Shortly after the CF gene was discovered, its link to chloride transport was established. A few years later, in 1993, a classification scheme for how CF mutations affected cell function resulting in that chloride transport defect was proposed (Figure 1).

This has provided a framework for drug discovery focused on particular types of CF mutations in which a drug would act directly upon CFTR to improve its function.

In 1998 the CF Foundation established the Therapeutics Development Program, which included a visionary drug discovery arm through which CFF would support industry as well as academic research. One of the early investments CFF made was in a small southern California biotech company, Aurora Biosciences, who had developed a “high throughput” approach to drug discovery based upon screening of huge numbers of chemicals in an automated cell culture assay that could detect compounds which made CF mutations work better. Later, Vertex Pharmaceuticals would acquire Aurora and incorporate their program into its CF program with continued support from CFF. In 2003–4 several compounds were discovered that seemed to help particular classes of CF mutations, in particular class III and class II defects. From these “hits” medicinal chemistry was employed to enhance potency and reduce toxicity. In 2004, the first “people ready” Class III agent, VX770, was synthesized. That same year the first active Class II agents were identified, and from these the first “people ready” compound, VX809, was synthesized in 2006. After appropriate animal studies, the stage was set to try and fix particular types of broken CFTR in patients.

This is a revolutionary development. Up to now, drugs that help people with CF (such as Pulmozyme®, Tobi®, Cayston®, hypertonic saline and azithromycin) work at a level beyond the basic malfunction of CFTR, on the resulting “vicious cycle” of airway obstruction, infection and inflammation. In contrast the Vertex drugs work “upstream” directly upon the problem protein itself CFTR, a process named CFTR modulation (Figure 2).

One key question was, how would we know a compound might work? What early clue could we use? The Therapeutics Development Network and other researchers went back to basics. The traditional diagnostic test for CF for 50 years has been the sweat chloride test. Could this be used as a “biomarker”, i.e., a readout that would match up with actual clinical effect? Studies of sweat chloride levels in various kinds of human subjects seemed to suggest the answer might be “yes.”

Our Center’s mission is to excel in cystic fibrosis care, to be partners with those we care for, and to be leaders in the discovery process that will produce the cure for cystic fibrosis.
VX770 was ready to enter clinical trials in 2006. It was decided to focus on patients with G551D because the drug had been shown to have a strong activity on this mutation in cell culture, and G551D is the most common Class III mutation, present in 4-5% of CF patients. In cell culture, VX770 allowed G551D to function so well that it could not be easily distinguished from normal CFTR (Figure 4).

After studies to determine safety and how the body handles VX770, a Phase 2 trial (a modest number of patients, 39; and a short time frame, 2-4 weeks treatment) was conducted to look at safety and effect on biomarkers like sweat chloride and NPD, as well as exploration of effect on lung function, symptoms, and other measures. The results were beyond all expectations: the biomarkers improved, lung function increased, and patients felt better, all within 2-4 weeks of treatment. Figure 5 shows a key result, the effect on sweat chloride, with a change so large that it might be associated with control of CF itself. The results of this study were published in the November 18, 2010 issue of The New England Journal of Medicine.

Based on this trial, the VX770 Phase 3 registration program (required for approval by the Food and Drug Administration) was initiated in 2009. The results of the pivotal Phase 3 “STRIVE” trial were announced on February 23, 2011. In this study 167 patients with a G551D CFTR mutation were randomized to receive VX770 (150 mg twice daily) or placebo for 48 weeks. Eighty seven percent of placebo and 93% of VX770 groups completed the trial and all but one patient elected to continue on an open-label extension (“PERSIST”) study. The main STRIVE endpoint, change in lung function as measured by FEV1 at 24 weeks, showed that the VX770 group improved by 10.4% while the placebo group declined by 0.2%, a highly significant and clinically meaningful difference. Importantly, the lung function benefit was seen by 2 weeks and fully sustained for 48 weeks. The relative change in FEV1 (i.e., compared to entry value) was 17%. Accompanying this effect, STRIVE also showed significant improvements in a patient-reported CF-specific quality of life measure called CFQ-R, a big weight gain of 3 kilograms (placebo patients had virtually no weight gain), and a decrease in sweat chloride from ~100 to less than 50 (this change was also seen by 2 weeks and sustained for 48 weeks). In clinical trials parlance, this can be termed not merely a home run; it was a grand slam. The full paper presenting these results has been accepted for publication.

In order to examine the safety and efficacy of VX770 in younger (and thus generally more mildly affected) patients, another trial (“ENVISION”) was conducted in 6-11 year olds using the same design and dose. This trial enrolled 52 patients with G551D. The results were announced on March 29, 2011. The effect was surprisingly strong and similar to STRIVE: lung function treatment effect was 12.5% absolute and 17.4% relative improvement in FEV1. Similar changes in sweat chloride, weight gain and CFQ-R were also found. Nobody discontinued the trial. ENVISION confirmed that VX770 was safe and effective in school age children with CF. ENVISION patients also continued on to the open-label PERSIST study. A critical issue for VX770 is whether it is safe and beneficial for CF patients with mutations other than G551D. This question has thus far only been studied for patients with F508del, the most common CF mutation. Worldwide, about half of all CF patients are homozygous for F508del (i.e., have two copies of this mutation, one from each parent). Another 35-40% carry one F508del with another mutation; thus 85-90% of all CF patients have at least one F508del. Besides patients with G551d/F508del in the VX770 trials discussed above, it was important to determine the drug’s effect in patients with homozygous F508del. This trial (“DISCOVER”) enrolled 140 patients homozygous for F508del who received VX770 for 16 weeks.

Figure 3. The relationship between sweat chloride (“biomarker”), clinical status (“phenotype”) and percent of functioning CFTR suggests that a drug capable of moving sweat chloride from 100 to 60 may possibly control or reverse the manifestations of CF.

Figure 4. VX770 works on Class III (regulation or gating defect) mutations like G551D by helping (“potentiating”) the CFTR chloride channel to stay open.

Figure 5. In the Phase 2 trial VX770 lowered sweat chloride levels from the severe CF range of ~100 into the normal range of less than 60.
There were no major safety issues or discontinuations. However lung function was not affected (only 1-2% increase), and sweat chloride was only slightly reduced (about 3, compared to >50 in G551D patients). Thus, VX770 appears safe but ineffective in the most common form of CF, involving F508del.

Enter VX809. This compound was designed to treat F508del. In cell culture experiments, VX809 can improve the chloride channel performance of F508del CF cells up to about 15% of normal level - enough, many believe, to provide potential clinical benefit. VX809 is termed a “corrector” because it helps correct the cell defect in F508del, namely the defective processing of CFTR that prevents it reaching the place it needs to go in order to work, the cell surface facing the airway. This is the Type 2 defect shown in the CFTR functional schema of Figure 1, and the effect of VX809 is depicted in Figure 6.

In clinical trials to date, VX809 has been well tolerated. In addition, as doses increased from 25 to 200 mg in CF patients homozygous for F508del given VX809 for 28 days, a progressive decrease in sweat chloride has been seen (Figure 7). However, the magnitude of decrease is probably not sufficient to be accompanied by clinical benefit. The scientific paper on this study is in press.

Currently, the results of the VX770 and V809 programs suggest that a combination approach may be safe and most effective. VX809 would be given to allow more F508del CFTR to reach the cell surface and VX770 would then boost its function (Figure 8).

Early results for the first part of this complex combination clinical trial were announced publicly on June 9, 2011. In this trial, 21 patients received placebos for 3 weeks, another 20 patients received VX809 200 mg daily for 2 weeks and VX770 150 mg twice daily for an additional week, and another 21 patients got a higher dose of VX770 (250 mg twice daily) during their third week on VX809. The results of this trial showed the combination of the two drugs was well tolerated, and the sweat chloride was decreased more on the 2 drug combination than on VX809 (in this trial and the preceding dose-escalation study) or VX770 (in the DISCOVER trial) as shown in Figure 9, with a substantial portion of the patients showing improvements in sweat chloride that might be associated with clinical benefit. Based on these results, the trial is being continued in a new group of patients exploring a variety of approaches to see if we can further increase the impact.

We can realistically hope that we may be on the verge of being able to fundamentally treat the genetic basis of CF in close to 90% of patients. Finally, it is also important to note that a separate program to treat Class I CFTR mutations has been in progress from PTC Therapeutics, with their drug PTC124 currently in Phase 3. This would cover another 5-10% of CF patients if effective. The revolution in fundamental treatment begun in 1989 is finally bearing fruit for patients and families. The Stanford CF Center has been deeply involved in all these trials every step of the way. Together, we will get to our goal.
Approximately 30% of all people with cystic fibrosis have cystic fibrosis related diabetes (CFRD). The additional diagnosis of CFRD has been shown to have a negative impact on lung function and survival in individuals with CF. Recent studies indicate that early diagnosis and treatment of CFRD improves outcomes. Screening for diabetes has become standard of care in CF centers across the United States.

We have a protocol in place at Lucile Packard Children’s Hospital for diagnosing, treating and monitoring CFRD. In response to the new CFRD guidelines, which were published as a joint effort by the American Diabetes Association, the Cystic Fibrosis Foundation, and the Pediatric Endocrine Society, we are in the process of updating our center protocol.

Our new protocol includes:

1) Routine screening for diabetes through the use of an oral glucose tolerance test for people 6 years and older.

2) Implementing in-patient screening as well, with blood sugars monitored first thing in the morning and 2 hours after meals for the first 48 hours of an in-patient stay. Individuals that are diagnosed with impaired glucose tolerance may receive a glucometer to test blood sugars at home.

3) CFRD should be managed by a multidisciplinary team, with individuals with expertise in CF and diabetes. We work closely with the Pediatric Endocrine division and will refer people diagnosed with CF related diabetes to their clinic. Individuals with CFRD are unable to produce enough insulin to maintain normal blood sugar levels. For this reason, insulin is the only recommended treatment. In addition, because individuals with CF need to maintain a very high calorie diet, usually 120-150% of the daily recommended intake for age, calories should never be restricted. Individuals with CFRD may be taught carbohydrate counting, a method of totaling carbohydrate intake at each meal and snack. Typically a carbohydrate to insulin ratio is provided which will allow a person to dose a certain amount of insulin for each gram of carbohydrate consumed at meals and snacks.

Our hope is that with a more comprehensive approach in identifying individuals with impaired tolerance and CFRD, we will help patients and families at our center to receive earlier treatment for CFRD, which will ultimately result in better nutrition and better lung function.

The Cystic Fibrosis Parent Advisory Council

The Cystic Fibrosis (CF) Parent Advisory Council is comprised of parents whose children receive care from the Stanford CF Center and Packard Children’s Hospital. We work in partnership with members of the pediatric CF Clinic team at Packard Children’s, with the shared goal of providing the highest quality of care and service to patients and families. To achieve this goal, the Council seeks to:

• Enhance communication between the CF Care Team and CF families;
• Develop resource materials to assist patients and their families;
• Provide input – from a family perspective - on issues relating to CF care;
• Assess and identify emerging needs of patients and families - such as the need for Spanish language and teen-focused resources - and work in partnership with the Care Team to address them.
• Serve as a voice for families receiving CF care at LPCH.

The Advisory Council meets monthly. If you have issues or ideas that you would like to share with the Council, please contact Siri Vaeth, Lead Parent, at svaeth@lpch.org.

In the Adult CF Advisory Council’s (ACFAC) first years, they’ve successfully encouraged the new Adult CF Center to start an Adult CF Support Group and created forms to give patients tools to communicate their medical routine and wishes to the CF team.

CF adults and their family are welcome at and encouraged to attend ACFAC monthly meetings as guests, or apply for council membership online. The ACFAC asks that CF adults and their families contact the council and make use of this unique resource and avenue for direct communication.

How to Contact the Stanford Adult CF Advisory Council:

WEBSITE: http://cfcenter.stanford.edu/acfac/
EMAIL: stanforddfac@gmail.com
PHONE: (650) 549-5102

There is an Adult CF Support Group which occurs on the first Friday of every month. The group is facilitated by the adult CF social worker, Meg Dvorak and covers a broad range of topics including stress, anxiety, loss, and maintaining balance. CF patients and caregivers are welcome to attend as long as the patient does not have a positive culture including MRSA, B cepacia, or multi resistant organisms. Web Ex and teleconference is available for those who wish attend but can’t come in person. Please contact Meg Dvorak at (650) 723-6273 or mdvorak@stanfordmed.org for more information.”
New Staff Members

MEG DVORAK, LCSW

Meg Dvorak, LCSW, has been a member of the adult cystic fibrosis team at Stanford since June 2010. Meg earned her bachelor’s degree in psychology at UCLA in 1993 and her master’s degree in social work at University of Pennsylvania in 1996. Meg is a licensed mental health clinician as of 1999. Meg has previously worked for the CF program at Kaiser Santa Clara and has 14 years of experience working with chronically ill populations in both pediatric and adult medicine. Prior to joining the CF team, Meg worked in the pediatric renal transplant program at LPCH for 9 years which has given her intensive training on transplant issues and the transitioning from pediatric to adult care programs. Additionally, Meg has 10 years of experience working in the Stanford ER. Meg has lectured on the following topics: compliance, anxiety and depression, benefits and resources for CF patients, fundraising for transplant, and school issues while living with chronic illness. Meg recently started a support group for CF adults and in the future would like to launch a mentoring program to link pediatric and adult CF patients.

CASSIE EVERSON, RC

Cassie Everson RC graduated from CSU, Sacramento with a Bachelor’s Degree in Health Science: Healthcare Administration in December 2006. As part of the Healthcare Administration program, she did an internship at the Kaiser facilities in the Sacramento area in the Women’s Health Center. This experience strengthened her already present desire to work in the healthcare field. In 2008, she moved to the Bay Area to attend the Foothill College Respiratory Therapy Program and in June 2010, she earned an Associate’s Degree in Science for Respiratory Therapy. Later on that year she joined the CF Research Team. As a child, she had a friend who had CF so she feels extremely privileged to be working with CF patients in research. For her, working in research provides hope. It is also conducive to building relationships because when patients come in for study visits, a lot of time is spent together. She sincerely looks forward to getting to know each and every patient and their families. In her free time, she enjoys reading, spending time with friends and family, and traveling with her husband. They just welcomed their first child, Olivia, on Oct 28, 2011.

DR. DARIO PRAIS

Dr. Dario Prais is a visiting physician from the Schneider Children’s Medical Center of Israel where he is the director of the chronic lung disease service. The Schneider Center provides care to approximately 120 CF patients. He was chosen from numerous applicants to come to Stanford to observe how we provide patient care, as well as to learn about our specific care protocols and various research procedures such as the Lung Clearance Index (LCI) and the Nasal Potential Difference (NPD).

What are the main differences that you see in cystic fibrosis care between our two centers?

- We don’t use the vest for chest physiotherapy like you do in the U.S. We use modalities such as autogenic drainage, manual chest PT (clapping), cough and breathing techniques, and exercise. We are also lucky to be able to have a physiotherapist make home visits as needed to all CF patients to provide CPT and in home exercise programs (frequency varies according to clinical status).
- We like to see our CF patients in clinic every 6 weeks. At the visits they usually see the whole team: the Dr, nurse, dietician, social worker, physiotherapist (respiratory therapist) and psychologist. The visits may last 4 to 5 hours.
- We separate our clinics: Pseudomonas positive patients are seen on different days from Pseudomonas negative patients.
- We have no separate adult program.
- In Israel we have no neonatal screening program so the average age of diagnosis is higher than in the U.S.
- In our clinic, a patient makes an appointment with the clinic (not a physician) and we have 4 physicians who regularly rotate through.

What do you hope to take back to Israel?

- A better understanding of research procedures such as LCI and NPD with the hopes of being able to eventually do them at our center.
- To collaborate with Stanford on some research projects in the hopes of publishing in the near future.
- To take back some ideas on how we can improve the delivery of CF care to our patients.
Ms. Mendoza understands how complicated diabetic management can be and also how much patient’s dread this diagnosis. She states that the acceptance of CFRDM can be seen in stages similar to the stages of grief experienced with diagnosis of any serious illness. Stages of grief progress from denial, then anger, bargaining, depression and finally acceptance. Ms. Mendoza starts with the patient’s understanding of diabetes and builds on the concepts that are unique to Cystic Fibrosis.

Ms. Mendoza can be reached in the Endocrine Clinic at 650-723-6961. Ms. Mendoza is available to Adult Cystic Fibrosis patients for follow up calls as patients navigate meter use or new insulin use.
The Power of Two CF Documentary Film Premieres Nationwide

The Power Of Two is a new feature length documentary film about hope, survival and the miracle of breath. The film offers an intimate portrayal of the sisterly bond between half-Japanese twins and LPCH CF Center patients, Anabel Stenzel and Isabel Stenzel Byrnes, their lifelong battle with cystic fibrosis (CF), survival through miraculous double lung transplants, and improbable emergence as authors, athletes and global advocates for organ donation and CF in the U.S. and Japan.

Featuring expert interviews as well as archival footage and deeply personal testimony from those whose lives have been impacted by CF and organ transplantation from the U.S. and Japan, this film provides unprecedented insight into the personal and societal aspects of this modern medical miracle affecting millions worldwide. The film also captures CF care in the United States and in Japan, where CF is under-diagnosed and under-treated, and transplantation is controversial due to cultural taboos.

Stanford CF Center Director, Dr. David Weill, Stanford lung transplant surgeon, Dr. Bruce Reitz, and LPCH CF patient, Anna Modlin, are also key characters. Watch the trailer for the movie here: www.ThePowerOfTwoMovie.com/the-film.

Without question, The Power Of Two provides hope and inspiration to anyone living with CF by telling the story of two lives, two cultures and two new chances of life. The film uses powerful personal stories of patients to educate and enlighten viewers about living with CF, patient advocacy, and cultural influences on health care access.

The feature directorial debut of Academy Award nominated producer Marc Smolowitz, The Power Of Two had its world premiere in August at the prestigious Oscar-qualifying showcase DocuWeeks in Los Angeles and New York. Since then, the film has been shown at over 10 film festivals and has won awards for Best Documentary, Most Socially Engaging documentary film, and an Audience Choice Award at three film festivals. The film premiered at Stanford Medical School on October 26, 2011 as part of the United Nations Association Film Festival, with over 100 attendees, many of whom were from the local CF community.

These and other film screenings are part of The Power Of Two’s Outreach & Community Engagement Campaign, which engages communities nationwide in critical health care discussions and inspire action around organ donation and transplantation, and awareness of cystic fibrosis and other chronic illnesses. Please see the website: www.thepoweroftwomovie.com/events for a list of cities where the film will be shown, or visit The Power of Two on Facebook and Twitter. Private community screenings can be arranged by contacting: www.thepoweroftwomovie.com/community-screening-faq/.

NEW QUALITY IMPROVEMENT PROJECT

Our pediatric team would like to introduce a new quality improvement project to determine if establishing a patient binder, which will include a standardized CF Action Plan, along with phone calls to families prior to scheduled appointments will improve organization for our patients and families, adherence with 3 month follow up CF Center clinic appointments and overall quality of life. We will provide a CFQ-R questionnaire (a 4 page survey designed by the CF Foundation), which will ask questions related to quality of life, at the start of this project and again 9 months later. We’ve already started handing out the surveys and binders. Keep your eyes open for them!
Pediatric CF Center Update
NEWS UPDATE!!!

The Pediatric CF Clinic at Packard Children’s will be moving. Our new Clinic location will be located at 770 Welch Road. The tentative date for relocating the clinic is currently scheduled for summer 2012. Once finalized, all the details of the move will be mailed out to the families that are seen at our CF Center. Starting January 1st our CF clinic days will be on Monday all day, Tuesday and Friday mornings. Look for a postcard detailing these changes in the mail soon. We have developed two new brochures for all our CF patients/families. They are; “Partners in Health: Infection Control” and “What to Expect During your Admission to Packard Hospital.” If you have not seen them yet, please ask Mary Helmers, RN, BSN Pediatric CF Nurse Coordinator for one.

The CF Center at Stanford Website has received a facelift!! It is now available in Spanish, too. If you have any recommendations or future ideas for the website, please click on the Submit Comments green tab…we would like to hear from you. Our website address is http://cfcenter.stanford.edu

Be a part of the cure for CF!
Volunteer for a clinical trial today. To learn more, visit http://cfcenter.stanford.edu, contact our research coordinators, or talk to your physician. The following trials are currently underway:

- Pulmonary Exacerbation Study
- Sweat testing in newborns with CF
- Chest CT and natural history of CF Lung disease
- Phase III study of VX-770 (for G551D)
- Phase II study of VX-809 and VX-770
- Advanced Diagnostic Testing for Lung Disease
- Cough in lung disease
- Exercise study
- ABPA study
- EPIC trial for early treatment of Pseudomonas
- Lung Clearance Index
- ISIS- Infant inhaled saline study
- PTC124 Phase III
- Inhaled Levoﬂoxacin
- HOLA
- Observational study looking at Hispanics and CF

CYSTIC FIBROSIS CENTER AT STANFORD
Pediatric Providers at Packard Children’s: Carlos Milla, MD, Center Director; Carol Conrad, MD; David Cornfield, MD; John Mark, MD; Richard Moss, MD; Terry Robinson, MD; Nanci Yuan, MD; Jacquelyn Zirbes, DNP, RN, CPNP.

Clinic Scheduling - Pediatrics (650) 497-8841
Clinic & Prescription Refill FAX, Pediatrics (650) 497-8837
Miguel Huerta, Patient Services Coordinator (Peds) (650) 498-2655
Mary Helmers, Pediatric Coordinator (650) 736-1359
Kristin Shetron, Pediatric Respiratory Therapist (650) 724-0206
Julie Meatel, Pediatric Nutritionist, Dietitian (650) 736-2128
Lindsey Evans, Pediatric Social Work (650) 736-1905
Jacquelyn Zirbes, Newborn Screening Coordinator (650) 721-1132

Adult providers at Stanford: David Weill, MD, Adult Program Director; Paul Mohabir, MD; Gundeep Dhillon, MD; Camille Washowich, MSN, ACNP; Erika Derakshandeh, RN, MSN, NP

Clinic Scheduling - Adults (650) 497-8510
Clinic & Prescription Refill FAX, Adults (650) 723-3106
Kathy Gesley, Adult Coordinators (650) 736-1358
Carol Power, Adult Respiratory Therapist (650) 736-8892
Lara Frett, Adult CF Registered Dietitian (650) 721-6666
Meg Dvorak, Adult CF Social Work (650) 723-6273

Research:
Colleen Dunn, Zoe Davies, Cassie Everson (650) 736-0388

For Urgent Issues:
Monday-Friday, 8:30 am to 5 pm, contact RN Coordinator
All other times, for children call (650) 497-8000 and for adults call (650) 723-4000 and ask for pulmonary physician on-call.
Visit our Web site at http://cfcenter.stanford.edu for more information about our center and CF.

To subscribe to this newsletter, please contact Cathy Hernandez by phone at (650) 724-3474 or by email at cathyh1@stanford.edu

Volunteer for a clinical trial today. To learn more, visit http://cfcenter.stanford.edu, contact our research coordinators, or talk to your physician. The following trials are currently underway:

- Pulmonary Exacerbation Study
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- Cough in lung disease
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- HOLA
- Observational study looking at Hispanics and CF