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Drug Repositioning: Extracting Added Value from Prior R&D Investments

Hermann A.M. Mucke, Ph.D.

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Hermann A.M. Mucke, Ph.D., spent 17 years in academia and industry before he founded H.M. Pharma Consultancy (www.hmpharmacon.com) in 2000 to become an independent pharmaceutical consultant, analyst, and science author. His last industry position was Vice President R&D in a European pharmaceutical company, which he helped to take public on the Frankfurt Stock Exchange in 1999. Since then, Dr. Mucke, who holds a Ph.D. in biochemistry from the University of Vienna (Austria), has become a consultant and advisory board member for several European and American pharmaceutical companies and a regular reviewer of drugs and patents for Thomson Current Drugs and Ashley Publications. Dr. Mucke is based in Vienna.

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Executive Summary

Drug repurposing (an approach to drug development that is also known as drug repositioning, reprofiling, or retasking) has become a matter of intense interest during the past few years. In brief, it is a strategy that calls for reinvestigating drug candidates that have not succeeded in advanced clinical trials, for reasons other than safety, for potential new therapeutic applications.

In the more conservative approach, termed "on-target repurposing," the drug's known pharmacological mechanism is applied to a new therapeutic indication, which in clinical terms might be quite far removed from the original one but is known to have the same pharmacological underpinning. About 80% of drug repurposing efforts that are currently ongoing (or have already resulted in a successful relaunch) have followed this route, which must not be confused with simple line extensions, *e.g.*, a cancer drug obtaining additional approvals for other types of cancer. The classic example is sildenafil, which was unsuccessful in its development as a new drug for common hypertension but became immensely successful as a drug for male erectile impotence; it then established itself as a drug to treat pulmonary arterial hypertension, a life-threatening chronic disease. One can hardly imagine two applications that are more different from each other medically, yet they share phosphodiesterase 5, an enzyme which sildenafil inhibits, as a common critical element in their respective symptomatic pathways. Even more innovative is "off-target repurposing," which looks at known molecules without prerogatives, looking for pharmacological mechanisms that have not yet been described for a known molecule. This approach uses what has been termed "systematic serendipity." In either case, having failed is not a criterion; the avenue is equally open to drugs that are being marketed or have once been on the market.

Some industry observers have decried repurposing as "drug recycling" and labeled it as another defensive marketing move by the pharmaceutical industry to squeeze out yet more return from its existing resources in a time when truly novel therapeutic approaches have become increasingly rare and new chemical entity approvals are dwindling. However, others have hailed it as a matter of economic and medical common sense not to shelve a drug candidate forever because it failed efficacy endpoints in Phase II or III trials. The motto should probably be what Gregory A. Petsko, D.Phil., a Gyula and Katica Tauber Professor of Biochemistry & Chemistry at Brandeis University, wrote in a May 2010 piece in *BMC Biology*:

> "Give me your tired, your poor, your Phase II failures... What if those drugs were not tried on the right disease? (...) What if the cure for Alzheimer's disease is sitting on some drug company's shelf, as a potential cancer drug that failed in Phase II? (...) People diagnosed with psoriasis are at greater risk of developing heart disease; in fact, in patients with severe psoriasis who are younger than 50 years old, the risk is comparable to that seen in diabetes. How many Phase II-failed psoriasis drugs have ever been tested in heart disease clinical trials? (...) So I REALLY want the Phase II failures. I want them for my own research and for your research. I want them because they could make a difference for a host of unmet medical needs."
>
> [Petsko GA. When failure should be the option. *BMC Biology*. 2010;8:61–3.]

Repurposing a drug or a failed advanced-stage candidate drug can have very different commercial implications. These will depend on where the drug comes from, how much accessible data exist, and how well the repurposer can exploit the new value chain created by a successfully repurposed drug. This will to a good part depend on what sort of intellectual property can be secured for the new use. Chapter 2 is dedicated to these issues, which can be tricky to argue: The repurposer fights an uphill battle against examiners who will scrutinize the prior art for any public facts that can be construed to have anticipated the new medical use of a known drug. Typically, methods-of-use patents (which usually is what a repurposer can hope for) are relatively weak when compared to composition-of-matter patents, which protect the active pharmaceutical ingredient itself; they are subject to off-label uses that effectively erode their market position. New court and patent office rules, as well as constantly improving data-mining technologies, make it much easier to find "obviousness" in the prior art—or even in a granted patent.

Tool sets combining state-of-the art genomic, proteomic, animal model, and bioinformatics technologies are employed to identify repurposing opportunities. Together with expert knowledge in pharmacology, these technologies define repurposing business strategies. These more technology-oriented aspects are discussed in Chapter 3, followed by an outline of the regulatory environment for repurposing in Chapter 4. Here, we discuss the applicable legal framework and show that while repurposing can remove the initial 1–1.5 years of preclinical and Phase I development time (the latter only if no new formulation has to be developed and tested), the later stages of the regulatory review process for repurposed drugs are the same as with new chemical entities. While reviewers might be more comfortable with the safety aspects of the drug (provided that existing data are sufficiently recent to meet current regulatory standards), the proposed use of the drug in a different target population and with a correspondingly different set of efficacy criteria will in many cases make late-stage reviews and the preapproval process as lengthy as any other.

Chapter 5 discusses exemplary cases of drug repositioning and illustrates how the task can be approached, depending on the intended goal. Chapter 6 profiles selected key companies in the repurposing business and how they have fared during the past decade. This section focuses on companies that offer platform-based services to identify repurposing options, but it also discusses the internal repurposing efforts of three top-ten pharmaceutical companies—Pfizer, Novartis, and Eli Lilly—and how these programs tie into their overall development strategies. Not much to our surprise, we found that the structure of repurposing-platform companies, as well as the structures of deals they make with larger companies, is similar to that of drug

discovery platform companies, and they suffer from similar vulnerabilities. Their success has been mixed. Like most other service providers, their businesses suffered severely from the economic crisis of 2008–2009 and its aftermath. For Big Pharma, drug repurposing is usually not something that is broadly discussed; such programs are for the most part already integral to these companies' discovery efforts.

Chapter 7 adds financial aspects to the discussion. If repurposing is successful, extension of the drug's useful lifetime before patent expiry (resulting from the initial steps not being required) will be the greatest benefit for larger companies. For smaller companies, much of the benefit of repurposing will be indirect, resulting from the ability to attract venture capital funding more rapidly and offer investors a more dynamic development perspective that (in the ideal case) will more or less begin with initiation of Phase II proof-of-principle trials. For one-product startup companies, repurposing might be the single best rationale for entering the drug development business with a head start, saving up to $5 million in direct, early-stage development costs.

In summary, we find that drug repurposing can take on many meanings in several dimensions. It spans the range from what (for a pharmacologist) might be blatantly obvious (at least in retrospect), to the cutting edge of innovation that completely reinvents a known molecule—exploiting a new mechanism, new dosing, and probably a different route of administration to address a disease or disorder that was not previously believed to offer any connection with the drug in question. Drug repurposing has also become a new business segment for the life science services industry. While it is easy for almost any existing contract research organization to directly monetize its existing services for the development of repurposed drugs, discovery of off-target repurposing opportunities is a matter of cutting-edge technology where high-content screening and multiplexed animal models are called for. For the decade ahead to 2020, we predict that such repurposing technology will see increasing integration as a standard process of resource utilization, de-risking, and acceleration of drug development.

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This drug repurposing (alternately called drug repositioning, drug reprofiling, or drug retasking) might require different dosing, different presentations, and new routes of delivery, but most of all it requires a deep understanding of biological mechanisms. While the overall degree of innovation would be somewhat lower than with the discovery of new targets and chemical entities, repurposing carries a much lower development risk. Further, the development timeline could be significantly accelerated, depending on how much is already known about the compound.

To reap the benefits, drug repurposing must be implemented through a planned process based on targeted deployment of cutting-edge innovation instead of serendipity. In a situation where *de novo* drug discovery has failed to efficiently supply pharmaceutical company pipelines, a therapeutic switch should be a crucial element of drug development strategy and lifecycle management. If conceived in this way, repurposing is not an inherently defensive measure in the way of "drug recycling," but rather an additional opportunity to optimize the return on earlier R&D efforts.

Robert Forrester, formerly CFO and Executive Vice President of CombinatoRx, put this very succinctly in an interview published by the magazine *Drug Discovery News* in October 2008.[1] "With new chemical entities, you just don't know what they will do in humans," he said, "but with approved drugs you already know what it does and what the side effects are, which is a huge advantage. You not only know the pharmacology and toxicology, but one knows that you can actually manufacture these things. Manufacturing can be a huge hurdle to new chemical entities. With reprofiling, you can do in two or three years what might otherwise take 5–10 years and maybe spend $10 million as opposed to something like $100 million." [Note: Mr. Forrester joined FORMA Therapeutics as its Chief Operating Officer in April 2010.]

This statement addresses one key aspect of repurposing: the search for new uses of drugs that have already been on the market. The other aspect of repurposing enters the game with drug candidates which, though found safe in man, have been discontinued from Phase II or III clinical development for lack of efficacy in the therapeutic indication they had originally been conceived for.

1.4. Finding Another Disease To Treat: On-Target and Off-Target

Drug repositioning through serendipity (based on clinical observation) has been with us since the beginning of the pharmaceutical industry. Rationalized repositioning can take several forms.

Sometimes the alternate opportunities for a class of drugs are immediately obvious. For instance, it takes little imagination to see that compounds developed for the treatment of solid tumors (because they inhibit angiogenesis) should also be useful for the treatment of non-cancerous conditions where aberrant angiogenesis causes problems, *e.g.*, choroidal neovascularization (a chronically progressive, blinding eye condition) or angioedema.

2.4. Data Support: An Indispensable Requirement for Second Use Patenting

Although there are still patent applications being published that claim new uses for known drugs without presenting any supporting data, the times when it was possible to get actual patent protection based on general principles alone are long past. Today, obtaining a new use patent requires hard biological data based on carefully designed experiments.

If such data are not included in the published patent application, this does not mean that none are available. Rather, in most such cases, it is part of the intellectual property strategy not to disclose crucial data in an early stage. In essence, this strategy consists of withholding the data in the original filing and presenting them only when the examiner demands them. (Frequently, the examiner will also demand an affidavit stating that the data had been available at the priority date, and/or substantial proof might be required as well.) The data, once submitted, will go into the patent file where they are (in principle) available to the public on request, but in a much more complicated fashion than would be the case otherwise—and significantly later.

While this practice can be justifiably called a misuse of the patent system (which is, after all, intended to make information publicly available in exchange for exclusivity of use), it is also an outgrowth of this same system's mechanisms. Early disclosure of more data than is needed might not only compromise the applicant's competitive position; these data might also be held against later applications by the same applicant when improvement of the original invention by a follow-on patent is intended. This is why corporate patentees, in particular, tend to disclose as little as possible.

How much data (and of what type and quality) will be needed to support a drug repurposing patent application will strictly depend on the case. The general principle "extraordinary claims require extraordinary support" applies.

There is a large amount of US patent law literature available concerning drug repurposing. For a review of the situation in Europe, see Curley and Easey (2009).[1a]

2.5. Case Study: Developer Actelion Claims Bosentan for Ovarian Cancer

Bosentan (originally a Roche compound) blocks the endothelial receptors ET-A and ET-B, which mediate the actions of the endogenous peptide endothelin, the most potent vasoconstrictor known to exist. The first patent on the compound, EP-526708, has a 1991 priority date. The Swiss company Actelion licensed bosentan and developed it into the first orally active medication with consistent and clinically significant efficacy in pulmonary arterial hypertension (PAH), a deadly orphan disease. Under the Tracleer trade name, bosentan was approved by the FDA in 2001 and by the EMEA in 2002. It became the prototype of an entire class of endothelin receptor antagonists which are now considered the gold standard in the treatment of most forms of PAH in adults.

3.4. Putting Informatics to Work

Clues to drug repurposing can reside in many elements that are accessible to bioinformatics. The best-known holistic sources for bioinformatics data are those that relate to genomes (and their polymorphisms), their transcriptomes (*i.e.*, the totality of the ribonucleic acids transcribed from a genome under defined conditions), and the proteomes (*i.e.*, the totality of proteins produced by an organism under defined conditions). Each of these "-omes" can pertain to the human or animal organism or some of its organs as well as to the etiological agents of diseases affecting them, and will take interactions between these systems into account.

However, in order to identify drug repurposing opportunities using informatics, it is not necessary to try to simulate such extremely complex interactions, as systems biology attempts to do. In much less challenging applications, molecular modeling of ligand-binding site interactions is almost equally promising. Computational strategies can then reveal these potential opportunities *in silico*. A large number of biomarker-based procedures are now available that provide quantifiable measures of disease severity, its progression, and a prognosis of its outcome. While they are frequently not broadly validated in the exact meaning of the term, such biomarkers (and particularly judiciously aggregated combinations, called complex biomarkers) can be used to obtain clues to repurposing strategies. Like phenotypic screening, this approach does not inherently rely on a complete understanding of the underlying molecular mechanisms—although it can accommodate such insights if they are available.

Case Study for Gene Expression: VVP808

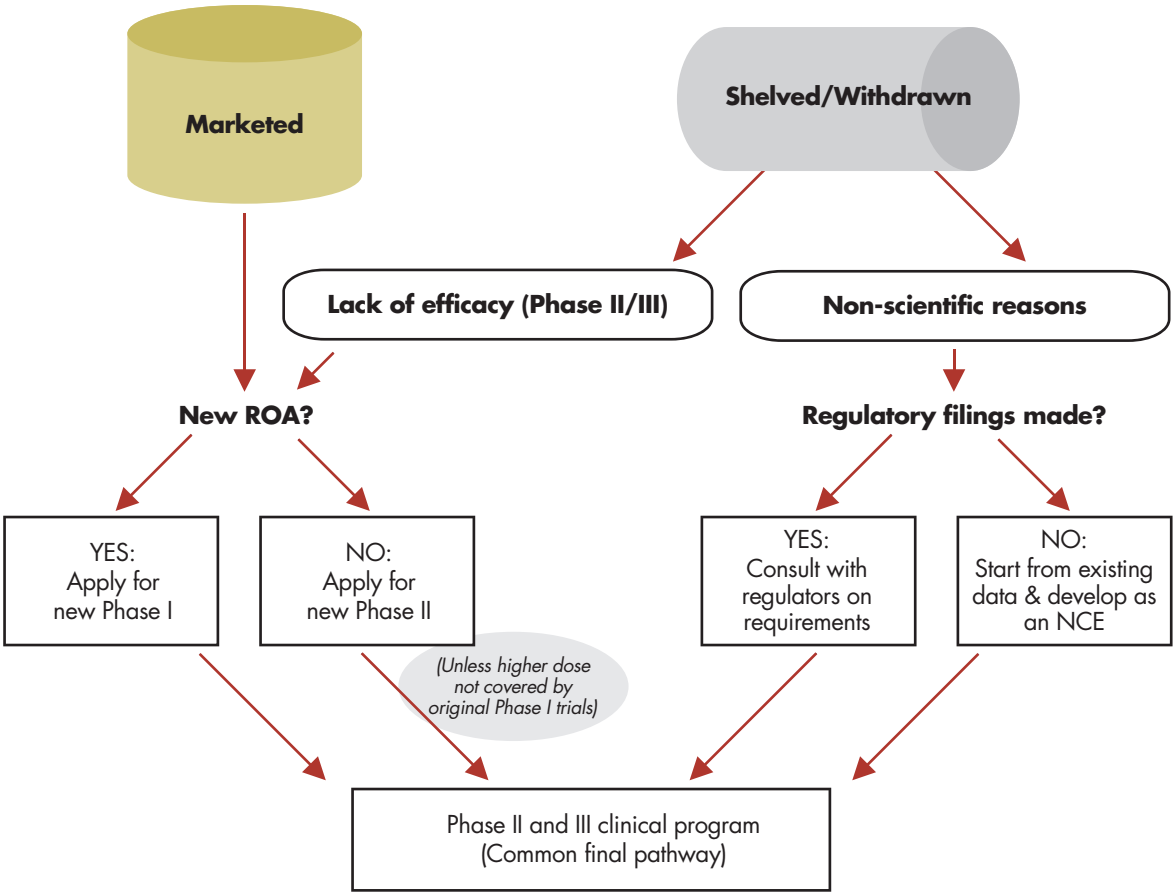
Verva Pharmaceuticals (Geelong, Victoria, Australia; www.vervapharma.com) develops therapies for diabetes and related metabolic conditions. The company, whose research facilities are at Deakin University, was created through a merger of Adipogen Pharmaceuticals Pty Ltd. and the ChemGenex subsidiary Autogen Research Ltd. in 2007. Verva has developed a microarray-based, target- and mechanism-independent drug discovery platform, the Gene Expression Signature (GES) platform, which is built on technology that was originally developed for cancer research. Different GES types may be employed to identify medications that are optimized for specific subgroups of diabetic patients, thereby providing for improved, personalized diabetes medicines.

The GES platform identified Verva's current lead product, VVP808, a nonthiazolidinedione insulin sensitizer that is entering a Phase IIa proof-of-concept study for type 2 diabetes. VVP808 is a repositioned drug. The company has only revealed: that it was used in North America as a therapeutic for glaucoma during the 1970s; that the enzyme-inhibitory activity for which it is used in glaucoma does not appear to be responsible for its insulin-sensitizing effect; and that the target through which it confers this activity is unrelated to the peroxisome proliferator-activated receptor (PPAR), dipeptidypeptidase-4 (DPP4), or other established diabetes targets.

According to Verva CEO Vince Wacher, PhD, VVP808's potential as a diabetes drug was discovered through differential gene expression signatures of normal fat cells, insulin-resistant fat cells (made by exposing normal fat cells to TNF-alpha), and insulin-resistant fat cells in the normal state and after exposure to

Figure 4.1 depicts highly schematized regulatory pathways for drug repurposing, depending on the history of the candidate compound.

Figure 4.1. Regulatory Pathways for Drug Repurposing: Marketed vs. Shelved/ Withdrawn Drugs



NCE = New Chemical Entity; ROA = Route of Administration

Source: H.M. Pharma Consultancy

The fact that regulatory timelines and cost are substantially reduced compared with development of new chemical entities is a decisive factor for the adoption of repurposing strategies. For small startup companies that rely mainly on venture capital, it is a very promising opportunity to implement a drug development program with a diminished burn-rate and faster time to market.

The Greek company PN Gerolymatos SA (Athens) secured a patent for the use of clioquinol in Alzheimer's disease (WO/98/06403), and in June 2002 the company announced that it also had clioquinol (which it had named Gero-46) in Phase II for Alzheimer's disease. In November 2004, Gerolymatos reached an agreement with Prana, under which Prana would get the rights in the United States and Japan while Gerolymatos would retain rights in Europe and elsewhere. Nothing has been disclosed since then, suggesting that the program has been discontinued.

Clioquinol certainly has problems on several levels that might prevent it from being successfully repurposed. Firstly, the mechanism that caused SMON in Japan is not understood, which implies an unknown risk. This is contrary to thalidomide, whose risk was purely teratogenic, therefore never existed in males and postmenopausal women, and can be minimized in reproduction-capable women by mandating a strict contraceptive regimen. Japan, a large market for Alzheimer's therapeutics, would hardly approve clioquinol given its previous disastrous experience with the drug, and regulators elsewhere would be extremely wary. Second, clioquinol has low CNS bioavailability after oral administration, which would necessitate high doses, and it would likely have to be used on a permanent basis—again, a bad constellation in the given environment. Thirdly, a successful developer would face the same problem that would have manifested for Bayer had its effort to repurpose metrifonate been successful: the active ingredient is not only off-patent, but available from a large number of competing wholesalers for list prices that go below $200 per kilogram. It would be all but impossible to avoid a parallel market if a clioquinol-based drug were launched at prices in the range of current drugs for Alzheimer's or Parkinson's disease.

Although there seem to be no active repurposing programs ongoing for clioquinol at this time, many tantalizing leads exist that point to applications beyond neurology. The University of Seoul has found that clioquinol is an activator of hypoxia-inducing factor-1alpha and has claimed its use in ischemic diseases (WO/2007/086663), while The Canadian University Health Network has claimed it for hematological malignancies (WO/2009/049410).

Astemizole: A Problematic Antihistamine with Significant Alternative Perspectives

Astemizole, a peripherally acting histamine H1 receptor antagonist, was discovered in 1977 and developed by Janssen-Cilag, which marketed it under the Hismanal trademark as a long-acting, non-sedating antiallergic and nasal decongestant in Europe. Johnson & Johnson-Merck Consumer Pharmaceuticals distributed it in the United States and Canada.

Janssen Pharmaceutica and its parent company ceased marketing of Hismanal worldwide during the first half of 1999. The FDA, which approved Hismanal in December 1988, co-announced the company's "voluntary withdrawal" of the product on June 21, 1999. The agency considered an OTC switch, but issued the first warning to consumers and healthcare providers in 1992 concerning rare cardiovascular adverse events, anaphylaxis, and serious drug interactions. Hismanal remained a prescription drug in the United States, and its labeling was changed several times thereafter to stress avoiding its use in combination with certain other medications, and for liver disorder patients to completely avoid it. Canada approved Hismanal as a prescription product in 1984, switched it to OTC status for adults in 1986, and removed it from the market in March 1999.

Chapter 6

COMPANIES IN THE DRUG REPURPOSING BUSINESS

In this chapter, we take a close look at exemplary cases of small life science companies that have focused their businesses on drug repurposing, either by routinely filling their own pipelines with such projects or by offering services related to repurposing. (Note that many more companies have been mentioned in Chapters 3 and 5.) We also investigate the drug repurposing operations that three large pharmaceutical companies have established and how they fit with these companies' overall strategies. Finally, we briefly discuss the Pharmaceutical Assets Portal, which is intended as a public-private facilitator for drug repurposing needs.

6.1. Business Models Centered On Drug Repurposing: Different From Those for Discovery?

A company that wants to set up a focused repurposing business needs to be research-driven and it needs to employ high technology. However, it will face more conceptual restrictions than an enterprise that wants to discover new drug targets or new chemical entities. This simply results from the fact that the pool of compounds from which to choose is, by definition, limited.

The prototypical drug discovery company will set out to push into a chosen territory of interest that is (relatively) unexplored, although (as discussed in the introductory chapter) this "virtual territory" has not turned out to be near-limitless (as some had hoped). Even so, the attitude of a drug discovery company has to in some ways be that of a serious digger during the gold rush.

If we accept this crude analogy for the moment, the drug repurposing company is more like a small, vigorous real estate redeveloper—the kind of entrepreneur who seeks hidden value in pieces of land, housing projects, or apartments that are traded below their inner value. The additional opportunities may not have lined up well with the original developer's intents and/or capabilities, unforeseen changes in the business environment might have made the real estate seem less attractive from the original developer's perspective, or development as originally intended might have simply failed. The redeveloper would examine this history carefully and then bring his own approach to bear.

Drug candidates that have been discontinued from clinical-stage development are shelved material assets. The desire to reactivate them is a matter of common sense. Reprofiling of such molecules to new therapeutic uses had been a valid economic proposition, independent of the business environment parameters. As Melior Discovery's president and CEO, Andrew Reaume, PhD, MBA, put it in an interview published in the January 1, 2008 issue of *Drug Discovery and Development*:[92]

> "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. 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."

Obviously, this statement is only a summary of what has several deeper dimensions with considerable differentiation. Taking a second look at existing assets (one's own, or those that are in the public domain) to see what else can be done with them is a strategic approach to drug development. In itself, it is not an answer to the problem of inadequate pharmaceutical productivity as measured by new marketed drugs. On the cost side, it puts the repurposer in a position between that of a generic drug developer and a developer of a new chemical entity. More importantly, however, it is a strategy for accelerating and de-risking drug development.

7.1. Cost Savings of Repurposing In Discovery and Development

The first issue to be factored into the calculation is the type of repurposing. On-target reprofiling—seeking therapeutic fields for a compound that are outside the originally intended use but exploit the pharmacological mechanisms for which the compound is known—has always been possible and sometimes even obvious, in a fashion commensurate with our insight into mechanisms and biological pathways. For instance, once a convincing case was made for the cholinergic dysfunction in Alzheimer's disease, it did not take a great leap of scientific or medical imagination to try cholinesterase inhibitors (known as antiglaucoma agents and prophylactics for nerve gas poisoning) in this new indication. Systematic discovery of such potential opportunities relies purely on innovative application of public knowledge. Establishing the new concept does not incur costs beyond those spent on searches of the peer-reviewed and patent literature. It is development—not discovery—that incurs the cost of on-target reprofiling.

Off-target reprofiling proceeds in an entirely different fashion. Originally a matter of exploiting purely serendipitous observations, it requires a systematization of the search for serendipity to be systematically successful. Although every pharmacologist knows that the majority of drug-like molecules act on more than one medically relevant target, the challenge remains to identify these targets in a context that also provides basic information on medical exploitability (as opposed to side-effect potential), and to do this with reasonable efficiency. This has become possible only with the development of complex biomarker diagnostics, high-content screening, and multiplexed animal models—all of which need to be established, validated, maintained, and additionally have their cost of operation. By their very nature, off-target findings obtained this way are almost always unexpected, might appear spurious, and sometimes are outright suspicious. (If it were otherwise, the effects would have been noticed during the initial development screening or during the compound's earlier medical use.) In off-target reprofiling, there is an incremental cost of discovery and preliminary result validation before development for a new indication can begin.

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