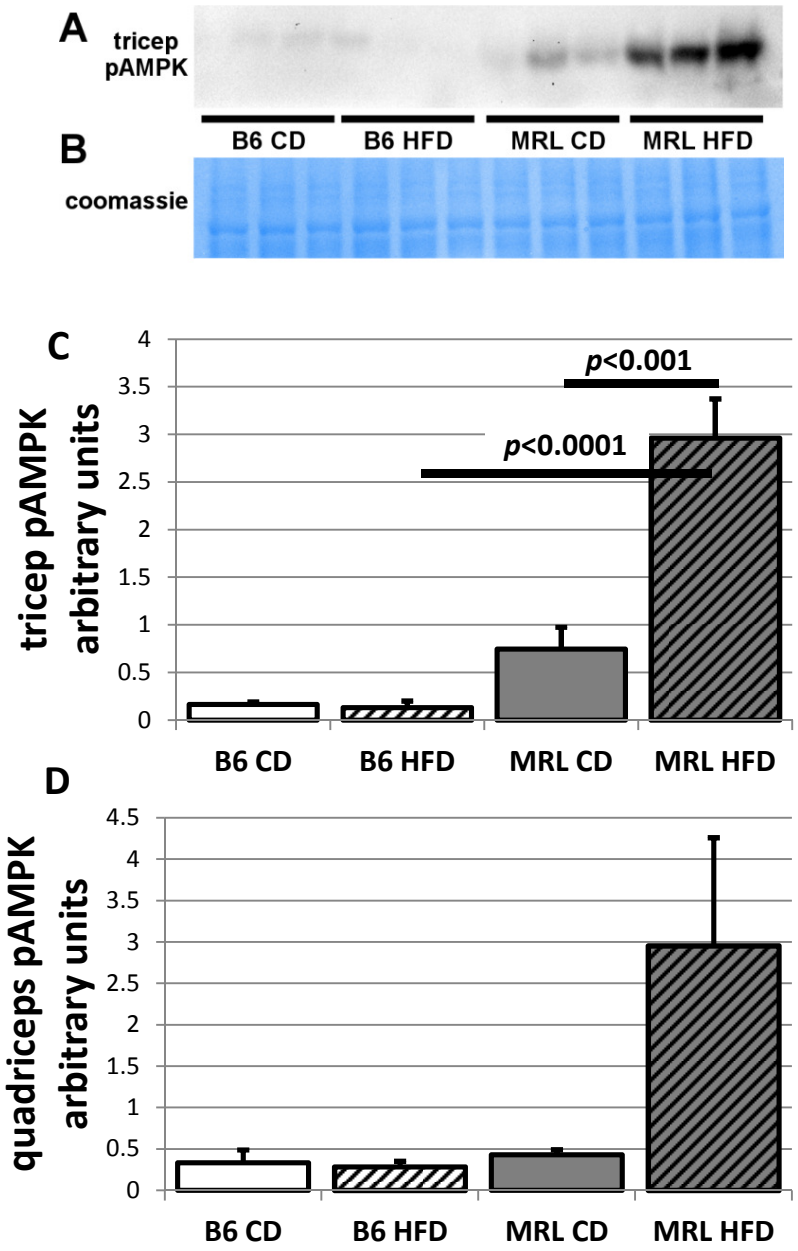
The MRL mouse strain is naturally resistant to high fat diet-induced hyperglycemia

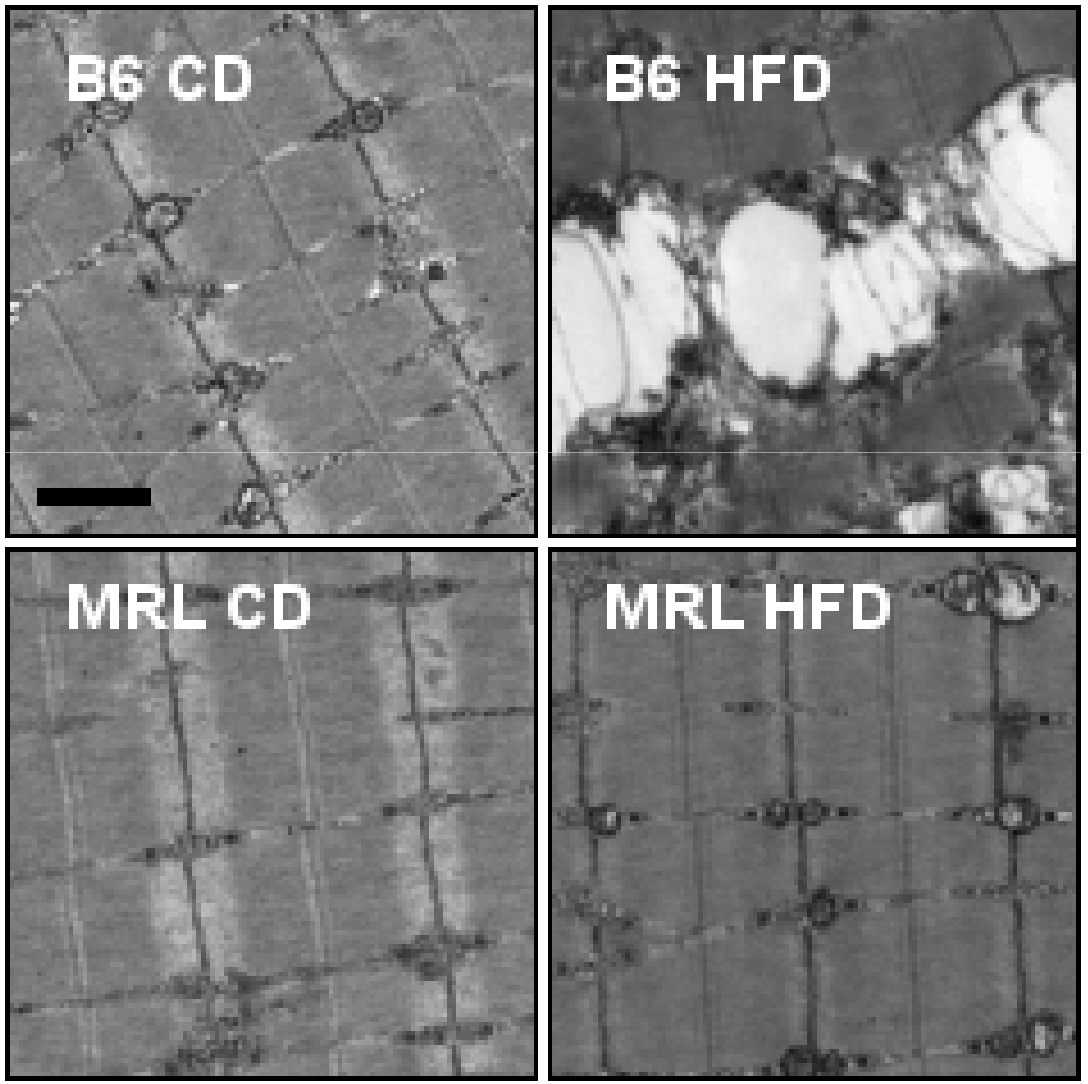
Ahlke Heydemann
University of Illinois at Chicago
Physiology and Biophysics
ahlkeh@uic.edu

pAMPK quantitation of 6 hour fasted animals

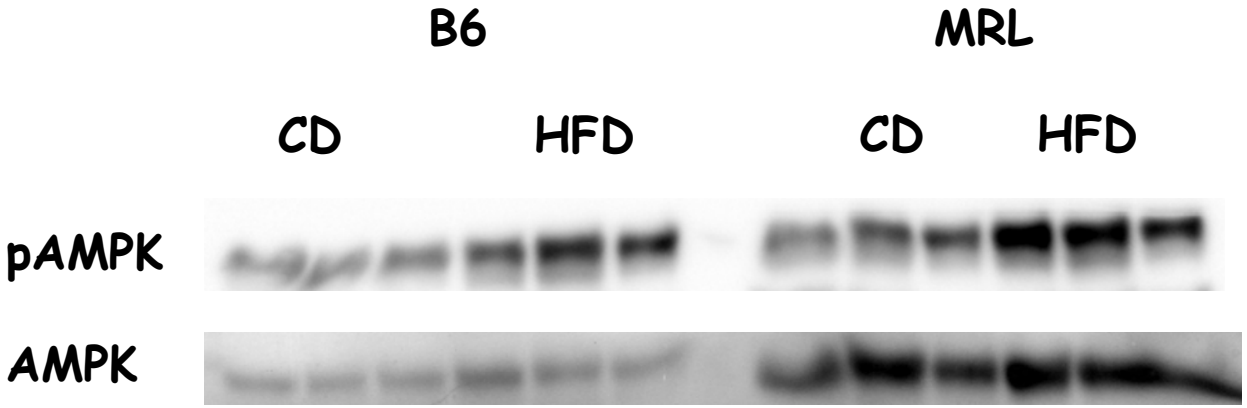


Mull, 2014

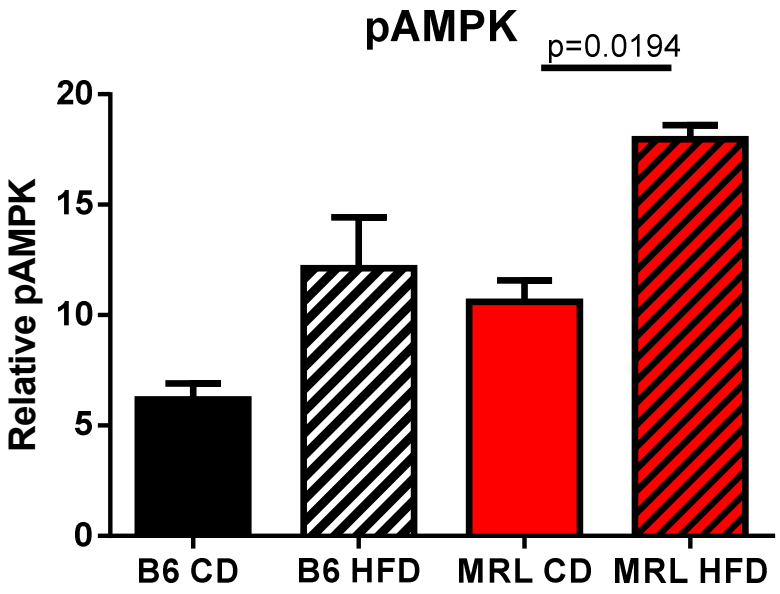
Quadriceps Tissue

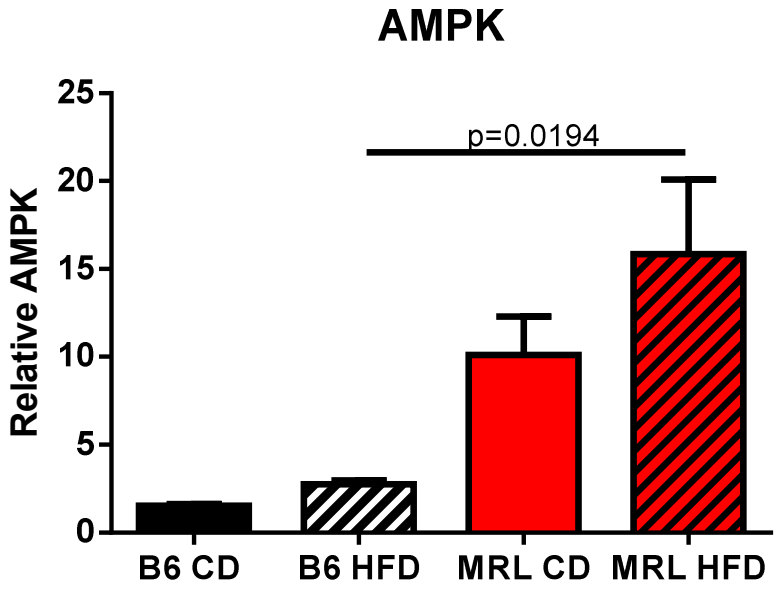


Mull, 2014



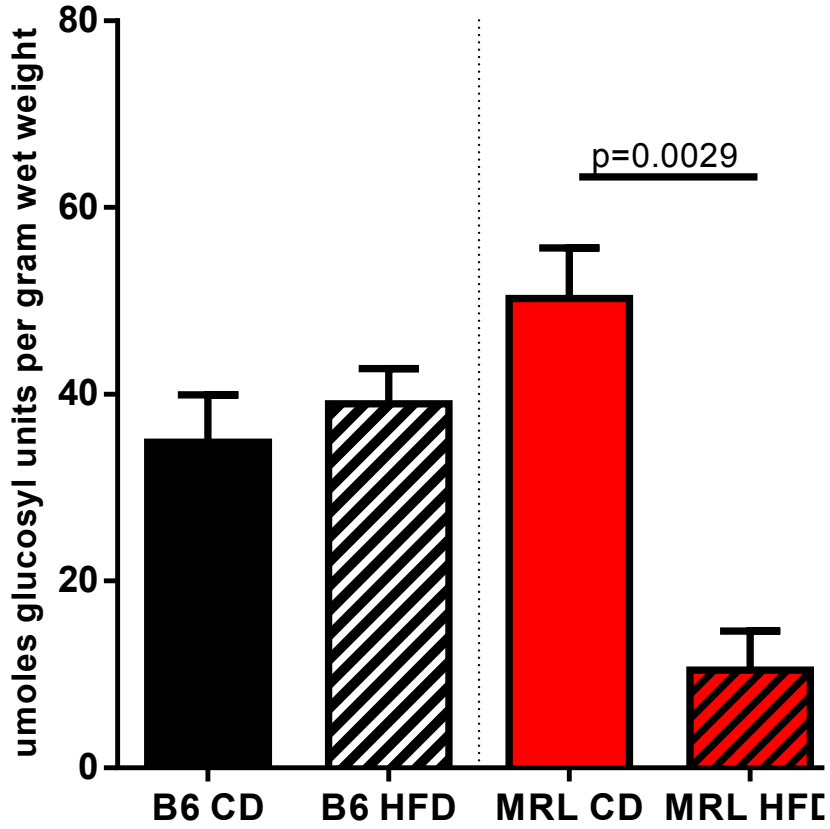
Liver tissue of 6 hour fasted animals at end of 12 week diets



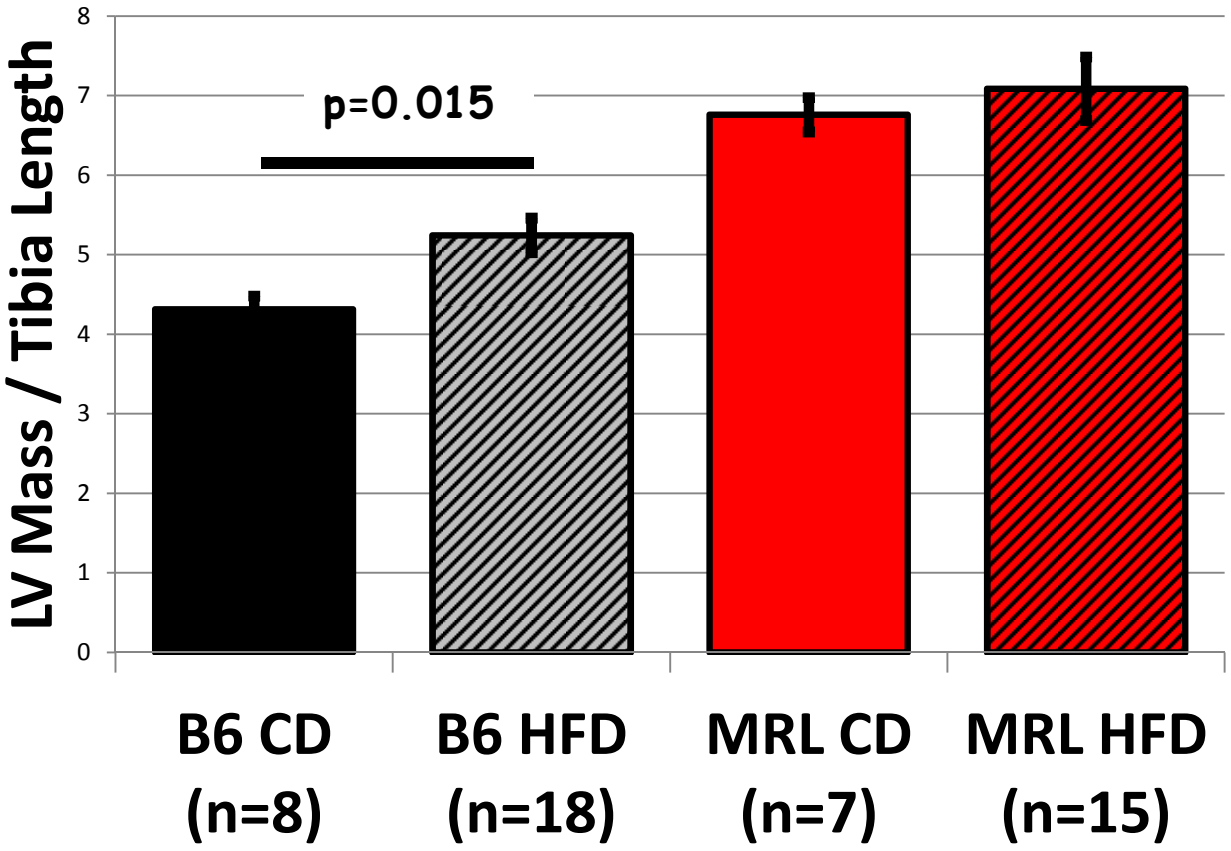


Liver Glycogen Assay

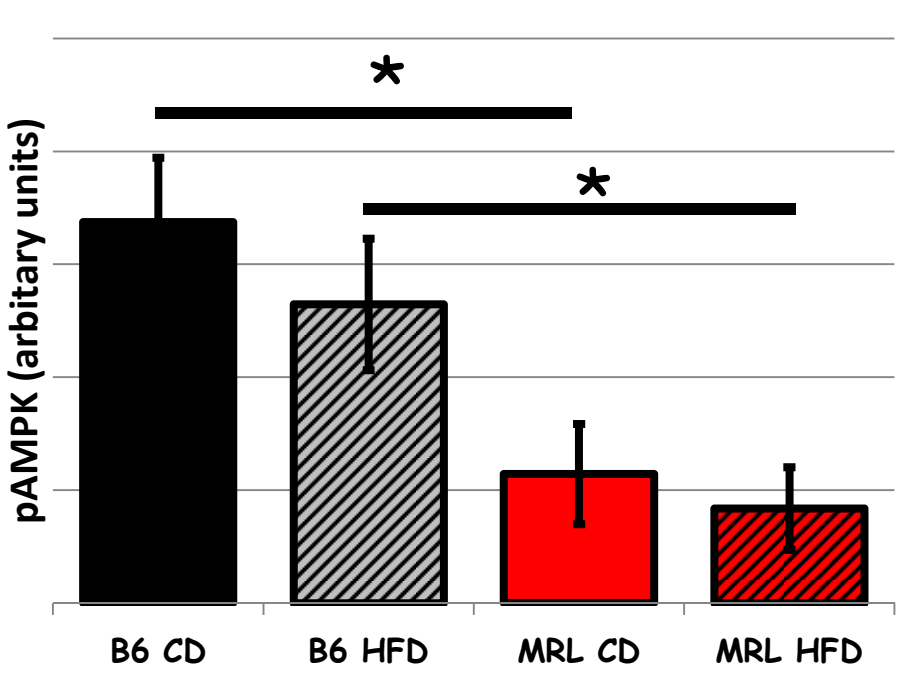
after 12 week diet, 6 hour fast

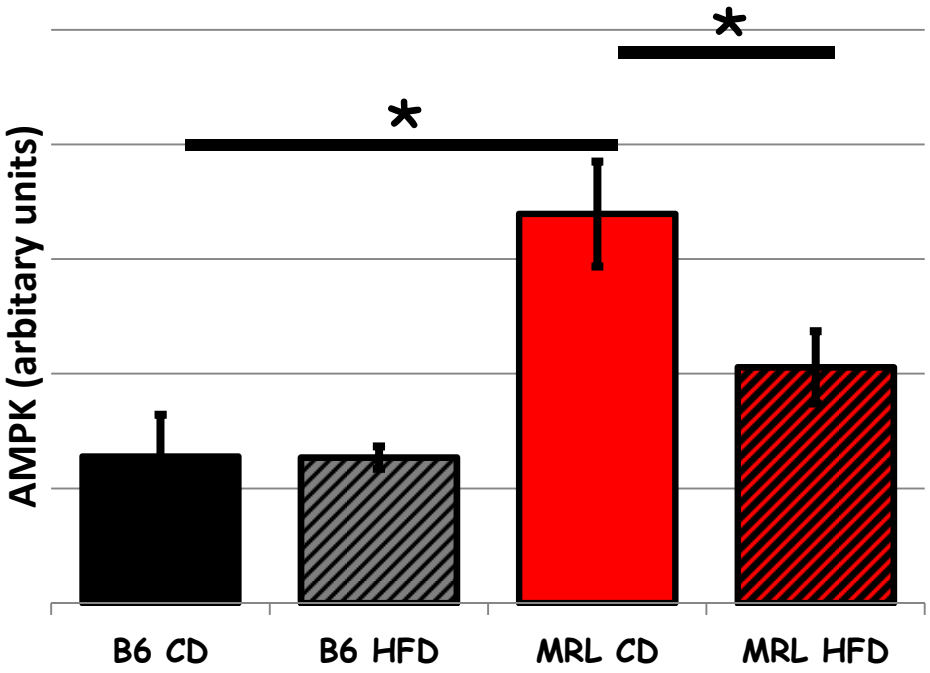


Heart size


LV Mass / Tibia Length
8
7
6
5
4
3
2
1
0
p=0.015
B6 CD
(n=8)
B6 HFD
(n=18)
MRL CD
(n=7)
MRL HFD
(n=15)

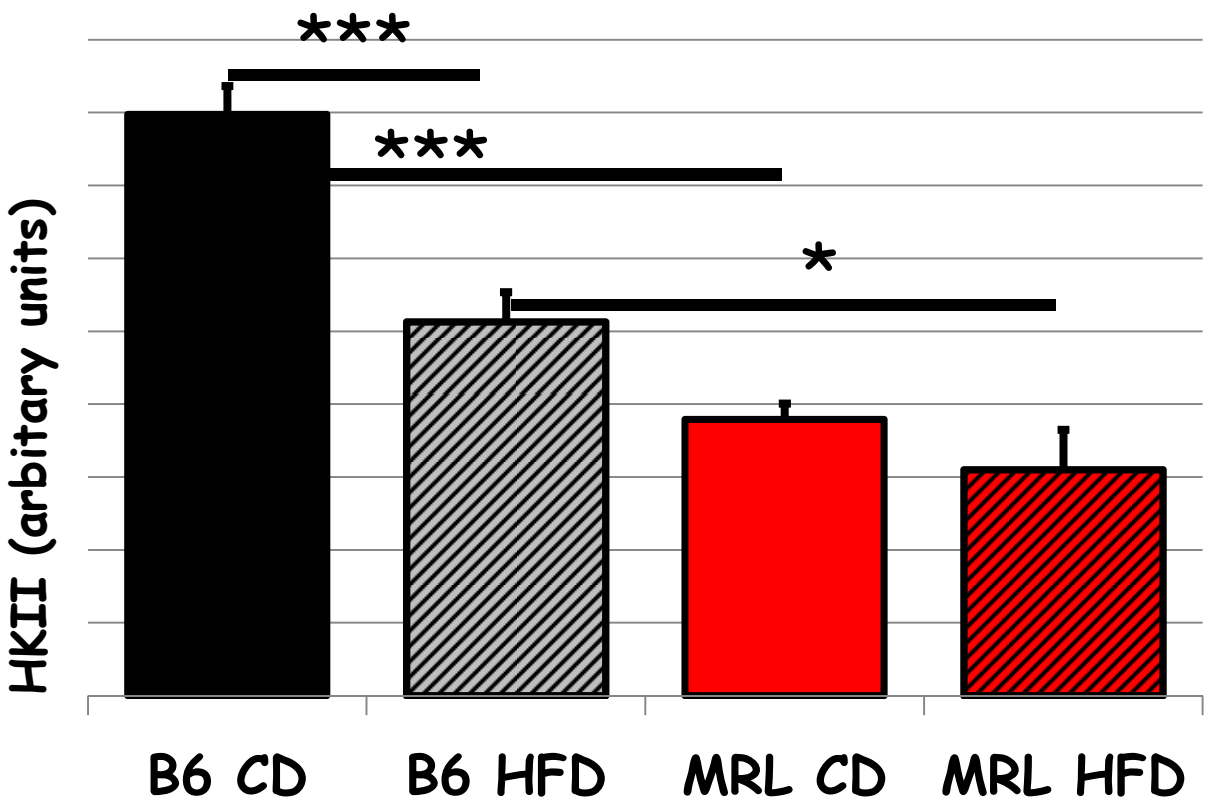
Cardiac: pAMPK comparison (n=9)





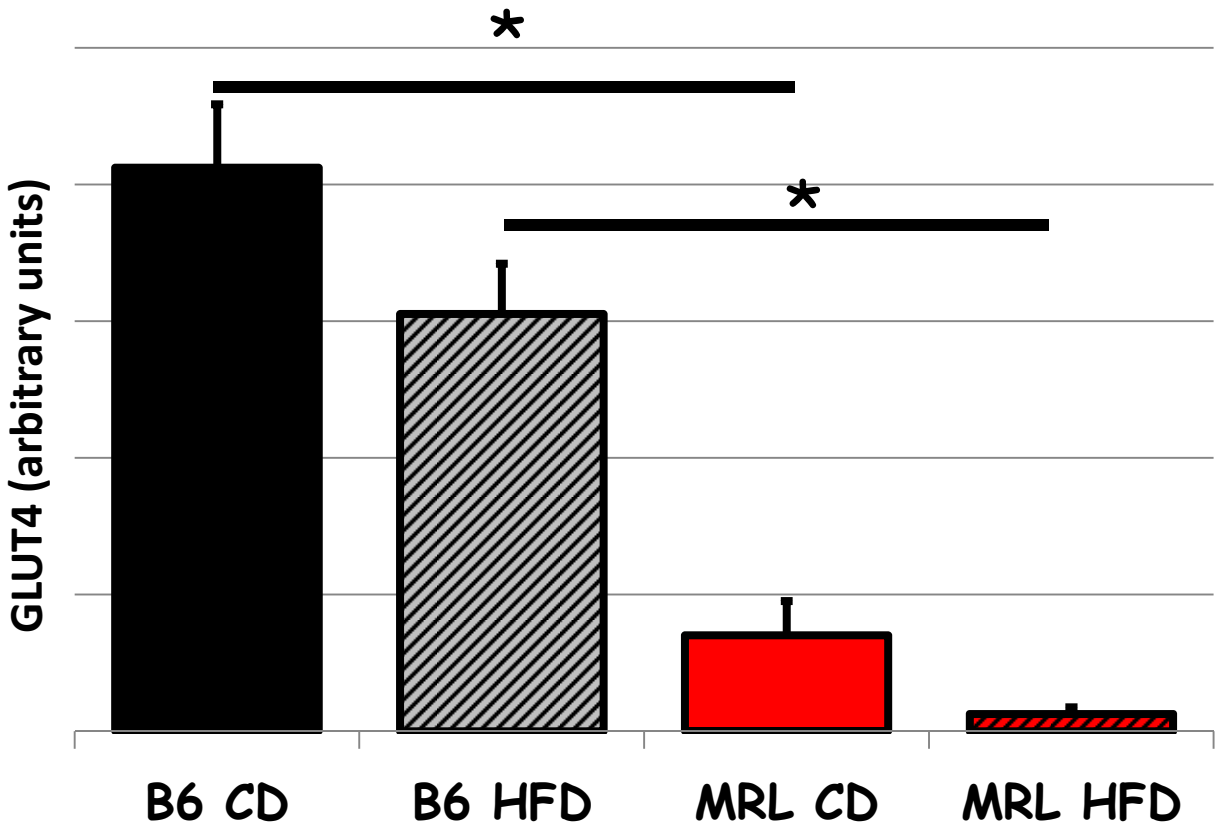
* $p<0.05$

Cardiac; HKII comparison (n=6)



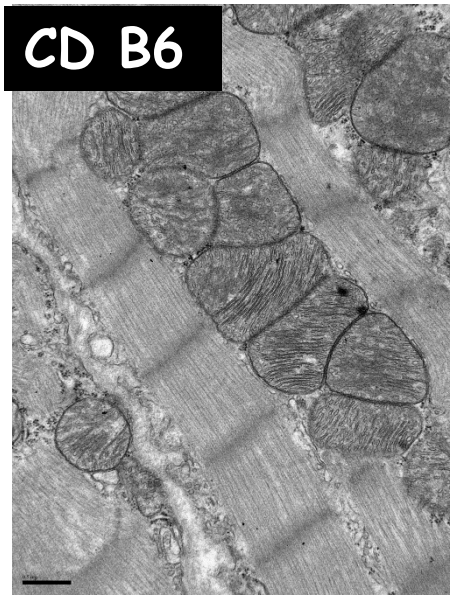
* $p<0.05$, *** $p<0.0005$

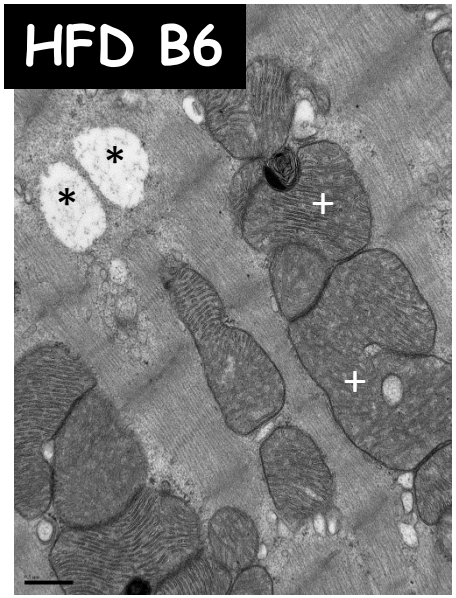
Cardiac; Glut 4 comparison (n=3)

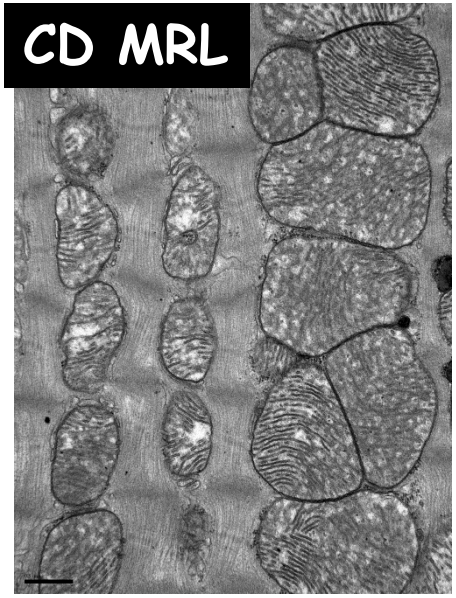


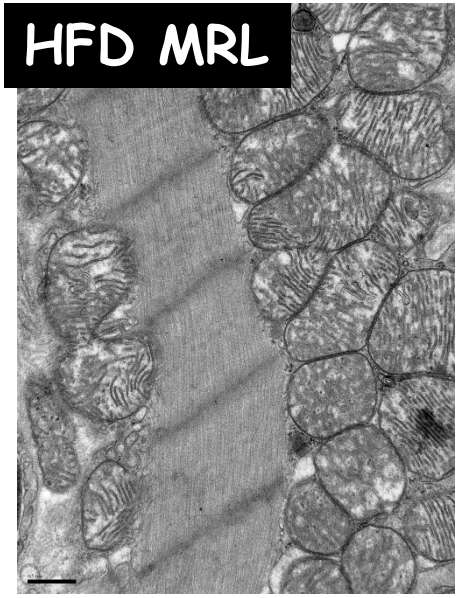
* $p<0.05$

Heart





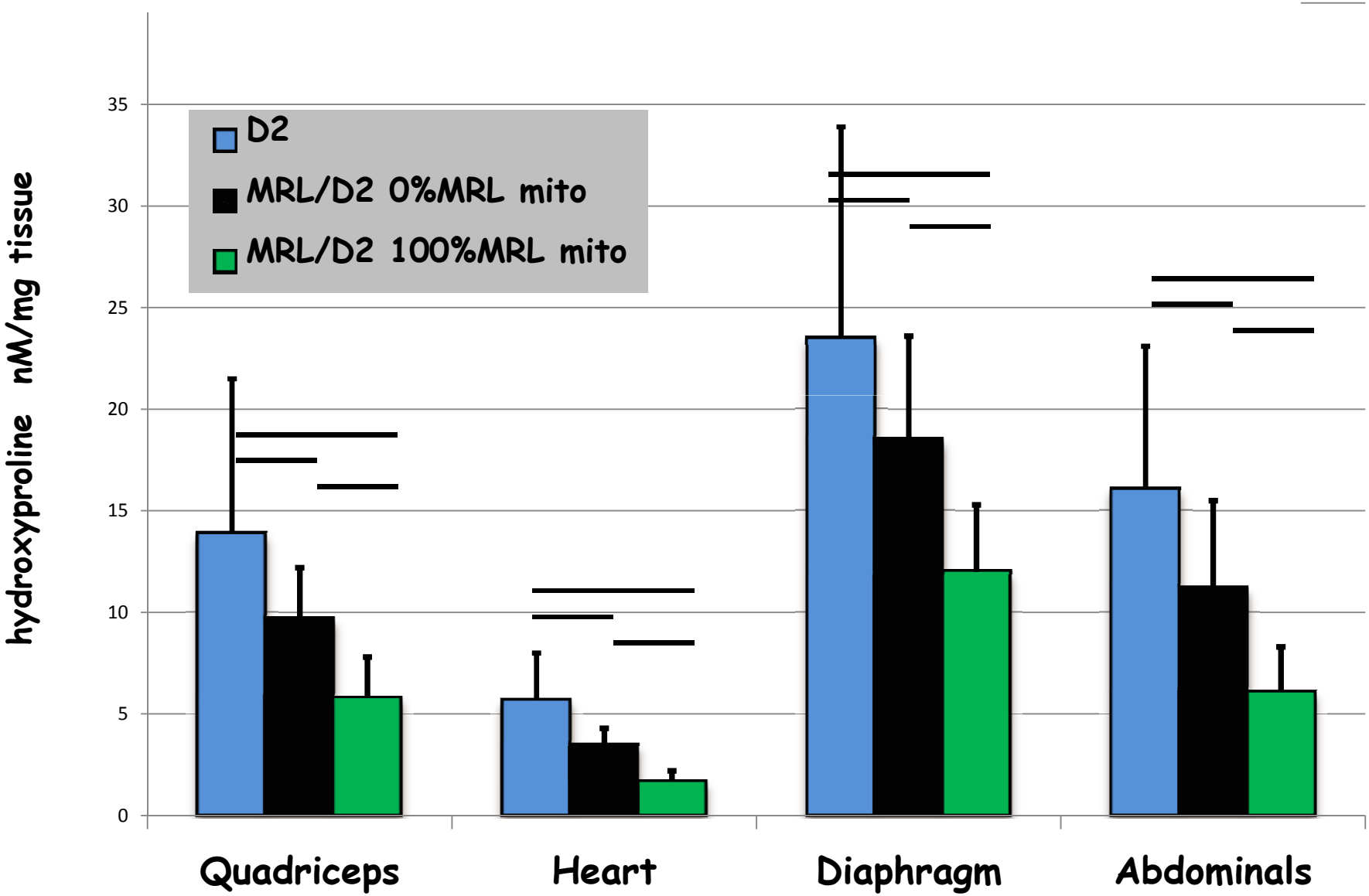




MRL mitochondrial heteroplasmies

- One mitochondria and cell containing more than one mitochondrial genome.
- MRL mice have 2; T3900C and an adenine tract length insert (Sachydyn 2008).
  - MRL cytosine at 3900
  - MRL more than 8 adenines in the tract
- Inherited from the mother
- Inherited independently
- Polymorphisms in $tRNA^{Met}$ and $tRNA^{Arg}$

Muscular dystrophy fibrosis



	Male		Female
P1	D Sgcg-/-	x	MRL
F1	$nuc^{M50D50}mito^{M}$, Sgcg+/-	x	MRL
N1	**$nuc^{M75D25}mito^{M}$**, Sgcg+/-)^2	x	MRL
N2	$nuc^{M88D12}mito^{M}$, Sgcg+/-	x	MRL
N3	$nuc^{M94D6}mito^{M}$, Sgcg+/-	x	MRL
N4	(**$nuc^{M97D3}mito^{M}$**, Sgcg+/-)^2	x	MRL

Current and future plans

Four pure-breeding resultant mouse lines;

$nuc^{M}mito^{M}$ Sgcg +/-

$nuc^{M}mito^{D}$ Sgcg +/-

$nuc^{D}mito^{M}$ Sgcg +/-

$nuc^{D}mito^{D}$ Sgcg +/-

Early generation sib-crosses

wild type mice;
- ear wound healing (2mm ear punch)

HFD, metabolic profile *

Sgcg-/- mice;
- Muscular Dystrophy panel *

* genome wide association studies with mitochondrial content as a covariate

Late generation sib-crosses

wild type mice;
- ear wound healing
- HFD, metabolic profile

Sgcg-/- mice;
- Muscular Dystrophy panel

University of Illinois at Chicago
UIC

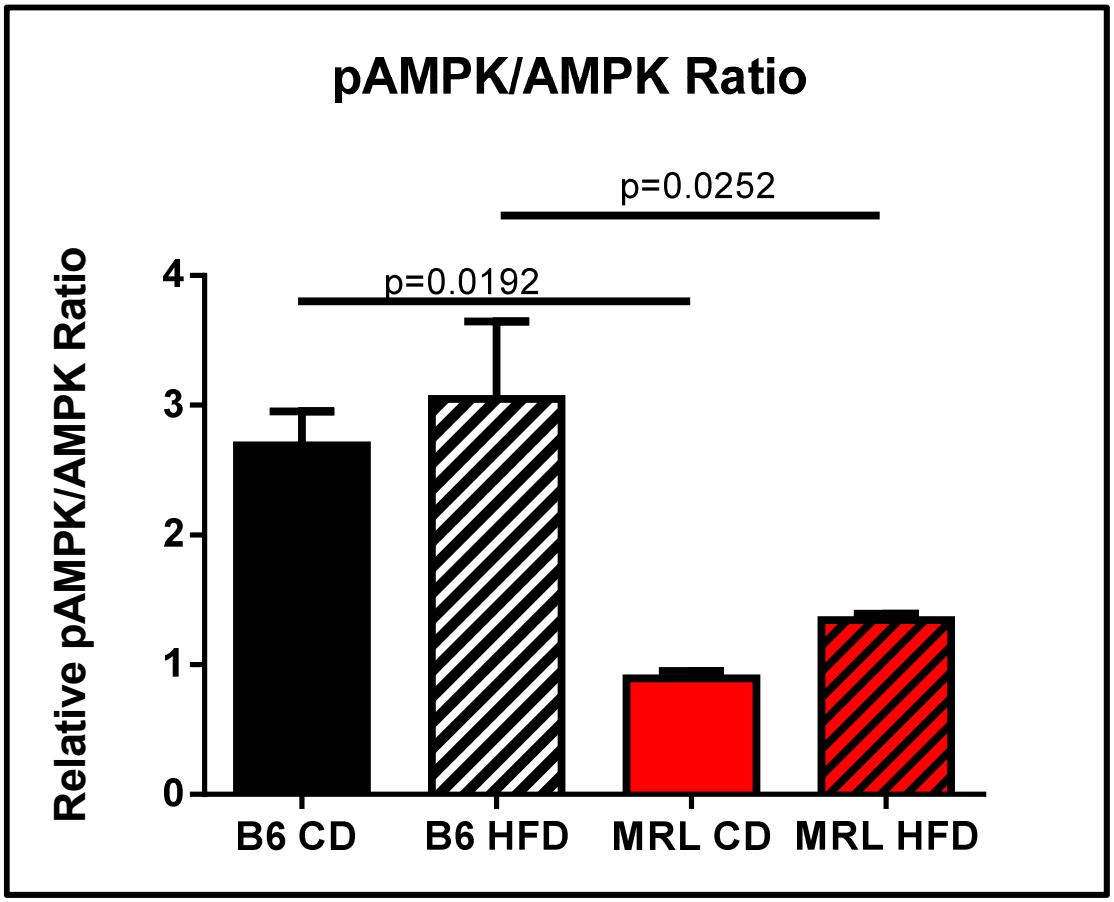
CCVR

Conclusions

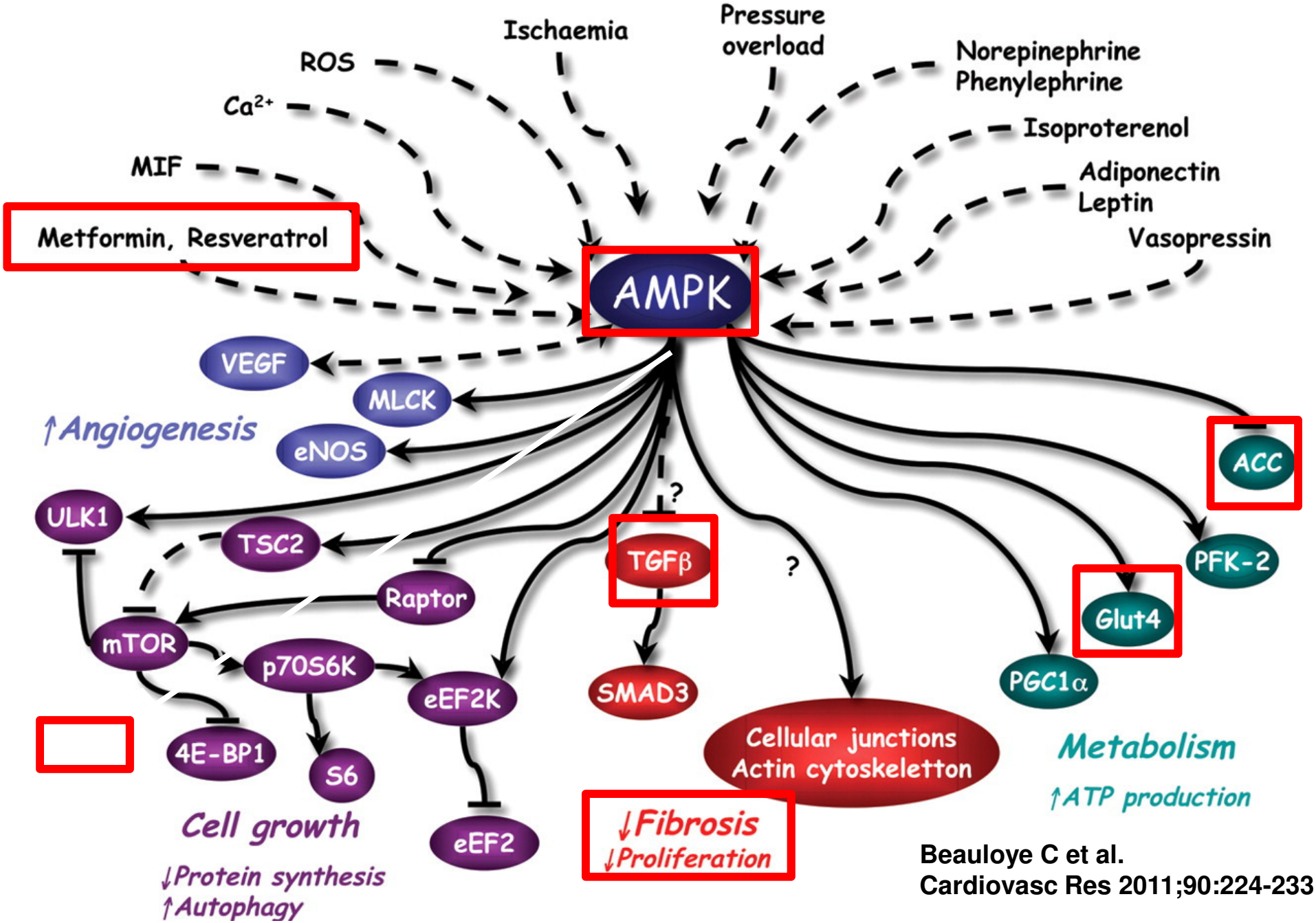
Wild type MRL mice can heal ear wounds, heal cardiac cryo-injuries, resist muscular dystrophy-mediated fibrosis, resist high fat diet-mediated type 2 diabetes.

Multiple pieces of data indicate MRL-introduced mitochondrial heteroplasmies beneficially alter metabolism.

Tirsit K. Berhanu
Nathan W. Roberts
Aaron J. Mull
Jenan Holley-Cuthrell
Magdalis Vega-Gonsalez


pAMPK/AMPK Ratio
p=0.0252
p=0.0192
Relative pAMPK/AMPK Ratio
4
3
2
1
0
B6 CD
B6 HFD
MRL CD
MRL HFD

Upstream stimulatory factors and downstream targets of AMPK in the heart.



Beauloye C et al.
Cardiovasc Res 2011;90:224-233