Accelerating Drug Development Through Repurposing, Repositioning and Rescue

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By: Nigel Walker

Academic researchers, tech-savvy startups, Big Pharma and biotech, nonprofits, government institutes and public-private partnerships are investigating existing drugs/drug candidates for the treatment of new indications

From Serendipity to Purpose

The pharmaceutical industry is facing intense pressure to reduce the cost of prescription drugs and also more rapidly develop novel medicines to treat unmet medical needs, including rare diseases. One approach that can significantly reduce the time, cost and risk of drug development is referred to as drug repurposing, or repositioning, reprofiling, re-tasking, etc. and involves the application of existing drugs (approved or unapproved candidates) for the treatment of previously unconsidered indications.

Drug repurposing is not new. Historically, however, it was largely the result of serendipity. Side effects and off-label uses of drugs have suggested potential new indications, according to Gini Deshpande, Founder & CEO of NuMedii, a drug discovery company that applies its proprietary big data platform based on integrative genomics, networkbased methods, large-scale machine learning, and chemoinformatics to improve efficacy.[1] Viagra (Pfizer's sildenafil) is one such example; the drug initially failed as an angina treatment in clinical studies, during which its effect on erectile dysfunction was noted.

Today, many organizations are purposefully investing in drug repurposing, repositioning and rescue (DRPx) programs. Drug repurposing refers to the use of exiting approved drugs for new indications, while repositioning involves the development of an existing, previously evaluated but unapproved active pharmaceutical ingredient for the treatment of a different disease.[2]

It is estimated that 30% of FDA approved new drug products[3] and repurposed drugs account for approximately 25% of pharmaceutical industry revenues.[4] The global market for drug repurposing is estimated to reach $31.3 billion in 2020, growing at a compound annual growth rate of 5.1% from $24.4 billion in 2015, according to BCC Research.[5]

The growing interest is driven by the advantages of working with existing compounds that have already undergone significant safety testing. Repurposed drugs have shorter development times (5-8 years) compared to those associated with new chemical entities (10-15 years).[1] As a result, costs can be as much as 60% of those for NCEs.[2] In addition, the risk is lower: approval rates for repurposed

treatments for rare diseases. There are only approximately 400 approved drugs for the more than 7000 currently identified rare genetic conditions.[6] Using existing APIs to validate the biochemical pathways and facilitate the discovery of new compounds can speed the development of drugs for patients with no current options. There are approximately 2,800 drugs and more than 4,000 compounds that have been discontinued at Phase II development, according to Deshpande, providing a "rich pool" of possible therapies.[1]

Many Successes

In recent years, many unsuccessful drug candidates and existing drug products have been successfully investigated and approved for other indications.

- Thalidomide, which was originally developed as a racemic mixture of enantiomers for the treatment of morning sickness but found to be teratogenic due to the effect of the (S)-(-)-isomer, was later successfully developed by Celgene as a single (R)-isomer product for the treatment of leprosy and multiple myeloma.[2]
- Celebrex, widely used for the treatment of osteoarthritis, works by inhibiting COX-2 receptors. Recently it has been shown that for patients that previously had colon cancer, taking Celebrex can reduce the risk of additional polyp formation without negative gastrointestinal effects associated with existing treatments.
- Common diabetes drug metformin has been shown to reduce the risk of breast cancer in diabetes patients and is being investigated as a treatment for cancer in many different clinical trials.[7]
- Acne medicine all-trans retinoic acid (ATRA), when combined with traditional chemotherapy, results in complete remission of acute promyelocytic leukemia in 90% of treated patients.[7]
- The antibiotic minocycline, which is used to treat acne and sexually-transmitted infections, also decreases the symptoms of patients with Fragile-X syndrome, a genetic disorder that leads to cognitive disabilities. It is being evaluated in clinical trials.[7]

Recent efforts have focused on identifying existing drugs that can be repositioned or repurposed as antibiotics for the treatment of infections caused by drug-resistant bacteria. In late 2016, Researchers at NIH's Institutes of Health's National Center for Advancing Translational Sciences (NCATS), Clinical Center and National Institute of Allergy and Infectious Diseases (NIAID) reported that they had tested approximately 4,000 approved drugs and other biologically active compounds for antibiotic effectiveness against drug-resistant bacteria using a newly developed screening method. They identified 25 compounds that suppressed the growth of two drug-resistant strains of Klebsiella pneumonia, which have caused fatal infections in hospitals across the US.[8]

In August 2017, Mohamed Seleem and colleagues at Purdue University received a $1.6 million grant from NIH to determine if two existing drugs can be repurposed to treat drug-resistant bacteria. Ebselen is a clinical molecule that is potentially effective against methicillin-resistant Staphylococcus aureus (MRSA), while auranofin, which is FDA-approved for the treatment of unresponsive rheumatoid arthritis, appears to be effective against Clostridium difficile.[9]

Widespread Effort

In addition to government organizations such as NCATS, there is a broad array of groups focused on identifying new uses for existing drug candidates and approved products. Public-private partnerships, nonprofits, academic researchers and companies, including Big Pharma firms and startups with advanced technologies specifically designed to facilitate DRPx activities, are all involved.

Cures Within Reach is perhaps the most well-known nonprofit group focused on drug repurposing. UK-based Findacure and Globalcures are others. Examples of public-private partnerships include the Center for Drug Repurposing (operated jointly by Ariel University and Drug Rediscovery Ltd.) and the Drug Repurposing Hub (a collaboration between the Broad Institute Cancer Program, the Center for the Development of Therapeutics, and the Connectivity Map group); and The Repurposing Drugs in Oncology (ReDO) project.

Startups with proprietary screening, computational and data-mining technologies include Biovista, GVK Bio, NuMedii, Excelra, and Recursion Pharmaceuticals, among others.

A large number of academic research groups are also actively seeking to find new treatments for rare diseases using existing compounds. In addition to Seleem's group at Purdue University, other groups can be found at the University of Pennsylvania, the Houston Methodist Research Institute, the University of Texas Health Science Center, McGill University and many other academic institutions.[10]

Large pharmaceutical companies have formed partnerships with many of these organizations to help

with Excelra, Biovista and NuMedi.[2] NCATs works with pharmaceutical companies to make data and sample of existing compounds available to academic researchers at no cost for evaluation with the intention of repositioning or repurposing them as new treatments.[10] Even publishing companies are becoming involved. In late 2016, Elsevier began collaboration with Findacure, providing analytics tools and access to literature data on known compounds.[11]

Regulatory Pathway

The regulatory pathway used to repurpose/reposition existing drugs is typically the 505(b)(2) application. The 505(b)(2) new drug application (NDA) was created by the Hatch-Waxman Amendments of 1984 and allows the filer to use data for previously approved ("reference" or "listed") drugs not developed by the NDA applicant. Changes that can lead to submittal of a 505(b)(2) application can be related to the formulation, dosing regimen or indication, among others.[12]

In the US, several pieces of legislation have been introduced that address drug repurposing,[12] including the Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act, or "Dormant Therapies" Act, introduced in the House in 2013 (H.R.3116), provides patent and exclusivity protection enhancements and is a reworking of the MODDERN Cures Act of 2011 (H.R.3497). The Orphan Product Extensions Now Accelerating Cures & Treatments (OPEN ACT) was introduced in the House (H.R.1223) in 2017 and is designed to encourage drug makers to repurpose existing drugs for rare and pediatric diseases.

The Promise of Big Data and Computing Power

When looking at the potential of an existing compound as a treatment for a new indication, scientific rationale, clinical viability, commercial viability and regulatory path all must be considered, according to Deshpande.[1] The indication must be a true clinical need, the mechanism of action must be appropriate, formulation and delivery with high bioavailability and efficacy must be manufacturable in a cost-effective manner and the market dynamics (competition, pricing, reimbursement etc.) must be appropriate.

Big-data analytics, advanced modeling software and high throughput screening techniques are making it possible to systematically and rapidly evaluate the thousands of existing compounds against different indications and cell lines to find molecules that show promise for biologically matching disease targets.[13] Similarly, significant advances have been made in the instrumentation and techniques for physically analyzing genomic data, which is allowing the identification of more specific disease targets for subgroups of patients.[11] Advances in the field of transcriptomics, or the study of active genes within cells, are also allowing the investigation of transcriptomic signals resulting from specific drugs.[6]

Biovista, for instance, maps the connections between drugs, molecular pathways, genes and other biologically relevant entities discovered by searching publically available data on generic compounds, from approval information, published literature, FDA's database of adverse events and other sources.[13] In addition to genomic-data driven methods, NuMedii also uses other types of 'omic' information in conjunction with literature and clinical information to identify possible candidates for a given disease target.[1] Cambridge biotech Healx is one company using transcriptomics as a new approach to drug repurposing.[6]

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