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Can Scientists Develop Drugs for Genetic Diseases by Studying Those Who Should Have Them, but Don't?

BY JESSICA KIM COHEN

NEW YORK – Some people with harmful genetic mutations never develop the diseases doctors would expect them to. Researchers hope to study these individuals and design new treatments for rare genetic conditions in a new phase of the Resilience Project.

The research program, dubbed the Resilience Project 2.0, builds on the original Resilience Project, which launched in 2013 and was led by researchers at the Icahn School of Medicine at Mount Sinai in New York and Sage Bionetworks, a biomedical data-sharing nonprofit, that had sought to explain why some patients with known pathogenic mutations don't get sick.

Now, under the Resilience Project 2.0 banner, collaborators seek to create a drug discovery platform to identify therapeutic targets for rare genetic diseases, not by homing in on variants in the disease-causing genes but by targeting variants in other genes encoding proteins that stave off the disease symptoms. These variants are known as second-site suppressor mutations.

"There are so many genetic diseases where there's a known alteration, but the known alteration isn't a direct path to a therapy," said Stephen Friend, president and cofounder of 4YouandMe, a nonprofit studying chronic diseases with digital tools. "Is there a way to find targets that haven't been considered?"

Friend is leading the Resilience Project 2.0 with Eric Schadt, dean for precision medicine and a professor of genetics and genomic sciences at the Icahn School of Medicine. Friend and Schadt cofounded Sage Bionetworks in 2009 and were two of the leaders on the original Resilience Project, in which they aimed to screen 1 million people for highly penetrant disease-causing mutations and identify healthy individuals who should have developed illnesses like Huntington's disease.

In the second phase of the project, Friend, Schadt, and other collaborators are looking to treat rare diseases caused by genetic mutations that are highly penetrant. They will start by identifying patients from biobanks like the US National Institutes of Health's All of Us Research Program and the UK Biobank who haven't developed a genetic disease, despite carrying a known pathogenic mutation — suggesting there might be an alteration in another gene that protects them. There are other factors that could inhibit disease onset besides genetics, Friend noted, such as environmental influences.

But if the Resilience Project 2.0 can identify second-site suppressors for even a subset of rare diseases, that would still be a promising foundation to possibly treat some patients, Friend said. They hope to collaborate with a coalition of investigators and advocates from academic centers and nonprofits and identify proteins encoded by second-site suppressors that could be exploited by drugs.

The researchers envision having collaborators from different institutions lead various teams, such as a group that identifies genes of interest, others that study mechanisms of suppression, and those that develop lead compounds.

In the original Resilience Project, researchers partly met their screening goal, analyzing genomic data from nearly 600,000 patients. From that analysis, they identified 13 so-called "resilient" patients who, for unknown reasons, seemed to continue to live healthy lives despite having a mutation that was strongly associated with a severe, childhood-onset Mendelian disease. However, since researchers weren't able to recontact the patients

whose genomic data they mined, they couldn't rule out the presence of unreported disease symptoms.

Now, in this second phase of the project, researchers will analyze existing genomic databases to identify drug targets. They hope that pinpointing and prioritizing drug targets that have shown promise at suppressing disease in real-world, existing datasets will be a more cost-effective drug development strategy.

Once they've identified "resilient" patients, they plan to use machine learning to analyze genetic and clinical data from their linked medical records to identify potential functional relationships between proteins and flag mutations that could be second-site suppressors. From there, collaborators will further explore and, hopefully, validate these mutations in cell lines, in vitro and in vivo functional assays, and other approaches.

After identifying promising candidates, they'll be able to design therapies and test them in patients within Phase I and Phase II trials. Researchers expect to develop small molecule and antibody therapies but are open to other, more affordable approaches, Friend said, acknowledging that there are some advanced techniques that may be cost-prohibitive for this effort. "We've assumed that most of the gene therapy approaches have patents and intellectual property that make it hard to make affordably," he said.

Friend wants to do this project in collaboration with patient advocacy groups that are already working on finding treatments for rare genetic diseases and can guide the work as founding partners. That includes weighing in on whether a promising candidate in early-stage studies should move into later-stage trials and enter the regulatory path, and if so, how to achieve that.

The project's leaders hope to raise awareness and find potential partners through an online survey to patient advocacy groups. Genetic Alliance — a nonprofit that works with patients and families to accelerate research into genetic diseases — will distribute the survey to organizations in its network.

Friend and Sharon Terry, CEO of Genetic Alliance, hosted a webinar last week to try to engage advocacy groups. During the webinar, Friend emphasized that most patients with a rare genetic disease don't have access to affordable treatments. While there are some rare diseases for which there are treatments, those might cost hundreds of thousands, if not millions, of dollars.

"I'm really looking for how we can get therapies that don't have that cost barrier," Friend told patient advocacy organizations on the webinar.

Biotech companies marketing rare disease treatments argue that the sky-high price tags are necessary to recoup development costs, as it's a massive investment to develop drugs that, ultimately, will be sold to a very small patient population. These challenges have led some companies to drop programs for rare diseases or seek partners.

Friend has been approaching foundations and nonprofits to see if they're interested in funding the Resilience Project 2.0, with the understanding that they won't see the fruits of their investment quickly. The project's leaders are looking for organizations that "are able to take a long-term view" of its potential, according to Friend. He hopes researchers involved in the project will identify a set of second-site suppressors that could be amenable for drug development within the next year, and then, he estimates it could take about three years to create possible drug compounds ready for clinical trials.

The Resilience Project 2.0 isn't looking to make a profit, and the work will be open source, without any patents filed, he added.

The biotech industry needs to try new drug discovery and development strategies, said Genetic Alliance's Terry, noting that the current model of drug development isn't working, especially for rare diseases. Even new treatments for more common conditions require hundreds of millions of dollars to develop, and without taking into account early discovery and preclinical work, nearly a decade to advance from clinical testing to the market. Most experimental drugs won't even make it to market.

In contrast, the leaders of the Resilience Project 2.0 hope their target identification approach using existing genomic data, focusing on suppressor genes, and the partnered development strategy will cut down costs and reduce the development timelines. It offers a promising opportunity to find a new drug development strategy for rare genetic conditions. "We have to stop doing business as usual," Terry said. "I'm very eager for us to try as many novel ways of working as we can."