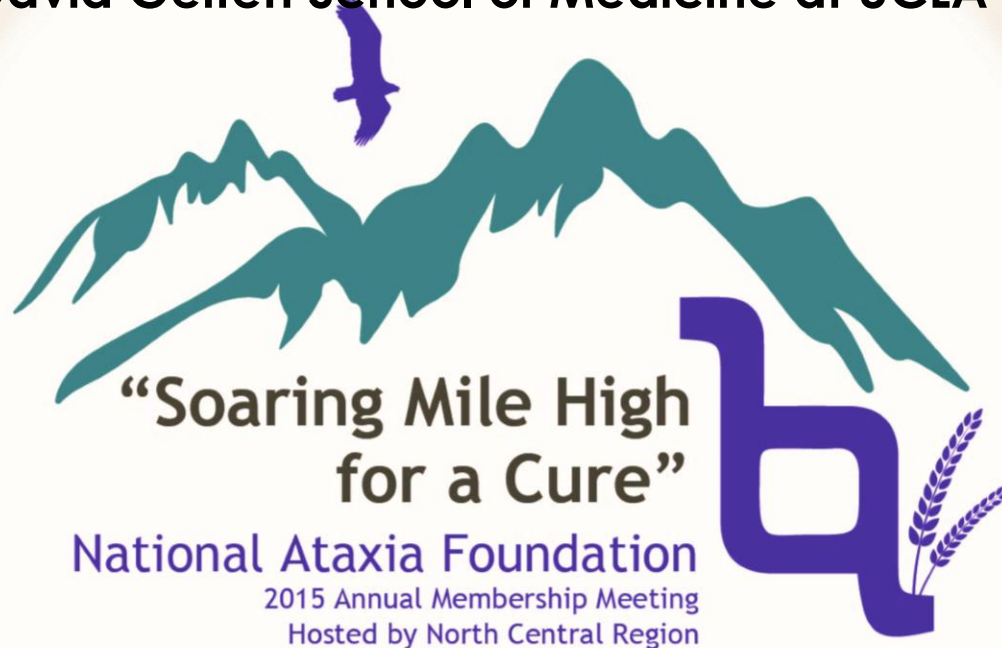


# The Ataxias: Research in FRDA, SCA, MSA

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# Presenter Disclosures

- Susan L. Perlman M.D.
- The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:
  - Investigational site for drug trials sponsored by:
    - Edison Pharmaceuticals
    - Shire/Viropharma
    - Teva Pharmaceuticals



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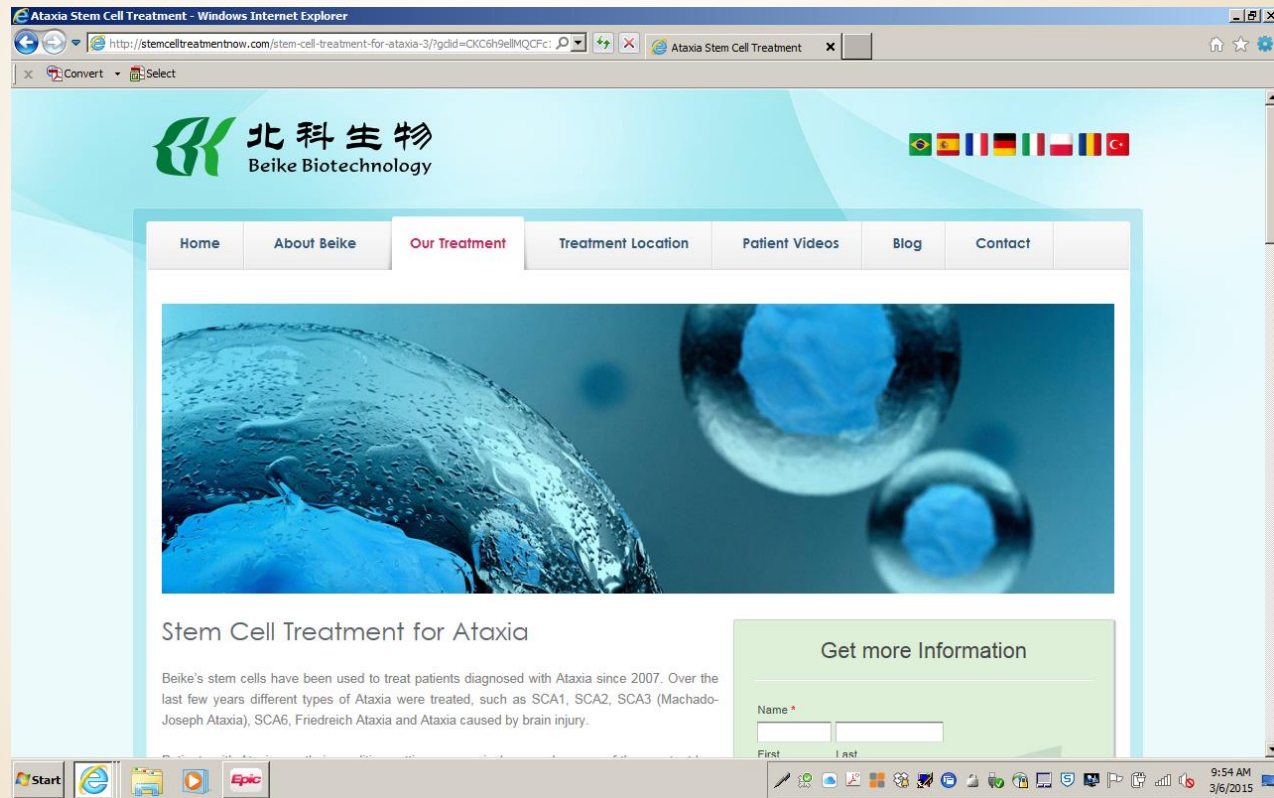



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However, no matter what you read  
on the Internet...  
there is still no cure for ataxia





**We are all interested in scientific discovery  
and constantly amazed at what science and technology  
are able to do...  
and intensely hoping that a cure for ataxia will come out  
of it.**

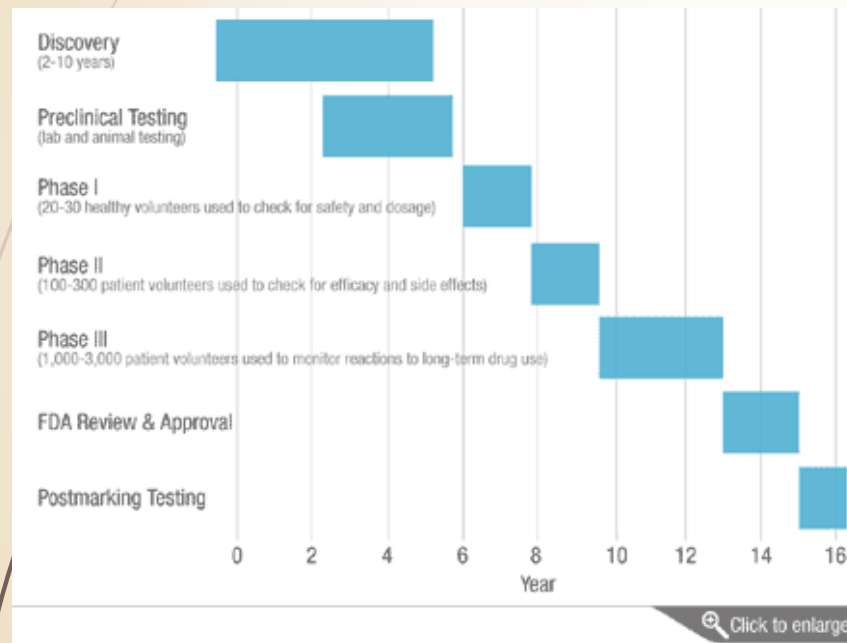
- ▶ Milestones in Neuroscience Research (from Eric Chudler PhD at the University of Washington, Seattle)
- ▶ 1824 - F. Magendie provides first evidence of cerebellum role in equilibration
- ▶ 1837 - Jan Purkyne (Purkinje) describes cerebellar cells; identifies neuron nucleus and processes (named for him in 1866)
- ▶ 1863 - Nikolaus Friedreich describes a progressive hereditary degenerative CNS disorder (Friedreich's ataxia)
- ▶ 1913 - Edwin Ellen Goldmann finds blood brain barrier impermeable to large molecules
- ▶ 1932 - Max Knoll and Ernst Ruska invent the electron microscope
  
- ▶ 1953 – Watson and Crick suggest a model for the structure of DNA
- ▶ 1977-96 – Techniques to sequence genetic material developed
- ▶ 1993 - The gene responsible for Huntington's disease is identified
- ▶ 1990-2003 – Human Genome Project
- ▶ The past 20 years have been an explosion of gene discovery in ataxia



# Examples in the History of Drug Development

- ▶ 1897 - Acetylsalicylic acid (aspirin) is synthesized by Felix
- ▶ 1898 - Bayer Drug Company markets heroin as non-addicting cough medicine
- ▶ 1899 - Bayer AG markets aspirin
- ▶ 1960 - Oleh Hornykiewicz shows that brain dopamine is lower than normal in Parkinson's disease patients
- ▶ 1961 - Levadopa successfully treats parkinsonism
- ▶ 1973 - Sinemet is introduced as a treatment for Parkinson's disease
  
- ▶ **13 years from the first bright idea about dopamine and PD until Sinemet released.**
- ▶ **Has this process been speeded up?**

# OFFICIAL PIPELINE FOR NEW DRUGS



- **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**



# Things You Need to Ask Yourself When Looking at a Research Study

- ▶ 1. Is it based in “good science?”
  - ▶ 2. Is it potentially dangerous?
  - ▶ 3. Is it being conducted ethically?
  - ▶ 4. Can I afford the time and money it may cost me?
  - ▶ 5. Is there any potential benefit for me?
  - ▶ 6. Is it something I could do on my own?
- ▶ Issues of study design that often come up include use of placebos, compassionate availability, and delays.



# The Bottom Line

- ▶ Every ataxia patient must participate in clinical trials—natural history, biomarker, drug treatment.
- ▶ Every researcher designing a clinical trial must make it accessible to all ataxia patients.
- ▶ There will be exceptions but...



# Every Ataxia Patient Must Participate in Clinical Trials

1. Registries will enable you to be found.  
These are rare diseases with very small numbers of patients who can participate. Every person counts.
2. Be knowledgeable about what makes a good clinical trial—don't make bad investments.
3. Speak up about the roadblocks to participation. Become involved in planning the trials.
4. Be prepared to make sacrifices.



# Every Researcher Designing A Clinical Trial Must Make It Accessible To All Ataxia Patients.

- ▶ Design trials that can use the fewest patients over the shortest period of time (this usually means testing better drugs and using biomarkers).
- ▶ What is the rationale for excluding certain patients? Can those excluded be used in other ways? Parallel or compassionate studies?  
But remember that a patient can participate in only one trial at a time and that participation in some trials may permanently disqualify participation in others.
- ▶ Reimbursing travel costs is essential for recruitment and compliance. Telemedicine?
- ▶ Don't expect the patients to make unreasonable sacrifices.

# Registries

- ▶ Ataxia patients are some of the most highly motivated research subjects around, but ...
- ▶ The Cooperative Ataxia Research Networks and the National Ataxia Foundation are not mind-readers.
- ▶ Every ataxia patient must be in a Registry.
  
- ▶ For all ataxias--  
<https://www.sanfordresearch.org/CoRDS/CoRDSRegistryForm>
- ▶ For episodic ataxia--  
<http://rarediseasesnetwork.epi.usf.edu/cinch/index.html>
- ▶ For Friedreich's Ataxia--<http://www.curefa.org/registry.html>

# TYPES OF CLINICAL TRIALS

<b>TYPE</b>	<b># SUBJECTS</b>	<b>LENGTH</b>	<b>AIM OF STUDY</b>
<b>N of 1</b>	1	Ongoing	Do I get better or stop getting worse on this drug?
<b>Pilot</b>	Up to 20 All get drug	Weeks to months	Is a larger study worth doing, will there be problems?
<b>Phase 1</b>	20-80 normal or patient in groups of 3 All get drug	2 years	Escalating doses to learn side effects, safety, best dose
<b>Phase 2</b>	20-300 Placebo and drug groups Compassionate trials do not use placebo.	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\$)
<b>Phase 3</b>	300-3000 Placebo and drug groups	3-5 years	To prove efficacy May include crossover design, open extension trial
<b>Phase 4</b>	100’s-1000’s Open drug use	Ongoing	To find out more about the effects of an approved drug.



## Research in FRDA, SCA, and MSA

- Since the last AMM, there have been 1748 articles about ataxia in PubMed.
- We will review each of them in detail...



# Research in FRDA, SCA, and MSA

- **Human Subjects**
  - natural history
  - biomarkers of disease onset and progression
  - mechanisms of tissue damage including genetics
- **Basic Science**
  - animal models
  - cellular models including iPSC
  - epigenetic controls
  - translational research
- **Treatment trials**
  - **Since the last AMM, there have been 79 publications about ataxia treatment.**
  - **Clinicaltrials.gov lists 57 open studies dealing with ataxia.**



# Collaborative Groups Doing the Research (and many more individual researchers)

**CRC-SCA—North American Collaborative Research Consortium for Spinocerebellar Ataxia** under the direction of Dr. Tee Ashizawa

**EUROSCA—European Integrated Project on Spinocerebellar Ataxia**  
under the direction of Prof. Olaf Riess

**CCRN—Collaborative Clinical Research Network for Friedreich's Ataxia**  
under the direction of Dr. Dave Lynch

**EFACTS--European Friedreich's Ataxia Consortium for Translational Studies**  
under the direction of Dr. Massimo Pandolfo

**Global MSA Taskforce, North American MSA Study Group, European MSA Study Group, and others**

under the direction of Dr. Ryan Walsh and others

# Recent and Active Studies in SCA

- ▶ **Natural History Study of and Genetic Modifiers in Spinocerebellar Ataxias**  
(SCA 1, 2, 3, 6; 12 US sites; visits every 6 months for 2 years)  
Separate blood/tissue banking study at U Utah.
- ▶ **Transcranial Magnetic Stimulation in Spino-Cerebellar Ataxia**  
(Genetic SCA; Beth Israel Medical Center in Boston; 5 days per wk for 4 wks)
- ▶ **Parkinsonism in Spinocerebellar Ataxia Type 6** (University of Chicago)
- ▶ **MRI/MRS imaging of the Brain in SCA1, 2, 3, 6** (U Minnesota)
- ▶ **MRI in SCA1, 2, 3, 6, 8** (Johns Hopkins)
- ▶ **Natural History of SCA7** (NIH)
- ▶ **Cerebellar Control of Voluntary Motion** (UC Berkeley; Princeton)
  
- ▶ **NOT YET RECRUITING**
- ▶ An Open-label Trial of Intravenous Immune Globulin (**IVIG**) in Treating Spinocerebellar Ataxias (SCA 1, 2, 3, 6, 10,11; U South Florida; 5 days per mo for 3 mo)
- ▶ Study To Assess Safety, Tolerability and Efficacy of **Intravenous Cabaletta** in Patients With Machado-Joseph Disease

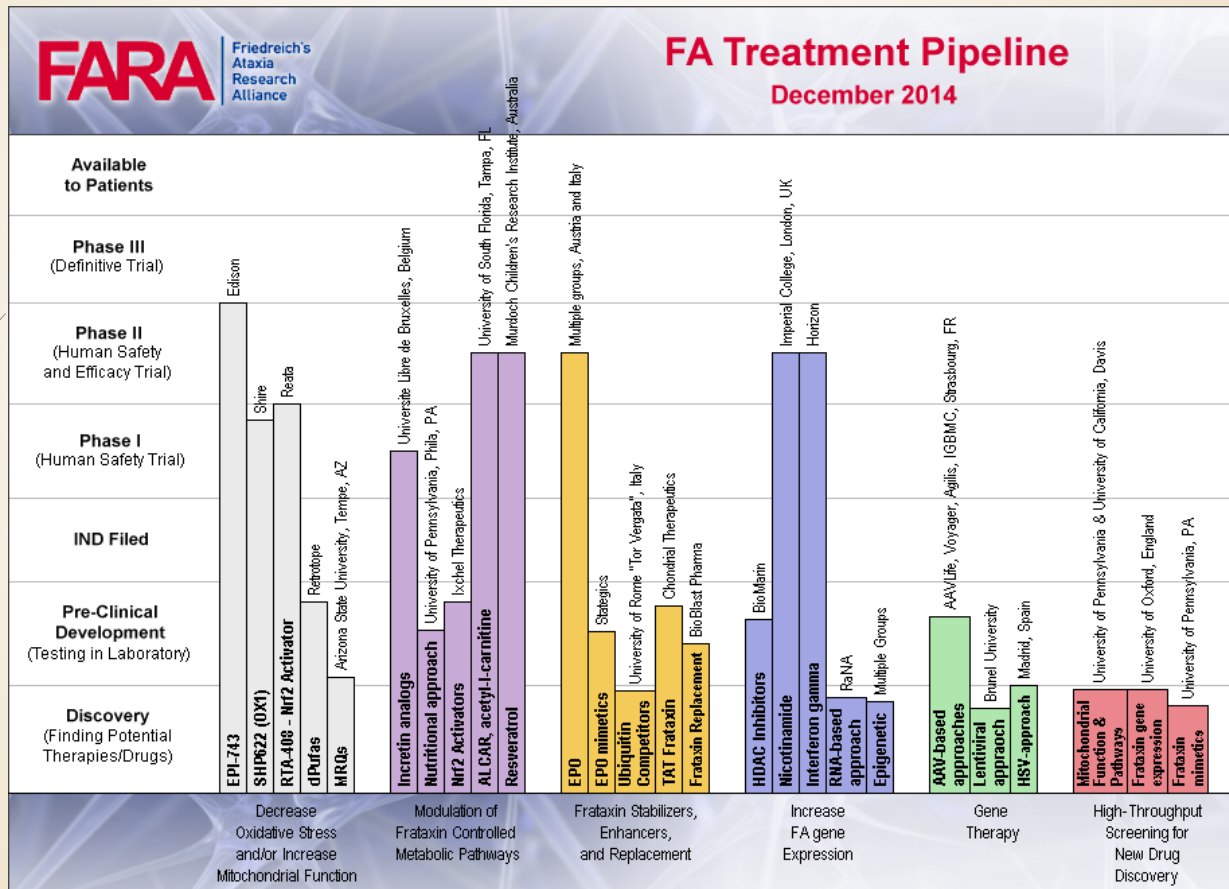
# SCA Pipeline—industry sponsored

Company	Agent	MOA	Status
Astra Zeneca	Myeloperoxidase inhibitor	Blocks microglial activation/inflammation.	Phase 2 For MSA
Others		Reducing neuroinflammation	
Ataxion	CNS ion-channel modulators	Stabilizes Purkinje cell electrical potentials	Pre-Phase 1
Bioblast	Trehalose	Prevent aggregate formation	Phase 2 for SCA3
Isis Pharma	ASO    ISIS-HTT <sub>Rx</sub>	Antisense drugs bind to messenger RNAs (mRNAs) and inhibit the production of disease-causing proteins	Pre-Phase 1 For Huntingtons disease
Prana Biotech	PBT2	Prevents the accumulation of toxic huntingtin proteins and the resultant damage inside neurons, and improve neuronal health and function by restoring normal copper and zinc levels which are disturbed when neurodegeneration takes place.	Completed Phase 2 study in Huntington's disease.

# Recent and Active Studies in Friedreich's Ataxia

- ▶ **Early and Longitudinal Assessment of Neurodegeneration in the Brain and Spinal Cord in Friedreich's Ataxia** (U Minnesota)
- ▶ **Cerebellar Control of Voluntary Motion** (UC Berkeley; Princeton)
- ▶ **Characterization of the Cardiac Phenotype of Friedreich's Ataxia** (Cornell NYC)
- ▶ **An Open-label Study of the Effects of Acetyl-L-Carnitine on Cardiovascular Outcomes in Friedreich's Ataxia** (U South Florida; every 6 months for 2 years)
- ▶ **RTA 408 Capsules in Patients With Friedreich's Ataxia – MOXIe**  
(UF at Gainesville, Emory, Ohio State, CHOP; 16-40y/o; multiple visits over 3 mo)
  
- ▶ NOT YET RECRUITING
- ▶ Efficacy, Safety, and Pharmacokinetic Study of ACTIMMUNE® (**interferon gamma-1b**) in Children and Young Adults with Friedreich's Ataxia
  
- ▶ FINISHING
- ▶ EPI-743 in Adults with Friedreich's Ataxia
- ▶ Safety and Pharmacology Study of VP 20629 in Adults With Friedreich's Ataxia

# Friedreich's Ataxia Pipeline



# Recent and Active Studies in Idiopathic Ataxia and MSA

- ▶ **MRI/MRS imaging of the Brain in MSA-C** (U Minnesota)
- ▶ **PET Imaging Study of Neurochemical and Autonomic Disorders in Multiple System Atrophy (MSA)** (U Michigan)
- ▶ **Exome sequencing genetic studies**
- ▶ **RECENTLY APPROVED**

NORTHERA (droxidopa) is indicated for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [eg. multiple system atrophy].

- ▶ **BEING STUDIED IN EUROPE**  
Phase I vaccine study (France); EGCG green tea extract (Germany)
- ▶ **FUTURE PLANS**—Global MSA Taskforce for a Research Roadmap



# Is Anyone Doing Research into Fatigue in Ataxia?

- ▶ Once medical issues, nutritional issues, sleep problems, depression, deconditioning have been ruled out...

- ▶ Functional MRI studies

Radiol Med. 2012 Dec;117(8):1398-407. Specogna I <sup>et al</sup>

**Functional MRI during the execution of a motor task in patients with multiple sclerosis and fatigue.**

- ▶ Patients with fatigue have greater activation of the motor-attentional network when performing a simple motor task.

- ▶ Neuro-inflammation studies

# Partners in Neurogenetics Research at UCLA

- Daniel Geschwind, M.D., Ph.D., Neurogenetics Program Director
- Susan Perlman, M.D., Ataxia Clinic Director (Ataxia Database, Drug Trials)
- Brent Fogel, M.D., Ph.D. (Molecular Genetics, Biospecimens bank)
- Robert Baloh, M.D. (Neuro-Otology)
- The Bartzokis group (Neuroimaging, Biomarkers)
- Yvette Bordelon, M.D., Ph.D. (Huntington's disease, Biomarkers, Drug Trials)
- Stephen Cederbaum, M.D. (Medical Genetics, Metabolic Disorders)
- Giovanni Coppola, M.D. (Molecular Genetics)
- Ming Guo, M.D., Ph.D. (Drosophila)
- Joanna Jen, M.D., Ph.D. (Episodic Ataxias, Drug Trials)
- Arik Johnson, Psy.D. (Psychology)
- Shamran Khamsa, M.D., Juan Alejos, M.D. (Cardiology)
- William Oppenheim, M.D. (Orthopedics)
- Noriko Salamon, M.D. (Neuroradiology)
- Ernest Wright D.Sc., Ph.D, Vladimir Kepe Ph.D., Jorge Barrio Ph.D. (Neuroimaging, Biomarkers)
  
- Clinic Coordinator (310) 794-1195
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- Nagmeh Dorrani, M.S. — Genetic Counselor (310) 206-6581
- Hillary Zebberman, MSW, social work consultant — Social Work Coordinator (310) 794-1225
-

# Thank You

- ▶ National Ataxia Foundation—  
sponsor of grants for our internal database, our DNA bank, our web-based database project, and the SCA3 Chantix study.
- ▶ The Collaborative Research Network for Spinocerebellar Ataxia—  
sponsor of the grant for the SCA Natural History Study.  
NINDS RC1 NS68897 and NIH Office of Rare Diseases Research
- ▶ Muscular Dystrophy Association and
- ▶ Friedreich's Ataxia Research Alliance—  
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- ▶ The Bettencourt Family Foundation
- ▶ The Norman Lapin Fund
- ▶ The Mariette Monnet Fund
- ▶ The Smith Family Foundation
- ▶ And to our patients and their families for their willingness to work with us and to share with us their ideas and hopes.