

# **Rationale and Design of a Clinical Study of RTA 408 in Patients with Friedreich's Ataxia**

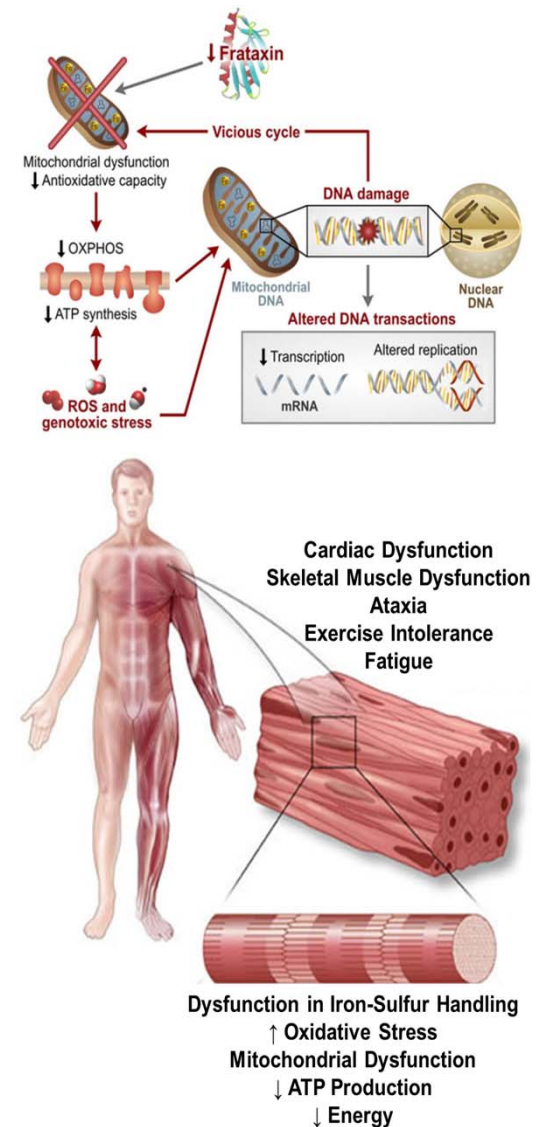
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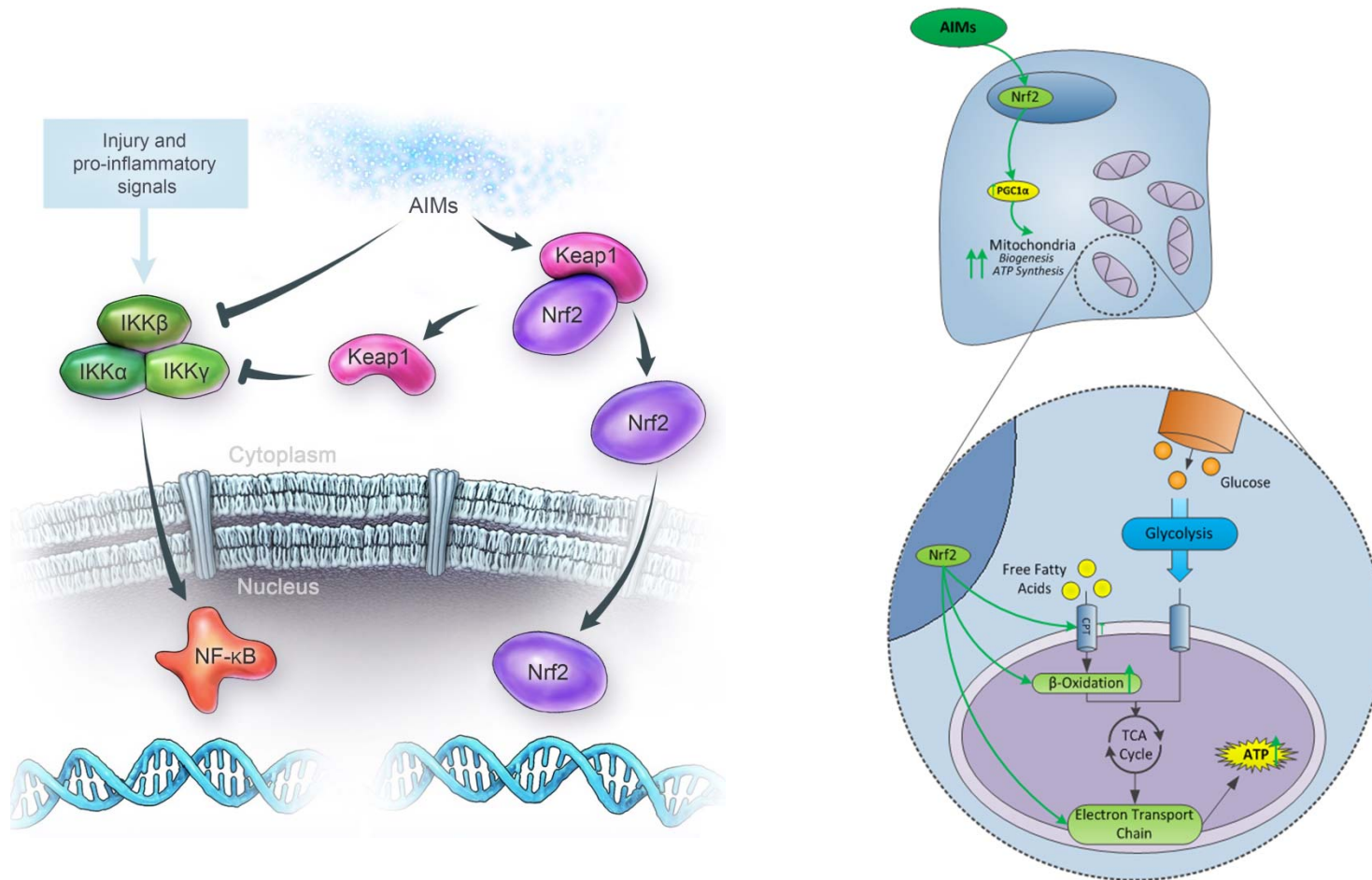
# Friedreich's Ataxia

- ▶ FA is a genetic disorder caused by a mutation in frataxin, an iron chaperone
- ▶ Frataxin mutation leads to:
  - ▶ Dysfunctional iron handling
  - ▶ Impairment of antioxidative defense mechanisms
  - ▶ Generation of excessive Reactive Oxygen Species (ROS)
  - ▶ Mitochondrial dysfunction/decreased energy production
  - ▶ Epigenetic silencing of frataxin
  - ▶ Dysregulation of Nrf2 signaling
- ▶ Clinical manifestations include:
  - ▶ Ataxia
  - ▶ Chronic fatigue and reduced exercise capacity
  - ▶ Heart disease, vision loss, and diabetes
  - ▶ Reduced quality of life
- ▶ No approved drugs

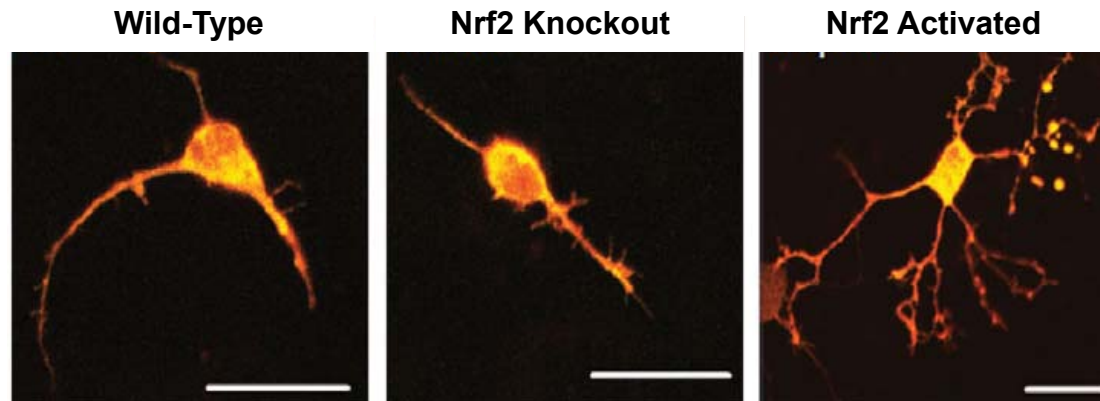
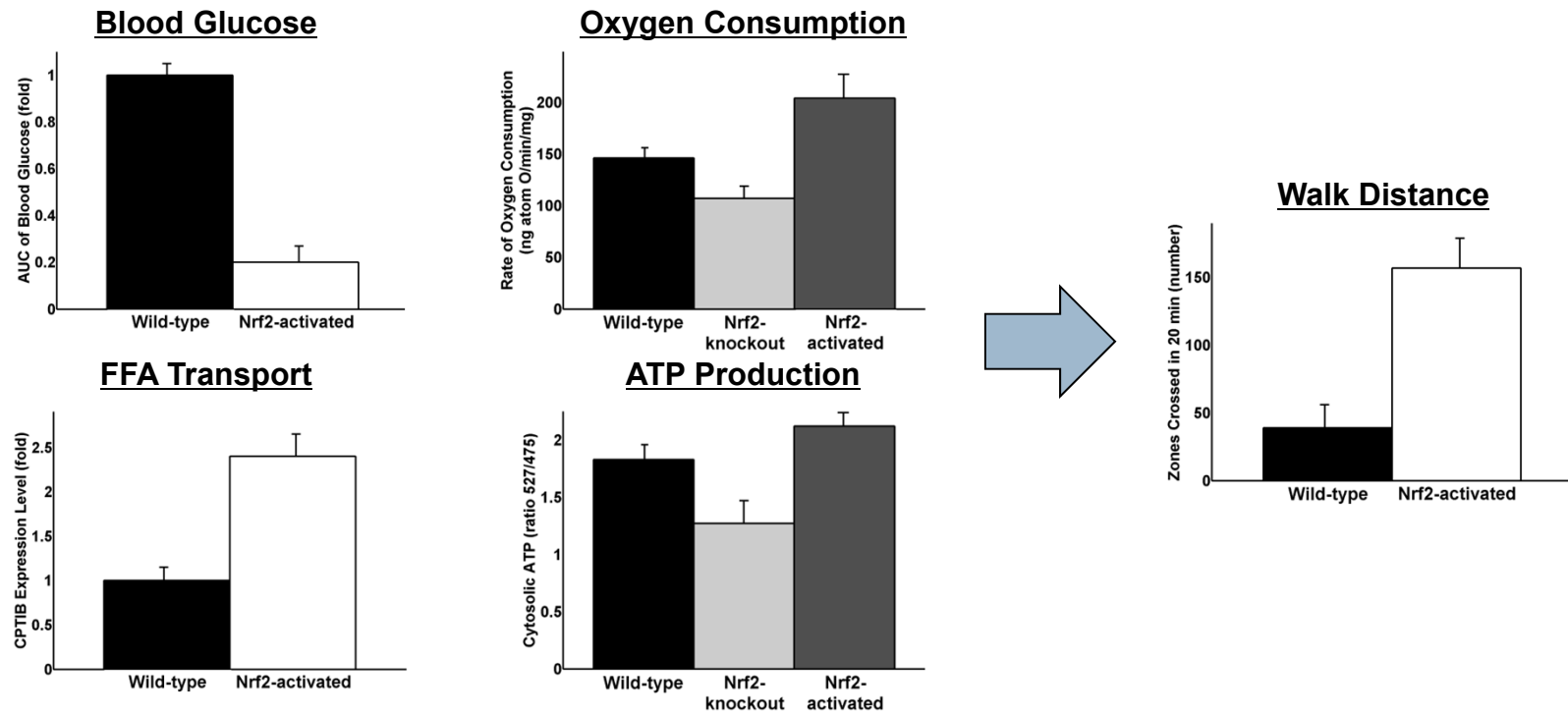


# Nrf2 Induction Activates Cell's Antioxidant and Detoxification Pathways and Suppresses NF-κB

- ▶ RTA 408 and analogs (AIMs) bind to Keap-1, activating Nrf2 and inhibiting NF-κB
  - ▶ Nrf2 induction increases 250+ antioxidant and detoxification enzymes and promotes ATP synthesis
  - ▶ NF-κB suppression reduces pro-inflammatory mediators



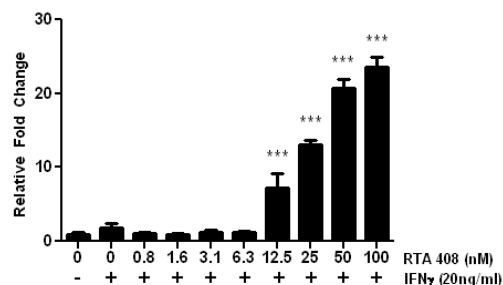
# Genetic Studies Validate Nrf2 as Mitochondrial Target that Improves Exercise Capacity



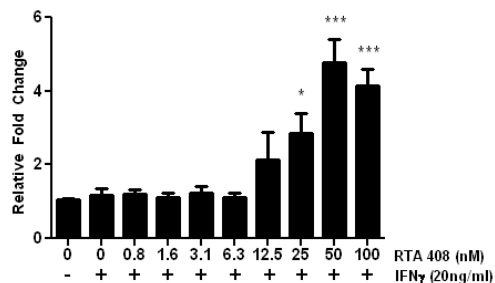
# RTA 408 Induces Nrf2 and Suppresses NF-κB at Low Nanomolar Concentration

## Nrf2 Target Genes

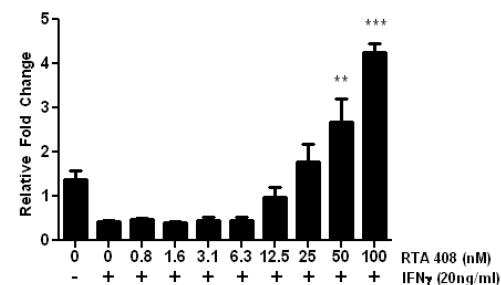
NAD(P)H dehydrogenase, quinone 1  
(*Nqo1*)



Thioredoxin reductase 1  
(*Txnrd1*)

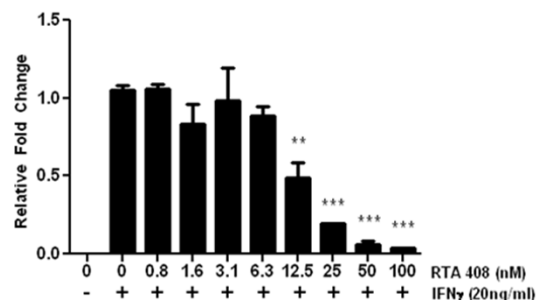


Glutamate-cysteine ligase, catalytic subunit  
(*Gclc*)

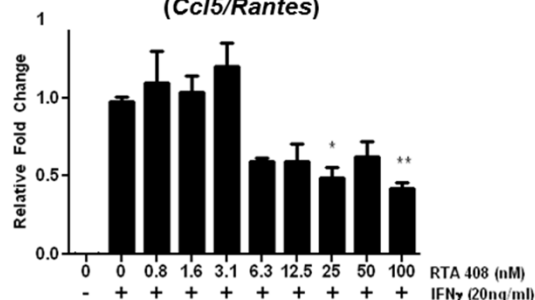


## NF-κB Target Genes

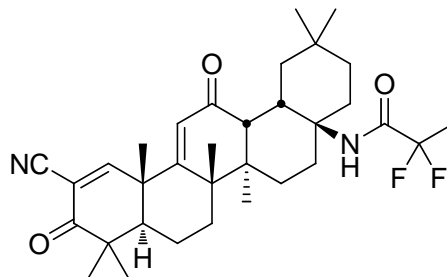
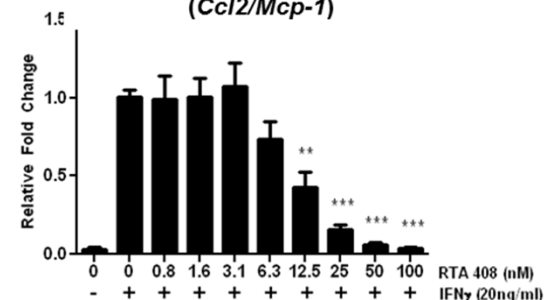
Nitric oxide synthase, inducible  
(*Nos2*)



Chemokine (C-C motif) ligand 5  
(*Ccl5/Rantes*)



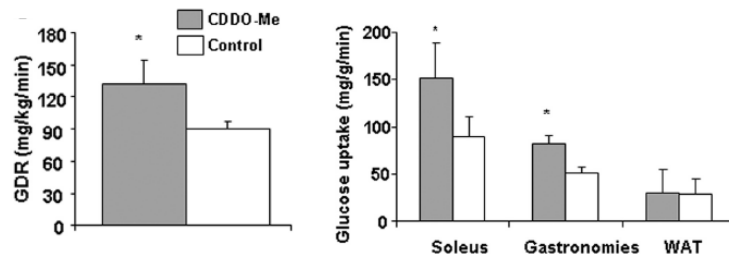
Chemokine (C-C motif) ligand 2  
(*Ccl2/Mcp-1*)



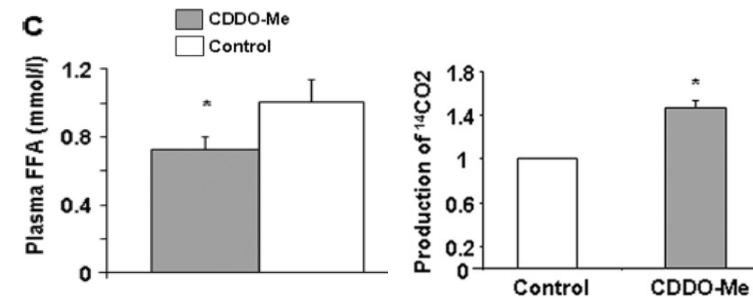
# RTA 408 and Analog Improve Energy Production in Preclinical Models

- ▶ RTA 408 analog bardozone methyl (also known as CDDO-Me) has been shown to improve glucose uptake, fatty acid oxidation, oxygen consumption and ATP levels
- ▶ Recent data demonstrate that RTA 408 improves mitochondrial function

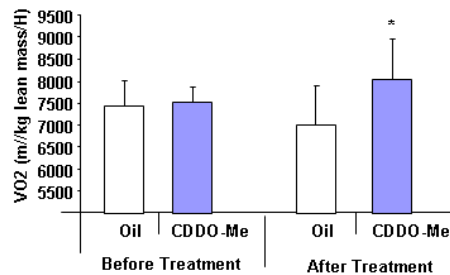
**BARD Increases Glucose Uptake**



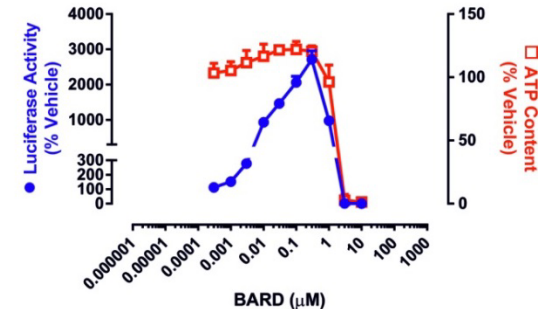
**BARD Increases Fatty Acid Uptake and TCA Flux**



**BARD Increases Oxygen Consumption**

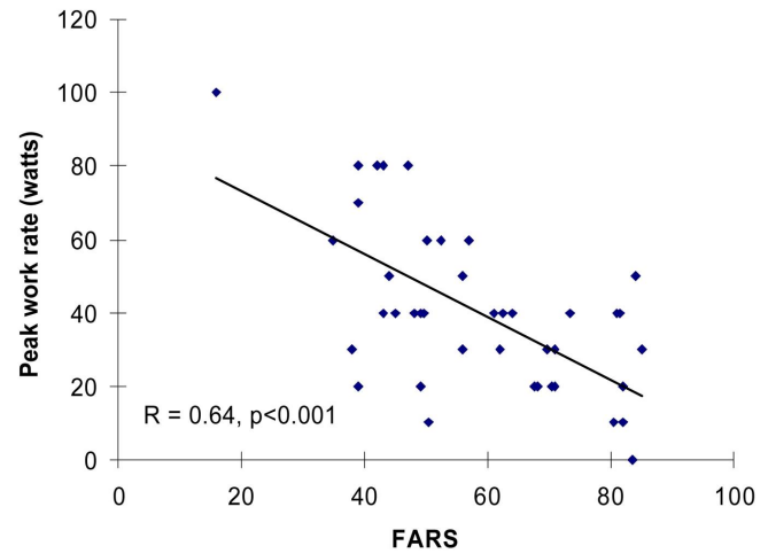
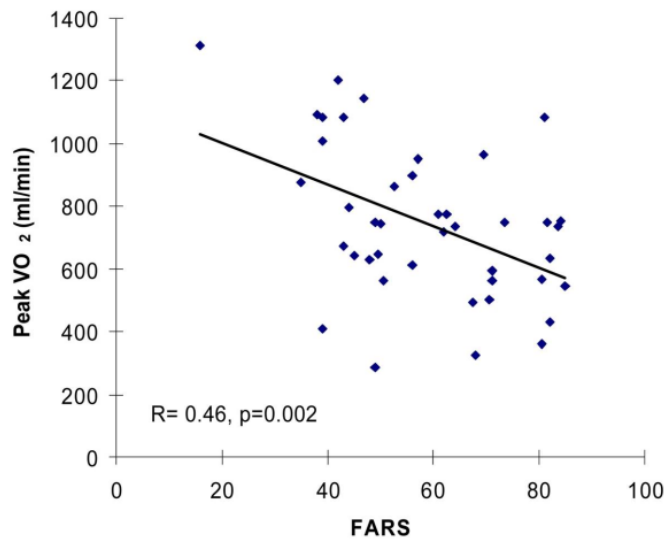


**BARD Increases ATP Levels**



# Bioenergetic Deficits are Key Features of FA

- ▶ Nrf2 signaling is grossly impaired in FA and contributes to oxidative stress, mitochondrial dysfunction and reduced ATP production
  - ▶ Reduced nuclear expression of Nrf2
  - ▶ Reduced levels of glutathione and antioxidant Nrf2 target genes
- ▶ In FA patients, oxygen consumption and exercise capacity are inversely correlated with FARS disease rating scale and length of frataxin mutation
- ▶ Peak VO<sub>2</sub> and work rate are determined during exercise testing on a recumbent bicycle



# Overview of Design and Objectives of NDA-Enabling FA Study



<b>Name</b>	MOXIe: A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia
<b>Design</b>	Randomized, placebo-controlled, double-blind, dose-ranging study
<b>Size</b>	40 to 52 patients
<b>Objectives</b>	<p>Primary:</p> <ul style="list-style-type: none"><li>• Peak work during maximal exercise testing</li><li>• Safety and tolerability of RTA 408</li></ul> <p>Secondary:</p> <ul style="list-style-type: none"><li>• Modified Friedreich's ataxia rating scale (FARS) score</li></ul> <p>Exploratory:</p> <ul style="list-style-type: none"><li>• SF-36 Health Survey Update score</li><li>• Fatigue Severity Scale score</li><li>• 9-hole peg test</li><li>• Timed 25-foot walk test</li><li>• Low-contrast letter visual acuity test</li><li>• Peak oxygen utilization during maximal exercise testing</li><li>• Pharmacodynamic markers of activity in platelet, cheek swab, and muscle samples</li></ul>



# Major Eligibility Criteria

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## Major Inclusion Criteria

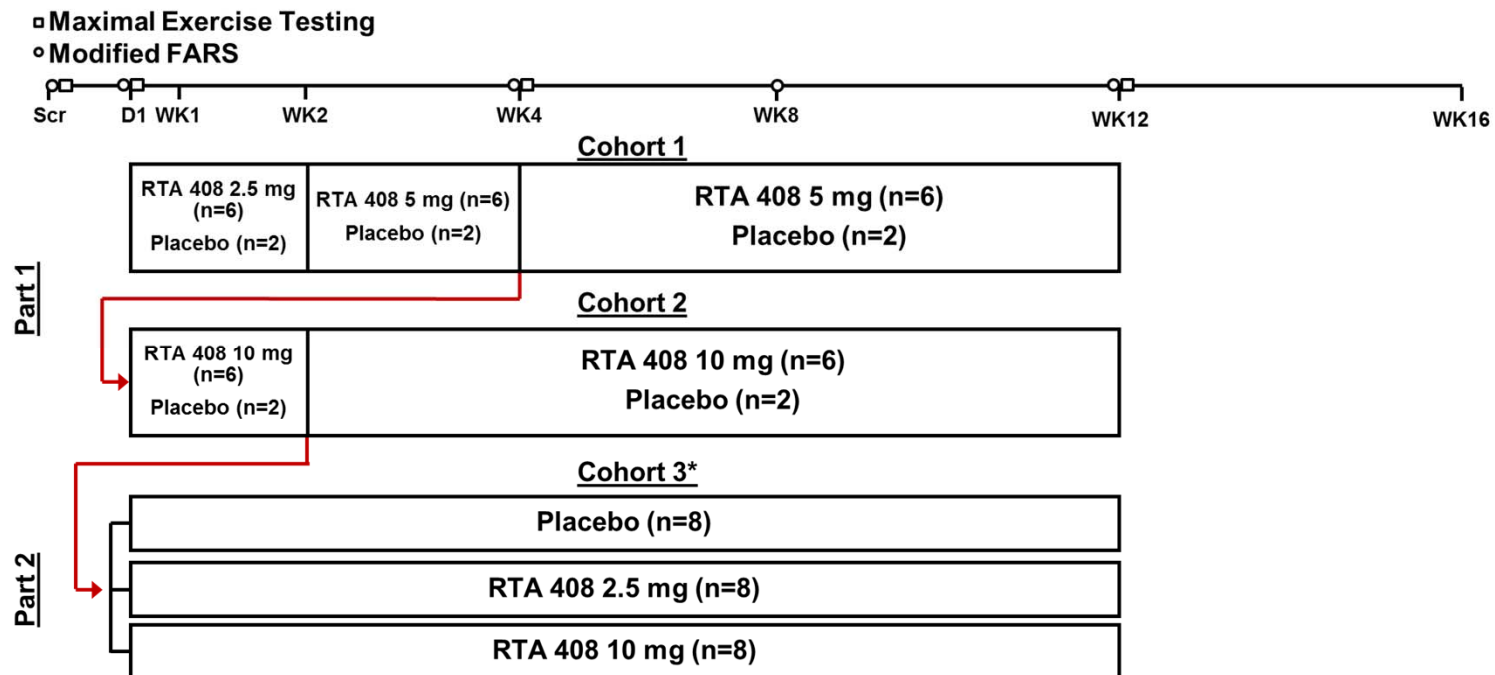
- Have genetically confirmed Friedreich's ataxia
- Have a modified FARS score  $\geq 10$  and  $\leq 80$
- Be male or female and  $\geq 16$  years of age and  $\leq 40$  years of age
- Have the ability to complete maximal exercise testing
- Have a left ventricular ejection fraction  $\geq 40\%$

## Major Exclusion Criteria

- Have uncontrolled diabetes (HbA1c  $> 11.0\%$ )
- Have B-type natriuretic peptide (BNP) level  $> 200$  pg/mL
- Have a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with Friedreich's ataxia

## Schema for Two-Part Study

- ▶ Part 1: Randomized, placebo-controlled, double-blind, dose-escalation study to evaluate the safety of RTA 408 at 2.5 mg/5 mg and 10 mg
- ▶ Part 2: Randomized, placebo-controlled, double-blind, parallel study to evaluate safety, efficacy, and PD of two dose levels (2.5 mg and 10 mg) of RTA 408
- ▶ All patients follow the same visit and assessments schedule



# Statistical Considerations

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<b>Sample size for Part 2</b>	24 patients (8 patients per treatment cohort)
<b>Power</b>	80%
<b>Hypothesized Improvement</b>	0.28 W/kg (assumes a common within-group SD of 0.28 W/kg)
<b>Two-sided <math>\alpha</math></b>	0.05
<b>Sample size recalculation</b>	If the SD for pooled, baseline peak work is greater than 0.28 W/kg or the distribution is not approximately normal, then an additional 12 patients will be enrolled in Part 2 (4 patients per treatment cohort)
<b>Method of analysis</b>	Change in peak work from Part 2 for patients treated with RTA 408 pooled (2.5 mg and 10 mg) compared to patients treated with placebo by repeated measures analysis of covariance

# Study Sites and DSMB

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- ▶ Sites
  - ▶ CHOP/Penn – Dr. Lynch
  - ▶ University of Florida – Dr. Subramony
  - ▶ Emory University – Dr. Wilmot
  - ▶ Ohio State – Dr. Hoyle
- ▶ Independent, multidisciplinary DSMB monitoring this study along with a similarly designed study in mitochondrial myopathy patients (MOTOR)
  - ▶ DSMB includes a cardiologist, neurologist, statistician, and patient advocate
  - ▶ DSMB coordinated by an independent statistical group
  - ▶ Monthly meetings for safety oversight

## Current Status

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- ▶ Part I, Cohort 1 (n=8) enrollment completed in less than 2 months at a single site
  - ▶ All patients dose-escalated to 5 mg with no safety concerns
- ▶ Part I, Cohort 2 (n=8) enrollment to open soon
- ▶ Monthly DSMB reviews underway with no identified safety issues
- ▶ Site activations nearly complete
  - ▶ 3 of 4 planned sites currently activated
  - ▶ 4<sup>th</sup> site expected to be activated by mid-April
- ▶ Part 2 (n=24 to 36) enrollment expected to begin in 2Q/3Q 2015
- ▶ Top-line data available 4Q 2015 or 1Q 2016

## Thank You

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- ▶ Thanks to all investigators, site personnel, data safety monitoring board members, patients, and FARA who will and have been participating in the design and conduct of MOXIe
  
- ▶ Questions?