

# NEW SERCA2A STIMULATOR COMPOUNDS RESTORE IMPAIRED SERCA2A FUNCTION IN A RAT MODEL OF DIABETIC CARDIOMYOPATHY

Arici Martina<sup>1</sup>, Torre E.<sup>1</sup>, Ferrandi M.<sup>2</sup>, Barassi P.<sup>2</sup>, Lodrini A.M.<sup>1</sup>, Luraghi A.<sup>1</sup>, Zaza A.<sup>1</sup>, Peri F.<sup>1</sup>, Rocchetti M.<sup>1</sup>

<sup>1</sup>Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy.

<sup>2</sup>Windtree Therapeutics Inc., Warrington, Pennsylvania.

## BACKGROUND

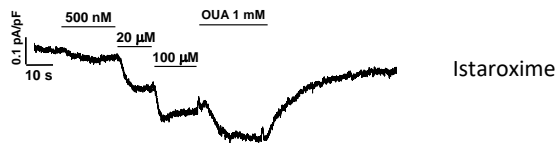
Recovery of SERCA2a function in heart failure may improve diastolic dysfunction. Istaroxime is a luso-inotropic compound resulting from SERCA2a stimulation and Na<sup>+</sup>/K<sup>+</sup>-ATPase (NKA) inhibition. New istaroxime follow on compounds (Cpds) have been recently developed to isolate pure SERCA2a stimulators able to restore cardiac pathologies with impaired diastolic function.

## AIM

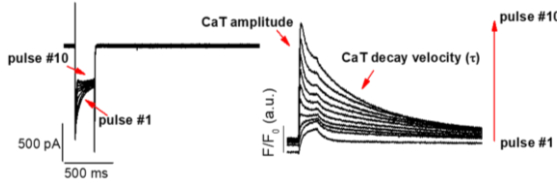
To characterize effects of istaroxime derivatives on SERCA2a and NKA, by using rat ventricular myocytes (CMs) from CTR and streptozotocin (STZ)-treated rats developing diabetic cardiomyopathy.

## METHODS

A. NKA current ( $I_{NaK}$ ) (holding current at -40 mV) in CTR CMs to evaluate affinity for rat NKA



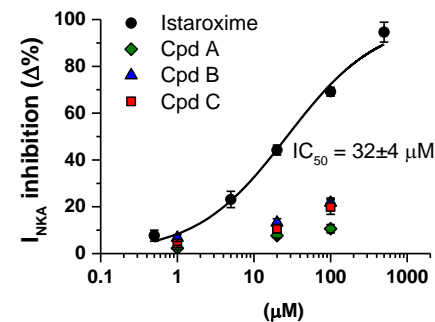
B. SR Ca<sup>2+</sup> uptake kinetics in STZ CMs to evaluate SERCA2a stimulation in a model with downregulated SERCA2a.



## MODEL



## RESULT\_1

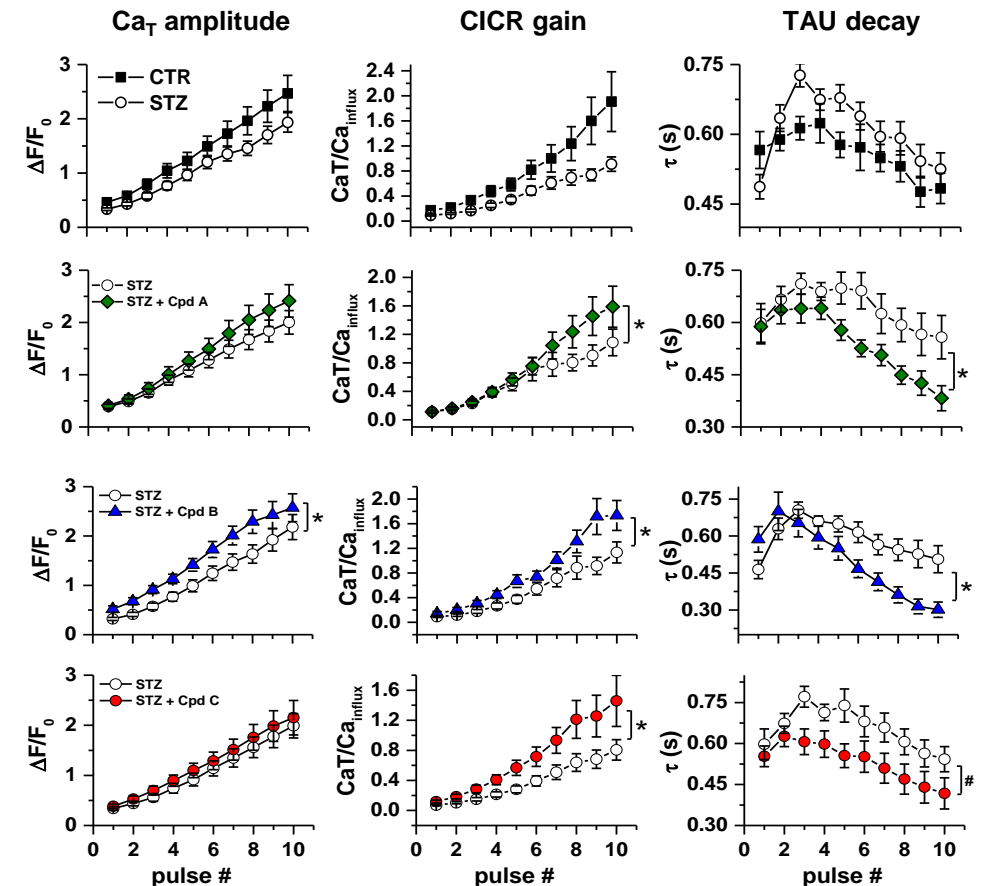


Effects of Istaroxime and its derivatives on NKA. Dose-dependent  $I_{NaK}$  inhibition by Istaroxime and its derivatives in CTR rat CMs.

## FUTURE PERSPECTIVES

1. Complete the *in vitro* Cpds effects in STZ-CMs
2. Test the *in vivo* Cpds effects in STZ-treated rats.
3. Understanding the role of SERCA2a stimulation by the new Cpds in smooth muscle cells to expand their therapeutic potential.

## RESULT\_2



SR Ca<sup>2+</sup> uptake kinetics in CTR and STZ-CMs with or w/o Cpds A, B and C. Average values of Ca<sub>T</sub> parameters measured during each of the first 10 pulses after SR depletion under NCX blockade.