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Commentary

Lessons learned for pandemic preparedness: A collaborative network is imperative

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The scientific community improvised to respond quickly to the SARS-CoV-2 pandemic without a template on how to work together on a global scale to understand and combat the virus. Here, we describe how we tackled impediments to success and the valuable lessons learned that prepare us for a future pandemic.

The ongoing SARS-CoV-2 pandemic has been a worldwide tragedy for the past three years, with millions of lives lost and many more irrevocably changed. However, the COVID-19 pandemic has also taught us several valuable lessons, including how working together and collaborating can have a profound impact, a lesson particularly important in the scientific world. Early in the pandemic, the Quantitative Biosciences Institute (QBI) at the University of California San Francisco (UCSF) established the QBI Coronavirus Research Group (QCRG), a collaborative entity focused on studying and understanding the recently emerged SARS-CoV-2 virus.[1] QCRG started in the San Francisco area and eventually included instutions and research groups across the globe. This piece describes these efforts, emphasizing what was learned and how these lessons can be applied to future pandemics as well as the study of disease in general.

Organic scaling up by commitment

In January 2020, when the genomic sequence of SARS-CoV-2 was first reported, the Krogan lab at UCSF cloned each of the ~30 individual genes associated with the virus. Our aim was to systematically study each of the genes and their protein products. We also wanted to generate a host-pathogen protein-protein interaction (PPI) map, as we had done with other viruses in the past.[2,3,4]

As the pandemic gained momentum, it became evident that one lab alone would not be able to generate data at a significant enough depth or speed. Therefore, we quickly approached 8 other groups who were also interested in working on the virus. These labs took on different roles to generate complementary datasets that could subsequently be integrated. Interest in the initial group increased and QCRG grew to 12 groups in February 2020, and by March, there were 42 labs comprising hundreds of scientists working together at QBI. Shortly thereafter, the university closed its doors, except to those working on COVID-19. In hindsight, responding with such speed turned out to be a great advantage, because many of the protocols, as well as inter-lab sharing and methodology, had already been established. We were therefore able to create distance schedules to coordinate shifts for tens to hundreds of scientists working around the clock.

However, ironically, our force quickly became a weakness. Over 100 scientists were trying to work together in the complex reality of remote and distance working. Communication was becoming an issue; we quickly realized that a Zoom session with 100+ people was not a communication tool but rather an invitation for chaos. QCRG quickly pivoted to form subgroups focused on distinct scientific areas of research, which were either focused on the technology being used to interrogate the virus (e.g., proteomic, genetic, structural, and bioinformatics approaches) or by the biological processes being hijacked during infection (e.g., chromatin regulation, ubiquitination, and protein trafficking). This allowed for smaller, focused meetings to direct research projects, with the project leads presenting to the larger integrated group. The coordinated strategy fell into place rather quickly and also gave trainees a significant role to play during the two years of lockdown. In parallel, channels on the collaboration software Slack[5] were formed, as were specific e-mail lists. Realizing the role that technology could play in scientific communication during these trying times was crucial, as was setting up a structure that facilitated research and empowered younger scientists.

International collaborations

Early on in the pandemic, UCSF did not have access to the SARS-CoV-2 virus and did not have established biosafety level 3 (BSL-3) containment protocols in place, which was crucial to studying and understanding the virus. QBI contacted the Institut Pasteur in Paris and the Icahn School of Medicine at Mount Sinai in New York, world-class research institutes known for their infectious disease research. Both institutes had access to the virus and systems in place to begin work immediately. Interestingly, relationships with these institutes and others were developed years prior to the crisis and did not necessarily have a distinctive objective beyond the bringing together of great scientists for collaborations and the progress of science. The pandemic revealed that possessing an extensive and, most importantly, active international network of scientists is invaluable. Without the help of our world-wide

partners, we would not have made the speedy headway that delivered a significant paper describing the first SARS-CoV-2-human PPI map and, based on this map, a list of drugs and compounds that could be repurposed to treat COVID-19.[6] This work, co-authored by more than 100 scientists , was initially posted as a preprint on BioRxiv in March of 2020 and published a month later.[6] This initial paper and the use of social media channels permitted us to advertise our set of plasmids expressing SARS-CoV-2 proteins, allowing us to distribute these valuable reagents to over 400 groups in over 40 countries in a very short period of time, helping to expedite COVID-19 research.[6]

The use of preprint servers such as BioRxiv represented another significant lesson learned during the pandemic: the value of immediate distribution of and access to critical information, although a formal peer-review process remained an essential component of the scientific process, enhancing our work. Prior to the pandemic, there was greater skepticism about the value of public sharing prior to acceptance in a peer-reviewed journal. During the pandemic, those who had significant findings that would benefit the general scientific community used BioRxiv more extensively to allow the data, methods, and potential drugs and compounds to be shared openly during a humanitarian crisis. The benefit of crowd-peer review was far greater than the risk of releasing an unreviewed paper.

As the group grew in size, so did its reputation, and both domestic and international institutions reached out to be part of the collaborative effort. A specific advantage was that QBI had already forged a number of significant international collaborations around the world, which allowed us to tap into diverse expertise and quickly fit new groups into the larger puzzle to move the research forward as quickly and effectively as possible.

Saying yes to industry

In addition to academic institutions, pharmaceutical companies, both big and small, reached out to see what they could do to help. The approach was unconventional and, for us, unprecedented; the companies were not seeking transactional relationships representing pay-for-return projects, but rather inquiring about how they could engage and contribute. Importantly, our increasingly large group had not only gathered momentum but also credibility with rapid publications that were being widely cited across the scientific community—efforts that gained us recognition with companies. Partnering with industry drew initial skepticism from some; however, the academic community alone could not perform all the needed tasks at the speed required to make the desired impact. For example, the pace at which Synthego, a CRISPR-focused company, could generate knockouts of host factors derived from the PPI map, or the ease with which a large pharmaceutical company could cross-reference compounds, were immediate assets. Benchling, a cloud-based platform for biotechnology research and development approaches, partnered with us, providing the buoyancy needed for our subgroups with respect to the sharing of information. Companies not typically in the science realm also reached out, such as Zoic Labs, a Hollywood visual graphics company, a testament to the fact that people wanted to be involved and wanted to help. Zoic Labs, which had previously worked on special effects for movies such as *The Life of Pi* and *The Titanic*, wanted to contribute to the scientific effort. They worked with a number of the QBI labs to create a visualization tool that represented the SARS-CoV-2-human PPI map in 3 dimensions, with the ability to map orthogonal datasets from other QCRG investigators. In the end, this unusual collaboration created a new way to visualize protein networks, initially with a focus on the SARS-CoV-2 virus, but which is now being used for a multitude of other disease areas and educational applications. We learned that the power of saying "yes" to unorthodox partners could bring about unexpected progress.

At the same time, in saying yes, the group also acquired extra work from smaller companies trying to make their mark in the ocean of pharmaceutical entities. Many had compounds they wanted to test in the successful pipeline that had been created. However, a lesson learned was that better methods had to be in place to identify the most promising relationships and efforts for both parties.

Big reward for communication

The QCRG was becoming bigger not only because of additional group members from labs around the world but also because of funding agencies.

During the pandemic years, we learned the value of clear and consistent communication. In order to succeed, the scientists needed to get their discoveries understood by the lay public, who, at the beginning of the pandemic, were living in fear. Amidst conspiracy theories and inaccurate news, there had to be a way to pierce through with real information presented in a digestible manner. We found that in order to get heard, and to tell our own story, we had to take control of our own narrative. QBI already had an active media team that went into high gear during the pandemic. Strategic use of Twitter, Instagram, Facebook, and YouTube helped to proliferate information and make the science more accessible. People on staff wrote blogs from a lay perspective, explaining how the science was being done, from A to Z, and why. Trainees were interviewed on newly formed programs like A QCRG Minute to highlight their research in one minute, in a tangible manner. Radio stations, newspapers, and television (TV) outlets were contacted regularly whenever there were both big and small discoveries that advanced the research. Personalized and focused emails from the scientists working on the research were directly sent to a UCSF donor group which became particularly interested in finding a solution for the pandemic. The staff at the institute wrote emails and lay pieces to convey the research to their family and friends, and that helped to ease a bit of the fear that people felt.

A lesson to be learned here is that while you can engage people, you cannot alleviate everyone's fear and not everyone will participate in the dialogue. At times, we were told that we were too enthusiastic and that it was tiring and unrealistic. Although hard to hear during a global psychological crisis and while combating depression in various employees, scientists, and others, it was important to still believe in what we were doing but also understand that we had to strike the right tone.

How to get support

It was important to get financial backing to fund the research projects for the hundreds of scientists who were doing their part to try to come to global solutions. At

the outset of the pandemic, most of the funding at UCSF was focused on supporting the very immediate and essential needs such as masks and ventilators and intended primarily to support doctors, nurses, and hospitals. Therefore, the discovery research ongoing within QCRG was not yet a priority. We learned that effective communication and the right kind of exposure attracts donors. QCRG was fortunate to find philanthropic champions who helped support the labs with unrestricted funds at a crucial juncture and allowed the research to flourish. However, this was not enough, and it was equally important to get commitment from the National Institute of Health (NIH), the major funding source for labs in the United States. In some cases, the NIH allowed for existing funds to pivot to help in the SARS-CoV-2 efforts, and this proved to be monumental. Importantly, the Defense Advanced Research Projects Agency (DARPA), given their own priorities in national security, was able to leverage existing awards at QBI and inject significant additional funding to advance our collaborative SARS-CoV-2 work. We learned that not only was having close relationships with our program officers crucial, but that transparent communication could also translate into financial support we did not know existed. Just recently, the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH created the Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern, a program for the discovery of direct-acting antivirals for not just SARS-CoV-2 but other viral families that have pandemic potential. The QCRG was one of the nine centers that were funded, and these collective efforts will almost certainly put us in a better position for the next pandemic.

Philanthropic and rapid support mechanisms accelerate progress

By believing in our approach, we were not only able to enable unprecedented progress as the group published over 50 collaborative papers in 2 years, but we were also able to garner unforeseen financial support. Philanthropists, in addition to gifting money to the group, also created a rapid grants mechanism that provided further oxygen to smaller research groups that were studying what would have been a higher-risk investment. In a particular example, FASTGRANTS, which provided quick funding to scientists working on SARS-CoV-2, allowed the QCRG structural biology subgroup to elucidate the novel structure of a SARS-CoV-2 protein, which is now enabling structure-based drug design. We learned that whereas the traditional grants process can be time-consuming on both sides, when you have an unconventional approach—such as some high net-worth individuals setting up a rapid opportunity that demands a page or less of explanation as an application and a two week turn around on decision making—you can achieve high impact in the short term with relatively modest funding.

Pandemic preparedness in the future

The lessons we learned in setting up the QCRG were many, and often the learning was by necessity. One of the most important lessons was that communication was key in all aspects of the endeavor. Setting up channels for communication early was incredibly important; for example, creating organized sub-groupings on the collaborative software Slack enabled people to work efficiently in a focused manner that was still open access communication to all involved. We set up a QBI TV channel that featured the scientists and their work, content that was echoed across various social media platforms ranging from Twitter to TikTok. We worked with a press release (PR) firm to help with messaging around the research as it was published and used Global Newswire to share news; efforts that, in turn, led to different entities reaching out to help or partake in the effort.

On the research side, at first, only the scientists directly engaged in SARS-CoV-2 work were involved. After a few months, we began to witness scientists working in other areas starting to feel excluded. It was essential to learn how to take a more disease agnostic approach to involve more people in the overall work. In fact, since COVID has impacts on virtually every organ, it was not difficult to include those working on cancer, cardiovascular diseases, or neurodegenerative diseases. This, in turn, revealed that similar pathways were being attacked by the virus and mutated in other disease states. We found that one thing informed the other, and a greater value was brought in as we considered the entire disease spectrum.

One of our international relationships with the Institut Pasteur in France, which had been formed before the pandemic, blossomed beyond our expectations as COVID unfolded. They had been testing the effects of compounds and drugs on viral replication in their BSL-3 facility, and the collaborations among scientists has kept growing. This particular relationship brought us support from the French government. As of October 2022, a formal agreement has been signed between UCSF-QBI and the Institut Pasteur to form a Center for Emerging and Neglected Diseases based in San Francisco at QBI. The objective is for this center to turn into the first Institut Pasteur in the United States (https://www.the-microbiologist.com/news). Importantly, the relationship has also brought support and attention from the NIH, the University of California system, and others as it progress.

We live in a reality that undeniably will involve more pandemics in the coming years. Climate change is no longer an alternative debate, but a reality. This, in turn, affects neglected and emerging diseases and expedites zoonosis. If we learned anything in the recent pandemic, it is that a cohesive team response can bring about more immediate and concrete results. As we look to the (immediate) future, by learning from the last three years, we need to have action plans in place to respond in an even more expedient manner to lessen the loss of human life.

WEB RESOURCES

Quantitative Biosciences Institute (QBI), http://qbi.ucsf.edu

Collaborations, http://qbi.ucsf.edu/collaborations

Zoic Labs visualization interactive map, https://ppi.zoiclabs.io/#/

Blog: Hunting for a cure for COVID-19: an insider's story, https://pharmacy.ucsf.edu/news/2020/03/hunting-cure-covid-19-insiders-story

A QCRG Minute, https://www.youtube.com/playlist?list=PLR9EaLfVfcwbcvhKgdxB4AHB8wzQ7pO03

Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern, https://www.niaid.nih.gov/research/antiviral-drug-discovery-centers-pathogens-pandemic-concern

QBI Coronavirus Research Group (QCRG), https://qcrg.ucsf.edu

Institut Pasteur and UCSF QBI team up to create center of excellence, https://www.the-microbiologist.com/news

"We were made for this": How Slack became king of the remote-work world, https://www.fastcompany.com/90490741/we-were-made-for-this-how-slack-became-king-of-the-remote-work-world

FASTGRANTS, https://fastgrants.org

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5. Slack is a trademark and service mark of Slack Technologies, Inc., registered in the U.S. and in other countries

6. Gordon, D.E., Jang, G.M., Bouhaddou, M., Xu, J., Obernier, K., White, K.M., O'Meara, M.J., Rezelj, V.V., Guo, J.Z., Swaney, D.L., et al. (2020). A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature *583*, 459–468.