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45 Years of Research, Education & Support
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My CF Life Becomes the Public Reality

By Erick Burton

If you had told me six months ago that in our shared dystopian future I'd spend my days on Zoom while working from home, that I'd make wearing a mask in public fashionable and avoiding handshakes look thoughtful, or that I'd be running a health risk assessment on everything and everyone, I would have pointed out that you'd described my standard Tuesday (and everyday life) perfectly.

What a strange feeling it is to be surrounded by people forced to track and respond to the threats that have become background noise to me. What a strange mix of empathy and entertainment it is to hear friends and family complain about dry and overwashed hands, or watch them learn about how often they touch their faces, or take the mental journey from "masks don't work," to "everyone must wear masks or we'll all die."

I stopped social contact with the world shortly after the first case of COVID-19 was identified as "community spread" here in the San Francisco Bay Area. From the beginning, it was clear that the potential severity of the outbreak was being downplayed. Severely limited test availability and information were keeping confirmed numbers low and people calm. It did not keep me calm. I filled the vacuum of information with translated Chinese studies along with information from epidemiologists and scientists. The disease was here and on the loose, airborne(ish), and had been spread for who knows how long by people with no symptoms.

Erick Burton and his wife Ashley Hartoch.

For me, daily anxiety and fear could be measured by the difference between the data and the public response to the crisis. In late February, my wife, who works at a

Continued on page 4

Physiological Patient-Derived Airway Culture Models for Testing Cystic Fibrosis Therapeutics

By Martina Gentzsch, PhD, Marsico Lung Institute/Cystic Fibrosis Research Center, University of North Carolina at Chapel Hill, NC

Cystic fibrosis (CF) is caused by mutations in the CFTR gene and results in inflamed and infected airways with mucus obstructions. Rescue of F508del CFTR, the most common mutation in CF, is now feasible with the recently approved CFTR modulator treatment, Trikafta. The remaining 10% of CF patients with rare CFTR mutations may also respond to Trikafta or other novel treatments. However, direct correlation of in vitro laboratory data with clinical responses has not been fully established for these individuals, and they therefore remain without CFTR modulator therapies.

To optimize use of recently developed CFTR modulators for patients with rare CFTR

Continued on page 4

My CF Life Becomes the Public Reality

Continued from Cover

a hospital, was told by her employer in a "calm down conference" that there was nothing to fear from people who were asymptomatic. That was it for us; without credible safety information from her hospital, it was time to act. The fight to get her "work from home" rights was fraught with challenges because we were on the leading edge of the wave. The Stanford Adult CF Clinic came through for us with a letter and we were able to secure her right to work from home in order to keep us safe. Closing that last open loop of exposure was a profound relief.

I operate a small business without the capital necessary to weather six months to a year with minimal income. Our sales dropped to zero overnight. With no real visibility of what aid or resolution might look like, I made the decision to shutter the company and get my employees as far to the front of the unemployment queue as I could manage. I'm hopeful we'll be able to re-open this year. That decision has been made countless times across the country and I'll be forever grateful to those who have kept the lights on for the rest of us (looking at you Stanford CF Research).

Erick, Ashley and friends rocking masks even before it was cool. (Pre-COVID-19)

For me, managing the stress and anxiety of this unprecedented time has come down to a few habits that a life with CF has reinforced. Identify as many threats and benefits as I can, make a plan for each, and execute them when the time comes. Keeping the conversation this simple makes the highwire act manageable. We will return to society when the consequences of becoming ill change. If it becomes a choice between financial hardship and safety, we're choosing safety. We will not lose focus on the importance of disciplined living in order to live well later. In the meantime, I'll concentrate on exercise, connecting with my tribe, and losing the 'Trikafta 15'.

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Continued from Cover

mutations, we utilized precision medicine strategies to examine CFTR rescue in patient-derived nasal and bronchial epithelial cells. Specifically, we evaluated CFTR function, protein expression, and maturation by analyzing CFTR protein levels, processing, mRNA quantities, protein-turnover, electrophysiological responses by short-circuit current, CFTR single-channel characteristics in lipid bilayers, and volume changes of spherical cultures in response to currently available modulator compounds. Using these methods, our studies revealed insights into defects and rescue approaches for many rare CFTR mutations.

In addition, we are studying the impact of the in vivo environment for CF disease prognosis, and applying this knowledge toward improving physiological tissue-specific bioassays for therapeutic testing. We developed advanced models that incorporated the inflamed CF airway environment and observed that CF airway inflammation (induced by application of fluid from CF lungs) substantially augmented rescue of CFTR by various therapeutics. Our findings demonstrate the feasibility of in vitro evaluation of CFTR modulators utilizing personalized medicine models combining patient-derived cultures with an inflammatory stimulus acquired from the same patient. Furthermore, mass spectrometry data on pharmacokinetics and pharmacodynamics of CFTR therapeutics were collected to reveal information for optimizing drug dosage.

These biochemical and functional studies elucidated the effects of CFTR-targeting compounds on CFTR processing and function at a cellular level, with the goal of providing predictions of clinical efficacy based on comparison of in vitro responses to in vivo outcome measures. We have demonstrated the utility of 2D planar and 3D spherical airway cultures as an assay platform to characterize rare CFTR mutations to guide therapy optimization, which illustrates the power of ex vivo and in vitro biochemical, physiological, and molecular techniques to quantitate CFTR rescue to support diagnosis and treatment.

Our studies improve the accuracy of in vitro models for CF drug development, pre-clinical testing, and evaluation of personalized therapies. This project has immediate translational potential in providing relevant models for accurate elucidation of mechanisms of CF pathophysiology and prediction of drug responses, thereby optimizing treatments that will improve the quality of life for all CF patients.

News from the Board

Continued from page 2

The funding of cutting-edge research remains key. CFRI's Board of Directors recently approved funding for inspired researchers at UC San Francisco and Michigan State through our Elizabeth Nash Memorial Fellowship and New Horizons Programs. In her cover article, CFRI-funded researcher Martina Gentzsch, PhD, provides an excellent overview of her work. As a member of CFRI's community, you are a part of this innovative research.

Thank you for your ongoing support. With your help we will continue to move closer to a cure, while enhancing the lives of those living with cystic fibrosis.

Peace and good health,

Bill Hult | *Board President*