

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## The Promise of Genomics-Based Drug Repurposing



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### H&O What is a repurposed drug?

**JD** A repurposed drug is an already-approved compound that is being tested for a new indication, or an experimental molecule that is being evaluated for indications beyond those evaluated during initial development.

### H&O How has drug repurposing primarily happened in the past?

**JD** Serendipity, at least in part, often underlies discoveries of new uses for already existing or shelved drugs. One of the reasons why is that we do not have full knowledge of the mechanism of action for many drugs on the market today. Aspirin is a great example of a common medication that we use without fully understanding how it works. Many drugs in clinical use today were discovered empirically, not necessarily through applied understanding of their precise molecular mechanism of action.

### H&O Is high-throughput screening a better approach for drug repurposing?

**JD** As we all know, one approach to rational, systematic drug repurposing is an assay in which many drugs can be screened for activity against a particular target. But this approach suffers from the same limitations that chemical screening has in general. Namely, a compound may test positive on a cell-based screen or target-based screen, but that activity usually does not translate into therapeutic activity in the vastly more complex context of human physiology. The percentage of compounds that move from such an assay into human use is very low.

Another limitation of high-throughput screening is that the assays often are focused on a single hypothesis. We screen compounds against a single target, or we search for a target for a single compound. But this narrow approach suffers from the fact that we do not know the full spectrum of targets that a small molecule may be hitting. Also, we do not understand the complexity of the alterations that may result from a compound hitting multiple targets. Furthermore, hitting targets A and B simultaneously may elicit a different reaction than hitting both targets at different times. I do think that phenotypic screens followed by deep molecular characterization and network analysis offer a path for screening approaches that better appreciate the complexity of biology and drug action.

### H&O How is genomics being used to investigate new uses for existing drugs or shelved compounds?

**JD** Research initially pioneered by the Connectivity Map project from the Broad Institute of Harvard and the Massachusetts Institute of Technology leveraged advances in genomics to enable a systems-based approach to drug repurposing and discovery. Instead of identifying the targets hit by a particular compound, say through a target-based screen, we can now measure and evaluate the genome-wide perturbation induced by a compound. In the case of the Connectivity Map, this perturbation was determined by transcriptional changes that result from exposing a cell line to a dose of the compound and measuring the changes in the transcriptome relative to untreated controls. By measuring all genes at one time, we can obtain a system-wide snapshot of how exposure to a particular drug affects the entire cell line.

An analogy is throwing a rock into a pond and taking a picture of the ripples. We are measuring the molecular ripples. We may not fully understand the physical or molecular dynamics between the rock and the water surface that generate the ripples, but we can know that a rock of a certain shape and size will generate a particular pattern of ripples.

The way in which a system responds downstream to a drug is complex; the response involves much more than just the targets that are engaged by the compound. In genomics, we capture the entire response as a pattern or signature. Genomics-based drug repurposing enables us to study genome-wide patterns of how drugs are changing biological systems. In the context of disease, we can look at tissue from a cohort or individual with a particular condition and tissue from a healthy individual and see which genes are changed. We can then use computational approaches that leverage the molecular patterns of drug and disease to draw inferences about therapeutic potential.

### **H&O** What are the advantages of a genomics-based approach to drug repurposing?

**JD** Similarly to drugs, there are many diseases for which we do not know the underlying causal mechanisms. But we can obtain a picture of the genomic patterns in tissue from affected and unaffected individuals and thereby obtain a molecular signature of a disease. So even if we do not know the underlying cause, we can know the differences in the gene expression pattern between people with a disease and those without that disease. Then, ideally we can take the genomic profile of a drug from the cell-line tests described above and match it to a disease according to its gene expression pattern. We can make predictions about how a drug might treat a disease based on what we know about how it affects genes.

Cancer cells have many different mutations that cause changes in how genes are expressed, or switched on or off. One of the main thrusts of current drug development is creating molecules that target these mutations one by one. But this approach has not led to the many miracle cures we were initially anticipating because the routes by which these targets trigger cancer cell proliferation are extremely complex.

With a systems-based approach, we can try to find drugs that will be able to shut down expression of genes that are switched on in tumors but not in healthy cells.

### **H&O** What is an example of a drug for which a new use has been found by this approach?

**JD** In 2013, I worked with a group led by Dr Julien Sage of Stanford University that used a computational drug repurposing approach to scan a broad range of compounds for

activity against small cell lung cancer. For each compound, we looked at the whole transcriptional pattern, a reflection of the cellular activity induced by the drug in relation to the disease. We had no prior hypothesis of which drug should be a match. It turned out that imipramine, a tricyclic antidepressant, was one of the strongest hits. Imipramine has about 8 different targets, none of which are considered to be cancer targets. And yet the compound had preclinical activity against this disease as well as against other neuroendocrine tumors.

If we had begun the research by asking whether a drug that targets these particular genes might be useful for cancer, the assumption would have been that this drug would not work because none of those genes are canonical cancer genes or cancer drug targets. But this data-driven approach does not require prior knowledge of what gene is or is not a cancer target. The data tell us which drugs match the tumor profile the most strongly. With genomic technology, we can measure more than we know.

### **H&O** Are you taking samples of DNA from patients at Mount Sinai and obtaining a snapshot of their genomic patterns?

**JD** DNA is somewhat limited in its utility for drug repurposing because it is very static relative to RNA and other molecular readouts. RNA actually tells us more about what is going on inside cells because it shows what genes are being expressed and to what degree. At Mount Sinai, we are using RNA sequences to look at the gene activity pattern in the tumor and try to match that to drugs.

There are caveats to this approach. Because RNA is unstable chemically and degrades rapidly, the logistics of collecting it can be complicated. For example, tumor tissue often needs to be flash-frozen immediately in the operating room in order to obtain a clear reading of the gene expression pattern.

Once RNA is obtained from a patient's tumor, we can see what genes might be overexpressed relative to normal tissue. We then check for relevant experimental compounds using large, public datasets of gene expression profiles, such as the Broad Institute's Connectivity Map, which is now part of a larger effort known as the Library of Integrated Network-Based Cellular Signatures, which is also maintained at the Broad Institute. These datasets show what genes are being up- or downregulated in cells when they are exposed to a particular drug. So we can look at the RNA sequences to see what genes are being turned on or off in the cancer, and then search for a drug that acts on those same genes according to these datasets. If the tumor upregulates particular genes, perhaps individually or coordinately in the same pathway or subnetwork, then we would look for a drug that downregulates, or suppresses, those genes.

## H&O Has this approach led to new treatments?

**JD** There is preclinical validation that topiramate, an anticonvulsant drug, has activity against inflammatory bowel disease (IBD), and also the example I mentioned above of imipramine for small cell lung cancer. These drugs have been validated in human cell lines. A survey of the translational medicine literature citing the Connectivity Map resource will reveal many other successful examples of genomics-guided drug repurposing.

Moving these repurposed drugs into clinical trials is difficult because it requires funding. But funding a study for a repurposed asset is challenging if there is no substantial intellectual property that a pharmaceutical company stands to gain. If imipramine turns out to be an effective compound for small cell lung cancer—and we do not have any data confirming that benefit at this point—will there be a pharmaceutical company ready to commercialize that indication? In order for doctors to prescribe an already approved drug for a new indication, there must be large clinical trials published in top-tier journals. The National Institutes of Health is trying to fill this gap with a new funding program from the National Center for Advancing Translational Sciences, but more funding is needed to bridge this gap.

## H&O Could drug developers create new drugs based on the research from repurposing studies?

**JD** Yes, because we are identifying new mechanisms of action for diseases and treatments. With data-driven and genomics-guided repurposing, it is possible to find totally new mechanisms of action that may not have been previously suspected would work on a given disease.

With topiramate for IBD, the drug is hitting the  $\gamma$ -aminobutyric acid (GABA)-A receptor combined with the carbonic anhydrase gene, cellular components that were not even on the radar for IBD previously. The preclinical evidence supporting the use of topiramate for IBD has led researchers to wonder how carbonic anhydrases and GABA-A receptors contribute to this disease. The potential benefit of imipramine for small cell lung cancer raises similar questions, leading researchers to examine the role of dopamines, calcium channels, and histamines in the development of the disease. That research in turn opens up new avenues for therapeutic discovery.

Thus repurposing can inform new mechanisms, even if the drug that led to the understanding is ultimately not developed for that indication. It may be that once a new mechanism is identified, pharmaceutical companies might check their storehouses for any potentially relevant experimental compounds, or perform medicinal chemis-

try on the scaffold of the approved compound to optimize for the repurposed indication.

At Mount Sinai, we are working with the multiple myeloma team to build computational models for relapsed disease using patient samples, which can then be used to search broadly across all approved drugs. We may even find that a drug already indicated for multiple myeloma may be repurposed for a specific group of patients. For one patient, bortezomib may be the best choice upon relapse. For another patient, lenalidomide may be a better option, or various combinations thereof.

## H&O Are you optimistic that efforts to repurpose drugs will bear fruit?

**JD** Yes. The level of technology available to us today—immune profiling, gene expression profiling, DNA profiling, microbiome profiling, epigenetic profiling, and imaging—means we are better equipped than ever to understand the entire network of systems that lend themselves to cancer, and hopefully to then identify compounds that can act against that system effectively.

We are looking at drugs that are already on the market—an approach often referred to as drug repositioning—but we are also working with private industry to access their shelved compounds to scan against alternative disease indications. Many pharmaceutical companies are eager to participate in this work.

The science is also improving. Many research groups are focused on drug repurposing. And genomics is not the only approach; some researchers, such as Dr Michael Keiser's group at the University of California, San Francisco, are using chemoinformatics and systems pharmacology approaches for drug repurposing. Our group is just publishing a study making specific computational predictions of how certain drugs would affect immune cells.

Several challenges still lie ahead. Clearly more work needs to be done to confirm that drug repurposing will ultimately benefit patients. We need demonstrations in humans of new uses for approved drugs or forgotten experimental compounds.

## Suggested Reading

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