Co-administration of inhibitors of HDAC6 and SGLT2 in murine HFpEF models results in additive improvements in cardiac structural and functional measures

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Combination of HDAC6 and SGLT2 Inhibitors Provides Additive Benefit vs Either Alone, Improves Diastolic Dysfunction without Reducing Ejection Fraction
Gene Expression Analysis Shows Differentiated Profile for HDAC6 Inhibitor; Highlights Orthogonal Mechanism of Action

INTRODUCTION

Background

Heart failure with preserved ejection fraction (HFpEF) is a form of heart failure characterized by diastolic dysfunction and associated with high morbidity, mortality and significant unmet need.

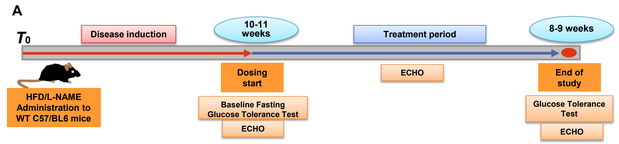
We have previously demonstrated that selective inhibition of histone deacetylase 6 (HDAC6) has direct and systemic effects on multiple pathways linked to HFpEF pathogenesis. In a mouse model of HFpEF using a high-fat diet (HFD) and L-NAME, positive effects on diastolic dysfunction and left ventricular thickness of the heart, as well as overall improvements in systemic inflammation and metabolism, were achieved. Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved by the FDA for HFpEF patients, works as expected in this model, confirming the potential clinical translatability of results seen with HDAC6 inhibitors. In head-to-head studies, the beneficial effects of HDAC6 inhibition have been shown to be comparable to empagliflozin, while demonstrating a distinct mechanism of action in gene expression analysis. (1)

TN-301, a highly selective HDAC6 inhibitor, is being advanced into clinical development for the potential treatment of HFpEF. In a Phase 1 clinical trial, TN-301 has been well-tolerated across a broad range of doses and demonstrated target engagement. (HFSA 2023; Poster #417/ Control #1761)

Purpose

In this study, utilizing TYA-018 (a TN-301-like HDAC6-specific inhibitor) we investigate the additive or synergistic effects of combining HDAC6 and SGLT2 inhibition to improve cardiac function in a two-hit mouse model of HFpEF.

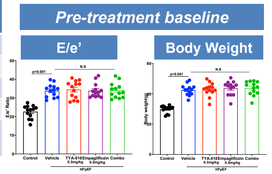
STUDY DESIGN



B

Group	Test Article	Dose (mg/kg, PO)	Number
Control	Vehicle	N/A	13
HFpEF (HFD / L-NAME)	Vehicle	N/A	13
	TYA-018	0.3	13
	Empagliflozin	0.5	13
	TYA-018 + Empagliflozin	0.3 & 0.5	13

C

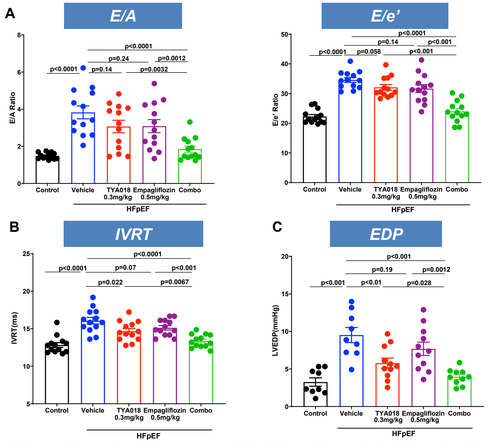


A. Mice were evaluated at 0-, 4-, and 8-weeks post-dosing by echocardiography and by terminal PV loop at endpoint (9 weeks), with cardiac tissue harvested and used for transcriptional profiling by RNA-Seq.
B. Treatment doses are selected empirically and in the lower treatment dose range to allow for comparing partial efficacy of each agent, as well as broader safety margin in clinical settings and increased patient accessibility and tolerability.
C. Pre-treatment evaluations including body measurements and diastolic function indicators were comparable across disease groups.

RESULTS

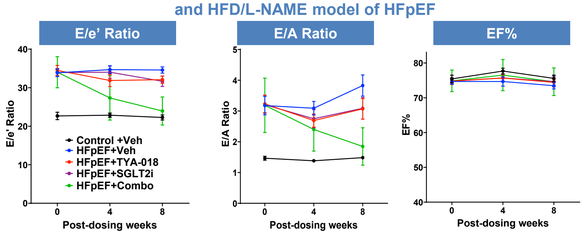
CARDIAC FUNCTIONAL IMPROVEMENTS OBSERVED AT 8-WEEKS OF TREATMENT

End-of-Study Echocardiographic Assessments of Cardiac Function by Non-invasive Doppler Analysis Conducted at 8 Weeks and Terminal PV Loop Analysis at 9 Weeks in Control and HFD/L-NAME Model of HFpEF



A-B. Echocardiography measurements (E/A, E/e', and Isovolumic Relaxation Time (IVRT) demonstrated that low doses of HDAC6- and SGLT2- inhibition did not robustly improve diastolic dysfunction, with only the combined treatment group showing consistently significant improvement relative to vehicle.
C. End diastolic pressure (EDP) by terminal PV loop showed HDAC6-inhibition and combined inhibition both significantly improved EDP relative to vehicle, with the combined inhibition group also showing improvement relative to HDAC6-inhibition alone.

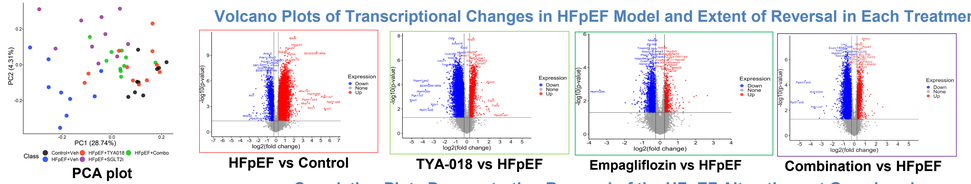
Longitudinal Echocardiographic Assessment of Cardiac Function in Control and HFD/L-NAME model of HFpEF



Substantial improvement of diastolic function indicators E/A and E/e' in the combined HDAC6- and SGLT2-inhibitors treatment group, as compared to vehicle or each treatment alone. At endpoint, both measurements were very close to Control group levels. Ejection Fraction (EF) did not show any marked change in any treatment group.

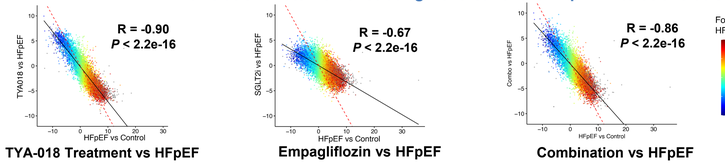
COMBINATION THERAPY RESTORES HEART TRANSCRIPTIONAL ACTIVITY OF HFPEF ANIMALS TO WT CONTROL

Volcano Plots of Transcriptional Changes in HFpEF Model and Extent of Reversal in Each Treatment Group



TYA-018 and Combination treatment demonstrate largest reversal of HFpEF transcriptional changes.

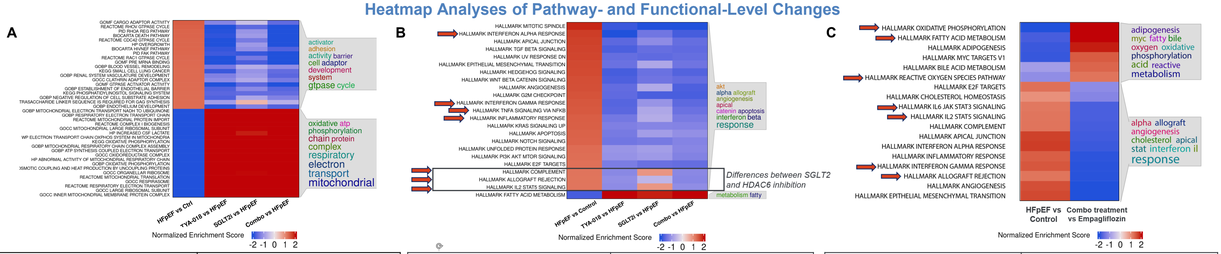
Correlation Plots Demonstrating Reversal of the HFpEF Alterations at Gene Level



Perfect reversal will have a correlation of -1 with the HFpEF effect. Our findings exhibit the substantial normalization of transcriptional changes at gene level in TYA-018 and Combination treatment groups.

COMBINATION TREATMENT SPECIFICALLY IMPROVES OXIDATIVE PHOSPHORYLATION, LIPID METABOLISM, AND PRO-INFLAMMATORY PATHWAYS AS SEEN IN GENE SET ENRICHMENT ANALYSES

Heatmap Analyses of Pathway- and Functional-Level Changes



Rho GTPase and FAK associated pathways are enriched in HFpEF vs Control and normalized substantially after all treatments.	Mitochondrial metabolism is negatively enriched in HFpEF vs Control, and normalized after all treatments	
Inflammatory pathways are enriched in HFpEF vs Control and normalized to larger degrees in Combination and TYA-018.	Fatty acid metabolism is depleted in HFpEF vs Control and normalized after all treatments.	
Significant Improvement in Cardiac Metabolism and Response to Reactive Oxygen Species.	Significant Reduction in Inflammatory State (JAK-STAT axis, IL2, TNFa), Fibrosis and Epithelial Mesenchymal Transition.	

A. Combination therapy significantly restores normal heart transcriptional activity at pathway level in HFpEF. Words in the word cloud on the right show most frequent terms in the gene set names and their font size represent relative frequency.

B. Combination therapy and TYA-018 reverse pro-inflammatory gene expression in HFpEF, and Empagliflozin does so to a lesser degree.

C. Combination therapy specifically improved OXPHOS and lipid metabolism above and beyond SGLT2i, and resulted in extensive inflammatory state retreat In Combination group.

CONCLUSIONS

In our comprehensive research on TN-301, a highly selective HDAC6 inhibitor for HFpEF treatment, we observed significant benefits. Both in vivo pharmacology and whole transcriptome RNA-seq analyses revealed additive and synergistic benefits of HDAC6 and SGLT2 inhibition. These effects significantly improved diastolic function and gene expression in the HFpEF heart. Further analysis emphasized distinct and complementary mechanisms of action from HDAC6 inhibition, reinforcing its potential as a standalone therapeutic and in conjunction with SGLT2 inhibitors. Corroborating previous data, it's evident that HDAC6 inhibitors, like TN-301, are potent treatments for HFpEF, and in select cases, surpass SGLT2 inhibitors. The synthesis of these findings underscores the potential of TN-301 for HFpEF treatment, both as a singular or combined approach.

REFERENCES

1. Ranjbarvaziri S, *et al.* American Heart Assoc. Congress. 2022
2. Schiattarella G, *et al.* Nature 2019
3. Lam CSP, et al. *Eur Heart J* (2018) 39, 2780–2792.
4. Data on file at Tenaya