FB-1083 demonstrates potent efficacy in preclinical models of Heart Failure with Preserved Ejection Fraction and Pulmonary Hypertension (MP 1670)

Natalie DeForest, Linda Goodman, Katharine Grabek, Ryan Sprenger, Rui Song, Evelyn Tran, Phil McNamara, Gennady Gorin, Noreen Henig, Robert M. Jones, Kacey Haptonstall, Ashley Hermans, Ashley Zehnder, **Bryan Burkey**
Fauna Bio, Emeryville, CA, United States

Abstract: 4369301

Scientific Sessions

November 7-10, 2025
New Orleans, LA

American Heart Association.

Financial Disclosure

List all disclosures from past 12 months

Presenter: Bryan Burkey
Employee FaunaBio Inc.

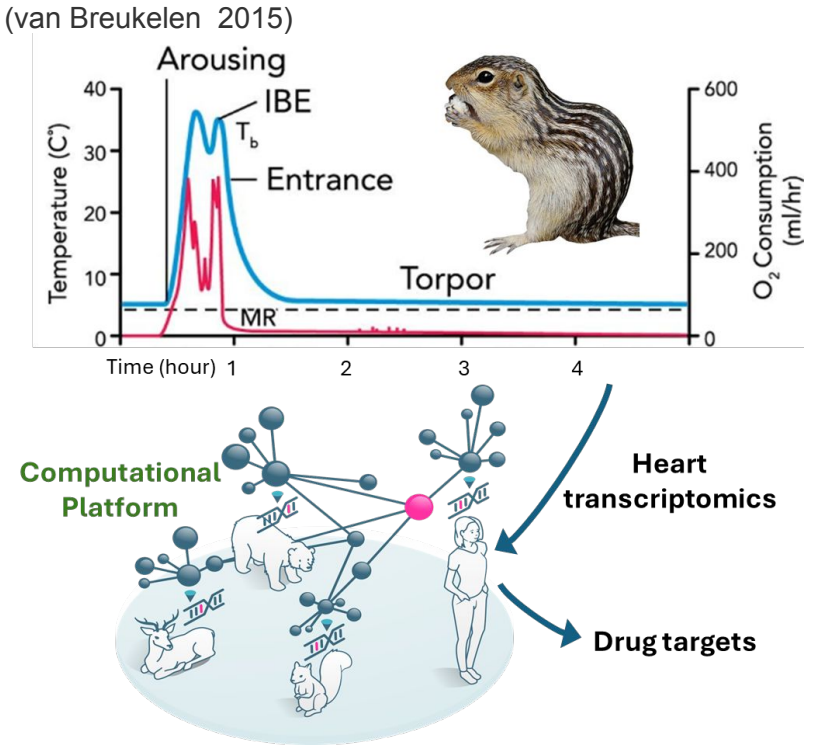
Co-authors: Natalie DeForest, Linda Goodman, Katharine Grabek, Ryan Sprenger, Rui Song, Evelyn Tran, Phil McNamara, Gennady Gorin, Kacey Haptonstall, Ashley Hermans and Ashley Zehnder
Employees of FaunaBio Inc.

Co-authors: Noreen Henig and Robert M. Jones
Consultant of FaunaBio Inc.

Discovery of Faun269g – a drug target for HFpEF / PH

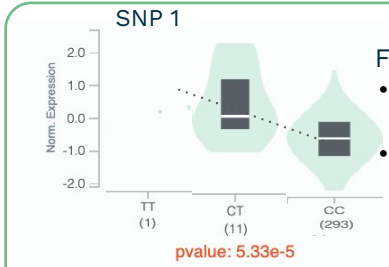
- The 13-Lined Ground Squirrel's unique physiology resists tissue damage
- Hibernation's rapid body temperature and metabolic changes mimic ischemia-reperfusion, yet without the tissue damage
- FaunaBio computational platform is designed to identify potential drug targets based on insights from tissue protection transcript signatures
- Faun269g is a gene target that can protect against pathologies like cardiac and pulmonary ischemia reperfusion and hypoxia tissue injury

Faun269g is Fauna Bio's anonymized gene ID



Faun269g human genomic association with HFpEF / PH

Faun269g cis-eQTL variant is causally associated with cardiopulmonary physiology

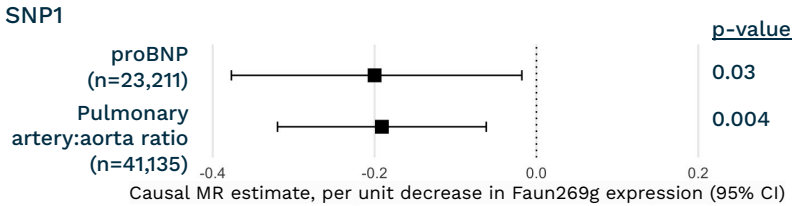


Faun269g cis-eQTL variant (SNP 1):

- located in the first intron of Faun269g
- associates with **decreased** Faun269g expression (p=5.3e-5, GTEx)

- SNP1 associates most significantly with **decreased pulmonary artery:aorta ratio** (PA:A) by cardiac MRI in an association study of SNP1 across CV phenotypes (beta = -0.0746, p-value=3.7e-4)

- SNP 1 is **causally associated with lower proBNP levels and pulmonary artery:aorta ratio** by Mendelian randomization



Putative loss of function and missense Faun269g variants associated with increased BHB

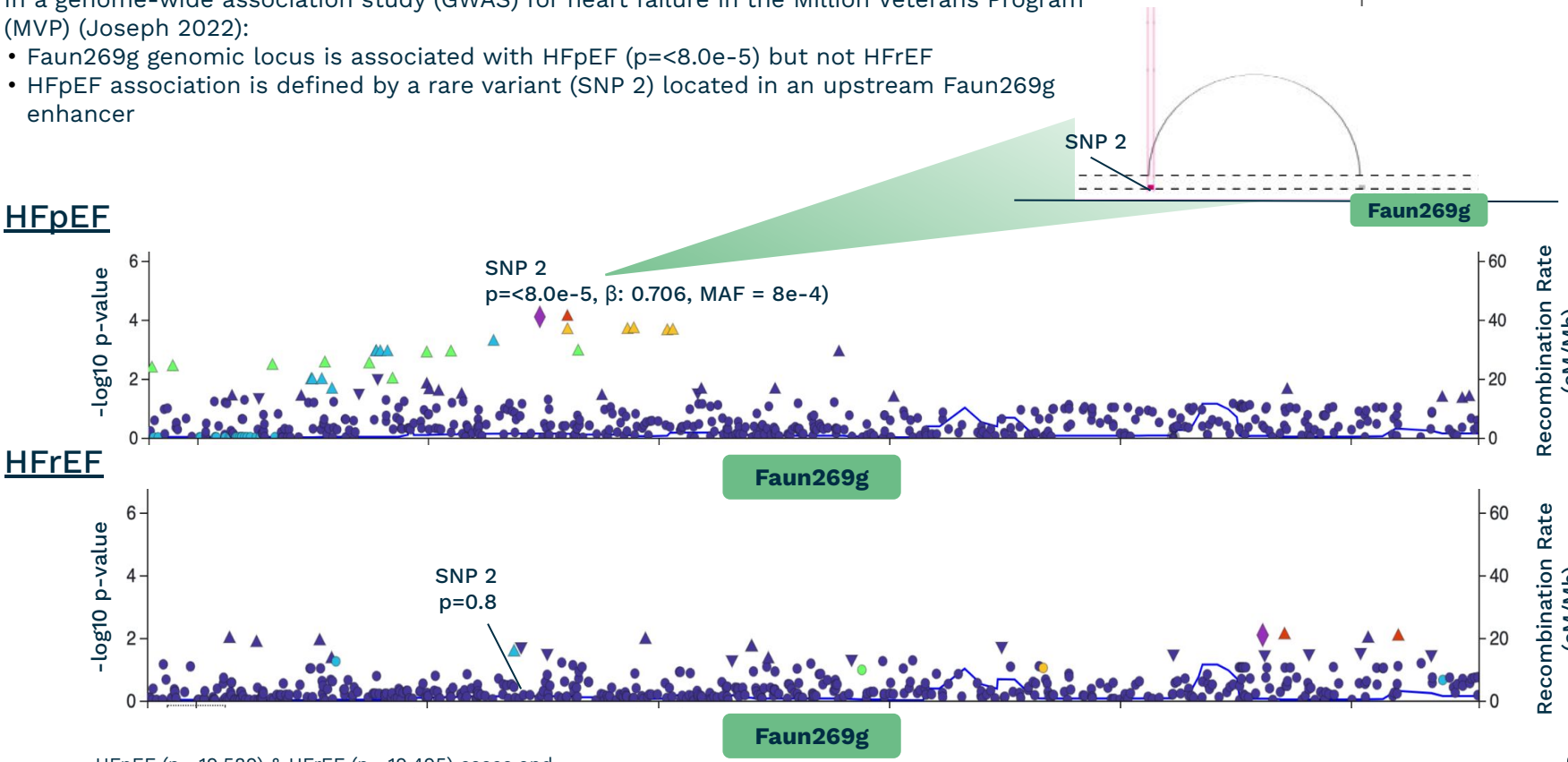
UK Biobank ~400k whole exome sequenced participants, gene-based association test (Karczewski 2022)

Phenotype	N samples	Beta	P-value	N variants (pLOF + missense)
3-Hydroxybutyrate (BHB)	93,741	0.003	0.002	194

Faun269g genomic locus associated with HFpEF but not HFrEF

In a genome-wide association study (GWAS) for heart failure in the Million Veterans Program (MVP) (Joseph 2022):

- Faun269g genomic locus is associated with HFpEF (p=<8.0e-5) but not HFrEF
- HFpEF association is defined by a rare variant (SNP 2) located in an upstream Faun269g enhancer

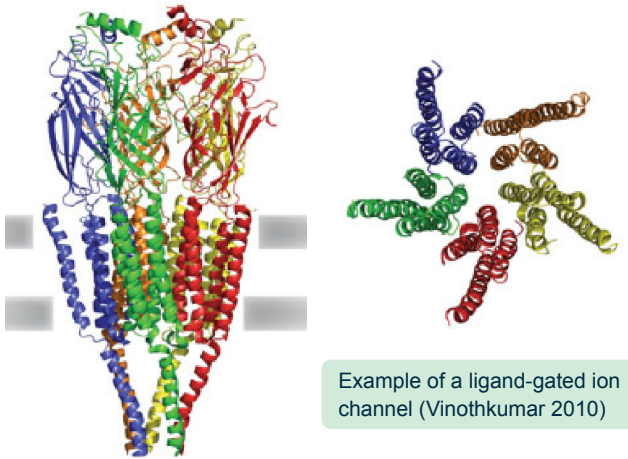


HFpEF (n = 19,589) & HFrEF (n = 19,495) cases and 258,943 healthy controls

FB-1083 is a small molecule antagonist of Faun269g

- Structure-based design was used to generate a range of compounds with potent antagonist effect on the ion channel
- Thorough screening identified dozens of attractive lead compounds with good potency, selectivity, and desired pharmaceutic attributes
- Extensive profiling identified FB-1083 as the lead candidate:
  - Antagonizes ligand activation of human Faun269g ion channel activity with an IC50 of 0.179 nM
  - Is >5,000-fold selectivity over other related receptors and safety targets
  - Has desired chemical properties with 4 step synthesis
  - Has desired PK and ADME properties suitable for once-daily oral dosing and low drug-drug interaction risk
  - Is well tolerated at high-doses in rats and dogs following two-week dose range finding studies

CryoEM of Ligand-Gated Ion Channel enabled rapid design and development of novel small molecule antagonists of Faun269g



Example of a ligand-gated ion channel (Vinothkumar 2010)

FB-1083 protects human cardiomyocytes from mitochondrial stress

- Mitochondrial dysfunction is a recognized factor contributing to HFpEF (Kumar 2019) and PH (Ryanto 2023)
- Faun269g ion channel localizes to the inner mitochondrial membrane of human cardiomyocytes
- FB-1083-treated human iPSC-derived cardiomyocytes stressed by overnight glucose and oxygen deprivation are protected from:
  - loss of cell viability
  - lowering of ADP/ATP ratio
  - and elevated reactive oxygen species
- The protective effect occurs at low nM drug concentrations and is lost if co-incubated with 10-fold excess of a selective ligand to the ion channel

Antagonism of Faun269g with FB-1083 protects mitochondrial function following cellular metabolic stress

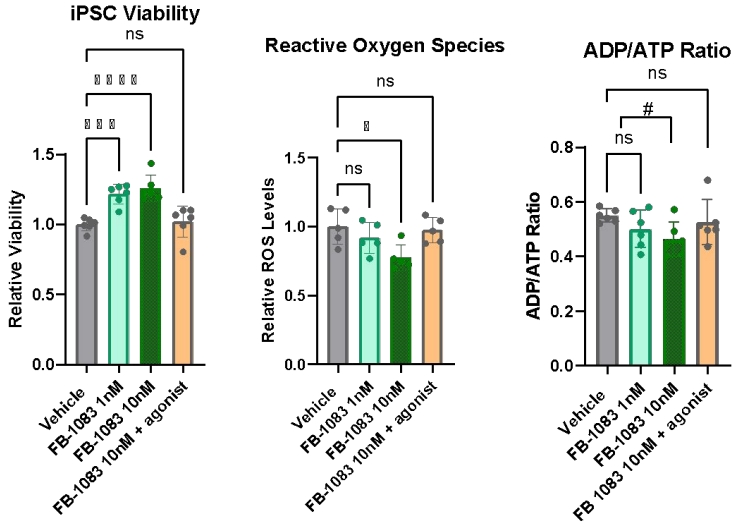
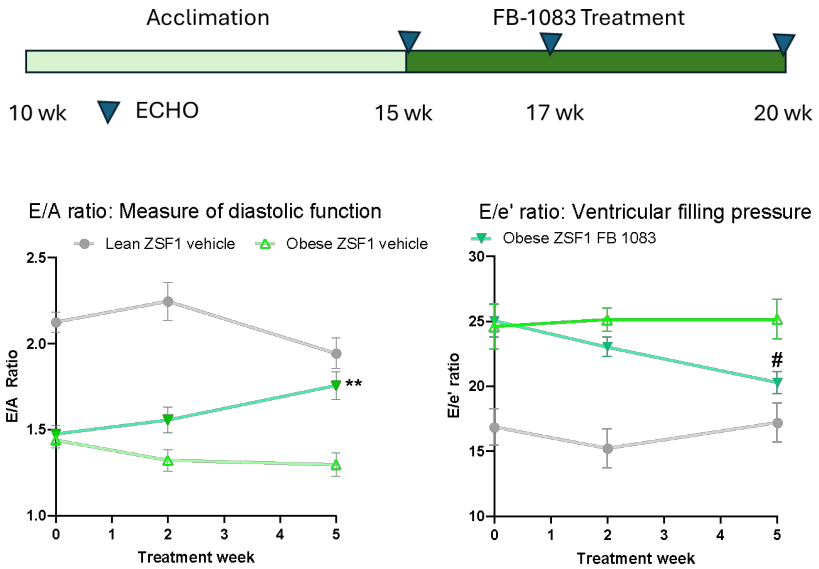


Figure legend: Human iPSCs were cultured 18 hours with low glucose and hypoxia in the presence or absence of compounds. Assays were performed 4 hours after restoration of standard culture media, with or without compounds. * P<0.05, *** p<0.001, **** p<0.0001 one-way ANOVA vs vehicle and # p<0.05, t-test vs vehicle

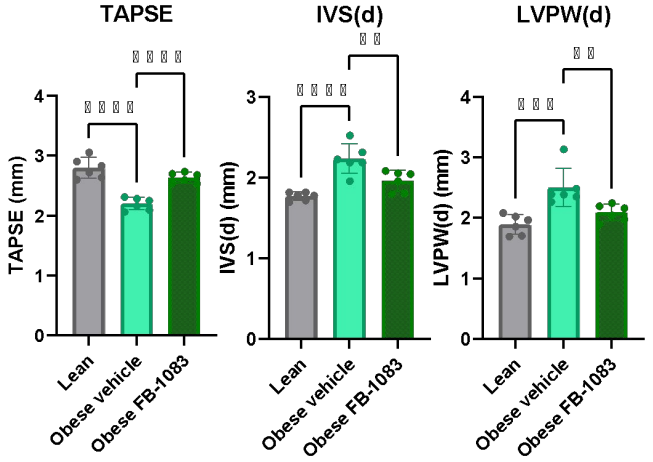
FB-1083 restores LV function in ZSF-1 rats with HFpEF

Obese ZSF-1 rats are used as a model of HFpEF as they develop left ventricular dysfunction while maintaining LV ejection fraction



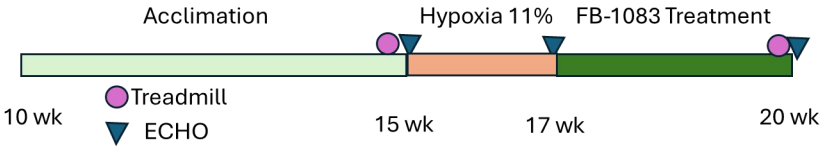
Effects of FB-1083 in a rat model of HFpEF:

- FB-1083 significantly reversed diastolic dysfunction (E/A ratio, $p<0.05$; E/e' ratio, $p<0.05$)
- FB-1083 improved right ventricular function (TAPSE, $p<0.005$)
- FB-1083 attenuated adverse cardiac remodeling (reduced LVPWd, $p<0.05$ and IVSd, $p<0.05$)



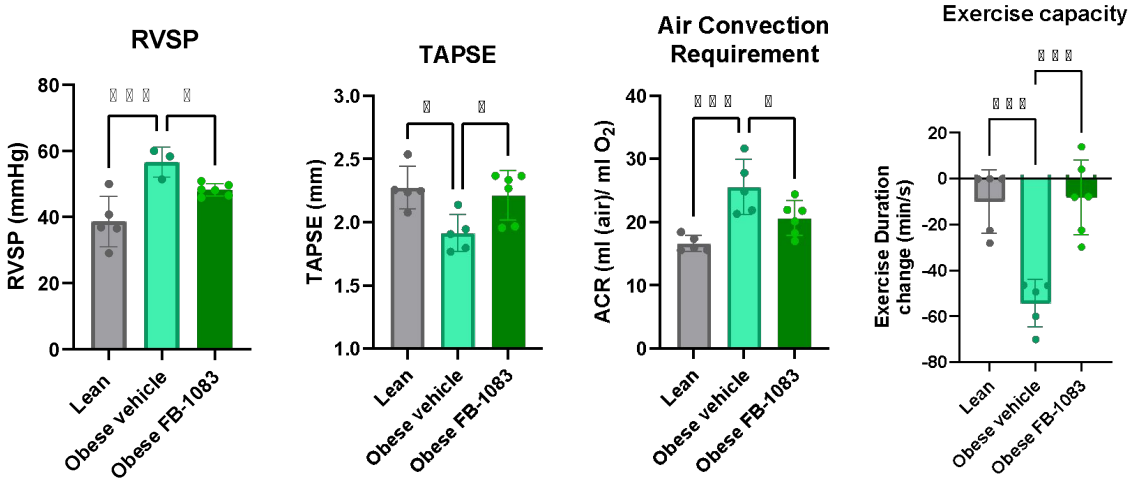
FB-1083 improves functional endpoints in HFpEF/PH

Obese ZSF-1 rats subjected to hypoxia develop PH in addition to HFpEF



Effects of FB-1083 in a rat model of HFpEF with PH:

- Reduced RVSP by 46%
- Significantly improved TAPSE scores by 83%
- Improved air convection capacity by 55%
- Fully prevented a decline in exercise capacity



Conclusions and references

Key takeaways:

- FB-1083 is a novel, small molecule compound with potential to treat patients with HFpEF, with or without PH
- FB-1083 is a potent and selective antagonist of Faun269g, a ligand-gated ion channel
- Human genomic analysis demonstrates associations of Faun269g with HFpEF, cardiopulmonary function and circulating factors associated with HFpEF
- FB-1083 attenuated stress-induced mitochondrial dysfunction in human derived cardiomyocytes
- FB-1083 is efficacious in rat models of HFpEF and HFpEF with PH
- Based on the strength of the preclinical data, IND-enabling studies for FB-1083 are on-going

References:

- Joseph J et. al. Nat Commun. 2022 Dec 14;13(1):7753.
- Kumar AA et.al Circulation. 2019 Mar 12;139(11):1435-1450.
- Ryanto GRT et.al. Antioxidants (Basel). 2023 Feb 3;12(2):372.
- van Breukelen F and Martin SL Physiology 2015 30:4, 273-281.
- Vinothkumar KR and Henderson R. Q Rev Biophys. 2010 Feb;43(1):65-158.