Fighting the Damocles Sword of Infectious Diseases Through Drug Repurposing

In the face of increasing levels of antimicrobial resistance, discovering new therapeutic uses for existing molecules is vital

Andrés Pizzorno PhD at Signia Therapeutics

Today's society faces a major challenge regarding the treatment of infectious diseases caused by viruses, bacteria, parasites, or fungi, which represent the second largest global mortality cause after cardiovascular diseases and the first in low income countries (1). Suboptimal vaccine efficiency (for those counted diseases for which effective vaccines are available), failure to develop a specific therapy, and/or the emergence of drug-resistant pathogens that become able to survive currently used therapies account for this major public health burden. In that regard, global unprecedented and accelerated rates of antimicrobial resistance are being faced, spurred by an inadequate use of these drugs and key shortfalls in infection control measures. Antimicrobial resistance leads to 700,000 deaths worldwide, and the WHO forecasts 13 million deaths due to infectious diseases in 2050, estimating that 10 million deaths will be directly attributable to antimicrobial resistance (2).

A Steady Decline in *De Novo* Drug Discovery

Developing *de novo* classical drugs is very costly and time consuming, with approximately only 12% of drug candidates that make it into Phase 1 clinical trials receiving the final market authorisation by regulatory authorities. In other words, for each approved compound, roughly 5,000-10,000 candidates were left behind at different stages of the classic drug discovery pipeline (3). Despite constant efforts from both the industry and academia, as well as major technological improvements in the last 30 years or more, the capacity to discover and develop new antimicrobials is still being outpaced by the (re)emergence of microbes and the ability of current ones to become resistant to the few treatments available. This scenario does not seem to be changing for the better. Indeed, this steady decline in drug discovery productivity, despite constant increase in pharmaceutical R&D expenses, has been labelled under the 'Eroom's Law', a backwards spelling of Moore's Law, which describes the exponential advances in other technological fields (eg, electronics) over time (4). The causes are multiple, including tighter safety regulatory requirements for drug approval, a restrictive 'single target-centred' approach for compound screening, the targeting of more intricate diseases, the limitations of reductionist experimental models to reproduce biological complexity, or even the overestimation of some very early target-based experimental results and consecutive overinvestment of financial and human resources. Besides, the real consequence is that this situation is hindering the ability to prevent and respond to outbreaks which spread easily, favoured by the globalisation of trade and travel, for which alternative drug discovery strategies are underscored.

New Lives for Existing Drugs

According to the National Institutes of Health's National Center for Advancing Translational Sciences, drug repurposing (also termed drug repositioning) is defined as the process of discovering new therapeutic uses for existing molecules (5). This process also comprises the evaluation and validation of the safety and efficacy for such second therapeutic indication. The apparently simple and generic concept of drug repurposing covers different approaches that can be independent or complementary to each other, such as:

- Finding a new clinical indication for a medicine or molecule, distinct for the initial intention that led (or not) to market approval
- The reformulation of the original molecule and/or the development of delivery mode alternatives to that of the first indication
- The combination of molecules to enable an additive or synergistic therapeutic effect on at least one of their respective indications

Among the multiple ways of (re)discovering new therapeutic uses for existing compounds, one approach, based on the concept of polypharmacology, is of particular interest in the field of infectious diseases. Polypharmacology involves the capacity of a specific drug molecule to simultaneously act on various targets, including either a single drug acting on multiple targets of a unique disease pathway or a single drug acting on multiple targets associated with multiple disease pathways (6). Although many different pathogens may or may not share similar molecular determinants that could be the target of the same drug (and also drug resistance hotspots), concerning infectious diseases, they can also exert their effects through exploiting, to different extents, a set of common cellular factors and pathways to subvert the host's cellular machinery to their profit, hence favouring microbial

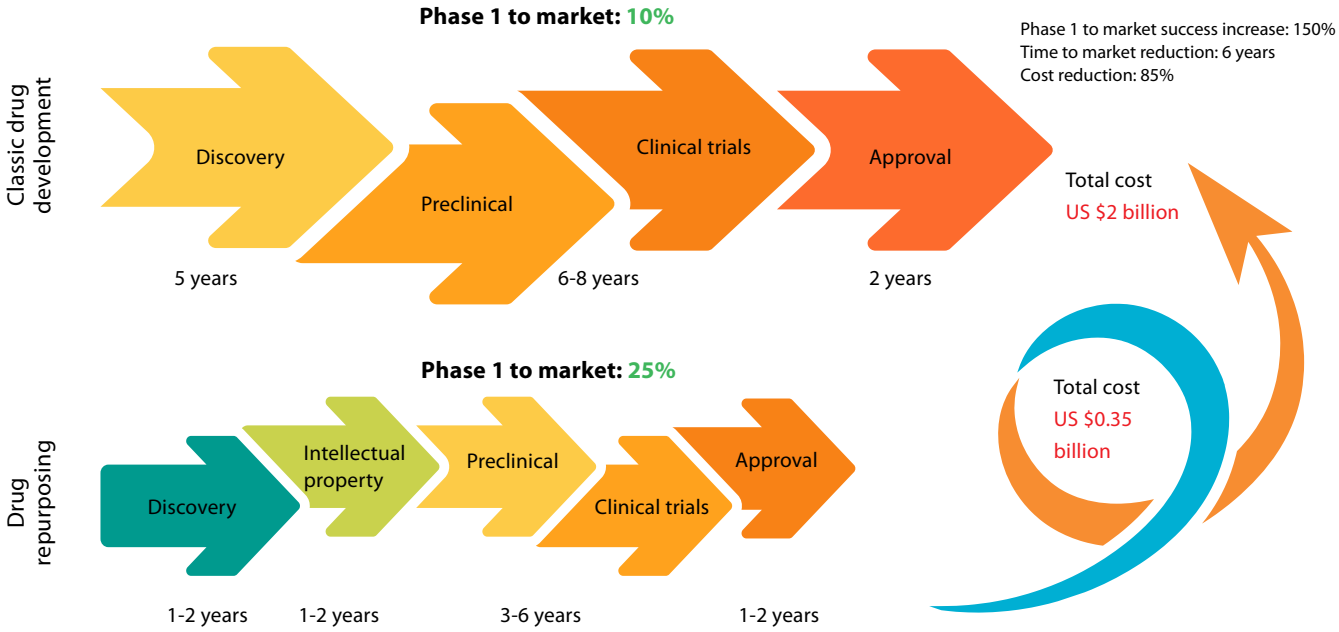

Figure 1: Comparison of classic *de novo* drug discovery and drug repurposing pipelines. Using already-existing extensive preclinical/clinical data as the starting point for drug repurposing in view of a novel clinical indication considerably reduces the high cost and time to market associated with classic *de novo* drug development

infection and pathogenesis. As a countermeasure, targeting host components on which pathogen replication depends instead on microbial determinants represents a real change of paradigm with significant advantages, such as the potential achievement of broad spectrum antimicrobial efficacy and the minimisation of pathogen drug resistance. In this way, the drug repurposing strategy could be of particular interest to fight emerging and/or recurrent pathogens for which there is no defence.

In practice, the key for drug repurposing relies on focussing on well-characterised molecules to take advantage of already existing extensive data concerning their toxicity, biodisponibility, pharmacokinetics, and preclinical/clinical *in vivo* effects (formulation, posology, etc) as the starting point for further development in view of a potential novel clinical indication. This strategy will enable bypassing a significant part of the long, risky, and expensive preclinical and early clinical evaluation associated with classic *de novo* drug discovery, hence considerably reducing the time to market, as well as the associated costs (see Figure 1) (7).

Additionally, drug repurposing can be applied to different types of molecules, including:

- Already-marketed molecules for which exclusivity patents are either still active or expired (publicly available)
- Molecules that are not marketed anymore for either safety or market purposes
- Molecules that have not reached the market for reasons such as failing to meet efficacy expectations for their primary indication in Phase 2/3 trials

Without undermining the historically proven potential of molecules belonging to the two first categories mentioned, those in the last category do represent a very attractive asset for drug repurposing. Indeed, the shelves of many drug developers are filled more than desired with drug candidates that did not make it through the 'Valley of Death' of advanced clinical evaluation, resulting in huge investment with little or no return. These high-value candidates are nonetheless thoroughly documented and validated in terms of preclinical and clinical data, safety, and probable undesired secondary effects and are also in the best possible scenario concerning intellectual property (IP) protection and patentability. The revalorisation potential of offering them an opportunity for a second life through drug repurposing is, at least, worth a try.

A Worthwhile Investment

The global market for infectious disease treatments (including diagnostic, vaccine, and pharmaceutical products) has been in constant growth for the last decade, reaching US $108.4 billion in 2015 and is expected to grow to US $183.2 billion by 2021 with a compound annual growth rate (CAGR) of 7.7% by 2021. Pharmaceutical treatments are the fastest growing segment of the market, accounting for US $78.3 billion in 2016, and are predicted to reach US $119.3 billion by 2021 (CAGR 8.8%) (8). In 2016, the total global drug discovery market was valued at US $35.2 billion, and estimates indicate that the market will grow to around US $71 billion by 2025, driven by the need to improve diagnostics and treatments (9).

Among the different drug discovery strategies, preference for drug repurposing is increasing mainly in the US (50% of the global market), as reflected by steady market growth.

> **Facing the incontestable reality, many infectious diseases still lack specific effective treatments, and, even though some traces of certain skepticism on the bankability of drug repurposing have not been yet completely extinguished, drug repurposing has arrived to stay**

Patent expiry in 2018		Patent expiry in 2019		Patent expiry in 2020		Patent expiry in 2021		Patent expiry in 2022	
Commercial brand	Generic name	Commercial brand	Generic name	Commercial brand	Generic name	Commercial brand	Generic name	Commercial brand	Generic name
Acanya	Benzoyl peroxide / clindamycin	Afinitor	Everolimus	Atrovent HFA	Ipratropium hfa	Bystolic	Nebivolol	Januvia	Sitagliptin
Adcirca	Tadalafil	Avastin	Bevacizumab	Byduredon	Exenatide	Crixivan	Indinavir	Oxecta	Oxycodone
Apidra	Insulin glulisine	Azasite	Azithromycin	Chantix	Varenicline	Emtriva	Emtricitabine	Pristiq	Desvenlafaxine
Astepro	Azelastine	Eliquis	Apixiban	Dexilant	Dexlansoprazole	Hysingla ER	Hydrocodone er	Selzentry	Maraviroc
Atripla	Efavirenz / emtricitabine / tenofovir	Emend INJ	Fosaprepitant	Inlyta	Axitinib	Perforomist	Formoterol	Victrelis	Boceprevir
Fentora	Fentanyl	Exelon patch	Rivastigmine	Namenda XR	Memantine er	Sutent	Sunitinib	Vimovo	Esomeprazole / naproxen
Finacea	Azelaic acid	Exjade	Deferasirox	Safyral	Drospirenone / ethinyl estradiol / levomefolate	Veramyst	Fluticasone fuoroate	Vimpat	Lacosamide
Follistim	Follitropin beta	Factive	Gemifloxacin	Saphris	Asenapine	Xarelto	Rivaroxaban		
Fortesta	Testosterone	Firazyr	Icatibant	Silenor	Doxepin	Zomig ns	Zolmitriptan		
Levitra	Vardenafil	Gilenya	Fingolimod	Sprycel	Dasatinib				
Lexiva	Fosamprenavir	Invega sustenna	Paliperidone	Tykerb	Lapatinib				
Lotronex	Alosetron	Orencia	Abatacept	Vigamox	Moxifloxacin				
Lyrica	Pregabalin	Prezista	Darunavir						
Makena	Hydroxyprogesterone	Ranexa	Ranolazine						
Namzaric	Memantine / donepezil	Rozerem	Ramelteon						
Pradaxa	Dabigatran	Tarceva	Erlotinib						
Promacta	Eltrombopag	Uloric	Febuxostat						
Remodulin	Treprostinil	Xyrem	Sodium oxybate						
Revlimid	Lenalidomide	Zyclara	Imiquimod						
Sensipar tablet	Cinacalcet								
Spiriva	Tiotripium								
Staxyn	Vardenafil								
Symbicort	Budesonide / formoterol								
Tekamlo	Aliskerin / amlodipine								
Tekturna	Aliskerin								
Tekturna HCT	Aliskerin / hctz								
Tikosyn	Dofetilide								
Treximet	Naproxen / sumatriptan								
Tyvaso	Treprostinil								
Vesicare	Solifenacin								
Xolair	Omalizumab								

Table 1: Drugs coming off-patent in the near future

Source: National Pharmaceutical Services® (www.pti-nps.com/nps)


Image: © Fotolia

The drug repurposing market represented US $24 billion in 2015 and is forecast to reach US $31 billion by 2020, with more than a 5% growth rate in the five-year period (9). Three factors, some aforementioned, could be called in to explain the major underlying reasons for the evolution of the drug repurposing market:

- The 'Eroom's Law' depicting the negative innovation dynamics in terms of increased R&D investment and reduced number of new marketed blockbuster drugs
- The correlation between the loss of private IP rights due to drug patent expiry deadlines (see Table 1) and the increasing number of generics, with the consequent negative financial impact for major drug developers
- The advent of novel technologies applied to research, notably in the case of computer-based Big Data approaches (data-mining, high-throughput 'omics' analysis tools, *in silico* chemo/bioinformatic databases, machine learning) that pave the way towards totally novel strategies for drug repurposing

In this context, more small and middle cap biotechnology and pharma companies, unsurprisingly, specialise in the drug repurposing domain spawn each year. Moreover, Big Pharma is not alien to this trend that could yield a marketable product in a relatively short time frame and with lower financial risk, for which some of them have seen up to 50% of their R&D human and financial resources strategically reoriented towards drug repurposing, even creating their own specialised departments: Indication Discovery Research Unit (Pfizer), Common Mechanism Research Group (Bayer), Systematic Drug Repositioning Group/Virtual Proof of Concept (GlaxoSmithKline), and New Indications Discovery Unit (Novartis) (10). Most importantly, this dynamic scenario seems to translate into an increased representation of drug repurposing in the global picture of drug discovery, accounting for 30% of the new drug products annually approved by the FDA (11).

Moving Forward

Facing the incontestable reality, many infectious diseases still lack specific effective treatments, and, even though some traces of certain skepticism on the bankability of drug repurposing have not been yet completely extinguished, drug repurposing has arrived to stay. The real challenge resides on defining to what extent the main actors of drug discovery (academia, industry, and regulatory agencies) are ready to break down some old barriers and create the best possible scenario to engage themselves in a more open and collaborative patient-oriented strategy that still makes everybody's ends meet. Yes, it is easier said than done, but, as Henry Ford once stated: "if everyone is moving forward together, then success takes care of itself."

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About the author

Andrés Pizzorno holds a PhD in microbiology-immunology from Laval University, Canada. With 10 years of research experience in the field of respiratory viruses, virus-host interactions, and antiviral strategies, he currently pursues his research activities at the VirPath Team of the Centre International de Recherche en Infectiologie in Lyon, France. Andrés is also co-founder and Project Manager of Signia Therapeutics, an innovative company based on a breakthrough proprietary drug discovery strategy to identify and repurpose already-marketed drugs rapidly, efficiently, and at low cost or to 'rediscover' unused drugs for new antimicrobial indications against several human pathogens.
Email: andres.pizzorno@signiatherapeutics.com