Developing New Biomarkers for Accurate Assessment of CFTR Function

By Andrey Malkovskiy, PhD, and Carlos Milla, MD

While novel drugs targeting the basic defect in the CFTR protein have been advanced, it is increasingly difficult to demonstrate the degree to which such therapies restore CFTR function in patients. Traditional measures such as pulmonary function or weight gain are “downstream” from the level of CFTR dysfunction present in patients, and are fraught with high variability that limits their utility. Accepted physiologic biomarkers such as nasal potential difference or intestinal short circuit currents give a closer readout of CFTR function, but the techniques required are cumbersome, difficult to standardize, and their sensitivity is limited. Although sweat chloride proved valuable for the initial Ivacaftor studies in patients with gating mutations, the signals have not been as robust for patients with more severe mutations. Thus, there is now a clear recognition...
Letter from the Executive Director

“To know even one life has breathed easier because you have lived. This is to have succeeded.”
— Ralph Waldo Emerson

Dear Friends,

I hope this note finds you and your loved ones enjoying a happy and healthy 2016! CFRI has had a busy start to the year. We achieved significant growth in 2015, and are now focused on our heightened efforts to fund cutting edge CF research, and to provide vital education and support services to our community.

In addition to funding researchers at seven university and medical centers nationwide, in 2016 we are offering a wide range of educational and psychosocial support programs, including our Discovery Series, monthly Caregivers Support Group, Embrace retreat for mothers of those with CF, National CF Family Education Conference, MBSR classes, and CF Summer Retreat. I am very excited to share that CFRI has launched a nationwide advocacy campaign, “Many Voices ~ One Voice,” to raise awareness of CF, and to encourage increased access to services and medications for all those with CF. Get ready for our exciting calls to action: we want your voice to be heard!

None of this is possible without you. Our research, advocacy, education, and support services are dependent upon the generosity of our community. You may have noticed that we have created many new opportunities for you to support CFRI. Whether through the Tea, online crowd funding campaigns, the Jessica Fredrick Memorial CF Research Challenge Fund, car donations, or special events, your participation is vital. You can help our loved ones with CF to breathe easier.

The sad truth is that we still have no cure. Our loved ones are still struggling to breathe. In recent months, numerous close members of our CFRI community have received lung transplants in the nick of time. Others have lost their battles. Cystic fibrosis remains a harsh and frightening disease. Each one of us plays a key role in the search for a cure. To be part of our shared mission to help others to breathe is, indeed, to have succeeded.

I am grateful to be a part of this strong, committed and compassionate community.

Warmly,
Sue Landgraf  |  CFRI
Executive Director and Mother of an Adult Daughter with CF

CFRI Community

News from the Board

Dear CFRI Community,

As we approach spring, I am pleased to share that CFRI’s first quarter has been one of vigorous activity on all fronts. Research proposals are being vetted, and we look forward to bringing more brilliant CF scientists into the CFRI “family” of researchers. Fiscally, we remain strong thanks to the support of our community and our corporate sponsors. It takes quite a village to accomplish all that CFRI does each year. On behalf of the Board of Directors, I thank you for being active members of this village.

While CFRI is located in Palo Alto, California, our reach is global. Our Spanish language materials are increasingly shipped to other Spanish speaking nations, where resources...
treatments. Of course, my CF could not be ignored because I had cancer, and every two weeks, in between treatments, I was required to do at home ‘tune-ups’ with IV antibiotics so that I could fight lung infections. At one point I was hospitalized with pneumonia.

The rigorous chemotherapy and radiation treatments made it difficult to continue my running routine and I eventually had to stop altogether. My running revival started back in 2010 after being in remission for five years. I wanted to become more proactive in regards to my cystic fibrosis and my overall health. Once I started running again, I realized how much mucus I was bringing up and how clear my lungs were feeling after each run. I started out by setting goals for myself such as running a 5k race. After I accomplished that, my new goal was a 10k, then a half marathon, and then a 16-mile mountain run. My next big goal is to run in a full marathon!

My lung function will drop and indicate that I need antibiotics or hospitalizations, but that always reminds me how important running is in my life and to my health, and I have luckily always been able to get my FEV1 back to my baseline, which is around 83% of predicted.

My husband, Adam, is my biggest support system. We were not sure if children were an option for us due to the complications of becoming pregnant because of CF-related thick cervical mucus, my lung health, and enduring impacts from chemotherapy and radiation therapy. We decided we wanted to try to have a baby, regardless of the improbability and potential risks involved.

To determine the possibility of our future children having CF, Adam was tested for the CF gene and found not to be a carrier. Just a few months later our prayers were answered when we found out that we were expecting a baby. My pregnancy went well as I stayed active the whole time by jogging (very slowly) and attending fitness boot camps. I strongly believe that running and exercise, along with adherence to my medical treatments, kept my body healthy and strong enough to conceive a child. In March of 2015, we joyfully welcomed our baby son, Leo, to the world.

As any parent knows, having a child is tough. There are no breaks or time outs in mommyhood. In between my treatments, there are feedings, changing of diapers, and clothes and a lot of rocking and bouncing. In Leo’s nursery I hung a treasured picture of my Tlingit great-grandmother carrying my grandfather on her back. This photo represents our family, culture and identity as Tlingit people, and is symbolic of strength and sacrifice. Each generation faces new obstacles and new remarkable innovations. I am thankful for my family and all they have sacrificed for me to be here.

Adam is a very positive person, who reminds me to never give up and to always keep trying. He works very hard so that he can provide a wonderful life for Leo and me. He gets up at five in the morning to exercise, works a 10-hour day, and comes home to help me with Leo, who is now one year old. He is always willing to set aside time so that I can go for a run or attend my weekly boot camp classes.

My main motivation for running has been to outrun cystic fibrosis and to prevent further lung deterioration. I am determined to run and exercise for my health. It is not just about me anymore, I have a child who needs me. I want Leo to grow up with his mom. I want to be able to teach Leo to be kind, humble, follow his dreams, strive for greatness, learn from failure, travel, read, be respectful, gain knowledge through experience, and to also pick himself up when life is tough.

Baby Leo is my inspiration to lace up my shoes and get out there and run. There are no excuses today, tomorrow or the next day; just reasons why I need to put one foot in front of the other and run.

To read Sabrina’s blog, go to www.sabrinawalkerfightscysticfibrosis.blogspot.com

Individual Counseling Support Available!

CFRI is proud to offer support for individual counseling services through our CF Quality of Life Program, a Living Legacy of Peter & Kathy Judge. Individuals diagnosed with CF and their family members are eligible. CFRI will cover individual co-pays, or provide up to $120 per session for five sessions of counseling with a licensed therapist. In order to be eligible for reimbursement, therapists must contact CFRI prior to service delivery to confirm participation in the program. For more information, contact Siri Vaeth Dunn at svdunn@cfri.org or 650.665.7565. Made possible through a grant from Vertex Pharmaceuticals.
News from the Board
Continued from page 2

for the CF community are in short demand. Participants in our CF Caregivers Support Group call in from around the country. Our Discovery Series is watched by viewers around the globe, and portions of our newsletter have been reprinted as far away as Australia. We are honored by this global involvement!

The Board of Directors is diving back into CFRI’s strategic plan, as we “check in” with our progress since the plan’s adoption last year. As you know, CFRI’s tagline is, “Research for Living ~ Partners for Life,” and the goals contained within the Strategic Plan link directly to this tagline, incorporating research, education, advocacy, resources, and support. If you wish a copy of the plan, please contact the CFRI office.

Thanks to your ongoing engagement, we will continue to improve and enhance the lives of those living with cystic fibrosis.

Peace and good health,

Bill Hult  |  Board President
In Honor of November 1, 2015 — January 31, 2016

Ben Abercrombie
Chelsa Aboud
Andrew Carl Acheson
Connor Acheson
Claire Alexander
Sadie Anderson
Mark Anthony
Jessica Arvidson
Haleigh Baker
Susie Baldwin
Bridget Barnes
Lucy L. Barnes
Nick Barnes
Jamie Barry
Joseph Batchelder
Baugh Family
Catherine Bell
Brett Bennett
Alison Best
Valerie Boisvert
Kara Borowski
Jack Boyd
Lacy Bradley
Joshua P. Brandon
Paige Brodsky
Brian Burks
Isabel Stenzel Byrnes
Brett Bennett
Catherine Bell
Brett Bennett
Alison Best
Valerie Boisvert
Kara Borowski
Jack Boyd
Lacy Bradley
Joshua P. Brandon
Paige Brodsky
Brian Burks
Isabel Stenzel Byrnes
Brett Bennett
Catherine Bell
Brett Bennett
Alison Best
Valerie Boisvert
Kara Borowski
Jack Boyd
Lacy Bradley
Joshua P. Brandon
Paige Brodsky
Brian Burks
Isabel Stenzel Byrnes

Honor Mothers Every Day:
2016 Mother’s Day Tea fundraiser kickoff is here!

Male or female, young or old, you can honor mothers year round while helping find a cure for CF. Mother’s Day Tea is CFRI’s biggest fundraiser of the year, and your help is critical to help us achieve our goal of raising $150,000.

Please participate as a Tea Sender! It’s easy: contact us at CFRI, and we will provide you with everything you need for this spring’s kick-off, including invitations and teabags. Mail the invitations to your family and friends, encouraging them to enjoy a cup of tea on Mother’s Day while reflecting upon their loved ones with cystic fibrosis (CF). Donors give in their honor — and in their memory — to further CFRI’s outstanding research, education and support programs, so as to improve the lives of people with cystic fibrosis.

If you don’t want to mail invitations, invite your friends and family to a virtual tea. Go to www.cfri.org and click on the “Fundraising” tab to find all the information you need to “brew” your tea!

There is tremendous cause for hope for those with CF, but still so much work to be done. CF remains the most common fatal genetic disease in the United States. Funds raised from our Mother’s Day Tea will support services for our CF community.

Please join us as a Tea Sender by calling our office at 650.665.7576, email cfri@cfri.org, or sign-up online at www.cfri.org.
Developing New Biomarkers for Accurate Assessment of CFTR Function
Continued from front cover

that better biomarkers and endpoints are required to more accurately assess CFTR function and efficiently identify drugs that offer the most promise of efficacy.

It is understood that mucus abnormalities are key to CF pathophysiology and we have conducted preliminary studies to discover biomarkers of this dysfunction. The application of Raman spectroscopy (RS) to mucus gel extracted from saliva has allowed us to clearly identify a RS signature corresponding to Thiocyanate (SCN-). The CFTR protein is known to conduct a number of anions, and this includes SCN-. We have found the SCN- signature to be very low or absent in salivary mucus from patients with CF. We hypothesize that the SCN- signal, normalized to the C-H peak of the solid salivary mucus fraction can serve as a quantitative means of assessing the level of CFTR function present.

In a preliminary study, samples from healthy individuals, individuals with CF, and from individuals with a partially defective CFTR gene and pancreatic sufficiency were analyzed. Sharp differences were noted between the groups, with patients with CF demonstrating very low to absent peaks and patients with partial CFTR dysfunction showing an intermediate level to that of healthy controls. We also assessed samples from patients with the G551D mutation under treatment with Ivacaftor and remarkably, all three patients had values above those seen in the CF patients and comparable to those seen in the healthy controls. One of these patients had samples assessed prior to and after the start of Ivacaftor, clearly demonstrating a response to therapy with increase in the peaks measured.

Our CFRI-funded research builds on our preliminary observations so as to develop a biomarker that could serve as a powerful tool to quantitate the degree of rescue of CFTR function in response to novel drugs. This method would provide non-invasive CF diagnostics and the monitoring of treatment efficacy for patients with CF that is on par or more sensitive than the existing diagnostic methods, and would be easier and faster to conduct than the current established methods. Further, this methodology could be applied as an additional means to determine residual function in patients with questionable diagnosis.

During the funded project period we will develop, refine and validate the methodology for the sampling and analysis of salivary mucus gel by Raman spectroscopy, including the development of a practical, reliable and reproducible kit so that samples could be collected at any medical facility or by the patients themselves, and then sent to a centralized facility by mail. Samples will be collected from volunteers known not to carry CFTR mutations. In addition, samples will be obtained from volunteers with CF who have their CFTR genotype fully characterized. We seek to equally enroll patients with pancreatic insufficiency and severe CFTR mutations, and patients with pancreatic sufficiency and CFTR mutations that confer residual function. Patients with CFTR gating mutations being treated with Ivacaftor will also be enrolled. Our sampling method primarily collects secretions from submandibular and sublingual glands. We will then assess the ability of SCN peak as a biomarker to distinguish between healthy controls and individuals with CF, including the ability to distinguish between CF subjects with varying degrees of CFTR dysfunction and individuals treated with drugs known to enhance CFTR function. In addition, for the CF patients, biomarkers will be assessed for any correlation with clinical characteristics of interest, in particular sweat chloride values and pulmonary function.

Carlos Milla, MD

CF Summer Retreat
“Blockbuster: Live in 3D!”
Please Join Us! August 16 - 21, 2016

The CF Summer Retreat, held at Vallombrosa Center in Menlo Park, California, provides a safe environment that enhances positive coping skills, social support, and education for people who share common experiences with CF. Adults with CF, their family members, friends, and health care providers are encouraged to attend. Register for whichever days fit your schedule. Rooms are available at Vallombrosa Center; scholarships are also available. To ensure good health for all, please use proper hygiene practices. All participants and guests with CF must comply with CFRI’s Infection Control Guidelines. See www.cfri.org for more information, or call 1.855.237.4669.
Jessica Fredrick Memorial 2016 CF Research Challenge Circle and Fund: Inspiring Others to Support the Search for a Cure

By Siri Vaeth Dunn, MSW

“One of the most important things you can do on this earth is to let people know they are not alone.” — Shannon L. Alder

I remember vividly the day of my daughter’s diagnosis. The year was 1995, long before cystic fibrosis (CF) was part of California’s newborn screening panel. In the 21 years since we entered the world of CF, there have been significant research breakthroughs that have translated to exciting therapies that enhance and extend the lives of those with CF, including my daughter’s. But the work is not done. CF remains the most common fatal genetic disease in the United States. The breakthroughs that we have witnessed reinforce the reality that continued funding of innovative CF research is the only way we will achieve a cure.

CFRI is pleased to have broadened its research funding in 2015, thanks to the leadership of our Jessica Fredrick Memorial CF Research Challenge Circle. CFRI needs your help to continue this forward momentum.

Thanks to a generous gift from the Daniel Tyler Health and Education Foundation, we have nearly reached our ambitious goal of $150,000 for the Jessica Fredrick Memorial 2016 CF Research Challenge Circle. Members of the Circle have made substantial gifts that are designated for CF research and used to match donations to the Jessica Fredrick Memorial 2016 CF Research Challenge Fund.

It is an exciting time to donate. Unless we are otherwise notified, all gifts received through this newsletter will be matched by the Circle and used to fund vital CF research.

Online MBSR Class for Individuals with CF Starts March 31, 2016!

Mindfulness Based Stress Reduction can have a positive impact on people coping with anxiety, pain and depression. Register today for this 8-week online class led by Dr. Julie Desch, which is offered at a significantly reduced fee. Sessions are every Thursday, March 31 through May 19, from 7:00 pm – 9:00 pm PST, and are open to those diagnosed with CF aged 16 years and older nationwide. To register, call 650.665.7576. Made possible through grants from Genentech and Vertex Pharmaceuticals.

There is still no cure for CF, and for every inspiring story of survival and hope, there are stories of tragic loss. Our Research Challenge Circle and Fund are named in memory of Jessica Fredrick. In a story that is familiar to many, Jessica – an active college student, dancer and CF advocate – lost her battle with cystic fibrosis while awaiting a lung transplant after her health declined suddenly.

To live with CF and its extreme challenges can be a very lonely experience. We still have much more work to do to improve and save the lives of our loved ones. But we cannot do it without you. Please contribute to the Jessica Fredrick Memorial 2016 CF Research Challenge Fund and support the search for a cure.

Please let our loved ones with CF know that they are not alone.
CFRI Mission
Cystic Fibrosis Research, Inc. exists to fund research, to provide education and personal support, and to spread awareness of cystic fibrosis, a life-threatening genetic disease.

CFRI Vision
As we work to find a cure for cystic fibrosis, CFRI envisions informing, engaging and empowering the CF community to help all who have this challenging disease attain the highest possible quality of life.

Visit our website at: www.cfri.org for more information about us and about cystic fibrosis. Call toll free: 1.855.cfri.now

CFRI’s 29th National Cystic Fibrosis Family Education Conference
Riding the CF Wave
July 29 – July 31, 2016
Sofitel San Francisco Bay • Redwood City, CA
Our annual conference brings together experts in the field of CF to provide the latest updates in research and care to our diverse CF community.

Speakers Include:
- Ginny Dieruf, Cody Dieruf Benefit Foundation, Bozeman MT
- Jordan Dunitz, MD, University of Minnesota Medical Center, Minneapolis MN
- Raksha Jain, MD, University of Texas Southwestern Medical Center, Dallas TX
- Dennis Nielson, MD, PhD, UCSF Benioff Children’s Hospital, San Francisco CA
- Alexandra Quittner, PhD, University of Miami, Miami FL
- Emily Schaller, Rock CF Foundation, Detroit MI
- Jennifer Taylor-Cousar, MD, National Jewish Health, Denver CO
- Jeffrey Wine, PhD, Stanford University, Palo Alto CA

Early Bird Registration (on or before 6/28/16)
- $185 per person
Regular Registration (6/29/16 and after)
- $215 per person
Registration includes meals, reference materials, presentations, receptions, and support groups.

CFRI-Funded Research Track:
Presentations on Saturday/Sunday by researchers from Stanford, UC San Francisco, San Diego State University, Children’s Hospital Los Angeles/University of Southern California

Research Track Only: Registration – $125 for Saturday and Sunday, including lunches, or $75 per day, including lunch.

To ensure good health for all, please use proper hygiene practices. All participants/guests with CF must comply with CFRI’s Infection Control Guidelines. See www.cfri.org for specifics.

For more information, visit www.cfri.org or call 1.855.cfri.now.

For their generous support of CFRI Community, special thanks to: Genentech, Vertex Pharmaceuticals, Gilead Sciences, AbbVie & Chiesi USA
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