A novel pipeline for drug discovery

Method · November 2022

DOI: 10.13140/RG.2.2.27116.64649

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A novel pipeline for drug discovery

By The Prepaire Team

Introduction

Foreword

Driven by rapid advances in computer hardware and publicly available datasets over the past decade, deep learning has achieved tremendous success in the transformation of many computational disciplines. These novel technologies have had a considerable impact on computer-aided drug design as well, throughout all stages of the development pipeline.
A flexible toolbox of neural architectures has been developed that is well-suited to represent the sequential, topological, or geometrical concepts of chemistry and biology; and that can either discriminate existing molecules or generate new ones from scratch.
Prepaire is using a proprietary algorithm based on Convolutional Deep Neural Networks (CNN) and Generative Adversarial Networks (GANs) to build reactive chemical and biological fitting models enabling the identification ligands to protein targets, protein-protein interactions, generating molecular structures with specified properties combining both functionality and drug ability, as well as preparing synthetic data for specific drug discovery and personalized treatment. Convergence of CRISPR, IPS and Genome sequencing has established a new clinical utility for disease treatment and prevention. Prepaire is enabling precision medicine with intending to integrate whole-genome sequencing with deep phenotyping to data-visualize clinical IPS panels. The platform combines the in-silico prediction with high throughput wet-lab validation in an iterative cycle that empowers continuous improvement and increases efficiency, accuracy, and reliability which are critical to drug R&D.
concurrence of state-of-the art Artificial Intelligence and chemical retrosynthesis has enabled companies like Prepaire to systematically integrate target identification, validation, lead discovery, optimization, drug synthesis, and preclinical testing into a single platform. AI accelerated drug discovery, allowing for a fast-track discovery and repurposing of the existing molecule, intelligent clinical design, and coupled with in-house manufacturing. Many of the bottlenecks in drug discovery and development could be alleviated if only we could predict earlier in the disease process which drugs are likely to work and for which patients.

These platforms accelerate the drug development process by integrating disease models spanning in-vitro cellular systems, and in-silico machine learning models. These models, combined with robotic chemical systems capable of navigating a chemical space based on learned general associations between molecular structures and reactivity, it is possible to identify and predict a range of high yield and highly efficient chemical reactions and products that ultimately lead to the discovery of new molecules or new uses for already existing molecules that can eventually become new speciality treatments. We use artificial intelligence with DL in all accessible formats, including neural, GANs, NLP, supervised, semi-supervised and unsupervised learning to build procedures and pipelines that will become key enablers for medical compliance and clinical approval whilst ensuring IP protection throughout the whole drug discovery process.

The successful outcome of these efforts will accelerate all steps of drug discovery and development, including target discovery, lead optimization, toxicity assessment, and trial design.

Historic overview

Modern drug discovery is a complex scientific area involving many different scientific disciplines ranging from chemistry, pharmacology, biology and medicine to applied mathematics, computational science, and artificial intelligence. From an historical perspective, drug discovery and prophylaxis have driven the evolution of medicine.

Even though providing a comprehensive history of medicine is not the objective of this short white paper, we believe that the following examples are illustrative about the origins of experimental biological and medical research.

During the second half of the 19th century, an obstetrician at the Vienna General Hospital, Ignaz Semmelweis, took a revolutionary approach to preventing death caused by puerperal fever. His department had an especially high mortality rate (18%) and he discovered that it was common practice for students to examine pregnant women directly after pathology lessons. By that time hygienic measures such as hand washing, or surgical gloves were not customary practice.

Semmelweis deducted that child bed fever was caused by *"decomposed animal matter that entered the blood system"*[1]. As a matter of fact, he succeeded in lowering the mortality rate to 2.5% by introducing hand washing and with a chlorinated lime solution before every gynaecological examination. Later, the surgeon Joseph Lister managed to introduce the general procedure of instrument sterilization in medical practice. The methods initiated by Lister are not very different from those applied today.

Arguably, the most important breakthrough regarding infections and infectious diseases is due to the works of Luis Pasteur. Pasteur discovered that tiny cell organisms caused disease and termed these organisms as **bacteria**. He also made the significant discovery that bacteria in fluids could be killed by heating. Pasteur also discovered that the administration of weakened chicken cholera bacteria immunized the animals against this illness and, as such, paved the way for the development of the first vaccines.

The circle for treating the first bacterial infections is marked by the discovery of the synthetic prodrug salvarsan and neosalvarsan by Paul Ehrlich in 1910 to treat *Treponema Pallidum*, a pirochaete bacterium that causes the sexually transmitted disease syphilis. Inspired by his own discovery of dyes that specifically stain bacterial cells, Ehrlich started screening a panel of synthetic drugs and subsequently identified salvarsan[2].

This short historic overview shows that the first 100 years of modern drug discovery were largely target and mechanism agnostic and primarily driven by chemocentric approaches (i.e. approaches based on a specific compound class which served as starting point for further optimization). These chemotypes were either discovered through ethnobotanical knowledge or derived from natural ligands and substances. Of course, serendipity was a key success factor for the early beginnings of modern drug discovery.

Background and methods

In 2006 there were about 1500 unique drugs acting through more than 350 different mechanisms[3]. Today, the portal drugbank.com features more than 12000 compounds acting on more than 48600 pathways. This exponential increase in available treatments and the understanding of their underlying mechanisms of action stem from the significant advances in cell biology, combinatorial chemistry, and artificial intelligence.

Target-based drug discovery has enabled a great expansion of chemotypes and pharmacophores available for the pharmacologist. New techniques like high-throughput screening (HTS), fragment-based screening (FBS), and crystallography in combination with molecular modelling, and combinatorial and parallel chemistry have created a considerable

[1] Semmelweis I., Etiology Concept and Profilaxis of Childbed Fever, University of Wisconsin Press, 1983.
[2] Eder J., Herring P.L., Ternds in Modern Drug Discovery, Springer, 2015.
[3] Overington JP, Al-Lazikani B, Hopkins AL (2006) How many drug targets are there? Nat Rev Drug Discov 5(12):993–996

diversity of chemical lead structures. This diversity can be used as a source for tool compounds to study unexplored biological space and find new drug targets or for phenotypic screening[4].

Compound collections used for high-throughput screening are typically based on chemically diverse molecules as well as on chemotypes from previous projects and can reach a size of 10–20 million substances. Compound collections can reach a size of 1–2 million substances. The compounds are screened in biological test systems, and hits, once validated by independent biochemical or biophysical methods, are further optimized to become drug candidates. The compounds are screened in biological test systems, and hits, once validated by independent biochemical or biophysical methods, are further optimized to drug candidates and clinical trials started with these compounds[2].

A specific variant of HTS is fragment-based screening. Fragment-based HTS is based on the idea that smaller molecules (usually with molecular weights below 250 Da) are better suited to sample the chemical space because it is much less complex for small molecules than it is for bigger ones [2]. For example, this approach has been recently applied to find pyrimidone inhibitors targeting the Chikungunya virus nsP3 macrodomain [2].

Today, the X-ray crystal structure of a drug target's binding pocket can now be solved early in the Discovery process, making it possible to combine the different lead-finding approaches into an integrated strategy. In this way, lead finding today may no longer be seen as a one-off activity at the beginning of a discovery project but rather as part of compound optimization. With this structural information, it is often possible to combine the different lead-finding approaches into a broader, integrated lead-finding strategy[5].

With these approaches, data from various omics sources such as genetics, proteomics, and metabolomics is integrated to unravel the intricate working of systems biology using machine learning-based predictive algorithms on available drug libraries. Machine learning methods offer efficient techniques enabling the discovery of new treatment targets. These biomarkers have the potential to help in accurate disease prediction, patient stratification and delivery of precision medicine[6].

AI methods in drug design

Despite the exponential growth in available healthcare data, only a small percentage of this newly created data is kept, as just 2% of the data produced and consumed in 2020 was saved and retained into 2021. In line with the strong growth of the data volume, the installed base of storage capacity is forecast to increase, growing to a compound annual growth rate of 19.2% between 2020 and 2025. Only in 2020, the installed base of storage capacity reached 64.2 ZB[7]. It is this exponential increase of available data combined with the growth in computation capacity that has driven the development of smarter electronic health records, and integration platforms as well as the ***Deep Learning Revolution***, which has taken the healthcare and pharma industry by storm by developing more efficient and effective models for diagnosis, patient management and treatment development.
Nevertheless, issues and pitfalls of drug development remain the same when it comes to drug development. It is a well-known fact that from the identification of a therapeutic compound, it takes roughly 12 years of research and development to obtain market approval, and that is only if the drug succeeds[8]. This long lead-time results in shortened exploitation times before the feared ***'drug patent cliff'***. Moreover, only one in 1,000 (0.1%) of drugs that enter pre-clinical

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[4] Eder J., and Herrling P.L., Trends in Modern Drug Discovery, Handbook of Experimental Pharmacology, Springer, 2015.
[5] Nielsch U., Fuhrmann U., Jaroch S., 'New Approaches to Drug Discovery', Springer 2016.
[6] Reel P.S., Reel S., Pearson, et al., 'Using machine learning approaches for multi-omics data analysis: A review', Biotechnol. Adv. 2021.
[7] Statista.com 2022
[8] https://www.azolifesciences.com/article/Modern-Challenges-of-Drug-Discovery.aspx

trials will succeed to be tested on humans, and only one in five (20%) of those that enter in-human trials make it to approval [8] . While these numbers have improved, there is still much room for further improvement to optimize the drug discovery process [8].

Graphical models

Graphical models (GM) are a branch of machine learning, which uses graphs to represent a given domain problem. From a strictly mathematical point of view, GMs can be considered a generalization of different well-established machine-learning (ML) and Deep Learning (DL) models. For example, the Naïve Bayes' algorithm, the Hidden Markov Model, the Restricted Boltzmann Machine (RBM) and Neural Networks belong to GM.
Probabilistic graphical models combine both probability and graph theory. The probabilistic part performs its reasoning under measured uncertainty whilst the graph part models the dependency, mutual information or correlation between the different variables in our drug-development problem. These models become even more relevant when the model variables can be modelled as exponential families because it is possible to rigorously demonstrate the statistical dependency between these variables[9].
For the case of drug-discovery, GM are used to assess the dependency between drugs and protein targets and find new molecules like those showing a strong statistical dependency with a given target. It is this these molecules that can be either synthesized de-novo or repurposed should they belong to an already existing library.

Deep Learning

Deep Learning (DL) has taken the drug-discovery space by storm. To name a few of the most recent state-of-the-art applications, DL has significantly accelerated the drug-discovery process and contributed to global efforts to stop the spread of infectious diseases. Besides enhancing the efficiency of screening, the efficiency of screening antimicrobial compounds against a broad spectrum of pathogens, deep learning also has the potential to reliably identify new targets, drug candidates and assessing antibiotic resistance of bacteria. The efforts of Deepmind[10] and Meta[11] have recently unravelled the 3D structure of the known proteome.
DL has been successfully used for the identification of drug candidates against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) including Favipiravir[12], Atazanivir, Remdesivir, Kaletra, Enalaprilat, Venetoclax, Posaconazole, Daclatasvir, Ombitasvir, Toremifene, Niclosamide, Dexamethasone, Indomethacin, Pralatrexate, Azithromycin, Palmatine, and Sauchinone[13].

DL encompasses algorithms that abstract data by using multiple processing layers composed of complex structures or multiple non-linear transformations. Compared with the shallow machine learning methods, a deep learning algorithm is a process for automatic feature engineering. Deep Learning frameworks such as convolutional neural networks (CNNs), Graph Neural Networks (GNNs), and Transformers have been successfully applied in the fields of bioinformatics and biomedicine with excellent results.

A CNN is a specialized type of artificial neural network (ANN) that uses the mathematical operator of convolution in place of general matrix multiplication in at least one of their layers. A CNN consists of an input layer, hidden layers and an output layer. In any feed-forward neural network, any middle layers are called hidden because their inputs and outputs are masked by the activation function and the final convolution. In a convolutional network, the hidden layers include layers that perform convolutions. Typically, this includes a layer that performs a dot

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[9] Ribas V., Ruiz-Rodriguez J.C., Vellido A., Romero E., 'Sepsis mortality prediction with the Quotient Basis Kernel', Artificial Intelligence in Medicine, 2014.
[10] https://alphafold.ebi.ac.uk/
[11] https://esmatlas.com/resources?action=fold
[12] www.prepaire.com
[13] Zhang Y., Ye T., Xi H., Juhas M., and Li J., 'Deep Learning Drug Discovery: Tackling the Severe Acute Respiratory Syndrome Coronavirus 2', Front. Microbiol., 2021.
[9] James Collins, MIT.

product of the convolution kernel with the layer's input matrix. As the convolution kernel slides along the input matrix for the layer, the convolution operation generates a feature map, which in turn contributes to the output of next layer. This is followed by other layers such as pooling layers, fully connected layers, and normalization layers.

A GNN is a class of ANN designed for processing data that can be represented as a graph. The key design element of GNNs is the use of pairwise message passing, such that graph nodes iteratively update their representations by exchanging information with their neighbours.

A Transformer is a DL model that adopts the mechanism of self-attention, differentially weighing the significance of each part of the input data. Transformers are designed to process sequential data such as drug SMILES with applications towards tasks of drug-target binding, or the assessment of side-effects for drugs.

The Protein folding problem

The binding between a protein and a molecule underlies how many drugs, including antibiotics, work. Most antibiotics, like penicillin, are simply small molecules that bind specifically to bacterial proteins. By binding to their protein targets, these drugs can interfere with the normal functions of proteins in many ways, including competing against physiological substrates and inducing protein conformational changes that render proteins inactive[14]. For antibiotics, we want these proteins to be needed for the cell to survive, so that the drugs targeting these proteins would lead to bacterial death [14].
This paradigm works similarly for anti-cancer and anti-viral drugs, and there are also cases where inhibiting the activity of some protein might be beneficial to a cell [14].

In general, being able to measure the binding between a protein and a molecule tells you about how a drug works and is a critical part of any drug development process. Many cases in which a drug succeeds or fails can be informed by knowing the protein target (or targets). A common reason for drugs failing is that they turn out to have multiple targets, and this promiscuity is often associated with drug side-effects [14].

Advances in AI algorithms and training have led to the development of software, such as AlphaFold[15], that can accurately predict the 3D shapes of proteins given their amino acid combinations.
Molecular docking has evolved and improved over the past 40 years, and nowadays open-source (eg, AutoDock Vina[16]) and proprietary (eg, Schrödinger[17]) software are commonly used. Predicting drug binding is probably one of the most difficult tasks in biology: these are many-atom interactions between complex molecules with many potential conformations, and the aim of docking is to pinpoint just one of them[18].

AlphaFold has now predicted over 200 million proteins from their amino acid strings. Researchers hoped that building such a large database would allow scientists to develop treatments targeting specific proteins associated with diseases such as cancer or dementia. Coming up with such medicines may require you to know the physical structure of the protein, which is where programs like AlphaFold can be used [14].
Breakthroughs such as AlphaFold are expanding the possibilities for *in silico* (computer simulation) drug discovery efforts, but these developments need to be coupled with additional advances in other aspects of modeling that are part of drug discovery efforts. One of AlphaFold's main contributions thus far has been to provide a comprehensive resource of predicted protein structures that we can now use for docking [14].

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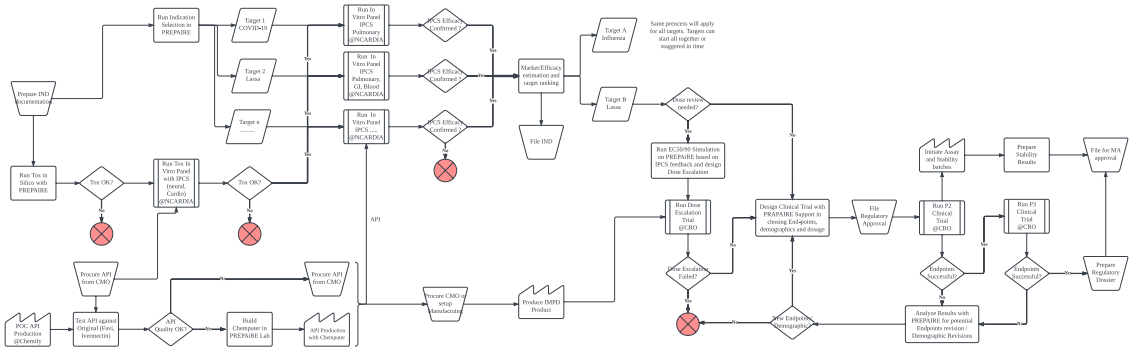
[14] https://www.theregister.com/2022/09/08/deepmind_alphafold_performance
[15] Jumper J., Evans R., Pritzel A., et al, Highly accurate protein structure prediction with AlphaFold, Nature 2021.
[16] https://vina.scripts.edu
[17] https://www.schrodinger.com
[18] https://www.salon.com/2022/09/24/no-ai-probably-wont-revolutionizedrug-development/

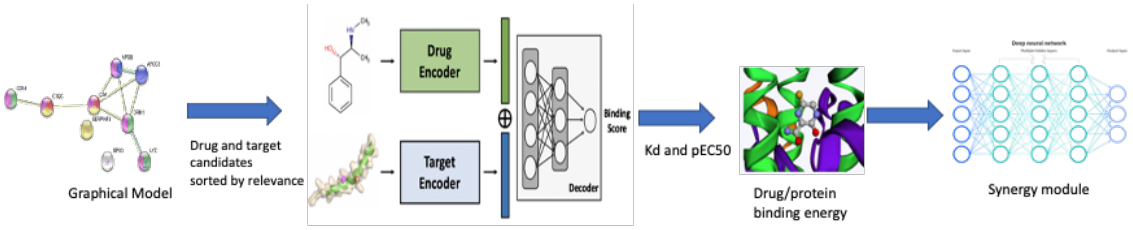
A new DL pipeline for drug discovery

In the current scenario of multiple potential viral threats, repurposing drugs for treating existing and potential new diseases offers the clear advantage to work with de-risked compounds. Working with existing drugs for new indications reduces the timeline to market, provides a clear risk profile and in addition leverages the existing manufacturing and CMCs data facilitating an immediate go-to-market in case of positive results. Repurposing can cut go-to-market from multiple years to months and costs by a 10x factor or more.

Concurrently the success experienced in the treatment of HIV and Cancer with combination therapies has driven pharma companies to replicate the approach also in other areas, by targeting multiple pathways in a synergistic or additive manner in to speed up recovery or improve recovery chances. The platform developed at Prepaire is perfectly suited for both tasks, empowering companies to create repurposed combination therapies in silico and obtain adequate IP protection before starting any in-vitro or in-vivo trial.



In this short paper we present an example of the application of GM and DL to drug repurposing in the Prepaire platform.



The first step in our pipeline consists in the development of a Graphical Model for the recommendation of drug candidates. In a first iteration of the Graphical Model, we assessed the dependencies between drugs and targets from DrugBank[19]. In the second iteration of development, this model is updated with networks and relationships from biosnap[20]. In this second iteration, particular attention has been given to the following networks and relationships:

1. Chemical-gene interaction network
2. Drug-target interaction networks
3. Disease-drug interaction network
4. Disease-function interaction network
5. Disease-gene association networks
6. Gene-function association network

[19] https://go.drugbank.com

[20] https://snap.stanford.edu/biodata/index.html

The figure below shows the neighbourhood map for a single drug from the developed Graphical Model.

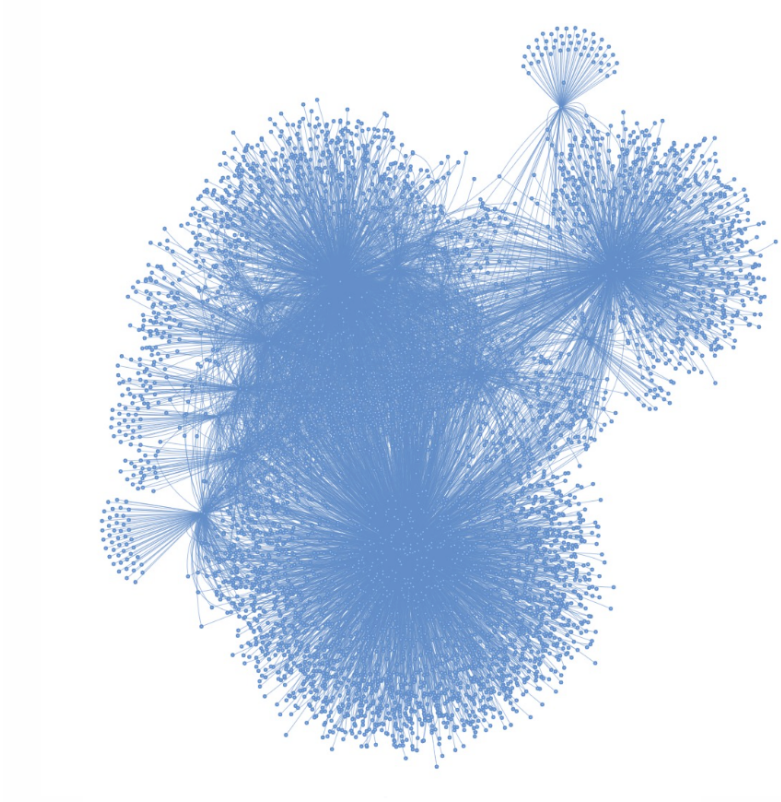


Figure 1: Neighbourhood map for Favipiravir

Our current Graphical Model design includes 4,000,000 edges and 175863 nodes out of which 16655 are drugs, 29984 proteins, 63962 biological functions, 144 Tissues, and 10120 genes. Finally, the different disease names and classifications have been filtered with the disease ontology[21] to decrease noise, redundant entries and, therefore, improve the relevance of the recommended drugs.

The figure below shows the pipeline for the recommendation engine based on our graphical model. On a first stage, we create a graph embedding that can be efficiently searched and provide a metric for the similarity between entities (cosine distance between embedding vectors and the Levenstein distance for names). The recommendation engine provides the ranked shortlist of the most relevant drugs from our graphical model.

[21] Disease-ontology.org

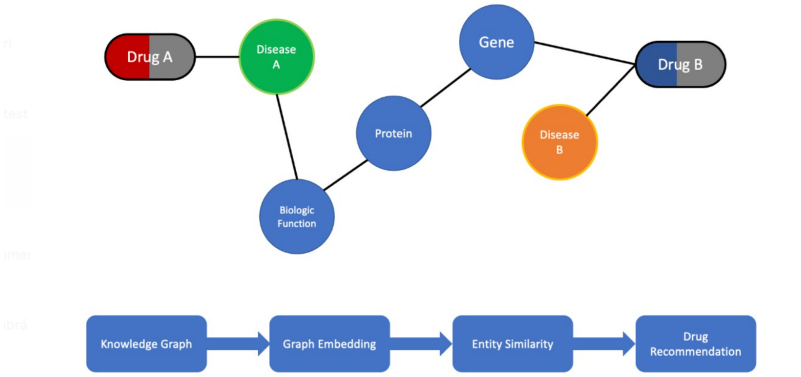


Figure 2: recommendation pipeline for drug candidates

The short-list from the recommendation GM is then processed with the drug-target interaction (DTI) module. This DTI module has been developed with two three-layered deep CNNs (1024 x 1024 x 512) and a learning rate of 0.0001. One CNN has been configured to predict pEC50 from the bindingDB[22] whilst the second has been configured to predict the log(Kd) from the same dataset. The inputs to this CNN have been encoded with an 8-layered Transformer (target) and another 3-layered CNN (drug). Data has been split into 80% for training, 10% for validation and 10% for testing. Both CNNs presented an MSE of 0.993, a Pearson Correlation of 78% and a concordance index of 80% on the complete SNAP dataset.

The synergy module comprises a 3-layered CNN with (512 x 512 x 256) and a learning rate of 0.001. This module has been trained with the drugcomb[23] dataset where 70% of data has been used for training, 10% for validation and 20% for testing. The synergy module presented an AUPRC of 74% with a cross-entropy loss of 11.23.

The drug repurposing pipeline outlined above has been applied to finding a combinatorial treatment for COVID-19 with Favipiravir.

Favipiravir is a broad spectrum anti-viral developed by Fuji Film Toyama and approved in 2014 against influenza. Due to its mechanism of action Favipiravir has been one of the first drugs to be introduced in the market for fighting against COVID-19. Favipiravir is approved in more than 20 countries and has been used on millions of patients worldwide.
Even with strong support of several meta-analysis4 and multiple clinical studies, the failure of some key studies in the United States5 has denied the drug the FDA approval. A post analysis of the failed trial has clearly pointed out some causes, including the potential of a wrong dosage due to the difference in BMI and metabolism between the original Japanese population and the American population involved in the trial.
In any case, Favipiravir remains one of the drugs used worldwide, that, at the right dosage, seems to be extremely effective against COVID-19 and viral infections caused by RNA viruses. Favipiravir is an off-patent drug with numerous generics in the market, especially in the south-east Asia, Turkey and India.

For this repurposing experiment, we have taken as a reference the nucleoprotein structure for the SARS-COV-2 virus as shown in the figure below. The preselected thresholds for a valid combination with Favipiravir have been set to a pEC50 < 2 log(μ Mol), a Kd < 6 log(n Mol), a Binding Energy < 7 kcal / mol and a synergy score > 80%.

[22] https://www.bindingdb.org/rwd/bind/index.jsp
[23] https://drugcomb.org/

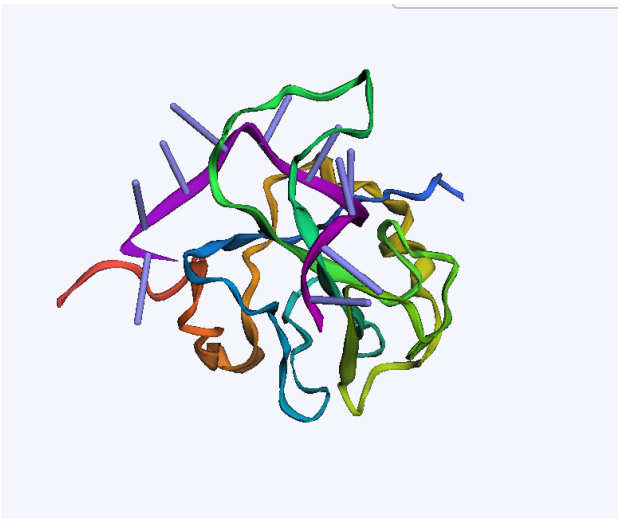


Figure 3: SARS-COV-2 nucleoprotein PDB 7ACT

Our search engine and recommendation module yielded 500 feasible molecules. Out of these 500 we short-listed the first 10 for which we present the main results in the table below.

Drug	Relevance	pEC50 log(μ Mol)	Kd log(nMol)	Binding Energy (kcal/mol)	Synergy
Favipiravir (reference)	74%	1.43	4.3	-4.95	n/a
Remdesivir	87%	2.24	6.12	-5.93	57%
Metenkefalin	82%	2.49	5.45	-7.16	58%
Opaganib	81%	1.79	6.36	-7.70	63%
Cutamesine	81%	1.69	5.63	-6.40	31%
Methoserpidine	79%	3.06	7.15	-7.17	80%
Methylthioinosine	79%	1.73	4.13	-5.34	44%
Ethyleniadiamine	79%	1.40	2.91	-2.99	75%
Moperone	78%	2.12	5.75	-7.66	64%
Razuprotafib	78%	1.77	4.13	-7.79	77%
Ivermectin	**78%**	**1.82**	**5.86**	**-9.52**	**82%**

Ivermectin is an antiparasitic drug approved by the FDA for intestinal strongyloidiasis and onchocerciasis, has been made popular by the fringe culture as a potential cure for SARS-COV-2. It is an off-patent drug provided by a wide range of manufacturers under different brand-names.

However, out of 32 clinical studies executed and completed with Ivermectin, none has resulted in a positive strong outcome for the drug. A particularly large trial involving more than 35001 patients in Brazil has strongly concluded that treatment with Ivermectin alone was not effective in providing any improvement in clinical outcomes for the patients.
At the same time, a meta-analysis2 on a subset of clinical trials has indicated the possibility of a certain potential effectiveness for Ivermectin against COVID-19, proposing the potential use of Ivermectin but, without a clear statistical significance, and more importantly without a clear explanation of its mechanism of action.
Conversely, outside the clinical setting, the self-administration of the wrong dose of the drug has resulted in severe side effects, mainly related to dosage issues or interactions with other prescribed drugs, leading the FDA to provide a specific warning against using Ivermectin for the treatment of COVID-19.

Conclusion

In this short paper we have presented a background for AI-based drug repurposing and use case for repurposing two drugs against the SARS-COV-2 nucleoprotein using the Prepaire platform.

Our experiments show that Ivermectin has a high binding energy with the nucleoprotein of SARS-COV2 due to its molecular size. Moreover, both pEC50 and Kd have respectively shown good potency and affinity against the virus.
Regarding Favipiravir, our in-silico experiments have shown that it is binding to the SARS-COV-2 nucleoprotein with high energy given the small size of the Favipiravir molecule. These results are confirmed with good pEC50 and Kd values.
From the results for both molecules, it is possible to hypothesize about the mechanism of action against COVID-19 as indicated by the docking and binding energy for both molecules. Finally, there is a significant probability of synergistic effects between the two drugs (82%), which shall be validated in-vitro in future studies.
The results from this study, supported in the issuance of a new patent by the USPTO for a combination therapy with Ivermectin and Favipiravir against COVID-19 and influenza.

About Prepaire

Prepaire is an AI-driven pharmatech company committed to discovering, repurposing, designing, and developing the best possible drugs in the fastest and most effective manner. Prepaire industrializes drug discovery using an autonomous operating system (OS) built across diverse technologies that continuously expand massive proprietary biological and chemical datasets. An internal pipeline is focused on leveraging a precision medicine platform in the antiviral space, while an extensive partnered pipeline broadens the approach to other therapeutic areas. Prepaire leverages sophisticated AI and ML algorithms to scale this new paradigm in medical science and healthcare, unconstrained by human bias. Prepaire unities technology, biology, and chemistry to advance the future of medicine. The Prepaire OS is the in-silico to an in-vitro fully integrated one-stop solution for discovery, repurposing, and personalized medicine.

Prepaire Development Team

B. Barbosa
A. Rothman
S. Carrol
J.M. Billaud
H. Francis
M. Georgakis
M. Markhovsky
F. Azar
C. Freer (*)
V. Ribas (*)

(*) corresponding authors
vicent@prepaire.com
carl@prepaire.com