Friedreich's Ataxia Research Alliance UPDATE

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FOCUS ON RESEARCH

This issue of the FARA Update focuses on presenting the significant progress in basic and clinical research, successful development of mouse models and the opening of the largest Friedreich's ataxia (FRDA) clinical trial to date. The Update includes summaries of research conducted around the world and funded by FARA and other grantmaking organizations.

A Glossary of FRDA Research and Genetic Terms is provided for the purpose of helping readers understand frequently used terms in scientific research articles.

FARA focuses on awarding grants for innovative research and supporting conferences and workshops where promising areas of research can be explored in depth. FARA's goal is to accelerate research leading to effective treatments and a cure for Friedreich's ataxia and the related, early onset sporadic ataxias. FARA places a premium on encouraging new investigators to enter the field and assists established investigators by offering seed-grant funding. This approach allows investigators to develop their ideas and preliminary data and compete successfully for larger sources of funding. *(cont'd, p. 2)*

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First Annual Friedreich's Ataxia Bass Tourney

Brent Moore (on right) organized and hosted a bass tourney to raise funds for FARA. "Taking an idea and seeing it develop into reality has been both satisfying and rewarding. Taking an initiative in life rather than the passive approach provided me with a sense of accomplishment." (cont'd, p. 4)

Friedreich's ataxia is a life shortening, debilitating and rare genetic neurodegenerative disorder. Onset of symptoms usually occurs between the ages of 5 and 15. Symptoms include muscle weakness and loss of coordination in the arms and legs; impairment of vision, hearing and speech; aggressive scoliosis (curvature of the spine); diabetes; and a serious heart condition. Most patients need a wheelchair full-time by their late teens or early twenties. There are no treatments or cures. Most childhood-onset patients with this disease die in early adulthood. FARA is a 501(c)(3) tax-exempt non-profit organization. 100% of FARA donations are dedicated to supporting research leading to a treatment or cure for this relentless and devastating disease.

Molecular Biology of the GAA triplet-repeat mutation in Friedreich's ataxia

SANJAY BIDICHANDANI, M.B.B.S., Ph. D.
University of Oklahoma Health Sciences Center
Department of Biochemistry & Molecular Biology

This FARA grant, along with the support of an anonymous FRDA family, allowed excellent progress to be made in Dr. Bidichandani's research. It was instrumental in leveraging additional funding from the Oklahoma Center for the Advancement of Science and Technology for further mutation analysis in FRDA. The progress achieved from the FARA grant resulted in leveraging additional funds for FRDA research in the amount of $6 for every $1 from FARA.

Dr. Bidichandani's research findings centered on the instability of GAA triplet repeats. He found a striking degree of somatic variability, with 89-97 percent of alleles differing significantly from the original progenitor alleles. The differences were large (contractions and expansions of 24-154% of original repeat lengths). And, there was a distinct bias towards contraction, with a significant correlation between the proportion of contracted alleles and the length of the progenitor allele. Contractions and expansions were equally prevalent when the changes were small (less than 5% of allele length), whereas contractions were 2-3 times more frequent in large changes (more than 15% of allele length). This bias toward contraction contrasts with the expansion bias in similar alleles of the CTG triplet repeat in myotonic dystrophy. According to Dr. Bidichandani, "A potential long-term implication of the finding is that if one were to try to contract these expanded repeats one would simply have to accelerate a process that our cells are carrying out anyway." Further research is needed, but this could be a future therapy.

Comparative Incidence of FRDA in Mexico and the Indo-European Populations

Under the same FARA grant, Dr. Bidichandani analyzed a cohort of recessive and sporadic ataxia patients from Mexico in which his findings indicate the incidence of FRDA to be less than 10%. This is significantly less than the frequency observed upon similar analyses involving the Indo-European and North African populations. This reduced incidence is likely to stem from the correspondingly reduced frequency of the "long normal" alleles among Mexicans. This finding has important clinical implications for the diagnosis of FRDA in Mexico and in Mexican Americans, the largest sub-group of Hispanics in the United States.

Construction of a human cell model for Friedreich's ataxia

PIERRE RUSTIN, Ph. D.
Research Director, Centre National de la Recherche Scientifique, Paris, France

This FARA grant is supporting the efforts of Dr. Rustin's team to create a FRDA cell model using cultured human skin fibroblasts. The aim of the project is to construct Frataxin-lacking cultured human cells to be used later to screen a large number of chemicals so as to identify new compounds able to rescue Frataxin-lacking cells.

The FARA funding directly supports a post-doctoral fellow, Dr. Niklas Darin, who is actually developing the FRDA cells. The Rustin team (Drs. Vanna Geromel, Darin, Agnes Rotig, and Rustin) will use the cells to (1) study the role of frataxin in iron-sulfur cluster synthesis and destruction, (2) understand the role of frataxin in mitochondrial iron import and (3) test different drugs against iron accumulation or free radical production. The team plans to translate the results of these cultured cell studies into tests using the FRDA mouse models, and then to take the most promising compounds into human trials.

FRDA Mouse Models Developed

The first mammalian models for evaluating treatment strategies for human FRDA patients are now available to FRDA researchers. This significant breakthrough was made possible by the diligent efforts of a number of scientists around the world. Two particular milestones in this collaborative effort are attributed to the team of Cossee M, Puccio H, Gansmuller A, Koutnikova H, Dierich A, LeMeur M, Fischbeck K, Dolle P, and Koenig M, and that of Puccio H, Simon D, Cossee M, Criqui-Filipe P, Tiziano F, Melki J, Hindelang C, Matyas R, Rustin P, and Koenig M.

Cossee et al last year generated a mouse model by deletion of exon 4 of the FRDA gene, leading to inactivation of the FRDA gene product (i.e., no frataxin protein production). They showed that deleting the exon on both alleles causes embryonic lethality a few days after implantation, demonstrating an important role for frataxin during mouse development. Puccio et al recently used a conditional gene targeting approach to generate two FRDA mouse models. One model manifests a frataxin deficiency in skeletal muscle while the other is frataxin deficient in neurons and cardiac muscle. Together, the two models present important, progressive, pathophysiological and biochemical features of the human disease. These features include cardiac hypertrophy, neurological dysfunctions (ataxia), and deficiencies in the iron-sulfur-cluster enzymes essential in the mitochondrial respiratory chain. These models also demonstrate time-dependent intramitochondrial iron accumulation that occurs after onset of pathology and after inactivation of the iron-sulfur-cluster enzymes.

In October, Pook MA, Al-Mahdawi S, Carroll CJ, Cossee M, Puccio H, Lawrence L, Clark P, Lowrie MB, Bradley JL, Cooper JM, Koenig M, and Chamberlain S., announced they had generated transgenic mice that contain the entire FRDA gene within a human YAC (Yeast Artificial Chromosome) clone of 370 kb. This demonstrated that human frataxin can effectively substitute for mouse frataxin and will likely facilitate generation of mice that more closely model FRDA in humans. The existing mouse models need to be proliferated and distributed to eager scientists, and refinements in the models are being pursued. **FARA has offered assistance in each of these efforts and is now reviewing applications.**

Sticky DNA, Triplexes and Therapeutic Strategies

Robert D. Wells, Ph.D.
Texas A&M University System Health Science Center, Institute of Biosciences and Technology

FARA has awarded Dr. Wells, a world leader in research on triplet repeats, a two-year grant to support his groundbreaking work. The goal of this FARA-funded project is to exploit the role of triplexes and sticky DNA in FRDA with the aim of developing therapeutic strategies.

This project will build on the research published earlier this year that Dr. Wells conducted with teams that included Naoki Sakamoto, Jacquelynn Larson, Ravi Iyer, Keiichi Ohshima, Laura Montermini, and Massimo Pandolfo. These teams explored the nature of molecular structures formed by the lengthy triplet repeats (GAA-TTC) in FRDA cells. They found an inverse correlation between the size of the repeats and the amount of frataxin protein produced. They concluded that sticky DNA inhibits transcription by sequestering the RNA polymerases (transcription molecules). They also explored the effect of interruptions in the long triplet repeats by introducing GGA-TCC interruptions into the GAA-TTC expansions. They found that the introduction of "more than 20% of GGA-TCC interruptions abolished the formation of sticky DNA."

In his FARA-funded project, Dr. Wells targets the inhibition of transcription and subsequent protein formation. He hypothesizes "that genetic destabilization of triplexes and/or sticky DNA with judiciously chosen ligands (oligonucleotides) may generate deletions and other mutations to attempt to reverse these inhibitions." The ultimate goal of the project is to develop the techniques for decreasing the length of the GAA-TTC expansions so as to destabilize their triplexes and/or sticky DNA structures. This is a promising approach for developing a genetic therapy for FRDA. (Focus on Research cont'd, p. 6)

Having Fun & Raising Much Needed Funds for Research

Everyone has a special interest, talent or hobby. How can YOU take YOUR special talent and put it to good use by raising funds for research?

100% of ALL FARA DONATIONS FUND RESEARCH

Canadian Bass Fishing Tournament - Cambridge, Ontario

(cont'd from p. 1)

Thirty-year old Brent Moore was phenotypically diagnosed with FRDA in 1990 and was genetically confirmed in 1997. After attending an ataxia conference last year, Brent left with some great memories of new friendships and inspiration. He started to brainstorm-- trying to find a way in which he could personally make a difference. Ever since Brent was old enough to hold a fishing rod, he's been consumed by the sport. It has been a life-long passion; its intensity has never swayed. "That's it," he thought to himself, "I'll organize a fishing tournament." This past July 14 was a warm and sunny day with a slight breeze in Cambridge, Ontario. Brent's original goal was to get 25 boats with 50 people to participate in the event, and he came within 2 boats of his goal. The tournament was a great success that enabled him to raise $1700 for FRDA research and heighten awareness of Friedreich's ataxia in his community. ***"Hopefully, others reading this will be inspired to take an active role in their communities, as well as an active role in funding FRDA research."-Brent Moore***

Theatrical Play - Chapel Hill, North Carolina

Sixteen-year old **Thomas Barnett** has Friedreich's ataxia and the entire Barnett family decided they wanted to do something to further research and help Thomas. They were joined by dozens of friends at United Church of Chapel Hill in producing, directing, and performing The Cole Porter musical "Anything Goes."

When it comes to raising funds for research, "Anything Goes" for the producers, director, actors and soundboard manager pictured above: Carrie, Paige, Thomas (with poster), Bill, Joanna and Kevin Barnett. BRAVO!

Thomas's mother, **Paige**, directed the show. His father, **Bill**, organized show publicity, pre-production fundraising and performed in the chorus. Sisters **Carrie and Joanna** and brother **Kevin** had character roles in the show. Thomas designed the show program and ran the sound board for the production. The group staged three performances over a three-day period.

The youngest cast members were first graders. Lead roles were filled by veterans of local and regional musical theater. Thomas's classmates at East Chapel High School, as well as students from Chapel Hill High, volunteered their time as cast members and in backstage support. The church was filled at all three performances by wonderfully warm, supportive and well entertained crowds. **The Barnett family more than doubled their fundraising goal for the event and all money raised was donated to FARA. In fact, the amount was sufficient to fully fund the research grant FARA awarded within the same week.**

St. Norbert's Hosts 2nd Annual Walkathon - Orange County, California

Chelsea Lane is a very little lucky girl. She is blessed with good friends at her school, St. Norbert's, who want to help find a cure for Chelsea. For the second year, the Lane family rallied their friends, family and local corporate and individual sponsors, as well as service and media personnel to raise funds for FARA. In the two events, the Lanes raised almost a quarter-million dollars for Friedreich's ataxia research. ***"I would like to extend my thanks to all of the families who made the Walkathons possible. I can more confidently say now, rather than a few years ago, that I feel a cure is getting a little closer and within our grasp." Sandy Lane***

Marked (^) in photo above, Sandy, Steve and Brianna Lane lead the way in FARA fundraising in their 2nd Annual "Walk for Hope and a Cure."

Above, Chelsea Lane flanked by KTLA TV's Gayle Anderson and dad, Steve. Below, Sandy and Steve Lane rally walkers.

The Lane family welcomes everyone to join them on May 18, 2002, for their 3rd Annual "Walk for Hope and a Cure." You can email Sandy at typesandy@aol.com for more information or call her at (714) 685-0096.

Jeans Day - Livonia, Michigan

Helps fund research to help our genes

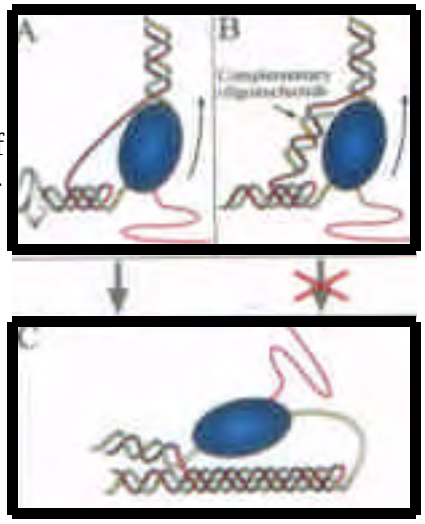
Key Plastics is a very caring company that comes up with different ideas to unify employees. One of the favorite activities is the "Friday Jeans Day". An employee may wear jeans to work if they contribute $5 - they then receive a sticker saying they paid. Marianne Fox, the mother of 2 children with Friedreich's ataxia, suggested that donations be made to FARA. "It was a fun event where everyone could participate. **I liked being able to suggest FARA and I will suggest FARA in the future in any way I can to get as much funding as possible for FRDA research."**

Testing for agents that improve transcription through GAA-TTC tracts

Edward L. Grabczyk Jr., Ph.D.
Louisiana State University (LSU) Health Sciences Center, Center for Molecular and Human Genetics

This FARA grant supported Dr. Grabczyk's efforts toward increasing the production of frataxin protein in FRDA cells by improving transcription through the GAA-TTC expansions. It also helped facilitate his transition from the National Institutes of Health (NIH) to LSU.
Working at NIH with Dr. Karen Usdin, Dr. Grabczyk proposed an explanation of the inhibition of FRDA gene transcription in which the triplex is a transient rather than fixed, permanent formation. In this model, as the RNA polymerase (transcription molecule) advances along the two DNA strands through the long GAA-TTC expansion, one of the two DNA strands (the non-template strand) ahead of the transcription molecule folds back and begins to coil with the two DNA strands behind the molecule, forming the triplex (A). If the triplex is sufficiently long, the transcription molecule is swung back toward it and stalls where they intersect (C), ending transcription prematurely and preventing formation of frataxin mRNA and frataxin protein. If correctly designed tracts of nucleotides (oligonucleotides) could be generated and delivered to the right places in the GAA-TTC expansions, Dr. Grabczyk hypothesizes that the sequence of the expansions could be interrupted sufficiently so that the non-template strand would not be drawn back into a triplex coil and the transcription molecule could advance properly through the expansion and complete transcription of the FRDA gene (B).

In fact, the Grabczyk/Usdin work **demonstrated in vitro that TTC-containing oligonucleotides can block triplex formation and alleviate transcriptional defect**. Dr. Grabczyk applied his FARA grant toward developing an appropriate transcription test system needed to extend the analysis of such interventions to human cells. Once completed, his "tandem reporter system" will be "specifically tailored to the study of transcription through GAA-TTC tracts in cultured human cells, and will provide quick, quantitative tests of efficacy for agents designed to increase frataxin mRNA levels. In addition, the system will extend and refine our understanding of the mechanism by which this triplet repeat reduces transcript yield in human cells. The insights gained in this pilot study will assist in the rational design of interventions aimed at alleviating frataxin mRNA insufficiency and lead to second generation vectors designed for use in high throughput screening."



Second Form of Friedreich's Ataxia Identified

This year a research team at the Cyprus Institute of Neurology and Genetics, Nicosia, reported the localization of a second FRDA locus to chromosome 9p23-9p11, now referred to as FRDA2. In 1996, the gene responsible for Friedreich's ataxia (now referred to as FRDA1) was mapped to a mutation in the STM7/X25 region of Chromosome 9. The gene map locus is 9q13. FRDA genetic testing became available and doctors and patients no longer had to rely on a verbal diagnosis based on physical examination indicating classic symptoms associated with FRDA. However, the following year, researchers at the Institut fur Humangenetik der Justus-Liebig-Universitat, Giessen, Germany, studied two patients who presented with classic physical symptoms indicating a FRDA diagnosis, though genetic testing did not detect a mutation in their gene locus indicating FRDA1. This year, a research team at the Cypress Institute (Christodoulou et al) successfully mapped a second FRDA locus to chromosome 9p23-p11. Patients who have been given a physician's verbal diagnosis of Friedreich's ataxia, but whose test results are negative for FRDA1, may wish to have their physician contact the Cyprus Institute at roula@mdrtc.cing.ac.cy for further information regarding FRDA2. This discovery may also help eventually to shed some light on additional genetic factors that may interact with the frataxin protein.

Clinical Trial of CoQ10 & Vitamin E in Friedreich's Ataxia

LODI R, HART PE, RAJAGOPALAN B, TAYLOR DJ, CRILLEY JG, BRADLEY JL, BLAMIRE AM, MANNERS D, STYLES P, SCHAPIRA AH, COOPER JM.
Department of Biochemistry, University of Oxford, London, United Kingdom

This team showed that CoQ10 taken with Vitamin E significantly improved bioenergetics in the heart and skeletal muscle of FRDA patients.

The team initially studied 18 FRDA patients along with 18 age- and sex-matched control subjects using Magnetic Resonance Spectroscopy (MRS) and echocardiography. Left ventricular hypertrophy was present in 8 FRDA patients while fractional shortening was normal in all. The team found that the phosphocreatine to ATP ratio for the FRDA patients as a group was 60 percent of the normal mean, and that, even in the FRDA patients with no left ventricular hypertrophy, this ratio was significantly below the normal level.

The team then evaluated 10 FRDA patients over a 6-month period of antioxidant treatment consisting of CoQ10 (400 mg/day) and Vitamin E (2,100 IU/day). Using Phosphorus MRS (31P-MRS) to measure energy metabolism in cardiac and calf muscle, they found that after only 3 months of treatment, the cardiac phosphocreatine to ATP ratio showed a mean relative increase to 178% and the maximum rate of skeletal muscle mitochondrial ATP production increased to 139% of their respective baseline values in the FRDA patients. These improvements were greater in prehypertrophic hearts and in the muscle of patients with longer GAA repeats, and the improvements were sustained after the 6 months of treatment. While these bioenergetic improvements were achieved after 3 months and sustained for the full course of treatment, the team did not detect any consistent benefits observable through other means (neurological or echocardiographic examinations). The team concluded that **"This study demonstrates partial reversal of a surrogate biochemical marker in FA with antioxidant therapy and supports the evaluation of such therapy as a disease-modifying strategy in this neurodegenerative disorder."**

Friedreich's ataxia, mitochondrial iron overload and chelation

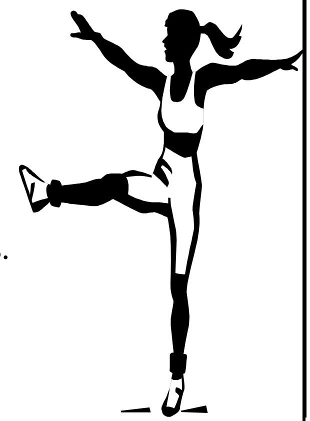
Des R. Richardson, Ph. D.
The Heart Research Institute
Sidney, Australia

Evidence indicates that iron overload in mitochondria, possibly accompanied by iron depletion in cytoplasm, is involved in FRDA. In a research project supported by the National Ataxia Foundation, Dr. Richardson ***is attempting to determine the role of frataxin protein in how cells handle iron.*** *He plans, then,* ***to further explore the possibility that chelation (removal) of iron from mitochondria might offer a therapeutic approach for the disease.***

FRDA's iron problem appears to involve maldistribution of iron within FRDA cells rather than simple overload throughout the cells. If iron chelation holds promise as a therapy, therefore, it will be important to remove iron selectively, from excessive amounts in mitochondria rather than from the cytoplasm around the mitochondria. Because some iron is essential to mitochondrial function (in iron-sulfur clusters, for example) it will also be important to remove only the iron in excess of the need. Dr. Richardson reports that his team has developed a series of iron chelators that, due to their high lipid solubility, enter mitochondria successfully. FARA has helped facilitate Dr. Richardson's collaborations with drug development companies that will be important if his iron chelators prove to be safe and effective in a FRDA therapy.

(Focus on Research cont'd, p. 10)

Second Annual Cardio Jam - Novato, California



Dreams can come true and the Cardio Jam helped to make that happen!

BJ Acker-Hitta put her expertise back to work this year in the MAD (Make a Difference) Cardio Jam at Rolling Hills Club. This year's Cardio Jam was a complete success--over $19,000 and still counting. The day's activities included outside aerobic classes starting with spin class, followed by a splash in the pool with an H2O aqua class. There was a 5k family walk that ended with a body pump class. Inside classes included cardio kickboxing followed by a spicy salsa class and finishing up with a heart-pounding step class. Concurrently with all the physical activity, there was a silent auction, which raised additional funds. FUN was had by all!

Bocce Ball Tournament - Marin County, California

Cindy and Bruce Olson have been active in FRDA fundraising for years. With a committee of 16 dear friends, they host a fall fundraiser in Minnesota. A dear friend, **Lisa Carmassi**, flies home each year for this event, with donated items to auction, checks from her friends, and eager to work. Lisa has now added a huge step by hosting her own supplemental event in California to raise money for FRDA research – she and her family host an annual bocce ball day. In 2000, they raised $1900 and this year over $4000! You could say they're on a roll! Cindy was able to attend this year to see firsthand what a special event this is.

"I have to say it was quite emotional to see all the love and energy that went into planning and preparing for this FUNdraiser! Beautiful Italian music was playing as we were embraced by the California sunshine at a bocce ball court filled with wonderful, caring people. Lisa recruited many great donations of food and sponsorships to assist her as she prepared the feast of barbecued ribs, Caesar salad, potato salad, sourdough bread and blackberry cheesecake. Donations from a local brewery and winery kept us well hydrated. It is so heartwarming to see this kind of outpouring of love. Looking back a number of years before our children were diagnosed with Friedreich's Ataxia, I can see this was all part of God's plan as Lisa and I became coworkers and friends. She truly is one of those special angels on earth!"
Cindy Olson

- -

PLEASE HELP FARA

Support research aimed at a treatment for Friedreich's Ataxia. Your donation promises a new legacy of scientific advancement and gives families genuine hope for the future. NO overhead costs --100% of your tax-deductible donation funds research. Donors receive this Update. Thank you.

Yes, I would like to help FARA with the enclosed tax-deductible donation in the amount of $________.

Your name: **Address:**

Mail to: FARA 2001 Jefferson Davis Highway, Suite 209 Arlington, VA 22202

Blues Festival - Loudoun County, Virginia

How much does it take to fund a research project that can help my friend Katrina? That was the question Neyna Webb asked FARA. Neyna's best friend, Katrina Rockett, has Friedreich's ataxia. Neyna's enthusiastic spirit and determination led her to organize and host two FARA fundraisers, including a Blues Festival, at local pubs in Sterling, Virginia. Neyna and her friends have raised thousands of dollars that will be used to fund more research grants.

Letter writing campaigns for the Holiday Season and Year 2002

Sue Kittel, the parent of 4 children, two of whom are FRDA patients, and the founder of the Friedreich's Ataxia Parents' Group (FAPG), has raised funds for FARA through her "Hope for the New Millennium." It can be printed on Holiday stationery and included with your holiday and Year 2002 greetings. It's a heartfelt and effective way to raise research funds for FARA.

Hope for the New Millennium….
I have hope.
That magic thing that I had lost or misplaced.
The future looks dark no more.
I do not even look at it,
except when necessary to make plans.
I try to let the future take care of itself.
The future will be made up of today and todays,
stretching out as short as now
And as long as eternity.
Hope is justified by many right-nows,
by the rightness of the present.
Wishing you the Brightest Year 2002,
that only HOPE can bring.

Please join me in my HOPE for a cure for Friedreich's ataxia, by mailing a donation in our family's name to:
FARA
2001 Jefferson Davis Highway Suite 209
Arlington, VA 22202-3604
(FARA= Friedreich's Ataxia Research Alliance, URL: http://www.frda.org)

Share <u>YOUR</u> FARA fundraising story

There are many more FARA fundraising stories to share. Email us with news and photos of your event to fara@frda.org so we can pass along your success story.

Organizing your FARA fundraiser?
Email or call FARA with any questions.

FDA Approves FRDA Idebenone Clinical Trial

On November 6, 2001, the Food and Drug Administration (FDA) approved the clinical trial of the antioxidant Idebenone in FRDA patients. FARA served on the committee responsible for preparing the submission to FDA and is assisting the National Institutes of Health (NIH) in enrolling patients for the trial. Phase I of the trial is scheduled to begin at NIH this winter. Phase Ia is to be an unblinded dose-escalation study to determine the maximum tolerated single dose of Idebenone for FRDA patients. Phase Ib will determine the maximum daily dose tolerated over a period of time. Phase II is being planned for next year and will require a larger number of patients at multiple locations (as yet undetermined). It will continue to test for safety at a dose level based on the results of Phase I. In Phase II, patients will also be monitored for indications that the drug has positive impact on FRDA symptoms. If successful, the trial will show whether Idebenone is safe, has beneficial effect on FRDA symptoms, at what doses it has maximum benefit, and against which symptoms it has such benefits. If the trial proves Idebenone to be safe and beneficial for FRDA patients, the FDA can approve it for use by FRDA patients in the United States, and doctors will be able to prescribe it for U.S. patients so FRDA families can use their health insurance to fill the prescriptions.

Patients are being enrolled for the trial in three age cohorts: adults (18 and older), adolescents (12-17 yrs), and children (5-11 yrs). Patients are still needed in all three cohorts. Enrollment qualifies a patient for participation in any phase of the trial and at any of its locations. Participants must have or obtain genetic confirmation of FRDA. Patients already taking Idebenone are eligible for participation. For additional information on how to be evaluated for enrollment, you should contact the National institute of Neurological Disorders and Stroke (NINDS) to express your interest in being considered. Contacting NINDS does not guarantee that you will be chosen as a participant, but it does guarantee that you will be considered. See details below.

FRDA CLINICAL TRIAL PATIENT RECRUITMENT UNDERWAY

The National Institute of Neurological Disorders and Stroke (NINDS) is currently recruiting FRDA patients for the clinical trial described above to determine if the antioxidant, Idebenone, is safe and beneficial for FRDA patients.

The Details: Phase I will be conducted at the NIH Clinical Center located on the main NIH campus in Bethesda, Maryland, just outside Washington, DC. Phase II will be planned for multiple locations. NIH will pay all participant expenses for travel, food and lodging.

For further information, please contact:
Ms. Jennifer R. Leib
Phone (301) 496-8969
Fax (301) 480-3365
Email: leibj@ninds.nih.gov

FARA Supports Development of Ataxia Scales

On the weekend of October 28-29, 2001, FARA helped fund and organize at the National Institutes of Health (NIH) the second session of the effort to further develop and refine the international cooperative ataxia scales. These scales consist of procedures and devices used to measure a patient's capabilities involved in the progressive symptoms of ataxia. Measurements include such things as speed of manipulating a nine-hole pegboard, walking with or without assistance, standing without assistance, the "pa-ta-pa" vocal ability test, and standard neurological examinations. Cardiology examinations for FRDA are being developed separately. The same doctors/raters and eight of the same FRDA patients as participated in the first session in July 2000, were again involved in this second session.

These two sessions were extremely important for two reasons. First, they will permit a validation and refinement of the international cooperative ataxia scales that will be useful to physicians and researchers worldwide in assessing the progression of all the ataxias as well as other movement disorders. **The results of these two sessions, in fact, are to be published and offered as validation of what is likely to become a new set of international ataxia scales.** Second, because the same patients and raters participated in both sessions, the results provide the scientific community with valuable "longitudinal data" across the 15 months between sessions. Such data permits assessments of the progression of the disease over time. In subsequent clinical trials, researchers will use these new ataxia scales to measure the progression of FRDA in their patients during the trial, and will compare the results with the untreated progression reflected in the "longitudinal data" so as to determine whether the drug or therapy being administered is beneficial.

Pictured above at October 28 ataxia scales session: (standing LtoR) Dr. Sub Subramony, Dr. Chris Gomez, Elaine Considine, Jennifer Leib, Dr. Rob Wilson, Dr. Tee Ashizawa, Dr. Bernard Ravina, Jeannie Markowitz, Dr. Paul Taylor, Dr. Kurt Fischbeck, Barbara MacDonald, Nancy Mercure; (seated LtoR), Glen Mitchell, John MacDonald, Jeff and Donna Littel, R.J. Mercure, Raychel Bartek (kneeling); (on floor) Michelle (Donna's dog) and Nicholas Mercure. Not pictured, Dr. Mark Hallet. Photo by Ron Bartek

Towards gene therapy for the peripheral nervous system manifestations of FRDA

Dr. IAN E. ALEXANDER, Head, Gene Therapy Research Unit
Division of Research
The Children's Hospital at Westmead, Australia

This FARA grant is helping advance Dr. Alexander's Friedreich's ataxia research program, emphasizing development of gene-based approaches to therapy, as he seeks additional funding from Australian national sources. ***He is focusing on one of the most difficult aspects of gene-based therapy - the delivery vehicle (vector) needed to deliver the genetic repair material to the right places in human cells.***

Earlier this year, Dr. Alexander's team (Jane Fleming, Samantha L. Ginn, Ron P. Weinberger, Toby N. Trahair, Jason A. Smythe, and Ian Alexander) demonstrated that particular virus vectors (lentivirus and recombinant adeno-associated virus - rAAV) are capable of accomplishing efficient and sustained transfer of cultured mouse and human dorsal root ganglion (DRG) sensory neurons.

In this FARA-funded project, Dr. Alexander will attempt to validate that the same virus vectors will encode the human frataxin cDNA (cloned messenger RNA) and undertake correction of FRDA cells *in vitro.* He will then evaluate the efficiency and persistence of the virus vector's transfer of genetic material to DRG sensory neurons in the conditional neuron-restricted, exon 4 deleted, FRDA mouse model developed by the French team (see "Mouse Models", p.3). Then he will investigate for any indication of improvement in the mouse model's DRG neuropathology resulting from the gene transfer.

The peripheral sensory neuropathy caused by progressive loss of DRG sensory neurons is a major component of FRDA pathology. **This research project will not only contribute to our understanding of the interplay of Peripheral Nervous System (PNS) and Central Nervous System (CNS) pathology in FRDA, but will serve as a stepping stone to larger animal studies and, ultimately, to human clinical trials of PNS-directed gene therapy.**

Symposium on the Hereditary Ataxias Clarifies FRDA

FARA awarded a conference grant to Dr. Arnulf Koeppen, Professor of Neurology, Albany Medical College, and Chief of Neurology Service at the VA Medical Center in Albany, New York, to assist him in organizing "THE HEREDITARY ATAXIAS", a symposium of the Society for Experimental Neuropathology under the auspices of the American Neurological Association. The symposium was held in Chicago, Illinois, on September 30th, 2001, and encompassed three presentations by leading Friedreich's Ataxia (FRDA) researchers who summarized what is known about the disease and clarified several aspects of its genetics and the protein deficiency involved.

Dr. Koeppen's presentation detailed the history, clinical features and neuropathology of FRDA. FRDA was first identified in 1863 by Dr. Nikolaus Friedreich, a German-born neuropathologist. In extremely detailed publications, Dr. Friedreich described the clinical manifestations of the disease, including degenerative atrophy of the dorsal spinal columns as well as cardiomyopathy. He had considerable insights into the heredity and pathogenesis of the disease.

Dr. Massimo Pandolfo, FARA Board Member, Professor of Neurology at the Universite Libre in Brussels and Chief of Neurology Services at the Erasmus Hospital, discussed the **molecular genetics of FRDA**. Key points from Dr. Pandolfo: Disease-associated repeats contain from about 70 to more than 1,000 GAA triplets, most commonly 600-900. Normal GAA repeat lengths range from about 6 to 40. However, the lengths are unstable during parent-child transmission. "Very large normal" GAA repeat lengths (about 34 to 70), if not inter-

rupted by another triplet (usually GAG), can be premutational and can expand to affected levels during parent-child transmission. About 90 percent of the time, the father's repeat lengths contract in parent-child transmission. The mother's repeat lengths may contract or expand at about equal probability. Repeat lengths are also unstable during somatic (non-reproductive) cell division, leading to some "mosaicism" (or variation) in repeat lengths in various cells.

A direct correlation has been established between the size of the GAA repeat lengths (especially the smaller of the two) and earlier age of onset, earlier need for a wheelchair, more rapid rate of disease progression, and presence of "non-obligatory" disease manifestations (e.g., cardiomyopathy, diabetes). However, differences in repeat lengths account for only about half of the variations in age of onset, indicating that other factors, such as modifying genes and mosaicism could possibly influence disease progression as well. A small percentage of patients have "point mutations," some of which are associated with milder symptoms, suggesting that the resulting mutated proteins retain some of the intended function.

At the Chicago Symposium, on Left, Dr. Rob Wilson, Dr. Massimo Pandolfo, Ms. Sandy Lane, Ms. Meir Bode.

On right, Dr. Arnie Koeppen. Ron Bartek, Ms. Meir Bode, Ms. Rochelle Litke. (photos by Marilyn Downing)

Dr. Robert Wilson, FARA Board Member, Chairman of FARA's Scientific Review Committee, and Associate Professor of Pathology and Laboratory Medicine, University of Pennsylvania, presented **evidence of the pathology caused by the frataxin protein deficiency**. The product of the FRDA gene is the frataxin protein, which moves to the mitochondria of the cells where it is involved in iron metabolism. When sufficient frataxin is present in the mitochondria, it appears to keep iron in its reduced, usable form (2+), and then facilitate its removal from the mitochondria. When, because of the FRDA gene mutations, sufficient frataxin protein is not present, excess (tenfold) iron accumulates in the mitochondrial. The iron is oxidized to its 3+ form and induces free radical oxidant damage, and energy production is diminished. Various antioxidants are being investigated in hopes of developing an antioxidant therapy in which the free radicals are sufficiently neutralized to allow mitochondrial repair processes to gain the upper hand over the chronic oxidative damage that apparently underlies the disease. Preliminary open trials of the antioxidant idebenone have demonstrated in FRDA patients a decrease in cardiac hypertrophy, suggesting a capacity for renewal of damaged mitochondria in heart muscle cells. Larger trials of idebenone will clarify the drug's effect.

The new journal, "The Cerebellum," plans to run the entire proceedings in an upcoming publication.

Glossary for FRDA Research and Genetic Terms

The Glossary is provided to you by the Friedreich's Ataxia Research Alliance for the purpose of understanding frequently used terms in scientific research articles regarding Friedreich's ataxia.*

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different forms of a gene (one from each parent) produce variation in inherited characteristics.

Amino acids: Molecules in the cytoplasm of each cell assembled in specific sequences determined by genetic code carried by mRNA to form proteins. Amino acids are referred to as the "building blocks" of proteins.

Antioxidants: Series of defenses that control or bind free radical molecules and mend damage. Vitamin E, CoQ10 and Idebenone are examples of antioxidants.

Apoptosis: Programmed cell death, the body's normal method of disposing of damaged, unwanted, or unneeded cells. In FRDA, apoptosis is the result of oxidative stress and free radical damage brought on by the reduced levels of frataxin produced by FRDA patients.

Ataxia: Incoordination; poor balance

Autosomal recessive: Autosomal-involving one of the first 22 "non-sex" chromosomes; Recessive- pattern of inheritance in which a patient must inherit two mutated genes, one from each parent, for the disease to develop. Each child of two carriers has a 1 in 4 chance of having the disease and a 1 in 2 chance of inheriting one abnormal gene. (see Carrier)

Carbohydrate intolerance: The inability of the body to completely process the nutrient carbohydrate that includes both starches and sugar into a source of energy for the body. About 20% of FRDA patients develop this intolerance.

Carrier: A person who has only one abnormal copy of a gene for a recessive genetic disease such as Friedreich's ataxia; a carrier will not develop the disease but could pass the affected gene on to offspring.

Cell: The basic unit of all living organisms. A small, watery, compartment consisting of a nucleus with 23 chromosome pairs with a complete copy of the organism's genome. The nucleus is surrounded by the watery cytoplasm with its mitochondria and amino acids, etc..

Chromosome: Threadlike package of genes and other DNA in the nucleus of a cell. Humans have 23 pairs of chromosomes; 46 in all. Each parent contributes one chromosome to each pair, children get half of their chromosomes from their mothers and half from their fathers. The FRDA gene is located on chromosome 9.

Coding Regions (or Exons): The regions of a gene that contain the code for sequences of amino acids to produce the gene's protein. Each exon codes for a specific portion of the amino acid chain of the gene's protein. In humans, a gene's exons are separated by long regions of DNA called introns. The FRDA gene has 5 exons.

Consanguinity: Genetic relatedness between individuals descended from at least one common ancestor.

Codon: Three bases in a DNA or RNA sequence which specify a single amino acid.

Computed tomography (CT) scan or magnetic resonance imaging (MRI): provides a picture of the brain and spinal cord; diagnostic tool for FRDA.

Deletion: A particular kind of mutation: loss of a piece of DNA from a chromosome. Deletion of a gene or part of a gene can lead to a disease or abnormality

Diabetes mellitus: Disorder in which abnormalities in the ability to make and/or use the hormone insulin interfere with the process of turning dietary carbohydrates into glucose, the body's fuel; 10% of FRDA patients develop this disorder.

DNA: Deoxyribonucleic acid; the double-helix chain inside chromosomes that carries the genetic instructions for making living organisms.

DNA bases (or nucleotides): Chemical units adenine, thymine, cytosine, and guanine, abbreviated A, T, C, and G. Certain bases always "pair" together (A with T; C with G), and different combinations of base pairs join in sets of three (triplets) to form coded messages. These coded messages are "recipes" for collecting amino acids to assemble different proteins.

Dysarthria: Slowness and slurring of speech associated with FRDA

Electrocardiogram (EKG): Gives a graphic presentation of the electrical activity or beat pattern of the heart; FRDA diagnostic tool

Echocardiogram (Echo): Records the position and motion of the heart muscle. FRDA diagnostic tool.

Electromyogram (EMG): Measures the electrical activity of muscle cells. FRDA diagnostic tool.

Exons: The regions of a gene that contain the code for sequences of amino acids to produce the gene's protein. Each exon codes for a specific portion of the amino acid chain of the gene's protein. In humans, a gene's exons are separated by long regions of DNA called introns. The FRDA gene has 5 such exons.

Fibroblasts: A type of cell found just underneath the surface of the skin. Fibroblasts are part of the support structure for tissues and organs.

Flanking Marker: an identifiable, polymorphic region of DNA located to the side of a gene; flanking markers are used in linkage analysis to track the coinheritance of the gene in question.

Founder effect: A gene mutation observed in high frequency in a specific population due to the presence of that gene mutation in a single ancestor or small number of ancestors

Frame Shift Mutation: When a number of DNA nucleotides not divisible by three is inserted or deleted. This causes a reading frame shift and all of the codons and all of the amino acids after that mutation are usually wrong. Frequently one of the wrong codons turns out to be a nonsense codon and the protein is terminated at that point. A small percentage of FRDA patients have this type of mutation.

Frataxin: The protein encoded by the FRDA gene and in short supply in FRDA patients. Research suggests that without a normal level of frataxin, certain cells in the body (especially brain, spinal cord, and muscle cells) cannot manage the normal amounts of "oxidative stress" which the mitochondria, the energy-producing power plants of cells, produce. Research using a yeast protein found that the shortage of this protein in the yeast cell led to a toxic buildup of iron in the cell's mitochondria. When the iron reacted with oxygen, free radicals were produced and the cell died (apoptosis).

Free radicals: Products of normal cell processes, but can destroy cells. Their devastating actions in FRDA re-

sult from molecules (e.g., oxygen) with an unpaired electron which makes the molecule unstable and electrically charged. It becomes stable by interacting with the nearest available molecule, randomly targeting proteins, fats, and even DNA, damaging the other molecules and causing cell death (apoptosis).

GAA Repeats: Repetition of three nucleotides, Guanine-Adenine-Adenine. Most FRDA patients have an abnormally long GAA-repeat expansion in the FRDA gene. In a normal frataxin gene, the GAA sequence is repeated 7 to 22 times, whereas FRDA patients can have up to 1,700 repeat sequences of GAA.

Genome: All the DNA contained in an organism or a cell, includeing the DNA in chromosomes within the nucleus and the DNA in mitochondria.

Genotype/Phenotype Correlation: Association between the presence of a certain mutation(s) (genotype) and the resulting physical trait (phenotype).

Gene: Functional and physical unit of heredity passed from parent to offspring. Humans have two copies of each gene - one inherited from the mother and one from the father. Genes are located at specific places on each of an individual's 46 chromosomes (23 pairs). Genes are pieces of DNA and most genes contain the information for making a specific protein.

Genetic code: Instructions in a gene that tell the cell how to make a specific protein. A, T, G, and C are the "letters" of the DNA code; they stand for the chemicals adenine, thymine, guanine, and cytosine, respectively, that make up the nucleotide bases of DNA. Each gene's code combines the four chemicals in various ways to spell out 3-letter "words" that specify which amino acid is needed at every step in making a protein

Genotype: Genetic characteristics of an individual rather than outward physical characteristics.

Heterozygous: having two different forms of a gene, one inherited from each parent (e.g., FRDA carrier).

Homozygous: having two identical forms of a gene, one inherited from each parent (e.g., FRDA patient).

Hypertrophic Cardiomyopathy: enlargement of heart walls of the left ventricle (frequent in FRDA patients).

Idebenone: a free radical scavenger; antioxidant

Intron: A noncoding sequence of DNA between exons that is initially copied into RNA but is cut out of the final RNA transcript. Introns are sometimes called "junk DNA" because they have no apparent function. However, about 96% of FRDA cases are due to expansion of the GAA trinucleotide repeat in intron 1.

Iron Overload: Research suggests that iron overload leads to a toxic buildup of iron in the cell's mitochondria. When the excess iron reacts with oxygen, free radicals are produced. Although free radicals are also products of normal cell processes, they can destroy cells that lack normal defenses.

Knock in: Insertion of genetic material; in a knock-in FRDA animal model, healthy frataxin genes are replaced with a mutant gene with GAA expansions. The knock-in models may reproduce the progressive neurological findings and neuropathological changes typical of FRDA.

Knock out: Disruption or deletion of genetic material. Knocking out the FRDA gene on one allele produces an asymptomatic model similar to a carrier of the FRDA gene. Knocking out both genes leaves the mouse with no frataxin protein and the model dies in the embryonic stage.

Locus: The place on a chromosome where a specific gene is located, a kind of address for the gene. FRDA1 = chromosomal locus 9q13; FRDA2 =chromosome 9p23-p11

Magnetic resonance imaging (MRI) or computed tomography (CT) scan: FRDA diagnostic tool; provides a picture of the brain and spinal cord.

Messenger RNA: Template for protein synthesis. The sequence of a strand of mRNA is based on the sequence of a complementary strand of DNA. Each set of three bases or nucleotides, called a codon, specifies a certain amino acid in the sequence of amino acids that comprise the protein. mRNA receives the gene's code, carries it into the cytoplasm where it assembles the specific amino acids in the specific sequence determined by the code and, thus, builds the gene's protein product.

Mitochondria: The energy-producing power plants of cells. Cellular degeneration in FRDA may be caused by mitochondrial dysfunction due to oxidative stress.

Mouse Model: A laboratory mouse useful for medical research because it has specific characteristics that resemble a human disease or disorder. Scientists can create mouse models by transferring new genes into mice or by inactivating certain existing genes in them.

Missense Mutation: This is usually a single substitution mutation and results in one wrong codon and one wrong amino acid. A small percentage of FRDA patients have this type of mutation. Example: the G130V point mutation.

Mutation: A permanent structural alteration in DNA. In most cases, DNA changes either have no effect or cause harm, but occasionally a mutation can improve an organism's chance of surviving and passing the beneficial change on to its descendants. The vast majority of patients with FRDA have identifiable mutations in the *X25/FRDA* gene (chromosomal locus 9q13).

Nerve conduction studies: FRDA diagnostic tool; measures the speed with which nerves transmit impulses.

Nonsense Mutation: A change in the base sequence that results in a nonsense (STOP) codon. Protein formation will be terminated at that point in the message. A small percentage of FRDA patients have this type of mutation.

Nucleotide: DNA base chemical unit (A, C, G, T). (See, also, DNA bases.)

Nystagmus: Rapid, rhythmic, involuntary movements of the eyeball (nystagmus). Common in FRDA patients.

Oxidative stress: Damage caused by free radicals. Humans are equipped with a series of defenses, or antioxidants, that control free radical molecules and mend damage. Free radical scavengers such as Vitamin E mop up free radicals and help prevent damage to critical cell structures. The lack of normal amounts of frataxin in FRDA patients leads to oxidative stress and cell death.

Phenotype: The observable traits or characteristics of an organism. With FRDA, observable traits could include ataxia, dysarthria and nystagmus.

Point Mutation: When one nucleotide (A, C, G, T) is substituted with another nucleotide. The number of chemical units remains the same, but there is an error or misspelling in the gene. About 4% of the people with FRDA will have one expansion in one copy of the gene and a point mutation in the other copy.

Premutation: In disorders caused by trinucleotide repeat expansions, an abnormally large allele that is not associated with clinical symptoms but that can expand into a full mutation when transmitted to offspring (full mutations are associated with clinical symptoms of the disorder)

Proteins: A large complex molecule made up of one or more chains of amino acids. Proteins perform a wide variety of activities in the cell. Frataxin is the protein encoded by the FRDA gene.

Ribonucleic Acid (RNA): A chemical similar to a single strand of DNA. In RNA, the letter U, which stands for uracil, is substituted for T in the genetic code. RNA delivers DNA's genetic message to the cytoplasm of a cell where amino acids are assembled to make proteins.

Scoliosis: A curving of the spine which, if severe, may impair breathing and balance.

Spinal tap: Evaluation of the cerebrospinal fluid; FRDA diagnostic tool.

Substitution: Replacement of one nucleotide in a DNA sequence by another nucleotide or replacement of one amino acid in a protein by another amino acid.

Superoxide dismutase (SOD): An enzyme that helps to detoxify certain harmful free radicals.

Transgenic: An experimentally produced organism, such as a mouse, in which DNA has been artificially introduced and incorporated into the organism's germ line, usually by injecting the foreign DNA into the nucleus of a fertilized embryo.

Triplet repeat expansion- In FRDA the GAA triplet is repeated too many times. Normally, the GAA sequence is repeated 7 to 22 times, but in people with Friedreich's ataxia it can be repeated up to 1,700 times. About 96 percent of Friedreich's ataxia carriers have a genetic triplet repeat expansion. A very small proportion of affected individuals have other gene coding defects responsible for causing disease. (See point mutation.)

****The Glossary of FRDA Genetic & Research Terms is for educational purposes only. Independent verification of all data is recommended. We shall not be liable for the completeness or accuracy of the data used in this Glossary of FRDA Genetic & Research Terms.***

Special acknowledgement to the National Human Genome Research Institute (NHGRI) Intramural Division; http://www.nhgri.nih.gov/DIR/VIP/Glossary/ and GeneTests-GeneClinics: Medical Genetics Information Resource [database online]. Copyright, University of Washington and Children's Health System, Seattle. 1993-2001. Available at http://www.geneclinics.org or http://www.genetests.org. Accessed November 16, 2001

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Please donate - your tax deductible contribution to FARA accelerates FRDA research.

THE RESEARCHERS' CORNER

REQUEST FOR GRANT APPLICATIONS

FARA will accept applications at any time from US & International Researchers

Research Grants. FARA will support research with grants provided by the organization itself and by assisting in seeking grants from other public, non-profit organizations that are exempt from federal income taxes under section 501(a) as organizations described in section 501(c)(3). **FARA** pursues a multi-tiered approach. **FARA**, itself, will provide one tier - smaller, shorter-term "seed" grants to attract new research investigators and assist existing investigators by supporting the early phases of their research (including funds for equipment and post-doctoral fellowships). These "seed" grants will permit investigators to collect preliminary data and test initial hypotheses. In some cases, significant findings might result, or additional investigators might be attracted to the field. In other cases, this preliminary research will better prepare the investigators to submit successful applications for larger, longer-term grants.

Workshop Grants. FARA supports scientific workshops designed to advance the research into treatments and cures for Friedreich's ataxia and the related sporadic ataxias. These workshops will be of two types - full-scale workshops and project-specific workshops.

Project-Specific Workshops - **FARA** intends also to support workshops arranged on shorter notice for small groups of investigators when face-to-face collaboration on a specific approach or insight promises a significant advance in **FARA**'s mission. In such cases, the workshop site will be selected so as to optimize collaboration and minimize costs.

Application Submission. Applications are to be submitted in electronic or paper form to **FARA** at the addresses below, from which they will be distributed to the scientific members of **FARA**'s Board of Directors and the Scientific Advisory Committee appointed to serve in the peer-review process. The Scientific Advisory Committee will request additional information from the P.I. when necessary.

Friedreich's Ataxia Research Alliance (FARA)
c/o Ronald J. Bartek, President
2001 Jefferson Davis Highway; Suite 209
Arlington, Virginia 22202 USA
Electronic application submissions will be accepted at fara@frda.org

Second FARA International Workshop — Initial Planning Underway

Planning for the next full-scale international workshop and conference on Friedreich's ataxia and the related sporadic ataxias has begun. FARA's mission includes the sponsorship of periodic, comprehensive, international workshops like the one it co-sponsored at NIH April 30-May 2, 1999. The '99 workshop brought together eighty of the world's leading scientists and identified promising avenues of approach to treatments. These workshops provide the opportunity for the full scientific community involved in pertinent research to come together to share findings and insights across the full spectrum of disciplines and approaches.

Researchers' Corner (cont'd from p. 19)

Availability of FRDA Cell Lines

The Coriell Cell Repositories provide essential research reagents to the scientific community by establishing, maintaining, and distributing cell cultures and DNA derived from the cell cultures. These collections are supported by funds from the National Institutes of Health (NIH) and several foundations. Coriell maintains and provides lymphoblast and fibroblast samples obtained from FRDA patients. These samples are reasonably priced and used by scientists around the world studying FRDA. To view the collection or place an order, visit the Coriell website at http://locus.umdnj.edu/

Internaf-Pro Invitation
International Network of Ataxia Friends

Internaf, an internet listserv supporting the ataxia community, is very privileged to have noted researchers in the field of hereditary ataxia, along with many other medical professionals, who participate via an anonymous invitation-only list which runs in tandem to the main Internaf list which serves patients and families coping with "an ataxia." If you are a health professional with an interest in ataxia and would like further details or an invitation to join, please contact the Internaf-Pro Coordinator, Fanny Chagnon at: internaf-pro-owner@yahoogroups.com

FARA Scientific Advisory Committee Expands

Two renowned leaders in triplet repeat disorder research, Dr. Henry Paulson and Dr. Robert Wells, have joined the Scientific Advisory Committee of the Friedreich's Ataxia Research Alliance. Henry L. Paulson, M.D., Ph.D, is an Assistant Professor of Neurology Programs in Genetics and Neuroscience at the University of Iowa College of Medicine. As an expert in triplet repeat disorders, he developed a zebrafish model for SCA3, a CAG triplet repeat disorder. Robert D. Wells, Ph.D., is the Director, Center for Genome Research at Texas A&M University System Health Science Center, Institute of Biosciences and Technology. The goal of Dr. Wells' current FRDA research is to develop the techniques for decreasing the length of the GAA-TTC expansions so as to destabilize their triplexes and/or sticky DNA structures. The expertise of these two scientists will be an invaluable asset to FARA in evaluating future FRDA research projects.

In and Around Washington D.C.

At the National Institutes of Health…

Bartek to Serve on NIH Advisory Council
"The privilege of serving on Council will provide me the opportunity to gain a deeper understanding of the NIH, our government's leading financial supporter of medical research."

Ron Bartek has been appointed to serve on the National Advisory Council for the National Institute of Neurological Disorders and Stroke. The Council, composed of physicians, scientists, and representatives from the public, advises the Institute Director on policy matters, reviews applications for research support and recommends funding for those applications that show promise of making valuable contributions to medical treatments that reduce the burden of neurological disease.
Bartek, who is President and co-founder of FARA, is a graduate of the US Military Academy at West Point and holds a Master's Degree from Georgetown University. His professional career includes 30 years of working with federal agencies in Washington, DC. He has represented the ataxia community before the US Congress and the Executive Branch in the support of medical research. Additionally, he serves on the Executive

Committee for the Chesapeake Chapter of the National Ataxia Foundation (NAF) and co-authors a quarterly legislative column, Window On Washington, for the NAF publication Generations. Ron is stepfather to three sons, Byron (17), Keith (16), and Stuart (13). Keith has Friedreich's ataxia.

On Capitol Hill …

Members of Congress Briefed on Friedreich's Ataxia
Congressional leaders had the opportunity to learn more about Friedreich's ataxia as FARA submitted testimony to the House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies. Representing FRDA patients, their families and the scientific community, FARA re-iterated its continued support of Congressional efforts to double the NIH budget. FARA will continue to work closely with Congress, the NIH, the research and patient community. Cooperation and collaboration will lead to accelerated scientific advancement.

Louisiana Congressman Billy Tauzin (right) testifies
in Washington, DC before the House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies regarding the importance of continued federal funding for the Center for Acadian Genetics and Hereditary Health Care. On the left is Keith Andrus, who is afflicted with Friedreich's ataxia, one of the genetic disorders that occurs at a disproportionately higher frequency in the south Louisiana Acadian community. The Center links a school of medicine, a biomedical research center, hospitals, rural clinics and a strong telecommunications network to provide urgently needed health services, health education regarding genetic diseases, and vital research into hereditary neurodegenerative disorders such as Friedreich's ataxia.

<u>WHAT THE NEWLY DIAGNOSED REALLY WANT TO KNOW</u>

Most patients and families had never heard the words "Friedreich's ataxia" until a loved one received the diagnosis. Many families enter into a very confusing and emotionally draining time, coupled with an intense desire to learn as much as possible about what to expect and what to do. **Patients, families and their medical providers now have understandable and helpful information to address their concerns**. Written by a patient family in collaboration with the scientific and medical community, the topics include:
Receiving the Diagnosis/Telling Your Child
Could My Other Children Have Friedreich's ataxia ?
What do the two numbers on the FRDA genetic test mean?
Genetically speaking, what happens in the body due to FRDA?
School - Your Child's Education
Telling Your Child's Classmates
Medical Care for Your Child
Coping - Where can I turn?
"A Message to the Newly Diagnosed" can be found on the FARA website at http://www.frda.org/education/message.htm.

Open to the public- Free admission

Dr. DiMauro to Speak on CoQ10 deficiency--Potential Cause of Familial Ataxia

Dr. Salvatore DiMauro, Professor of Neurology at Columbia University, New York City, will be keynote speaker at the Annual Medical Meeting of the Chesapeake Chapter of the National Ataxia Foundation on Saturday, February 9, 2002, 9am, at Montgomery College in Rockville, Maryland (just outside Washington, DC).

Dr. DiMauro's published research indicates that primary CoQ10 deficiency is a potentially important cause of familial ataxia and CoQ10 administration seems to improve the clinical picture by showing increased strength, improvement in ataxia and less frequent seizures. DiMauro will discuss the expansion of this research and patient recruitment. For further details and directions, please contact carljlauter@erols.com or visit the CCNAF website at http://www.geocities.com/HotSprings/Oasis/4988/

Friedreich's Ataxia Parents' Group - FAPG

Are you are a parent coping with a child diagnosed with childhood onset ataxia? ***This forum is a MUST!*** FAPG has remedied the isolation and loneliness many parents feel dealing with the challenges of raising children with these rare degenerative diseases. The forum is a closed email group with over 200 subscribers. Discussions and posts revolve around coping, research, parenting issues, accessibility issues, education, employment, and medical care. To join, visit http://www.fortnet.org/fapg or email kittel@webaccess.net

Through the Eyes of a Child — A glimpse into the world of a child with FRDA

Amanda (Mandie) Rieffenberger wrote the book, Through the Eyes of a Child, to work through the feelings and issues she faced as a result of her diagnosis of Friedreich's ataxia. The book was written over the course of three years in Mandie's life. When she completed the book in 1996, she diligently worked to get her book published in order to share her experiences with others. **The book has been used in elementary and secondary school programs and in collegiate level courses for therapists and physicians**. It is a useful resource in helping children who face FRDA, as well as educating other family members and the community. To Order Through the Eyes of a Child, email rieff1@home.com or call 1/605/882-2343; $10 per copy, plus $2.50 S/H.

International Network of Ataxia Friends

Ataxia patients of all ages & Family - Internet mailing list

Ataxia patients and their families are invited to join an internet listserv that provides support and serves as an information exchange vehicle. Subscribers help each other by asking questions, making comments and providing answers on how to make life with ataxia easier. There are currently over 400 subscribers from more than 40 countries worldwide. Subscriptions to INTERNAF are free and the list is unmoderated.

To subscribe to INTERNAF, send an email to internaf-subscribe@yahoogroups.com

The Corporate Business Connection -- Matching Gift Programs

If your employer offers a Matching Gift Program, your contribution to FARA could be doubled or even tripled! Because each employer has different requirements, please take a moment to contact your personnel office for your company's specific matching gift form and information. Complete your company's matching gift form and send it with your gift to FARA. Thanks to the many donors who have doubled or tripled their donation to FRDA research with their company's matching gift.

United Way -Another Way to Help!

The United Way begins its annual fundraising drive each fall in nearly every community in the United States. It provides a way for charities to obtain funds by individuals contributing one-time donations or a small portion of their monthly paycheck through payroll deduction. Most organizations listed are based locally. However, the majority of United Way chapters allow individuals to write in the charity of their choice, regardless of where it is based.

FARA's 501(c)(3) nonprofit status and participation in the United Way's Combined Federal Campaign (#7970) qualifies us for the local United Way write-in option.
Contact your company's United Way chairperson to ask if there is a write-in option. Your co-workers may also be interested in donating to a cause dealing with someone they personally know. If you have any questions, contact us at fara@frda.org

Federal Workers Giving at the Workplace
Combined Federal Campaign
Federal employees can contribute to FARA through the Combined Federal Campaign (CFC), the annual fund-raising drive conducted by Federal employees in their workplace each fall. Each year Federal employees and military personnel raise millions of dollars that benefits non-profit charities. Federal employees can obtain a pledge card from their agency. **To designate FARA enter the four-digit code 7970 on your pledge card.**
Please ask your friends and family who are federal employees to consider making a CFC contribution to FARA.

YOUR PERSONAL CHECK

Elizabeth and Peter Maer of Fairfax, Virginia, are among many who write personal checks to FARA in honor of friends and neighbors who are afflicted with FRDA.

The Maers: ***"We met our neighbor Keith for the first time back in 1986 when his family moved in next door. He was only 6 months old. Over the years we've celebrated joyful events such as graduations and birthdays and we've grieved over the loss of family members. We remember Keith climbing trees and jumping on the trampoline and are saddened as he awaits the delivery of his first wheelchair. We felt the best way to help Keith was to support research through a personal donation."***

Miniature Golf Tournament

Leo Lazaropolous (pictured at right) was at it again this year-- raising money for FRDA research! Leo's mom, Krissa, described the fundraising miniature golf tourney as an "eventful event". Despite Leo's high fever and his brother getting a big piece of glass in his foot when he went into the water trap to fish out someone's sunglasses, it was a fun time for a worthy cause. We are all grateful for Leo's tremendous commitment to supporting research.

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In Memoriam

FARA extends its deepest condolences and sympathy to all the families who lost loved ones this year.

The loss of a family member or close friend is never an easy time for anyone involved. The memorial gifts FARA received this year help accomplish our mission to find a treatment or cure for Friedreich's ataxia. May you find comfort in knowing that these memorial donations are a gift of hope-- something promising that rises above the sadness and grief of death.

FARA DIRECTORS AND OFFICERS

MAIL TO: