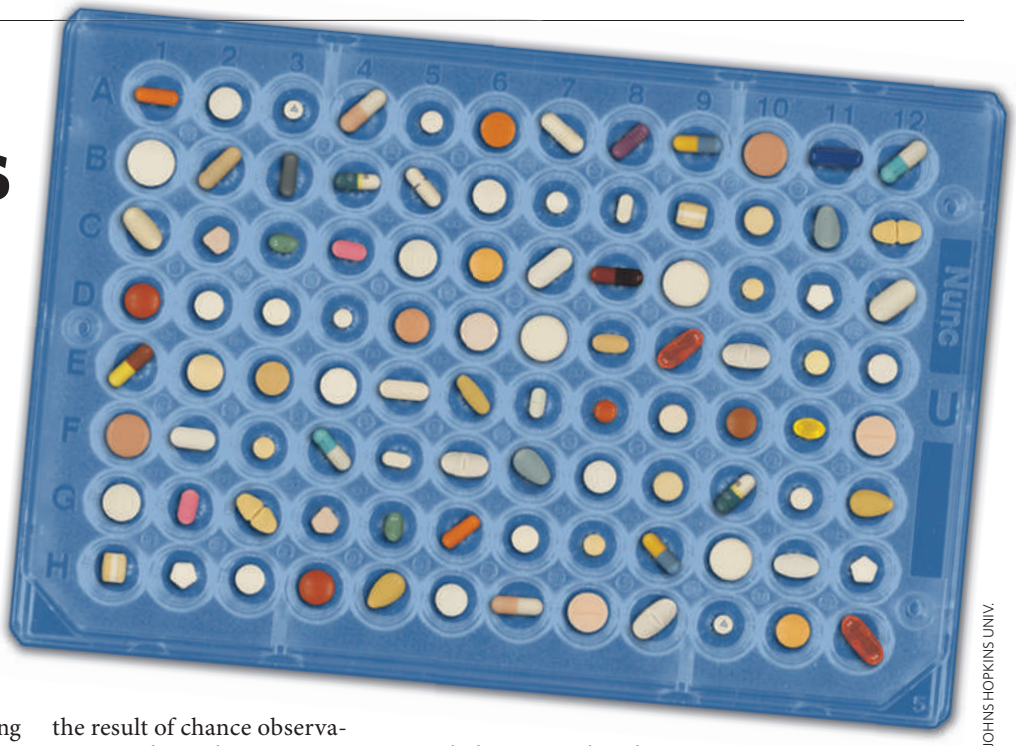
COMMENTARY

New uses for old drugs

It takes too long and costs too much to bring new drugs to market. So let's beef up efforts to screen existing drugs for new uses, argue **Curtis R. Chong** and **David J. Sullivan Jr.**



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Fast, affordable drug development is a vision that contrasts sharply with the current state of drug discovery — which also neglects too many diseases of the poor. An analysis[1] of 68 approved drugs estimated that it takes an average of 15 years and US$800 million to bring a single drug to market. And despite a doubling in research spending by the US National Institutes of Health (NIH) to $27 billion in 2003, the number of new drugs approved by the US Food and Drug Administration (FDA) each year remains constant at 20–30 compounds[2]. At this rate it will take more than 300 years for the number of drugs in the world to double.

The current costly and time-consuming paradigm of drug discovery is ill-equipped to combat rapidly emerging diseases, such as avian flu, drug-resistant pathogens and diseases that have a small financial market. One solution is to identify new uses for existing drugs. As the pharmacologist and Nobel laureate James Black said, "the most fruitful basis for the discovery of a new drug is to start with an old drug." Because existing drugs have known pharmacokinetics and safety profiles and are often approved by regulatory agencies for human use, any newly identified use can be rapidly evaluated in phase II clinical trials, which typically last two years and cost $17 million[1]. In this way, drug developers can bypass almost 40% of the overall cost of bringing a drug to market by eliminating much of the toxicological and pharmacokinetic assessments[1].

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This back-to-basics approach is growing in popularity. At least 17 existing drugs are in various stages of clinical and animal testing for new uses (see Supplementary information), and a further 24 are already being remarketed by the pharmaceutical industry for new uses[3]. Although most successful crossovers have been the result of chance observations or educated guesses, exceptions include the antibiotic ceftriaxone, which is a potential treatment for amyotrophic lateral sclerosis[4], and whose new activity was discovered following the screening of 1,040 compounds from the National Institute of Neurological Disorders and Stroke (NINDS) custom collection in Gaylordsville, Connecticut. In the past, individual labs were limited to screening perhaps hundreds of compounds. Now, clinical drug collections like the NINDS library and the Prestwick Chemical Library in Washington DC offer more than 1,000 approved drugs for small-scale lab screening. In our view, what is needed is a more systematic approach to drug rediscovery that takes these valuable resources to the next level.

Historically, 'repurposing' old drugs has proved successful in bringing new therapies to the developing world. Today, even with the billions of research dollars available to create new drugs through public–private partnerships, and the promise of genomic data, there remains an enormous unmet need for therapies for neglected diseases[5]. A recent example of a repurposed drug is miltefosine, initially developed for breast cancer but now used for treating visceral leishmaniasis[6]. This disease is caused by a sand-fly-transmitted parasite and kills an estimated 500,000 people each year. In fact, miltefosine failed phase II testing for tumour reduction and the drug was never approved by the FDA for cancer therapy. However, *in vitro* and animal studies indicated anti-infective activity, and phase II trials confirmed miltefosine as a viable treatment for visceral leishmaniasis[6].

Cost cutting

Cost is one reason to revisit existing drugs: roughly 1,000 of the 10,000 or so drugs ever tested in clinical medicine are covered by patents, so most drugs can affordably be redeployed in the developing world. Safety is another compelling reason. Phase IV clinical studies, which monitor post-marketing safety, cost around $100 million per drug to perform in developed countries[1] and are nearly impossible in countries without an established healthcare infrastructure. Because many existing drugs have undergone phase IV surveillance in millions of patients, the same stringent safety standards required by users in developed countries can be offered to patients with neglected diseases in the developing world.

Despite the promise of finding new uses for existing drugs, a comprehensive collection of the approximately 9,990 drugs known to clinical medicine does not exist. This number includes 2,933 unique drugs approved by the FDA since 1938 (ref. 7), 1,107 drugs in the 2006 FDA Orange Book, 888 drugs in the 2006 Physician Desk Reference, and 7,057 drugs that are either approved abroad or have entered phase II clinical trials, as indicated by a US Adopted Name or International Non-proprietary Name[8]. Excluding antiseptics, pharmaceutical aids, therapeutic plant or animal extracts, and vaccines, we estimate that there are 8,850

unique drugs worth screening (see Supplementary information).

The largest publicly accessible collection of existing drugs is the Johns Hopkins Clinical Compound Library (JHCCL; www.jhccsi.org), where we both work. This now has 1,500 available compounds, which together with the NINDS collection represents 22% of drugs that have ever entered the clinic[7]. An estimated 1,600 additional approved drugs can be purchased by researchers, expanding coverage to nearly 40% of the existing drug space (Fig. 1). These compounds are the low-hanging fruit as far as cost and patent restrictions are concerned.

Building the library

To build a library of all 8,850 clinical compounds will require organic synthesis or donation of the remaining 60%. A comprehensive library should also include major drug metabolites, as these often have distinct pharmacological properties. For example, fexofenadine, which is a non-sedating antihistamine, lacks the cardiotoxic side effects of its parent terfenadine[9], and isoniazid (for tuberculosis) and primaquine (for malaria) are not active unless first metabolized[10]. Adding metabolites might increase the size of the library by as much as 25%.

Existing collections, such as the NINDS and Prestwick libraries, provide access to mostly FDA-approved and marketed drugs (Prestwick offers mainly off-patent compounds). Although screening drugs for new uses does not, as we understand it, violate existing patents, whether they cover drug synthesis or use, patented drugs will be the most difficult and expensive to obtain for screening, perhaps costing as much as $1,000 per compound.

Chemical synthesis of drugs and metabolites that cannot be purchased will be costly, perhaps running to several millions of dollars. This is a substantial investment, yet, in our view, identifying just one new clinical use for an existing drug would more than make up for the resources invested in the library, given the expense of conventional drug development. Compared to the effort and resources already devoted to *de novo* drug discovery, such as the 2003 NIH Roadmap Molecular Libraries Initiative, which aims to screen more than 100,000 novel compounds at a cost of $250 million annually, a smaller clinical compound library is a worthy target for public–private funding.

And although a collection of 10,000 compounds sounds ambitious, it pales in comparison with the libraries of novel unmarketed compounds (100,000 or more) held by pharmaceutical companies. Unlike *de novo* drug discovery, which requires specialized robotics to screen hundreds of thousands of compounds, the smaller size of the proposed clinical compound library makes screening feasible in virtually any laboratory. JHHCL currently provides its collection of drugs in 24 × 96-well plates, and this could easily be scaled up to 27 × 384-well plates for a library of 10,000 or more. At this scale, specialized screening centres (as used by the NIH Roadmap initiative) will not be necessary.

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Once the clinical compound library is complete, it should become a public resource available to the scientific community for screening on any disease target. As an open repository, the collection should be distributed rapidly and provided at minimal cost to investigators from both academia and industry with reasonable screening proposals. The existing JHCCL collection is now available to any laboratory for a small charge of $5,000 to cover shipping and replacement costs. In our view, access to the library should complement the decentralized, independent spirit of academia and should not entail a lengthy or complicated review process. An excellent example of an open repository is the synthetic and natural products collection maintained by the Developmental Therapeutics Program of the National Cancer Institute[11].

The only requirement to access the library should be agreement to deposit results in an open database upon publication, just as the raw data from structural biology and microarray experiments are made publicly available now. To aid the interpretation of initial screening results, researchers will need a comprehensive public database containing the pharmacokinetics and clinical properties of the drugs in the library. For example, knowledge of the peak blood-plasma levels of drugs is helpful in determining whether novel activities discovered by screening are clinically significant. These data are often held by drug manufacturers or the FDA, but are not always publicly available in the scientific literature, although they can be found after some time and expense in the patent literature.

Genetic information on the biological target of each drug in the database will assist in identifying other diseases for which it mioght be used. The not-for-profit bioinformatics resource DrugBank in Canada has already linked genetic targets with around 1,000 drugs[12]. JHCCL has plans for a relational database of this sort, although curating such information requires additional resources. Still, Wikipedia has already compiled descriptions of more than 1,800 drugs currently in use by relying on the work of volunteers.

Finding new uses for existing drugs is a proven short cut between the lab and the clinic. We challenge the scientific community to create a comprehensive clinical drug library and use it to screen every neglected disease by 2011. To build on past successes in drug rediscovery will mean screening all known pharmacological space in a systematic way. ■

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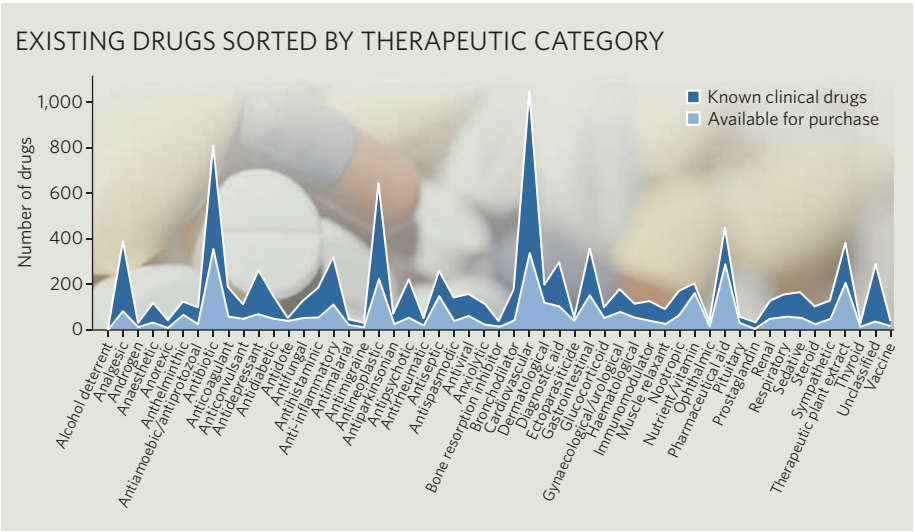

Figure 1 | The existing universe of 9,990 drugs and their availability.

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Supplementary information is linked to the online version of this article at www.nature.com/nature

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