Empagliflozin Mediates Acute and Chronic metabolic changes in a Cardiospecific mechanism of Action

Sarnoff Fellow:	Nicholas Forelli
Preceptors:	Zoltan Arany, MD, PhD
Host Institution:	The University of Pennsylvania, Perelman School of Medicine
Sponsor:	Richard Kitsis, MD
Medical School:	Albert Einstein College of Medicine

Background: Sodium-glucose cotransport inhibitors (SGLTi), such as empagliflozin, have rapidly become a mainstay therapy for patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Despite their significant clinical benefit, a clear cardiac mechanism of action has yet to be established. Our work aims towards uncovering the biochemical basis for the use of SGLT2i in heart failure. In our approach we've developed a methodology to study steady-state metabolism in human myocardium *ex vivo* which has elucidated that SGLT2i have a direct cardiometabolic effect.

Methods: Stable isotopes of lactate, 3-hydroxybutyrate, valine, glutamine, and glucose were infused into human myocardial tissue in control and empagliflozin treated groups. Isotopic labeling and metabolic flux were determined through liquid-chromatography high-resolution mass spectrometry (HRMS).

Results: Labeled citric acid cycle intermediates are increased in empagliflozin treated groups within our acute treatment groups. Enrichment in isotopic malate, fumarate, and succinate within a 70-minute isolated cardiac perfusion suggest acute metabolic changes occur with empagliflozin.

Conclusion: Our data suggests that empagliflozin mediates acute metabolic changes in a cardio-specific mechanism of action.