Antidepressants Give Cancer Cells the Blues

Stephan C. Jahn, Ph.D.
Department of Medicinal Chemistry and UF Health Cancer Center, University of Florida, Gainesville, FL
Email: scjahn@ufl.edu

Abstract

With the ever present need for novel treatments of human diseases, processes that accelerate the progress from bench to bedside are constantly being sought. While developing a new small molecule from the ground up takes a great deal of time and resources, repurposing drugs that have already been approved for the use of other indications allows their clinical use to occur in a very timely manner. Here, we highlight a new bioinformatics approach to finding new uses for old drugs, using data that are already available, that was recently published by Jahchan *et al.*

Introduction

There are multiples hurdles that must be cleared before a new small molecule can be used in the clinic. Once an active molecule is identified and characterized it must be tested for safety in lengthy and costly clinical trials as well as analyzed pharmacokinetically before being approved by the United States Food and Drug Administration (FDA). One approach to accelerate the entry into clinical use is to repurpose a previously approved drug. As safety testing as well as absorption, distribution, metabolism, and excretion (ADME) characterization has already been completed, all that is generally needed is proof of efficacy in treating the new condition.

Oftentimes, this repurposing can be done logically. What is considered a side effect of an off-target action in using a drug to treat one condition may be a desired effect in another. For example, thalidomide, which was developed in the 1950s to treat morning sickness during pregnancy, caused severe birth-defects in some children. These side effects were found to be due to its antiangiogenic and immunomodulatory properties. Conversely, these activities make thalidomide a useful anticancer drug [1] and it is also used to treat leprosy [2]. Additionally, a second logical repurposing strategy is to utilize the fact that one target can play multiple roles in the body. Finesteride, which blocks the conversion of testosterone to dihydrotestosterone, was originally approved to treat enlarged prostates but was later repurposed to prevent male pattern baldness through the same mechanism, being marketed by Merck as Propecia.

On the other hand, repurposing can be done through other mechanisms that find previously unknown relationships. High-throughput phenotypic screens can find new uses through undiscovered mechanisms while molecular docking has successfully been used to find currently approved drugs that bind to a desired protein, causing an anticipated effect [3]. Recently published online in Cancer Discovery, an article by Jahchan et al. presents a novel bioinformatics approach to discovering new uses for current FDA approved drugs [4].

Authors' Results

Seeking to discover FDA approved drugs to treat small cell lung cancer (SCLC), a fast progressing disease with no suitable treatments available, the authors compared gene expression profiles of cells treated with 3,600 current drugs to gene signatures of SCLC. Of the compounds predicted to antagonize these neuroendocrine tumors, many were known to interact with neurological pathways as well as calcium signaling, both of which are known to be important in SCLC [5-7]. This process is summarized in Figure 1.

Imipramine and clomipramine are tricyclic antidepressants, promethazine is a histamine H1

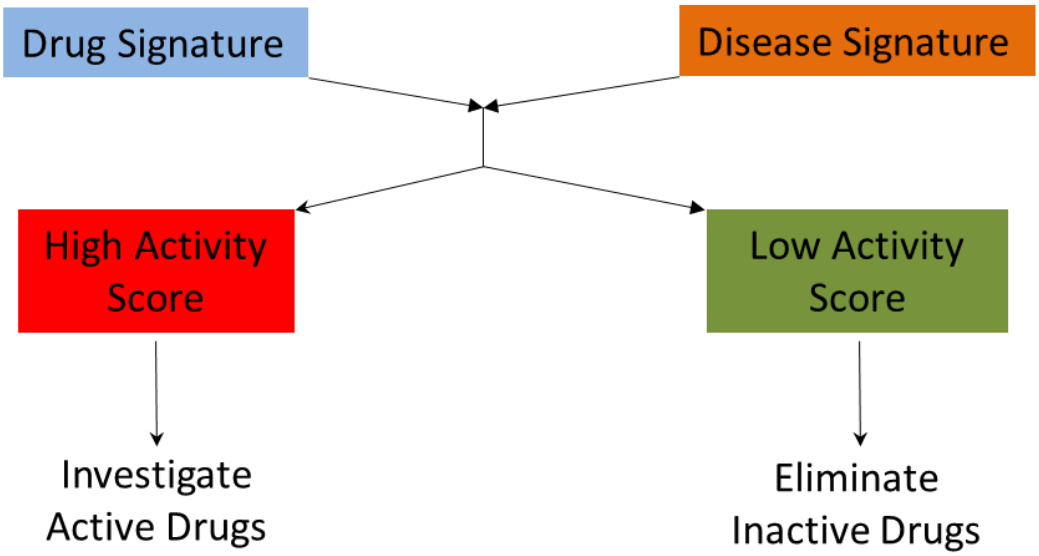

Figure 1. Drug repurposing through the use of currently available bioinformatics data. Gene signatures from cells treated with FDA approved drugs are compared to those of the target disease. Ability of each drug to oppose this malignancy is computed to yield is computed as an activity score. Low scoring drugs are eliminated while high scoring drugs and further investigated experimentally.

antagonist, tranylcypromine and pargyline are monoamine oxidase inhibitors, while bepridil is a calcium channel blocker, and all were identified in the screen. All except the monoamine oxidase inhibitors showed growth inhibition of the small cell lung cancer cell lines H82, H69, and H187, but not A549 and LKR13, which are non-small cell lung cancer cell lines. Additionally, one representative drug from each promising drug class was tested and showed efficacy against allograft and xenograft tumors in NOD SCID Gamma mice initiated by either injection of SCLC cell lines or transplantation of primary human tumors, with imipramine and promethazine showing the best results. Additionally, 30-day treatment of *Rb*/*p53*/*p130* mutant SCLC mice with imipramine or promethazine reduced tumor burden, by both number and volume, and blocked liver metastasis, compared to saline treated controls.

As no targeted therapy is currently available for small cell lung cancer, treatment regimens generally combine cisplatin with etoposide, however this oftentimes leads to resistance. To assess the ability of imipramine to inhibit the growth of chemoresistant tumors, lung tumors from *Rb*/*p53*/*p130* mutant mice that had regressed after cisplatin treatment were grown in culture or transplanted to NOD SCID Gamma mice. The tricyclic antidepressant imipramine continued to show efficacy even under these conditions.

Visual observations showed that treatment of small cell lung cancer cells with imipramine or promethazine induced cell death and further assays identified the presence of apoptotic cells. Co-treatment with zVAD-FMK, an apoptosis inhibitor, blocked cell death in a dose dependent manner. This death was not observed in non-small lung cancer cells or the normal lung epithelium in treated mice, indicating the specificity toward SCLC.

Treatment with imipramine or promethazine induced a rapid decrease in cellular calcium levels and increased levels of reactive oxygen species. This was seen to coincide with a rapid increase in c-Jun, JNK, and stress MAPK signaling. Through a series of experiments with various agonists and antagonists, the authors concluded

that these drugs inhibit tumor growth through blocking signaling downstream of G-protein coupled receptors (GPCRs), inhibiting production of cAMP and thus the activation of PKA, in turn activating the c-Jun/JNK pathway. Indeed, the JNK inhibitor SP600125 largely prevented cell death, indicating its importance in the cell death cascade

Interestingly, it was found that both imipramine and promethazine also potently inhibited the growth of other neuroendocrine tumors, including pancreatic neuroendocrine tumors, among others. These newfound treatments have already entered phase II clinical trials, a benefit of their earlier approval by the FDA. This study presents two important findings. First, it shows that tricyclic antidepressants and other related drugs may prove useful in treating both untreated and chemoresistant neuroendocrine tumors. Second, it opens the doors for a new method of repurposing drugs that is fast, inexpensive, and not labor intensive. It will be exciting to see what new uses can be discovered for the compounds already stocked in the nation's pharmacies.

Acknowledgements

I thank Dr. Julien Sage for his openness to this research highlight and the reviewers for their helpful critiques.

References

1. Breitkreutz I, Anderson KC (2008) Thalidomide in multiple myeloma--clinical trials and aspects of drug metabolism and toxicity. Expert Opin Drug Metab Toxicol 4: 973-985.
2. Prasad PV, Kaviarasan PK (2010) Leprosy therapy, past and present: can we hope to eliminate it? Indian J Dermatol 55: 316-324.
3. Leung CH, Chan DS, Kwan MH, Cheng Z, Wong CY, et al. (2011) Structure-based repurposing of FDA-approved drugs as TNF-alpha inhibitors. ChemMedChem 6: 765-768.
4. Jahchan NS, Dudley JT, Mazur PK, Flores N, Yang D, et al. (2013) A Drug Repositioning Approach Identifies Tricyclic Antidepressants as Inhibitors of Small Cell Lung Cancer and Other Neuroendocrine Tumors. Cancer Discov.
5. Wistuba, II, Gazdar AF, Minna JD (2001) Molecular genetics of small cell lung carcinoma. Semin Oncol 28: 3-13.
6. Moody TW, Chan D, Fahrenkrug J, Jensen RT (2003) Neuropeptides as autocrine growth factors in cancer cells. Curr Pharm Des 9: 495-509.
7. Onganer PU, Seckl MJ, Djamgoz MB (2005) Neuronal characteristics of small-cell lung cancer. Br J Cancer 93: 1197-1201.