Review article:
Challenges and Opportunities in Repurposing of Drugs: Mini Review
Sindhu S¹ and Murugan S²

Abstract:
Repurposing of drugs is an emerging area in the field of medicine. Formulation of new drugs for treating a new clinical condition takes time and consumes a lot of investment. Therefore, there is much attention given towards repurposing of old drugs for new therapy. Majority of drugs approved by FDA for a particular treatment has found applications in the treatment of various other clinical conditions too. In other words, it can be said as ‘reusing’ of a drug. This mini review focused on the use of repurposed drugs for bacterial infections and cancer treatment. Apart from the benefits of repurposing of drugs, there are some challenges needed to be addressed. Therefore, in this review paper the use of repurposed drugs in treatment of communicable (bacterial infections) and non-communicable (cancer) diseases were discussed.

Keywords: Repurposing of drugs; phase V clinical trial; lifestyle drugs

Introduction
Drug repurposing, is also known as re-profiling, repositioning, reusing and rediscovery of drugs. The main objective of drug re-profiling is to explore the possibility of using approved drugs for treatment of new diseases. The de novo drug discovery and development can take at least 13 years and cost close to 2 billion dollars. Re-profiled drugs can overcome initial cost and time when compared to formulation of new drugs. Moreover, the rates for repurposed compounds that reach the market are 25% from Phase II and 65% from Phase III clinical trials, in comparison to new molecular entities are 10 and 50%, respectively. Drug re-profiling allows investigators to bypass toxicity studies and so it appears to be cost and time-effective.

According to Sir James Black (1998), “The most fruitful basis for discovery of a new drug is to start with an old drug”. The repurposing of drugs is sustained by two scientific concepts namely: known target with a new medication and known drug with a new target. FDA has approved many repurposed drugs which were currently introduced into the market. Some of the examples include thalidomide by Celgene corp; which was initially prescribed for nausea and insomnia in pregnant women in 1950, but later it was approved by FDA for the treatment of leprosy in 1998 as Thalomid. Likewise, Azidothymidine which was used for treatment of cancer is now repurposed as an HIV therapeutic and vice versa. Similarly, olaparib, an anticancer agent is under trial for 3rd degree burn. Table 1 shows the list of few FDA approved repurposed drugs.

Table 1: Repurposed drugs for several indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual usage</th>
<th>Repurposed to treat</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Anti-diabetic</td>
<td>Pancreatic cancer stem cell</td>
<td>7</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Breast cancer</td>
<td>Anti-bacterial activity</td>
<td>8</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Leukaemia</td>
<td>Parkinson’s disease</td>
<td>9</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Breast cancer</td>
<td>Osteoporosis</td>
<td>10</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Anti-diabetic</td>
<td>Liver disease, weight loss</td>
<td>11,12</td>
</tr>
</tbody>
</table>

1. S Sindhu
2. S Murugan
   Department of Biotechnology, School of Agriculture and Biosciences, Karunya Institute of Technology and Sciences, Coimbatore- 641 114, India

Correspondence to: S Murugan, Department of Biotechnology, School of Agriculture and Biosciences, Karunya Institute of Technology and Sciences (Deemed to be University) Coimbatore- 641 114, India, E-Mail ID: micromurugans@gmail.com, murugan@karunya.edu
Opportunities of repurposed drugs in bacterial infections

Bacterial infections have become a major threat to the human population as it becomes a leading cause of death. The overuse, misuse and lack of new antibiotics have led to the development of drug resistant bacteria which is a public menace. These bacterial infections with multiple drug resistance may increase the mortality and morbidity in Intensive Care Unit patients. The multidrug resistance of bacteria occurs mainly due to two mechanisms: (i) accumulation of multiple genes on resistance (R) plasmids, with each coding for resistance to a single drug, within a single cell and (ii) by the action of multidrug efflux pumps, each of which can pump out more than one drug type. Examples of few drug resistant microbes include: i) *E. coli* resistant to cephalosporins and fluoroquinolones, ii) *Klebsiella pneumoniae* resistant to cephalosporins and carbapenems, iii) *Staphylococcus aureus* resistant to methicillin, iv) *Streptococcus pneumoniae* resistant to penicillin, v) Non-typhoidal *Salmonella* resistant to fluoroquinolones, vi) *Shigella species* resistant to fluoroquinolones, vii) *Neisseria gonorrhoeae* resistant to cephalosporins, viii) *Mycobacterium tuberculosis* resistant to rifampicin, isoniazid and fluoroquinolones.

Currently researchers are working on developing new antibiotics with some criteria like (i) focussing on new targets and processes like bacterial cell-cell communication that upregulates virulence; (ii) usage of alternate antimicrobials like bacteriophages; (iii) designing inhibitors of bacterial resistance, such as blockers of multidrug efflux pumps. In addition to the development of new antibiotics a different approach of “New uses of old drugs” is a booming concept in pharmaceutics. Clinical survey reports suggested that nearly 24 drugs which are already in use are remarked for new treatment. Some of the FDA approved repurposed drugs for treating bacterial infections were mentioned in Table 2.

Table 2 : Repurposed drugs for bacterial infections

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Use</th>
<th>New Use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Anti-viral</td>
<td>Parkinson’s disease</td>
<td>13</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Pain killer</td>
<td>Heart attack</td>
<td>14</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Sedative</td>
<td>Leprosy</td>
<td>15</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>HIV/AIDS</td>
<td>Cancer</td>
<td>16</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Anti-inflammatory</td>
<td>Anti-microbial</td>
<td>17</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rheumatoid arthritis and Psoriasis</td>
<td>Transplant rejection</td>
<td>18</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Urinary tract infection</td>
<td>Tuberculosis</td>
<td>18</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Rheumatoid arthritis</td>
<td>Anti-diabetic</td>
<td>52</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Hypertension and Angina</td>
<td>Erectile dysfunction</td>
<td>54</td>
</tr>
<tr>
<td>Miltefosine</td>
<td>Breast cancer</td>
<td>Anti-leishmanial</td>
<td>22</td>
</tr>
</tbody>
</table>

Challenges and Opportunities in Repurposing of Drugs: Mini Review
Sindhu S and Murugan S

Opportunities of repurposed drugs in Cancer Treatment

In the recent days, cancer is a major threat for the community. The cause of cancer due to genetic defects accounts only for 5-10%, whereas 90-95% cases were due to environmental factors and lifestyle\(^3\). Some of the methods of treatment include surgery, chemotherapy and radiation therapy. In addition complementary treatments like molecular therapy, immunotherapy, apoptosis regulation, anti-angiogenesis therapy, differentiation therapy, signal-transduction therapy, targeted radionuclide therapy and nucleic-acid-based therapies. Moreover, tumour resistance to anticancer drugs is a major problem faced now days\(^5\). The FDA approved drugs for cancer has declined since 1990s. Due to the lack of enough medications the new concept, drug repurposing of FDA approved non-cancer drugs were developed\(^6\). Apart from new introduction of drugs discovered for treating cancer, only 5% of drugs enter into phase I clinical trials are continuously used for cancer treatment, therefore already existing non-cancer drugs are tested for its anticancer activities\(^4\). Previous research reports showed that the treatment using a single agent of drug is less effective than combination therapies as the DNA mutations due to cancer is greater. Therefore repurposing of non-cancer drugs which have undergone preclinical and clinical studies may offer effective treatment for cancer patients\(^7\). Some of the FDA approved drugs for cancer treatment were depicted in Table 3.

Table 3 : Repurposed drugs for cancer treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Use</th>
<th>New Use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Diabetes</td>
<td>Breast Cancer</td>
<td>36</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>Anti-helminthic</td>
<td>Lung Cancer</td>
<td>37</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Stroke</td>
<td>Colorectal Cancer</td>
<td>38</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Anti-malarial</td>
<td>Suppress growth of tumour cells</td>
<td>39</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Osteoporosis</td>
<td>Breast Cancer</td>
<td>40</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Nausea</td>
<td>Bone marrow cancer</td>
<td>41</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Gastric or duodenal ulcer</td>
<td>Colorectal cancer</td>
<td>42</td>
</tr>
</tbody>
</table>
However, reports of successful drug repurposing for cancer treatment were limited. Therefore, there is a large gap towards repurposing of drugs for treatment of cancer, thereby researchers have plenty of opportunity in exploring the FDA approved non-cancer drugs for treating cancer.

**Challenges with repurposing of drugs**

Apart from benefits, repurposing of drugs faces huge challenges due to which there are limitations in the market for repurposed drugs. Repurposing clinical trials cost a huge amount of money, demonstration of safety needs, efficacy establishment, lack of patent protection and commercialization. Despite the advantages like low cost, less time consuming, the financial support for drug repurposing approaches has been lacking, shorter patent duration, and low return on investment. Moreover, FDA offers only a period of three years exclusively for a new use of previously used drug for a new indication, which is very short period of time to regain the invested money and in case a loss for the pharmaceutical industry.

Making Medicalization of certain physiological conditions could be a basis for repurposing of drugs e.g. Sildenafil is used for hypertension and was repurposed for erectile dysfunction. This concept has been discussed under lifestyle drugs. According to Ringel, a drug that has already failed because of toxicity issues cannot be used for new indications. He also suggested that by understanding well about the disease targets and mechanisms, it is possible to overcome market imperfections that prevent repurposing. Some companies are trying to develop platform to build disease matrices and molecules to treat those diseases.

Moreover, not all repurposed drugs are successful. For example, bevacizumab, the kinase inhibitor which has been repositioned to many cancers, failed to show its efficacy for gastric cancer in phase III trials. Likewise, multi-kinase inhibitor, sunitinib which was approved for treatment of Gastrointestinal Stromal Tumour (GIST’S), renal carcinomas and pancreatic neuroendocrine tumours failed in its clinical trials for treatment of breast cancer, prostate cancer and Non-small Cell Lung Cancer. The other risks of repurposing of drugs may include side effects for new indications, as the drug has been already used for some other purpose. There should be thorough clinical trials prior to the usage for repurposed drugs. There may be some changes in the concentration of dosage to treat a new indication or may be in the root of administration, as though perfect clinical trials must be carried out.

**Conclusion**

This mini article is written in a point of view to develop knowledge and awareness among the research community about the upcoming trend “Repurposing of drugs” for communicable and non-communicable diseases. Therefore, repurposing of drug is a blessing for people suffering from diseases caused by multiple drug resistant organisms across the globe. Drug reprofiling therefore has its own benefits and consequences which must be thoroughly studied before making it as a practise. Therefore, a clear view on benefits and consequences of drug-reprofiling can be obtained.

**Conflict of interest:** None

**Source of Fund:** Nil

**Ethical Clearance:** Not Applicable

**Author’s Contribution**

Data gathering and idea owner of the study: Sindhu S and Murugan S

Study Design: Murugan S

Data gathering: Sindhu S

Writing and submitting: Sindhu S and Murugan S

Editing and approval of final draft: Murugan S
References:


13. Lee HM and Kim Y, Drug Repurposing is a new opportunity for developing drugs against neuropsychiatric disorders. Schizophr Res Treatment, 2016; 6378137.


24. Karak P, Kumar KA, Mazumdar K, Mookerjee M and Dastidar SG. Antibacterial potential of an antispasmodic


48. Kim S, Ding W, Zhang L, Tian W and Chen S. Clinical response to sunitinib as a multigated tyrosine-kinase inhibitor (TKI) in solid cancers: a review of clinical


