Insights From The Kalydeco Journey: A Real Life Story of Progress and Possibility

By Siri Vaeth-Dunn

In one of the most anticipated presentations of the 2012 National CF Family Education Conference, Dr. Eric Olson (Ph.D.), Vice President and Leader of the Cystic Fibrosis Franchise at Vertex Pharmaceuticals, and Dr. Michael Boyle (M.D.), Director of the Johns Hopkins Adult CF Center, shared their unique perspectives on the exciting journey that led to the Food and Drug Administration’s (FDA) recent approval of Kalydeco for use by cystic fibrosis (CF) patients with the G551D mutation. For many of these patients, who comprise approximately 4% of the CF population, Kalydeco (also referred to as VX-770 or Ivacaftor) has had a dramatic impact on their health and sense of well-being. For the 96% of people with CF who have other mutations, the science behind Kalydeco will lead to the development of new therapies that are showing promising results in clinical trials.

“I’m going to walk you through a story,” said Dr. Olson, as he opened his fascinating presentation, “The Science of Possibility: Building on More Than 30 Years of CF Research to Discover and Develop Innovative CF Therapies.” When telling a story, he explained, “Wherever you start, you leave out much that came before.” His prologue included Dr. Paul Quinton’s pivotal research from 1983 that led to a new understanding of the role of the sodium chloride channel in cystic fibrosis.

(RESEARCH)

A Role for CFTR in Bacterial Killing by the Airways

By Horst Fischer, Ph.D.

CF is caused by a defect in the CFTR gene. When CFTR was cloned more than 20 years ago, it was immediately noticed that it forms a chloride channel in epithelial cells. However, the relation between the defective CFTR and CF lung disease remained elusive. The major function of the airways is to filter particles and microbes out of the airstream so that the lung remains clean and uninfected. The normal lung has an arsenal of antimicrobial factors that quickly and efficiently kill microbes. In CF, this critical function is impaired, which almost always leads to colonization of the lung with microbes and to persistent lung infections.

Because the only difference between a normal lung and the young, uninfected CF lung is the CFTR defect, it was reasonable to assume that CFTR has a role in bacterial defense, which would be defective in CF. Several years ago, we found that CFTR is also a channel for bicarbonate. Bicarbonate is an important pH buffer in the body and we proposed that CFTR’s function as a bicarbonate channel would alkalinize the airway surface liquid. This was consistent with the finding of clinical studies that the airway pH was more acidic in CF than in normal subjects. However, the finding of an acidic airway surface
Notes from our Executive Director – Fall 2012

It has been an exciting summer at CFRI! Our 25th annual National Cystic Fibrosis (CF) Family Education Conference saw a continued increase in attendance, as acclaimed speakers addressed a variety of CF issues. A review of the CF Therapeutic Pipeline by Felix Ratjen, M.D., gave us a context for specific therapies and drugs that were presented at this event. New information on the recently approved Kalydeco opened up exciting discussions about more possible discoveries in the near future.

At the same time, the message was clear for patients: whether you are eligible for Kalydeco now or for a new product in the future, do not abandon your ongoing therapies. No drug to date repairs past damage caused by CF, and keeping the body as healthy as possible will maximize the opportunity for good outcomes as new drugs become available.

Many of the Conference presentations are reviewed in this issue, and DVDs of different sessions can be ordered from CFRI. The talk given on Kalydeco by Eric Olsen, Ph.D., and Michael Boyle, M.D., and the “Ask the Experts” panel were broadcast, and can be viewed on our website http://www.CFRI.org/resources.shtml under CFRIlive™.

Your generous contributions enable us to fund top-quality CF research, vetting new projects that can then go on to the next phase of development. On page 1, Horst Fischer, Ph.D., describes his current research at the University of California, Berkeley. Research at this level leads to breakthroughs in scientific understanding, which in turn lead to improved treatments for CF.

As we move into an era where there are more adults than children with CF, we cheer those who stretch their limits at the USA Transplant Games. Anabel Stenzel gives us a window into that event, held this year in Grand Rapids, Michigan. See p. 17.

The CFRI “2012 RetrEAT: Nourishment for the Soul” was a wonderful gathering of those living with CF, who came together on the beautiful Vallombrosa campus. Exercise, arts and crafts, boating, educational presentations, and rap sessions contributed to a rich experience. To share in the “good feeling” of this unique week, go to: http://youtube/1XkkXKhv8Ls.

Many donors participated in our CFRI Golf Tournament at the renowned California top 100 course, Pasatiempo, in Santa Cruz. Thanks to Scott Hoyt and his committee, the players had a great time on the greens, and also enjoyed a fabulous auction and delicious dinner.

Thank you to our volunteers, who participate at all levels to help us create these top-quality events. This year we were joined by a special intern, Kevin Lin, who shares his impressions of his experience at CFRI on page 14.

We are all grateful to our sponsors for supporting the events we offer. They make it possible for us to keep registration costs low so that those who need the information and the community resources are able to attend. Mark your calendars with the dates noted below!

Finally, keep your eyes open for CFRI’s new look in the new year. With the help of Kriss Benson, a graphic designer and CFRI volunteer, we are updating our logo, and working to present a more consistent “face” to our community. We are excited to begin this process in January, 2013.

Warm wishes,
Carroll Jenkins

Save the Dates

CFRI Teen and Adult Retreat
June 23 – 30, 2013
Vallombrosa Center
Menlo Park, CA

CFRI 26th National CF Family Education Conference
August 2 – 4, 2013
Sofitel San Francisco Bay
Redwood City, CA

CFRI Golf Tournament
August 5, 2013
Pasatiempo Golf Club
Santa Cruz, CA
One Puzzle, Many Pieces: Fitting Together Multiple Approaches for Best Outcomes in CF

By Bridget Barnes

I have spent more of my life caring about CF than I haven’t,” Dr. Felix Ratjen revealed in his morning presentation, “Solving CF Puzzles: New Drugs in the Pipeline.” As Division Chief of Pediatric Respiratory Medicine at The Hospital for Sick Children in Toronto, Canada, Dr. Ratjen emphasized that there are many pieces needed to solve the CF puzzle, and “no one piece fixes the problem but rather, all the pieces fitting together.” To help understand the “puzzle pieces” leading to good outcomes in CF care, Dr. Ratjen outlined the various means to achieve that end.

Acknowledging that the lungs are the primary location of disease in cystic fibrosis patients, Dr. Ratjen spoke about the many treatment strategies that have been developed over the years, vastly improving survival rates for people with CF. Reviewing how lung disease develops in CF, Dr. Ratjen said, “the flux of salt influences the flux of water, and they need to be in the right balance to break up the mucus and stop infection.” He also touched on the standard treatment strategies currently used for CF, which have dramatically improved outcomes for CF patients. The list of drugs that are currently being studied or have been approved was graphically depicted on the Cystic Fibrosis Foundation’s “Therapeutics Pipeline.”

Dr. Ratjen described how CF drugs are divided into different categories such as gene therapy, CFTR modulation, restoring airway surface hydration, mucus alteration, anti-inflammatory, anti-infective, and transplantation and nutrition, each targeting a specific piece of the CF puzzle.

Noting that “good nutrition is key to survival in cystic fibrosis,” Dr. Ratjen added, “the high-fat diet we use today came from Toronto.” In a 1988 study that compared the Toronto CF center, which used a high-fat diet, with the Boston center, which used a low-fat diet, patients in the Toronto group on average weighed 6 pounds more and lived nine years longer than their Boston counterparts. In Canada in 2007, there were more adult patients with CF than children. Dr. Ratjen pointed out that, “Canada has done well over time and has more adults than pediatric patients due to aggressive disease management.” Overall lung function has improved in patients and the median FEV1 predicted for a 30-year-old patient in Canada was almost 80% in 2007. “It is better than it has been, but not at a point to stop,” Dr. Ratjen explained. “We want to do better in the future.”

New targets of therapy and their potential impact are also being studied and implemented. Hydration therapy with agents such as hypertonic saline is now a mainstay in CF care and a “simpler way” to clear accumulated mucus and prevent infection. Gene therapy will take longer to develop as there is currently no major gene therapy trial going on in the US, and only one in the UK, where the results have been “so-so.” According to Dr. Ratjen, we “won’t see much development of gene therapy in coming years.”

While it may be years before gene therapy is available, treating the defect itself currently offers another very promising approach to transporting the CFTR protein to the surface of the cell. In CF there can be one of two different problems with the “ion pump” that moves the CFTR protein. Either the ion pump is not present, or the ion pump is there, but does not function properly. The way to fix the problem is: 1) get the pump to where it needs to be on the surface of the cell, known as a “corrector;” 2) make the pump perform better, a “potentiator;” or 3) create an alternative pump which works on other ion channels. With the recent approval of Kalydeco (VX-770), a “potentiator,” and three other drugs that target the basic defect in CF currently in trials, Dr. Ratjen said there are “very exciting possibilities” in store. He also noted it is important to learn from what has not worked, such as denufosol. “Denufosol has a short half-life lasting approximately 50 minutes, so the study results may have been affected. With Kalydeco, we saw a huge initial bump-up in lung function, very different from denufosol.”

With regards to drug development in cystic fibrosis, Dr. Ratjen focused on hypertonic saline and bronchitol as examples of hydration therapy in CF. “Cilia transports mucus, and the airways need enough fluid so the cilia can ‘wave.’” Coincidentally, the solution to this problem was found on a wave. Australian surfers with CF found that saltwater helped clear clogged mucus, leading to better lung function and the development of hypertonic saline. Bronchitol (or inhaled mannitol), is a sugar that draws water to the airways, which is delivered as a dry powder and requires no nebulizer. A study of CF patients using bronchitol showed a 7% increase in lung function, and it is now available to adult patients in Europe.

Airway infection in cystic fibrosis caused by pathogens specific to the disease is a chronic concern. “Staph aureus is the most common bug, not pseudomonas,” according to Dr. Ratjen. “It’s changed because we have been more aggressive on pseudomonas than Staph.” He added, “Prevention of chronic infection has become paramount and is a major treatment target.” To combat pseudomonas, several studies compared intravenous to inhaled therapies. As an anti-infective, inhaled tobramycin (TOBI) is considered the standard of care to date. It achieves high (continued on page 22)
Antioxidants, Probiotics and Vitamins: The Vital Importance of Nutrition and Screening

By Siri Vaeth-Dunn

Anyone who has glanced at a health or fitness magazine lately has likely seen references to antioxidants, probiotics and vitamins. While beneficial for most people, they can be especially crucial for those with cystic fibrosis (CF). In her enlightening presentation, “Nutrition Essentials for CF: Antioxidants, Vitamin D and More,” Terri Schindler, M.S., a registered dietitian at the CF Center at Rainbow Babies and Children’s Hospital in Cleveland Ohio, shared valuable information about nutrition and its impact on those with CF.

As presented by Schindler, antioxidants are “substances that are capable of counteracting damaging effects of oxidation in tissues, as they neutralize free radicals,” which are believed to lead to cellular damage. Key antioxidants include vitamin E, C, Beta-carotene and selenium. Studies on the impact of antioxidant supplementation on lung disease and pulmonary exacerbations have had conflicting results. While some researchers have found that patients with CF using antioxidant supplements had a reduction in CF-related pulmonary exacerbations, others found that antioxidant supplementation “caused no harm…but showed no benefit.” Schindler emphasized that in addition to oral supplements, people should strive to eat foods that are high in antioxidant micronutrients.

Vitamin D has long been recognized as a key component to optimal bone health, as it assists in the absorption of calcium and phosphorus. Schindler cited a study which clearly indicated the inverse relationship between vitamin D levels and bone fractures. Vitamin D has been found to reduce the risk of falls in post-menopausal women by nearly 50%, and leads to significant improvement in neuromuscular function in the elderly. In light of the increased risk of osteopenia and osteoporosis for those with CF due to poor nutrient absorption, the importance of adequate vitamin D levels is paramount.

In addition to bone health, Schindler noted that vitamin D supplementation is associated with a “significant reduction in the risk of influenza and the common cold.” A recent study suggested that vitamin D might also serve as an effective anti-inflammatory. Common sources of vitamin D include ergocalciferol (D2), which is available by prescription, cholecalciferol (D3), which is “what we make in our skin from exposure to UV-B light,” and what is commonly found in over-the-counter supplements and sunlight. Noted Schindler, “the body can synthesize vitamin D from only ten to fifteen minutes of sunlight on the arms and legs without sunscreen.” The Cystic Fibrosis Foundation (CFF) recently published new guidelines for vitamin D, suggesting that levels should be checked near the end of winter, when levels are usually lowest. The CFF recommended the use of D3 (cholecalciferol) instead of D2 (ergocalciferol), with the goal of “a minimal 25-hydroxyvitamin D concentration of 30 ng/ml (75 nmol/liter)” for those with CF.

Schindler discussed the possible benefits of probiotics for those with CF, as the antibiotics commonly prescribed to them often wreak havoc with the beneficial bacteria and flora in the intestinal tract. The introduction of probiotics, “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host,” may be helpful in addressing antibiotic-associated diarrhea. A small study of 10 CF patients who were treated for six months with probiotic supplementation – specifically, lactobacillus GG – found a significant reduction in pulmonary exacerbations, though there was no notable difference in pulmonary function levels or inflammatory markers. Schindler stressed that patients should confer with their doctors prior to taking probiotics. It is important to “pick a product from a trusted manufacturer and to choose a product with the right quantity of colony forming units.” Probiotics may be dangerous for those people who have had lung transplants and it is especially critical that they consult with their doctors prior to use.

Schindler discussed several “hot topics” in CF nutrition, including the use of growth hormones, insulin therapy, and vitamin K. The height of many children with CF is impacted due to impaired nutritional absorption. A multi-center clinical trial of growth hormone treatment for children with CF found that use of the growth hormone rhGH improved growth, lean body mass, and lung function. Schindler addressed the benefits of slow-release insulin therapy for those people with CF who have impaired glucose tolerance. A three-year study in which CF patients with insulingenesis (a deficiency of insulin secreted by the pancreas) were treated with low-dose insulin found that this therapy helped to prevent lung function decline. Vitamin K, a fat-soluble vitamin which assists with blood clot formation and bone health, is commonly prescribed as part of the CF care regimen. Vitamin K deficiency is linked to hemoptysis (bleeding in the lungs or bronchial tubes). Schindler stressed that vitamin K is “often not found in over-the-counter vitamin supplements, and that it has a history of being under-dosed.”

Other “hot topics” include the prevention (continued on page 23)
What are the top ten adult Cystic Fibrosis (CF) Centers in the United States doing to achieve the best health outcomes for their patients? In his engaging talk, “Providing the Best Care for Adults with CF: A Partnership with Patients and Families,” Dr. Michael Boyle presented a very clear set of guidelines based on information he gathered in his study. Among his many duties as Director of the Adult Cystic Fibrosis Program and Assistant Professor of Medicine at the Johns Hopkins Medical Institutions in Baltimore, Dr. Boyle led the Adult CF Quality Improvement project inspired by “the idea of how we as caregivers, patients, and families can work together to get the best outcomes.” He visited each of the ten centers to learn how they deliver their care and distilled the best common practices employed by each.

The following questions served as the basic criteria for discovering what leads to better health for adults with CF: 1) Does what we do as caregivers, patients and families make a difference in the severity of CF, or is the course determined by genetics? 2) How can we create a partnership between caregivers and patients to assure the best possible care? 3) What are the strategies to help young people with CF become successful adults with CF?

As to whether or not severity of lung disease in CF is attributable solely to genetics, or whether other factors play a role, Dr. Boyle reported, “When looking at identical twins, their FEV1 was similar when living at home together, but after living apart there was four times more variability.” Showing a slide with a mother holding an apple pie, Dr. Boyle jokingly concluded, “The recipe for a good outcome is to provide everyone with a mom.”

Today, when more than half of the people living with cystic fibrosis are adults, Dr. Boyle cited examples of adults who take responsibility for themselves and added, “It’s actually healthier for this age group with CF to have inspirational peers in their lives than a doting mom.” In a study at Johns Hopkins that followed the clinical and pharmacy records of 95 CF patients for twelve months, Dr. Boyle reported, “patients do better if they take their medications and have them available in their medicine cabinets.” The study showed, “If 80% of one’s medications were being filled, there were no exacerbations. If medications were only being filled 40 to 60% of the time, exacerbations increased,” demonstrating that compliance is crucial.

Partnering with caregivers is also a vital component in ensuring that adults with (continued on page 18)
A New Perspective on CF Care
Presented at Annual Conference

By Bridget Barnes

In order to convey the dramatic improvements that have taken place in cystic fibrosis (CF) care over the past 30-plus years, Dr. Karen Hardy, Director of Bay Area Pediatric Pulmonary at Children’s Hospital Oakland and California Pacific Medical Center in San Francisco, shared stories about her early days as an intern. Asked by Isabel Stenzel-Byrnes to do “CF 201,” Dr. Hardy, with no notes in hand, gave an insightful and comparative analysis of how the treatment of CF has changed over the years during her presentation entitled, “CF Care: Getting A New Perspective.”

Dr. Hardy’s first patient was a 17-year-old girl with cystic fibrosis on oxygen full time “who touched my heart.” According to Dr. Hardy, “she wanted to know my age and if I was good with IVs. When I said ‘Yes,’ she said, ‘Good, I only have one vein left.’ Her goal was to survive to her 18th birthday.” It was this fateful meeting that led Dr. Hardy to pursue a career specializing in CF clinical care. She completed her fellowship in 1986 in Pediatric Pulmonary Disease and Cystic Fibrosis at Saint Christopher’s Hospital for Children in Philadelphia, which had 400 patients. She recounted how Dr. Stan Field, one of her mentors, was also there to learn about pediatric patients, as he was beginning to consider transition at that time. His influence made Dr. Hardy a big proponent of transition as she recognized that children need to “graduate” and move forward to an adult center. This idea was one of the many precursors that changed the way CF care is imagined and delivered today.

In 1989 the CFTR gene was discovered. “It was a very exciting year and everyone was optimistic thinking that within a decade we’ll have a cure,” Dr. Hardy recounted. “But we didn’t.” In the meantime, big advances were made in mucus alteration with the development of Pulmozyme and anti-infectives such as Azithromycin and TOBI. Hypertonic saline was also approved and made available to patients with CF as a way to improve airway surface liquid. All of these therapies improved lung function.

In describing the ways in which treatments have changed over the years, Dr. Hardy noted, “CF has truly changed from a fatal illness to a chronic disease.” As more medications have been discovered, the focus has been on merging therapies in an effort to reduce treatment time without compromising the benefits. Dr. Hardy used the example of nebulizers for bronchodilation, which “are not necessary anymore,” as MDI’s (metered dose inhalers) are quicker, just as effective and far more portable.

There are multiple ways of clearing mucus from the lungs including autogenic drainage, active cycle of breathing, using a vest, PEP or flutter, as well as a number of aerosol treatments. Dr. Hardy clarified the order in which aerosol treatments have been found to be most effective. “Start with a bronchodilator or metered dose inhaler (MDI) to open up airways, then breathe in hypertonic saline, which adds fluid and moves mucus, and finally Pulmozyme, which chops up the rafts of mucus.” She also explained that adding PEP or flutter to vest therapy, “helps keep airways open that have grown floppy with age.” Non-medical treatments such as trampoline, pogo stick, all wind instruments, running, swimming, horseback riding, or any sport with high impact are also very beneficial.

Saving the best for last, Dr. Hardy talked about Kalydeco, “the exciting new Vertex product,” which targets the basic defect in cystic fibrosis and restores ion transport to the cell surface. A couple of patients in her clinic with the G551D mutation are using the new drug and according to Dr. Hardy, “the results have been amazing, and patients may be able to decrease other treatments.” She concluded her talk by joking that she was “the opening act for Paul Quinton, who we’re all here to see,” and enthusiastically noted once again how dramatically different and positive the CF treatment landscape has become. Dr. Hardy won CFRI’s Professional of the Year Award in 2011, and was Best Bay Area Doctor in 2009.
Dr. Paul Quinton: Inspiring CF Researcher and Role Model

By Rod Spadinger

For many years, it was generally assumed that those diagnosed with cystic fibrosis (CF) would live a brief and relatively unproductive life. Several decades ago, that may have been accepted as truth. However, Dr. Paul Quinton, who spoke at the 25th National CF Family Education Conference, defies the odds each and every day. As we learned during his presentation, “Kicking Butt With CF at 67!” Dr. Quinton’s life is the extreme opposite of brief and unproductive.

Dr. Quinton, currently a professor of Biomedical Science at the University of California, San Diego, was born in 1944, a time when cystic fibrosis was largely unknown by the medical community. While in the fifth grade, Dr. Quinton failed a school Tuberculosis test and it was discovered that something was wrong with his lungs. As a result of the relative obscurity of CF, he was not diagnosed with cystic fibrosis until the age of 19 years. Until that point, it was assumed that he merely had stubborn respiratory infections that could not be properly treated. Dr. Quinton’s first diagnosis was that of chronic bronchitis.

While a sophomore at the University of Texas, Dr. Quinton read literature that led him to a self-diagnosis of cystic fibrosis. It was then that he was introduced to Dr. Gunyon Harrison of Baylor University, his first physician who was a specialist in the treatment of CF patients. Dr. Harrison was able to medically confirm through a series of sweat tests that Dr. Quinton did, indeed, have cystic fibrosis.

Early in Dr. Quinton’s career, while working at the University of California, Riverside, he analyzed the sweat ducts of CF patients, and with the assistance of his colleagues, was able to discover an abnormality in these ducts. The team concluded that the problem with the ducts was due to their impermeability to chloride. As such, the chloride could not get out across the duct, could not be reabsorbed back into the blood, and wound up on the surface of the skin. This is the basis for the thick and sticky mucus that permeates the bodies of CF patients.

During his presentation, Dr. Quinton shared some personal moments about his life as a CF patient. He divulged that when he was first diagnosed with cystic fibrosis, he chose to keep the discovery largely to himself, informing just a few people about his condition. It was only when his experience with CF appeared in the San Jose Mercury newspaper, that he was able to freely disclose his situation.

Dr. Quinton concluded his presentation with thoughts about how he felt about death, and whether he is fearful. He remarked that to him, death is inspirational: it drives us to live. Further, it is his view that the challenge of death can inspire people to be more than they otherwise would.

The rich and full life that Dr. Quinton leads provides an example to all living with cystic fibrosis that being diagnosed with CF is not the beginning to an end. Rather, it is merely a beginning with boundless possibility.

Reflections on My First CFRI Conference

By Maria Fioccola

The 25th Anniversary of the National Cystic Fibrosis Family Education Conference was held at the Sofitel San Francisco Bay, in Redwood City, California. This year’s theme was “Facing CF Together with Confidence.” I traveled from Chicago to attend the conference for the first time.

You may wonder how I got involved from so far away. An adult with cystic fibrosis (CF), I am on the Board of Directors for USACFA (United States Adult Cystic Fibrosis Association) and Secretary for the Northwestern University Patient Advisory Board. I learned about the CFRI conference through fellow board members who have attended in the past. I was honored to be asked to attend on behalf of USACFA, but needed help with expenses. Fortunately, I received a scholarship from CFRI, USACFA helped with my airfare, and the Sofitel offered CFRI Conference attendees a discounted room rate. With the essentials taken care of, I was ready to book my trip!

I was nervous at the thought of traveling alone and visiting a new city and I was grateful for the patience and help from the CFRI staff! Upon arriving in San Francisco, I was greeted by Mary Convento, who drove me to...
Airway clearance is the never-ending, time-consuming, life-sustaining ritual practiced in every cystic fibrosis (CF) household. We constantly wonder about it. “Am I doing the best I can?” “Should I be doing anything differently?” “Is airway clearance really worth the time and effort?” Mary Lester, a Registered Respiratory Therapist at the Medical University of South Carolina (MUSC) in Charleston, directly addressed these concerns during her presentation, “Effective Airway Clearance Treatments.”

Lester advocates that airway clearance is for everyone. Since no airway clearance method has proven to be superior to others, respiratory therapists must help patients decide which method will work well for them. Lester informs her patients about all the options, listens to patient opinions, and then works with individuals to determine which method is best for them. Some factors she considers when selecting airway clearance techniques are the patient’s motivation, the patient’s goal, the caregiver’s goal, effectiveness, patient age, and ease of learning and teaching.

With twelve years experience as the lead respiratory therapist at MUSC, Lester emphasized that airway clearance is an active process. Since it can be rather boring, patients need to figure out how to stay involved. Illustrating that patients can integrate treatments into an active lifestyle, Lester described the routine of a particularly creative patient. This motivated CF adult has machines set up in his car so that he can do airway clearance as he drives to and from work. How does Lester know his set up works? The patient coughs, coughs, and coughs some more.

The Medical University of South Carolina serves a wide population. Being the only adult CF center in South Carolina, MUSC has almost twice as many adult patients as pediatric ones. With newborn screening, many CF children are being diagnosed at birth. While young babies are consistently given chest physiotherapy with a bronchodilator, effective airway clearance techniques typically change for an individual over time. As with older patients, it is recommended that infants begin TOBI at the first positive culture for Pseudomonas aeruginosa. Hypertonic saline use is recommended at a later age. According to the results of a recent study on the effectiveness of inhaled hypertonic saline on infants (known as ISIS), infants can tolerate a 7% saline solution, but do not significantly benefit from it.

Lester recommends giving “lots of thought about when to get a device, because you don’t want it to be put in a closet.” She does not discuss a high-frequency chest wall compression (HFCWC) device until after a child turns two. A HFCWC device is more commonly known as a “vest,” and there are now three vest manufacturers to choose from. Since different types of airway clearance may be more effective than others at different stages of life, Lester believes patients should know all of the options for chest physiotherapy. In addition to HFCWC, recommended therapies include autogenic drainage and IPV (intrapulmonary percussive ventilator). Autogenic drainage is unique in that the patient can perform it alone and in a sitting position; however, autogenic drainage requires training and intense focus and concentration. To help clear sputum, an IPV delivers shorts bursts of air into the airways. Nebulized medicine can be administered at the same time. Once patients are informed about their airway clearance options, Lester acknowledges that the final decision may still be based on a “gut feeling.”

Finally, Lester endorses exercise. Consistent research has not shown if exercise can replace airway clearance techniques. However, experience shows that exercise is an important adjunctive therapy. With exercise, it’s easy to follow Lester’s main guidelines. Be creative. Be consistent. And be sure to cough.

“...exercise is an important adjunctive therapy.”
Men with CF Are Having Children!

By Rod Spadinger

Among the category of challenges that men with cystic fibrosis (CF) face is the topic of male reproductive capacity. For many years, it was assumed that men with CF were not able to father children due to infertility issues. Over the past few years, however, barriers have been breached with science, which now allows men with CF to reproduce. At the 25th National CF Family Education Conference, Dr. Paul Turek, infertility specialist and founder of The Turek Clinic, delivered a presentation entitled, “Men With CF Are Having Children!” As detailed by Dr. Turek, the majority of men with cystic fibrosis are capable of having children, albeit with the aid of technology.

The primary reason that men with CF are unable to reproduce naturally is the result of a tube, called the vas deferens, which was not properly formed prior to birth due to complications related to the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein. This causes mucus to clog the vas deferens while it forms, leading to its deterioration and absence in newborns. Approximately 99% of men with cystic fibrosis are missing the vas deferens. Termed Congenital Absence of the Vas Deferens (CAVD), this anatomical defect provides a reproductive roadblock for men, as the vas deferens is the tube that connects the sperm-producing testicles to the penis.

The good news, as detailed by Dr. Turek, is that there are well-defined and successful surgical sperm retrieval procedures for men with CF who are missing the vas deferens. Choices include retrieving it from the epididymis, an organ above the testicle where sperm is stored, or via testis (testicular) sperm. According to Dr. Turek, the quality of the sperm is generally identical, regardless of from where it is retrieved.

The most successful method of retrieving epididymal sperm is through Microsurgical Epididymal Sperm Aspiration (MESA). In this process, a small incision is made in the scrotal skin and, aided by the use of optimal magnification, tubules of the epididymis are examined and opened, which allows for the identification and collection of quality sperm. Percutaneous Epididymal Sperm Aspiration (PESA) does not require an incision. Instead, a needle penetrates the scrotal skin and retrieves sperm that is found. The most successful method of retrieving epididymal sperm is through Microsurgical Epididymal Sperm Aspiration (MESA). In this process, a small incision is made in the scrotal skin and, aided by the use of optimal magnification, tubules of the epididymis are examined and opened, which allows for the identification and collection of quality sperm. Percutaneous Epididymal Sperm Aspiration (PESA) does not require an incision. Instead, a needle penetrates the scrotal skin and retrieves sperm that is found.

“The good news... is that there are well-defined and successful surgical sperm retrieval procedures for men with CF who are missing the vas deferens.”

Dr. Turek prefers MESA to PESA because MESA allows the surgeon to identify and extract quality sperm tubules, whereas PESA is a “random” technique that does not allow the surgeon to be certain that the extracted sperm are of good quality. Because of this, MESA typically needs to be performed only once, while PESA procedures often need to be repeated.

To a lesser extent, CF male fertility may also be challenged by very little epididymis to store sperm, or merely low sperm production. A significant obstacle for men with CF with low sperm production is that sperm is difficult to find and subsequently retrieve in the testicle. To address this, Dr. Turek has developed a mapping procedure that enables the surgeon to determine whether or not sperm exist in the testicles. In this instance, the testicle must be entered surgically, with the most successful procedure being Testicular Sperm Extraction (TESE). With TESE, a small piece of testicular tissue is removed through an incision in the skin, allowing for the extraction of the sperm.

Once sperm is retrieved from the patient, Intracytoplasmic Sperm Injection (ICSI) is performed. With this procedure, the extracted sperm is inserted via a needle into the cytoplasm, the inner part of a woman’s egg. ICSI is preferred to in vitro fertilization, where the sperm is placed near the egg, because the sperm retrieved is not mature enough to fertilize the egg without the directed assistance that ICSI provides.

Thanks to the enormous efforts and expertise of physicians such as Dr. Paul Turek, the possibility of men with CF having biological children has become a reality.

Paul J. Turek, M.D.

“Intracytoplasmic Sperm Injection (ICSI) is performed. With this procedure, the extracted sperm is inserted via a needle into the cytoplasm, the inner part of a woman’s egg. ICSI is preferred to in vitro fertilization, where the sperm is placed near the egg, because the sperm retrieved is not mature enough to fertilize the egg without the directed assistance that ICSI provides.”
When Heather Walter’s daughter was diagnosed with cystic fibrosis (CF), the news triggered a wide range of emotions. During her thought-provoking presentation, “PTSD (Post Traumatic Stress Disorder): Confronting High Anxiety with Confidence,” Dr. Walter, a professor of organizational communication at the University of Akron, recalled that when her daughter’s doctor shared the devastating news, he told her that children with CF were living into their twenties. Much to Dr. Walter’s shock, this information was “presented like good news.” Dr. Walter recounted that as she was “falling into the CF world,” the stress and disorientation caused her to feel “defined by the diagnosis.” She likened her experience to having arrived in a new country, where she was faced with a completely unfamiliar language and culture. She felt, in a word, traumatized.

In her search to understand this new CF world, Dr. Walter employed her academic research skills and discovered the work of a Brazilian psychiatrist, Mariana Cabizuca, from the Institute of Psychiatry at the Federal University of Rio de Janeiro. Dr. Cabizuca and her associates conducted a study to assess the prevalence of post-traumatic stress disorder (PTSD) among parents of children with CF. In their article, “The Invisible Patients: Post Traumatic Stress Disorder in Parents of Individuals with Cystic Fibrosis,” the researchers found that 6.5% of study respondents had “full PTSD,” while 19.4% of surveyed parents had “partial PTSD.”

PTSD is an anxiety disorder caused by exposure to some form of traumatic event that often involves the threat of injury or death. Usually associated with those who have experienced extreme violence, including rape victims and war veterans, there is now a growing understanding that the diagnosis of a life-threatening disease triggers the same anxiety response. Typically there are three responses to PTSD: re-experiencing/re-living, avoidance, and arousal. People who “re-experience,” are often faced with intrusive recollections, nightmares and flashbacks, and continue to relive the traumatic events. Situations that remind people of the original event can cause strong reactions. In Dr. Cabizuca’s study, 63% of the parents experienced the re-living of the diagnosis.

Those who respond with “avoidance,” often feel detached from others. They avoid anything related to the traumatic event that may trigger symptoms. People with avoidance often have a sense of foreboding about the future, and diminished interest in their usual activities. While only 11% of people in the Brazilian study reported this, Dr. Cabizuca hypothesized that those who are experiencing avoidance were unlikely to participate in a study and were therefore likely under-reported.

The third common symptom of PTSD is “arousal,” a state of hyper-vigilance and hyper-alertness. People experiencing this arousal often suffer from insomnia, are unable to relax, and may have an exaggerated response to anything that startles them. Of the parents in Dr. Cabizuca’s study, 63% reported experiencing this symptom.

How to manage the symptoms of post-traumatic stress disorder? Dr. Cabizuca recommended that CF care teams ask parents of patients about their emotional health and the possibility of psychological/psychiatric treatment. For many, knowing that they are not alone may be enough to alleviate the symptoms. Participation in support groups can be useful – both online and in-person. The social worker at the CF Center can provide direct support, or referrals to other counselors. Behavioral therapy is very effective for some, as are anti-anxiety medications.

Dr. Walter shared the personal lessons she has learned since her daughter’s diagnosis. First and foremost, “There is help out there.” She noted the importance of understanding that some days, “avoidance is not a bad thing.” And due to the nature of the disease, it is likely that each new “sub-diagnosis” – for example, new infections and cystic fibrosis related diabetes – can trigger the stress of the initial diagnosis. Most importantly, symptoms of PTSD should not be ignored. As Dr. Cabizuca wrote about the parents in her study, “their suffering remains ‘invisible’ to the medical system, leading to under-diagnosis and under-treatment.”

To read the article by Dr. Cabizuca go to: http://www.scielo.br/scielo.php?pid=S0101-60832010000100002&script=sci_arttext&tlng=en
Women With CF Are Having Children!

By Siri Vaeth-Dunn

The first successful pregnancy and birth by a woman with cystic fibrosis (CF) was documented in 1959. At a time when few people with CF survived early childhood, this was a remarkable event. As the median life expectancy for those with CF increases, as well as their quality of life, more women with cystic fibrosis are exploring pregnancy and in 2010, 225 women with CF delivered babies. In her illuminating presentation “Women with CF Are Having Children!” Dr. Lynn Westphal, Associate Professor of Obstetrics and Gynecology at Stanford School of Medicine, discussed the reproductive options currently available to women with CF.

Most women with CF are fertile, but those considering pregnancy will require additional medical care. According to Dr. Westphal, the physician’s first step is to conduct fertility testing with the patient, including measuring the levels of follicle-stimulating hormone (FSH). Should these tests indicate that fertility is not an issue, there are other considerations before proceeding. The woman’s partner must be tested to assess whether he is a carrier and the couple should receive genetic counseling. Dr. Westphal stressed that women should try to reach at least 90% of their ideal weight, and optimize their health through adherence to their medical regi-

women. They should also review their medications with their doctor and be screened early for diabetes. Dr. Westphal emphasized that a successful pregnancy requires well-coordinated multidisciplinary care.

Most women with cystic fibrosis who are hoping to bear children will have some form of procedure utilizing assisted reproductive technology (ART). Most often, women undergo ovarian stimulation, in which they are given follicle-stimulating hormones with the goal of the development of multiple follicles. The next step, according to Dr. Westphal, is the collection of oocytes (eggs), which are retrieved using a needle through the top of the vagina. The eggs are then fertilized. With traditional in vitro fertilization (IVF), 50,000 to 200,000 sperm are mixed with the collected eggs. In some cases, intracytoplasmic sperm injection (ICSI) is utilized, in which a single sperm is directly injected into each egg.

By the third day, the embryos have 6 to 8 cells, and Dr. Westphal noted that biopsies of the embryos are usually conducted at this stage. Pre-implantation genetic diagnosis/screening (PGD/S) involves removing one or two cells from each embryo in order to test for genetic defects. PGD/S, said Dr. Westphal, is “well proven for the diagnosis of a single genetic defect.” The accuracy of this screening is estimated to be 85%, and women may choose to have chorionic villus sampling (CVS) or amniocentesis at a later date for more accurate results.

Once the embryos have been selected, they are transferred to the uterus via catheter, guided by ultrasound. While IVF implantation often results in multiple babies, this could have serious implications for women with cystic fibrosis. As such, Dr. Westphal noted that usually only one or two embryos are transferred. If the implantation is successful, “the patient will be passed to a high-risk obstetrician at around 10 weeks.”

Women with CF who have undergone lung transplantation have successfully had children, but it has additional risks. Dr. Westphal suggested that women have a minimum of three years of stable health post-transplant before considering pregnancy. She also cautioned that organ rejection is more frequent during pregnancy.

For those women with CF who are unable to carry a pregnancy, Dr. Westphal suggested gestational surrogacy, in which the woman goes through all the steps of IVF, but the fertilized embryo is then transferred to another woman, who will serve as a surrogate and carry the baby to term. Noting that California is “surrogate friendly,” Dr. Westphal warned that, “regulations regarding surrogacy vary by state and country.”

Much progress has been made in cystic fibrosis care, with expanded life expectancy and improved quality of life. A tangible measure of this progress is the number of women with cystic fibrosis who – regardless of how they achieve it – have successfully become mothers.
Chapter One began with the question, “Is it possible to find drugs or therapies or small molecules that could restore the function of the CFTR (cystic fibrosis transmembrane conductance regulator) protein?” The discovery of the CFTR gene in 1989 led to focused work on understanding how the CFTR protein worked, and why various mutations led to “a misfunction or dysfunction” of the sodium chloride channel. “Understanding the gene was one thing,” Dr. Olson said, “also important was identifying the mutations and clinical phenotypes that they manifested.”

Fortunately, new methodologies were being developed for high throughput screening, in which hundreds of thousands of molecules could be tested to look for “any particular activity to block a protein, turn on a protein, or any other pharmacological activity,” said Dr. Olson. In 1996, Aurora Biosciences in San Diego, California “had the technology in a niche market,” whereby they “specialized in building florescent-based technology for screening and identifying drugs that could affect ion channels, sodium chloride and calcium channels.” According to Dr. Olson, Aurora formed an agreement with the Cystic Fibrosis Foundation to focus on CF. Through this pilot program, Aurora found molecules that appeared to “turn on or restore the CFTR function.” In 2001, Vertex Pharmaceuticals purchased Aurora. The research challenge, shared Dr. Olson, was that, “Most enzymes block or stop a protein from doing its function. We were trying to make the protein come to life and function.” In 2004, VX-770 showed the potential to do this, and in 2005, the VX-770 development team was formed and transferred to Cambridge, Massachusetts.

The G551D mutation is a “class III” mutation, in which the CFTR protein has been made and is sitting at the epithelial surface, but the channel will not open. As such, this mutation has the greatest potential for research success. As Dr. Boyle explained succinctly in his later presentation, “Kalydeco binds to CFTR…and opens the gate more frequently, with more chloride conductance. Ivacaftor (Kalydeco) is a potentiator that increases CFTR channel opening time.”

In the “discovery phase,” as described by Dr. Olson, researchers cultured airway epithelial cells from autopsies and transplant patients. Airway cilia in those with CF are immobilized by mucous and unable to sweep away particles and bacteria, leading to a cycle of inflammation and infection. When the cilia of G551D lung cells were treated with VX-770 in the lab, they began to move. The moving cilia showed the potential of VX-770 to repair the “gating” problem with the channel, and soon after, Vertex conducted a phase 1 clinical trial in healthy people to determine safety and dosing.

Based on the results of this, VX-770 was advanced to phase 2 trials. Dr. Olson noted that based on the small number of adult patients with the G551D mutation, it was a challenge to find twenty subjects for the study. The main outcome of the trial was to measure changes in the sweat chloride. Dr. Olson shared, “One of the more emotional times of my whole career was when two physicians called me into the office to show me the data from the study with the patients.” The data showed dramatic drops in sweat chloride. “We knew we were on the right track, and that it was possible. Spring of 2008 will forever live in my memory.” Not only did the study mark an important proof of concept, Dr. Olson said, but also, “Proof of principle. It showed you could give someone with CF a pill, and that this drug could get into the body and restore the function of the protein.”

Based on the promising results of the phase 2 trials, Dr. Olson and his team at Vertex worked simultaneously with the FDA and European regulators to initiate a pivotal phase 3 trial, which began in 2009. When the first results were seen in February 2011, “the race was on,” to provide all the necessary information together for both the FDA and European regulators. Said Dr. Olson, “It was a nerve-wracking time. Never underestimate the amount of work required to bring a product to manufacture and to market. Whether for 1,000 people or a million, it requires the same amount of work.” VX-770, renamed Kalydeco, was approved by the FDA in January 2012.

The work on Kalydeco is only a part of Dr. Olson’s story. Another promising molecule, VX-809, had been discovered by Vertex researchers and was being explored as a “corrector,” to address patients with the Delta F508 mutation. Delta F508 is a class II mutation, which causes the CFTR protein to misfold, and prevents it from reaching the epithelial surface. Eighty percent of people with CF have a class II mutation. In an early study, patients homozygous for Delta F508 were given VX-770. While they did not have a significant clinical response, Dr. Olson noted that the study “gave important information for a combination approach.” He added, “In June, 2011, we saw for the first time that a corrector and potentiator could work together to improve CFTR function.” VX-809 - the corrector - helps move the protein to the cell surface, while the potentiator, VX-770, helps the protein channel to open and function. Dr. Olson noted that he and his colleagues are currently, “in the middle of dissecting that data.”

As for the future, Dr. Olson was very enthusiastic. “Now that we know the science that led to this, we think that this same science can be applied to a much
larger group of patients. We have another drug in clinical development. The team in San Diego is still screening, doing chemistry, and looking for even better molecules. We are on a very strong scientific foundation, and someone will harvest that and develop new therapies.”

While Dr. Olson provided insights from the development side of Kalydeco, Dr. Michael Boyle, as Director of the Adult CF Center at Johns Hopkins Medical Center, was able to share his personal perspective as both a principle investigator for the Vertex combination trial, and a CF practitioner who witnesses firsthand the effects of Kalydeco. Noting that, “Dr. Olson is limited about what he can say,” Dr. Boyle had more liberty to provide encouraging details from the field.

“The most striking result from the phase 3 study, looking at the 48-week data, was that the FEV1 of those treated with Kalydeco improved by approximately 10% after two weeks, and continued to show this significant difference throughout the study,” said Dr. Boyle. “This has been confirmed in a follow-up study, following patients for an additional two years.” In addition to the improvements in lung function, Kalydeco is, “correcting CFTR throughout the body, making a difference in some of the key clinical outcomes.”

Kalydeco’s impact on sweat chloride levels, which so moved Dr. Olson in early clinical trials, has held true in clinical practice. Dr. Boyle shared that patients treated with Kalydeco had their sweat chloride levels drop from approximately 100 mmol to less than 60 mmol. This is significant, in that 60 mmol is used as the cutoff for cystic fibrosis diagnosis.

According to Dr. Boyle, adult patients treated with Kalydeco had an average weight gain of approximately 7 pounds, and a 55% reduction in pulmonary exacerbations. Those taking Kalydeco consistently cited an improved quality of life. A phase 3 study was conducted with children aged 6 to 11 years old with at least one G551D mutation. The results from this study, said Dr. Boyle, “were almost identical to the results for adults.”

While the study results were resoundingly positive, Dr. Boyle noted that Kalydeco’s “real life application” was equally encouraging. “People who were on the study drug knew they felt better.” They told Dr. Boyle that they noticed a “significant decrease in cough, and also increased energy.” Many cited “a general sense of well-being.”

Dr. Boyle emphasized that those who take Kalydeco must still adhere to their previous medical regimen, including respiratory therapy. Kalydeco “cannot undo previous lung structural damage that a patient already has.”

Noting that bronchiectasis and previous scarring are irreversible, Dr. Boyle emphasized that Kalydeco, “does restore some of the physiology that will help to prevent future damage.” In the future, he added, “maybe we will be able to use it with kids who have not experienced lung damage,” thus preserving their lung function.

CF pulmonologists have long stressed the critical importance of doing what is necessary to preserve lung function. With the approval of Kalydeco, this advice is resonating with Dr. Boyle’s patients – particularly with teens – because it represents the potential for new treatments in the near future.

In acknowledging that Kalydeco is only approved for use by a small percentage of CF patients, Dr. Boyle pondered who else might benefit from the drug in the future. The “low-hanging fruit,” according to Dr. Boyle, are those with other class III mutations, as well as those with class IV mutations, where the CFTR protein is already at the surface.

Combination therapy holds great promise for those who carry the Delta F508 mutation, as 87% of people with CF carry at least a single copy, while approximately 50% are homozygous for the mutation. In addition to the corrector VX-809, Vertex is studying VX-661, which also helps traffic CFTR up to the surface to help act as a channel. A recent study of people homozygous for the Delta F508 mutation included, “28 days of monotherapy with VX-809 to get the protein to the surface, followed by 28 days of combination therapy with VX-809 and Ivacaftor (Kalydeco).” According to Dr. Boyle, while the data is not published yet, top line data indicated a “mean absolute improvement of 6% in lung function.”

Due to the results, Vertex and clinical investigators will advance to phase 3 trials. At the same time, VX-661 is in phase 2 trials with 120 patients. Said Dr. Boyle, “At the end of day, we spoke a lot about Ivacaftor (Kalydeco), but there is a lot of promise and potential with VX-809 and VX-661 to help with trafficking, and hopefully to see the results that we have seen with Ivacaftor.” Dr. Boyle encouraged patients to talk with their doctors, and to “Please look to see what studies are ongoing if you are eligible, so you are guaranteed the drug.”

In closing, Dr. Boyle noted that while many questions have been answered, there are others to consider, including: “What are the long-term effects of Ivacaftor on CF individuals with G551D? Can we protect younger patients’ lungs? Will Ivacaftor be beneficial in other classes of mutations with preserved CFTR function? Will VX-809 or VX-661 in combination with Ivacaftor be beneficial in Delta F508 so as to help 87% of other patients? Will we be able to develop other strategies for those with a lack of CFTR in class I mutations?”

The future holds promise for those living with CF. As Dr. Olson noted, “This is clearly not the end of a story – in fact, we think we’re just at the beginning.”
Life Lessons and More for a CFRI Intern

By Kevin Lin

Excuse me? I sat in silence. Frozen. How could one question provoke so deeply? The voices in the room began to fade into the sounds of the air conditioning. I became fixated on that one question.

Let’s back up. Allow me to introduce myself. My name is Kevin Lin and last summer I worked at CFRI for five weeks as a marketing intern, before my senior year of high school. At first, I did not know what I was getting myself into. I expected to be cast off in an office corner. But I was wrong. I was taken in by the staff as one of their own, able to take initiative on office projects while learning about the inner workings of a non-profit.

At the CFRI Conference, it was rewarding to see that all my work, including the name badges, the brochure covers, the handouts, and the press releases I wrote to promote this event had their “prime time” in the spotlight.

After the conference ended, I went straight into the Teen and Adult Retreat. The experience was eye-opening. There was no non-CF/CF tension at all, as I had initially expected. From breath-concentrated yoga, to rocking out U-Jam style, to having engrossing lunch conversations, to participating in enlightening group talks, I was welcomed as one of the group. I was also able to participate in the daily rap sessions - group gatherings where we vented, talked, and explored certain issues relating to CF.

Which leads me back to my fixation on the question which sent off flashing red panic alarms for me. It was the second day of the retreat at a rap session. The conversation at the time was geared more towards people with CF, so I wasn’t concentrating fully. As I sat there, caught off guard, someone asked: “What is your mission statement in life?”

I didn’t know. I didn’t know and it scared me. Here I was, 17 years old, a senior in high school and off to college soon, not knowing what I wanted. I thought about this question in the shower, at my desk at CFRI, and during car rides. Even now, I don’t know.

But what I do know is that by the end of my internship, I learned valuable life lessons and a bit more about myself. By the end of my time at CFRI, besides figuring out what PFT’s measured and what the FEV1 test was, I learned to appreciate even the smallest of loves, to go out and try new experiences, and to do what makes me happy. Looking back years from now, I won’t remember all the name tags I created or the raffle prize I won. But I will remember the lives I’ve touched and the knowledge that I have a supportive community to fall back on. Thank you Carroll, David, JoAnn and Mary. Thank you Retreaters. Thank you CF Community for letting me catch a glimpse of my life’s mission statement.

For information about internships at CFRI, please contact Mary Convento at 650.404.9975 or mconvento@cfri.org.

Wine for a Cure Hosts Elegant Reception

Last May, Wine for a Cure held an outstanding benefit for CFRI, which included a wine reception hosted by the Winemaker’s PourHouse, featuring local vintners from Livermore, California. Music by singer-songwriter Chris LeBel set the tone for an intimate event. NBC Bay Area reporter Bob Redell, Master of Ceremony for the afternoon, recognized Tara Goodearly and others with cystic fibrosis (CF) as heroes facing the challenge of this disease.

Carroll Jenkins was presented with the 2012 Caregiver of the Year Award for her dedication to the CF community and for ten years of service as Executive Director at CFRI.

The reception was followed by a screening of the award-winning film, The Power of Two at Cinema West, and a special Q&A opportunity with the cast, crew and other special guests.

Thanks to Diana Heppe, Robin Modlin and wonderful volunteers, over $10,000 was raised for CFRI. A special thanks to: The Pleasanton Lions Club, Doug and Jan Heppe, and all of the generous sponsors who made this possible.

Surf’s Up!

On September 29th, a wonderful benefit dinner and auction was hosted by “Friends Cure CF” at the Best Western Seacliff Inn in Aptos, California. Inspired by the Altano family, funds were raised for the Living Breath Foundation and CFRI.

Generous donations supported the cause: to impact the critical needs of CF patients, to help them “breathe easy.” Thanks to the Seacliff Inn for their hospitality, to the Altanos and to all the volunteers who created this lovely evening.

Tara Goodearly and Bob Redell
This year was my first time going to CFRI’s Teen and Adult Retreat. It was an experience I will never forget. From the people whom I met, to good times shared, that one week was like nothing I had ever experienced.

I had never done anything involving the CF community before, except for Great Strides. I always thought, “I have CF and I can deal with it in my own way.” However, the Retreat isn’t just a place to get information and advice from your peers on how to work with health care providers, or to learn how to deal with what’s going on; it’s so much more! It is a place to be understood, a place to get to know others going through the same hardships you’ve been through, and to understand what may lie ahead. This event is more than just a get-together of people going through the same thing. For that one week, it quickly becomes like a family and a home. The hardest thing about attending the retreat was having to leave. I can’t wait for next year!
Each year at the annual conference, CFRI recognizes a top professional and volunteer, to honor their extraordinary contributions to the cystic fibrosis (CF) community. Nominations are received from across the country, and winners are selected by past recipients of these awards.

This year’s 2012 Professional of the Year Award was awarded to Dr. Moira Aitken, an outstanding physician who is devoted to the improvement of CF clinical outcomes and to the advancement of clinical care in cystic fibrosis. She is currently Professor of Medicine at the Division of Pulmonary and Critical Care at the University of Washington in Seattle, and Director of their Adult CF program and Pulmonary Clinic. Dr. Aitken graduated from the Medical School at Edinburgh University in Scotland and continued postgraduate training at Western General Hospital in Edinburgh, the Royal Infirmary in Edinburgh and the University of Washington. Practicing since 1985, Dr. Aitken has been the recipient of many honors during her career.

Dr. Aitken established one of the first adult CF centers in the United States at the University of Washington, where she continues to provide critical leadership of the Adult CF Clinic, as well as daily work “in the trenches” of clinical care. She actively supports the Adult CF program within the hospital and maintains a positive, “can-do” attitude, always advocating for more CF resources. Dr. Aitken’s clinic offers 24-hour access to patients and she has coordinated with many physicians throughout the northwest to deliver the best CF care close to the homes of patients.

Dr. Aitken has devoted a significant part of her career to CF research, and as a member of the Royal College in Edinburgh, she has published over 100 original research papers. As a teacher, she is known for her “ceaseless enthusiasm,” and she takes the lead in training adult fellows in the care of CF patients at the University of Washington. Dr. Aitken’s unique mix of qualities — accessibility, skill, compassion, and honesty — lead to significant bonds with her patients. As a quintessential mentor, brilliant scientist and compassionate clinician, Dr. Moira Aitken has all the ingredients of a great doctor.

The 2012 Dave Stuckert Memorial Volunteer of the Year Award, named after one of CFRI’s earliest presidents, was awarded to Laura Tillman. Born in 1948 and not diagnosed with CF until age 47, Tillman has been educating herself and others since 1995 on how to best live a full life with cystic fibrosis. She has been director of the United States Adult Cystic Fibrosis Association (USACFA) since 2003 and as their current President, leads the field in sharing the voices of adults with CF. Tillman writes a regular column for USACFA’s quarterly publication, CF Roundtable, in which she shares vital information gathered from the internet and other sources on a myriad of topics.

Tillman’s involvement with the CF community includes serving many organizations, including the Michigan Pulmonary Disease Community, Inc., and the University of Michigan Medical School Mentoring Program for CF doctors. She has participated in podcasts, panel discussions and webcasts, sharing her CF experience with others. She is also a highly valued volunteer for CFRI. Over the years as a Conference Committee member, Laura Tillman has given her time and expertise in helping with planning, participating on panels, facilitating support groups, encouraging attendance and volunteering in the hospitality area. She is also a regular columnist for CFRI news, and synthesizes information from a variety of sources to examine in depth a particular topic regarding CF. Laura Tillman is a CF community treasure: always willing to assist others and share her positive outlook.

CFRI applauds these two remarkable women, who do so much to enrich and support the CF community.

Send in Your Nomination!

Seize the opportunity to recognize the efforts of someone who makes a real difference in the world of CF today.

To make a nomination for the CFRI Professional or Volunteer of the Year contact the CFRI office for 2013 guidelines:
dsoohoo@CFRI.org
Team Northern California returned victorious from the 2012 Transplant Games of America, held this year in Grand Rapids, Michigan from July 27 to July 31. Twenty-one athletes, ages 17 to 65 – all of whom have had organ transplants – competed among 1000-plus athletes from over 38 teams nationwide in 13 sports. “Team Nor Cal” brought home 57 medals, including 36 gold, 13 silver, and 8 bronze, in swimming, track and field, tennis, table tennis, badminton and cycling, ranking fourth in the nation.

In addition, the women’s relay teams in track and field, and swimming, won gold in four events.

Thirteen family members of organ donors also joined Team Northern California. All of these families lost loved ones and chose to give life to others at a time of tragedy. Four athletes were adults with cystic fibrosis (CF) who have received lung transplants and are members of the “CFRI family.” They included Tom Martin, Anna Modlin, Isabel Stenzel-Byrnes and myself. Together, we brought home 21 of the team’s medals. As a CFRI Board member who has attended six Transplant Games, I served as this year’s manager for Team Northern California, and won 4 gold, 3 silver, and 2 bronze medals in track and field and swimming. Much like our CF community gatherings, the Transplant Games are like a family reunion, a love fest. The event is a celebration of health, yet inspires a mix of grief, loss, love and hope as we celebrate the miracle of transplant, while mourning the loss of our donors. At the Games, we push our bodies to the max, as if our donors are watching.

The Transplant Games are part summer camp, part carnival, and part educational conference mixed with friendly sport competition and encouragement. We celebrate all the gifts that transplant offers: health, the ability to achieve new levels of fitness, fellowship, learning from others around the country, the generosity of sponsors, and the commitment and leadership of the medical community.

Says Tom Martin, “This was my third time at the Transplant Games and I’m always inspired by the enthusiasm and friendly competition.” He adds, “It’s a great privilege and honor that I’m able to compete. This year, I finally won the gold in the 100m dash (track and field), all thanks to my teammates’ support and encouragement.”

Twenty months ago, Anna Modlin received a double lung transplant. This year she attended the Transplant Games for the first time, winning five gold medals in swimming. Modlin reflects, “These were my first Games since my transplant. They gave me a sense of accomplishment and a level of physical fitness I haven’t had in many years. It was a transformative experience and has encouraged me to get more involved and to work harder spreading organ donation awareness and to continue my fitness goals.”

These were the fifth Transplant Games for Isabel Stenzel-Byrnes, who received a double lung transplant in 2004, and who brought home six gold medals in swimming. “The most rewarding experience of the Games for me was participating in the 4 x 50 women’s medley and the 4 x 50 women’s free relay swim event with Anna Modlin, my sister Anabel, and another teammate. After sharing the challenging journey of cystic fibrosis with the Modlin family for over 20 years, what a celebration it was to be healthy enough to swim together,” explains Stenzel-Byrnes, who is 40 years old. “The Transplant Games of America is an extraordinary, life-affirming event that provides indescribable hope. To see an entire generation of people with CF living 10, 15, 20 years post-double lung transplant makes me believe in a long and happy future!”

The Transplant Games of America is a biannual event that raises critical public awareness about the life-restoring impact of organ donation, and the immense need for the public to register as organ donors so that more lives can be saved.

Team Northern California is grateful for the support of many sponsors, including Genentech, Inc., Stanford Hospital & Clinics, the California Transplant Donor Network, University of California, San Francisco Transplant Programs, XDX Inc., LifeStars Jewelry, Black Diamond Pavers and Landscapers, Blood Centers of the Pacific, and the San Francisco Bay Area Transplant Recipient International Organization (TRIO). For more information or to join Team Northern California in 2014, visit: www.teammorcal.org or find your local team at www.transplantgamesofamerica.org. To register to be an organ donor, please visit: www.donatelifeamerica.net.
CF receive the best possible care. Dr. Boyle studied both the top ten CF centers (based on their pulmonary and nutritional outcomes), and low performing centers as well. He developed a comprehensive survey to capture the details of each center’s clinical practice and collected data by visiting the centers and conducting interviews. Dr. Boyle found that centers and patients with outstanding outcomes shared the following practices.

- Maximize use of time at clinic visits.
- Have a pre-clinic meeting with the “team” prior to patient’s appointment.
- Encourage the patient to prepare for clinic as well, with a list of key concerns and questions about ways to improve his or her care.
- Involve patients in their care at an early age by regularly giving them feedback; a visual image is very effective, such as a graph of their FEV1 results, so they can “literally see” how they’re doing.
- Make sure centers provide, and patients understand, their health data, such as FEV1 trends, weight and Body Mass Index (BMI), microbiology (cultures), key labs and radiology (x-ray).
- Schedule Chest CT “interventions.” Dr. Boyle showed a picture of the lungs of a 22 year old adult with 92% predicted FEV1. “It actually showed damage, which can inspire a person to do treatments. In fact, I had one patient put it on his fridge for visual feedback.”
- Send the patient home from his or her clinic visit with a care plan, detailing recommendations for airway clearance, nutrition, pulmonary medications and diabetes, if appropriate.
- Recommend a home spirometry device to measure FEV1 daily to keep track of trends and identify exacerbations before they need treatment.
- Maintain an aggressive attitude toward treatment, treat small declines, and do not hesitate to use antibiotics.
- Don’t allow long stretches of missed clinic visits or medications.
- “Make it personal,” by working closely with the patient to overcome obstacles to adherence, such as cost, anxiety, depression, fear and embarrassment.
- Encourage honesty between doctor and patient. “With adults,” Boyle noted, “anxiety and depression are big barriers.”

But how does one best prepare a child with CF to be a successful adult with CF? A successful transition from childhood to adulthood depends on learning healthy habits at an early age. “Seven of the top ten adult CF centers grew out of the top ten pediatric centers, demonstrating that what we do during the pediatric years can set the trajectory for adulthood,” Dr. Boyle explained, emphasizing that the transition from being a child to an adult starts at a young age. According to the data collected for the survey, preparing for successful adult care employs the following principles:

“Transition, not transfer; start early; and, parental guidance is essential, but it is also absolutely essential that you not help your child with everything.” Quoting the famous coach John Wooden, Dr. Boyle said, “The worst thing you can do for someone you love is to do that which they could and should do for themselves.” The ideal transition is, “less parent, more child.”

Specific goals for successful transition were established for each age group in two-year increments ranging from 12 to 21, with increasing levels of responsibility as the patient gets older. For example, “Naming your medications and reasons for taking them,” is a goal for a 12 year old, whereas “Describing choices about smoking and drinking and their effect on health in CF,” is suggested for an 18 year old. At 21, the goal is for the patient to manage his or her care, and handle everything from scheduling appointments to being aware of details about insurance and discussing strategies for future coverage with their caregivers. Patients living with CF need to “develop a sense of self-responsibility, not perfection,” Dr. Boyle explained, and it is important for parents to remember, “It is not only your child who is transitioning, you are as well.”

In concluding, Dr. Boyle reiterated, “What we do makes a difference. It’s not all genetics. Partner with your caregivers to assure you receive the best possible care. And developing strategies towards self-responsibility, not perfection, helps young people with CF become independent and healthy adults.”

Teeing Off for CFRI at Beautiful Pasatiempo

Scott Hoyt, the father of two daughters with cystic fibrosis, hosted CFRI’s 28th Annual Golf Tournament at Pasatiempo Golf Club, a USA “Top 100” course in Santa Cruz, CA. A beautiful and challenging course!

Thanks to volunteers and sponsors, and all who made the day special. Next year’s CFRI event will be on August 5, 2013. Hope to see you there!
Probiotics for Cystic Fibrosis

By Laura Tillman

Probiotic organisms are live microorganisms (yeast or bacteria) that, when ingested in sufficient quantities, provide health benefits for the person consuming them. Most probiotics are similar to the bacteria that are found naturally in the gut. They prevent colonization, cell binding and invasion by disease causing organisms; they have direct antimicrobial activity; and they exert a controlling influence on the host immune response. The strongest evidence for the clinical effectiveness of probiotics has been in their use for the prevention of symptoms of lactose intolerance, treatment of acute diarrhea, reduction of antibiotic-associated gastrointestinal side effects and the prevention and treatment of allergy manifestations. Research has also suggested that probiotics improve digestive function, improve lactose tolerance to lactose, decrease Helicobacter pylori colonization of the stomach and manage relapse of some inflammatory bowel conditions.

In CF patients, the antibiotics that are taken to kill the bacteria found in the lungs also kill the bacteria and yeast that are normally found in the gut. In many patients this can lead to diarrhea – specifically called antibiotic associated diarrhea (AAD). The two most common probiotics used in CF patients are Lactobacillus species and Saccharomyces boulardii. The University of Maryland and their Center for Integrative Medicine recommend a probiotic supplement (containing Lactobacillus acidophilus), 5 - 10 billion CFUs (colony forming units) a day, for maintenance of gastrointestinal and immune health in CF.

The benefits of probiotics in CF patients are shown in the following research:


In some cases, cystic fibrosis may include intestinal inflammation and bacterial overgrowth. The authors concluded that probiotics improved not only clinical but also biochemical intestinal function in cystic fibrosis patients.

http://tinyurl.com/boczysj


The researchers looked at how Lactobacillus GG (LGG) affects the lungs of CF patients. They found that cystic fibrosis patients who took LGG regularly had fewer bouts with respiratory infections than those that didn’t take LGG.

http://tinyurl.com/d3rua7n

**Intestinal Inflammation is a Frequent Feature of Cystic Fibrosis and is Reduced by Probiotic Administration.** Bruzzese E.; Raia V.; Gaudiello G.; et al. A. Aliment Pharmacol Ther. 2004;20:813-819. The researchers looked at the benefits to the intestines in this study. They found that cystic fibrosis patients who take Lactobacillus GG may have a reduction in the intestinal inflammation that often causes them pain.

http://tinyurl.com/cwz322c

**Probiotic Supplementation Affects Pulmonary Exacerbations in Patients with Cystic Fibrosis: a Pilot Study.** Weiss B.; Bujanover Y.; Yahav Y.; et al. Pediatr Pulmonol. 2010 Jun;45(6):536-540. The authors found that probiotics reduce pulmonary exacerbation rates in patients with CF and that probiotics may have a preventive potential for pulmonary deterioration in CF patients.

http://tinyurl.com/bytez9xd

**Probiotic Post-Transplant: Important Warning**

For transplant patients, both the Optic Probiotics website and the Livestrong.com website state that probiotics are not recommended for individuals who are severely immunosuppressed. Immunosuppressed patients do not have the ability to mount an appropriate response to any microbe with which they come in contact.

Microbes, even those that are normally considered beneficial, can sometimes cross the gut barrier and grow in the blood or in the internal organs where the nutrients are high and the competition for nutrients is low. Growth in these areas can cause a systemic infection. Also, individuals on steroids are at increased risk of absorption of probiotics into the bloodstream, causing serious systemic infections. Antibiotic resistance is another potential risk with probiotic use.

**Investigation of Probiotic Use Among Inpatients at an Academic Medical Center.** Jacques Simkins, M.D., Anna Kaltasas, M.D., Brian P. Currie, M.D., MPH; Presentation given at the Fifth Decennial International Conference on Healthcare-Associated Infections; March 19, 2010. Probiotic use has become very common; related infections have been described in immunosuppressed patients and those with impaired intestinal integrity. Certain probiotic package inserts now contain warnings regarding their use in such patients. Probiotic use was common in patients with moderate to severe immunosuppression and in patients with impaired intestinal immunity. Even though the incidence of related bloodstream infections was low, these cases could have been prevented.

http://tinyurl.com/d3nxnc7


Organisms contained in probiotics are generally regarded as non-pathogenic and safe to administer. The authors report a case of pus accumulation caused by Lactobacillus in a human immunodeficiency virus-infected lung transplant recipient receiving a probiotic containing Lactobacillus rhamnosus GG. The article compares the incidence of Lactobacillus infections in heart and lung transplant recipients at the authors’ institution before and after the

(continued on page 22)
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drug concentrations at the site of infection, and minimizes systemic exposure to the drug. In Canada, tobramycin is available as a powder and delivered through a portable breath-actuated inhaler. Adult patients favor this method as it can be done more quickly than inhaled TOBI, has better delivery, and is more convenient.

“Inflammation is tricky business in cystic fibrosis,” according to Dr. Ratjen, noting that it is an important immune response, but can create a worsening cycle in the lungs. What is the right balance between infection and inflammation? “It’s much easier to treat an inflamed joint than an area where there is bacteria,” Dr. Ratjen explained. “Ibuprofen is the only approved anti-inflammatory for CF and is not used much.” A 2004 study investigating pulmozyme as an ancillary treatment for airway inflammation found that those who used pulmozyme had an indirect result of clearing infected mucus from their airways, reducing inflammation and preventing infection. Azithromycin, an oral antibiotic and anti-inflammatory drug, was also studied in CF patients with mild disease. Patients who took the drug had fewer infections and less inflammation.

In looking to the future and what is on the research horizon, Dr. Ratjen emphasized, “We need to develop multiple, parallel pipelines and not just a single approach. To solve the CF puzzle, all pieces must fit together.”

RESEARCH (continued from page 1)

liquid in CF was controversial initially (because it turned out to be very difficult to measure) and it did not offer a clear explanation for CF lung disease because no defense functions were clearly affected by pH changes.

The finding of a new defense factor in the lung provided a major breakthrough. Phagocytic white blood cells are the body’s champions of bacterial killing, and we reasoned that the lung epithelium might use a similar mechanism. Christian Schwarzer, then a CFRI-funded postdoctoral fellow, identified an NADPH oxidase (now called DUOX) in lung epithelial cells that was an isoform of the bactericidal NADPH oxidase found in phagocytes. This finding suggested that the lung epithelium kills bacteria just the same way as phagocytes do. We found that DUOX is an epithelial defense factor that generates hydrogen peroxide (H$_2$O$_2$) in the airways, which (in the presence of additional factors) efficiently kills bacteria. Others found that when DUOX is inactivated, the airways completely lose their antimicrobial activity. In addition, for every mucosal H$_2$O$_2$ produced, DUOX also generates an intracellular proton that needs to be released or otherwise DUOX is blocked. In other words, DUOX is pH sensitive and is blocked by acidity. For DUOX to operate properly, a release mechanism for intracellular protons is required.

We investigated a number of known proton transporters and found that the airway epithelium expresses a proton channel (called HVCN1) that had previously been described in phagocytes. Thus, the airway epithelium expresses a defense mechanism that is quite similar to the mechanism found in phagocytes to kill microbes. In phagocytes, a pH dependence of killing has been noted experimentally but because the blood pH is very well buffered, their operation is not significantly limited by pH. In contrast, the airway surface liquid is extremely thin (1 microliter per square centimeter), and its buffering power is largely dependent on the bicarbonate that is delivered into it by CFTR. Thus, our recent findings suggest that a properly buffered airway pH is critical for normal airway defenses.

The parallel operation of the CFTR bicarbonate channel and the HVCN1 proton channel is intriguing as they determine the final airway pH and support proper DUOX activity. Currently, we are investigating the intimate relation between the three factors, which we call the CFTR-HVCN1-DUOX axis. All three factors operate together as one antimicrobial complex and we aim to identify the best way to normalize its function in CF.

I wish to thank CFRI for its outstanding contributions to CF research. CFRI provides leadership and maintains a vibrant community of CF researchers.

PROBIOTICS (continued from page 19)

introduction of this probiotic, and discuss the potential mechanism for Lactobacillus within the probiotic to cause infections and to spread.

http://tinyurl.com/cmu74nf

Side Effects of Probiotics.
Ningthoujam Sandhyaran. Buzzle.com. Last updated: November 16, 2011. The author states that according to medical studies, there is a possibility that probiotics interact with immunosuppressive medications, leading to life-threatening conditions. He concludes that those who are on immunosuppressive drugs should avoid probiotic use.

http://tinyurl.com/cherxqn
of kidney stones, constipation and distal intestinal obstruction syndrome (DIOS), and the importance of early screening for colon cancer. Kidney stones are more common among people with CF than the general population. Schindler explained that there is often an absence of the intestinal bacteria *Oxalobacter formigenes*, and that there are commonly low citrate levels in the urine of those with CF. She stressed that “there is an inverse relationship between calcium intake and kidney stones, and that maintaining a high fluid intake, having adequate calcium in one’s diet, and possibly the use of citrate supplementation or probiotics may help to prevent kidney stones.”

Schindler discussed the difference between DIOS and constipation. DIOS may cause a complete obstruction of the intestine, and often causes extreme abdominal distention, vomiting and excruciating pain. The use of oral GoLYTELY® is usually prescribed for a partial obstruction, while a complete obstruction usually requires GoLYTELY® administered via a nasogastric tube, along with a gastrografin enema. Schindler stressed that anyone who suspects that they have DIOS should immediately call their CF center, as this is a medical emergency unique to CF.

It is now understood that there is an increased incidence of gastrointestinal (GI) cancers for those with CF, particularly colon cancer. This risk is further increased post-transplant. Schindler listed the potential symptoms of colon cancer, including “blood in the stools, abdominal pain, weight loss, persistent constipation and unexplained anemia.” She strongly advocated for earlier GI cancer screening for those with cystic fibrosis, noting that at her CF center in Cleveland, “we start at 35 with colonoscopies.”

In closing, Schindler reviewed her “take home advice,” for those with CF, which included working with a CF center registered dietitian to achieve nutrition goals. She stressed the importance of maintaining proper vitamin levels, including A, B, D, E and K, and encouraged patients to discuss probiotics with their doctors. “Ensure adequate calcium and fluid intake to reduce the risk of kidney stones.” Schindler encouraged patients to call their CF center if they experience abdominal pain, but stressed that they should “not adjust the enzyme dose if abdominal pain and constipation are the only symptoms,” unless they have consulted with the dietitian. Adults with CF should also talk with their doctor’s about early screening for colon cancer.

By following Schindler’s advice, people with CF may improve their health, and quality of life.
CFRI’s Mission

Cystic Fibrosis Research, Inc. exists to fund research, to provide educational and personal support, and to spread awareness of cystic fibrosis, a life-threatening genetic disease.

CFRI’s 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.

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