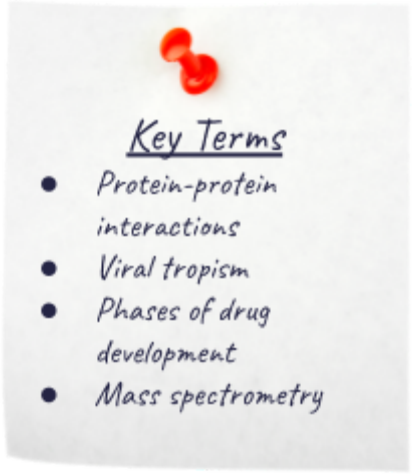
D4P Discussion Guide

Lindsey Lopes and Emily Costa present on what drugs could be repurposed to treat COVID-19

D4P Discussion Guide: https://bit.ly/2SKEd1n

A SARS-CoV-2 protein interaction map reveals targets for drug repurposing · David E. Gordon, Gwendolyn M. Jang, Mehdi Bouhaddou, Jiewei Xu, Kirsten Obernier, Kris M. White, Matthew J. O'Meara, Veronica V. Rezelj, Jeffrey Z. Guo, Danielle L. Swaney, Tia A. Tummino, Ruth Huettenhain, Robyn M. Kaake, Alicia L. Richards, Beril Tutuncuoglu, Helene Foussard, Jyoti Batra, Kelsey Haas, Maya Modak, Minkyu Kim, Paige Haas, Benjamin J. Polacco, Hannes Braberg, Jacqueline M. Fabius, Manon Eckhardt, Margaret Soucheray, Melanie J. Bennett, Merve Cakir, Michael J. McGregor, Qiongyu Li, Bjoern Meyer, Ferdinand Roesch, Thomas Vallet, Alice Mac Kain, Lisa Miorin, Elena Moreno, Zun Zar Chi Naing, Yuan Zhou, Shiming Peng, Ying Shi, Ziyang Zhang, Wenqi Shen, Ilsa T. Kirby, James E. Melnyk, John S. Chorba, Kevin Lou, Shizhong A. Dai, Inigo Barrio-Hernandez, Danish Memon, Claudia Hernandez-Armenta, Jiankun Lyu, Christopher J. P. Mathy, Tina Perica, Kala B. Pilla, Sai J. Ganesan, Daniel J. Saltzberg, Ramachandran Rakesh, Xi Liu, Sara B. Rosenthal, Lorenzo Calviello, Srivats Venkataramanan, Jose Liboy-Lugo, Yizhu Lin, Xi-Ping Huang, YongFeng Liu, Stephanie A. Wankowicz, Markus Bohn, Maliheh Safari, Fatima S. Ugur, Cassandra Koh, Nastaran Sadat Savar, Quang Dinh Tran, Djoshkun Shengjuler, Sabrina J Fletcher, Michael C. O'Neal, Yiming Cai, Jason C. J. Chang, David J. Broadhurst, Saker Klippsten, Phillip P. Sharp, Nicole A. Wenzell, Duygu Kuzuoglu, Hao-Yuan Wang, Raphael Trenker, Janet M. Young, Devin A. Cavero, Joseph Hiatt, Theodore L. Roth, Ujjwal Rathore, Advait Subramanian, Julia Noack, Mathieu Hubert, Robert M. Stroud, Alan D. Frankel, Oren S. Rosenberg, Kliment A Verba, David A. Agard, Melanie Ott, Michael Emerman, Natalia Jura, Mark von Zastrow, Eric Verdin, Alan Ashworth, Olivier Schwartz, Christophe d'Enfert, Shaeri Mukherjee, Matt Jacobson, Harmit S. Malik, Danica G. Fujimori, Trey Ideker, Charles S. Craik, Stephen N. Floor, James S. Fraser, John D. Gross, Andrej Sali, Bryan L. Roth, Davide Ruggero, Jack Taunton, Tanja Kortemme, Pedro Beltrao, Marco Vignuzzi, Adolfo García-Sastre, Kevan M. Shokat, Brian K. Shoichet & Nevan J. Krogan· *Nature* · April 30, 2020 · PDF LINK · doi: https://doi.org/10.1038/s41586-020-2286-9



In this installment of D4P, graduate students Lindsey Lopes (Rockefeller University) and Emily Costa (Weill Cornell Medical College/ Memorial Sloan Kettering) present data on the possible interactions between human proteins and SARS-CoV-2 proteins, and how this information can provide clues into using drugs already on the market for the treatment of COVID-19. The presenters put this research into context by demonstrating the process—from molecule to medicine—for getting a drug on the market via FDA approval.

questions for learners	discussion points for educator
1. *What kind of cells were used in this study, and what are the limitations of using a cell line for the purposes of testing drug compounds?*	The authors conducted their experiments in human kidney cells and monkey cells. Cells that are used in the lab are called cell lines, and they are different from the cells in our body because they're adapted to grow in a lab environment. These adaptations often allow the cells to be immortalized, or in other words, grow almost indefinitely, which is not a feature of healthy cells. Also, factors like genetics, other medical conditions, and other prescribed drugs would all affect how a patient responds to a particular therapy, and cell line experiments don't account for those factors. Regarding COVID-19, the cell lines used in an experiment may greatly differ from the cells that are infected *in vivo*.
2. *What is a protein-protein interaction, and how does this relate to the*	Protein-protein interactions are specific, physical contacts between two or more proteins, held together through intermolecular forces. Protein-protein interactions are often critically important in carrying out

mechanism of drug action?	cellular processes, including processes that are important for SARS-CoV-2 infection in humans. Understanding protein-protein interactions is important when designing drugs. For example, a drug could work by preventing a specific protein-protein interaction that would otherwise be important for the disease to develop in humans.
3. *What is mass spectrometry and how did the researchers use this technology in the paper?*	Mass spectrometry is a technology that scientists use to determine the identity of a molecule or compound. The scientists in this paper used mass spec to identify which human proteins interact with proteins from SARS-CoV-2. Through identification of the specific proteins that interacted with each other, scientists were able to create an interaction map, or interactome, that gave clues into the possible human cellular processes that are impacted by SARS-CoV-2 infection.
4. *This study identified 332 interactions between human proteins and SARS-CoV-2 proteins. How was this information used to determine next steps?*	Once the researchers had identified these 332 protein-interactions, they searched for drugs that are known to bind the human proteins in the protein-protein interactions. They then tested these drugs in viral infectivity assays to see if any of them reduced the ability of SARS-CoV-2 to infect cells. The drugs that showed some impact on SARS-CoV-2 infection were identified and further studies will be conducted to provide evidence for drug efficacy in combating SARS-CoV-2 (or not).
5. *How did the protein maps created in this study reveal novel aspects of SARS-CoV-2 infection in humans?*	The protein maps revealed that some of the human proteins that interacted with SARS-CoV-2 proteins are from the same pathway or cellular process. This could mean that SARS-CoV-2 relies on these processes when it's infecting our cells. When a virus, like SARS-CoV-2, uses host cellular proteins as part of its biology, those proteins are called host factors. A well-known example of a host factor for SARS-CoV-2 is the ACE-2 receptor. Since the virus needs certain host factors for its biology, the presence or absence of host factors determines whether the virus can infect certain cells, tissues, or even species. This is known as viral tropism. The idea that these protein maps revealed potential new host factors and insights into SARS-CoV-2 tropism, and thus infection was further supported by the viral infectivity assays. In these assays, the researchers saw that drugs that bind Sigma receptors and disrupt protein production were especially effective at reducing infection, suggesting that these processes are important to SARS-CoV-2 infection.
6. *What are the stages of drug discovery, and how does the effort to repurpose an existing drug differ from getting FDA approval for a brand new drug?*	The phases of drug development starts off with laboratory experiments. After a drug shows promising results in these preclinical studies (using cells, animals, etc.), the FDA can give permission to use it as an investigative new drug (IND) for clinical trials. There are at least three stages of clinical trials, all for testing the safety and efficacy of a drug. Phase I trials use healthy patients to test the dosage and safety of the IND, followed by Phase 2 trials with patients who have the disease in question. Finally in Phase 3 trials, more patients (hundreds to thousands) are included for longer periods of time, to narrow down doses and look for rarer side effects. If the drug passes Phase 3 trials, it becomes FDA-approved and enters the market. This can take 10 to 12 years in total. By repurposing a drug with a known safety profile - like some of the drugs tested in this paper - a few of these stages can be skipped and the process is shortened.