Chronic EDG-7500 treatment prevents left atrial metabolic dysfunction in a Yucatan mini-pig model of genetic non-obstructive hypertrophic cardiomyopathy

Ben Barthel[1], Luuli Tran[1], Alexa A. Krause[2], Taylor J. Kelty[2], Grace M. Meers[2], R. Scott. Rector[2], Alan Russell[1], & Craig A. Emter[1]

[1]Edgewise Therapeutics, Boulder, CO, USA; [2]University of Missouri- Columbia; Columbia, MO, USA

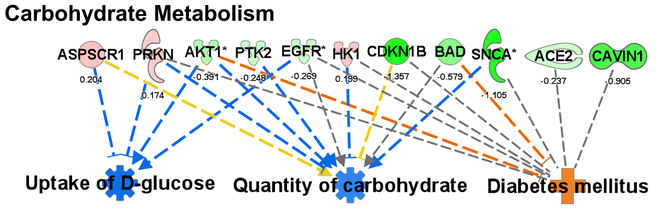
Study Aims

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

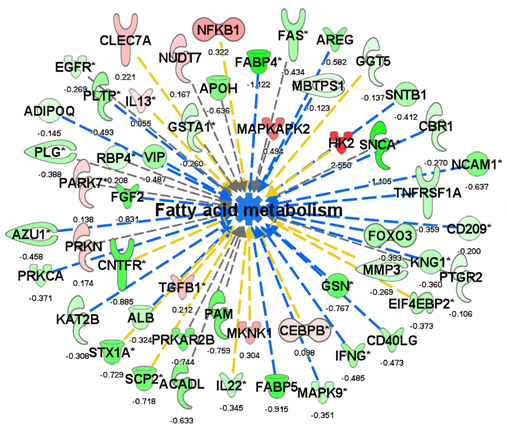
Background

- **In the R403Q pig, left atrial energetic impairment is characterized by functional and proteomic shifts in preferred substrate utilization and energy production systems indicative of decreased oxidative capacity.**

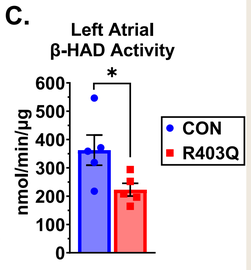
A. Carbohydrate Metabolism



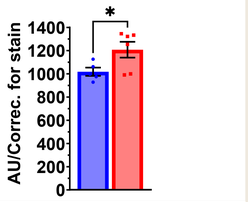
B. Fatty Acid Metabolism



C. Left Atrial β-HAD Activity

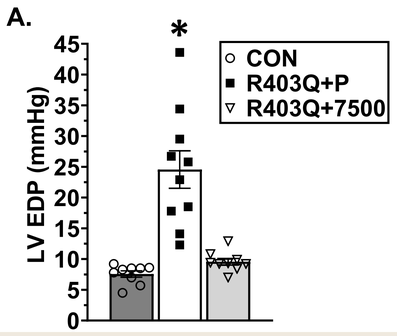


D. Left Atrial Lactate Dehydrogenase

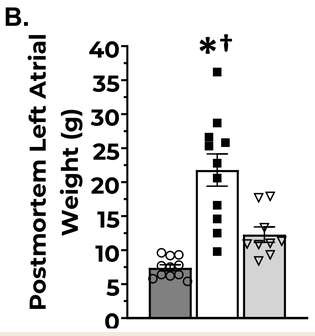


- **In the R403Q pig, chronic EDG-7500 treatment prevents LV diastolic impairment & LA remodeling**

A.



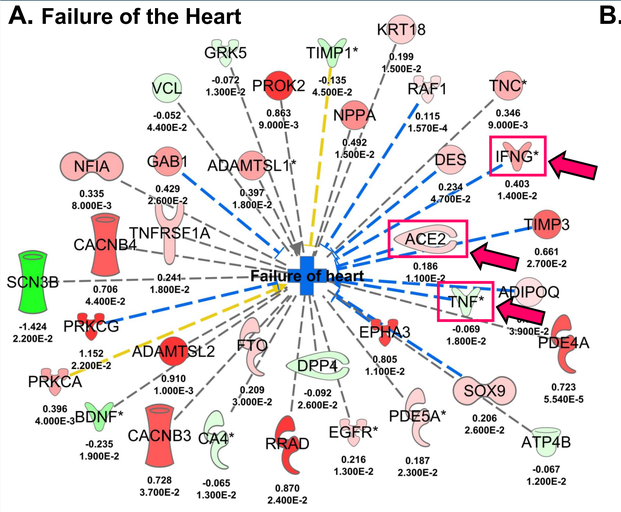
B.



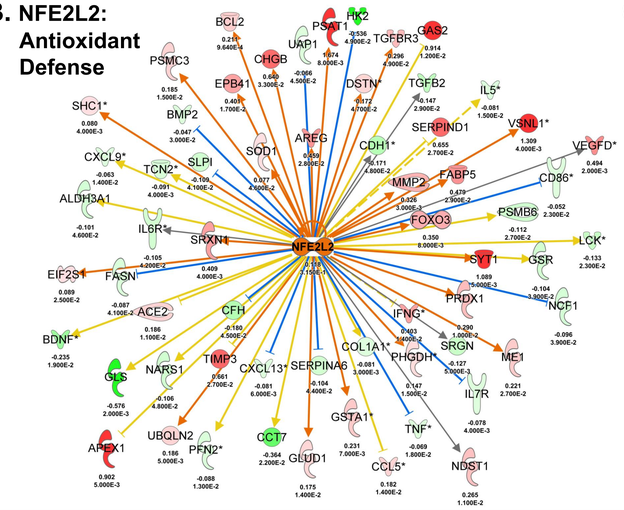
Results

EDG-7500 decreases enrichment of left atrial protein networks associated with heart failure & activates antioxidant and mitogenesis signatures. ***Comparison - EDG-7500 vs. placebo; P < 0.05***

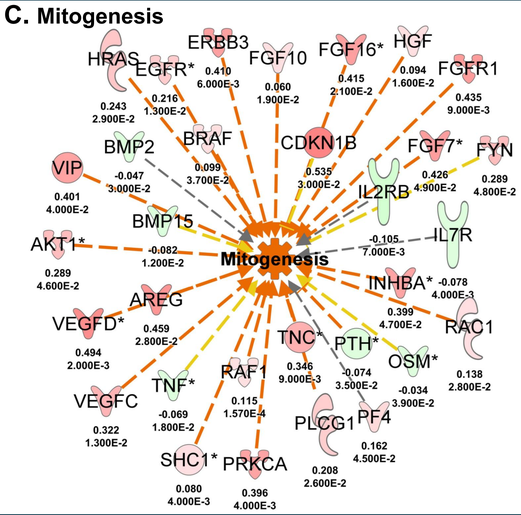
A. Failure of the Heart



B. NFE2L2: Antioxidant Defense

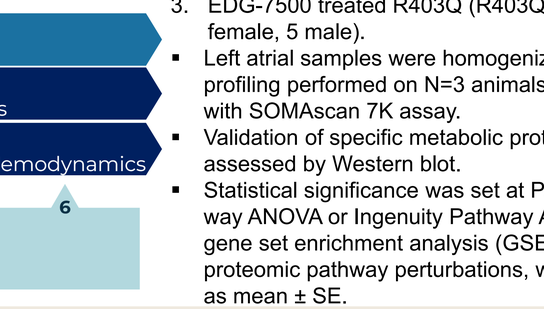


C. Mitogenesis

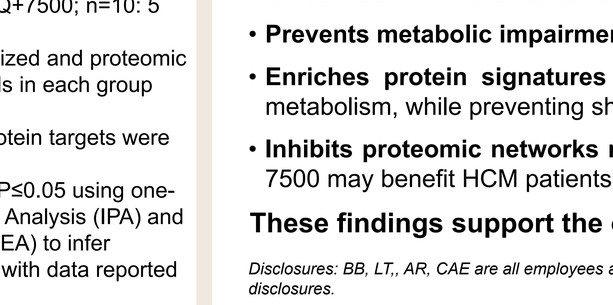


EDG-7500 enriches left atrial metabolic networks associated with the activation of lipolysis and carbohydrate metabolism while preventing shifts towards glycolysis. ***Comparison - EDG-7500 vs. placebo; P < 0.05***

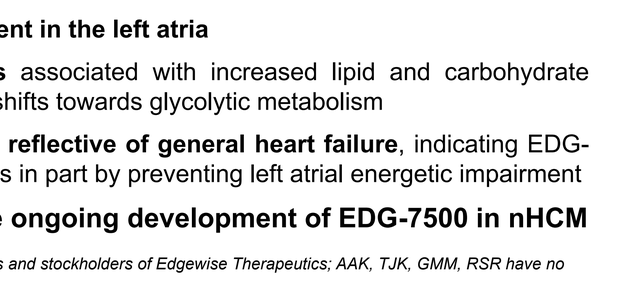
A. Lipolysis



B. Carbohydrate Metabolism



C. GSEA w/ Gene Ontology – Normalized Enrichment Score

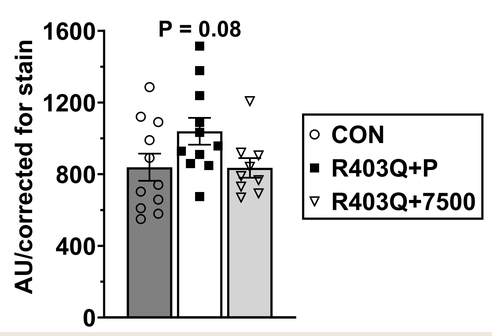


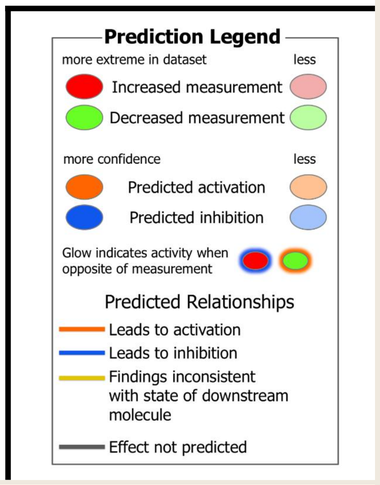
D.

Left Atria Top Downregulated Proteins. ***Comparison – EDG-7500 vs. placebo***

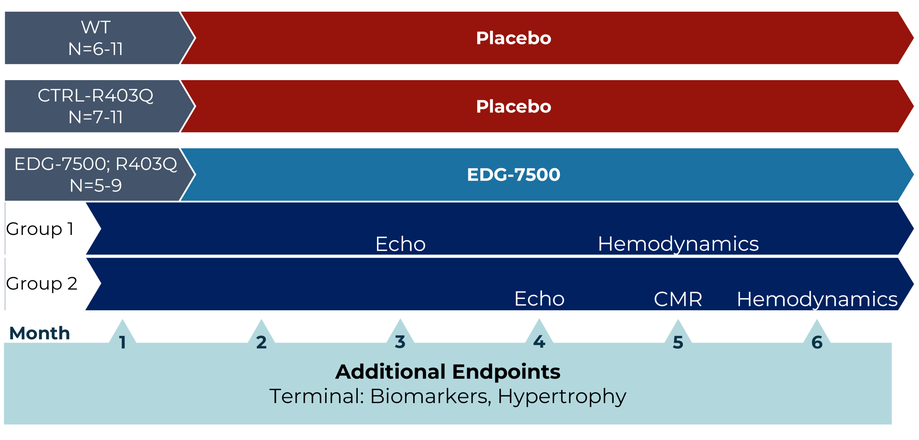
Protein	Log2 fold-change	P-Value
Sodium channel subunit beta-3	-1.424	0.022
EF-hand calcium-binding domain-containing protein 14:C-term	-1.17	0.008
LRP	-0.848	0.043
Phosphoglucomutase-2	-0.663	0.000694
Glutaminase kidney isoform, mitochondrial	-0.576	0.002
Hexokinase-2	-0.536	0.049
Protein disulfide-isomerase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

E. Left Atrial Lactate Dehydrogenase





Study Design



Animals were randomly assigned into 3 groups:

1. Placebo-treated wild-type control (CON; n=11: 6 female, 5 male)
2. Placebo-treated R403Q (R403Q+P; n=11: 6 female, 5 male)
3. EDG-7500 treated R403Q (R403Q+7500; n=10: 5 female, 5 male).

- Left atrial samples were homogenized and proteomic profiling performed on N=3 animals in each group with SOMAscan 7K assay.
- Validation of specific metabolic protein targets were assessed by Western blot.
- Statistical significance was set at P≤0.05 using one-way ANOVA or Ingenuity Pathway Analysis (IPA) and gene set enrichment analysis (GSEA) to infer proteomic pathway perturbations, with data reported as mean ± SE.

Conclusions

In a mini-pig model of non-obstructive HCM (nHCM) caused by heterozygous *MYH7* R403Q mutation, proteomic analysis indicates chronic EDG-7500 treatment:

- **Prevents metabolic impairment in the left atria**
- **Enriches protein signatures** associated with increased lipid and carbohydrate metabolism, while preventing shifts towards glycolytic metabolism
- **Inhibits proteomic networks reflective of general heart failure**, indicating EDG-7500 may benefit HCM patients in part by preventing left atrial energetic impairment

These findings support the ongoing development of EDG-7500 in nHCM

Disclosures: BB, LT,, AR, CAE are all employees and stockholders of Edgewise Therapeutics; AAK, TJK, GMM, RSR have no disclosures.