

A Circuitry that Drives Ventricular Maturation

Daniel P. Kelly, M.D.



Disclosures

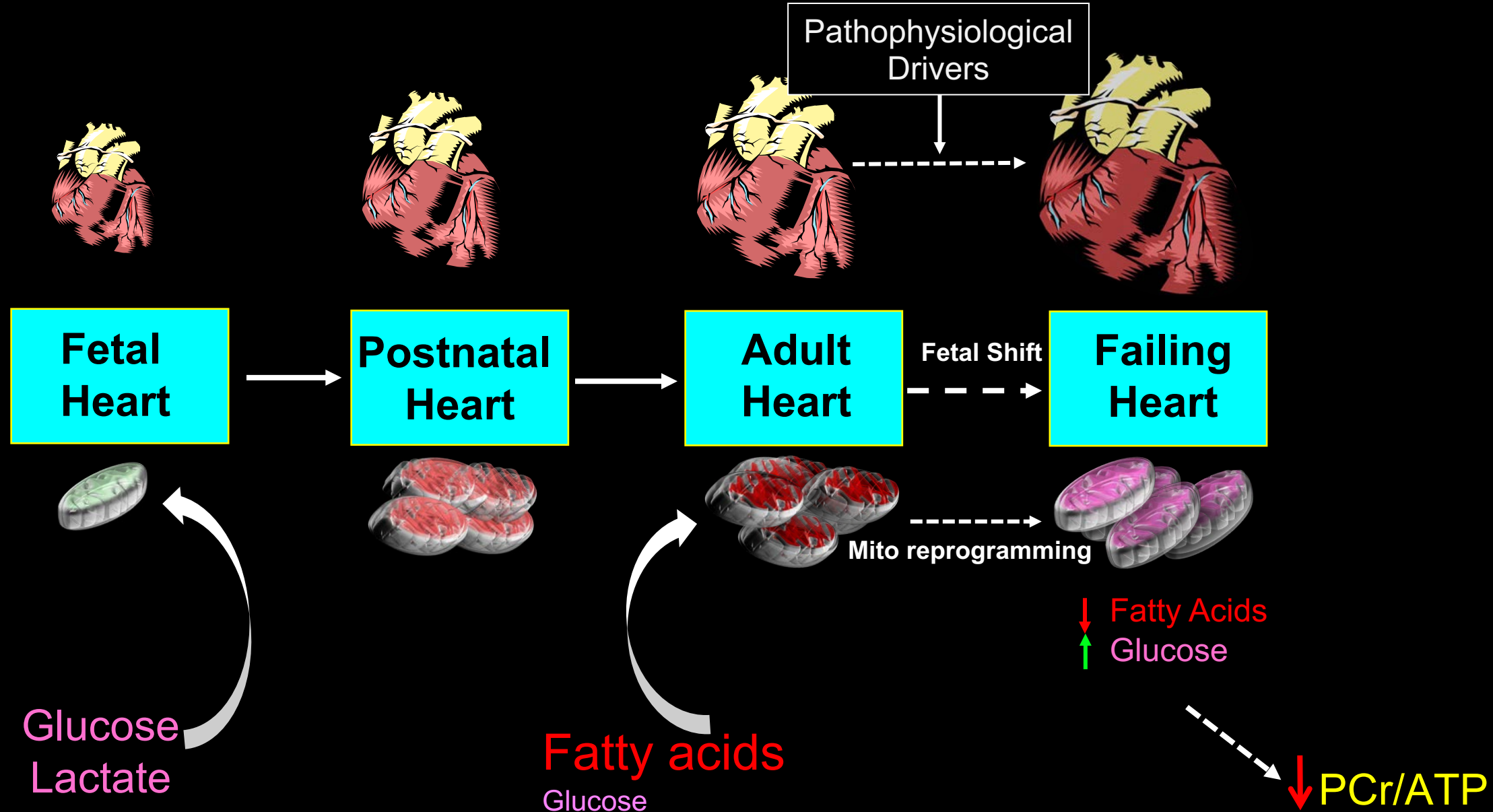
Scientific Advisory Boards/Consultant:

- Pfizer
- Amgen
- GSK
- BMS

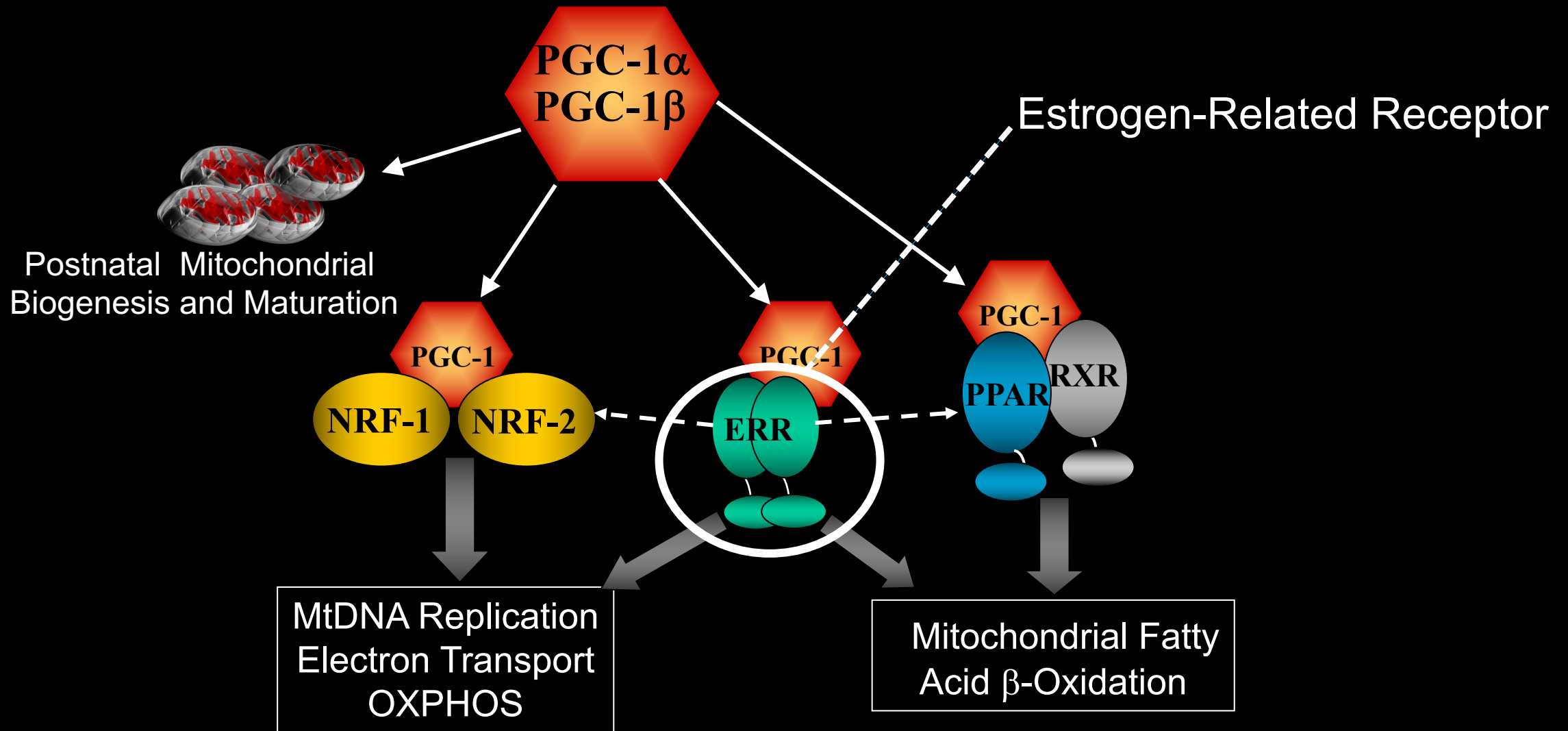
Research Support:

- Amgen
- Pfizer

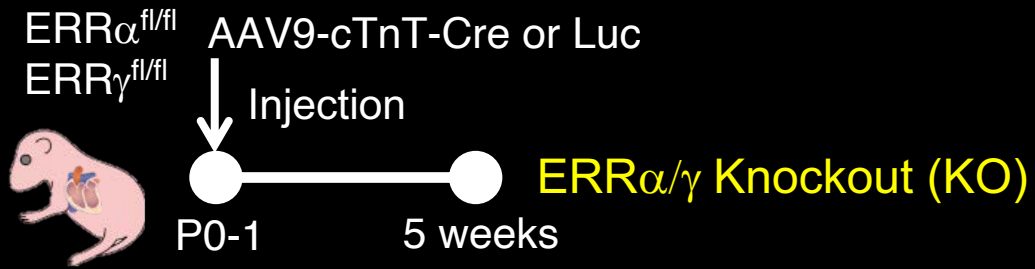
Mitochondrial Maturation and Re-programming in the Developing and Failing Heart



Building and Programming Cardiac Mitochondria: The PPAR γ Coactivator 1 (PGC-1)-Nuclear Receptor Transcriptional Regulatory Cascade

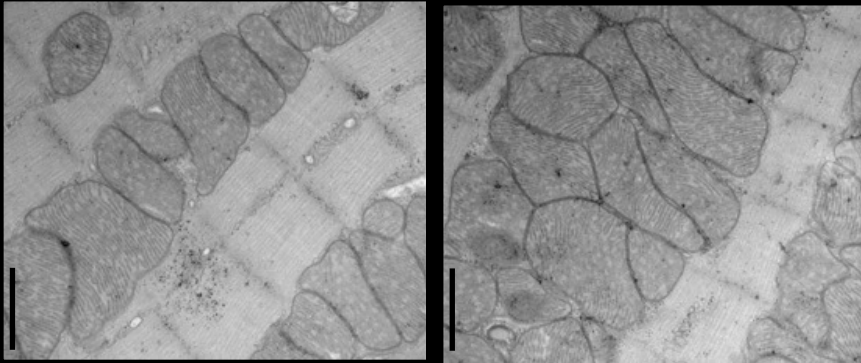


Postnatal Cardiac $ERR\alpha/\gamma$ Deficiency Results in Cardiomyopathy with Mitochondrial Abnormalities and Ventricular Non-Compaction Phenotype

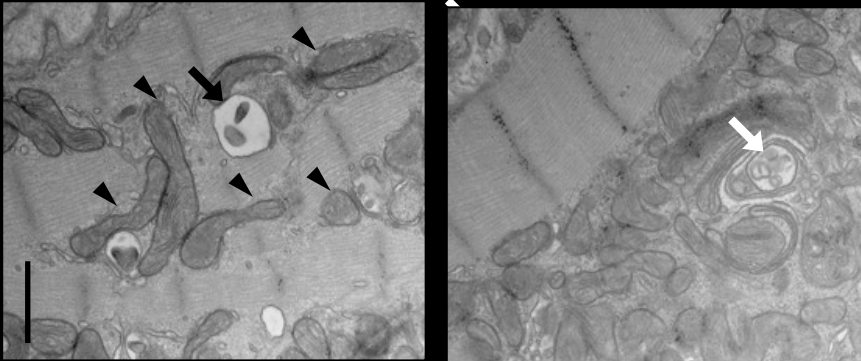


Mitochondrial Abnormalities

WT

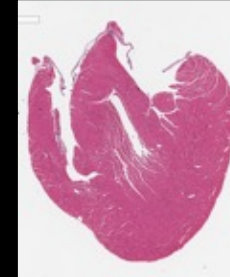


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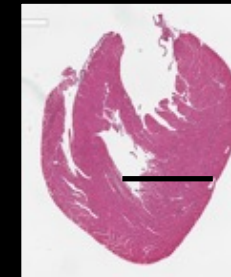


Dilated Cardiomyopathy

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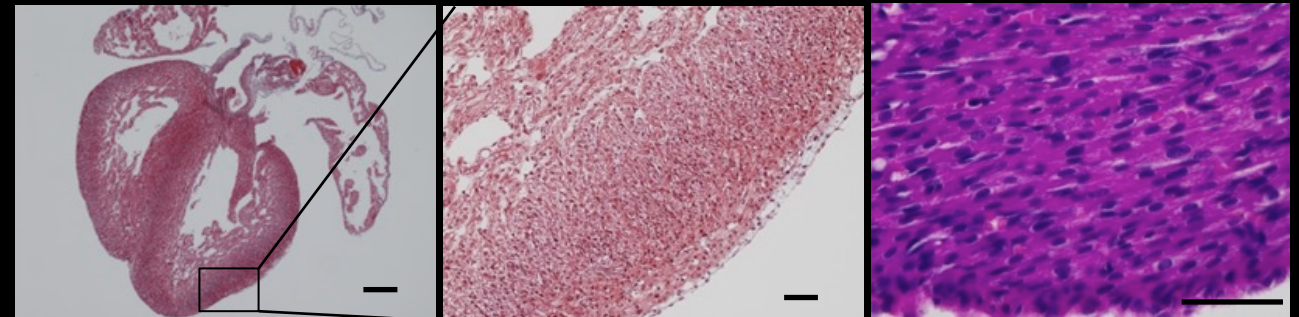


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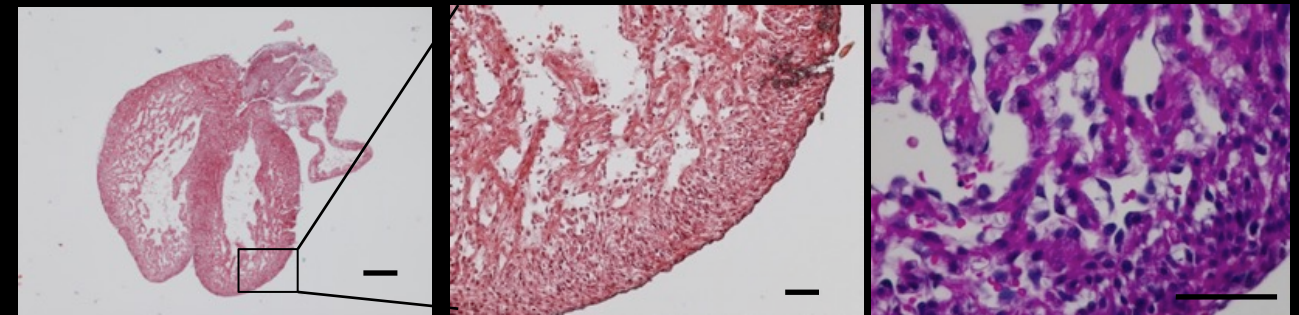


Ventricular Non-compaction

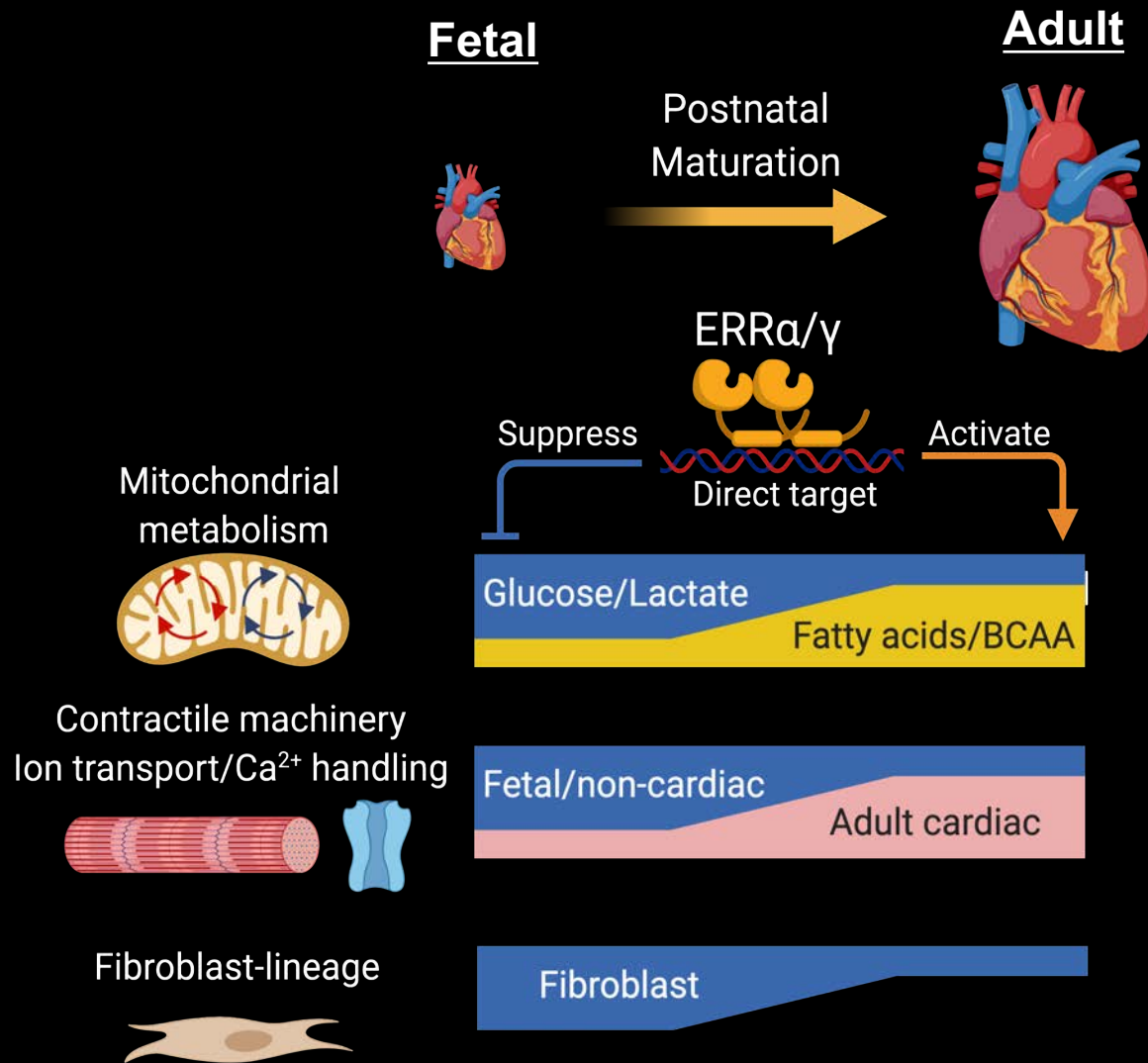
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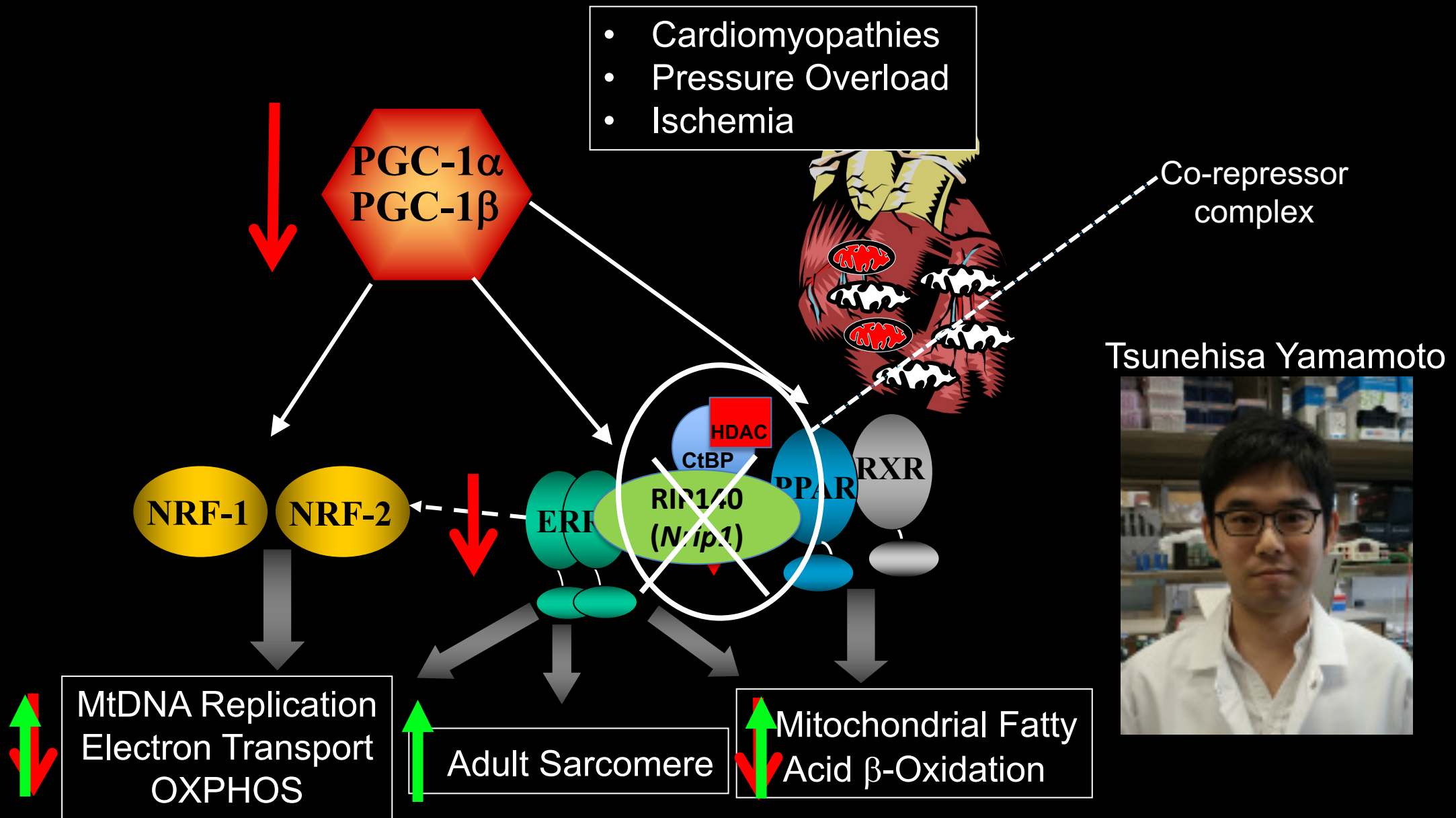


Estrogen-related Receptors (ERRs) Serve as Master Regulators of Cardiac Ventricular Maturation



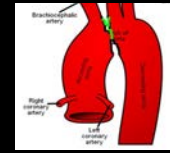
- ERRα/γ are necessary for mitochondrial and contractile postnatal maturation.
- ERR functions as a suppressor of non-cardiac genes, including the fibroblast lineage.

Targeting the ERR Co-Repressor RIP140 (*Nrip1*) to Maintain Normal Cardiac Mitochondrial and Contractile Function in the Failing Heart



Cardiac-specific RIP140 Deletion Attenuates Heart Failure in Mice

csRIP140^{-/-}

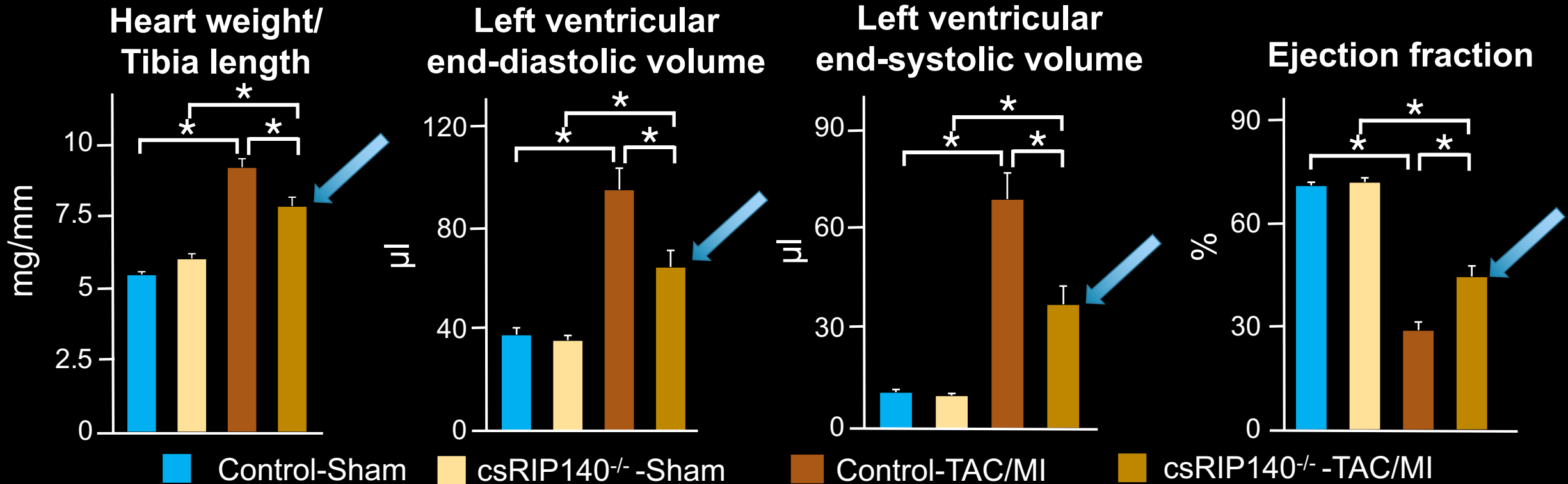


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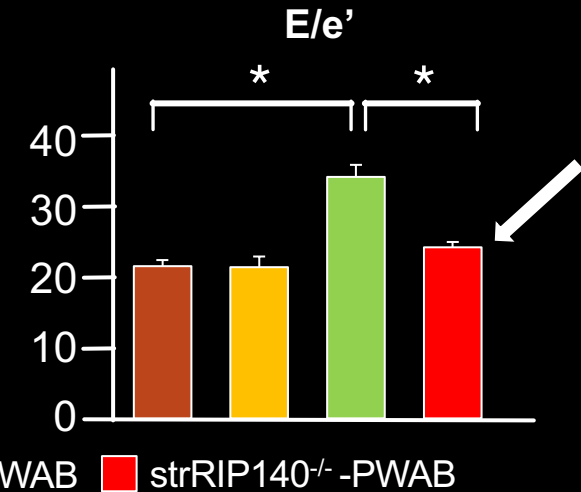
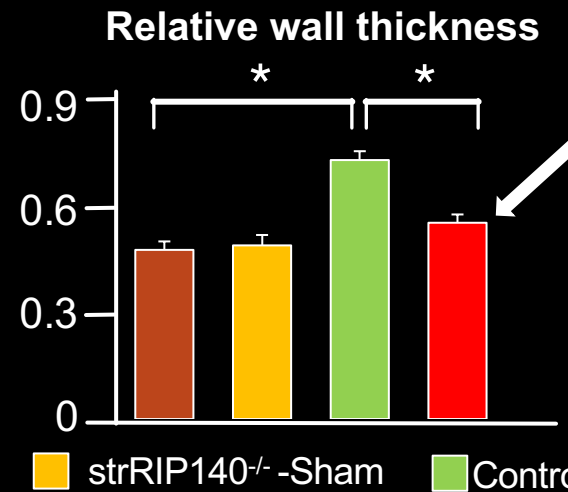
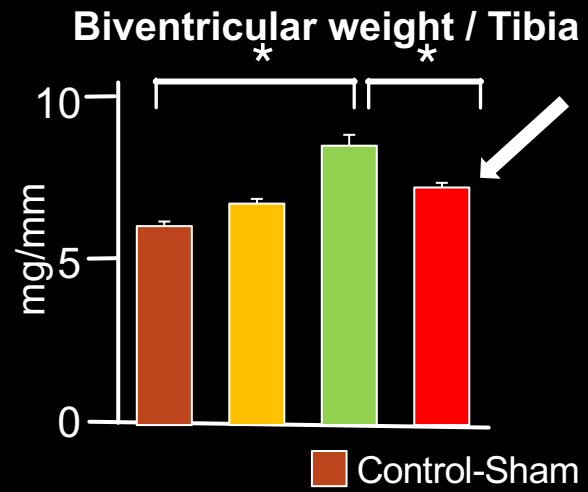
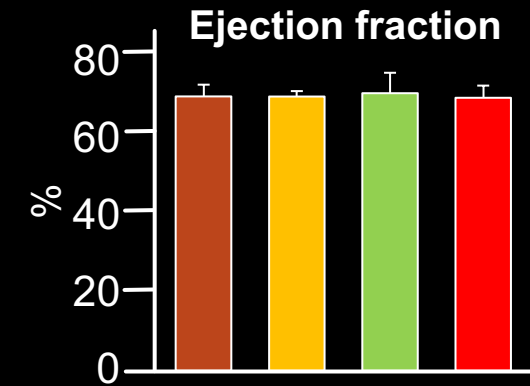
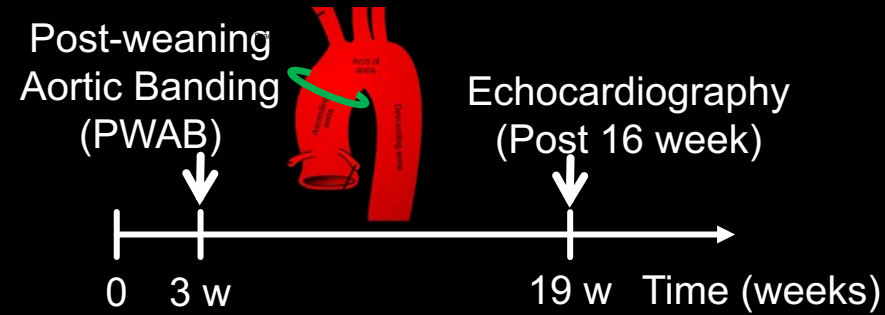


TAC/MI

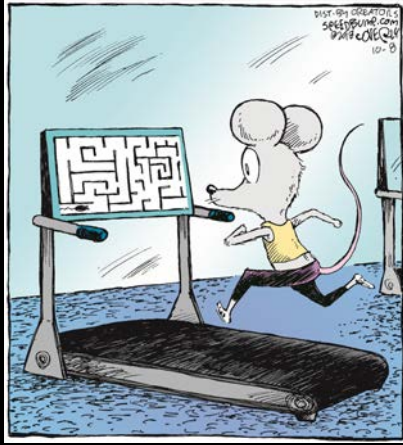
Echocardiography
(Post 4 week)



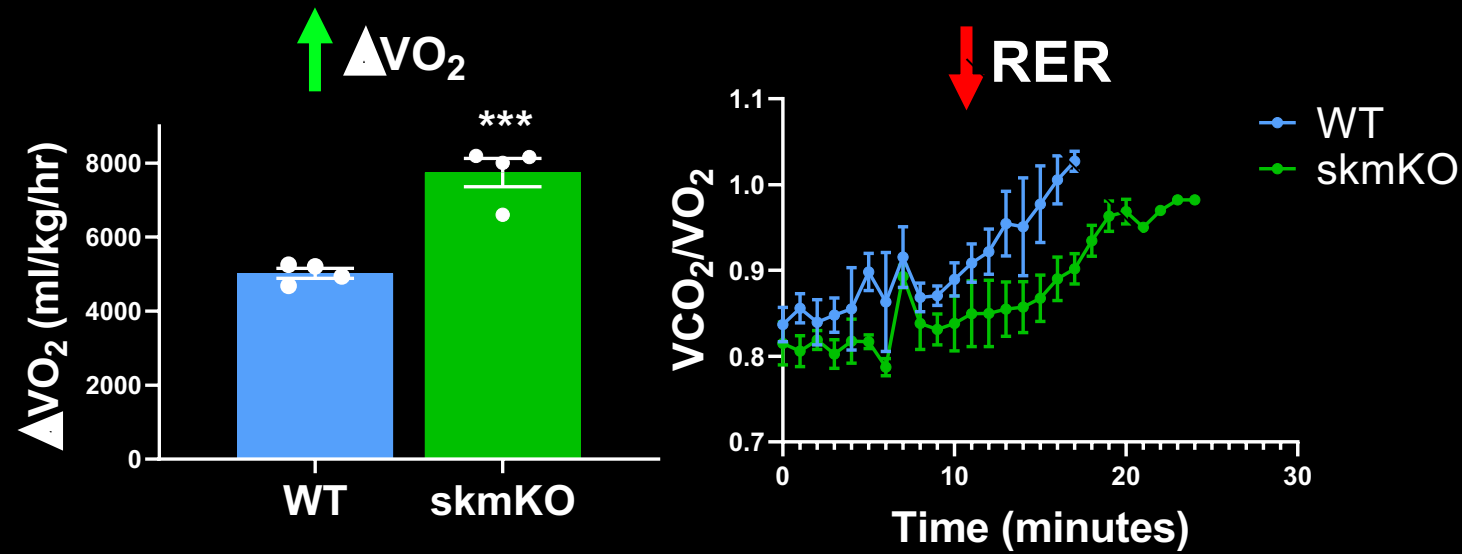
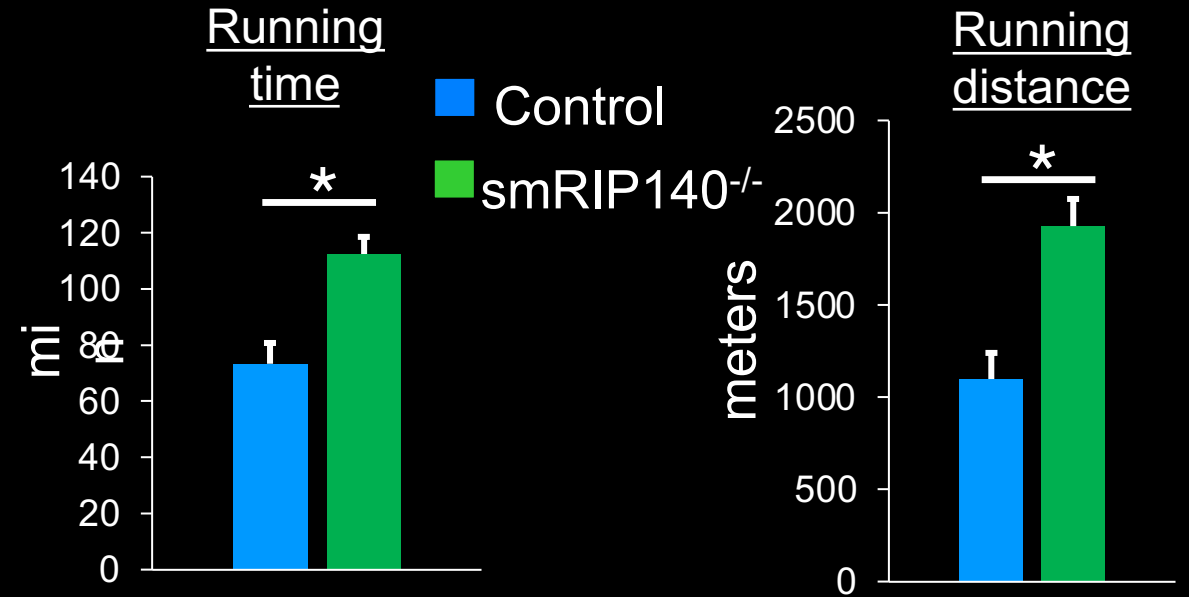
RIP140 Deficiency Defends Against Cardiac Hypertrophy and Diastolic Dysfunction in a Chronic Progressive Pressure Overload HFpEF Model



Mice with Muscle RIP140 Deficiency Exhibit Marathon Mouse Phenotype



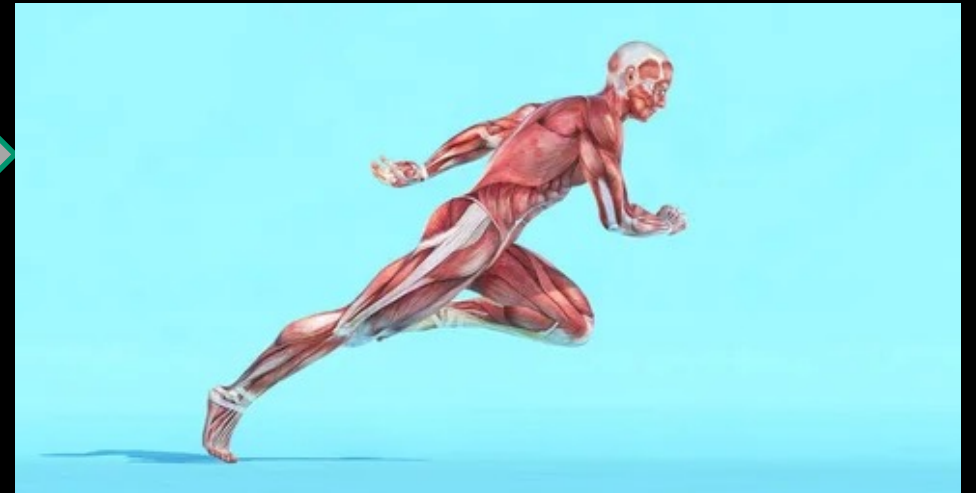
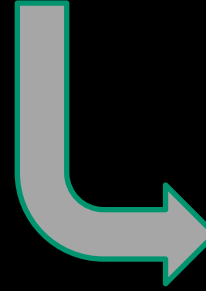
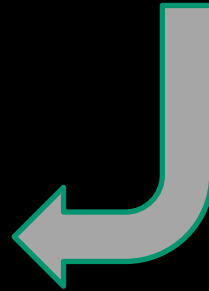
Elizabeth (Bee)
Pruzinsky



Re-balancing Mitochondrial Function as an Emerging Therapy for Heart Failure and Muscle Diseases

RIP140 Inhibitors

Ketone Supplementation (Plenary Session V)



Kelly Lab

Teresa Leone
Tomoya Sakamoto
Peihong Ma
Russ Callaway
Richie Madnick
Tsunehisa Yamamoto

Tim Matsuura
Bee Pruzinsky
Justin Berger
Sarah Sulon
Ling Lai

Mouse Phenotyping and Metabolomics Cores

Ling Lai (Penn,CVI)
Joanna Griffin (Penn CVI)
Chris Petucci (Penn)
Clarissa Shoffler (Penn)
Joe Baur (Penn, IDOM/DRC)

Collaborators

Kirill Batmanov (Penn)
Ken Margulies, Alexia Vite (Penn)
Debbie Muoio (Duke)
John Newman/Eric Verdin (Buck Institute)
Gary Lopaschuk (U Alberta)
Peter Crawford (SBP, U Minn)
Doug Lewandowski (SBP, OSU)
Fabio Recchia (Temple)
Daan Westenbrink (U Groningen)

