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The making of the Biohub

The Chan Zuckerberg Biohub is both an institute and an academic network devoted to accelerating research via cutting edge technologies and open science. Its focus on single-cell analysis and infectious disease has placed it front and center in the pandemic.

Laura DeFrancesco

A global pandemic is something Joe DeRisi has been preparing for his entire career. What he didn't expect was that the viral scourge would ravage so close to home. DeRisi was in the process of standing up sequencing technology to help researchers in ten low- to middle-income countries detect known, emerging or novel pathogens. In early January, during a visit to one such station in Phnom Penh, Cambodia, his cloud-based IDseq tool, developed for scanning metagenomics data, sequenced the first full length COVID-19 genome in country — in a few days, rather than the weeks it usually takes when samples are sent away for analysis.

Before long, the virus had arrived on his doorstep in San Francisco, California, and DeRisi and his colleagues pivoted to throw their considerable technological expertise and infrastructure at it. They set up a COVID-19 testing lab and recruited several hundred skilled volunteer researchers from around the Bay Area. With the help of California governor Gavin Newsom, as well as the administrators at their sister institution the University of California, San Francisco (UCSF), the necessary permits were acquired and a fully functional and accredited clinical lab was launched — this time in just eight days.

The pivot on a dime was possible because the Biohub is funded by the Chan Zuckerberg Initiative (CZI) — a philanthropy set up by pediatrician Priscilla Chan and tech titan Mark Zuckerberg to leverage technology, community-based solutions and collaboration to accelerate education, justice, opportunity and science. Together with Steve Quake of Stanford University, DeRisi is co-president of CZI Science's Biohub, the first major collaboration to come out of CZI's Science initiative. The Biohub is an experiment combining the complementary strengths of three Californian academic institutions: Stanford, UCSF and UC Berkeley. The Chan

Leading the charge: Biohub co-presidents Joe DeRisi of UCSF and Steven Quake of Stanford University were instrumental in designing the Biohub before taking the helm. Credit: Tyler Mallory, Chan Zuckerberg Biohub

Zuckerberg Biohub's core principles of enabling technology, collaboration and open science are what enabled its turbocharged response to the pandemic.

What is the Biohub?

In 2015, Priscilla Chan and Mark Zuckerberg pledged 99% of their wealth derived from Facebook shares over their lifetimes to launch CZI. The initiative takes on numerous scientific as well as societal issues, among them prison reform, the homeless problem in the Bay Area, and equity gaps in remote learning. In 2016, the couple announced they were expanding CZI to include science, and as part of that announcement, they pledged \$3 billion over ten years to support science and technology that would make it possible to cure, prevent or manage all diseases by the end of the century. After broad consultations in the scientific community, the couple made the first major investment of CZI Science, with \$600 million in endowment over 10 years, to form the Chan Zuckerberg Biohub. "Folks from across the board were willing to talk with us, share ideas, share where they think there is an unmet need," Chan says. Chan is a scientist/pediatrician herself and takes the lead on science issues.

But it's not all Chan. Zuckerberg's fingerprints can also be seen in the emphasis on developing technologies that cut across fields, as opposed to focusing on particular diseases as much of other philanthropic

science does. One question Chan asked of all the consultants was how can science be accelerated. By distilling down the answers, CZI came up with an answer: "giving researchers the tools and technologies they need to do their best work," she says.

Chan also wanted "to change the incentive structure away from tenure or publishing papers, allowing researchers to go deep on an issue." Thus, the Biohub instituted an extramural program with roughly a third of its funds to support research considered too risky to receive federal funding (Fig. 1). To foster collaborations, their grantees, who work in

disparate areas of biological science, meet twice a month to share their findings and discover areas of common interest that they might not otherwise be aware of.

Catherine Blish, a Stanford immunologist and Biohub investigator since 2017, says the environment of sharing has been more important than the money. "The investigator meetings are a fantastic opportunity to learn about new approaches, new ways of applying old approaches, and generally stretch the boundaries of what seems possible. Dozens of new collaborations have developed based on lunchtime conversations at these meetings," she says. A recent *Nature Medicine* paper from Blish's lab illustrates the value proposition. "Through Biohub connections, we were able to share the data in a readily accessible portal, well before our paper was accepted, so that investigators throughout the world could use it to test hypotheses."

With DeRisi and Quake at the helm, Chan and Zuckerberg had the perfect pair to head such a project. With a background in physics, Quake has developed numerous enabling life science technologies, which have been the foundation for over a dozen startups. DeRisi built an early version of a cDNA microarrayer while a graduate student in Pat Brown's lab at Stanford, a technology that transformed the field of gene expression profiling in the nineties. His other inventions include the Virochip, a microarray containing probes for all known viruses, and more recently IDseq, a cloud-based tool for analyzing next-generation sequence data. IDseq delivers to sequencing labs around the globe the considerable computing power required to fish for pathogens in metagenomics data. "A lot of those places were hamstrung by the inability to analyze the data or even

Fig. 1 | Chan Zuckerberg Biohub's work. Source: Chan Zuckerberg Biohub.

Box 1 | Open science on steroids

One point of commonality between CZI founders and co-presidents is a commitment to open science. In 2017 Chan and Zuckerberg donated an undisclosed sum to the preprint server bioRxiv, along with technical support to develop better tools for creating machine-readable and searchable platforms for manuscripts. Again in 2020, as the pandemic put stress on preprint servers — which went from publishing a few percent of Ebola and Zika virus pandemic-related manuscripts in 2014–2015 to publishing fully half of COVID-19 manuscripts, more than 18,000 as of August — the couple supported the medical preprint server medRxiv with a \$2 million donation. This is only one part of CZI's Open Science initiative, which supports various platforms that facilitate

data sharing across disciplines, such as ASAPbio, protocols.io and the Essential Open Source Software for Science initiative.

Both Quake and DeRisi are vocal advocates for open science. Quake said that when he and Joe were brought into the discussion on ways of accelerating science, they decided that the most practical way to do that was to eliminate publication delay. Using a back-of-the-envelope calculation, Quake estimates that getting rid of publication delays [could speed up scientific discovery by fivefold](#). “If you think of one discovery depending on the next, the earlier people know what their colleagues are doing the faster they can benefit from that.” So they made it a rule that everyone they fund has to publish all their work — not just the work that the Biohub funds —

as a preprint when they submit for peer review. Surprisingly, to Quake, everyone agreed. “I thought we’d get pushback, but we didn’t. Amazingly, everyone agreed to do it. We hit the zeitgeist right.”

Quake is clear that preprints remain primarily a means of rapid communication among the research community. He generally doesn’t speak with the press about research findings until they are associated with a later peer-reviewed publication. “It’s there for experts and we’re not out there pounding the drum,” he says. He thinks excessive media attention to preprints will recede once the pandemic is over. “In normal times, science is not front-page news. We go unnoticed except by the experts,” he says.”

participate in this sort of thing. So that really led to this concept of IDseq, to bridge the compute and storage barrier and make metagenomics sequencing accessible to low- and middle-income countries where the infectious disease burden is the heaviest,” DeRisi says.

Reaching out

The CZ Biohub now employs 100 scientists, engineers, data scientists and operational support personnel at their site, a 60,000-square-foot building in San Francisco, and provides funding to another 100 projects at the three universities through their investigator program. According to Gajus Worthington, COO of the Biohub, “These awards are selected based primarily on assessment of individual scientific potential and the catalytic effect that additional unrestricted cash would have on the scientists’ research.” The Biohub has spent \$190 million, a little more than half (\$107 million) in investigator awards.

The administrative structure has some similarities to the venerable Howard Hughes Medical Institute (HHMI) in that it funds both intramural and extramural research. (Both DeRisi and Quake were HHMI investigators before becoming leaders of the Biohub.) One difference is that, except for Quake and DeRisi, the Biohub investigators retain their university affiliations, whereas HHMI’s investigators are employees of HHMI while retaining university affiliation in all other ways.

One scientist whom Chan consulted early on was Rockefeller’s Cori Bargmann, a neuroscientist with experience as a co-chair of another grand science adventure: the

Brain Initiative from the NIH, started under the Obama administration. She helped design the program that, since its inception in 2013, has invested almost a billion dollars in research funding for neurotechnology tools to map brain circuitry. In 2016, Bargmann was brought on as head of science at CZI, and in that role she works closely with DeRisi, Quake and others to define priorities and foster collaborations between the various arms of the CZI. “This is part of my history — going from thinking of myself only as a scientist to thinking, hey, I can help other people do good work too,” she says.

According to Bargmann, in designing the Biohub, they engaged in the proverbial thinking outside the box: “You don’t want to just duplicate what everybody else is doing and throw a few more dollars in,” she says. “We wanted to push forward the development of certain types of tools that could be used in many different diseases.” As an example, she points to the single-cell platform developed by Quake and collaborators. In 2018, the first of what would be a torrent of publications [came out in *Nature*](#): the so-called Tabula Muris, a compendium of single-cell transcriptomes from 100,000 cells derived from 20 organs of the mouse *Mus musculus* (see [Bioengineering Community post](#)).

Although a boon for basic researchers, the cell atlas program has already had a real-world impact in the fight against COVID-19. Datasets generated at the Biohub have been contributed to the [COVID-19 Cell Atlas](#), a collaborative effort to compile all that’s known about cells infected with COVID-19. In addition, researchers from the Bill & Melinda Gates

Foundation dipped into the Biohub’s Tabula Sapiens lung atlas to verify an observation they made — that COVID-19 infection affects surfactant-producing cells in the lung. (Surfactants make breathing easy by reducing surface tension at the air-liquid interface of alveoli.) This relates to ongoing Gates-supported projects to develop therapies for premature infants, many of whom suffer from deficiencies in surfactants. Having verified this result, the foundation is sponsoring [a clinical trial in patients with COVID-19 in Southampton, UK](#).

In the trenches

The pandemic response at the CZI has been broad and deep — everything from supporting the transitioning of the Biohub to a diagnostic testing service to setting up a database for COVID-19-related research within bioRxiv and medRxiv (see Box 1) and community outreach at many levels. The Biohub was on it from day one. According to Quake, they didn’t close for even a day; whereas most labs in the Bay Area were shut down, pandemic-essential work at the Biohub was allowed to go on. In addition to the diagnostic lab, there are efforts to test serological assays, sequence genomes, and produce proteins for assays and vaccines, as well as design vaccines. They even helped launch an engineering project at Stanford led by David Camarillo to design a single-use ventilator, the COVID-19 Rapid Response Ventilator, which is now being manufactured.

The diagnostic lab fell into the lap of Emily Crawford, who had been working with Joe DeRisi as a postdoc before

Biohub infectious disease team leader Emily Crawford stepped up to lead a team of researchers to convert their labs to a fully functional CLIA lab. Credit: Chan Zuckerberg Biohub

becoming a group leader in the Biohub's infectious disease initiative three years ago. Her lab was working on integrating next-generation sequencing into the clinical care of infectious diseases, to improve discovery of pathogens in a sequencing milieu where the vast majority of the reads map to human sequences — “to find those needle-in-a-haystack pathogen genes,” she says. More recently, she was working on a rapid, CRISPR–Cas12-based diagnostic for tracking antibiotic resistance, which has some parallels to pandemic tracking: with a quick diagnostic, you can see if and where antibiotic resistance is spreading and hopefully tamp it down. As she was trying to eliminate an amplification step in the process, which would have made Cas12 more adaptable as a rapid diagnostic, COVID-19 came along and all work came to a halt.

Because of her lab's relationship with the clinical testing lab at UCSF through various sequencing projects, it was natural that they would come to the Biohub for help with COVID-19 testing. Crawford was put in charge of the COVID-19 task force and quickly (and thankfully) found herself surrounded by eager volunteers, with all manner of expertise needed to create a fully functioning CLIA (Clinical Laboratory Improvement Amendments) clinical lab — including administrators who took on the task of keeping the supply chain full, no easy

lift. With a capacity to run a thousand tests a day — many times what the UCSF clinical lab was able to do at the time — they were able to reach out to the larger community, prisons, nursing homes and eventually public health agencies throughout the state of California. “Some counties do screening of homeless encampments or farm worker communities, who work with uninsured people. We've made a conscious effort to promote our testing services in those areas. Since we are able to provide free testing, we want to make sure it goes to communities where they might not have other options,” says Crawford.

As part of the COVID-19 task force, Biohub data analyst Josh Batson and infectious disease group leader Amy Kistler have set up the COVID Tracker program. This program provides free whole-genome sequence data as part of surveillance in the Bay Area and beyond, listing not just who is infected, but where and how. By analyzing the relationships among cases in a company or community, they can provide critical feedback on whether infection containment efforts are working. When a company has a few cases, for example, looking at the sequences can tell whether the infection was spread at the company or whether the cases were independently brought in from outside. (One mutation, on average, occurs once every two weeks, or roughly every two or three transmissions.) Batson recalls

an example in which Humboldt County in northern California had a small number of cases and wanted to know whether they were experiencing community transmission. By comparing the sequences, Batson was able to give them a definitive answer: they weren't.

Their genome analyses also have shown that the early COVID-19 cases in Santa Clara were tamped down by the lockdown put in place in the five Bay Area counties in early March. A new variant that has spread globally and is now prevalent throughout the United States and Europe was not detected in those early Santa Clara cases, according to Batson. But since June, all the cases in the Bay Area have had the variant, which suggests a second, independent introduction from the East Coast or beyond.

Another big piece of the COVID-19 task force is data sharing: a pipeline has been created so that the data — some 1,100 SARS-CoV-2 genomes to date — are made accessible to the research community as quickly as possible, by uploading the data to several public databases and incorporating them into phylogenetic trees. “The international collaboration on bioinformatics pipelines for SARS-CoV-2 has been a beautiful thing; scientists all over the planet are focused on every minute detail of this genome, and we're all learning from each other in real time,” says Batson.

As a molecular biologist as well as an epidemiologist, Kistler is “living the vision. From a research perspective, this is really a rare opportunity, as the virus emerges in a particular geographical location, to be able to watch it spread and watch it evolve,” she says.

Alex Marson, an immunologist at UCSF and the Gladstone Institutes who has been part of the Biohub's extramural investigator program since its earliest days, found himself heading up a cast of over 50 researchers, doing quality control on some of the many serological tests that flooded the market in the rush to fill in gaps created by insufficient COVID-19 diagnostics. “Test performance analysis lagged behind the availability of the tests, and I had a huge interest in our lab in contributing and using our knowledge of immunology during the crisis,” he says. The group tested ten lateral flow assays and two enzyme-linked immunosorbent assays (ELISAs) with serum obtained from patients at different time intervals from the onset of symptoms. They observed a range of outcomes: some tests performed better at detecting antibodies and some had higher rates of false positives, information that is critical to using the tests in a clinical setting. “It was an outpouring of energy; even that long list [of authors] belies the full extent of the

people and the effort that went into it,” says Marson.

Whereas Marson has handed off the serological testing to the National Cancer Institute after some back and forth, for others, there is no end in sight. For Batson and Kistler, their goal is to be a catalyst and disseminate this knowledge on capacity building within public health communities. “Five years from now, we shouldn’t be doing this work, we should be doing the next thing and know that we helped get this going,” says Batson. “We hope that a lot of this capacity will transfer over to public health and there will be reinvestment in public health,” which they all agree was not up to the task of handling a pandemic. Crawford feels driven to continue with what she is doing. “I feel fortunate to have been in a position that it was so clear from the very beginning that my professional skills were exactly what was needed. I don’t have a single ounce of regret about continuing in the vein I am now,” she says.

The future of philanthropy science?

Four years into the CZI Biohub experiment, it may be too soon to judge whether it’s on the path to accomplishing its goals. Gerald Rubin, founding director of HHMI’s freestanding laboratory arm, the Janelia Research Campus, says it took about ten years before he was confident that what they were doing was going to work, as well as what parts were working less well.

Marson thinks that they have yet to tap the full potential of the Bay Area. So much is happening — with the Biohub, the Parker Institute for Cancer Immunotherapy, Jennifer Doudna’s Innovative Genomics Institute, and Marson’s own newly announced Gladstone-UCSF Institute of Genomic Immunology. “There’s enormous amount of opportunity in the Bay Area, and the Biohub is a main part of bringing it all together,” he says.

There are further parallels between HHMI and the Biohub, which is not surprising because all the principals at CZI and the Biohub were once part of HHMI. Rubin feels that the value of both these institutes lies in the ability of their investigators to take on risky science. “We’re trying to do things that are difficult to do in universities because of the siloing that goes on in universities, and the way people are evaluated — physicists are judged by other physicists not by biologists.” At Janelia, they picked big problems requiring a diverse set of skills that cross disciplines — like building a better microscope and determining the basic circuitry of the brain, which grew into the Brain Initiative — and threw money at them. “I applaud the Biohub for setting up a distinct research culture; we need to explore a wider variety of non-academic research models. In my mind 1–2% of research is funded in that way; we should probably have 10–20%,” he says.

Bargmann is placing her bets on young investigators to seed the future of research. In some of their grant programs, investigators have to be within ten years of receiving their advanced degree. (Rubin did something similar at Janelia, hiring some investigators straight out of graduate school.) Bargmann gives a couple of reasons for CZI focusing on junior scientists. “We have seen that it’s not easy for young scientists to get funding from federal organizations. So, we feel that we are stepping into a place where there is potential. But we are also doing it because there’s evidence that people often do their most creative and ground-breaking work in their 30s,” she says.

When the Biohub will return to its mission, or whether pandemic response will become a permanent part of their mission, remains to be seen. For now, the researchers involved wouldn’t change a thing. As Crawford sums it up, “There are great medium- and long-term benefits to all the research going on, and I don’t want to lose sight of that, but we have to meet the moment and realize there are ways that we can make relatively small personal sacrifices, of putting our lives on hold for a little bit, to really have an impact.” □

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