Recycling Existing Drugs
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Drug-makers explore the possibilities and re-hydrate dried-up pipelines by repositioning their existing compounds.

Nowadays, it seems every industry in the world is "going green." Conservation, recycling, cleaner energy, and hybrid cars are the realities that fill our lives. This greening trend has spawned new industries and companies that have found recycling and conservation to be quite profitable. Even Google is trying to help the conservation movement by getting into the “cleaner energy” game.

Drug companies are also trying to conserve, but for a different reason. They are trying to conserve effort: the years of time and gobs of money they have put into drugs that eventually failed to reach the market for a variety of reasons. Very often, a compound fails to reach the marketplace due to a poor safety profile.

Now, imagine recouping losses of billions of dollars spent to develop a drug by simply finding a different disease to treat with it. Or, how about taking a drug already on the market, with perfectly good sales for one indication, and making more money on same drug for a different indication. Repositioning has made all these previously impossible tasks possible.

Repurposing for Biodefense

Some researchers like Rae Lyn Burke, PhD, senior director, Center of Excellence for Infectious disease and Biodefense, SRI International, Menlo Park, Calif., are playing the repurposing game a little differently. SRI's work fits into two large research programs. The first is funded by the National Institutes of Health (NIH), Bethesda, Md., and is headed by SRI's Jon Mirsalis. They are focused on determining the utility of old antibiotics against the biothreat agents Bacillus anthracis (the cause of anthrax) and Yersinia pestis (the cause of bubonic plague). The first aims to determine if antibiotics like doxycycline and ciprofloxacin have utility against anthrax and whether gentamycin, levofloxacin, doxycycline, and ceftriaxone have utility against plague. Of course, the ultimate objective of the project is to get a new label claim for these antibiotics. One major difference in Burke’s repurposing approach is the way the drugs are tested for efficacy. "We"re actually not doing human trials ourselves. That is the intent of the repurposing effort that one does not need to do that. Essentially, it is because you can’t do human trials for using these agents," says Burke. The reason that this research only needs to be done in animals is that it falls under the animal rule—guidelines passed by the US Food and Drug Administration (FDA) for cases like this one where testing an investigational drug against a life-threatening disease is unethical. The approval process for these drugs is currently ongoing and Burke says there is a great deal of urgency.

Their second program, called an Accelerated Path to Safe and Effective Therapeutics for Bioterrorism Agents (APCET), and funded by the Department of Defense is a much broader repurposing effort. "This process is absolutely different than what everyone else is doing in the area of repurposing. It is really a novel concept," says Burke. The novelty, she says, comes from the fact that Burke et al. screens a large library of FDA licensed drugs to find compounds that show efficacy against these biothreat agents. In this wide-scale screening project, Burke doesn’t care about the initial indication of the antibiotics or other drugs screened, only for new potential utility against these biothreat agents.

Because all of the drugs had already been licensed for human use by the FDA, their safety profiles, pharmacokinetics, and mechanism of action were already known. However, Burke does not eliminate the possibility that the doses might have to be changed for the new indication. But, she says, when a drug is being developed, a broad range of dose levels are evaluated. "We will have to use the two-animal rule to get a re-label claim," says Burke. "And so we will have to explore what is the M.O.A. for the new indication

"Repositioning is not really a new idea. The concept was floated in the early 1990s, but rapidly gained momentum in the post-genomic era when drug developers realized that there are far fewer targets than the 100,000 to 150,000 initially slated," says Andrew Reaume, PhD, MBA, president and chief executive officer, **Melior Discovery, Inc.**, Exton, Pa. "There was not a deep well of targets. So determining how we were going to find new drugs became a big dilemma for the industry and repositioning became one of the answers."

Fast-forward to 2003 when Tom Barnes, PhD, senior vice president of discovery at **Gene Logic Inc.** (now called **Ore Pharmaceuticals**) in Gaithersburg, Md., and a small team was shopping around for venture capitalists to fund a spin-off of a drug repositioning business from his former employer, **Millennium Pharmaceuticals**.

"Drug repositioning had been happening all the way along, but as a serendipitous process, where occasionally other activities are discovered in drugs and then they can be exploited," says Barnes. "What we have sought to do is to try to uncover these hidden activities in a more systematic way."

But they were not the first to try it. **Sosei Pharmaceuticals** in Japan tried before Ore but in a different way. Ore Pharmaceuticals combined the gene expression database and computational techniques developed by Gene Logic with several drug annotation technologies acquired from Millennium. They also developed partnerships with Pharma by taking their late-stage clinical failures, and finding potential new indications for them, with the goal of having the partner rapidly return them to the clinic.

So, the drug-repositioning space has really only existed in its current form since the beginning of the decade. At first, there were only two companies: Sosei and **CombinatoRx**, Cambridge, Mass. Then, a number of other companies like Ore Pharmaceuticals that either looked at existing drugs or retooled themselves to do repositioning sprouted up. "So there are a number of players in this space. But at the same time, it should also be pointed out that pharma itself is taking a hard look at doing this internally. For example, Pfizer has mounted a fairly visible high-profile effort to better annotate its live portfolio of molecules," says Barnes.

Some of Ore's current Pharma partners include Pfizer, Roche, Organon, Eli Lilly, Abbott, and Merck-Sorono. "[Ore Pharmaceuticals] is looking across a large number of diseases, more than 400, and we’ve got multiple technologies that are looking at these molecules," says Charles Dimmler, chief executive officer of Ore Pharmaceuticals. They have started looking at more than 100 molecules and finished many of them. Ore's process of interrogating these molecules for new activities includes developing a hypothesis and then validating them in preclinical animal testing. "We report a new hypothesis rate fairly similarly to other repositioning companies, which is about one-in-three molecules looked at—a fairly high rate. Of course, not all of those new hypotheses are commercially viable, but obviously a good subset is," says Barnes. Their validation has also been successful: they have not yet had any animal validation failures.

Is repurposing just serendipity?
Like Ore Pharmaceuticals, Melior’s business is also rooted in drug repositioning. And, like Ore, it is their technology that allows them to provide repositioning services to their business partners. Specifically, Melior's technology is "a platform comprised of 35 animal models (disease models) representing a broad range of therapeutic areas," says Reaume.

Melior tests a partner's compound against all of these disease models to uncover unexpected uses in a "non-hypothesis driven" manner—a system that has been successful both in their

and any info about a dose."

What about finding a common target for drugs screened against these biothreats? Although there is an impetus to find a common target, and consequently attain broad-spectrum efficacy, right now they do not anticipate that there will a single target for all of the different compounds tested. But, according to Burke, the real strength of the project is that because the M.O.A. for the screened compounds is already known, the new indications will have a faster track to efficacy than typical discovery efforts. In addition, she says, the fact that their results will be published will allow for off-label use of these antibiotics by any licensed physician in the event of bioterrorist attack. "We have not been developing drugs against biothreat agents for commercial application, but rather for the good of the country," says Burke.

own drug discovery efforts, as well as in the company's collaborations with pharma and biotech partners.

"Once we have their compounds, we perform preliminary work, which consists of a reasonably thorough pharmacokinetics and maximum tolerated dose analysis to very carefully describe the in vivo qualities of these compounds, which in turn allow us to design custom-dosing regimens for these compounds," says Reaume. Then, multiple doses are administered to all of the 35 different disease models via the drug delivery route determined by the previous characterization work. And, of course, the goal is to identify unpredicted therapeutic activity.

But a finding of unpredicted activity is not truly serendipity. According to Reaume, "most new indications on compounds tend to be on-target effects, meaning that the M.O.A. [mechanism of action] for the unexpected therapeutic activity more than 90% of time is driven by the same molecular target as the original indication." Reaume uses Viagra as an example. Viagra, a phosphodiesterase-5 (PDE-5) inhibitor, was originally developed as an anti-hypertensive, but is now used to treat erectile dysfunction (ED). And it is the PDE-5 that is the molecular target responsible for Viagra's new therapeutic activity. So much for serendipity!

Viagra is just one example of the successful repurposing/repositioning approach, an approach that has clearly increased in popularity over the last five years. In fact, of the top 50 selling pharmaceuticals in 2004, 84% have had additional indications approved since their initial US licensure (source: http://www.msi.co.uk/article-read.php?DL_ID=37&from=articles Accessed December 21, 2007). "Over the last five years, there certainly has been a steady approval [of repositioned drugs]," says Barnes, "but it still does not represent a very major part of new approvals."

A natural progression

Despite not taking up the lion's share of pharmaceutical development, drug-repositioning is still pulling its own weight. And the results of repositioning for reducing risk of such development are quite clear.

"I think looking at repurposing compounds is a very natural progression for the industry in general," says Sabrina Johnson, MS, chief business officer and chief financial officer, **Cypress Biosciences**, San Diego, Calif. Although Cypress has been around for quite a while longer, they really only started in the drug repositioning space in 2001. It all started with a vision to develop a treatment for fibromyalgia that was better than the existing treatment modalities. But because there are no internal drug discovery programs at Cypress, they must rely on existing compounds that can treat the disease they set out to treat. They then set out to find compounds that met these criteria for fibromyalgia. This simple vision eventually led them to find Milnacipran, a drug for which they filed a new drug application at the end of 2007.

Selected long-standing pharmaceuticals that had been repositioned during or prior to 2004. (Source: *Nature Reviews* Drug Discovery (August 2004) 3, 673-683)

Generic Name	Trade Name, Original Indication (originator)	Trade Name, Repositioned Indication (repositioner)
Celecoxib	Celebrex, osteoarthritis and rheumatoid arthritis (Pfizer)	Celebrex, familial adenomatous polyposis, colon & breast cancer
Minoxidil	trade name N/A, hypertension (Pharmacia & Upjohn)	Rogaine, hair loss (Pfizer)
Topiramate	Topamax, epilepsy (Johnson & Johnson)	trade name N/A, obesity (Johnson & Johnson)
Lidocaine	Xilocaine, local anesthesia (AstraZeneca)	trade name N/A, Oral corticosteroid-dependent asthma (Corus Pharma)
Buproprion	Wellbutrin, depression (GlaxoSmithKline)	Zyban, smoking cessation (GlaxoSmithKline)
Fluoxetine	Prozac, depression (Eli Lilly)	Sarafem, premenstrual dysphoria (Eli Lilly)
Duloxetine	Cymbalta, depression (Eli Lilly)	Duloxetine SUI, stress urinary incontinence (Eli Lilly)

"When we started our fibromyalgia program in 2001, we were the only company we knew about that was utilizing that approach. And now, there are more companies utilizing that approach," says Johnson. "Even if you just look at big Pharma companies, they are taking their own product and examining the scope of possibilities. You know … more drugs with more indications."

Melior Discovery Repositioned Therapeutic Candidates

Compound	Previous Indication	Originator	Previous stage of development	New Indication	Current Status
MLR-1023	Gastric ulcer	Pfizer	Phase III (discontinued ca. 1980)	Diabetes	IND-enabling studies
MLR-1045	Peripheral vascular disease	Hoeschst Marion Roussel	Phase II (discontinued ca. 1995)	Irritable bowel syndrome	Preclinical
MLR-1130	Alzheimer's disease	Hoeschst Marion Roussel	Phase III (discontinued ca. 1990)	Atopic dermatitis	Preclinical

Reaume also thinks that drug repositioning is a fruitful strategy that will see greater use in the future. He notes that in big Pharma there is increasing buy-in, acceptance, and infrastructure built up around repositioning.

Barnes opines that repositioning is here to stay, and adds that molecules with drug-like properties have multiple and unexpected activities that can be revealed. "Given that," he says, "the industry—that is to say, those who own these molecules—will develop and maintain an interest in going through their closets and their pantries looking for these old molecules and trying to figure out which one of them is worth bringing forward."

Experts all agree that the concept of repositioning is built on the fact that there is more to a particular drug than the originally-intended indication for which it was initially licensed. They also agree that inherent in the repurposing model is the efficiency brought to it by having a preexisting safety profile. This is in striking contrast to the traditional discovery model where it takes tremendous time and effort to constantly develop something a new drug from scratch. The main thing they all agree on: repositioning is here to stay.

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