Mitochondrial Myopathy

New Therapies
MitoAction Webnair

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Northeast Ohio Medical University

What is a Myopathy?

- a muscle disorder
- muscle fibers do not function normally
- results in weakness (or cramps or stiffness)
- the weakness is due to a primary process in the muscle
  - - not a problem with the brain, nerve, tendon, etc.

Inherited forms [edit]

- (G71.0) Dystrophies (or muscular dystrophies) are a subgr
  weakness, often leading to use of a wheelchair, and eventu
- (G71.1) Myotonia
  - Neuromyotonia
- (G71.2) The congenital myopathies do not show evidence
  include, but are not limited to:
  - (G71.2) nemaline myopathy (characterized by presenc
  - (G71.2) multi/minicore myopathy (characterized by mul
  - (G71.2) centronuclear myopathy (or myotubular myopa
- (G71.3) Mitochondrial myopathies, which are due to defect
- (G72.3) Familial periodic paralysis
- (G72.4) Inflammatory myopathies, which are caused by pr
- (G73.6) Metabolic myopathies, which result from defects in
  - (G73.6/E74.0) Glycogen storage diseases, which may
  - (G73.6/E75) Lipid storage disorder

Acquired [edit]

- (G72.0 - G72.2) External substance induced myopathy
  - (G72.0) Drug-induced myopathy
    - Glucocorticoid myopathy is caused by this class of
  - (G72.1) Alcoholic myopathy
  - (G72.2) Myopathy due to other toxic agents
- (M33.0-M33.1)
  - Dermatomyositis produces muscle weakness and skin
    drugs like corticosteroids or immunosuppressants. (M3
  - Polymyositis produces muscle weaknesss. It can often
  - Inclusion body myositis is a slowly progressive disease
- (M61) Myositis ossificans
- (M62.89) Rhabdomyolysis and (R82.1) myoglobinurias

What are the Main Causes of Myopathies in Adults?

- Inflammatory: polymyositis, inclusion body myositis
- Endocrine: thyroid, parathyroid, adrenal, pituitary
- Toxic: alcohol, steroids, narcotics, colchicine, chloroquine
- Critical illness
- Metabolic
- Paraneoplastic

Lab Evaluation

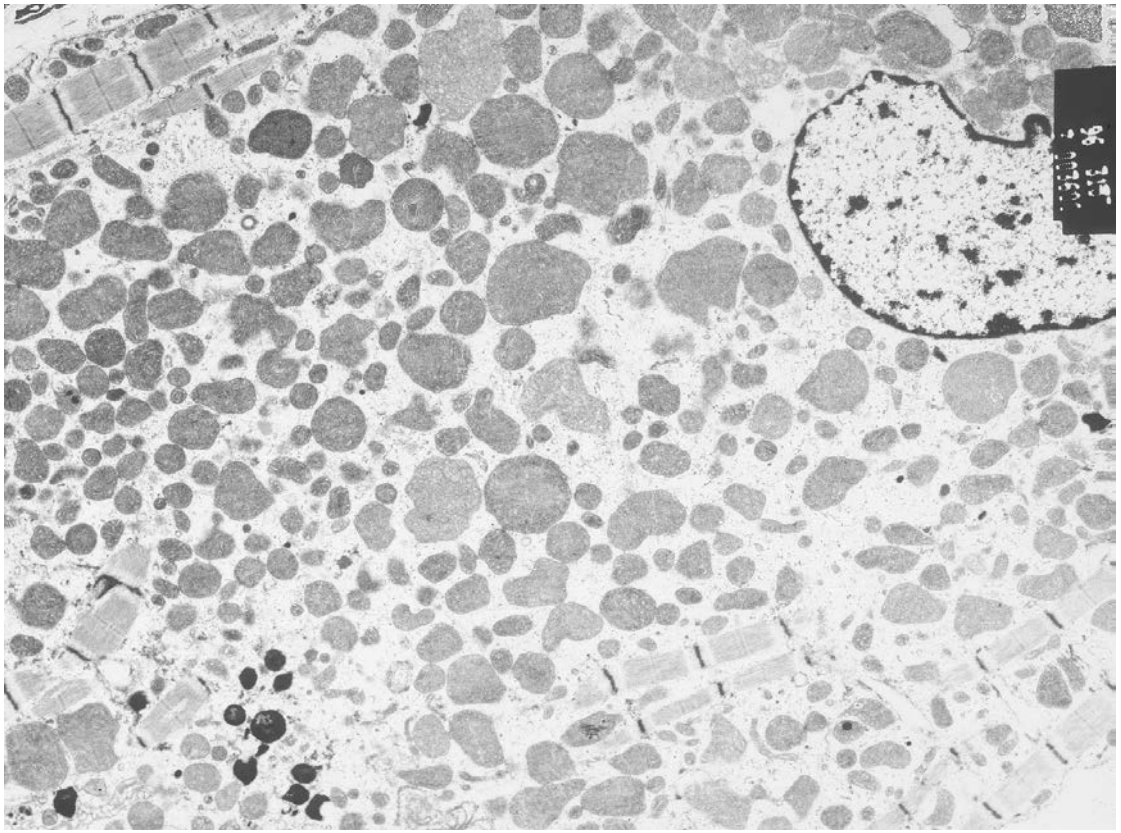
1. CBC
2. CMP
3. Free T_4, TSH
4. Fasting early morning cortisol
5. ESR, C-reactive protein, ultra-sensitive C-reactive protein
6. Vitamin B12 level and methylmalonic acid
7. CK
8. Fasting glucose, 2 hour glucose tolerance test and/or HbA1c
9. Paraneoplastic Panel, SPEP, urine monoclonal proteins/M-protein
10. Polysomnogram (even without complaints of snoring or sleep apnea)
11. Polysomnogram and multiple sleep latency test (for excessive daytime sleepiness)

1. Endocrine
   A. Hyper- or hypothyroidism
   B. Adrenal insufficiency
   C. Diabetes mellitus
   D. Hypoparathyroidism and related disorders
2. General medical illnesses
   A. Obstructive sleep apnea
   B. Metabolic syndrome
   C. The deconditioned state
   D. Fibromyalgia
   E. Chronic fatigue syndrome
3. Inflammatory: SLE and other collegen vascular disorders, inclusion body myositis
4. Paraneoplastic: anti-Hu, anti-Yo, anti-NMDA receptor, opsoclonus-myoclonus, GARS
5. Muscle–hepatic disorders
   A. Congenital muscular dystrophies: central core disease, multimini core disease, Ullrich–Bethlem myopathy (*COL6* disorders)
   B. Muscular dystrophies: OPMD, other dystrophies (note: ragged-red fibers are common in the muscular dystrophies)
   C. Channelopathies (*RYR1* mutations)
   D. LPIN disorders
   E. Glycogen synthesis disorders
   F. Fatty acid oxidation disorders
6. Chronic renal failure with acidosis or loss of amino acids (note: systemic carnitine deficiency occurs in patients on dialysis)
7. Vitamin deficiencies: B12 deficiency, other cobalamin disorders, vitamin E deficiency, micronutrient disorders seen in patients having undergone bariatric surgery, on chronic TPN, self-induced restrictive diets, inflammatory bowel disease, or s

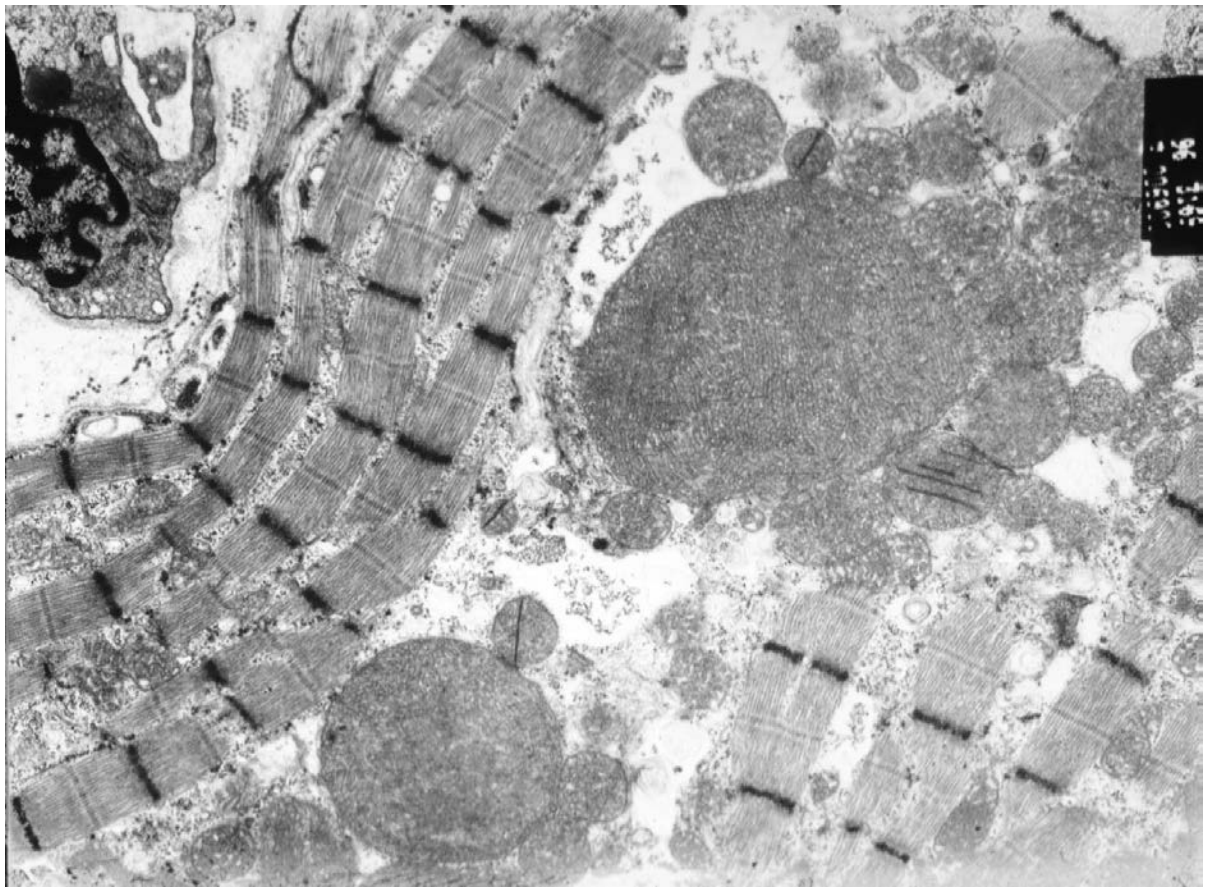
G71.3 Mitochondrial Myopathy

- Those disorders due to defects in mitochondria
- Note: many of the other myopathies will result in
  - -ragged red fibers
  - -decreased electron transport chain function
  - -the exact same weakness that occurs in mitochondrial myopathies

Massive Mitochondrial Proliferation



Giant Mitochondria & Paracrystalline Inclusions



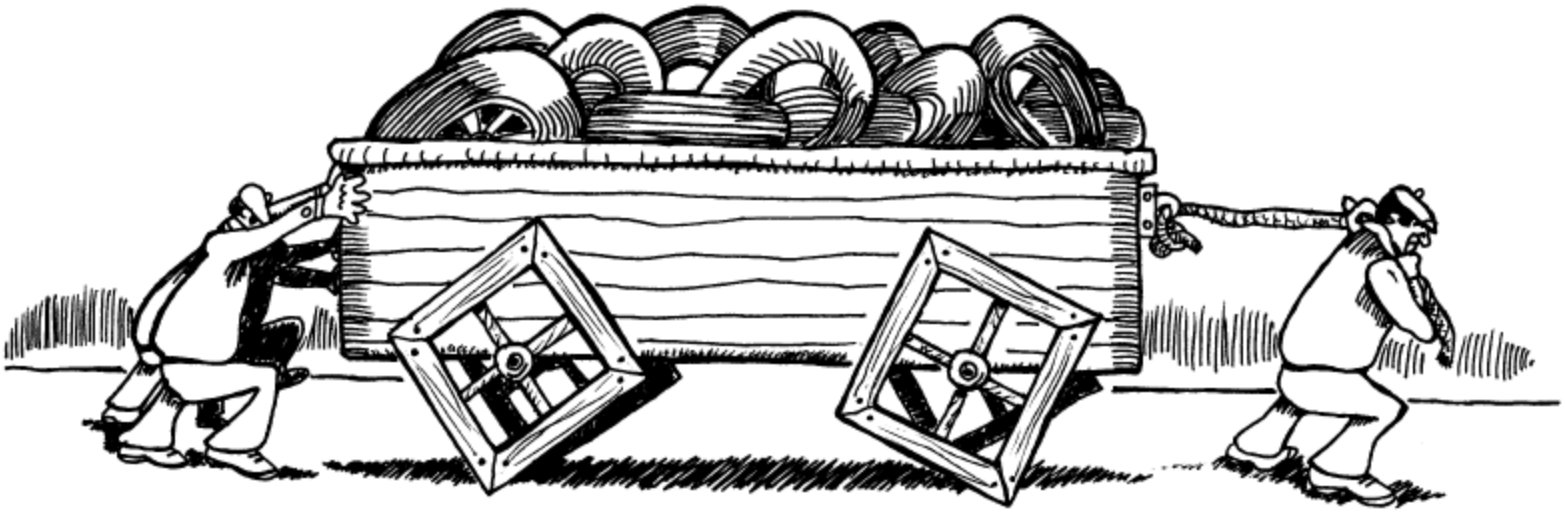
Genetic Testing

1. Mitochondrial DNA select point mutation testing (preferred muscle, cheek swab/saliva, urine sediment but can be done on blood).
2. Mitochondrial DNA whole genome testing (preferred muscle, cheek swab/saliva, urine sediment, but can be done on blood).
3. Long-range polymerase chain reaction or Southern blot (preferred muscle, but can be done on cheek swab/saliva or urine sediment; blood not reliable).
4. Sequencing and deletion/duplication testing of specific nuclear genes, or panel of genes.
5. Massive parallel sequencing (NextGen) of large numbers of nuclear genes, including that all known mitochondrial-targeted genes, look-alike disease genes, or whole exome along with a high-density single nucleotide polymorphism microarray.

Treatment for Myopathy

- Some myopathies are treatable & curable
- Supportive care
  - - physical therapy
  - - assist devices and bracing
  - - rare truly responsive cases
    - - CoQ10 deficiency
      - Creatine defects

Clinical Trial Work



Quarter

LOS	3rd NN	No Show	% Closed Charts
-136	Neuro, NS	NSG 11%	SI % : 95%
-1500 YTD		Neuro 15%	SI % (Aug)
	PME	NBH 0%	ES % (Sept)
		PSG 12%	
		OBP 17%	

LOS / [illegible] CYE

104, 116, 109, 96

NOSC ON-STAFF

Clinical Time	4
Non-Clinical	0
Registry	5
Completed	4
Pubs	3

Total
Open IRBs ___
Pts on Stds ___

Huron Healthcare 2015-6

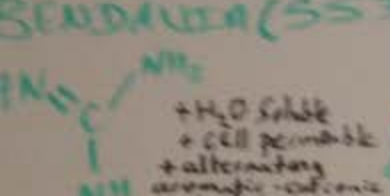
a) Ambulatory & Provider Standardization
b) Research @ ACH
c) Regional Ambulatory ACHP & Subspecialty

RECRUITMENT

NEURO ☐ Director ☐ Epilepsy
☐ Neuro ☐ MV ☐ Manopelli
PHYSIATRY ☐ Director
DB PEDS ☐ ___ ☐ ___

Raptor
RP-103-002
n=2

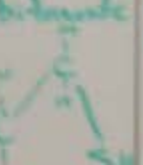
Stealth Biotherapeutics
BENDAVIA (SS31)



SPINAL-201
N = 8
-2

NAMDC
Registry 94
Biobank 27
Alpers 4

Raptor Pharma
RP-103-001
Cysteamine bitartrate



Edison Pharma
EPI-743-13-023 (SCA2)
EPI-743-12-002 (LHON)

Scope of the Problem

- 100s of distinct disorders
  - 37 mtDNA genes
  - ~1100 nuclear genes
- Age: birth – 100 (birth – 60s)
- Major organ systems: brain, muscle, nerve, heart, liver, pancreas, eye, ear, kidneys
- Therapies: symptomatic care, exercise, vitamins

Goals of Therapy

- Brain
  - reduce seizures
  - improve attention and concentration
  - improve intellectual functioning
  - prevent headaches
  - prevent strokes
  - improve motor control
  - MRI, SPECT
- Muscle
  - improve strength
  - lessen pain
  - lessen fatigue
  - reverse cardiomyopathy
  - improve gut transit
- Liver
  - improve synthetic function

- Nerve
  - improve autonomic function
  - lessen pain
  - improve nerve conduction (all tissues)
- Pancreas
  - improve β-cell function
  - improve insulin production
- GI
  - improve gastric motility
  - improve intestinal motility
- Renal
  - improve tubular function
- Eyes
  - prevent further retinitis or optic atrophy
- Ears
  - prevent further hearing loss
- Systemic
  - growth - prevention of failure to thrive

How Do We Measure Success?

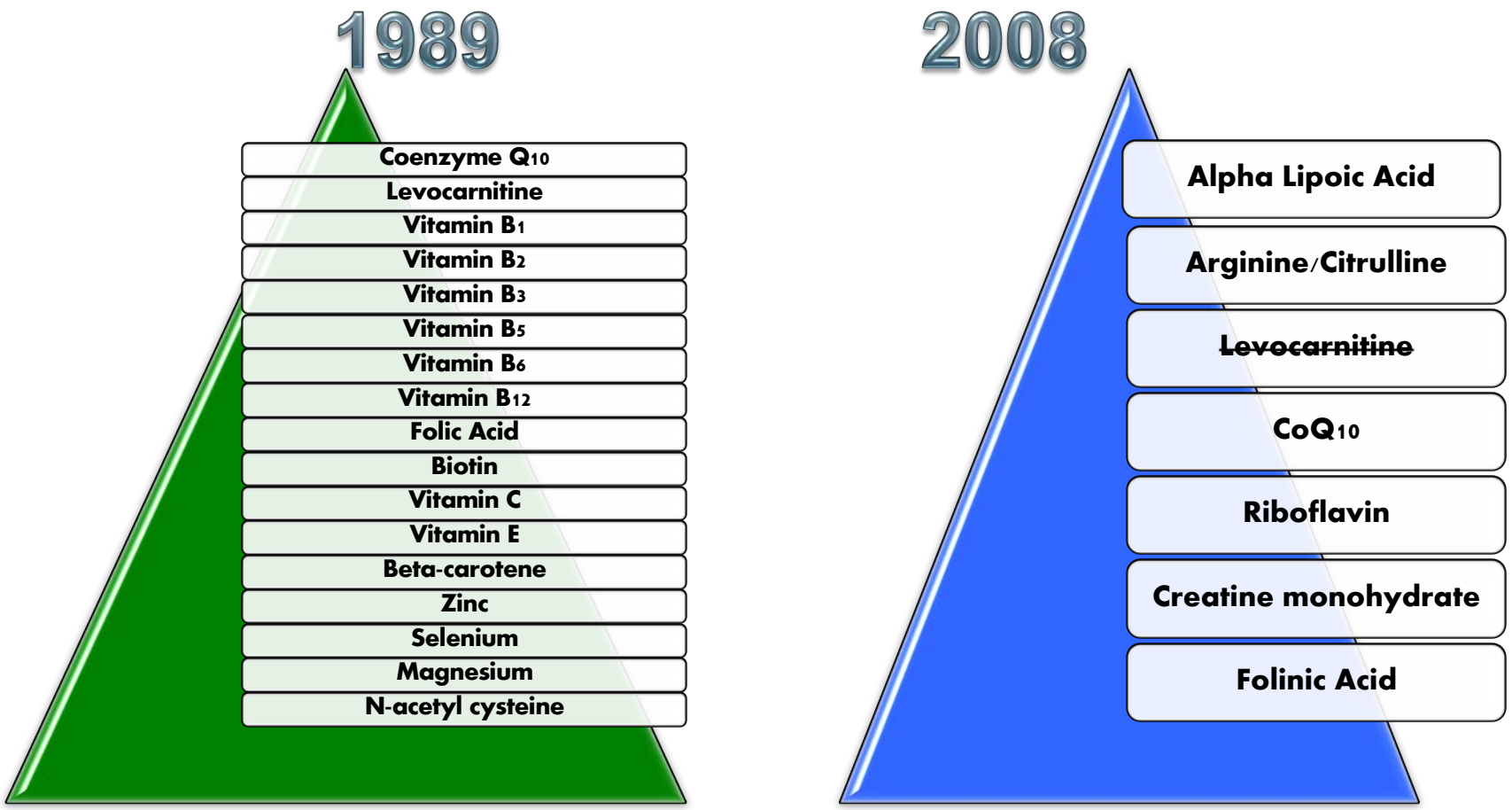
- Brain
  - Seizure count
  - Age-appropriate neuropsychological testing
  - Headaches Diary
  - Stroke Count
  - Dozens of motor tests
- Muscle
  - Strength Testing (dozens of different tests)
  - OT and PT evalutations
  - Lessen fatigue
  - Cardiac contractility
  - EKGs
- Liver
  - Sequential liver function studies, enzymes
  - Ultrasounds
- Pancreas: Amylase, lipase, stool fat, HbA1c

- Nerve
  - Sequential autonomic function studies
  - Pain diary
  - Sequential NCV
- GI
  - Qualitative testing of motility
  - Symptom diary
- Renal
  - GFR and fractional excretion studies
- Eyes
  - Sequential Va and Vf testing
- Ears
  - Sequential audiology
- Systemic
  - growth charting
  - Cardio-Pulmonary Exercise VO_2 max
  - Analyte studies

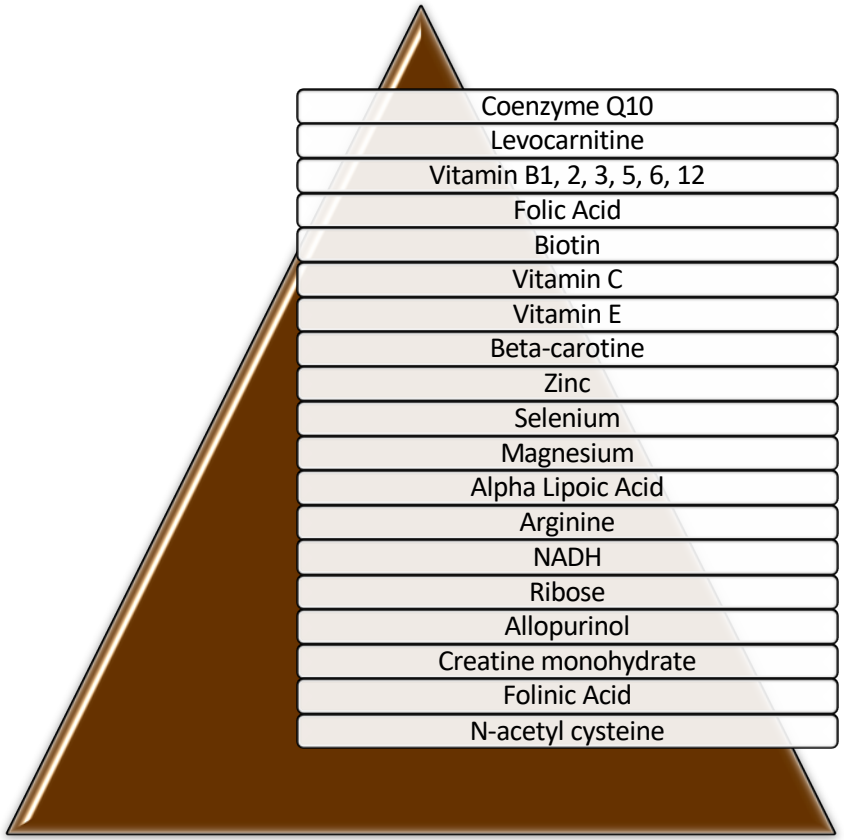
Rationale for Vitamin and Cofactor Therapy

- Stimulate poorly functioning enzymes
- Antioxidant activity to reduce oxidative stress and effects
- Alternative energy sources
- Improve muscle bulk
- Scavenge free-fatty acids and poisonous organic acids
- Bypass blocked components of the electron transport chain

Mitochondrial Therapy Before Molecular Diagnostics

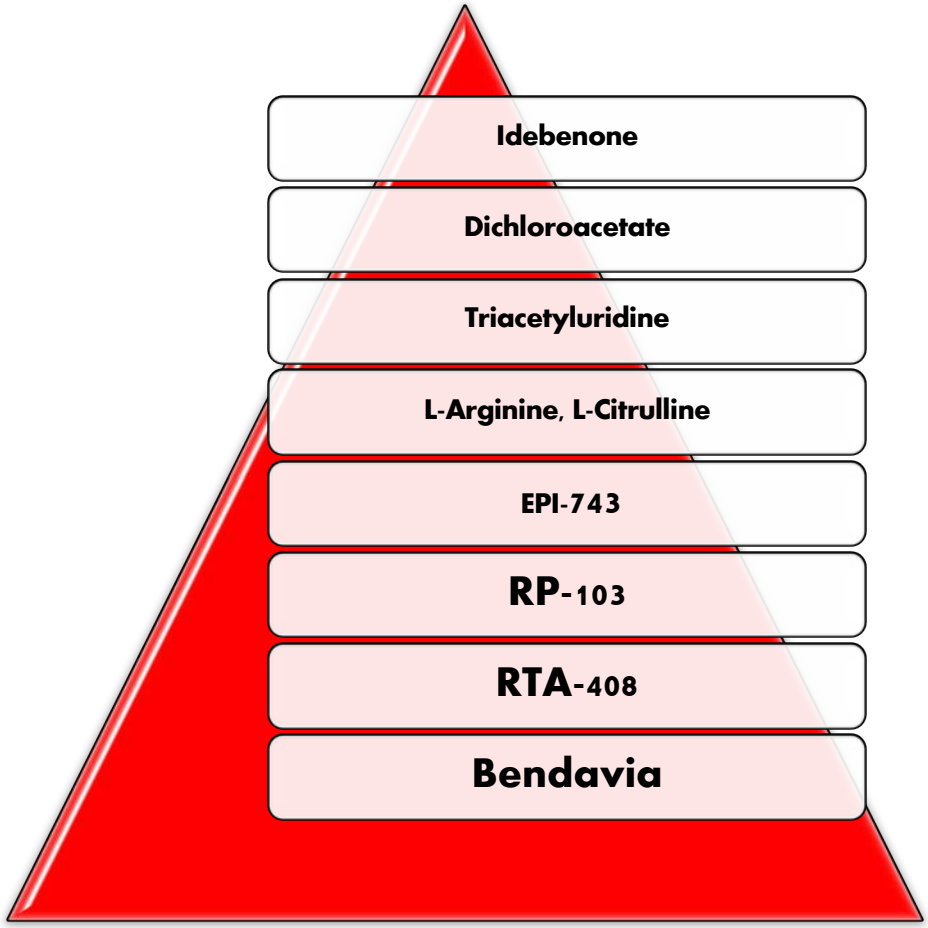


Shotgun Mitochondrial Therapy
Why it Does Not Make Sense



- 1 approach to 100s of diseases
- No ability to judge efficacy
- *Expensive*
- Only able to be carried out by overly compulsive parents or patients
- Prescribers viewed as "vitamin pushers"
- Seldom meets therapeutic goals

Mitochondrial Therapy New Investigation



My Typical Treatment

- Maximal exercise ± physical, occupational or speech therapies
  - endurance training
  - resistance training
- Sleep Hygiene - Polysomnograms for Everyone
- Hydration and more hydration; Early IV hydration during viral illnesses
- Basic Supplements: Derived from Evidence, Experience and Costs ($ and other costs)
  - CoEnzyme Q10 - 5-20 mg per kg per day
  - B2 100-600 mg per day
  - Creatine monohydrate 0.1 grams per kg per day; max 5 grams a day
  - Alpha-Lipoic Acid 300 mg bid for an adult
  - Folinic Acid for CSF folate-deficient patients: 5-25 mg tid
  - l-arginine 0.15-0.3 gram per kg per day; 4-24 grams a day for an adult
  - l-citrulline 0.1 grams per kg per day
  - ? Antioxidants (Gamma-E 400 IU, C 500 mg bid, Selenium, Zinc)
- Miralax polyethylene glycol for constipation
- Avoid Stress
  - Illness, fever, starvation, sleep
  - treat illness, fever, starvation and sleep disturbance

Clinical Trials

- Randomized Clinical Trials
- (Placebo Controlled, Crossover Design, Double Blind)

WHAT IS THE FDA LOOKING FOR?

Functional Improvement using Verified Tools and Scales
Fewer Adverse Events
Altered Natural History

WHAT IS THE FDA NOT LOOKING FOR?

Lower Lactic Acid Levels
Improved Brain MRIs
Reduced RRF Count or ETC Enzymology
Normalization of Abnormal Organic Acids


PROJECT OVERVIEW CDE SEARCH CRF SEARCH FORM BUILDER CONTACT
NINDS Common Data Elements
Harmonizing Information. Streamlining Research.
CDEs
Tools
Learn
Public Review Period: November 20, 2014 – January 16, 2015
New CDE Recommendations for Mitochondrial and Neuromuscular Diseases (CMD, DM, FSHD)
Mitochondrial Disease
Data Standards
Overview
History and Acknowledgements
References
Updates
Feedback and Suggestions
Public Review Period for Mitochondrial Diseases CDEs: November 20, 2014 – January 16, 2015

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Neurological Assessments

- Ingrid Tein, MD, FRCP - *University of Toronto*, **Co-Chair**
- Laurence Bindoff, MD, PhD - *University of Bergen and Haukelanc* **Co-Chair**
- Bruce Cohen, MD, FAAN - *Akron Children's Hospital, Akron, OH, USA*
- Michio Hirano, MD - *Columbia University Medical Center*
- Matthew Klein, MD, MS, FACS - *Edison Pharmaceuticals*
- Thomas Klopstock, MD - *Friedrich-Baur-Institute, Munich, Germany*
- Saskia Koene, MD - *Radboud University Nijmegen Medical Centre, Netherlands*
- Pascal Laforêt, MD, PhD - *Groupe Hospitalier Pitié-Salpêtrière Assistance Publique-Hôpitaux de Paris, Paris, France*
- Margherita Milone, MD, PhD - *Mayo School of Graduate Medical Education, Rochester, MN, USA*
- Jan Smeitink, MD, PhD - *Radboud University Nijmegen Medical Centre, Netherlands*

NINDS Mitochondrial Disease Neurological Assessment CDE Recommendations
Public Review Comments Due January 16, 2015
NINDS Mitochondrial Disease Neurological Working Group
Recommendations Public Review

Instrument / Scale Name *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification (e.g., Core, Supplemental, Exploratory)	Description *Brief description of the instrument/measure*	Scoring Information *Total range of scores and range of subscales if appropriate*	Time to Administer	Comments / Special Instructions	Population / Age range / Validation	Copyright Information *Explains whether the instrument / measure has copyright protection and if so, provides information on how to obtain it from the publisher.*	References *References that contain additional information about the instrument / measure.*
Barry Albright Dystonia Scale (BADS)	Supplemental - Highly Recommended for measuring dystonia.	The BADS evaluates dystonia in eight body regions (Appendix SII, supporting information published online).	Each of the scoring criteria for each region are scored from 0 to 4. The maximum total score is 32, calculated by summation of the region scores. Assess the patient for dystonia in each of the following regions: eyes, mouth, neck, trunk, each upper and lower extremity (8 body regions).		Advantages: Good intrarater reliability. Less training required to administer, relatively easy to administer. Uses parental input. Provides a more temporally integrated estimate of dystonia. Directions: Assess the patient for dystonia in each of the following regions: eyes, mouth,neck, trunk, each upper and lower extremity (8 body regions). Write the scores on the lines provided. Rate severity based only on dystonia as evidenced by abnormal movements or postures. When assessing functional limitations, do not score as dystonia-induced functional limitation if other factors, such as weakness, lack of motor control, cognitive deficits, persistent primitive reflexes, and/or other movement disorders are contributing to functional limitation. Must be administered by a trained professional.	Pediatrics / Adult	Barry MJ, VanSwearingen JM, Albright AL. Reliability and responsiveness of the Barry-Albright dystonia scale. Dev Med Child Neurol 1999; 41: 404-411	
Peabody Development Motor Scale II	Supplemental - Highly Recommended for measuring deterioration and short-term improvement in pediatric patients		Scores include 1) a Gross Motor Quotient which is a composite of the Reflexes, Stationary, Locomotion and Object Manipulation subtests, 2) a Fine Motor Quotient, a composite of the Grasping and Visual-Motor Integration subtests, and 3) a Total Quotient, a combination of the gross and motor subtests.	Administration Time: 45-60 minutes	Administration Skills: MA (psychologist, OT, speech pathologist, social work, special ed) or BA Occupational therapies with certification Limitations: Valid up to age 5 years. Has not yet been validated in mitochondrial disease.	Birth – Age 5 years		

NINDS Common Data Elements

Ingrid Tein
Bruce H. Cohen

End Points

Newcastle Pediatric Mitochondrial Disease Scale

Adverse Event Count

Primary Investigator's Menu Choice of Scales

Berry-Albright Dystonia Scale

Quality of Life Scales

6-Minute Walk Test

Gross Motor Function Scale

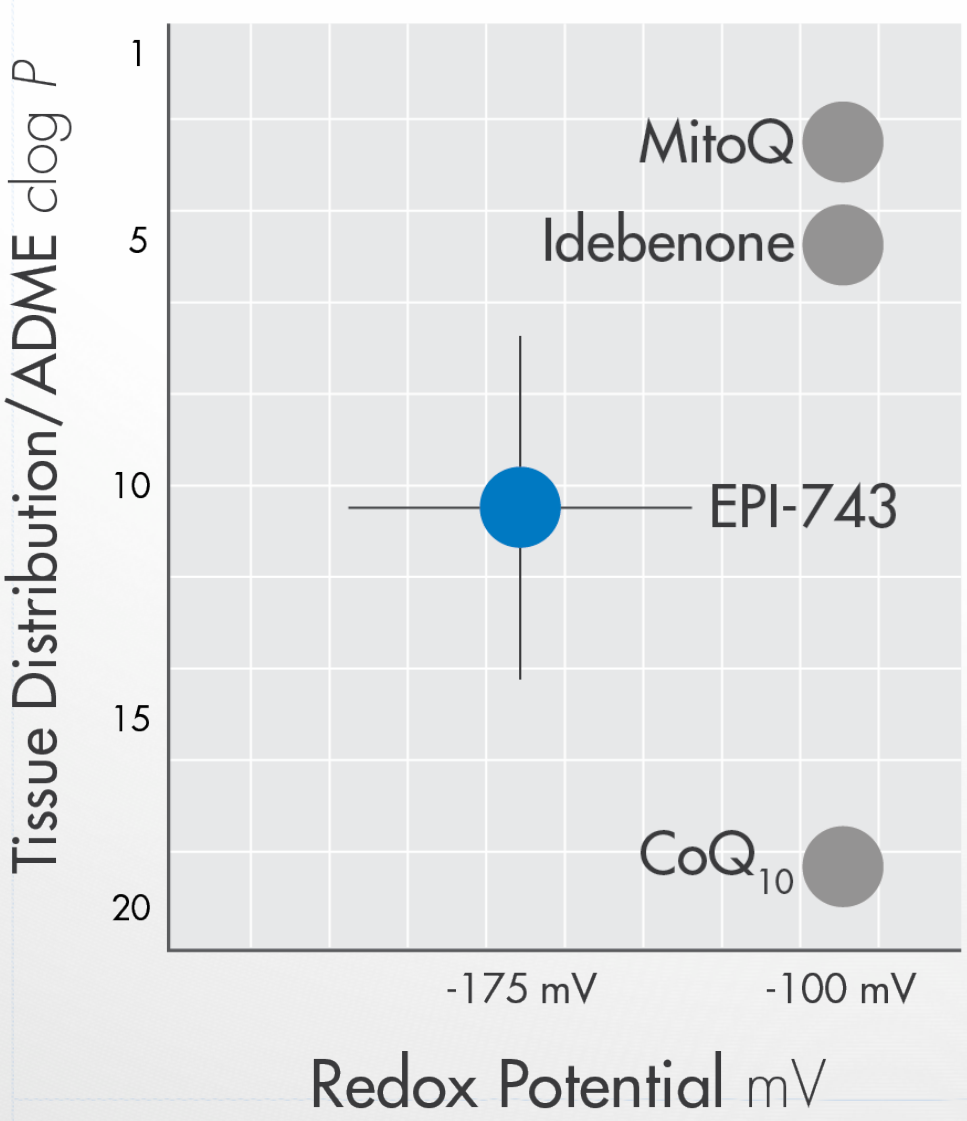
Seizure Calendar

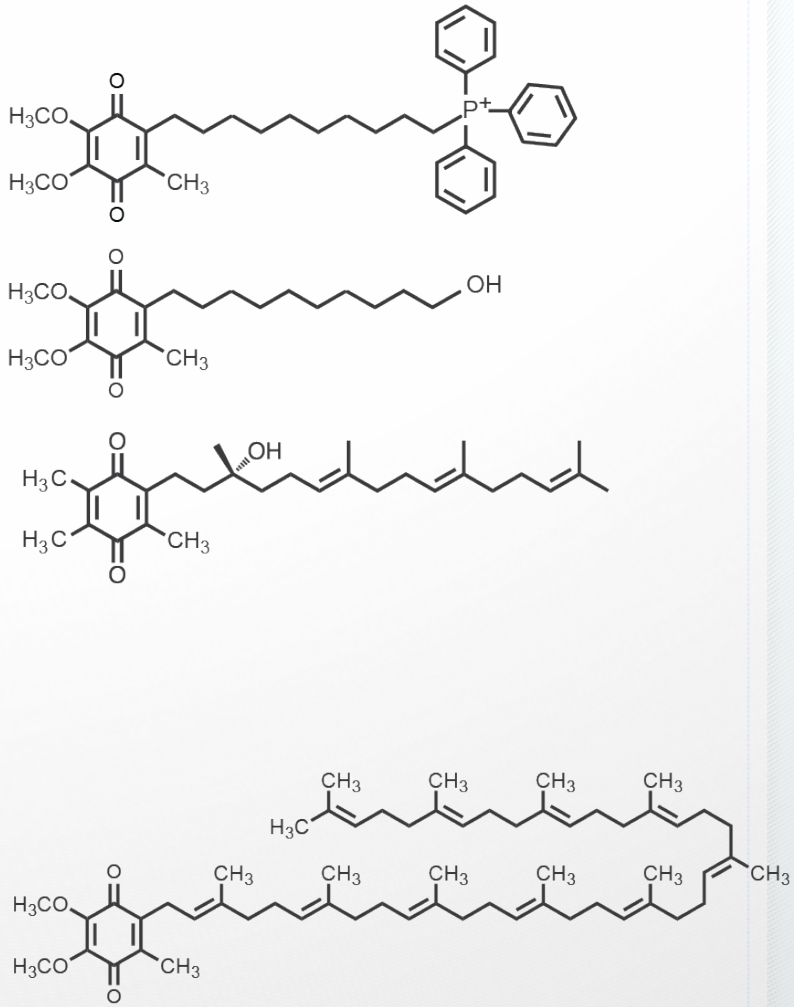
Friedreich Ataxia Rating Scale

Designing the Perfect Phase 3 Study

- It has to excite the patients and investigators
- Financially Viable
- Perception must be Worth the Travel
- Double-Blind
- Placebo Controlled
- Some Type of Crossover
- For studies that do not crossover; treatment and non-treatment arms must be similar (enough)

EPI-743 has unique redox and pharmacologic properties





EPI743

EPI-743 Leigh syndrome: RCT

- Akron, Baylor, Stanford, Seattle
- 36 patients, randomized to drug at 5mg/kg/day or 15 mg/kg/day vs Placebo (1:1) x 6 months
- All patients on placebo get put on drug at 6 months at 15mg/kg/day, others on drug continue at their dose
- Primary Outcome Measures: Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) Sections 1-3

Outcome Measures

- NPMDS (Scales I-3)
  - Change from baseline to 6 months will be compared between subjects in active and placebo treatments
- Secondary Outcome
  - Neuromuscular Function
    - Gross Motor Function Measure
    - Barry Albright Dystonia
  - Respiratory Function
    - Need for tracheostomy
  - Disease Morbidity
    - Total # of hospitalizations
  - Glutathione cycle biomarkers
    - Blood levels compared between active and placebo groups
  - # of AEs
  - Mortality

Open-Label, Dose-Escalating Study to Assess Safety, Tolerability, Efficacy, PK and PD of RP103 in Children With Inherited Mitochondrial Disease (RP103-MITO-001)

Open-Label, Dose-Escalating Study to Assess Safety, Tolerability, Efficacy, PK and PD of RP103 in Children With Inherited Mitochondrial Disease (RP103-MITO-001)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2014 by Raptor Pharmaceuticals Inc.

Sponsor:
Raptor Pharmaceuticals Inc.

Information provided by (Responsible Party):
Raptor Pharmaceuticals Inc.

ClinicalTrials.gov Identifier:
NCT02023866

First received: December 17, 2013
Last updated: November 19, 2014
Last verified: November 2014
History of Changes

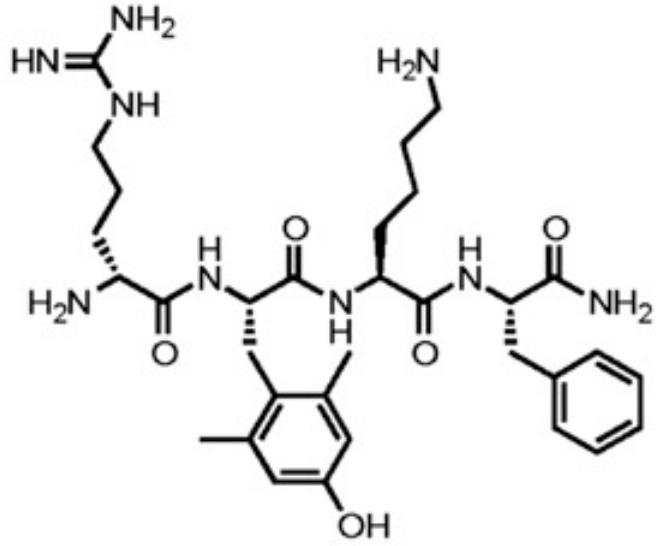
Up to 25 patients will be enrolled if there is no toxicity up to the level of 1.3 g/m2/day of **RP103.** Initial sample size estimate is 25 subjects. Interim analyses will occur after 4 and then 12 subjects complete the study through Week 24. There is a possibility of stopping for efficacy or for futility after either interim analysis. If the study is not stopped early, final analysis will occur after 25 subjects have completed through Week 24.

The rationale for choosing patients with inherited mitochondrial disease who are age 2 and older is based on available clinical data collected in previous and current **RP103** studies in other indications, in subjects aged 2 years and older.

Mitochondrial Myopathy Trials

Bendavia – Stealth Biotherapeutics

RT-408 – Reata



SS-31

d-Arg-2′, 6′-dimethyltyrosine-Lys-Phe-NH2

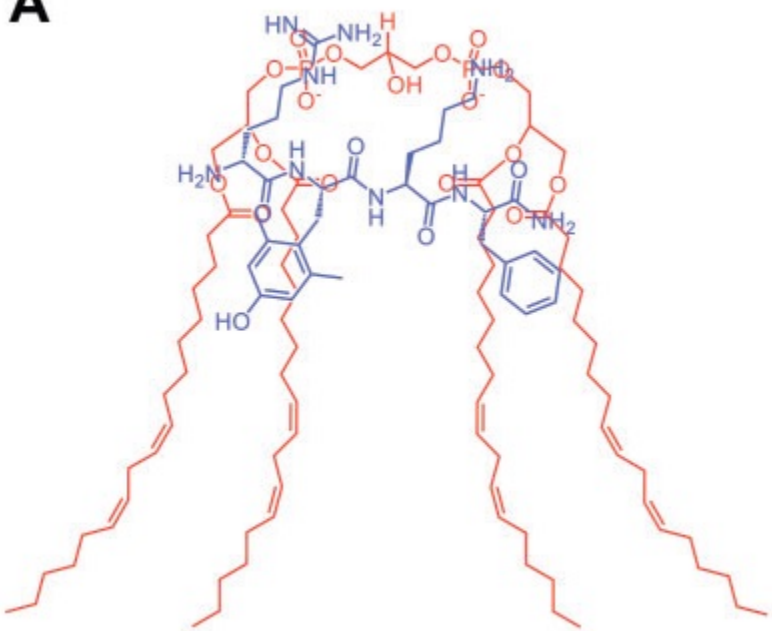
Cardiolipin and the Inner Mitochondrial Membrane

lipid component

- no cholesterol
- high concentration of cardiolipin
  - 20% of total lipid in IMM
  - 4 fatty acid tails-double phospholipid
  - stabilizes the proteins of the IMM

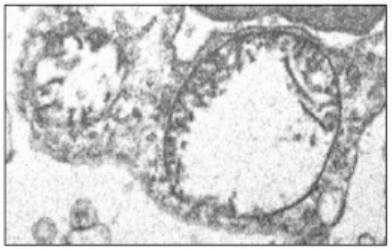
SS-31 Stabilzes Cardiolipin

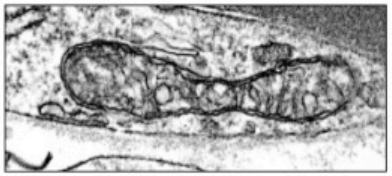
A

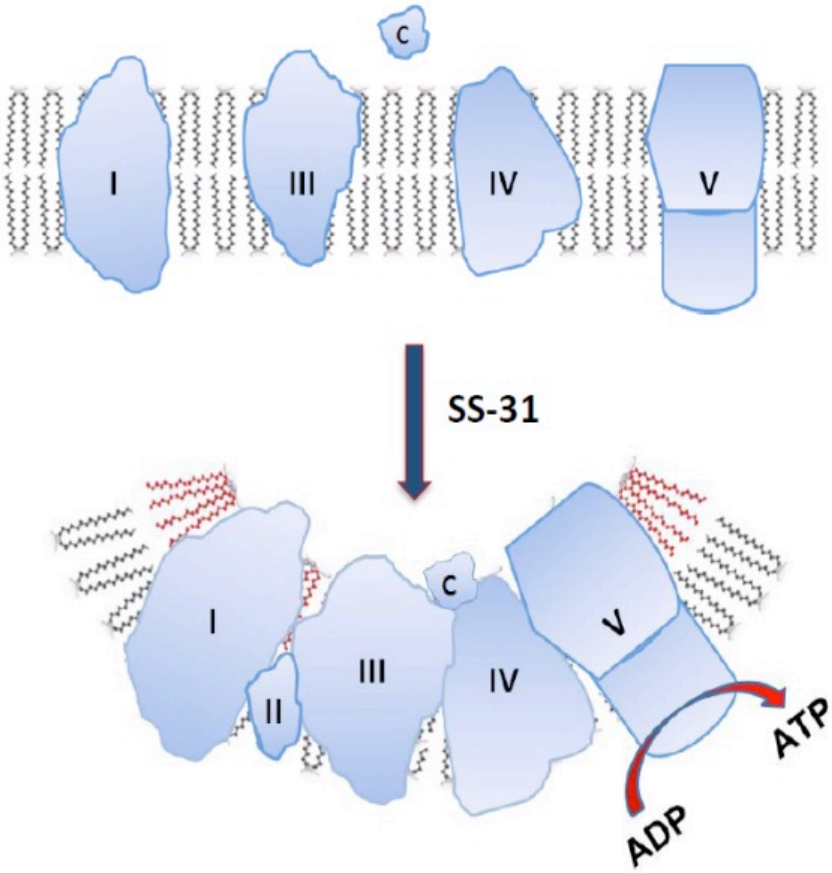


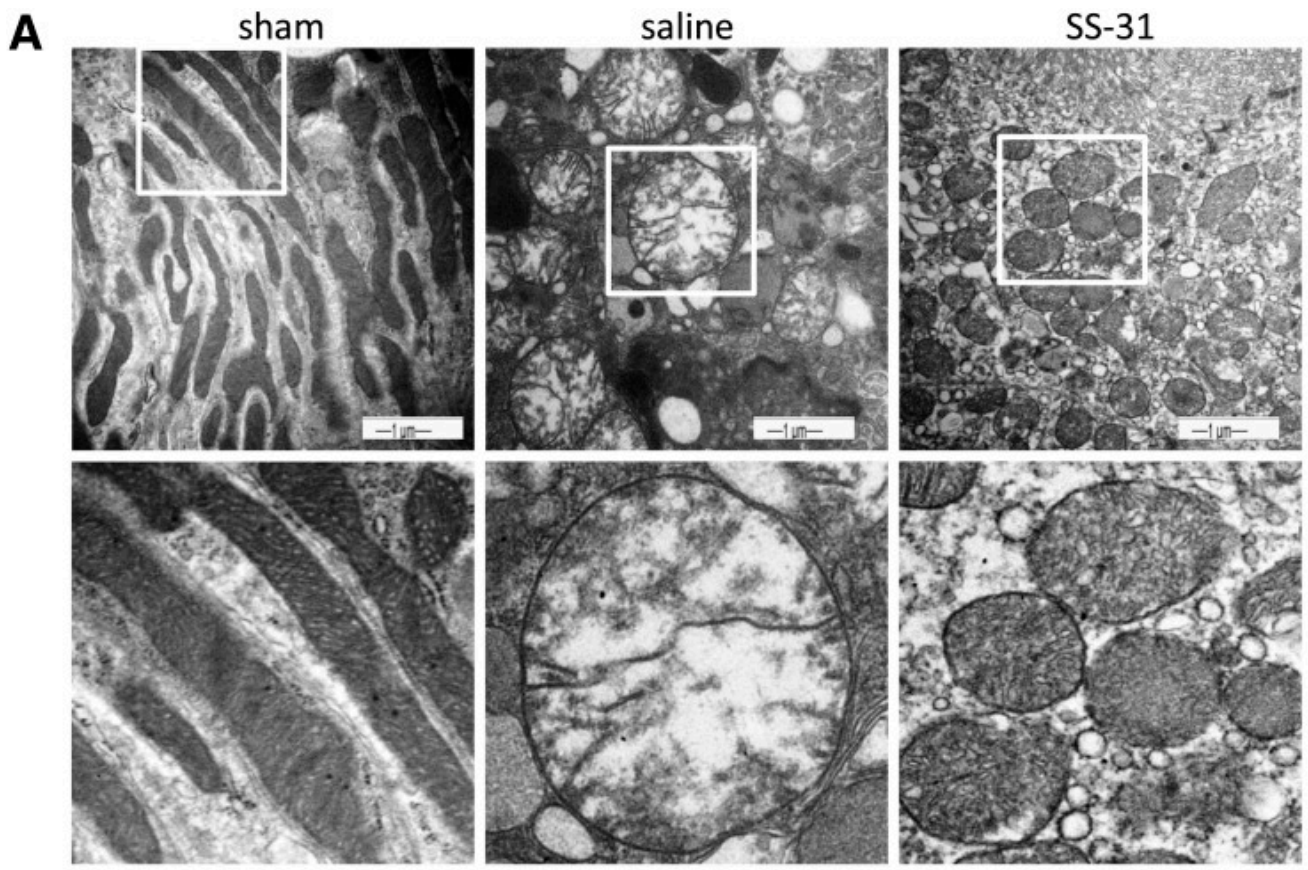
SS-31 restores cardiolipin and promotes bioenergetic efficiency

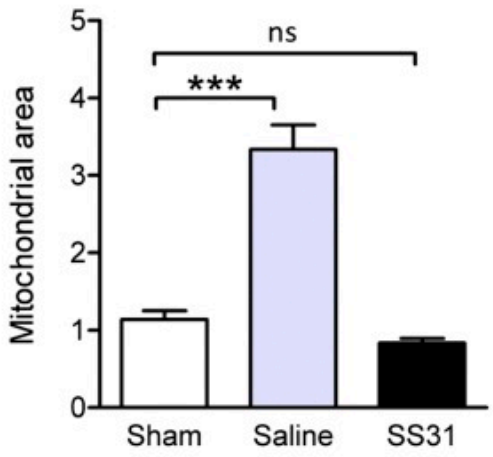
Looks matter!!!

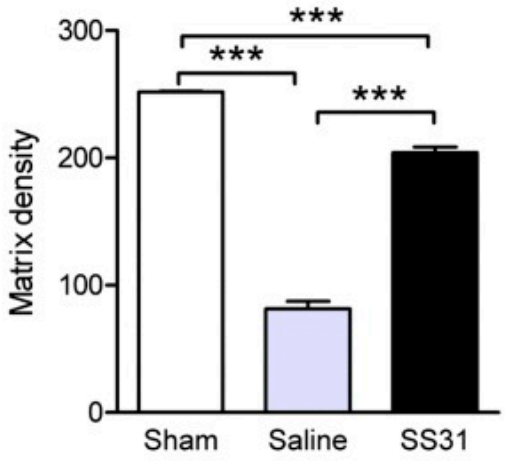






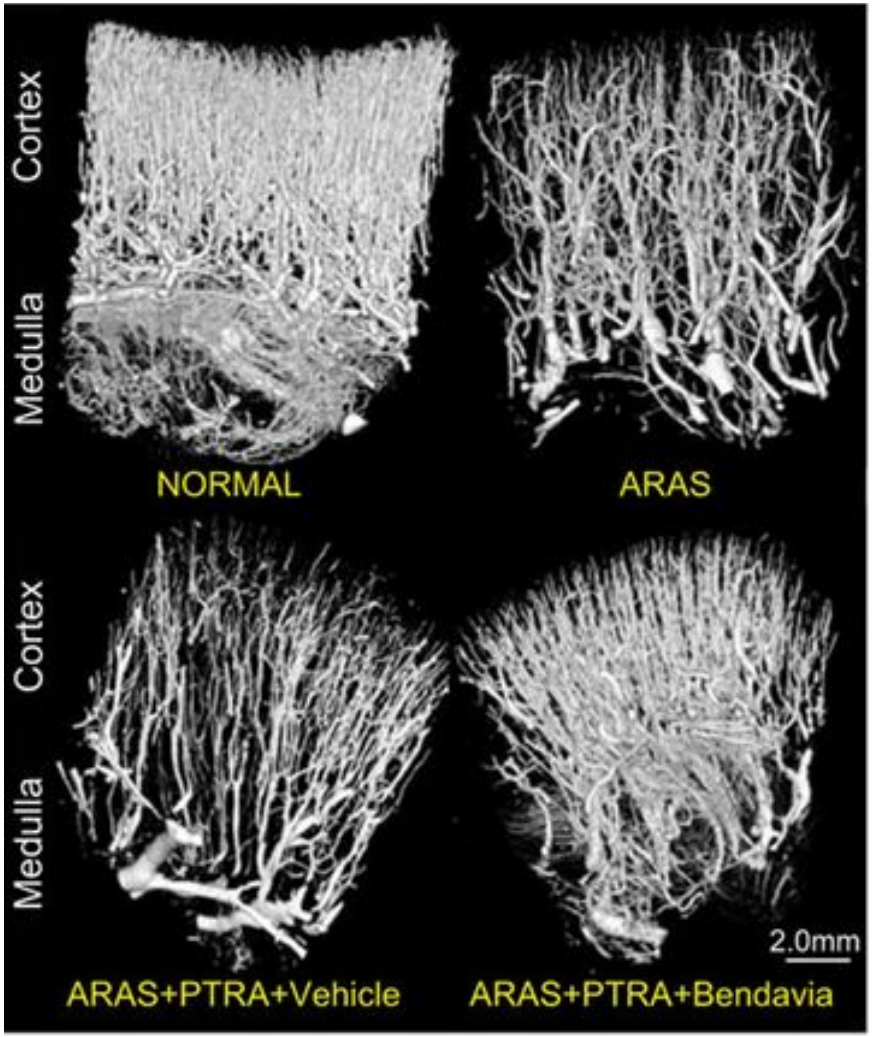


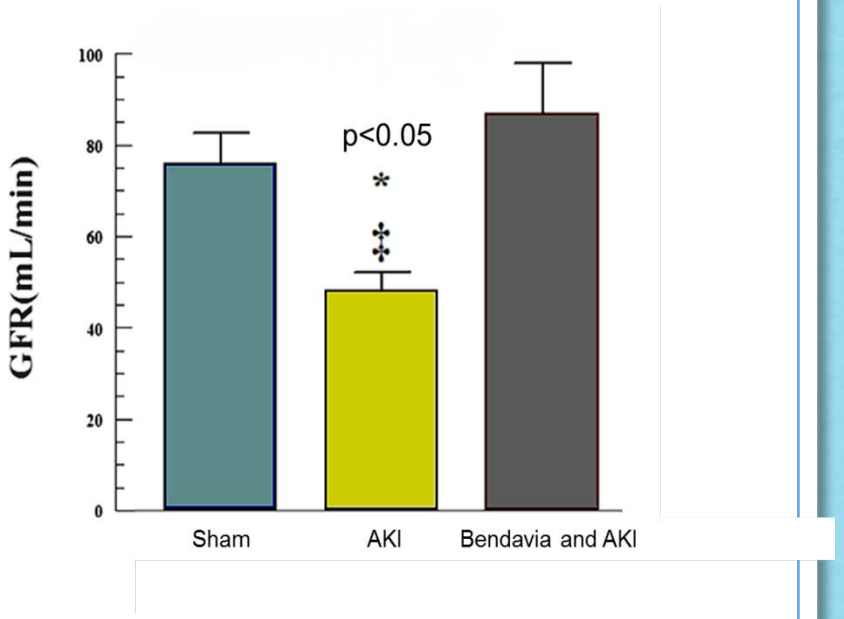




Birk et al
JASN 24: 1250-61, 2013
Ischemia Model

Reperfusion Injury after Renal Revascularization



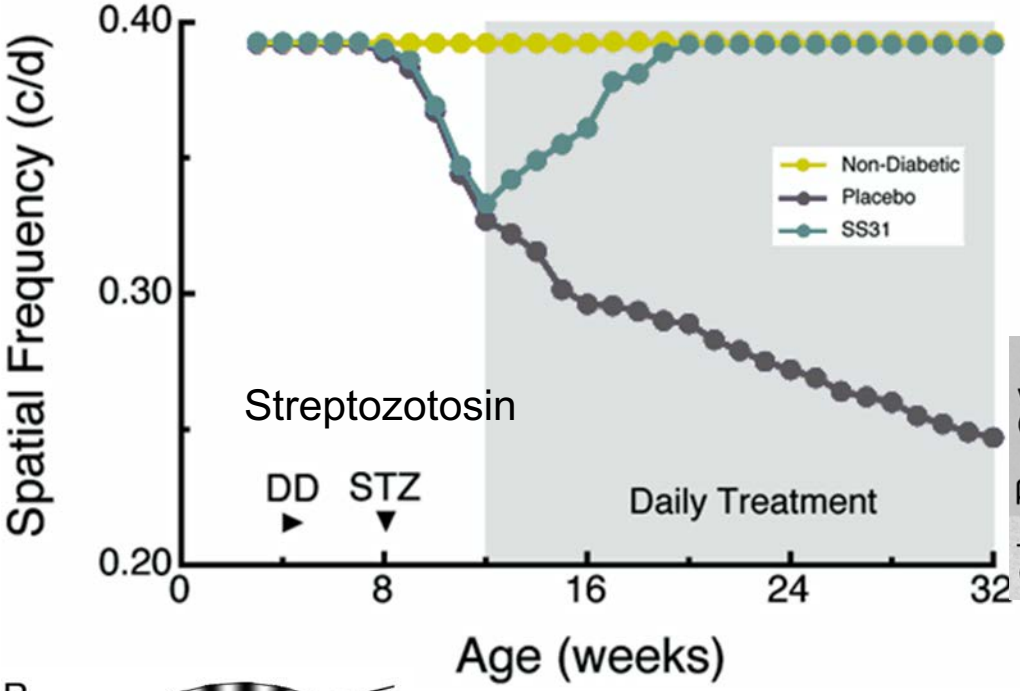


American Heart Association.

Eirin A et al. Hypertension. 2012;60:1242-1249

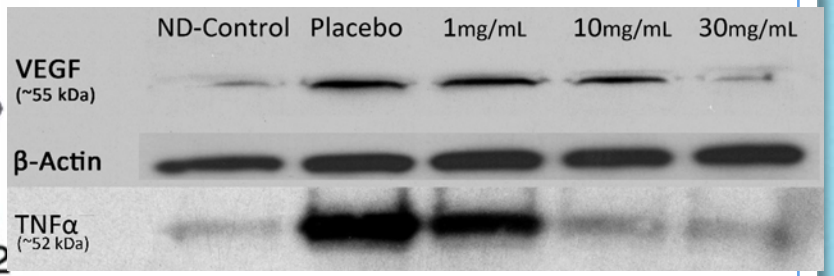
Ocuvia in Diabetic Retinopathy

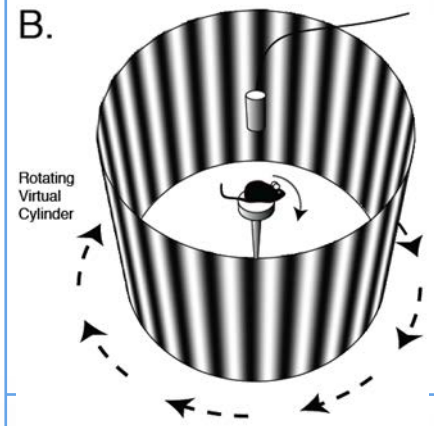
Restores **Visual Function**

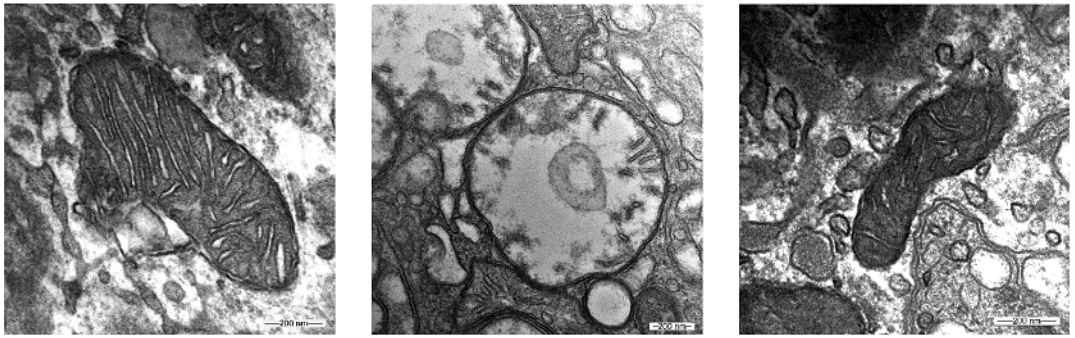


Ocuvia has no effect:

- On normal animals
- On blood glucose or body weight







Design:
3 cohorts of 12 patients (genetically confirmed, mitochondrial myopathy) each, 9 of 12 get drug, 3 of 12 get placebo, given IV over 5 consecutive days, each successive cohort gets ascending doses. Dose 0.01, 0.1, 0.25 mg/kg/hr x 2 hrs x 5 doses.

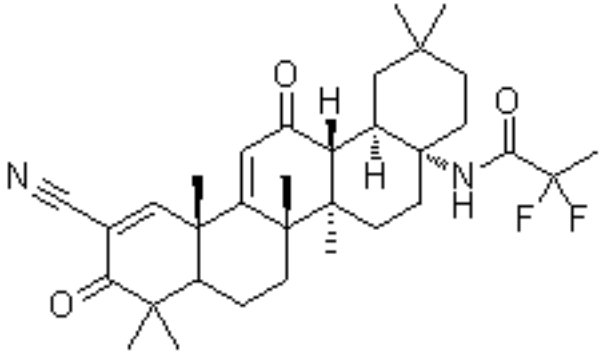
Primary:
Safety and Tolerability of ascending doses

Secondary:
-6 minute walk test
-cardiopulmonary exercise testing (CPET)
-PK
-PD

Exploratory:
plasma, blood and urine biomarkers and other functional measurements

SPIMM 201 - Phase I-II Clinical Trial

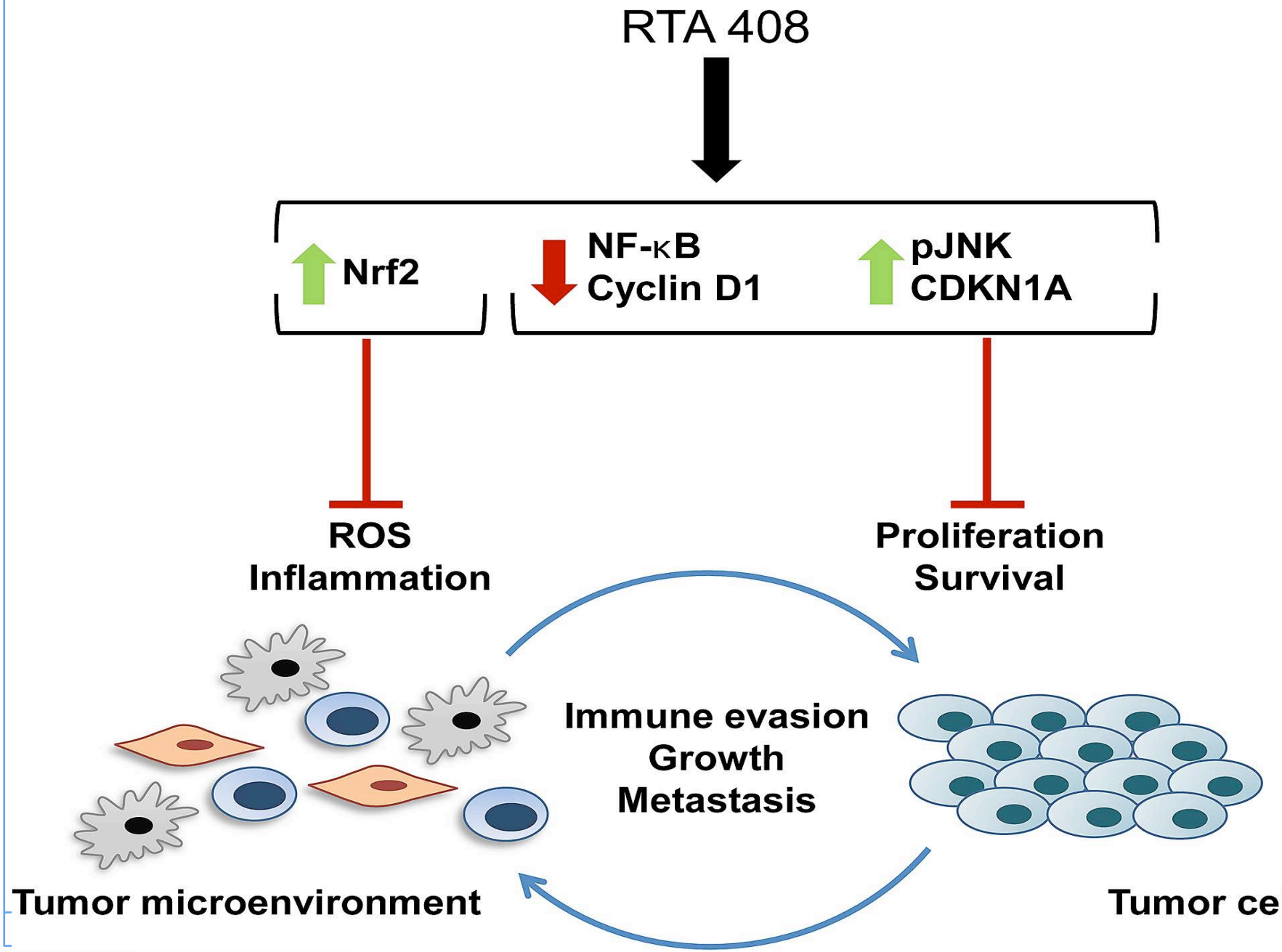
RTA-408



a synthetic triterpenoid

Broad Anticancer and Anti-Inflammatory Action

Animals, plants and fungi all create triterpenes, with arguable the most important example being squalene as it which forms the basis of almost all steroids


RTA 408
Nrf2
NF-κB
Cyclin D1
pJNK
CDKN1A
ROS
Inflammation
Proliferation
Survival
Immune evasion
Growth
Metastasis
Tumor microenvironment
Tumor cells

RTA-408

- Potent Activator of Nrf2 and inhibitor of NF κB (nuclear factor kappa-light-chain enhancer of activated B cells)
- Increases mitochondrial respiration
- Increases mitochondrial biogenesis
- Increases antioxidant capacity

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Mitochondrial Myopathy (MOTOR)

- Inclusion Criteria
  - Mitochondrial myopathy
  - Ages 18-75
  - No changes in exercise, have the ability to complete maximal exercise testing but a peak workload of < 1.5 Watt/k
- Exclusion
  - Uncontrolled diabetes, significant heart disease, abnormal basic labs and not be on a list of several dozen drugs that activate the P450 2C8 or 3A4 system

A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Mitochondrial Myopathy (MOTOR)

- USA
  - UCLA
  - Mass General Boston
  - Akron Children's
  - Children's Hospital of Philadelphia
  - University of Pittsburgh
  - Baylor (Houston)
  - Institute for Exercise and Environmental Medicine (Dallas)
  - University of Texas (Houston)
- Denmark-University of Copenhagen

- 12 week study

Outcome Measures

- Primary
  - Measure the change of peak workload (in watts/kg) during exercise testing
- Secondary
  - Measure the change in distance walked during a 6-minute walk test