A novel drug candidate targeting the adrenergic regulation of the SERCA2 complex protect the heart from myocardial infarct injury

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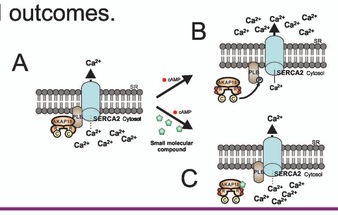
INTRODUCTION

The β-adrenergic receptor-cAMP-protein kinase A (PKA) signaling pathway regulates heart rate and contractility. Central in this regulation is the supramolecular complex PKA/AKAP18δ/PLB/SERCA2 (Fig 1A). This complex controls the adrenergic effect on Ca^{2+} re-uptake and heart relaxation (Fig 1B). Discrete control of PLB phosphorylation is facilitated by the AKAP18δ, which holds PKA and PLB in close proximity. We aimed to find small molecular compounds that disrupt the AKAP18/δ-PLB protein-protein interaction (PPI) (Fig 1C) as this may protect from ischemia reperfusion injury (IRI) in the treatment of acute myocardial infarction. Total infarct size is a key indicator of post MI outcomes.



CONCLUSION

First small molecule to target the AKAP18δ-PLB interaction. We propose that specifically blocking the adrenergic regulation of SERCA2-activity is beneficial and provide evidence that small molecular PPI disruptors that have such a mechanism-of-action reduce infarct size and preserve cardiac function.

RESULTS

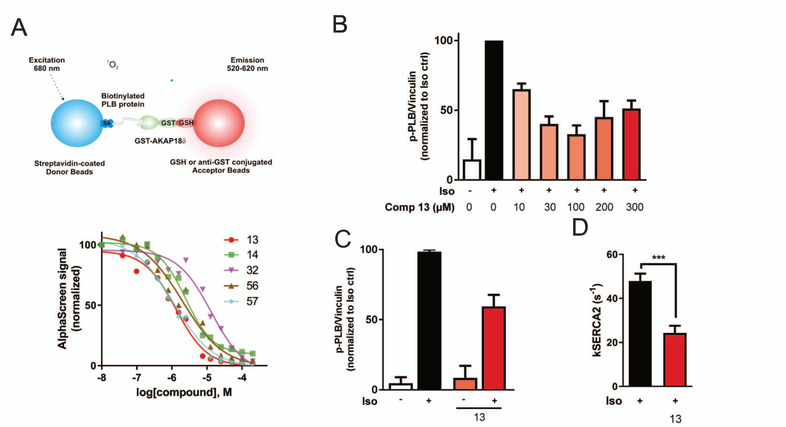


Figure 2: ***In vitro*** **testing of compound 13**. A) Principle of the bead-based Alphascreen assay. AKAP18 and PLB binding with increasing concentration of diferent compouns. C) PLB phosphorylation (p-PLB) on H9C2 cell line. D) p-PLB on rat adult cardiomyocytes. E) SERCA2 activity determined by field stimulated cardiomyocytes.

Anesthesia	IV injection 5 min	Monitoring 30 min	Iso/saline 5 min	Harvest tissue

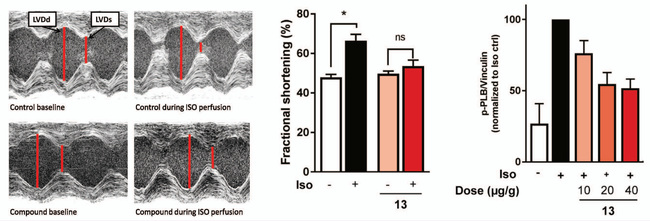
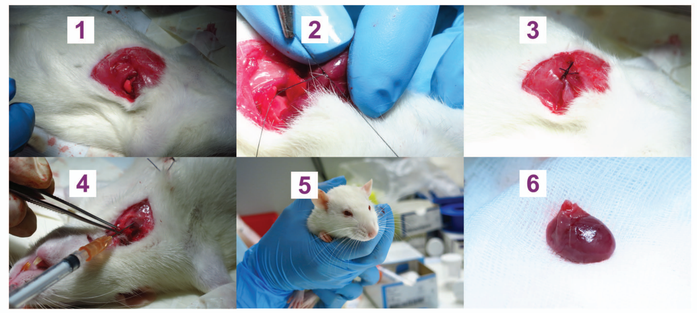
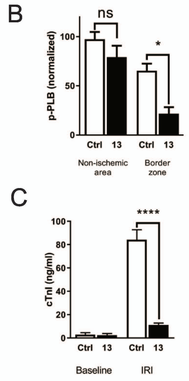


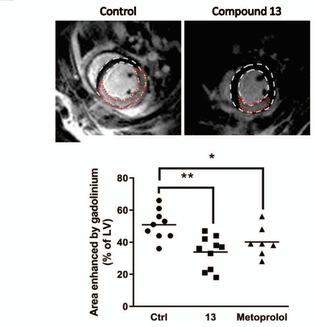
Figure 3: ***In vivo testing of compound 13*** **-** Initial efficacy data on rats. A) Illustration of the protocol. Compound blocks Isoproterenol effect on the heart contractility measured by echocardiography (fractional shortening; FS=(LVDd-LVDs)/LVDd*100) and phospholamban phosphorylation.

Ischemia	10 min	IV injection	20 min	Reperfusion	60 min	Harvest heart





Day 0	Ischemia	10 min	IV injection	20 min	Reperfusion
Day 1	MRI with LGE to measure infarction size				
Day 9	Echo, BP and harvest tissue				



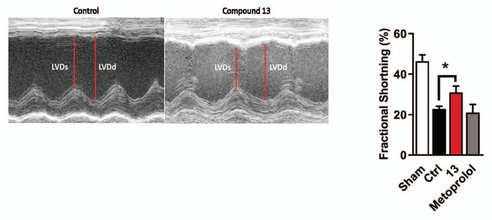


Figure 4: IRI disease model . A) Illustration of the protocol for the ischemia reperfusion injury (IRI) model. B) Compound 13 decrease p-PLB in the border area, but not in the non-ischemic region. C) Compound decreases troponin in blood. D) IIIlustration of the protocol for the IRI model. E) MRI analysis showed a decrease in area enhanced by gadolinium in animals treated with compound 13 and with Metoprolol. F) Echocardiography on day 9 show that treated animals have better contractility.

DISCLOSURE:
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