Drug repurposing: progress, challenges and recommendations

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Abstract | Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, repurposing of 'old' drugs to treat both common and rare diseases is increasingly becoming an attractive proposition because it involves the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines. Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges that need to be addressed. In this Review, we present approaches used for drug repurposing (also known as drug repositioning), discuss the challenges faced by the repurposing community and recommend innovative ways by which these challenges could be addressed to help realize the full potential of drug repurposing.

Despite advances in technology and enhanced knowledge of human disease, translation of these benefits into therapeutic advances has been far slower than expected[1,2]. The challenges facing the global pharmaceutical industry are multifold and include high attrition rates[3,4], increased time to bring new drugs to the market in some therapeutic areas and changing regulatory requirements, which can all contribute to higher costs. The escalating cost and length of time required for new drug development mean that for every dollar spent on research and development (R&D), it has been estimated that less than a dollar of value is returned on average[5], which could make the pharmaceutical industry a less desirable choice for investors.

Drug repurposing (also called drug repositioning, reprofiling or re-tasking) is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication[1]. This strategy offers various advantages over developing an entirely new drug for a given indication. First, and perhaps most importantly, the risk of failure is lower; because the repurposed drug has already been found to be sufficiently safe in preclinical models and humans if early-stage trials have been completed, it is less likely to fail at least from a safety point of view in subsequent efficacy trials. Second, the time frame for drug development can be reduced, because most of the preclinical testing, safety assessment and, in some cases, formulation development will already have been completed. Third, less investment is needed, although this will vary greatly depending on the stage and process of development of the repurposing candidate[6]. The regulatory and phase III costs may remain more or less the same for a repurposed drug as for a new drug in the same indication, but there could still be substantial savings in preclinical and phase I and II costs. Together, these advantages have the potential to result in a less risky and more rapid return on investment in the development of repurposed drugs, with lower average associated costs once failures have been accounted for (indeed, the costs of bringing a repurposed drug to market have been estimated to be US$300 million on average, compared with an estimated ~$2–3 billion for a new chemical entity[7]). Finally, repurposed drugs may reveal new targets and pathways that can be further exploited.

Historically, drug repurposing has been largely opportunistic and serendipitous; once a drug was found to have an off-target effect or a newly recognized on-target effect, it was taken forward for commercial exploitation. Indeed, the most successful examples of drug repurposing so far have not involved a systematic approach; repurposing of sildenafil citrate for erectile dysfunction relied on retrospective clinical experience, and repurposing of thalidomide for erythema nodosum leprosum (ENL) and multiple myeloma was based on serendipity[1]. Sildenafil was originally developed as an antihypertensive drug, but when repurposed by Pfizer for the treatment of erectile dysfunction and marketed as Viagra, it held a market-leading 47% share of the erectile dysfunction

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drug market in 2012, with worldwide sales totalling $2.05 billion[8]. Thalidomide, a sedative originally marketed in some countries in 1957, was withdrawn within 4 years owing to its infamous link with severe skeletal birth defects in children born to mothers who had taken the drug during the first trimester of their pregnancies[1]. However, it was serendipitously found to be effective first in the treatment of ENL[1] (in 1964) and decades later in multiple myeloma[9] (in 1999). It has had substantial commercial success since in multiple myeloma and also led to the development and approval of even more successful derivatives, such as lenalidomide (Revlimid, Celgene), which had global sales in 2017 of $8.2 billion[10]. TABLE 1 shows other selected successful drug repurposing examples along with the repurposing approaches employed, most of which so far have derived from an understanding of the pharmacology of the drug or retrospective analyses of the clinical effect of a drug when prescribed for its original indication.

Such successes have also encouraged the development of more systematic approaches to identify repurposable compounds. These approaches have resulted in the identification of a number of promising candidate drugs, some of which are in advanced stages of clinical trials, with the potential for use in the treatment of both common and rare diseases (for which repurposing is a key — and sometimes, the only — route for drug development; see BOX 1). However, important technical, regulatory and organizational challenges remain that impede the advancement of drug repurposing. In this Review, we provide an overview of various approaches that aid drug repurposing, including the use of novel types of big data. We also discuss the major challenges encountered and how recent public–private partnerships in drug repurposing might help in addressing some of these challenges. Finally, we provide recommendations that could accelerate the realization of the full potential of drug repurposing.

Approaches used for drug repurposing

Typically, a drug repurposing strategy consists of three steps before taking the candidate drug further through the development pipeline: identification of a candidate molecule for a given indication (hypothesis generation); mechanistic assessment of the drug effect in preclinical models; and evaluation of efficacy in phase II clinical trials (assuming there is sufficient safety data from phase I studies undertaken as part of the original indication). Of these three steps, step 1 — the identification of the right drug for an indication of interest with a high level of confidence — is critical, and this is where modern approaches for hypothesis generation could be most useful. These systematic approaches can be subdivided into computational approaches and experimental approaches (FIG. 1), both of which are increasingly being used synergistically. Drug repurposing based on clinical data is encompassed within these two broad areas.

Computational approaches

Computational approaches are largely data-driven; they involve systematic analysis of data of any type (such as gene expression, chemical structure, genotype or proteomic data or electronic health records (EHRs)), which can then lead to the formulation of repurposing hypotheses[11] (FIG. 1). The most commonly used computational approaches, together with drug repurposing examples, are discussed below.

Signature matching. Signature matching is based on the comparison of the unique characteristics or 'signature' of a drug against that of another drug, disease or clinical phenotype[12,13]. The signature of a drug could be derived from three general types of data: transcriptomic (RNA), proteomic or metabolomic data; chemical structures; or adverse event profiles, which we discuss in turn below.

Matching transcriptomic signatures can be used to make drug–disease comparisons (estimating drug–disease similarity)[14] and drug–drug comparisons (drug–drug similarity)[15]. In the first case, the transcriptomic signature of a particular drug is derived by comparing the gene expression profile of biological material, such as a cell or a tissue, before and after treatment with the drug; the resultant differential gene expression signature (the molecular signature of the drug) is then compared with a disease-associated expression profile that has been similarly obtained through differential expression analysis of disease versus healthy conditions. The extent of negative correlation between the gene expression signature of the drug and that of the disease (that is, the genes upregulated in the disease are downregulated with the drug and vice versa) would then allow inference of whether the drug may have a potential effect on the disease[16,17] (see the case study of topiramate in BOX 2). This computational approach relies on the signature reversion principle (SRP), where it is assumed that if a drug can reverse the expression pattern of a given set of genes that are a hallmark for a particular disease phenotype (that is, the drug signature will be closer to that obtained for the healthy state), then that drug might be able to revert the disease phenotype itself. Despite this principle being quite simplistic, it has been demonstrated for metabolic disorders[18] and successfully exploited to identify novel drug repositioning opportunities in a wide range of therapeutic areas[19–24]. The SRP has also been successfully

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Table 1 | **Selected successful drug repurposing examples and the repurposing approach employed**

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sales for minoxidil were US$860 million in 2016 (Questale minoxidil sales report 2017; see Related links)
Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction drug market, with global sales in 2012 of $2.05 billion[8]
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	1998 and 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved substantial clinical and commercial success in multiple myeloma
Celecoxib	Pain and inflammation	Familial adenomatous polyps	2000	Pharmacological analysis	The total revenue from Celebrex (Pfizer) at the end of 2014 was $2.69 billion (Pfizer 2014 financial report; see Related links)
Atomoxetine	Parkinson disease	ADHD	2002	Pharmacological analysis	Strattera (Eli Lilly) recorded global sales of $855 million in 2016
Duloxetine	Depression	SUI	2004	Pharmacological analysis	Approved by the EMA for SUI. The application was withdrawn in the US. Duloxetine is approved for the treatment of depression and chronic pain in the US
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab[144])	Global sales of rituximab topped $7 billion in 2015 (REF.[145])
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015 (see Related links)
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis[146]	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod (Gilenya) reached $3.1 billion in 2017 (see Related links)
Dapoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and a number of European countries; still awaiting approval in the US. Peak sales are projected to reach $750 million
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Qsymia (Vivus) contains topiramate in combination with phentermine
Ketoconazole	Fungal infections	Cushing syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years (see Related links)
Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of aspirin to help prevent cardiovascular disease and colorectal cancer[52]

ADHD, attention deficit hyperactivity disorder; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MS, multiple sclerosis; SUI, stress urinary incontinence.

employed to identify drugs that could be repositioned as chemo-sensitizers based on anticancer drug-resistance signatures[25].

Drug–drug similarity approaches aim to identify shared mechanisms of action of otherwise dissimilar drugs (drugs that belong to different classes or that are structurally dissimilar). This principle is called guilt by association[26] and can aid the identification of alternative targets of existing drugs and uncover potential off-target effects that can be investigated for clinical applications[12]. A shared transcriptomic signature between two drugs could therefore imply that they also share a therapeutic application, regardless of the similarity or dissimilarity in their chemical structures[27] (see the case study of fasudil in BOX 3). This principle has proved effective even when comparing transcriptional signatures that are reflective

Box 1 | **Repurposing in rare diseases: opportunities and challenges**

From the perspective of unmet medical need, drug repurposing for rare diseases offers a great opportunity. There are more than 7,000 rare diseases, and over 95% of them lack a US Food and Drug Administration (FDA)-approved therapeutic agent (Global Genes RARE Diseases; see Related links). Drug repurposing is a particularly attractive approach for rare diseases for both scientific and commercial reasons. Scientifically, these conditions are often poorly characterized pathophysiologically and lack a clear understanding of the biological pathways important in disease development. Computational techniques for predictive repurposing (as discussed in the main text) offer a relatively quick and mechanistically agnostic method of identifying testable hypotheses that may be translated into the clinic; this may also be the only route for drug development in certain rare diseases where there is a lack of information on disease pathophysiology. Conversely, with the growth in large-scale genome-sequencing initiatives (BOX 5), it may be increasingly likely that data indicate that a particular genetic variation causes a rare disease, potentially opening up opportunities to rapidly repurpose drugs that target the protein in question if they are already available.

Commercially, there are specific regulatory measures that are meant to encourage research into rare diseases; these measures can provide commercial exclusivity in situations where repurposed products cannot be protected by a patent or if that patent is weak. The Orphan Drug Act (ODA; 1983) was the first of its kind to be enacted, reflecting concerns that the economics for developing a drug for a rare disease were unfavourable, as the costs of research and development (R&D) can only be amortized over a relatively small number of patients. As a result of the ODA, approximately 360 drugs and biological products have been approved by the FDA since 1983 for rare diseases, compared with fewer than 50 such products in the 17-year period before 1983 (REF.[109]).

US legislation enables fast-track FDA approval, marketing protection, tax incentives and clinical research funding in rare diseases. The market protection means that once a drug is approved, a generic version in that indication cannot be marketed for 7 years, in addition to the normal patent protection. The developer can also receive tax concessions, grants and regulatory fee waivers. Following the success of the ODA, similar legislation was enacted in Singapore, Japan, Europe and Australia, with each jurisdiction having a slightly different definition of an orphan indication and applicable commercial incentives (see table). For instance, in the US, an orphan designation may apply if the prevalence is less than 200,000 (approximately 6.25 in 10,000), whereas in Europe, the corresponding figure is 5 in 10,000 (corresponding to approximately 250,000 patients in the 28 European Union member states).

Table | **Legislation in major markets offering commercial incentives for orphan drug development**

	United States	Japan	Australia	European Union
Legislation date	1983	1993	1997/8	2000
Prevalence[a]	Fewer than 200,000 (6.25 per 10,000)	Fewer than 50,000 (4 per 10,000)	Fewer than 2,000 (1.1 per 10,000)	Fewer than 5 per 10,000
Market exclusivity	7 years	Re-examination period extended from 4 to 10 years	None	10 years
Fee waiver	Yes	No	Yes	At least partial

[a]In the US, a rare disease is defined as one that affects fewer than 200,000 persons; however, this definition varies among countries.

The regulatory protection in rare diseases is particularly important given the relative weakness of patent protection for repurposed generic products, which is often confined to method-of-use-type intellectual property. Thus, there is much repurposing activity in this area. A comparison of the FDA approvals database with those drugs that have received orphan drug designation revealed 236 that were promising for the treatment of a rare disease though not yet approved for marketing for that condition[109].

of a secondary mode of action, which could be shared, for example, by a group of pharmacologically diverse mild correctors of a given disease phenotype[28,29].

Both drug–disease and drug–drug similarity approaches involve matching of transcriptomic signatures and therefore rely heavily on publicly accessible gene expression data. The Connectivity Map (cMap), which was established in 2006 by the Broad Institute, consists of gene expression profiles generated by dosing of more than 1,300 compounds in a number of cell lines[30] (Connectivity Map; see Related links). cMap information can be considered as a proxy phenotypic screen for a large number of compounds and has been successfully used to make drug repurposing predictions for a number of disease conditions. The third instalment of the cMap data repository (cMap 3.0) is now available within the US National Institutes of Health (NIH) Library of Integrated Network-based Cellular Signatures (LINCS; see Related links). It encompasses transcriptional signatures generated with tens of thousands of compounds upon treatment of hundreds of human cell lines. This enormous resource can be used along with other important public repositories of transcriptomic data, such as the Gene Expression Omnibus (see Related links) and Array Express (see Related links), which contain raw gene expression data from hundreds of disease conditions in humans and animal models. Manual curation or dedicated computational tools[31] can then be used to interrogate these disease signatures in association with the cMap data to identify novel drug–disease connections and potential drug repositioning opportunities[32,33].

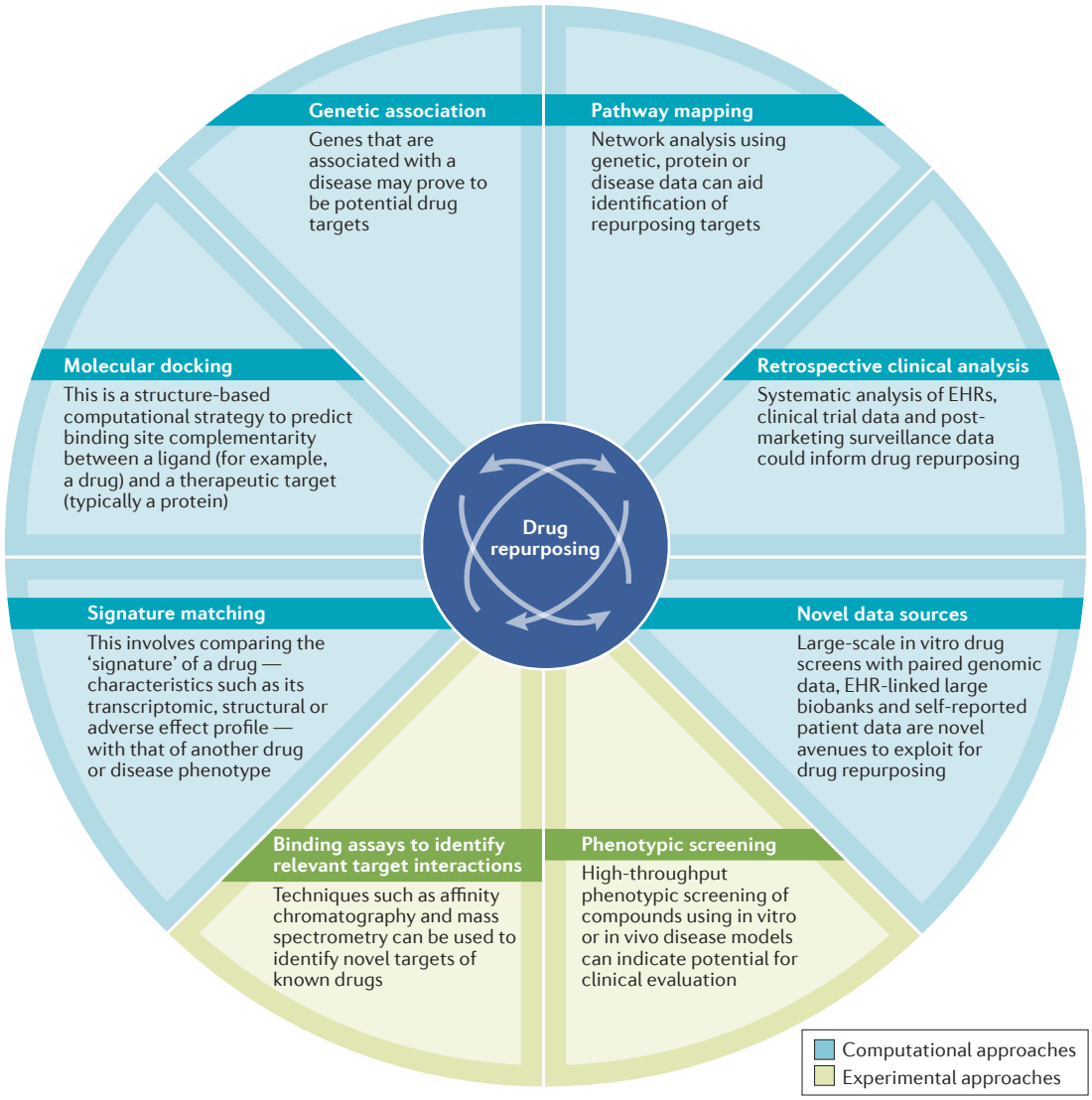

Figure 1 | **Approaches used in drug repurposing.** Various computational approaches can be used individually or in combination to systematically analyse different types of large-scale data to obtain meaningful interpretations for repurposing hypotheses. Challenges for such analyses are discussed in BOX 5. Experimental approaches can also be used to identify repurposing opportunities. EHR, electronic health record.

The second type of signature matching used in drug repurposing is based on chemical structures and their relationship to biological activity[34]; comparing the chemical signature of one drug with that of another drug to see whether there are chemical similarities could suggest shared biological activity. The process involves selecting a set of chemical features for each drug and then constructing networks based on the shared chemical features. This is exemplified by the statistics-based cheminformatics approach undertaken by Keiser and colleagues[12] to predict new targets for 878 US Food and Drug Administration (FDA)-approved small-molecule drugs and 2,787 pharmaceutical compounds. Using a similarity ensemble approach (SEA) to evaluate the 2D structural similarity of each drug to each target's ligand set, they were able to identify 23 new drug–target associations.

Chemical similarity approaches have their pitfalls: errors in chemical structures as well as physiological effects that exist beyond the structural relationship (for example, a metabolite of the original drug with a modified structure could be the active molecule) could limit the use of this approach in drug repurposing[14].

Finally, every drug has a relatively unique adverse effect profile that could be used as a proxy for its phenotype. Matching the adverse effect signature of drugs is based on the hypothesis that two drugs that cause the same adverse effects may be acting on a shared target or protein or on the same pathway[14]. It is also possible that the adverse effect phenotype of a particular drug may resemble that of a disease; this would suggest shared pathways and physiology by both the drug and the disease. Peer Bork's group used the adverse effect similarity

Box 2 | **Drug–disease similarity approach to identify topiramate in IBD**

Dudley and colleagues[16] compared the gene expression signature of inflammatory bowel disease (IBD) derived from publicly available data obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus with the gene expression profile of 164 drugs obtained from the Connectivity Map (cMap). Therapeutic predictions for drug–disease pairs were derived based on the extent of negative correlation between the gene expression signature of the drug and that of the disease. One of the strongest therapeutic predictions they obtained for IBD was the corticosteroid prednisolone, which is widely used to reduce inflammation associated with IBD. Another drug that showed a stronger correlation with both Crohn's disease and ulcerative colitis — two important clinical manifestations of IBD — was topiramate, an antiepileptic drug with GABA agonistic activity.

The authors validated the potential efficacy of topiramate in IBD using a trinitrobenzenesulfonic acid-induced rat model of IBD, in which it significantly reduced diarrhoea, visual manifestations of colitis on endoscopy and microscopic manifestations of disease on colonic biopsy. Functional enrichment analysis indicated that genes involved with gastrointestinal disease, inflammatory response and other immune-related functions were divergently expressed between the drug-affected and disease-affected conditions, further highlighting some of the potential mechanisms by which topiramate may act in IBD. However, a recent retrospective cohort study using administrative claims data from the MarketScan databases in the US failed to show a beneficial effect of topiramate in IBD[110]. Nevertheless, it is interesting to note that GABA has been recently suggested to play a potential role in gastrointestinal inflammation[111]. Thus, an appropriately designed and powered randomized clinical trial would be required to definitively answer the question of whether topiramate can be used therapeutically in IBD.

approach to identify novel drug–target relationships for 746 approved drugs[35]. They used the Unified Medical Language System (UMLS) ontology for medical symptoms and extracted relevant adverse effect profiles from drug package inserts, weighted them based on frequency and scored these drugs based on adverse effect similarities. This approach not only confirmed previously known drug–drug pairs that shared the same protein target but also identified new shared targets for 754 drug pairs. A different approach was used by Yang and Agrawal to match adverse drug effects with disease[36]; they combined adverse effect information derived from drug labels with drug–disease relationships obtained from the PharmGKB database and were able to predict repurposing indications for 145 diseases.

Although this is a logical approach to use for identifying repurposing opportunities, the difficulty in mining adverse effect information from drug package inserts and the lack of well-defined adverse effect profiles and causality assessments for a number of drugs[14] could limit its use. However, artificial intelligence technologies that can undertake text mining and natural language processing represent potential future opportunities to overcome these limitations.

Computational molecular docking. Molecular docking is a structure-based computational strategy to predict binding site complementarity between the ligand (for example, a drug) and the target (for example, a receptor)[37]. If there is prior knowledge of a receptor target involved in a disease, then multiple drugs could be interrogated against that particular target (conventional docking: one target and multiple ligands). Conversely, drug libraries could be explored against an array of target receptors (inverse docking: several targets and one ligand) to identify novel interactions that can be taken forward for repurposing. Using high-throughput computational docking, Dakshanamurthy and colleagues[38] performed molecular fit computations on 3,671 FDA-approved drugs across 2,335 human protein crystal structures. They discovered that mebendazole, an anti-parasitic drug, has the structural potential to inhibit vascular endothelial growth factor receptor 2 (VEGFR2), a mediator of angiogenesis; this was also confirmed experimentally.

However, there are several issues with the use of molecular docking for drug repurposing. First, 3D structures for some protein targets of interest may not be available, particularly because drug targets are often membrane proteins, such as G protein-coupled receptors (GPCRs), although substantial progress has recently been made in GPCR crystallography[39]. Second, there is a lack of well-curated macromolecular target databases that provide accurate structural information[40], although this is getting better[41]. Finally, the utility of docking algorithms to predict the affinity of binding has been questioned[42] and, while it is improving, there can be differences between different software packages, and some limitations in predictability (for instance, mode of binding and entropic effects) still remain[43].

Genome-wide association studies. There has been a large increase in the number of genome-wide association studies (GWAS) conducted over the past 10 years following advances made in genotyping technology, the completion of the Human Genome Project and dwindling genotyping costs. GWAS aim to identify genetic variants associated with common diseases and thereby provide insights into the biology of diseases; the data obtained may also help identify novel targets, some of which could be shared between diseases treated by drugs and disease phenotypes studied by GWAS and thereby lead to repositioning of drugs[44]. Sanseau and colleagues[44] refined the catalogue of published GWAS traits from the US National Human Genome Research Institute (NHGRI) and found that genes that were associated with a disease trait were more likely to code for proteins that are 'druggable' or 'biopharmable' than the rest of the genome, with the GWAS gene set enriched by 2.7-fold in targets being pursued by the pharmaceutical industry. They also found 92 individual genes with a GWAS trait that was different from the original drug indication, suggesting that it is possible to evaluate drugs that target the products of these 92 genes for a new disease indication (see the case study for denosumab in BOX 4). Another recent study by Grover and colleagues[45] used a bioinformatics approach to match gene targets identified for coronary artery disease with drug information obtained by integration of three different drug–target databases (DrugBank, Therapeutic Target Database and PharmGKB) to identify potential repositioning opportunities.

However, there are challenges in the use of GWAS information for drug repositioning, and its utility at present is unclear. GWAS signals in gene-rich loci with strong linkage disequilibrium may make identification of causal gene and/or gene variants difficult[44]. Another

Box 3 | **Drug–drug similarity approach to identify the potential use of fasudil in amyotrophic lateral sclerosis**

Iorio and colleagues[27,112] used the 'guilt by association' principle to construct a drug network using publicly available transcriptomic profiles of drugs, which allowed them to identify drugs with a similar transcriptional signature and therefore a perceived similar mechanism of action. Using gene expression profiles of each drug across multiple treatments on different cell lines and/or at different dosages obtained from the Connectivity Map (cMap), they computed a representative transcriptional response for each drug. A drug network was then constructed in which two drugs were connected to each other if their optimal transcriptional responses were similar according to a similarity measure developed by the authors (called drug distance). This resulted in a drug network of 1,302 nodes (drugs) and 41,047 edges (indicating similarities between pairs of drugs) purely based on transcriptomic profiles of drugs within this network consisting of drugs with a similar transcriptional signature and therefore a perceived similar mechanism of action.

Using this network, the authors correctly predicted the previously known mechanism of action of nine anticancer compounds, thereby validating this predictive model. Importantly, they also predicted previously unknown mechanisms for drugs such as fasudil, a Rho-kinase (ROCK) inhibitor, based on its proximity to known autophagy enhancers such as 2-deoxy-D-glucose and tamoxifen, and validated their prediction using an in vitro fibroblast model[112]. Autophagy plays a key role in the pathogenesis of amyotrophic lateral sclerosis (ALS)[113], a neurodegenerative disease with no cure. Preclinical studies in animal models of ALS showed that fasudil can increase motor neuron survival in transgenic mice expressing mutant superoxide dismutase 1 (SOD1), the causal gene for congenital forms of ALS[114]. The beneficial effects of fasudil in preclinical models of ALS were also confirmed in other preclinical studies[115,116]. This has now led to an open-label, single-centre clinical trial in China to investigate the efficacy and safety of fasudil in ALS (NCT01935518).

issue is the lack of information on the direction of effect of the gene variant; functional studies will need to be conducted to ascertain this before deciding whether an activator or a suppressor is required to control the disease[44]. GWAS data do not provide detailed pathophysiological information, and hence, rational use of GWAS data is advocated before predicting repurposing targets[46]. It should also be noted that the current understanding of the human genome is not final and there may be many more new genes discovered[47].

Pathway or network mapping. Pathway-based or network-based approaches have been widely used to identify drugs or drug targets that may have potential in repurposing[48]. As discussed above, even though some of the potential targets found by GWAS or other means may make themselves directly amenable as drug targets, quite often, these genes may not be ideal druggable targets. In such circumstances, a pathway-based strategy may provide information on genes that are either upstream or downstream of the GWAS-associated target and could be exploited for repurposing opportunities[49]. Network analysis involves constructing drug or disease networks based on gene expression patterns, disease pathology, protein interactions or GWAS data in order to aid identification of repurposing candidates. Some of the signature matching studies discussed earlier also make use of the network analysis approach[27,50]. A recent study by Greene and colleagues[51] combined genetic variant information arising from GWAS with tissue-specific functional interaction networks using a technique termed network-wide association study (NetWAS) to identify disease–gene associations much more accurately than GWAS alone. By applying this strategy to hypertension and by querying the resultant data against drug–target data from DrugBank, they observed that targets of antihypertensive drugs were enriched to a greater extent among the top genes from NetWAS than with GWAS. Pathway analysis of gene expression data sets from studies involving a wide range of respiratory viruses in human host infection models identified 67 common biological pathways that may be important in respiratory viral infections[48]. Interrogation of these pathways against the DrugBank database identified several drugs with a potential effect against host-viral targets. These included pranlukast, a leukotriene receptor 1 antagonist used in asthma, and amrinone, a phosphodiesterase inhibitor used in the treatment of congestive heart failure. It has been postulated that both of these drugs could be useful in treating viral infections owing to their potential ability to alter the immune response.

Retrospective clinical analysis: use of electronic health records. The best example of retrospective clinical analysis leading to repurposing (or rescue if the drug had otherwise failed for its primary indication) of a candidate molecule is sildenafil[1]. Other examples for repurposing opportunities arising from retrospective clinical and/or pharmacological analyses include aspirin in colorectal cancer (the US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of aspirin to help prevent cardiovascular disease and colorectal cancer[52]), raloxifene in breast cancer (Evista; approved by the FDA to reduce the risk of hormone-receptor-positive breast cancer in postmenopausal women who have not been diagnosed but are at higher-than-average risk of disease) and propranolol in osteoporosis[53]. However, the above cited examples did not arise as a result of a systematic analysis of clinical data. A systematic approach for analysing clinical data is now increasingly suggested for identifying drug repurposing opportunities[54].

Retrospective clinical data can be obtained from various sources, including EHRs, post-marketing surveillance data and clinical trial data. EHRs contain an enormous amount of data on patient outcomes, both structured and unstructured. The diagnostic and pathophysiological data, including the results of laboratory tests as well as drug prescribing data, are more structured; however, EHRs also contain considerable amounts of

unstructured information, such as clinical descriptions of patient symptoms and signs (which are important in defining disease phenotype) and imaging data. This wealth of data present in EHRs could be used as a source for identifying signals for drug repurposing[11]; in addition, the enormous amount of EHR data also provides high statistical power[55]. Paik and colleagues[55] extracted clinical signatures from over 13 years of EHRs from a tertiary hospital, including >9.4 million laboratory tests from half a million patients, in addition to diverse genomics signatures to identify over 17,000 known drug–disease associations; this approach led to the identification of terbutaline sulfate, an anti-asthmatic, as a promising candidate for the treatment of amyotrophic lateral sclerosis (ALS).

The UK Clinical Practice Research Datalink (CPRD), the Yellow Card scheme of the Medicines and Healthcare Products Regulatory Agency (MHRA), EudraVigilance (a European database of suspected adverse drug reaction reports managed by the European Medicines Agency (EMA)), the FDA Adverse Event Reporting System (FAERS) and the World Health Organization (WHO) global database for adverse drug reactions (VigiBase) all contain valuable patient, disease and drug data that could serve as important sources for drug repurposing analyses. However, great challenges still lie ahead in accessing and using EHR data, including ethical and legal obstacles that limit access to the data and difficulty in extracting the unstructured information present in these databases. Building more research capability into EHR databases could help improve their utility for various downstream opportunities such as drug repurposing. Natural language processing and machine-learning techniques could also prove valuable.

Post-marketing surveillance data and clinical trial data are two other important big data sources, but access may be limited for commercial or confidentiality reasons. However, there is increasing realization that opening up access to such wealth of information can aid further drug development research. In October 2016, the EMA started providing direct public access to clinical trial data submitted by pharmaceutical companies and has published reports on six different drugs to date (European Medicines Agency Clinical Data; see Related links). The data can be used for independent reanalysis by academics and researchers and may indicate drug repurposing leads.

Novel sources of data for drug repurposing. Immortalized human cancer cell lines (CCLs) have been used in high-throughput drug screens against hundreds of compounds (both approved and experimental) to test their effect on cell viability[56,57]. In a number of studies, the pharmacological data sets resulting from these screens have been paired with comprehensive genomic characterization of the probed CCLs, thereby allowing identification of interactions between molecular features of the cell and drug response (pharmacogenomic interactions)[58–61]. Mining such publicly available data sets containing paired genomic and pharmacological data on large panels of CCLs has been suggested as a novel resource for identifying drug repositioning opportunities. CCLs are of course imperfect models: they might have acquired molecular alterations providing selective advantages for in vitro culture and are often biased towards certain molecular subtypes. However, despite these limitations, studies have shown how identifying pharmacogenomic interactions recapitulate therapeutic genomic markers already in clinical use, with a strength of association that is comparable to that observed in the clinic[58–61].

More recently, CCL studies have also been integrated with the genomic characterization of large cohorts of primary tumours to prioritize the identified pharmacogenomic interactions on the basis of the clinical prevalence of the involved genomic alterations[60]. Strikingly, many of the novel identified pharmacogenomic interactions were specific to cancers of a given tissue type and involved drugs that are already in clinical use for other diseases or for cancers of other tissue types. The data arising from these types of study could be used to identify drug repurposing opportunities. Furthermore, this novel investigative avenue would offer an additional advantage: identification of the genomic alteration involved in a pharmacogenomic interaction with a repurposable drug would allow it to be prescribed to a very well-defined subpopulation of patients, thus advancing personalized cancer therapy.

Box 4 | **Use of GWAS-identified targets for potential repurposing of denosumab in Crohn's disease**

Denosumab (Prolia, Amgen), which is marketed for the treatment of postmenopausal women at high risk of fracture with osteoporosis, is an antibody that targets tumour necrosis factor ligand superfamily member 11 (TNFSF11), also known as RANKL. TNFSF11 has also been shown to be activated in Crohn's disease, in which a substantial proportion of patients have osteopenia and osteoporosis[117]. Moreover, a *TNFSF11* genetic variant (rs2062305) has also been associated with Crohn's disease by genome-wide association studies (GWAS)[118].

This prompted Sanseau and colleagues[44] to speculate about a potential role for denosumab in Crohn's disease. Using human B-lymphoblastoid cells and osteoblasts, they found that the Crohn's disease-associated *TNFSF11* variant was associated with the differential expression of *TNFSF11* and was able to explain population variation in *TNFSF11* expression in both cell types representing distinct cellular lineages relevant for both inflammatory and bone disease. This provided further support to postulate a causal link between *TNFSF11* and Crohn's disease and the potential for repurposing denosumab in Crohn's disease. A recent preclinical study explored the efficacy of daily denosumab injection in a mouse model of colitis induced by dinitrobenzenesulfonic acid[119]. Denosumab was found to decrease pro-inflammatory cytokines and modify the gut microbiota diversity in this animal model, further supporting its potential use in treating manifestations of inflammatory bowel disease. The same investigators are currently conducting an open-label phase I/II trial of denosumab in patients with active Crohn's disease (NCT02321280). The study is due for completion in July 2019.

Box 5 | **The challenges of big data**

Advances in technology such as next-generation sequencing and continuously reducing costs mean that researchers can generate large quantities of experimental data; these include data generated by high-throughput DNA and RNA sequencing, mass spectrometry, metabolomics and transcriptomic data, phenotyping and many more. Added to this are large amounts of clinical data that are increasingly becoming available from electronic health records (EHRs), clinical trials and biobanks. Such data are often referred to as big data — data sets that are so large or complex that traditional data processing methods are inadequate[120].

Big data are important for improving our understanding of disease and developing strategies for disease prevention and treatment. However, we are facing an increasing gap between our ability to generate big biomedical data and our ability to integrate, analyse and interpret the data[67]. This is further compounded by our ability to generate large amounts of data in a minimal amount of time. Another problem with big data is that they are disparate and heterogeneous, which makes data integration extremely difficult[120,121]. Integrating multiple types of data has proved to increase the power of analysis[122], and there are already some examples in drug repurposing where this strategy has been utilized at a limited scale[123,124]. However, much of the data generated are unstructured, such as imaging and structural data, and this adds another layer of complexity. There is an urgent need for technology solutions that can combine heterogeneous data sets and integrate, analyse and interpret them.

Finally, another bottleneck lies in accessing various types of data[120,121]. Although the publicly available databases for transcriptomic data are well known and contain standardized data, such databases are rare for other types of data, such as clinical trial data and structural, in vitro or imaging data. For example, access to clinical trial data is limited at the moment, and even if access is obtained, this may involve mining of enormous amounts of data (for example, the clinical trial data published by the European Medicines Agency for only two drugs, carfilzomib and lesinurad, constitutes ~260,000 pages of information in over 100 clinical reports). Therefore, it is important to have publicly accessible repositories that hold data in a standardized format and have the necessary tools to mine such data.

EHR-linked large DNA biobanks could be another frontier in accelerating drug repurposing research[62]. GlaxoSmithKline utilized China Kadoorie Biobank (CKB)[63], a prospective cohort of half a million individuals, to examine the role of *PLA2G7* gene variants in major vascular disease[64] following the failure of two consecutive phase III trials for darapladib (an inhibitor of the *PLA2G7* gene product Lp-PLA_2) in coronary heart disease and acute coronary syndrome[65,66]. *PLA2G7* gene variants did not show any association with major vascular disease, providing further support for findings from the phase III trials. Although a biobank resource was used to confirm the lack of efficacy of a drug in this case, the same approach could be used to confirm gene targets for drug repurposing. Tapping into resources offered by large biobanks that are linked to EHRs, such as the UK Biobank, may be a valuable approach for assessing potential drug targets.

Advances in sequencing technologies are enabling the collection of large quantities of comprehensive genomic data from many individuals that could be useful for drug repurposing. For example, the HiSeq X Ten system developed by Illumina (San Diego, California) is able to sequence more than 18,000 whole human genomes per year (the volume of which will be 3.6 petabytes or 3,600 terabytes)[67]. Large-scale projects harnessing such technologies include the 100,000 genome project launched in the UK in 2014 (REF.[68]), which has a focus on rare diseases and cancer, and the All of Us research programme in the United States (formerly called the Precision Medicine Initiative[69]), which will genotype 1 million individuals. This is in addition to various initiatives by other countries (for example, China has announced its own precision medicine genome sequencing initiative, with an estimated cost of $9.2 billion[70]) and private consortia (for example, AstraZeneca's genome sequencing initiative in drug discovery (see Related links) in collaboration with Human Longevity in the US, the Wellcome Trust Sanger Institute in the UK and The Institute for Molecular Medicine in Finland, which will involve 2 million individuals). Data from these projects could provide new insights into the genetic basis of disease and indicate therapeutic targets for both new drug discovery and opportunities for drug repurposing, as with GWAS discussed above. This could be particularly valuable for rare diseases (BOX 1) if causative genetic variations are identified in proteins for which potential candidates for drug repurposing are already available. For example, the phosphatidylinositol 3-kinase α-selective inhibitor, alpelisib (BYL719), which has been developed for the treatment of PIK3CA-altered tumours[71], was recently shown to be effective in a mouse model of, and in 19 human subjects with, PIK3CA-related overgrowth syndromes (PROS) based on the fact that affected patients have somatic, mosaic gain-of-function mutations in the *PIK3CA* gene[72].

Nevertheless, it should be noted that the nature of the big data from such projects and from the use of other high-throughput technologies poses considerable challenges for analysis and effective application, both in new drug discovery and drug repositioning (BOX 5).

Finally, online self-reported patient data have been suggested as another new potential source for drug repurposing[11,73]. One example is self-reported data on the usage of lithium carbonate by patients with ALS, which were used to derive useful conclusions about the efficacy of usage[73]. Even though no effect of lithium on disease progression was identified, the approach suggests that data reported by patients over the Internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drugs already in use. Use of patient-reported outcome data collected over the Internet offers advantages such as faster data collection, reduced cost and enhanced patient engagement; however, this approach also carries considerable risks in terms of bias and, potentially, patient safety if it involves patient self-prescribing.

Experimental approaches

Binding assays to identify target interactions. Proteomic techniques such as affinity chromatography and mass spectrometry have been used as approaches to identify binding partners for an increasing number of drugs[74]. In an era of chemical biology for target validation, analyses of the targets and off-targets of drugs and drug repurposing have become natural bedfellows. For example, the Cellular ThermoStability Assay (CETSA) technique has been introduced as a way of mapping target engagement in cells using biophysical principles that predict thermal stabilization of target proteins by drug-like ligands that possess the appropriate cellular affinity[75].

Examples of early successes with this technique include the confirmation of cellular targets for the tyrosine kinase inhibitor (TKI) crizotinib[76] and the detection of quinone reductase 2 (NQO2) as a cellular off-target of acetaminophen (paracetamol)[77]. A need to address the promiscuity of protein kinase inhibitors has long been recognized[78], and the prediction that protein kinases will represent the major drug targets of the 21st century[79] may still be fulfilled. This has increased efforts to develop better probe compounds for preclinical research that can inform clinical drug development and repurposing through an evidence-based pharmacological 'audit trail' in cells[80]. It is also important to note that the 'mistakes' made in various kinase drug discovery approaches have much to contribute, and early-stage unbiased affinity approaches are particularly useful for understanding the likely effects of compounds in cells, which include paradoxical kinase activation by inhibitors[81] that underlie mechanistic off-target tumour initiation in patients[82]. For example, to understand the complexity of compound effects, Brehmer and colleagues incubated HeLa cell lysate extracts with a matrix containing covalently attached gefitinib; mass spectrometry of the resultant elutes identified more than 20 different protein kinases as putative gefitinib targets[74]. Broader efforts have also been employed to evaluate kinase inhibitors by employing affinity matrices containing 'kinobeads', which capture proteins before analytical quantification[83], often revealing interesting novel off-targets for well-known drugs[84,85]. Similar approaches have now revealed many of the molecular on and off targets for important clinical agents, such as the first-to-market (and relatively specific) BCR–ABL inhibitor imatinib[86], which has been successfully repurposed to treat KIT-driven gastrointestinal stromal tumours[87], the newer BCR–ABL inhibitors nilotinib and dasatinib, and the very promiscuous kinase inhibitor ponatinib.

Chemical genetics can also provide a better understanding of the relationship between binding and efficacy in the cellular context[88]. In turn, these findings can be rapidly translated into new clinical areas or to address drug-resistance outcomes of prolonged exposure that are near-inevitable phenotypic responses to kinase inhibitor therapy in cancer[89,90]. Many of these studies stem from industry-driven high-throughput direct binding or catalytic assays, in which small-molecule–kinase binding is analysed in a kinome-wide fashion using a variety of in vitro and increasingly organism-based assays to generate heat maps of biologically important interactions[91,92]. In one such study, Karaman and colleagues[92] used an in vitro competition binding assay to evaluate 38 kinase inhibitors against a panel of 317 distinct human protein kinases; their analysis identified a total of 3,175 binding interactions. Interestingly, some kinase inhibitors such as sorafenib and dasatinib showed higher affinity to secondary kinase targets than their known primary target, potentially informing (or invalidating) their use in patient populations. In the kinase field in particular, non-kinase targets of small molecules originally designed to inhibit protein kinases are increasingly recognized[93] and are leading to repurposing opportunities in cancer[19], as Zika virus modulators[94] and as potential agents to treat antibiotic-resistant microorganisms[95].

Phenotypic screening. Phenotypic screening can identify compounds that show disease-relevant effects in model systems without prior knowledge of the target(s) affected[96]. In the context of drug repurposing, if the compounds screened are approved or investigational drugs, this may indicate repurposing opportunities that can readily be pursued. Typically, in vitro phenotypic screens use a wide range of cell-based assays in a 96-well format. For example, Iljin and colleagues[97] conducted high-throughput cell-based screening of a library of 4,910 drug-like small-molecule compounds in four prostate cancer and two non-malignant prostate epithelial cell lines with proliferation as the primary end point. They identified disulfiram, a drug used for alcohol abuse, to be a selective antineoplastic agent, which was then validated using genome-wide gene expression studies. Whole-organism phenotypic assays are also utilized in drug repurposing; Cousin and colleagues[98] used a zebrafish model to evaluate 39 FDA-approved medications for use in tobacco dependence and found that compounds such as apomorphine and topiramate modified nicotine-induced and ethanol-induced behaviour in this model.

Barriers to drug repurposing

As highlighted in the introduction and in TABLE 1, there have already been notable successes for drug repurposing. Nevertheless, repurposing does not always succeed; TABLE 2 shows selected drug candidates for which repurposing failed, mostly at the stage of phase III trials. Some failures in late-stage development are obviously to be expected, as with the development of completely new drugs, although these failures should be less likely to be due to toxicity because the safety profiles of the candidates were previously characterized. However, there are also other reasons for failure in the repurposing field (including failure to even begin to pursue a promising candidate beyond initial studies) related to barriers that are specific to drug repurposing, including patent considerations, regulatory considerations and organizational hurdles.

Patent considerations

There are a number of legal and intellectual property barriers to drug repurposing[1,6]. Difficulties associated with patenting a new repurposed indication and enforcing patent rights are the critical hurdles in incentivizing drug repurposing, as they have a great impact on the potential profit expected from the repurposed product[1]. It is possible to protect a new repurposed medical use of a known drug molecule in most of the major pharmaceutical markets, provided the new medical use is new and inventive (that is, non-obvious). However, many of the potential repurposing uses are already known in the scientific literature or in clinical practice. Even though they may not have been proved to work through clinical testing, prior scientific knowledge of the repurposed use may limit the ability to obtain patent protection unless the patentee can somehow differentiate their patent claims over the information that is already available in the public domain. In order to obtain granted patents for a new repurposed medical use, the patentee will also

Table 2 | **Selected examples where drug repurposing failed**

Drug name	Original indication	New indication	Date	Repurposing approach used	Outcome of repurposing
Latrepirdine	Antihistamine	Huntington disease	2011	Pharmacological analysis	Phase III trial (known as HORIZON) by Pfizer and Medivation was unsuccessful[147] (Pfizer phase III HORIZON trial; see Related links)
Ceftriaxone	Antibiotic	Amyotrophic lateral sclerosis	2014	High-throughput drug screening in animal models	Phase III trial failed to show efficacy[148]
Topiramate	Epilepsy	Inflammatory bowel disease	2014	Transcriptome-based signature matching	Successful in a rodent model of inflammatory bowel disease but failed in a retrospective cohort study[110]; no randomized clinical trial conducted to date

be required to present data in the patent application demonstrating that the drug is a credible treatment for the new indication concerned.

For drugs that are off-patent, a new method-of-use (MOU) patent can be obtained for a new repurposed use of an old generic drug (if, as discussed above, that use is new and inventive and can be supported by suitable data to render the new use credible). However, enforceability can become a major issue here if the new repurposed indication makes use of available formulations and dosage forms of the generic drug[99]. This is because the generic drug may be widely available from other manufacturers and prescribed by clinicians for other non-patented indications. The generic manufacturer can legitimately label their product only for the non-patented indications (so-called 'skinny labelling'), and provided that they do not encourage use in the patented indication in some other way, it will be difficult to allege that they are infringing on the new MOU patent. In this scenario, it can be difficult to stop off-label use for the newly patented repurposed indication, thereby reducing the potential profitability of the product[99]. However, off-label use can be limited if the new repurposed indication requires a unique formulation and/or a dosage regimen that cannot easily be achieved with the available generic versions of the drug. Given the above described challenges, it may be important to consider how and to what extent the intellectual property can be secured for a repurposed output at the beginning of the project.

The market exclusivity for repurposed drugs has been recognized as a major hurdle. This is exemplified by the Off-Patent Drugs Bill 2015–16 that was introduced in the UK Parliament in June 2015. This bill was meant to address the situation in which a drug that has an expired patent is discovered to be effective for a new indication that is not within the scope of its licence. It was supported by a number of medical charities but failed to pass into legislation (UK Parliament Off-Patent Drugs Bill 2015–16; see Related links). Subsequently, the Association of Medical Research Charities (AMRC) in collaboration with a wide range of stakeholders, including the National Institute for Health and Care Excellence (NICE), the MHRA, Royal Colleges and representatives from industry, published a report (Association of Medical Research Charities; see Related links) in November 2017 making recommendations on how drug repurposing can be facilitated for the benefit of patients in the UK. The report lists different ways in which sponsors can work with the MHRA to pursue a licensing route; it also makes recommendations to develop financial incentives that would encourage generic manufacturers to participate in drug repurposing and a mechanism for testing the drug repurposing framework. In the US, the OPEN ACT (Orphan Product Extensions Now Accelerating Cures and Treatments) provides an additional 6 months of exclusivity (Orphan Product Exclusivity Extension) to the patent life of a marketed drug being repurposed for a rare disease (EveryLife Foundation for Rare Diseases OPEN ACT press release; see Related links). Other ways of maximizing chances of patentability are by developing new formulations, dosage forms or newer derivatives with a similar therapeutic effect or by obtaining exclusive marketing approval in new geographic regions[1].

Regulatory considerations

Regulatory considerations are critical determinants for the development of repurposed drugs. BOX 6 describes regulatory pathways for repurposed drugs in the US and in Europe and the eventual exclusivity benefits that repurposed drugs receive.

A study by Murteira and colleagues[100] evaluating the regulatory path associated with repurposed and reformulated drugs observed that within the EU (the UK, France and Germany were studied), the centralized procedure was the most important route for the submission of repurposed drugs for approval. In the US, according to the classification of Murteira and colleagues[100], 'new drug application (NDA) chemical types' type 1 (new molecular entity), NDA type 6 (new indication) and supplemental new drug application (sNDA) (new indication) were used solely for drug-repurposing submissions, while NDA type 3 (new dosage form) and NDA type 4 (new combination) were used for either drug repurposing or drug reformulation. The study also found that in both the EU

Box 6 | **Regulatory pathways for repurposed drugs in the EU and the US**[a]

European Union

- Directive 2001/83/EC (particularly articles 6, 8(3), 10(3) and 10(5)) provides the main legal basis for drug applications for repurposed drugs. The application process for repurposed drugs in Europe can be filed via three different routes: centralized, decentralized or national application (mutual recognition).
- The application should contain information on pharmaceutical (physicochemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and clinical trials. Some of the data requirements can be met by bibliographic data. In addition, for article 10 (abridged) applications that refer to data of a reference medicinal product, data requirements may be reduced.
- Safety characterization may be supported by prior clinical experience (such as trial data or post-marketing data).
- All applications should be accompanied by a risk management plan.
- All applications under article 8(3) require a Paediatric Investigation Plan or waiver, to be agreed with the European Medicines Agency (EMA) before application.
- A new indication for an approved drug could be added using a variation application.

United States

- The drug application for repurposed drugs can be filed according to one of the possible regulatory paths, namely, section 505(b)(1), section 505(b)(2) or section 505(j).
- To make minor changes (label, new dosage or strength, etc.) in a product that already has an approved new drug application (NDA; or biologics license application (BLA) for biologic products), a company must submit a supplemental NDA (sNDA; or sBLA for biologic drugs).

[a]See Related links.

(France: 83.3%; Germany: 88.9% and UK: 93.8%) and the US (69.6%), the majority of repurposing cases were approved before patent expiry of the original product.

For repurposed drugs with a designated orphan indication, the market exclusivity provided in the EU/EEA is 10 years of protection from market competition with similar medicines with similar indications and an additional 2 years if they complied with an agreed Paediatric Investigation Plan (PIP). All orphan drug applications must be submitted via the centralized procedure. For repurposed drugs without an orphan designation, 10 years of data exclusivity are available for Article 8(3) (complete dossier) applications. Applications for new indications of well-established substances submitted under Article 10(5) may be granted 1 year of data exclusivity. However, data exclusivity provisions do not apply for variations to existing marketing authorizations.

In the US, the FDA offers a period of 3 years of data exclusivity for a new use of a previously marketed drug; however, 3 years is too short a period to recoup the money a company has invested in repurposing a particular drug. In addition, as discussed under the above section on patent considerations, off-label use of a repurposed generic drug may further devalue the product.

Organizational hurdles in industry

Pharmaceutical companies are realizing the potential in drug repurposing outside their primary disease area of focus and opening up collaborations with smaller biotech firms and academic communities. The AstraZeneca Open Innovation Platform (see Related links) is one such example to promote external collaborations to synergize research in drug repurposing with access to well-characterized compounds suitable for repurposing through translational, preclinical experiments and clinical phase II studies. Other notable examples include the Center for Excellence for External Drug Discovery at GlaxoSmithKline, Centers for Therapeutic Innovation at Pfizer and Bayer's Grant4Indications initiative (see Related links).

However, repurposing in the pharmaceutical industry can be met with some organizational hurdles, particularly if the repurposed indication is not within the organization's core disease area or the compound has been discontinued in development and thus there is no longer a 'live' project within the R&D division to provide dedicated support for the new indication[1]. This would mean that there is a lack of personnel who can work on a potential drug repurposing project as well as limited funding and resources to progress the idea within the company. One way to address these challenges with clinical studies is to use external resources for drug supply via contract manufacturing organizations, regulatory support and pharmacovigilance. Alternative funding routes can be considered, as outlined in the next section, to ensure that robust scientific hypotheses can be tested when it would otherwise not have been possible to take it forward within the company. In addition, increasing the choice of compounds would provide more repurposing opportunities, especially for compounds that target novel mechanisms. However, the majority of these compounds are generally live in development, and there are perceived risks with sharing these compounds outside of the pharmaceutical company, such as new safety risks identified and risk to intellectual property ownership. Sharing successful examples of repurposing compounds still in live development may help to dispel concerns in this respect.

Collaborative models for drug repurposing

There is increasing realization among pharmaceutical and academic research leaders that new business models are needed to drive the field of drug repurposing. A collaborative strategy that combines the strengths of pharmaceutical companies, biotechnology companies, academic researchers, venture capitalists, publicly funded research charities and other funders and stakeholders has been recognized as a key route for drug repurposing[5]. Such collaboration will involve greater sharing of drug-related data by pharmaceutical companies and novel ways of sharing intellectual property that may be generated between the pharmaceutical industry, academia and other stakeholders.

There are three key components to successful drug repurposing collaborations: identification of scientific experts with novel ideas in emerging areas of disease biology, alternative funding routes and enthusiastic engagement among all parties involved. Several repurposing initiatives have recently been established between the pharmaceutical industry, grant funding organizations and academic scientists to address some of the challenges in drug repurposing. Two of the most important examples of this type of collaboration are the Mechanisms for Human Diseases Initiative,

a partnership between the Medical Research Council (MRC) and AstraZeneca, which was launched in 2011 (REF.[101]), and the Discovering New Therapeutic Uses for Existing Molecules initiative launched in 2012 by the NIH–National Center for Advancing Translational Sciences (NIH–NCATS) in partnership with eight pharmaceutical companies[102].

The MRC–AstraZeneca initiative initially listed 22 discontinued compounds on which AstraZeneca provided detailed information regarding the drug's potency, selectivity, pharmacology, pharmacokinetics, safety and various other characteristics. The MRC call for concept proposals attracted more than 100 proposals from 37 different UK institutions, of which 15 were eventually funded by the MRC following peer review, totalling £7 million in funding. The NIH–NCATS programme listed 57 compounds from eight different pharmaceutical companies in its first round, and nine proposals were funded in 2013, totalling approximately $12.7 million. The level of interest shown by academic researchers in both these programmes showed that these were seen as exciting, unprecedented opportunities to access molecules that were otherwise unknown to the public domain[101]. It should be noted that there were considerable differences between the MRC and NCATS programmes: the MRC programme was more focused on understanding the mechanisms of disease, whereas the NCATS programme specifically focused on repurposing existing drugs with each proposal, including a phase II proof-of-concept clinical study in the new indication. There was company involvement in the reviewing of the MRC programme proposals in the initial stages (but not full proposals, with all funding decisions taken by the MRC), but there was no company involvement in the NCATS programme (although they could decide whether they wanted to enter into a collaboration with a research partner or not); there were also differences in the way funding was provided[101]. However, in each case, the MRC and the NCATS acted as trusted intermediaries facilitating collaboration between academia and industry[5]. A detailed interim assessment of progress to date on these two programmes has been published by Frail and colleagues[101].

Although it is too early to definitively assess the success of these pilot government-sponsored programmes given the long time frames of drug development, initial indications suggest some positive outcomes. Saracatinib, initially developed as an anticancer agent by AstraZeneca, is currently being investigated in five separate clinical and preclinical programmes between the MRC and the NCATS for a variety of non-oncological conditions (pain, psychosis, lymphangioleiomyomatosis, chronic otitis media and Alzheimer disease)[101] (see the case study in BOX 7). Another promising example

Box 7 | **Saracatinib: repurposing opportunities based on increasing knowledge of its pharmacology**

Saracatinib (also known as AZD0530) is an anticancer compound developed by AstraZeneca. It is a potent, orally bioavailable inhibitor of SRC tyrosine kinase family members, which regulate tumour cell adhesion, migration and invasion[125]. Although it was found to be clinically well tolerated, phase II studies showed only limited benefit as a single agent for oncological conditions, and it was therefore deprioritized[126,127]. However, increasing understanding of the role of SRC kinases in multiple diseases has now led to a number of repurposing initiatives for saracatinib.

Repurposing of saracatinib for Alzheimer disease

FYN, an SRC kinase family member, is implicated in triggering Alzheimer disease. Kaufman and colleagues[128] showed that saracatinib potently inhibits FYN in a mouse model of Alzheimer disease; they also showed that the drug enters the central nervous system and is detectable in cerebrospinal fluid of mice and humans at concentrations that inhibit FYN. This was followed by a phase Ib study, which confirmed the safety and tolerability of saracatinib in patients with Alzheimer disease[129]. The drug is currently undergoing a phase IIa clinical trial to investigate its efficacy in treating Alzheimer disease (NCT02167256).

Saracatinib as an analgesic to treat cancer-induced bone pain

Approximately 70% of patients with breast, lung or prostate cancer experience bone metastases and associated bone pain[130]. SRC kinase is part of the *N*-methyl-D-aspartate (NMDA) receptor complex and plays a major role in the pathophysiology of pain hypersensitivity[130]. De Felice and colleagues[130] used a rat model of cancer-induced bone pain to show that SRC plays a role in its development and that SRC inhibition using saracatinib ameliorates cancer-induced bone pain. The potential analgesic effect of saracatinib in cancer patients with bone metastases is currently being tested in a phase II clinical trial (NCT02085603). The estimated study completion date was March 2018; no results have been published to date.

Saracatinib as a therapeutic strategy for lymphangioleiomyomatosis

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutation in either the tuberous sclerosis complex 1 (TSC1) or TSC2 tumour suppressor genes[131]. Lymphangioleiomyomatosis (LAM), a pulmonary manifestation of TSC, is a progressive cystic lung disease affecting primarily women of childbearing age. Increased levels of active SRC kinase have been observed in LAM lungs together with increased SRC kinase activation in $TSC2^{-/-}$ cells[131]. A randomized clinical trial to examine whether SRC inhibition using saracatinib represents a potential therapeutic strategy in LAM is ongoing (NCT02737202).

SRC inhibitors as potential antipsychotics

SRC kinases are suggested to mediate psychosis induced by hallucinogens such as psilocybin[132]. A clinical study is currently underway within the Medical Research Council (MRC) Mechanisms of Human Disease Initiative to evaluate the potential role of SRC kinase inhibitors in blocking psychosis.

(not part of the MRC–AstraZeneca initiative but an academic-investigator-led study in collaboration with AstraZeneca and funded by the MRC) is the development of neurokinin 3 receptor antagonists for the treatment of menopausal hot flushes[103] (see the case study in BOX 8). TABLE 3 shows some of the most promising late-stage clinical candidates arising from deliberate repurposing efforts, including those funded by the MRC and the NIH–NCATS.

These two crowdsourcing collaboration models have clearly been shown to be a pathbreaking strategy in bringing open collaboration and innovation in drug repurposing research. The subsequent rounds of these two calls have now increased the number of pharmaceutical industry partners: the MRC Industry Asset Sharing Initiative in 2016 had seven pharmaceutical industry partners and made more compounds (68 in total) available for academic access. It has also led to the generation of other similar public–private partnerships in drug repurposing, such as the partnership between AstraZeneca and the National Research Programme for Biopharmaceuticals (NRPB) in Taiwan in 2013 (REF.[104]).

Collaboration models also exist between patient advocacy groups, philanthropic organizations and academics, particularly to explore repurposing opportunities for generic marketed drugs in rare diseases (Cures Within Reach and Duchenne UK; see Related links). The open innovation and collaborative models need to be extended to partnerships between patient charities, advocacy groups, academic scientists and pharmaceutical companies at an earlier stage in drug development; this could increase opportunities to access specific disease populations, experts in the specific disease and alternative funding routes for clinical studies.

Two other public–private partnership initiatives that exist mainly in preclinical research to aid future drug repurposing are in the area of human kinome research; these are the GlaxoSmithKline-led Published Kinase Inhibitor Set (PKIS)[105] and the Oxford-based Structural Genomics Consortium (SGC)[106]. GlaxoSmithKline's PKIS1 (rapidly followed by PKIS2 and PKIS3) is an annotated set of 367 small-molecule kinase inhibitors with known interactions with multiple protein kinases that is available as an open-access tool to academic researchers[105]. This set can be re-examined in a variety of in vitro and cellular assays and has already shown the potential to uncover important new understanding across the academic and industrial sectors[107,108]. The SGC's focus is on the determination of 3D structures of human proteins of biomedical importance on a large scale, which are then released into the public domain through the Protein Data Bank[106] to benefit researchers in identifying potential protein binding partners.

Box 8 | **Repurposing of neurokinin 3 receptor antagonists in postmenopausal hot flushes**

The decline in oestrogen levels in postmenopausal women results in hot flushes characterized by intermittent episodes of sweating and heat sensation; 70% of postmenopausal women experience hot flushes, which can have a substantial negative impact on quality of life[133]. Hot flushes are also experienced by patients undergoing hormone deprivation therapy for breast and prostate cancer, young women who have had an oophorectomy and hypogonadal men[133]. Hormone replacement therapy (HRT) is the most commonly used treatment for hot flushes[134] but has fallen out of favour because of its adverse effects and contraindications[135]. Selective serotonin reuptake inhibitors, gabapentin and clonidine can also be used to treat hot flushes but are less effective than HRT and are associated with various adverse effects[135].

Thermoregulatory centres in the hypothalamus are thought to play a crucial role in mediating the hot flush response[136]. Growing evidence over the past 20 years has suggested a key role for the hypothalamic hormone neurokinin B (NKB) in the aetiology of hot flushes[134]. NKB is a member of the tachykinin family of peptides; it is encoded by the *TAC3* gene and binds preferentially to the neurokinin 3 receptor (NK3R, encoded by the *TAC3R* gene). Pioneering studies by Rance and colleagues[136] showed for the first time the role of KNDy (kisspeptin, NKB and dynorphin) neurons in the arcuate nucleus in regulating the reproductive axis. Hypertrophy of KNDy neurons and higher levels of NKB were observed in postmenopausal women[137]. Animal studies have also shown that micro-infusion of a selective NK3R agonist, senktide, into the rat median preoptic nucleus induced a rapid, dose-dependent drop in core temperature[138]. Clinical studies conducted by Dhillo and colleagues showed that intravenous infusion of NKB can induce hot flushes in healthy women[135]. Genome-wide association studies identified genetic variants in the TACR3 locus to be associated with the risk of vasomotor symptoms[139]. Together, these findings suggested a critical role of NKB–NK3R signalling in the aetiology of hot flushes and prompted investigation of NK3R antagonism as a strategy for its treatment.

NK3 receptors are known to play a key role in dopaminergic function and may be involved in the pathogenesis of schizophrenia[140]. This led to the development of several NK3 receptor antagonists, such as osanetant and talnetant, in the 1990s and 2000s; however, various clinical studies failed to demonstrate any significant efficacy for NK3R antagonists in schizophrenia[140,141], leading to the discontinuation of NK3R drug development programmes. The accumulating evidence on the role of NKB and NK3R in the aetiology of hot flushes prompted Dhillo and colleagues, in collaboration with AstraZeneca, to undertake a phase II trial of an oral selective NK3R antagonist, AZD4901 (now known as MLE4901 after being out-licensed to Millendo Therapeutics), in women having severe hot flushes. MLE4901 significantly reduced the total weekly number of hot flushes compared with placebo, demonstrating the efficacy of an NK3R antagonist in menopausal hot flushes for the first time[103]. Around the same time, the biotech Ogeda (which has since been acquired by Astellas Pharma) also reported the efficacy of another NK3R antagonist, fezolinetant, in the treatment of hot flushes[142]. A third NK3R receptor antagonist, NT-814, is currently undergoing phase II clinical trials for hot flushes (NCT02865538)[143].

Table 3 | **Selected late-stage clinical candidates arising from deliberate drug repurposing studies**

Drug	Old indication or drug classification	New indication	Latest update	Funder
Saracatinib	Experimental anticancer drug	Alzheimer disease	See BOX 7	NIH–NCATS
		Cancer-induced bone pain	See BOX 7	MRC
		Lymphangioleiomyomatosis	See BOX 7	NIH–NCATS
		Psychosis	See BOX 7	MRC
AZD4017	11β-HSD1 inhibitor	Idiopathic intracranial hypertension	A phase II trial is ongoing[149], and recruitment has been completed (NCT02017444)	MRC
Zibotentan (ZD4054)	Experimental anticancer drug that obtained fast-track status from the FDA for prostate cancer	Renal scleroderma	A phase II trial is ongoing (Zibotentan in Better Renal Scleroderma Outcome Study (ZEBRA)); it was expected to finish in October 2017 (NCT02047708)	MRC
		Peripheral arterial disease	A phase II trial is ongoing (a phase II clinical trial to assess the safety and effects of zibotentan on exercise-induced calf muscle perfusion in patients with intermittent claudication (Rutherford II or III)). Recruitment has been completed (NCT01890135)	NIH–NCATS
LY500307	Benign prostatic hyperplasia	Schizophrenia	A phase II trial is ongoing (The Efficacy and Safety of a Selective Estrogen Receptor Beta Agonist (LY500307) for Negative Symptoms and Cognitive Impairment Associated with Schizophrenia (Beta)). Currently recruiting; estimated study completion date of June 2018 (NCT01874756)	NIH–NCATS
PF-05190457	Ghrelin receptor inverse agonist	Alcoholism	A phase II trial is ongoing (A Novel Compound for Alcoholism Treatment: A Translational Strategy Sponsored by National Institute on Alcohol Abuse and Alcoholism). Recruiting currently; estimated completion date of December 2019 (NCT02707055)	NIH–NCATS
Ribavirin	Antiviral, used in hepatitis C infection	Acute myeloid leukaemia and breast cancer	Some evidence already from phase II trials that demonstrated clinical efficacy in acute myeloid leukaemia[150] (NCT00559091)	Leukemia & Lymphoma Society
Denosumab	Osteoporosis	Crohn's disease	See BOX 4	Not available
Nelfinavir	HIV	Various cancers	Multiple clinical trials are ongoing in NSCLC, rectal cancer, myeloma and other types of cancers to investigate the effect of nelfinavir (See ClinicalTrials.gov)	Multiple funders
AZD4901 (MLE4901)	Neurokinin 3 receptor antagonist	Menopausal hot flushes	See BOX 8	MRC

11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1 (cortisone reductase); FDA, US Food and Drug Administration; MRC, Medical Research Council; NIH–NCATS, National Institutes of Health–National Center for Advancing Translational Sciences; NSCLC, non-small-cell lung cancer.

Recommendations for drug repurposing

Bearing in mind the opportunities and challenges for drug repurposing discussed above, we conclude by putting forward six recommendations to help realize the full potential of drug repurposing.

First, there is a need for better integrative platforms for data analysis. The benefits of big data and how it can aid identification of repurposing opportunities are clear. However, data access and integration remain a bottleneck, particularly for clinical data (including clinician notes in patient case records). There is a need for advanced technological solutions that can reduce the need for manual curation and help integrate different types of omics data (BOX 5) such that subsequent analyses can be more refined and analysed in user-friendly formats by more 'non-experts'.

Second, improved access to industry-generated preclinical and clinical compounds is needed. The MRC and NIH–NCATS initiatives are a step in the right direction, but there needs to be an increase in the number of compounds that can be accessed by academic researchers, ideally in large libraries. The processes involved

also need simplification, especially at the level of material transfer agreement signatories and compound dissemination.

Third, there is a need for greater access to data from industry-sponsored phase II–IV clinical trials. This could allow external scientists to mine for new findings in the data that could open repurposing opportunities, in particular for discontinued programmes.

Fourth, newer safety liabilities of repurposed drugs should be studied. There is a continuing need to ascertain any new safety implications associated with repurposed drugs. These may arise as a result of new interactions between the drug and the disease for which it is repurposed, use in new populations or differences in the dosing schedule (for example, chronic rather than intermittent dosing).

Fifth, there is a need for further funding opportunities for drug repurposing initiatives in general, including funding of appropriate technology, supporting compound access and sharing of drug repurposing libraries. There is also a need for innovative sources of funding for drug repurposing initiatives in rare diseases in particular (BOX 1), such as crowdsourcing and parent entrepreneurs.

Finally, measures are needed to incentivize drug repurposing, particularly to address the patent and regulatory barriers discussed above. Such measures could include better data exclusivity periods for repurposed indications, royalty arrangements with generic companies or other legislative changes to ensure that there is sufficient opportunity for retrieval of investment in drug repurposing programmes.

1. Ashburn, T. T. & Thor, K. B. Drug repositioning: identifying and developing new uses for existing drugs. *Nat. Rev. Drug Discov.* **3**, 673–683 (2004).
2. Scannell, J. W., Blanckley, A., Boldon, H. & Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* **11**, 191–200 (2012).
3. Pammolli, F., Magazzini, L. & Riccaboni, M. The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discov.* **10**, 428–438 (2011).
4. Waring, M. J. et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat. Rev. Drug Discov.* **14**, 475–486 (2015).
5. Roundtable on Translating Genomic-Based Research for Health (Board on Health Sciences Policy) Institute of Medicine in *Drug Repurposing and Repositioning: Workshop Summary* (eds. Johnson, S. G., Beachy, S. H., Olson, S., Berger, A. C.) (National Academies Press, Washington DC, 2014).
6. Breckenridge, A. & Jacob, R. Overcoming the legal and regulatory barriers to drug repurposing. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/nrd.2018.92 (2018).
7. Nosengo, N. Can you teach old drugs new tricks? *Nature* **534**, 314–316 (2016).
8. Phillips, D. J. Pfizer's expiring Viagra patent adversely affects other drugmakers too. *Forbes* https://www.forbes.com/sites/investor/2013/12/20/pfizers-expiring-viagra-patent-adversely-affects-other-drugmakers-too (2013).
9. Singhal, S. et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N. Engl. J. Med.* **341**, 1565–1571 (1999).
10. Urquhart, L. Market watch: top drugs and companies by sales in 2017. *Nat. Rev. Drug Discov.* **17**, 232 (2018).
11. Hurle, M. R. et al. Computational drug repositioning: from data to therapeutics. *Clin. Pharmacol. Ther.* **93**, 335–341 (2013).
12. Keiser, M. J. et al. Predicting new molecular targets for known drugs. *Nature* **462**, 175–181 (2009).
13. Hieronymus, H. et al. Gene expression signature-based chemical genomic prediction identifies a novel class of HSP90 pathway modulators. *Cancer Cell* **10**, 321–330 (2006).
14. Dudley, J. T., Deshpande, T. & Butte, A. J. Exploiting drug-disease relationships for computational drug repositioning. *Brief Bioinform.* **12**, 303–311 (2011).
15. Iorio, F., Rittman, T., Ge, H., Menden, M. & Saez-Rodriguez, J. Transcriptional data: a new gateway to drug repositioning? *Drug Discov. Today* **18**, 350–357 (2013).
16. Dudley, J. T. et al. Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. *Sci. Transl Med.* **3**, 96ra76 (2011).
17. Sirota, M. et al. Discovery and preclinical validation of drug indications using compendia of public gene expression data. *Sci. Transl Med.* **3**, 96ra77 (2011).
18. Wagner, A. et al. Drugs that reverse disease transcriptomic signatures are more effective in a mouse model of dyslipidemia. *Mol. Syst. Biol.* **11**, 791 (2015).
19. Hsieh, Y. Y., Chou, C. J., Lo, H. L. & Yang, P. M. Repositioning of a cyclin-dependent kinase inhibitor GW8510 as a ribonucleotide reductase M2 inhibitor to treat human colorectal cancer. *Cell Death Discov.* **2**, 16027 (2016).
20. Huang, C. H. et al. Identify potential drugs for cardiovascular diseases caused by stress-induced genes in vascular smooth muscle cells. *PeerJ* **4**, e2478 (2016).
21. Kunkel, S. D. et al. mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. *Cell Metab.* **13**, 627–638 (2011).
22. Malcomson, B. et al. Connectivity mapping (ssCMap) to predict A20-inducing drugs and their antiinflammatory action in cystic fibrosis. *Proc. Natl Acad. Sci. USA* **113**, E3725–E3734 (2016).
23. Mirza, N., Sills, G. J., Pirmohamed, M. & Marson, A. G. Identifying new antiepileptic drugs through genomics-based drug repurposing. *Hum. Mol. Genet.* **26**, 527–537 (2017).
24. Shin, E., Lee, Y. C., Kim, S. R., Kim, S. H. & Park, J. Drug signature-based finding of additional clinical use of LC28-0126 for neutrophilic bronchial asthma. *Sci. Rep.* **5**, 17784 (2015).
25. Wei, G. et al. Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance. *Cancer Cell* **10**, 331–342 (2006).
26. Chiang, A. P. & Butte, A. J. Systematic evaluation of drug-disease relationships to identify leads for novel drug uses. *Clin. Pharmacol. Ther.* **86**, 507–510 (2009).
27. Iorio, F., Isacchi, A., di Bernardo, D. & Brunetti-Pierri, N. Identification of small molecules enhancing autophagic function from drug network analysis. *Autophagy* **6**, 1204–1205 (2010).
28. Hegde, R. N. et al. Unravelling druggable signalling networks that control F508del-CFTR proteostasis. *eLife* **4**, e10365 (2015).
29. Iorio, F. et al. A semi-supervised approach for refining transcriptional signatures of drug response and repositioning predictions. *PLOS ONE* **10**, e0139446 (2015).
30. Lamb, J. et al. The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* **313**, 1929–1935 (2006).
31. Wang, Z. et al. Extraction and analysis of signatures from the gene expression omnibus by the crowd. *Nat. Commun.* **7**, 12846 (2016).
32. Pacini, C. et al. DvD: an R/Cytoscape pipeline for drug repurposing using public repositories of gene expression data. *Bioinformatics* **29**, 132–134 (2013).
33. Zhang, S. D. & Gant, T. W. sscMap: an extensible Java application for connecting small-molecule drugs using gene-expression signatures. *BMC Bioinformatics* **10**, 236 (2009).
34. Oprea, T. I., Tropsha, A., Faulon, J. L. & Rintoul, M. D. Systems chemical biology. *Nat. Chem. Biol.* **3**, 447–450 (2007).
35. Campillos, M., Kuhn, M., Gavin, A. C., Jensen, L. J. & Bork, P. Drug target identification using side-effect similarity. *Science* **321**, 263–266 (2008).
36. Yang, L. & Agarwal, P. Systematic drug repositioning based on clinical side-effects. *PLOS ONE* **6**, e28025 (2011).
37. Kitchen, D. B., Decornez, H., Furr, J. R. & Bajorath, J. Docking and scoring in virtual screening for drug discovery: methods and applications. *Nat. Rev. Drug Discov.* **3**, 935–949 (2004).
38. Dakshanamurthy, S. et al. Predicting new indications for approved drugs using a proteochemometric method. *J. Med. Chem.* **55**, 6832–6848 (2012).
39. Cooke, R. M., Brown, A. J., Marshall, F. H. & Mason, J. S. Structures of G protein-coupled receptors reveal new opportunities for drug discovery. *Drug Discov. Today* **20**, 1355–1364 (2015).
40. Kharkar, P. S., Warrier, S. & Gaud, R. S. Reverse docking: a powerful tool for drug repositioning and drug rescue. *Future Med. Chem.* **6**, 333–342 (2014).
41. Huang, H. et al. Reverse screening methods to search for the protein targets of chemopreventive compounds. *Front. Chem.* **6**, 138 (2018).
42. Warren, G. L. et al. A critical assessment of docking programs and scoring functions. *J. Med. Chem.* **49**, 5912–5931 (2006).
43. Pagadala, N. S., Syed, K. & Tuszynski, J. Software for molecular docking: a review. *Biophys. Rev.* **9**, 91–102 (2017).
44. Sanseau, P. et al. Use of genome-wide association studies for drug repositioning. *Nat. Biotechnol.* **30**, 317–320 (2012).
45. Grover, M. P. et al. Novel therapeutics for coronary artery disease from genome-wide association study data. *BMC Med. Genom.* **8** (Suppl. 2), S1 (2015).
46. Wang, Z. Y. & Zhang, H. Y. Rational drug repositioning by medical genetics. *Nat. Biotechnol.* **31**, 1080–1082 (2013).
47. Willyard, C. New human gene tally reignites debate. *Nature* **558**, 354–355 (2018).
48. Smith, S. B., Dampier, W., Tozeren, A., Brown, J. R. & Magid-Slav, M. Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis. *PLOS ONE* **7**, e33174 (2012).
49. Greene, C. S. & Voight, B. F. Pathway and network-based strategies to translate genetic discoveries into effective therapies. *Hum. Mol. Genet.* **25**, R94–R98 (2016).
50. Iorio, F., Saez-Rodriguez, J. & di Bernardo, D. Network based elucidation of drug response: from modulators to targets. *BMC Syst. Biol.* **7**, 139 (2013).
51. Greene, C. S. et al. Understanding multicellular function and disease with human tissue-specific networks. *Nat. Genet.* **47**, 569–576 (2015).
52. US Preventive Services Task Force. Final recommendation statement. Aspirin use to prevent cardiovascular disease and colorectal cancer: preventive medication. *US Preventive Services Task Force* https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer (2017).
53. Cavalla, D. & Singal, C. Retrospective clinical analysis for drug rescue: for new indications or stratified patient groups. *Drug Discov. Today* **17**, 104–109 (2012).

54. Jensen, P. B., Jensen, L. J. & Brunak, S. Mining electronic health records: towards better research applications and clinical care. *Nat. Rev. Genet.* **13**, 395–405 (2012).
55. Paik, H. et al. Repurpose terbutaline sulfate for amyotrophic lateral sclerosis using electronic medical records. *Sci. Rep.* **5**, 8580 (2015).
56. Huang, Y. H. & Vakoc, C. R. A. Biomarker harvest from one thousand cancer cell lines. *Cell* **166**, 536–537 (2016).
57. Weinstein, J. N. Drug discovery: cell lines battle cancer. *Nature* **483**, 544–545 (2012).
58. Barretina, J. et al. The cancer cell line encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* **483**, 603–607 (2012).
59. Basu, A. et al. An interactive resource to identify cancer genetic and lineage dependencies targeted by small molecules. *Cell* **154**, 1151–1161 (2013).
60. Iorio, F. et al. A landscape of pharmacogenomic interactions in cancer. *Cell* **166**, 740–754 (2016).
61. Seashore-Ludlow, B. et al. Harnessing connectivity in a large-scale small-molecule sensitivity dataset. *Cancer Discov.* **5**, 1210–1223 (2015).
62. Wei, W. Q. & Denny, J. C. Extracting research-quality phenotypes from electronic health records to support precision medicine. *Genome Med.* **7**, 41 (2015).
63. Chen, Z. et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int. J. Epidemiol.* **40**, 1652–1666 (2011).
64. Millwood, I. Y. et al. A phenome-wide association study of a lipoprotein-associated phospholipase A2 loss-of-function variant in 90 000 Chinese adults. *Int. J. Epidemiol.* **45**, 1588–1599 (2016).
65. O'Donoghue, M. L. et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA* **312**, 1006–1015 (2014).
66. White, H. D. et al. Darapladib for preventing ischemic events in stable coronary heart disease. *N. Engl. J. Med.* **370**, 1702–1711 (2014).
67. Eisenstein, M. Big data: the power of petabytes. *Nature* **527**, S2–S4 (2015).
68. Peplow, M. The 100,000 Genomes Project. *BMJ* **353**, i1757 (2016).
69. Collins, F. S. & Varmus, H. A new initiative on precision medicine. *N. Engl. J. Med.* **372**, 793–795 (2015).
70. Cyranoski, D. China embraces precision medicine on a massive scale. *Nature* **529**, 9–10 (2016).
71. Juric, D. et al. Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: results from the first-in-human study. *J. Clin. Oncol.* **36**, 1291–1299 (2018).
72. Venot, Q. et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* **558**, 540–546 (2018).
73. Wicks, P., Vaughan, T. E., Massagli, M. P. & Heywood, J. Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. *Nat. Biotechnol.* **29**, 411–414 (2011).
74. Brehmer, D. et al. Cellular targets of gefitinib. *Cancer Res.* **65**, 379–382 (2005).
75. Martinez Molina, D. et al. Monitoring drug target engagement in cells and tissues using the cellular thermal shift assay. *Science* **341**, 84–87 (2013).
76. Alshareef, A. et al. The use of cellular thermal shift assay (CETSA) to study crizotinib resistance in ALK-expressing human cancers. *Sci. Rep.* **6**, 33710 (2016).
77. Miettinen, T. P. & Bjorklund, M. NQO2 is a reactive oxygen species generating off-target for acetaminophen. *Mol. Pharm.* **11**, 4395–4404 (2014).
78. Eyers, P. A., van den, I. P., Quinlan, R. A., Goedert, M. & Cohen, P. Use of a drug-resistant mutant of stress-activated protein kinase 2a/p38 to validate the in vivo specificity of SB 203580. *FEBS Lett.* **451**, 191–196 (1999).
79. Cohen, P. Protein kinases—the major drug targets of the twenty-first century? *Nat. Rev. Drug Discov.* **1**, 309–315 (2002).
80. Blagg, J. & Workman, P. Choose and use your chemical probe wisely to explore cancer biology. *Cancer Cell* **32**, 9–25 (2017).
81. Hall-Jackson, C. A. et al. Paradoxical activation of Raf by a novel Raf inhibitor. *Chem. Biol.* **6**, 559–568 (1999).
82. Su, F. et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N. Engl. J. Med.* **366**, 207–215 (2012).
83. Duncan, J. S. et al. Dynamic reprogramming of the kinome in response to targeted MEK inhibition in triple-negative breast cancer. *Cell* **149**, 307–321 (2012).
84. Klaeger, S. et al. Chemical proteomics reveals ferrochelatase as a common off-target of kinase inhibitors. *ACS Chem. Biol.* **11**, 1245–1254 (2016).
85. Troutman, S. et al. Crizotinib inhibits NF2-associated schwannoma through inhibition of focal adhesion kinase 1. *Oncotarget* **7**, 54515–54525 (2016).
86. Wisniewski, D. et al. Characterization of potent inhibitors of the Bcr-Abl and the c-kit receptor tyrosine kinases. *Cancer Res.* **62**, 4244–4255 (2002).
87. Blanke, C. D. et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J. Clin. Oncol.* **26**, 620–625 (2008).
88. Sloane, D. A. et al. Drug-resistant aurora A mutants for cellular target validation of the small molecule kinase inhibitors MLN8054 and MLN8237. *ACS Chem. Biol.* **5**, 563–576 (2010).
89. Bago, R. et al. The hVps34-SGK3 pathway alleviates sustained PI3K/Akt inhibition by stimulating mTORC1 and tumour growth. *EMBO J.* **35**, 1902–1922 (2016).
90. Carter, T. A. et al. Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. *Proc. Natl Acad. Sci. USA* **102**, 11011–11016 (2005).
91. Davis, M. I. et al. Comprehensive analysis of kinase inhibitor selectivity. *Nat. Biotechnol.* **29**, 1046–1051 (2011).
92. Karaman, M. W. et al. A quantitative analysis of kinase inhibitor selectivity. *Nat. Biotechnol.* **26**, 127–132 (2008).
93. Munoz, L. Non-kinase targets of protein kinase inhibitors. *Nat. Rev. Drug Discov.* **16**, 424–440 (2017).
94. Xu, M. et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat. Med.* **22**, 1101–1107 (2016).
95. Sun, W. et al. Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria. *Emerg. Microbes Infect.* **5**, e116 (2016).
96. Moffat, J. G., Vincent, F., Lee, J. A., Eder, J. & Prunotto, M. Opportunities and challenges in phenotypic drug discovery: an industry perspective. *Nat. Rev. Drug Discov.* **16**, 531–543 (2017).
97. Iljin, K. et al. High-throughput cell-based screening of 4910 known drugs and drug-like small molecules identifies disulfiram as an inhibitor of prostate cancer cell growth. *Clin. Cancer Res.* **15**, 6070–6078 (2009).
98. Cousin, M. A. et al. Larval zebrafish model for FDA-approved drug repositioning for tobacco dependence treatment. *PLOS ONE* **9**, e90467 (2014).
99. Kremer, S. & Jones, R. Repurposed drugs: second time lucky. *Life Sciences Intellectual Property Review* http://www.lifesciencesipreview.com/article/repurposed-drugs-second-time-lucky (2014).
100. Murteira, S., Millier, A., Ghezaiel, Z. & Lamure, M. Drug reformulations and repositioning in the pharmaceutical industry and their impact on market access: regulatory implications. *J. Mark. Access Health Policy* https://doi.org/10.3402/jmahp.v2.22813 (2014).
101. Frail, D. E. et al. Pioneering government-sponsored drug repositioning collaborations: progress and learning. *Nat. Rev. Drug Discov.* **14**, 833–841 (2015).
102. Allison, M. NCATS launches drug repurposing program. *Nat. Biotechnol.* **30**, 571–572 (2012).
103. Prague, J. K. et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* **389**, 1809–1820 (2017).
104. [No authors listed.] AstraZeneca, Taiwan's NRPB launch drug discovery collaboration. *Genetic Engineering & Biotechnology News* https://www.genengnews.com/gen-news-highlights/astrazeneca-taiwan-39-s-nrpb-launch-drug-discovery-collaboration/81248991 (2013).
105. Drewry, D. H., Willson, T. M. & Zuercher, W. J. Seeding collaborations to advance kinase science with the GSK Published Kinase Inhibitor Set (PKIS). *Curr. Top. Med. Chem.* **14**, 340–342 (2014).
106. Knapp, S. et al. A public-private partnership to unlock the untargeted kinome. *Nat. Chem. Biol.* **9**, 3–6 (2013).
107. Billin, A. N. et al. Discovery of novel small molecules that activate satellite cell proliferation and enhance repair of damaged muscle. *ACS Chem. Biol.* **11**, 518–529 (2016).
108. Elkins, J. M. et al. Comprehensive characterization of the Published Kinase Inhibitor Set. *Nat. Biotechnol.* **34**, 95–103 (2016).
109. Xu, K. & Cote, T. R. Database identifies FDA-approved drugs with potential to be repurposed for treatment of orphan diseases. *Brief Bioinform.* **12**, 341–345 (2011).
110. Crockett, S. D., Schectman, R., Sturmer, T. & Kappelman, M. D. Topiramate use does not reduce flares of inflammatory bowel disease. *Dig. Dis. Sci.* **59**, 1535–1543 (2014).
111. Auteri, M., Zizzo, M. G. & Serio, R. GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation. *Pharmacol. Res.* **93**, 11–21 (2015).
112. Iorio, F. et al. Discovery of drug mode of action and drug repositioning from transcriptional responses. *Proc. Natl Acad. Sci. USA* **107**, 14621–14626 (2010).
113. Lee, J. K., Shin, J. H., Lee, J. E. & Choi, E. J. Role of autophagy in the pathogenesis of amyotrophic lateral sclerosis. *Biochim. Biophys. Acta* **1852**, 2517–2524 (2015).
114. Takata, M. et al. Fasudil, a rho kinase inhibitor, limits motor neuron loss in experimental models of amyotrophic lateral sclerosis. *Br. J. Pharmacol.* **170**, 341–351 (2013).
115. Gunther, R. et al. Rho kinase inhibition with fasudil in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis-symptomatic treatment potential after disease onset. *Front. Pharmacol.* **8**, 17 (2017).
116. Tonges, L. et al. Rho kinase inhibition modulates microglia activation and improves survival in a model of amyotrophic lateral sclerosis. *Glia* **62**, 217–232 (2014).
117. Moschen, A. R. et al. The RANKL/OPG system is activated in inflammatory bowel disease and relates to the state of bone loss. *Gut* **54**, 479–487 (2005).
118. Franke, A. et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat. Genet.* **42**, 1118–1125 (2010).
119. University of Manitoba. The effect of denosumab, the inhibitor for receptor activator of nuclear factor kappa-B ligand (RANKL), on dinitrobenzensulfonic acid (DNBS)-induced experimental model of crohn's disease. *University of Manitoba MSpace* https://mspace.lib.umanitoba.ca/handle/1993/32400?show=full (2017).
120. Gligorijevic, V., Malod-Dognin, N. & Przulj, N. Integrative methods for analyzing big data in precision medicine. *Proteomics* **16**, 741–758 (2016).
121. Chen, Y., Elenee Argentinis, J. D. & Weber, G. IBM Watson: how cognitive computing can be applied to big data challenges in life sciences research. *Clin. Ther.* **38**, 688–701 (2016).
122. Ritchie, M. D., Holzinger, E. R., Li, R., Pendergrass, S. A. & Kim, D. Methods of integrating data to uncover genotype-phenotype interactions. *Nat. Rev. Genet.* **16**, 85–97 (2015).
123. Luo, Y. et al. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. *Nat. Commun.* **8**, 573 (2017).
124. Napolitano, F. et al. Drug repositioning: a machine-learning approach through data integration. *J. Cheminform* **5**, 30 (2013).
125. Hennequin, L. F. et al. N-(5-chloro-1,3-benzodioxol-4-yl)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a novel, highly selective, orally available, dual-specific c-Src/Abl kinase inhibitor. *J. Med. Chem.* **49**, 6465–6488 (2006).
126. Fury, M. G. et al. Phase II study of saracatinib (AZD0530) for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). *Anticancer Res.* **31**, 249–253 (2011).
127. Gangadhar, T. C., Clark, J. I., Karrison, T. & Gajewski, T. F. Phase II study of the Src kinase inhibitor saracatinib (AZD0530) in metastatic melanoma. *Invest. New Drugs* **31**, 769–773 (2013).
128. Kaufman, A. C. et al. Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. *Ann. Neurol.* **77**, 953–971 (2015).
129. Nygaard, H. B. et al. A phase Ib multiple ascending dose study of the safety, tolerability, and central nervous system availability of AZD0530 (saracatinib) in Alzheimer's disease. *Alzheimers Res. Ther.* **7**, 35 (2015).
130. De Felice, M., Lambert, D., Holen, I., Escott, K. J. & Andrew, D. Effects of Src-kinase inhibition in cancer-induced bone pain. *Mol. Pain* **12**, 1744806916643725 (2016).

131. Tyryshkin, A., Bhattacharya, A. & Eissa, N. T. SRC kinase is a novel therapeutic target in lymphangioleiomyomatosis. *Cancer Res.* **74**, 1996–2005 (2014).
132. Dickerson, J. & Sharp, F. R. Atypical antipsychotics and a Src kinase inhibitor (PP1) prevent cortical injury produced by the psychomimetic, noncompetitive NMDA receptor antagonist MK-801. *Neuropsychopharmacology* **31**, 1420–1430 (2006).
133. Stearns, V. et al. Hot flushes. *Lancet* **360**, 1851–1861 (2002).
134. Prague, J. K. & Dhillo, W. S. Neurokinin 3 receptor antagonism — the magic bullet for hot flushes? *Climacteric* **20**, 505–509 (2017).
135. Jayasena, C. N. et al. Neurokinin B administration induces hot flushes in women. *Sci. Rep.* **5**, 8466 (2015).
136. Mittelman-Smith, M. A., Williams, H., Krajewski-Hall, S. J., McMullen, N. T. & Rance, N. E. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. *Proc. Natl Acad. Sci. USA* **109**, 19846–19851 (2012).
137. Rance, N. E. & Young, W. S. 3rd. Hypertrophy and increased gene expression of neurons containing neurokinin-B and substance-P messenger ribonucleic acids in the hypothalami of postmenopausal women. *Endocrinology* **128**, 2239–2247 (1991).
138. Dacks, P. A., Krajewski, S. J. & Rance, N. E. Activation of neurokinin 3 receptors in the median preoptic nucleus decreases core temperature in the rat. *Endocrinology* **152**, 4894–4905 (2011).
139. Crandall, C. J. et al. Association of genetic variation in the tachykinin receptor 3 locus with hot flashes and night sweats in the Women's Health Initiative Study. *Menopause* **24**, 252–261 (2017).
140. Griebel, G. & Beeske, S. Is there still a future for neurokinin 3 receptor antagonists as potential drugs for the treatment of psychiatric diseases? *Pharmacol. Ther.* **133**, 116–123 (2012).
141. Evangelista, S. Talnetant GlaxoSmithKline. *Curr. Opin. Investig. Drugs* **6**, 717–721 (2005).
142. Fraser, G. L. et al. Clinical evaluation of the NK3 receptor antagonist fezolinetant (a.k.a. ESN364) for the treatment of menopausal hot flashes. *Endocrine Society* https://www.endocrine.org/meetings/endo-annual-meetings/abstract-details?ID=32994&ID=32994 (2017).
143. Cully, M. Deal watch: neurokinin 3 receptor antagonist revival heats up with Astellas acquisition. *Nat. Rev. Drug Discov.* **16**, 377 (2017).
144. Protheroe, A., Edwards, J. C., Simmons, A., Maclennan, K. & Selby, P. Remission of inflammatory arthropathy in association with anti-CD20 therapy for non-Hodgkin's lymphoma. *Rheumatology* **38**, 1150–1152 (1999).
145. Storz, U. Rituximab: how approval history is reflected by a corresponding patent filing strategy. *mAbs* **6**, 820–837 (2014).
146. Brinkmann, V. et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. *Nat. Rev. Drug Discov.* **9**, 883–897 (2010).
147. Bezprozvanny, I. The rise and fall of Dimebon. *Drug News Perspect.* **23**, 518–523 (2010).
148. Cudkowicz, M. E. et al. Safety and efficacy of ceftriaxone for amyotrophic lateral sclerosis: a multi-stage, randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* **13**, 1083–1091 (2014).
149. Markey, K. A. et al. Assessing the efficacy and safety of an 11beta-hydroxysteroid dehydrogenase type 1 inhibitor (AZD4017) in the Idiopathic Intracranial Hypertension Drug Trial, IIH:DT: clinical methods and design for a phase II randomized controlled trial. *JMIR Res. Protoc.* **6**, e181 (2017).
150. Assouline, S. et al. Molecular targeting of the oncogene eIF4E in acute myeloid leukemia (AML): a proof-of-principle clinical trial with ribavirin. *Blood* **114**, 257–260 (2009).

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Competing interests
S.H. is an author on this manuscript and works for the Medicines and Healthcare Products Regulatory Agency (MHRA), UK; the opinions expressed in this review are her own and should not be attributed to the MHRA/European Medicines Agency (EMA). A.D. is a director of PharmaKure Ltd.

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