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HONORARY LECTURE

Drug Repurposing: Then, Now, and in the Future

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ABSTRACT

Contrary to the definition of a drug, drug repurposing usually involves the redevelopment of an active pharmaceutical ingredient (API) for a substantially different medical use; only rarely is this done with an off-the-shelf drug approved for a different disease. There is a qualitative difference between API redevelopment and additional approvals for an existing drug; to qualify as repurposing, the additional therapeutic indication must not be closely related to the original one. Using the mechanism for which the drug is approved and marketed to treat a different disease context is called on-target repurposing, and while the new use may seem obvious in retrospect, it requires ingenuity to connect the dots of evidence leading to it. Off-target repurposing is even more innovative: it relies on a newly discovered mechanism, or one that was known but only considered in terms of the drug's side effects. While clever pharmacological thinking and occasional serendipity have long driven repurposing, algorithmic approaches are now making their mark, and more recently, artificial intelligence applications are taking drug repurposing to unprecedented levels.

KEYWORDS

Artificial Intelligence; Electronic Health Records; Drug Approval; Drug Repositioning; High-Throughput Screening Assays; International Classification of Diseases; Machine Learning; Molecular Docking Simulation; Risk Assessment.

WHAT EXACTLY IS DRUG REPURPOSING?

As of November 30, 2023, PubMed had indexed 4954 papers under the MeSH term "drug repositioning" (synonymous with "drug repurposing" according to the United States National Institutes of Health), including 1327 review papers. Is another review on this topic necessary for the scientific community?

The answer appears affirmative. Discussions with drug developers, regulatory scientists, health technology assessment specialists, healthcare providers, and active ingredient manufacturers in the pharmaceutical sector reveal a diversity of interpretations of this term. This variability in definitions leads to confusion on multiple levels.

Confusion No. 1: Drug or API?

The confusion begins with the blurred distinction between an active pharmaceutical ingredient (API) and a drug. As defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an API is "*any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.*"

But this clear distinction is widely ignored. For example, the official definition of the MeSH term "drug repositioning" states that it refers to "*the deliberate and methodical practice of finding new applications for existing drugs*." However, a cursory review of research papers indexed under this term in PubMed shows that most are not about drugs but rather about the API contained in them, to suggest its potential utility in medical conditions not covered by regulatory approval.

In principle, an extension of the drug's utility through supplementary indication approvals might even result in actual repositioning of the particular unchanged off-the-shelf drug for a new, unrelated medical purpose. That can be part of drug life cycle

management but is quite uncommon nowadays due to its poor alignment with pharmaceutical marketing strategies.

In practice, "repurposing" implies that the API would be redeveloped into a new drug presentation. Pure medical necessity often suggests or requires this: an alternate route of administration might better serve the new target population than the original one, dose units might differ, or release kinetics might be advantageously altered. Therefore, much of what is termed drug repurposing or, even more inaccurately, drug repositioning, should correctly be referred to as "API redevelopment."

Confusion No. 2: The New Therapeutic Indication

During the Covid-19 pandemic, it was occasionally claimed that remdesivir, an adenosine analog originally intended for the treatment of hepatitis C but later developed and approved for Ebola and Marburg virus infections, had been "repurposed" for Covid-19. However, using a drug that interferes with RNA-dependent RNA polymerase against another single-stranded RNA virus severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) requiring this key enzyme hardly qualifies as repurposing; remdesivir had always been known as a broad-spectrum agent for such viruses.[1] Nor would it be regarded as repurposing if a drug with initial marketing authorization for a particular type of solid tumor received supplementary approval for another type of cancer; this would rather be use extension.

But how should a "substantially different medical condition" (as opposed to the approved one) be defined? Indeed, this distinction might not be easy to make in some cases. A pragmatic approach could define repurposing as redeveloping an API for a medical condition that is in a different axis in the World Health Organization International Classification of Diseases (ICD 10/11) and/or in a different High Level Group in the Medical Dictionary for Regulatory Activities (MedDRA) as maintained by the ICH. In the above example concerning a cancer drug, its redevelopment for choroidal neovascularization would clearly be considered repurposing because the new target disease is not a cancer.

WHY DO WE REPURPOSE DRUGS?

Commonly offered explanations often miss the core reasons.

The notion that we are depleting drug-like chemical space is easily refutable. The PubChem database currently contains 115 million compounds, most of which can be considered drug-like. The ZINC20 ligand discovery database holds tens of millions of small molecules that are not only ready for virtual screening with popular docking software but are also commercially available.[2]

Are we approaching the limits of useful targets? Although more realistic, this is unlikely: some 3000 human proteins are considered druggable in principle, and methods to target those previously deemed "undruggable" (i.e., those lacking defined pockets for ligand interaction) are constantly being developed.[3] While it is true that there might be only 400–1400 unique classes of binding pockets shared among different proteins (not all equally relevant), their uniqueness is gradual, and the effects of ligand binding depend on the characteristics of the proteins that harbor them.

Synthesizing vast libraries of novel molecules and screening them against a given target almost always results in at least one lead compound, for which patents could be secured, unlike repurposed agents where only the new use and formulations might be patentable. So, why is repurposing attractive, barring pure scientific interest?

The simple answer is cost—not just direct costs saved in early discovery phases, animal studies, and initial clinical trials (which are minimal compared to phase II and especially phase III programs), but also factors often overlooked by academic researchers such as the following:

- *Risk*: An agent that has been widely used for years or at least has been in advanced clinical trials without significant side effects is much less likely to fail for safety reasons than a new chemical entity. Lower development risk means a reduced need for set-asides to cover potential investment losses, more predictability in return on investment, and hence, greater appeal to external investors.
- *Time to market*: Accelerating market access by even a single year compared to a new chemical entity can significantly improve the cost-effectiveness of a drug development project: it means earlier returns on investment and free resources for new projects, bolstering the bottom line. If a quicker market launch results in a first-in-class drug or one with unique selling points, there is a strategic advantage that may be difficult for competitors to match.

These factors have driven drug repurposing historically and will continue to be key motivators as long as drugs are developed in a capital-intensive, profit-oriented economic environment.

Methods of Drug Repurposing: Past and Present

Traditionally, there are two primary approaches:

- *On-target* repurposing leverages an agent's established mechanism to address a distinctly different disease. It encompasses applications in systems medicine, wherein altering a known target in varied pathways can yield unique effects. The impetus for on-target repurposing usually lies in creatively "connecting the dots" of existing evidence.
- *Off-target* repurposing involves harnessing a previously unknown, overlooked, or side-effect-related pharmacological mechanism of an agent, initially approved for a different purpose. This approach requires a higher degree of inventiveness, making it easier to obtain use patents.

In the past, ingenious pharmacological thinking predominantly contributed to repurposing. For instance, redeveloping marketed cholinesterase inhibitors like galantamine based on the cholinergic hypothesis of Alzheimer's disease in the 1990s is a notable example.[4] Similarly, repurposing the selective serotonin reuptake inhibitors fluoxetine and paroxetine for premature ejaculation treatment capitalized on the inhibitory effect of elevated brain serotonin levels on ejaculation, a side effect observed in men with otherwise normal sexual function.[5]

Currently, on-target repurposing accounts for 80–90% of discoveries in this domain, as evidenced by hundreds of research papers and patent applications published annually. A recent example is international patent disclosure WO/2023/165465 from Jinan University, claiming the amyotrophic lateral sclerosis drug riluzole, an N-methyl-D-aspartate (NMDA)/kainate receptor blocker, for oligospermia. This research stemmed from the known effect of glutamate on testicular toxicity and male infertility.

So far, off-target repurposing has not led to significant drug approvals, though scientific interest in these findings is high. The pharmacologically promiscuous statins, developed as hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors for dyslipidemia treatment, are prime candidates for this type of innovative repurposing. Simvastatin, for instance, has been claimed for a range of conditions including pancreatitis, sepsis, intervertebral disc degeneration, various cancers, asthma, cocaine addiction, glaucoma, and osteoarthritis in patent applications since 2010. Such discoveries often result from high-throughput screening, in silico docking, and occasionally serendipity.

THE FUTURE OF DRUG REPURPOSING

Although traditional strategies remain productive, artificial intelligence (AI) is rapidly transforming the landscape of drug repurposing. Stripped of all hype, the fact remains that AI might be better suited to repurpose known agents than to design new chemical entities. For publishing novel repurposing methods, the GitHub open-access software repository has become almost as important as PubMed.

Data are essential for any complex algorithm, and there is no shortage of data that are either freely accessible or can be mined post-anonymization. Peer-reviewed literature and patent documents are rich orthogonal sources of scientific information, though they have been barely correlated until recently.[6] (Patents, as a source of scientific information, differ in motivation from peer-reviewed papers.)

Advanced cheminformatics, particularly when integrated with structural protein target information provided by the open-source AlphaFold software package which has resolved the long-standing challenge of predicting three-dimensional protein folding from amino acid sequences,[3] can identify ligand–target interactions that had not even been imagined so far. The on-target repurposing challenge of "connecting the dots in new ways" can be tackled on a much larger scale with machine learning.

Electronic health records maintained by hospitals and insurers constitute a different type of data treasure. They encompass observational patient data across various types and levels, all linked to medications. AI-assisted data mining and deep learning can uncover correlations that might otherwise go unnoticed, and can even facilitate the creation of frameworks for identifying potential repurposing candidates.[7] Utilizing these methods on datasets from 169,000 patients treated for posttraumatic stress disorder at U.S. Veterans Administration centers led to the discovery that certain inhibitors of the non-structural hepatitis C viral protein NS5A were significantly associated with symptom improvement (international patent application WO/2023/102535).

Another vast data resource exists within large regulatory authorities, which receive preclinical and clinical data from drug developers and researchers conducting investigator-initiated clinical trials. While these data are confidential, they could provide immense opportunities for drug repurposing if eventually made publicly available, even decades later.

The application of rapidly advancing AI technologies to these databases opens nearly limitless possibilities. Machine learning[8] and graph theory[9] approaches have increasingly been applied to drug repurposing over the past decade. However, this expansive field is beyond the scope of this review.

The quest for new applications of known pharmaceutically active agents presents inexhaustible opportunities. With the continuous influx of extensive data and emerging technologies, we are poised to fully exploit these potentials.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

DATA AND CODE AVAILABILITY

Data and code availability does not apply.

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REFERENCES

1. Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019;169: 104541. DOI: 10.1016/j.antiviral.2019.104541.
2. Irwin JJ, Tang KG, Young J, et al. ZINC20—a free ultralarge-scale chemical database for ligand discovery. J Chem Inf Model. 2020;60(12): 6065–6073. DOI: 10.1021/acs.jcim.0c00675.
3. Xie X, Yu T, Li X, et al. Recent advances in targeting the "undruggable" proteins: from drug discovery to clinical trials. Sig Transduct Target Ther. 2023;8(1): 1–71. DOI: 10.1038/s41392-023-01589-z.
4. Mucke HA. The case of galantamine: repurposing and late blooming of a cholinergic drug. Future Sci OA. 2015;1(4): FSO73. DOI: 10.4155/fso.15.73.
5. Zhang D, Cheng Y, Wu K, Ma Q, Jiang J, Yan Z. Paroxetine in the treatment of premature ejaculation: a systematic review and meta-analysis. BMC Urology. 2019;19(1): 2. DOI: 10.1186/s12894-018-0431-7.
6. Mucke H. Relating patenting and peer-review publications: an extended perspective on the vascular health and risk management literature. Vasc Health Risk Manag. 2011;7: 265–272. DOI: 10.2147/VHRM.S14454.
7. Ozery-Flato M, Goldschmidt Y, Shaham O, Ravid S, Yanover C. Framework for identifying drug repurposing candidates from observational healthcare data. JAMIA Open. 2020;3(4): 536–544. DOI: 10.1093/jamiaopen/ooaa048.
8. Napolitano F, Zhao Y, Moreira VM, et al. Drug repositioning: a machine-learning approach through data integration. J Cheminform. 2013;5(1): 30. DOI: 10.1186/1758-2946-5-30.
9. Gramatica R, Matteo TD, Giorgetti S, Barbiani M, Bevec D, Aste T. Graph theory enables drug repurposing – how a mathematical model can drive the discovery of hidden mechanisms of action. PLoS One. 2014;9(1): e84912. DOI: 10.1371/journal.pone.0084912.