

Ataxia Research Update - 2008

NAF Annual Meeting, Las Vegas

Research - 2008

“Blazing a Trail in Research”

**Thanks to ataxia patients and families.
2008, NAF distributed \$750,000 to investigators
for ataxia research (2007 - \$580,000).**

AIM 2008

Organized by Dr. John Day

Attended by 120 ataxia researchers from around the world.

Many young investigators.

Basic to translational to clinical research.

2007 RESEARCH – THE BRIDGE TO HOPE

**Ataxia
Patients and Families**



Preclinical Research

Clinical Trials

Basic Research

Treatment

AIM - 2008

Basic Science

Identification of Ataxia Genes:

SCA 11

SCA 15

SCA 28

ARCA1

ARSACs

New pathways to disease.

AIM - 2008, Basic Science

Pathogenic pathways:

Intracellular Protein Trafficking (Spectrin Ataxias)

SCA5

ARCA1

16q ADCA

Cayman ataxia

Friedreich Ataxia

Iron chaperone for Fe-S protein synthesis.

SCA11

Tauopathy???

Friedreich Ataxia - Translational & Clinical Research

Completion of a Phase II clinical trial, idebenone

HDAC inhibitors

Additional High through put screens

➔ Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial

Nicholas A Di Prospero, Angela Baker, Neal Jeffries, Kenneth H Fischbeck

Lancet Neurol 2007; 6: 878-886

Findings Idebenone was generally well tolerated with similar numbers of adverse events in each group. One child receiving high-dose idebenone developed neutropenia after 6 months, which resolved after discontinuation of treatment. 8OH²dG concentrations were not increased, and did not significantly change with idebenone treatment. Whereas an overall analysis did not show a significant difference in ICARS, FARS, or ADL total scores, there were indications of a dose-dependent response in the ICARS score. A second, pre-specified analysis, excluding patients who required wheelchair assistance, showed a significant improvement in ICARS (Bonferroni $p=0.03$) and suggested a dose-related response in ICARS, FARS, and ADL scores.

Interpretation Treatment with higher doses of idebenone was generally well tolerated and associated with improvement in neurological function and ADL in patients with FA. The degree of improvement correlated with the dose of idebenone, suggesting that higher doses may be necessary to have a beneficial effect on neurological function.

Next step a phase III trial.

Friedreich Ataxia - HDAC inhibitors

HDAC inhibitors means to overcome silencing of FRA gene seen with mutant GAA repeats.

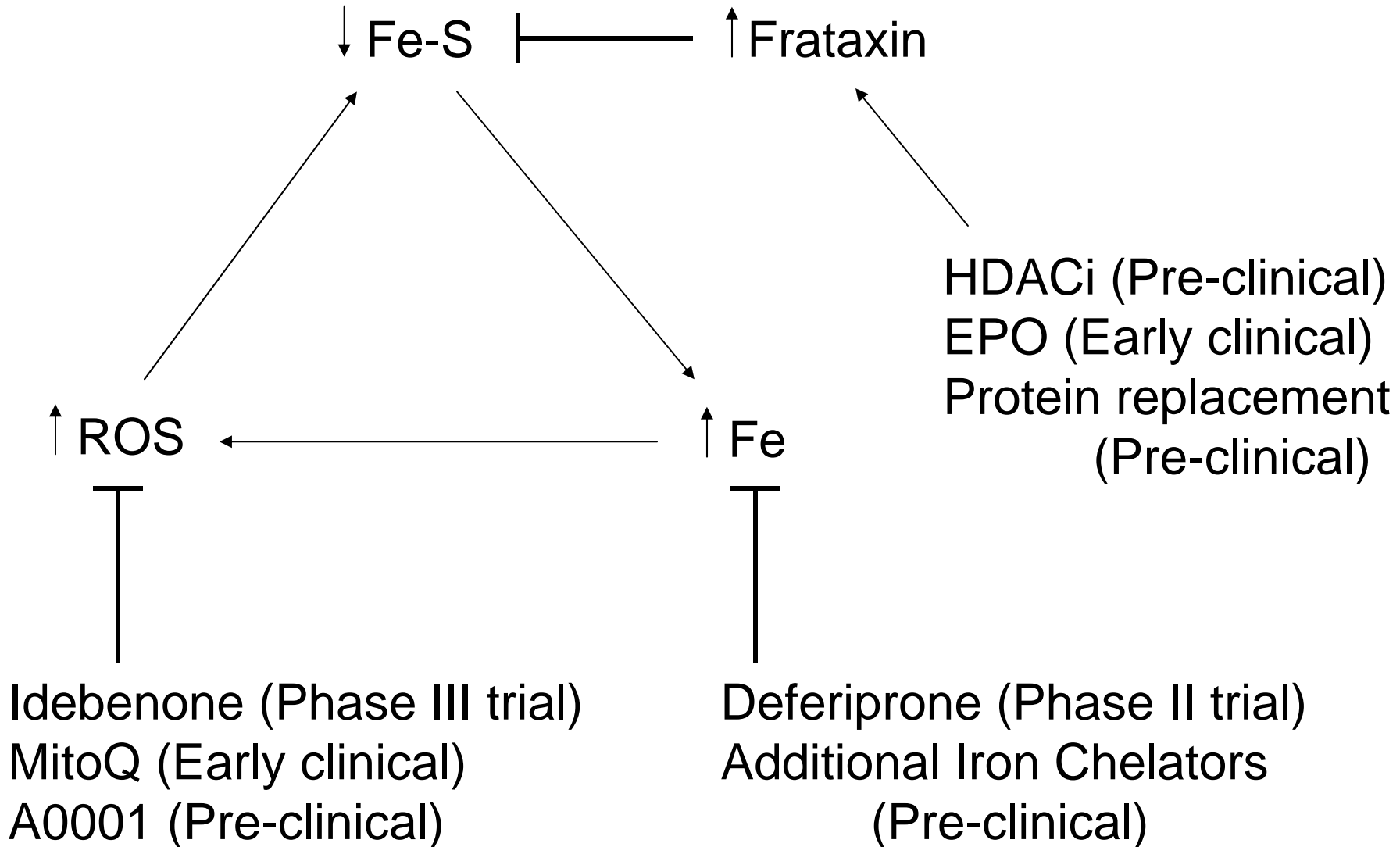
J. Gottesfeld compound 106:

Effective in activating FRA gene in cells.

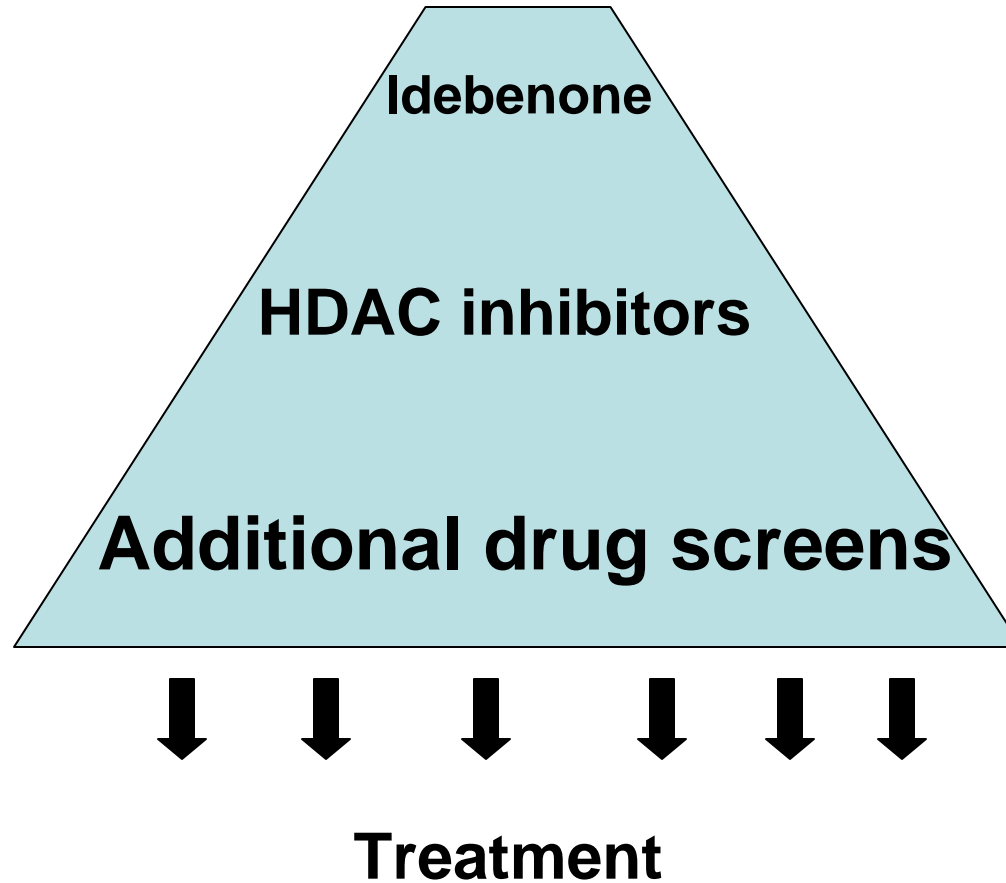
Effective in activating FRA in a mouse model.

Licensed to Repligen, synthesis of more active derivatives, toxicity studies in animals, and provide derivatives to investigators for testing in FRA mice.

Underlying Vicious Cycle in FA



Expanding the Probability of a Treatment



SCA1 - Translational & Clinical Research

Lithium

Lithium carbonate trials in SCA1 mice (0.5 - 0.87 mM, blood) improves coordination, & learning.

Lithium carbonate pilot safety trial (10 patients for 3 months) at the NIH to begin by end of this summer.

If Lithium is tolerated by SCA1 patients will move to a multicenter double-blind test of efficacy.

SCA1 - Basic & Translational Research

Additional drug target:

Interaction of ataxin-1 with another cellular protein RBM17 has a critical role in disease.

This interaction is regulated by the phosphorylation of ataxin-1 at amino acid serine 776.

Kinases, proteins that phosphorylate other proteins are major targets for drug development.

Phosphorylation of ataxin-1, a target for drug development

Sporadic Ataxias

Genetic ataxias provide pathways to disease alterations in which might underlie sporadic ataxia.

For example:

FRA tells us that alterations in iron homeostasis can lead to ataxia.

SCA1, perhaps alterations in phosphorylation of ataxin-1 leads to ataxia.

The Challenge:

To connect insights learned from genetic ataxias to the sporadic ataxias.

Our Expectations for the AIM/NAF 2009 & 2010

Expand the Probability of Treatments

Basic research:

Identify additional pathways to disease.

Additional ataxia genes.

Translational Research

More drug targets for ataxias.

Clinical Research

Drug trials for ataxias.

Connect disease pathways learned in the genetic ataxias to disease pathways operative in the sporadic ataxias.

Thank You
Ataxia Patients and Families