Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 1027–1031

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Application of Artificial Intelligence in COVID-19 drug repurposing

Sweta Mohanty [a], Md Harun AI Rashid [b], Mayank Mridul [c], Chandana Mohanty [a, *], Swati Swayamsiddha [d, **]

[a] School of Applied Science, KIIT University, Bhubaneswar, Odisha, India
[b] Samsi Rural Hospital Rutua-1, Malda, West Bengal, India
[c] School of Computer Engineering, KIIT University, Bhubaneswar, Odisha, India
[d] School of Electronics Engineering, KIIT University, Bhubaneswar, Odisha, India

ARTICLE INFO

Article history:
Received 19 June 2020
Received in revised form
26 June 2020
Accepted 29 June 2020

Keywords:
Artificial intelligence
Machine learning
Deep learning
COVID-19
Coronavirus
Drug repurposing
Drug repositioning

ABSTRACT

Background and aim: COVID-19 outbreak has created havoc and a quick cure for the disease will be a therapeutic medicine that has usage history in patients to resolve the current pandemic. With technological advancements in Artificial Intelligence (AI) coupled with increased computational power, the AI-empowered drug repurposing can prove beneficial in the COVID-19 scenario.
Methods: The recent literature is studied and analyzed from various sources such as Scopus, Google Scholar, PubMed, and IEEE Xplore databases. The search terms used are 'COVID-19', ' AI ', and 'Drug Repurposing'.
Results: AI is implemented in the field design through the generation of the learning-prediction model and performs a quick virtual screening to accurately display the output. With a drug-repositioning strategy, AI can quickly detect drugs that can fight against emerging diseases such as COVID-19. This technology has the potential to improve the drug discovery, planning, treatment, and reported outcomes of the COVID-19 patient, being an evidence-based medical tool.
Conclusions: Thus, there are chances that the application of the AI approach in drug discovery is feasible. With prior usage experiences in patients, few of the old drugs, if shown active against SARS-CoV-2, can be readily applied to treat the COVID-19 patients. With the collaboration of AI with pharmacology, the efficiency of drug repurposing can improve significantly.

1. Introduction

Novel coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), continues to spread aggressively. With a mortality rate of about 7%, 213 countries and territories around the world have reported a total of 7,817,195 confirmed cases with a death toll of about 430,397. It started with patients reporting pneumonia-like symptoms of unknown etiology, in the Wuhan district of China (Hubei Province), and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1,2]. SARS-CoV-2 is a class of enveloped viruses with a positive-sense RNA genome. They come under the *Betacoronavirus* group, having the same phylogenetic similarity with the previous severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1,3]. Thus it is the 3rd coronavirus epidemic, and as a result of evolution of the virus, the spread of COVID-19 is more severe than that of the previous SARS-CoV and the MERS-CoV [2].

The SARS-CoV-2 pandemic has forced researchers to invent new strategies for rapid antiviral treatment. Host-based antiviral agents target host cellular machinery essential for viral infections or innate immune responses to interfere with viral pathogenesis [4]. It can be augmented by employing well-validated drug discovery approaches. There are two basic strategies in drug discovery, conventional drug development and drug repositioning [5]. Besides the success rate being very low, the conventional way typically takes 10–15 years, is very expensive and needs high investments. Drug repositioning, instead reuses old drugs for exploring new therapeutics, making it more efficient, economical, and riskless [6]. More than 80 pioneering clinical trials have been instigated at

* Corresponding author.
** Corresponding author. Kalinga Institute of Industrial Technology (KIIT), Deemed to be University, Bhubaneswar, Odisha, 751024, India.
E-mail addresses: chandanamohanty@gmail.com (C. Mohanty), swati.swayamsiddha@gmail.com (S. Swayamsiddha).

https://doi.org/10.1016/j.dsx.2020.06.068
1871-4021/

present to test coronavirus treatment, including potential old drugs and investigational new drugs [7]. Recycling and reusing old drugs, recovering shelved drugs and increasing patients' lives makes drug repositioning an appealing system of drug discovery. It requires a thorough in-depth knowledge of present practices acquired by assessing both biological and pharmaceutical learning and interpreted mechanism-of-action of drugs.

In this regard, the pharmaceutical industry is also looking for novel leading-edge technologies to track, monitor and restrict the dissemination of COVID-19 disease [2,8]. AI is one such parallel technology that can provide support against this virus by population screening, medical help, notification, and suggestions about infection control. AI is also implemented in the field design through inception of learning-prediction model and performs a swift virtual screening to accurately display the congruent outputs. With a drug repositioning strategy, AI can briefly screen drugs that have potential to fight minacious diseases such as COVID-19. Being an evidence-based medical tool, this technology has the potential to improve the drug discovery, planning, design treatment and outline follow-ups of the COVID-19 patients. This review describes the current application of AI in Drug Repurposing for treating COVID-19 pandemic.

2. Drug Repurposing

Drug discovery is a high-risk, lengthy and expensive process [9,10]. According to a report by the Eastern Research Group (ERG), while it takes 10–15 years to develop a new molecular entity, the success rate is only 2.01% [6]. The concept of drug repurposing reuses old drugs for the treatment of a never-considered therapeutic indication. It is an experimental approach of identifying the pre-approved, discontinued, shelved and investigational drugs for authorized restatement for the treatment of other diseases. Conventional drug development usually includes five stages: (i) discovery and development, (ii) pre-clinical research, (iii) clinical research (iv) FDA review and (v) FDA post-market safety monitoring and development. However, there are only four steps in drug repurposing: (i) compound identification (ii) compound acquisition (iii) clinical research and (iv) FDA post-market safety monitoring and development (Fig. 1) [6]. A repositioned drug goes directly to preclinical testing and clinical trials omitting the initial steps, thus narrowing down the risks and lowering the costs. Fundamental principle in drug repurposing is that a common molecular pathway is associated and accountable for numerable diseases and a multitude of explicit information that is accessible on the formulation, dose, toxicity, pharmacology and clinical trial data of the authorized, approved, shelved or discontinued drugs [11].

3. Drug repurposing for COVID-19

Drug "repurposing" in this article refers to the use of existing approved drugs for the treatment of a never-considered therapeutic indication - in this case, COVID-19. The discovery and development of new molecular entities being lengthy, time-killing and high-priced for clinical trials to earn regulatory authorizations or sanctions, the momentary passage thus to potential treatments is the repurposing (repositioning) of prevailing approved drugs for the treatment of COVID-19. In this context, Chloroquine (CQ) and it's Hydroxyl analogue Hydroxychloroquine (HCQ) have been reported in the treatment of viral infection. These drugs have antimalarial activity and also showed *in vitro* treatment against COVID -19 [12]. Similarly, an antiviral drug Remdesivir primarily used in the treatment of Ebola virus clinical studies exposed new successful effects against COVID-19 *in vitro*. It is an adenosine analogue, basically integrates into nascent viral RNA chains and shows in early termination [13]. Lopinavir and Ritonavir were used in the ministration of COVID-19 patients. These two antiviral agents mainly affect proteolysis in coronavirus replication cycle [14]. Ribavirin is an analogue of ribonucleic and inhibitor of RNA polymerization. This drug has shown *in vitro* activity against SARS-CoV-2 in preclinical studies [1].

Furthermore, Tocilizumab, an immunosuppressive drug, was also used in the treatment of COVID-19 patients *in vivo* in China. This is chiefly employed to aid rheumatoid arthritis tested in COVID-19 patients. The drug successfully mitigates the clinical symptoms of viral infection, but the numbers of patients investigated in the study were very few [15]. The Anti-flu drug of Japan is revealed significant results in clinical trials over 340 patients [16]. In China, this drug is accepted for the treatment of Influenza and also shown to be efficient against a different type of viruses including SARS-CoV-2. Similarly, Ascorbic acid (Vitamin C) combination with other antiviral drug has shown to be supportive in the treatment of COVID-19 patients. In this context, more studies are suggested for a future drug against COVID-19 [17].

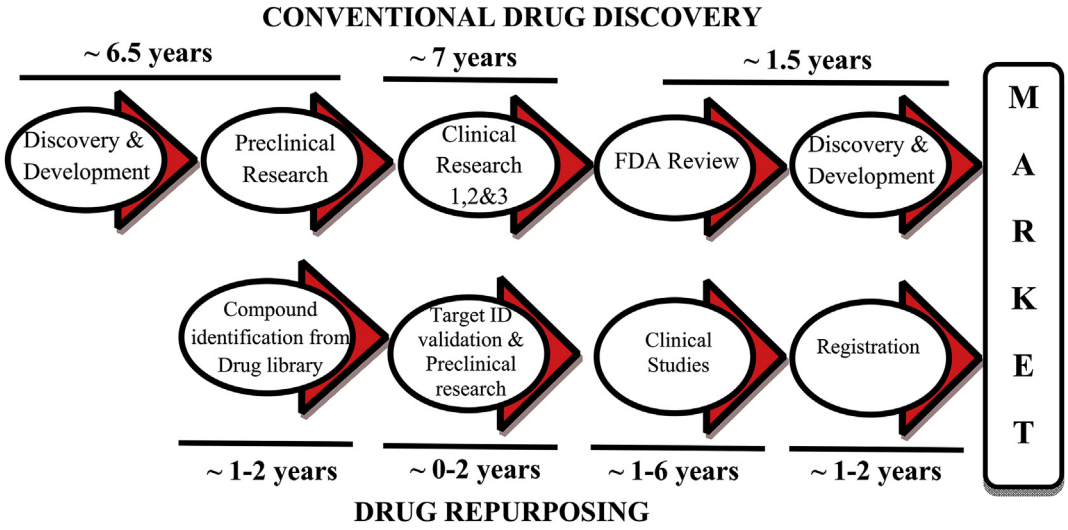

Fig. 1. Different steps followed to discover new drugs against drug repurposing.

4. Proposed AI techniques for drug repurposing

The main hindrance in drug repositioning is diagnosing and identifying the unique drug-disease relationship. To address this issue, a variety of approaches have been developed including computational approaches (such as AI), biological experimental approaches, and mixed approaches. Thus there are chances that the application of the AI approach in drug discovery is feasible [18]. Researchers have found many similarities between the COVID-19 virus and the 2003 SARS Virus and based on the existing data that caused SARS, AI learning models can be created to predict drug structures that could potentially treat COVID -19 [19]. Notwithstanding effectively affirmed repurposed drugs, there is a requirement for recognizing more repurposed drugs [19]. AI and machine learning (ML) can support this procedure by rapidly recognizing drugs having adequacy against COVID-19 and thus overcome any barrier between a large number of repurposed drugs, laboratory/clinical testing, and final drug authorization. A good amount of information, discharged by different health agencies and organizations is accessible on open stages [20]. AI likewise contains a subfield called ML, which utilizes factual strategies with the capacity to learn with or without being modified by an external user. Machine learning is divided into supervised, unsupervised, and reinforcement learning [21]. Supervised learning contains characterization and relapse strategies where the prescient model is created dependent on the information from information and yield sources i. e output. Unsupervised learning includes bunching strategies by gathering and deciphering information dependent on input information only. Another field of ML is deep learning. It uses AI neural network with multiple hidden layers apart from the input and output layer. Deep learning permits machines to take care of complex issues in any event, when utilizing an informational index that is exceptionally differing and unstructured. The more Deep learning calculations learn, the better they perform. The development of DL was seen with the expanding measure of information and the nonstop development of computer power. The striking distinction that DL makes is the adaptability in the design of neural systems such as repetitive neural networks (RNN), convolutional neural networks (CNN), deep belief networks (DBN), and completely associated feed-forward systems. The whole explanation will be better understood by Fig. 2. It presents the AI-empowered drug repurposing strategy. We need a Repurposed Drug Database, Open Chemical/Drug Database as an input to the model. Then different algorithms could be applied to the input and the required drug could be obtained [22].

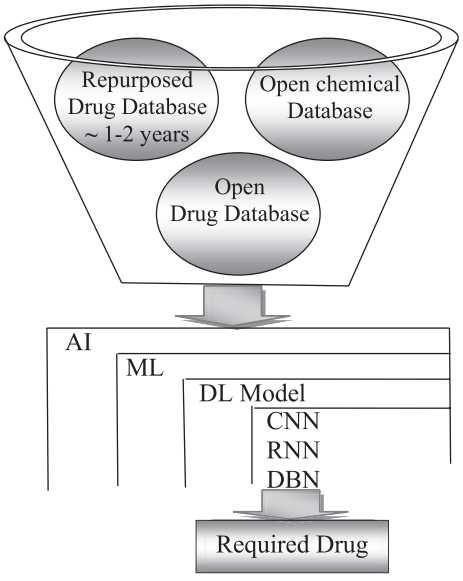

Fig. 2. Artificial intelligence (AI) empowered drug repurposing. Abbreviations: Machine learning (ML), Deep learning (DL), Repetitive Neural Networks (RNN), Convolutional Neural Networks (CNN), Deep Belief Networks (DBN).

The best and the truly necessary technique during circumstances is to order this unique medication information with the goal that AI scientists can apply their calculations to determine noteworthy bits of knowledge. For this, the world offices and policymakers need to step up to push huge pharma organizations and exploration labs to unite with littler examination associations and pool information sources. To foresee increasingly exact outcomes, specialists need arrangements of good information which is as of now not accessible and are therefore constrained by lack of data or too much noisy data. Associations over the globe are taking vital activities to utilize AI for testing which is empowering, be that as it may, there is a requirement for progressively symptomatic testing [8].

A few associations have begun to use these advancements to quicken COVID-19 medication disclosure and better fathom how the resistant framework battles the infection. Toward the beginning of April, pharmaceutical organizations GlaxoSmithKline (GSK) and Vir Biotechnology joined forces to progress coronavirus treatment advancement utilizing computerized reasoning and CRISPR. Furthermore, in the scholarly area, the Harvard T. Chan School of Public Health as of late united with the Human Vaccines Project to dispatch the Human Immunomics Initiative, which uses man-made reasoning models to quicken antibodies for a scope of infections, including COVID-19 [23]. A group from Southern Illinois University (SIU) as of late built up an information representation device that uses GPS data to show users the locations of known COVID-19 cases. Google and Apple have likewise collaborated to build up a contact following application powered by Bluetooth innovation. These methods may prove effective in the data collection in a great and accurate amount [23]. Organizations are running experimentation explores different avenues regarding effectively approved drugs, having built up wellbeing profiles in people, based on fundamental comprehension of the infection. With regards to COVID-19, hydroxychloroquine (endorsed to treat Malaria) and remdesivir (for Ebola) are the two most popular instances of this up until now [24]. So, the data set of the effectiveness of these medicines may be a good input for an AI model. The organizations which are utilizing AI for repurposing existing medications for COVID-19 are listed in Table 1.

5. Conclusion

This article explores the recent advances of AI-empowered drug repurposing for COVID-19. In the age of big data, drug repurposing can be done efficiently by using deep learning methods. The AI-based drug repurposing is a cheaper, faster, and effective approach and can minimize the failures in clinical trials. The repurposed drug can directly enter the advanced phase for trial without the initial trials and toxicity tests. Though presently the AI-empowered drug repurposing is in its nascent stage, this approach is a promising solution for the development of potential drugs for the cure of COVID-19. The computational intelligence aided drug molecule design and re-positioning of drug molecules can help in the prediction of excellent anti-viral therapeutics. However, the prediction efficiency can increase with a systematic training database and development of relevant learning algorithms. With technological advancements in AI coupled with increased computational power, the AI-empowered drug repurposing can prove beneficial in the COVID-19 scenario.

Table 1
List of companies using AI for drug repurposing.

Company name	Description and Implication of AI in drug repurposing	References
BenevolentAI	The UK based organization is known as a mammoth in the AI medicate revelation industry. The organization has been utilizing AI to repurpose all current affirmed drugs against the novel coronavirus. Inside a month, they limited competitors down to the six most encouraging particles with baricitinib, a medication rheumatoid joint pain sedate, being generally encouraging for treatment.	[21,25]
Innoplexus	The Indo-German organization started by assessing the capability of treatments like Hydroxychloroquine and Remdesivir against 2019-nCoV by utilizing information originating from patients. Their AI stage proposed higher viability for a mix of chloroquine and tocilizumab (a medication for rheumatoid joint pain), chloroquine and remdesivir, and the third mix of hydroxychloroquine with clarithromycin (an anti-microbial) or plerixafor (antiretroviral).	[24,26]
Deargen	The Korean organization, as a team with Dankook University, anticipated the action of accessible antiviral medications against the novel coronavirus and the AI stage recommended atazanavir (a medication for HIV treatment) to have high power. Abbvie is running a preliminary with its comparative HIV-antivirals lopinavir and ritonavir in Wuhan.	[27]
Gero	The Singaporean organization recognized 9 medications utilizing its AI stage. Among the top particles anticipated to have adequacy against the coronavirus are niclosamide and nitazoxanide, wide range hostile to parasitic, and against viral medications.	[28]
Cyclica	The Canadian organization reported screening of 6700 atoms that are FDA affirmed or if nothing else in Phase I human preliminaries on their AI-based medication repurposing stage MatchMaker. They have joined forces with China's Institute of MateriaMedica for *in vitro* and *in vivo* evaluation.	[29]
Healx	The UK based organization is utilizing its foundation to reveal bi-and tri-mixes of affirmed drugs against the infection. While the organization's capacities lie in uncommon infections, they are remarkably situated to use the information on why mortality is higher with comorbidities of respiratory and heart frameworks.	[30]
VantAI	The New York-based organization is utilizing a frameworks science way to deal with comprehend the interchange between collaborations of the viral proteins with perhaps over 500 human proteins through the span of disease. The organization is planning to recognize drugs against focuses on that may have been disregarded by different organizations and has just revealed a few promising objective pathways, for instance obstructing the infection's movement in the Golgi contraption (a viral re-bundling framework in the human cell that helps in additionally spread), and is at present screening around 300 leads with a CRO to tentatively research sway on viral contamination further.	[31]

Declaration of competing interest

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

The following authors have affiliations with organizations with direct or indirect financial interest in the subject matter discussed in the manuscript:

Author's name Affiliation.

Dr. (Mrs) Chandana Mohanty Associate professor.

School of Applied Science, KIIT University, Odisha 751024, India.

Dr. Md. Harun AI Rashid Ratua Rural Hospital −1, Malda, West Bengal, India.

Dr. (Mrs) Swati Swayamsiddha Associate professor.

School of Electronics Engineering.

KIIT University, Bhubaneswar, Odisha, India.

Sweta Mohanty School of Applied Science, PhD Student KIIT University, Odisha 751024, India.

Mayank Mridul School of Computer Engineering, KIIT University, Bhubaneswar, Odisha.

References

[1] Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020;55(6):105948.
[2] Swayamsiddha S, Mohanty C. Application of cognitive internet of medical things for COVID-19 pandemic. Diabetes Metab Syndr 2020;14(5):911−5.
[3] Xiaoling X, Mingfeng H, Tiantian L, Wei S, Dongsheng W. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci Unit States Am 2020;117(20):10970−5.
[4] Li C, Wang X, Wang H. Repurposing host-based therapeutics to control coronavirus and influenza virus. Drug Discov Today 2019;24(3):726−36.
[5] Patil V, Singhal S, Masand N. A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: efficacy, safety and clinical trials. Life Sci 2020;1(254):117775. https://doi.org/10.1016/j.lfs.2020.117775.
[6] Xue H, Li J, Xie H, Wang Y. Review of drug repositioning approaches and resources. Int J Biol Sci 2018;14(10):1232−44.
[7] Sanders JM, Pharamd LM, Tomajsz ZJ. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020;323(18):1824−36.
[8] Ting D, Carin L, Dzau V, Wong T. Digital technology and COVID-19. Nat Med 2020;26(4):459−61.
[9] DiMasi JA, Faden LB. Competitiveness in follow-on drug R&D: a race or imitation? Nat Rev Drug Discov 2011;10(1):23−7.
[10] Carter PH, Berndt E, DiMasi JA, Trusheim M. Investigating investment in biopharmaceutical R&D. Nat Publ Group 2016;12(6):56−71.
[11] Ngo H, Garneau T, Sylvie G, K D. A complex game of hide and seek: the search for new antifungals. MedChemComm 2016;7(7):1285−306.
[12] Rolain J, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents 2007;30(4):297−308.
[13] Gautret P, Lagier J, Parola P, Hoang V, Meddeb L, Mailhe M. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;10(11):52−69.
[14] Guida J. Chloroquine, Hydroxychloroquine and Covid-19: a systematic review of literature. InterAm J Med Health 2020;3(2):1−10.
[15] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323(18):1775−6.
[16] Chan J, Chan K, Kao RY, To K, Zheng B, Li CP. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67(6):606−16.
[17] Chan J, Yao Y, Yeung M, Deng W, Bao L, Jia L. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015;212(12):1904−13.
[18] Mohs R, Greig N. Drug discovery and development: role of basic biological research. Alzheimer's Dementia. Transl Res Clin Interv 2017;3(4):651−7.
[19] GNS H, Saraswathy G, Murahari M, Krishnamurthy M. An update on drug repurposing: re-written saga of the drug's fate. Biomed Pharmacother 2019;110(2):700−16.
[20] Paul S, Mytelka D, Dunwiddie C, Persinger C. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010;9(3):203−14.
[21] Mak K, Pichika M. Artificial intelligence in drug development: present status and future prospects. Drug Discov Today 2019;24(3):773−80.
[22] Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 2020;6(14):1−18.
[23] K J. How will big data analytics factor into the next phase of COVID-19? Health it analytics. https://healthitanalytics.com/news/how-will-big-data-analytics-factor-into-the-next-phase-of-covid-19; 2020.

[24] S A. How AI is fighting COVID-19: the companies using intelligent tech to find new drugs. Pharmaphorum 2020. https://pharmaphorum.com/views-analysis-digital/how-ai-is-fighting-covid-19-the-companies-using-intelligent-tech-to-find-new-drugs.
[25] Richardson P, Corbellino M, Stebbing J. Baricitinib for COVID-19: a suitable treatment?—Authors' reply. Lancet Infect Dis 2020;2(393):52–65.
[26] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White K. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;20(6). https://doi.org/10.1038/s41586-020-2286-9.
[27] Scudellari M. Five companies using AI to fight coronavirus. IEEE Spectrum 2020. https://spectrum.ieee.org/the-human-os/artificial-intelligence/medical-ai/companies-ai-CoV.
[28] Kurji N. China's Institute of Materia Medica Partners with Cyclica on Innovative drug repurposing for COVID-19. Cyclica News; 2020. https://www.cio.com/article/3292616/how-singapore-is-using-artificial-intelligence.html.
[29] Siddiqui A. China's Institute of Materia Medica Partners with Cyclica on Innovative drug repurposing for COVID-19. China's Institute of Materia Medica Partners With Cyclica for COVID-19; 2020. https://www.biospectrumasia.com/news/48/15552/chinas-institute-of-materia-medica-partners-with-cyclica-for-covid-19.html.
[30] Guilliams T. Healx joins forces with Boehringer Ingelheim to discover new treatment approaches for rare neurological diseases. Healx News 2019. https://healx.io/healx-joins-forces-with-boehringer-ingelheim-to-discover-new-treatment-approaches-for-rare-neurological-diseases.
[31] Vant AI. DE NOVO AI powered drug design. https://www.vant.ai/who-we-are/index.html; 2020.