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Themed Section: Inventing New Therapies Without Reinventing the Wheel: The Power of Drug Repurposing

EDITORIAL

Inventing new therapies without reinventing the wheel: the power of drug repurposing

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Current drug development strategies devote extensive effort to identifying the molecular mechanism of action of new drug candidates. Often, if more than one unrelated enzyme or protein is affected by a certain agent at similar concentrations, the agent is considered to be 'non-specific' (or not specific *enough*) and thus of questionable therapeutic utility. However, specificity for drugs is surprisingly not only a function of concentration, as thought in pharmacology books, but also a function of time: the more a drug is studied, the more likely it is that additional targets or indications will be discovered. In 1993, the Nobel Laureate Sir John Vane – who spent his career studying drugs and their modes of action – said that 'The specificity of drugs decreases over time' (Sir John Vane – while making this comment to a group of young investigators including one of the authors of this Editorial (C.S.) – also stated that he believes that this quote originally belongs to another prominent pharmacologist, Sir James Black (also a Nobel Laureate). In spite of extensive internet searches, we were unable to verify the origin of the original quote.). On the one hand, additional targets might mean trouble for a drug candidate under development. On the other hand, new molecular targets and new pharmacological actions may present new therapeutic opportunities for clinically used drugs – in the framework of therapeutic repurposing.

Drug repurposing (also termed *drug repositioning* or *drug re-profiling*) is generally defined as the re-application of known drugs to target new indication(s). The known drugs might already be in clinical practice for a different indication or might have been 'retired' from further development due to lack of efficacy, perceived risk of adverse effects or perhaps non-science-related issues, for instance commercial/marketing considerations. *Drug rescuing*, on the other hand, refers to situations where the drug candidate failed to make the initial intended indication but were later on successfully introduced for a different indication (Barratt and Frail, 2012; Sharlow, 2016).

The 'classical' process of drug development is estimated to have approximately 90% attrition rate, meaning that 90% of those drug candidates that have been extensively studied in preclinical models, lack toxicity in rodents and large animals and are well tolerated by humans do not reach drug approval stage (Kola and Landis, 2013; Waring *et al.*, 2015; Mullard, 2016). Re-entering the development pipeline for a clinical-stage drug saves time and money: it reduces the cost of development and time (usually 12–14 years) it takes to move a drug from preclinical stage to the stage of approval. According to some estimates, the cost is only $40–80 million in total for FDA approval through the repurposing route, compared to the $1–2 billion it takes to develop a drug starting from hit selection *in vitro*. However, this figure for repositioning may be too optimistic as it does not take into consideration the costs of failed repurposing trials (Bertolini *et al.*, 2015; Ishida *et al.*, 2016; Cha *et al.*, 2018). In the often-quoted figure of $1–2 billion as the cost of new drug development (see Tufts Center for the Study of Drug Development; http://csdd.tufts.edu/) (Scannell *et al.*, 2012), a significant portion is made up

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by the large Phase III trials that – in most cases – remain mandatory to validate the new indication for the repurposed drug and to receive regulatory approval. But one can argue that repurposed drugs do not necessarily need a formal approval to be helpful for patients. Repurposing efforts – if they demonstrate robust efficacy for a different disease – could provide doctors with a rationale for off-label use, perhaps in patient populations that have limited therapeutic options.

Frequent discussion points related to repurposing are commercial ones (e.g. new indications may undermine existing markets). One of the most debated issues relates to the intellectual property protection. As discussed extensively (Smith, 2011; Sternitzke, 2014; Naylor *et al.,* 2015; Nosengo, 2016), while structure-of-the-matter patents are generally no longer valid and therefore cannot be used to protect the repurposed drug, a host of other patenting and intellectual property approaches ('use patents', patents around different dosing, different routes of administration, combination patents, claims related to combined usage of diagnostic and therapeutic approaches, etc.) are still available to protect the repurposer's investment.

Some of the 'classic' examples of successful repurposing are thalidomide, ropinirole, minoxidil and methotrexate. Thalidomide's original 'life' was a scary one, probably one of the most-cited cautionary tales in drug development and approval. This sedative – approved in 1950s and later withdrawn due to birth defects – has received a 'new lease on life' in the late 90s and became a very successful drug. It was approved in the U.S. in 1998 to treat leprosy and in 2012 to treat multiple myeloma. Ropinirole – originally developed for Parkinson's disease – is now used to treat restless legs syndrome and selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. Gabapentin and pregabalin – originally developed as anti-epileptics – are now commonly used to treat neuropathic pain and anxiety disorders (as well as seizures). Minoxidil – originally an anti-hypertensive agent – was reformulated as a topical treatment after patients using it noticed hair re-growth. Methotrexate – originally a chemotherapy drug – has been repurposed for the therapy of various autoimmune disorders including arthritis. And the list goes on (Barratt and Frail, 2012; Sharlow, 2016). Some drugs could even be 'repurposed' while under development. One well-known example is sildenafil that was originally being tested for cardiovascular indications but was serendipitously found to facilitate erectile responses. Sildenafil's repurposing (as well as repurposing of other agents) was not the result of a discovery of the inhibitory action of the drug on a different 'receptor' but rather resulted after realizing that the targeted receptor was more important in a different biological response than the intended use. Sildenafil was later re-purposed in a less random way, as a drug to treat pulmonary hypertension, and many additional indications emerged since, including myocardial reperfusion injury and chronic heart failure (discussed by Korkmaz-Icöz and colleagues in this themed section (Korkmaz-Icöz *et al.,* 2018a)). Naturally – like in all areas of drug development – there are no guarantees or magic bullets: in late-stage/pivotal repurposing trials, the chance that the trial will fail is still several fold higher than the chance that the trial will succeed (Barratt and Frail, 2012; Novac, 2013).

Driven by the speed and moderate cost of repurposing and inspired by the many success stories, scientists are now employing more sophisticated methods from systematic physical screening to bioinformatics-based approaches (e.g. Deftereos *et al.,* 2011; Cheng *et al.,* 2012; Issa *et al.,* 2013; Jin and Wong, 2014; Cichonska *et al.,* 2015) to identify new uses for existing drugs. This themed section on drug repurposing collates a number of reviews and original research papers on the topic. The authors of the reviews offer their unique perspectives derived from working in diverse environments: pharmaceutical companies with active repurposing programmes (Teva Pharmaceutical Industries) (Cha *et al.,* 2018); governmental research institutions that specialize in this approach of drug development, such as the National Center for Advancing Translational Sciences (Zheng *et al.,* 2018); and academic investigators who have a background of interest in certain pathways or mechanisms where repurposing opportunities present themselves (Berger *et al.,* 2018; Korkmaz-Icöz *et al.,* 2018a). In addition, the themed section compiles a number of original research papers, with new experimental data indicating the potential of repurposing the clinically used PARP inhibitor olaparib for non-oncological indications (Ahmad *et al.,* 2018; Korkmaz-Icöz *et al.,* 2018b); the long-acting PTH analogue LY627-2K (originally in development for osteoporosis) for the therapy of hypoparathyroidism-associated hypocalcaemia (Krishnan *et al.,* 2018); the clinical-stage drug development candidate dexpramipexole for stroke (Muzzi *et al.,* 2018); the 'age-old' antibiotic rifampicin as a neuroprotectant in traumatic brain injury (López-García *et al.,* 2018); various clinical-stage glycogen phosphorylase inhibitors for type I diabetes (Nagy *et al.,* 2018); the FDA-approved food additive β-caryophyllene for the therapy of alcoholic steatohepatitis (Varga *et al.,* 2018); and various non-steroidal anti-inflammatory drugs (e.g. ibuprofen) as potential therapeutics for acute pancreatitis (Bombardo *et al.,* 2018). In this themed section most of the original research papers use rational (hypothesis-driven) approaches to identify various repurposing opportunities, while other studies (e.g. López-García *et al.,* 2018) used mechanism-agnostic, phenotypic screening of libraries of clinically used drugs and drug candidates.

The editors hope that the articles contained in this themed section will prove to be useful not only to scientists in the field but also to colleagues, as well as students interested in learning more about the approaches, techniques and considerations behind drug repurposing.

Conflict of interest

The authors declare no conflicts of interest.

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