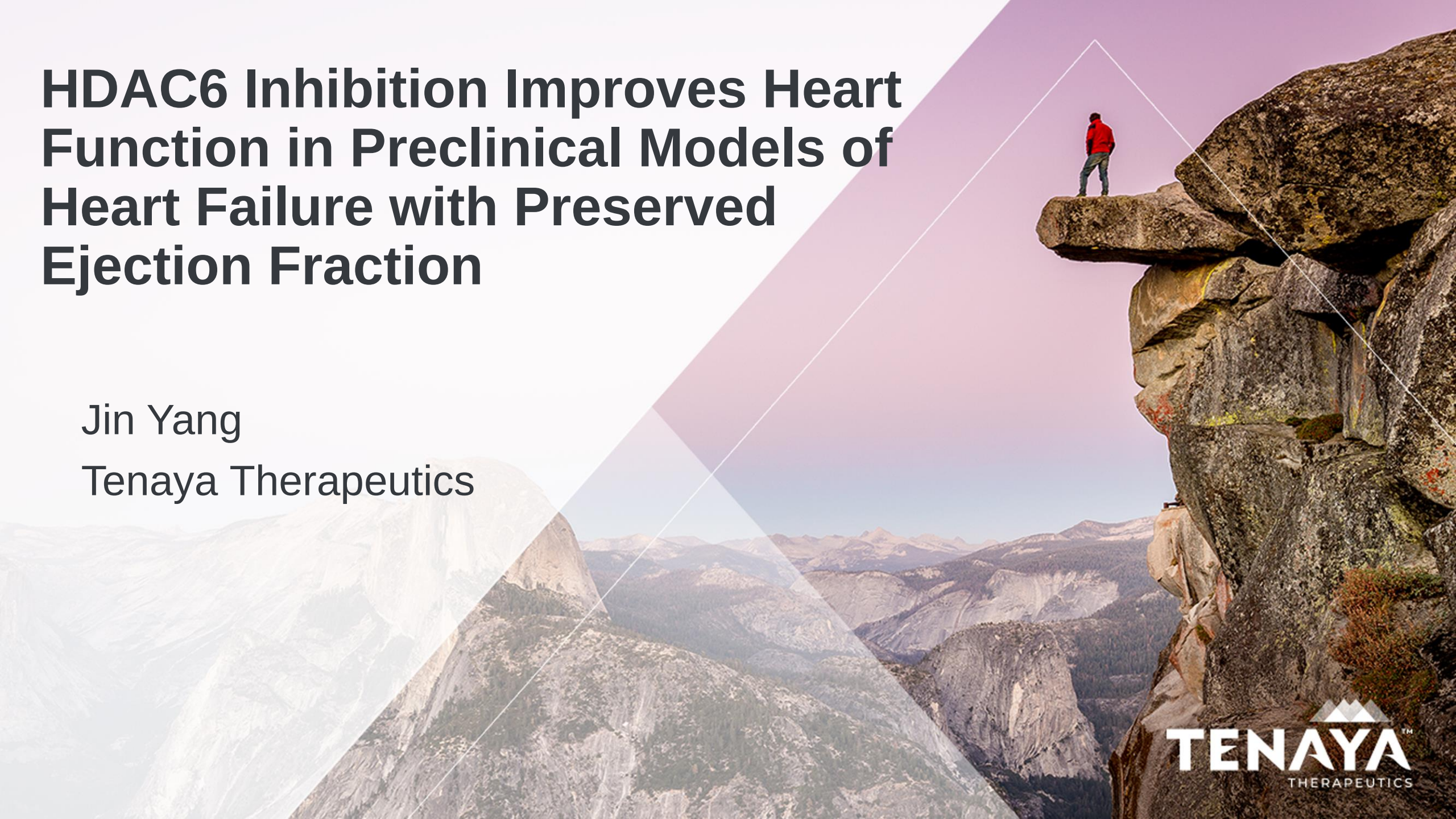
HDAC6 Inhibition Improves Heart Function in Preclinical Models of Heart Failure with Preserved Ejection Fraction

Jin Yang

Tenaya Therapeutics



HDAC6 is a Potential Therapeutic Target for HFpEF

Epidemiology

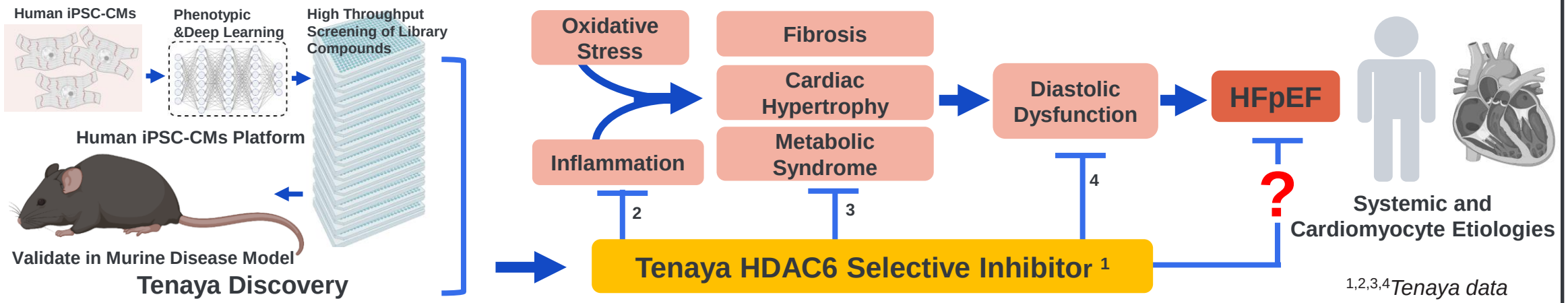
- Patients with HFpEF represent ~50% of HF patients, and is most common form of HF in patients > 65yo
- Estimated to be > 3MM patients diagnosed with HFpEF in USA alone
- Prevalence is rapidly increasing, anticipated to increase by > 45% by 2030

Standard of Care

- Few effective treatments; no disease modifying therapies that improve clinical outcome

HDAC6 & HFpEF

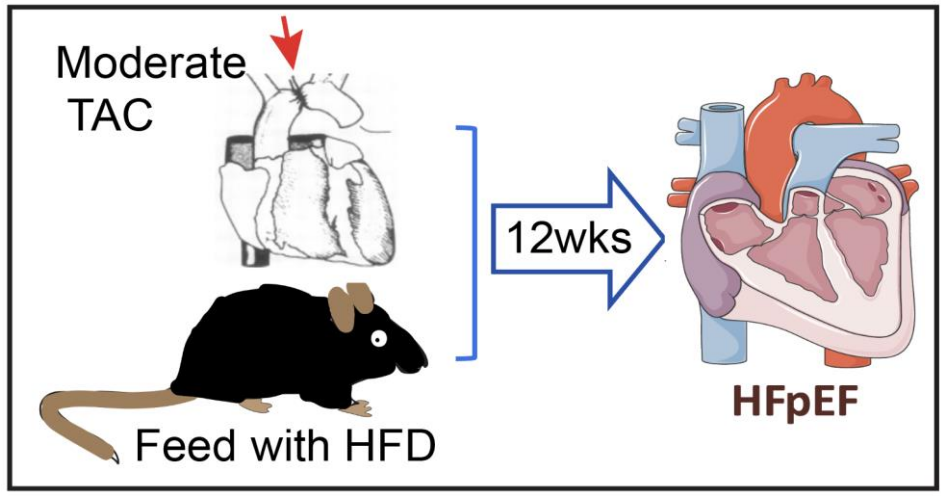
The Role of HDAC6 in multiple components of HFpEF pathophysiology is supported by Tenaya data



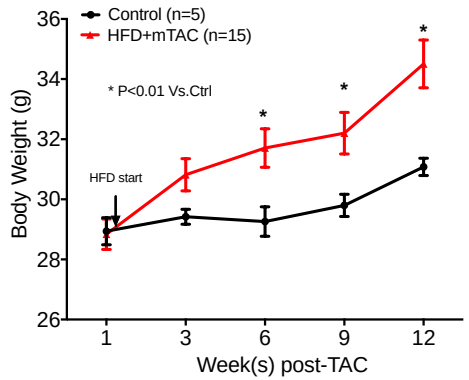
To assess whether TYA-11631, a histone deacetylase 6 (HDAC6) selective inhibitor, improves cardiac structure and heart function in preclinical models of diastolic dysfunction with preserved ejection fraction

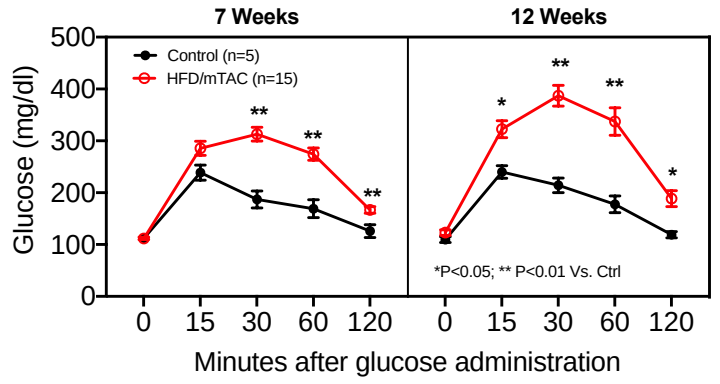
Establishment of a Novel Mouse HFpEF Model

High Fat Diet/Moderate TAC Model Recapitulates HFpEF Phenotypes



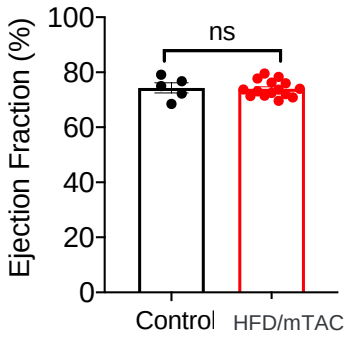
Obesity/Glucose Intolerance



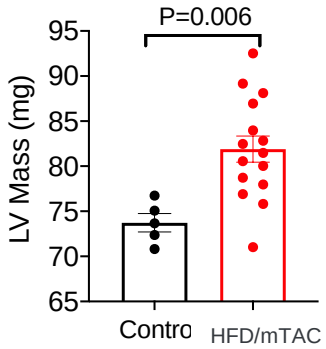


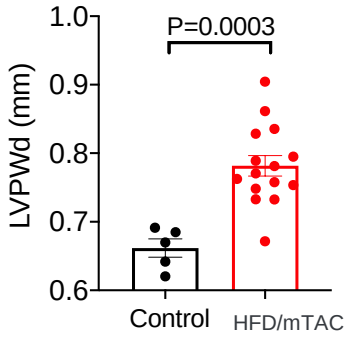
Glucose-tolerance tests were performed by IP injection of glucose (2 g/kg) after 6-h fasting

Ejection Fraction Preserved

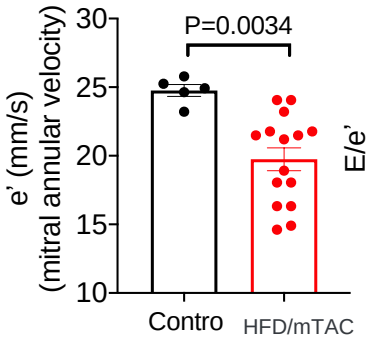


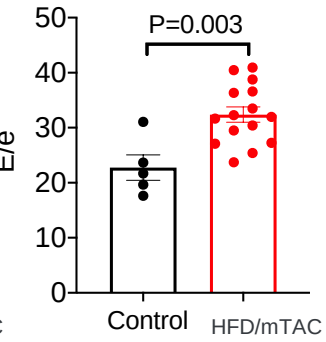
LV Remodeling with Concentric Hypertrophy





LV Diastolic Dysfunction with Impaired Relaxation & Filling





Test TYA-11631 (selective HDAC6 inhibitor; PO, QD) in the established *HFpEF* (HFD/mTAC) Model

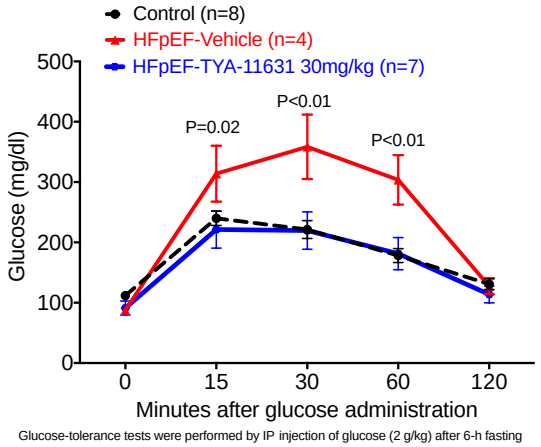
Randomization & Group

Group	Test Article	Number
Control	Vehicle	5
HFpEF (HFD/mTAC)	Vehicle	7
	TYA-11631	8

TYA-11631 Efficacy in HFpEF (HFD/mTAC) Model

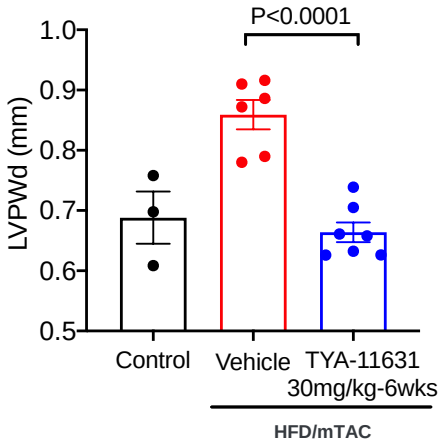
Treatment with TYA-11631 for 6wks Significantly Improved Glucose Tolerance, Hypertrophy and LV Diastolic Function

Glucose Tolerance Test

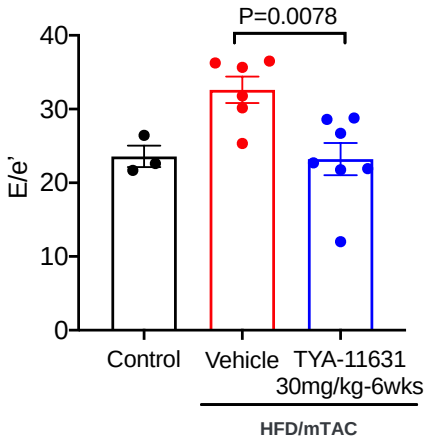


Glucose-tolerance tests were performed by IP injection of glucose (2 g/kg) after 6-h fasting

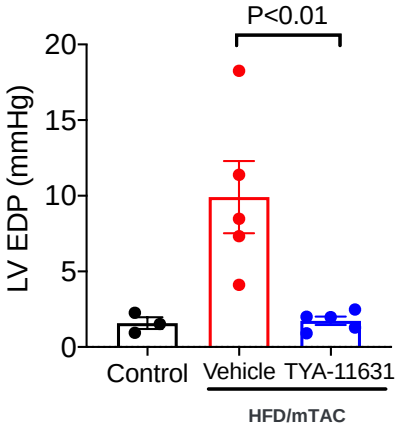
Hypertrophy



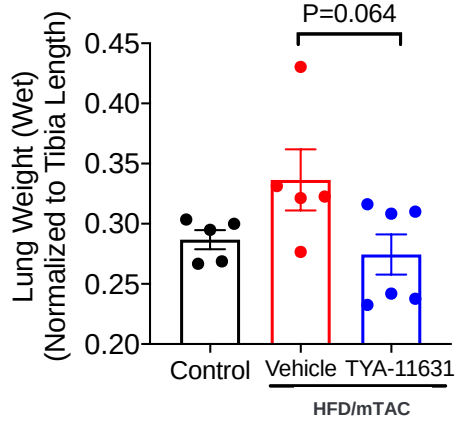
E/e'



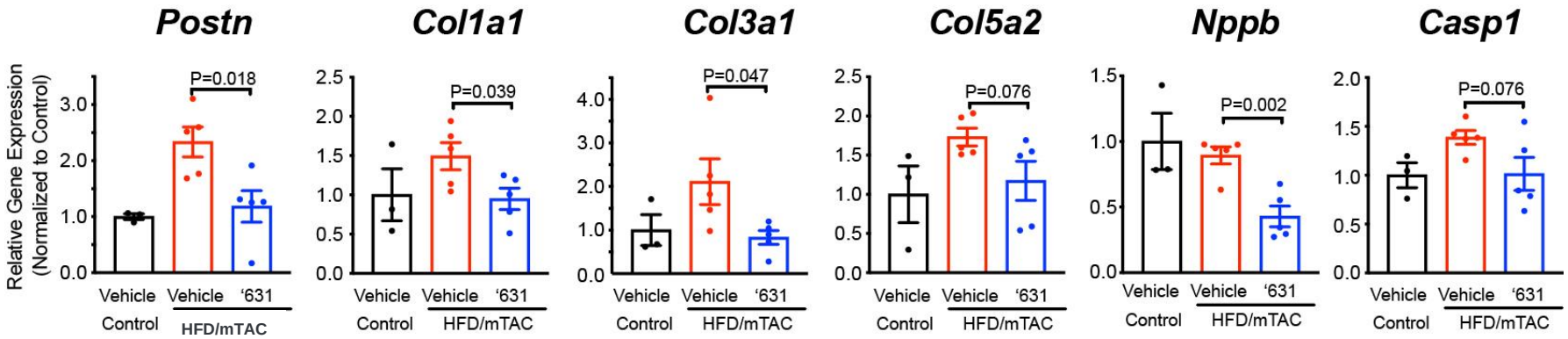
EDP



Lung Weight



Targeted Biomarker Analysis From HFpEF Mouse Hearts



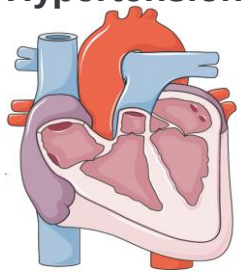
Gene analysis shows reduction of gene expression associated with fibrosis, cardiac function, and inflammation in hearts from TYA-11631 treated HFpEF animals

TYA-11631 Efficacy in a Second HFpEF Model Induced by HFD/L-NAME

Wildtype C57/BL6 mice
Feed with high fat diet containing 0.1% L-NAME

8wks

Obesity
Hypertension



HFpEF

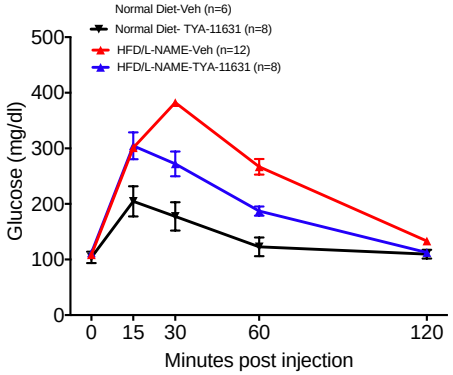
Nature **568,** 351–356 (2019). Joe Hill's lab

- **WT Mice on HFD/0.1% L-NAME for 8wks developed obesity, hypertension and diastolic dysfunction, recapitulating HFpEF phenotypes in humans**
- **Test TYA-11631 (PO, QD) in the established *HFpEF* (HFD/L-NAME) Model**

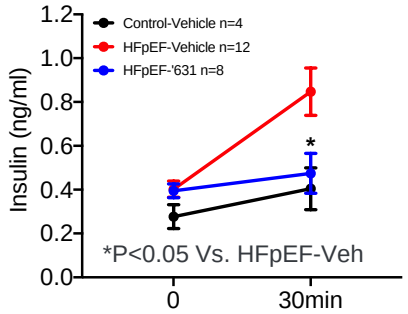
Randomization & Group

Group	Test Article	Numb.
Control	Vehicle	5
	TYA-11631 30mg/kg	7
HFD/L-NAME	Vehicle	12
	TYA-11631 30mg/kg	8

GTT

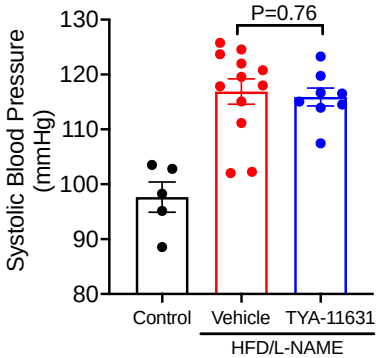


Insulin

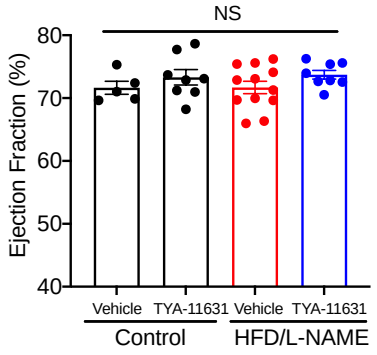


* Plasma insulin level during GTT at 0 and 30min post IP injection of glucose

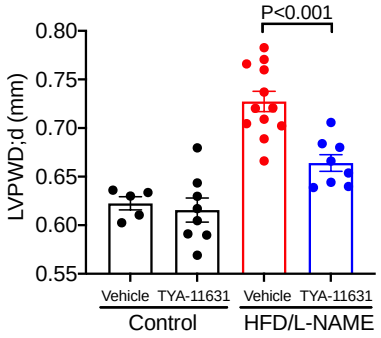
Blood Pressure



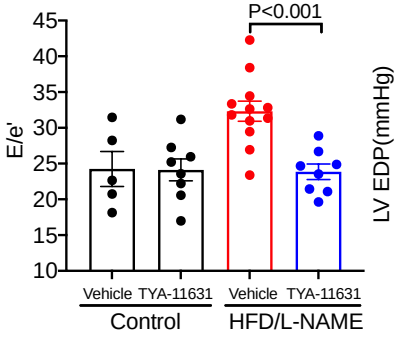
Ejection Fraction



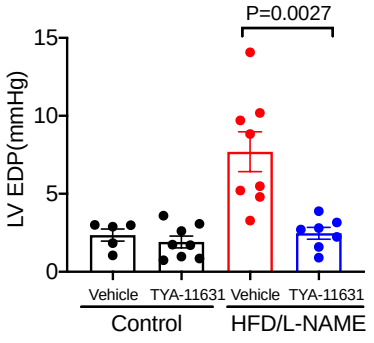
Hypertrophy



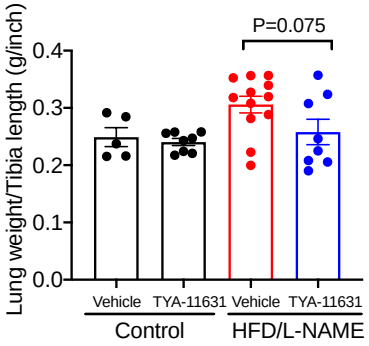
E/e'



EDP



Lung Weight



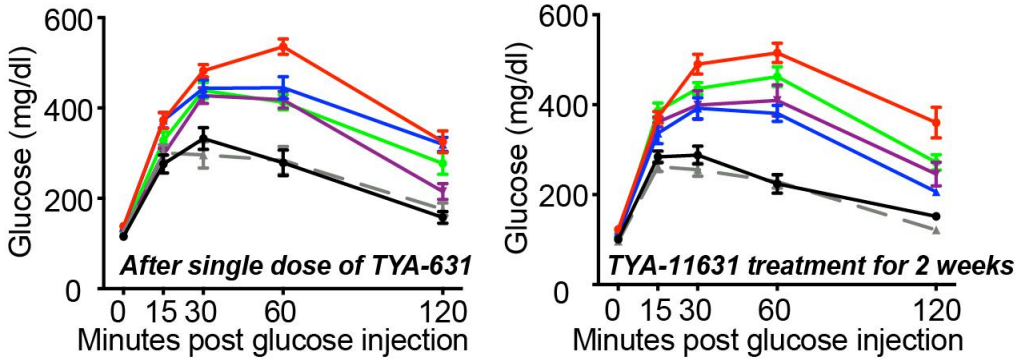
Treatment with TYA-11631 (30 mg/kg) in HFD/L-NAME model for 9 Weeks improves glucose tolerance, insulin sensitivity, LV remodeling and diastolic function. No adverse effects have been observed.

TYA-11631 Efficacy in Diet Induced Obese Model & Summary

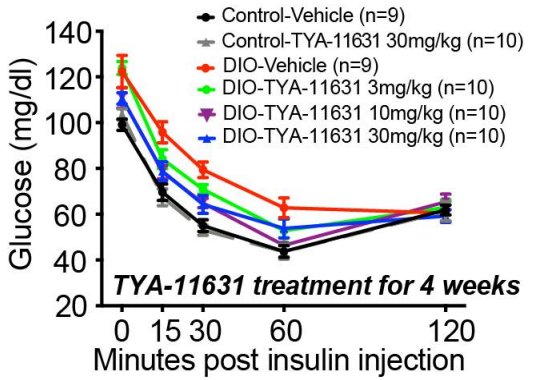
To further assess potential of TYA-11631 treatment to impact glucose metabolism, additional studies have been perused in a died induced obese mouse model

- Dose-dependent improvements were observed in metabolic defects, including glucose tolerance and insulin sensitivity
- TYA-11631 treatment inhibited inflammatory genes in adipose tissue

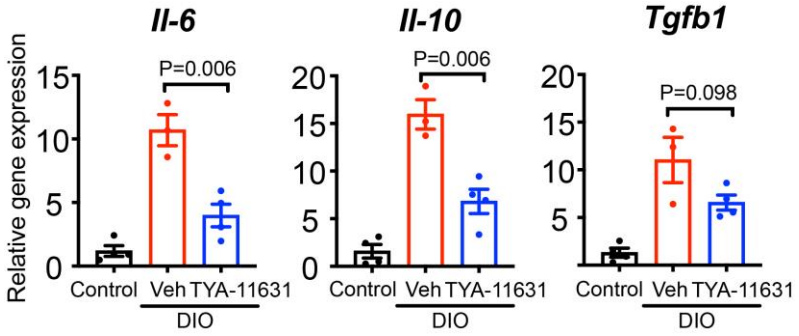
Improvement in Glucose Tolerance (Acute & Chronic)



Improvement in Insulin Resistance



Reduction of Inflammatory Genes in Adipose Tissue After a Single Dose of TYA-11631 (30mg/kg)



- **Robust Efficacy of TYA-11631 (HDAC6 selective inhibitor) has been demonstrated in two HFpEF models and DIO mice across multiple functional endpoints including:**
  - Diastolic dysfunction
  - Cardiac remodeling
  - Metabolic parameters
- **TYA-11631 holds promise as an effective therapeutic for the treatment of HFpEF in humans**