

EDITORIAL

Repurposing drugs in your medicine cabinet: untapped opportunities for cancer therapy?

“As a society we have the chance to mine for potential therapeutic gold in our existing non-cancer drug supply. We owe it to patients to overcome the economic and social impediments that stand in that path.”

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Many forms of cancer lack efficacious treatments, despite continuing advances in our understanding of molecular biology, and the development of precisely targeted agents that exploit relevant drivers and pathways of malignancy. To date the effectiveness of most tumor cell-focused molecularly targeted agents, in terms of event free and overall survival appears to be modest [1]. What is more, these new drugs come with a high price tag as companies seek to recoup development costs and to generate a return on investment (in part a consequence of a high attrition rate in oncological drug development, high regulatory burdens and expensive clinical trial costs) [2].

In the developing economies of the world, where cancer incidence is rising, the problems of unmet patient need is exacerbated by these high costs, putting many cancer treatments out of reach of patients and imposing strains on local health systems [3].

An alternative approach to seeking new drug treatments for cancer is not to start with molecular targets in mind, but to assess those drugs – approved for any indication – in our existing armamentarium

which show some evidence of anticancer activity. This is the field of drug repurposing in oncology and there is now an increasing interest in the use of non-cancer drugs as anticancer therapeutics.

There are two main advantages of repurposing. Firstly, by starting with well-known and well-characterized drugs we can draw on existing and detailed knowledge of pharmacodynamics, pharmacokinetics, bioavailability, toxicities, established protocols and dosing. This body of knowledge is far in excess of what can be gained in early phase clinical trials of new agents, particularly for first in class drugs. This is not to say that repurposed drugs do not need Phase I trials, since they may be used for cancer in schedules and combinations that differ from their accepted use, but it does represent a considerable short-circuiting of the preclinical phase of the drug development life cycle [4].

Secondly, many of the candidate drugs for repurposing are available at low cost; indeed many are available as generics. This is in stark contrast to the very high costs associated with the newest agents emerging from current pharmaceutical pipelines.

KEYWORDS

• drug repurposing • health economics • health policy • off-label drugs • ReDO Project

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While this is of secondary concern compared with the question of clinical efficacy, it is a key concern to stressed health systems, insurers and ultimately patients. It suggests that in cost–utility calculations, repurposed drugs would score more highly assuming that they demonstrate clinical efficacy.

The range of candidate drugs for repurposing in oncology is actually extremely wide. In fact, the difficulty is not to find candidate drugs but to filter the long list of potential agents so that we may focus on those with the most evidence of efficacy at physiologically relevant doses, with low toxicity and at low cost. The Repurposing Drugs in Oncology (ReDO) Project is an international collaboration aiming to identify the candidate drugs with the highest clinical potential and to bring them to the attention of the research and clinical oncology communities [5].

Drugs are considered high-potential targets if they meet the following criteria:

- Are well-known and widely used clinically. Availability as a generic is an advantage, but on-patent drugs are not excluded;
- Have good toxicology. Low toxicity even with long-term use is seen as a distinct advantage;
- Have a relevant putative mechanism of action – although it is accepted that sometimes drugs have off-target effects independent of the main mechanism of action for which the drug has been developed;
- Show a high level of evidence of anticancer activity – *in vitro*, *in vivo* and human data. Human data in particular is scored significantly more highly. For preclinical evidence results in syngeneic, orthotopic transplantable models or genetically engineered mice, is rated more highly than other forms of *in vivo* models;
- Show evidence of anticancer efficacy at standard dosing or at dosing which is known not to be associated with significant toxicity;
- The drug is not currently being widely pursued as an active agent in oncology.

Examples of the drugs that the ReDO project has identified as high-potential agents includes mebendazole (anthelmintic) [6], cimetidine (H₂-receptor antagonist) [7], nitroglycerin (vasodilator), diclofenac (NSAID), itraconazole (antifungal) and clarithromycin (antibiotic). Other noncancer drugs that are being actively

investigated in clinical trials in cancer include metformin, aspirin and hydroxychloroquine. Thalidomide is an example of a noncancer drug that has successfully been repurposed as a treatment for multiple myeloma.

It should be noted that these high-potential agents have diverse initial indications and putative mechanisms of action. They may be cytotoxic or may instead exert an anticancer effect by acting on one or more aspects of the tumor microenvironment. For example, they might:

- Disrupt key pathways that mediate resistance to existing treatments – for example, affecting drug efflux or other mechanisms of resistance;
- Interfere with tumor neo-angiogenesis or tumor vascularization;
- Stimulate host immunity and/or reverse cancer-associated immunosuppression;
- Disrupt key proliferative pathways – for example, disrupting microtubule dynamics.

It should be apparent that individually none of these mechanisms is likely to be sufficient to attack the multifaceted disease process that is cancer. It is imperative, therefore, that we think systemically when exploring the potential of repurposed agents and consider repurposed agents in combination with existing anticancer treatments and in combination with each other.

Some repurposed drugs might be used short-term in combination with existing chemotherapies or targeted therapies. Others may be used in more chronic or continuous dosing, an obvious overlap with the movement towards metronomic chemotherapy. In this case there is an emphasis on low toxicity, in contrast to the classical dose-dense Maximum Tolerated Dose protocols of standard chemotherapy [8]. The focus is not on maximum cytotoxic effect and massive tumor kill, but in altering the tumor microenvironment such that the ‘life support’ systems of the tumor are attacked. In common with metronomics, many of the drugs being investigated for repurposing are suitable for chronic treatment at doses that do not cause adverse effects and consequent toxicity with a negative impact on patient quality of life.

Identifying these high-potential agents, summarizing the data, identifying probable combination protocols and making all the data available to researchers and clinicians is relatively straightforward. However, the more intractable task is to move these agents into definitive trials

to provide the necessary evidence of safety and efficacy in order to change clinical practice.

Given that many of the drugs being investigated for repurposing are either coming to the end of their patent lifetime or are already available as generics, there is an obvious issue with economic incentives. There are considerable costs attached to the process of taking drugs through Phase I to Phase III clinical trials, and beyond that to statutory approval and adoption in clinical practice. Without IP protection, there is no economic incentive for pharmaceutical companies to make the considerable investment in this process. These drugs can be considered 'financial orphans,' agents with known efficacy that languish without adoption by agencies or companies with the incentive to take them to market [9]. Clearly this is a social issue of the utmost importance requiring innovative solutions to what is essentially an economic issue, not a medical one. Collaborations between non-profit organizations, governments, regulatory agencies, health insurers and patients' organizations should be encouraged to lead to such a paradigm shift.

Finally, there exists another key impediment that demands action. The trend in recent years has been on ever larger Phase III clinical trials of new cancer agents. In part, this trend has been driven by the need to adequately power trials so that the often incremental improvements in overall or progression-free survival wrought by these new agents can be measured [10]. Well-designed, well-run and adequately powered clinical trials with repurposed drugs do take place, although not on the scale of the trials in some of the new targeted agents. Large trials are not necessarily needed if the repurposed drug(s) lead to substantial improvements in outcomes or if a specific population of patients can be identified in whom the drug is most likely to show clinical benefit. Even after such data

becomes available, there will be the challenge of 'marketing' it to practitioners, since commercial entities are unlikely to get involved, unless the intervention in question is used as an adjunct to a standard of care drug that carries commercial interest.

A case in point is the H₂RA cimetidine (Tagamet). A number of clinical trials established that peri-operative and postoperative cimetidine provided a survival benefit when given as an adjunct to curative surgical resection of colorectal cancers, a finding confirmed in a subsequent Cochrane review [11]. However, to date, these results have not been translated into clinical practice, despite the fact that there is an acknowledged need for new treatment strategies.

We are faced with the challenge of meeting the existing and future unmet needs of cancer patients in both advanced and developing economies. In the repurposing of non-cancer drugs for oncology we are seeking new treatments that meet these needs in as short a time-frame as possible and at a cost that is affordable both in developed and developing countries. As a society we have the chance to mine for potential therapeutic gold in our existing non-cancer drug supply. We owe it to patients to overcome the economic and social impediments that stand in that path.

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