Cell

Silicon Valley Meets Biomedical Research in the Chan Zuckerberg Initiative

The Chan Zuckerberg Initiative, the philanthropy launched by Facebook CEO Mark Zuckerberg and his wife Priscilla Chan, drew attention with its stated goal of helping to "cure, manage, or treat all diseases" by the end of the century. They intend to do it through funding basic research and addressing gaps in biomedical technology.

When pediatrician Priscilla Chan and her husband Mark Zuckerberg of Facebook announced their intention to found a research-funding philanthropy that will try "to cure, prevent or manage all diseases by the end of this century," many observers were skeptical. The goal is massive. After all, the US federal government invested more than 30 billion dollars in the National Institutes of Health in the 2016 fiscal year alone, and even though the Zuckerbergs have pledged to eventually donate 99% of their fortune to the philanthropy, the newly launched Chan Zuckerberg Initiative (CZI)'s science budget so far is only 3 billion. However, CZI's science strategy—at least in its first decade of existence—will focus not on diseases themselves but on developing technologies and tools that biomedical scientists can use to explore a wide range of questions.

"We have to recognize that there are a lot of other funding agencies out there—that we are 1% of the size of the NIH budget, smaller than Howard Hughes [Medical Institute]—and so we need to think about what we can do that's unique and impactful," says CZI President Cori Bargmann. "By developing tools and technologies, we can raise everyone's game and advance all of science," she added.

The Chan Zuckerberg Initiative is not the first private philanthropic LLC to tackle basic research, but they hope to leverage their Silicon Valley connections to tackle technology problems in biomedicine that other organizations haven't. "We've heard a number of philanthropists struggling with the issue of how to help with this [data analysis and data management]," says MIT professor and president of the Science Philanthropy Alliance Marc Kastner. The Zuckerbergs consulted with the Science Philanthropy Alliance during the earliest stages of planning the CZI, but neither Kastner nor the alliance is formally CZI-affiliated. "Part of the problem is just the salary structure because these kinds of folks [computer analysts] can get such high salaries in industry," he continues. "The Chan Zuckerberg Initiative seems to really be tackling this head-on by hiring really outstanding computer scientists and developers and letting them address some of the problems that the scientific community has."

Rather than letting software engineers choose the problems, the CZI has turned to researchers themselves. CZI leadership met with several non-CZI-affiliated researchers in a series of workshops, the most recent of which was hosted at Stanford, and asked: how can we help biologists analyze their data?

Cori Bargmann, President of Science of the Chan Zuckerberg Initiative

In these conversations, two areas stood out as places where improved computational tools could make a world of difference: single-cell data (such as transcriptome data that track changes in cells over time) and next-generation microscopy (where rendering an image or video requires computing thousands upon thousands of three-dimensional data points). Both are areas where the amount of data being collected is growing exponentially but the analytical tools are not.

"When I was a graduate student, I would do an experiment, and it would take me a month," says Bargmann. "And I would look at the results for ten minutes, I would think about it, and then I would spend another month doing the next experiment. Now it's the exact opposite. Someone in my lab can take a movie in ten minutes that takes them the next month to analyze. So it's a tremendous challenge to understand the sort of dense signals we can generate from the cutting-edge microscopes and from movies and four-dimensional datasets."

Distributing the analytical tools needed to make sense of these datasets may prove even more vital than distributing the lab equipment. Some programs, like Janelia Farm's Advanced Imaging Center, follow a model in which biologists can visit the center, collect the data they need over the course of about a week, and then return their home institution to analyze the data there. If this model became more widespread, it would allow researchers at smaller institutions to ask questions that can only be answered with advanced lab equipment. However, researchers at those institutions would still need tools to find signals in their data. That's where the Silicon Valley and its fondness for computing clouds comes in.

"Part of our job is to make it easy for any one scientist to use the giant volume of data with a collection of cloud tools that are simple yet powerful," says CZI's chief technical officer and former Amazon executive Brian Pinkerton. "A lot of these [scientific] institutions have data centers of their own or they rely on government data centers … Public clouds are now where it's easy to get cheap computing, so it's a lot better to have your data on

Steve Quake (left) and Joe DeRisi (right), Co-Presidents of the Chan Zuckerberg BioHub

those than locked up on a data server in the closet.''

Data sharing is a core value for the organization. The CZI not only encourages authors to publish in open-access journals and make datasets publicly available online, they go a step further and ask that all code developed in support of CZI-funded studies be published on public code depositories such as GitHub.

Many of the CZI's initial efforts focus on The Human Cell Atlas Project. The goal is to build a publicly available database that will organize molecular data gathered by hundreds of labs into a coherent map of ''every cell type in the human body.'' The Atlas will likely include gene expression data, microscope images, and interaction networks that show how cell types affect each other, among other types of data. CZI is not the only organization involved in the Cell Atlas Project but, rather, is part of a scientific network that also includes the Wellcome Trust's Sanger Institute, as well as organizing committee members from 17 institutions in 10 different countries.

''We want to create a catalogue of all the cell types in the human body in both health and disease. We think that's going to be a really fundamental resource not just for basic science and physiology but a powerful new resource for development of therapies for a variety of human disease,'' says Stanford biophysicist Stephen Quake. Quake is also co-president, along with UCSF's Joe DeRisi, of the Chan Zuckerberg BioHub, a biomedical research center that Chan and Zuckerberg have established in San Francisco. The CZ BioHub is a non-profit organization, separate from the Chan Zuckerberg Initiative LLC, but the two organizations share some common goals: both are focused on developing technology platforms for enabling basic research, with the long-term goal of addressing all human diseases.

Quake says that there will probably be a draft version of the Cell Atlas database in about five years but notes that molecular sequencing technology is changing rapidly and that ideas about what constitutes a ''cell type'' vary widely. (In fact, one of the ice-breakers at the Stanford Cell Atlas meeting was Quake asking all of the attendees to write their estimate of the number of cell types in the human body on their name tags. The range was ''huge,'' Quake says.)

However, genomics researchers largely agree that a comprehensive database of cell types is needed. ''Nearly everything that we've done in genomics/'omics' to date using tissues from human or really any multicellular organism has been confounded by cellular heterogeneity … Until we are able to obtain single-cell resolution, we'll be fundamentally stuck,'' genomicist Jay Shendure of University of Washington wrote in an email to *Cell*. Shendure attended the Stanford Cell Atlas Meeting but is not affiliated with the CZI or the CZ BioHub.

''Comprehensive cell atlases of human as well as model organisms will be foundational resources, much like the reference human genome is, for understanding normal physiology and development, as well as what goes wrong in disease,'' he wrote.

Shendure also mentions that one potential pitfall ahead of the Cell Atlas project is the temptation to publish a draft atlas as quickly as possible at the expense of a well-thought-out framework for the data. He writes, ''I hope that there is a phase that supports the development and integration of diverse technologies that support this long-term goal, rather than prematurely turning this into a data production project.''

However, some observers are still skeptical. Shobita Parthasarathy, a professor of public policy at University of Michigan who analyzes large-scale biotech projects, notes that Human Cell Atlas is very similar to the Human Genome Project and that the CZI's emphasis on collaboration closely mirrors the collaborative spirit of the Obama administration's Cancer Moonshot program. ''I'd argue that the Cancer Moonshot was, in fact, more innovative because it really explicitly addressed questions around data sharing and intellectual property, and the CZI doesn't, as far as I can tell from their public statements,'' she says. ''So it's not clear to me what exactly is so new.''

Another common criticism of the CZI is that the leadership may be underestimating the difficulty of translating and distributing the benefits gained from biotech projects. Today, many diseases go untreated, not because we lack the scientific knowledge to treat them but because of a lack of economic incentives for drug manufacturers or because of difficulty convincing patients to opt in to new treatments. So far, the science arm of the Chan Zuckerberg Initiative seems to be focused exclusively on basic biology research.

Many, however, are welcoming the CZI's emphasis on basic research. ''I am very enthusiastic about CZI's emerging plan to take a lead role in the development of a[n] open-access cloud-based database and associated informatics tools that will enable researchers from all over the world to get access to the Human Cell Atlas data and make fundamental discoveries about human biology,'' NIH director Francis Collins wrote in an email to *Cell*. ''While basic science is also the cornerstone of NIH's diverse portfolio of biomedical research, our resources are currently insufficient to pursue all of the opportunities that are emerging at this remarkable time,'' Collins added.

The leadership of CZI itself remains optimistic that they can make an impact where few other groups have in biotechnology. ''We are in a really strong position to bring modern computer science and artificial intelligence and machine

learning to biology on a larger scale than has been possible,'' says Bargmann. ''We have the connections in the community. We have the local expertise. This is an opportunity that has not yet reached its full development in the existing system. The algorithms that Amazon uses to sell you books are more sophisticated than the algorithms we have for searching the literature. We have an opportunity here to help turn that around.''

Pinkerton, the chief technical officer, agrees, saying ''We have some goals, we're relentlessly attacking those goals, we want to make a big impact. We're not going to be satisfied with doing something small.''

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