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Review

Artificial Intelligence Enabled Drug Repurposing for Precision Therapeutics: A Systems Pharmacology Approach

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Abstract:
The pharmaceutical sector is caught in a critical situation, where the conventional de novo drug discovery has become unsustainable due to high costs, long development time, and poor success. Simultaneously, this need of precision therapeutics requires solutions to enable the treatment to be tailored to particular subpopulations of patients. Drug repurposing is a tactical shortcut, making use of the available safety history of pre-existing compounds to expedite the development of therapy. The hypotheses of this review are that convergence of artificial intelligence (AI), big data and systems pharmacology can provide a reinventive, integrative framework that drives this novel paradigm. We describe how AI-based models, which are based on systems-level network analysis, can be used to predict new drug-disease relationships in a systematic way- not by chance but by hypothesis-guided precision repurposing. The discussion includes major pillars of methodology, such as signature-based matching and knowledge graph reasoning to deep learning on biological networks. Using illustrative case studies in oncology, rare diseases and pandemic response, we show how an integrative AI workflow, in the context of candidate prioritization and mechanistic elucidation, is operationalized. The achievement of this potential, however, depends on addressing the major challenges, such as data heterogeneity, limitations of algorithms as black boxes, and translation problems in validation and regulation. Finally, AI-based systems pharmacology will be a paradigm shift of more efficient, guided, and patient-centric therapeutic discovery.

Keywords: Artificial Intelligence (AI), Drug Repurposing (Drug Repositioning), Systems Pharmacology, Precision Therapeutics (Precision Medicine), Network Medicine

Introduction

Pharmaceutical research and development are at a deep inflection point, and its own success history is stretched, and a confluence of technological revolutions has been rejuvenated. The historical mode of de novo drug discovery, which was previously the unquestioned driver of medical innovation, is becoming less sustainable and strategic

realignment is in favor of more productive approaches such as drug repurposing and precision therapeutics. This change is not only a matter of convenience but a necessity and the result has been a perfect storm of economic pressures, scientific complexity, and patient demand. It is artificial intelligence (AI), big data analytics, and systems biology thinking, which offers the necessary structure to bring these fragmented strategies to a cohering, transformative new approach to biomedicine [1].

The Expertise of Increased De Novo Drug Discovery and Schedule

Discovery of new therapeutic molecules has been the staple of modern medicine. This de novo process, in which a biological target is identified, and millions of compounds are screened and leads optimized and a candidate shephered through years of clinical trials is a wonders of human ingenuity. It is a monument of increasing danger, however, and of decreasing returns. The statistic that is quoted most about the cost of getting a new drug to the market being over 2.6 billion dollars and taking 10-15 years is not just a talking point; it is now a symptom of a structural crisis. It is a paradoxical law of Eroom (Moore law in reverse) that even with exponential changes in technology, the rate of new drugs approved each billion dollars spent on research and development has been declining about 50 percent every nine years [2-4].

The causes of such an unsustainable course of action are complex. The low-hanging fruit of single and well-understood targets in diseases such as hypertension or infection, has been picked. Modern problems, such as neurological disorders, complicated autoimmune diseases, most cancers, have complex, poorly characterized biological networks in which the effects of the targeted regulation of a single target are sometimes inadequate or associated with unwanted side-effects that are not easily predictable. In addition to this, the regulatory threshold to safety and efficacy has been appropriately increased, hence requiring larger, longer and more complicated clinical trials. The attrition rate is also disastrous, with more than 90 percent of candidates who proceed to clinical testing lost, in the majority of the cases because of insufficiently high efficacy or unexpected toxicity. This risky model compels the pharmaceutical companies to focus on potential blockbuster medication to a large population of patients in the name of getting a payoff, unintentionally neglecting rare diseases and niche patient groups. The de novo pipeline, although it is still necessary to fulfill literally unmet needs, is therefore a bottleneck, a stressor to the finances and the creative capabilities of even the largest of the institutions [5].

Drug Repurposing: A Strategic Shortcut to New Therapies

Drug repurposing (or repositioning) has become an efficient and viable complementary approach in direct response to this bottleneck. It is the discovery of new therapeutic applications of existing drugs-compounds with established safety profiles, established manufacturing processes and in many cases, previously approved by the regulatory authorities. The benefits are undeniable: it will be possible to cut years of development timeline and save orders of magnitude, millions versus billions and even tens of millions. The fact that these compounds are de-risked, and have already passed Phase I safety trials, enables researchers to shortcut much of the preclinical toxicology and formulation effort, enabling them to quickly move to proof-of-concept in patients [6].

In history, successful repurposing incidents were accidental such as the finding of the use of sildenafil in the treatment of erectile dysfunction during its development to treat angina. It is an intentional systematic effort nowadays. The plan is especially powerful during crises, which is reflected by how fast dexamethasone and remdesivir were deployed during the COVID-19 pandemic. Nevertheless, there are challenges associated with repurposing. The apparent suspects of most diseases have frequently been subject to test. Hurdles that involve science are the ability to comprehend the new mechanism of action within a different disease setting and the appropriate group of patients. There are also serious commercial and legal challenges such as extension of the life of the patent, gaining regulatory acceptance of the new indication, and developing effective pricing and reimbursement programs of older, frequently generic drugs. Nevertheless, repurposing is an essential instrument of providing new drugs more promptly,

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and it is particularly applicable to underserved regions by conventional research and development [7].

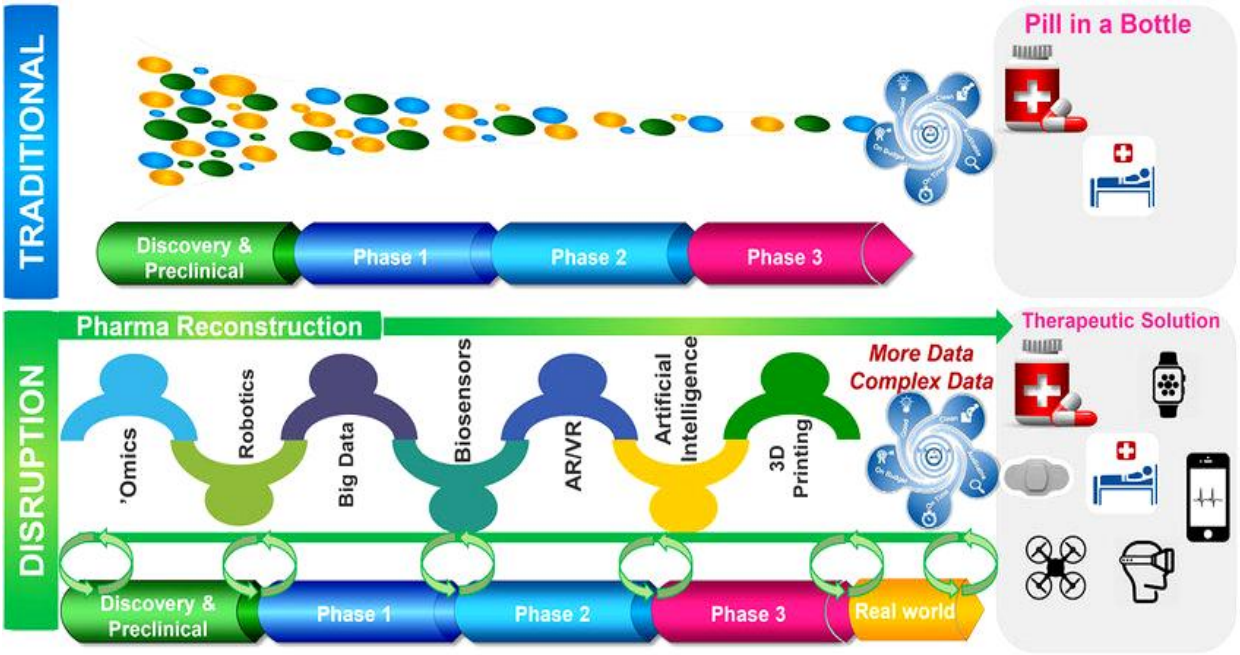

Fig: 1 Innovation in the traditional drug development paradigm moving from the randomized controlled trial to gain regulatory approval to an all-encompassing collection of real-world evidence in the context of a therapeutic solution

The Promise and Challenge of Precision Therapeutics

At the same time, medicine is experiencing a paradigm shift in its approach to a one-size-fits-all paradigm to one of precision therapeutics. This paradigm is steered by the revolution of genomics with an aim of aligning the right drug at the right patient at the right time, with reference to the molecular drivers of their disease. The pledge is two-fold, increased efficacy dramatically in those who will respond and avoidance of unnecessary cost and toxicity in those who will not. Repeated successes, including imatinib of BCR-ABL-positive chronic myeloid leukemia and a series of kinase inhibitors against cancers with targeted genetic mutations have confirmed the approach, producing near-miraculous results when narrowly-focused subpopulations are affected [8].

However, the achievement of a vision of precision medicine across all diseases is riddled with challenges. The majority of disorders do not resolve to one, simple genetic change. They are polygenic, environmental, and the complicated interactions of a variety of cell types in a tissue microenvironment. This biological heterogeneity renders the determination of the exact "molecular signature" of targeted intervention incredibly hard. Moreover, the very strategy of focusing on small groups of patients poses a business dilemma: with the patient groups getting stratified and narrowed down to smaller and smaller biomarker-specific segments, the old-fashioned blockbuster approach to the economy becomes unsustainable. This requires new models of drug valuation, development and access. Therefore, although precision medicine holds a future of extremely more effective and customized treatment, the way to achieve it fully is lost in a maze of scientific rigidity and economic re-pricing [9].

The Confluence of Forces: AI, Big Data in Biomedicine, and Systems Thinking

At the intersection of these three forces, which include the failed de novo pipeline, the expedient nature of reusing, and convoluted hope of accuracy, a revolution confluence is being created. The three are the artificial intelligence, big data in biomedicine and systems thinking, the catalysts. Combined, they offer the intellectual and technological framework that would help them to transcend the weaknesses of each

approach separately. Big data provides the fuel. We are now producing more multi-omic data (genomics, transcriptomics, proteomics, metabolomics) than ever, high-resolution medical imaging, electronic health records and wearable evidence in the real world and repositories of structured and unstructured scientific literature that are growing daily. This information contains the trends of sickness and treatment outcome, however it is too large and complicated to be analyzed without human input [10-12].

Machine learning and deep learning, in particular, are the engines that will decipher these patterns, with the help of AI. In the de novo discovery process, AI-based methods are able to forecast new drug-target interactions, generate new, optimized molecular structures using design (generative chemistry), and screen compound libraries in a manner that is both superhumanly fast and accurate. Repurposing AI can be used to mine disparate datasets- linking drug-induced changes in gene expression to clinically-related genetic signatures, or discovering unanticipated correlations between clinical outcomes in real-world data- to provide high-probability hypotheses of previously unknown drug-disease pairs. In the context of precision medicine, AI plays a crucial role in the combination of multi-omic data to deconvolute disease subtypes, discover predictive biomarkers, and align patient-specific traits with the most effective treatments [13].

This is supported by systems thinking: a shift in a reductionist one target one drug perspective of disease to a holistic definition of disease as a disruption in a complex biological network. AI-based models that have been trained on big data are the only models that can be used to model such networks. They can also forecast the ripple effects of perturbing a single node (with a drug), which can be used to propose combination therapies to complex diseases, determine biomarkers of network state, and to uncover previously unanticipated mechanisms of action of both new and old drugs. It is a system-pharmacology perspective that connects repurposing to precision medicine; it enables us to view how an approved drug would reorganize a maladaptive network in a particular patient group based on their molecular signature [14].

This intersection is forming a new, iterative flywheel R&D. Patient data that is analyzed using AI advances disease intelligence and makes new targets or repurposing candidates. These candidates are then also tested and generated new data provides feedback to enhance the AI models. The cycle boosts learning and minimizes expensive dead-enders. It facilitates precision repurposing - not only identifying a new disease to apply a drug, but also specifying the group of patients who will have it be useful. It also directs de novo discovery to targets and chemical matter with an increased chance of success in particular situations. Strategic drug repurposing has unique paradigms and practices, which are gradually coming together and getting amplified by the systems pharmacology integrative approach and the computational capabilities of artificial intelligence. The ancient classification of repurposing strategies is the activity-based strategies and in silico-first strategies. Activity-based approaches e.g. phenotypic screening start with a measurable biological phenotype e.g. a drug is causing an intended effect on a cell or tissue disease model then proceed backward to understand how it happens. This black-box empirically powerful but might be a sluggish process, is known as the function-first-path. On the other hand, in silico-first paradigm uses computational technologies to forecast repurposing opportunities prior to the lab experiment. It is a hypothesis-guided method, where large datasets are examined to determine new drug-disease relationships and give priority to the candidates to be experimentally validated, thus speeding up the discovery process and saving resources [15].

Under these streams of methodology, the strategic intent may be further differentiated into, therapeutic switching and target-based repurposing. Therapeutic switching Therapeutic switching can be the use of a drug in a totally different drug area than its initial indication, and often the use of a drug is based upon serendipitous clinical findings or similarity in symptom alleviation (e.g. an antidepressant in neuropathic pain). However, Target-based repurposing is based on molecular justification. It targets new diseases in which the primary pathogenic target or off-target profile of the drug is known. It involves a thorough knowledge of the

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polypharmacology of the drug i.e. its capacity to bind to various biological targets and the molecular architecture of the disease. It is at this point that systems pharmacology comes in as the critical integrative model and pushes the discipline out of the reductionist one drug, one target, one disease paradigm [16-20].

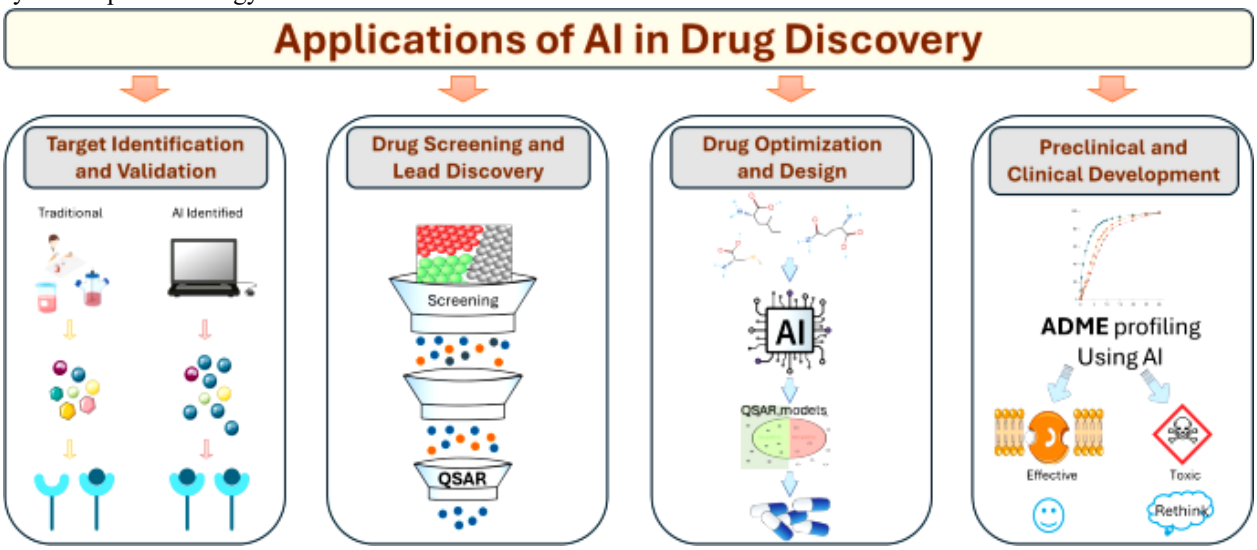

Fig: 2 AI-Enabled Systems Pharmacology Workflow for Drug Repurposing

The systems pharmacology is the next level of molecular target obsession to network medicine. It hypothesizes that diseases are due to the distortion of complex intracellular and intercellular networks and that the effect of drugs is due to the change in the state of this network. This perception replaces a drug as the key to one lock, but as a message that resonates within a biological circuit. It is highly facilitated by its major principles. First, it has a feature of polypharmacology, but not a bug, a systematic mapping of the drug interactions with the proteome. Second, it uses network analysis to simulate disease-specific interactomes, which identify key nodes and pathways whose regulation can be used to restore health. Third, it links molecular actions to phenotypic responses in cells, tissues and organisms, forming causal relationships between network perturbation and therapeutic outcome [21]. Through comparison of the overlaps between the drug and disease network signature, systems pharmacology can make rational predictions about which known compounds would have to push an ailing network back to health. This process is multi-scale and cannot be made without artificial intelligence and machine learning (AI/ML). AI/ML offers the computing toolset to identify significant trends in the high-dimensional, noisy biology data. Learning algorithms that are supervised are trained with labeled information, e.g., known pairs of drugs and diseases, to make predictions about new associations or group drugs according to their likely efficacy in treating a particular condition. Unsupervised learning methods, including clustering, discover latent structures without assigned labels, discovering new disease subtypes or grouping drugs based on their systems-scale effects, which may sometimes identify unexpected repurposing possibilities. Certain fundamental AI/ML methods have become fundamental. Deep Learning architectures are especially powerful: Convolutional Neural Networks (CNNs) are especially well-suited to process image-based data, such as high-content screening or histology, Graph Neural Networks (GNNs) are the only models that can directly operationalize systems pharmacology concepts, and Recurrent Neural Networks (RNNs) are uniquely well-posed to process sequential data, such as time-series gene expression. Natural Language Processing (NLP) is a process that searches through the large volumes of unorganized knowledge that is found in the scientific literature, patent databases, and clinical notes and finds, or extracts, the implicit relationships between things to produce novel hypotheses. Lastly, Knowledge Graphs are data models that combine all

of these disparate data streams, structured databases, network models, and NLP-extracted relationships into one unified queryable representation of biomedical knowledge. This enables complex reasoning, e.g. through the use of shared genes, pathways and comorbidities to link a drug to a disease and thus discover mechanistically-supported repurposing opportunities that would otherwise be obscured by siloed analysis [22-25].

The AI-Enabled Toolkit for Repurposing

The artificial intelligence approach to drug repurposing is fundamentally transformative: based on a synergistic base, a robust, multi-faceted data layer that drives advanced algorithmic models. This infrastructure is self-perpetuating with different biological and clinical information educating smart systems, who subsequently produce new knowledge, which improves our comprehension of the information, itself. Data layer is the fuel of AI engine, which brings together different streams of information into a knowledge space. Omics data: a multi-dimensional view on biological states, Omics data gives a comprehensive description of molecular profiles, a combination of genomics, transcriptomics and proteomics data. Such datasets display the molecular patterns of disease and the global effect of drug perturbations and are the basis of signature-based matching. Recovery discovery is based on the human pathophysiology through Clinical and Real-World Data (RWD), which is obtained based on the electronic health records (EHRs) and large-scale biobanks. RWD has connected molecular signatures with clinical phenotype, discovered treatment outcome at the population scale, and unexpected drug-disease course interactions, providing a treasure trove of real-world confirmation of computational hypotheses [26]. The known drug-target interactions, protein structures, and metabolic pathways are compiled into structured chemical and biological bodies of knowledge, thus, providing the established rulebook of pharmacology. These human-selected resources provide the ground truth of training algorithms. Lastly, Natural Language Processing (NLP) of literature mining unlocks the immeasurable, unstructured knowledge contained in millions of scientific papers and clinical records, and gets latent relationships and contextual evidence that might otherwise go undiscovered in structured databases. Such streams of data, when combined, form an interrelated substrate on which computational operations can be performed. In order to derive meaningful hypothesis concerning repurposing out of this data deluge, a hierarchy of algorithmic approaches and models is used. The signature-based techniques, like the gene expression connectivity mapping (an example of which is the LINCS project), compare the transcriptional fingerprint that a drug induces to the fingerprint of a disease condition. The fundamental idea is that a signature drug which is antithetical to a disease signature (negative association) is a candidate therapeutic that provides a potent, high-throughput screening paradigm in silico. The principles of systems pharmacology are operationalized using network-based methods. They superimpose drug and disease data on complex protein-protein interactions, signaling pathways, and metabolism reactions. These models can rank drugs in terms of their network distance to a disease and prioritize those that interact with neighboring or central nodes of the network by identifying overlapping sets of nodes, the disease module, and can rank drugs based on their network distance to the disease, giving those with neighbors or neighbors a higher priority [27].

Machine Learning predictors are more direct and inference based. Classifiers and regression models are trained on known examples to learn the intricate relationships that are used to predict new drug-target interactions (DTI) or drug-disease associations (DDA), and typically take into account features of chemical structures, protein sequences, and phenotypic data. This is greatly boosted in Deep Learning architectures. GNNs are singularly efficient at modeling the intrinsically relational data of biological systems, reasoning about meaningful representations of molecular structure (drug structures) and of enormous interaction networks. Transformer models, known to be successful in NLP, learn and process biological sequences (e.g., protein amino acid chains), as well as large volumes of scientific text, producing contextualized embeddings that learn rich semantic relationships [28].

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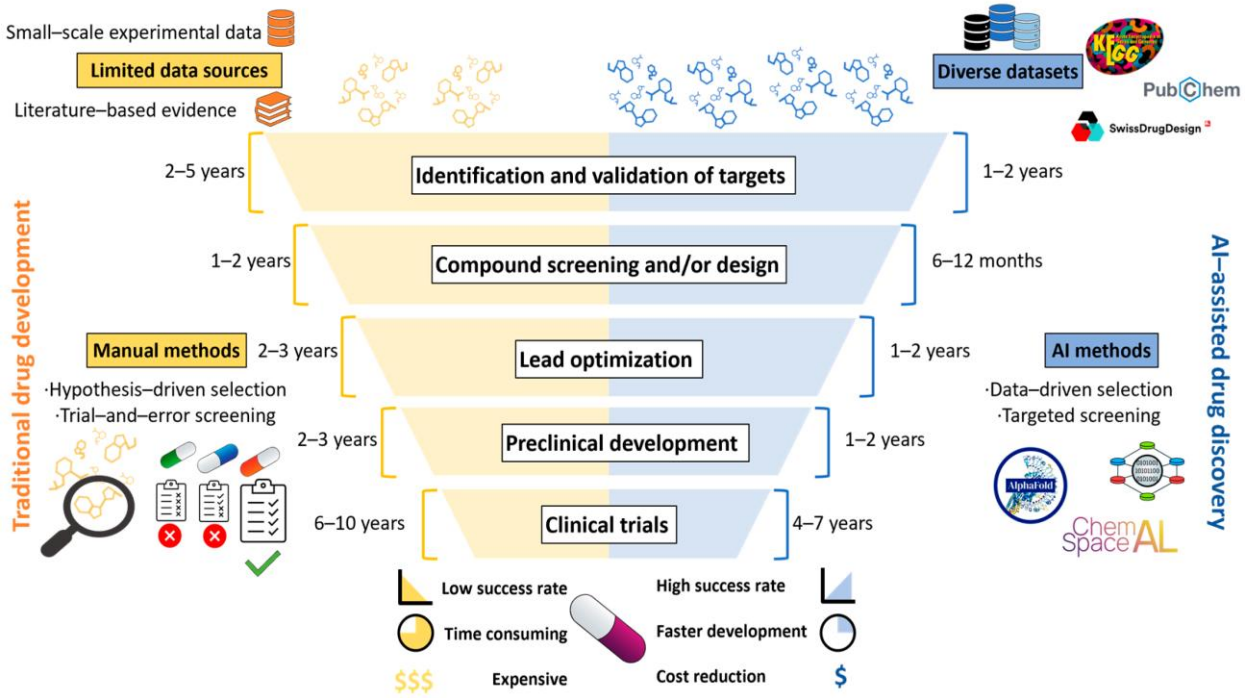

Fig: 3 The evolving landscape of AI-assisted drug discovery. The integration of AI-driven approaches can potentially revolutionize each stage of the process, leading to accelerated timelines, reduced costs, and improved success rates

Knowledge graph embeddings represent the best point of data integration. In this case, drugs, diseases, genes and side effects, and their associations (treats, inhibits, associates_with) are combined into a huge heterogeneous graph. Then AI models are trained on the low-dimensional (vector) representations (embeddings) of each entity, and the learners are placed in a mathematical space where geometrical relationships (such as proximity) are represented with biological or pharmacological relationships. This allows complex multi-hop inference and hypothesis learning- such as the inference of a new drug-disease relationship by walking through common targets or comorbidities. Lastly, the generative AI transcends to creation instead of prediction. Although it is mainly seen in de novo drug design, in repurposing it can be applied to optimize existing drug structures to new target profiles or, of greater importance, to design rational combination therapies by computing the synergistic network effects of two or more drugs [29].

Implementing the Systems Pharmacology Pipeline

The drug repurposing integrative AI workflow is considered a paradigm shift in that serendipity is replaced by systematic, hypothesis-based discovery. This pipeline starts with accurate definition of problems and data curation, where heterogeneous data of the real world, genomics to electronic health records, are combined and harmonized. This drives development of multi-scale systems to model the biology of disease in molecular, cellular, tissue, and organismal scales, to form a digital twin of disease pathophysiology. These models are then interrogated using AI-driven inference, and the priorities of drug candidates are their prediction of the ability to reverse or modulate the disease network signatures. Lastly, in silico validation revises these predictions with mechanistic simulations e.g. docking experiments or network perturbation experiments to clarify a candidate putative mode of action prior to the expensive wet-lab experiments [30]. This framework has been found to be helpful in wide-ranging therapeutic sphere. It complements non-oncology drugs with tumor genomic vulnerabilities in oncology. In rare diseases, it makes use of limited patient information by using models constructed on common pathway biology. Network medicine methods have revealed new targets in network maps of protein interactions in complicated neurological

diseases. The COVID-19 pandemic clearly illustrated how quickly this strategy can be implemented where AI platforms in a short period of time screened thousands of already available drugs to identify potential antiviral and anti-inflammatory agents that could be subjected to clinical trials [31-33].

Nevertheless, there exist serious obstacles to the massive implementation. Challenges in data, such as data bias, noise, and silos, reduce model resilience, and strict compliance with the principles of FAIR (Findable, Accessible, Interoperable, Reusable) is required. Algorithms do still have problems (such as the so-called black box problem), where explainability is lacking, and it is harder to understand the mechanistic interpretation, and that is why Explainable AI (XAI) is needed. Moreover, the generalizability of a model is usually a problem outside of the training data [34]. The most daunting one is the translational gap: an in silico prediction would have to cross the valley of death to be in vivo and clinical validated. This process is made difficult by non-standard regulatory approaches to AI-informed repurposing, ambiguous intellectual property environments around ancient drugs, and dis-incentive economic incentives of drug companies. Therefore, although the idea of AI-driven repurposing is a powerful instrument, it completely depends on the ability to address these combined scientific, technical, and translational obstacles [35].

Conclusion

Artificial intelligence and systems pharmacology are coming together to signify a critical evolution in the field of research in biomedical studies. Such synergy turns drug repurposing into an endeavor that is sporadic and uncoordinated into a systematic and scalable driver of accuracy therapeutics. The systematic prediction of how known drugs could restructure diseased biological systems in patient cohorts can now be done by building multi-scale network models and using state-of-the-art AI inference algorithms. The paradigm, which is known as preciseness repurposing, solves both problems of therapeutic innovation directly: to deliver with increased speed, and to increase the personalization. The AI-enabled toolkit, which is based on connectivity mapping, graph neural networks, knowledge graph reasoning, and other tools, is a potent way to come up with high-confidence hypotheses as demonstrated by applications in oncology and pandemic response. The workflow reduces the original discovery schedule by a significant factor, and eliminates the risk to clinical validation. However, there has been consistent obstacles on the way to the bedside of a patient since the in silico prediction. Existence of biomedical data quality and interoperability, lack of transparent regulatory and financial routes of repurposed generics, and interpretability of complex AI models are significant impediments to translation. The future development thus depends on the interdisciplinary cooperation. It needs to be guided by the principles of FAIR data, construct answerable AI (XAI) systems to build biological understanding, and actively participate in dialog with regulators to influence adaptive approval routes.

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