March 13, 2014

Dear Friends,

FA researchers at the Fred Hutchinson Cancer Research Center in Seattle received FDA approval in 2012 for a Phase I/II clinical trial of gene therapy for FA-A patients 18 years of age or older. They have now announced that their clinical trial has been approved for pediatric FA patients 4 years or older by the Food and Drug Administration. Attached is a copy of the official announcement letter sent to FARF along with the inclusion and exclusion criteria. Please note that more information about the trial can be found at *www.clinicaltrials.gov*. The identification number for the trial is NCT01331018.

The trial opens May 1, but you may contact them sooner. If you are interested or have questions, please contact Jennifer Adair, PhD, at jadair@fhcrc.org or 206-667-7110.

As the letter explains, this would be the first gene therapy trial for FA patients using a lentiviral vector to deliver un-mutated copies of affected genes to the cells of the patient's body in order to treat bone marrow failure.

Teresa Kennedy, Director of Family Support Services, asked the researchers important questions about the trial that would be useful for FA families. Their answers are included with this letter.

The opening of this trial represents an exciting re-start of a therapy for FA that has experienced ups and downs for more than a decade. The Fund has co-sponsored four meetings of an international gene therapy working group, chaired by FARF Scientific Advisory Board member, Jakub Tolar, MD, from the University of Minnesota. At the group's last meeting, held in October 2013 in Boston, updates on the clinical trials in Seattle, Indiana, and Madrid, Spain, were presented. None of these trials have currently enrolled patients, but hope to in the near future.

The trial at Fred Hutchinson is only open to FA-A patients, but the researchers hope to use information and data from this preliminary trial to extend their trial to other complementation groups in the future.

We will keep you posted.

Sincerely,

Laura Hays, PhD
Executive Director
Fanconi Anemia Research Fund

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

February 28, 2014

Hans-Peter Kiem, MD
Transplantation Biology
Clinical Research Division
Mail Stop D1-100
Tel: 206.667.4425
Fax: 206.667.6124
E-mail: hkiem@fhcrc.org

Fanconi Anemia Research Fund, Inc.
1801 Willamette Street, Suite 200
Eugene, OR 97401

Re: **A Phase I/II Clinical Trial of Gene Therapy for Patients with Fanconi Anemia (A Complementation Group)**
IND Sponsor: Hans-Peter Kiem, M.D.
Protocol PIs: Pamela Becker, M.D., Ph.D. and Hans-Peter Kiem, M.D.
Study contact: Jennifer Adair, Ph.D.

To Whom It May Concern:

We are happy to notify the FARF that our Phase I clinical trial of gene therapy for FANCA patients was approved to enroll pediatric patients by the Food and Drug Administration and we have secured additional funds from the Gene Therapy Resource Program of the National Heart, Lung and Blood Institute to allow enrollment of 3-5 FANCA patients. Patients may begin enrollment as early as May 1st, 2014.

This is the first lentivirus-vector based gene therapy study for patients with Fanconi anemia. The trial incorporates novel gene delivery by a safety-modified lentivirus with improved techniques for *ex vivo* handling of FA patient blood cells and will be conducted at the Fred Hutchinson Research Center in Seattle, WA in conjunction with the Seattle Cancer Care Alliance and the University of Washington Medical Center. Importantly, due to the extended time required to obtain pediatric approval and secure additional funds for this study, Genzyme/Sanofi will no longer supply the mobilization agent, plerixafor (Mozobil®), which was to be administered in combination with Neupogen® (filgrastim or G-CSF). Since previous research has shown that Neupogen® alone is not sufficient to promote collection of the desired stem cell numbers in FA patients, we have modified the protocol to include bone marrow harvest only. This will also reduce risk to the patients by eliminating the possibility of apheresis and bone marrow harvest in the same day. Moreover, bone marrow harvest is the stem cell collection method currently being used in gene therapy for immunodeficiencies and other genetic diseases affecting pediatric patients. Another advantage of this approach is that it will minimize the amount of time that patient stem cells are maintained outside the body, which is critical for the fragility of FA cells.
I have included a modified version of the trial description previously provided to the FARF with this letter. This information and more can also be found on the National Clinical Trials Registry web page (www.clinicaltrials.gov; NCT #01331018).

We look forward to working with the FARF in conduct of this trial, partnering to identify potential patients, as well as communicating the exciting results of these initial studies.

Thank you for your continued support in this endeavor. Please contact me if you have any questions or concerns.

Sincerely,

Hans-Peter Kiem, M.D.
José Carreras / E. Donnall Thomas Endowed Chair in Cancer Research
Associate Head and Member, Program in Transplantation Biology
Fred Hutchinson Cancer Research Center
Professor of Medicine / Adjunct Professor of Pathology University of Washington School of Medicine

Clinical Trial Description in Question/Answer format:

1. **Who is eligible?**
   The trial is for patients affected by Fanconi anemia, ages 4 years and older in the complementation group A (FANCA). Patients from the United States and around the world may enroll in the study. The expected enrollment is three to five patients. Patients need to meet specific inclusion criteria, but they need not be in severe bone marrow failure in order to participate. (Go to www.clinicaltrials.gov for specific criteria. The registry number for the trial is #01331018.)

2. **What is the time commitment?**
Patients who successfully enroll in the trial are expected to be in Seattle for 6-8 weeks.

3. **Where does the trial take place?**
   All procedures will be done at the Seattle Cancer Care Alliance, Seattle Children's Hospital or the University of Washington Medical Center. Most procedures are performed on an outpatient basis, but inpatient stays of at least one night are required during the administration of the gene therapy.

4. **What is the gene therapy process?**
   The first 2-3 weeks of the trial include pre-treatment evaluations. Patients will then undergo a bone marrow harvest to collect stem cells. Researchers will examine the number of stem cells in the collection. If there are enough stem cells, the cells will incubate overnight in the presence of a reducing agent and a vector to correct the defective FANCA gene. The next day, the researchers will infuse the gene-corrected cells back into the patient. After patients receive the gene-corrected cells, they will be monitored in Seattle for engraftment through peripheral blood samples taken once a week for four weeks. If successful, researchers will notice a *sustained* increase in patient blood counts, essentially curing the bone marrow failure aspects of FA.

5. **What happens next?**
   Once the patient returns home, i.e., in month #2 after the infusion, peripheral blood collection and testing is done every two weeks. In months #3 through month 12, the collection and testing drops to once per month. These samples can be taken in a patient's local community and shipped overnight to Seattle for testing. Patient follow-up lasts for 15 years after the infusion.

6. **What if the gene therapy doesn't work?**
   Unsuccessful gene therapy does not preclude a stem cell transplant in the future if needed. There is no predicted impact, one way or the other, on the future success (or failure) of a more traditional stem cell transplant.

7. **What are the risks?**
   According to Dr. Kiem, the infusion procedures involved in this trial are considered "standard" and there are no expected side effects of infusing a patient's own cells. The lentivirus vector that is used to correct the cells "has now been used for many years, for more than a decade," said Dr. Kiem. Dr. Kiem explained that this same vector has been used in large animal models (dogs and monkeys) with no side effects. In France, researchers have used this same type of vector in gene therapy to treat and benefit adrenoleukodystrophy (ALD) or "Lorenzo's Oil" disease, and researchers in Italy have used the same type of vector to treat patients with a similar type of disease called metachromatic leukodystrophy (MLD), and a different rare genetic disease called Wiskott-Aldrich syndrome (WAS). These patients are doing well, with no side effects from the gene therapy. In addition, the same type of vector is also being used in the United States to treat children with severe combined immunodeficiency (SCID) or "bubble boy" disease.

8. What about the costs?

The treatment-related medical expenses of this trial are covered by the institutions participating in the trial. Patients will be responsible for travel and living expenses while in Seattle, such as airfare, lodging and food. As a reminder, the Fanconi Anemia Research Fund can assist with making referrals to potential resources that patients may qualify for. In addition, the Fund has limited resources for which patients may apply for help with travel and living expenses while participating in certain clinical trials, including this one.

9. Not FANCA?

While this trial is specifically for FANCA patients, the researchers are hopeful that with success, future gene therapy trials will open for patients in all complementation groups.

10. Additional questions?

For questions about the clinical trial, please contact Jennifer Adair, PhD at (email: jadair@fhcrc.org or telephone: 206-667-7110). For questions about the Fund's clinical trials scholarship fund, please contact Teresa Kennedy (email: teresa@fanconi.org or telephone: 1-888-326-2664).