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# AI Can Find Many Drugs To Repurpose For COVID-19, But Real-World Results Mixed

by Alaric DeArment

A study presented at a recent MIT-sponsored conference used network medicine to uncover dozens of potential opportunities for existing drugs to be repurposed for COVID-19.

Artificial intelligence and machine learning (AI/ML) has allowed for the identification of a number of compounds with potential use in treating COVID-19, but the results from those that have made it into clinical development have been rather mixed, according to a presentation at a recent conference on AI/ML in drug discovery, both for drugs repurposed as antivirals against SARS-CoV-2 and as anti-inflammatory agents.

The presentation, at the 30 October AI Cures Drug Discovery Conference sponsored by the Massachusetts Institute of Technology, looked at graph neural networks for identifying drug repurposing opportunities for COVID-19. AI Cures comprises a group of machine learning and life science researchers using AI/ML to find drugs for COVID-19 and other emerging pathogens. It is one of multiple efforts around the world to use computers to find potential COVID-19 therapies: In July, Fugaku – the world's fastest supercomputer, installed in Kobe, Japan – was deployed for the same purpose, under a partnership between the Riken research institute and Fujitsu. (Also see "*Coronavirus Update: Japan's Supercomputer Joins COVID-19 Drug Hunt*" - Scrip, 6 Jul, 2020.)

"The traditional methodologies that rely on development and iterative development of drugs are really not feasible these days, and so we need new strategies that can rapidly identify repurposing opportunities and then be quickly deployed in real work," said presenter Marinka Zitnik, a machine learning and computational biomedicine researcher at Harvard University. "And so the question that we are tackling here is really how can we find these new tricks for drugs that are already in the market or that are in late clinical stages of drug development, and how can we repurpose them in a much more fast manner at the pandemic scale to COVID-19 in particular."

## AI For Teasing Out Repurposing Opportunities

Zitnik's approach employs network medicine, a field that involves applying the scientific study of networks to the identification, prevention and treatment of disease.

"The effect of a drug is not really limited only to molecules to which the drug directly binds in the human body," she said. Rather, it's that "the effect of drugs propagates through underlying biological networks."

Similarly, she said, diseases may not exist independently of one another, but may share a number of genes despite their distinctiveness.

"And so, because of that, [the] effect of a drug on a disease is inherently a network phenomenon," she explained.

The approach by Zitnik's team involved taking 6,340 drugs and then using AI algorithms, network diffusion and network proximity to rank them based on expected efficacy against SARS-CoV-2. They focused in particular on 918 drugs that had been screened in VeroE6 cells, as well as those under clinical development, in order to capture the medical community's assessment of drugs with potential efficacy in COVID-19. That was further narrowed down to 77 drugs that successfully reduced viral infection, of which 76 did not bind to proteins targeted by SARS-CoV-2, thus indicating they rely on network-based actions. The results – posted on a preprint server – offer a potential method to find drugs that could be repurposed for future pathogens and neglected diseases faster than de novo drug development.

"It is possible that some drugs that lacked activity in VeroE6 cells may nevertheless show efficacy in human cells, like loratadine, which inhibited viral activity in the human cell line Caco-239," Zitnik told *Scrip*. Her study ranked loratadine at position 95, but showed it had no effect on VeroE6 cells.

## Drug Repurposing: A Mixed Bag In COVID-19

Drug repurposing isn't a new concept, and it certainly isn't limited to COVID-19. Perhaps the most well-known repurposed drug at the moment is *Gilead Sciences, Inc.*'s Veklury (remdesivir), which won US Food and Drug Administration approval 22 October as a treatment for SARS-CoV-2 infection and had been used for months under emergency use authorization. (Also see "*Coronavirus Update: Gilead's Veklury Gets Full FDA Approval, Roche Partners With Atea*" - Scrip, 23 Oct, 2020.) But before remdesivir was tested in the clinic for SARS-CoV-2, and even before it was tested for SARS-CoV-1 or MERS-CoV, the drug was developed for ebolavirus.

The practice of repurposing is long standing though – *Celgene Corporation*'s business was largely built on a repurposing of the infamous morning sickness drug thalidomide under the brand Thalomid, first for leprosy and then for multiple myeloma.

Still, the urgency of the COVID-19 pandemic and the shortage of available treatments or vaccines has made repurposing a significant part of the overall effort to find new ways to prevent or treat the disease.

To date, these repurposing efforts have met varying degrees of success. In addition to Veklury, the steroid dexamethasone has been successful as a treatment for severe cases of COVID-19 thanks to its anti-inflammatory effects.

On the other end of the spectrum, there have been several high-profile failures. Hydroxychloroquine and chloroquine – both of which showed strong activity in Zitnik's study – have prominently flopped in clinical trials. *AbbVie Inc.*'s Norvir (ritonavir) did not show any effect in the study's screen, and fellow AbbVie drug Kaletra – which combines it with lopinavir – has also not been effective in COVID-19. (Also see "*Coronavirus Update: RECOVERY Finds Kaletra Ineffective, Indian Company Joins Vaccine Race*" - Scrip, 30 Jun, 2020.)

*Roche Holding AG*'s Actemra (tocilizumab), a monoclonal antibody that targets IL-6 and is used to treat cytokine release syndrome in patients receiving CAR-T cell therapy for blood cancers, has nevertheless shown disappointing results when tested for cytokine storm in COVID-19. (Also see "*Coronavirus Update: Roche's Actemra Fails In Phase III COVID Study*" - Scrip, 29 Jul, 2020.)

The same is true of *Sanofi* and *Regeneron Pharmaceuticals, Inc.*'s Kevzara (sarilumab), also an IL-6 inhibitor. (Also see "*Coronavirus Update: Moderna Hold Up, Sanofi and Regeneron's Kevzara Fails In Phase III*" - Scrip, 3 Jul, 2020.) The companies subsequently announced a partnership to develop Regeneron's novel antibody cocktail for SARS-CoV-2, REGN-COV2, which is pending at the FDA. (Also see "*Roche Signs Up To Be Regeneron's Global Partner For COVID Antibody*" - Scrip, 19 Aug, 2020.)

"In other words, some of the drugs ranked high by the algorithm may show efficacy, even if they are not among the 77 strong- or weak-effect drugs with positive outcomes," Zitnik told *Scrip*.

## Other Potential Pandemic Treatments

Two drugs highly ranked in the study that have not been tested in clinical trials are azelastine, an antihistamine for allergy symptoms of the upper airways, and the heart failure drug digoxin.

"Our findings, coupled with extensive experience in their use in the clinical community, argue for their consideration in clinical trials," Zitnik told *Scrip*.

Others include folic acid and methotrexate, which impair folate metabolism and address inflammation in autoimmune diseases. The acid reflux drug omeprazole alters lysosome acidification and binds to nonstructural protein 3 (nsp3). That protein enhances SARS-CoV-2's ability to evade the immune system, and blocking it was found to interfere in viral formation,

Zitnik said, adding that other benzimidazoles also bind to nsp3.

ClinicalTrials.gov lists two Phase I/II studies in Brazil, one posted 20 April and another posted 30 October, that use methotrexate contained in nanoparticles for COVID-19, while the drug is also included as part of two larger studies using other drugs. Folic acid is also included in several clinical trials. Omeprazole is included in three clinical trials of COVID-19, though not as the primary intervention.