



KHRS 2021 Scientific Session
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**Biological pacing by non-viral TBX18 Gene Transfer
and TGF- β inhibition**

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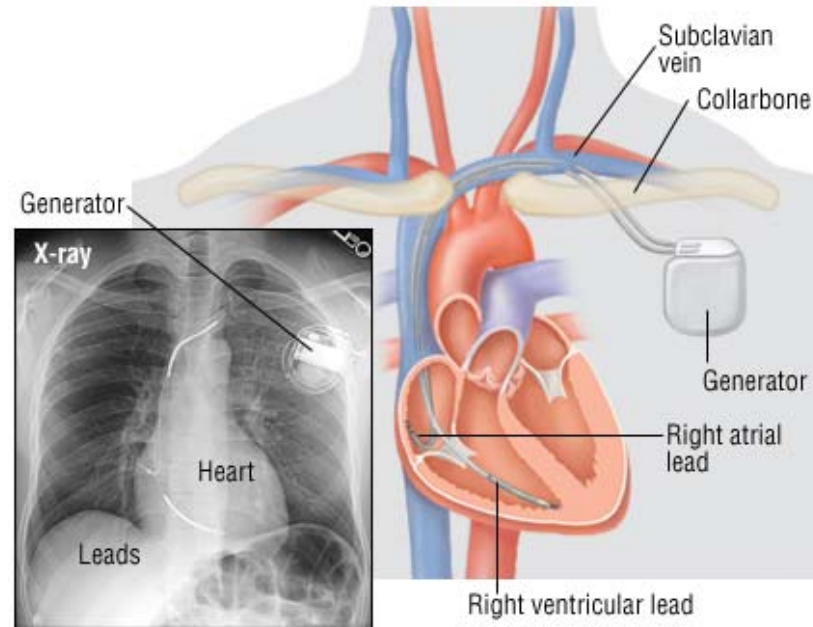
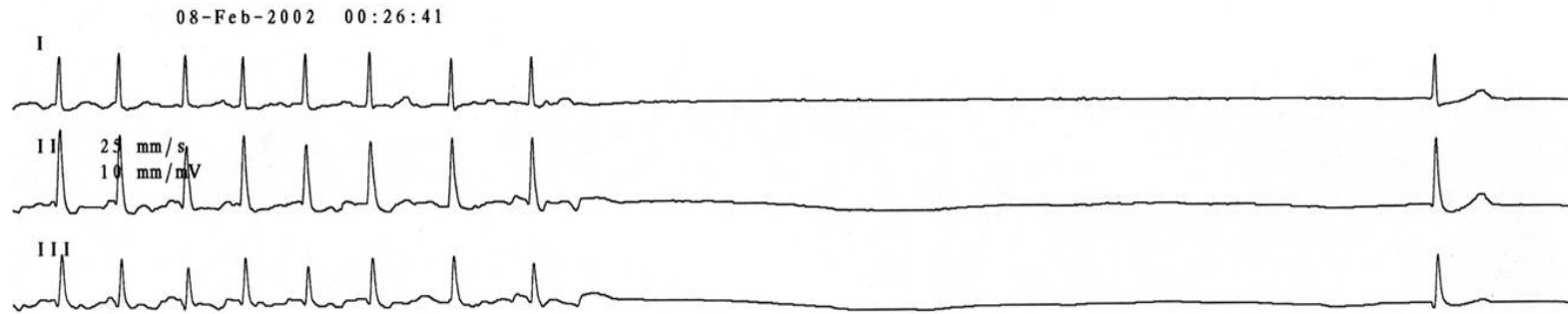
Korean Heart Rhythm Society COI Disclosure

Name of First Author:

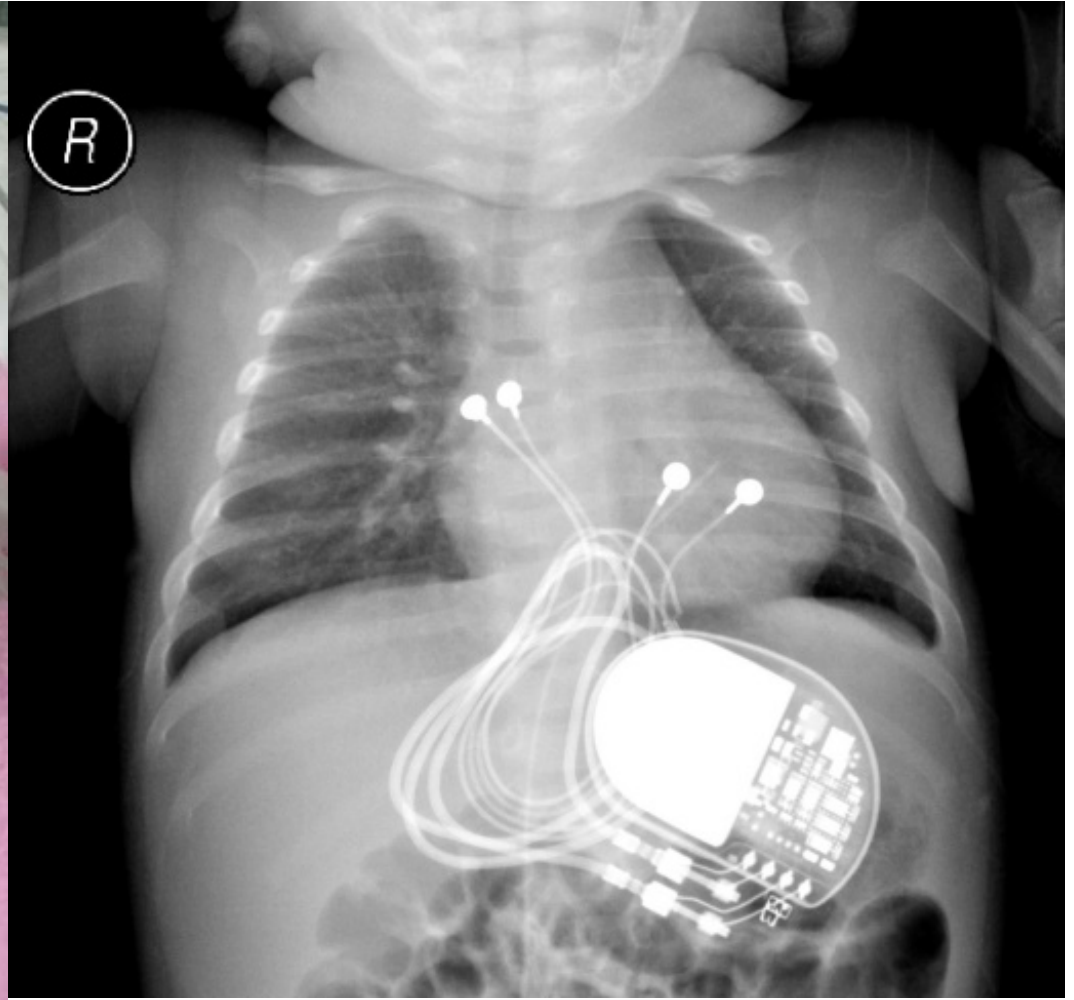
The authors have no financial conflicts of interest
to disclose concerning the presentation

1. What is 'biological pacemaker'?

Pacemaker



Problem of current implantable pacemaker



Problem of current implantable pacemaker



Evolution of pacemaker

Paradigm Shifts in Cardiac Pacemakers

1950s

AC-powered pacemakers tethered to an extension cord (Furman)



1950s

Battery-powered transistorized "wearable" pacemakers (Lillehei/Bakken)



1958

First fully implantable pacemaker (Elmqvist/Senning)



2015

Implantable pacemaker—basic system had not evolved significantly



2016

Leadless pacemaker—the entire device is placed within cardiac chambers

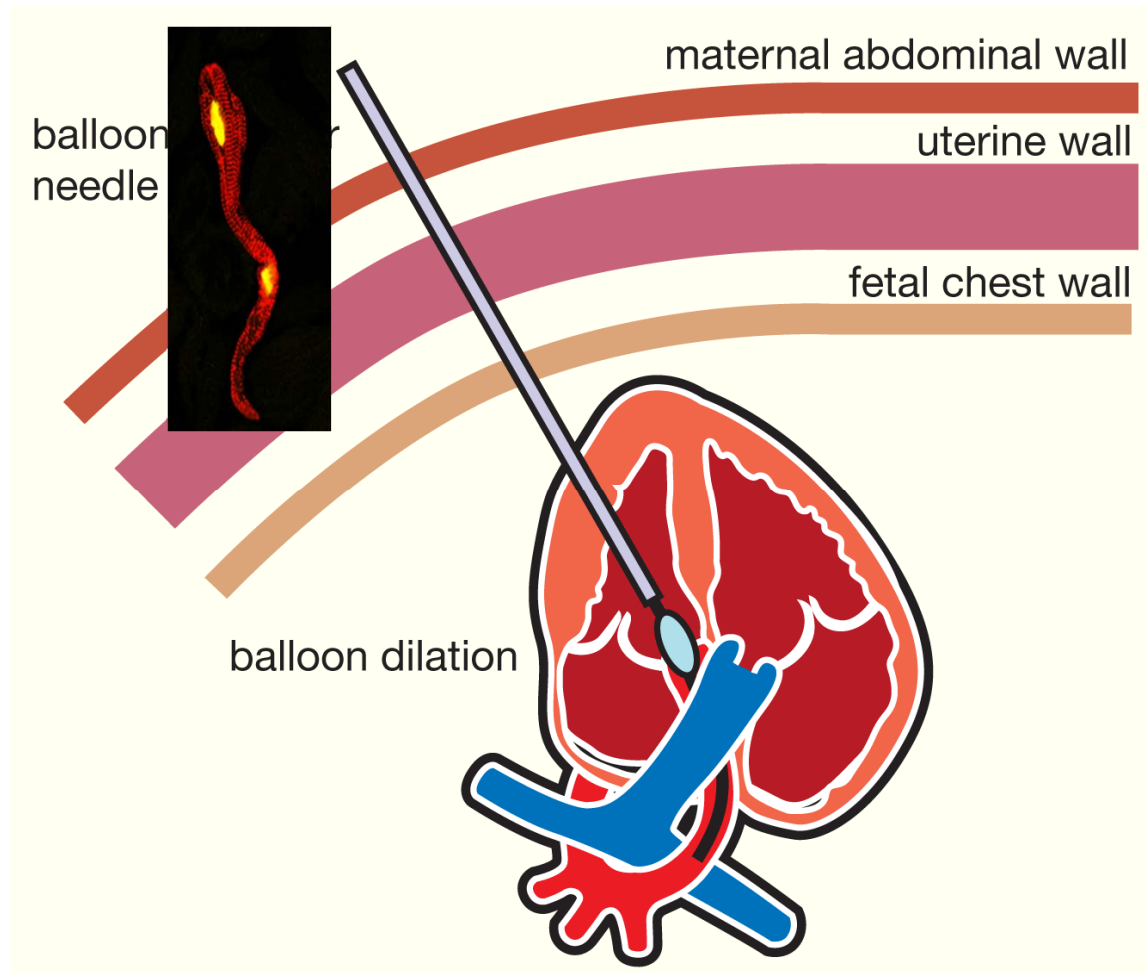


Future

Biological Pacemaker—fundamental treatment of heart block without "foreign body"



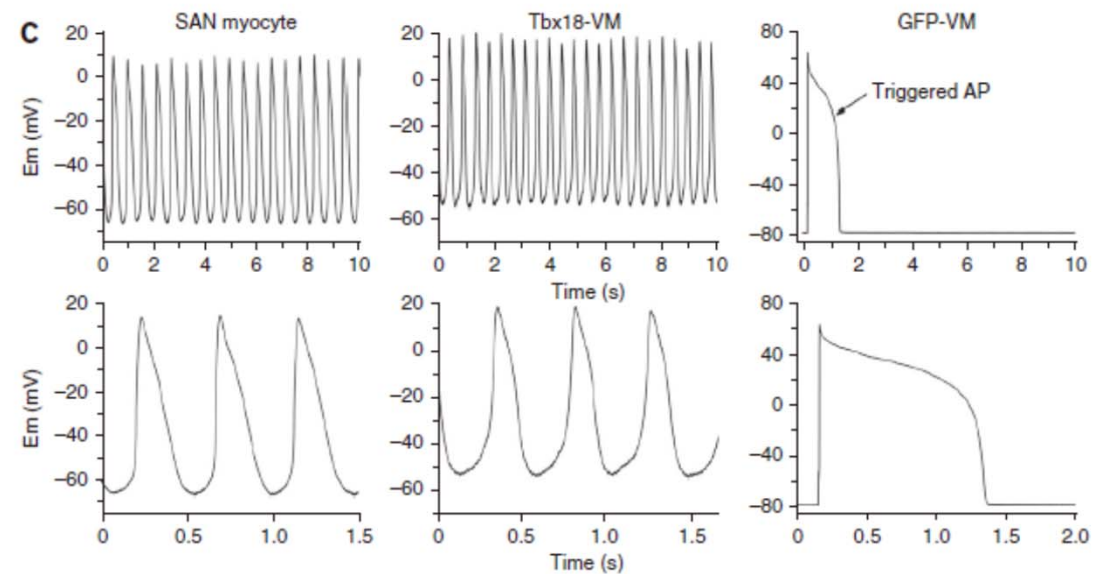
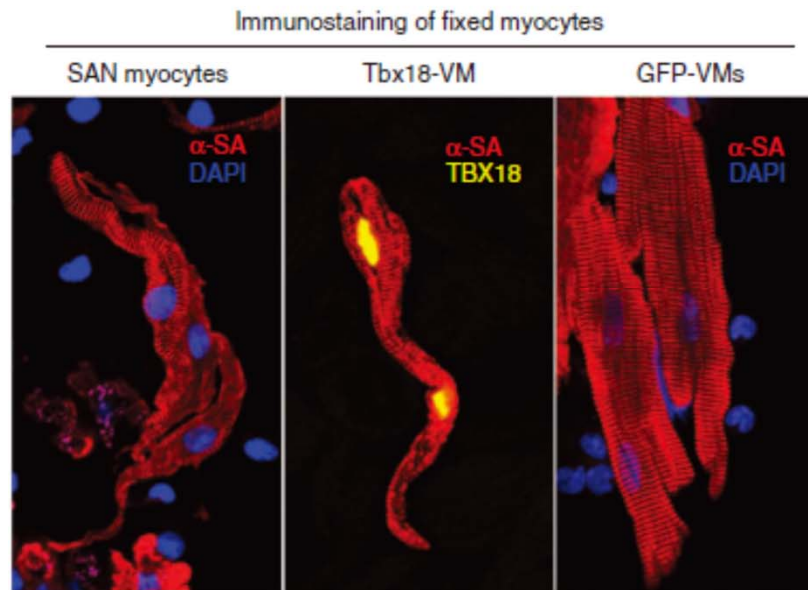
Biological pacemaker



Direct conversion of quiescent cardiomyocytes to pacemaker cells by expression of *Tbx18*

Nidhi Kapoor^{1,2}, Wenbin Liang^{1,2}, Eduardo Marbán¹ & Hee Cheol Cho¹

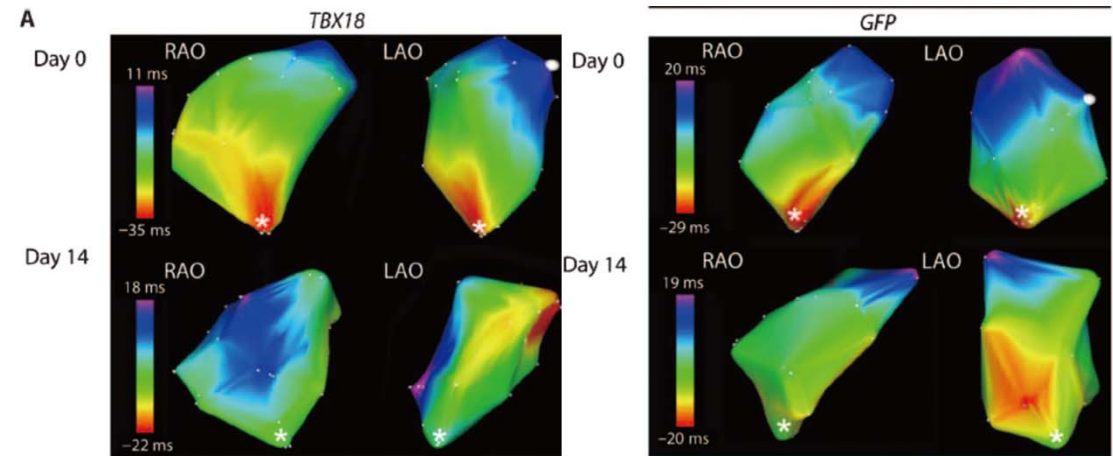
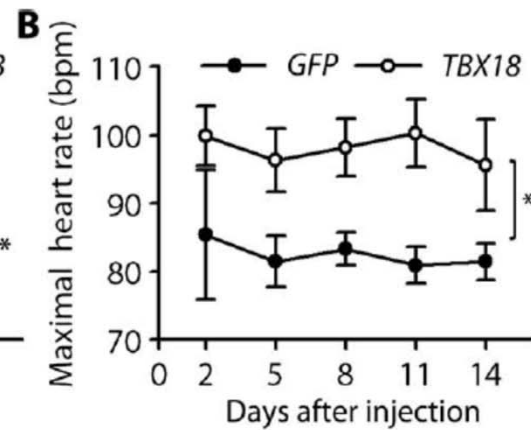
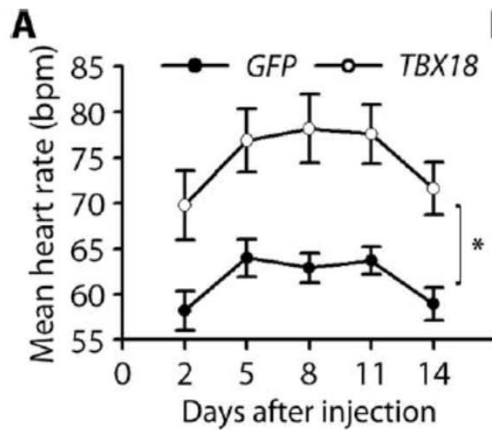
nature
biotechnology



GENE THERAPY

Biological pacemaker created by minimally invasive somatic reprogramming in pigs with complete heart block

Yu-Feng Hu,^{1,2} James Frederick Dawkins,¹ Hee Cheol Cho,¹ Eduardo Marbán,^{1*} Eugenio Cingolani^{1*}

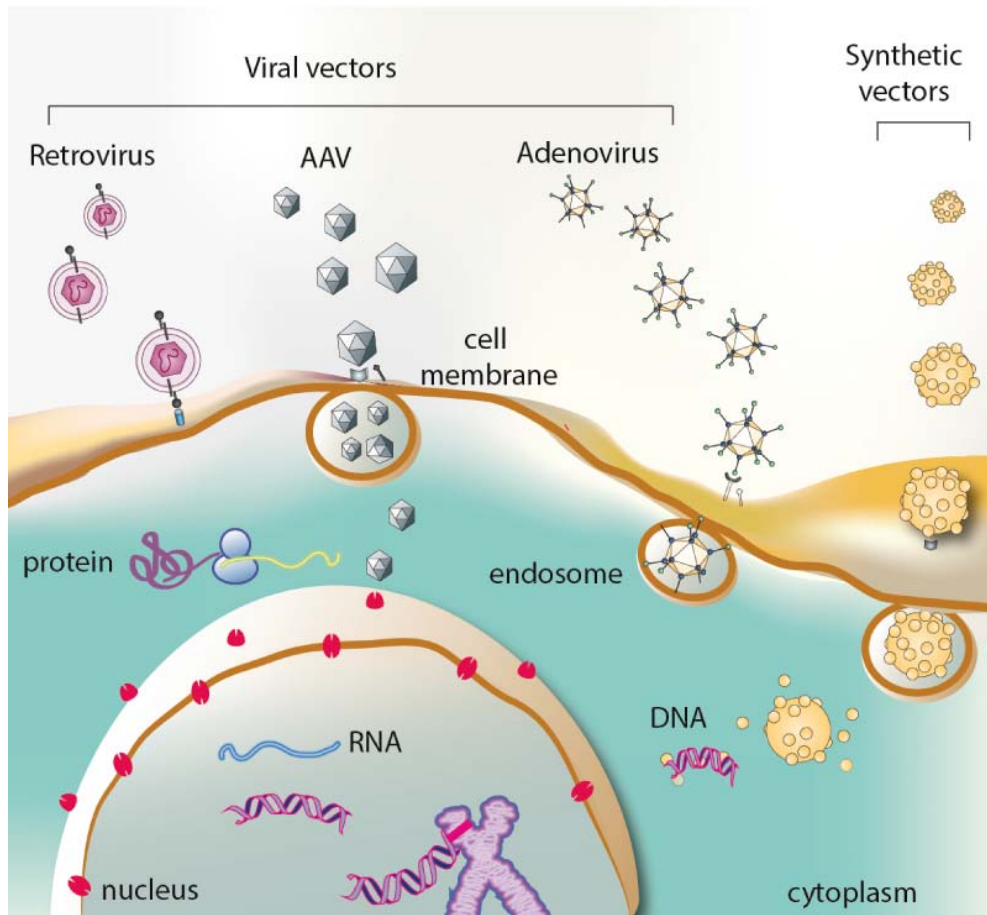


Movement to US - 07/13/2019



2. Vector change: from adenovirus to mRNA

Adenovirus vector vs. modified. mRNA vector



Potential advantages of mRNA gene transfer

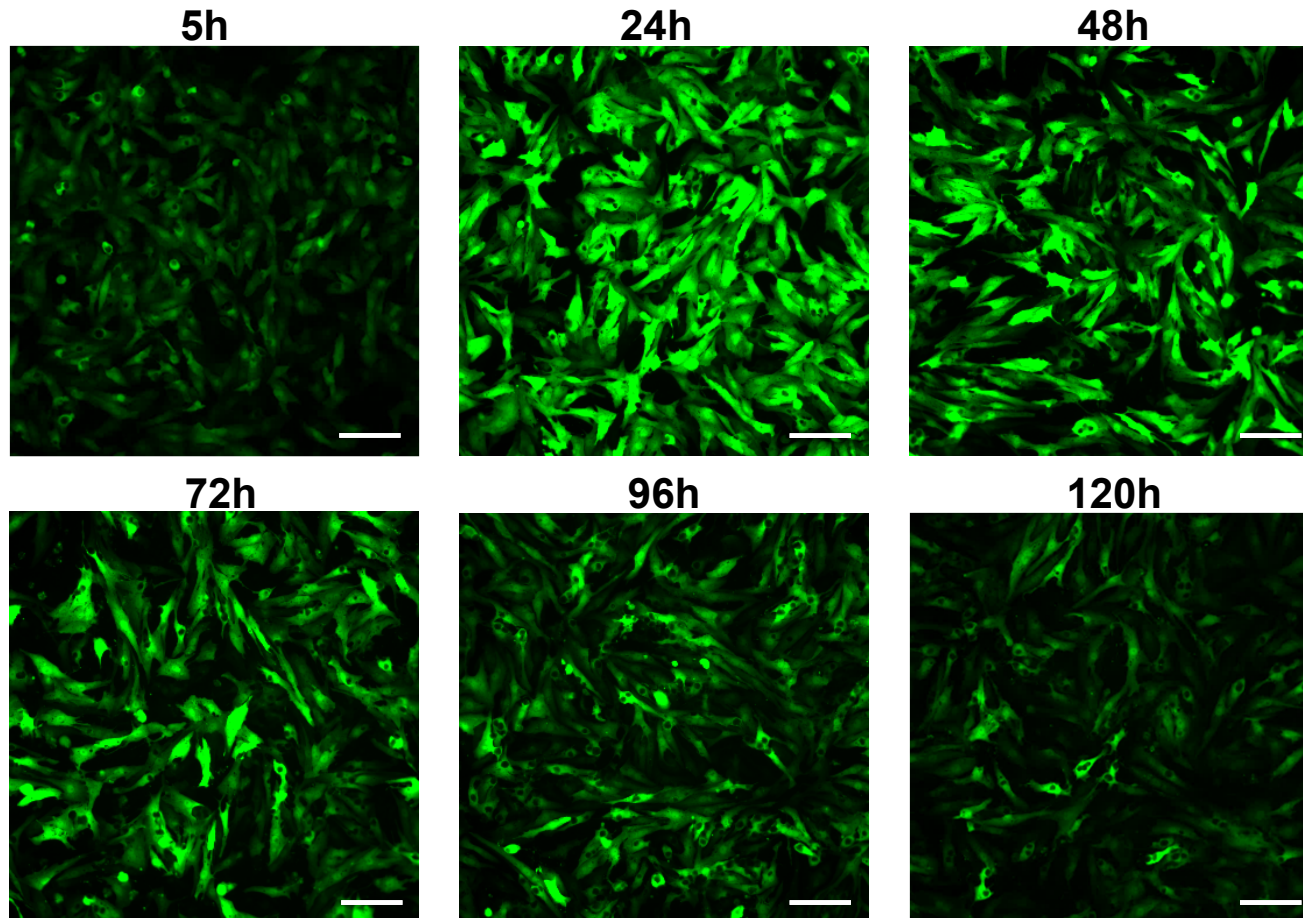
- ✓ Fast peak expression
- ✓ Less or no immunogenic response
 - Repeat injection possible
- ✓ No genomic integration
 - Long-term safety
- ✓ Human use compatibility, in the future

Gene transfer of modified mRNA to cardiomyocytes are fast and highly efficient

GFP mRNA:

333ng/well in a 96-well plate

Neonatal rat ventricular myocytes (NRVMs)



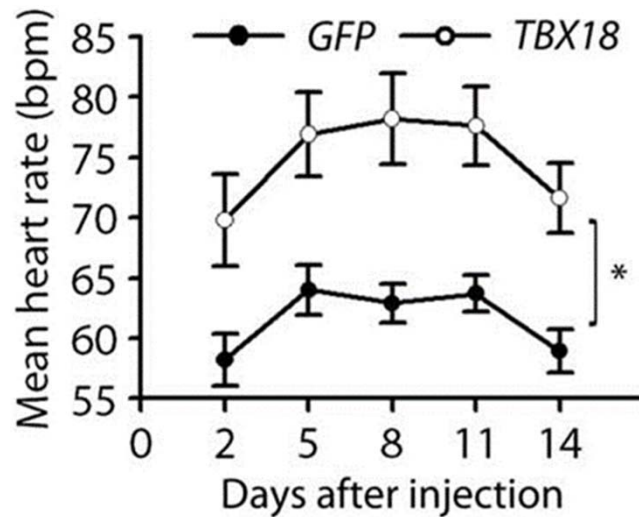
Data from *Jinmo Gu*

**3. For long duration pacing,
Incorporation of TGF- β inhibitor: A8301**

TGF β inhibition

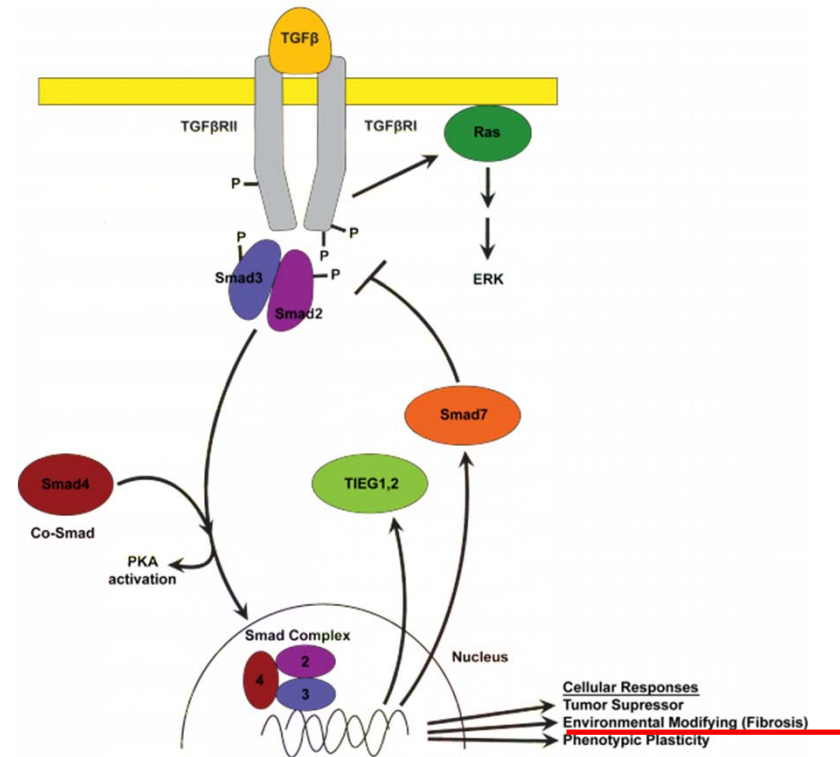
TBX18 iPM with EMT inhibition can produce stable long-term pacing

Function of TBX18 iPM decrease 11days after injection

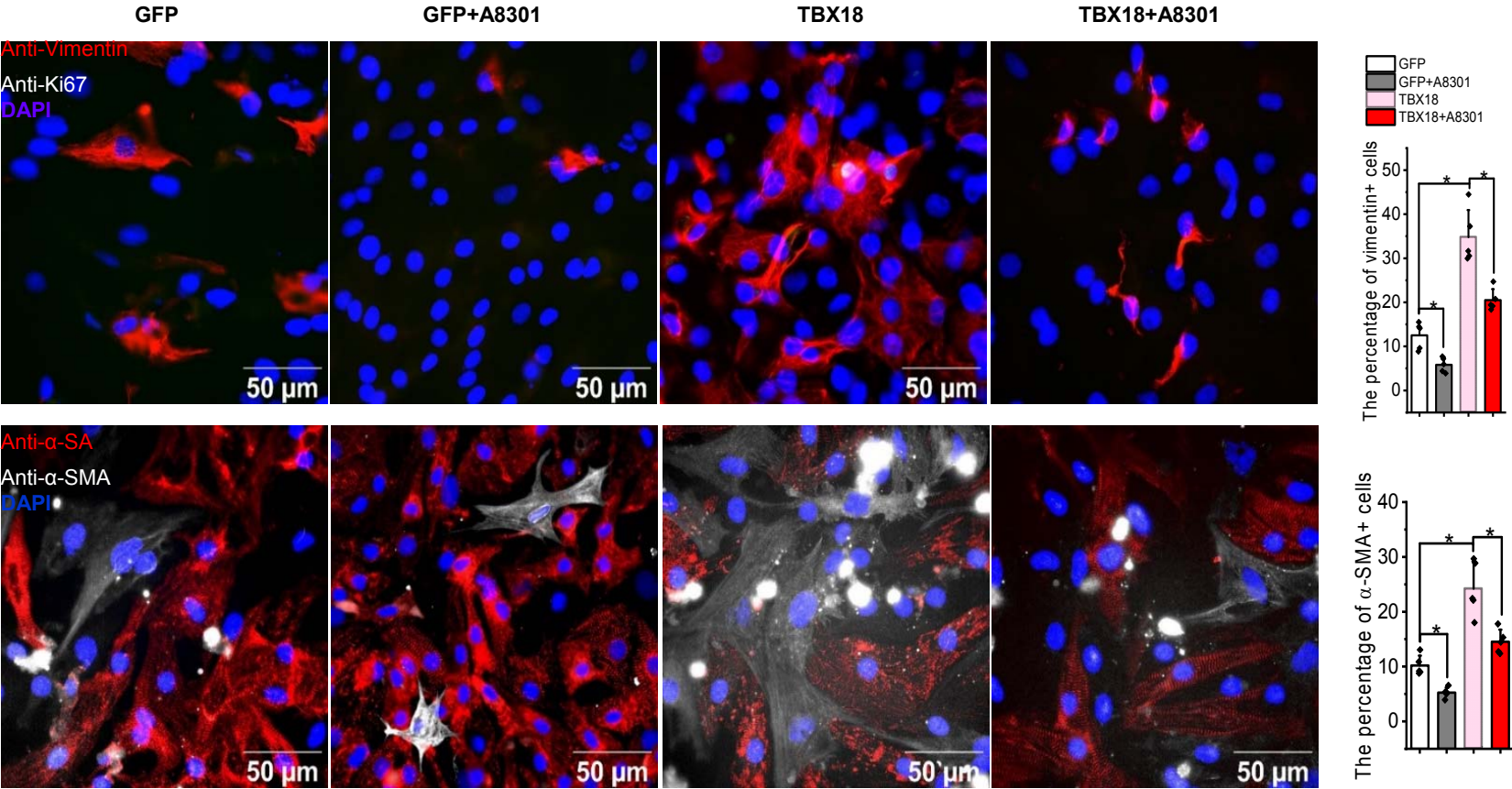


Hu et al., Sci Transl Med 2014

TGFβ signaling pathway is correlated with fibrosis which can contribute source-sink of TBX18 iPM



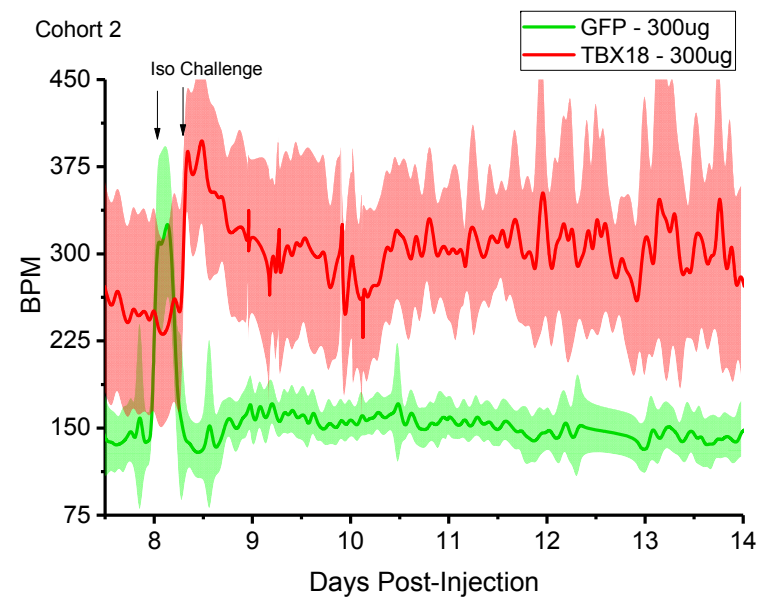
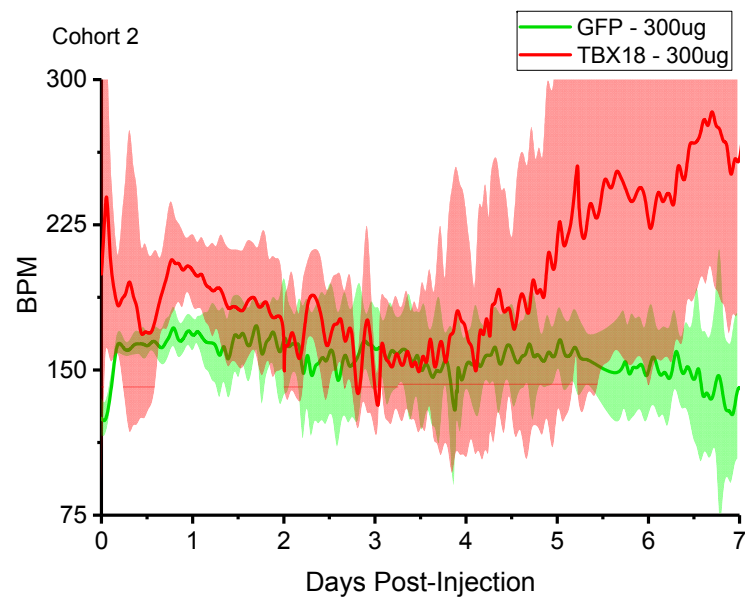
Fibroblast proliferation and differentiation into myofibroblast



Comparison in rat CAVB model : GFP vs. TBX18+A8301

Day -7 ; Complete AV block creation Day 0 ; TBX18 injection & Telemetry implantation Day 7 ; Iso test Day 14

TBX18mRNA + A8301 VS GFPmRNA (n=2, each group)



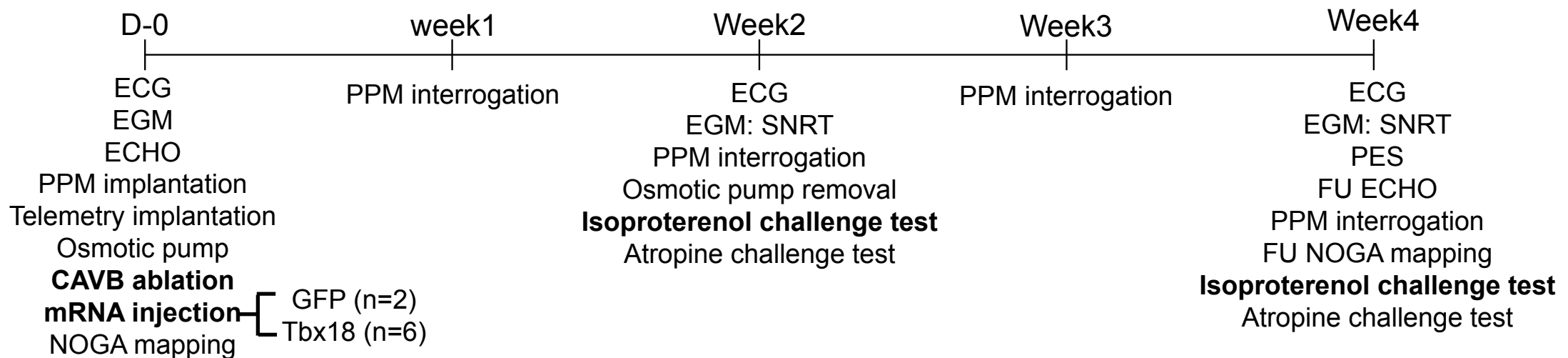
4. Pig study

**Induced biological pacemaker by TBX18 modified mRNA
in porcine CAVB model**

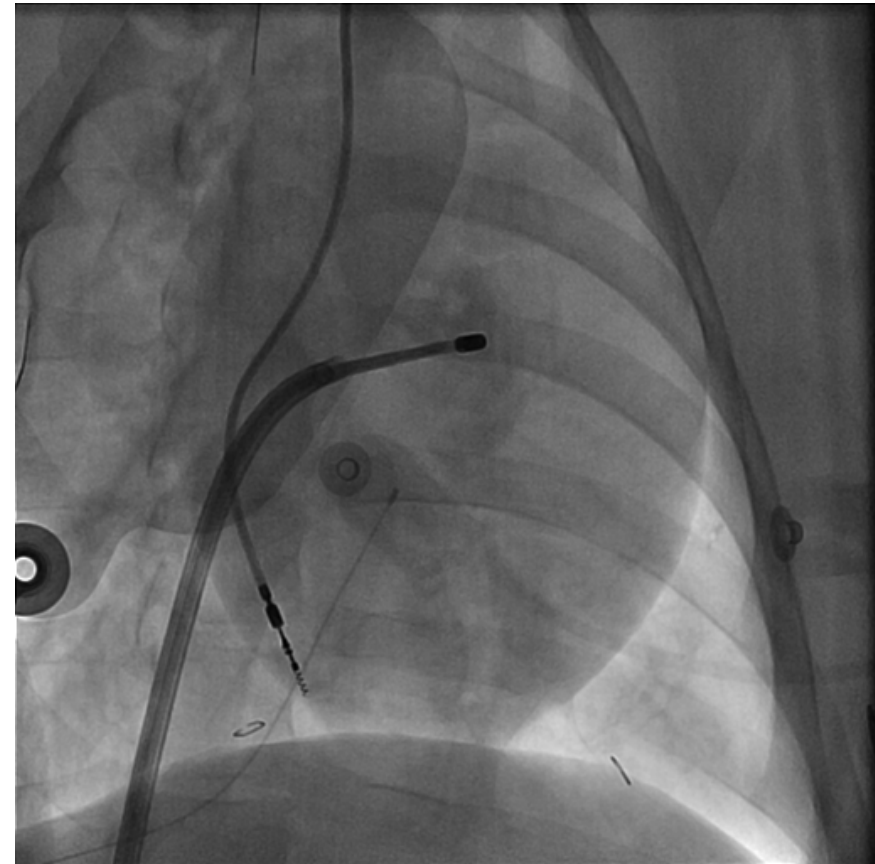
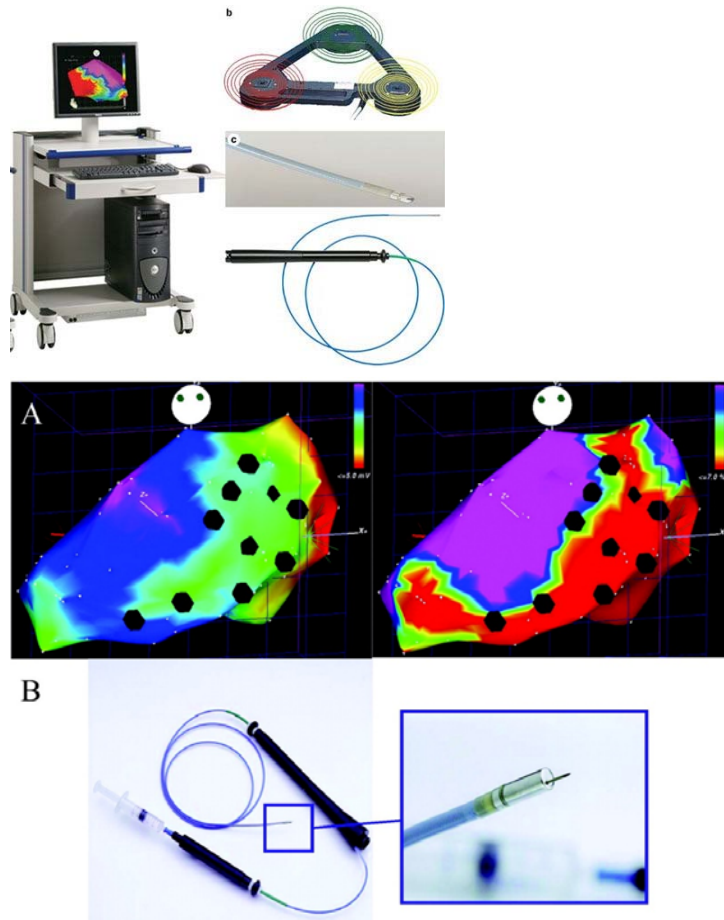
Pig study design

Control animals (n=2): GFP mRNA + TGF β inhibitor (A83-01)

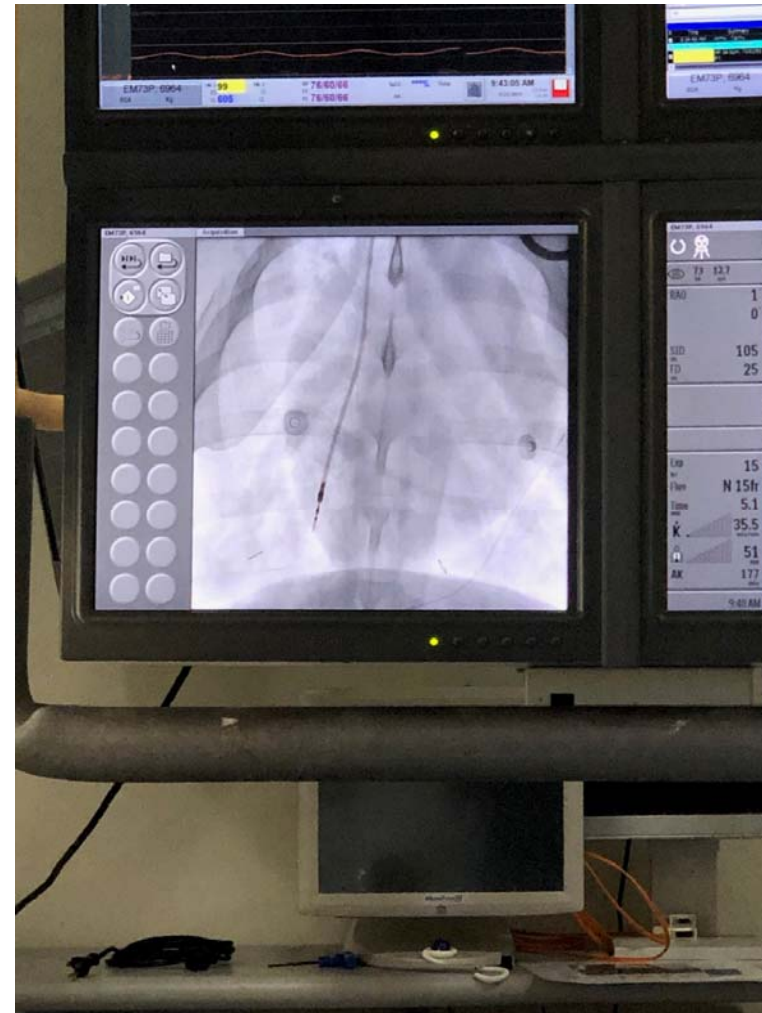
Experimental animals (n=6): TBX18 mRNA + TGF β inhibitor (A83-01)



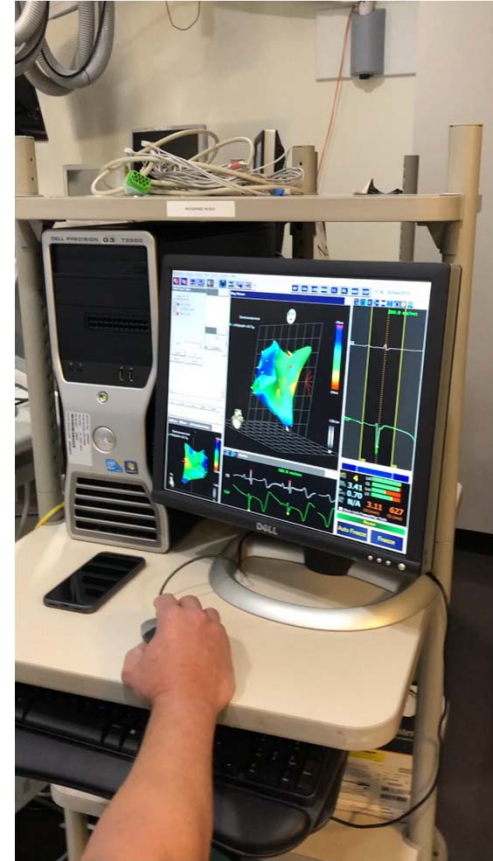
CAVB model & mRNA injection



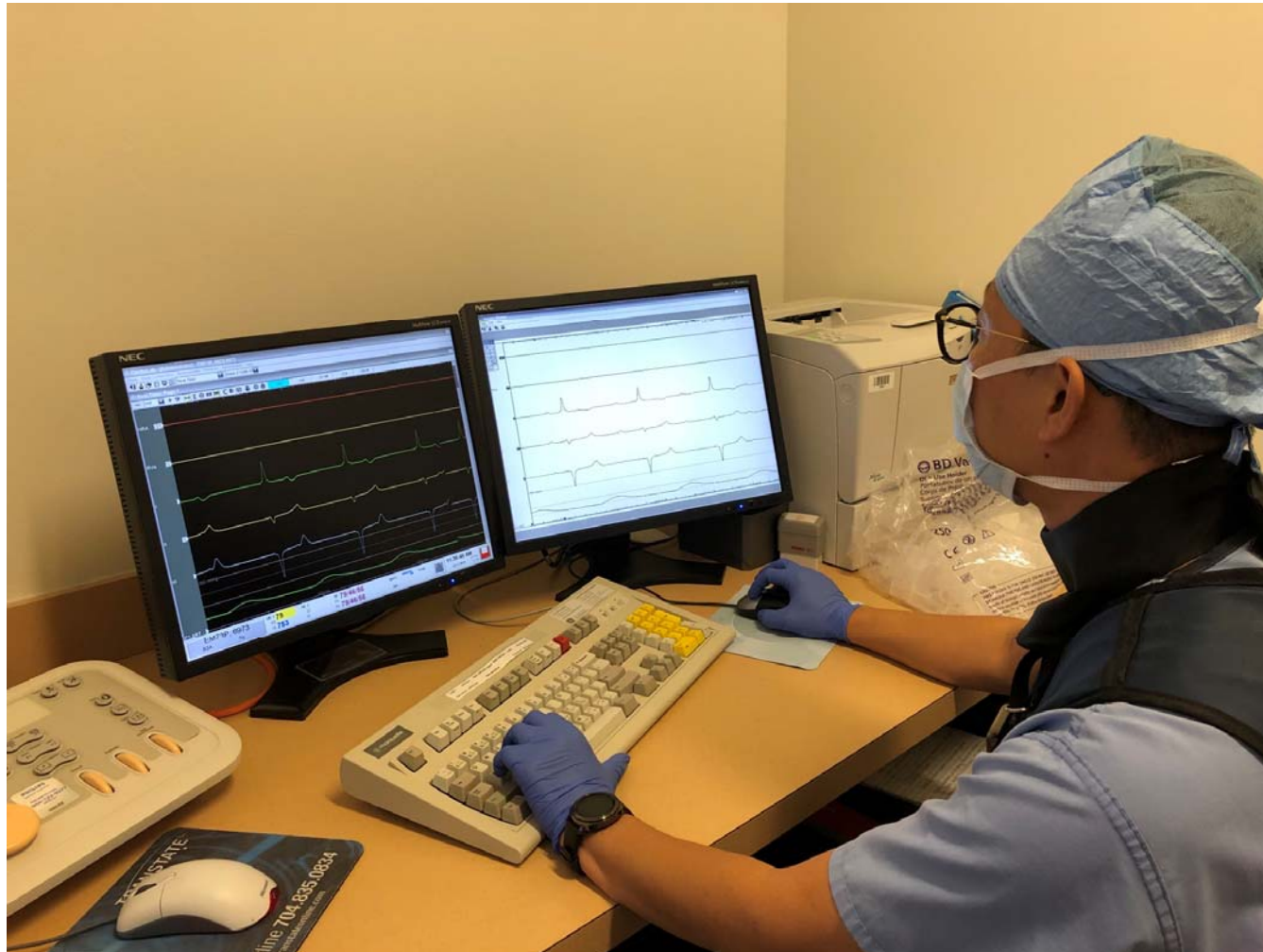
Pacemaker implantation



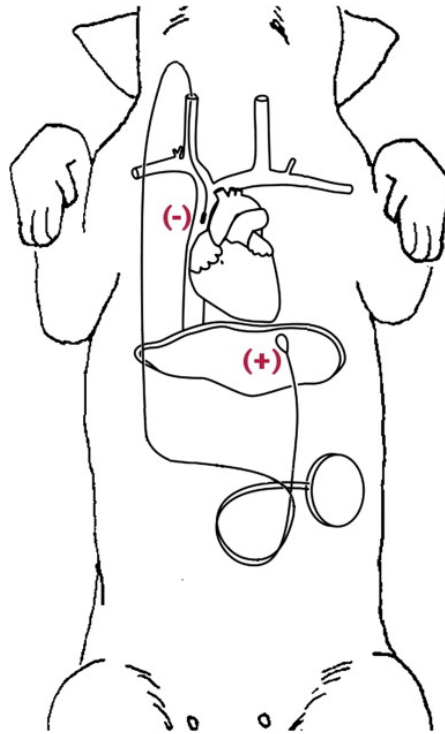
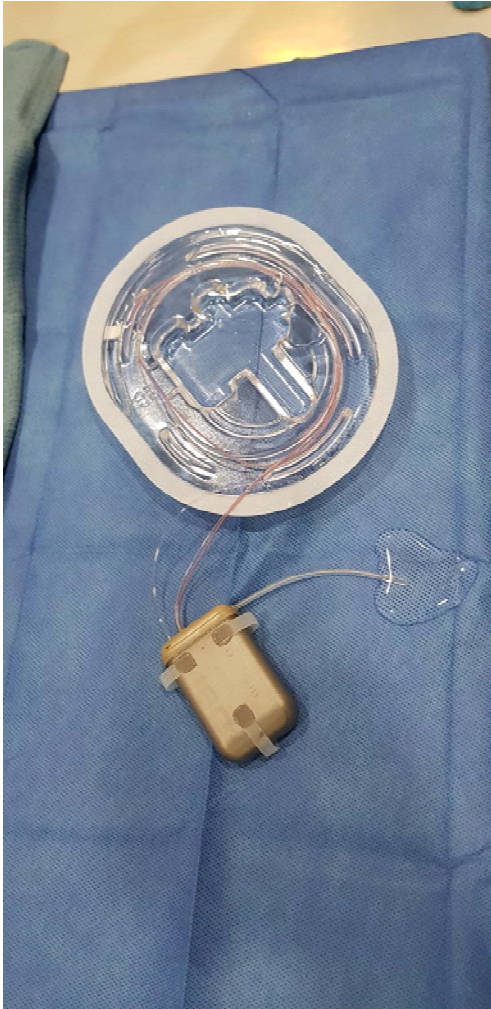
Electrical map, NOGA map, Fluoroscopy



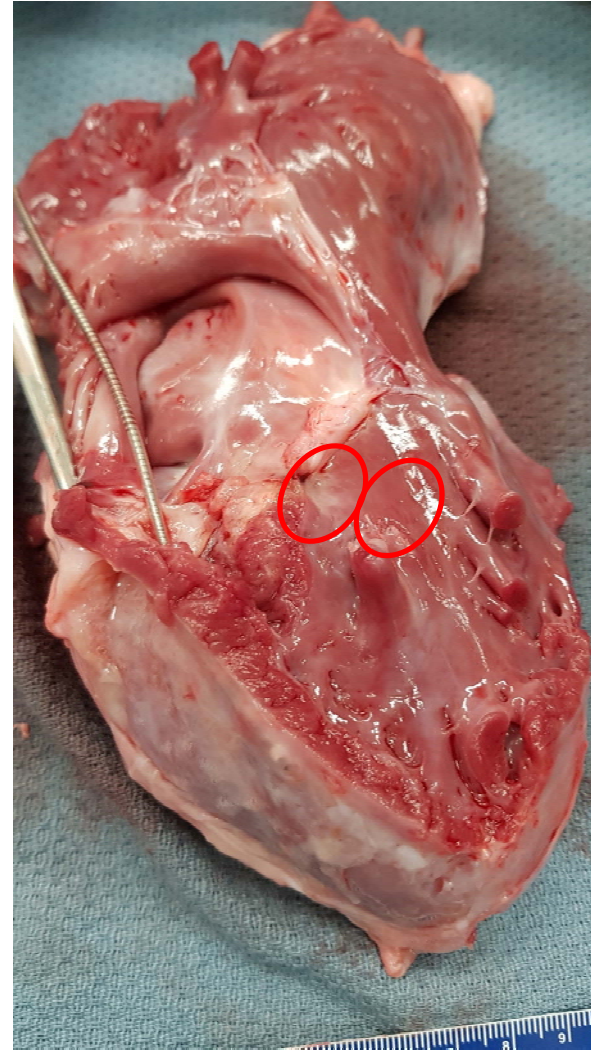
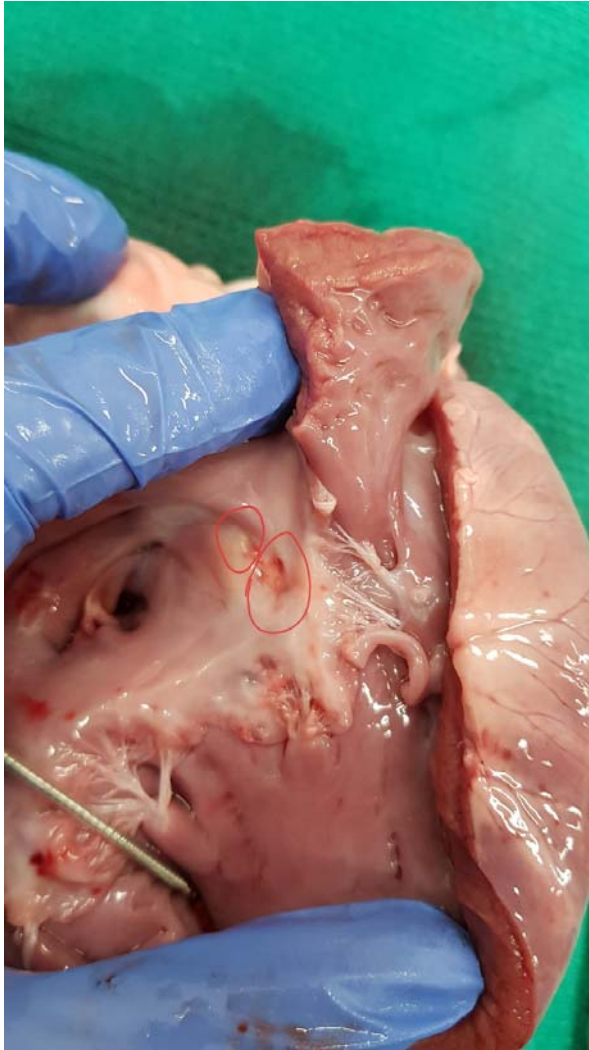
Real time EGM



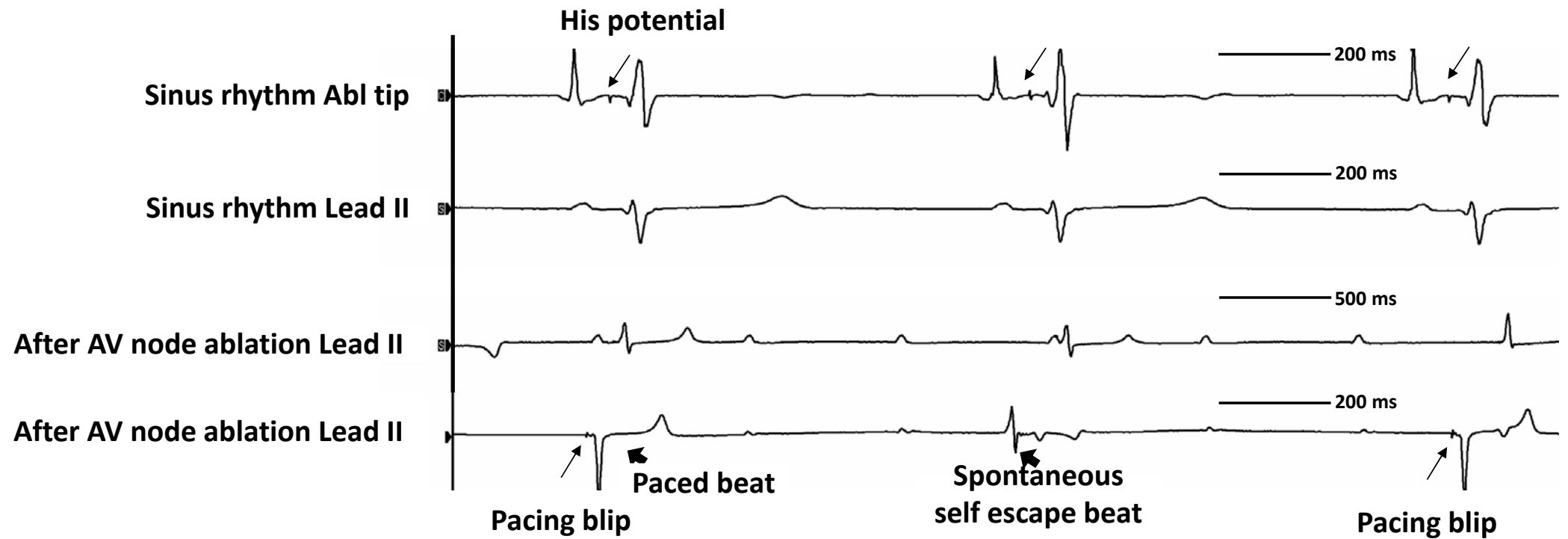
DSI: telemetry



Autopsy



Creation of AV block



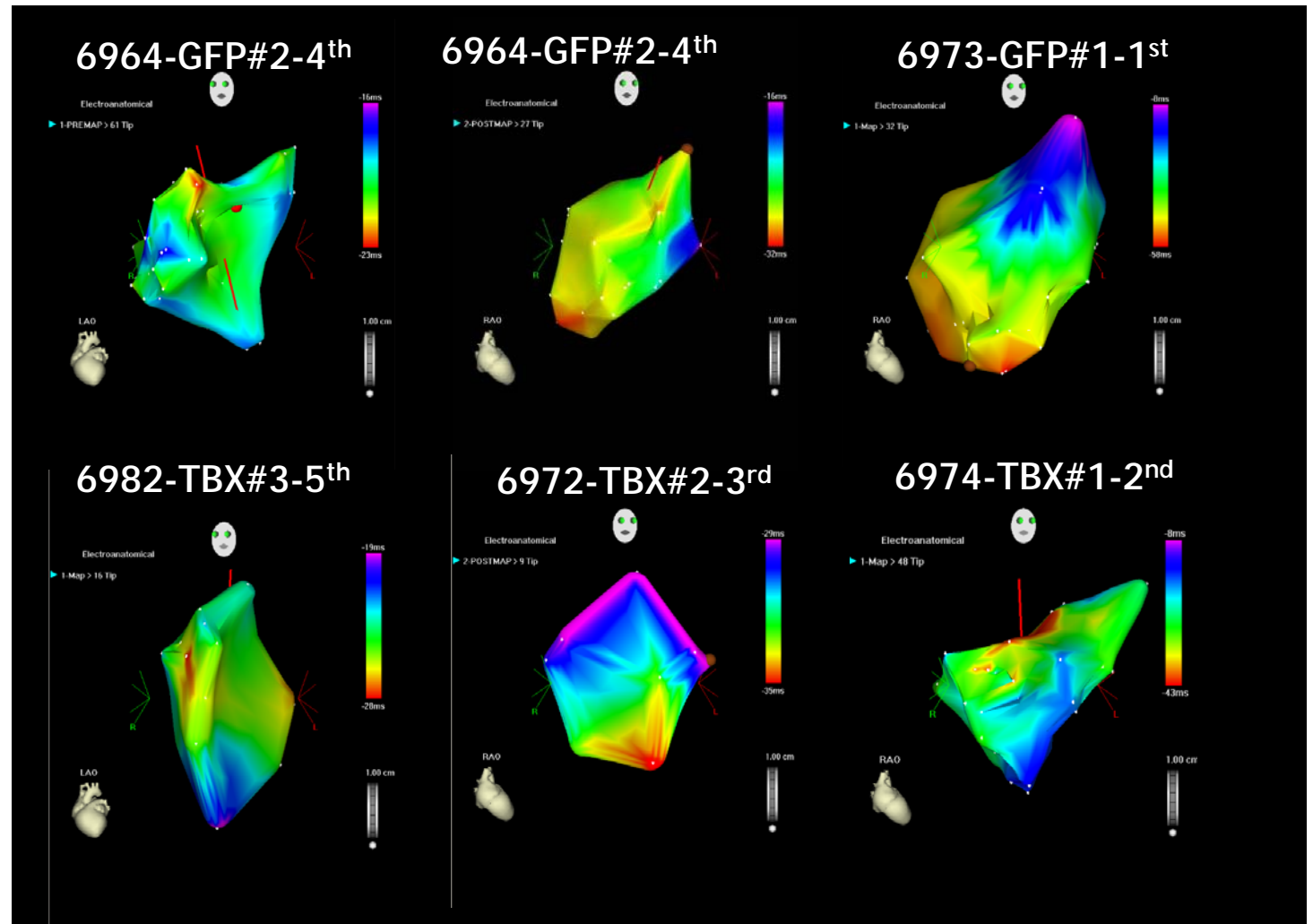
**Baseline –
before CAVB
LAO view**

**Baseline –
after CAVB
RAO view**

**Week 4
RAO view**

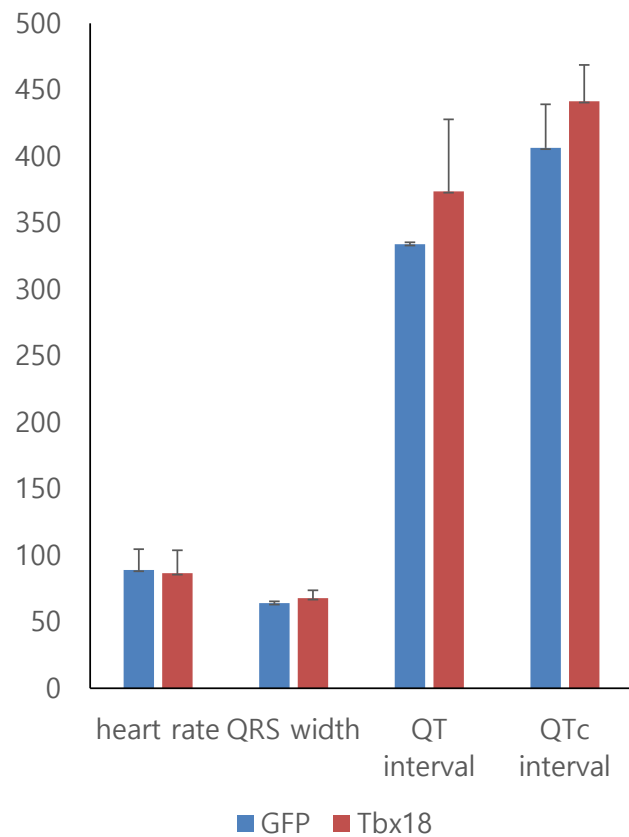
GFP

Tbx18

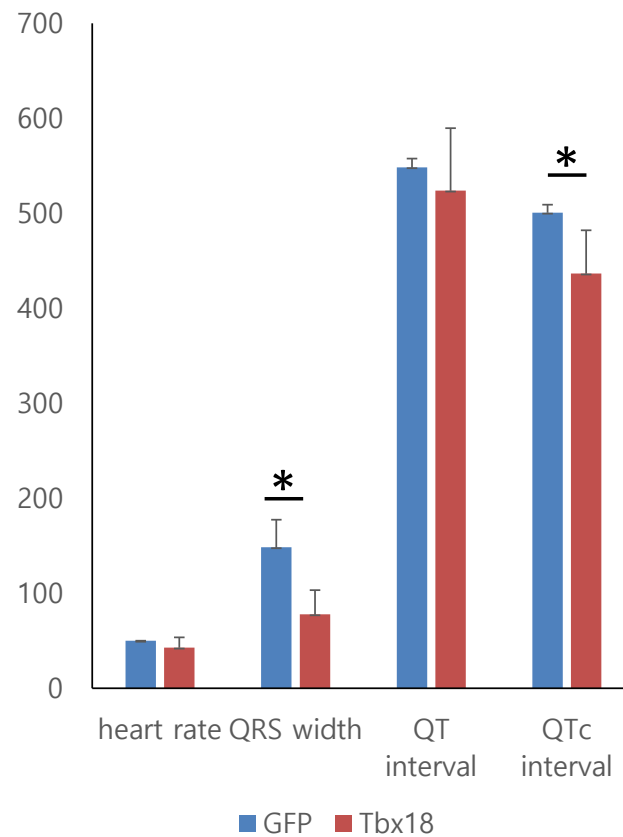


Change of ECG parameters

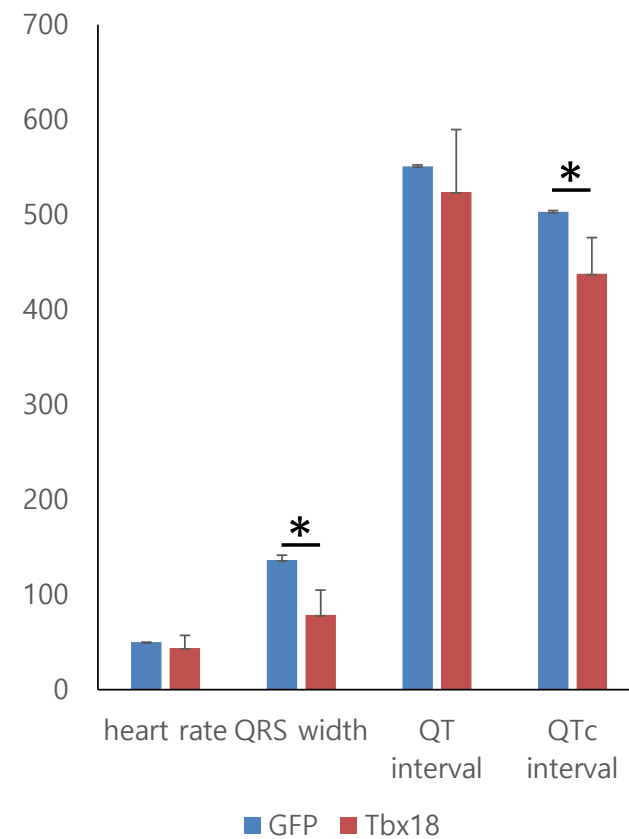
D-0



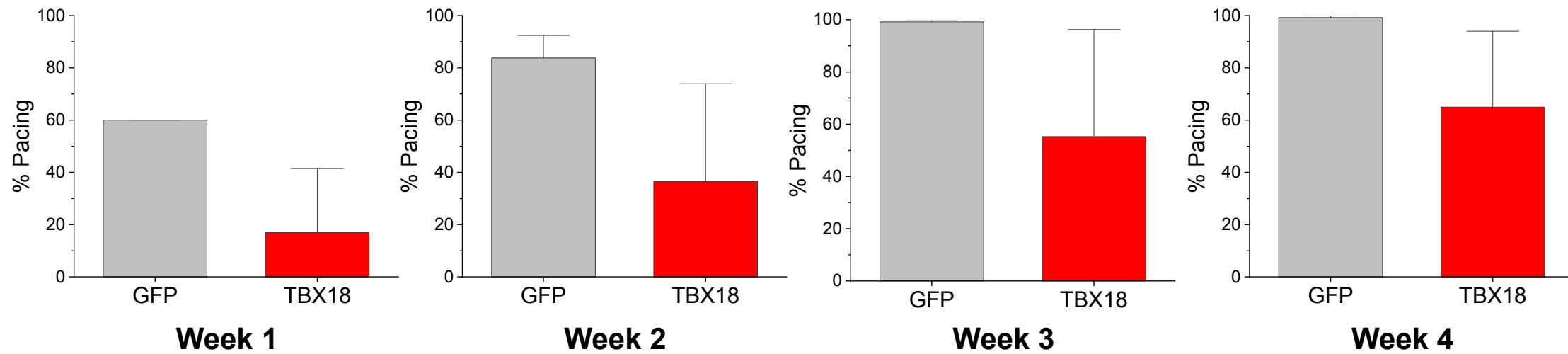
D+14



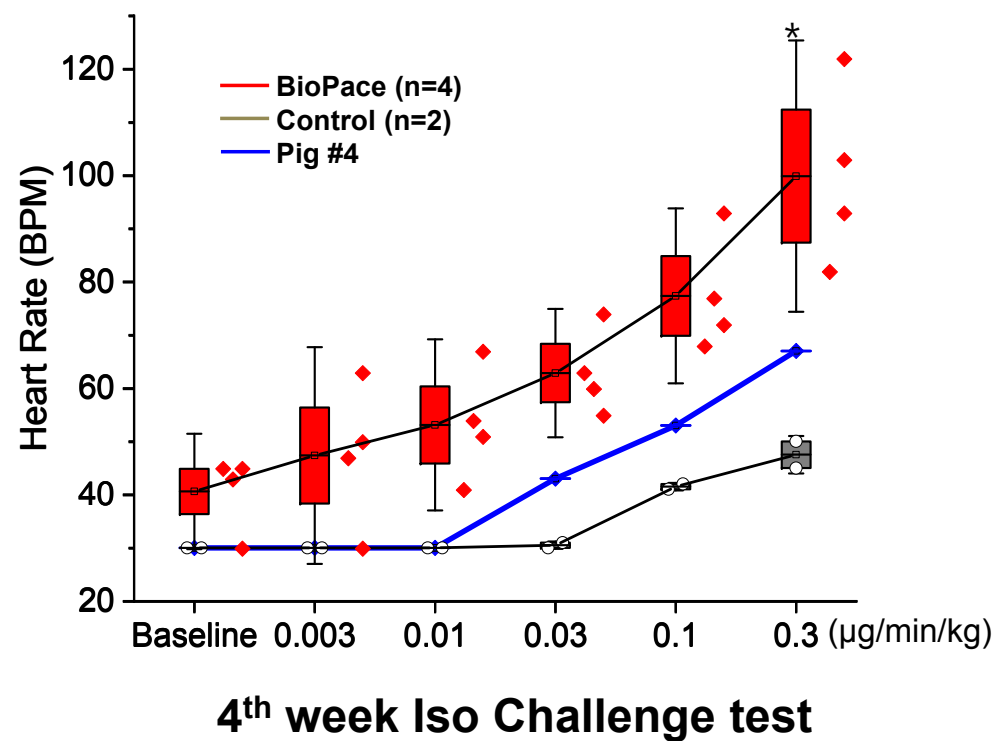
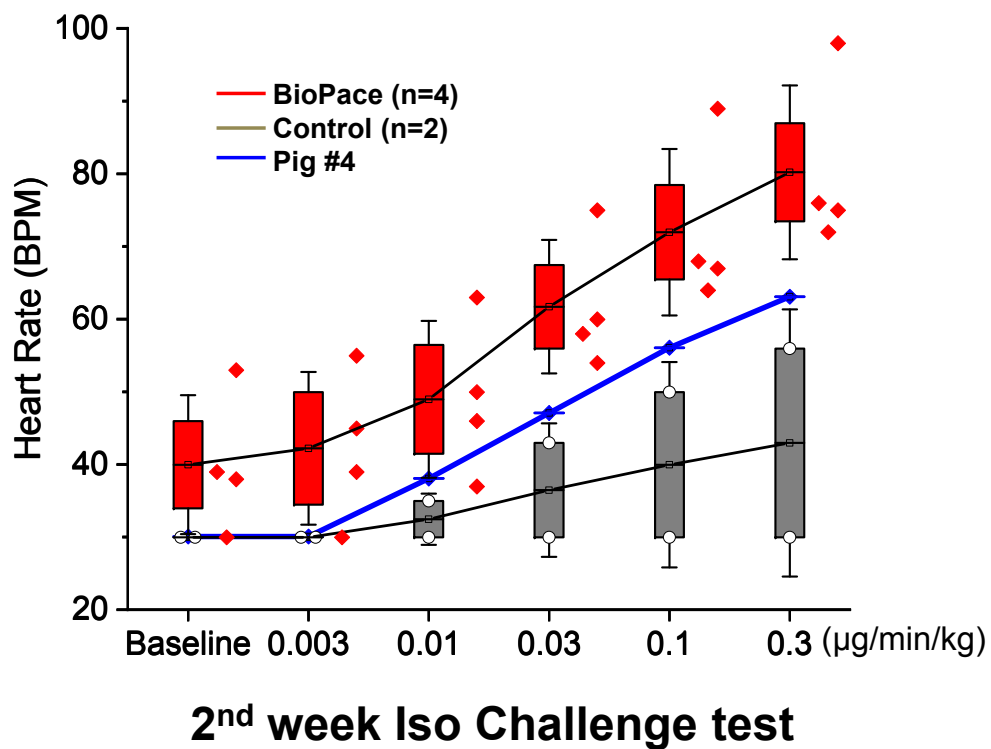
D+28



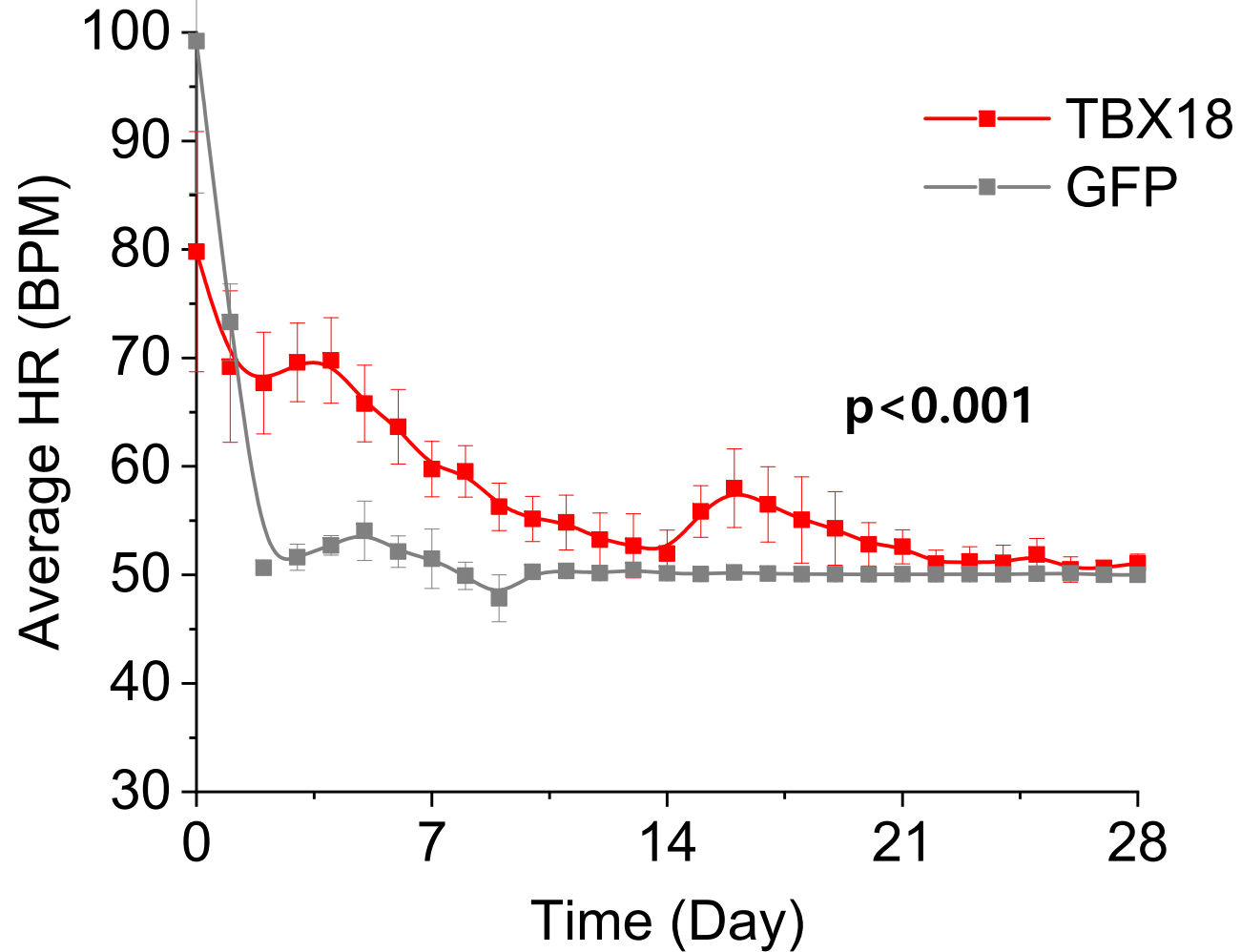
Pacemaker Dependence



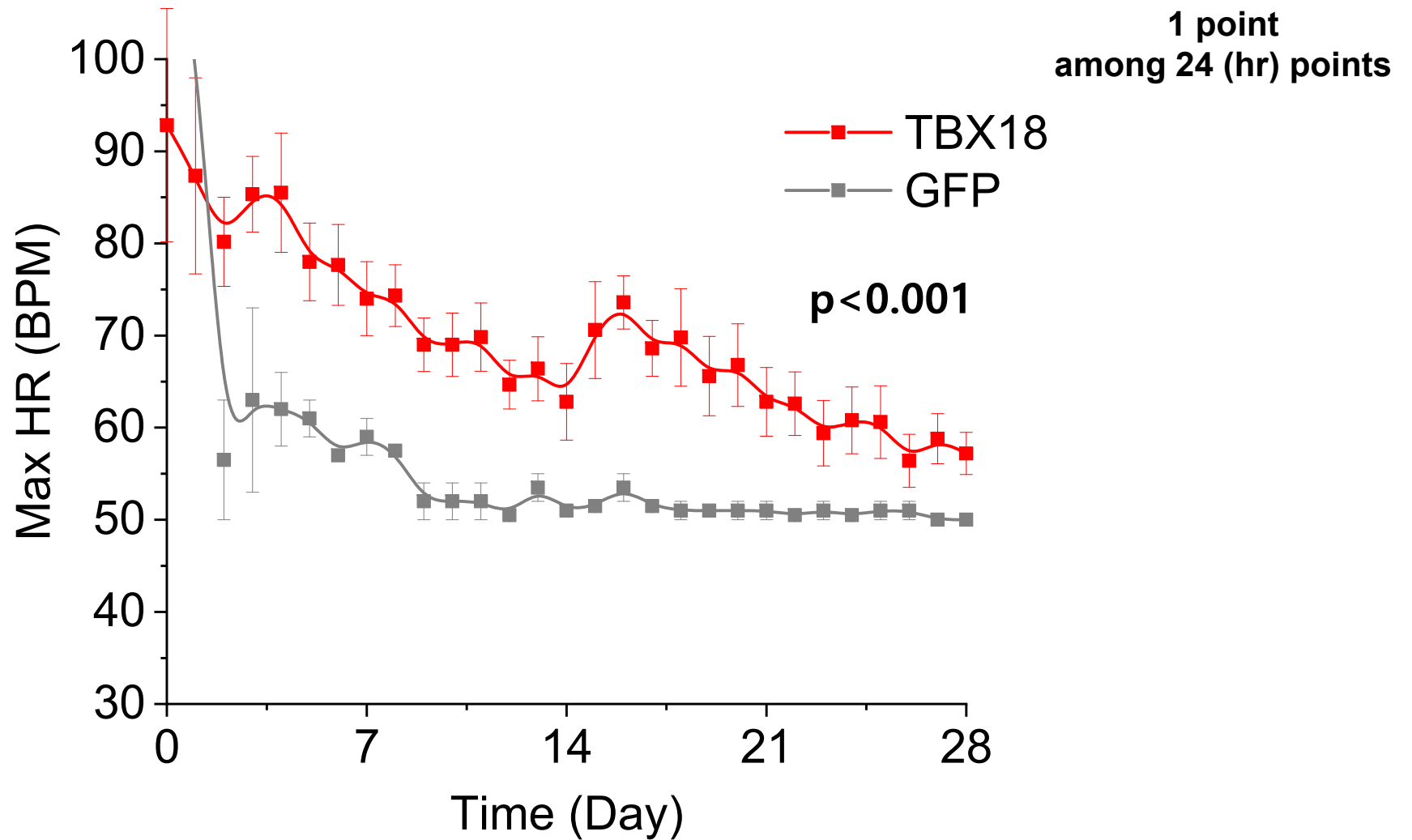
Isoproterenol Challenge test



2019 GFP vs. TBX18 - mean BPM - #Day (00:00~00:00)



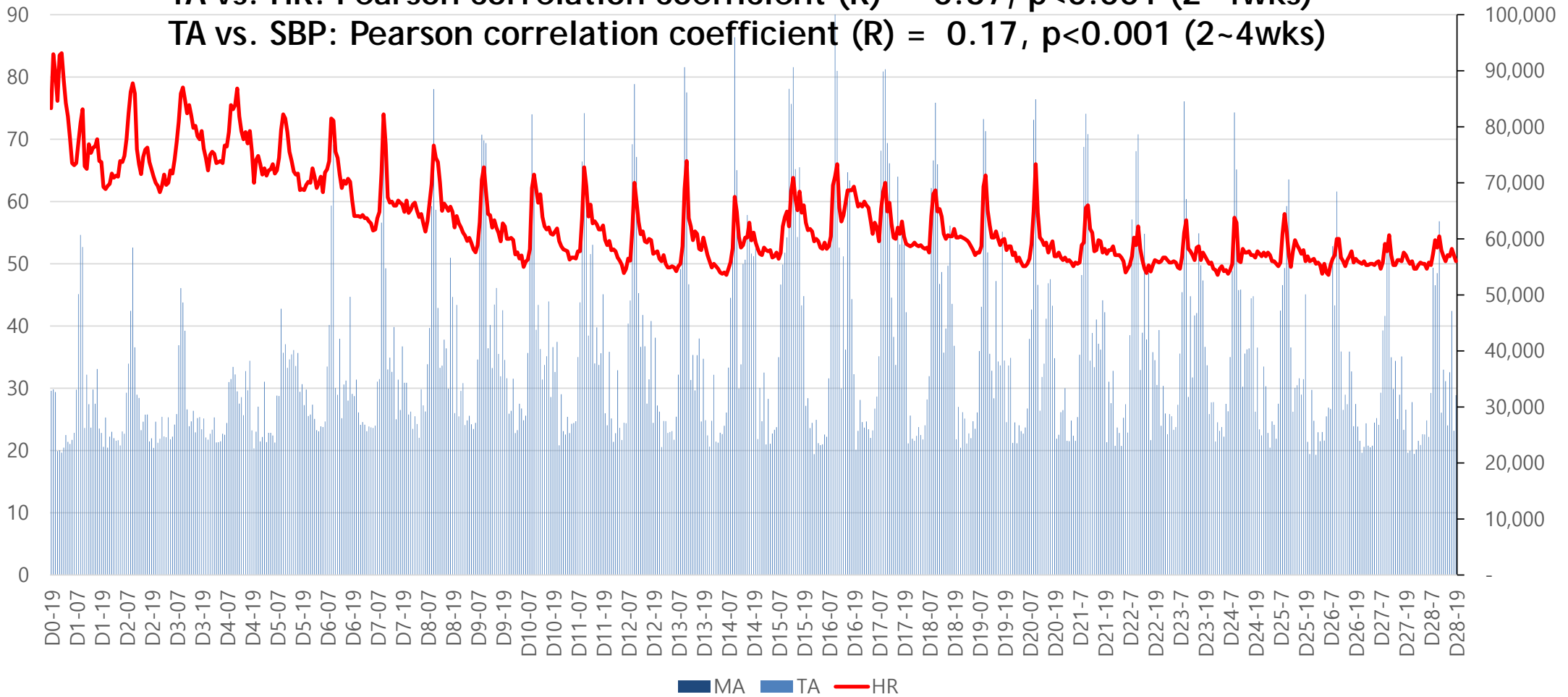
2019 GFP vs. TBX18 - Max BPM -00:00~00:00 - 1 Hr interval



2019 TBX18 Total activity vs. HR

TA vs. HR: Pearson correlation coefficient (R) = 0.67, p<0.001 (2~4wks)

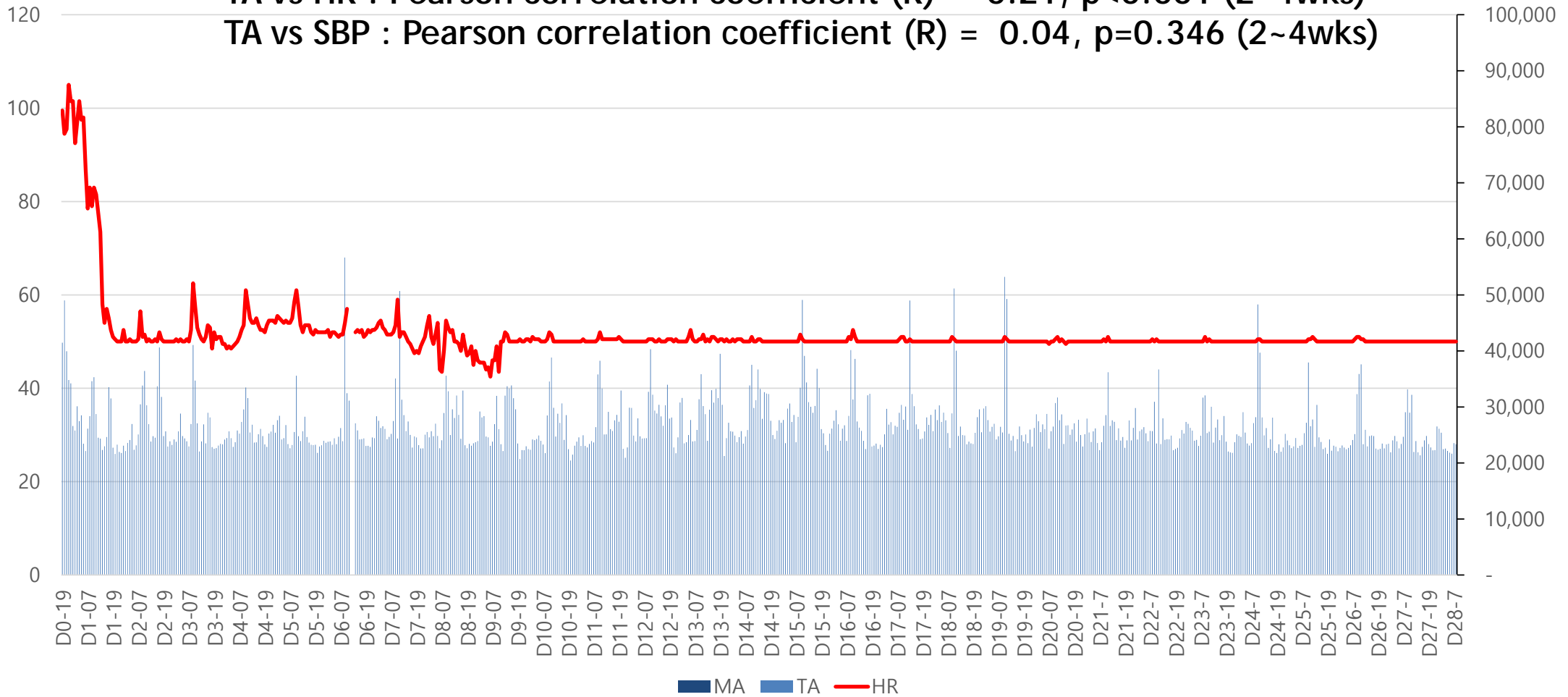
TA vs. SBP: Pearson correlation coefficient (R) = 0.17, p<0.001 (2~4wks)



2019 GFP Total activity vs. HR

TA vs HR : Pearson correlation coefficient (R) = 0.21, p<0.001 (2~4wks)

TA vs SBP : Pearson correlation coefficient (R) = 0.04, p=0.346 (2~4wks)





Conclusion



1. Induced biological pacing by TBX18 mod.mRNA had higher mean and Max heart rate than controls.
2. Induced biological pacing by TBX18 mod.mRNA lasted for more than 4 wks.
3. Induced biological pacing by TBX18 mod.mRNA was well matched to biological activity.
4. Induced biological pacing by TBX18 mod.mRNA was safe without arrhythmogenicity.

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Thank you for your attention !!

