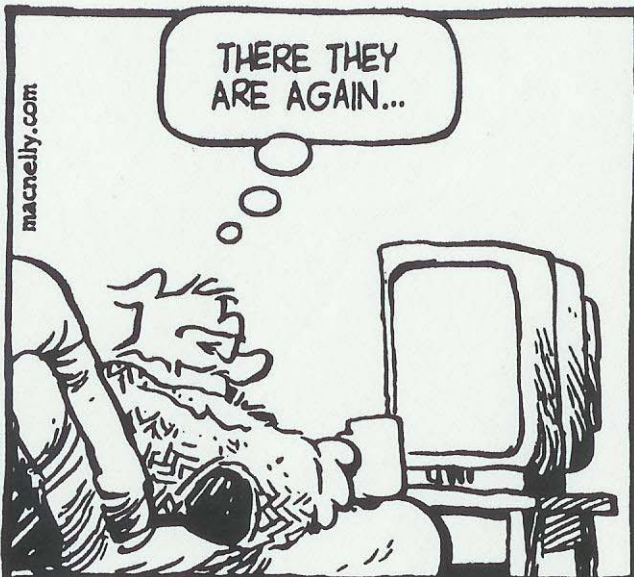


FRDA CLINICAL TRIALS

Susan L. Perlman, M.D.
Clinical Professor of Neurology
UCLA Medical Center



©1996 Tribune Media Services, Inc. All Rights Reserved

TRIBUNE MEDIA SERVICES, INC. ALL RIGHTS RESERVED.

March 30, 2008

2008 NAF Annual Membership Meeting

Pay Attention

- **This is not just about Friedreich's.**

March 30 in History

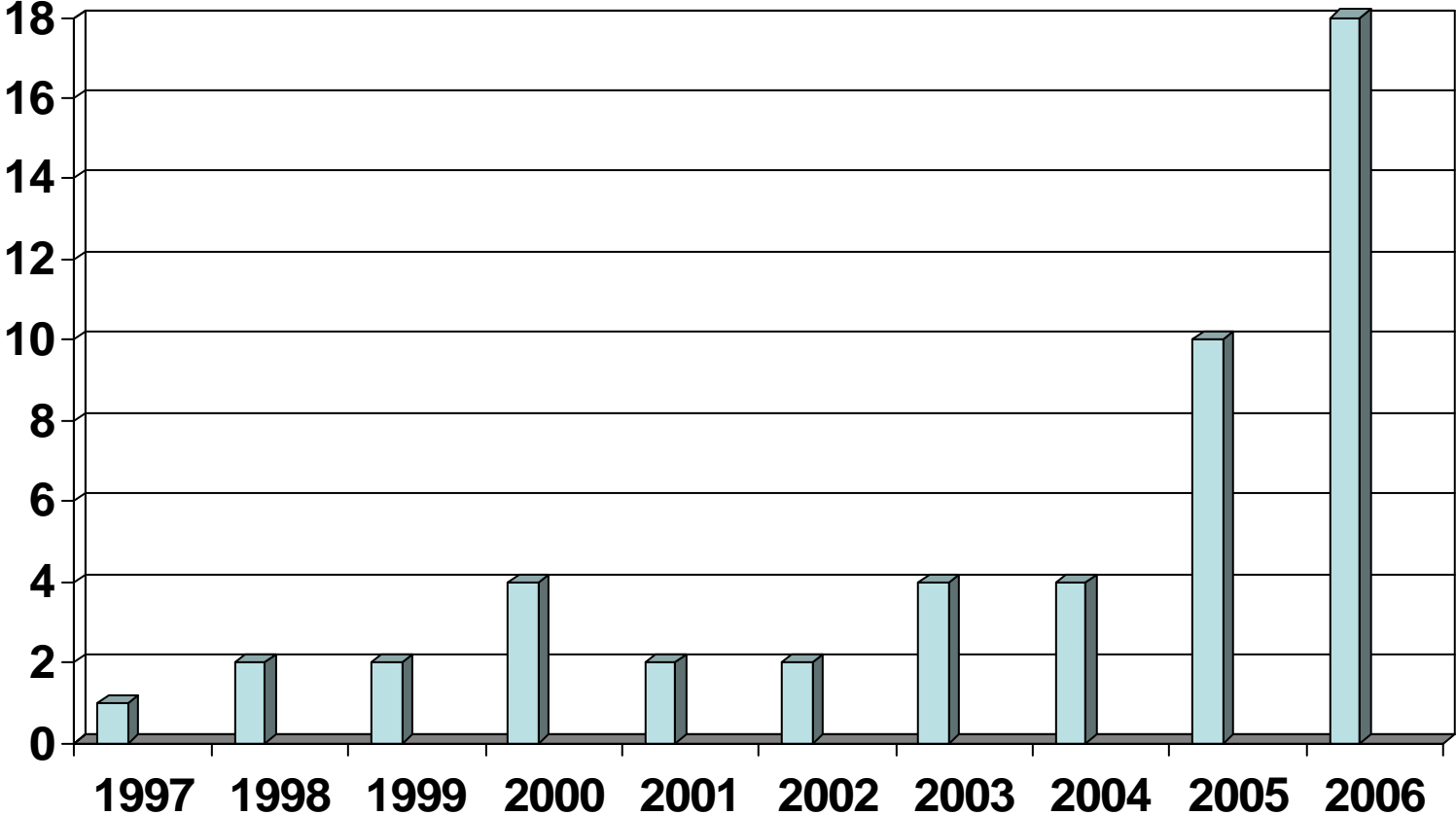
Thanks to Wikipedia

- Seeing as how this is a leap year, March 30 is the 90th day of the year. Only 276 days left to accomplish everything we need to.
- 1858 - Hymen Lipman patents a pencil with an attached eraser.
That's 150 years of second chances.
- 1867 - Seward's Folly, Alaska is purchased for \$7.2 million, about 2 cent/acre (\$4.19/km²).
- 1981 - President Ronald Reagan is shot in the chest outside a Washington, D.C., hotel by John Hinckley, Jr.
- Birthdays--1746- Francisco Goya; 1853 - Vincent van Gogh; 1950 - Robbie Coltrane (Hagrid); 1968 - Celine Dion
- Deaths--1840 - Beau Brummell; 1965 - Philip Showalter Hench, American physician, recipient of the Nobel Prize in Physiology or Medicine (1950) for the use of cortisone for Rheumatoid Arthritis. First disease-modifying therapy for a non-infectious disease (penicillin-Nobel Prize 1945) and a non-deficiency disease (insulin-Nobel Prize 1923).

March 30 also an ancient Roman festival dedicated to Salus

- **In Greek mythology, Hygieia (Roman equivalent: Salus) was a daughter of Asclepius, the demigod of medicine.**
- **She was the goddess of health, cleanliness and sanitation.**
- **While her father was more directly associated with healing, she was associated with the prevention of sickness and the continuation of good health.**
- **One of her sisters was Panacea (all-healing).**
- **And let us not forget her neglected stepbrother Placebo.**

US STUDIES FUNDED BY FARA, MDA, NAF, AND NIH FOR FA



March 30, 2008

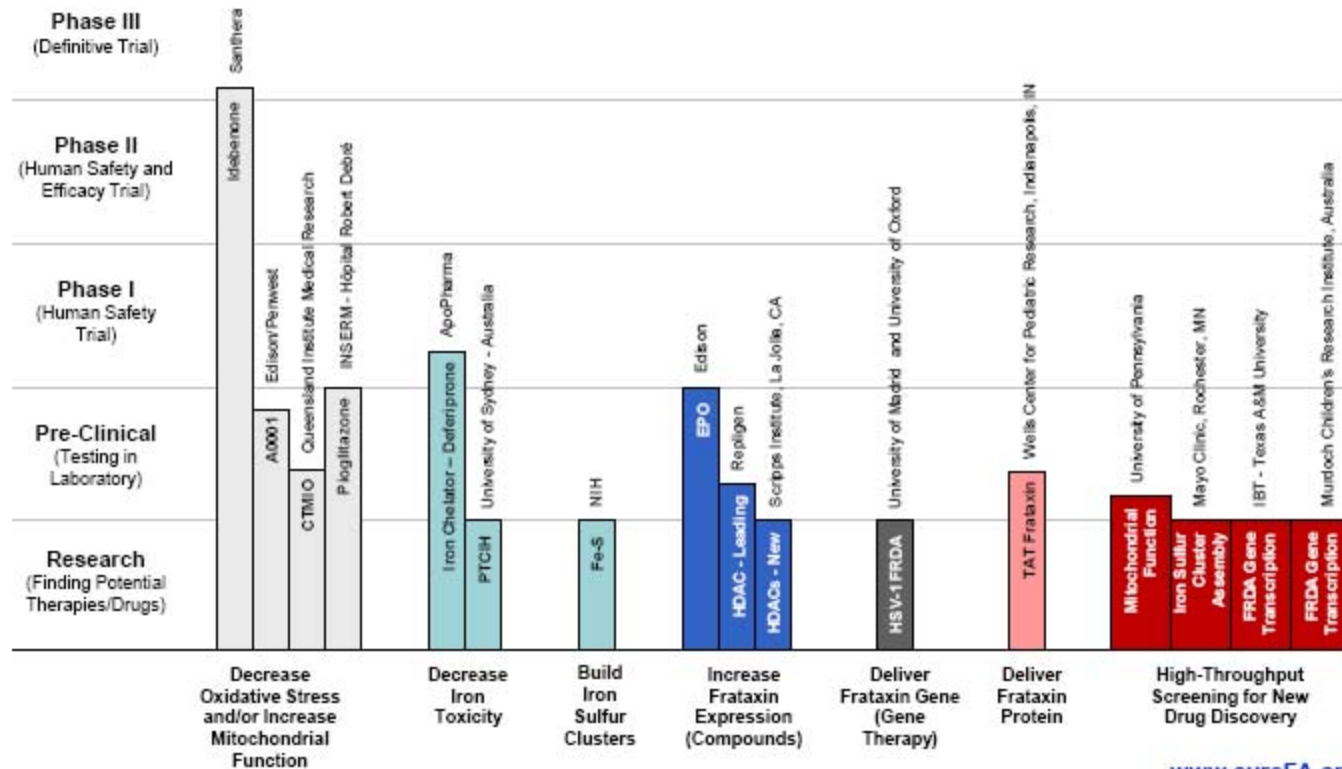
2008 NAF Annual Membership Meeting

Friedreich's Ataxia Pipeline

October 2007

Available to Patients

FARA has supported, and is supporting, these efforts by providing various combinations of direct funding, essential clinical infrastructure, advocacy and awareness efforts.



www.cureFA.org

Current FRDA Clinical Trials

clinicaltrials.gov

- Idebenone Phase 1A-completed (5/01-4/06)
- Idebenone Phase 1B-completed (2/04-4/06)
- Idebenone Phase II-active, no longer enrolling (9/05-)
Note—almost 7 years to move from Phase I to Phase III
- **Idebenone Phase III-active, enrolling (12/07-)**
- Epoetin alfa Phase II-active, enrolling in Italy (2/08-)
- Deferiprone Phase I/II-not yet enrolling in US
active in France (3/05-)
- **2 epidemiological studies-**
one completed
one active (FACOMS- Friedreich's Ataxia Clinical Outcome Measure)

Phase III Trial with SNT/MC17/idebenone

- **Aim of the Study**

To show idebenone's clinical benefit on neurological and cardiac function in patients with Friedreich's Ataxia

- **Inclusion Criteria**

Genetically diagnosed with Friedreich's Ataxia

Of either sex between 8 and 17 years of age

Able to walk at least 10 meters (33 feet) without accompanying person (may use a cane or walker)

Did NOT participate in the Phase II idebenone study run by the NIH

- **Treatment**

2 study sites—Children's Hospital of Philadelphia and UCLA

51 patients; 6 months' duration

3 treatment groups: placebo, medium and high idebenone doses

5 clinic visits (travel costs are fully reimbursed)

Option for 1-year open label extension study at high dose

Proposed FRDA Clinical Trials

- **MitoQ—Indefinite hold.**
 - Preclinical studies initiated 2003.
 - Phase I/II study had intended US start date in early 2007.
 - FDA concerns about thoroughness of animal safety studies resulted in withdrawal of IND application in August 2007.
 - Pending additional animal safety studies and results of New Zealand-based study in patients with Parkinson's disease, **Phase I study FA patients may be reconsidered in early '09**
- **Deferiprone—Indefinite hold.**
 - Experience outside US in 7500 patients with iron overload.
 - Pilot study in France in 2007 in FA patients.
 - Phase I/II study had intended US start date in late 2007.
 - FDA concerns about thoroughness of animal safety studies resulted in withdrawal of IND application in March 2008.
 - Pending additional animal safety studies and results of European Phase I/II study now in progress, **US Phase III study may be reconsidered in early '09.**
- **Erythropoetin (EPO)—Phase I/II study planned for late 2008.**
- **EPI-A0001 (Edison)—Phase I study healthy volunteers planned for Summer 2008**
 - Phase II study FA patients possible early 2009**
- **HDAC inhibitors (Scripps, Repligen)—FDA application for Phase I study planned late 2008.**

Clinical Trials Questions

- How do drugs get chosen for testing?
- What about “N of One” Trials?
- If it’s a safe enough drug for testing, why all the focus on protecting the participant?
- If it’s a good drug, why doesn’t everyone respond the same?
- Is it fair to exclude some patients from clinical trials?

How do drugs get chosen for testing? What about “N of One” Trials?

March 30, 2008

2008 NAF Annual Membership
Meeting

PRO'S AND CON'S OF CANDIDATE DRUGS FOR HUMAN TRIALS

- **Rationale--do we expect it to work?** Basic Science
- **Efficacy--has it worked in animal or pilot human trials (even “N of One” trials)?**
- **Safety**
- **Do the anticipated benefits outweigh the risks?**
- **Availability--designer drugs vs. already available ones. What's in it for the drug company?**
- **Cost (and where to get the money from)**

EFFICACY--CAN WE SHOW THAT THE DRUG ACTUALLY MAKES A DIFFERENCE?

- **Symptomatic benefit vs. disease-modifying**
- **Is the candidate drug strong and specific?**
- **How much does the disease change over how much time? Natural history.**
- **How accurately can this change be measured? Rating scales, QOL measures.**
- **Can biomarkers show clinically meaningful change quicker? 1° vs. 2° outcome measure.**
- **Can enough researchers and patients be found? Research centers and registries.**

FOR EXAMPLE: UMBILICAL STEM CELL TRANSPLANTATION FOR BRAIN DISEASE

- Symptomatic benefit vs. disease-modifying

NO ATTEMPT TO CONTROL FOR OTHER TREATMENTS, OTHER EFFECTS.

- Is the candidate drug strong and specific?

NO EVIDENCE AS TO WHAT ITS REAL EFFECT IS.

- How much does the disease change over how much time? Natural history.

TIMELINE WRONG FOR TRUE DISEASE-MODIFYING EFFECT.

- How accurately can this change be measured? Rating scales, QOL measures.

HAVE BEGUN TO USE VALIDATED MEASURES.

- Can biomarkers show clinically meaningful change quicker? 1° vs. 2° outcome measure.

NO BIOMARKERS USED TO MONITOR EFFECTS.

- Can enough researchers and patients be found? Research centers and registries

HIGH INTEREST IN MANY COMMUNITIES BUT FEW ETHICAL CONTROLS.

FOR EXAMPLE: LITHIUM FOR ATAXIA

- **“Lithium Carbonate and Choline Chloride in Cerebellar Ataxia.”**
- **10 patients (3 FA, ILOCA 3, 2 Etoh, 1 AHC, 1MS)**
- **Partial improvement with CC, marked with both**
- **1984!**
- **How did this miss getting into the pipeline?**
- **I was involved with a clinical drug trial for ataxia then**
- **I knew about choline**
- **This article was published in the Indian Journal of Pharmacology and there was no PubMed back then**
- **There were no patients on the Internet.**

TYPES OF CLINICAL TRIALS

TYPE	# SUBJECTS	LENGTH	AIM OF STUDY
N of 1	1	Ongoing	Do I get better or stop getting worse on this drug?
Pilot	Up to 20 All get drug	Weeks to months	Is a larger study worth doing, will there be problems?
Phase 1	20-80 normal or patient in groups of 3	2 years	Escalating doses to learn side effects, safety, best dose
Phase 2	20-300 Control and drug groups	2 years	To assess potential for good effects, as well as side effects. Also designed as “futility” study—to show a drug doesn’t not work(fewer subjects, less\$)
Phase 3	300-3000 Control and drug groups	3-5 years	To prove efficacy May include crossover design or open extension trial
Phase 4	100’s-1000’s Open drug use	Ongoing	To find out more about the effects of an approved drug.

The Pathway to Approval of a New Drug Goes Through the FDA

- If it's a safe enough drug for testing, why all the focus on protecting the participant?

Well-designed safety studies in animals and people are required by the FDA.

People cannot be unfairly coerced into participation.

- If it's a good drug, why doesn't everyone respond the same?

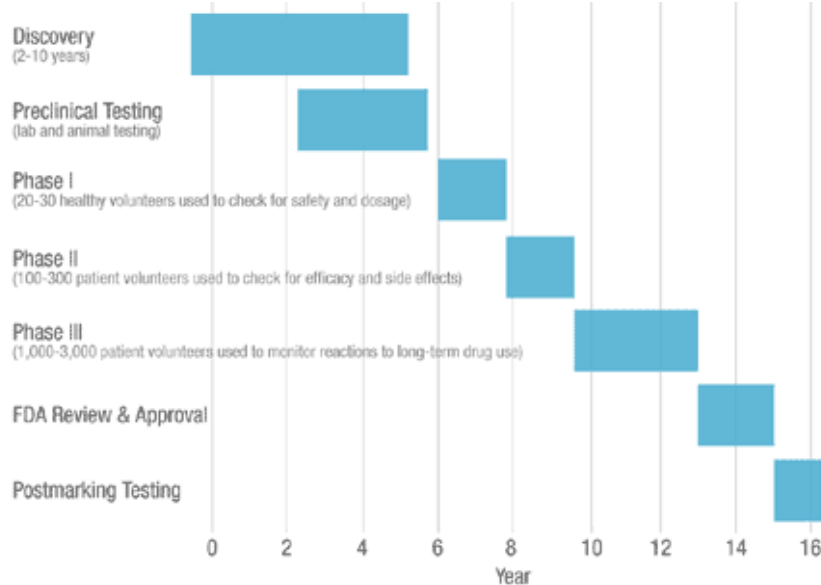
Well-designed Phase I, II, and III trials are required, with placebo controls, to be absolutely certain that the drug is responsible for observed good effects. The placebo effect is very real.

DO WE REALLY NEED PLACEBOS?

- Gold Standard for Phase III clinical trials is the **double-blind, placebo-controlled, randomized** study.
- The “placebo effect” is very real and accounts for all the other effects not related to the drug directly.
- Dramatic differences between the placebo and drug groups will usually result in all subjects being placed on drug before the end of the trial. Open extension studies are usually done.
- If it would be dangerous for a potential subject to end up on placebo, that subject would not be enrolled in the study. This includes the subject having to stop other medications to enter the study.
- **Active placebos may be used once the first drug is approved.**
- Use of historical controls or subject acting as own control may require a longer study to prove benefit of drug.

OFFICIAL PIPELINE FOR NEW DRUGS

Up to 15 years and \$500-700million to get to market



Click to enlarge

- **Discovery**—clinicians and scientists working out the cause of the disease, the “dominos” that fall over, and targeted candidate drugs.
- **Preclinical testing**—test tube and animal studies.
- **Phase I**—dosing, safety
- **Phase II**—safety, possible efficacy
- **Phase III**—efficacy
- **FDA Approval**
- **Phase IV**--Post-marketing studies for long-term side-effects and good effects.
- To help with promising drugs for serious diseases with unmet needs:
- **NIH**—Rapid Access to Intervention Development (RAID)
- **FDA**—Orphan Drug Status

FUNDING

A PUBLIC-PRIVATE PARTNERSHIP

- **Discovery—clinicians and scientists working out the cause of the disease, the “dominos” that fall over, and targeted candidate drugs.**
\$25-80,000 per yr over many years
- **Preclinical testing—test tube and animal studies.**
\$100,000 per year for at least 2 yr
- **Phase I and Phase II--**
\$500-700,000 per year for 4 yr
\$2-4 million to get to this point
- **Phase III—\$4-5 million (\$10K/subject)**
- **FDA Approval**
- **Post-marketing studies for long-term side-effects and good effects and possible other uses of the drug.**
- **Government**
Private research foundations
- **Government**
Private research foundations
Pharmaceutical companies
- **Government**
Private research foundations
Pharmaceutical companies
- **Pharmaceutical companies**

Is it fair to exclude some patients from clinical trials?

- The number of patients and the type of patients (age, level of disability) chosen for a clinical trial are determined in order to achieve the best results in the shortest time with the least cost.**
- But, the drug when approved will certainly be used by all ages and all levels of disability.**
- A compromise with the drug company and the FDA might be in order.**

WHAT'S ON THE HORIZON FOR NON-FA ATAXIAS?

- **Are we ready to begin clinical trials?**

MULTIPLE TARGETS TO TREAT THE CAUSES OF TRIPLET REPEAT DISEASES

- **Mutant DNA/RNA** **inhibit other genes**
 make protein with extra-long polyglutamine
 may not make enough normal protein to do
 the normal job of the gene
- **Extra-long polyglutamine binds with/soaks up other proteins**
- **Extra-long polyglutamine is chopped up into fragments.**
- **Fragments bind with other proteins and are taken into the nucleus where they form aggregates and trigger excitotoxicity and apoptosis.**
- **Fragments “clog up” proteosomes and deprive cell of needed functions.**
- **Mitochondrial function is also deranged/free radicals build up.**
- **Certain nerve cells are more sensitive to these stresses than others.**

SOME TARGETS ARE ACTIVE IN NON-GENETIC ATAXIAS TOO

- **Mitochondrial function is also deranged/free radicals build up.**
- **Certain nerve cells are more sensitive to these stresses than others.**

CANDIDATE DISEASE-MODIFYING TREATMENTS ALREADY PILOTED IN ANIMALS AND PEOPLE WITH TRIPLET REPEAT DISEASE (HD) AND NON-GENETIC DISEASE

- Oxidative Stress, Free Radicals/Mitochondria
 - vitamin E, coenzyme Q10* (entering Phase III studies for HD)
 - creatine*
 - alpha lipoic acid*
 - tauroursodeoxycholic acid (TUDCA)*
 - ethyl-EPA (LAX-101)*
 - Dimebon*
- Apoptosis/Excitotoxicity
 - anti-glutamate(*remacemide, riluzole, memantine*)
 - anti-caspase-1 (*minocycline, ethyl-EPA*)
- “Declumping”--reduce fragment load
 - anti-caspase 3 (*minocycline* and others)
 - anti-caspase 6
 - anti-transglutaminase (*cystamine*)
- “Declumping”--reduce aggregation
 - inhibition of GSK-3beta (*lithium chloride*)
 - trehalose*
- Transcriptional re-regulation--upregulating expression of genes inhibited by mHtg. (*Valproic acid*), SAHA/suberoylanilide hydroxamic acid, *phenylbutyrate*, Scripps)
- Transcriptional hijacking--small inhibitory RNAs to block the production of mHtg

NATURAL HISTORY STUDIES TO UNDERSTAND THE BEHAVIOR OF THE DISEASE

- **FARA and MDA have funded and completed a 3-year natural history study for FA, to determine the normal course of the disease.**
- **EUROSCA has completed a 2-year natural history study of the most common SCAs.**
- **The Cooperative Ataxia Group and NAF have the foundation to begin a natural history study of the SCAs in the US if it would be necessary. International collaboration can save researchers a lot of unneeded work.**

RATING SCALES TO MEASURE THE DISEASE

- **FARA and MDA have assisted in the validation of 2 rating scales for FA trials (FARS, FACT).**
- **EUROSCA has validated 2 rating scales for ataxia (ICARS—international cooperative ataxia rating scale; SARA—scale for the assessment and rating of ataxia) and has worked with instrumental scales like the FACT.**

AVAILABLE BIOMARKERS

- **Imaging—MRI, fMRI, MRS, SPECT, PET**
- **Measures of level of protein product of gene.**
- **Measures of free radical-related chemicals.**

RESEARCH CENTERS

- **NIH—basic and clinical research**
- **Basic research—many centers at many institutions large and small.**
- **Clinical centers—present/?future for genetic disease**
U Penn@Philadelphia, UCLA
California Pacific Medical Center
UCD, UCSF, UCSD
U Washington-Seattle, U Colorado, U Iowa, U Texas
@Galveston, LSU, U Mississippi@Jackson, U South
Florida, Emory U, Mass Gen, Rochester U,
U Chicago, U Minnesota

REGISTRIES

- FA

<http://www.faresearchalliance.org/registry>

- FA, SCA, SPORADIC ATAXIA

<http://cooperative-ataxia-group.org/register.htm>

Non-FRDA Clinical Trials

North American and International

- **The Cooperative Ataxia Registry is a clinical trial. Every ataxan-sign up!**
- **The Cooperative Ataxia Database and Rating Scales will support longitudinal natural history trials and provide a resource for genetic studies.**
- **Epidemiologic studies have already commenced in Europe. Dr. Subramony has started one in the US.**
- **The first clinical drug trial (Phase I Lithium in SCA1) will be starting within a few weeks at the NIH. Other non-FA trials are right behind.**

THANK YOU

- **National Ataxia Foundation**—
sponsor of grants for our internal database, our DNA bank, and our web-based database project.
- **Muscular Dystrophy Association and**
- **Friedreich's Ataxia Research Alliance**—
sponsors of our grant for the collaborative project on “Clinical Outcome Measures in Friedreich's Ataxia”.
- **The Smith Family Foundation**
- **Dr. David Lynch and the CCRN**
- **And to our patients and their families for their willingness to work with us and to share with us their ideas and hopes.**
- **Clinical trials won't work without you!**