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Repurposing Existing Drugs for New Indications

An entire industry has sprung up around resurrecting failed drugs and recycling existing compounds for novel indications.

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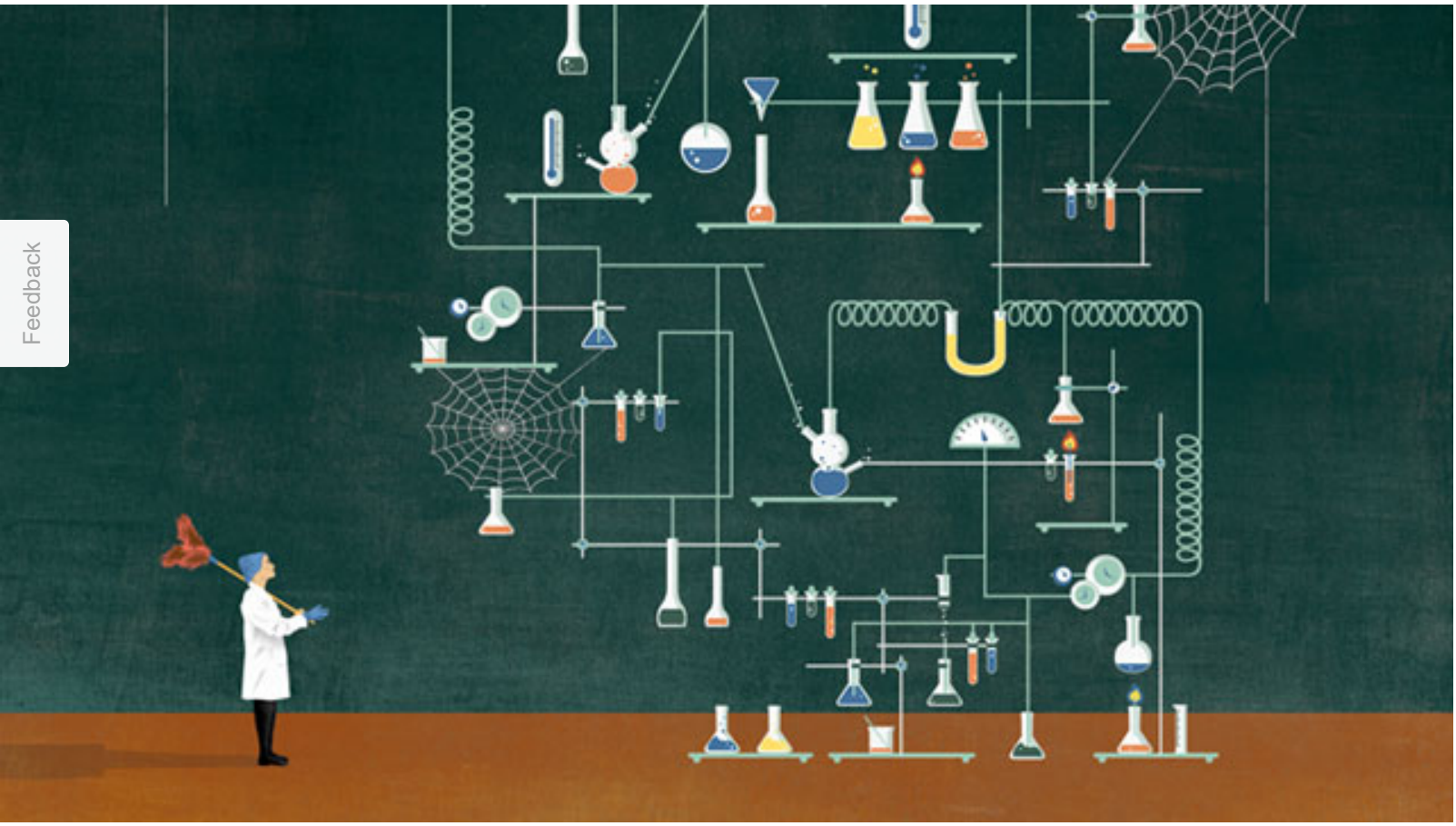


In 2010, Bruce Bloom, CEO of Illinois-based Cures Within Reach, reviewed the organization's decade-long track record of bringing new treatments to patients. He found that the nonprofit had funded 190 novel drug projects, but "couldn't find any instance where it was directly helping patients," says Bloom. Cures Within Reach had also funded 10 different drug repurposing projects, seeking to test existing drugs for novel indications. Of the 10 projects, four generated enough evidence to give physicians confidence to treat patients off-label, which doctors can do at their discretion, particularly when there is no approved therapy for a condition or when a patient has exhausted all available treatment options.

"We then polled 200 researchers and clinicians, and 66 percent of researchers told us they had a [repurposing] project ready for investigation, and 25 percent of clinicians had clinical observations they wanted to test in a trial," says Bloom. "This convinced us that there is a ton [of opportunities] out there for repurposing."

Thalidomide, originally approved in Europe in the 1950s as a sedative and in the U.S. in 1998 to treat leprosy, was one of the initial compounds researchers suggested to Bloom's organization for repurposing—in this case, to treat multiple myeloma. In 2000, Cures Within Reach—which itself receives funding exclusively from nongovernment

sources including private foundations—helped support a thalidomide Phase 2 trial at the Mayo Clinic. Because the drug had already been tested as a leprosy treatment, the researchers were able to bypass Phase 1 safety and dosing trials, which can take years to complete. Based on those results, in combination with a handful of other trials of the drug, the US Food and Drug Administration (FDA) approved thalidomide for multiple myeloma in 2012. Bloom estimates it cost only $40–$80 million in total to secure this FDA approval, compared to the average of $1–$2 billion it takes to develop a drug from scratch.[1]

Other researchers are taking similar approaches to find promising therapies already developed for one disease that could help treat another. Many academics have found promise in drugs that have long been on the market—inexpensive generics whose patents have expired. And a handful of nonprofit companies have cropped up to help usher these discoveries, which lack monetary incentive, to the clinic.

Some companies hoping to recoup returns on their investments are also looking to repurpose existing drugs still under patent, such as those that were shelved after unsuccessful trials. Because resources have already been devoted to these unapproved therapies, companies see value in attempting to revamp them for a new indication. "A portion of the cost and risks of drug development has already been surpassed, which is a huge cost benefit," says Craig Wegner, head of AstraZeneca's Emerging Innovations Unit in Boston.

Generic drugs found to work for a new disease are in a state of purgatory.

—Craig Wegner, AstraZeneca

Meanwhile, the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) aims to bridge the industry-academia divide by opening pharma's storehouse of compounds to university researchers for study of their mechanisms and potential uses. The center, established in December 2011, funded nine drug projects in 2013 and another four in 2015. Ongoing phase 2 clinical trials grew out of these projects and the center announced funding of several new projects in 2017. "There has been an incredible amount of energy around repurposing in the last five years that was not there previously," says Bloom.

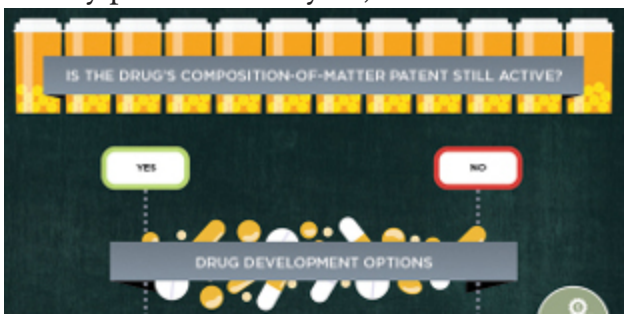
Most successful cases of drug repurposing have been largely serendipitous discoveries. Sildenafil, sold as Viagra since 2005, was tested as a treatment for erectile dysfunction only after erections emerged as a side effect in Phase 1 trials for cardiovascular disease. The antihypertensive minoxidil was reformulated into the topical cream Rogaine after patients using it experienced hair regrowth. But driven by such repurposing success stories, researchers are now taking more-tactical approaches to pinpoint new uses for existing and failed drugs, relying on new high-throughput techniques such as large-scale screens and bioinformatics strategies to mine data for drug-disease connections.

"More and more," says Bloom, "people are thinking of repurposing as a faster, cheaper, safer way to drive therapies to patients and as a method of creating a smarter way of new drug development."

Academia takes the lead

Heath Schmidt of the University of Pennsylvania's Perelman School of Medicine teamed up with Penn clinical researcher Rebecca Ashare to test galantamine's ability to help smokers kick their habit. Galantamine, an acetylcholinesterase inhibitor approved in 2001 for the treatment of Alzheimer's disease, blocks an enzyme that degrades acetylcholine, a neurotransmitter in the brain that's been linked to cognition that also binds to some of the same neuronal receptors that mediate nicotine's rewarding effects. "The idea is that if you can increase acetylcholine signaling in the brain, you could decrease nicotine-related behaviors such as tobacco smoking," says Schmidt.

In 2012, the team launched a Phase 2 short-term efficacy trial, and in a study published last year, found that smokers who took the acetylcholinesterase inhibitor for two weeks had decreased satisfaction from smoking and smoked an average of 12 percent fewer cigarettes compared with smokers who took a placebo.[2] "The known safety and side effects can make a trial much more efficient," says Ashare. The researchers have already launched a second Phase 2 trial to study the drug's effects on longer-term smoking cessation.



REPURPOSING STRATEGIES: Researchers are looking for novel uses for existing and failed drugs, which may save them time and money in brining new therapetuics to market.
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Schmidt and Ashare are not alone. Many academic researchers are turning their attention to existing drugs as a potential goldmine of therapies that are cheaper and faster to move into the clinic, and they're getting more methodical in their approach. Stephen Wong, a biomedical engineer at the Houston Methodist Research Institute in Texas, switched his focus from novel drug discovery to repurposing nine years ago when he realized the breadth and depth of clinical trials and basic science information available online. That has "really changed everything for drug development," he says. Wong's lab culls and archives publicly available omics research databases, journal articles and conference abstracts, human clinical trial data, patents, and Houston Methodist's database of longitudinal patient records, as well as privately generated omics data from preclinical disease models. The researchers then mine the information to identify molecules and combinations of molecules that match disease targets and pathways using artificial intelligence algorithms. "We call our technology the DrugX engine," says Wong. "It's like Google but for drug discovery."

The search engine spits out dozens of potential matches for laboratory and animal testing. Wong's team then turns to disease-specific clinicians and researchers who can help narrow down the list. "If we get 1,000 possibilities from our search engine, an expert can likely tell me which few we should actually validate," Wong says. The lab's efforts have led to several Phase 2 clinical trials (skipping Phase 1 safety trials in all cases), including an ongoing one testing the malaria drug chloroquine, administered in combination with chemotherapy, for metastatic breast cancer.[3]

Hua Xu's lab at the University of Texas Health Science Center in Houston also hopes to repurpose drugs, relying exclusively on clinical data. "[Doctors] monitor for bad side effects of drugs, but then we started to think, 'Why couldn't we use electronic health records to find potentially good effects of drugs?'" he says. Xu's group found, for example, that patients with breast, colorectal, or lung cancer who took metformin for type 2 diabetes had better overall survival compared with diabetic cancer patients who took other diabetes medications.[4]

In 2014, the growing popularity of drug repurposing led Hermann Mucke—a biochemist who has run his own consulting firm to advise pharma companies and academic institutions on potential repurposing opportunities for nearly 17 years—to help launch a dedicated journal, *Drug Repurposing, Rescue, and Repositioning*, currently published twice a year as special issues of *ASSAY and Drug Development Technologies*. "Our mid-term goal is to publish regularly as a stand-alone journal," says Mucke, who serves as the editor. "There is more than enough research going on in the field to warrant this."

While academic labs continue to churn out new leads, they often encounter difficulties garnering industry interest to support trials for a new use of a generic drug. After Eric Verdin, president and CEO of the Buck Institute for Research on Aging in Novato, California, and his colleagues identified two possible clinical uses for an aspirin derivative in mice,[5,6] for example, the team was unable to find a partner to move the compounds into clinical trials. "I'm becoming disenchanted with drug repurposing," Verdin says. "It's impossible to get funding from venture capitalists or even from our institution's intellectual property office." Verdin said he was advised to modify the molecules to

make them unique, such that they would be patentable and generate revenue. “But [if the generic version works], this is completely the opposite of what one should do with this type of discovery,” he says.

“Repurposed generic drugs do not appear to be good business cases,” agrees researcher Michael Pollak, a cancer researcher at McGill University in Montreal. “That’s the reality of repurposing.” Metformin—a widely used generic and typically the first line of treatment for type 2 diabetes—is a good example. Although the drug may slow the growth of some types of tumors and may even prevent certain cancer types,[7] trial funding has come predominantly from academia. Despite hundreds of small clinical trials, a lack of coordination between academic institutions and industry has resulted in slow development and no clear answer on the drug’s efficacy in thwarting cancer growth. “No company expects to make a profit from metformin’s use in cancer,” Pollak says.

Due to this lack of monetary incentive, “generic drugs found to work for a new disease are in a state of purgatory,” says Wegner. Indeed, no generic drug has ever been approved for a new indication by a manufacturer without modification of the drug’s delivery or its dose, which would provide renewed patent protection. Someone needs to step up to help move preliminary findings about these cheap and available drugs into the clinic where they can help patients, Wegner adds. “This is where foundations, advocacy groups, and the NIH can play a huge role.”

Nonprofits tackle generics

Feedback

The unused surplus of widely available, cheap, and potentially beneficial therapies is exactly what the Massachusetts-based nonprofit GlobalCures wants to tap into. “Our goal is to repurpose ‘financial orphans’—drugs for which there is evidence of efficacy but that have not gone through rigorous Phase 3 trials because there has been no financial incentive,” says cofounder Vikas Sukhatme. GlobalCures catalogs case reports and anecdotal remissions submitted by patients, as well as published preclinical and retrospective human data on noncancer drugs that show promise as anticancer therapies.

“We have trial protocols written and principal investigators all ready to go,” says Sukhatme, who studies tumor metabolism and immunotherapy at Harvard Medical School. “It costs $5 million to $10 million for a [small] trial, and we have ideas for 10 to 20 such studies that could be started immediately.” Which of those trials will move forward depends on funding, which GlobalCures hopes to receive from NIH grants, private foundations, and donors. “Priority is given to studies that might have the greatest impact in the shortest time frame and use inexpensive medications,” says Sukhatme.

The Belgium-based nonprofit Anticancer Fund also supports trials testing agents that have “low commercial interest for industry but that have potential to help patients,” says Gauthier Bouche, the organization’s medical director. Leveraging its network of collaborators, the Anticancer Fund sifts through published human data, anecdotes regarding off-label drug use, and high-throughput screening results in cultured human cells to decide which approved compounds are worthy of clinical trials for new indications. The organization has teamed up with GlobalCures to write manuscripts and editorials summarizing the

How much cheaper is it to repurpose a dru to develop a new one?

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It takes about 12 years and approximately $2 lion to discover a candidate compound and through all the preclinical and clinical tests r for US Food and Drug Administration appro according to a recent estimate from analysts London- and New York–based investment fi (formerly AllianceBernstein; *Nat Rev Drug D* 11:191-200, 2012). To save money, companie demic institutions, and nonprofits are gettin drug repurposing, where a pharmaceutical c pany has already done the heavy lifting of p ical development as well as Phase 1 and som

outcomes of studies investigating noncancer drugs for different tumor types, and the researchers are working to better understand the regulatory hurdles when seeking to test a drug for a new indication.

A repurposed drug does not necessarily need approval to be considered a success, however. Bloom says that about 80 percent of repurposing efforts at Cures Within Reach aim to demonstrate efficacy of generic drugs for a new indication, providing doctors with enough information to make an informed decision on off-label use. “Our goal is to complete a robust proof of concept trial that gives physicians enough information for off-label use in a patient population that has no other reasonable treatment,” he says. To earn FDA approval, the nonprofit would have to secure millions of dollars to run large clinical trials. “The cost of securing marketing approval far outweighs the possible financial return,” says Bloom.

This was the approach the organization took when it started investigating the use of the generic mTOR inhibitor sirolimus for pediatric autoimmune lymphoproliferative syndrome (ALPS), a chronic disorder in which blood cells accumulate in the body, causing damage to many organs and sometimes leading to lymphoma. In 2008, in a small trial funded by Cures Within Reach, five of six patients treated had complete remissions.[8] After publishing the results the following year, the news began to spread among clinicians and patients. The inexpensive drug, originally approved in 1999 as a prophylactic treatment to prevent rejection of renal transplants, is now prescribed off-label for ALPS (and, more recently, for other similar autoimmune disorders in children).[9]

“Prior to the work in ALPS, the kids that were refractory to steroids or other drugs had no therapy; they suffered and died,” says Bloom. “Now they have a therapy, and physicians know it is available, and it works. The patients are getting the care, and that is a success.”

In bed with industry

There are also players in the repurposing field looking to turn a profit. Like academics and nonprofits in the field, biotechnology companies focused on drug repurposing are also finding innovative ways to mine publicly available information on existing compounds to uncover new drug-disease connections. (See “Teaching an Old Drug New Tricks,” *The Scientist*, April 2011).

Phase 2 and 3 human trials. Even with clinic
in hand, however, it is no small feat to condu
cessful Phase 2 and Phase 3 trials required b
FDA for approval of a new indication. In fac
late-stage trials are arguably the most costly
of clinical testing. A Phase 3 trial program ca
anywhere between $40 million to $300 mill
cording to AstraZeneca’s Craig Wegner.

“That developing a known drug for a repurp
indication would be hugely cheaper than for
single new chemical entity is a common
misunderstanding,” says pharmaceutical con
consultant Hermann Mucke. “The most exp
parts of a drug development program, the la
stage trials, apply to a repurposed developm
[including of failed drugs] to the same exten
said, he adds, “repurposing takes some of th
out, making drug development more predic
particularly for rare diseases.”

When the AB analysts compared traditional
development and repurposing costs, bringin
new molecular entity to market still seemed
more expensive than drug repurposing—on
der of $1 billion to $2 billion, compared with
$300 million to repurpose—“but these figur
heavily slanted to favor repurposing,” says W
The $1 billion figure includes the totality of
the compounds a company generates and te
prior to clinical trials, including those that n
make it to human trials, according to Wegne
timated repurposing costs are “not attrition-
adjusted, even though most repurposing effo
also fail,” he says. “Repurposing can be less
expensive, but it isn’t the magnitudes people
talking about.”

In 2008, University of California, San Francisco, pediatric endocrinologist and bioinformatician Atul Butte launched NuMedii to capitalize on his new data-mining technology that identifies potential links between drug profiles and the molecular pathways of disease. “All of the information we put into our system”—including available data on marketed drugs, generic compounds, and unapproved drugs abandoned by pharmaceutical companies during development—“is carefully curated to enable us to come up with potential clinically and commercially viable data,” says Gini

Deshpande, NuMedii's cofounder and CEO. "We use a lot of omics data and take an unbiased perspective to find where there may be yet undiscovered biology that we can leverage." The company then tests the most promising candidates in animal models. NuMedii has yet to take a candidate drug into the clinic, but has several "clinic-ready" compounds, according to Deshpande.

If one of the drug candidates NuMedii revives is not a generic, but a shelved, patented drug owned by a pharmaceutical company, the biotech can partner with the pharma firm for further development or obtain rights to the compound and carry on solo. But other routes exist. Some in the field are pulling for collaboration—not just among companies, but with academics of diverse expertise as well. "Drug development using bioinformatics is incredibly complex," says Bloom. "Right now, different companies and labs have each started to figure out a piece of the puzzle." Mucke adds: "The real interesting things will come if you use each to its full advantage and cross-link them together."

Fostering such collaborations is one of the main goals of the NIH's NCATS program, which aims to uncover new uses for the compounds pharmaceutical companies still own but whose development has been halted. NCATS asks that companies make some of these shelved compounds—and the accompanying preclinical data—available to academic researchers at no cost. The program then provides this information as well as a supply of the drug to research labs that can study new, clinically relevant activity of the drug. The company retains full control of the rights to the drug and the ability to file for the new indication. For U.K.-based AstraZeneca, the program allows the company to tap the knowledge and experience of outside experts for a disorder that may not be on the company's radar, says Wegner. "The program can benefit patients, the investigators, possibly AstraZeneca, and at the minimum, advance science."

"There have even been instances where our program elected not to fund a project, and the pharmaceutical company stepped in and provided funding, working with researchers on their own," says Christine Colvis, who heads the NCATS program. NCATS currently has 10 ongoing projects, including eight Phase 2 clinical trials. One of NCATS's most advanced projects involves AstraZeneca's shelved cancer drug saracatinib, which in 2012 was found to target amyloid-β signaling in the brain and to rescue synapse loss in mice.[10] A Phase 2 trial of saracatinib for Alzheimer's patients completed enrollment at the end of 2016.

"What I like about drug repurposing is that it can solve two issues: improved health-care impact and reduced health-care cost," says Bloom. "That's a big driver for us."

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