Second act

Drug repurposing gets a boost as academic researchers join the search for novel uses of existing drugs.

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In February 2011, the British drug company AstraZeneca shelved its experimental drug zibotentan, intended for the treatment of non-metastatic prostate cancer in men who do not respond to hormonal treatments. Despite early promise, the drug failed to improve patients' survival in trials. But more than a year later, the drug might get a second wind, this time as a potential treatment for Alzheimer's disease, thanks to a partnership between industry and academia. With AstraZeneca crowdsourcing the search for potential new applications for its drugs in the academic community, the partnership could lead to treatments not apparent during the original development of the drug.

Crowdsourcing innovation is a concept that has gained increasing favor in biological research, with notable examples such as Foldit (1), a popular computer game that harnesses

human intuition to solve the baffling puzzle of how cellular proteins fold, and DIYBio (2), a movement launched by a team of amateur biologists who perform sophisticated research in garage labs.

But there are few precedents for a systematic, large-scale crowdsourced approach to drug discovery adopted by the pharmaceutical industry, which is sometimes perceived as fiercely guarding its intellectual capital. The case of zibotentan is one example of an increasingly favored approach to drug discovery, one with the potential to save money, time, and lives.

Because zibotentan, code-named AZD4054, blocks a human protein called the endothelin A receptor, implicated in narrowing blood vessels, University of Bristol, Bristol, UK neuropathologist Seth Love reasons that the drug

might help restore normal blood flow in the brain of patients with Alzheimer's disease, the progression of which has been tied to constricted blood vessels in the brain's cortex (3). To that end, Love's group, one of 15 UK-based research teams awarded a competitive grant through the partnership between the Medical Research Council (MRC) and AstraZeneca, will begin testing the effects of zibotentan, together with a high blood pressure drug, on cerebral blood flow in a rat model of the disease.

If the drug's promise bears out, Love hopes to test its effect on cognitive function in patients. "There's a vicious cycle that under normal circumstances accelerates the progression of Alzheimer's disease, and we might be able to interfere in that pathway," says Love.

Stemming from a governmental push to boost life sciences research in the United Kingdom and launched in December 2011, the partnership is aimed at uncovering

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hidden biological pathways implicated in diseases and, as an eventual dividend, potential new therapeutic uses for any of the 22 compounds shelved by AstraZeneca. Among the compounds are candidates previously tested for a range of indications, including cancer, pulmonary disease, diabetes, schizophrenia, and rheumatoid arthritis; some were found to be safe for use in people in the context of the tested indications but were shelved owing to a variety of reasons, including lack of efficacy, whereas others are currently suitable only for preclinical testing.

Public funding and crowdsourced innovation propel drug discovery.

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With a budget of $11.1 million disbursed among 15 successful applicants over 3 years, the research council hopes to provide UK-based researchers access to compounds that might otherwise languish within the company's vaults, thus harnessing academic competition for the benefit of patients. Yet "the primary purpose of these proposals is not to identify repurposing opportunities of these molecules. It's to use these molecules to better understand mechanisms of human disease," says Chris Watkins, head of the MRC's translational research unit who helped launch the partnership with AstraZeneca.

The combined approach to tackling human disease championed by the British government, industry, and academia has been seen as a forerunner to a similar initiative in the United States. In May 2012, the Bethesda, Maryland-based National Center for Advancing Translational Sciences (NCATS), the translational research arm of the National Institutes of Health (NIH), announced its own effort to find new uses for therapeutic compounds shelved or abandoned by pharmaceutical companies after initial efforts largely led to inadequate showings of efficacy for the tested indications.

Through similarly competitive grants, the NCATS will award six to eight awards totaling $20 million in 2013 to successful proposals from researchers seeking novel uses for any of 58 shelved compounds contributed by eight drug companies; all 58 compounds have been shown to be safe for use in people. An NIH scientific review committee, which excludes representatives from the participating drug companies, will select successful proposals.

"It's been quite a large part of our strategy through the MRC and the NIH to engage the academic community and external science in this way," says Don Frail, Vice President of Science within AstraZeneca's New Opportunities iMED initiative. A wealth of safety-related information on the compounds—such as dosing, pharmacokinetics, and disease-related biomarkers—already collected by the drug companies, the reasoning goes, should give academic researchers a leg up in their search for new uses for these shelved drugs, potentially speeding the pace and lowering the cost of drug development.

Some perspective: While it can take up to 15 years and $1 billion to bring a new drug to market, according to some estimates, more than 90% of drugs fail to make it past the early development and toxicity testing stages of the drug pipeline (4, 5). "If this is wildly success-

ful, then we may think about expanding the number of compounds that we would have on the list," says NCATS program director Christine Colvis.

Compared with piecemeal drug repurposing partnerships between individual researchers and drug companies, the NCATS initiative, says Colvis, helps streamline otherwise-unwieldy aspects of intellectual property and information exchange between academic researchers and industry. As a measure of the strength

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of a crowd-sourced approach to drug repurposing, says NCATS director Christopher Austin, "The response from the biomedical research community to this new initiative has been encouraging; we have received nearly 160 applications for the majority of the 58 available compounds, and have found there is no shortage of ideas for potential new therapeutic uses for these molecules."

Jeff Nye, head of external innovation in neuroscience at New Jersey-based Janssen Pharmaceuticals, says, "What we gain is the world of researchers looking at these mechanisms and asking themselves and the literature what they could be possibly used for." Janssen Pharmaceuticals, a Johnson & Johnson company, contributed three compounds to the NCATS initiative.

Under the NCATS initiative, says Colvis, any intellectual property generated by researchers successful in winning grants related to new uses for the compounds is subject to the Bayh-Dole Act, legislation that applies to intellectual property generated by federally funded research. As such, any new IP generated by a grant applicant within the NCATS initiative will belong to the applicant's institution, but the drug company partnering with the applicant will have the first right of refusal to license the IP.

Old Idea, Fresh Boost

While the involvement of government institutions in the effort to find new uses for known drug compounds has generated a drumbeat of publicity for the initiatives, the idea of repurposing is old hat in the drug

industry. For decades, drug companies have attempted to repurpose drugs for indications other than those initially foreseen, with several notable successes. For example, Pfizer's immunosuppressant drug tofacitinib, which blocks a signaling molecule called JAK kinase, was originally designed to prevent transplant rejections and approved in November 2012 by the Food and Drug Administration (FDA) for treating rheumatoid arthritis, a potentially debilitating autoimmune disorder (6).

The drug eflornithine, effective in treating African sleeping sickness, a parasitic scourge in Central Africa, got a second act in 2001 when the drug's manufacture was resumed, thanks partly to its profitable, then-novel use in the removal of unwanted facial hair in women (7). And the oft-cited poster child drug for repurposing, sildenafil citrate, or Viagra, was unsuccessfully tested as a treatment for angina but revealed by happenstance to be a blockbuster drug for erectile dysfunction.

The benefits of drug repurposing to pharmaceutical companies facing drying pipelines and expiring patents, to nonprofit organizations seeking cures for rare and neglected diseases, and to patients battling intractable conditions need no overstatement, but, from a scientific standpoint, repurposing relies on nuanced understanding and intricate dissection of the often-interwoven genetic pathways underlying human disease. Advances in genomics technologies have helped basic researchers make strides in addressing some of those challenges.

One example of a systematic effort to help researchers glean a panoramic view of disease-related pathways in human cells through genomics is a project dubbed "The Connectivity Map," a public database of gene expression signatures tied to diseases, drugs, and drug candidates. Conceived by Broad Institute molecular biologist Todd Golub, his then-associate Justin Lamb, and others and published in *Science* as a pilot project in 2006 (8), the map serves as a sort of genetic almanac for researchers who wish to look up gene expression profiles triggered in lab-grown human cells by chemical compounds, to use software tools to match such patterns with diseases, and to unearth novel connections between drugs and diseases. Currently more than 16,000 researchers have access to a database of more than 7,000 gene expression profiles representing more than 1,300 chemical compounds. "We have well north of half a million profiles in an [expanded] database that will soon be

made publicly available. It represents about 4,000 small molecule compounds in different cell types," Golub says. Several of those compounds, he adds, are drug candidates and FDA-approved drugs.

"The most astonishing aspect of the Connectivity Map project…was the extraordinary appetite of external disease biology experts to engage with these data. I think therefore that using gene expression profiling to capture a functional fingerprint, if you like, of these compounds and letting the outside world look at those data is incredibly valuable," says Lamb, now president and CEO of Cambridge, MA-based biotech startup Genometry, which provides gene expression profiling services.

Matching Drugs and Diseases

A testament to the map's usefulness in drug repurposing, Stanford University biologist Atul Butte and his team used data from the map to provide experimental proof of novel uses for two FDA-approved drugs. Published in a pair of 2011 reports in *Science Translational Medicine*, the findings proved the idea that drugs can be repurposed by mining publicly available gene expression databases for diametrically opposite expression profiles triggered by diseases and drugs (5, 9). The researchers pored through the NIH-sponsored Gene Expression Omnibus database, identified genetic profiles for 100 diseases as defined by the levels of messenger RNA molecules—molecular middlemen that help translate the genetic code into proteins—that reliably rose or dropped in cells from patients with those diseases, and compared the profiles with gene expression signatures triggered by 164 drugs in the Connectivity Map.

The result: Two well-known drugs—used to treat ulcer and epilepsy—showed promise against lung cancer and inflammatory bowel disease. Strikingly, the drugs worked when tested in animal models of both new indica-

tions, suggesting that gene expression data can presage a drug's hidden properties. By combining disease- and drug-related gene expression data, the researchers leapfrogged months of spadework tied to traditional methods of drug development that can involve screening therapeutic molecules en masse.

"We're going from computational prediction to a dose in humans here at Stanford in about 15 months or so," Butte says, referring to planned clinical trials of a similarly rediscovered class of psychiatric drugs that showed promise in treating lung cancer. Providing context, he estimates, "I think if one were starting with cancer samples, trying to identify a target, then some compounds that might hit that target, then seeing…if those compounds had preclinical efficacy, then creating enough drug to launch a clinical trial, it would take on the order of 5–7 years." Speaking of the NCATS initiative, he adds, crowdsourcing innovation is likely to help salvage at least some of the tens of thousands of drugs thus far shelved by drug companies.

Asked how AstraZeneca chose which compounds to make available for the initiatives, Frail responded: "Both the MRC and the NIH set forth specific criteria for the compounds that could be included, which then dictated our decision as to which compounds to include... The safety profile and the availability of drug

supply were other factors considered."

The promise of such crowdsourcing of drug discovery is tempered by skepticism over the likelihood of finding truly new uses for drugs that pharmaceutical companies often test in a variety of biological contexts. John LaMattina, a partner in the Boston-based venture capital company Puretech Ventures and former president of global research and development at Pfizer, New York, says that several oft-cited instances of successful drug repurposing represent cases where the biological pathways underlying the diseases in question overlap or are closely related. Which is why, he adds, alluding to tofacitinib and Viagra, "It's not really repurposing in my mind." That said, he concedes, drug companies might not necessarily pursue all possible therapeutic effects for every drug candidate.

And even if the yield is low, the efforts might still benefit patients without recourse to other treatments. "This notion of open innovation is getting increasing traction in the pharmaceutical industry, and I don't think it should be restricted to the small number of existing drugs or late-stage clinical efficacy failures," adds Lamb.

Whether such open innovation can ultimately lead to better health for patients while remaining profitable for drug companies remains to be seen.

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