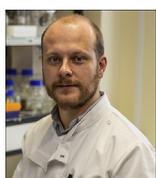




editorial



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Renovation as innovation: is repurposing the future of drug discovery research?

Repurposing is increasingly hailed as a solution to the problems of the high costs and poor productivity of drug development. Instead of starting with a disease and beginning the laborious and expensive task of discovering a new drug, researchers can initiate the discovery process with a drug in hand, and simply look for the right disease. The question is: Will repurposing fulfill its promise and, if so, should we scale back our commitment to basic research and novel drug discovery, and focus instead on second-chance drugs?

With repurposing success stories, such as Viagra and thalidomide, as inspiration, the National Institutes of Health (NIH) offers grants to take advantage of failed drugs as 'partially developed therapeutic assets' that have 'cleared several key steps along the development path,' and can, therefore, 'accelerat[e] the pace of . . . development' [1,2]. The US Food and Drug Administration (FDA) and the Medical Research Council have followed suit with repurposing initiatives, while governments and foundations have offered grant funding, and companies have provided access to large libraries of compounds [3–5], all with the goal of turning pharmaceutical failures into medical successes by testing unsuccessful compounds in different diseases.

Despite all the excitement (a new scientific paper with repurposing in the title appears nearly every day), there has been impressively few data on success rates. So far, repurposing advocates have told compelling stories about the well-known examples, but all of the numbers have been estimates and projections. These estimates have ranged from 30% [6] to as high as a potential 75% success rate [7].

If such high success rates are possible, policy-makers would need to rethink their longstanding commitments to basic biomedical research, where any successful outcomes will be more time-consuming, more expensive, and considerably less likely. With thousands of partially developed compounds with which to work, and the FDA approving new molecular entities at the rate of only about 20 or so each year, a 75% (or even 30%) success rate for repurposing the thousands of failed drugs would satisfy the regulators' and payors' ability to absorb new medicines for a century or more.

In light of newly available data, repurposing certainly has promise, but it would be premature to abandon fundamental research in its favor. We have analyzed the complete clinical development history of 834 drug candidates that started clinical trials between 1980 and 2012. The analysis clearly shows that repurposing can be expected to yield important new medicines, but those successes are unlikely to occur at the high projected rates (Table 1).

In considering redirecting old drugs, it is important to distinguish between what might be the lower hanging fruit (i.e., finding new uses for already approved drugs) and the harder to reach variety: turning failed drugs into successful ones in other diseases. Both 'repurposing' and 'repositioning' have been used to describe either or both of these phenomena, although most of the policy arguments for repurposing revolve either around failed drugs or successful ones that are redeveloped for entirely new therapeutic areas.

When it comes to evaluating the prospects for repurposing, there are two key questions to ask: (i) What are the chances that we will find a good reason to try a drug against a disease other than the one for which it was developed? And (ii) once we have formulated that hypothesis, what is the likelihood of success?

Overall, 21% of the products we reviewed were approved by the FDA and launched commercially for the first indication against which they were tested. With a successful drug in hand, the pharmaceutical industry has regularly sought to the expand its use in the same therapeutic area, such as testing a breast cancer drug in ovarian cancer [6]. Such line extensions were attempted for only 31% of the initial successes, but they had a high success rate: 67% of the products had at least one additional success in the same therapeutic area (e.g., cancer, autoimmune disease, cardiovascular disease, etc.) as the first indication.

More relevant to the repurposing question is how these successful drugs fared in different therapeutic areas. A considerably smaller percentage of these initial successes entered clinical testing in a different therapeutic area, and the success rate dropped dramatically. Only 18% of the products were tried in another area, and only 33% of those attempts succeeded.

The alchemy involved in turning failures into successes is even more complicated. Only 16% were tried in another indication, and most were in the same therapeutic area, with only 10% of the initial failures tried in a different area altogether. Whether the therapeutic area was the same or different, the success rate was the same: 9%.

Despite the difficulty of finding a good hypothesis in these classic repurposing cases, and then proving it with clinical results, the rewards can be substantial. Some of these once-failed drugs have become valuable commercial and medical products. Two of them, infliximab and etanercept, both initially developed for treating sepsis, are approved for the treatment of rheumatoid arthritis, and were ranked among the top five best-selling drugs in 2016 [8].

Interestingly, and adding to the challenges presented by repurposing, we could find no predictive pattern among the successfully repurposed products. The success rates for small and large molecules were similar, and the successes were distributed across a range of therapeutic areas. The only pattern that did emerge clearly was that most of the attempts, and most of the successes, were in the same therapeutic area, which is outside of the main theme of repurposing, that of finding entirely new uses for existing molecules.

How promising are these success rates? Despite ever more sophisticated methods for conducting pharmaceutical research, clinical success rates have remained disappointingly low. The most recent major study [9] reported an ~10% success rate for all of the therapeutic indications for which potential new medicines have entered clinical trials. Additionally, various publications have cited a 5% success rate from the start of formal pre-investigational new drug toxicology testing [10].

These low rates of success have been accompanied by inexorably increasing drug development costs, a phenomenon sometimes called 'Eroom's law,' which states that the 'efficiency of research and development of new drugs . . . halves every nine years or so . . . Moore's law for microprocessors in reverse' [7]. In this environment, it is not surprising that the promise of repurposing partially developed drugs has generated considerable enthusiasm from patients, payors, regulators, policymakers, and biopharmaceutical companies.

Based on our new data, does repurposing deserve all the attention it has been getting? To be sure, initial successes are a reasonably good

TABLE 1

Repurposing rates ('attempts') and corresponding commercial launch rates ('success') in the same and different therapeutic area as the first attempted clinical development path for two subgroups: first attempted clinical development path yielding a market launch ('first success'); and first attempted clinical development path terminated ('first failure')

Repurposing	Same therapeutic area	Different therapeutic area
First success, <i>N</i> = 167	Attempts: (52/167) = 31% Successes: (35/52) = 67%	Attempts: (30/167) = 18% Successes: (10/30) = 33%
First failure, <i>N</i> = 667	Attempts: (104/667) = 16% Successes: (9/104) = 9%	Attempts: (65/667) = 10% Successes: (6/65) = 9%

indicator of successful follow-ons, and initial failures do not necessarily signal the ultimate failure of the product. Accordingly, for those products for which large amounts of time and resources have been invested in research, development, large-scale manufacturing, and clinical testing, there can be good reasons to consider the possibility of repurposing, even after an initial clinical failure.

At the same time, turning base metal into gold has been difficult for a long time, and repurposing is unlikely to fill our future medicine cabinets singlehandedly, especially if we focus only on products that we hope will be effective in another disease setting. Of the 834 new molecules entering clinical trials, less than 2% were ultimately launched in a therapeutic area other than the one in which they were originally tested. Most new medicines were the products of *de novo* discovery that succeeded in the originally expected therapeutic area. Accordingly, as promising as repurposing might be, basic research remains essential. It will not only help us understand where failed drugs might have a second chance, but, more importantly, will also continue to create a fertile environment for the often unexpected discoveries that can launch entirely new classes of medicine.

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Conflict of interest

D.L.D. has financial interests in numerous biotechnology companies.

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