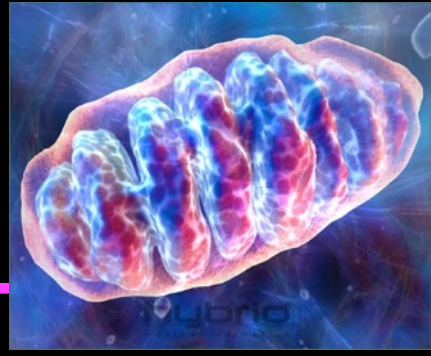
Exercise and nutrition in Mitochondrial Disease.

Mark Tarnopolsky, MD, PhD, FRCP,

Depts. of Pediatrics (Neuromuscular + Neurometabolic Disease) and Medicine (Cell Biology/Metabolism, Neurology and Rehabilitation), McMaster University, Hamilton, CANADA

Disclosure



- Genzyme, Transgenomics – speaker honorarium 2009, 2010, 2011, 2012, 2013.
- Amicus Therapeutics, Biomarin - consultant, 2011, 2012.
- Wyeth – research funding 2009-2010.
- GSK - speaker honoraria 2011.
- Genzyme - research funding, 2011.
- CEO and founder ***Exerkine*** Corp.

Pathological Disorders

Physiological Adaptation

Atrophy

Strength

drugs, nutrition,
exercise

obesity, T2DM,
mitochondrial disease
immobilization,
neuropathy
sarcopenia/aging,
cancer,
statin myopathy
corticosteroids

nutrition,
exercise

drugs, nutrition,
exercise

Mitochondrial
Dysfunction

Endurance

Nutritional Inadequacy in Patients with Muscular Dystrophy

- N = 51 MD patients (DM1, LGMD, FSHD).
- N = 14 DMD patients (< 16y).
- Prospective dietary analysis for 3 days separated by 5 months.
- Mean values reported.
- Compare to Canadian DRI.

Motglah, et al, *Muscle and Nerve*, 2005

% NOT meeting the DRI.

- Energy = 68/64
- Vit A = 45/14
- Vit C = 40/14
- Vit D = 78/71
- Vit E = 98/78
- Vit K = 86/85
- Thiamine = 26/14
- Riboflavin = 33/7
- PRO = 16/0
- Vit B6 = 31/7
- Folate = 82/42
- Vit B12 = 23/0
- Pantothenate = 80/35
- Biotin = 90/17
- Calcium = 72/64
- Iron = 29/21

ADULT/PEDIATRIC

MD vs Mitochondrial disease.

Motagleh, and Tarnopolsky, *Muscle Nerve*, 2005, Tarnopolsky, et al, *Muscle Nerve*, 1997.

	DM1 (29)	MD (21)	MITO (9)
BMI (> 30)	10 %	18 %	14 %
BMI (< 18.5)	13 %	9 %	14 %
Energy (< RNI)	62 %	82 %	43 %
PRO (< RDI)	10 %	5 %	14 %
FAT (> 30 %)	55 %	86 %	57 %
Vit. E (< ADMR)	90 %	86 %	44 %
Vit C (< ADMR)	31 %	18 %	14 %

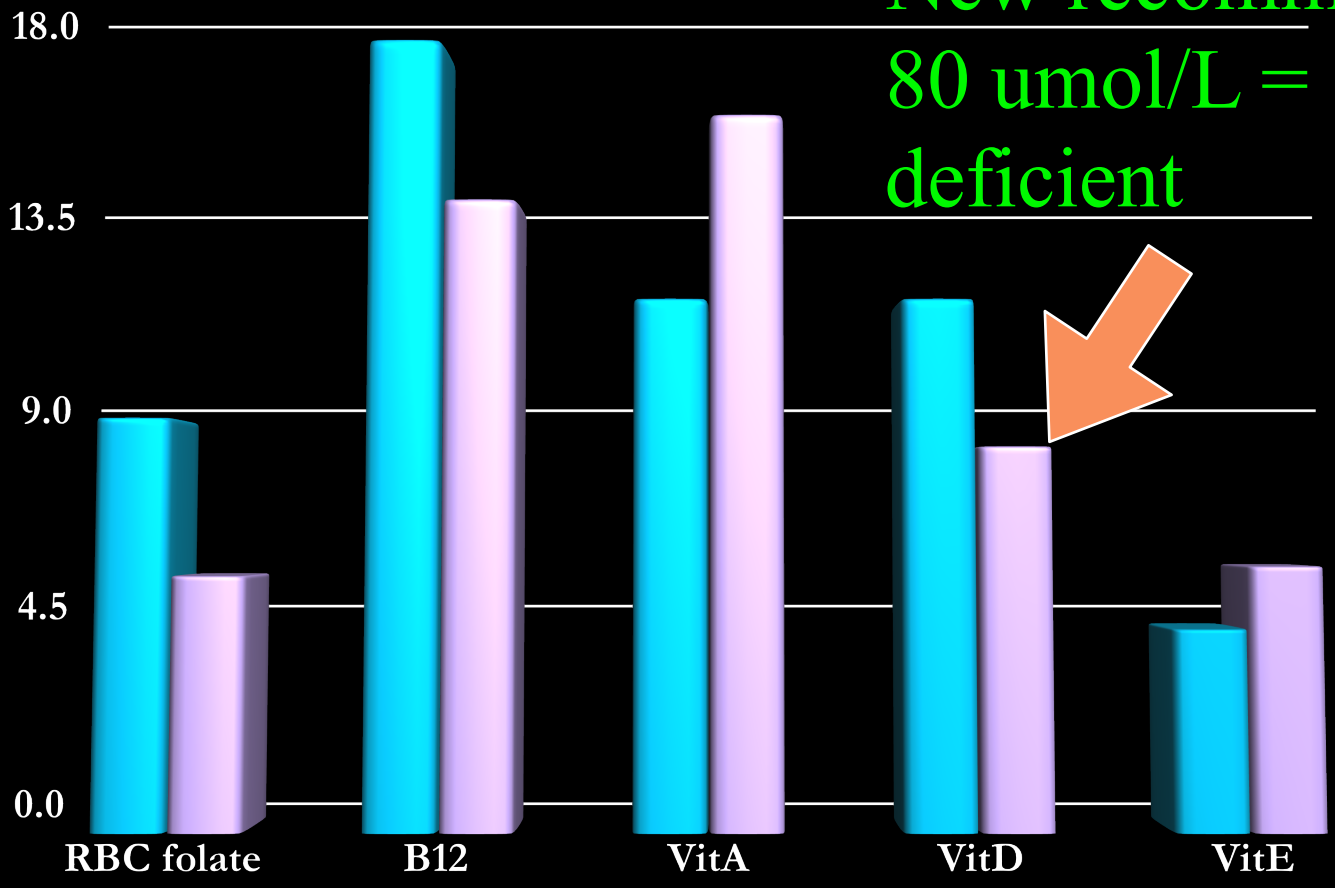
Serum Vitamin Levels

- July 1, 1996 ➡ June 15, 2001.
- McMaster University Neuromuscular Clinic
- N = 1852 (♂ = 905; ♀ = 947) blood tests with at least one vitamin level sent:
  - RBC folate
  - B12
  - Vitamin A
  - Vitamin D (25-OH)
  - Vitamin E

Tarnopolsky M., et al.,
MS in preparation, 2012

Serum Vitamin Levels

New recommendations: > 80 umol/L = 85 % deficient



Tarnopolsky M., et al., MS in preparation, 2012

What about other deficiencies?

- 1. carnitine - if low - 10 - 15 mg/kg/d.
- 2. MELAS - L-arginine - acute = 0.5 g/kg acute and q12 h X 4. Oral = 1,000 mg bid adults - citrulline - often low: ? replace - 750 mg bid.

Secondary carnitine deficiency and impaired docosahexaenoic (22:6n-3) acid synthesis: a common denominator in the pathophysiology of diseases of oxidative phosphorylation and beta-oxidation.
Infante JP, Huszagh VA., FEBS Lett. 2000 Feb 18;468(1):1-5.

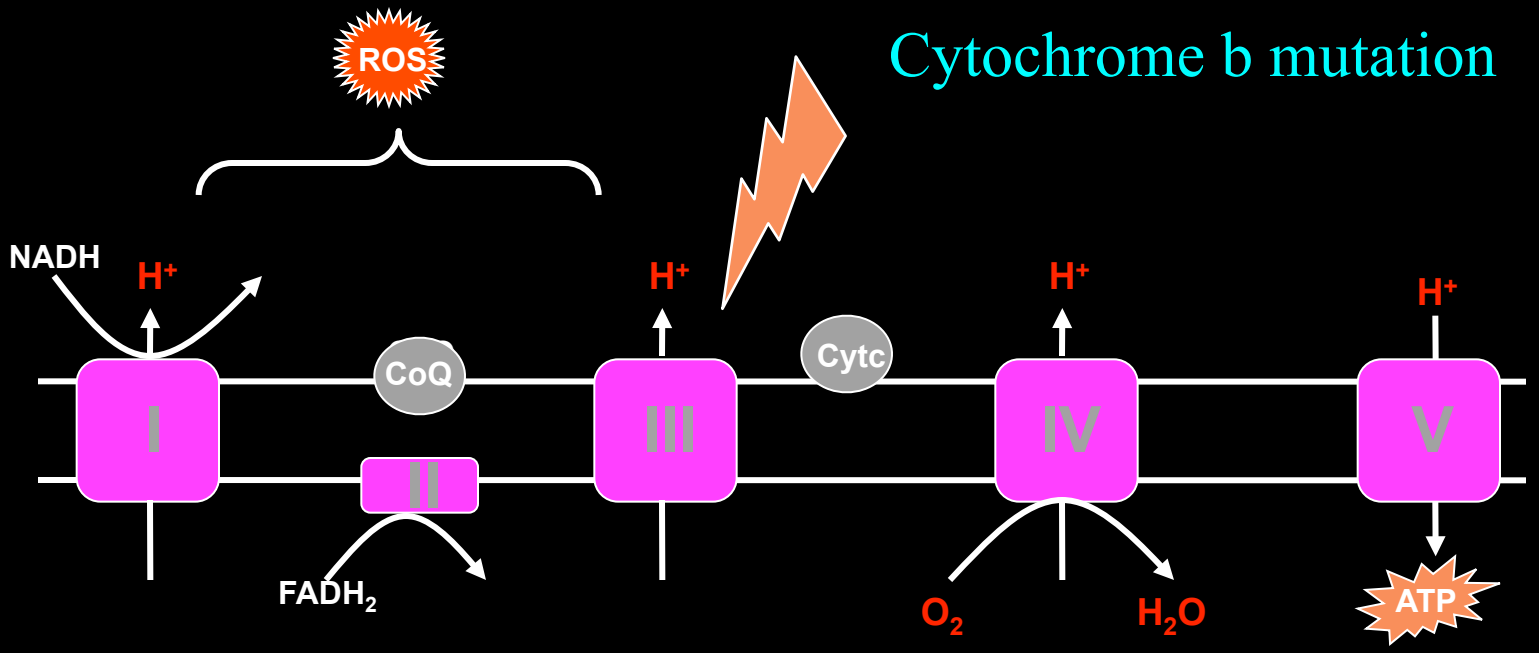
Habitual Diet – General conclusions/suggestions:

- Energy intake is low.
- Low expenditure; ? Low RMR.
- Food preparation/eating may be difficult.
- Fear of swallowing.
- Suggestions:
  - Swallowing study if any suggestion of dysphagia.
  - Take a balanced multivitamin.
  - Check for deficiencies in patients – Rx as appropriate.
  - A deterioration in function in mitochondrial disease could be a vitamin deficiency.
  - G-tube early in kids falling off growth curve.

Habitual Diet – General suggestions – Continued.

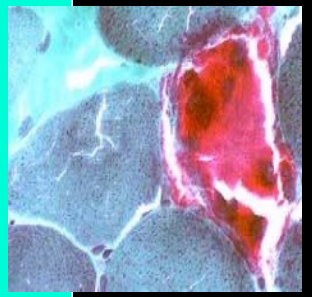
- Avoid fasting for prolonged periods (> 10 h).
- More frequent meals.
- Consider high fat in complex I with seizures or PDH deficiency.
- Avoid iron supplements unless iron deficient anemia.
- Avoid ethanol (excess can lead to paracrystalline inclusions).
- Avoid MSG and other migraine triggers (red wine, aged cheese, etc.) in MELAS patients with migraines.

Consequences of Mitochondrial Dysfunction



- ATP
- Alt. E. Source
- ROS
- Lactate

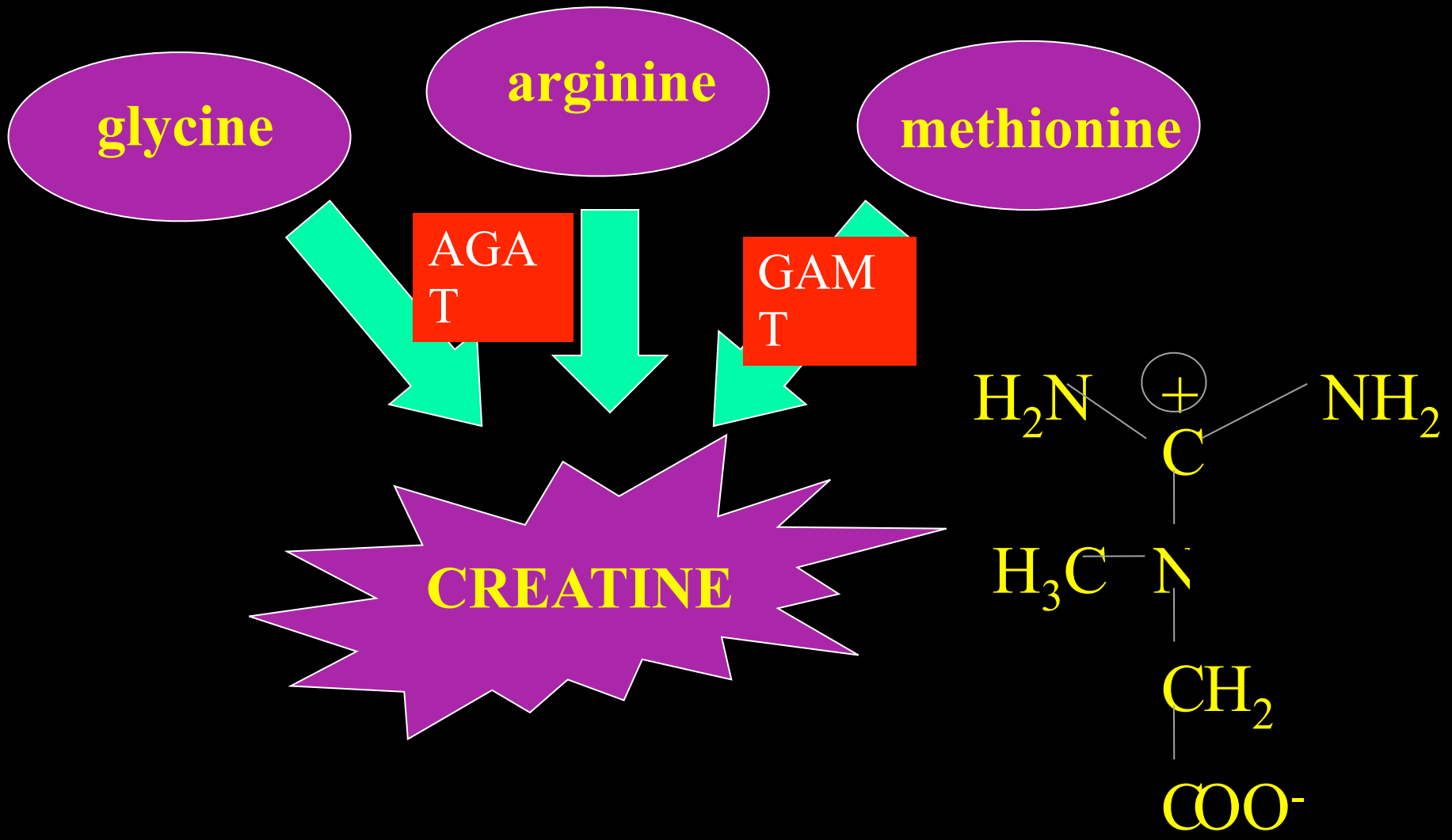
- Mito proliferation
- Anti-oxidant enzyme



Mitochondrial Disease R_x Strategies

Bypass Defect	**(CoQ_{10}, succinate, riboflavin).**
Reduce Lactate	**(Dichloroacetate, thiamine)**
Anti-Oxidants	**(Vit E, lipoic acid)**
Alternative Energy	**(Creatine monohydrate)**
Exercise training	**(Aerobic vs strength)**
Vasodilatation	**(L-arginine)**
Folate deficiency	**(folate, folinic acid)**
Nucleotide precursors	**(triacetyluridine)**

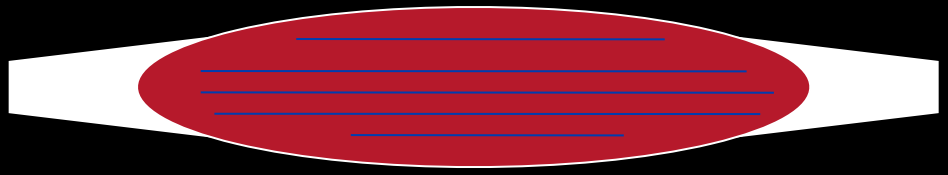
Creatine


glycine
arginine
methionine
AGA T
GAM T
CREATINE
H_2N
+
NH_2
C
H_3C
N
CH_2
COO$^-$

Creatine physiology:

Exogenous consumption: (~ 1 g/day)

Skeletal Muscle (~ 90 % of Creatine) → Creatinine



1 – 2 g/d

GA

KIDNEYS

AGAT

LIVER

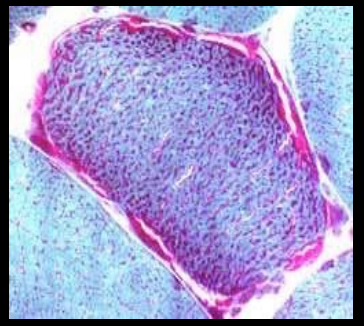
GAMT

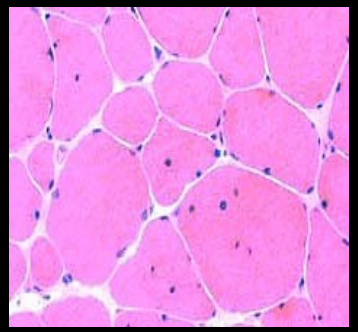
?

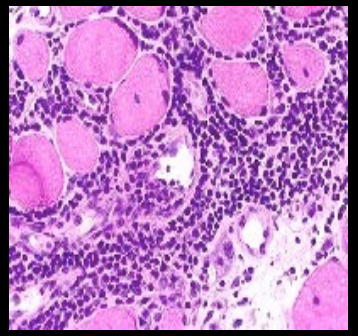
PANCREAS

Low muscle TCr/PCr stores.

- Mitochondrial DNA disorders.
- Muscle dystrophy.
- Inflammatory muscle disease.







(Tarnopolsky and Parise, *Muscle + Nerve*, 1999).

Potential Benefit in Mitochondrial Disorders.

- ↑ Fat-free mass
- ↑ Strength/Power
- ↓ Neuro-toxicity (ALS, HD, PD)
- ◦ Anti-oxidant (direct and indirect)
- ◦ Anoxia protection
- ↑ Mitochondrial function (*mdx, ?* humans)
- ↓ Apoptosis ↑ ΔΨm (traumatic brain injury)

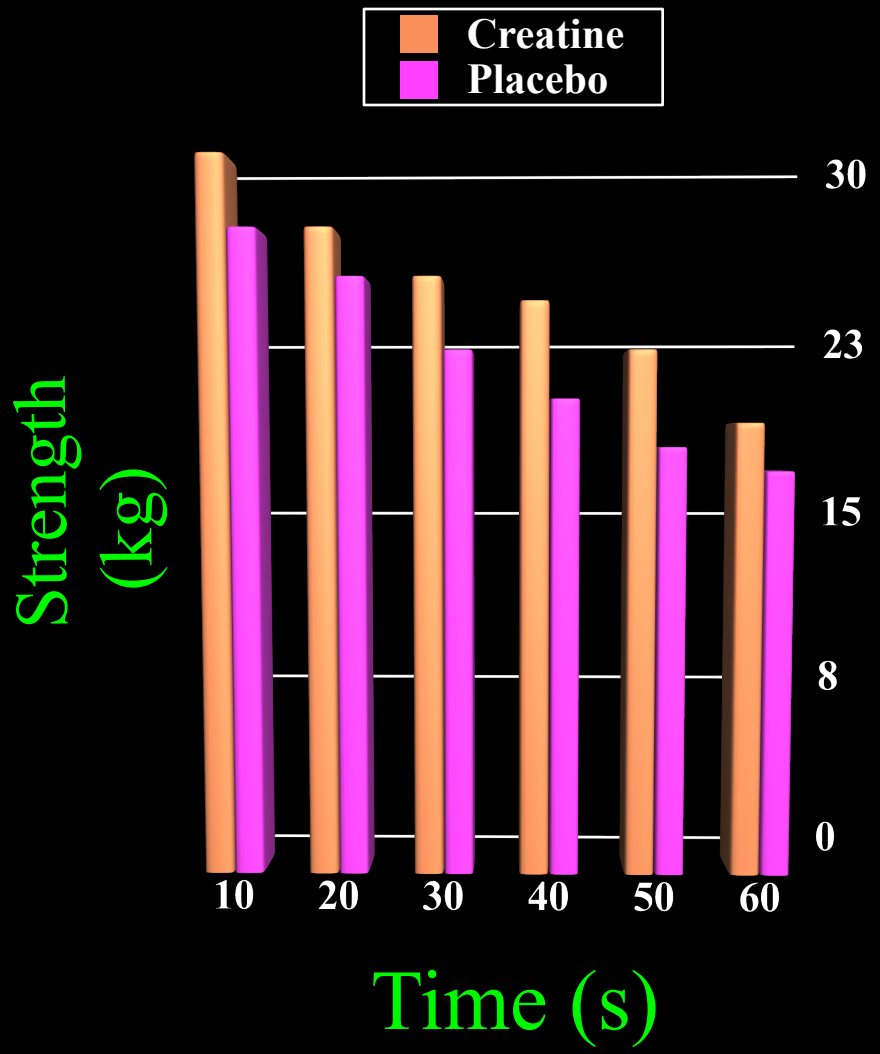
Creatine in Mitochondrial Disorders

Study	N	Dose	Outcome	S.E.s
Komura, 2003	5	0.08 - .35 g/kg/d, 4y	+ 12.1 %	nil
Barisic, 2002	1	20g>5g/d X 28mo	+ CNS, MRS	? Renal
Cacic, 2001	1	~ 0.15 g/kg/d	+ symptoms	nil
Klopstock, 2000	16	20g/d X 4 weeks	+ 23 % (N.S.)	nil
Borchert, 1999	4	0.15 – 0.2 g/kg/d	+ symptoms	nil
Tarnopolsky, 1997	7	10g/d > 4g/d (3 wk)	+ high intensity	nil
Hagenfeldt, 1994	1	5 g/d	+ exerc./HA	nil

Creatine in Mitochondrial Disorders.

Tarnopolsky MA, et al, *Muscle Nerve*, 20:1502- 1509,1997.

- N = 7, RCT, cross-over.
- CM 10g/d X 2 week and 4 d/d X 1 week:
- ⇑ handgrip and dorsi-flexion power.
- ➡ VO2max.



Not performing well?

- 26 y male triathlete.
- Study volunteer.
- EM for lipids.

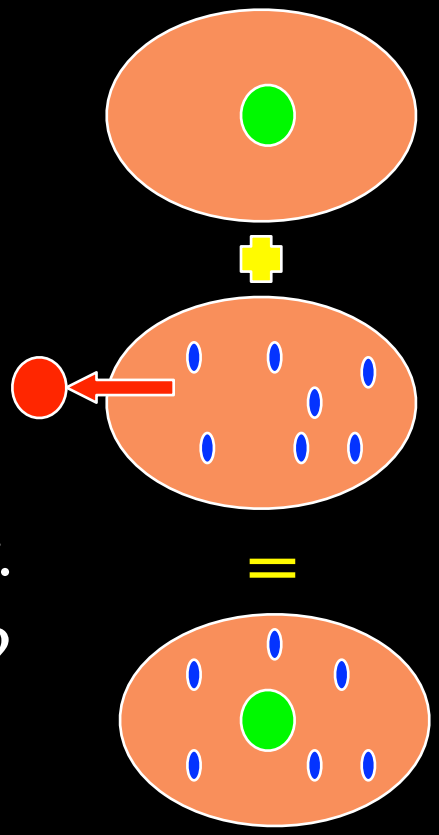
- Surprised to find paracrystalline inclusions in muscle.
- Discovered a novel cytb

Tarnopolsky MA, et al, *Muscle Nerve*,

in vitro testing of therapy?

- Generation of cybrids.
- Expose to stressors:
  - Oxygen and glucose (OGD).
  - SIN1 – peroxynitrite donor.
- Protection from Rx ?

Cybrid generation:

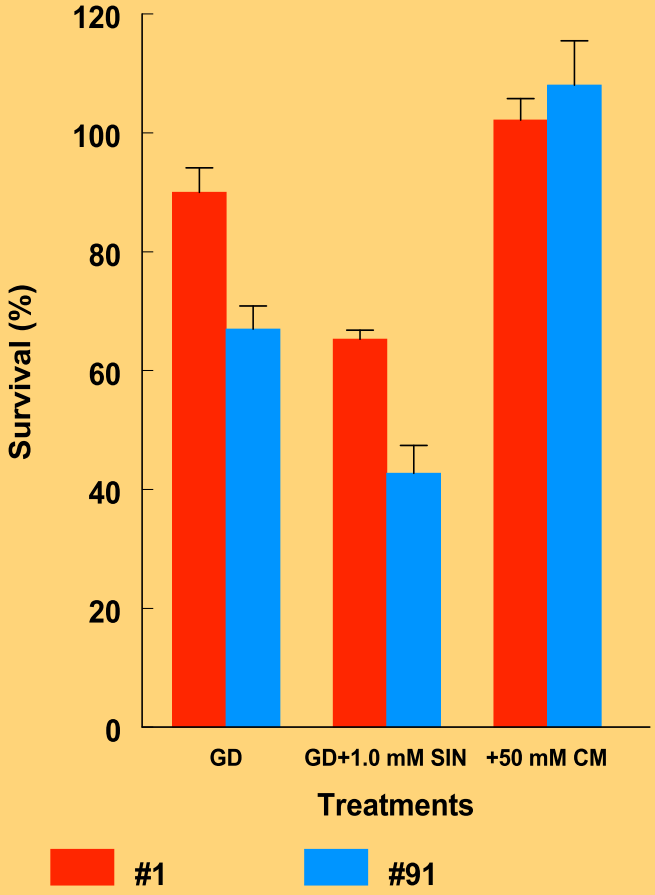


1. Deplete mito. in immortalized cell (EB).

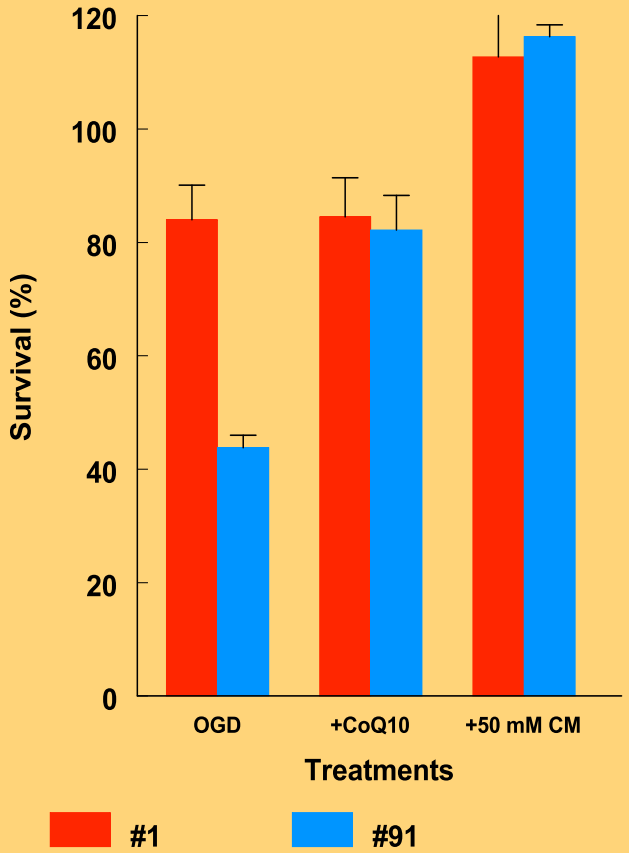
2. Enucleate the patient's + con. cells (centrifuge).

3. Fuse cells with PEG.

Glucose deprivation + SIN-1



Oxygen and glucose deprivation

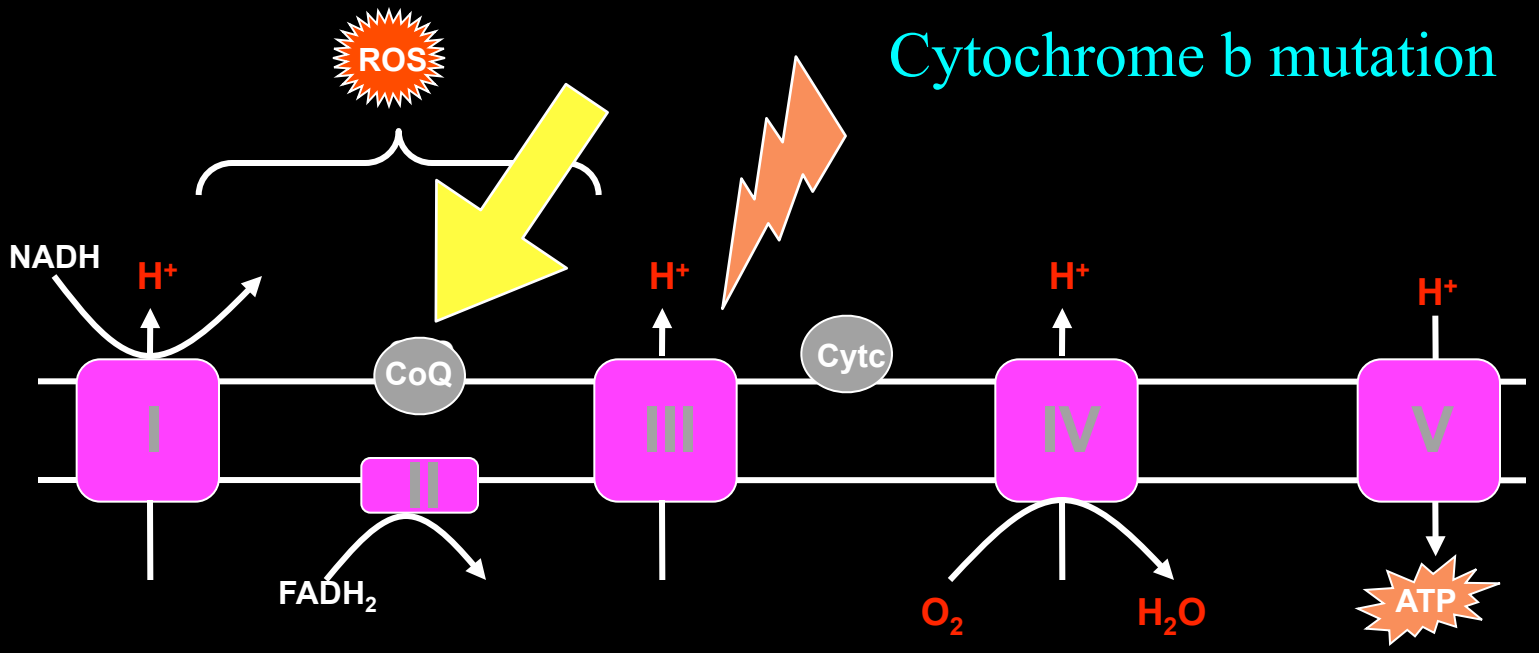


Cybrid #1 – normal mtDNA
Cybrid #91 – cyt b mut mtDNA
Creatine monohydrate – 50 mM
CoQ10 - 10 ug/ml

SUMMARY

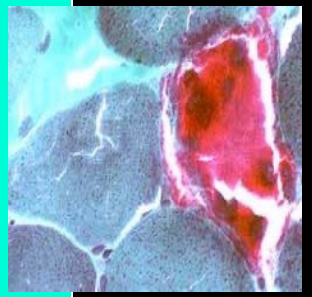
- CM supplementation can decrease paracrystaline inclusions in muscle (no change in mtCK total protein; possibly due to decreased oxidative stress and octameric:dimeric transitions).
- Effects on cellular function are subtle and need further examination (High intensity function is enhanced (Tarnopolsky, et al, *M+N*, 1997)).

Consequences of Mitochondrial Dysfunction



- ATP
- Alt. E. Source
- ROS
- Lactate

- Mito proliferation
- Anti-oxidant enzyme



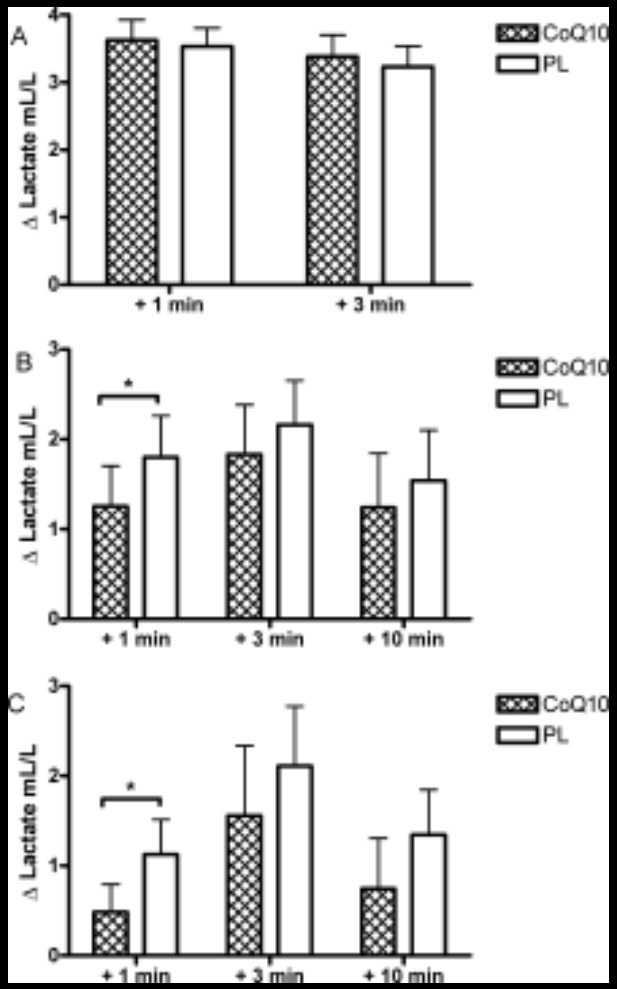
Mitochondrial Disorders - CoQ10 Rx (3 – 5 mg/kg/d)

- POSITIVE: Reichmann, 1998 (9), Matsuo, 1999 (2), Barbiroli, 1999 (10), Barbiroli, 1997 (6), Chen, 1997 (8), Schoffner, 1989 (1), Nishikawa, 1989 (10), Bresolin, 1988 (7), Ogasahara, 1986 (5), Bendahan, 1992 (2), Ikejiri, 1996 (1), Ogasahara, 1985 (1), Yamamoto, 1987 (1), Desnulle, 1988 (1), Ihara, 1989 (2), Abe, 1999 (2), Chan, 1998 (9), Glover, 2010 (30). (108)
- NO EFFECT: Matthews, 1993 (16), Gold, 1996 (8). (24)
- SAFETY: Shults, et al, Arch Neurol, 2002 – PD – safe and well tolerated up to 1,200 mg/d. Matthews – some GI side effects; children with COQ10 deficiency – very high doses.
- FORMULATION: Liquid or gel – not powder.

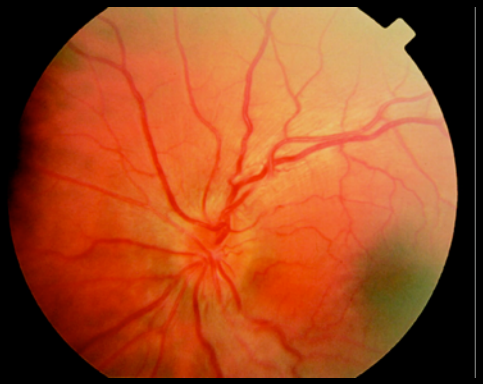
A randomized trial of coenzyme Q10 in mitochondrial disorders.

Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. Muscle Nerve. 2010 Nov;42(5):739-48.

- N = 30 mito. myopathy.
- RCT - 8 weeks, cross-over, double-blind.
- 900 mg po bid COQ10.
- MRS, lactate, oxidative stress, exercise capacity



Idebenone and LHON



- N = 85 LHON.
- 24 weeks, RCT.
- 900 mg/d idebenone.
- primary = best recovery of V/A.
- No effect with ITT.
- Sub-group with discordant V/A -

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy.

Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, Atawan A, Chattopadhyay S, Schubert M, Garip A, Kernt M, Petraki D, Rummey C, Leinonen M, Metz G, Griffiths PG, Meier T, Chinnery PF

Brain. 2011 Sep;134(Pt 9):2677-86. Epub 2011 Jul 25.

Idebenone increases mitochondrial complex I activity in fibroblasts from LHON patients while producing contradictory effects on respiration.

Angebault C, Gueguen N, Desquiret-Dumas V, Chevrollier A, Guillet V, Verny C, Cassereau J, Ferre M, Milea D, Amati-Bonneau P, Bonneau D Procaccio V, Reynier P, Loiseau D.

BMC Res Notes. 2011 Dec 22;4:557.

Clinical Trials in Mito Disease.

- Small numbers/OPEN studies.
- Outcome variables (ie. Anti-oxidant not likely to alter strength, exercise capacity in short-term).
- Often redundant "cocktails" (i.e., multiple anti-oxidants).
- Often single agents.
- Suggest: target the 3 "final common pathways"

(↑ ROS; ↓ Alt. E source; ↓ ETC flux)

Mitococktail

- Given that there are several final common pathways of mitochondrial dysfunction – targetting most of them should be more beneficial.
- Examples:
  - Chemotherapy (ALL survival rates).
  - *mdx* mouse (Payne, E, *Muscle Nerve,* 2006).
- ? Mitochondrial disease?

Mitococktail

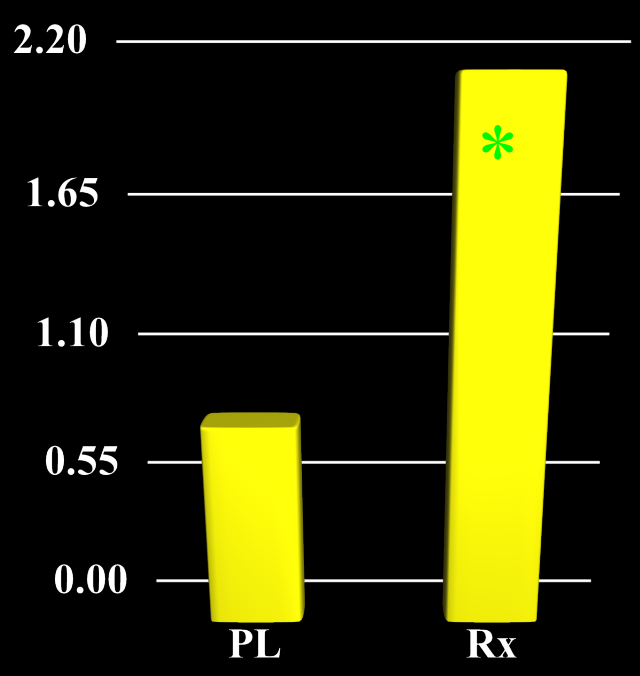
(Marriage, *Mol Gen Metab.*, 81:263-, 2004).

- N = 12 (6 LHON; 3 CPEO, 3 misc.).
- Pre, 3,6,12 months (open):
  - COQ10 @ 5 mg/kg (~ 210 mg/d); carnitine 500 mg/d; B complex (1,2,3,5,6,12, folate), vitamin K (0.4 mg/kg), vitamin C 1000 mg)
- CoQ10 – increased 5 fold:
  - Increased ATP production in lymphocytes at 12 months, no effect on lactate.

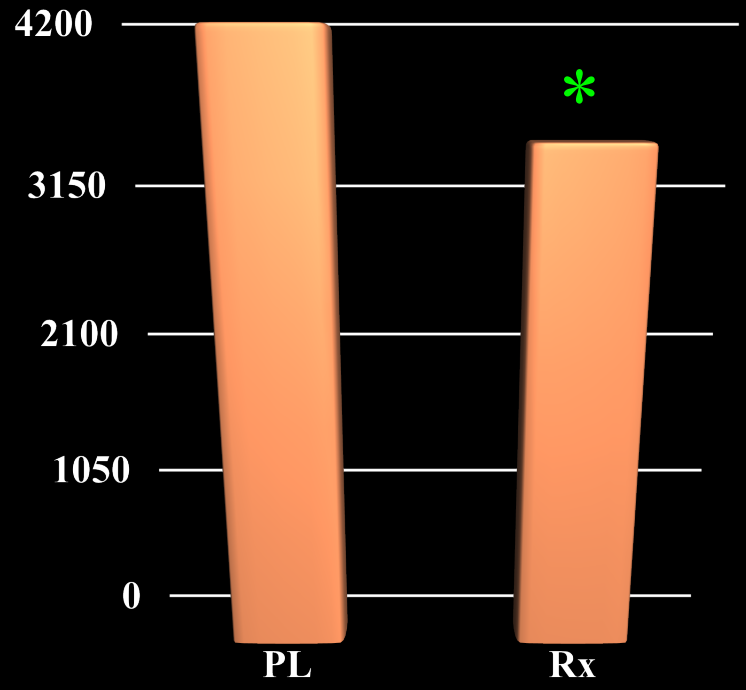
RCT in Mitochondrial Diseases

Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.

- 2 month RCT, 2 month W/O, cross-over: CoQ10 120 mg bid + 150 mg Vit E + creatine 3 g bid + LA 300 mg bid in 16 patients with definite mitochondrial disease.

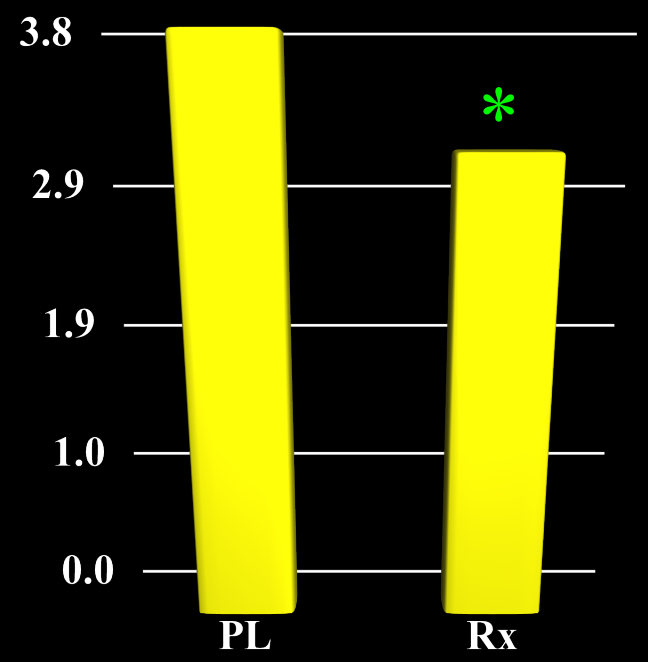


CoQ10 (ug/mL), P < 0.001

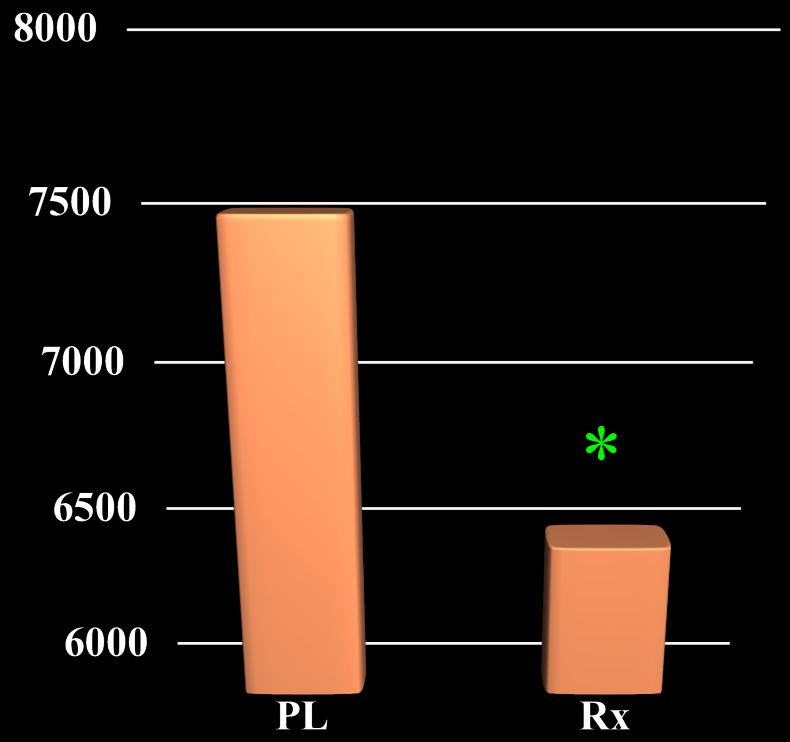


8-OH-2dG (ng/g creatinine), P = 0.065

RCT in Mitochondrial Diseases

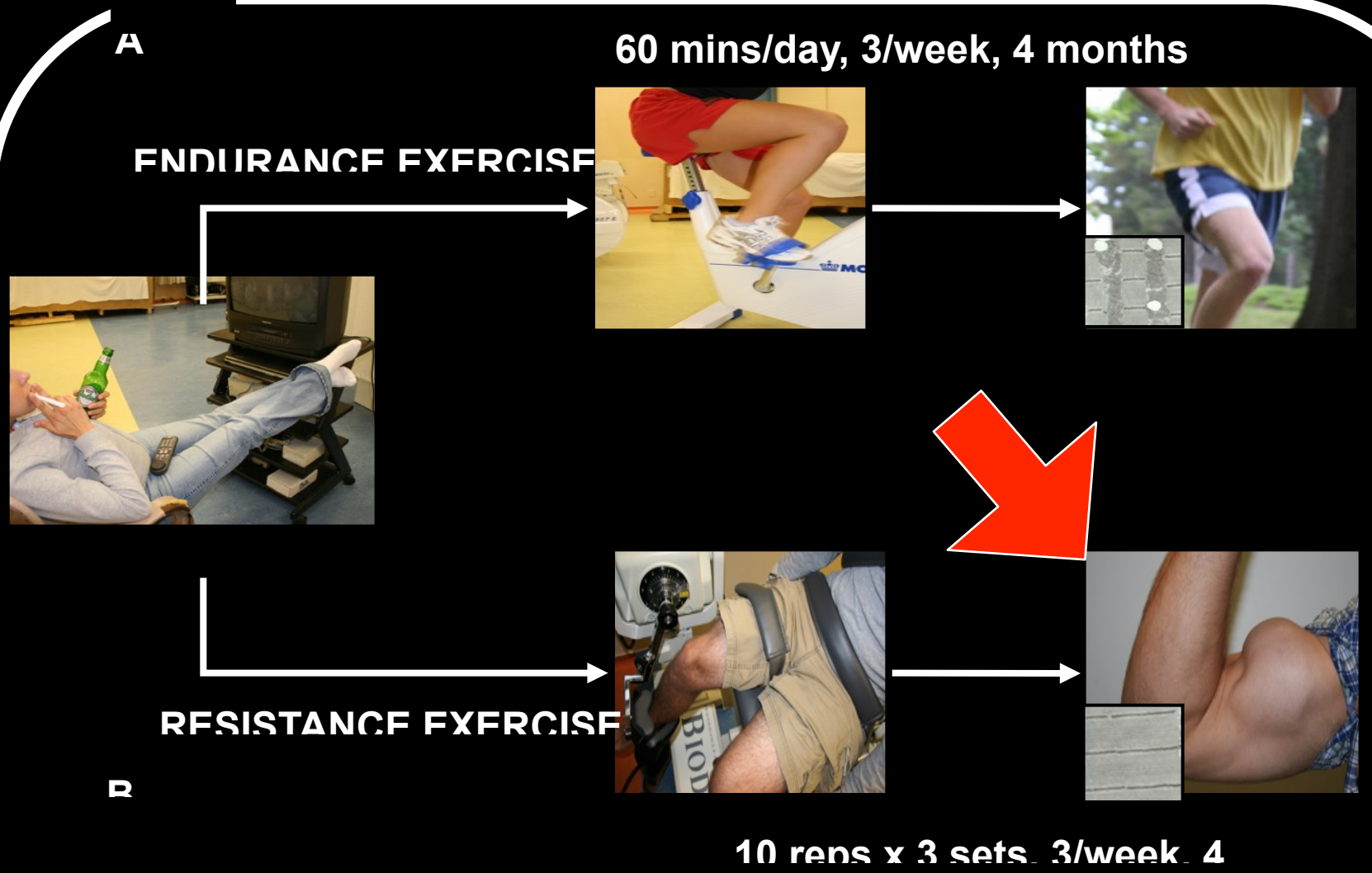


Lactate (mmol/L), P < 0.05



8-isoprostanes (umol/g creatinine), P < 0.05

Rodriguez, et al., *Muscle and Nerve,* 35:235-, 2007.

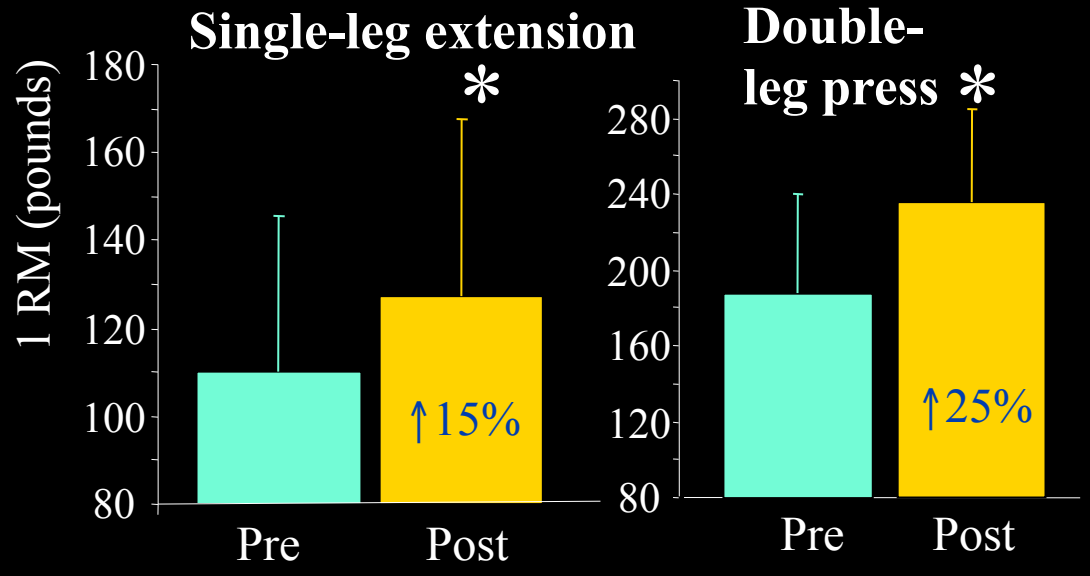


Contractile Activity Determines

Resistance training in Mitochondrial myopathy

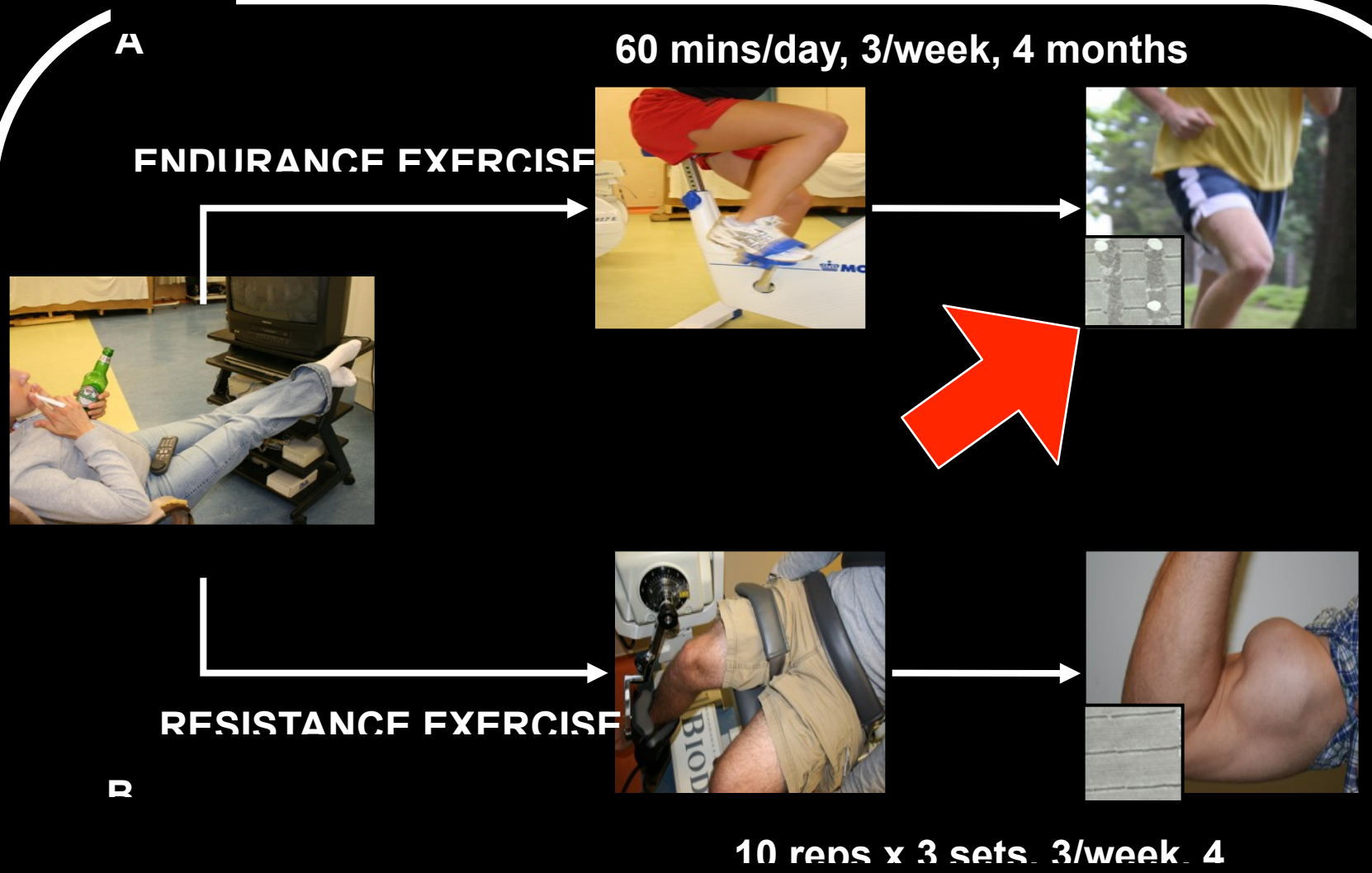
- **Group of 8 patients:** (39±9 y) with single large-scale deletions.

- **Training Protocol**
  - Bilateral leg extension/flexion, leg press
  - 12 weeks, 3 x per week at 80-85% 1RM (3 to 6 sets, 6-8 reps)



CK pre: 187 ± 115 U/L
CK post: 166 ± 159 U/L

Taivassalo, Gardner, Haller and Turnbull, *Brain*, 2009.



Contractile Activity Determines

Endurance exercise training

- N = 20 MITO (14 point mutations in mtDNA; N = 16 healthy controls).
- 12 week cycle @ 70 % VO_{2peak}, 4 X/week.
- ⬆ CS (67 %); ⬆ VO_{2peak} (67 %); (same in controls).
- No increase in CK or muscle morphology.

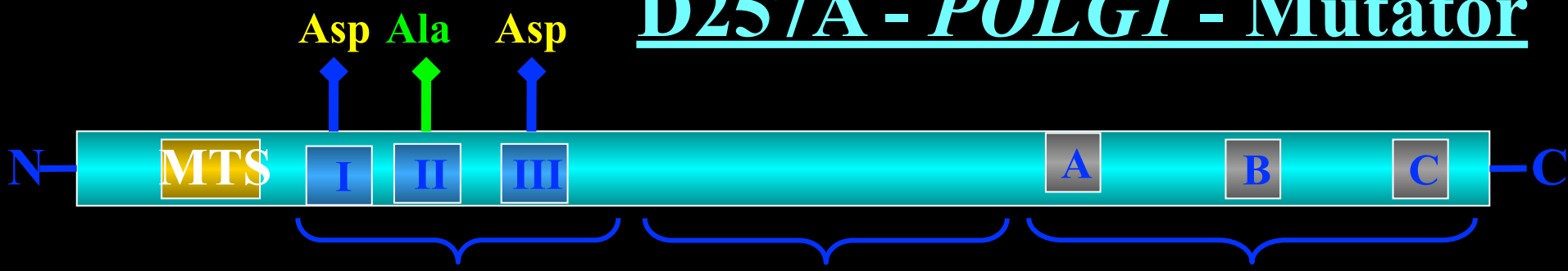
Jeppesen T., et al., *Brain* 129:3402-, 2006

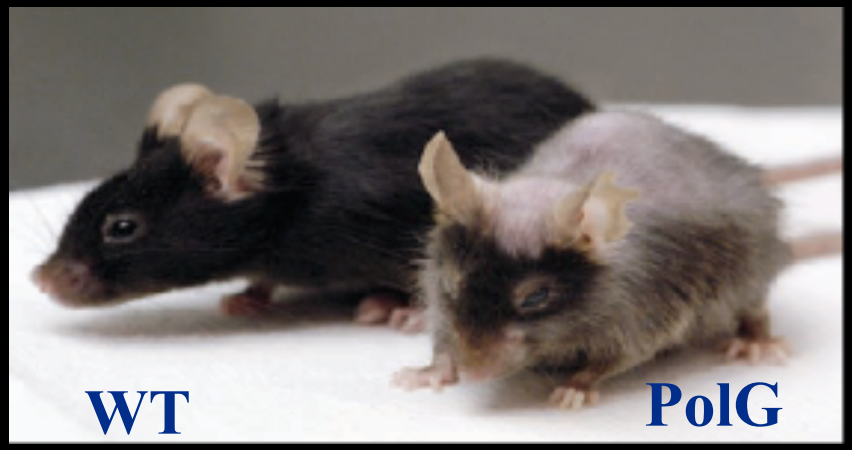
Endurance exercise training

- N = 8 MITO (single deletions).
- 14 weeks cycle training.
- 14 weeks of deconditioning.
- ⬆ sub-max work rate; O_2 extraction; SF-36 (QOL).
- No change in mtDNA content or mutation burden.
- Returned to baseline after 14 weeks.

Taivassalo, et al., *Brain* 129:3391-, 2006

D257A - *POLG1* - Mutator





- ↓ Lifespan
- ↑ Oxidative Stress.
- ↑ Inflammation.
- ↓ Telomeres.

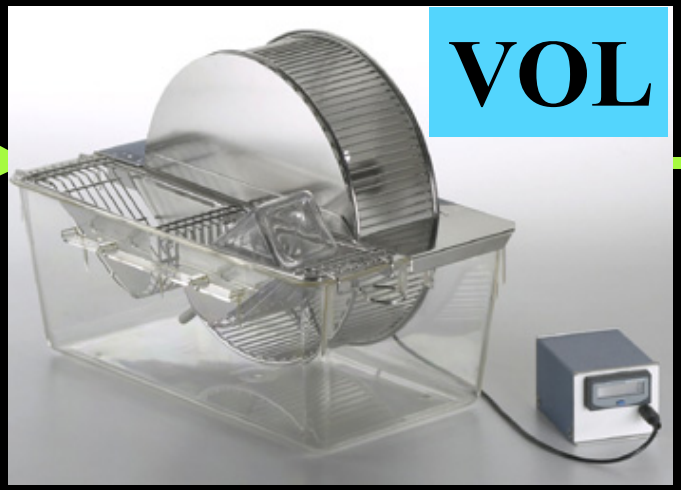
Safdar, A., et al., 2013.
Kauffman, B., et al., 2013.

- ↑ Sarcopenia

Prolla, T., *Science*, 2005.
Larsson, N., *Nature*, 2004

Putting an END to AGING…

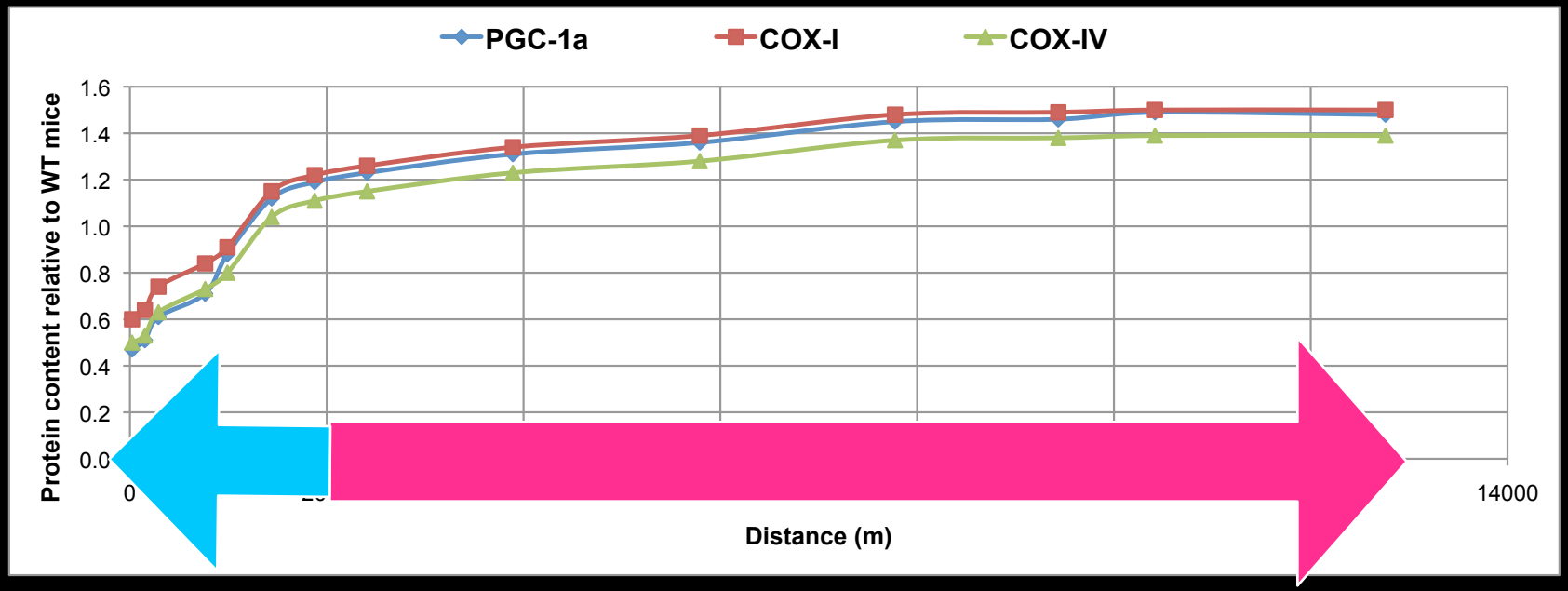
3 Groups of POLG (3 months > 8 months):



SED

Exercise attenuates many aging features.

Voluntary Endurance Exercise - DOSE RESPONSE



Stokl, Safdar et al., 2011 *in preparation*

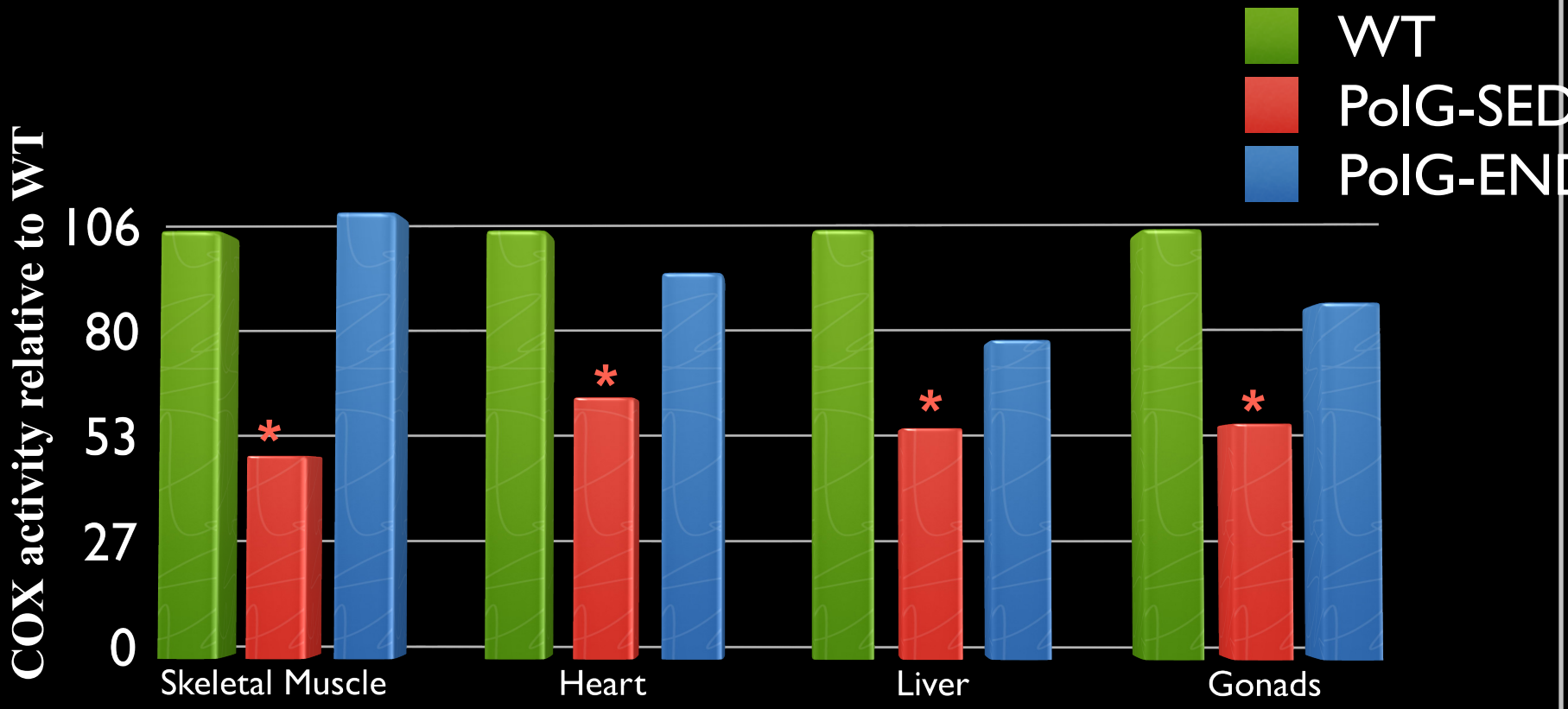
P < 0.05

Voluntary Endurance Exercise - DOSE RESPONSE on Mitochondrial Ultrastructure

Stokl, Safdar et al., 2012 *in preparation*

Magnification: 7,500X

Endurance Exercise Promotes Systemic Mitochondrial COX Activity

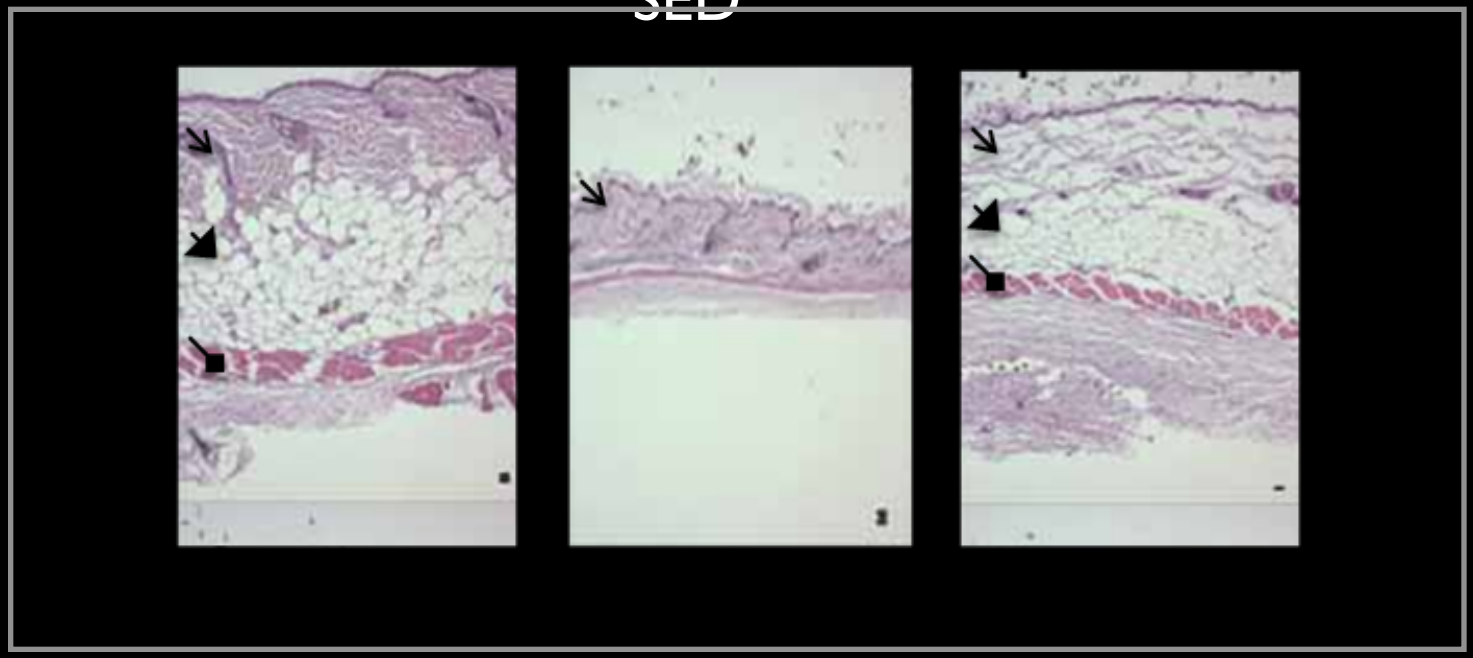


Safdar et al., *PNAS*, 2011.

P <

Endurance Exercise Prevents Skin Histological Alterations

WT | PolG-SED | PolG-END



Safdar et al., *PNAS*, 2011.

$P < 0.05$

Encouraging exercise in children

- Make it fun/play.
- Start slowly and gradually increase intensity.
- Listen to body.
- Mix up different types of exercise (ENDUREX).
- Warm-up/stretch.
- Avoid: fasted, concurrent illness, myalgia.

ENDURANCE

RESISTANCE

Thanks

- The lab:

Dr. A. Safdar

Dr. J. Crane

Dr. L. McNeil

Dr. A. Saleem

Dr. A. Gomez

Dr. M. Akhtar

Dr. M. Nilsson

Dr. D. Ogborn

Mr. B. Hettinga

- Local Collaborators:

Dr. G. Parise

Dr. J. Bourgeois

Dr. M. Gibala

Dr. S. Phillips

Dr. G. Steinberg

Dr. J. Schertzer

- National/ International Collaborators:

Dr. S. Melov

Dr. J. Thompson

Dr. M. Falk

Dr. D. Simon

Dr. A. Hubbard

Dr. B. Kaufmann

Dr. K. Khrapko

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