SERGE BLOCH

New tricks for old drugs

Faced with skyrocketing costs for developing new drugs, researchers are looking at ways to repurpose older ones — and even some that failed in initial trials.

BY NICOLA NOSENGO

When a young physician opted to do a short stint in Grant Churchill's pharmacology lab as part of his medical training, he asked for a task that would quickly teach him the tools of the trade. "So I thought, 'I have a good project for you'," says Churchill.

That was in 2010, and Churchill's group at the University of Oxford, UK, was looking for ways to treat bipolar disorder without using lithium — a drug that often works well, but is plagued with side effects. So Churchill asked the physician, Justyn Thomas, to screen all of the 450 compounds in the US National Institutes of Health (NIH) Clinical Collection, a library of drugs that had passed safety tests in humans but, for various reasons, had never reached the market. "That stuff is just sitting there, and it doesn't take much effort," says Churchill, "so you think you just have to try."

Thomas pipetted a few drops of each compound into Petri dishes filled with bacteria that had been genetically engineered to manufacture the human enzyme suppressed by lithium — and eventually got a hit. A compound originally intended for people who had experienced a stroke also damped production of the enzyme, suggesting that it might give patients the same benefits as lithium[1]. After experiments in mice showed that the drug, ebselen, could get through the chemical barrier that protects the brain — something only a few compounds can do — Churchill's group did a small-scale trial and found that ebselen could be used safely in healthy volunteers[2].

The University of Oxford has now teamed up with a pharmaceutical company to run clinical trials of ebselen for bipolar disorder. The researchers are able to skip the phase I safety trials because the drug had already passed them, and are going straight to phase II: testing the drug's efficacy against bipolar disorder. Churchill is well aware that ebselen could fail this trial, or the larger, more stringent ones needed to test whether the drug works better than lithium. But he is already proud of what his team has achieved. "As an academic group with no company money," he says, "we were able to go from identification of the molecule to a human trial with a very limited budget."

Such stories are becoming more and more common: taking drugs that have been developed for one disorder and 'repositioning' them to tackle another is an increasingly important strategy for researchers in industry and academia alike. These efforts take inspiration from some classic success stories. One is sildenafil, an angina medication developed in 1989 that

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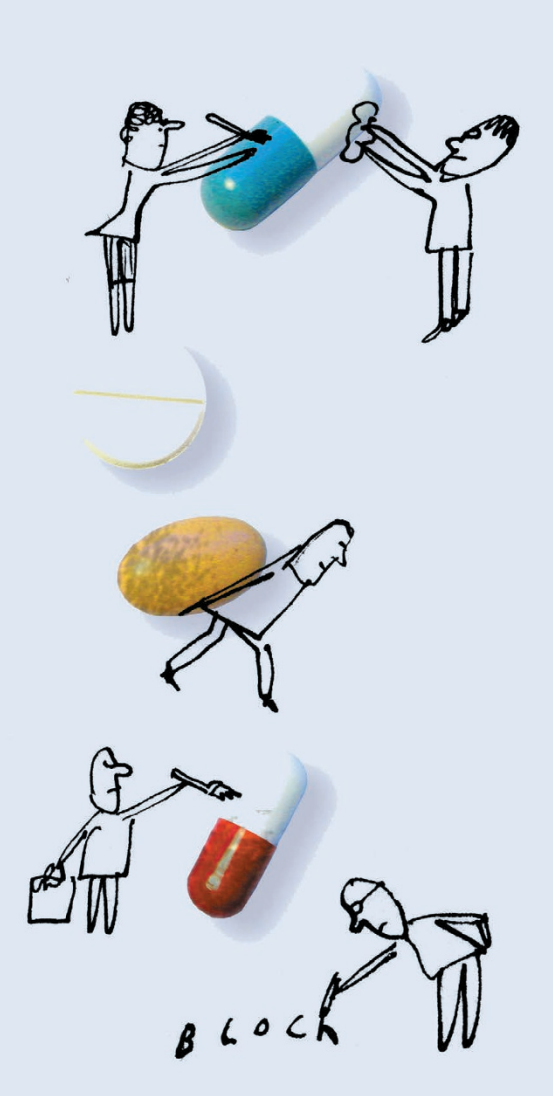

is now marketed as Viagra and used to treat erectile dysfunction. Another is azidothymidine, which failed as a chemotherapy drug but emerged in the 1980s as a therapy for HIV.

Increasingly, the serendipity responsible for those earlier discoveries is giving way to systematic searches for candidates. Partly, this is the result of advances in technology. These include big-data analytics that can now uncover molecular similarities between diseases; computational models that can predict which compounds might take advantage of those similarities; and high-throughput screening systems that can quickly test many drugs against different cell lines.

But for the pharmaceutical industry, the real impetus is economics. Getting a drug to market currently takes 13–15 years and between US$2 billion and $3 billion on average, and the costs are going up — even though the number of drugs approved every year per dollar spent on development has remained flat or decreased for most of the past decade[3] (see 'Eroom's law'). The 3,000 or so drugs that have been approved by at least one country therefore represent a vast untapped resource if they can be used against another condition — as do the thousands more that stalled in clinical trials. Many of them, like ebselen, can probably skip the phase I trials and pose a substantially lower risk of producing dramatic side effects in later phases — thereby slashing those development costs compared with completely new compounds. Some estimates suggest that repositioning a drug costs on average $300 million and takes around 6.5 years. "My feeling is that the proportion of drugs that in theory could be repositioned is probably around 75%," says Bernard Munos, a senior fellow at FasterCures, a drug-development advocacy organization in Washington DC, and a member of the advisory council of the National Center for Advancing Translational Sciences (NCATS) at the NIH.

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But the fraction is probably quite a bit smaller in practice, he concedes. Repositioned drugs still have to make it through phase II and III clinical trials for their new purpose — trials that respectively eliminate 68% and 40% of every compound that gets that far. And many drugs also face economic barriers, such as being off-patent, that could dissuade pharmaceutical companies from getting involved. "Can some repositioning projects work? Sure. Can it work systematically as a profitable business model? That, I don't believe," says John LaMattina, a former president of research and development at Pfizer, and now a senior partner at the health-care technology research firm PureTech in Boston, Massachusetts.

Nonetheless, some 30 articles on cases of drug repositioning are now being published in scientific journals every month — a sixfold increase since 2011. A dedicated journal, *Drug Repurposing, Rescue and Repositioning,* was launched last year. Three or four drug-repositioning companies are created every year. And some estimates[4] suggest that the number of repositioned drugs entering the regulatory-approval pipeline is rising, and could account for about 30% of all drugs approved every year.

"We've gone past the stage where we had to explain to everyone what we were talking about," says Andreas Persidis, chief executive of Biovista in Charlottesville, Virginia, one of about 40 companies that now specialize in drug repositioning. "Now it's a recognized field, and we're in the typical second stage of scientific trends, when lots of people jump on the bandwagon."

STARTING POINT

The easiest target for repositioning is generic drugs. They have been on the market for years, their safety profiles are well known and they are easy and cheap to obtain for clinical trials because their original patents have expired. And, if they involve new formulations or applications to new disorders, they can still be covered by patents or be granted three years of market exclusivity by the US Food and Drug Administration (FDA). So they remain attractive targets for companies.

Biovista, for example, starts by automatically scanning through all the publicly available information on generic compounds, from scientific papers and patents to the database of adverse events compiled by the FDA. Then it creates a kind of cellular social network, mapping all the connections that it has found between drugs, molecular pathways, genes and other biologically relevant entities. The thinking is that the more connections that a drug has in common with a disease, the more likely it is to be a good candidate for repositioning.

This is how Biovista discovered that pirlindole — a generic antidepressant that was developed and is used in Russia — might be a potential treatment for multiple sclerosis. In mouse models[5], the drug slows down the progression of the disease, and is now about to progress to a proof-of-concept study in humans. The company has secured a new patent on pirlindole, as well as on another candidate treatment for multiple sclerosis, still another for epilepsy and three for cancer.

Another source of knowledge is what doctors see in the clinic. "Every drug that's been around for some years has about 20 off-label uses, two-thirds of which are started by practising physicians," says Moshe Rogosnitzky, who heads one of the first academic centres for drug repositioning, established last year at Ariel University in Israel. "But the other doctors don't know about them, because clinicians have a hard time publishing their results."

So Rogosnitzky and his group systematically canvas these practitioners in Israel and 12 other countries, try to work out a mechanism of action for each reported effect and help the physicians to get patent protection and attract money for further trials. They also help more people to get the drug on an off-label basis. Next July, the group will start a phase II trial to reposition a generic angina drug, called dipyridamole, to treat dry eye disease, a frequent complication for people who have undergone bone-marrow transplants and risk losing their sight because their eyes stop producing tears.

FAILED BUT NOT FORGOTTEN

Another favourite target is the long list of failed drugs. Most of them pass phase I trials, but do not get past phase II because they don't have the same effect in humans that they had in animals. "Still, there are not many compounds that have some biological activity and are safe in humans, so for heaven's sake let's try to do something else with them," says Gregory Petsko, a

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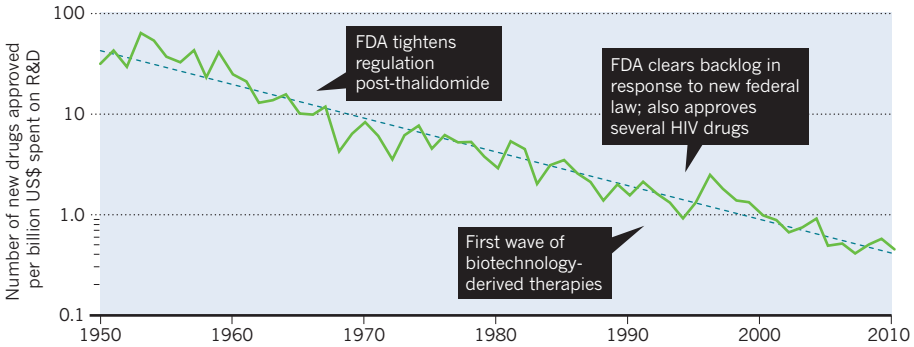
EROOM'S LAW

The efficiency of research and development of new drugs in the United States halves every nine years or so. Drug developers sometimes call this Eroom's law — Moore's law for microprocessors in reverse. Repositioning drugs could help to counter this decline.



12–16 years, **~$1 billion to $2 billion**

A SHORTER TIMESCALE

Because most repositioned drugs have already passed the early phases of development and clinical testing, they can potentially win approval in less than half the time and at one-quarter of the cost.

~6 years, **~$300 million**

SOURCES: J. W. SCANNELL *ET AL. NATURE REV. DRUG DISCOV.* **11**, 191–200 (2012); CYTHERA PHARMACEUTICALS

neuroscientist at Weill Cornell Medical College in New York City. The problem is that, apart from really old ones like ebselen, they tend to be locked in the industry's drawers.

"Sometimes, companies make official announcements when they abandon a molecule, but in most cases they don't," says Hermann Mucke, a biochemist who in 2000 founded the Vienna-based firm HM Pharma Consultancy, which now makes a business from hunting through discontinued compounds. "So we monitor a number of sources and look for drugs that have quietly disappeared from pipelines, or for clinical trials that were announced and never led to a publication." When they feel there may be room for repositioning, Mucke and his staff approach the owner of the drug and try to strike a deal that will allow them to do further tests and development — and share in any profits that result. They are also creating a database of drugs that have been approved but are no longer manufactured, and of drugs that have been abandoned during development. "We are developing it for our own use," he says. "But if we can find investors, we would like to turn it into a public resource."

In the absence of such a public resource, both the UK Medical Research Council (MRC) and NCATS have struck deals with major pharmaceutical companies, convincing them to pick some abandoned compounds from their pipelines and release enough information for academic groups to work out whether repositioning might be feasible. "There's a lot of research that could be done but is not happening, simply because academic people are not aware of what pharmaceutical companies are doing," says Christine Colvis, who heads the NCATS drug-repurposing effort.

Although the MRC programme officially aims to help researchers to understand the biology of diseases, many of the groups that it funds end up doing interesting repositioning work, too. At the University of Manchester, UK, for example, physician–scientist Jacky Smith is testing a compound that was originally developed to treat heartburn to see whether it can help people with chronic cough.

The NCATS programme has drawn criticism, however. "It's good that some groups have had access to some drugs, but that leaves out the vast majority of us," says Petsko. "And there's no guarantee that the compounds in those lists were really the most interesting ones." NCATS spent $12.7 million on 9 projects in 2013, and 8 of those have progressed to phase II trials. They include a former psoriasis drug that is being tested as a smoking-cessation therapy, a failed diabetes pill that is getting a second chance as a treatment for alcoholism, and a failed cancer drug that is now a potential therapy for Alzheimer's disease. A year from now, says Colvis, the first results of those studies will be published, and if all goes well, at least some of them will progress further. In the meantime, NCATS invested $2 million last year in another round of projects.

TURNING THE TABLES

In the long run, says Munos, drug repositioning could disrupt big pharma's business model in much the same way that digital music upended big record companies in the 1990s. "When current efforts start resulting in a flow of market approval," he says, "and we see many small companies developing drugs for a few millions of dollars, there will be a lot of interesting competition with traditional companies."

That optimism is not universal, however. "Not all repositioning projects that work on paper are really feasible," says Tudor Oprea, a bioinformatics researcher at the University of New Mexico in Albuquerque who monitors the field in addition to doing his own repositioning work. For instance, he says, side effects that would be acceptable for a life-threatening disease might not be acceptable for a chronic one. And the standard business case for repositioning — that costs are slashed because safety tests are already in the bag — works only if the dose and mode of administration remain similar. If the new disease requires a significantly higher dose, the drug will have to go through phase I trials again. In the end, says Oprea, development costs can be similar to those for a new molecule.

LaMattina wonders whether the opportunities are really as plentiful as proponents suggest. When companies test a new molecule, he says, they do a wide array of tests on various targets and cell types because they want to anticipate the effects. So if a drug really has interesting effects beyond the expected one, industry scientists will find out for themselves. "It's a bit naive to think that companies overlook all these opportunities to do business," he says. "It's typically people in academia, who don't know what happens in the industry, who think they can do it."

But Persidis argues that many companies are too specialized to benefit from all the repositioning opportunities they have in-house. They may have expertise and market penetration in neurology, but not in oncology, and moving a drug from one field to the other could be out of their strategy. "People like us keep getting business," he says, "and that's because larger companies do appreciate having an external partner looking at their drugs from a different angle."

In the end, says Atul Butte, a bioinformatician at the University of California, San Francisco, drug repositioning is a complement to the discovery of new molecules, rather than an alternative. "We just need more of both," he says. "In modern medicine, we're becoming better at figuring out that each disease is actually five or ten different ones. There are simply not enough companies out there to develop new drugs to treat them all." ■

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