SPRING 2014

FA Family Newsletter

issue 55

A semi-annual publication of the Fanconi Anemia Research Fund, Inc.

Boisterous Debate, New Findings, and the Award of Merit Highlight the 25th Annual Scientific Symposium

Dr. K.J. Patel receives Award of Merit

The 25th Annual Fanconi Anemia Research Fund Scientific Symposium, held last October in Houston, was attended by almost 200 scientists, clinicians, board of directors, and family representatives from 19 countries, including first-time attendees from Pakistan and Lebanon.

Ten sessions over four days commenced with FA 101, an introduction to the clinical and biological aspects of FA, popular with both newcomers to the field and long-time veterans alike. Forty-five abstracts were presented in oral sessions including Head and Neck Squamous Cell Carcinoma, Aldehydes and Enzymology, Experimental Hematology, FA Protein Interactions and Structure, and, for the first time, Endocrinology and Development. An additional 66 abstracts presented as posters covered a wide range of FA research and treatment topics.

The symposium also featured two special sessions—Design and Conduct of Clinical Trials and a To Transplant or Not to Transplant debate—as well as a keynote presentation by Jeffrey Myers, MD, PhD, MD Anderson Cancer Center, Houston, entitled Genomics, Cancer, and Personalized Medicine. The clinical trial session included presentations on trials with NAC, gene therapy, and reduced busulfan bone marrow transplantation.

An exciting new addition to the meeting's agenda was a mentorship lunch for early investigators. Young investigators packed a meeting room

continued on page 2

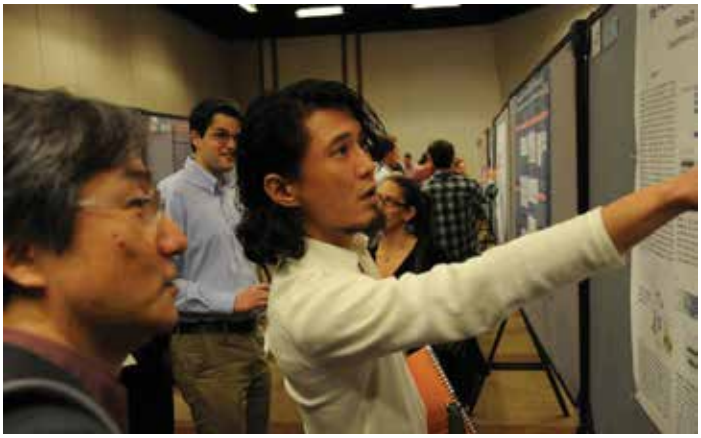
Record Attendance at Adults with FA Meeting

The fifth Meeting for Adults with FA was held March 21-24 in Baltimore, Md. A record 42 adults with FA aged 18 to 61—including two grandparents—attended from 11 countries. This was a huge increase from the previous meeting in October 2012 in which 24 adults with FA participated. The Fanconi Anemia Research Fund allocated nearly $30,000 for travel assistance to adults with FA who otherwise would not have been able to attend.

Presentation topics at the meeting included FA 101; Personal Relationships; Aldehydes; Wellness through Food; Gynecology for Women with FA; and Head and Neck Cancer. In addition, the meeting offered support groups for adults with FA, their parents, partners and spouses, as well as opportunities to participate in oral cancer screenings and other research projects.Watch for more on this meeting, including presentation reports, in the Fall 2014 *FA Family Newsletter*.

25th Annual Symposium

continued from page 1



Poster sessions sparked lively discussions.

to hear from and ask questions of an international panel of researchers who had recently made the transition to being a primary investigator. The enthusiastic response ensures this lunch will be an annual feature to help early investigators further their careers in the FA field.

The annual Symposium banquet was a celebration of all that has been accomplished, with an understanding that there is still a long way to go. The Award of Merit was presented—for only the sixth time in the Fund's history—to K.J. Patel, MD, PhD, MRC Laboratory of Molecular Biology, Cambridge, UK, for his seminal work on discovering the major role of aldehydes in Fanconi anemia cell hypersensitivity. As inscribed on his award, Dr. Patel's "innovation, perseverance, and leadership have advanced the science of FA, raised its visibility, and opened up exciting new opportunities for therapeutic interventions." David Frohnmayer, cofounder of the Fund, presented the award and medal accompanied by the British and Kenyan national anthems, Dr. Patel's countries of origin.

Jordi Surrallés, PhD, Universitat Autònoma de Barcelona, Spain, and his group received Discovery Awards for the identification of *FANCQ*. Other awards were given for the best basic, clinical, and translational posters presented at the Symposium. The evening included the always poignant video, Faces of FA.

"I nearly missed my flight because I enjoyed the interaction in the concluding Town Hall session. This was a good chance for newcomers to get perspective in the field."

"The biggest strength of the Symposium, and long-term achievement of the FARF, is uniting the focused interests of basic researchers with the most pressing clinical needs of FA families."

"Excellent meeting. More motivated than ever to get back to the bench to make important discoveries to improve the lives of FA patients and their families."

"An incredible meeting at which people not only learn, but interact with people working at the top of Fanconi anemia research. This influences faster progress."

—from participant evaluations

Long-term Study Looks at Mosaicism in FA Patients

Mosaicism is not uncommon in individuals with Fanconi anemia. Jordi Surallés, PhD, Universitat Autònoma de Barcelona, Barcelona, Spain, states that over 20% of Spanish FA patients are mosaic. He defines an individual with FA as mosaic if a significant percentage of peripheral blood T-cells have no chromosome breaks following a diepoxybutane (DEB) test. This happens when one allele with a disease-causing mutation reverts to normal. Dr. Surrallés showed that *the clinical significance of mosaicism depends on which type of cell undergoes the reversion*. For example, reversion in a very early stem cell can lead to correction of all cell lines, whereas reversion in a more mature progenitor cell would affect only specific blood lineages. Reversion in a lymphocyte progenitor cell affects only that one cell line.

To better understand the clinical impact of mosaicism, Dr. Surrallés examined the long-term hematological status of several FA mosaic individuals and observed distinct patterns, from quick or slow normalization of blood counts to lineage-specific normalization, or only transient improvement followed by a decrease towards pancytopenia.

In conclusion, mosaicism often, but not always, results in clinical improvement. It provides a useful model to better understand the outcome of future gene therapy clinical trials.

Advances Reported In Head and Neck Cancer Research

Jeffrey Myers, MD, PhD

Sanne Martens-de Kemp, PhD

Stephanie Smetsers, MD, PhD Student

Flavia Teles, DDS, DMSc

Individuals with Fanconi anemia are at a high risk of developing head and neck squamous cell carcinoma (HNSCC). Treatment options are often limited to surgery with or without post-operative radiation because cisplatin-containing chemotherapy protocols are too toxic for FA patients. Early diagnosis and treatment of cancer, or preferably pre-cancer, might improve the clinical management of HNSCC in individuals with FA. Targeted therapies which only affect the cancer or pre-cancer cells could also be beneficial. Four presentations highlighted research that may lead to these goals.

Characterizing HNSCC Tumors

In the Symposium's keynote presentation, Jeffrey Myers, MD, PhD, MD Anderson Cancer Center, Houston, described how research into understanding tumor biology will help improve the diagnosis, prognosis, and treatment of HNSCC. By sequencing the entire DNA in tumor tissue from non-FA patients, he and others discovered which mutations are most frequently involved in HNSCC and compared these to the clinical, pathological, and molecular progression of the cancer. In this manner, researchers might devise new methods for early detection, identify the therapies that might be most effective for a patient's tumor, and develop new therapies targeted for specific mutations.

The DNA that comprises non-FA HNSCC tumors is varied and complex. Mutations most often occur in tumor suppressor genes (like *TP53* and *NOTCH1*), and tumors behave differently depending on whether or not they are HPV-positive. Characterization of the mutations in FA HNSCC tumors is still being studied. There are suggestions that they may have different characteristics than those in the general population. A highly collaborative approach for determining the characteristics of HNSCC tumors, such as The Cancer Genome Atlas funded by the National Institutes of Health, will yield the best results for developing targeted therapies against these cancers that are the least toxic to non-cancerous tissue.

Finding Drug Targets

Sanne Martens-de Kemp, PhD, Vrije University Medical Center, Amsterdam, presented work done to identify genes that may serve as good drug targets for the earliest signs of cancer. Researchers screened FA HNSCC tumor cell lines for expression of 362 genes that are essential for non-FA tumor cells to grow. The majority of the 362 genes were also essential for FA tumor cells. They studied FA pre-cancerous cell lines to identify which of these genes could best be targeted by small molecule drugs. The work indicated a possible gene target for FA pre-cancerous cells, *PLK1*, which this group will investigate further. Future plans are to establish more FA cell cultures and look for the best druggable targets to test in these cultures and then in living organisms.

> Four presentations highlighted research that may lead to early diagnosis and treatment of head and neck cancer as well as targeted therapies.

Screening for Early Diagnosis

Stephanie Smetsers, MD, PhD student, Vrije University Medical Center, Amsterdam, is analyzing a non-invasive screening tool for monitoring the mucosal lining of the

continued on page 4

continued from page 3

mouths of individuals with FA to detect pre-cancerous changes by identifying cancer-associated genetic alterations. She and her group brushed the oral cavities of 141 non-transplanted individuals with FA to obtain mucosal cells, isolated the DNA, and determined the presence of specific genetic alterations in the chromosomes that predict malignant progression. These alterations are called loss of heterozygosity (LOH). A control group of 144 individuals without FA (50 low-risk and 94 medium-risk) was also brushed.

No LOH was found in the control group, whereas LOH was found in 14 individuals with FA (9.9%) at a median age of 25.5 years. Researchers sampled 58 of the individuals with FA more than once, including 8 of the 14 with LOH. LOH persisted in all the following samples. In the FA group, 4 of the 14 individuals with LOH and only 1 of the 127 individuals without LOH developed HNSCC during the study period.

Individuals with FA who show LOH should be monitored intensively to detect and remove visible pre-cancerous lesions as early as possible. A screening test that will also be suitable for transplanted FA individuals is currently under development.

Identifying Possible Causes

Flavia Teles, DDS, DMSc, Forsyth Institute, Cambridge, Mass., and her group are working toward identifying the underlying factors that initiate FA-associated oral cancer by studying the oral microbial and inflammatory profiles of individuals with FA. She presented the initial results of this ongoing study which is funded by FARF. Previous investigations have suggested associations between certain micro-organisms and local inflammation with oral cancer development. Dr. Teles collected saliva and tongue biofilm samples from 10 individuals with FA and their non-FA siblings, and compared the levels of up to 108 micro-organisms and 21 cytokines which are regulatory proteins. Species of *Candida* (yeast) and *Streptococcus* (bacteria) were higher in those with FA. There were also higher pro-inflammatory cytokines in the FA group. These findings may suggest that micro-organisms and inflammation could play a role in the increased susceptibility of individuals with FA to oral cancer, and could point the way for the development of better diagnostic, prevention, and treatment strategies.

Researcher Receives Major Grant to Expand FARF-funded Study

Elizabeth Eklund, MD, Northwestern University, Chicago, received a major grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, part of the National Institutes of Health) in December to continue work originally funded by the Fanconi Anemia Research Fund. Dr. Eklund received a two-year pilot study grant from the Fund in 2010 for a project entitled *Impaired Emergency Granulopoiesis in FA Leads to Immuno-deficiency and Predisposes to Acute Myeloid Leukemia.* Results from the study were presented at the 2013 Scientific Symposium. (Please see article on page 5.)

In notifying the Fund of her award, Dr. Eklund wrote, "I want to thank the FARF again for the support over these past years for my pilot project in Fanconi anemia. This was a completely new area of research for me and I would never have gotten the project started without the FARF. I just received the award from the NIDDK for the project that is the outgrowth of the FARF studies. Funding should start after the first of the year and I can't thank the FARF enough."

Dr. Eklund is one of many researchers who have been awarded major funding after receiving a pilot study grant from the FARF. As such, donors to the Fund have seen their gifts multiply many-fold, and FA science has advanced more rapidly than ever thought possible!

Why Infections Are Dangerous for Individuals with FA

Fanconi anemia families have long observed that a severe illness like chicken pox often reduces the blood counts of individuals with FA. Liping Hu, PhD, from the lab of Elizabeth Eklund, MD, Northwestern University, Chicago, explained that emergency granulopoiesis (EG) may contribute to this problem. EG is the rapid production of infection-fighting white blood cells in response to infection or inflammation. Studies in Dr. Eklund's laboratory suggest that the stress of EG may overwhelm DNA repair capabilities and lead to apoptosis (cell death) in the bone marrow of FA patients. Dr. Eklund's laboratory also found that repeated EG episodes may result in early signs of progression to leukemia.

For these studies, Dr. Eklund subjected Fancc-deficient mice and normal mice to a stimulus that mimics infectious challenge. Normal mice had a dramatic increase in granulocytes (also referred to as neutrophils, a type of white blood cell) in circulation, and an expansion of granulocyte precursor cells in the bone marrow. Fancc-deficient mice showed no increase in circulating granulocytes, and large numbers of apoptotic precursor cells were present in the bone marrow after just one cycle of EG. Most of the Fancc-deficient mice died after one or two cycles of EG, whereas no normal mice perished. Leukemic cells were present in the blood and bone marrow of Fancc-deficient mice that survived three cycles of EG. Dr. Eklund concludes that repeated infections result in the death of bone marrow cells and lead to anemia, granulocytopenia, and preleukemia in FA mice.

FA patients need to be protected from infection. Dr. Eklund suggests that prophylactic antibiotics may be beneficial, as is routinely prescribed in other congenital immune-deficiency disorders. Drugs that inhibit interleukin-1beta (the major cytokine [see box] that stimulates EG) are approved for human use in rheumatoid arthritis and could be another approach to this problem.

What Are Cytokines?

Cytokines are a diverse group of proteins that serve as molecular messengers between cells. There are different types of cytokines. Some interact with cells of the immune system in order to regulate the body's response to disease, inflammation, and infections. Others, called "colony-stimulating factors," induce the production of blood cells.

Stressing Stem Cells to Divide Leads to Stem Cell Exhaustion and Aplastic Anemia

Amelie Lier, PhD student, Heidelberg Institute for Stem Cell Technology and Experimental Medicine, German Cancer Research Center, Heidelberg, Germany, described experiments in her laboratory aimed at creating an FA animal model and increasing understanding of the cause of bone marrow failure in FA.

Ms. Lier treated Fanca-deficient and control mice with infusions of certain cytokines (including interferon-alpha, granulocyte colony-stimulating factor, and thrombopoietin) that stress bone marrow cells to exit quiescence and divide into committed progenitor cells.

Hematopoietic stem cells from both normal and FA mice demonstrated elevated DNA damage after treatment. Of note, the level of DNA damage was two-fold higher in FA stem cells compared to stem cells from mice with a functional FA pathway. In the normal mice, four rounds of treatment led to a permanent reduction of primitive hematopoietic stem cells, but these mice still had sufficient primitive hematopoietic stem cells to sustain blood production. In the FA mice, stem cell depletion was even more pronounced. Additional rounds of treatment led to severe aplastic anemia in the FA mice, but not in the normal controls.

Ms. Lier concludes that cytokines that stress stem cells to divide lead to DNA damage and bone marrow failure in mice with FA. This model can be used to test drugs that might prevent this outcome.

Expanding Our Understanding of Aldehydes and Fanconi Anemia

Gerry Crossan, PhD

Lucas Pontel, PhD

Nigel Jones, PhD

Markus Grompe, MD

Recent newsletters describe the promising research on Fanconi anemia and aldehydes, which are highly reactive chemicals that can injure cell DNA. Aldehydes may come from outside the body, but they also are produced inside the body as a result of normal metabolism. Normally, aldehydes are broken down by aldehyde dehydrogenases and this process prevents damage to the DNA. Any aldehydes that avoid detoxification can damage DNA, but a working FA pathway would ordinarily repair such an injury.

Two aldehydes, formaldehyde and acetaldehyde, are by-products of the body's own metabolism. Three researchers at the Scientific Symposium advanced our understanding of how formaldehyde and acetaldehyde may be driving bone marrow failure in FA. A fourth described a chemical compound called cysteamine that has the potential to ameliorate that failure.

Gerry Crossan, PhD, MRC Laboratory of Molecular Biology, Cambridge, UK, and his colleagues looked at the mouse equivalent of an aldehyde dehydrogenase called Aldh2 which breaks down acetaldehyde formed in the body. When Aldh2 and the FA pathway (Fancd2) are inactivated, adult mice have a 600-fold decrease in functional blood stem cells. However, these mice have normal numbers of stem cells before they are born. The data suggest that the breakdown of acetaldehyde and the FA pathway are not necessary for the initial generation of blood stem cells before birth. Yet, without them, the blood stem cell pool dies, often leading to bone marrow failure after birth.

Lucas Pontel, PhD, also of MRC Laboratory of Molecular Biology, and his group used a mouse model to inactivate another aldehyde dehydrogenase that normally breaks down formaldehyde, called ADH5 in humans. These mice were also deficient for the FA DNA repair pathway due to inactivation of Fancd2. Although these mice were born alive, they rapidly developed bone marrow failure and showed some signs of early leukemia. Their blood cells also accumulated broken chromosomes. The profound depletion of blood stem cells in the mice seems more severe than what is experienced from removing Aldh2. This result may indicate that formaldehyde is a greater threat to FA bone marrow than acetaldehyde.

Nigel Jones, PhD, University of Liverpool, UK, and his group exposed mouse cells lacking either Fanca or Fancg protein to acetaldehyde and formaldehyde. Interestingly, even though the FA DNA repair pathway was not working in either cell type, cells lacking Fancg were more sensitive to formaldehyde than Fanca cells. This difference indicates that Fancg may be involved in another DNA repair pathway that mitigates the DNA damage caused by some aldehydes. Further, it points to the possibility that there may be subtle differences among FA patients of major complementation groups that may have to be taken into account in any future therapies.

Markus Grompe, MD, Oregon Health & Science University, Portland, Ore., and his group studied a small molecule called cysteamine that reacts with and detoxifies aldehydes. Cysteamine easily penetrates cells, is not degraded in the liver, and is FDA-approved for the treatment of another disease. His group fed cysteamine to mice with the potential to produce pups that were missing both Aldh2 and Fancd2. The mice that were fed cysteamine produced more viable offspring lacking both Aldh2 and Fancd2 than the mice that were not fed cysteamine.The results suggest that cysteamine can at least partially neutralize acetaldehyde inside the body without ill effects. Dr. Grompe's laboratory is performing further studies to determine whether cysteamine can positively impact blood cell formation and cancer prevention with a view to someday creating a human clinical trial.

Current and Upcoming Clinical Trials Aim to Benefit Patients

Jakub Tolar, MD, PhD, University of Minnesota, Minneapolis, chaired a special session on clinical trials for individuals with FA. He observed that the true goal of conducting FA research is to develop therapies and take them directly to patients. Four researchers presented ongoing and future trials that aim to accomplish this goal.

Gene Therapy Trial

Early this year, researchers and clinicians in Spain opened a gene therapy trial for patients aged one to 21 in the FA-A complementation group. Patients must lack a suitable family stem cell donor and be deficient in at least one blood cell line. Julian Sevilla, PhD, Hospital Infantil Universitario Niño Jesús, Madrid, stated that this trial addresses issues that have contributed to previous gene therapy trial failures. Researchers will try to increase the number of stem cells collected by improving the collection method; they will use a lentiviral instead of a retroviral vector to transduce stem cells more efficiently; and they will reduce the time stem cells are outside of a patient's body. The purpose of this trial is to determine the safety of gene therapy.

Multi-Institutional Alternative Donor Stem Cell Transplant Study

Farid Boulad, MD, Memorial Sloan-Kettering Cancer Center, New York, provided an overview of the remarkable improvement in bone marrow transplantation outcomes since the late 1990s. The purpose of the multi-center study is to improve on these results and to reduce secondary malignancies by (1) decreasing the risks of graft-versus-host-disease (GvHD) using T-cell depleted grafts, and (2) substituting busulfan for radiation.

Five centers participate in this study: Cincinnati Children's Hospital Medical Center; Memorial Sloan-Kettering Cancer Center; Boston Children's Hospital; Children's Hospital of Wisconsin, Milwaukee; and Fred Hutchinson Cancer Research Center, Seattle. To date, these centers have transplanted 37 patients with an overall survival rate of 86%. Dr. Boulad emphasized the importance of these large studies to answer important questions that affect patient survival while minimizing the risks of GvHD.

Oral Cancer Prevention Trial

Head and neck cancer in FA is very difficult to treat due to the extremely toxic effects of chemotherapy and radiation in this population. Dr. David Kutler, MD, Weill Cornell Medical Center, New York, stressed the importance of finding drugs to prevent these cancers in FA patients.

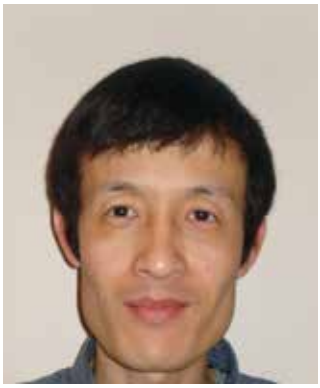
Dr. Kutler described a large, on-going phase II multi-center trial of the drug pioglitazone (brand name Actos) that has shown promise in treating oral pre-malignant cells in the non-FA population. They will look to see if the drug reduces leukoplakia and erythroplakia, which are white or red ulcerative patches in the mouth that may progress to oral cancers. In an earlier randomized trial, 15 of 22 patients in the pioglitazone group had a positive clinical and/or histologic response, compared to no response in the placebo group. The current study will expand the time of trial to six months, and will determine safety and efficacy of this drug. Understanding why FA patients develop oral cancers and including this population in chemoprevention trials will be crucial in helping to prevent these deadly cancers.

Prospective Phase 1/2 Study of Oral N-Acetylcysteine to Evaluate Effectiveness in FA Patients

In vitro experiments and animal trials do not predict the effectiveness of N-acetylcysteine (NAC) in people, according to Rabin Tirouvanziam, PhD, Emory University, Atlanta. NAC inhibits oxidative stress and inflammation by stimulating the production of glutathione. It is primarily processed in the liver and has systemic effects throughout the body. In human trials, NAC was found to inhibit various disease processes in chronic inflammatory conditions such as cystic fibrosis and chronic obstructive pulmonary disease. A multi-center study is being developed for 40 individuals with FA to determine if this drug can improve blood counts and protect cells from DNA damage. Researchers anticipate that this trial will open in the latter half of 2014.

The true goal of conducting FA research is to develop therapies and take them directly to patients.

Potential Drug Therapy Shows Promise for FA



Sirt1 is a protein that suppresses inflammation and may have beneficial effects in treating a number of age-related diseases. Compounds that activate Sirt1, called STACS, may be drug candidates for treating FA.

Researchers at Oregon Health & Science University (OHSU), Portland, Ore., use Fancd2-deficient mice to test various compounds as possible therapies for FA. These FA mice have measurable hematopoietic defects, including a smaller pool of early stem cells, as compared to control mice. Qingshuo Zhang, PhD, OHSU, observed that FA mice and normal mice treated with a STAC displayed increased early hematopoietic stem and progenitor cells as well as the number of platelets and white blood cells in *both* groups of mice. Although this drug "looks safe at this point," additional safety tests are necessary. Dr. Zhang concludes that this STAC compound may have potential to boost certain stem and mature blood cells in individuals with FA.

To Transplant or Not to Transplant: Point/Counterpoint

Families and individuals affected by Fanconi anemia often struggle with the issue of whether or not to undergo a stem cell transplant. Stella Davies, MBBS, PhD, MRCP, Cincinnati Children's Hospital and Blanche Alter, MD, MPH, National Cancer Institute, Bethesda, Md., gave a lively discussion of the pros and cons of this decision.

Stella Davies

Twenty years ago, individuals with FA did not go to transplant unless they *had* to, according to Dr. Davies. Outcomes were "so-so" with matched sibling donors and very poor for those with unrelated donors (only 1/5 survived). Today, because of several factors (Dr. Davies cited fludarabine, removal of radiation, and better donor availability), 91% of FA patients with aplastic anemia survive with no clinically harmful graft-versus-host disease (GvHD). Donor matching has also greatly improved, and there is a much larger pool of available potential donors. Donors registered worldwide now number 20.8 million, compared to 0.2 million in 1989.

The greatly improved survival number still means an individual with FA has a 9% chance of not surviving transplant. This weighs heavily on family members. The decision to transplant means accepting an immediate risk for a later benefit. Dr. Davies added that social networking can be very disheartening, because persons in the network "carry everyone's burden."

Blanche Alter

Dr. Alter stated that there is no single "right" answer to this difficult decision as it depends on a variety of factors. This should be a shared decision, made through close communication between the treating physician and the family. Dr. Alter noted that experts can have different opinions, and that assessing risk is imprecise. Families need to examine their subjective view concerning the quality of life offered by each outcome. On the positive side, families hope that transplant will cure marrow failure and prevent acute myeloid leukemia (AML). On the other hand, they need to weigh the possibility of death or survival with GvHD. If something goes wrong, parents may question the decision they made and wonder: "Did my child and family miss out on good time?" It can be very difficult to move forward.

Dr. Alter believes we must gather more data on risk. We need to document clones in the bone marrow that do not lead to leukemia. We need to know more about oncogenic changes in the marrow that predict AML.

Special Considerations for BRCA2 Patients

Both Drs. Davies and Alter addressed the special situation of individuals with FA in the *BRCA2* complementation group. Dr. Alter studied outcomes in 36 *BRCA2* patients. The most common cancer in this group was brain cancer, but this group also had a very high risk of leukemia. There is a 97% probability of death by age seven. Dr. Alter suggested that transplant might not be the best option for these patients.

Dr. Davies noted that Cincinnati has not performed transplants to *prevent* AML with persons in the *BRCA2* group. (Transplant survival rates given above do not include *BRCA2* or AML patients.) She stated that these individuals will experience complications other than those affecting the bone marrow. Parents "may choose to do less." It is essential that parents have open and honest discussions with treating physicians and transplant experts on the unique complications in this complementation group.

Oral Swabs Studied to Detect Human Papillomavirus in FA

Human papillomavirus (HPV) is implicated in a subset of head and neck cancers in the general population, and these cancers are on the rise. People with Fanconi anemia are at increased risk of head and neck cancer, but it is not clear that these cancers are due to HPV infection. Rachel Katzenellenbogen, MD, Seattle Children's Research Institute, studied oral swabs from individuals with FA to determine the prevalence of HPV DNA in the oral cavity of these individuals, and the specific HPV subtypes involved.

Dr. Katzenellenbogen's team collected oral swabs from 67 FA individuals. The mean age of this group was just over 18; 30 males and 37 females participated in the study. Twenty-six individuals reported previous sexual activity. Five individuals with FA were HPV-positive. This is similar to the prevalence reported in the general population. Those 18 and older were more likely to be HPV-positive. Oral health and tobacco usage did not affect the results. One of the HPV-positive patients submitted a second oral swab four months later and it, too, was HPV-positive.

The types of HPV detected were not the most common for head and neck cancer in the general population. HPV type 16, although the most common in head and neck cancers generally, was not present in these individuals. It is not known if any of the types detected could lead to clinical disease. *None of the HPV types detected in the oral swabs of this group of individuals with FA are included in either FDA-approved HPV vaccine*. Additional studies are needed to follow persistence of HPV in the oral cavity, and whether HPV could lead to clinical disease in individuals with FA.

FA Appears to Increase Risk of HPV

Individuals with Fanconi anemia are predisposed to head and neck cancer and gynecological cancers. In the general population, there is an association between these cancers and human papillomavirus (HPV). Researchers at Cincinnati Children's Hospital Medical Center hypothesize that individuals with FA may be uniquely susceptible to HPV infection. There is a need to know if earlier vaccination is warranted in this unique population.

Melinda Butsch Kovacic, MPH, PhD, described a longitudinal study involving 132 individuals with FA and their siblings and other relatives, seen at Cincinnati Children's Hospital Medical Center and at the Fund's Family Meetings over a five-year period. DNA was extracted from oral rinse samples and tested for 37 HPV subtypes.

Dr. Butsch Kovacic found that 10.6% of persons with FA were HPV-positive compared to 2.7% of siblings and 2.5% of parents and siblings together. Sexual exposure greatly increased the risk 6.5-fold in FA individuals. Dr. Butsch Kovacic concludes that FA increases the risk of HPV-positivity.

Over the time of the testing, 14 individuals with FA were HPV-positive, six of them younger than 13 years of age. While HPV16 was the most common subtype, other positive types included 6, 11, 18, 51, CP6, and 84. Approximately half of the HPV-positive individuals had been vaccinated. Infection might have occurred prior to vaccination, and some of these subtypes are not covered by the vaccine. *Interestingly, subsequent samples from eight of 14 HPV-positive individuals all tested negative*.

Dr. Butsch Kovacic found no association between HPV-positivity and birth type (vaginal versus C-section), a mother's abnormal pap smear, or breast feeding. And while the prevalence of HPV was high in individuals with FA, especially after sexual exposure, a significant number later developed sufficient antibodies to eliminate the infection. Long-term incidence is not known.

Of concern is the prevalence of HPV subtypes not covered by immunization. Future studies need to examine further the roles of bone marrow transplantation, immune deficiency, and possible routes of HPV transmission in individuals with FA.

Researchers Look at HPV Exposure and Vaccination in FA

Researchers at Cincinnati Children's Hospital Medical Center have shown that a large number of individuals with FA have some kind of immune deficiency. Is the HPV vaccine therefore effective in these individuals? Do they need a booster? Should the vaccination be given at an earlier age? What is the natural exposure/infection of these persons to HPV as determined by their antibody response? Parinda Mehta, MD, Cincinnati Children's Hospital Medical Center, described a study to begin to answer these questions.

Sixty-four individuals with FA participated in this study; 28 had received an HPV vaccine. Median age was 15.5, with a range of 2-42. Dr. Mehta tested blood serum (plasma) to detect antibodies to HPV. "Positive serology" or "seropositive" means antibodies against HPV were detected.

Overall, 90% of vaccinated FA patients showed positive serology. Of those who had completed the three-shot vaccination series, 100% showed positive serology to HPV16 and 83% were seropositive to HPV18, the two subtypes of greatest concern in causing cancers.

Thirty percent of unvaccinated patients also showed positive serology, meaning they had been exposed to HPV and had naturally mounted antibodies against this virus. Three of 11 unvaccinated FA children under the age of nine (25%) were seropositive, indicating HPV exposure.

Dr. Mehta also measured overall immune function in FA individuals and found that 49 individuals or 75% of those studied had one or two problems indicating immune deficiency. While a high majority of persons mounted a serological response to the HPV vaccine, this does not mean that the response is adequate in offering protection. Additional studies are needed to determine the vaccine's adequacy, the need for a booster shot, and the best age to begin vaccination.

Early Identification of Ovarian Problems

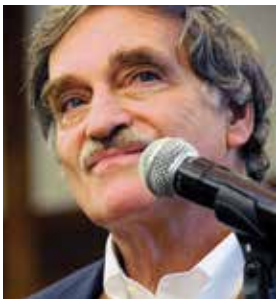
Women with Fanconi anemia may experience a loss of normal function of their ovaries before age 40, so they do not produce normal amounts of estrogen or release eggs regularly. They may have irregular or occasional periods for years and though they may become pregnant, fertility is reduced. They may also develop osteoporosis and menopausal symptoms. This condition is called primary ovarian insufficiency (POI), and is different from early menopause where periods stop altogether and pregnancy cannot occur. Currently, POI is diagnosed by elevated serial follicular stimulating hormone (FSH) levels in blood, by amenorrhea (absence of menstruation), or by absent fertility.

POI should be diagnosed as early as possible in order to better manage its complications, possibly with estrogen replacement or other treatments. Neelam Giri, MD, National Cancer Institute, Bethesda, Md., and her group studied how declining levels of a hormone called anti-Müllerian hormone (AMH) could be used to detect POI at an earlier stage than FSH. Eggs are produced in follicles in the ovaries, and small growing follicles produce AMH. The AMH level can indicate the degree of potential egg reserve present in the ovaries and does not vary significantly with the menstrual cycle or hormone supplements as can FSH. A trans-vaginal ultrasound can be used to detect ovarian reserve, but it may not be as practical as AMH in young individuals. In healthy females, the levels of AMH rise until puberty and remain elevated in early adult life, followed by a gradual decline to negligible levels 5 to 10 years before menopause.

Dr. Giri's group compared the AMH levels of women less than 41 years of age. They examined 22 FA females (7 to 37 years of age), 20 of their unaffected relatives, and an additional 21 unrelated healthy females. AMH levels were very low or absent in the majority of FA females, including adolescents, implying poor ovarian reserve which is consistent with POI.

Monitoring AMH levels in FA females is a simple and reliable way to assess ovarian function in order to manage POI complications as early as possible. It also offers the possibility that treatment with AMH may delay the onset of POI. However, use of AMH as a treatment requires much more research, starting with mouse models before attempting human trials.

Compound May Offer Protection from Radiation Damage for Non-Malignant Cells



Individuals with Fanconi anemia are at high risk for head and neck squamous cell carcinoma (HNSCC). Radiation therapy is a mainstay of treatment for these cancers in the general population, but sensitivity to radiation in individuals with FA compromises its use. A radioprotector for tissue surrounding the tumor would be very valuable in decreasing mucositis and overall treatment toxicity.

In a series of experiments, Joel Greenberger, MD, University of Pittsburgh Cancer Institute, has demonstrated that a special compound, JP4-039, targets the mitochrondria (specialized subunits in cells that function in energy production) and protects non-cancerous cells from radiation damage. JP4-039 scavenges and sops up free radicals, thus protecting normal tissue. Tumor cells, which have low levels of mitochondria, are not protected. Dr. Greenberger concludes that JP4-039 can protect the oral mucosa in FA patients from the damaging effects of radiation therapy, while still allowing radiation to kill the cancer cells. This compound suggests the possibility of a targeted treatment of oral cancer in the FA population.

Central Nervous System Abnormalities and Fanconi Anemia

Stavros Stivaros, PhD, Stefan Meyer, MD, PhD, University of Manchester, UK, and their colleagues determined the frequency and patterns of central nervous system (CNS) structural abnormalities in 19 patients diagnosed with Fanconi anemia by studying magnetic resonance imaging of their brains. The individuals ranged from 5 to 47 years old and possessed physical anomalies other than CNS that ranged from subtle to severe. CNS abnormalities in these patients were common and variable with a striking similarity between siblings, although 5 of the 19 had normal CNS imaging.

The type of CNS abnormalities most often observed were midline abnormalities of the brain affecting the pituitary gland, a part of the endocrine system which secretes hormones that control growth, sexual development, metabolism, and reproduction. A structural anomaly called Chiari I malformation was also common, which can cause various symptoms such as headaches or balance problems. The group also observed less frequent CNS structural abnormalities of various types and severity.

The number and kinds of CNS malformations detected implies that the FA pathway performs a significant role in early CNS development and may continue to provide protection for CNS cells. **It would be prudent to diagnose CNS abnormalities for individuals diagnosed with FA as part of their overall medical assessment.**

Gene Therapy Trial Approved for Patients Age Four and Up

A clinical trial of gene therapy for individuals in the *FANCA* (FA-A) complementation group recently received approval from the FDA to enroll pediatric patients. The trial, conducted by Hans-Peter Kiem, MD, Fred Hutchinson Cancer Research Center, and Pamela Becker, MD, PhD, University of Washington, both in Seattle, was initially approved for FA-A adults only. The trial is the first lentiviral-based gene therapy study for patients with FA. It incorporates novel gene delivery by a safety-modified lentivirus using newly improved techniques. The trial is now open to individuals with FA-A, ages four years and older. Enrolled patients are expected to be in Seattle for 6-8 weeks.

For more information, please contact:
Jennifer Adair, PhD, Study Contact
phone: 206-667-7110
email: jadair@fhcrc.org

For information about FARF's clinical trials scholarships, please contact:
Teresa Kennedy, Family Support Services Director
phone: 1-888-FANCONI
email: teresa@fanconi.org

Exploring Resilience

By Nancy Cincotta, MSW, MPhil
Psychosocial Director, Camp Sunshine

Resilience can be cloaked in many different ways in relation to Fanconi anemia. The question is not, "Are you resilient?" but rather, "How are you resilient?"

Whether you are the person who fills out college applications during bone marrow transplant, or the mother who beautifully photographs her child throughout the course of treatment, or the child who scales a climbing wall as a literal last step en route to transplant, each act is an indicator of resilience. Then there are those who undergo experimental treatment knowing it will have the potential to help someone else in the future. This is an act of courage and bravery that exemplifies resilience.

Thinking about resilience

Is the strength to deal with FA and the ability to bounce back a given trait, or can it be cultivated?
What do you do every day that gets you through to the next day?
Where do you find beauty, joy, and hope?
In whom or what do you have faith, and how do you carry that with you through good days and bad moments?
How do you learn, endure, and find strength in the face of adversity?
How and when do you decide you are going to tell the world about life with FA?
Are those around you—parents, partners, siblings, and friends—enablers of resilience?
How do you choose friends who will enable, not disable, you in life's journey?
What allows you to grow and thrive as a person with FA?
What strength comes from within and what comes externally?
Are some families or individuals more resilient?
Is your ability to cope different when you grow up with FA or when you learn about FA in later life?
When you have already developed coping skills, do those carry over to coping with the diagnosis of FA?
Is the ability to bounce back and to have fun a testimony to your personal resilience, or is it a combination of personal characteristics, your support system, and your environment that affords you that strength?
Does your own "personal resilience profile" lead you to seek knowledge, take care of medical issues, and carry on with an optimistic spirit?

What creates or encourages resilience?

Telling your story.
Open communication and sharing life's experiences.
Education; knowing how to find and act on good information.
Finding strength in connecting with others, and developing cohesion within the FA community.
Believing in a cure and seeking it.
Doing research and learning from others.
Connecting with scientists and researchers to enable a cure.
Participating in research.
Pursuing your dreams.
Connecting with and learning from others with FA.
Finding creative and expressive outlets.
Moving forward, even if life presents you with setbacks.
Retreating when necessary.
Engaging and being active with the Fanconi Anemia Research Fund for support, education, and research.
Finding hope.

Defining resilience as a source of strength in individuals and family members facing FA

Do you think resilience can be cultivated? Do you have a "personal resilience portfolio?" Learned optimism and cultivated resilience are concepts to explore in coping with FA.

If you are someone with FA, or a sibling, parent or spouse to a person with FA, please email me your thoughts on how your resilience developed in relationship to coping and growing with FA. This article is the first in a series on this topic. Your feedback is needed to continue the dialogue about resilience. If you have any additional thoughts about different types of resilience, please send those as well. I look forward to hearing from you at nancycincotta@gmail.com.

In Loving Memory

"For some moments in life there are no words."

Peng Xiong, 3/23/85 - 12/27/13
Christopher Chaffins, 10/14/78 - 3/2/14
Tanay Dharmadhikari, 4/25/05 - 3/5/14

Feeling Lucky, Giving Back

By Sanjeev Singh Parmar

My name is Sanjeev Singh Parmar and I am a "now-adult" survivor of Fanconi anemia. I was diagnosed by my pediatric hematologist in the winter of 1987, and received a bone marrow transplant at the British Columbia Children's Hospital in the summer of 1988.

By a strange twist of fate, my hematologist had neglected to request genetic screening a year earlier (which he had fully intended to do, but for some reason had never submitted the test requisition). The delay in my diagnosis proved vital, as a safe radiation protocol for young children undergoing bone marrow transplantation had yet to be developed. By the time I was diagnosed, a safer, low-dose radiation protocol had been developed and circulated around the world. (Lucky me!)

Despite some initial confusion involving my younger sister and some false-positive results, it was eventually determined that my older brother (now himself a physician) was an ideal donor match. (Lucky again!) At the time of my transplant I was eight years old, my older brother was 10, and my younger sister was five. As far as I am aware, I was the first person with Fanconi anemia to have a successful bone marrow transplant in Canada, and one of the first in North America.

My mom and sister relocated from Calgary to Vancouver to be with me during my transplant and recovery (months and months spent in isolation as "the boy in the bubble" and then home schooling for half of grade four). My dad and brother remained on the other side of the Rocky Mountain range in Calgary. The family was apart for almost half a year all told. It was a very difficult time for my family, and I greatly appreciate all that they sacrificed to help save my life. (Lucky a third time!)

I am now 34 years old, happily married, gainfully employed, and, for the most part, healthy. My wife, Caroline, and I reside in Calgary where I practice law as a corporate and securities lawyer for a national law firm and my wife works as an accountant for an international engineering firm. We have been married for more than three years, and are planning on expanding our family in the near future.

I have been extremely lucky, several times over. I know it. And I was not alone at any point in my journey. I had a great group of people on my side, and a great older brother. I don't think I will ever be able to fully repay everyone—my doctors, my family, my teachers, my friends—who helped me get as far as I have in my life. All I can do is to try and give back to the community in whatever small way that I can.

Congratulations!

Congratulations to Miriam Behers (FA, 47) for earning an associate's degree as a Certified Occupational Therapist Assistant.

Way to go, Miriam!

Study Underway to Detect Oral Cancer in FA

If you or someone in your family is diagnosed with oral cancer, please consider participating in a research study funded by FARF to determine if saliva can be an early detection tool for oral cancer. Contact Teresa Kennedy as soon as possible after diagnosis and before treatment at teresa@fanconi.org or 888-FANCONI. Teresa will coordinate your participation with David Wong, DMD, DMSc, the study's principal investigator. For more information, visit Research Highlights on our website.

How FA Made Our Lives… *Better*?

By Lori Salo

Our journey with Fanconi anemia started when our first daughter, Emily, was born in November of 1994 in San Diego. Erik and I had careers, a house, and a plan for the future which included raising three children in Colorado with a nanny. We had it all figured out, and our five-year plan to move to Colorado took one-fifth the time. We had the closing set on our house, and we would be in Colorado when Emily was just a few weeks old. We were going to hire a nanny and I would continue to work for the government.

Then it happened. Our world came crashing down around us when Emily was born and within two weeks we got the diagnosis of FA. Our world stopped, and at the same time, everything seemed to be spinning out of control. The doctors said to expect her to be with us for three to five years. What? That was not in the plan. We still moved to Colorado; we just postponed it by two months. Then I held this very demanding little baby in my arms almost 24/7 knowing that every moment she was with us was a gift and we would lose her way too soon.

Well, as everyone who has had a sick child knows, things don't always go according to the plans. There was just no way I was going to let somebody else raise my daughter while I worked. I was selfish and I wanted every minute she was here with us to be *with* us. This was one of the first gifts that FA gave us. Priorities changed.

The next gift FA gave us came when we hesitantly entered the room full of FAmilies at the Fanconi Anemia Research Fund's Family Meeting at Camp Sunshine that next May. We were overwhelmed and still somewhat in denial. We just couldn't possibly belong to this club. By the end of the meeting that year, we had made friends who are like family to us and we knew that we were not alone in our battle. The losses and successes of our FAmily through the years have taught us to enjoy each day and let minor annoyances go.

Emily Salo

We celebrated when Miranda, our second daughter, came along just before Emily turned two. What a miracle we had! A perfect match, and Emily's counts were hanging on. Then a few months later, Emily's marrow crashed and with only two weeks' warning, we were headed to transplant. There are no words to describe transplant because every patient's journey is individual, but they all have one thing in common: It will be the hardest thing you ever do as a parent or patient. The summer of 1997 left us changed forever. We celebrated our success while we mourned for many families that left the Minnesota transplant center without their babies. It was the best of times and the worst of times for sure. I have a picture of Emily with four other FA kids at transplant, and she is the only one who is still here. We were devastated at each loss, while we had to stay strong for Emily.

Emily's transplant was a success, and the little girl I thought would never attend school at all has survived and flourished. It would have been easy as parents to shelter and spoil her, but we stood strong and treated her like a healthy child. She has grown into an amazing young lady. Every time I think of her graduating high school last May, my eyes well up with tears of joy. I can't help but be proud of the woman she has become, and excited about what the future holds for her. I don't think she would be a better person if she didn't have FA. She would definitely be luckier, but as much as we *hate* FA, I am grateful for the people we now call FAmily and the lessons that it has taught us.

Emily is now thriving as a student at Colorado State University! She has found her passion in blues dancing and is having the time of her life! Here is to ***living***—with or without FA!

Oral Cancer Fact Sheets Available

Regular screenings for oral cancer are critically important for people with FA. The Fund has fact sheets about squamous cell carcinoma to share with your dentist and ear, nose and throat doctor (ENT). **FA patients and families are encouraged to take a fact sheet to every dentist and ENT visit.** The fact sheets—in English, Spanish, Afrikaans, Dutch, French, German, Hebrew, and Italian—are available on our website or by calling our office.

Our New Normal

By Brian Anderson

When I reflect on the past few years, I am both grateful and saddened by our new perspective on the brevity of life and the importance of choice. Despite the unfairness of our children's diagnosis and their future of ongoing medical concerns, we are determined to soldier on, for the future will hold times of great joy as well as the deepest opposite. My name is Brian. My wife, Sultana, and I live with our three children, Elias, seven years old, Isaac, three, and Avery, one, in the Seattle area. Both Isaac and Avery have Fanconi anemia.

Allow me to go back. In 2010, we lived in Spokane, Wash. Sultana and I were fresh out of college, married with one child, and enthused to embrace life. It was during this momentary sense of self-accomplishment that we decided to have a second child. Almost immediately, ultrasounds showed that Isaac appeared small in size and microcephalic. I believe this was when our future, perspective, and everything changed. Uncertainty grew prior to Ike's birth and when he finally joined us, we began the slow process of discovering his ailments. He was born with a malformed thumb, café au lait spots, and microcephaly. Months later, still impatiently awaiting answers, we learned that we were pregnant with Avery. Shortly thereafter, we received the phone call that Isaac tested positive for Fanconi anemia.

Tragically, Avery's ultrasounds began to suggest the same disorder. While many expectant parents focus on their hope for a boy or a girl, we simply wished and pleaded that our third child would arrive healthy and spared from the same diagnosis as his or her brother. Avery's birth was one of elation, worry, excitement, and fear. Ultimately, we remained calm and hopeful upon our Avery's positive diagnosis in August 2012. As so many other families have experienced, the odds, while somewhat promising, can get completely tossed out the window.

The day we found out that Isaac tested positive for a genetic disorder, we made the choice to accept the reality of our situation and lead as "normal" a life as possible. We seized the opportunity to relocate near Seattle hospitals. I chose to pursue a more challenging career. Sultana's passion guided her to choose a job counseling the formerly homeless. Sultana's mom, Cherie, chose to quit her job to help us raise our children. As a family, we choose to focus on the positives (like celebrating Eli's good health and being grateful that he is a bone marrow match for Isaac). My point is this: We had the choice to allow this terrible disease to define our present

and future, yet we try to move past it and appreciate that FA has allowed us a new perspective.

Although we cling to hope and acceptance, we nevertheless remain affected by periods of fear, sorrow, and anger for what our children endure. Life now is different after endless blood counts and tests, the first bone marrow aspiration, the thumb surgery, and countless appointments with specialists. And it certainly does not get easier to restrain a sobbing and confused toddler for his standard quarterly blood draw, only to discover that his platelets continue to decline. But we accept this as our new normal; it's what we choose to do and, luckily, normal is relative.

With the support of family and friends, we move forward. Amid hardship and grief there is resiliency, strength, and determination. And as difficult as this battle becomes, we will not give up.

Help Advance FA Research!

Researchers are working hard to find effective treatments and a cure for Fanconi anemia, but they can't do it alone. **FA researchers need you.** Please consider donating tumor tissue for FA research.

Contact Teresa Kennedy at teresa@fanconi.org or 888-FANCONI.

Families Join Forces to Fundraise

By Cynthia Vandermeys

My family is relatively new to the Fanconi anemia world. Both of our children were diagnosed in the spring of 2012. Jacqueline was five and Alex had just turned nine. Alex's counts were so dangerously low that we went to transplant at the Cincinnati Children's Hospital only weeks later. As we all do when we first get diagnosed, we contacted the Fanconi Anemia Research Fund. Teresa Kennedy, the Director of Family Support Services, informed me that there was another family in our town with an FA child—Lorraine and Kevin McQueen. I got a call from Lorraine soon after. I can't tell you what a blessing it has been to have a motivational, uplifting individual to help support us through this! She invited us to their annual Play for FA event that May. We went. I cried. Then we went home and packed for Cincinnati.

When we returned home after transplant, I asked the McQueens if we could join forces with them to fundraise. There was no hesitation on their part. Every year, the McQueens host fundraising events for FARF, ranging from a black tie casino night to a down-home barbeque with a band and a live auction. They are very successful, usually raising $60,000 to $80,000!

So, we added our contacts to the McQueens' invitation list. They added our family's story to their Play for FA website. My husband, Gerard, and I helped solicit donations along with the myriad tasks involved in putting on an event. The invitations, donation and sponsor letters include pictures of all our children. The pictures are also displayed during our events and, boy, are they powerful. Walking into an event, seeing the faces of children you know, and learning what they are going through really speaks to people!

During our first visit to the FARF's FA Family Meeting last June, I was asked how we had helped raise more than $40,000 through Play for FA when our children were only recently diagnosed, and were only one year post-transplant. The answer was simple: drive, determination, and the McQueens. We are fortunate that we are not going at this alone.

But after attending last year's Family Meeting, I was determined to do something more for our children's future. Lorraine and I discussed it, and we concluded, "Okay, game on! We can do this!" So, with only two months, we put together a fundraiser that raised nearly $10,000 for FARF.

Here is how we did it. I sent a message out via Facebook and Caringbridge asking for help. Several people replied and we met one Sunday afternoon. The children played while we decided on the fundraiser's details: **Place**: Neighborhood pool. **Date**: Saturday after Labor Day. The pool is already officially closed, but this was a huge draw because families were able to get in one last swim. The kids loved that! **What**: Swimming, live band, BBQ, cornhole tournament, desserts, silent auction. **How**: Okay, this is the scary part, but let me tell you it just all came together. One father is in a band and volunteered the music. Another volunteered to organize the cornhole tournament. Another family who owns an Italian ice shop donated the dessert. Someone even knew a group of guys that grill for charitable causes—they provided the unbelievably yummy dinner! Our brother-in-law works for a beer distributor who donated several cases of beer. Drawing on Lorraine's expertise of putting together silent auction packages, we revised previous donation letters, and received enough for almost 30 auction packages. I have found that if you ask and have a donation letter handy, you will be surprised how many businesses and people will donate. We grouped donated items into packages and they were a big hit! FARF provided credit card swipers, so paying for items was a breeze.

I would be remiss if I didn't mention all the support we got from FARF. They mailed out our invitations and donor and sponsor letters. They paid for linens we used to dress up the tables for dinner, desserts, and the silent auction, which we can use for future fundraisers. FARF also covered the cost of the lifeguards for the night. There are many people to help and give encouragement. And FARF is there to back you up.

One other thought. Use your Christmas card mailing list, use your children's school directory, and send a letter about your family. Tell them what FA is about. Tell them that almost 89 cents of every dollar donated to FARF goes to family support and FA research. That is outstanding. Tell them you are having an annual drive and that you would love their support. Send the letter to FARF along with your mailing lists. They will mail them. And your friends and family will want to help and support you.

I know we are lucky to have another FA family, Lorraine and Kevin McQueen, to help us with fundraising. But, WE ALL have the support of the Fanconi Anemia Research Fund.

Fund is Lucky Recipient of Foundation's Generous Efforts

Every year, a group of 13 volunteers gather each month around the dining room table of Lucky Duck Foundation founders, Pat and Stephanie Kilkenny, with one mission: to raise money for the Fanconi Anemia Research Fund and other charities. "I call them my Lucky 13," said Stephanie of the group comprised of an architect, PR professionals, moms, and others.

The Kilkennys, who live in Del Mar, Calif., began the Lucky Duck Foundation in 2005 to raise funds and awareness for charitable causes. Since its inception, more than $3,700,000 has been donated to select charitable organizations. "The best part of being on the Lucky Duck Foundation Committee is raising awareness of causes that are dear to our hearts, including the Fanconi Anemia Research Fund," says Navjot Rai, a Committee Member since 2009.

Pat, a University of Oregon alumni and former Athletic Director, and his wife, Stephanie, chose the Fanconi Anemia Research Fund as a beneficiary because of a personal tie. Longtime friends of Fund founders Dave and Lynn Frohnmayer, the Kilkennys want to do everything they can to help eradicate the disease that claimed the lives of two of the Frohnmayers' five children. "We are honored to be able to help them in their quest for a cure," states Stephanie.

The name Lucky Duck Foundation is a nod to Pat's Irish heritage and his University of Oregon roots. The organization raises the majority of its funding at its annual Swing & Soiree, a golf tournament and auction put on at the Santaluz Club in San Diego. Last September, 128 golfers participated in the shotgun shamble golf tournament, and 300 guests gathered for the evening reception hosted by professional golfer Peter Jacobsen and NBA great Bill Walton. The event raised $700,000, the result of live and silent auctions, event registration, and the Kilkennys' generous matching donation. Of that total, $200,000 went to the Fanconi Anemia Research Fund for research and education.

The committee is already hard at work planning the 2014 Swing & Soiree to be held on September 29th at the Santaluz Club. While serving on the committee is a big commitment—in addition to fulfilling their respective roles in communications, administration or events, committee members canvas neighborhoods to promote the Swing & Soiree and accumulate auction items—no one is asking for a pat on the back. "I hope that with each and every Lucky Duck Foundation donation we are one step closer in providing scientists with the resources they need to find new treatments to help those afflicted with Fanconi anemia," says Rai.

FARF Can Help You Fundraise

More than 90% of the Fanconi Anemia Research Fund's annual budget comes from family fundraising. We're here to help make your events a success. We can:

- Provide sample fundraising letters and help you edit your letter
- Use your photos to personalize your letter, event invitation or brochure
- Use your mailing list to send your letter or invitation from our office
- Provide ideas, information, and display materials for events
- Provide a PowerPoint or video presentation to use at your event
- List your event on our website
- Send a thank-you letter and tax receipt to your donors

We ask that all fundraising events be covered by liability insurance. Insurance for a one-time event is often available through a family's homeowner's insurance policy as a relatively inexpensive insurance rider. Please contact the Fund if you need assistance obtaining or paying for this required insurance.

Please ask your donors to make checks payable to the Fanconi Anemia Research Fund. When a donation is received, we'll generate a letter of thanks with a tax receipt, and we'll notify you that a donation has been made in your behalf.

We appreciate all your efforts to raise funds for FA research and family support. You are making a difference!

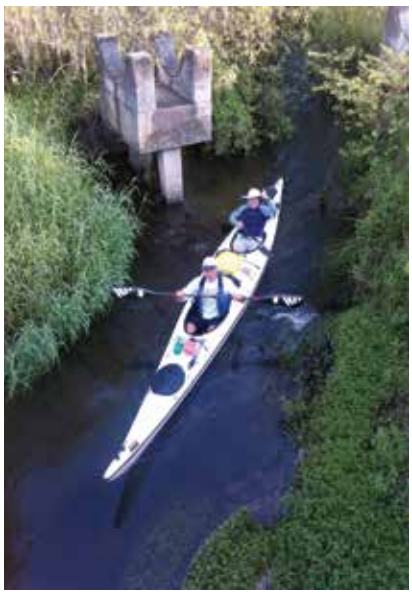
Kabuki Helps Helps FARF

A small company with a big vision, Kabuki Helps brings creative books and educational games to children to make learning fun while supporting worthy causes—like the Fanconi Anemia Research Fund. Each Kabuki Helps product was carefully created by a parent or teacher to enhance learning, and 10% of every sale is donated to one of five select charities.

When you purchase an item from the Kabuki Helps website, look for the drop-down menu to select a charity during checkout, and choose "Fanconi Anemia." The next time you're in the market for a new children's book or game, why not support FA research at the same time? Find Kabuki Helps at www.kabukihelps.com.

ONE for Wyatt Inspires a Village

ONE for Wyatt began in 2008. Steve Kliemkiewicz was training for his first Sandman Triathlon when his son, Wyatt, was diagnosed with Fanconi anemia. Steve couldn't participate in the race that year because the family was preparing for Wyatt's bone marrow transplant. After the family returned home to Virginia Beach, Va., Steve decided to train again. A good friend and fellow racer suggested using the race as an opportunity to fundraise for FA. That first year, six racers raised about $6,000. Last year, 25 runners raised $150,000! Wyatt's mom, Jen, says they have received amazing support from friends and family, and the greater community has really embraced their fundraising efforts. Wyatt's friends hosted lemonade stands at local businesses throughout September (race month) and raised more than $500. In addition, the kindergarten class at Wyatt's school hosted a lemonade stand, raising more than $100. Many contribute to ONE!



Team BrAvery Continues Its Challenges

Last October, Team BrAvery paddled about 320 miles from the headwaters of the Florida Everglades near Orlando, down the Kissimmee River, across Lake Okeechobee, and through the Everglades National Park to Flamingo to raise money for Fanconi anemia research. The team's adventures have raised more than $20,000.

Orion and Lisa Marx's daughter, Avery, age 10, has FA. She received a successful bone marrow transplant in 2010 and is doing very well. Her grandfather, Charlie Scott, and the Marx family are always working on ideas to help FARF. Orion's office held a well-attended bone marrow donor recruiting drive and a LOT of the family's friends came out to register as bone marrow donors.

For the past three years, the Marx family, aka Team BrAvery, have raised funds for FA research, trying to do it in a little different way. They plan outdoor adventures that not only challenge them physically, but also provide an educational opportunity for Avery's class. Each of their trips focuses on history and/or geography, and the Team always makes sure Avery's teachers get information to add to the class lessons. That's value-added fundraising!

The next Team BrAvery Challenge is planned for July. For more information, visit www.goteambravery.com.

Family Legacies

Mary Traynor Grabher was diagnosed with FA at age 51. A wife, mother, and college-level English teacher, Mary researched FA exhaustively after her diagnosis and became an inspiration to others. Sadly, Mary died two years later. Family and friends remember her loving and optimistic nature and rare quality of seeing the best in everyone.

Near the end of her life, Mary shared an essay with her sister-in-law, Linore Burkard, that she had written in college about family ties. Charmed by the story and knowing that nothing was more important to Mary than family, Linore recently adapted and published the essay as a children's picture book entitled *Grandmother, Mother and Me*. Proceeds from the book will help support Mary's adopted special-needs daughter and the Fanconi Anemia Research Fund. *Grandmother, Mother and Me* can be purchased from Amazon and through most booksellers.

Eli's Gift

To Our Friends at FARF:

Enclosed please find donations totaling $1204 for your organization to use as it sees fit. Our son Eli Lana collected this money in honor of his own birthday as a way of giving back to you for all you have done for him and for all those who have Fanconi anemia. These donations reflect the support of a number of people who love Eli, and through him wish to support the organizations that have helped our family.

From the bottom of our hearts we thank you for everything you do and we are so glad to have you in our lives. We are lucky to have an organization like FARF to support our family and many others by funding research, funding Camp Sunshine, and much more. Eli will celebrate the 3-year anniversary of his bone marrow transplant this April, a tremendous feat in the world of FA. We know you share in this joy with us.

Thanks again,
The Lana family

Focusing on Fundraising

Sandy Carter, grandmother of Lea Branov, age eight, is putting her excellent eye and photographer's expertise to work raising money for Fanconi anemia research and family support. Through Sandy Carter Photography on the Etsy website, Sandy offers nearly 100 original fine art photographs for sale. Stunning color and black and white images include scenes from world travels as well as human studies and animals—including some very photogenic chickens. Not only does Sandy donate all of her proceeds to the Fanconi Anemia Research Fund, she generously matches her sales 100%. That's right—each sale equals a double donation!

Visit Sandy's shop at www.etsy.com/shop/sandycarterphoto. For $50 or less, you are sure to find a beautiful and unique print to grace your home or office, or to gift—and fundraise for FA at the same time. Thank you, Sandy!

Double Your Money

Who wouldn't want to double his or her money? Especially when it means double the funds for Fanconi anemia research and family support. Many employers sponsor matching donation programs to charitable organizations such as the Fanconi Anemia Research Fund. Most of these programs match your contribution dollar-for-dollar, doubling your personal donation. Please check with your company's Human Resources or Payroll Department to see if your employer offers charitable donation matching.

Family Fundraising Efforts Impressive in 2013

In 2013, FA families raised an impressive $1,870,643 for Fanconi anemia research and family support! This is almost $300,000 over the total family fundraising in 2012. In all, 185 families raised funds; 106 families raised more than $500. Almost 89 cents of each dollar donated went directly to research and family support to make a difference in the lives of individuals and families affected by Fanconi anemia. Thank you to the FA families listed below for their fundraising efforts in honor or memory of loved ones.

$608,000 and up
Dave, Lynn, and Amy Frohnmayer

$100,000 - $160,000
Kendall & Taylor Atkinson Foundation w/ the Nash and Atkinson Families
Steve and Jennifer Klimkiewicz
Kevin and Lorraine McQueen

$53,000 – $89,000
John and Kim Connelly
Francesca Hutchins-Huff
Peg Padden
Glen Shearer

$20,000 - $33,000
Mike and Tracy Brannock
Kerrie and Mauro Cazzari
Mark De Groot and Hanneke Takkenberg
Jim Hamilton
Peter and Tara Himmelreich
Todd and Kristin Levine
Orion and Lisa Marx
Peter and Janice Pless
Nigel and Ann Walker

$10,000 – $19,999
Jimmy and Jenny Armentrout
Robert and Barbara Capone
David and Mary Ann Fiaschetti
Andre Hessels and Rutger Boerema
Brian Horrigan and Amy Levine
Charles and Katy Hull
Kaps for Kendall
Susan Ortiz
Mark and Diane Pearl
George and Kathryn Reardon
Bob and Andrea Sacks

$5,000 - $9,999
Ryan and Becky Brinkmann
Susan and Skip Gannon-Longstaff
Deane Marchbein and Stuart Cohen
Dan and Nikki McCarthy
Tyler Morrison and Rachel Altmann
Jack and Lisa Nash
Gerard and Cynthia Vandermeys

For the fundraising events calendar and helpful fundraising materials and tools, visit www.fanconi.org

$1,000 - $4,999
Michael and Jennifer Aggabao
Juanita and Ron Arroyo
Mark and Linda Baumiller
Israel and Mary Jo Becerra
Richard and Tena Boson
Chris and Jennifer Branov
Donald and Danielle Burkin
Christopher Byrd
David and Kim Chew
Joseph and Nancy Chou
Daniel and Melinda Coleman
Chris and Susan Collins
David and Kari Doctor
Brian and Jennifer Dorman
David and Kelly Dunnock
Mitch and Erin Furr
Ben and Stephanie Griggs
Alan and Rachel Grossman
Owen Hall and Margaret Kasting
Lisa and John Hayden
Patti and Mike Hilbert
Jeff and Beth Janock
John and Karilyn Kelson
Erik Kjos-Hanssen and Turid Frislid
Sejin Kwon and Jee-Ai Kim
Mark and Angela Lamm
Tim and Mary Ann Lana
Tanner and Jessica Lindsay
Gregory and Lynnette Lowrimore
Bill and Jackie Lucarell
Tue Marker and Kirstine la Cour Rasmussen
Gianna and Lauren Megna
Adam and Olivia Mindle
Jim and Holly Mirenda
Ron and Fredi Norris
Lorraine O'Connor
John and Dianne Ploetz
Mark Ritchie and Lisa Mingo
Kevin and Katie Rogers
Rick and Lynn Sablosky
Ron and Elesa Schaefer
Bryan and Karen Siebenthal
William and Mary Underriner
Mike and Beth Vangel
Marc Weiner
Michael and Kim Williams

Up to $999
Dorian Adams
Kelly Adams
Andrew and Vicki Athens
Ken and Jeanne Atkinson
Cherie Bank
John and Audrey Barrow
Willie and Jeanette Beetge
Conrad and Joan Bender
John and Francene Berglund
Domenico Bertolucci and Federica Bonati
John and Elaine Beyer
Randy and Nancy Bloxom
Jeffrey and Donna Boggs
Michael and Diane Bradley
Jeanette Clark
Mary Eilleen Cleary and Gleaves Whitney
Tyler and Teresa Clifton
Natalie Curry
Brian and Margaret Curtis
Bill and Pat Danks
Darrel and Kalani DeHaan
Wendy Delzell
Pat and Mary DiMarino
Antonino and Marie Di Mercurio
Lindsay and Sandra Dunn
Gene and Lynn Eddy
Ginger Eggers
Sharon Ellis
Billy Jo and Debbie Estep
Curt and Crystal Fales
Justin and Britteny Ferrin
Nancy Finnegan
Martin and Tamara Francois
Fabio and Sune Frontani
Liz Funk
Thomas Germann and Jennifer Bland
Stan Gilbert and Chris Brunner
Maria and Josh Godwin
Allen Goldberg and Laurie Strongin
Andrew and Jennifer Gough
William Graham
David and Paula Guidara
Doreen and Shawn Gummoe
Mitchell and Tirzah Haik
Abdul Hameed
Eric and Elisabeth Haroldsen
Bob and Victoria Hathcock
Shane and Colleen Irvin
Lila Keleher
Christopher and Dana Lamb
Eugene and Renee Lemmon
Peg LeRoux
Joey Linsenmann
Eric and Beth Losekamp
Donnie and Jerri Lott
Steve and Alison McClay
David and Samantha McDowell
Kevin and Barbara McKee
Catherine McKeon
Charles and Cecelia Meloling
Lynn Welfare Mendenhall
Michael Menna
Ian and Tricia Mitchell
George and Sabine Mohr
Sydney and Betsy Moore
Des Murnane and Mai Byrne
Kenny and Lisa Myhan
Tony and Lina Nahas
Jack and Tammy Neal
David and Catherine Newmann
Robert and Mary Nori
Fred and Nancy Nunes
Michael and Katharine Ormond
Stacia Pattison
Derek and Ginger Persson
Michael and Kay Proctor
Lynn and Shirley Quilici
Mario and Yolanda Ramirez
Pedro and Marina Ravelo
Jack and Tannis Redekop
Leonard and Jan Riley
Dov Rom
Stanley and Lisa Routh
Mike Sanders
Richard and Dolores Satterlee
Bill and Connie Schenone
Severt and Beatrice Score
Thomas and Brenda Seiford
Matt and Diane Senatore
Jack and Debbie Siegel
Alain Silverston
Jim and Carol Siniawski
Ariel Sitzerman and Gabriela Bernal
Kevin and Joanne Smith
Mitzi Speelman
Alfons and Karin Staab
Greg and Brandi Stuart
Mary Tanner
Peggy Templeton
Bruce and Loreen Timperley
Charles and Doris Trotta
Tom and Kathy Uno
Ronald and Sharon Van't Hof
Louis and Theresa Viola
Matt and Barbara Violassi
Joe and Wendy Vitiritto
Mike and Wendy Wade
Jian Yang and Jing Nie
Sean and Kristin Young
Tom and Marge Zaborney

Your FA Research Dollars at Work

From September 2013 to February 2014, the Fanconi Anemia Research Fund awarded $368,111 in research grants to the following projects:

Investigators: Michael Garbati, PhD, and Grover Bagby, MD, Oregon Health & Science University, Portland, Oregon
Title: *The Role of Aldehyde Dehydrogenases in Protecting Fanconi Anemia Hematopoietic Stem Cells During the Inflammatory Response*
Amount: $141,911

Investigators: Ashwin Shinde, MD candidate, and Joel Greenberger, MD, University of Pittsburgh Cancer Institute, Pennsylvania
Title: *Protection with JP4-039 of Normal Oral Cavity and Oropharyngeal Tissue During Radiotherapy of Cancer in Fanconi Anemia D2-/- and HPV+ K14E7 FancD2-/- Mice*
Amount: $50,000

Investigator: Andrew Deans, PhD, Institute for Medical Research, Fitzroy, Australia
Title: *A Biochemical System for Testing the Function of Unclassified FANC Protein Variants*
Amount: $176,200

The Fund is committed to supporting research to further our mission of finding new treatments and a cure for Fanconi anemia. Over our 25-year history, we have awarded 194 research grants and one service grant to a total of 102 investigators at 56 institutions worldwide. The amount of research dollars awarded totals more than 16.5 million dollars!

Online Fundraising Tools Available

Qgiv and Hobnob are online fundraising tools available through the Fanconi Anemia Research Fund. Through Qgiv, we can accept online donations directly on our website. Hobnob offers people a customizable fundraising page for events, enabling online registrations and donations in advance and at the event. Contact FARF for details on how Qgiv and Hobnob can enhance your fundraising!

New! Donate While You Shop on Amazon

The Fanconi Anemia Research Fund is now a participating charity in the AmazonSmile program which donates 0.5% of the purchase price of eligible products to selected charities. Simply visit smile.amazon.com, select the Fanconi Anemia Research Fund as your charity, and start shopping! You'll find the same prices, selection, and shopping experience that you are used to on Amazon.com. You can use your existing Amazon account on AmazonSmile, and once you select your charity on your first visit it is retained with your account. So, just remember to do your Amazon shopping at AmazonSmile. It's that easy!

amazonsmile

23rd Annual FARF FA Family Meeting at Camp Sunshine Casco, Maine — June 27-July 2, 2014

Questions or need financial assistance for travel?

Please contact Teresa Kennedy at teresa@fanconi.org or 1-888-FANCONI.

Meet the Staff

It is not uncommon for families or researchers newly acquainted with the Fanconi Anemia Research Fund to be surprised to learn that we have just a single office. Or that the Fund has a staff of five. Meet the Fund's staff—those hard-working folks who make it all happen in a small office in Eugene, Oregon.

As the Executive Director of the Fund, **Laura Hays**, PhD, oversees all daily operations, manages staff, guides research, plans meetings, and much, much more. Before joining the Fund, she worked in Fanconi anemia research for 10 years as an assistant professor at the Oregon Health & Science University in Portland, Ore. Laura says, "My favorite part of the job is the great people I work with and the wonderful interactions with FA families and scientists."

Teresa Kennedy, MA, is the Director of Family Support Services. She has been with the Fund since 2008. Teresa communicates with hundreds of families and individuals with FA from around the world, providing them with the Fund's educational materials and support. She also networks with FA researchers and clinicians. In addition, Teresa plans the Family Meeting and the Meeting for Adults with FA. She is impressed by the dedication of FA researchers and clinicians, and is continually inspired by the families and individuals with FA served by the Fund.

Kim Larsen, Conference Planner and Communications Editor, has been with the Fund since 2004. She organizes the annual Scientific Symposium as well as other science meetings and the Fund's annual planning meetings. She is managing editor of the FA Family Newsletter and the Donor Newsletter, and edits many Fund materials and family fundraising letters. Kim enjoys working towards successful meetings and publications, and especially interacting with scientists, clinicians, and newsletter contributors along the way.

Kristi Keller, Bookkeeper and Administrative Assistant, has been with the Fund since 2005. She is responsible for the day-to-day financial activities of the Fund. She enters all donations into the Fund's database and accounting programs, as well as prepares and mails all donation thank you letters and tax receipts to donors. Kristi also assists families with various fundraising activities.

Cynthia Freeman, Special Projects Coordinator, provides family fundraising support such as preparing letters, flyers, and personalized brochures and shipping the FARF tabletop display and banner for fundraising events. She tracks and completes state registrations and registrations for federal and state charitable donation campaigns. Cynthia is responsible for updating and producing the annual Family Directory and the Treatment and Testing Resource Guide. She coordinates audiovisual support at the Scientific Symposium as well as video conferencing for board meetings.

facebook

Find us on Facebook at

www.facebook.com/fanconianemiaresearchfund

Changes to the Boards

The Fanconi Anemia Research Fund saw changes to its Board of Directors and Scientific Advisory Board recently as terms expired. The Board of Directors adopted term limits several years ago to infuse both boards regularly with new members and fresh ideas.

We say good-bye and thank you to Kevin Rogers whose term on the Board of Directors ended. Kevin, an FA parent, served on the Board since 2009, providing expert financial advice as the leader of the Board's investment review committee. We are very grateful that Kevin has volunteered to continue as a special advisor to this committee.

Marc Coltrera, MD, head and neck surgeon and professor, University of Washington, Seattle, gave valuable, wise advice as a member of the Scientific Advisory Board which he joined in 2005. Dr. Coltrera initiated an abstract submission website for our Scientific Symposium which he has volunteered to keep providing. We are delighted that he will continue to advise and support the work of the Fund.

Erich Sturgis, MD, a head and neck surgeon at the MD Anderson Cancer Center in Houston, departed the Scientific Advisory Board at the end of his term. Dr. Sturgis served on the Board since 2007. We are extremely grateful for his input and guidance in our efforts to address the head and neck squamous cell carcinomas that affect individuals with Fanconi anemia.

Grover Bagby, MD, Oregon Health & Science University, Portland, Ore., stepped down as chair of the Scientific Advisory Board. Dr. Bagby has served as chair since the Board's inception in 1989. Thankfully, he will continue as a member of the Scientific Advisory Board. We recognized Dr. Bagby's enormous contributions with a Lifetime Achievement Award bestowed at the 2012 Fanconi Anemia Scientific Symposium. His passionate curiosity, dedication to inquiry, and excellent leadership skills are invaluable to our efforts.

We are very grateful to these retiring board members!

Fanconi Anemia
RESEARCH FUND, INC.

1801 Willamette St, Suite 200
Eugene, Oregon 97401

RETURN SERVICE REQUESTED

Mission: To find effective treatments and a cure for Fanconi anemia and to provide education and support services to affected families worldwide.

Use of Logo

A reminder to our families with FA: Please use our logo or letterhead only after you have consulted staff at the Fanconi Anemia Research Fund and received approval. This step is necessary to be sure our messages are accurate and consistent, and it helps avoid legal complications. We are happy to collaborate on fundraisers and mailings.

Editors' Note and Disclaimer

Statements and opinions expressed in this newsletter are those of the authors and not necessarily those of the editors or the Fanconi Anemia Research Fund. Information provided in this newsletter about medications, treatments or products should not be construed as medical instruction or scientific endorsement. *Always consult your physician before taking any action based on this information.*

HOW YOU CAN HELP

Donations Online:	Donate via the heart button on the Fund's website (www.fanconi.org) or through www.networkforgood.org or www.paypal.com
Donations by Phone:	Call us at 541-687-4658 or toll free at 888-FANCONI (888-326-2664) (USA only)
Donations by Mail:	1801 Willamette St., Suite 200, Eugene, OR 97401

Please go to www.fanconi.org to learn about other ways to donate.

1801 Willamette St., Suite 200, Eugene, OR 97401
phone: 541-687-4658 • 888-FANCONI (888-326-2664) (USA only)
fax: 541-687-0548 • email: info@fanconi.org • web: www.fanconi.org