Edgewise THERAPEUTICS

Scientific Sessions

EDG-7500, A NOVEL CARDIAC SARCOMERE MODULATOR, PREVENTS LEFT ATRIAL METABOLIC IMPAIRMENT IN YUCATAN MINI-SWINE WITH HYPERTROPHIC CARDIOMYOPATHY CAUSED BY HETEROZYGOUS *MYH7* R403Q MUTATION

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American Heart Association.

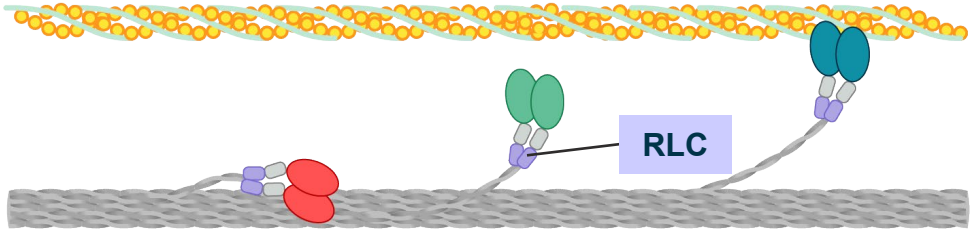
#ScientificSessions26

DISCLOSURE SLIDE

Craig Emter, PhD, is an employee of Edgewise Therapeutics.

EDG-7500 is an investigational agent that is not approved for use by any regulatory authority in any territory and its safety and efficacy have not been established.

EDG-7500 TARGETS THE REGULATORY LIGHT CHAIN (RLC)



Two main actions of EDG-7500	1	2
	EDG-7500 reduces the stiffness of the lever arm • Slowing early contraction, speeding relaxation	**EDG-7500 moves myosin heads toward actin** • Speeding of late systolic contraction

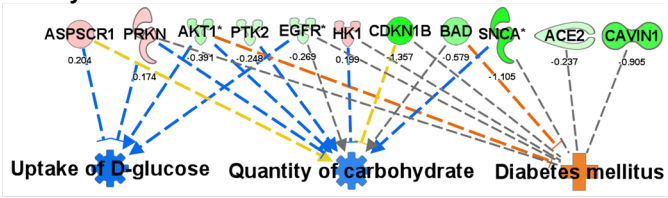
Emter et al. *JCI Insight*. 2026; doi.org/10.1172/jci.insight.203086
RLC, regulatory light chain.

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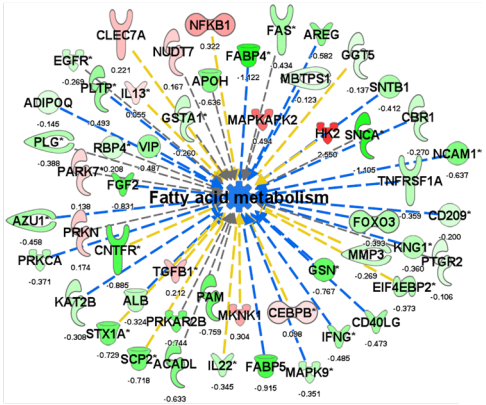
R403Q HCM PIGS DEVELOP LEFT ATRIAL METABOLIC IMPAIRMENT AND DIASTOLIC DYSFUNCTION

Energetic impairment is characterized by proteomic and functional shifts indicative of decreased oxidative capacity alongside diastolic impairment and left atrial remodeling.

A. Carbohydrate Metabolism



B. Fatty Acid Metabolism



Prediction Legend

more extreme in dataset — less

- Increased measurement
- Decreased measurement

more confidence — less

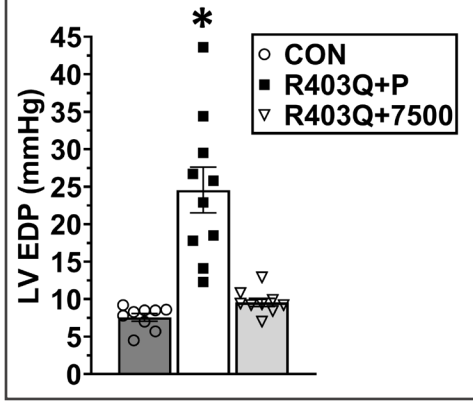
- Predicted activation
- Predicted inhibition

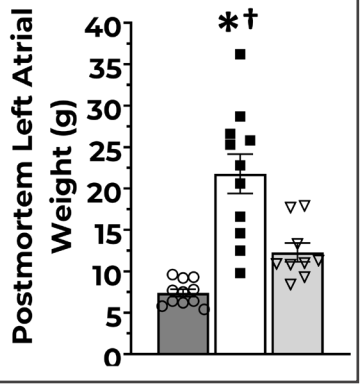
Glow indicates activity when opposite of measurement

Predicted Relationships

- Leads to activation
- Leads to inhibition
- Findings inconsistent with state of downstream molecule
- Effect not predicted

- In the R403Q pig, chronic EDG-7500 treatment prevented LV diastolic impairment & LA remodeling

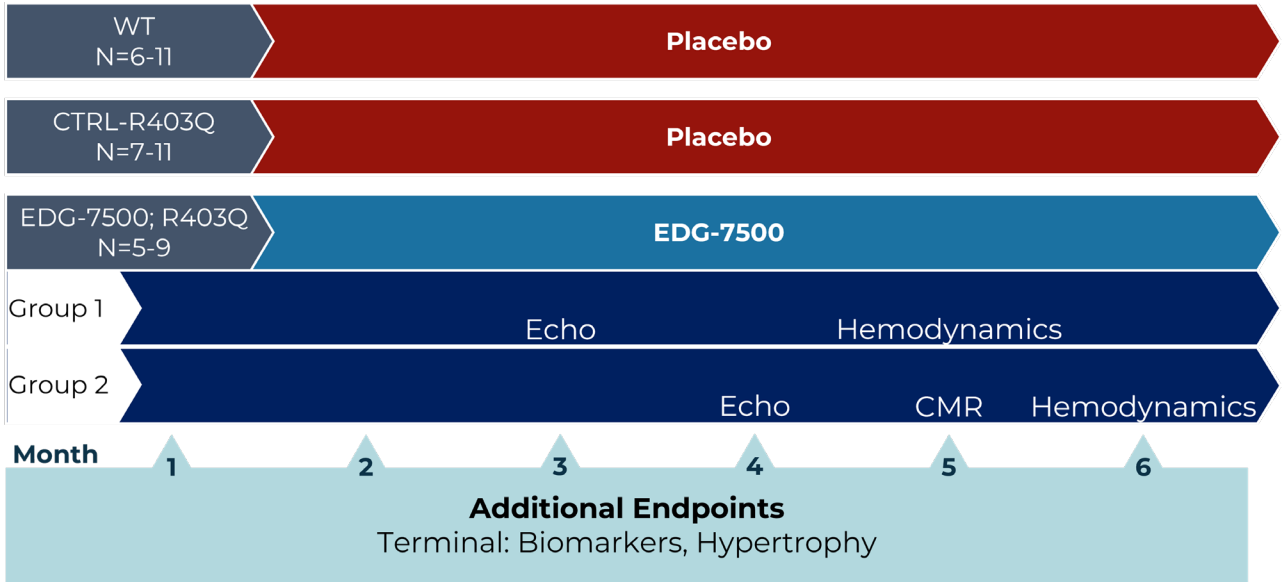




Krause et al. *Journal of Applied Physiology*, 2025; doi:10.1152/japplphysiol.00339.2025
Emter et al. *JCI Insight*, 2026; doi.org/10.1172/jci.insight.203086

CON, control; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; P, placebo

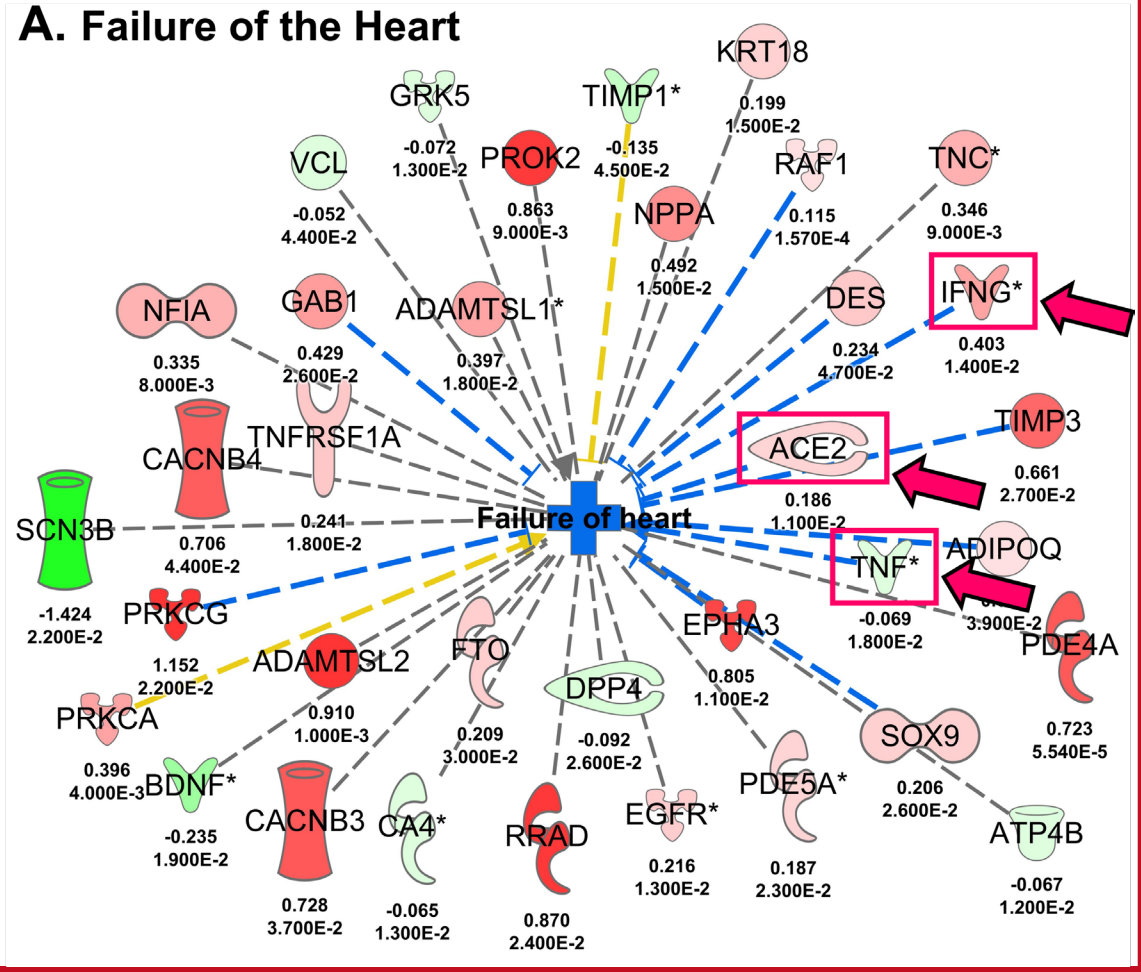
STUDY DESIGN – PROTEOMICS USING INGENUITY PATHWAY ANALYSIS (IPA) AND GENE SET ENRICHMENT ANALYSIS (GSEA)



Study Aim - To determine if EDG-7500 can prevent left atrial metabolic dysregulation in a mini-pig model of nonobstructive HCM (nHCM) caused by heterozygous *MYH7* R403Q mutation.

Emter et al. *JCI Insight*, 2026; doi.org/10.1172/jci.insight.203086
CMR, cardiac magnetic resonance; WT, wild type.

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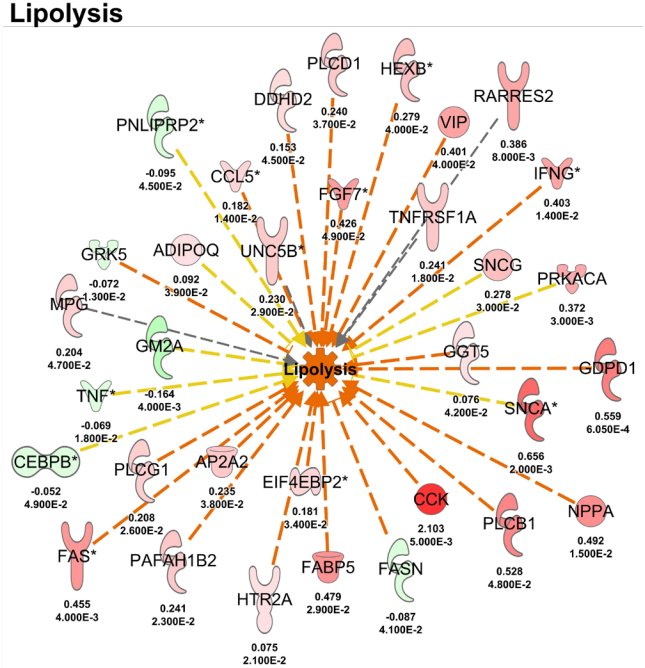
In the R403Q pig, chronic EDG-7500 treatment decreased left atrial enrichment of key networks associated with heart failure (blue cross signifies inhibition).

In R403Q+7500 compared to R403Q+Placebo animals, chronic treatment (6 months) with EDG-7500 inhibited:

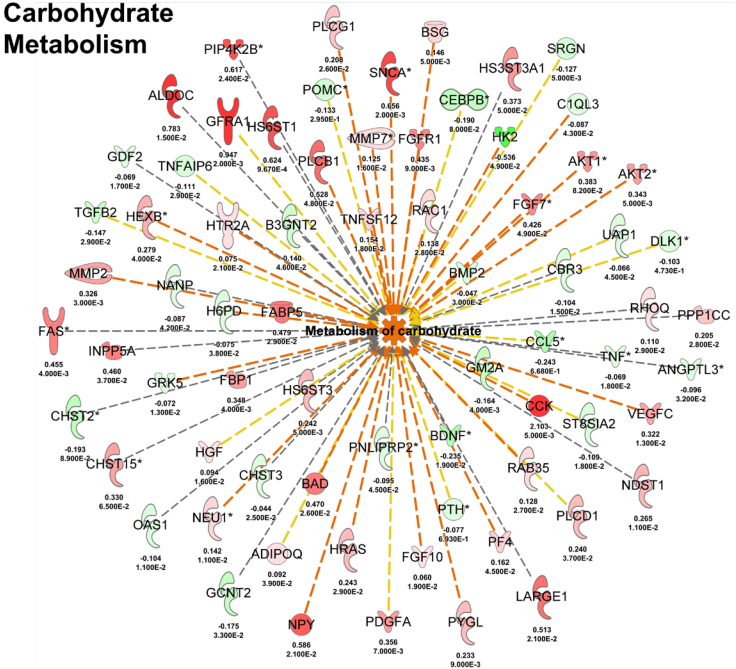
1. Angiotensin converting enzyme-2 (ACE2)
2. Tumor necrosis factor (TNF)
3. Interferon-gamma (IFNG)

IN THE R403Q PIG, CHRONIC EDG-7500 INCREASED ENRICHMENT OF PROTEIN NETWORKS ASSOCIATED WITH THE ACTIVATION OF LIPOLYSIS & CARBOHYDRATE METABOLISM

1



2



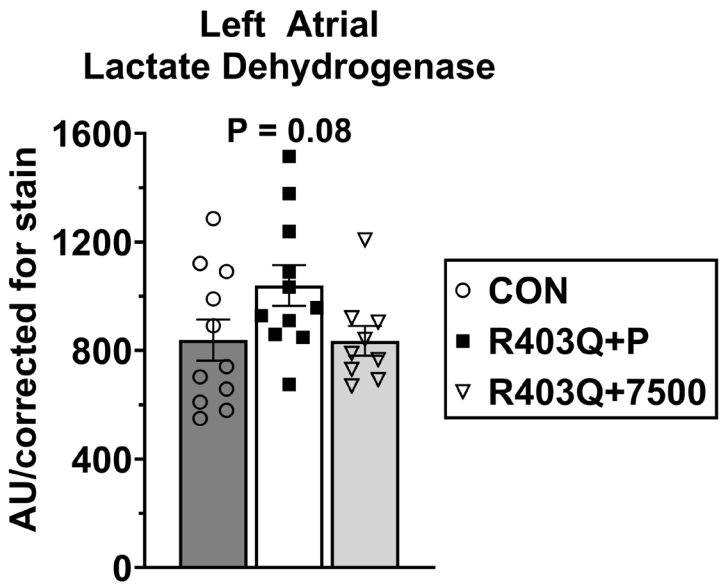
EDG-7500 treatment reverses pathologic findings, shifting metabolic pathways back towards more diverse substrate utilization

IN THE R403Q PIG, CHRONIC EDG-7500 DECREASED TOP-LEVEL FLUX INTO GLYCOLYSIS AND GLYCOGENOLYSIS

1

Left Atria Top Downregulated Proteins. *Comparison – EDG-7500 vs. placebo		
Protein	**Log2 fold-change**	**P-Value**
Sodium channel subunit beta-3	-1.424	0.022
EF-hand calcium-binding domain-containing protein 14:C-term	-1.17	0.008
LRP	-0.848	0.043
Phosphoglucomutase-2	-0.663	0.000694
Glutaminase kidney isoform, mitochondrial	-0.576	0.002
Hexokinase-2	-0.536	0.049
Protein disulfide-isomerase [11450-110]	-0.504	0.000765
Protein Wnt-16 [21942-14]	-0.486	0.05
Glutaredoxin-1	-0.348	0.044

2

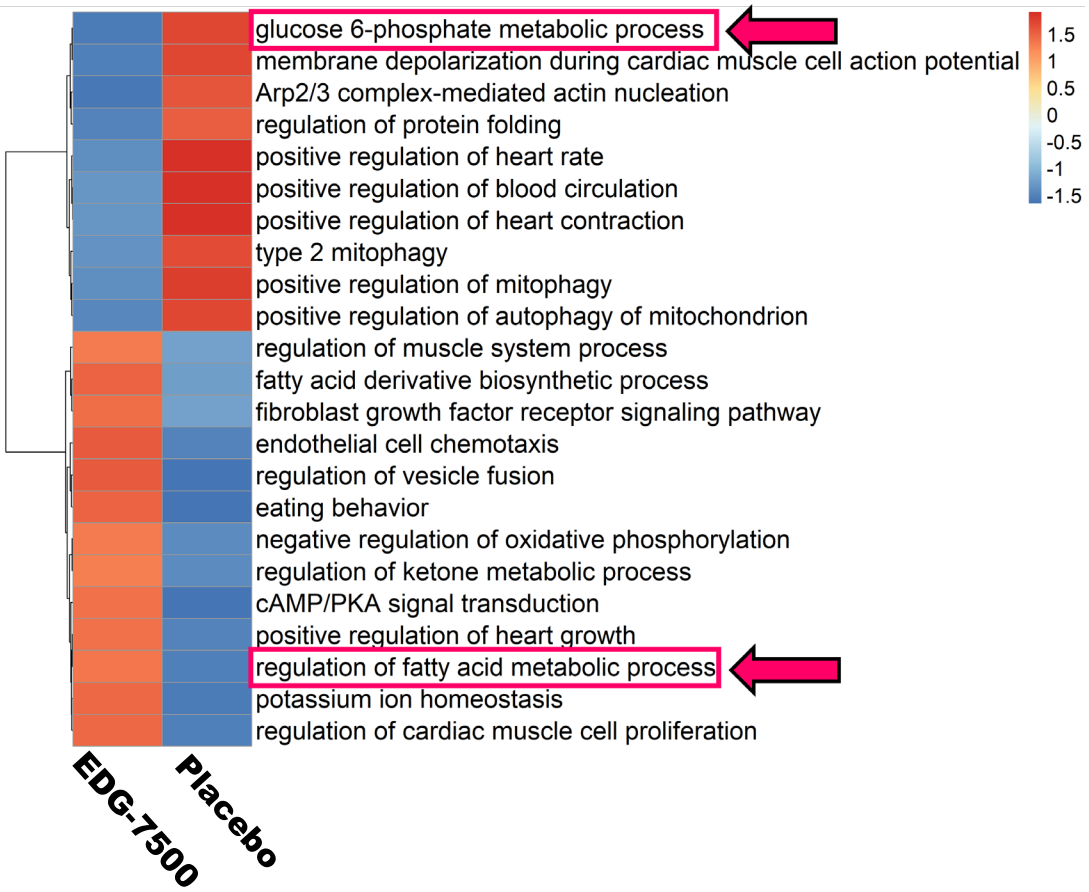


Following chronic EDG-7500 treatment, network indicators of decreased glycolytic flux suggest a shift back towards more flexible substrate use

Krause et al. *in preparation*, 2026
CON, control; LA, left atrial; P, placebo.

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GSEA w/ Gene Ontology – Normalized Enrichment Score



In the R403Q pig, chronic EDG-7500 treatment decreased pathological shifts towards glycolytic flux.

In R403Q+7500 compared to R403Q+Placebo animals, chronic treatment (6 months) with EDG-7500 prevented:

1. Increased glucose 6-phosphate metabolism
2. Decreased regulation of fatty acid metabolism

These findings overall metabolic substrate utilization may be moving back towards a more normal balance

PROTEOMIC ANALYSIS INDICATES CHRONIC EDG-7500 TREATMENT PREVENTED METABOLIC IMPAIRMENT IN THE LEFT ATRIA OF PIGS WITH HCM CAUSED BY HETEROZYGOUS *MYH7* R403Q MUTATION.

1

Inhibits proteomic networks reflective of general heart failure, suggesting EDG-7500 may benefit HCM pathology in part by preventing left atrial energetic impairment.

2

Enriches protein signatures associated with increased lipid and carbohydrate metabolism.

3

Prevented shifts towards **glycolytic metabolism.**

4

By decreasing left atrial wall stress in this preclinical model of nHCM, EDG-7500 may reduce energetic need and **preserve more normal substrate utilization and diverse energy production systems.**