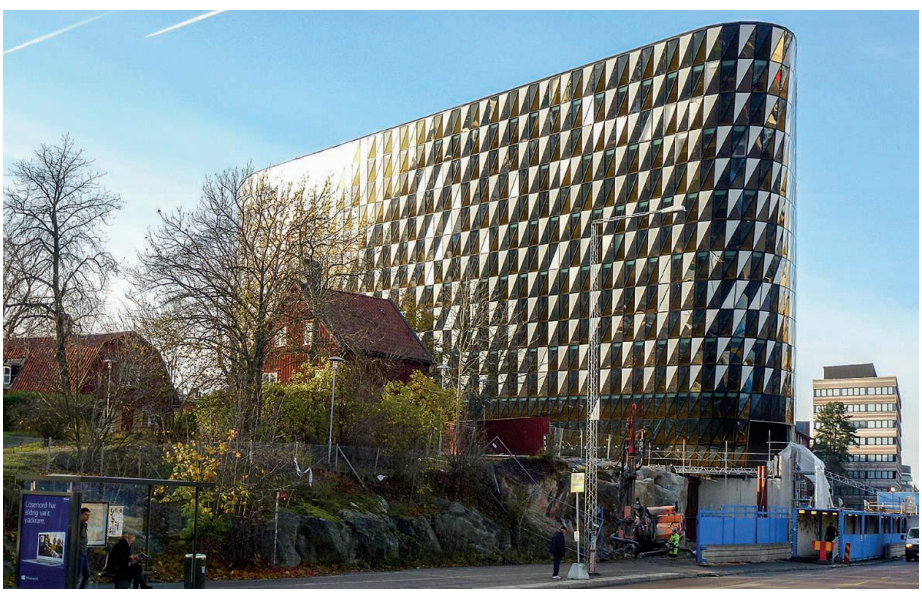
on 31 August, and KI's own report a few days later. Both concluded that Macchiarini should never have been hired; administrators ignored "strikingly negative" references from Macchiarini's previous employers as well as irregularities in his CV. Once he was on board, the reports found, loose oversight allowed him to skirt ethical regulations. "There was a stunning lack of interest in learning more about his work before extending his contract," said Sten Heckscher, a former president of Sweden's Supreme Administrative Court who headed the KI investigation.

In response to the reports, Swedish Minister for Higher Education and Research Helene Hellmark Knutsson fired the country's chancellor in charge of all public universities, Harriet Wallberg-Henriksson, who was KI's vice-chancellor when Macchiarini was hired. The minister also dismissed all remaining KI board members who were active during Macchiarini's tenure. (Five board members had already stepped down.) Nobel Assembly leaders asked Wallberg-Henriksson and Hamsten to resign their memberships.



The Karolinska Institute in Stockholm fired Paolo Macchiarini last March.

Meanwhile, a CEPN report issued on 9 September found scientific misconduct in a paper on rat esophagus implants that Macchiarini published in *Nature Communications* in 2014. Among other problems, the panel found no data to support the claim that the recipient animals had recovered and gained weight. (The journal says it's investigating.) As *Science* went to press, the agency was about to release another report, on papers describing the artificial scaffolds. Conclusions about two key *The Lancet* papers describing successful human implant surgeries are expected later this year.

Macchiarini, who faces criminal inquiries, including possible manslaughter charges, did not respond to *Science*'s requests for comment last week. Swedish television, however, reported on 5 September that he again denied any wrongdoing.

Swedish scientists are left wondering how things went so terribly wrong. Macchiarini was exceptionally persuasive, notes Anders Ekbom, a clinical epidemiologist at KI. In January, *Vanity Fair* reported that Macchiarini had told an NBC news producer with whom he had an affair that he had treated many world leaders, including two popes; he also convinced her that Pope Francis would marry them. Rosling says the *Vanity Fair* story helped KI leadership see that they, too, had been deceived: "It pinpointed that there was a deep personality problem with Macchiarini."

Another part of the problem, according to the KI report, was "a growing fixation on excellence" at the university and "the aspiration to close the gap between research and its application in healthcare." The fixation is natural, Rosling says: "There is nothing more wasteful and boring than mediocre research. We need spectacular new research findings," he says. But although hiring Macchiarini may have been understandable, he says, "the serious thing here is the failure to rectify the mistake."

Ekbom hopes the dismissals and resignations will give KI a fresh start. "If something good comes out of it—better routines, better safety—the net outcome after this drama will be a better Karolinska," Gerdin adds. "That is what we hope." ■

BIOMEDICINE

Cystic fibrosis foundation opens drug discovery lab

Funded by a drug royalty bonanza, lab seeks novel ways to target mutations

By **Bijal P. Trivedi**

The Cystic Fibrosis Foundation (CFF) is once again breaking new ground. In 2000, with little beyond symptomatic relief available for the inherited, life-threatening condition, the Bethesda, Maryland–based foundation hired a biotech company to develop more effective treatments. The move, unprecedented for a disease advocacy organization, paid off in two new drugs, the first to target the molecular root of the disease. But there is still no cure, and cystic fibrosis (CF) patients continue to die—467 in the United States alone in 2014. So on 19 September, the foundation is setting another precedent by officially opening its own independent laboratory in Lexington, Massachusetts, to speed drug development, funded primarily from the success of the two drugs it helped bring to fruition.

The goal of the new CFF Therapeutics Lab, says Preston W. Campbell III, the foundation's CEO and president, is to generate and share tools, assays, and lead compounds, boosting its partners' chances of finding treatments. Frustration with academic technology transfer agreements was a key motivation, he notes. University-based researchers funded by the foundation have to seek approval from their institution's legal department before sharing assays, cells, or any intellectual property, a hurdle that can take a year to negotiate. "This was killing us," Campbell says, "[but] if we created our own laboratory, we could not only focus on the things we wanted to focus on, we could also share them freely."

Margaret Anderson, executive director of FasterCures, a Washington, D.C.–based think tank and arm of the Milken Institute, believes other disease philanthropies will be watching the experiment. "I'm excited … and I would venture to say that the disease foundation community is going to be excited about it, too."

CF, which afflicts 30,000 people in the

For many with cystic fibrosis, available treatments only address symptoms, such as lung mucus buildup.

United States and some 70,000 worldwide, results from mutations in the gene for the CF transmembrane conductance regulator (CFTR)—a cell membrane protein that is crucial for salt-water balance in the lungs, pancreas, and gastrointestinal (GI) tract. The most common of the 1800 or so known mutations disable the ion channel, causing viscous mucus to clog the lungs and leading to serious infections and—without a lung transplant—early death.

The picture started to brighten with the arrival of the two drugs that CFF codeveloped with a California firm later acquired by Vertex Pharmaceuticals, headquartered in Boston. Orkambi, approved by the Food and Drug Administration in 2015, partially corrects a misfolding in the CFTR protein in people who carry two copies of F508del, the most common and deadly CF mutation. But Orkambi doesn't work alone—it requires another drug to make the CFTR protein functional. Kalydeco, approved in 2012, opens ion channels wedged shut by a rarer mutation, but it is also given with Orkambi. In 2014, CFF sold the rights to future royalties for these drugs to Royalty Pharma for $3.3 billion—money that it plans to fold back into research. Part of this windfall is funding the new lab, which has a budget of $6 million for 2016.

Its research is potentially critical because although the two recent drugs are game changers for some with CF, neither cures the disease, and they help only about half of all CF patients (see chart, right). In addition, both are extremely expensive, costing hundreds of thousands of dollars a year or more per patient—a price tag that has raised eyebrows, given CFF's role in their development.

To seek out new and better therapies, the lab—which has been up and running since December 2015—devotes about 70% of its activity to original research, with the remainder centered on developing resources for the rest of the scientific community. Its first priority is screening compound libraries to find a second generation of drugs targeting the F508del mutation; at least 90% of CF patients carry a single copy of this mutation.

The lab's director, Martin Mense, is an electrophysiologist who began studying the CFTR protein at The Rockefeller University in 2000 and then ran CF biology programs at two biotech firms. His team is also using high-throughput screening to identify compounds that suppress "nonsense mutations," which truncate the CFTR protein enough to cause the ion channel to malfunction. "We definitely have a number of molecules with interesting activity," says Mense, who is hoping to find something that corrects multiple CF nonsense mutations. That's a practical approach, because for some mutations the patient populations are so small that it is unrealistic to develop a drug for each one. If the lab succeeds, the benefits would go beyond CF, Campbell says, as many other diseases are caused by similar mutations.

The lab now employs about 23 scientists, drawn from both academia and the drug industry, but it has room for twice that number. Mense and William Skach, vice president of research affairs at CFF who leads its basic research, drug discovery, and preclinical therapeutic development, plan to add staff to bolster the lab's expertise in gene editing and stem cells. They envision editing stem cell genomes to reproduce rare patient mutations; the altered cells would then be differentiated into airway epithelium cells and used to screen for promising drug candidates.

Skach is also hoping to explore possible treatments: extracting patients' own stem cells, editing out their CF mutation, and repopulating their lungs, pancreas, and GI tract with healthy cells. Ultimately, he would like to edit out the mutation right in a patient's body. "If we can use gene-editing tools to fix the mutations in CF patients, then we can basically cure CF once and for all. That's where we want to go," he says. The foundation is moving swiftly in that direction. In 2015, CFF funded 50 labs and several companies to develop editing technology for the condition. "This is all rather futuristic by today's terms," Mense admits. "But you have to think a little bit ahead."

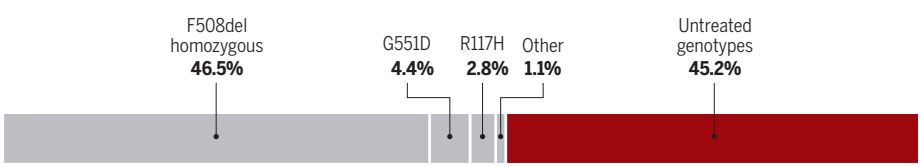
The new lab's in-house expertise will help the multibillion-dollar foundation evaluate the many outside projects it is asked to fund each year, says Eric Olson, the former head of Vertex's CF program, who oversaw the development of Kalydeco and Orkambi. "If you don't have people who have done those kinds of experiments, generated that kind of data, know the pluses and minuses of the experimental system, it is tougher to do true due diligence and evaluate," says Olson, now chief scientific officer at Syros Pharmaceuticals in Cambridge, Massachusetts, and a member of the board of trustees for CFF and the CFF Therapeutics Lab.

The foundation says it has no intention of developing drugs from scratch and stresses that it doesn't want to crowd other academic labs or companies out of CF research with its new venture. "We don't care who's successful," Campbell says. "We want success." ■

Bijal P. Trivedi, a writer based in Washington, D.C., is working on a book on cystic fibrosis.

A drug cabinet half-empty

Although two recently developed cystic fibrosis drugs can treat several mutations causing the disease (gray), nearly half of the people in a 2014 patient registry had mutations that don't benefit from either drug.



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