Repurposing approved drugs for COVID-19 at an accelerated pace

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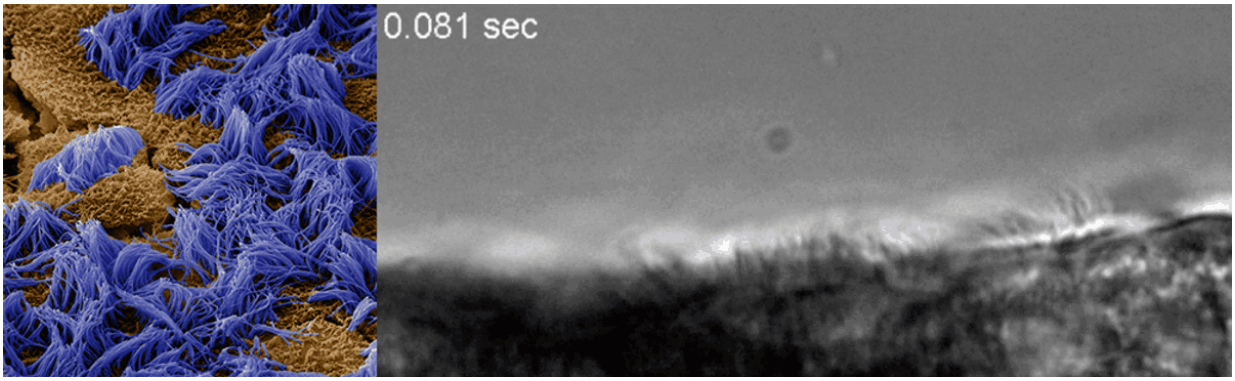


Human organ chips recapitulate the base-level functions of human organs in small cartridges that simulate conditions inside the human body. Cells in the Lung Chip, shown here, have characteristic hair-like cilia on their surfaces that behave like they do in vivo. Credit: Wyss Institute at Harvard University

The United States' Defense Advanced Research Projects Agency (DARPA) has signed an Agreement worth up to $16 million over the next year with the Wyss Institute for Biologically Inspired Engineering at Harvard University to identify and test FDA-approved drugs that could be repurposed to prevent or treat COVID-19. This highly collaborative effort leverages the Institute's computational drug discovery pipelines and human Organ Chip technologies, and has already found multiple approved compounds that show promise against the SARS-CoV-2 virus that causes COVID-19.

The team, led by Wyss Founding Director Donald Ingber, M.D., Ph.D., is continuing to evaluate many more drugs, and lead compounds are being tested in high-throughput cell-based assays with CoV-2 virus in the lab of Matthew Frieman, Ph.D., Associate Professor of Microbiology and Immunology at the University of Maryland School of Medicine. The most promising drugs are being transferred to the lab of Benjamin tenOever, Ph.D. at the Icahn School of Medicine at Mount Sinai for testing in COVID-19 animal models. Human Organ Chip technology is also being set up in the Frieman and tenOever labs with equipment supplied by Wyss spinout Emulate, Inc., so that they can carry out experiments analyzing the human response to COVID-19 infection in vitro.

"Over the past few years, the Wyss Institute has been building up its computational approaches to identify compounds as potential therapeutics and validate them using our human Organ Chip microfluidic culture technologies, but the emergence of COVID-19 has really galvanized us to quickly integrate all of our capabilities and bring full force to bear on that challenge," said Ingber. "Our initial successes allowed us to obtain this new support from DARPA, which we hope will greatly accelerate the development of drugs that might be used to prevent the spread of disease in large populations, as this is precisely what is needed before we can all go back to something close to life as usual." Ingber is the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS), and is a co-founder of Emulate, Inc.

In addition to identifying and testing compounds for potential use against the virus, the Wyss team has established relationships with the Beth Israel Deaconess Medical Center (BIDMC) and SUNY Downstate Medical Center, where they are collecting clinical specimens from COVID-19 patients and carrying out RNA analysis using the sequencing

core at the Broad Institute of Harvard and MIT, which will then provide data that can be fed back into the Institute's computational discovery pipeline.

Computing a COVID-19 cure

There are no treatments or vaccines for this novel coronavirus because it is just that: novel. "Treatment" for those infected largely consists of supportive care so that their immune systems have the best shot at overcoming the virus on their own, but many patients unfortunately do not survive the viral onslaught. To date, testing FDA-approved drugs to determine if they can be repurposed to treat COVID-19 has not yet been pursued in a careful and systematic way. As a result, there has been much speculation in the media regarding unproven and/or off-label use of approved medications as potential therapies.

Ingber recognized that drug discovery efforts already underway at the Wyss Institute could be adapted to meet this need, and created the Institute's Coronavirus Therapeutics Project Team. Composed of members with diverse skill sets from analytical chemistry to machine learning to pathophysiology and virology, the team has quickly shifted their work to focus nearly exclusively on finding and testing drugs that could potentially treat COVID-19.

Ken Carlson, Ph.D., a Senior Staff Scientist at the Wyss Institute who is also the Project Lead of the Coronavirus Therapeutics Project Team, says that the pandemic has accelerated the pace of the Institute's drug discovery and development pipeline by many months. "The processes that we're now putting in place are bringing the Wyss up to par with the world's leading drug development companies and institutions, and we have the potential to even go beyond the current standard because we're using novel approaches rather than what has typically been done by others," said Carlson, who has more than 25 years of experience in the

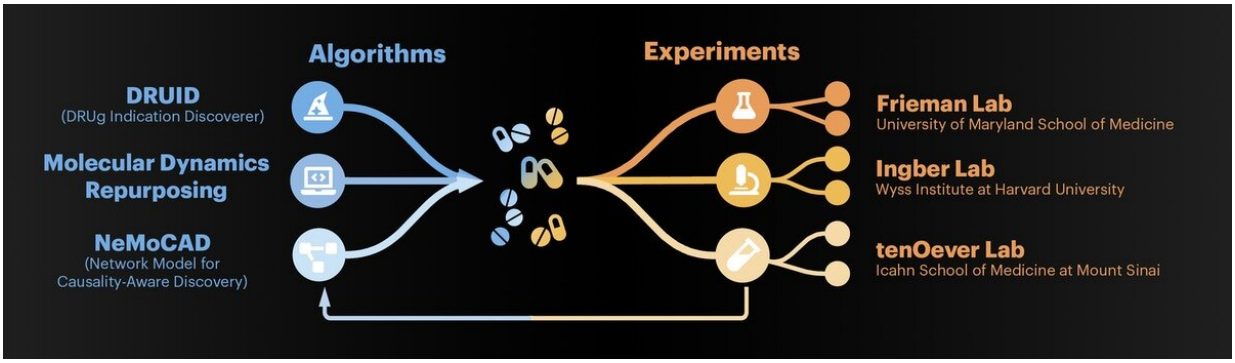
biopharma industry.

Some of those novel approaches include three computational pipelines that the Wyss Institute has developed recently to harness the power of data analytics, machine learning, and computer science to address a number of different diseases. These different approaches are now being deployed to rapidly evaluate existing drugs for potential activity against COVID-19.

The first uses a proprietary machine learning algorithm called DRUID (DRUg Indication Discoverer) developed by Senior Staff Scientist Diogo Camacho, Ph.D. and his team that sifts through gene expression data generated with tens of thousands of known drug compounds and identifies those that have the potential to revert a disease-state expression pattern and phenotype back to a normal one. It was previously used to successfully identify compounds that have the potential to fight cancer and is now being used to analyze the gene expression patterns of human lung cells infected with the CoV-2 virus, and how different drugs change those patterns.

The second approach, Molecular Dynamics Repurposing, created by Senior Staff Scientist Charles Reilly, Ph.D. and his team, uses multiscale computer-based molecular simulation techniques to create virtual versions of molecules whose properties can be modeled and analyzed. The team has used it to model the Spike protein found on the novel CoV-2 virus and develop small molecules targeted against a specific region of the protein. When tested in cultured cells infected with both pseudotyped and native CoV-2 viruses, some of these novel compounds inhibited infection in early studies. As part of the DARPA program, the team is now integrating this information with structural data from other drugs that inhibit CoV-2 infection to identify additional FDA-approved compounds that might have even more potent effects.

The third, NemoCAD (Network model for causality-aware discovery), engineered by Senior Engineer Richard Novak, Ph.D. and his team, uses a network analysis-based algorithm to compare genetic networks found in COVID-19 patients with those in healthy patients, and identifies drugs that could change network state to that of a healthy patient. In past work, the team used this approach to identify existing approved drugs that can reversibly induce suspended animation in tadpoles or normalize behavioral abnormalities in a mouse model of Rett syndrome.



Multiple computational pipelines are being used at the Wyss Institute to identify existing FDA-approved drugs that show potential activity against the SARS-CoV-2 virus that causes COVID-19. These drugs are then tested in the Frieman, Ingber, and tenOever labs in a variety of model systems to validate them. Credit: Wyss Institute at Harvard University

"There are so many great, creative scientific ideas happening all the time at the Wyss Institute, and bringing together these different projects into a unified process makes them even stronger because data about a compound that is acquired using one method can then be shared with everyone else who is working on that compound from a different angle," said Rani Powers, Ph.D., a Senior Staff Scientist who is leading efforts to coordinate and integrate all computational efforts and data relating to

the Therapeutics Discovery program. "Each compound that we're testing has a story that we'll be able to follow, showing its journey from computational modeling to in vitro assays to animal models, and we'll be able to see how the different assays performed on a compound provide a unique piece of the puzzle we're trying to solve."

From computers to Organ Chips to animal models

The Wyss cell biology team, including Ingber, Senior Staff Scientist Rachelle Prantil-Baun, Ph.D., Staff Scientist Girija Goyal, Ph.D., and postdoctoral fellows LongLong Si, Ph.D. and Haiqing Bai, Ph.D., recently uploaded a preprint to bioRxiv describing how they used cultured human lung cells in Lung Airway Chips to identify two approved compounds that inhibit infection with a CoV-2 pseudovirus at concentrations similar to those observed in human blood in clinical studies. But for any of these drugs to be quickly approved for use in patients, they need to be tested against the real CoV-2 virus. To make sure their candidate drugs could continue their journey toward the clinic, Ingber teamed up with Frieman and tenOever, whose labs have dedicated spaces with the capability to safely conduct tests with the novel CoV-2 virus, and together they have created a full drug-testing pipeline that demonstrated the compounds' safety and efficacy against the virus in animal models.

As part of the DARPA grant, Frieman and tenOever are also setting up Organ Chip testing programs in their own labs so that they can infect human Lung Chips with the CoV-2 virus and study human organ-level inflammatory responses. The most active anti-CoV-2 compounds or drug combinations are being tested in tenOever's CoV-2 animal models to validate efficacy, optimize dosing, and assess toxicity. Throughout the DARPA program, the team also will be engaging with other government partners and regulators to expedite the translation of drugs that are found to be effective inhibitors of CoV-2 infection for use in patients.

"Through our cell and lung-on-a-chip-based anti-viral testing system, we will be able to better predict candidate therapeutics for priority in animal models and eventually human trials," said Frieman.

"The Wyss Institute always been a very collaborative institution, but addressing the COVID-19 crisis has required that we reach beyond our walls and beyond the immediate Boston community to identify partners who can build on our technological advances and add their own unique capabilities, much like handing off a baton to a teammate in a relay race, to achieve our shared goal of identifying existing drugs that can prevent this horrible disease," said Ingber. "I'm confident that what we're doing both internally and externally is going to help all of us cross the finish line together over the coming months."

Provided by Hansjörg Wyss Institute for Biologically Inspired Engineering