New Indications and a Sense of (Re)purpose

What do metformin, Viagra and Avastin have in common? They are all used to treat conditions besides those they were originally developed to treat. Drug repositioning, or repurposing, describes the process of deploying therapeutics to new indications. The impetus to find additional applications for currently prescribed drugs, as well as novel uses for shelved compounds, is becoming increasingly important as the drug development pipeline dwindles.

The crux of the problem is money. It typically takes over a decade and in excess of a billion dollars to bring a drug to market. This imposes severe financial pressure on the R&D departments of pharmaceutical companies and non-commercial entities embarking on drug development. Failures that occur later on in the development process are particularly expensive. The magnitude of the problem is difficult to ascertain, but a conservative estimate is that <10% of mature preclinical de novo compounds make it to product launch. This attrition means that the majority of unsuccessful compounds are dropped or stalled, never to be heard of again. Not only is this a costly and inefficient process, but important data concerning drug safety profiles and synthesis are never published, creating a black hole for valuable information.

While the notion of drug repositioning is not new, the drive to rescue compounds from the brink of obscurity has gained momentum as a means to stimulate the currently flawed drug development model. There are two forms of repositioning: drug-centered, whereby promiscuous drugs act on more than one biological target (such as metformin which activates AMPK in diabetes and a variety of molecular targets in cancer); and disease-centered, in which diseases that share pathophysiological mechanisms can be affected by the same drug (such as Viagra, which is used to treat erectile dysfunction and pulmonary arterial hypertension by causing vasodilation via a reduction in cyclic guanosine monophosphate degradation).

From a business standpoint, repositioning makes sense as a great deal of information about the pharmacokinetics, toxicity and manufacture of a drug is already known. This knowledge can offer an advantage over de novo drugs that have yet to pass these scientific and regulatory barriers, translating to a shorter time to market and improved success rate. However, there is an argument that resurrecting failed and abandoned compounds might have a negative impact on scientific innovation and the pursuit of novel drugs. This is true to some extent, but drugs can act in unexpected ways in new indications, enabling a deeper understanding of a disease that can stimulate new avenues of research. This was recently exemplified by the use of glitazones to treat chronic myeloid leukemia (CML) as reported in Nature on September 2, 2015. These peroxisome proliferator-activated receptor-y agonists are traditionally used to treat diabetes, but Prost and colleagues found that they were also able to target the CML leukemia stem cell pool, achieving a complete molecular response in all CML patients tested.

Drug repurposing also provides the opportunity to foster collaboration between industry and academia. This relationship is mutually beneficial: academic researchers are allowed access to well-characterized, clinical-relevant compounds to test in new indications, and the industrial partner potentially gains knowledge of new molecular targets, and the etiology and pathophysiology of disease. At the recent 28th European College of Neuropsychopharmacology (ECNP) Congress in Amsterdam, The Netherlands, David Nutt gave a passionate talk about the Medicines Chest, an initiative whereby the ECNP acts as broker between researchers and industry to provide pharmacological compounds for human experimental medicine studies. So far, 23 pharmaceutical companies are on-board with >30 compounds in the chest.

This enterprise has been mirrored by similar efforts worldwide to unite stakeholders committed to drug-repurposing. The UK Medical Research Council oversees the Industry Asset Sharing Initiative in which seven industry partners offer deprioritized molecules to research scientists. A recent success was AZD3355, a GABA-B receptor agonist, originally used to treat gastro-esophageal reflux and repurposed to treat chronic cough. In the United States, the National Center for Advancing Translational Sciences (NCATS) also has a Repurposing Drugs Program that is divided into early-stage repurposing (high-throughput screens of already approved compounds), and late-stage repurposing (regulatory-quality data packages to support a drug’s entry into clinical trials for new disease indication). A recent achievement came from a partnership between NCATS-associated academic scientists and AstraZeneca through the repurposing of saracatinib. Originally developed to treat cancer, saracatinib was recently shown to restore brain function in mouse models of Alzheimer’s disease and entered a Phase 2a clinical trial within 18 months — a process that would take up to a decade using an untested compound.

Despite these successes, repurposing drugs can be a controversial business. Pharmaceutical companies can remove a perfectly active drug from one indication, reformulate it in a minor way without any chemical alteration (for example modifying the dose or altering the formulation), and rebrand it for a new indication at a substantially higher price. Limiting the availability of the anti-cancer drug Avastin (bevacizumab) for wet age-related macular degeneration (AMD) is a well-reported example, as it has comparable efficacy (according to NIH’s comparison of AMD treatments trials), and is far less costly than the prescribed alternative Lucentis (ranibizumab). While some claim that off-label use of bevacizumab to treat wet AMD is unsafe, many doctors feel this is a cynical pharmaceutical maneuver that prioritizes profit ahead of patients. This debate is ongoing and
bevacizumab is not, at present, approved by the US Food and Drug Administration or European Medicine Agency as a treatment for wet AMD.

Finding new uses for existing compounds makes financial and scientific sense even though its implementation can be challenging. It is worth remembering that a unifying need to improve disease treatment should prevail and that sometimes, contrary to the old adage, you can teach an old dog new tricks.