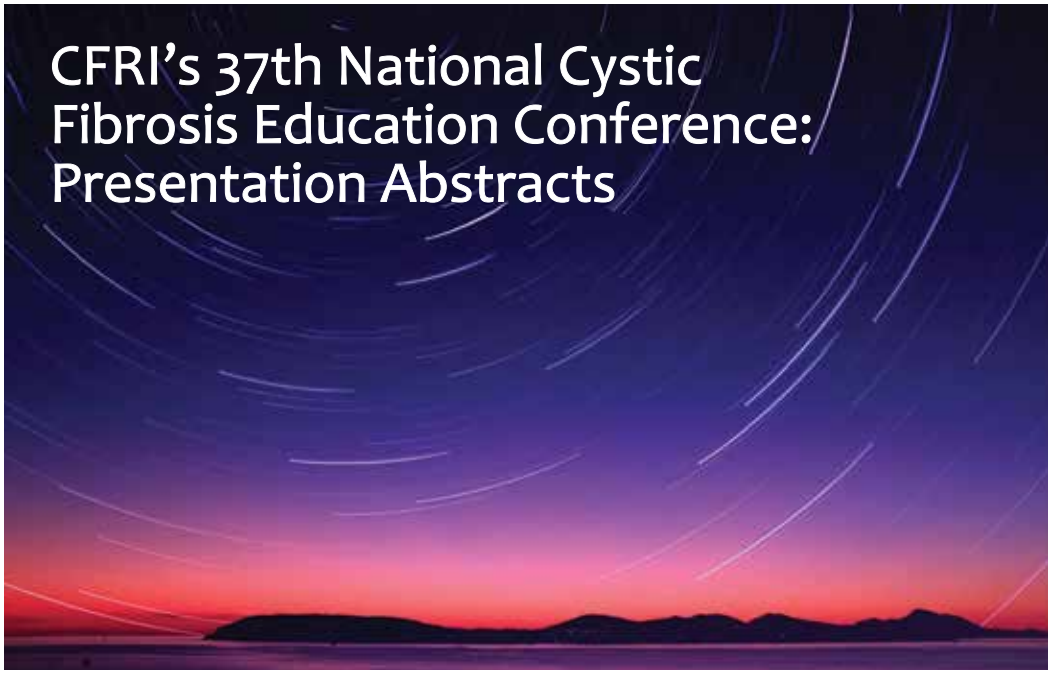
CFRI community
49 Years of Research, Education, Advocacy, & Support
Fall 2024

CFRI's 37th National Cystic Fibrosis Education Conference: Presentation Abstracts



CFRI held its 37th National CF Education Conference, *Transforming CF Together*, as a hybrid event July 26 - 28, 2024. Over three days, attendees from across the country and globe heard from nationally-renowned speakers on a wide range of CF-related topics. These presentations are now available for viewing on CFRI's YouTube channel: **https://tinyurl.com/ycf55jvb**. The abstracts of the presentations appear below.

The Power of Passion

Nicholas Kelly, MS, RD, LD — *Cleveland, OH*

Nicholas Kelly

Do you know what it's like to be told you have a chronic disease, what it takes to fight despite obstacles, and thrive in the face of adversity? That is Nick's life.

Nick's story starts at three months old, when he was diagnosed with cystic fibrosis. Although interesting, this is not what made his story unique. Nick was diagnosed by his mother, a fact further explored later. Despite his diagnosis Nick went on to thrive, becoming a dietitian, speaker, author, artist, advocate and much more.

Nick's advocacy is something he holds dear, as he loves to share knowledge and passion. He believes in the importance of being informed. As his favorite quote says, "A candle doesn't lose anything lighting another candle." Nick hopes to be the light that dispels some of the darkness surrounding CF. He is dedicated to shining a light on research, addressing inadequacies, advocating for the community, and driving the mission to make CF stand for "Cure Found."

Book Reading: *Love, Courage and Miracles*

Robin Modlin, MA — *Livermore, CA*

Embark on a heart-warming journey through a tale of love, courage, and miracles. Robin shares excerpts from her book, as she confronts her daughter Anna's life-limiting prognosis, navigates the challenges of cystic fibrosis, and witnesses Anna's

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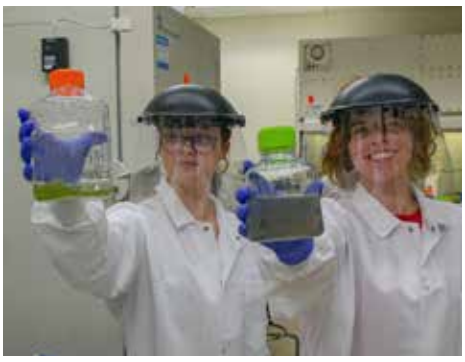

CFRI-supported PhD student Kayla Raygoza and UCI undergrad researcher Faith Cribbs holding phage-rich sewage samples from the Hyperion Treatment Plant.

How Everyday Molecules and Bacteriophages Can Help Eradicate Tough CF Infections

Katrine Whiteson, PhD and Sage Dunham, PhD — *UC Irvine*

The increase in antibiotic-resistant bacteria and the lack of new antibiotics has created an urgent need for new treatments. One promising approach is to use bacteriophages, or phages — viruses that target specific bacteria — to treat infections that don't respond to regular antibiotics. Phages are the natural predator of bacteria in every imaginable environment on Earth, and although they have been studied for medical use for more than 100 years, antibiotics were the preferred treatment throughout most of the 20th century. The rise of antibiotic resistance has renewed interest in phage therapy.

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How Everyday Molecules and Bacteriophages Can Help Eradicate Tough CF Infections

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In the Whiteson lab at UC Irvine, teams of brave students search wastewater samples from several treatment plants in Southern California to find phages that can target resistant bacteria from people with CF, including bacteria like *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. Samples from the wastewater treatment plant in Escondido, CA have been particularly rich in *Stenotrophomonas* phages – that is where most of the several dozen new phages discovered at UCI came from.

With the help of medical collaborators, we have been collecting bacterial isolates from people with CF and testing whether our phages can kill them. Often there are some bacteria that the phages cannot kill. To boost the phages' potential to kill some of the more difficult strains of bacteria, we are combining phages, antibiotics and other helper molecules into cocktails and testing them under conditions that mimic CF airway environments. So far, we have tested a variety of alcohols along with 2,3-butanedione (diacetyl), 2,3-butanediol, essential oils, and other everyday molecules, including fatty acids.that range from small, acidic molecules such as acetic acid (vinegar) to larger carbon chains resembling soap. Many of these molecules are known to inhibit bacterial growth and have been used since medieval times. Fortunately, chemist and CFF post-doctoral fellow Dr. Sage Dunham has helped us past many hurdles, especially related to the solubility of the compounds we want to work with.

We have found that all tested fatty acids slow the growth of *S. maltophilia*, but short-chain fatty acids (SCFAs) rely heavily on pH to work and don't help phages much. In contrast, medium-chain fatty acids (MCFAs) can stop growth independent of pH and work synergistically with phages. Octanoic acid, a type of MCFA, seems to enhance the effectiveness of phages across different types of bacteria, including both gram-negative ones like *S. maltophilia* and gram-positive ones like *Enterococcus*. We are now expanding our tests with MCFAs to conditions that better mimic the CF infection environment, such as different oxygen levels and artificial lung fluid, and applying them to other CF pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

CFRI's 37th National Cystic Fibrosis Education Conference

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miracle resurrection through a double lung transplant. Together, they defy the odds and are fueled by hope, gratitude and a quest for meaning and healing.

Robin Modlin

Follow them as they meet a Tibetan lama who opens their world with ancient healing rituals, have an audience with the Dalai Lama, and in one of her darkest hours, Anna experiences a healing blessing from a magical blue budgie. With her newfound lungs, Anna triumphs, realizing unexpected dreams and invites exciting adventures into their lives.

Love, Courage, and Miracles is more than a story. It is a testament to the unbreakable bond between a mother and daughter entwined with the challenges of a devastating disease. Their journey is a powerful narrative of survival and living life to the fullest, showcasing the transformative power of love, acceptance, and hope.

Modeling Epithelial Immune Cell Interactions in Cystic Fibrosis

Amy Ryan, PhD —
University of Iowa, Iowa City, IA

Amy Ryan

Mucociliary clearance is a key mechanical defense mechanism of human airways, and clearance failure is linked to major respiratory diseases, including cystic fibrosis. Despite Highly Effective Modulator Therapy (HEMT) benefits, persistent lung inflammation and compromised pathogen clearance in people with CF (pwCF) suggests inadequate targeting of lung innate immunity or potential drug tolerance. These issues highlight a need to further understand the interplay between immune cells and airway epithelial cells during injury, repair, and regeneration.

Our research focuses on developing models to elucidate these dynamics. We have recently generated lung-on-chip models incorporating CF primary bronchial epithelial cells and elucidated the structural parameters of airway epithelia that predict clearance function in both ex vivo and in vitro tissues. From these we developed physics-based models to translate measurable parameters to quantitatively benchmark the human-relevancy of mucociliary clearance in experimental models, and to characterize distinct disease states.

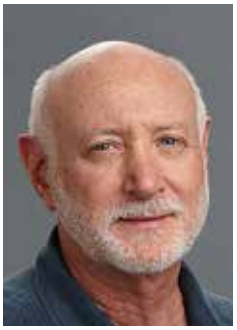
Furthermore, we have engineered ΔF508 mutant THP-1 cells, using CRISPR/Cas9 technology, to investigate the role of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) in innate immune functions. We compared isogenic wild-type, ΔF508 mutant, and CFTR knock-out THP-1 cells, differentiated into macrophage-like cells, and tested their responses with CFTR modulators (ivacaftor, elexacaftor, tezacaftor). Our findings indicate dose-dependent effects of these modulators on inflammatory responses, TNFα release, phagocytosis, bacterial killing, cell migration, and expression of pro-inflammatory markers in both ΔF508 and wild-type macrophages. Notably, lower concentrations of modulators attenuate inflammation, while higher doses, especially in combination, may exacerbate immune dysfunction.

These insights into how HEMTs impact macrophage function highlight potential mechanisms underlying immune complications observed in CF patients despite treatment. Future investigations incorporating patient-derived macrophages could reveal additional therapeutic targets to mitigate these challenges. Moving forward, our integrated approach combining physics-based models, gene-edited immune cells, and lung-on-chip technologies promises to deepen our understanding of inflammation's role in airway stem cell function and functional mucociliary clearance. This multidisciplinary framework holds promise for advancing personalized cellular therapies for CF and other lung diseases.

Aging in the New Age of Cystic Fibrosis

Richard Moss, MD —
Stanford University, Palo Alto, CA

In the 15 years since the clinical trials of Kalydeco® (ivacaftor) in G551D-carrying people with CF (~4% of the total CF popula-



Richard Moss

tion) showed a potential transformative early benefit, confirmed and vastly expanded by the effects of the triple drug Trikafta® (elexacaftor/ tezacaftor/ ivacaftor, ETI) on 85-90% of people with CF in the Global North, the entire worldwide CF community has come to realize that we have entered a new age, where the potential of a full lifespan is now predicted for those diagnosed, eligible and on CFTR modulator treatment from an early age. What the rosy predictions may neglect is the realization that aging with, instead of prematurely dying from, CF presents its own set of formidable new challenges, for lifelong "highly effective" CFTR modulator therapy [HEMT] with ETI is not a cure. Aging on top of defective, not fully corrected CFTR function and established disease impacts on many organs despite HEMT, recent studies confirm, is associated with a panoply of many CF- (and transplant-) related complications and early vulnerability to an expanding array of age-associated diseases such as diabetes, a variety of cancers, cardiovascular disease, obesity, osteoporosis, and other health challenges. The huge issue of the ineligible minority with HEMT-unresponsive CFTR mutations remains a new mountain to climb. In addition, there is increasing recognition of the further problems of HEMT intolerance and heterogeneity of response, CF underdiagnosis in much of the world and among many ethnicities (partly due to genotypic heterogeneity and partly to many socioeconomic factors), lack of access to HEMT in many countries and exorbitant lifelong cost. In this overview talk, Dr. Moss addresses many of these aspects of our new age of CF, and presents CFRI's new programmatic efforts to raise expertise of caregivers for aging CF patients as well as providing accurate information and empowerment to all people with CF everywhere.

Culture Shift: CF Lung Infections in the Modulator Era

Lucas Hoffman, MD, PhD —
University of Washington, Seattle, WA

CFTR modulator therapy has dramatically changed the pace, course, and overall

Lucas Hoffman

nature of CF lung disease for many, but not yet all, people with CF. Even before these transformative treatments were introduced, the "ecology" of CF airway infections – the types and prevalences of different bacteria in the respiratory samples from people with CF - had changed considerably over the years as treatments, social practices, and hospital policies changed. At the same time, our understanding of how microbes infect people with CF in the first place, and how those microbes adapt and change during infections, has grown enormously, aided by new technologies, concepts, and insights from a variety of fields. We are only now updating these models of CF lung infection pathogenesis in the context of CFTR modulator treatments, with some studies suggesting the need for large-scale revisions of how we diagnose, treat, and think about these infections, guided both by ongoing research and what our patients are telling and showing us.

In this presentation, Dr. Hoffman reviews the "cast of characters" - the microbes that are most frequently detected and other less common but equally important ones - involved in CF airway infections. We'll see how these infections have changed over the years, as treatments and policies have changed. He talks about the benefits and risks of current treatments, especially antibiotics, and the meaning of antibiotic resistance, and how these concepts might change in the context of CFTR modulators. In addition, Dr. Hoffman discusses the implications of the ongoing decreasing rates of expectoration among many people with CF, a trend that preceded the introduction of highly-effective CFTR therapy but that has greatly accelerated since. In particular, he reviews what this trend means for diagnosing CF respiratory infections, as well as work on the horizon to improve detection of infections in this new era.

Sexual and Reproductive Health in CF

Natalie E. West, MD, MPH —
Johns Hopkins University, Baltimore, MD

With improved therapies, people with cystic fibrosis (CF) are living longer and healthier

Natalie E. West

lives. People with CF have an increasing number of questions regarding their sexual and reproductive health. This talk will summarize important issues during puberty, adulthood, and menopause that specifically affect people with CF.

A wide range of sexual and reproductive health topics including puberty, transgender and gender nonbinary identities, contraception, cyclical hemoptysis, fertility, contraception, and parenthood will be addressed.

More people with CF are expressing the desire to become pregnant, as people with CF are living longer lives. In the last 4 years, the pregnancy rate of women with CF has tripled in the United States. The impact of highly effective modulators has improved the health of many people with CF, which is allowing them to consider all reproductive options. Care during pregnancy, management of CF medications during pregnancy, and outcomes with the use of highly effective modulator therapy during pregnancy and lactation will be discussed, as there are retrospective studies available, as well as a large ongoing prospective pregnancy clinical trial. 95-97% of men with CF have congenital bilateral absence of the vas deferens, which leads to infertility in men with CF. Assisted reproductive technology is available which can be used to assist in having biological children.

Other options for family building include fostering, adoption, and surrogacy. Gaps in knowledge, current evidence, and management strategies to optimize care in people with CF will be discussed. The impact of the approval and increased use of highly effective modulator therapy on sexual and reproductive health care needs and outcomes remains to be seen. However, due to the positive impact on health and longevity, it is expected that people with CF will increasingly face concerns and decisions. Optimizing sexual and reproductive health care as the face of CF changes is imperative to meet these emerging needs throughout the lifespan.

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Panel: Coping with Cancer and CF

Elyse Elconin Goldberg, MA; Thomas Horal; Colleen Lewis; Christine Nash, MBA — *Los Gatos, CA; San Jose, CA; Philadelphia, PA; Lafayette, CA*

Moderated by Jean Hanley, MD — *Manhattan Beach, CA*

Elyse Elconin Goldberg

Thomas Horal

Colleen Lewis

Christine Nash

As adults with cystic fibrosis are living longer, additional health complications are emerging. Some of these are related to having CF; others are made more complex by a CF diagnosis. There is increased awareness of the higher risk of certain cancers for adults with CF, most notably gastrointestinal cancers. There is a higher risk of pancreatic cancer; the risk of colon cancer for those with cystic fibrosis is five to ten times higher than that of the general population. Breast cancer rates are higher for women with CF, with evidence of the role of sex hormones, particularly estrogen, impacting the pathophysiology of CF.

For individuals with CF who have received a double lung transplant, the risk grows significantly; colon cancer risks are over 25 times higher than the general population due to the immunosuppressants required to ward off organ rejection. With the immune system suppressed, cancers are more likely to develop and spread, most significantly GI, esophageal and skin cancers. In this session, panel participants share their personal experiences with diverse cancer diagnoses. A sibling will describe her brother's battle with pancreatic cancer, while three adults with CF will describe their individual journeys with breast cancer, skin cancer and colon cancer. Awareness, detection and early intervention are key. Panelists will share insights and perspectives on detection and treatment, as well as the mental health implications of this dual diagnosis.

Jean Hanley

Panel: Advocacy, Access and Health Equity in Cystic Fibrosis

Rachel Alder; Jaelyn Cooper, MHA; Alicia Maciel, MBA; Abhijit Tirumala — *Salt Lake City, UT; Little Rock, AR; Brea, CA; Saratoga, CA*

Moderated by Kimberly Morse, MSW, LCSW — *Children's Hospital Los Angeles, Los Angeles, CA*

Rachel Alder

Jaelyn Cooper

Alicia Maciel

Abhijit Tirumala

Despite the fact that cystic fibrosis occurs in every race and ethnicity, there remains a misperception – both in the general public, and among medical care providers - that the disease only impacts people of European descent. As a result, many people of color with CF are misdiagnosed for years and are thereby unable to benefit from CF therapies and care. People of color are more likely to have rare mutations that are missed by states' newborn screening panels, exacerbating the likelihood of a late diagnosis. And these rare mutations are far less likely to be responsive to CFTR modulator therapies, thereby leaving fewer therapeutic options. Current CF therapies were largely approved through clinical trials with very few people of color participating. For CF patients and families for whom English is not a first language, it may be challenging to access resources and support. During this dynamic panel discussion, we will hear from members of our CF community who will share their personal experiences and insights navigating bias to develop productive partnerships with care teams and fellow community members so as to improve medical care and quality of life. All panelists provide examples of optimal care and interactions, while stressing the importance of self-advocacy and community engagement.

Kimberly Morse

Exploring Nucleic Acid Based Approaches to Treat People with CF

Jennifer Taylor-Cousar, MD, MSCS — *National Jewish Health, Denver, CO*

Jennifer Taylor-Cousar

Cystic fibrosis (CF) was first described as a clinical entity by Dr. Dorothy Andersen in 1938. At that time, people with CF unfortunately did not survive past early childhood. In subsequent years, the establishment of comprehensive care and treatments directed at the signs and symptoms of CF improved the quantity and quality of lives for people with CF. In 1989, the CF transmembrane conductance regulator (CFTR) gene was discovered; it was thought that the development of gene therapy to cure CF would be imminent. However, in early gene therapy clinical trials, ineffective vector (transport mechanism)

transduction (transfer of the corrected gene) into lower airway cells along with immune-mediated side effects temporarily prevented advancement of this approach to treating CF.

While deficits in early gene therapy technology precluded its initial development for CF, focus shifted to addressing the downstream protein dysfunction caused by variants in the CFTR gene. Since 2012, four CFTR protein modulators have been approved. In populations comprised primarily by people of European descent, >90% of people are variant eligible for CFTR modulators. However, side effects and access preclude CFTR modulator use by some variant-eligible people with CF. Critically, there are also people with CF whose variants make them unable to benefit from CFTR modulators. To achieve effective therapies for all people with CF, nucleic acid based therapies are being developed.

The goal of nucleic acid based therapies (NABT) is to deliver the correct instructions to the cell for making a functional CFTR protein. Examples of nucleic acid based therapy include gene editing (making specific changes to the gene), gene therapy (replacing the entire gene), mRNA [messenger ribonucleic acid] therapy (using the corrected blueprint for the protein) and antisense oligo nucleotide (ASO) therapy (using a very small amount of matching RNA to correct the blueprint). The various approaches are each associated with advantages and challenges including potential variant-agnostic treatment (e.g. therapies that are effective regardless of CFTR variant), differences in delivery requirements for each potential therapy, potential immune reactions to therapeutic delivery of the therapies, and possible barriers for redosing. Nonetheless, gene therapy, mRNA and ASO treatments are currently in clinical trials for pwCF.

In this session, Dr. Taylor Cousar reviews lessons learned from historical NABT efforts, pre-clinical data supporting renewed clinical investigative efforts, and ongoing clinical trial designs and updates.

Strategies to Address Medical Trauma

Samantha Johnson, MA, CCLS;
Kate Yablonsky, LCSW —
Stanford Children's Medicine, Palo Alto, CA; Stanford Health Care, Palo Alto

Over the course of a lifetime with chronic illness and interaction with the medical

Samantha Johnson

Kate Yablonsky

system, people with cystic fibrosis and their families are at high risk of experiencing medical trauma. This is an under-discussed but very real form of trauma that can have a significant impact on quality of life. In this session, a pediatric Child Life Specialist and Adult CF social worker review signs and symptoms of medical trauma and discuss strategies for people with CF and their loved ones across the lifespan to effectively process and integrate these experiences.

Living Proof: Nearly Seventy Years with Cystic Fibrosis

Luanne McKinnon, PhD —
Albuquerque, NM

Luanne McKinnon, PhD (b. 1955) has cystic fibrosis and is a thirteen-year survivor of a successful bilateral lung transplant. Her presentation, "Living Proof: Nearly 70 Years with Cystic Fibrosis" is a colorful recounting of her life with CF, from a diagnosis in 1969 through the arc of CF care that, like a travel log, leads us from Texas to Europe to New York City, Scotland and France, then New Mexico to Palo Alto. She will speak about her uncanny good fortune to live at a time, in the long history of CF, in which research and healthcare have mitigated so much suffering. Ms. McKinnon's presentation weaves a brief historical account of the discovery of CF in 1938 into the broader, compassionate scope of living under the "double rainbow" of hope and doing the work required to be here now.

Luanne McKinnon

"Living Proof" is presented in two parts. Part 1 is a personal testimony. Part 2 is an imaginative piece about the life of her mother's sister who died in 1935 from symptoms echoing CF. Inspired by the late Isa Stenzel Byrnes, who during one of her last creative writing workshops posed the question, "How do we honor those we have lost?" Ms. McKinnon will share an excerpt from her memoir-in-progress entitled, *Pneuma, Latin for soul and breath*. The CFRI audience is the first to hear this.

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