

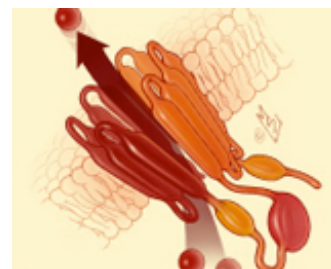


eLITERATURE
REVIEW

eCysticFibrosis Review

Presented by the Johns Hopkins
University School of Medicine and the
Institute for Johns Hopkins Nursing

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Special Edition: Highlights of the 34th European Cystic Fibrosis Conference

Welcome back to eCysticFibrosis Review. We're starting Volume 3 off with a special two-part series reporting on some of the key information presented at the European Cystic Fibrosis Society (ECFS) meeting in Hamburg, Germany June 8-11 2011.

In addition, many of these reports include links to streaming video of eCysticFibrosis Review Program Director Dr. Peter Mogayzel discussing the data with the presenters. Look for the



to link to this feature.



In this Issue...

Physicians and researchers from around the globe came to Hamburg for the 34th European Cystic Fibrosis (CF) Congress to share the latest information from an ever-growing number and diversity of clinical trials. While advances in delaying the loss of pulmonary function and optimizing growth have notably improved the patient survival rate over the last 30 years, quality of life issues still remain. However, the growing body of information available to physicians—as presented at the symposia, workshops, and poster exhibit at the ECFC—provided clinicians with new knowledge to improve the management of their patients.

Among the highlights of the Congress discussed in this issue are:

- **Infections:** Many CF investigators believe that understanding the role of the risk factors affecting the CF patient is the first place to begin controlling infection. Lung pathogens change through a patient's lifetime, however, the effects of different organisms simultaneously colonize the lung is unclear. The role of anaerobes in CF pathogenesis is the subject of some debate, with researchers presenting opposing arguments.
- **Nutrition:** New information reaffirms the value of breastfeeding as the best form of early nutrition, as well as the direct relationship between nutritional status and lung function.
- **Gene Modulation:** Significant enthusiasm surrounded the new investigational compound, VX-770, which is designed to interfere with the basic genetic flaw in CF and promise to dramatically slow disease progression. To this end, investigators identified other gating mutations like the archetype G551D, which showed a good response to the potentiator VX-770 *in vitro*. Although safe to use, VX-770 had no apparent clinical benefit for patients with F508del mutations.
- **Therapies:** New research has found that therapies such as mannitol effectively restore depleted airway surface fluids, clearing the clogged airways of patients with CF.
- **Clinical Trials:** In general, researchers have found that a slower disease progression and an increase in effective therapeutic agents calls for new approaches to future studies and are developing more effective animal models to elucidate the pathogenesis of CF lung disease.

Program Information

[CME/CE Info](#)
[Accreditation](#)
[Credit Designations](#)
[Intended Audience](#)
[Learning Objectives](#)
[Internet CME/CE Policy](#)
[Faculty Disclosures](#)
[Disclaimer Statement](#)

Length of Activity

Physicians
1 hour
Nurses
1 contact hour

Release Date

July 25, 2011

Expiration Date

July 24, 2013

Next Newsletter Issue

September 7, 2011

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Step 1.
Please read the newsletter.

Step 2.
See the Post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access the post-test.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify patients likely to benefit from the CFTR channel potentiator VX-770
- Describe the age-associated shift in lung microbiota and the risk factors associated with microbial acquisition
- Explain how infant diet guidelines improve weight and body mass index (BMI) and help ward off early *Pseudomonas aeruginosa* infections
- Compare effective mucus clearing agents
- Describe the role of anaerobes in cystic fibrosis (CF) lung disease
- Explain how future clinical trials must adapt to a changing CF population

IMPORTANT CME/CE INFORMATION

▼ Program Begins Below

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LAUNCH DATE

This program launched on July 25, 2011, and is published monthly; activities expire two years from the date of publication, ending July 24, 2013.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

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IN THIS ISSUE

- [GENE MODULATION: VX-770 - Gating Mutations And Beyond](#)
- [INFECTIONS: Microbial Diversity and Risk Factors](#)
- [NUTRITION: Feeding In Infancy Is Predictive of Childhood Health Status](#)
- [TREATMENT THERAPIES: Mannitol and Denufosal for Mucociliary Clearance](#)
- [INFECTIONS: Do Anaerobes Matter?](#)
- [INFECTIONS: Adapting Clinical Trials](#)

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Unlabeled/Unapproved Uses

The authors have indicated that there will be reference to the following unlabeled or unapproved uses of drugs: Ataluren/PTC-124, Denufosal, Mannitol, Tobramycin, VX-770, VX-809.

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GENE MODULATION: VX-770 - Gating Mutations and Beyond

Workshop 5: Translational Research in CF

Abstract 61: VX-770 in Subjects with Cystic Fibrosis Who Are Homogenous for the F508del-CFTR Mutation. Patrick Flume, MD. [Abstract from the 34th European Cystic Fibrosis Congress; June 8-11, 2011; Hamburg, Germany.](#)

Abstract 62: Investigational Compound VX-770-Potentiated, Multiple CFTR Channel-Gating Mutants *in Vitro*. Fred van Goor, PhD. [Abstract from the 34th European Cystic Fibrosis Congress; June 8-11, 2011; Hamburg, Germany.](#)

VX-770 improves chloride ion flow through the CFTR channel. It showed safety and efficacy in patients with G551D gating-mutations, which make up 4% of the overall CF population. A recent *in vitro* study that tested the effects of VX-770 on other CFTR-gating mutations substantiated the potentiating effect of the compound and identified three gating mutations in addition to the G551D archetype gating mutation, according to Fred Van Goor, PhD of Vertex Pharmaceuticals, San Diego. These data support investigations of the potential benefit of VX-770 in patients with CF who have CFTR gating mutations beyond G551D.

Dr. Van Goor and his team induced 90 of the 1800 CFTR mutations into Fischer rat thyroid cells (FRT) and tested the effects of VX-770 by patch-clamp tests, which use an electrode on the epithelium, to electrically monitor the opening and closing of the channel.

VX-770 increased chloride transport *in vitro* and increased the CFTR channel-open probability in all CFTR-gating mutations tested, as well as or better than G551D-CFTR. The study compared these results to normal cells, which exhibit a full response, and to cells with F508del mutations, which had a very minimal response to VX-770.

In a separate investigation, researchers studied the safety of VX-770 in patients homozygous for the F508del mutation. This mutation (50% of patients with CF are homozygous and approximately 70% have at least one copy) has shown a minimal CFTR activity of 15%.

Describing the DISCOVER trial that included 140 patients with CF (F508del homozygotes, ≥ 12 years, $FEV_1 \geq 40\%$ predicted), Patrick Flume, MD of the Medical School of South Carolina, noted that the safety and tolerability profiles of the drug were good. The results showed that the overall adverse event frequency was similar between VX-770 and placebo.

The patients were randomized 4:1 to receive either VX-770 (n=112, 150mg twice daily) or placebo (n=28) for a treatment period of four months. The overall adverse events frequency was 87.5% in the VX-770-treated patients and 89.3% in the placebo-treated patients, the most common adverse events being respiratory. Serious adverse events frequency was 13% (VX-770) and 21% (placebo). Pulmonary exacerbations were higher in the placebo group (39%) compared to the treatment group (25%). After 16 weeks of treatment, Flume reported no statistically significant difference in FEV_1 , other spirometry parameters, subject-reported respiratory symptoms (CFQ-R), weight gain, and pulmonary exacerbations. The change in the sweat chloride was statistically significant, but modest at about 3 mmol/L, compared to placebo.

"The sweat chloride responses to VX-770 treatment were intriguing, although no clinical benefit was noted. This would be consistent with the studies done in bronchial epithelial cells that suggest minimal CFTR activity in F508del patients, which this molecule could potentiate," Dr. Flume said.

Take home message: *Gating mutations other than G551D have been identified that show a response to VX-770 in vitro. Clinical studies are needed to show in vivo efficacy. At the given dose, VX-770 had no apparent clinical benefit in patients with CF with F508del mutations. The safety profile supports continued evaluation of VX-770.*





Dr. Peter Mogayzel and Dr. Patrick Flume discuss the VX-770 DISCOVER trial.

[back to top](#)

INFECTIONS: Microbial Diversity and Risk Factors

Symposium 7- Making Sense of Metagenomics

Microbial Diversity in the CF Lung. Susan Lynch, PhD

Symposium 14 – The CF Lung and the Environment

Risk factors for Environmental Acquisition of Microorganisms. John Moore, PhD

CF physicians can attest to the fact that mixed microbial communities populate the airways of patients with CF, but how many understand the intricacies and dynamics of airway microbiota? In an investigation that looked at 53 patients with CF of various ages, mutation types, and pulmonary health status, Susan Lynch, PhD of the University of California in San Francisco, determined characteristic bacterial community structures and specific organisms in younger versus older patients with CF.

Dr. Lynch found that CF airway microbiota are diverse and dynamic, with more than 1837 taxa (43 phyla) of organisms that change their composition and number throughout a patient's lifetime. She found that communities in older patients were less diverse and more phylogenetically restricted than in younger patients. Major shifts in the airway composition were associated with poor pulmonary function. Furthermore, she established an association between specific organisms and mutation types. "Community composition is related to mutation type, but we cannot really yet tease apart whether that is due to the mutation *per se* or the treatments that are administered because of the mutation severity," she noted. Moderate phylogenetic shifts were evident during lung exacerbations, with the most severe perturbation occurring on antimicrobial administration.

The patients in this study (27 male/26 female patients, ages ranging from 9 months to 72 years, normal to severe pulmonary health status, and homozygous F508del [n=19], heterozygous F508del [n=19], non- F508del [n=13] *CFTR* mutations received no antibiotics for two months before analysis. The study showed that the airway microbiota recovered a similar composition between 1-2 months after the cessation of antibiotic therapy, with some organisms never reaching their balance in that composition. Dr. Lynch observed that this selection for certain organisms and the associated pulmonary function decline was evident in patients with long-term CF.

Gerd Döring, MD of Tübingen University, Germany, who moderated the ECFC session on *Making Sense of Metagenomics*, maintained that Dr. Lynch's findings could determine whether a particular therapy was achieving desired or other results. Dr. Lynch confirmed that the investigation outcomes helped provide some understanding of what antimicrobials do and where they are appropriately used. "CF goes beyond a single pathogen paradigm. It is the microbial neighborhood of the organism that defines how it acts. With less competition, an organism can be more pathogenic. In fact, although a radical idea, it might be good to manipulate the microbiota to promote beneficial diversity and to modulate the behavior of some of those organisms into competing with others so they don't dominate the airway," Lynch said.

In the *CF Lung and the Environment symposium*, Dr. John Moore of the Northern Ireland Public Health Laboratory, UK, maintained that the key to controlling infection was gaining more control over the patient's exposure to a plethora of risk factors. His presentation discussed risk factors in patients with CF, counting antibiotics and adding the patients themselves to the list of factors setting them at risk. "The chronic use of antibiotics erodes bacterial richness and allows successor pathogens to flare up. Furthermore, the CF patient himself is a risk factor. Certain types of *CFTR* mutations seem to attract *Pseudomonas aeruginosa*, but all types predispose the body to *Pseudomonas aeruginosa* and other infections of the lung," Dr. Moore explained.

Dr. Moore reported that patients with residual *CFTR* function (class 4 and 5 *CFTR* mutations) were infected by different organisms than patients with minimal *CFTR* activity (class 1-3

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mutations.) Genotypes with minimal CFTR functionality were associated with increased risk and earlier age of infection by multiple organisms.

Take home messages: *Patients with CF are exposed to a huge number of pathogens that change in number and dominance throughout their lives. Patients genetics and their antibiotic therapy are both risk factors in and of themselves for infection.*



VIDEO: Dr. Peter Mogayzel and Dr. John Moore discuss CF infection risk factors.

[back to top](#)

NUTRITION: Feeding in Infancy is Predictive of Childhood Health Status

Poster Presentations:

Poster 279. Lai HJ, Shoff SA, Wu GS, Zhang Z, Tippets BM, Farrell PM et al. Growth and pulmonary outcomes during the first two years of life of breastfed and formula-fed infants diagnosed with cystic fibrosis through the Wisconsin Routine Newborn Screening Program. *Am J Clin Nutr.* 2011; 93:1038-1047. [Poster exhibited at: 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Poster 280. Verling W, Davies J, Kaye H, Legg J. Improving nutritional outcomes at 2 years of age in a population of 303 new CF diagnoses over the last 15 years. [Poster exhibited at: 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

The role of nutrition in CF is a vibrant topic that emphasizes the importance of early intervention strategies to optimize growth, and ward off infection, and minimize lung damage within a child's first two years. With so much to tell, the poster exhibits at the ECFC abounded with educational and practical information about the role of nutrients in patients with CF and how best to exploit them. Two studies that looked at early nutrition in infants with CF found that the way in which infants were fed could set the stage for disease development later in life.

Although optimal feeding for infants is still largely unknown, the US CF Foundation infant care guidelines recommend breast milk for early feeding, with no specifications on exclusiveness or duration. In a study that reviewed the medical records of 103 children born with CF between 1994 and 2006 through the Wisconsin Routine NBS program, a group of investigators from the University of Wisconsin found that more pancreatic-sufficient infants were breast fed (67%) compared to pancreatic-insufficient (49%) or infants with meconium ileus (MI) (54%). Pancreatic-insufficient infants who were breast-fed had fewer *P. aeruginosa* infections in the first two years of life than those who were fed formula exclusively.

In this study population, breast-feeding was prevalent (about 50%), but exclusive breastfeeding was shorter and less common (<25% of infants beyond one month). Half of the exclusively formula-fed infants received formula with high caloric density. None of the infants with pancreatic sufficiency (PS) was exclusively formula-fed; however, 40% of infants with pancreatic insufficiency (PI) and >80% of infants with MI were strictly formula-fed. Pancreatic-insufficient infants who were exclusively breast-fed for less than two months achieved adequate weight gain and experienced fewer positive *P. aeruginosa* in the first two years of life compared to those who were exclusively formula-fed. PI infants exclusively breastfed more than two months had reduced weight gain, more positive *P. aeruginosa* during the first two years of life, and a worse Wisconsin chest x-ray score at two years of age compared to infants exclusively breast-fed for one month.

A second study confirmed the importance of optimizing an infant's early growth, saying that a child's nutritional status at two years of age was shown to be predictive of pulmonary function (FEV₁) by mid-childhood. Investigators from Southampton University NHS Hospital reviewed growth parameters in infants whose CF diagnosed from 1994 through 2008 from the South and West UK CF database, including: annually recorded heights, weights, and BMI scores and converting those parameters to standard deviation scores (SDS). They compared SDS values for the age ranges 0 to 1 and 1 to 2 years over a 15-year period and found that the

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data demonstrate significantly improved early life growth indices for the studied population, which is likely to reflect increased attention to nutritional status within the first two years of life.

The findings revealed that from 1994 through 2008, among the 303 children whose CF was diagnosed in the first two years of life, there was a significant increase in weight SDS over the study period for 0 to 1 years ($p < 0.001$) and 1 to 2 years ($p < 0.05$). BMI SDS also increased significantly at both 0 to 1 years ($p < 0.05$) and 1 to 2 years ($p < 0.05$) over the same period. No significant changes in height SDS were identified.

Take home message: *Breastfeeding seems to ward off *P. aeruginosa* infection in infants with CF. Growth and BMI indices are improving, which suggests that dietary guidelines are effective.*

[back to top](#)

TREATMENT THERAPIES: Mannitol and Denufosal for Mucociliary Clearance

Workshop 5 - Translational Research in CF

Abstract 77: Phase III Study (CF - 302) of Inhaled Dry Powder Mannitol in Cystic Fibrosis. Results from the Six-month Open-Label Phase. Moira Aitken, MD, FRCP. [Abstract from the 34th European Cystic Fibrosis Congress: June 8-11, 2011; Hamburg, Germany.](#)

Symposium 12- Pipeline Update

Improving Mucociliary Clearance. Scott Donaldson, MD

The clearance of mucus from the lungs of patients with CF is an integral component of daily therapy. Inhaled mannitol is an osmotic agent that increases the water content of the airway surface liquid and improves the clearance of mucus with the potential to improve lung function and respiratory health. The six-month follow-up of a Phase III open label study (CF-302) of inhaled dry powder mannitol in CF revealed a sustained improvement (8% at twelve months) in lung function, suggesting durability of the response to treatment, according to Moira Aitken, MD of the University of Washington, who spoke for the CF-302 Investigators at the ECFC in Hamburg.

"The safety profile for inhaled mannitol was maintained over a twelve-month treatment period. No new safety issues arose with longer treatment durations, and adherence was high. The control patients who rolled over and received 400 mg during the follow-up phase showed an improvement in lung function. This is consistent with the improvement seen in the phase II trial," Dr. Aitken noted.

All of the study participants (n=242/260 patients completed the six-month open-label phase CF-302 study) received mannitol 400 mg twice daily. They maintained the increase in FEV₁ seen in the first six months of the trial, with an 8.2% improvement from baseline at week 52 (87.2 mL). Patients randomized to control had an FEV₁ improvement of 6.3% (84.0 mL) change from baseline at week 52. The study visits occurred at 26 weeks, 38 weeks, and 52 weeks. The phase II studies (multicenter randomized, double blind, controlled, six-month studies, followed by a six-month open-label phase), CF-301 and CF-302, showed a change in FEV₁ from baseline of 121 ml and 106 ml, respectively. The subjects were randomized 3:2 (mannitol 400 mg 2x/day:control 50 mg 2x/day). The patients had a confirmed diagnosis of CF, ≥ 6 years of age, FEV₁ ≥ 40 -90% predicted, standard therapy continued, no hypertonic saline allowed, and a negative mannitol tolerance test.

At the ECFC Pipeline Update Symposium, Scott Donaldson, MD, of the University of North Carolina at Chapel Hill, who spoke, reported on a different mucociliary clearing agent that did not fare as well in phase III clinical trials. Reporting on behalf of the Tiger 2 study that tested the effects of denufosal 60mg 3x daily on 450 patients with CF (mean patient age 15 years, mean FEV₁ 90% predicted, 40% with *P. aeruginosa*, 24% with previous hospitalizations for pulmonary exacerbations) for 48 weeks, Dr. Donaldson noted that patients randomized to the denufosal group did not achieve better FEV₁ values than the placebo group in TIGER2. Furthermore, no patient subset had any advantage when analyzed, although exacerbations were reduced, he said.



Denufosol tetrasodium is a selective P2Y₂ agonist that enhances mucosal hydration and mucus clearance by activating chloride ion secretion and cilia beat and inhibiting epithelial sodium ion transport through a non-CF CFTR mechanism in the lung. The development of denufosol targeted mild patients with CF, Dr. Donaldson said.

Dr. Donaldson continued: "There are a number of explanations of why this agent did not reach the expected results: maybe we do not understand the biology of the *in vivo* system, or the receptor activation is already near maximum in CF, or desensitized. It could also be that denufosol is not potent enough in CF."

Take-home message: *Mannitol seems suitable as an osmotic agent to restore the depleted airway surface liquid in CF patients, while denufosol showed slow and low increases in FEV₁. Unfortunately, the lack of clinical efficiency has led to the decision to stop development of this latter drug.*

[back to top](#)

INFECTIONS: Do Anaerobes Matter?

Symposium 7- Making Sense of Metagenomics

Pro: Anaerobes Matter. Gerd Döring MD

Con: Anaerobes Don't Matter. Steven Bell MD

Poster Presentation:

Poster 158: Einarsson G, Parks K, Gilpin D, Tunney M, Elborn JS. In vitro co-culture of *Pseudomonas aeruginosa* and *Prevotella* spp: Interaction between bacteria common to CF lung infection. [Poster exhibited at: 34th European Cystic Fibrosis Congress: June 8-11, 2011: Hamburg, Germany.](#)

The role of anaerobes in the progression of CF lung disease is poorly understood. At the ECFS in Hamburg, investigators discussed the relevance of the high numbers of anaerobic bacteria detected in the sputum and airways of patients with CF.

Mucus plugs provide an ideal anaerobic microenvironment for both facultative and obligate anaerobes. Despite the fact that researchers have demonstrated the prevalence of anaerobes in CF airways, the debate persists as to how seriously to take them. Gerd Döring MD, Tübingen University, Germany, who co-chaired a session on metagenomics, believes anaerobes should be treated and not ignored. "We do not specifically test for or diagnose anaerobes in patients with CF, but they are there. When we do find them, we generally do not single them out for treatment, but we should. If we targeted anaerobes we could learn whether or not they make a difference in lung function," Dr. Döring said.

He explained that *Prevotella intermedia* (a gram-negative obligate anaerobe) is more cytotoxic than *P. aeruginosa* (a gram negative facultative anaerobe) when grown under anaerobic conditions, and although it does not multiply rapidly, it persists in the sputum and lungs of patients with CF. *P. intermedia* is cytotoxic and just as toxic as *P. aeruginosa* for neutrophils and monocytes under anaerobic growth conditions. Furthermore, it is well adapted to anaerobic growth in contrast to *P. aeruginosa*, and has been shown to lower the toxicity of *P. aeruginosa* in animal models, suggesting that *P. intermedia* competes with *P. aeruginosa* in an anaerobic environment, Dr. Döring noted.

In vitro mixed cultures of these two organisms were grown by Gisli Einarsson, MD and his colleagues from the CF & Airways Microbiology Research group, Belfast, UK, who presented their results by poster. The study revealed that *P. intermedia* failed to promote the growth of *P. aeruginosa*. By contrast, however, co-cultures of *P. intermedia* with live *P. aeruginosa* cells resulted in a one log₁₀ increase in *P. intermedia* growth at 32 hours.

Further study results showed that cell-free supernatants from either aerobically or anaerobically grown *P. aeruginosa* had a similar effect on *Prevotella* growth. The coinoculation of *P. intermedia* with cell-free *P. aeruginosa* culture supernatants increased *Prevotella* by one log₁₀ at 28 to 56 hours, compared to when grown alone. The evidence suggests that *P. aeruginosa* may play an important role in promoting growth of *P. intermedia* within the CF lung.

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However, not all the CF experts agreed. Steven Bell, MD of the Adult Cystic Fibrosis Unit, Brisbane, Australia, who shared the stage with Dr. Döring at the ECFC session, debated that the presence of *P. intermedia* in sputum samples was not indicative of its presence in the lungs. Evidence suggests that anaerobic cultures of CF lung tissue obtained by thoracotomy showed few patients with anaerobes in the lower respiratory tract. "Patients found to have an anaerobic organism by culture are also frequently infected with *P. aeruginosa*, but anaerobes are isolated just as frequently from patients with and without exacerbations, suggesting a colonizing rather than a pathogenic role," Dr. Bell observed.

Dr. Bell argued that expectorated sputum is likely to be contaminated with bacteria residing in the upper airways, oropharynx, and sinuses. CF mice models homozygous for F508del showed a dramatic increase in dental caries, along with a similarly dramatic increase in anaerobes in the upper airways. Periodontal disease may be contributing to some of the anaerobes we are detecting, he said.

Take-home message: *Anaerobes are likely present in the lungs of CF patients, however, their role in the pathogenesis of CF lung disease is unclear. Larger studies of aerobic and anaerobic bacterial CF lung infections, including antibiotic treatments, are urgently required to better understand their clinical significance.*



VIDEO: Dr. Peter Mogayzel and Dr. Gerd Döring discuss anaerobic CF infections.

[back to top](#)

INFECTIONS: Adapting Clinical Trials

Workshop 15 - Translational Research in CF

CF Research: Challenges for the next 5 years? Preston Campbell, MD

Plenary - Cystic Fibrosis 2011

Models of Inflammation: From Bench to Bedside. Markus Mall, MD

Clinical trial designs for CF must adapt to changing disease, according to Preston Campbell, MD of the US CF Foundation, who co-chaired a workshop at the ECFC on Translational Research.

Dr. Campbell reported that patients with CF have an increased life expectancy, but that continued poor lung function call for better therapies. Since disease progression is slowing down, researchers will require larger patient samples over time to demonstrate the effect of new therapies. Also, the growing number of approved therapies taken simultaneously calls for physicians to be wary of drug-drug interactions. Placebo studies are likely to become more difficult to perform as patients' welfare largely depends on the continued intake of a complex and varied drug regime.

Dr. Campbell expects more studies focusing on infants and young children, which is evidence that as a community, CF specialists have transitioned from trying to just treat disease to trying to determine the natural history of how to maintain health in this population and maximize the benefits, he said.

For post-approval studies, Dr. Campbell believes that after a drug is approved, regulatory bodies and payers are likely to require longer-term efficacy and safety monitoring (phase IV studies). CF patient registries can provide a data entry mechanism for these studies to capture relevant clinical, safety, and treatment data, and registries will have to be compliant with regulatory guidelines.

Markus Mall, MD of the Division of Pediatric Pulmonology & Allergy and Cystic Fibrosis Center of Heidelberg University, Germany, sees other changes on the horizon for CF studies. In his plenary lecture, Dr. Mall noted that chronic inflammation was still a major problem in CF, causing irreversible structural damage to the lung, which is life-limiting for most patients. He described the future of animal models as crucial to our understanding of inflammation in CF.

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"We now have critical evidence that depletion of the airway surface liquid both by CFTR-mediated chloride ion secretion and increased absorption through the epithelial sodium channels is the early initiating lesion of this cascade. But we still have very limited evidence about the complex *in vivo* pathogenesis of chronic inflammation. These observations are difficult to make in patients without the use of invasive techniques, necessitating better animal models," Dr. Mall said.

Mouse models have been used since 1992. Today, CF researchers have several mouse models to work with and develop new ones frequently. A switch from the mouse model was long awaited because mice do not develop CF lung disease. Researchers are making their first observations on ferret and pig models, which seemed better suited to approximate human CF lung disease, with severe mucus obstruction in the large and small airways, chronic inflammation, and bronchiectasis. The pig model will be central for studies on preventing bronchiectasis and its complications. Also, improved research tools, like molecular profiling and pulmonary function imaging in animal models, will move progress along, he maintained.

"Studying the data along the translational chain helps to understand the pathogenesis of inflammation. We can use this to develop new sensitive biomarkers for early detection of inflammation and develop pre-clinical proof of concepts, both for new compounds that come out of the chemistry pipeline but also to test new therapeutic strategies, like preventive versus late-onset therapies. I believe that if we put these components together in an intelligent way, it will really help us to accelerate the development of effective therapies for CF lung disease," Dr. Mall said.

Take home message: *Slower disease progression and more concomitant therapeutic agents necessitate new approaches to future studies in patients with CF. New animal models promise to elucidate the pathogenesis of CF lung disease.*

[back to top](#)

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