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Drug Repurposing: Resurrection of Drugs

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ABSTRACT

There are innumerable definitions out there but in the most concise way can say it is a strategy by which newer values are generated from a drug by targeting diseases other than those for which it was originally intended. Drug repurposing takes much less time than the new drug. Advantages of drug repurposing over novel drug treatments are cost-effectiveness, time, and success rate. Repositioning of drugs lowers the overall cost of drug development. In other words, we can say, Drug repurposing is a boom for drug development arena. It shows that older drugs have a potential to revolutionize new medicine.

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INTRODUCTION:

There are innumerable definitions out there but in an almost concise way can say it is a strategy by which newer values are generated from a drug by targeting diseases other than those for which it was originally intended (1). In other words, to find new uses of existing, marketed, failed drugs(2). Currently, there are over 7,000 diseases worldwide that don't have effective treatments. This affects over 500 million people and it includes conditions such as cancer, Multiple Sclerosis, Alzheimer's, and many rare diseases. To overcome this crisis and get the better treatment it's a time to give a boost. Why should we look for drug repurposing? There is an obvious reason behind all these strategies. Drug repurposing takes much less time than a new drug. Advantages of drug repurposing over novel drug treatments are cost-effectiveness, time, and success rate (3).

1. Drug repurposing for diseases:

In 2012, more than 14 million people were diagnosed with cancer and there were 8.2million estimated cancer deaths(4). The repurposingofexisting non-cancer drugsisapotential source ofnewtreatmentoptions for cancerpatientswithhigh unmet medicalneeds. While scientific researchisprogressing rapidly inthe field ofdrug repurposing, theimplementation of drug repurposing stillfaces important financial andregulatory hurdles thatshouldbeaddressed to optimize clinicaladoption (5).

Cancer:

Non-steroidal anti-inflammatory (NSAID) is an original attribute of Aspirin and widely used due to itsanalgesic and antipyretic properties too (6). At low dose intake, it also shows anti-platelet and anti-thrombosiseffects through inhibition of COX-1, which involved in thesynthesis of Thromboxane A2, thekeyfor aggregation of platelets(7). According to data from in vivo and in vitro experiments, observational studies and trials have firmly shown that Aspirin has anti-neoplastic effects (8).The reported study established that regular use of aspirin significantly reduced colorectal, gastric, breast, biliary cancer after systemically trials (9). The anti-neoplastic property of Aspirin has been attributed to its mitigation of cyclooxygenase (COX) enzymes that promote carcinogenicity through PGE2 (9).Aspirin has also been linked to increases in 15-hydroxyprostaglandin dehydrogenase (15-PDGH) which is responsible for an inactivation of PGE2(10).Moreover, Aspirin blocks PGE2-induced secretion of CCL2and thereby recruitment of myeloid-derived suppressor cells(11). But

frequent use of aspirin shows therisk of cardiovascular disease for patients above 40 years(12).

Neurodegenerative diseases:

Formerly Auranofinwas being used for the treatment of arthritis but is now being investigated for potential therapeutic action in other diseases such as cancer, neurodegenerative disorders, HIV, anti-diabetic, parasitic infections and bacterial infections(13).The mechanism of action of Auranofin is to inhibit the oxidoreduction of enzymes that are capable of maintaining intracellular levels of reactive oxygen species(ROS).Inhibition of these enzymes ultimately leads to apoptosis and oxidative stress(14). Auranofin acts as an anti-inflammatory, changing cytokine levels by increasing interleukin-8(IL-8) and mitigating interleukin-6(IL-6) secretion from lipopolysaccharide-stimulating human monocyte. Auranofin also induces the anti-inflammatory enzyme hemeoxygenase (HOX)-1 in the human monocyte cell line THP-1 cells, guarding neuronal cells against oxidative stress potentiated by hydrogen peroxide(15). Moreover, Auranofin inhibits the neurotoxic effects of induced by primary human astrocytes(16). Auranofin also inhibits neuronal cells from microglia toxins Tumor necrosis factor (TNF) and nitric oxide. And it has also shown to reach the CNS in low concentrations(0.2-5lmol/L)(17).Auranofin may no longer be the drug of choice for rheumatoid arthritis, but there is potential for new applicationsin the treatment of bacterial infection, cancer, and parasitic infections and neurodegenerative diseases(18).

Tropical diseases:

World health organization (WHO) defines that Neglected tropical diseases (NTDs) are a diverse group of communicable diseases that prevail in subtropical and tropical conditions. According to World health organization, there are 17 infectious diseases (19).Originally Eflornithine was used to treat cancer, now being utilized as a topical agent for hirsutism. Eflornithineinhibits polyamine biosynthesis that leads to inhibition the growth of trypanosomes by the similar mechanism of action (20).Eflornithine has been successfully repositioned for Human African trypanosomiasis (HAT), also known as sleeping sickness. Trypanosomabrucei, T.b. gambienseand T.b. rhodesiense these are causative agents for aHAT. It's been prevalent in sub-Saharan Africa, HAT causes disruptions in sleeping patterns and leads to death in severe condition (21). Moreover, Eflornithine T.b. brucei infection in mice when given as a two percent solution in water; it is nontoxic. Due to use as a single

agent for so many years, eflornithine requires large dose. The combined use of nifurtimox-eflornithine mitigates drawbacks. Also, by combining Eflornithine with nifurtimox, the dose required, the complexity of administration and the cost of treatment reduced. Most importantly, Eflornithine is effective against stage 2 HAT whereparasite crosses the blood-brain barrier (BBB), and nifurtimox- eflornithine combined therapy (NECT) has become the most promising treatment for second stage T.b. gambiense infections (22).

Diabetes:

Diabetes growing faster worldwide and creating new drugs are is need to mitigate the chances of diabetes. Approximately 380million people are suffering currently (as per theInternational Diabetes Federation data) (23).Type 2 diabetes is solely based on regulation of blood glucose level. Various mechanisms contribute to aberrant glycemic control makes it the multifactorial disease. Parasitic worm infestations in humans were treated withNiclosamide ethanolamine (NEN) got approval by the US FDA. NEN is claimed to be amitochondrial uncoupling agent, it prevents diabetes in mammals by impacting energymetabolism. The demonstrations were made in mice, which depicted anincrease in expenditure ofenergy and increased lipid metabolism. The effectsdelayed the onset of diabetes, suggesting it would be a novel antidiabetic agent which iswell tolerated and non -toxic pharmaceutical agent(24, 25).

Sclerosis:

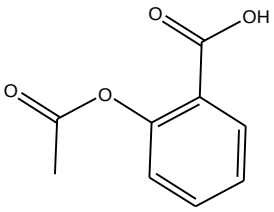
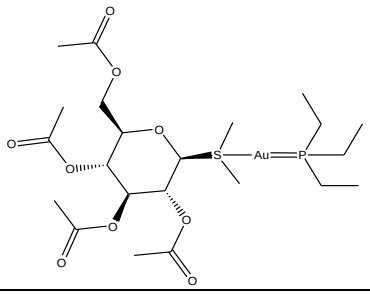
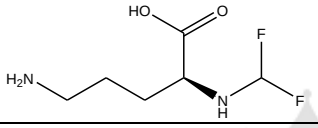
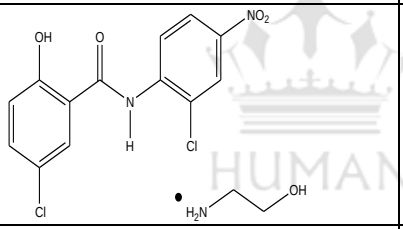
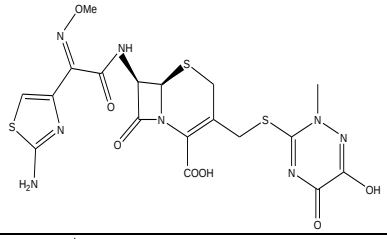
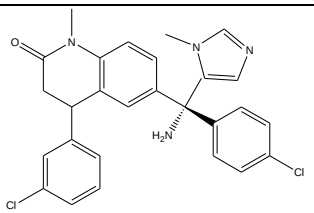
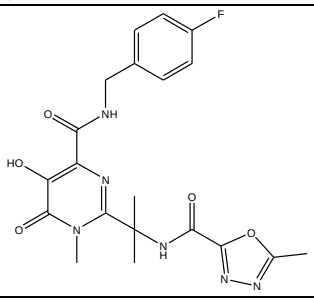
A potent stimulator of GLT-1expression was identified as a prime property of Ceftriaxone. In an Animal model, the rats showed mechanical hypersensitivity, induced by reduced carrageenan levels. They were treated systemically. A treatment ofceftriaxone (10-200 mg/kg) alone was given to rats through systemic acute intraperitoneal for 7 days (26). A synergistic action was observed whenceftriaxone was directed along with similar acting drugs like ibuprofen, paracetamol, celecoxib, or levetiracetam. An excitatory amino acid transporter 2 (EAAT2), is predominantlyexpressed in astrocytes is humanortholog of GLT-1 (27). The reduction in hyperexcitability of postsynaptic neurons isobserved when glutamate is taken up and the synapse is cleared. This new property ofceftriaxone leads the pharmaceutical ingredient to repurpose, thus used to cure amyotrophiclateral sclerosis. Moreover, the reduction of spinal tumor necrosis factor / (TNF/) andinterleukin 1b is expectedin line with the cytokine inhibiting effects of various antibiotics (28). Thus a reduction in synaptic

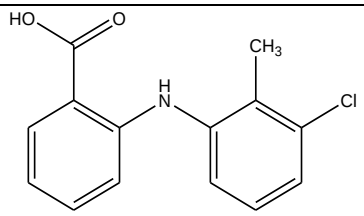
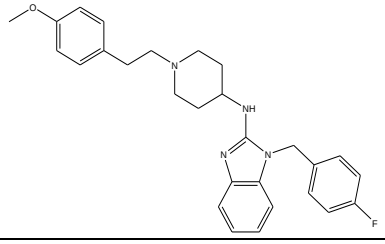
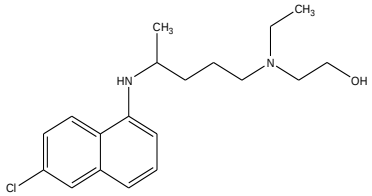
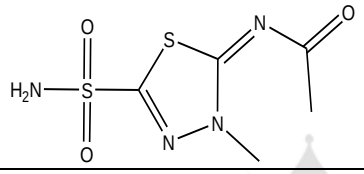
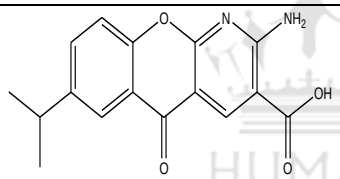
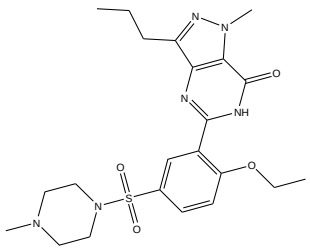
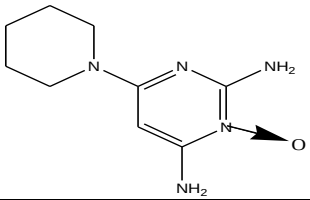
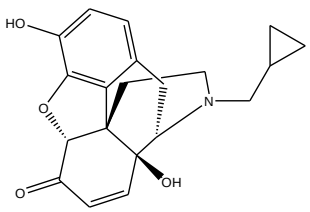
glutamate concentrations occurs by upregulation of glutamate transporter (GLT-1) expression caused by Ceftriaxone. ReductionofspinalTNF/ and IL-1b concentrations (29).

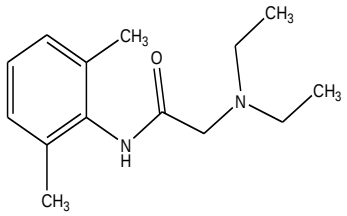
Malaria:

To treat malaria, protein farnesyltransferase inhibitors are administered. Proteinfarnesyltransferase (PFT) is an enzyme that transfers a Farnesyl group as a post-translationalmodification of specific proteins, including oncoproteins such as RasGTPase. Some well-developed cancer therapeutics contains PFT inhibitors (30). P.falciparum lacks type I protein geranyl geranyl transferase, an enzyme found in mammalian cells that is similar in structure to PFT which is type I protein lacked by P falciparum. P.falciparum does contain type II protein geranyl geranyl transferase, which acts on Rab GTPases. In mammalian cells treated with a PFT inhibitor (PFTI), proteins that are normally farnesylated can become geranylgeranylated by type I geranyl geranyl transferase. As P. falciparum lacks type I protein there can be high toxicity of PFTIs to malarial cells as this rescue is not possible. (31).Based on this hypothesis, Tests were carried out to check the ability of PFTIs in clinical and preclinical development to inhibit in vitro growth of P. falciparum parasites. By screening, the display of excellent potency in assays was observed using the isolated PfPFT enzyme and whole-cell P. falciparum organisms. A series of tetrahydroquinoline (THQ) PFTIs, typified by compound 12, was identified. Alongwith it, in a mice efficacy model of malaria, there was no observed toxicity in treated 12 eliminated parasitemia in 60% of mice. In order to improve clearance, oral bioavailability, preclinical metabolism and pharmacokinetic studies were conducted on agroup of most promising compounds from this campaign (32). Compared to controls in theefficacy study the rats treated with 13 showed significant reduction parasitemia after just three days of treatment, because of the rapid clearance the injections were requiredevery 8h for effective treatment. N-dealkylatedtetrahydroquinoline a major metabolitewas identified in a metabolism study. To block metabolism which takes by this pathway, thesynthesis of 2-oxo tetrahydro quinolines was stressed upon (33). Several compounds in this series showed significant improvement in clearance over their matched tetra hydroquinoline (THQ) analogs. After a period of time,PFT's which had the appropriate collection of potency and satisfactory pharmacokinetic properties for further development.Nevertheless, parasite PFT's remain a validated target for drug discovery. Above case study shows, it is possible to find parasitic enzyme inhibitors. We can hit human targets by knowledge of repurposing chemical entity (34).

Table: 1 (1-34)

Sr. No.	Drug	Structure	Original use	Proposed action
1	Aspirin		Antipyretic Analgesic Anti-inflammatory Antithrombosis	Anti neo-plastic
2	Auranofin		Rheumatoid arthritis	Neurodegenerative, Parasitic infections, cancer
3	Eflornithine (DFMO)		Cancer	Trypanosomes
4	Niclosamide ethanolamine		Parasitic worm infestations	Antidiabetic
5	Ceftriaxone		Hypersensitivity	Antinociception
6	Protein farnesyltransferase		Anticancer	Antimalarial.
7	Raltegravir		HIV-1 integrase; Antiviral activity.	Metnase; Adjuvant therapy in a cancer patient.

8	Tolfenamic acid		Cyclooxygenases, non-steroidal anti-inflammatory drug for short-term treatment.	Antiviral activity against Sin Nombre virus.
9	Astemizole		Histamine H1 receptors; antihistamine for treatment of allergy	Inducer autophagy; as adjuvant therapy in prostate cancer
10	Hydroxychloroquine		Malaria, rheumatoid arthritis	Anti-inflammatory
11	Methazolamide		Glaucoma	Suppresses hepatic glucose production
12	Amlexanox		Oral aphthous ulcers	Anti-inflammatory
13	Sildenafil		Agina	Erectile dysfunction
14	Minoxidil		Hypertension	Hair loss
15	Naltrexone		Opioid addiction therapy	Alcohol withdrawal therapy

16	Lidocaine		Local anesthetic	Antiarrhythmic

2. Knowledge of therepositioning of drug:

With respect to funding, the studies and observations would improve the research along with logistics. Research studies also insights the strong points and the weak points of performing repurposing of a drug in the academic setting.

4. The Benefits of Drug Repurposing:

Less Risky: Having success rate of 1 in 10000 (30% in 2012) amongst the new chemical entities in overall research of pharmaceuticalsand process of design. The reasons include the lengthy and rigorous standards imposed by thegovernment; it has ahigh probability of rejection. It is a difficult task to get a new drug approved.

Faster: The novel drug discovery takes approximately 20-30 years whereas if the drug is designated repurposed, it needs only 4 years.

Cheaper: Bringing new drug takes much time and with many expenses for pharmaceutical companies. Thetests on laboratory animals are narrowed down using repurposed drugs.Vol. 8,

CONCLUSION:

Drug repositioning making an opportunity to treat innumerable diseases.These efforts have led to benefits current aura of drugs market. Repositioning of drugs lowers the overall cost of drug development. In other words, we can say, Drug repurposing is a boom for drug development arena. It shows that older drugs have a potential to revolutionize new medicine. Moreover, it lowers the credibility of computational study for repurposing. Drug repurposing has become indispensable in today's world and pharma industries looking forward to it. So, drug repurposing is a new hope.

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