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R E V I E W A R T I C L E

Pharmacy Research Translational and Transformational

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A B S T R A C T
One important challenge in modern drug discovery is to accelerate the search for new and more potent therapeutic molecules but in a more assertive manner as thus far, conventional approaches are extremely costly, time consuming and largely ineffective. Pharmaceutical companies have spent billions of dollars in development but only a small percentage of candidates have made it to the market. Novel artificial intelligence algorithms provide an alternative route for a more comprehensive search of candidates in already available and large databases of pharmaceutical compounds. Also, those algorithms reduce the number of experiments needed *in vitro* and *in vivo*, given that only the most promising candidates are further analyze. A hub for bench-to-bedside-to-community is required for conducting the pharmaceutical research has towards more efficient applied outcomes improving public health. This requires a structured, well-organized, reproducible and continuous relationship between three main backbones of translational research i.e. bench-side, bedside and community.
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A R T I C L E I N F O

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C O N T E N T S

1. Introduction

The development and subsequent market penetration of new pharmaceuticals is a critical yet time consuming and expensive process that has increased in cost by nearly 150% over the last decade. In 2016, the development of just one medicine was estimated at around $ USD 2.6 billion. This is mainly attributed to the costs of pre-clinical and clinical trials where ethical issues and complications are encountered very often. As a result, only 10% of the pharmaceuticals that reach trials finally obtain FDA approval. For these reasons, such large investments have often limited the development of drugs for medical conditions where the niche market is not sufficient for a payback in a reasonable time frame. Even for some molecules of urgent need such as the antibiotics, where resistance is increasingly worrisome worldwide, there has

been an stagnation in the discovery of alternative candidate molecules for over a decade[1-9]. As a result, these issues in the discovery and production of pharmaceuticals have been seen as an opportunity to explore new approaches that combine both experimental and computational routes to accelerate the development. In this regard, some of the most successful experimental approaches include soil-dwelling, Rule of 5 (Ro5), genomics, proteomics, phenotypic screening, binding assays to identify relevant target interaction, turbidimetric solubility measurements and high throughput solubility measurements. Despite the progress, such approaches still rely on large investments in sophisticated infrastructure for automated manipulation of samples and data collection and processing. The developed algorithms still lag behind in precision and effectiveness and the obtained candidates might require considerable experimental testing. This combined approach is therefore leading to the repurposing of known molecules for new and more potent treatments, which is attractive for both companies and the patients. To reduce the time for screening and implementation of new therapeutic candidates even further, recent advances in artificial intelligence (AI) have provided more effective search algorithms that rely on the capacity to model relationships between the variables, which can also be trained to discover patterns in significantly large data sets simultaneously. Machine Learning-based algorithms have been particularly useful for improving drug discovery because they can analyze large data sets and learn the optimal representation for specific tasks rather than using hand-craft fingerprints, which are difficult to achieve otherwise.

Moreover, computational techniques such as Support Vector Machines (SVM) and Random Forests (RF) have been successfully applied for the design of pharmaceuticals with high specificity and selectivity, and improved physiological behavior in terms of important parameters such as circulation times, bioavailability and biological activity, toxicity and potential side effects[10-15]. These developments have been enabled by the availability of large public databases with information about the physicochemical and biological properties of pharmaceuticals. With this information it is possible to train deep learning models, which allow virtual screening over large data sets by means of efficient optimization algorithms and new computational capabilities. The main result was the identification of the antibiotic potential of halicin, which for the first time allowed the successful re-purpose of this molecule fully *in silico*. Halicin was originally researched for the treatment of diabetes due to the inhibition potential of the enzyme c-Jun N-terminal kinase but was abandoned because of low performance. This finding provides remarkable evidence for the notion that AI is a suitable route for the screening and eventual development of new drugs. Moreover, it offers the opportunity of a reduction in both the required investment for development and the potential risks to be undertaken in pre-clinical and clinical trials. Finally, it is possible to assure that from the beginning of the development, candidate molecules comply with requirements imposed by regulatory frameworks in terms safeness and reliability[16-25].

The current global COVID-19 pandemic is a compelling example of the urgent need for automating drug discovery, as this situation is the result of a novel coronavirus (SARS-CoV-2) capable of infecting humans at an extremely fast pace. To respond to this contingency, novel antiviral treatments and vaccines need to be developed in an extraordinarily short time. In this regard, according to the experts and even with the unprecedented resources allocated by governments, the shortest possible period for developing and deploying a COVID-19 vaccine is of about eighteen months. The European Union has raised $ 8 billion for collaborative development and universal deployment of diagnostics, treatments and vaccines against SARS-CoV-2. This is also the case of the U.S. and German governments, which are planning to invest in vaccine and treatments development and distribution over $ 2 billion and $ 812 million, respectively.

The developments in the field of computer vision to the critical task of active molecule prediction, which mainly involves the estimation of whether a molecule is able to bind to particular membrane receptors. Starting from the publicly available AD Dataset, we formalized active molecule prediction as a detection problem for which we designed an experimental framework that allowed us to evaluate results with the aid of normalized Precision-Recall curves. According to our newly proposed framework, the state-of-the-art technique only performs with a 1% efficiency, however, it was reported to show an AUC score of 52%. In search for a superior performance, we developed an algorithm based on deep learning for active molecule prediction, which we called PharmaNet[26-29].

PharmaNet was designed on the basis of natural language processing (NLP) techniques given that in this case the most important information lies in the sequence of each of the elements. Consequently, we implemented recurrent neural networks (RNNs) as the baseline for PharmaNet due to their demonstrated performance in problems involving language. Specifically, we considered a Gated Recurrent Unit (GRU) cell as it enables the analysis of atom sequences in an information flow direction that finalizes in the current element by analyzing the ones before it. These architectures have been used previously explored for similar tasks such as those required for property prediction and the generation of molecules according to properties of interest. For instance, Marwin et al. trained Long Short-Term Memory (LSTM) cells to learn a statistical chemical language model for the generation of large sets of novel molecules with similar physicochemical properties to those in the training set. The LSTM network receives as input a canonical Simplified Molecular Input Line Entry System (SMILES) representation of the molecules[30-25]. The theoretical benefit of translational research has been previously described. For translational research to be successful, a two-way dialogue between scientists and

clinicians is necessary, to foster cooperation towards common goals and the setting of complementary strategies, whereby work in one area informs efforts in the other. Translational research enables researchers to capitalize on recent technological breakthroughs and advances in basic sciences, such as the mapping of the human genome, the availability of techniques such as proteomics and metabonomics that enable the detection of small changes in tissue composition, and improvements in imaging platforms that enable a better understanding of the functional changes in normal and disease states. This is particularly relevant with unprecedented drug targets; discarding ineffective mechanisms early on enables more efficient use of resources and better-focused efforts on targets that are more likely to deliver effective medicines[36].

Target biomarkers:

Target biomarkers are measures of direct pharmacological effects that result from interaction with the target receptor, enzyme or transport protein. Because they are not linked to a specific disease or condition, they are useful, regardless of the indication being evaluated. Proof of pharmacology and building knowledge of dose– response with new chemical entities, it is important to define the pharmacologically active dose range before embarking on large proof-of-concept (POC) studies. This particularly applies to unprecedented drug targets, where it is important that the efficacy hypothesis is adequately tested. By conducting the POC study using doses known to display the appropriate pharmacology, appropriate decisions whether to proceed or not can be made on the drug target rather than just an individual compound. In some instances, the upper end of a pharmacological dose range can be characterized by the emergence of dose-limiting side effects related to that drug class. Doses up to and including the maximum tolerated dose can then be studied in POC studies to determine the therapeutic window. With more selective compounds, however, drug-class side effects might represent a loss of selectivity or extra-pharmacological effects. In this case, the therapeutic margin can be defined by demonstrating the dose ranges showing the selective pharmacological activity relative to the appearance of nonselective side effects[37-38].

Peripheral drug targets

Soluble biomarkers can be used to determine a pharmacological response to various drug classes. This approach is particularly relevant for enzyme inhibitor mechanisms, where measurement of the substrate provides direct evidence of pharmacological effect. Neutral endopeptidase is a metallopeptidase enzyme involved in the degradation of several endogenous peptides, including atrial natriuretic peptide (ANP), brain natriuretic peptide, enkephalins, bradykinin, angiotensin II and endothelin 1. Candoxatril is the orally active prodrug of candoxatrilat, a neutral endopeptidase inhibitor (NEPi) assessed as a treatment for hypertension and congestive heart failure. In rodent studies, candoxatril causes a dose-dependent increase in plasma and urinary ANP levels and an associated rise in plasma and urinary cyclic GMP (cGMP), the second messenger mediating the ANP effect[39-40].

CNS drug targets

Drug targets in the central nervous system (CNS) present parti-cular challenges because it is important to show that pharma-cological activity is due to the CNS drug–target interaction rather than a peripheral effect. For CNS drug targets, it is possible to show pharmacological effects in different ways: (i) peripheral effects, such as the inhibition of prolactin secretion by the anterior pituitary with dopaminergic drugs [10]; (ii) physiologi- cal effects due to central drug activity, such as altered sensor-imotor processing and motor reaction time seen with dopaminergic drugs; and (iii) brain imaging techniques. Brain imaging technology platforms such as functional mag- netic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) are being investigated to assess their usefulness in characterizing central pharmacody- namic effects. For example, fMRI [blood oxygenation level- dependent (BOLD) technique] has been used to characterize the pharmacological effect of dopamine antagonists in preclinical and clinical studies. Sulpiride, an atypical antipsychotic agent used to treat schizophrenia, causes bilateral increases in BOLD signal intensity in the frontal cortex following single dose administration in anaesthetized rats[41-42].

Disease-oriented biomarkers

Disease-oriented biomarkers are preclinical or clinical measures of efficacy that are specific to the indication of interest. We use this term to include all measures that can be used to predict a desired outcome in a study using registration endpoints such as questionnaire or diary data to record symptom relief in an outpatient study design. The following examples illustrate the translation of preclinical and clinical biomarkers. The use of genomics in drug development one of the key factors in developing improved medicines is a better understanding of the molecular basis of the complex diseases we treat. Genetic association studies have a role in define the pathways linked with disease processes and have yielded several novel drug targets, as exemplified below. Pharmacogenomics can also be used to streamline drug development by characterizing the genetic polymorphisms of a given drug target and using these data to explain any variability in drug response or to select an enriched patient population for efficacy studies. The availability of DNA samples from large phase III or IV studies enables whole-genome association studies to be conducted, widening the horizon for novel target identification. Candidate gene linkage studies Clinical observations could lead to candidate gene studies that can identify polymorphisms associated with particular disease phenotypes. This, in turn, can lead to new drug target being identified. This is illustrated by the discovery of CCR5 antagonists for the treatment of HIV infection. It was observed that certain human chemokines can prevent HIV from entering T lymphocytes and that some individuals repeatedly exposed to HIV-1 remain uninfected. Moreover, CD4+ lymphocytes and macrophages from these individuals were shown to be relatively resistant to HIV-1 infection in vitro. Genetic analysis showed that this was associated with a homozygous defect (32 base pair deletion) in their CCR5

gene, leading to a lack of expression of the CCR5 (C-Cchemokine receptor-5) receptor on the cell surface of the CD4+ T lymphocytes [28]. Subjects who are heterozygous for this deletion have partial resistance to infection, and individuals who are HIV-1 seropositive have a slower decrease in their CD4 T-cell count and a longer AIDS-free survival relative to those with the wild-type CCR5 gene. These findings led to further work to characterize the role of the human CCR5 receptor, and resulted in a new class of anti-HIV therapy. The search for a selective CCR5 antagonist resulted in the development of maraviroc, a new compound that is safe and efficacious and is now in late-stage development for HIV with encouraging results to date. This drug discovery program reflects the use of applied genetics to find novel targets, in this case a host target that is expected to confer a degree of immunity against HIV-1 infection[43-47].

Optimizing drug response

Besides linkage studies that might yield novel targets, pharmaco-genomics can also be used to develop personalized medicines –where the therapy is targeted at individuals most likely to respond. This is particularly true for several recent oncology approaches. For example, tumour analysis from women with breast cancer identi-fied that 30% of patients had tumours that overexpressed the HER-2/neu oncogene. These women were found to have a poorer prognosis, with HER-2/neu overexpression associated with greater degree of lymph node metastasis, reduced disease-free survival and shorter life expectancy. This gene encodes a receptor related to the epidermal growth factor receptor (EGFR) family. Studies in a xenograft mouse model with implanted human tumour overex-pressing HER-2/neu showed that a monoclonal antibody against this receptor slowed tumour growth. These findings led to the development of the HER-2 monoclonal antibody trastuzumab (Herceptin1), and clinical studies confirmed its efficacy in women with breast cancers overexpressing this receptor. This anti-body is now licensed as a treatment for patients over expressing HER-2, which constitute 30% of breast cancer patients.

Indication discovery

Translational research has an important role in identifying new indications for established therapies a process we have termed ‘indications discovery’. New drug target hypotheses can be generated through preclinical experiments on novel target organs or can result from clinical observations, such as side effects or additional pharmacological effects beyond those expected from efficacy in the main indication. Sildenafil, a selective PDE5i, is a good example of a drug assessed for one indication but was subsequently licensed for a different one. This drug was originally intended for the treatment of angina as an alternative to nitrate therapy. However, its relatively short half-life and haemodynamic interaction with nitrates led to discontinuation of development in this indication. Following chance observations of enhanced penile erections in healthy volunteers, its potential as a treatment for MED was assessed in an animal model of erectile function and in clinical biomarker studies. This led to the drug being developed and subsequently licensed as the first effective oral treatment for this condition.

2. Conclusion

Translational research can benefit for drug discovery and development. Pharmacogenomics lead to the discovery of new mechanisms as well as help to define patient subpopulations with exaggerated drug response, thus enabling enriched clinical trial designs and the potential for personalized medicines. These measures of pharmacology used to determine the active dose range and hence aid dose selection for efficacy testing and enable appropriate decision making in POC studies. Translational biomarkers are particularly useful in linking the efficacy seen in preclinical studies with potential therapeutic benefit. Translational biomarkers useful for identifying novel indications for late-stage compounds or established drugs, opening up new markets for molecules that might have an established safety profile in the main indication. Translational research is a rapidly developing area that offers great promise, and this article describes how its successful application can reduce the cost of research and development and assist in the delivery of important new medicines of the future.

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