CellPress
OPEN ACCESS

Backstory

One common enemy, a pandemic, uniting interdisciplinary teams

Marie-Elizabeth Barabas,[1] Rituparna Chakrabarti,[1,*] and Michelle Muzzio[1]

Over the past year and a half, we have experienced an unprecedented shift in our daily life due to COVID-19. Not just that, the pandemic has set a new course in science to face head-on a previously unknown virus that wreaked havoc globally.

As soon as SARS-CoV-2 was discovered, research groups worldwide started probing its biology (Kumar et al., 2020; Fox et al., 2020), while others developed diagnostic tests (Kilic et al., 2020) or investigated public-health measures to control it (Kilic et al., 2020; Fox et al., 2020). Scientists raced to find treatment strategies (Kumar et al., 2020; Gorgulla et al., 2021), and others assessed the consequences of the pandemic on mental health (Zhang et al., 2021), which affected the personal and professional lives of millions. Many of those who were not trained virologists or epidemiologists dove into interdisciplinary collaborations to further understand the molecular mechanisms of the disease and the prolonged impact of this worldwide phenomenon (Zhang et al., 2021; López Prol J, 2020). At the same time, many researchers across career stages dealt with uncertainties, project delays, loss of family members and friends, and careers put on hold due to lockdowns (Muzzio, 2020; Fu et al., 2021).

Nevertheless, science has never progressed so rapidly, and certain fields would not have shown as much growth if it were not for the pressing urgency to put an end to the pandemic and unite against one common

Figure 1. Global research teams uniting to fight COVID-19 pandemicImage by Miroslava Chrienova from Pixabay

enemy. In this backstory, the *iScience* editorial team interviewed authors of six papers published in 2020-2021 in *iScience* to delve into their journey about what it was like to be a researcher during a pandemic and how their interdisciplinary work accelerated COVID-19 research to impact society and policies.

INSPIRATIONS AND BEGINNINGS

What was the motivation to launch your project?

Hakho Lee (Massachusetts General Hospital, Harvard Medical School): My lab focuses on developing point-of-care diagnostic technologies, and the ravaging pandemic motivated us to design biosensors for fast COVID-19 detection. We started by reviewing the current status and challenges in COVID testing. This process helped us to sort out which types of tests are most effective for a given clinical context.

Shahid Mukhtar (University of Alabama at Birmingham): We mainly focused on lung epithelial cells, although other areas of the body are affected by COVID-19 because that appeared to be the area of main problematic symptoms. The motivation of the paper was how we could contribute effectively to COVID-19 research using our lab's expertize in network science.

Rebecca Powell (Icahn School of Medicine at Mount Sinai): Although my doctoral and postdoctoral work was focused on HIV vaccine design and the immune response to HIV, when I became a mother, my personal interest in lactation brought me into the milk immunology field. When the pandemic hit NYC in early March 2020, I knew this was an opportunity to learn about the generation of milk immunity to a completely novel pathogen, something which as a field we don't understand much.

Xiaochu Zhang (University of Science & Technology of China): We didn't expect the outbreak of the COVID-19 pandemic. Our lab focused on the neural basis of mental disorders with neuroimaging tools. The initial motivation to launch our project is to investigate how to predict the future depressive degree of nonclinical depressed populations based on their current cognitive biases.

Javier López Prol (University of Graz) and Sungmin O (Max Planck Institute for Biogeochemistry): Amid slowing economic activity due to COVID-19, we decided to examine changes in electricity consumption to offer early insights into the economic impacts of the pandemic and resulting lockdowns. We forecast daily electricity consumption under a business-as-usual scenario and then compare it with actual consumption for the most affected EU countries and US states (as of July 2020).

Christoph Gorgulla and Haribabu Arthanari (Harvard Medical School): Over the past several years, we have developed a new computational drug discovery platform, VirtualFlow (https://virtual-flow.org/), which allows us to carry out ultra-large virtual screenings in a very short time published early March 2020 (Gorgulla et al., 2020). Thus, VirtualFlow seemed to be the perfect tool to quickly find new drug candidates for COVID-19. Leveraging the structural information available on SARS-CoV-2, we targeted proteins critical for the virus survival and function. In total we targeted 40 sites each with ~1.1 billion molecules. We partnered with Google, who generously provided us with computation time in the Google Cloud and technical support.

Did you start the research before the pandemic and how did you shift gears?

Lee: The shift was straightforward, as we already validated the technology with bacteria. One of the biosensors that we developed before the pandemic had to be redesigned to detect SARS-CoV-2.

Mukhtar: During the first week of lockdown in Alabama, we felt we could contribute to the world while the whole world was on standby mode. Prior to COVID-19 pandemic, we were already using network science and bioinformatics of protein-protein interactions to identify important proteins or nodes in a network. Therefore, we started off assessing the topological features of the binding partners of SARS-CoV2 in lung epithelial cells to understand pathogenesis.

Powell: Before the pandemic, I lead multiple projects studying milk immunity to flu and HIV. Many of the techniques used in those studies translated easily to the COVID-19 project. Immediately we began to enroll local COVID-19-recovered milk donors, and I traveled around the city during the NYS PAUSE to collect their samples. We were, therefore, able to generate data on the SARS-CoV-2 milk antibody response very quickly. These data demonstrated that in milk, a robust secretory IgA response to the SARS-CoV-2 Spike

[1]iScience, Cell Press

*Correspondence: r.chakrabarti@cell.com

https://doi.org/10.1016/j.isci.2021.102992

protein was extremely common after infection and that this response was highly dominant over other antibody classes.

Zhang: The pandemic erupted when we were on a stage of assessing participants' future depressive indices. Then, we realized that this provides us with an opportunity to study the effect of this pandemic on the relationship between cognitive biases and future depressive degrees. A global pandemic can give enough influence to our life, e.g., social distancing, etc.

López Prol and O: We have been working on climate change issues, in the fields of social and natural sciences, respectively, for the last six years. Mitigating and adapting to climate change requires interdisciplinary collaboration. This is also the case for the COVID-19 pandemic. When the pandemic started and seeing the seriousness of the situation, we thought that we should contribute to understanding what was happening to the best of our abilities because the information at the time was very uncertain. The main results are summarized in a Twitter thread (https://twitter.com/lopez_prol/status/1313825998861938690?s=20), and an interactive version can be accessed through an open-access online application (https://jlprol.shinyapps.io/covid/).

Mitigating and adapting to climate change requires interdisciplinary collaboration. This is also the case for the COVID-19 pandemic.

Gorgulla and Arthanari: Though we were working on structure-based drug discovery, the SARS-CoV-2 virtual screen was uncharted waters for us, both in terms of the number of target sites and the number of molecules targeted per site. Our results from the ~50 billion docking instances are available to the research community and can be accessed interactively through our website (https://vf4covid19.hms.harvard.edu/).

CHALLENGES

What are the main challenges you faced so far or project for the future?

Lee: We faced many practical challenges – lockdown, shortage of reagents and common lab supplies. But a more important technical hurdle was to come up with an efficient way to pre-process samples before actual sensing. Building a robust yet economical cartridge for sample handling required many design iterations.

Mukhtar: The concern was that the lack of "wet lab validation" or benchwork during the lockdown and how to return to the lab safely. I felt responsible for publishing our findings sooner rather than later, so we decided to publish only the network biology analysis.

Powell: Probably the biggest challenge is that there are so many questions to answer since COVID research is such a novel field that it is hard to know what to study first. Especially now that COVID-19 vaccines have come into play, and everyone needs answers about their effect on milk immunity.

López Prol and O: For this study in particular, challenges were related to the speed and uncertainty of the day by day unfolding events.

Gorgulla and Arthanari: One of the main challenges was in removing the roadblocks in upscaling our screen to ~200,000 CPUs and handling the demand on the file handling on the scale of billions of files. Access to BSL-3 facilities that can test our compounds with SARS-CoV-2 is another bottleneck, and there exists long waiting times.

How interdisciplinary helped to move the project further during the COVID-19 pandemic? What are the key factors that stimulate such interdisciplinary research, and how do you apply those in your paper?

Lee: Building a working biosensor is like making a car. You need to seamlessly put together many distinct, for example, mechanical, electrical, and chemical parts. Furthermore, they must work together (almost) 100% of the time, like we expect a car to start regardless of the weather, which requires expertize from diverse fields.

Mukhtar: We took an interdisciplinary approach to combine past virology-based benchwork and comprehensive datasets from 4 other studies to decipher the significant proteins targeted by SARS-CoV-2 and create mathematical modeling to assess the regulatory factors.

Powell: My research has led to various collaborations with other academics across the world, as well as pediatricians and OB-GYNs, and non-academic partners, to try to use the milk I have collected and am continuing to collect to answer many of the outstanding questions about the milk immune response to COVID-19 and milk immunity in a more general context. I think my willingness to share these milk samples and let others benefit from my highly successful recruitment has been vital in these partnerships.

Zhang: An interdisciplinary approach helped us do research that impacted both psychology and public policies during the COVID-19 pandemic. It provides us with the opportunity to study the pandemic's effect and conduct research that directly impacts public mental health.

López Prol and O: We were lucky to meet in the interdisciplinary PhD Program DK – Climate Change (https://dk-climate-change.uni-graz.at/en/), run by the Wegener Center for Climate and Global Change (https://wegcenter.uni-graz.at/en/) at the University of Graz. This interdisciplinary training was essential to answer the question at hand: from the handling of weather variables such as temperature to developing reliable forecast methods.

Gorgulla and Arthanari: We used to have weekly meetings accommodating different time zones in Germany, Austria, Israel, Ukraine, Switzerland, and the United States because of our global team. Video conferencing and instant messaging kept the project going and we were getting used to discussing science in this new setting. During the early lockdowns we were able to run all the virtual screens in a matter of a few weeks, order some of the best compounds, and they arrived around the time when the labs started to reopen.

RESEARCH METHODS

How did you approach developing the methodology for the needs of your interdisciplinary project?

Lee: The urgency of the pandemic helped forging and speeding up joint projects with my colleagues – we united against our common threat. My existing collaborators immensely helped by accommodating my fellows in their lab and sharing resources. I was also able to connect with new collaborators who tirelessly collected clinical samples.

Zhang: After the pandemic outbreak, we changed our original plan and divided the nonclinical depressed participants into two groups for the needs of the project. One group's future depression degree was assessed before the pandemic, and the other groups were assessed during the pandemic. This approach helped us investigate the effect of the global pandemic on people's depression degree.

López Prol and O: Given the possible applications of our data for further research, we also try to make the results as accessible as possible; first, by writing our article in a language understandable for a broad audience; second, by disseminating our results on social media; and finally, by creating an interactive platform.

The urgency of the pandemic helped forging and speeding up joint projects with my colleagues – we united against our common threat.

COLLABORATIONS

What are other disciplines or new communities that should look to this field with interest?

Lee: The sheer amount and depth of data we are generating is stunning. Data science will be integral to analyze these data and distill them into actionable public health policies.

Mukhtar: Biochemists and pharmacologists are interested in the protein-protein interactions, which might identify actionable targets for different stages of infection.

Powell: Medical doctors and lactation specialists so that they can provide evidence-based guidance to patients.

Zhang: We believe that this research brings together psychologists and neuroscientists and will accelerate the conversation with the public and government to work together making better policies for public mental health.

We believe that this research brings together psychologists and neuroscientists and will accelerate the conversation with the public and government to work together making better policies for public mental health.

Gorgulla and Arthanari: Researchers who are interested in small-molecule therapeutics especially the experimental drug developers, are increasingly become interested in artificial intelligence/machine learning (AI/ML)-based approaches, we hope that this workflow will allow them to get initial hit compounds quickly, laying a solid foundation for further experimental validation.

GOVERNANCE

How does it feel like doing research which has a direct impact on society and policies?

Lee: It is extremely rewarding that I can contribute to such a global question, but at the same time I feel the increasing responsibility of sharing my research outcomes precisely with validations, so that the public benefits and is better informed.

Mukhtar: I hope my work feeds into evidence-based decisions to treat COVID-19 patients. Our work can help better predict responsiveness to FDA (other regulatory bodies)-approved drugs. I'm proud that our research has a direct impact here.

Powell: As a working mother, who has been affected directly by policies surrounding breastfeeding, this is where my personal and scientific interests truly align and affecting changes in this area through research is very important to me.

As a working mother, who has been affected directly by policies surrounding breastfeeding, this is where my personal and scientific interests truly align and affecting changes in this area through research is very important to me.

López Prol: As an economist, my object of study is society itself. For this reason, it is vital to be aware of the potential implications of the results, be careful to differentiate between positive and normative statements and be transparent on how our values and assumptions mediate the latter. Usually, the results of a paper do not suffice by themselves to propose specific policies. They are rather a grain that, combined with other research, can provide a more comprehensive perspective and lead to informed policy decisions. The different responses to the pandemic across countries with dramatically different outcomes showed us the importance of basing political decisions on scientific evidence.

Gorgulla and Arthanari: Our investigations are typically closer to basic research and this project, although far from human trials, was the closest we have been to speed up the research during an urgent public health crisis.

Where did you get help from or seek advice to execute your project?

Lee: Being in a hospital setting and doing clinical research, I have many clinical colleagues and mentors. Their inputs are critical to make practical systems to address real needs in clinics.

Mukhtar: We designed the COVID-19 study ourselves, but we found assistance with virologists and our collaborators who could help interpret the data to determine what is physiologically relevant.

We designed the COVID-19 study ourselves, but we found assistance with virologists and our collaborators who could help interpret the data to determine what is physiologically relevant.

Zhang: Without strong funding support from Information Science Center of University of Science and Technology of China and access to big instrumentation core facilities doing such time-sensitive research would have been difficult.

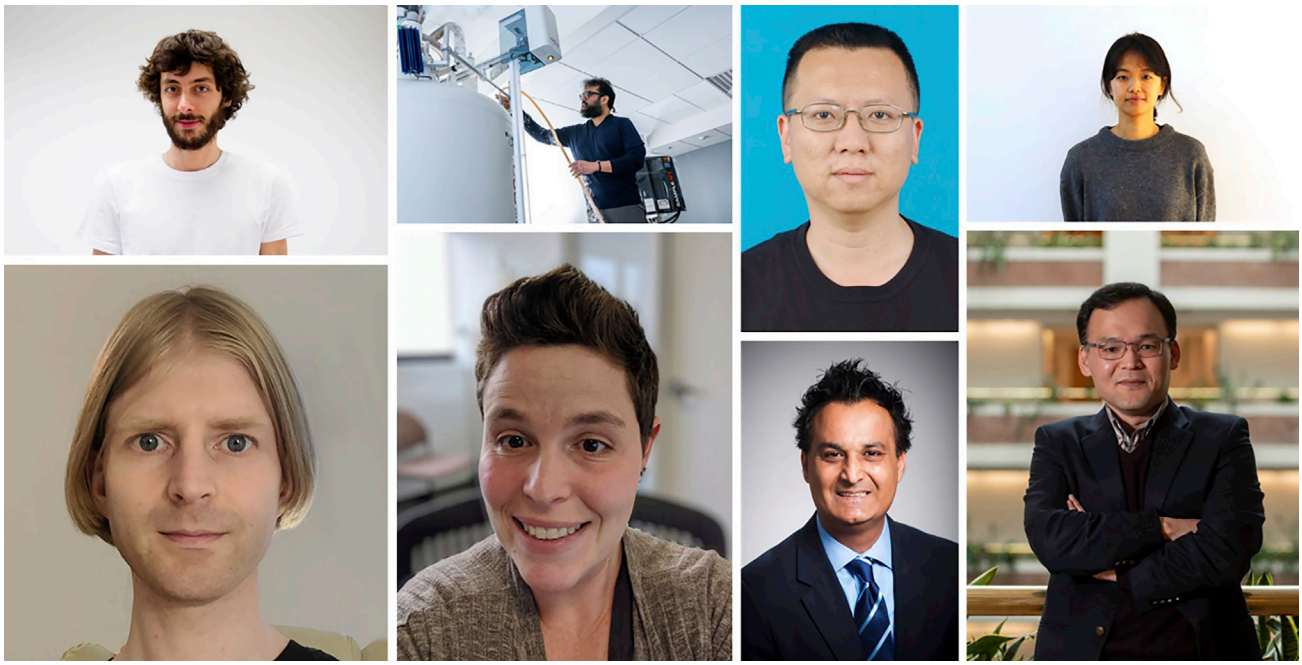

Figure 2. Researchers interviewed in this backstory who all found themselves shifting gears to join the scientific momentum to fight against COVID-19 with interdisciplinary research methods

Top (from left): Javier López Prol, Haribabu Arthanari, Xiaochu Zhang, and Sungmin O. Bottom (from left): Christoph Gorgulla, Rebecca Powell, Shahid Mukhtar, and Hakho Lee.

López Prol: During the pandemic, daily interaction between researchers was limited. I realized how understated the importance of informal discussions, e.g. while taking a coffee or having lunch with colleagues, is. Still, I was able to discuss online with my colleagues at the German Institute for Economic Research (DIW Berlin), where I was working at that moment, and particularly with the Deputy Head of the Department of Energy, Transport and Environment Wolf-Peter Schill. In that sense, it is also important to appreciate the support and flexibility of the Austrian Science Fund, through the Schrödinger fellowship, to let researchers focus on basic science while at the same time tackling some of the most pressing societal issues, such as climate change and the energy transition, or the pandemic in this case.

Gorgulla and Arthanari: Engineers and computer scientists at Google were remarkably supportive and we worked together as a team to remove any computational roadblocks and scale VirtualFlow in the Google Cloud. We had a team of researchers with expertize in virology, structural biology, drug discovery, medicinal chemistry, and computational chemistry, with whom we had several discussions, debates, and consultations.

What is your recipe for projects' governance (e.g. getting funding, project planning and management)?

Lee: I am still learning. Increasingly, I realize the importance of project management and try to develop required skill sets by taking classes and reading relevant books. The most important factor, however, remains the same — people, whom you respect, trust, and collaborate to secure long-term funding.

Mukhtar: I encourage independence of my students to investigate side projects, and our COVID-19 project came from one of my students, Nilesh Kumar. This has allowed my lab to grow in unexpected directions and adapt current funding to cover these projects.

Powell: Certainly, persistence amidst all the rejections you will inevitably receive before actually getting a project funded is key. In fact, this project was initiated with no funding to see it through because I knew it was critical to recruit and generate data ASAP. Finally, about six months into the project, I did receive grant funding for this work.

Zhang: We had a well-designed project that allowed us to account for unexpected circumstances and gave us the flexibility to switch from our original idea.

Gorgulla and Arthanari: Project management worked for us because everyone was ready to go beyond the call to help and augment the research. The genesis of this project was not planned, and a classic example of necessity is the mother of invention. The team assembled organically and everyone contributed without ego or an expectation of where they would be on the author list in the final paper. We feel that the pandemic extracted the best from us and forged new friendships.

The genesis of this project was not planned, and a classic example of necessity is the mother of invention. The team assembled organically and everyone contributed without ego or an expectation of where they would be on the author list in the final paper. We feel that the pandemic extracted the best from us and forged new friendships.

FINAL THOUGHTS

What's next? What breakthroughs do you imagine or hope to see in upcoming years? What questions does your research open up now?

Lee: I envision a gradual yet tectonic shift in how we detect and treat diseases. First, more liquid biopsies and other non-invasive assays will be adopted into a main clinical workflow. These technologies would be a cost-effective means for detecting diseases and monitoring treatment. Second, we will see the democratization of (bio)sensors in our daily lives. These "sensors for life" will promote preventive healthcare by enabling us to monitor our general well-being, environments, and early signs of illness. Toward this vision, my immediate focus is on coming up with a hassle-free, automatic way to process samples.

Mukhtar: Single-cell sequencing is a powerful tool, and we hope to integrate this into our lab's work in terms of COVID-19 research and cancer biology. We are especially interested in what causes cancer cells to move and migrate in the body, using transcriptomics and single-cell sequencing.

Eventually, we would like to understand the long-term issues in other organs/tissues affected by COVID-19, beyond lung epithelial cells. Why are some populations of people more severely affected by COVID-19, measured by proteomics, metabolomics and Genome-Wide Association Studies (GWAS) studies.

Powell: The data in this paper are only a preliminary look at the milk antibody response to COVID-19, and we have since followed up this study to include many more samples as well as durability and functional data. We have a particular interest in secretory IgA, as it is the most resilient class of antibodies meant to survive in milk and relatively harsh mucosal areas. Given that we have determined that most of the IgA elicited after SARS-CoV-2 infection is in secretory form, we are investigating if this sIgA can be extracted for therapeutic use. We will study this in hamsters in the coming months.

There are many questions to be answered, including how long does this antibody response last, does it change qualitatively over time, what are the functions of these antibodies, is there cellular milk immunity at play in the milk, is this response truly protective for babies, and if so, how much milk is required to achieve protection? There are also now many questions about the COVID-19 vaccines and milk immunity, which we will also be studying.

Zhang: Our research revealed that a more negative memory bias was associated with a greater decrease in future depression degree during the COVID-19 pandemic in the nonclinical depressed population. This may indicate a promising strategy for treating depression. Besides, our findings also put up a challenge to the traditional cognitive model of depression. We hope to see that we can better understand depression or some other mental disorders in the upcoming years.

López Prol and O: Generally, scientific research is taken for granted, unnoticed, and often undervalued. The pandemic has shown us how vital science is to improve societal well-being when it is most needed.

This research opens more questions than it answers. The first avenue of future research would be to update the results and expand the analysis to other countries. Then, it would be interesting to see the impact of

specific policies on electricity consumption and economic activity. Finally, how the relationship between electricity consumption and economic activity changed during this pandemic, and whether these changes will be permanent or only temporary while the containment measures are in place. There will certainly not be a shortage of questions to answer.

Gorgulla and Arthanari: Though vaccines represent the immediate therapeutic option, having an arsenal of small-molecule therapeutics against an array of protein targets will provide us ammunition to combat the next pandemic. Here we present atypical viral targets, such the methyltransferase, phosphatase, and helicase which represent novel viral targets. We are currently experimentally validating the hits in biophysical and cellular experiments.

CONCLUSION

There are some common themes across these six interviews. The COVID-19 pandemic is an important global issue that sparked changing research focuses in many labs to address the urgent need for research in this area, but, at the same time, it presented many unique challenges, such as lockdowns that slowed research progress and affected the morale of research teams. An important aspect of shifting gears in research was forming collaborations, reaching out to mentors, and adapting approaches. Further, research started in response to the pandemic's unprecedented needs, opening a plethora of new fields of research, formed in part from the merging of fields.

REFERENCES

Fox, A., Marino, J., Amanat, F., Krammer, F., Hahn-Holbrook, J., Zolla-Pazner, S., and Powell, R.L. (2020). Robust and specific secretory IgA against SARS-CoV-2 detected in human milk. iScience *23*, 101735. https://doi.org/10.1016/j.isci.2020.101735.

Fu, N., Hou, Y., Li, K., Li, M., Tang, S., and Yu, C. (2021). A time of transition: stories from starting a new research program in 2020. iScience *24*, 102308. https://doi.org/10.1016/j.isci.2021.102308. PMID: 33997667.

Gorgulla, C., Boeszoermenyi, A., Wang, Z.F., Fischer, P.D., Coote, P.W., Padmanabha Das, K.M., Malets, Y.S., Radchenko, D.S., Moroz, Y.S., Scott, D.A., et al. (2020). An open-source drug discovery platform enables ultra-large virtual screens. Nature *580*, 663–668. https://doi.org/10.1038/s41586-020-2117-z.

Gorgulla, C., Padmanabha Das, K.M., Leigh, K.E., Cespugli, M., Fischer, P.D., Wang, Z.F., Tesseyre, G., Pandita, S., Shnapir, A., Calderaio, A., et al. (2021). A multi-pronged approach targeting SARS-CoV-2 proteins using ultra-large virtual screening. iScience *24*, 102021. https://doi.org/10.1016/j.isci.2020.102021.

Kilic, T., Weissleder, R., and Lee, H. (2020). Molecular and immunological diagnostic tests of COVID-19: current status and challenges. iScience *23*, 101406. https://doi.org/10.1016/j.isci.2020.101406.

Kumar, N., Mishra, B., Mehmood, A., Athar, Mohammad, and Mukhtar, M. Shahid (2020). Integrative network biology framework elucidates molecular mechanisms of SARS-CoV-2 pathogenesis. iScience *23*, 101526. https://doi.org/10.1016/j.isci.2020.101526.

López Prol J, O.S. (2020). Impact of COVID-19 measures on short-term electricity consumption in the most affected EU countries and USA states. iScience *23*, 101639. https://doi.org/10.1016/j.isci.2020.101639.

Muzzio, M. (2020). The generation of virtual defenders. iScience *23*, 101118. https://doi.org/10.1016/j.isci.2020.101118.

Zhang, P., Piao, Y., Chen, Y., Ren, J., Zhang, L., Qiu, B., Wei, Z., and Zhang, X. (2021). Outbreak of COVID-19 altered the relationship between memory bias and depressive degree in nonclinical depression. iScience *24*, 102081. https://doi.org/10.1016/j.isci.2021.102081.