Repurposing non-cancer drugs to treat cancer

Drug repurposing, sometimes also referred to as drug repositioning, is a drug development strategy that seeks to reuse licensed drugs for new indications [1,2]. The advantages of repurposing existing well-characterized and widely used drugs are many and obvious, for example the reuse of established pharmacokinetic and toxicology data (including rare adverse events), and low costs (especially for generic medications). This could lead to a significant reduction in the development life-cycle, for example by reducing the need for early-phase clinical trials assessing safety and tolerance.

Examples of successful repurposing are fairly common in medicine. One example is sildenafil (Viagra), which was developed for hypertension and angina, but repurposed for erectile dysfunction and then subsequently licensed for pulmonary arterial hypertension. Another example is methotrexate, one of the first commonly used chemotherapeutics in cancer, now routinely used for severe psoriasis and rheumatoid arthritis. Methotrexate is not the only cancer drug being repurposed for non-oncological conditions; however, examples of non-cancer drugs being repurposed for treating cancer have only a single example, viz. thalidomide. Thalidomide was widely used as a treatment for morning sickness before infamously the association with birth defects was discovered. The drug has subsequently been licensed by the FDA for the treatment of leprosy, and later by the FDA and EMA for the treatment of multiple myeloma.

However, a growing number of clinicians and researchers believe that there are many more agents that can make a positive contribution to cancer treatment. The Repurposing Drugs in Oncology (ReDO) project – an international collaboration looking specifically at this issue – founded by two not-for-profit foundations – the Anticancer Fund, based in Brussels, and GlobalCures, based in Massachusetts [3]. The project strategy has been to identify approved drugs with the potential to make a clinical difference and bringing them to the attention of clinicians and researchers by summarising and publishing the data in peer-reviewed journals. In parallel, the parent organisations involved in ReDO have also been collaborating with a range of investigators in different clinical trials to establish the efficacy of some of the drugs they have identified (http://www.anticancerfund.org/projects/currently-ongoing).

Selecting drug candidates

An initial surprise was the high number of potential repurposing candidates; in fact the problem has been to identify the most promising targets rather than simply identifying possible targets. The major criteria used in target selection are:

- The drug should be well-known and widely used clinically;
- Low toxicity, particularly if it is for long-term use;
- There is a relevant putative mechanism of action;
- It shows strong evidence of anticaner activity. Human data is valued significantly more highly than in vitro and animal data.
- Preclinical data in syngeneic, orthotopic transplantable models or genetically engineered mice is rated more highly than other forms of in vivo models;
- There is evidence of anticancer efficacy at standard dosing or at a level that is not associated with significant toxicity;
- The drug is not currently being widely pursued as an active agent in oncology.

The last criterion is important as there are a number of candidate drugs currently under intense scrutiny and clinical investigation in oncology, including aspirin, metformin and some statins. ReDO therefore focuses on drugs that have yet to achieve the kind of momentum illustrated by, for example, the Add Aspirin trial (http://www.addaspirintrial.org/).

To date there are published articles on six candidate drugs: mebendazole [4], cimetidine [5], itraconazole [6], nitroglycerin [7], clarithromycin [8] and diclofenac [9] – Table 1 gives details. Other targets with high potential currently being investigated include the non-selective beta-blocker, propranolol, the anti-malarial, chloroquine, and angiotensin II receptor antagonists (losartan, telmisartan, etc.).

Dirty drugs?

It is apparent from Table 1 that the range of agents with potential for reuse in oncology encompasses an extremely diverse set of drug families. Many different mechanisms of action are at work and only a few of these drugs are directly cytotoxic. Instead many of them have effects on the tumour microenvironment or the immune response, which include:

- Disruption of key pathways that mediate resistance to existing treatments, for example, affecting drug efflux or other mechanisms of resistance;

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While the promise of repurposing is that these drugs are relatively cheap, easy to access and potentially easy to adopt clinically, the promise can only be realised if there is convincing evidence of efficacy. There are numerous clinical trials in progress exploring combinations of repurposed drugs and existing standard of care therapies, including:

- Breast cancer (NCT01806259) – **Ketorolac** 30 mg IV, pre-incisional in patients undergoing curative resection;
- NSCLC (NCT01210378) – Transdermal nitroglycerin patch with standard of care (chemo-radiotherapy);
- Pediatric optic nerve gliomas (NCT02115074) – Combination of *celcoxib* and *fluvastatin*;
- Osteosarcoma (NCT02517918) - Metronomic cyclophosphamide, methotrexate, *zoledronic acid* and *sirolimus* in patients with advanced pre-treated osteosarcoma;
- NSCLC – A prospective phase II, randomized multi-centre trial of a bio-modulatory treatment with 3 oral drugs (*clarithromycin, pioglitazone* and *metronomic treosulfan*) in patients with NSCLC after platinum failure. However, there are some cases where the body of evidence in favour of a drug includes high-quality randomised Phase III trials. One of the most striking examples is the classical H2 histamine receptor antagonist, cimetidine. Clinical trials of cimetidine have been carried out in a range of cancers including colorectal, gastric, renal cell carcinoma and melanoma [5]. The results from colorectal cancer are the most extensive; a Cochrane review concluded that “cimetidine appears to confer a survival benefit when given as an adjunct to curative surgical resection of colorectal cancers” [10]. Cochrane analysis of the 5 cimetidine trials meeting the inclusion criteria, which included 421 patients, yielded a statistically significant improvement in overall survival (HR 0.53; 95% CI 0.32 – 0.87).

**Perverse Incentives**

While the scientific case for repurposing is being made by ReDO and other investigators [11,12], and is now being discussed more widely in the oncological community [13,14], there are significant obstacles in the path to clinical adoption of repurposed drugs.

The first issue is related to the fact that many of the drugs of interest are generics and no longer covered by patent protection. Given the costs associated with running large randomised controlled trials, the lack of patent protection means that pharma companies cannot guarantee a return on their investment should they fund trials. The situation with combination therapies is still more complex, with multiple companies involved the situation requires extended legal negotiations and contracts, all of which require an investment in time and money which cannot be recouped. One upshot of this is that it is often more expensive for institutions to run a trial using cheap generic drugs than it is to run a trial using a significantly more expensive proprietary agent. This leaves many potentially useful treatments languishing as ‘financial orphans’ [15].

The example of cimetidine is

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### Table 1 - High-potential drugs for repurposing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Original Indication</th>
<th>Relevant Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebendazole</td>
<td>Anti-parasitic</td>
<td>Microtubule disruption, Hedgehog pathway inhibition, anti-angiogenic</td>
<td><em>In vitro, in vivo and some human case studies. PS3 independent, also targets XIAP. Currently in trials in glioblastoma.</em></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Antacid</td>
<td>Cellular proliferation, immunomodulatory, cell adhesion</td>
<td>Evidence that post-operative use reverses immunosuppression. Currently in trial in colorectal cancer.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Antifungal</td>
<td>Hedgehog pathway inhibition, anti-angiogenic, targets cancer stem cells, reverse MDR</td>
<td>Hedgehog a target of interest in multiple cancers. In trials in BCC, prostate and NSCLC.</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Vasodilation</td>
<td>Chemo/radio-sensitisation, anti-hypoxic (HIF1-alpha)</td>
<td>HIF1-alpha a target of interest in multiple solid tumours. Current trials in NSCLC.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Antibiotic</td>
<td>Autophagy inhibition, anti-angiogenic, immunomodulatory</td>
<td>Most evidence in multiple myeloma and some lymphomas. Currently in trials in MM, lymphoma and NSCLC.</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>NSAID</td>
<td>Anti-angiogenic, COX-2/PGE2 inhibitor, immunomodulatory</td>
<td>Pre-clinical and epidemiological data exists, but currently no trials are in progress. The related drug ketorolac in being trialled in breast cancer.</td>
</tr>
</tbody>
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- Inhibition of tumour neo-angiogenesis/vascularization;
- Stimulation of host immunity and/or reversal of cancer-associated immunosuppression;
- Targeting of oncogenic pathways, for example, Hedgehog signalling;
- Disruption of key proliferative pathways, for example, disrupting microtubule dynamics.

Many of these drugs were developed for clinical use at a time when our knowledge of the molecular biology of cancer was far less developed. In contrast to the modern paradigm of drug development – which identifies relevant molecular pathways and then designs specifically targeted agents – many of these older drugs serendipitously have multiple clinically relevant pathways. While once these old drugs were considered ‘dirty drugs’, we can now more usefully classify them as multi-targeted agents.

However, even with these multi-targeted agents, it is unlikely that any single drug will be sufficient to treat cancer. Therefore a key consideration in investigating these repurposed drugs is to consider how it is that they may be used therapeutically. Typically this means combinations of one or more repurposed drugs with existing therapies. The ReDO papers have explicitly addressed this issue and have identified combination treatments that may be of value in specific clinical settings.

**Clinical Trials**

While there is human data to show an anticancer effect for the candidate drugs, much of this is either retrospective or from small early-phase prospective trials.

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instructive in showing that, even with data from multiple Phase III trials, a drug with efficacy may not make it into clinical practice. One factor may be related to the issue of licensing or label extension for a new indication. In normal practice a repurposed drug is typically granted a marketing authorization for a new medical indication by the regulator (the MHRA in the UK). In the absence of a specific license clinicians are often reluctant to prescribe a treatment ‘off-label’, even if evidence of efficacy exists. Off-label prescribing is not the long-term strategy that manufacturers cannot guarantee a return on their investment should they seek a new license or label extension.

Conclusion
Drug repurposing holds much potential to deliver new therapies to patients in an accelerated time-frame and at reduced costs compared to de novo drug development. While there is a renewed level of interest in this strategy, there are significant impediments to progress associated with financial incentives and social policy issues.

References
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