

- Note that the opinions expressed within the abstracts and presentations are those of the authors/presenters alone and do not necessarily reflect the opinions of WADA.

PPAR δ and the Creation of the Marathon Mouse

Gene Doping Symposium--WADA
Karolinska Institute, Stockholm
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What are PPARs?

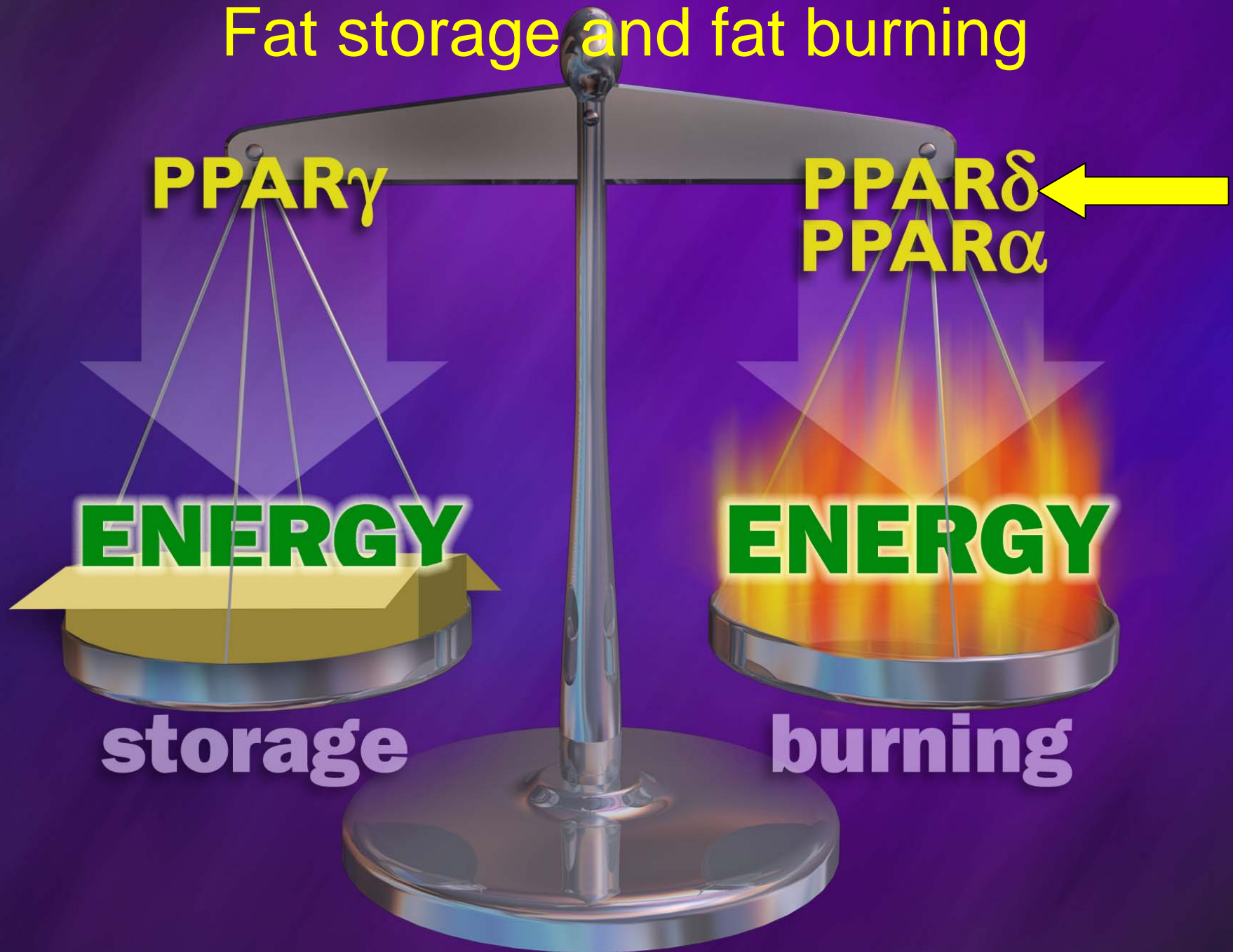
The PPARs (peroxisome proliferator-activator receptors) comprise a set of three related nuclear hormone receptors (PPAR α , γ & δ) that control broad aspects of lipid metabolism.

They are expressed in different tissues and are naturally activated by a variety of dietary and endogenous long chain fatty acids (FFAs).

PPAR γ promotes fat storage

PPAR δ promotes fat burning in muscle and other tissues

Fat storage and fat burning



Revving Up Metabolism

PPAR δ



synthetic
ligand
GW1516

The PPAR δ Marathon Mouse

The PPAR δ Marathon Mouse

A strain of mice was engineered to express an activated PPAR δ transgene (termed **VP-PPAR δ**) in their skeletal muscle. The strain is viable, fertile and overtly normal.

Muscling in on endurance



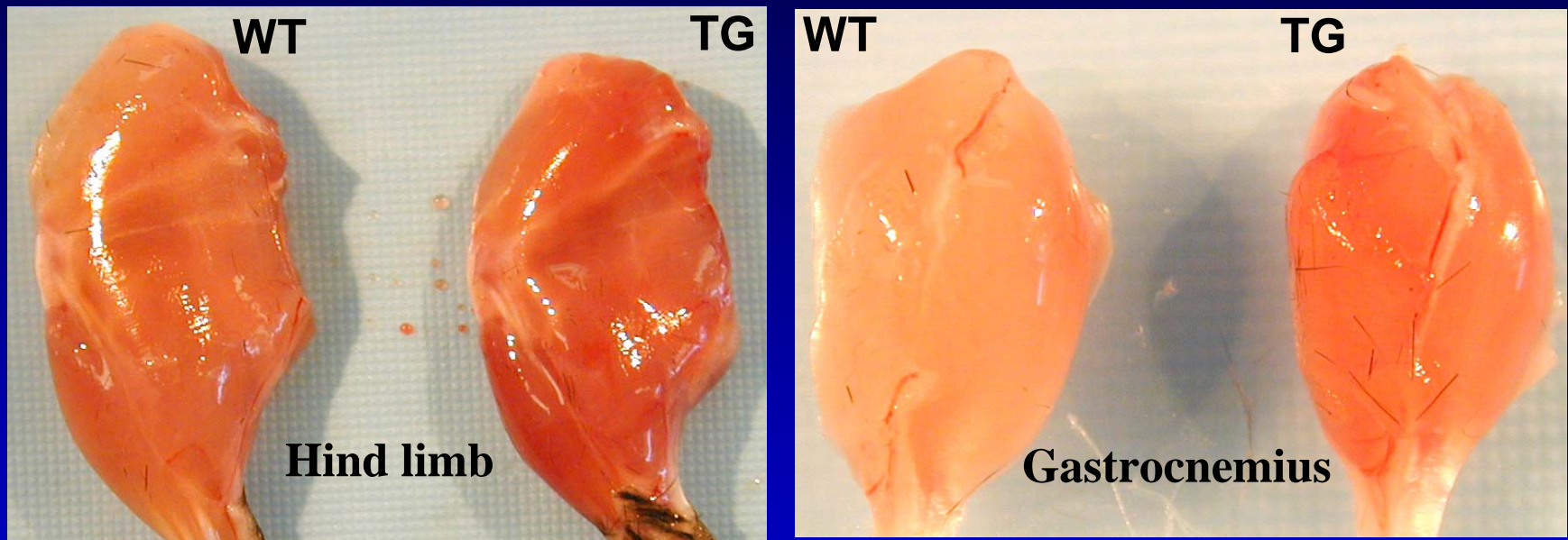
Muscling in on endurance



Or.....

We will also treat wild type (i.e. normal) littermates with the orally active PPAR δ specific drugGW 1516

Red Muscle Increased in Transgenic Mice

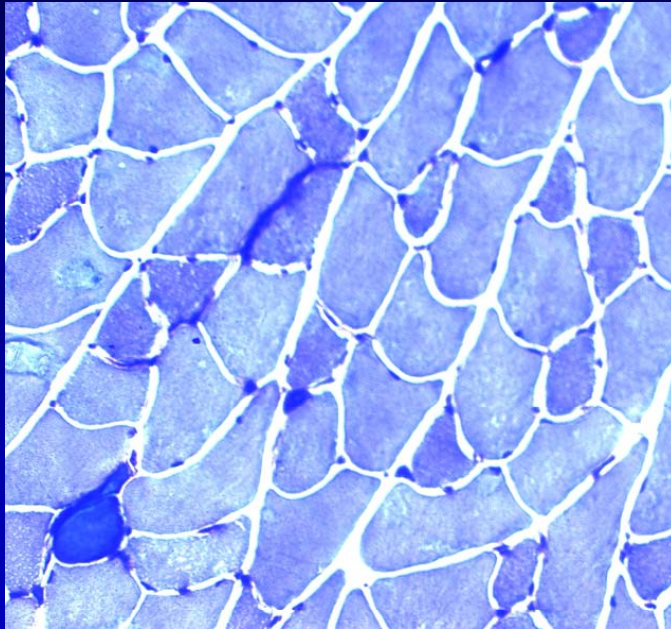


pink - glycolytic
fast twitch type II
rapid fatigue

color change - ?shift to
slow twitch, myosin-rich
non-fatiguing fibers

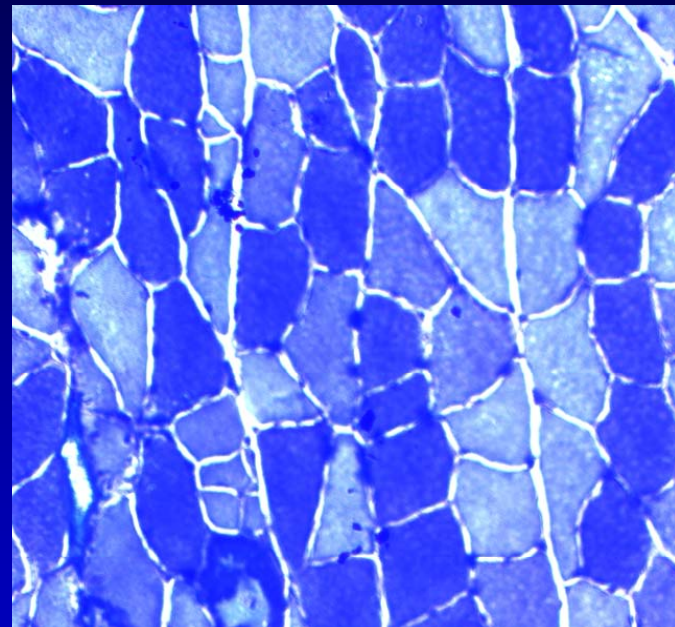
ATPase staining - PPAR δ promotes formation of Type I Fibers in Type II Muscle

WT
Fast



(Burns sugar)

TG
Slow



(Burns Fat)

Activation of mitochondrial genes associated with oxidative phosphorylation



A

better

B

worse

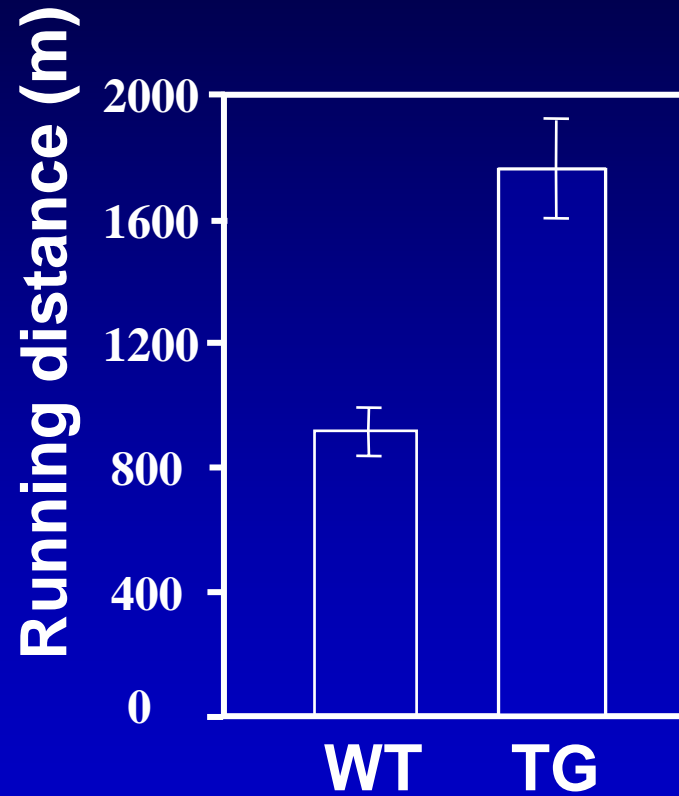
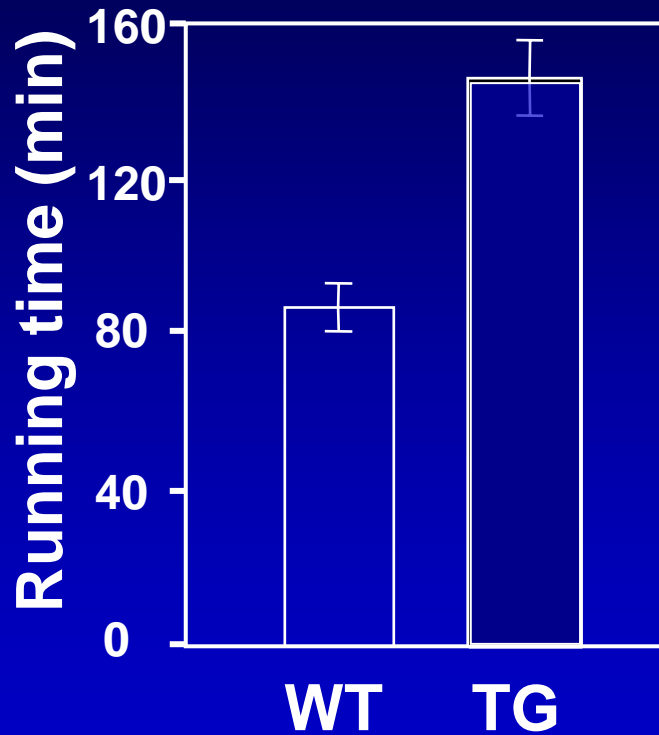
C

same

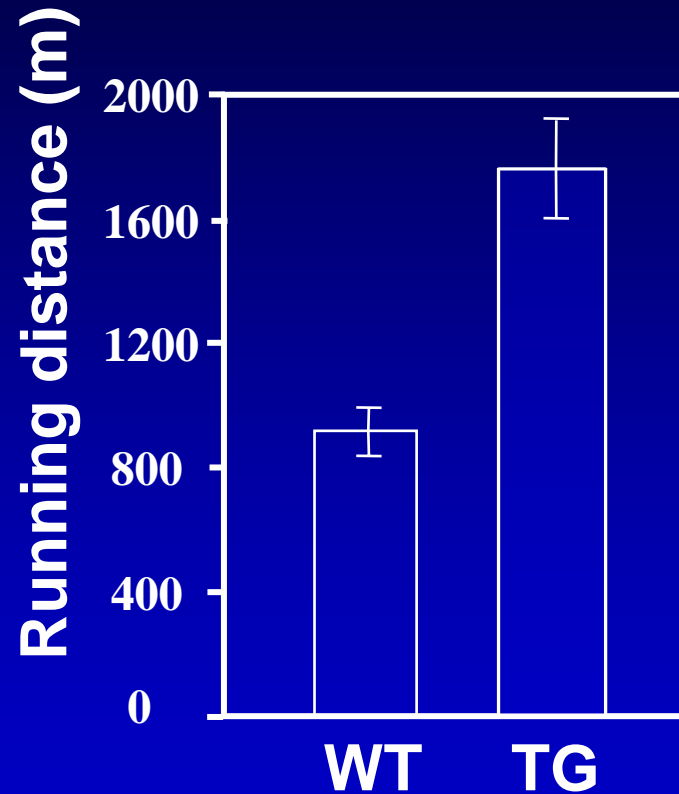
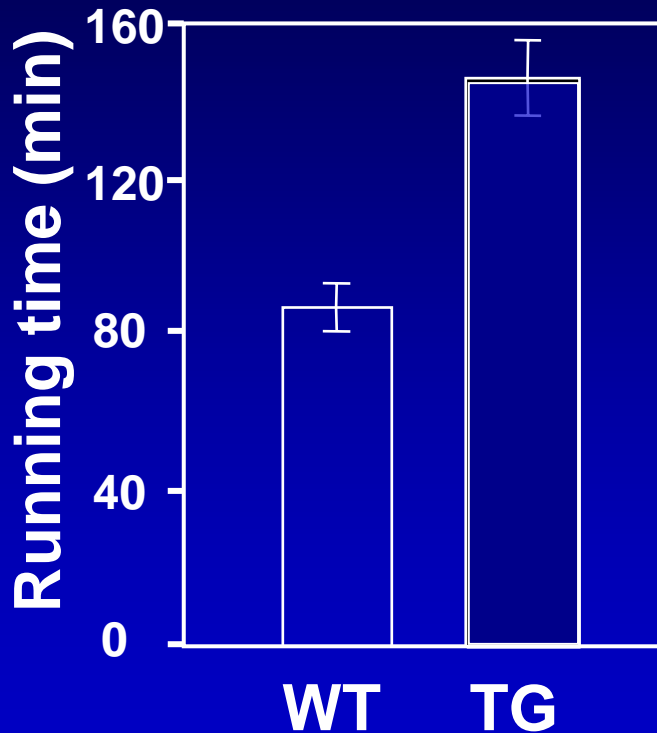
QuickTime™ and a
Sorenson Video 3 decompressor
are needed to see this picture.

Marathon Mouse treadmill challenge

Improved Exercise Performance in Transgenic Mice

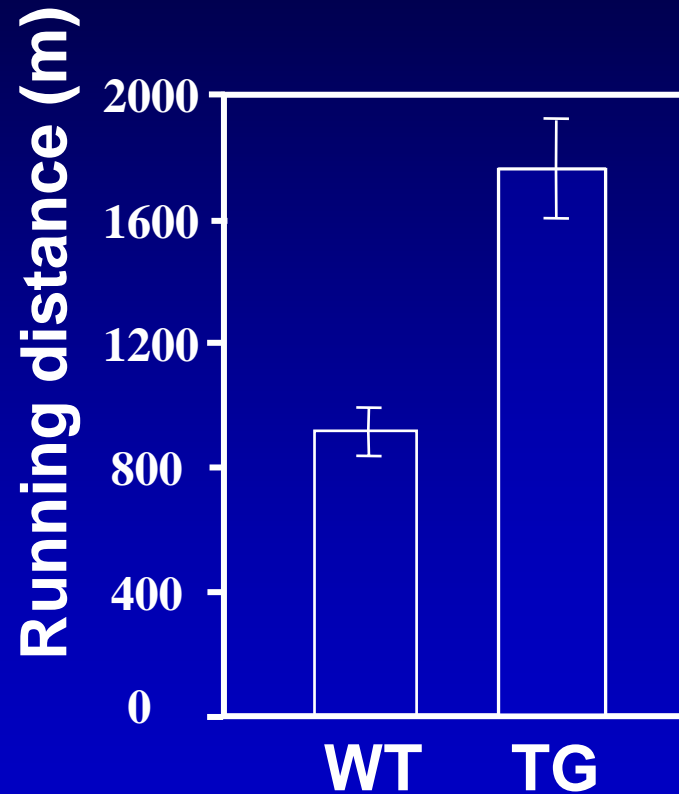
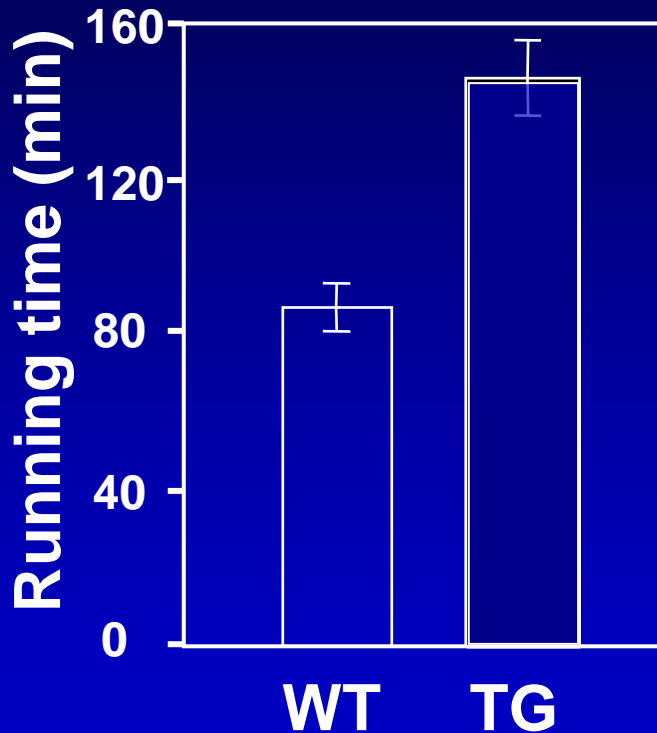


Improved Exercise Performance in Transgenic Mice



What about PPAR δ null mice?

Improved Exercise Performance in Transgenic Mice



Total running time only 20 min !

Under study - does GW1516
enhance performance in mice?

The Future



will there be a magic pill?

Clinical Applications

muscle wasting diseases

weight loss mechanisms related to
increased oxidative metabolism

Opportunity for abuse

inquiries from athletes, coaches, a
horse trainer

Some Conclusions

- **PPAR δ directed metabolic changes produces a mouse with a long distance running phenotype**
- **It is possible to alter a single component of a complex system (i.e. muscle fiber energy burning) to entrain the rest of a physiologic network.**
- **Genetically produced “delta” muscle fibers confer high performance even in the absence of exercise**
- **Exercise physiology can be predictively manipulated**
- **The PPAR δ receptor and its drugs are clear targets of potential athletic abuse**

**The work on the Marathon Mouse was
Lead by Yongxu Wang
Now “running” his own lab at U Mass**

**Thank You All!!!!
and sorry I was unable to join you**