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FA Family Newsletter

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57

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New Discoveries, Lively Debates, and 25th Anniversary Celebrations Highlight the Annual Scientific Symposium



Francis Collins, MD, PhD, Director of the National Institutes of Health

The 26th Annual Fanconi Anemia Research Fund Scientific Symposium, held last September in Bethesda, Md., was attended by 211 scientists, clinicians, Fund board members, and family representatives from 17 countries, including Egypt, South Africa, and the Czech Republic. Nine sessions over four days commenced with FA 101, an introduction to the clinical and biological aspects of FA, popular with both veterans and newcomers alike. Researchers presented 39 abstracts on subjects including Head and Neck Squamous Cell Carcinoma; Malignant Transformation; Aldehydes and Bone Marrow Failure; Experimental Hematology; Expanding FA Clinical Phenotype; FA Proteins: Structure and Function; FA Therapeutics: Past, Present, and Future; and Mutation to Phenotype. An additional 68 abstracts

were presented as posters on a wide range of subjects.

Francis Collins, MD, PhD, Director of the National Institutes of Health in Bethesda, opened the meeting by praising the progress in FA research engendered by the Fund, and encouraging new FA research and the scientists performing it. Dr. Collins also acknowledged the major contributions of the Fund's co-founders, stating that, "Dave and Lynn Frohnmayer have really transformed this world that they entered."

The Symposium featured two special sessions—Solid Tumors and, for the first time, Provocative Case Studies. The tumor session included presentations on head and neck, gynecologic, and skin cancers. The provocative cases focused on individuals in the FANCD1/BRCA2 complementation group, as well as head and neck cancer and other topics. In addition, there were keynote presentations by Christian Abnet, PhD, MPH, National Cancer Institute, Bethesda, Md., on environmental carcinogenesis, and

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Screening Therapeutic Drugs Using FA Cells



Jordi Surrallés, PhD

Jordi Surrallés, PhD, Universitat Autònoma de Barcelona, Spain, described his lab's recent work on screening substances for their potential efficacy in treating Fanconi anemia. The goal is to identify compounds that have the best chance to reduce DNA damage in FA cells, with a view to developing them into drugs that would ameliorate the hematological symptoms of FA and prevent cancer formation.

Dr. Surrallés employed two cell-based drug screening systems to measure the impact of candidate drugs: 1) a flow cytometry technique to test the capacity to alter chromosome fragility and cell cycle; and 2) induced pluripotent stem (IPS)

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New Discoveries, Lively Debates, and 25th Anniversary Celebrations Highlight the Annual Scientific Symposium

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by Aninyda Dutta, MD, PhD, University of Virginia School of Medicine, Charlottesville, on DNA replication and its interplay with FA pathways.

The mentorship lunch option for early investigators, started last year, was expanded so that the investigators were grouped by career stage and location. Appropriate mentors with similar backgrounds were chosen for each group to allow more intimate and specific discussions. Also, for the first time, there was a clinical investigators' lunch for medical professionals that also performed FA research. The overall response for both lunches was very positive, with 22 investigators and 58 mentors attending, and will be carried forward in subsequent years.

The annual Symposium banquet celebrated the 25th anniversary of the Fund. The celebration included inspiring and well-received talks by FA parents Diane Pearl, Lorraine McQueen, and Lorne Shelton. Additional presentations included a scientific history of the Fund by Scientific Advisory Board member Grover Bagby, MD, Oregon Health & Science University, Portland, and remarks by Dave Frohnmayer, Fund co-founder. Awards were given to Emilie Dubois, Laval University, Québec City, Canada, Eugenio Zapata Aldana, MD, Hospital Civil de Guadalajara, Guadalajara, Mexico, and Surya Amarachintha, PhD, Cincinnati Children's Hospital Medical Center, Ohio, for the best basic science, clinical, and translational posters, respectively, presented at the Symposium. The evening concluded with a video that

recapped the Fund's 25 years, highlighting research advancements and family support.

Participant evaluations attest to the great value of the meeting:

"It was my first time at a FARF meeting. It was very enriching for me. Immersion in cutting edge molecular biology—and the clinical sessions were very good. The session with interesting cases was incredible! I'm very excited for the next meeting."

"This conference is the most inspiring for me as a scientist. The format and dedication of parents and fundraisers is truly amazing."

"Thank you for organizing such an impeccable conference. It definitely focuses on research that is relevant to FA patients."

"This was a very well designed symposium. An excellent conference. I am very impressed."

Screening Therapeutic Drugs Using FA Cells

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cells created from FA patient fibroblasts to test the ability to restore blood cell production.

The lab screened antioxidants, compounds affecting aldehydes, synthetic androgens, and anti-inflammatory compounds. Among their findings, they discovered that resveratrol, N-acetyl cysteine (NAC), quercetin, and danazol significantly reduced spontaneous and induced DNA damage and cell cycle arrest in human FA cells in vitro. ALDA1 (which promotes aldehyde breakdown) had no effect. They also found that the anti-inflammatory doramapimod decreases genome instability without affecting the cell cycle and improves the FA IPS cells' ability to produce blood progenitors.

Dr. Surrallés presented the results of testing 84 compounds, the majority of which were antioxidants. The lab found 20 potentially effective drugs worthy of further investigation and development. It appears that the screening platforms utilized could be extremely useful in the identification of potential new therapies, which could then be tested in mouse models for in vivo efficacy and safety.

The research presented is in its early stages and has only been performed on cell lines, a pre-clinical model. Nevertheless, researchers involved in this study hope their work will identify candidate drugs that will eventually improve the survival and quality of life of individuals with FA.

Study Shows Transplant Seems to Increase Cancer Risk, Even with Reduced Toxicity Conditioning Regimens



Eunike Velleuer, MD



Ralf Dietrich

Eunike Velleuer, MD, Children's Hospital, University of Dusseldorf, Germany, and Ralf Dietrich, FA parent, German Fanconi Anemia Patients Organization and Research Fund, explored the incidence of oral lesions and signs of malignant transformation in transplanted compared to non-transplanted FA patients. **Dr. Velleuer concluded that transplanted patients show twice as many oral lesions and nearly twice as many cancers as those who have not undergone transplant. Patients who develop cancer following a transplant are generally younger than those who have not undergone transplant.**

Over a period of one year (June 2013- May 2014), Velleuer and Dietrich examined the oral cavities of 300 FA patients from 14 countries at family and patient meetings, home visits, or in hospitals. Their sample included 195 patients who had undergone transplant using various conditioning regimens, and 105 non-transplanted patients. Physicians in

Dusseldorf subsequently analyzed brush samples of all oral lesions for signs of malignant transformation.

Velleuer and Dietrich detected 179 oral lesions in 195 transplanted patients (an average of 0.92 lesions per patient), and 43 oral lesions in 105 non-transplanted patients (0.41 lesions per patient). Samples showing malignant transformation were present in 10 of the 195 transplanted patients (5.1%) and in 3 of 105 non-transplanted patients (2.9%). The median age of transplanted patients with malignant transformation was 28.5 years (range 17.2 to 42.1 years). Three of the transplanted patients with malignant transformation were under the age of 20. The three non-transplanted patients were 30.5, 31.1 and 40.3 years of age at time of cancer diagnosis, all older than the median age of patients post-transplant.

The ultimate goal of performing FA research is to develop new therapies, screening methods and prevention strategies.

This early study suggests that, in spite of reduced toxicity regimens, transplant still seems to increase the risk of malignant transformation in FA patients. This study emphasizes the importance of early and frequent screenings to detect oral cancers, when treatment is most effective.

Editors' note: This data has not been analyzed by a transplant center or by specific variations in regimen and treatment. The conclusions must therefore be regarded as preliminary and subject to further investigation.



FA Guidelines for Diagnosis and Management

The Fanconi Anemia Research Fund is pleased to announce the publication of *Fanconi Anemia: Guidelines for Diagnosis and Management, Fourth Edition*. Published in 2014, the updated guide replaces the third edition.

Every family registered with the Fund has been sent a printed copy of the new *Guidelines*. If you would like additional copies, please use the link on the Guidelines page of our website or contact the Fund. The complete electronic version is also available on the Fund's website.

Results of Multi-Center “Chemotherapy Only” Transplant Study Presented



Parinda Mehta, MD

Parinda Mehta, MD, Cincinnati Children’s Hospital Medical Center, Ohio, presented results of 45 Fanconi anemia patients transplanted at one of five centers using a chemotherapy only preparatory regimen. Dr. Mehta concludes that this chemotherapy only protocol leads to excellent overall survival and low toxicity.

The protocol uses busulfan instead of radiation, with the goal of decreasing short- and long-term toxicity, including secondary solid tumors. Centers participating in this study are Cincinnati Children’s Hospital Medical Center; Memorial Sloan-Kettering Cancer Center, New York; Boston Children’s Hospital; Children’s Hospital of Wisconsin, Milwaukee; and Fred Hutchinson Cancer Research Center, Seattle. The vast majority of patients were transplanted at Cincinnati Children’s Hospital (29 patients) and Memorial Sloan-Kettering (10 patients).

Between June 2009 and May 2014, forty-five patients enrolled in this multicenter study. Forty patients were under

the age of 18; five were 18 or older. Donor source was mismatched related or unrelated donors.

Forty-three patients engrafted. One had a late graft failure and one could not be evaluated because of early relapse of myelodysplastic syndrome. Toxicity included oral mucositis (N=23), hypertension (N=12), and hyperbilirubinemia (N=10). One of the early patients developed hepatic veno-occlusive disease, after which the busulfan level was decreased. No further veno-occlusive disease was seen in the next 42 patients. Acute GvHD (grade I-IV) was seen in four patients, and three patients developed limited chronic GvHD, all of which responded to therapy. Twenty-six patients experienced infection.

Thirty-six of the 45 patients are alive and disease-free at a median follow-up of 21.3 months; one patient is alive but has relapsed. Overall survival is 80%.

Of note, this study included highly mismatched donors, including 4/8 mismatched donors.

Children fared far better than adults in this study. Only one of the five adults survived, suggesting that a better protocol is needed for these patients. A new risk-adjusted regimen will account for specific patient characteristics, including disease status and age.

Long Term Use of Oxymetholone Leads to Stem Cell Exhaustion



Qingshuo Zhang, PhD

Qingshuo Zhang, PhD, Oregon Health & Science University, Portland, Ore., studied 18-month-old Fanconi anemia mice in the *Fancd2* complementation group to assess the therapeutic efficacy of oxymetholone in this animal model and to better understand its mechanism of action. Like their human counterparts, these mice had reduced bone marrow cellularity, red cell macrocytosis (large

red cells), and low blood counts. Chronic oxymetholone treatment significantly improved these hematological parameters by stimulating the proliferation of hematopoietic stem and progenitor cells. But oxymetholone therapy caused acceleration of the cell cycle and ultimately resulted in stem cell depletion.

Dr. Zhang concludes that oxymetholone therapy should begin before the marrow runs out of stem cells and might not provide a permanent rescue of hematopoiesis. Better treatment methods are needed, even in good early responders. He believes that it is extremely likely that danazol (but not resveratrol or NAC) influences blood cell production in the same way as oxymetholone.

Largest Study of Effectiveness of Oxymetholone Therapy Presented



Lisandro Ribeiro, MD

FA patients with bone marrow failure who lack a suitable stem cell transplant donor have often undergone androgen therapy using the drug oxymetholone. An early 1961 report stated that only 50% of FA patients respond to this drug and that the response was rarely long-term.

Lisandro Ribeiro, MD, Federal University of Parana,

Brazil, Bone Marrow Transplant Unit, presented the largest retrospective study ever conducted on the effectiveness of oxymetholone in FA. Unlike the 1961 report, he concludes that oxymetholone is an effective and well-tolerated therapy for most FA patients who develop bone marrow failure and lack a suitable donor, and its use may provide time to search for better donors.

Dr. Ribeiro described 49 FA patients who underwent oxymetholone therapy between 2005 and 2013. Patients had hemoglobin counts of less than 8 g/dL, platelets under 30,000 or an absolute neutrophil count of less than 500 when therapy began. Median duration of treatment was 525 days.

Forty FA patients (82.6%) showed hematological response and were no longer transfusion dependent at a median of three months after the beginning of treatment, and 50% had a response in all three blood lineages. Nine patients achieved hemoglobin levels of 12g/dL and platelets of greater than 100,000, which Dr. Ribeiro considered a “complete response.” Nineteen out of 46 patients with low neutrophil counts at the beginning of treatment had an improvement in the neutrophil count. Twenty-nine patients subsequently underwent stem cell transplant; 25 of these patients are alive and well. Nine patients did not respond to oxymetholone.

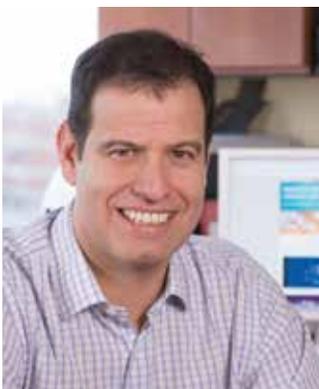
All patients developed variable degrees of virilization and most had elevated liver enzymes. One patient discontinued therapy after developing pelliosis hepatitis.

Androgen therapy is effective and well tolerated in most FA individuals, but better long-term treatment options are needed.

The bottom line is that Dr. Ribeiro’s research suggests a valuable role for androgen therapy.

Editors’ note: Drugs such as danazol and oxandrolone are alternative androgens that cause less virilization and have been effective in improving blood counts in many FA patients.

BRCA1 is a Fanconi Anemia Gene



Roger Greenberg, MD, PhD

Twelve years ago, researchers discovered that the breast cancer susceptibility gene known as *BRCA2* was a Fanconi anemia gene, now known as *FANCD1/BRCA2*. Roger Greenberg, MD, PhD, University of Pennsylvania, Philadelphia, presented information implicating the most common breast cancer susceptibility gene, *BRCA1*, as an FA gene, as well.

BRCA1 had not previously been confirmed as an FA gene because most embryos with homozygous *BRCA1* mutations don’t survive to birth. Dr. Greenberg reported, however, on an adult with two *BRCA1* mutations, multiple phenotypic features of FA, and breast cancer at 23 years of age.

BRCA1 has now been officially named as a Fanconi anemia gene by the HUGO Gene Nomenclature Committee, and is also known as *FANCS*.

The link between *BRCA1* and FA has important implications for adults of child-bearing age who have been identified as *BRCA1* carriers, and for women with early-onset breast or ovarian cancer who have yet to undergo genetic testing.

Gene Discovery Reported



Josephine Dorsman, PhD



Anderson Wang, DPhil

Two scientists, Josephine Dorsman, PhD, Vrije Universiteit Medical Center, Amsterdam, Netherlands, and Anderson Wang, DPhil, The Rockefeller University, New York, reported the discovery of a new Fanconi anemia-like gene, *RAD51*.

The scientists described one 12-year-old and one adult

in this new complementation group. Marrow function is normal to date in both cases, but they noted other anomalies affecting the radius, thumb, spinal cord and in one case, neurological function. Dr. Wang found that *RAD51*-deficient cells in his patient are not sensitive to ionizing radiation, but they are extremely sensitive to DNA crosslinking agents. However, it is unclear how patients with *RAD51* mutations would respond to radiation. Treatments must be tailored to each individual patient.

In contrast with other FA genes, both labs found the mutations in *RAD51* to be *de novo*, in other words the mutations are not present in the parents, but arise as new mutations in the children. Furthermore, these are heterozygous mutations, leading to disease (FA) with a mutation in just one copy of the gene. These are important differences between *RAD51* and other FA genes, with implications for diagnosis and treatment.

Unusual Characteristics May Suggest a Specific Complementation Group



Isabell Rost, MSc, PhD Student

At our September Scientific Symposium, Isabell Rost, MSc, PhD Student, University of Wuerzburg, Germany, discussed an atypical FA patient. The unusual phenotype of this patient suggests that she may belong to one of the rare complementation groups.

Mary (not her real name), was diagnosed with FA at age three. She has physical

anomalies associated with FA—short stature, abnormal thumb, microcephaly, hearing loss, kidney malformation, and diabetes. In addition, she has cerebral atrophy, visualized on an MRI, a feature occurring at unknown frequency in older individuals with FA. Mary also has some skin sensitivity to sunlight and, although in her late 40s, has never had severe bone marrow failure, an abnormal clone, or a malignancy. Molecular studies placed her in the *ERCC4/XPF/FANCO* complementation group. Two other individuals with FA are in this group: one of them also has sensitivity to sunlight; the other died at age four. Patients who have not yet been assigned to a specific group and who have sunlight sensitivity should be tested for mutations in *FANCO*.

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 Laura Hays as soon as possible after diagnosis and before treatment at laura@fanconi.org or 888-FANCONI. Laura will coordinate your participation with David Wong, DMD, DMSc, the study's principal investigator. For more information, visit Research Highlights on our website.

Town Hall Stimulates Lively Discussion and Controversy



Eva Guinan, MD

The 2014 Scientific Symposium concluded with a Town Hall, giving all participants an opportunity to review, synthesize, and look to the future. Eva Guinan, MD, Dana-Farber Cancer Institute, Boston, and member of the Fund's Scientific Advisory Board, chaired the Town Hall and asked thought-provoking questions that encouraged

healthy discussion and debate. Topics ranged from clinical to molecular, but an important theme was implications for Fanconi anemia patients from the new findings presented during the conference.

Joel Greenberger, MD, University of Pittsburgh Cancer Institute, Pa., made an impassioned case for re-educating radiation oncologists to individualize their treatment of FA patients. While some FA patients are hypersensitive to radiation, others are not. It's important to use a therapeutic trial on a patient to determine the most appropriate treatment. This is important information for patients to share directly with their doctors.

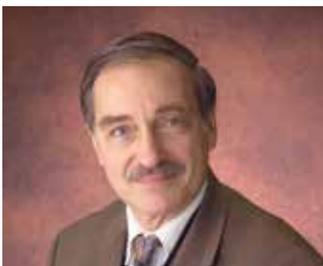
The FA patient's perspective was heard when Christopher Byrd, JD, Fanconi Anemia Research Fund board member, spoke about the importance of the work done by Eunike Velleuer, MD, University of Duesseldorf, Germany, and Ralf Dietrich, German Fanconi Anemia Patients Organization and Research Fund. Dr. Velleuer and Dietrich see patients around the world, inform them about oral health, and use brush samples of visible oral lesions for their studies on head and neck cancer. Byrd called their approach "helpful, realistic, and empowering."

Markus Grompe, MD, Oregon Health & Science University, Portland, and Laura Hays, PhD, Fanconi Anemia Research Fund, offered opposing views on whether it's time

for an Alda-1 type drug to be tried within humans. Alda-1 stimulates the production of an enzyme that helps break down aldehydes in the body and makes them less toxic (see Family Newsletter #56 about aldehydes). Dr. Grompe advocated for more time to do trials in animals. Dr. Hays noted that the Fund is partnering with Aldea Pharmaceuticals to offer a clinical trial of a compound similar to Alda-1 in the near future.

Many Symposium participants debated the nuances of the definition of FA. Should two newly-discovered genes be considered FA genes or FA-like genes? Is FA a spectrum? While there were no definitive answers reached, the HUGO Gene Nomenclature Committee has officially designated *BRCA1* as *FANCS*, although *RAD51* has not been designated as an FA gene. While this may seem like splitting hairs, these definitions impact many aspects of research such as the availability of funding, the eligibility of patients for clinical trials, and the focus of scientific investigations.

Throughout the Symposium, presenters were asked to describe the implications of their research for patients. During the Town Hall participants were reminded of the real-world context and impact of their work. FA patients and families frequently face challenging medical choices such as using androgens vs. going quickly to transplant, or whether to use total body irradiation (TBI) during transplant or only chemotherapy. How can they make the best decisions that take into account the most up-to-date information? Those who have the ability to travel to an FA center benefit from the knowledge and experience of a range of specialists coordinating the care of an FA patient. But worldwide, there are many places with limited resources and without FA centers. The FARF continues to play important roles in connecting families with information and specialists, ensuring those specialists share the latest information at scientific meetings, and by funding the research that continues to advance our understanding of the disease and improve treatments.



Joel Greenberger, MD



Christopher Byrd, JD



Markus Grompe, MD



Laura Hays, PhD

Inhibiting PARP Proteins: A Possible Therapy For FA Individuals with Head and Neck Tumors



Susa Wells, PhD

It is crucial to find new treatments for Fanconi anemia patients with head and neck cancers, because at present the five-year survival rate for these patients is less than 20%. Problems involve both the toxicity of present therapies and the high rate of recurrence. PARP inhibitors may

offer one possible solution.

Anne Lombardi, MD, in collaboration with Susa Wells, PhD, both from Cincinnati Children's Hospital Medical Center, Ohio, stated that, although FA cells are sensitive to chemotherapy, FA cancer cells develop a type of resistance due to hyperactivation of PARP proteins. PARP proteins bind to damaged DNA and activate DNA repair pathways. PARP hyperactivation may be one method by which FA cancer cells overcome FA pathway loss and become resistant. Therefore, the amount of therapy FA patients can tolerate is

probably insufficient to kill enough cancer cells to prevent recurrence.

Knowing this may lead to a new therapy for FA head and neck cancer patients. PARP inhibitors, drugs that prevent the proteins from activating DNA damage repair, could lead to the death of cancer cells. FA cancer cells were sensitive to these drugs in laboratory experiments.

Many questions need to be answered before PARP inhibitors can be used in FA patients. All FA cells in the body, including blood cells, rely on PARP to repair DNA. Therefore, PARP inhibitors can affect non-malignant FA cells in addition to cancer cells. Effects on the bone marrow may be fewer in individuals who have non-FA bone marrow due to transplant, but safety of the drugs must be investigated in the context of FA before they can be used in either transplanted or non-transplanted patients. Local delivery of PARP inhibitors to cancer cells only would be the ideal therapy.

Despite remaining questions and challenges, this discovery is an important one for FA patients, as it may improve survival of FA individuals with head and neck cancers.

27th Annual Fanconi Anemia Research Fund
SCIENTIFIC SYMPOSIUM

SAVE THE DATE!

September 17-20, 2015
Toronto, Ontario

Provocative Cases Presented in New Session

A new session highlighting provocative case studies was introduced at the 2014 Scientific Symposium. The idea behind this session was that scientists and physicians could grasp a great deal about Fanconi anemia by learning about the wide range of medical issues that characterize individuals with FA. The Fund invited treating physicians to submit

provocative case studies for report at the meeting. Eleven cases were selected for oral and/or poster presentations. Participant evaluations showed that this session was extremely well received; many suggested it should be continued. Five of these presentations are summarized here.

Atypical Presentations of *FANCD1/BRCA2* In Two Individuals



Kimberly Rickman, MD-PhD student

An individual with the *FANCD1/BRCA2* complementation group often has a distinctive phenotype from other Fanconi anemia groups. Leukemia and specific solid tumors have earlier onset and occur at higher rates. There is also a higher incidence of VATER congenital anomalies. At

the cellular level, high levels of chromosomal damage occur spontaneously and in response to DNA crosslinking agents. Kimberly Rickman, MD-PhD student, The Rockefeller University, New York, presented an atypical case of two siblings with mutations in both *FANCD1/BRCA2* gene alleles from the International Fanconi Anemia Registry.

Both siblings had congenital abnormalities at birth, including skeletal, kidney, gastrointestinal, and cardiac anomalies, as well as a cleft palate and microcephaly, but did not develop any of the typical early childhood

malignancies of this complementation group. The patients, now young adults, have not progressed to any hematological abnormalities or solid tumors.

When the entire DNA of these individuals was examined with whole exome sequencing, it revealed two *FANCD1/BRCA2* mutations. The specific mutations were an “exon 11 frameshift mutation” that causes early truncation of the protein, and a “missense mutation in exon 20” which codes for a DNA binding domain. Lymphoblast cells derived from the individuals showed typical sensitivity to cross-linking agents, but only displayed intermediate chromosomal breakage levels when treated with the crosslinking agent DEB.

It may be helpful to further test the cells of these patients to determine if they are sensitive to other DNA damaging agents and if they are deficient in homologous recombination, a procedure the cell normally carries out as part of the repair of some types of DNA breaks.

Any individual diagnosed in this complementation group should have early and frequent cancer screening. Individuals presenting with atypical FA phenotypes should be screened for *BRCA2* mutations.

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.

Expanding the Clinical Paradigm of *FANCD1/BRCA2*



Kara Maxwell, MD, PhD

Kara Maxwell, MD, PhD, University of Pennsylvania, Philadelphia, described a young woman who had developed multiple basal cell carcinomas by age nine. Though controlled with surgical removal, repeated instances of skin cancer continued to develop.

When the patient was 23, her dermatologist referred her to Dr. Maxwell and Katherine

Nathanson, MD, also University of Pennsylvania, for further testing. The patient was overweight and presented with high blood pressure, multiple café au lait spots, and small bones. She had a normal complete blood count and normal bone marrow, with no evidence of an abnormal clone. The patient's older sister had died of cancer as a child. Suspecting a genetic cancer predisposition, her team of physicians monitored her carefully for cancer. At age 24, a colonoscopy revealed 13 polyps, one of which was an adenocarcinoma. Surgery, a

prophylactic total colectomy, was successful and she recovered well, but she continued to require removal of polyps from her remaining rectal pouch.

When the patient returned two years later, Drs. Maxwell and Nathanson performed whole exome sequencing, which revealed biallelic mutations in *BRCA2*. They called in the patient's father and siblings to more thoroughly investigate the patient's family history. They discovered that her older sister had developed multiple cancers including Wilms' tumor, acute lymphoblastic leukemia, and medulloblastoma. This sister succumbed at age nine to acute myeloid leukemia. Three other family members also had cancer, including both prostate and breast cancer.

Further testing confirmed the diagnosis of FA. In 2013, a screening brain MRI showed a possible brain tumor. The patient underwent brain surgery and the lesion was determined to be a developmental abnormality. In 2014, she presented with abdominal pain. Imaging revealed widely metastatic small cell neuroendocrine carcinoma, an aggressive and terminal cancer. Despite tolerating four cycles of modified doses of chemotherapy, she died of cancer at the age of 28.

Case Study of a *FANCD1/BRCA2* Family



Karel Svojr, MD, PhD

Karel Svojr, MD, PhD, University Hospital Motol, Prague, Czech Republic, reported on three siblings with FA who developed cancer at very young ages. Their mother suffered from breast cancer in her 30s; the father had no history of cancer. Three of the four children of this couple were small for their ages, had microcephaly, and had *BRCA2* mutations.

Child #1 was diagnosed at age one with T-cell lymphoblastic leukemia. The child was given chemotherapy, and achieved a remission at day 33. Toxicity included severe

pancytopenia and sepsis. During maintenance therapy, the child developed secondary acute monocytic leukemia. The parents refused further treatment and the child died 18 months after initiation of treatment.

Child #2 was diagnosed at age three with Wilms' tumor, which was treated with the chemotherapeutic drugs vincristine and dactinomycin. This child is now in remission and has not experienced additional complications.

Child #3 was diagnosed with a large brain tumor (medulloblastoma) at four years of age. The tumor was surgically removed, and the child was treated with vincristine, doxorubicin, and methotrexate, leading to severe pancytopenia and infection. The child recovered from these complications but relapsed after only six weeks, leading to another round of surgery and chemotherapy. The cancer returned again after five months, leading to the child's death.

Atypical FA Family Highlighted by Multiple Pregnancies and Son with AML



Neelam Giri, MD

Neelam Giri, MD, National Cancer Institute, Rockville, Maryland, presented the cases of three close relatives with Fanconi anemia, each raising a provocative question and challenging our understanding of this genetic disorder.

Patient #1: This woman presented with FA in her 40s. She had a bone marrow transplant (BMT) from an identical HLA-matched

sibling, but died just two weeks after the transplant. Dr. Giri's question: Should the same treatment guidelines apply to adults as well as children, since the risks associated with BMT are higher in older patients?

Patient #2: A sister who was tested as a potential donor for Patient #1 was also found to have FA. She was in her 50s at

the time of this diagnosis. The chromosomal breakage test was "slightly abnormal" in her blood but was diagnostic of FA in skin fibroblasts. She was diagnosed as mosaic. Her bone marrow cellularity was normal, but she was found to have a cytogenetic clone in her bone marrow. She currently has slight cytopenia. Patient #2 has had five normal pregnancies resulting in normal births. She has no clinical features suggestive of FA. Although she has an abnormal clone, the appearance (morphology) of her bone marrow cells is normal. Dr. Giri's question: Does this patient meet the definition of myelodysplastic syndrome because of the presence of a cytogenetic clone in her bone marrow?

Patient #3: The son of Patient #2 is heterozygous (a carrier) for FA, having a splice mutation in *FANCA*. At age 30, this patient developed acute myelogenous leukemia (AML), and underwent a bone marrow transplant. He relapsed and subsequently died. Dr. Giri's questions: Does heterozygosity increase the risk of AML? And is this the first case of an FA carrier to develop AML?

Egg Preservation For Young Females With FA



Marc Bierings, MD

Marc Bierings, MD, PhD, Utrecht University Children's Hospital, Utrecht, Netherlands, presented the case of an 18-year-old woman who was recently diagnosed with Fanconi anemia, but presented with only slight thrombocytopenia. She was struggling with two important questions: 1) if and when to proceed to transplant, and 2)

whether or not to preserve her oocytes for future pregnancy.

With respect to the second question, a female may experience early menopause and reduced fertility after transplant-related chemotherapy. While not true in every case, transplant can be catastrophic for fertility. This young woman did not want to take that chance and did not want alternatives to having her own biological child such as oocyte donation, a gestational carrier, or adoption.

There are ethical considerations and unknowns with oocyte preservation, and doctors' attitudes about it can vary. Is it ethical to submit someone to painful surgery to

extract their eggs if it is unknown how likely it is to yield a future pregnancy? It is unclear whether FA oocytes survive cryopreservation in all young adult women. Another consideration is maternal life expectancy, which should be discussed with the patient. However, it is not clear whether the matter should be discussed at the time of preservation or at the time of fertilization and whose responsibility it is to instigate the discussion.

Other questions arise. Should all females have their eggs preserved before transplant regardless of their age? Currently, only menstruating women can have their oocytes preserved, and beforehand the entire ovary must be cryopreserved. Whether this technique works with an individual with FA is unknown. Should the parent be allowed to make the decision for a young girl and how young is too young?

In the case of this 18-year-old, medical professionals involved with her care did all they could to preserve the chance for this young woman to become a mother. It is recommended that all women undergoing transplant have a discussion with their doctors regarding fertility options as part of the standard of care, including counseling to cover the many issues involved.

Supporting Research by Participating in a Gene Therapy Clinical Trial

By William Bloxom



Will Bloxom (FA, 22), first FA patient in the world to undergo gene therapy with a lentiviral vector, pictured with Pamela Becker, MD, PhD, Hans-Peter Kiem, MD, PhD, and Jennifer Adair, PhD.

I will begin by thanking everyone who was able to donate to the Fanconi Anemia Research Fund this past year. In many ways Fanconi anemia is a rather “hands off” condition. Besides being germ- and injury-conscious there are very few things that the average parent or patient can do to actively combat this disease. It can be rather disheartening at times. The one area where you do have power, however, is in research.

A little background about myself is in order. I was born in 1992 and diagnosed with FA in 1997. I was blessed—or cursed from another perspective—with a rather mild form of the disease resulting in few physical abnormalities and low but stable blood counts. I still spend my fair share of time at the hospital, but at 23 years old I’ve not needed a bone marrow transplant and had not received a blood transfusion

until this past October. I graduated last May with a degree in Communications, and I would love to pursue a career making games. However, I put my post-graduate job search on hold to participate in a gene therapy clinical trial at the Seattle Cancer Care Alliance (SCCA) in Seattle.

As many of you are already aware, past attempts at gene therapy for FA patients using retroviral vectors have proved problematic. Last May though, I learned about a new gene therapy clinical trial using lentiviral vectors. Past research has shown that lentiviral vectors are a more suitable option for gene therapy, and they have been successfully used in Europe to treat other diseases. I did some research and decided that there would be no better time than just after graduation for me to help the research along, so I enrolled. After some preliminary testing, I was approved for the trial and flew out to Seattle from my home in Maryland in September.

The procedures involved in the trial were rather pedestrian in nature, consisting of a bone marrow harvest and then a simple re-infusion of the gene modified cells. Although both went off without a hitch, I will say that enduring a bone marrow harvest while having already depleted blood counts was rather frightening. I received an autologous blood transfusion directly after the withdrawal, but it still took nearly a month before I was feeling back to my old self.

This experience, while not the most pleasurable, is probably one of the most meaningful things I will do in my life. I did not pursue a career in medicine or biology as I figured I deal with health problems enough on a personal basis. Entering this trial, though, has allowed me a chance to give back to all those who are suffering more debilitating forms of the disease. I encourage everyone to keep abreast of research opportunities and to participate when you feel so inclined. These trials are the frontline in the fight. It is in these trials that the science and medicine are being pushed forward.

I would like to take this opportunity to thank all the doctors and staff out at the SCCA. I’ve been seen by many doctors at prestigious hospitals including Johns Hopkins and Memorial Sloan Kettering, and can therefore say with some authority that the little SCCA clinic is second to none.

If anyone would like to contact me about more specific elements of the trial you can find me on Facebook at William Bloxom or you can email me at wbloxom@comcast.net.

For information on the clinical trial: <https://clinicaltrials.gov/ct2/show/NCT01331018>

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. Post-mortem tissue donations are also invaluable in helping us understand and treat the cancers that affect so many individuals with FA.

For more information, contact Laura Hays at laura@fanconi.org or 888-FANCONI.

Gene Therapy for FA: An Update

The Fifth International Fanconi Anemia Gene Therapy Working Group Meeting was held in October in Milan, Italy. The meeting was hosted by Luigi Naldini, MD, San Raffaele-Telethon Institute for Gene Therapy, Milan, and again jointly sponsored by the Fanconi Anemia Research Fund and Fanconi Hope, a national charitable trust in the United Kingdom. Eighteen scientists and clinicians from six countries, including Italy, Spain, United Kingdom, and Germany, attended the productive meeting along with two representatives from Fanconi Hope. The meeting was

expertly moderated by Jakub Tolar, MD, PhD, University of Minnesota, Minneapolis. Highlights include Jennifer Adair, PhD, Fred Hutchinson Cancer Research Center, Seattle, reporting on the first FA individual treated with the newly established and improved gene therapy protocol developed by the Working Group, and Bob Dagleish and Thomas Carroll, MD, both from Fanconi Hope, presenting on what questions FA families may ask when deciding between gene therapy and bone marrow transplant.

Congratulations!



Patrick and Alissa O'Toole recently adopted Makayla Ann who just turned one year-old. Makayla joins big brother, Tyler, to make a happy family of four.



Kendyl Biby (FA) and Michael Green were married on October 18, 2014.

24th Annual FARF Fanconi Anemia Research Fund Family Meeting Camp Sunshine, Casco, Maine



June 25-July 1, 2015 for first-time families only • June 26-July 1, 2015 for returning families

Questions or need financial assistance for travel?

Please contact Laura Hays at laura@fanconi.org or 1-888-FANCONI.

Taking Risks



Our names are Aliza and Flavio Canonica and we are the lucky parents of two cute and lively children: Sofia (11) and Plinio (6). We live in an Italian-speaking village in Ticino, Switzerland.

Sofia was born with severe abnormalities and wrongly diagnosed with Holt-Oram syndrome. The genetic doctor told us it was a very rare syndrome

strictly related to Sofia, so that the likelihood of having another child with the same disease would be very small. The diagnosis seemed to be the right one: Sofia had no thumbs and multiple heart defects. Yet, we found nothing about kidney abnormalities in Holt-Oram syndrome, which Sofia also had. For this reason, my husband was skeptical about the diagnosis.

Sofia underwent three operations per hand. After the last operation, we were happy and thought that the worst time in our life was over. We did not imagine that our destiny could be even worse.

Sofia was well and growing like other girls, although a little smaller than average. At five years old, she showed a lot of hematomas on her skin. We were worried, but the doctor was not. We had full trust in him, but I wondered what the black marks on her skin were.

Sofia was growing up smart, full of energy and life, and loved by her friends. We felt ready for another child.

In 2008, Plinio was born. He also showed some health problems, despite his healthy and strong appearance. At the age of 2 months, he had surgery for hiatal hernias and a gastroscopy because of blood in his milk regurgitations. It was very hard for me to accept that something was also wrong with him. It was too much to bear, and we still didn't know the right diagnosis for Sofia. Plinio also had frequent nosebleeds and used his hands in a peculiar way, but we thought he was just copying his sister.

A genetic screening finally showed that Sofia did not have Holt-Oram syndrome. She was selected for a German study about a Holt-Oram-like syndrome. In May 2012, we went to Zurich for the follow-up of this study. They asked us to bring Plinio. The new genetic doctor quickly noticed

Plinio's thumbs. She was quite sure that Plinio had the same disease as Sofia.

Soon they confirmed the diagnosis for Sofia: Fanconi anemia. Our first reactions were tears, desperation, fear, panic. I didn't want to know too much about the disease because it was too much to bear. Yet, after a few days we began to search for help. A few months later, we received another call from the hospital in Zurich: the diagnosis for Plinio was the same: FA.

In June 2013, we met Ralf Dietrich, Eunike Velleuer, and Amy Frohnmayer in Duesseldorf. After months of loneliness and deep despair, we were not alone. We had met people who could share this experience with us, and help us understand.

Sofia's platelets were dropping and we were too scared to think about a bone marrow transplant. At our first FA family meeting in Germany that November, we spoke with Dr. Boulad, who convinced us to try androgens first. Sofia started taking danazol and her platelets are now stable.

Last summer we went to the Family Meeting at Camp Sunshine. It was a real dream for me and my husband. Having two children with FA is a tragedy. However, we have tried to find the positives. We meet very special people from all over the world, people with whom we can share something very important: the love for our children, for life, and for the present time. We enjoy every single day and don't complain about little things anymore.

In September, Sofia began secondary school. She is a good student, enjoys music, horseback-riding, and being among friends. Plinio began primary school and is a very kind, sweet boy, loved by his friends and teacher. Despite frequent nosebleeds and a lazy eye, Plinio is fine at the moment.

Last May, we founded the Swiss Fanconi Anemia Association (ASAF) in order to raise funds and awareness. We know that our battle is tiny, since it concerns a very small number of patients in the world, but for us it has become the reason of our existence. This disease has opened our eyes to the real meaning of life, the pleasure of small things, of falling asleep in the evening united under the same roof.

We decided to tell our story because, in the most difficult moments of our lives, we were comforted by reading the stories of other families. Hopefully, we too, in our small way will comfort others and contribute to supporting research. We are very grateful to all the FA associations in the world, who help to bring doctors and patients closer, giving hope to people suffering from FA. If you take risk, you may win or lose, but if you don't, you always lose.

Learning How to Dance Life

By Amy Frohnmayer



Tell me, what is it you plan to do with your one wild and precious life? (Mary Oliver)

If you were to dance your life, what would it look like? A close friend posed this question recently and despite a host of hip hop

and ballet classes that have demonstrated unfailingly my lack of skill on the dance floor, I delivered. I summoned the chronological pieces of my story and danced them all...the carefree spirit of childhood, the grief, the joy, the anger, the uncertainty, the love...

Needless to say, it was an eclectic dance. My journey with FA, like that of so many others, has not been free of emotional trials. My two sisters died of this disease at ages 12 and 24. The threats of a bone marrow transplant and cancer diagnoses have loomed like shadows. Trusting the future enough to make long-term plans remains a challenge I work, with intention, to overcome again and again.

And. My life is extraordinarily beautiful.

FA has been my greatest teacher. Through the fires of fear and loss, and the lens of a condensed time perspective, this illness has made me inescapably aware of the preciousness of life, and it has motivated me to do everything within my power to live fully and well.

For me, caring for the body and nourishing the spirit go together hand-in-hand in the process of crafting a balanced, healthy, and deeply satisfying life. I run almost every day because it helps me connect with nature and reminds me that regardless of future uncertainties, I am powerfully alive *now*. I note foods that have been implicated as potent antioxidants and anti-inflammatories and keep a list of these on my fridge as a reminder. I soak my mouth with ginger and black raspberry mixtures because these have demonstrated anti-carcinogenic properties. Though they are disruptive, I stay on top of medical appointments because they are just too important to skip. I infuse tools, such as meditation, self-compassion, and creativity, into my life to combat the toxic effects of stress.

Finally, I make meaning. FA has taught me that life is fragile. As a result, I care a lot about discovering, and living a life grounded in, the themes that feel most important to me. Right now, these are appreciation of beauty, nature, gratitude, love and generosity, and being deeply present. I also believe that we are in charge of how we measure miracles. The trick is finding little ones scattered through every day, from coffee-infused morning sunrises to connecting deeply with another person.

As I grow older, I am understanding with inescapable clarity that life with FA, as with any life, will never be devoid of loss and pain. My heart has broken so many times that I have found no other choice but to soften in response to the painful things—to accept them as darkness that completes the palette of an unbelievably colorful life. And at the same time, I owe it to myself, and to this world, to pursue with all my heart the things I can do to make this life beautiful. I will never be able to control all of the music. I am simply learning how to dance this life with a little more grace.

In Loving Memory

“For some moments in life there are no words.”

Ben Hilton.....7/25/84 - 11/8/14

Nikelle Schaefer.....1/10/71 - 12/20/14

Piper Bentley6/24/05 - 1/13/15

Anthony Arroyo2/23/98 - 2/13/15

Boikanyo Rampa.....6/7/06 - 3/14/15

Alicia Reed.....11/18/02 - 3/19/15

Fear of Finding Community

By Rachael Alaniz



I am the mother of two beautiful children. Aria is my four-year-old living with Fanconi anemia and Daisy is her five-year-old big sister. Shortly after Aria's birth, we realized Daisy wasn't developing normally and subsequently

learned she has a random genetic mutation called a CASK mutation. My children are beautiful and complex. They're a different kind of perfect, and I treasure each day my husband and I get to enjoy with them. I've spent the last few years connecting with families who I feel understand the issues affecting our daily life; deaf-blindness and profound cognitive delays for Aria and autism for Daisy. It wasn't until recently that I introduced our family on the Fanconi Anemia Research Fund's private family support group on Facebook. It wasn't that I didn't know FARF existed or that I was unaware of a support group or a camp we could attend. I waited so long because I was afraid. I was afraid of finding community in a diverse population plagued by tragic stories of child loss. I now realize my fears were unfounded.

In considering joining the Family, I was paralyzed by the fear of countless questions. Will people understand that, when I think of FA, the last thing I consider is bone marrow? To Aria, FA is an exhausting list of physical deformities impacting the ways our family goes about daily life. For us, FA is deaf-blindness closely followed by uncontrolled seizures, painful enteral feedings, upper and lower limb deformities, and kidney disease. FA is wheelchairs, IV poles, and accessibility issues. It's selling the dream home we purchased while pregnant with our first child in favor of a handicap accessible home; a home in which you'll learn to live a different kind of dream. FA is the knowledge that I'll never hear my child say "I love you" and hope that she understands how fiercely she is loved even though we've yet to find a reciprocal communication system that would prove she understands.

When I considered joining the ranks of other FA families I felt the fear of self-inflicted alienation. I wonder if I'm alone

in my feelings of marginalization when FA receives national attention. Not seeing a child even remotely resembling mine on these broadcasts stings, but not as bad as when people question our family if it's even the same disease. The need always to explain that our journey is simply different than that of those featured by the media is an emotionally exhausting one. I wonder if people will think of me as ungrateful for the awareness and funds raised simply because I wish the diversity of the disease were better represented. I feared the inevitable bone marrow transplant conversation, and explaining why we are not considering transplant for our child to those who feverishly search for a donor for theirs. I feared people wouldn't understand that, while I often feel like we drew the FA short straw, I also understand how lucky we are to have a beautiful daughter still living with us and realize those whose children have lost their FA battle would give anything for each day I have with mine.

In doubting that I would find community within the diverse FA population, I feared no one would understand our journey, in the same way I feel ill-equipped to understand theirs. But then I realized that even with my inability to understand the journey of those experiencing the day-to-day of FA differently than our family, I still feel a tremendous amount of compassion for them as I lament alongside them. I decided if I can feel compassion and grief for those whose experiences differ from mine, they could probably feel the same for my family.

So, I dipped my toe in the FA pool of support. I discovered that all of my fears were unfounded and my feelings of alienation self-imposed. I found that, while all those who contacted me privately included a discussion of bone marrow transplantation, I received an outpouring of support and understanding when I explained the path we have chosen for Aria's care. I discovered a loving community welcoming my daughter with open arms. To my surprise, I realized that the severity of Aria's physical presentation might make me an asset to the community, having experienced much of the medical problems discussed online. I found that I'm neither alone nor misunderstood. I found that Aria is already loved.

After dipping my toe into the FA pool, I am surprised that I'm eager to jump in head first and meet some of my FAmily at the Family Meeting this summer. Thank you for immediately making me feel like a member of the FAmily.

Touchdown, Team FA



The Fisher family

The New Year's Day Rose Bowl in Pasadena, Calif. was unique this year in more ways than one. The game was a meeting of the #2 University of Oregon Ducks and the #3 Florida State University

Seminoles in a semi-final of the inaugural College Football Playoff between the four top teams. Both of these teams have a connection with Fanconi anemia, and the high profile game helped bring awareness and much-needed funds towards finding a cure.

Dave Frohnmayer, co-founder of the Fanconi Anemia Research Fund with his wife, Lynn, led the University of Oregon as President from 1994 to 2009, after serving as the Dean of its School of Law. The Frohnmayers have a daughter, Amy, 28, with FA and have lost two other daughters to the disease. Jimbo Fisher, head coach of the Florida State University football team since 2010, and his wife, Candi, have a 9-year-old son, Ethan, who was diagnosed with FA less than four years ago. Soon afterwards the Fishers founded the Kidz1stFund to raise awareness and funds to fight FA.

Over the past quarter century, the Fanconi Anemia Research Fund has raised more than \$29 million to educate and support affected families and has funded 202 research projects towards better treatments and a cure. In just under four years, Kidz1stFund has donated \$2.8 million to the University of Minnesota Masonic Children's Hospital, the largest treatment center for FA patients in the U.S.

With the big game pending, the Frohnmayers and the

Fishers joined forces in support of their shared goal. "It's a terrible fate our families share, but one we use to fuel our fight against FA," coach Jimbo Fisher said. "With the nation's attention on the Rose Bowl, we have both an opportunity and responsibility to raise awareness for a much more critical victory in our sights."

In the spirit of the game, the Fanconi Anemia Research Fund and Kidz1stFund together organized a friendly competition in which both sides win. The Touchdown Fan Challenge allowed supporters to pledge money for each touchdown made by their favorite team. Proceeds pledged to the UO Ducks went to the Fanconi Anemia Research Fund. Proceeds pledged to the FSU Seminoles went to the Kidz1stFund. The Challenge was highlighted in newspapers, TV interviews, and social media, and fans signed on.

Both teams are to be congratulated for their outstanding seasons. As the clock ran out in the fourth quarter, the Oregon Ducks' eight touchdowns had not only led them to the Rose Bowl win, but raised a phenomenal \$12,548 through the Touchdown Challenge for FARE. In addition, the Fund received an anonymous \$20,000 donation for a grand total of \$32,548. A huge thank you to the fans of both teams who pledged support for the Fanconi Anemia Research Fund and Kidz1stFund! You provided a win for all of us looking for a cure for Fanconi anemia.



The Frohnmayer family

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!

Chellie's Challenge



Marcella “Chellie” DiSandro died from complications of Fanconi anemia last September. She was 28. Less than two months before she died, “Chellie’s Challenge” was created to honor Marcella’s fight with FA and raise funds for the Fanconi Anemia Research Fund. In notifying the

Fund, Marcella’s aunt, Laura Robertson, wrote, “Marcella is the strongest person I know and in her final stages wanted to give something back for future Fanconi anemia patients. She has been so overwhelmed by the outpouring of generosity and care from everyone!” The online “Challenge” told Marcella’s story and raised an amazing \$51,445. Here is the story that touched so many.

Sadly, cancer first touched Marcella’s life when her older sister, Adriana, died at the age of nine from leukemia, after battling cancers for all of her young life. Marcella was only three years old at the time. Her family history with cancer is a heartbreaking one. Her own journey with the disease also started at a young age when she developed an extensive form of skin cancer. She had to be extremely careful in the sun and religious about checking her skin. Though controlled with surgical removal, the instances of skin cancer continued to develop despite her diligent efforts. And so Marcella raised the question: Why?

In 2010, Marcella took her question to her doctor who suggested a possible hereditary link between her and her sister’s cancers. She encouraged Marcella to pursue genetic testing which brought her to the team at the University of Pennsylvania.

Thorough testing led her doctors to determine that there was undoubtedly a genetic link, but they had yet to pinpoint a specific disorder. Based on their findings, they speculated that Marcella would encounter at least five different cancers in her life. They suggested that she undergo bi-yearly, preventative body scans to detect cancer as early as possible. Now her real journey with cancer began.

At the age of 24, these scans were justified when colon cancer was detected. Miraculously, surgery was successful and she recovered well. Marcella could now add survivor to her list of attributes. She felt lucky and scared at the same time about what the future would bring.

As Marcella continued to carefully monitor her health, her doctors continued to seek answers for her condition. After further genetic testing, the diagnosis of Fanconi anemia was finally attributed as the link between Marcella’s condition and that of Adriana’s. Her family was faced with the prospect of loss again. Fanconi anemia is a genetic disorder that primarily affects bone marrow and the reparation of cells in the body. Individuals with this disorder can develop a variety of cancers throughout their lives and have shortened life spans. Fighting FA was now added to Marcella’s list of challenges.

The next few years were filled with numerous procedures, including frequent medical scans and surgeries. She faced her challenges one day at a time. One such scan revealed an abnormality in her brain that required her to undergo an invasive, awake craniotomy in June 2013. Her bravery was incredible! She recovered and went back to work. Again, surviving another battle.

Despite diligent, preventative measures and frequent monitoring, in 2014 she was given the heartbreaking diagnosis of small cell neuroendocrine carcinoma, an aggressive and terminal cancer. She has fought this final cancer with continued bravery. By choosing to undergo chemotherapy treatments Marcella has given the greatest gift to everyone around her—time. Time to love her, time to spend with her, and time to watch her bravery shine through at insurmountable levels.

Treatments have made Marcella very sick and after four months of aggressive chemotherapy and many hospital stays, her doctors feel that her body can no longer handle further chemo. She recently made the decision to start in-home hospice and is being cared for by her family. As always, love, laughter, family, and friends surround Marcella during this final journey.

Marcella has one last fight to fight and needs your help. She would like to leave a legacy behind by raising money for this rare genetic condition. Her favorite quote “Everybody dies, but not everybody lives” is so well demonstrated by this final expression of love to help those who might have this future fight with FA.

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

Family Fundraising Efforts 2014

In 2014, FA families raised an impressive **\$1,630,267** for the Fanconi Anemia Research Fund to support families and research. In all, 194 raised funds, with 99 raising more than \$500. More than 88 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 FA. Thank you to the FA families listed below for their fundraising efforts in honor or memory of loved ones.

\$740,000 and up

Dave, Lynn, and Amy Frohnmayer

\$100,000 - \$190,000

Kendall & Taylor Atkinson Foundation w/ the Nash and Atkinson Families
Kevin and Lorraine McQueen

\$39,000 - \$79,000

Peg Padden
Glenn Shearer
Steve and Jennifer Klimkiewicz
Robert and Barbara Capone

\$20,000 - \$26,000

Todd and Kristin Levine
Dan and Nikki McCarthy
Mark De Groot and Hanneke Takkenberg

\$15,000 - \$19,999

Orion and Lisa Marx
Kerrie Brannock

\$10,000 - \$14,999

Gerard and Cynthia Vandermeys
Pedro and Marina Ravelo
Emily and Neil Robison
Juanita and Ron Arroyo
Brian Horrigan and Amy Levine
Charles and Katy Hull
Bob and Andrea Sacks

\$5,000 - \$9,999

David and Mary Ann Fiaschetti
Jimmy and Jenny Armentrout
Ryan and Becky Brinkmann
Chris and Jennifer Branov
Deane Marchbein and Stuart Cohen
Jack and Lisa Nash
Patti and Mike Hilbert
Peter and Janice Pless
Mark and Diane Pearl
Rachel Altmann and Tyler Morrison

George and Kathryn Reardon
Joseph and Nancy Chou
John and Karilyn Kelson

\$1,000 - \$4,999

Nigel and Ann Walker
Michael and Joanna Peros
Daniel and Melinda Coleman
Israel and Mary Jo Becerra
Alan and Rachel Grossman
Louis and Theresa Viola
Bill and Connie Schenone
Andre Hessels and Rutger Boerema

Ron and Fredi Norris
David and Kelly Dunnock
Donald and Danielle Burkin
Mark and Linda Baumiller
Ron and Elesha Schaefer
Ben and Stephanie Griggs
Kaps for Kendall
William and Mary Underriner

Lori Petersen,
Jeff and Beth Janock
Darrel and Kalani DeHaan
Owen Hall and Margaret Kasting
Gregory and Lynnette Lowrimore
Ian and Tricia Mitchell
Chris and Susan Collins
Sheila Meehan
Susan Ortiz
Tony and Lina Nahas
Tim and Mary Ann Lana
Michael and Kim Williams
Bryan and Karen Siebenthal
Richard and Dolores Satterlee
Matt and Diane Senatore
Mike and Beth Vangel
Richard and Tena Bosen
Lorraine O'Connor
Randy and Nancy Bloxom
Jeffrey and Donna Boggs
Jim and Holly Miranda

John and Kim Connelly
Egil Dennerline
David and Kim Chew
Sejin Kwon and Jee-Ai Kim
Mark and Angela Lamm
Maureen Russo

Up to \$999

Sean and Kristin Young
Ken and Jeanne Atkinson
Brian and Jennifer Dorman
Jeff Hoffman
Robert and Jennifer Kiesel
Antonino and Marie DiMercurio
Chris Byrd
Gene and Lynn Eddy
Tammy and Ben Hilton
Tom and Mary Eileen Cleary
Lynn and Shirley Quilici
Liz Funk
David and Kari Doctor
Merry Cable
Justin and Britteny Ferrin
Lester and Nancy Jansen
Brian and Margaret Curtis
Scottie and Jessica Dillon
Stan Gilbert and Chris Brunner
Marzban Hathiram and Mahazareen Dastur
Peter and Tara Himmelreich
Lila Keleher
Tom and Marge Zaborney
Joe and Wendy Vitiritto
Stanley and Lisa Routh
Lindsay and Sandra Dunn
John and Dianne Ploetz
Andrew and Vicki Athens
Julie and Gerald Barbier
George and Sabine Mohr
Peter and Donna Abramov
Tanner and Jessica Lindsay
Ed and Janice Duffy
Shane and Colleen Irvin
Eugene and Renee Lemmon

Bill and Jackie Lucarell
Mark Ritchie and Lisa Mingo
Jim and Carol Siniawski
Rick and Lynn Sablosky
Greg and Brandi Stuart
Marc Weiner
Bob and Alice Nicholson
Chris Scaff
Cherie Bank
John and Audrey Barrow
Joseph and Tracey DeMarco
David and Stacy Ownby
Albina Parente
Alain Silverston
Wesley and Sue Wycoff
Lisa and John Hayden
Joel and Jennifer Ramirez
Robert and Mary Nori
Andrew and Jennifer Gough
Natalie Curry
Bob and Victoria Hathcock
William and Amy Lewis
Catherine McKeon
Paul and Debra Sundsvold
Sharon Ellis
Thomas and Brenda Seiford
Bennetsen, Jasmine
Fred and Nancy Nunes
Abid Usmani and Shahid Reshma
Wendy Delzell
Billy Jo and Debbie Estep
Michael and Katharine Ormond
Jack and Tammy Neal
Mir Saleem and Umber Ellahi
Nancy and Scott Finnegan
Susan and Skip Gannon-Longstaff
Gary and Melody Ganz
Abdul Hameed,
Paul and Catherine Rodwell
Lorne Shelson and Annette Waxberg
Michael and Kay Proctor
Christopher and Dana Lamb

John and Betty Mozisek
Jack and Debbie Siegel
Sydney and Betsy Moore
Mokrane Simoussi
Marzban Ardesir
John and Francene Berglund
Anthony Glavac and Sabrina Bowmer
Curt and Crystal Fales
Pat and Maria Gleason
Brian and Pamela Heilig
Eddie and Maly Lee
Zachary and Shannon Mekker
Adam and Olivia Mindle
Griff and Cecilia Morgan
Leonard and Jan Riley
Dan and Bonnie Rosen
Mike Sanders
Severt and Beatrice Score
Ariel Sitzerman and Gabriela Bernal
Debby Slater
Mitzi Speelman
Alfons and Karin Staab
Jian Yang and Jing Nie
Kayla Lackey
Doreen Gummoe
Jeanette Clark
Mitch and Erin Furr
Kenny and Lisa Myhan
Charles and Marie-Pierre Bichet
Greg and Diane Hayes
Joey Linsenmann
Kevin and Barbara McKee
Joshua and Crystal Pepper
Steve Perkins and Karen Magrath
Christian Ryder
Sharon Saunders
Richard Briga
Bill and Pat Danks
Henry and Gwen McNutt
Mary Tanner
Elizabeth and Graham Walker

PayPal Giving Fund

Do you want a simple way to increase giving to the Fanconi Anemia Research Fund? Welcome to the PayPal Giving Fund. EBay sellers are encouraged to give a percentage of their proceeds to a nonprofit certified by PayPal Giving Fund each time they list an item for sale. Participating sellers are rewarded for their generosity with special eBay Giving Works features. The nonprofit receives recognition in the listing and benefits from the seller's success. PayPal Giving Fund and eBay collect and distributes the donation, and handles the tax receipt.

EBay members can also choose to make an online gift with PayPal. The Donate Now tab lets anyone with a PayPal account donate. For more information, see www.paypalgivingfund.org/index.html.



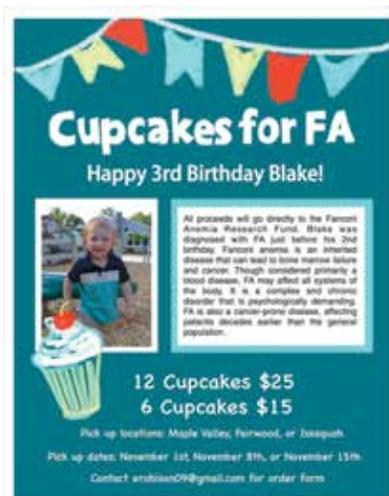
Michael Capone (left) and Farid Boulad, MD (right)

A Winning Story

Barb Capone told her Fanconi anemia story, the people voted, and she won \$4,000 for the Fanconi Anemia Research Fund! The Rare Life Award is an annual recognition program created to honor individuals who exhibit courage, leadership, survival, devotion, and heroism. Barb was among the top 20 nominees, selected from 191 stories submitted. She was one of six runners-up, receiving \$4,000. You're our hero, Barb.

Scare Away FA

Wyatt Klimkiewicz and his cousin, Shane, both 10 years old, conjured up a spookily successful Halloween party to benefit Fanconi anemia research. Sixty costumed friends, neighbors, and classmates appeared to help "Scare Away FA", jump in the bounce house, and play video games in the gaming bus. Wyatt's mom, Jennifer, says that Shane is always looking for ways to support his best friend, Wyatt, who has FA. The boys asked their guests to make a donation to the Fanconi Anemia Research Fund, and donate they did. "Scare Away FA" raised more than \$2,900!



Cupcakes for FA

Cupcakes were the order of the day on Blake Robison's 3rd birthday in November. Emily Robison, Blake's mother and cake decorator and baker extraordinaire, decided to put her skills to good use to benefit FA. With a fun graphic design, online ordering, a choice of a half or full dozen cupcakes, four gourmet flavors, three pick-up locations and dates, the "Cupcakes for FA" birthday fundraiser made it easy to place an order and donate. Family members donated all of the ingredients and supplies. The fundraiser was promoted on Facebook and social media, and built on the following generated from the family's previous fundraiser (250 Miles for FA; see the FA Family Newsletter, Issue 56).

The plan was that Emily's mom would assist with baking. Unfortunately, Emily was placed on bed rest for some issues with her pregnancy just before the first baking day. Without missing a beat, Emily's mom, who is not a baker herself, made the cupcakes under Emily's careful direction. The cupcakes turned out beautifully, and raised nearly \$2,600 for the FA Research Fund. Emily reports, "Overall, it was a ton of work and exhausting (especially since I was supposed to be on bed rest!), but we are excited to do it again next year. We have learned a lot and hopefully can raise even more for Blake's 4th birthday."



Lighting a Path

After planning the “Lighting the Path for a Cure” fundraiser, the Arroyo family had cancelled the event to focus on the health of Anthony, then 16. But Anthony really wanted to see it through, so at the last minute the plans were put back into action. That was good news for the 150 people who attended.

The event was held at Anthony’s school, Buchanan High, which was aglow with lights lit with every \$10 donation. Awesome entertainment was provided by Anthony’s choir group. Along with the school’s marketing class, the group also designed and sold t-shirts emblazoned with “Buchanan Bears Fight Together” on the front and “Team Arroyo Find a Cure” on the back. Food and desserts sold out—including cookies beautifully decorated with the Fanconi Anemia Research Fund’s logo made by Anthony’s aunt Theresa. His cousins volunteered and were kept busy all night. A highlight of the fundraiser was the Shave your Head Challenge. Anthony was going through chemotherapy at the time and losing his hair. Family and friends lined up to donate their money and their hair in support. Although Anthony was physically exhausted, he was present for as long as he could. Long enough to watch his best friend have his head shaved and accept a banner signed by his whole choir group which read “This is your home”. “Lighting the Path for a Cure” was a great success in every way and raised nearly \$12,500, making the path to a cure much brighter.



Shall We Dance?

By Julia Pless

Having to do a senior project for high school gave me the perfect opportunity to try my hand in fundraising. Seeing as how this was my first fundraiser, I hit quite a few bumps. Some things didn’t end out the way I thought they would, but they all worked out just fine. I had quite a few options of different fundraisers I could have done, but in the end I decided to have a Dance-A-Thon. Planning the Dance-A-Thon and getting everything I needed was hard and took lots of time. When it came time to set it all up, however, we had tons of fun. We had music, prizes, food, decorations, and a Chinese auction. We had awesome Halloween decorations and we even asked those who were coming to dress up in a costume. I had a lot of help and support from all of my friends and family. In all we raised \$1,450 for FARF and I couldn’t be happier. I had a great time and I hope to have more fundraisers in the future!



Julia, fourth from left, with Dance-A-Thon friends

Getting on Board

The Burkin family of Perrysburg, Ohio got on the fundraising bus with a trip to Greektown Casino in Detroit, Mich. in honor of Hope Burkin, 14. Hope’s mother, Danielle, grandparents, Don and Kathy Burkin, and a small committee of friends set the date, got to work selling tickets, and filled two chartered buses. About 70 attendees traveled 70 miles on the day trip that included a casino voucher and a 50/50 raffle. Snacks and beverages were sold on board. A fun time was had by all, and nearly \$600 was raised for Fanconi anemia research and support in the process. That’s a good bet!

Changes to the Boards

The Fanconi Anemia Research Fund saw changes to its Board of Directors and Scientific Advisory Board recently as terms expired and members assumed new positions. Fixed terms were adopted for the Board of Directors several years ago to bring in fresh faces and new ideas.

On the Board of Directors (BOD), we say good-bye and thank you to Brian Matthews, PhD, whose term, plus one extended year, ended in 2014. Dr. Matthews, who has been on the board since 2011, is a scientist and was a vital member of the Fund's proposal review committee. He served as the BOD's secretary and treasurer. We are grateful to Brian for his years of dedicated service.

Sharon Schuman, PhD, who joined the BOD last year, was elected the new secretary and treasurer after Dr. Matthews' departure. Dr. Schuman is a long-time volunteer and supporter of the Fund with excellent writing and organizational skills. Her annual FA concerts have raised over \$250,000 for FA research.

On the Scientific Advisory Board, Christopher Mathew, PhD, resigned after spending 15 years on the board. Dr.

Mathew is a geneticist and helped identify at least seven FA genes. He has been a vital member of the board and the FA research community and received the Fund's Distinguished Service Award in 2011. We are delighted that he will remain a part of the research community.

In addition, Raymond Monnat, MD, has graciously assumed the chair position on the Scientific Advisory Board. Dr. Monnat is Professor of Pathology and of Genome Sciences at the University of Washington in Seattle. His research focuses on the molecular mechanisms that insure genome stability, and how these modulate cancer or disease risk and the response to therapy. Dr. Monnat has been an integral member of the FA research community and has served on the Scientific Advisory Board since 2000. We are excited to welcome him as the new chair!



Raymond Monnat, MD

The Legacy of Co-Founder David Frohnmayer



When David Frohnmayer died on March 10, 2015, after battling prostate cancer for over five years, we knew we had lost an irreplaceable leader, mentor, and friend. As a law professor, state legislator, Oregon's Attorney General, and for 15 years, president of Oregon's flagship public university, he sharpened

his ability to solve even the most intractable problems. Faced with Fanconi anemia, he was thus able to marshal well-honed talents and resources to confront the most difficult task of all—cracking into the mysteries of a fatal disorder, about which almost nothing was known, even as it dismantled the health of two daughters and menaces a third.

It's one thing to relish a challenge, but quite another not to get to choose that challenge—to be forced to respond to an assault that must have seemed sudden, relentless, unfair, depressing, and, for a loving father, unspeakable. Dave and Lynn, like other FA parents, were dragged against their will

into the battle against this disorder—a battle that never lets up its demands, no matter what health crisis might erupt at home.

Instinctively Dave and Lynn knew that they would get nowhere without reaching out to others—families who not only shared FA but could help raise funds and furnish scientists with data; organizations that sought to understand other rare diseases; and scientists who volunteered their time to help choose projects that could be leveraged into major grants that would eventually identify 18 genes. The Frohnmayers encouraged collaboration and sought out researchers with interdisciplinary perspectives, some uncovering links to main-stream conditions like head and neck cancer and breast cancer, others discovering more effective FA therapies. David Frohnmayer devoted himself to pushing this progress forward and gathering the funds to make it happen.

Now we have to do all this and more, without his encouraging, humble, relentlessly questioning presence. We will never be able to replace him, but we can and will carry forward this quest in a way that would make him proud.

Your FA Research Dollars at Work

From September 2014 to April 2015, the Fanconi Anemia Research Fund awarded \$513,000 in research grants to the following projects:

Investigator: Henri van de Vrugt, PhD, Netherlands Cancer Institute, Amsterdam

Title: *Correcting Fanconi anemia mutations by CRISPR/Cas9 genome editing to explore a novel therapeutic strategy*

Amount: \$125,000

Investigator: Yigal Dror, PhD, The Hospital for Sick Children, Toronto, Canada

Title: *A prospective phase III study to evaluate the cysteine and glutathione prodrug Nacetylcysteine (NAC) for safety and amelioration of DNA damage, oxidative stress, and hematological anomalies in patients with Fanconi anemia*

Amount: \$188,000

Investigator: Toshiyasu Taniguchi, MD, PhD, Howard Hughes Medical Institute, Seattle

Title: *Phosphatases that regulate the Fanconi anemia pathway*

Amount: \$200,000

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 funded 202 research grants totaling over 17 million in research dollars given to 105 investigators at 58 institutions worldwide.

Many companies and businesses will match their employees' donations to charities. It is a great way to donate to FARF and double the overall donation!

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!

facebook

Find us on Facebook at

www.facebook.com/fanconianemiaresearchfund

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!

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.*

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- Donations by Phone:** Call us at 541-687-4658 or toll free at 888-FANCONI (888-326-2664) (USA only)
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