DRUG REPOSITIONING/REPURPOISING:

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1. INTRODUCTION

It’s no secret that drug discovery and development is a costly, complex, and time-consuming process, often taking 14 years and $1 billion plus in R&D costs, with no guarantee of success. But what if the odds of extending the usefulness of an approved drug, or finding a useful indication for a failed drug, could be improved? Drug repositioning or repurposing accounts for approximately 30% of drugs and vaccines recently approved by the US Food and Drug Administration.\(^1\) Recycling an approved drug for a different indication or rescuing a candidate that may have failed in a Phase 1 study and developing it to treat a different condition are faster and more cost-effective than trying to develop a new drug from scratch, and carry less risk to companies and to patients. It’s no wonder that more pharmaceutical companies are investigating this approach to extend the life of their portfolios.

2. APPROACHES THAT WORK

Different approaches are used for drug repositioning, depending on whether the desired outcome is drug-centric (i.e., predicting new indications for an existing drug), or disease-centric (i.e., identifying a disease with no effective drugs on the market, and then identifying an approved or failed drug as a potential treatment option). There are a variety of different approaches to drug repositioning, including:

- **Knowledge-based**: Providing comprehensive bioinformatics/cheminformatics analyses of available information from drug-target networks, chemical structures of drugs and targets, clinical trials and other input.

- **Signature-based**: Exploring functional connections between biological events using an enhanced gene-signature design, assisted by pathway analyses.

- **Pathway- or network-based**: Reconstructing disease-specific pathways using disease “omics” data analyses.

- **Targeted mechanism-based**: Developing mechanistic therapeutic models using treatment “omics” data analyses.

Published scientific literature contains tremendous amounts of information from both research and clinical studies than can help shed light on alternative applications for approved or failed drugs. Elsevier, as a leading provider of scientific content and advanced tools for text mining and disease pathway analysis, has partnered with several of its customers to explore potential alternative uses for two drugs already on the market.
3. CASES IN POINT: ADALIMUMAB, IMATINIB

Pathway Studio’s proprietary text-mining technology provides access to an unparalleled amount of data from the published literature—both Elsevier journals and those of other top publishers—enabling researchers to rapidly and accurately pinpoint promising avenues to pursue for drug repositioning. Companies have applied this technology to successfully identify new indications for, among others, the TNF-inhibitor adalimumab, and the anti-cancer drug, imatinib. In both cases, a straightforward, user-friendly approach yielded the desired outcomes.

FOR ADALIMUMAB, THE APPROACH INVOLVED:

Identifying indications reported in the literature: Full-text documents in PubMed, PubMed Central and more than 12,000 Elsevier journals were mined to extract potential adalimumab indications. Of the 53 indications identified, 23 were supported by more than one reference—giving further support to those as potential targets. Additional indications were also extracted from clinical trial data, and from patents mentioning Humira or adalimumab in the title, abstract or claims.

Predicting indications from the literature data: We examined the data supporting those indications for reports of other anti-TNF drugs; from diseases with contributing TNF activity; and from diseases with upregulated TNF activity. In total, 158,069 abstracts mentioning the keyword “TNF-alpha” were identified. After importing those results into Pathway Studio, relevant diseases, syndromes, physiological effects and toxicities were further categorized—e.g., as diseases with upregulated TNF activity, upstream or downstream of TNF.

Predicting indications using curated pathway data: We then applied specialized analytical functions (Sub Network Enrichment Analysis) in Pathway Studio to identify diseases linked to TNF signaling, and characterized a number of proteins associated with TNF pathways contributing to the disease.

Integrating results to support data-driven decision making: Based on these text and data-mining approaches, a total of 491 possible adalimumab indications were identified and prioritized based on the evidence discovered. There are some trials for currently non-approved indications that, while not influenced by our report, validate the concepts from the analysis. Recent trials for areas identified in the Elsevier analysis include Hidradenitis Suppurativa, completed 2014,3 and Behcet syndrome (ongoing).4

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3 http://clinicaltrials.gov/ct2/show/NCT01468207?term=humira+hidradenitis&rank=1
Validating fibrosis as a new imatinib indication using pathway analysis, mining of clinical trials and patent mining: Taken together, these approaches enabled the identification of imatinib’s role in down-regulating fibronectin (FN1), the major protein activated in fibrosis, and in inhibiting the FN1 pathway. This resulted in eight clinical trials of imatinib for seven fibrosis-related diseases, and one US patent claiming an imatinib application for liver fibrosis.

Beyond these two examples of drug-centric repositioning, Pathway Studio also has been utilized successfully for disease-centric positioning—for example, to identify CYR 61 as a novel glioblastoma target, and an approved breast cancer drug, fulvestrant (Faslodex), as a potential treatment.

A SIMILAR, MULTIFACETED APPROACH WAS UNDERTAKEN USING IMATINIB:

We identified six protein targets from an initial collection of 344 potential indications in the literature. These targets were grouped into two families of targets: ABL kinase paralogs and PDGF receptor paralogs. Each of these indications was ranked based on the evidence supporting it via protein-disease interactions found in the literature. From this initial list, the client asked Elsevier to focus only on diseases in their key therapeutic areas—resulting in 10 potential indications for prioritization. Four types of fibrosis were linked by the largest number of references to the ABL and PDGF receptor targets, and were chosen for further validation.
4. LOOKING AHEAD

In an era of precision medicine, this quote from noted chemist Christopher Lipinski is particularly apt: “Although a bit of an exaggeration, there is a lot of truth in the saying that ‘we do not need to find new drugs; rather we need to find the patients who can benefit from existing drugs.’” It is now commonly accepted that most approved drugs are not selective for a single target or signaling pathway. Using the best possible tools to discover and delineate disease and treatment mechanisms is critical not only to successful drug repositioning, providing significant economic benefits to pharmaceutical companies, as well as significant health benefits to the appropriate patients.

5 Technical Program Abstracts, Fall 2012 American Chemical Society National Meeting, Chemical Information Bulletin; 64 (3): Fall 2012
http://bulletin.acscinf.org/node/347
Are you interested in learning how Pathway Studio can support your drug discovery efforts?