



# FAMILY NEWSLETTER

#25 A Semi-annual Newsletter on Fanconi Anemia for Families, Physicians and Research Scientists Spring, 1999

## Mark Your Calendars for Our Annual Family Meeting!

Our 8th annual family meeting will be held at Aurora University's George Williams Lake Geneva campus in Williams Bay, Wisconsin from August 13-18, 1999. As we discovered last year, the campus includes a picturesque lake front complete with swimming and boating, an eighteen-hole golf course, tennis courts, a full-sized gymnasium, shuffleboard, nature trails and campfire sites. Lake Geneva is an easy, less than two-hour drive from Chicago's O'Hare airport. Families can also fly into Milwaukee, Wisconsin.

We have a new format to enable more families to attend. Two days of

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*Grover Bagby, MD, addressing the 10th International Fanconi Anemia Science Symposium in Denver, Colorado.*

## Fanconi Anemia Scientific Symposium

- Three Genes Account for Approximately 85% of All FA Cases
- Mouse Bone Marrow Can Be Cured of FA Defect
- New Strategies May Improve BMT with Mismatched Donors

Eighty-three researchers, treating physicians, and a few family members met in Denver, Colorado for the Tenth Annual FA Scientific Symposium, November 1-2, 1998. This meeting was sponsored by the FA Research Fund, Inc., the Collins Medical Trust, the Rose E. Tucker Charitable Trust, and the Samuel S. Johnson Foundation.

Twenty-six scientists gave formal presentations. In addition, thirteen participants presided at a poster session, where they discussed research

results in an informal setting. Evaluations of this symposium again emphasized the tremendous value of regular scientific workshops.

Research topics covered four general areas: gene identification and characterization; protein function studies; hematopoiesis, apoptosis, leukemogenesis and oncogenesis; and developmental models and experimental therapies. Some highlights:

- Scientists and publications now

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### HIGHLIGHTS

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## Discovery of “Homing” Receptor May Improve Transplant Success

**Israeli researchers boost receptor-bearing cells from 10% to 90%**

The February 5, 1999 issue of the journal *Science* describes a discovery by scientists at the Weizmann Institute of Science in Rehovot, Israel, which might improve bone marrow transplant outcomes. Dr. Tsvee Lapidot describes the identification of a “homing” receptor that guides blood-producing stem cells to bone marrow during transplant.

The following excerpt is quoted from *Reuters Health*, February 4, 1999:

“During marrow transplant, stem cells are injected into the bloodstream of the transplant patient, in the hopes that at least a minority of them will re-populate the marrow cavities of the patient’s bones. However, in most cases only about 10% of injected cells end up colonizing the marrow. These low rates of stem cell migration can seriously limit long-term chances of transplant success.

Lapidot and his team sought to determine if a specific receptor found on the surface of stem cells might act as a ‘homing’ device, naturally attracting the cell to the marrow. In studies in which human stem cells were injected into mice, the authors found that only those stem cells with the CXCR4 receptors migrated successfully to the marrow.

The CXCR4 receptor seems to be ‘attracted’ to SDF-1, a compound released by bone marrow cells. ‘We discovered that human stem cells are sort of like sailing boats,’ Lapidot explained. ‘A sailing boat will pick up

the wind only if its sail is put up on the mast; similarly, stem cells will migrate to the bone marrow only if they display a specific receptor on their surface that allows them to pick up the signals from marrow cells.’

Even though just 10% of stem cells are naturally equipped with the CXCR4 ‘sail,’ all may have the potential to grow the receptor. In fact, by culturing stem cells in the laboratory with natural growth factors, the Israeli researchers were able to boost the number of CXCR4-bearing stem cells to more than 90%.

Transplants involving large populations of stem cells equipped with CXCR4-homing ability might greatly increase bone marrow transplant success rates, the investigators explain. Clinical trials involving use of the procedure are already under consideration, according to the Weizmann Institute statement.”

*In response to the above article, John Wagner, University of Minnesota, wrote “We have been very much aware of the chemokines that enhance homing and have been working with the one in the news release as well as others for a while. I am very excited about this and think that this should be pursued. This finding could be very beneficial to all patients but especially FA patients.” ♦*

## FA Patients and Cancer

During the past two years, the FA Research Fund staff have received numerous calls from patients and families, reporting occurrences of solid tumor malignancies and seeking guidance concerning treatment. Unfortunately, data concerning solid tumors have not been well documented. Dr. Blanche Alter prepared a questionnaire for FA families who have experienced cancer. If you or a loved one has experienced a malignancy, we would deeply appreciate your willingness to participate in this survey. Contact Leslie Roy at the FARE office, and she will mail you a questionnaire. Your experiences could be very valuable in helping physicians understand this complication and devise helpful therapy for patients.

Over the past two years, 21 patients have reported solid tumor malignancies to the FA Research Fund and the German support group. Two of these patients experienced two separate kinds of cancer. Eight patients were male, thirteen were female. Six cancers involved female reproductive organs; the other cancers were evenly divided between the sexes. The vast majority of these patients developed cancer after their mid-20s. Only three occurred prior to age 12, six during the 20s, eight during the 30s and four after age 40. Twelve patients are alive, six died from cancer, and three died from other causes.

The following statistics are too small to be predictive, but may have some relevance. The most common kind of cancer reported was squamous cell carcinoma of the mouth,

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## Pursue Mouth Tissue Irregularities Aggressively

by Lynn Frohnmayer

We know of too many FA patients who have recently developed cancer of the mouth. When our daughter, Amy, complained of a small area in the back of her mouth which caused her some discomfort and seemed to have irregular tissue, we rushed her immediately to her pediatrician. He suspected leukoplakia, and sent us at once for a biopsy by an ear, nose and throat specialist, Dr. Chris Hiatt.

The tissue was benign. The biopsy revealed salivary gland tissue which had become irritated. We asked about indicators of the earliest signs of malignancy. Hiatt would have been concerned if the biopsy had revealed leukoplakia or erythroplasia.

Leukoplakia is a thickening of the lining of the tissue, and it appears as a whitish area. It can be caused by trauma (biting, dentures, tobacco usage, etc.) and can be benign or premalignant. Eighty percent of premalignant

conditions of the mouth are leukoplakia, according to Hiatt.

Erythroplasia, which accounts for 20% of premalignant mouth tissues, presents as a velvety, irregular, raised area which persists. The patient does not feel discomfort and usually does not know this abnormal tissue is present. However, most dentists would notice and recognize this tissue as abnormal.

**We repeat Dr. Elise Bolski's words from our *Science Letter* #24. "Suspicious lesions, including ulcerations, persistently swollen tissue and leukoplakia should be subjected to biopsy." For FA patients, Bolski recommends that dental check-ups should begin at the age of 18 months and continue semi-annually. ALL dentists treating FA patients should be aware that cancer of the mouth is a common problem especially with older FA patients. ♦**

### **FA Patients and Cancer**

*continued from page 2*

head and throat (8 cases). This was followed by cancer of the female reproductive organs, primarily cancer of the vulva (6); cancer of the esophagus (2); anus (2); liver (2); bladder (1); bone (1); and B cell non-Hodgkins lymphoma (1).

In future publications, we will attempt to provide articles from physicians concerning early warning signs and prevention of malignancies. Some observations can be made independent of expert medical opinion, however. The older FA patient is at risk for solid tumor malignancies. Dentists, gynecologists and all treating physicians **MUST be made aware of this risk factor**. Physicians knowledgeable about FA agree that abnormal-appearing tissue in high

risk areas should be biopsied to rule out premalignant or malignant conditions.

Factors which pose a cancer risk for the population in general (we refer the reader to Appendix C of the *FA Handbook*, "Toxic Agents to Avoid" by Joyce Owen, Ph.D.) especially must be avoided by FA patients. The FA patient who smokes, drinks, breathes second-hand smoke or is careless about issues involving good hygiene and nutrition is taking life-threatening risks. Unprotected sex with multiple male partners might create a health problem for a female population already at risk for gynecological malignancies.

*See related articles on pages 14-15.*

## Joenje to Study FA Malignancies; Requests Samples

Hans Joenje, PhD, Free University of Amsterdam, asked the FA Research Fund to inform FA patients of his desire to establish a tumor study. Joenje is collecting solid tumor samples. Older FA patients frequently develop solid tumors, most frequently oral squamous cell carcinomas. The reason for this is presently unknown. Cell lines derived from such tumors may be extremely valuable for research. Cell lines that may result from specimens sent to Joenje's lab will be made available to the research community.

If you are diagnosed with a solid tumor malignancy and would like to participate in Joenje's study, your doctor should contact the EUFAR secretariat in Amsterdam to arrange for shipping.

EUFAR Secretariat and Cell Repository:

Phone: 011 31 20 444 82 73

Fax: 011 31 20 444 82 85

Free University

Department of Human Genetics

Der Boechorststraat 7

NL-1081 BT Amsterdam

The Netherlands

The tumor sample should be excised aseptically and ideally be 4-5 mm thick and 2 cm deep. The sample should be packaged by courier, ensuring a guaranteed arrival within 16 hours. The less time for transport, the higher the chance of success in establishing a cell line. Exact protocol details are available by contacting the FA Research Office. ♦

# Mutation Screening and Complementation Analysis for Fanconi Anemia Complementation groups FA-A, FA-C and FA-G

By Arleen D. Auerbach, Ph.D.

My laboratory is currently offering mutation screening to all Fanconi anemia families, and complementation group analysis in certain cases. Mutation studies are useful to families, because we can offer carrier screening to extended families if we can identify the FA-causing mutations. A major goal of these studies is to make correlations between the specific mutations causing FA in the different complementation groups and the severity of the clinical course of the disease.

Our current strategy for newly ascertained patients is to use mutation-specific assays to test for the 6 common mutations in FANCC and the 2 recurring mutations in FANCA. Patients are then screened for mutations in FANCG (see below). Non-G, non-C patients will be screened for FANCA mutations, starting with those previously found in their ethnic group.

Transduction of patient's cells with retroviral vectors containing genes for FA-A, FA-C and FA-G will be used in some cases for complementation analysis. The time it takes to determine complementation group and mutations for a particular patient is unpredictable, depending on what we find. We have had results in some patients in a few weeks, while we have not yet been able to identify any mutations in other patients.

Four disease-causing mutations in FANCG were described in the initial cloning report for FANCG. To identify additional mutations in FANCG, we have screened a panel of 211 DNA samples from ethnically diverse FA patients. Families with known mutations in FANCA (123 families) and FANCC (53 families)

were excluded from this study. The ethnic origins of the patients were highly varied. Twenty-two of the 211 patients in the initial screen have been found to be in FA complementation group G, based on identification of at least one pathogenic mutation in FANCG. Many of the patients not identified as FA-G could be in FA-A, as most FA-A patients have private mutations that were not yet screened for, or in the complementation groups for which the genes are still not isolated. We have identified a total of 17 different FANCG variants in the IFAR patients; 15 of these are probably pathogenic mutations. Genotype-phenotype correlations are being analyzed in the 38 FA-G patients identified with these mutations. Most of the FANCG mutations are associated with a severe phenotype; three appear to have a milder clinical picture.

Over 50 mutations in FANCA have been identified by our laboratory. Except for the two most common mutations found on about 5% and 2% of FANCA genes, few FANCA mutations are shared between affected individuals. The mutation spectrum of FANCA also includes large

genomic deletions that are difficult to detect. The heterogeneity of the mutation spectrum and the frequency of intragenic deletions makes the molecular diagnosis of FA a formidable task.

Results of a study to correlate genotype with phenotype in 123 FA-A families (148 patients including affected siblings) is still in progress. Preliminary findings indicate that the majority of patients in complementation group A have a relatively mild phenotype in terms of age of onset of hematologic manifestation of the disease, leukemia diagnosis, and age of death, as well as the number and type of major congenital malformations. As with complementation groups C and G, certain mutations are correlated with a severe phenotype.

My thanks to FARF for its generous support of my work.

Any interested family in North or South America should contact me by e-mail if possible or by regular mail:

Laboratory of Human Genetics  
and Hematology  
The Rockefeller University  
1230 York Ave., Box 77  
New York, NY 10021  
auerbac@rockvax.rockefeller.edu

## Alert

Most of the families in the International Fanconi Anemia Registry (IFAR), a database which tracks clinical and genetic data on FA families, are already in this study. However, it is very important that we hear from families who have not contacted us in the last year in order to get our 1999 IRB (Institutional Review Board)-approved consent forms signed by each individual in the mutation study. New York State requires that we discard precious DNA, some of which was obtained from FA patients who are now deceased, unless we get these consent forms signed. Thus we need to hear from families with living as well as those with deceased FA patients.

Contact Arleen Auerbach at the above address for appropriate forms.

# Subtyping of Fanconi Anemia Patients by Retroviral Gene Transfer and Immunoblotting

Alan D'Andrea and Markus Grompe

Three of the eight known FA genes have been cloned (FANCA, FANCC, and FANCG), and mutations in these genes account for more than 80% of FA patients. Subtyping of FA patients is an important first step toward identifying candidates for FA gene therapy. In addition, precise knowledge of the complementation group permits DNA-based prenatal diagnosis and carrier detection. We have recently established a tight collaboration of the FA cell repositories of the Oregon Health Sciences University (Grompe) and the Dana-Farber Cancer Institute (D'Andrea) and have begun a systematic subtyping analysis of FA cell lines (peripheral blood lymphoblast lines and skin fibroblast lines). Subtyping can be performed by one or more of the following procedures:

## (1) Direct mutational screening of the three cloned FA genes

Disease-causing mutations have been found in FANCA, C and G patients using a variety of techniques. For several technical reasons, direct mutation detection is impractical in most situations. The one exception is FA in Ashkenazi Jewish individuals. In this group a single mutation accounts for 85% of all disease chromosomes, and therefore, mutation analysis for this allele is the most practical approach in this patient group. In all other settings, each mutation analysis represents a lengthy research project. Mutation analysis can be performed on either lymphoblast or fibroblast cell lines.

## (2) Somatic cell fusion studies

FA complementation groups his-

torically have been defined by the study of cell-cell fusions (somatic cell hybrids), using either lymphoblasts or fibroblasts. The patient's cell line is fused to an index cell line of a defined complementation group. If the fused cells (hybrids) remain sensitive to DNA cross-linking agents, then the patient belongs to this complementation group. This technique is still useful today, particularly for complementation groups in which the gene has not yet been cloned. If a patient does not belong to groups A, C or G, this somatic cell hybrid analysis remains the only method available. While highly reliable, this technique is very labor intensive, time consuming and expensive. The Oregon FA repository continues to perform this test on all patient cell lines which have been excluded from groups A, D or G.

## (3) Retroviral complementation

This method has only recently become available. In principle it is quite similar to the analysis of somat-

ic cell hybrids. The cell line of an FA patient of unknown complementation group is infected with a high efficiency retrovirus carrying the FANCA, FANCC, or FANCG normal gene. The retrovirus-infected cell line is then analyzed by either chromosome breakage analysis (Oregon FA repository) or cell cycle analysis (Harvard). The chromosome analysis is carried out in the laboratory of Dr. Susan Olson at Oregon Health Sciences University. If a given cell line is corrected by one of the retroviral vectors, that indicates that the patient belongs to this complementation group. Overall, this is the most rapid and efficient method of subtyping available at present. The disease-causing mutation itself is not detected, but the defective gene is unambiguously identified. This information is sufficient to define candidates for gene therapy. In addition, DNA-based prenatal diagnosis and carrier detection can be performed using linkage analysis.

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## New Names for FA Genes: FANCA-FANCH

Readers should be aware that as of November 1998, the scientific community is using new abbreviations to refer to Fanconi anemia genes. This change is in response to gene reference standardization efforts by the Nomenclature Committee of the Human Genome Project.

We recognize that there may be initial confusion, so please use care in reading scientific articles. In the past, scientists referred to the different FA genes as FA-A, FA-B, FA-C up to FA-H, representing the eight known

Fanconi anemia genes. They now refer to these genes as FANCA, FANCB, FANCC up to FANCH. The different complementation groups will still be referred to as complementation group A, complementation group B, complementation group C, etc. A patient in complementation group A may still be referred to as an FA-A patient, or as a FANCA patient (a patient defective in the A gene). The disease, Fanconi anemia, will still be abbreviated as FA.

Confusing, isn't it!! ♦

## Your FA Research Dollars at Work January 1 - December 31, 1998

Arleen Auerbach, PhD ..... <i>The Rockefeller University, New York</i> "Comprehensive Analysis of FA Mutations & Their Genotype Phenotype Correlations"	\$75,640
David T. Curiel, MD..... <i>University of Alabama, Birmingham</i> "A Novel Vector Strategy to Accomplish Gene Therapy for Fanconi Anemia"	\$69,000
Maureen Hoatlin, PhD, Assistant Professor ..... <i>Oregon Health Sciences University, Division of Hematology/Oncology</i> "Production and Characterization of Polyclonal and Monoclonal Antibodies Specific for FA-A"	\$66,637
Alan D'Andrea, MD, Associate Professor ..... <i>Dana-Farber Cancer Institute, Boston</i> "Rapid Subtype Analysis of Fanconi Anemia Patients by Retroviral-Mediated Transfer of FA Genes"	\$47,500
Hagop Youssouffian, MD..... <i>Department of Molecular and Human Genetics, Baylor College of Medicine</i> "Localization and Regulation of the FA-A Protein"	\$52,885
Yan Xie, MD ..... <i>Hubei Medical University, Department of Hematology/Oncology</i> "Toward a Diagnostic Service for Fanconi Anemia in Central China"	\$18,900
<b>Total Research Funded 1998:</b>	<b>\$330,562</b>

## New Study Hopes to Improve Transplant Outcomes

John Wagner, MD, is looking for bone marrow samples to determine whether FA patients have normal stroma (supportive tissue of the bone marrow). This study could impact future treatments for patients with or without bone marrow transplants. Dr. Wagner says, "If we find that the stroma is defective, then we have ideas on how to transplant normal stroma that might improve engraftment after BMT. Moreover, it might be possible to transplant normal stroma without doing a bone marrow

transplant, and this might delay the onset of pancytopenia." Wagner would like FA families to be informed of his study, and to consider sending him an additional marrow sample if their child is undergoing a bone marrow aspiration.

For details regarding collection please have your physician contact:  
John E. Wagner, MD  
Pediatric Bone Marrow Program  
University of Minnesota  
(612) 626-2961  
wagne002@maroon.tc.umn.edu

## Interleukin 11 Trial Opens for FA Patients

A clinical trial to determine if the cytokine Il-11 (Interleukin 11) can improve the platelet count in children with Fanconi anemia is now open at the Riley Hospital for Children in Indianapolis, Indiana. Il-11 is a growth factor that directly stimulates the bone marrow to increase platelet production. It is administered as a daily injection. Il-11 has been approved for the prevention of severe thrombocytopenia and reduction of the need for platelet transfusions in patients receiving chemotherapy. The clinical trial is to determine if Il-11 is safe and if the platelet count can be raised in children with Fanconi anemia. Further information can be obtained from Dr. James Croop at 317-274-8784 or [jcroop@iupui.edu](mailto:jcroop@iupui.edu). ♦

## Symposium on Gene Therapy Planned

At the 1998 Scientific Symposium in Denver, a number of gene therapy researchers agreed to meet in the spring of 1999 for a one day mini-symposium focused on gene therapy and the progress of gene therapy trials.

This symposium will take place on Saturday, May 15 at the Chicago Airport Hilton. The FA Research Fund will pay for travel, food and lodging. At the present time, fifteen researchers from Europe and the United States plan to attend.

Any scientist reading this article who might wish to attend as a participant or observer should contact Joachim Schulz at the Fanconi Anemia Research Fund. ♦

## FA Scientific Symposium

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officially refer to FA genes as FANCA, FANCB, FANCC, etc. (See article on page 5.)

- Eight complementation groups have been identified. Three FA genes have been isolated (FANCA, FANCC and FANCG) and these genes account for approximately 85% of all cases of FA.

- Hans Joenje believes that some patients do not belong to any one of the eight complementation groups identified. In other words, it is likely that more than eight genes, when mutated, can cause this disease.

- Joenje studied eleven older FA patients and discovered that three would now be diagnosed as "normal" if only blood cells had been used for diagnosis. Their skin cells (fibroblasts) were still sensitive to agents used to diagnose FA. Joenje believes that, in some cases, skin cells must be studied for an accurate diagnosis of FA.

- Chris Mathew noted that many different disease mutations account for FANCA. One notable exception is that three mutations account for over 90% of all FANCA cases in the Union of South Africa.

- Arleen Auerbach stated that there are at least 187 different disease mutations in FANCA. This gene, therefore, is notably different than FANCC which has six primary mutations. She has identified two mutations which account for 2% and 5% respectively of FANCA cases; all the rest were unique to individual families. Because of the huge range of mutations, it is difficult to make correlations between a mutation and how it affects patients.

- Auerbach has assigned 148 patients to FANCA. In general, she finds that this is a "mild" complementation group, with fewer physical anomalies and later age of onset of

hematological disease. However, a large number of older patients in this group have solid tumor malignancies. FANCC patients tend to have earlier hematological problems, a high incidence of leukemia and multiple anomalies.

- Alan D'Andrea finds that the FANCC and FANCA proteins are expressed in the cytoplasm of the cell, bind together in a complex, and move into the nucleus. The protein products of other FA genes may provide the "glue" which allows this process to occur in normal individuals. In contrast, Frank Kruyt believes that FANCC and FANCA function in different subcellular compartments. Additional research is needed to clarify these differences.

- Blanche Alter presented data which suggest that the presence of an abnormal clone in FA patients may not be predictive of a bad outcome. However, morphologic myelodysplasia (which means that at least two cell lines obtained from a bone marrow aspirate have an abnormal appearance in greater than 25% of the cells) is correlated with an adverse outcome.

- The laboratory of Robert Arceci is working to develop antileukemic immune responses which would avoid the toxicity of intensive chemotherapy for AML. Studies in both mouse systems and human leukemias are underway.

- Johnson Liu and Christopher Walsh updated the group on progress and complications of gene therapy. Walsh presented data showing that mouse bone marrow can be "cured" of FA through a combination of gene therapy and destruction of the host FA marrow. His upcoming gene therapy trial for complementation group A, however, will not include ablation of the FA patient's marrow.

- John Wagner discussed the challenges of FA transplants using unre-

lated or related, mismatched donors. Twenty-nine FA patients have undergone BMT with donors other than matched siblings, using the protocol developed in Minnesota. Survival rate is approximately 35%. Thirty-five percent did not engraft. No single risk factor predicted graft failure, although there was a trend toward increased risk of graft failure in patients with myelodysplasia, lymphocyte mosaicism and lower number of donor cells. Infection (especially aspergillus) and multi-system organ failure accounted for poor outcomes. Increasing total body irradiation from 450 cGy to 600 cGy did not improve outcome. Wagner is now actively pursuing new strategies to improve engraftment. These strategies include use of new agents that may augment immunosuppression, induce tolerance of the host to the donor's stem cells, or increase the number of transplanted stem cells which reach and settle in the bone marrow.

Many presentations focused on the possible function of FA proteins and theories which might explain the underlying defect of this disease. Understanding these complicated issues could suggest therapeutic interventions.

The editors have included an outline of the symposium, giving the name of each presenter and the title of his or her presentation. Given the sheer volume of this material and its highly technical nature, we have not prepared a *Science Letter*. If you wish a copy of one or more of these abstracts, please contact the FA Research Fund and the appropriate material will be mailed to you promptly. ♦

# Preclinical Studies of Fanconi Anemia Gene Therapy at Children's Hospital, Boston

*Eric Nisbet-Brown, M.D., Ph.D. and Alan D. D'Andrea, M.D.*

*Dana-Farber Cancer Institute, Children's Hospital, Harvard Medical School*

Gene therapy offers the potential for cure of the hematological abnormalities of Fanconi anemia and for prevention of the development of leukemia. Children's Hospital and Dana-Farber Cancer Institute have recently committed to a major initiative in pediatric gene therapy, with particular emphasis on pediatric hematological diseases including Fanconi anemia. Dr. Alan D'Andrea has recently received a substantial grant from the Charles H. Hood Foundation of Boston to establish the infrastructure necessary for such a program, which will focus on Fanconi anemia. This program involves extensive collaboration with several groups of investigators, including Eva Guinan, M.D., Richard Mulligan, Ph.D., and Colin Sieff, M.B., Ch.B.

Working with Mulligan, who is internationally recognized for his work on retroviral vectors for gene therapy, we have developed retroviruses which allow us to correct the cellular abnormalities in Fanconi anemia types A, C and G. Over the last year, we have completed construction of a facility which allows us to produce vectors which meet the stringent standards of the Food and Drug Administration for treatment of patients. These clinical-grade viruses contain the DNA which codes for the FANCA or FANCC proteins, which has been packaged in a viral particle that allows it to infect a number of different cell types. (We are still working on a clinical-quality FANCG virus). After cells are incubated with virus, the virus' DNA is taken up by the cell and then

becomes incorporated into the cell's own DNA as the cell divides. All cells derived from the infected cell then will express the 'new' DNA. In the case of Fanconi anemia, this means that all cells resulting from division of an infected cell will express the FA protein, thus correcting the abnormalities that result from lack of the protein.

Work done previously in D'Andrea's laboratory by Dr. Michael Pulsipher showed that we can use retroviruses coding for FANCA or FANCC to rapidly type cells from Fanconi anemia patients. Cells from Fanconi anemia type A patients will be corrected only if they are infected with the FANCA but not the FANCC virus, and vice versa. We have now developed a research-quality virus which allows us to do the same for Fanconi anemia type G patients. Since types A, C and G account for over 80% of FA patients, we can now subtype the majority of patients within a few weeks, rather than the months previously needed for somatic cell fusion studies and direct mutational screening.

We have also used the clinical-quality virus to study gene transfer into human bone marrow cells from normal people and from patients with Fanconi anemia. We have previously shown, using a research-grade virus, that bone marrow cells from FA-A or FA-C patients show markedly increased growth in tissue culture after correction with the appropriate virus, and that the infected cells are resistant to treatment with Mitomycin-C, which kills FA cells. Before we can extend these studies to

treatment of patients, we must first obtain approval from the FDA. The FDA will require that we show that the viruses are safe and that they correct the defect in FA cells. These pre-clinical studies divide into several phases, which we are currently pursuing actively. We know, from previous work, that overexpression of the FANCA protein in cells in tissue culture does not impair their growth. In addition to studies on cells in tissue culture, we are using the FA-A retrovirus to infect normal human bone marrow, and assaying the growth of blood cell colonies. To date, it appears that infection with the FA-A virus does not decrease the growth of colonies nor does it change the proportions of different colony types (red blood cells, granulocytes and monocytes) which we see.

Another major difficulty in previous studies has been that only a very small fraction of human bone marrow 'stem cells' (cells that can repopulate the whole hematopoietic system) can be infected to express proteins in the long-term. Expression of most proteins falls to undetectable levels in less than a year, limiting the applicability of gene therapy. We are using several approaches to try to overcome this limitation. First, we are using vesicular stomatitis virus (VSV) capsids for gene transfer. The type of capsid is particularly important, as it disguises the virus and allows it to infect the cells. VSV infects a wide range of different cell types, and this may allow better gene transfer into bone marrow stem cells than previous retroviruses. Second,

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## Preclinical Studies

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we are using highly concentrated viruses—up to 1000-fold more concentrated than in previous studies—in our work. It seems reasonable that more concentrated viruses should be better able to infect cells. Finally, we are optimizing the conditions for infection, to improve the efficiency of gene transfer. This involves a number of different factors, including the duration and temperature of infection, oxygen levels in cultures (Fanconi anemia cells are sensitive to high oxygen levels), pre-stimulation and post-stimulation of the marrow cells, and the use of chemicals such as Polybrene or fibronectin to increase viral uptake. To date, these approaches appear to be paying off. Using a highly-sensitive test developed by Mulligan's group with Dr. John Gribben at DFCI, we can show expression of virus-derived FANCA protein in up to 80% of bone marrow colonies. This is substantially higher than in previous work.

It is very important that we continue this work using cells from patients with Fanconi anemia. We are totally dependent on the generosity of Fanconi anemia patients and their families for bone marrow samples which are large enough to enable us to address questions, such as the effects of different infection conditions, and to compare different protocols. Most of the marrow specimens we have obtained have been from patients with advanced disease prior to bone marrow transplant, with some degree of aplastic anemia and probably decreased numbers of stem cells. At this stage in our work, we critically need bone marrow from younger patients, with more cellular marrows and higher stem cell content. We now have a protocol open at our institution which allows volun-

## Gene Therapy Trial Approved

The University of North Carolina Gene Therapy Center, directed by Chris Walsh, has received FDA approval to begin a gene therapy trial for the treatment of Fanconi anemia group A patients. Current therapy for FA patients is bone marrow transplantation. However, most patients lack a suitable donor and usually die from aplasia or acute leukemia. Thus, alternative therapies must be investigated.

The biochemical defects of FA are not yet known. FA bone marrow stem/progenitor cells are defective in their ability to divide and grow. This leads to bone marrow failure or leukemia. There are at least 8 FANCA genes (FANCA through FANCH). Walsh's group has shown that the FANCA or group A gene can be transferred to FA patient bone marrow progenitor cells and correct the growth defect. By using a retrovirus carrying a normal copy of the FANCA gene they plan to test whether they can correct the growth defect in FA-A patients.

Progenitor cells removed from the peripheral blood following a ten day

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tary donation of adequate amounts (15 cc or 1 tablespoon) of bone marrow to allow us to carry out comparative studies.

We are developing a treatment protocol for patients with Fanconi anemia type A. This gene therapy protocol will need local review and will then be submitted to the FDA for review, together with our preclinical data. Once this approval has been obtained, we should be able to offer clinical gene therapy within several months. We are also interested in extending this strategy to FA-C and FA-G patients. ♦

course of G-CSF will be isolated and targeted by the virus. The cells will then be reinfused into the patients without any bone marrow treatment or conditioning typically performed in bone marrow transplants. If sufficient progenitor cells are corrected they could have a growth advantage and repopulate the marrow. The procedure will require only one night in the hospital. Patients will be required to send blood and bone marrow for testing both before and after the patient's entry. Only patients in complementation group A without a histocompatible sibling donor are invited to participate. Inquiries can be referred to:

Dr. Chris Walsh  
UNC  
Chapel Hill, NC  
phone (919) 966-9116  
fax (919) 966-0907  
e-mail: cwalsh@med.unc.edu

Dr. Walsh's laboratory will screen marrow to confirm that patients are in complementation group A. His laboratory will not perform mutation analysis. ♦

### 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.

## Cancer Diagnosed Due to Patient's Persistence

*Paula Guidara, age 44, was diagnosed with Fanconi anemia at the age of five after the diagnosis of an older sister. Two of Paula's sisters have died from FA. Paula has experienced no hematological problems, but has the typical short stature of FA patients, café-au-lait spots, and the experience of early menopause in her thirties. Paula writes of the obstacles she encountered in getting a diagnosis of mouth cancer:*

Four years ago my dental hygienist noticed a white area on the palate of my mouth and notified the dentist. I was lucky that she noticed it because it was an area that I could not see nor did it hurt. I also complained to my dentist of areas on my gum and cheek that were sore and didn't seem to be healing. After waiting three months and not seeing any healing, my dentist sent me to another doctor to get an opinion of the areas in question. My dentist thought it looked like a whitish, grey area that could have been burned due to hot food.

In fact I went to three different doctors in three years. None of the doctors took a biopsy and the last one diagnosed the problem as possibly "lichen planus," a non-life-threatening problem. Since it was not troublesome, they did not bother to biopsy the areas.

Again this summer, at my check-up, I requested a second opinion about the areas in question. The oral surgeon who saw me also suspected "lichen planus," but did several biopsies due to the fact that none of the

previous doctors had. One week later the diagnosis returned as microinvasive squamous cell carcinoma on the palate. The gum and cheek areas were labeled moderate and severe epithelia dysplasia. I immediately opted for surgery the next day (August 5). Luckily, I was only out of work for 1 1/2 days.

Although my surgeon excised the area on my palate, he suggested cryosurgery (removal of tissue by freezing) for the other areas. I wasn't comfortable with that course of treatment. Five medical professionals agreed that we should be aggressive and excise the areas that showed dysplasia. My second surgery was scheduled for October 7. I was out of work only three days.

I must say that this was a frightening, upsetting experience for me. I had never had any major surgery or hospitalizations before. I had wonderful support from family and friends and lots of prayers. I am sure that is why I was able to handle this mentally as well as I did. Healing was slower than I expected. It was a bit uncomfortable, but was tolerable.

I feel that I have kept myself at a low risk for cancers by never having smoked, consuming only small amounts of alcohol, and not using mouth rinses. I also get pap smears every six months and mammograms every year. I use sunscreen and visit the dentist every six months for cleanings and especially oral cancer screenings. I try to eat as healthily as I can, take two ACES vitamin pills each day, and drink green or black



*Paula Ceresa Guidara*

tea. I believe that a study done at the National Cancer Institute, NIH suggests that green and black tea may protect against esophageal cancer.

Currently I am feeling great. My ear, nose and throat doctor checks my mouth every month for anything suspicious. I did have some suspicious areas in December. Biopsies were done, and surgery was being considered when suddenly, within one week, everything healed up.

My advice to others is to continue to go for check-ups for all parts of your body. Biopsy any suspicious areas that are sore or precancerous looking because conditions can change over time. Lastly, try to stay busy, think of others instead of yourself, keep your immune system up and be positive. This works for me! ♦

## A Cancer Survivor's Ordeal

Hello. My name is Audrey Hettinga. I am a 30-year-old adult with FA and have also been diagnosed with cancer. I lost my brother, Minze, to this disease in 1981. He lived a pretty normal life until he developed acute myelogenous leukemia at the age of 17. He passed away seven months later.

In 1992 a biopsy revealed that I had mild dysplasia (abnormal-appearing cells) both inside and outside the entrance to my vagina. I requested this biopsy because that area was red and irritated to the touch and had an abnormal odor. I had laser treatments to get rid of the dysplasia. Five years later I was still under the close eye of Dr. King, who was continuing to do biopsies and had completed seven laser treatments. Having this disorder is a common female problem. Generally it takes one or possibly two laser treatments and the condition is gone. As you know, we FA fighters are an exception to the rule. So we were unsuccessful at licking the dysplasia with normal laser treatments.

After several conversations and visits with Dr. Liu, we decided gene therapy might be an option for me. In March 1998, I went to Washington, D.C. to have gene therapy. Now I go to Washington, D.C. every three months to have bone marrow biopsies and to check if the gene therapy is affecting anything within my system.

On a scale of 1 to 5, my dysplasia was rated at 3 in March 98. I was told if it were to go away, it was a 1, and if it went up to a 4 or 5, it was cancer. In May 1998, it was at 5. I was diagnosed with vulvar carcinoma (cancer of the vulva and vagina). The big scary word CANCER!

Up until this point I had lived a fairly normal life of an adult with FA

with only minor complications. Now I was diagnosed with cancer. Where could we go from here? Surgery seemed the safest way to remove the tumor without facing the complications and risks that either radiation or chemotherapy would cause. Surgery might also disfigure me, a young female who was recently engaged.

This cancer is commonly found in women 50 and older and is a very curable cancer. But once again, having FA caused an exception to the rule.

A day prior to surgery, as I sat through a couple of hours of explanation of what they were going to do to my body, the doctor decided to take one more look at the tumor. He was in for a surprise. In just two weeks, the tumor had grown enormously. It usually would have taken three months to get to this size. Now what could we do?

The surgery was cancelled immediately. My doctors decided that radiation was the next best option, even knowing that it was highly toxic to FA cells. They really didn't know how my body would respond, but they would keep a close eye on me.

The radiation started out okay, but half way through the course of therapy my neutrophils dropped considerably and I had second degree burns. Treatments were stopped for six weeks so I could heal. In August, I was scheduled to finish the final treatments. In September they did internal radiation which, to say the least, was not the most pleasant experience. By October I had finished treatments. All together I received 4500 cGy in 25 sessions to my external perineum area and 1500 cGy internally to my vagina. This was a reduced dosage, given the severity of my reaction.

It is now February 1999. I go for monthly check ups. There is no evi-



*Audrey Hettinga*

dence of cancer. I now get to deal with the side effects from the radiation, and they are severe. I am unable to have children. I can't sit for long periods of time due to discomfort. I have to do daily exercises to keep my vagina open. To me, sex is supposed to be natural and part of a relationship, but now it is uncomfortable and seems like work. I am engaged to marry Jay. I don't know how long it will be for us to understand each other on that level again. It will be a long process. But as long as everything stays stable, I will get back to normal, or as good as it's going to get. God only knows what that will be.

I have had to deal with all of the changes that have happened to me physically as well as emotionally one day at a time. I know it may sound easier said than done, but that is how we have to deal with it. And we must be thankful for every day we have. I know our faith has helped mom and me. I also strongly believe in herbs and vitamins. Yes, I know they may not cure my illness, but I am not going to give in, and if I can improve the quality of my life for however long it may be, I will do it. Take care. I hope to see you all at summer camp. ♦

## Memorial for Caryl Brock

by Lisa Benegas

My American Hero is someone I have known since preschool. Her name is Caryl Brock. She died on November 30, 1995 of Fanconi anemia. She is my hero because she was very courageous and brave. She was thirteen-years-old and had already been in the hospital many times. She was placed in intensive care in Wylers Children's Hospital in September and remained there off and on until she died.

She loved to be with her friends and family. She liked to go to the movies, roller skating, and swimming. Caryl also liked sports. She was an ice skater, a volleyball player, and a cheerleader.

She also loved her pets. She had a

dog, Samantha, two cats, BJ and Phil, and a bird. She loved all kinds of animals.

She was very kind and loving towards all people, no matter who they were. If she ever saw anyone sad or lonely, she'd go cheer them up with her big, bright smile. Caryl had a great personality and sense of humor. She always had something funny to say. She was very optimistic and was always cheerful.

Caryl and I had been friends since we were three years old. She was and always will be my best friend and I admire her very much. Even though she was only thirteen when she died, in my eyes, she was the most loving and caring person who ever lived.



Caryl Brock

Through Caryl's death we have learned to value life and friendship. And Caryl, if you're listening, we want you to know that we love you, we miss you, and you'll always be my hero. Thank you! ♦

## The Best Therapy

by Carol Siniawski

The first few months after our son Jake was diagnosed were really tough. You all know what I am talking about. I had a rough time trying to get through each day with this new terrible stress in my life. It took me a while, but I now have a plan that works really well for me. I want to share it with others, in the hopes of helping them find ways to cope.

The first thing I decided to do was to get well educated on FA, genetics, blood cells—whatever the current pertinent topic was for Jake's latest medical situation. Becoming an informed, knowledgeable parent has helped me tremendously. It has been good for me mentally, of course, but also has helped me emotionally. I feel a little more in control, now that I know more of the details and can ask informed probing questions. It's a

feeling of empowerment. I felt so helpless at diagnosis. This was a wonderful change.

The second thing that helped me emotionally was trying to help others. I remember how much Lynn Frohnmayer helped me emotionally over the phone, when Jake was first diagnosed. She still may not realize how helpful that was, and I don't remember whether I thanked her. I thought to myself, just weeks after diagnosis, how strong Lynn was and how I never thought I'd ever be able to reach that point. I'd never be able to have so much to offer to another. That was five years ago, and I have grown a lot since then.

The first time I helped another FA family understand something emotionally or technically really made me feel good. This was my first

step to becoming strong like Lynn. I subconsciously started paying closer attention to other opportunities where I could help another family. I grew stronger by helping others to grow stronger. Then I started offering to talk to newly diagnosed families to see if I could help them "over the hump" of diagnosis. I also wrote articles for the *Family Newsletter*, sharing my experiences so others could avoid learning the hard way, as I sometimes did.

As I look back, I underestimated the power of helping others. It's been wonderful for me. You may not think that you have much to offer, just as I thought in the beginning, but you have more to give than you think. Don't underestimate yourself or the power of giving, as I did. It's great. Try it! ♦

## Dale Keegan Offers Comfort

*Dale Keegan, who lost her talented daughter, Anna, following a bone marrow transplant, wrote to comfort another grieving mother. We quote, in part, from her letter:*

"I heard the news of your loss and realized that I really didn't know how to write to you and offer any comfort, as this terrible tragedy made me realize that I truly don't know how to deal with my own Anna's death. So I'm not much damned use to anyone else in his or her sorrow. It really is an indescribable experience. Life becomes a constant battle to remain positive and not to allow everything to seem pointless.

As you said in your letter, the only consolation is that our children would have hated the quality of life they had at the end. My overwhelming feeling was one of relief for Anna when the suffering had become endless and she was finally spared any more. Where there's life there's hope certainly, and we fight like hell to hang on to that hope. But it becomes a selfish exercise when our hope is offering only suffering to these amazing children of ours.

We all approach these hurdles from our own vantage point and my fourteen-year-old son, John, repeatedly expresses concern over how your children are feeling. I can't imagine what it feels like to lose a brother or a sister. But John feels a great empathy with your family. He and Anna were extremely good friends—he says he's lost his very best buddy. I think he was at least lucky to have known that deep friendship when he did. Julia, our 21-year-old is lost, too, and is very impatient with people's apparently small problems and irritations. She becomes quite angry with them, which I hope passes, for hers and others' sakes!

## In Loving Memory

Caryl Brock  
6/3/82 - 11/30/95

Kent Hite, Jr.  
2/13/87 - 10/26/98

Jesse Barnes  
5/14/88 - 1/25/99

Joanne Rowland  
4/3/80 - 1/17/99

Paige Ellis  
5/26/67 - 2/16/99



*Our sorrows and wounds are  
healed only when we touch  
them with compassion.*

Please take some time out for yourself, so you can sustain yourself for what lies ahead. And please learn to see the humor in as many things as you possibly can. Enjoy as much laughter as you can feasibly squeeze out of life with your other children. This is Anna's legacy to us. She managed to find something funny in every situation right up until a few days before she died. And laughter is certainly a great medicine. Julie, John and I use it greedily.

Anna requested that her ashes be buried under a Magnolia tree. We established an endowment at Eden Gardens, a beautiful public park in Auckland, and Anna's ashes are buried at the roots of a magnificent young tree right at the top of the hill. Her name plaque is beside her tree. It had the most glorious flowers this spring. I'm sure she would approve.

Anna's great musical talent lives on in the form of two cups for musical competition and performance, and a scholarship. I was asked to present these awards at two separate

concerts, and I know she would have been proud of the talented recipients.

One of the millions of Anna's projects was to create embroidery designs. In her long days in the hospital she drew wonderful graphs. I hope to complete the two embroideries she designed and graphed.

She planned to learn calligraphy and to attend life-drawing classes this year, so this term I have enrolled in both and have really enjoyed these challenges. No art gallery will be beating a path to my door, I know, but it is most satisfying to try out some new and interesting skills.

I am very conscious of some small satisfaction I experience in helping to complete some of Anna's unfinished business. I don't mean to become obsessive about it, but just to work through and complete these things on her behalf. I don't know if any of this is helpful to you, but I only offer it as a suggestion of how I am trying to cope with the loss of Anna.

My love and most deeply felt sympathy to you all." ♦

## My Daughter's Journey with FA

by Joan Peters of Prince Edward Island, Canada

I became aware of this wonderful organization only in the spring of 1998 and how happy I was to hear of it. I sure could have used the support of this organization when I felt like my world had fallen apart.

My story begins in August 1985 when our beautiful baby girl, Terri-Lee, was born. She had one thumb missing and the other thumb was just not right. Besides that, she was very small, weighing only 3 lbs, 5 ozs. The doctors didn't give us any reason to be too concerned. They said lots of babies are born small and some are born with problems more serious than missing thumbs. So we didn't think too much about it. But the doctors said they were going to do some tests to determine why she was small and missing a thumb. After what seemed to be millions of tests, our daughter was diagnosed with Fanconi anemia, four months after she was born.

After many consultations with doctors in Nova Scotia and in Ontario, we found out just how bad this disease was. We were devastated! We were told that she could go on with very minor problems for a long time and, then again, maybe not. They would monitor her closely. The end result for her was a bone marrow transplant. After many discussions between doctors, we were told that they would do her transplant in Toronto, Ontario, using the Paris protocol. Why use the Paris protocol, we asked? Because Toronto had done only four Fanconi anemia transplants, and none was successful. Just what we need to hear: more bad news. But Paris had a success rate of 50%, so doctors would use the Paris protocol.

Most important was to get a good match for Terri-Lee. We were all tested and our six-year-old daughter, Krista, was a perfect match. Finally, something was going right.

During the next six years we visited many doctors and had many tests done. Terri-Lee had a few transfusions. We took one day at a time. In 1991, six years after our daughter was born, we got the dreaded call. The time was right. We had to go to Toronto for the transplant.

We arrived in Toronto on April 13, 1991, and after chemotherapy, radiation and many tests, Terri-Lee was transplanted on May 1, 1991. Every day, we just waited and waited for something to happen. Of course, we expected her to lose her hair (this was a big thing for a six-year-old) and develop mouth sores, but other than that, nothing out of the ordinary happened. We were very apprehensive as we and the doctors felt that things were going too well. Our donor, Krista, who was ten at the time, did extremely well. We just couldn't believe it. At least, we didn't have to worry about her anymore.

After about ten days, the doctors told us that it seemed that Terri-Lee's bone marrow was beginning to work, but not to get our hopes up too soon. You can be sure we didn't, because we thought, everything is going so smoothly, something is bound to happen. But every day, the reports were good. Her bone marrow was working and things were looking really good for her. The doctors were amazed with her progress, and on the 21st day, they came and gave us the good news. We could leave the hospital, but still needed to stay in Toronto. We were so happy just to



*Terri-Lee and Krista Peters*

get out of the hospital. We visited the hospital every day for approximately three weeks and then went home to Prince Edward Island. What a happy day.

It is now 7 1/2 years later, and all is well. As of today, she has not had a setback and is doing perfectly fine. Of course, we still visit doctors once a year for many tests, but so far, so good. We continue to hope and pray that our nightmare is over and she will continue to thrive.

But we do have one concern. For 13 1/2 years of age, our daughter is very petite. She weighs only 44 1/2 pounds and stands 4 feet tall. She hasn't much of an appetite, although we continually push her to eat. The doctors attribute her size to Fanconi anemia and say that a lot of the kids with this disease are small. I'm very curious to find out if this is so. Being a teenage girl, her size is bothering her quite a bit. The doctors told us we could put her on growth hormones but then, the chances of her developing cancer would be 50%.\* I told them to forget it. I'd rather have a small child than a sick one.

*continued on page 20*

## Living With Fanconi Anemia

Hi, my name is Jessica Paulson. I am 17 3/4 and have Fanconi anemia. When I was 15 months old, I was diagnosed because of failure to thrive.

I have been very lucky that I have had no blood problems so far. My blood counts remain normal. They check me every six months, which I hate. It seems like every time I find someone who knows how to draw blood without too much pain, that person moves away after a while.

What I have had to put up with is the fact that I am short. Even though I am 17, my bone age is that of a 12 year old.

Also, the kids at school treat me differently. I have the body of a 12-year-old, but most boys want a girl with the body of a 17-year-old. I have years of growing left and, when others are looking a bit old, I'm going to look young. Most people think that looking their age is bad, but I would give just about anything to look my age, even if I were 50.

One thing that really makes me upset is that, when I have gone to camp to be with others like myself, most of the other teens treat me differently, too. They should know that this disease affects all of us in different ways and be accepting of every-

one, but then again, why should they be any different?

I do get sick a lot with colds, flu and strep. This causes me to miss a lot of school so I have to work hard at staying caught up. I won't share food and drinks with anyone which is hard for some kids to understand. They say that I'm not sick. I tell them they carry germs that their bodies can fight off, but my body can't and I don't need to take the chance. Most people understand after a while.

Among some of the questions that I am asked is, "Why haven't you had your extra thumb removed?" I tell them that this is the least of my problems and ask if they think having it removed is going to make my hand look normal? I don't think so. My thumb doesn't hurt me, and besides, why would I want to go through pain like that when I don't have to.

I have chosen not to abuse my body by taking drugs (smoking, drinking, etc.). That makes some people uncomfortable, but when they really get to know me they find out I'm just a normal teenage girl who is short, with a mind of her own. I love going to movies and parties, I love chatting on the phone and joining internet chat lines. I love to read



*Jessica Paulson*

and listen to music.

I am a senior this year. In order to graduate, all seniors have to do a seven-month-long "Senior Project." It involves choosing a subject, finding a mentor, researching, writing a lengthy paper and doing some sort of visual. The final step is giving a speech in front of community members who judge you. You must complete and pass your project if you want to graduate. What better topic for me to explore than Fanconi anemia. I am ready to tell the world about myself and this deadly disease. I am enrolled in a speech class and have already given a short speech on FA. It went really well! Wish me luck for the rest of my project. I'll let you all know how it went. ♦

### Use of Logo

This is just a reminder to our FA families: please use our logo or letterhead only after you have consulted the staff of the FA Research Fund, and received their approval. This is necessary to be sure our messages are accurate and consistent. It also helps to avoid legal complications. We are happy to collaborate on fundraisers and mailings.

## Protect Children Against Excessive Sunlight

With spring upon us and summer fast approaching, FA families should make sure that patients (all of us, in fact!) are protected against damaging rays from the sun. Your editor consults a dermatologist on a regular basis due to youthful carelessness. This physician recommends wearing hats. He also insists that sunscreen be applied on a daily, routine basis, that the SPF be 15 or higher, and that the product offer both UVA and UVB protection.

Your local pharmacy will have a large variety of products which should meet the needs of all family members.

A company called Down Under Wear makes children's play clothing suitable for beach and swim wear which, they claim, provides outstanding protection from the sun's rays. You can call them toll free at (877) 266-2971 or FAX (714) 220-0415 for a brochure and additional information. ♦

## We Welcome New Families Who Have Joined Our Support Group

Ann Anderson

151 Quaker Lane  
North Scituate, RI  
(401) 934-2537

**Thomas Konikowski** ~ DOB  
5/13/87

Rudolph & Diane Brand

41415 Yarrow Central Road  
Chilliwack, BC  
Canada V2R 5G5

**Danielle** ~ DOB 2/3/94,  
deceased 2/19/95

**Jeremy** ~ DOB 5/30/95

**Monique** ~ DOB 11/24/98

**Fiona** ~ DOB 8/27/97

**Richard Briga**

909 Skyview Drive  
Scranton, PA 18505

(717) 343-4403

DOB ~ 9/7/57

Sibling BMT in Minnesota  
11/17/98

Daniel and Lucy Del Toro

1121 Hollowood Ct.  
Perris, CA 92571

**Dena** ~ DOB 2/18/97

**Marissa** ~ DOB 11/29/89

**Violet** ~ DOB 9/17/91

Marie DiMercurio

32915 Birchwood  
Chesterfield, MI 48047

(810) 716-0702

**Fabrizio** ~ DOB 11/9/98

**Alejandria** ~ DOB 7/21/97

Fabio and Sune Frontani

Via Crocco #14/4

Genova

Italy 16122

011 39 010 215566

Fabfro@hotmail.com

**Carlotta** ~ DOB 8/7/92

Greta ~ DOB 5/9/96

Francesco ~ DOB 10/8/98

Albert and Edna Gray

503 E. Parker St.

Baxley, GA 31513

(912) 367-0005

**Albert, Jr.** ~ DOB 3/24/94

**Peggy Longacre** ~ DOB 10/10/92

Kelly and Frank Hamilton

Rt. 2, Box 1655

Mannford, OK 74044

(918) 865-4084

**Frankie (Francis)** ~ DOB  
7/16/96

**Alexis** ~ DOB 12/11/90

**Cassie** ~ DOB 8/07/88

Lisa and Chris Munday

5829 Spring Hollow

Toledo, OH 43615

(419) 861-1166

**Cody** ~ DOB 9/28/92

**Chelsea** ~ DOB 6/27/91

Michael and Sally Parum

701 SE 4th St.

Grand Prairie, TX 75051

(922) 264-8225

**Trent** ~ DOB 12/27/88

**Brett** ~ DOB 2/21/85, deceased  
10/4/92

**Matt** ~ DOB 6/7/83

Names in bold print indicate  
person with Fanconi anemia.

### Helpful Publications

Leslie Roy suggests several publications which might be of help and interest to FA families. They are:

*Bone Marrow Transplants, A Book of Basics for Patients*

Published by:

BMT Newsletter

1985 Spruce Ave.

Highland Park, Illinois 60035

(708) 831-1913

The BMT Newsletter also produces an excellent newsletter which covers a wide range of topics related to bone marrow transplants.

*Emotional Aspects of Childhood Leukemia: A Handbook for Parents*

*Bone Marrow Transplantation and Peripheral Blood Stem Cell Transplantation*

*I'm Having a Bone Marrow Transplant*, a coloring book by bone marrow transplant patients

Published by:

The Leukemia Society of America

600 Third Avenue, New York, NY 10016

(212) 573-8484

(800) 955-4LSA, (Public Information Resource Line)



# Valuable Materials Available Through the National Marrow Donor Program

By Carol Siniawski

This past year I was selected to be a member of the Patient Services Committee of the National Marrow Donor Program. We work with the NMDP's Office of Patient Advocacy. We provide information, support, education, and even intervention for those families making decisions about unrelated bone marrow transplants.

Our Patient Services Committee is made up of family members of those who are currently searching for a donor or have undergone a bone marrow transplant. Committee members volunteer their time and efforts. Our sole purpose is to represent the family's best interest.

During my orientation to the NMDP, the OPA and the PSC, I was

surprised, impressed and amazed at all the information readily available. We have been searching for five years for a donor for Jake and I had never seen some of these well written resources. Did you know that two different folders are available to families to help them better understand the search process, the transplant process and even provide some data on different transplant centers? A new financial guide is geared towards helping families with the financial aspects of a BMT.

We have information for the doctors treating patients who will need an unrelated BMT. There is much material on donor recruitment, should you decide to have a marrow

drive to add people in your community to the National Registry. Many pamphlets are geared towards specific ethnic groups like Hispanics, Native Americans or Asian and Pacific Islanders.

This material makes very helpful and interesting reading. Please call the NMDP's Office of Patient Advocacy at its toll free number, (888) 999-6743, and ask for anything I have mentioned here. If the response is anything less than warm and helpful, let me know. As part of the Patient Services Committee I need to know that the needs of patients and their families are being met. Let me know if you have any great ideas for our future work. ♦

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## Subtyping of FA Patients

*continued from page 5*

### (4) Immunoblotting

Antibodies to the FANCA, FANCC and FANCG proteins have been produced in the D'Andrea lab. Extracts from patient cell lines are probed with these antibodies to detect absence of the FANCA, FANCC or FANCG proteins. While rapid, this method can yield false positive results. For example, the FANCA protein may be absent in the cell line of a patient of complementation group B. Therefore this test is best used in conjunction with retroviral complementation.

### Updates:

D'Andrea lab: We have recently used a combination of retroviral gene transfer and immunoblotting to con-

firm successfully the FA subtype of 26 FA patients and families. More recently we have extended these studies to determine the subtype of several other FA patients.

Grompe lab: We have performed retroviral complementation analysis on 19 additional fibroblast cell lines. Of these, 16 belonged to complementation group A and one was from group G. The other two cell lines were from complementation groups other than A, C and G. We are planning to complete the complementation analysis on approximately six cell lines per month until all cell lines in the repository have been sub-typed.

To submit cells for complementation analysis, please consult Grompe's *Appendix in Fanconi Anemia: a Handbook for Families and Their Physicians*. This contains all the

details about who should submit cells, what information to send, how to collect and ship the cells, and who pays for the shipping and testing. Grompe can be reached at:

Dr. M. Grompe  
Department of Medical and  
Molecular Genetics, L103  
Oregon Health Sciences  
University  
3181 SW Sam Jackson Pk Rd  
Portland, OR 97201

Tel: (503) 494-6888  
FAX: (503) 494-6882  
email: grompem@ohsu.edu

Dr. D'Andrea can be reached at:  
a\_d'andrea@macmailgw.dfci.harvard.edu ♦

# FAMILY FUNDRAISING

## Family Fundraising Efforts

In 1998, proceeds from family fundraisers accounted for 70% of the FARF total budget. This is truly an outstanding effort, especially if one considers that our families already carry the emotional and financial burden of living with Fanconi anemia. Family fundraisers will remain critical to the success of our mission. Given the competitive nature of today's fundraising climate, many of our fundraising strategies will be based on convincing donors and foundations to match our efforts.

Our support group has grown to 540 families worldwide. However, only sixteen families conducted special fundraising efforts including letter campaigns, United Way promotions, dinners, marathons, auctions and school assisted fundraisers. We know it is not easy to raise funds, especially for those families who make fundraising an annual event. The task becomes tiresome, and the responsibility weighs heavily. **But the burden should not fall on a handful of families. It needs to be shared by each and every one affected by this disease. If just one of our primary fundraising families were unable to continue, our efforts to advance science would be seriously jeopardized and, perhaps, would end altogether.** On the other hand, if each family raised at least \$1,000 annually, it would help to meet the ever-increasing need for more science dollars.

Congratulations and a big thank you to all the families who made special efforts toward raising a total of \$371,428 during the second half of the year. The sixteen families who did special fundraisers raised

\$308,600 of our total. This includes generous stock donations of \$27,000. United Way contributions, Combined Federal Campaign donations, and personal and memorial contributions account for the rest of the total. Because of the above efforts, we exceeded the Summerville Challenge Grant goal of \$60,000.

Funds raised during the second half of 1998 were attributed to the following families:

**\$220,000+**

Dave & Lynn Frohnmayer

**\$30,000+**

Andrew & Vicki Athens

**\$14,000+**

Allen Goldberg & Laurie Strongin  
Chris & Susan Collins

**\$5,000+**

Deane Marchbein & Stuart Cohen  
Eric & Beth Losekamp  
Pat & Maria Gleason  
Jack & Lisa Nash  
Jim & Carol Siniawski

*continued on page 19*

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## Regional Networks to be Created in 1999

A generous grant from the Meyer Memorial Trust enables us to establish regional networks of FA families. During the upcoming year, we plan to hold half-day meetings in four or five regions in the United States. Meetings will enable families to learn more about Fanconi anemia and current therapies from guest speakers, to share information about local medical resources and expertise in FA, and to join forces to increase our fund-raising capacity.

Most of us with this illness feel extremely isolated. Those who have not attended a family meeting may never have met another family with this disorder. Some families who have lost children to this illness may feel that they no longer have a role to play in our support group. Participating in regional networks in a variety of different capacities should enable

families to learn from one another, decrease isolation and strengthen our resolve and ability to combat this devastating illness.

### Your Help Is Needed for Regional Organization

The FA Research Fund will contact families and researchers to schedule a number of regional meetings for the spring, summer and fall of 1999. Staff members from FARF will attend. Families can help in a number of ways. They can locate a meeting place, host a meeting in their home, phone other families to invite them to attend, arrange presentations by local physicians, or write a report for our family newsletter. **Please get in touch with the FA Research Fund if you can volunteer some of your time and ideas to make regional networks a success.** ♦

## Family Fundraising Efforts

*continued from page 18*

### \$2,000+

Keleher Family  
Jack & Tannis Redekop  
Erik & Lori Salo  
Bill & Connie Schenone  
Rene LeRoux  
Marc & Sandy Weiner

### \$700-1200

Donna DellaRatta  
Teddi Matlack Gray  
Susan Jackson  
Jeff & Beth Janock  
Robert & Jennifer Kiesel  
Steve & Alison McClay  
Gil & Peggy McDaniel  
Griff & Cecilia Morgan  
Des Murnane  
Rick & Lynn Sablosky  
Jeff & Debby Slater  
Robert & Lynn Tharp  
Mark & Susan Trager  
Steve & Melissa Turner  
Mike & Beth Vangel

### Up to \$700

Ken & Jeanne Atkinson  
Cherie Bank  
Mark & Linda Baumiller  
Gilbert Bodier  
Diane & Michael Bradley  
Richard Briga  
Bob & Carole Cavanaugh  
Brian & Margaret Curtis  
Bill & Pat Danks  
Day Family  
Pat & Mary DiMarino  
Sam & Chantal Doughty  
Elzinga Family  
Gary & Melody Ganz  
Tom & Monica Garry  
Dave & Paula Ceresa Guidara  
Michael & Tirzah Haik  
Ida Hodge  
Chris Hull  
John & Irene Kalman  
Nobuo & Ayako Kawasaki  
Terry & Therese Robertson

John & Karilyn Kelson  
Kwon Family  
Gayle Licari  
Dennis & Sharon Lower  
Greg & Lynette Lowrimore  
Bill & Jackie Lucarell  
Glen & Roberta Magill  
Jack & Pam McCarty  
Cecelia Meloling  
John & Barbara Miller

David & Sheila Muhlen  
Ron & Fredi Norris  
Paulson Family  
Leonard & Jan Riley  
Glen & Maureen Russo  
Bob & Andrea Sacks  
Severt & Beatrice Score  
Robert & Linda Scullin  
Bryan & Karen Siebenthal  
Richard & Janice Thomas



*Dancing the night away at Lake Geneva*

## Annual Family Meeting

*continued from front page*

science presentations will be held over the weekend followed by two days of psycho/social sessions. Families can attend either session or stay for the entire meeting.

The science meeting will begin with dinner on Friday, August 13, and end early afternoon on Sunday, August 15. Researchers and treating physicians will address topics such as FA 101 (a session for those families new to this disease), post-transplant issues, leukemia and other cancers, diagnosing FA and related syndromes, guidelines concerning treatment options, a new protocol for sibling transplants, new approaches to unrelated or mismatched transplants and gene therapy.

The psycho/social portion of the

meeting will begin Sunday afternoon, August 15, and continue through Wednesday morning, August 18. Leslie Roy and Nancy Cincotta will lead discussions relevant to coping and living with FA. Other agenda items, such as nutrition and/or coping with learning disabilities, may be included, depending upon families' interests. A comprehensive children's program will be offered during all presentations for the duration of the entire meeting.

Evening activities will include a magic/juggling show, Karaoke night and bonfires. The meeting should prove highly educational, emotionally supportive and fun!

Families have received information related to cost and a pre-registration form. **We hope to see all of you in Wisconsin this coming August!** ♦



Esther Lombardi



Katie Douglass

## New Staff at the Fund

Esther Lombardi joined our team in mid-December as Family Services Assistant, a new position supported by a generous grant from the Meyer Memorial Trust. Esther will assist us with establishing the Regional Network of FA families.

Katie Douglass joined us in mid-January, taking Caryl Stone's place. Both Esther and Katie bring with them an impressive set of skills and the heartfelt desire to support our mission. ♦

## My Daughter's Journey with FA

*continued from page 14*

I would be really interested in hearing about other children and if they are of a small stature.

I thank you for listening to my story and I hope it may give courage to you. Our miracle happened and it could for you. I also wish each and every one of you the very best in the future.

Sincerely,  
Joan Peters  
Hunter River R.R. #3,  
Prince Edward Island,  
Canada COA INO  
Home : (902) 963-2227  
Fax: (902) 892-0452  
e-mail: jpeters@cupe.ca

*quent risk of cancer at 50%. If such a study exists, please inform us. Specialized centers can perform tests to determine whether an FA patient has a growth hormone deficiency or might benefit from this therapy. Previous newsletters have carried extensive articles on the risks and potential benefits of the use of human growth hormone. This therapy should be discussed carefully with an endocrinologist knowledgeable about Fanconi anemia. ♦*

*\*Editors' note: We are unaware of any study which suggests that the administration of human growth hormone to FA patients places the subse-*



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Katie Douglass

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# 10TH ANNUAL FANCONI ANEMIA SCIENTIFIC SYMPOSIUM

November 1-2, 1998

Denver, Colorado

## PROGRAM OF PRESENTATIONS:

### SESSION I GENE IDENTIFICATION AND CHARACTERIZATION

**Chair: Manuel Buchwald**

**Hans Joenje:** Complementation studies - Update 1998

**Robb Moses:** Amplification of 3p correlates with the reversion of FA-D fibroblasts

**Martin Digweed:** Localization of a Fanconi anemia gene to chromosome 9p

**Johan de Winter and Quinten Waisfisz:** The Fanconi anemia group G gene is identical with human *XRCC9*

**Chris Mathew:** Mutation detection in the *FANCA* gene: strategy and outcome

**Arleen Auerbach:** A spectrum of mutations in *FANCA* and genotype-phenotype correlations

**Anna Savoia:** Molecular analysis of FA genes

### SESSION II PROTEIN FUNCTION STUDIES

**Chair: Hagop Youssoufian**

**Alan D'Andrea:** Functional interactions of the FA proteins

**Gary Kupfer:** A patient-derived mutant form of the FA protein, *FANCA*, is defective in nuclear translocation

**Frank Kruyt:** The FA proteins, *FANCA* & *FANCC*, function in different subcellular compartments

**Muriel Lambert:** A deficiency in a 230kDa DNA repair protein in FA complementation group A cells is corrected by *FANCA* cDNA

**Maureen Hoatlin:** Development of monoclonal antibodies able to distinguish between wild-type and L554P mutant *FANCC* proteins

### POSTER PRESENTATIONS:

**Sat Dev Batish:** Prenatal diagnosis for FA using cytogenetic and molecular techniques

**Steven Arkin:** A flow cytometry based screening test for FA

**Sat Dev Batish:** Retroviral gene transfer into Fanconi anemia T lymphocytes as a diagnostic tool

**Hans Joenje:** Oligonucleotide-mediated genetic correction of FA mutations: fact or fiction?

**Peter Verlander:** Evidence of somatic mosaicism in hematopoietic precursor cells in an FA group A patient

**W. Clark Lambert:** Undiminished rates of DNA synthesis in FA lymphoblastoid cells treated with the interstrand DNA crosslinking agent 4, 5', 8-tri-methyl psoralen activated by long wavelength ultraviolet radiation

**Dora Papadopoulo:** The fidelity of recombination pathways involved in the processing of double strand breaks is affected in FA cells

**Laura McMahon & Nydia Ramos:** A 230 kDa DNA repair protein which is deficient in FA complementation group A, B, C, and D cells forms a complex with the *FANCA* and *FANCC* proteins in the nucleus

**Kenneth Grossman:** SNMID, a yeast mutant specifically sensitive to DNA crosslinks, is not corrected by overexpression of human SNMI cDNA

**Irene Garcia-Higuera:** Identification of nuclear proteins that bind to *FANCA* and *FANCC*

**Pia Huber:** Interactions of Fanconi anemia proteins

**H.J. van de Vrugt:** A murine homologue of the FA complementation group A gene

**Eric Nisbet-Brown:** Enhanced clonogenic survival of primary bone marrow progenitor cells from FA patients following retroviral-mediated gene transfer

### SESSION III HEMATOPOIESIS, APOPTOSIS, LEUKEMOGENESIS, AND ONCOGENESIS

**Chair: Blanche Alter, MD**

**Margaret Baron:** Induction and modulation of hematopoiesis and vasculogenesis by embryonic signaling molecules

**Steven Arkin:** DNA damage is a triggering event for apoptosis in Fanconi anemia

**Randall Phelps:** Deficiency in S-phase delay in FA-C

**Holger Hoehn:** Cellular phenotypes in FA as a function of age and complementation group

**Blanche Alter:** Myelodysplasia as a predictor of outcome

**Grover Bagby:** The *FANCC* gene product suppresses a storm of death signals

**Robert Arceci:** Costimulatory targeting conjugates that stimulate antileukemic immune responses

**Chaim Roifman:** Novel therapy of acute myeloblastic leukemia

### SESSION IV DEVELOPMENTAL MODELS AND EXPERIMENTAL THERAPIES

**Chair: Grover Bagby, MD**

**D. Wade Clapp:** Hematopoiesis in *FancC* mice

**Madeleine Carreau:** *FancC*<sup>-/-</sup> mice have fewer CD 34<sup>+</sup> hematopoietic cells and an impaired hematopoietic reconstitution ability

**Freerk Arwert:** The *FancA* gene in the mouse (*FancA* KO mouse and FANCA mouse homologue)

**Johnson Liu:** Fanconi anemia: molecular pathophysiology and treatment strategies

**Chris Walsh:** Selected growth advantage of gene corrected Fanconi anemia group C KO mice

**John Wagner:** Unrelated donor hematopoietic cell transplantation (HCT): current results and future directions

**William H. Fleming:** Toward in utero transplantation for Fanconi anemia

**David Curiel:** Tropism-modified adenoviral vectors for cell-specific gene delivery