Usage of the calcineurin variant CnAβ1 with gene therapy to treat heart failure

Madrid, 2 July 2014

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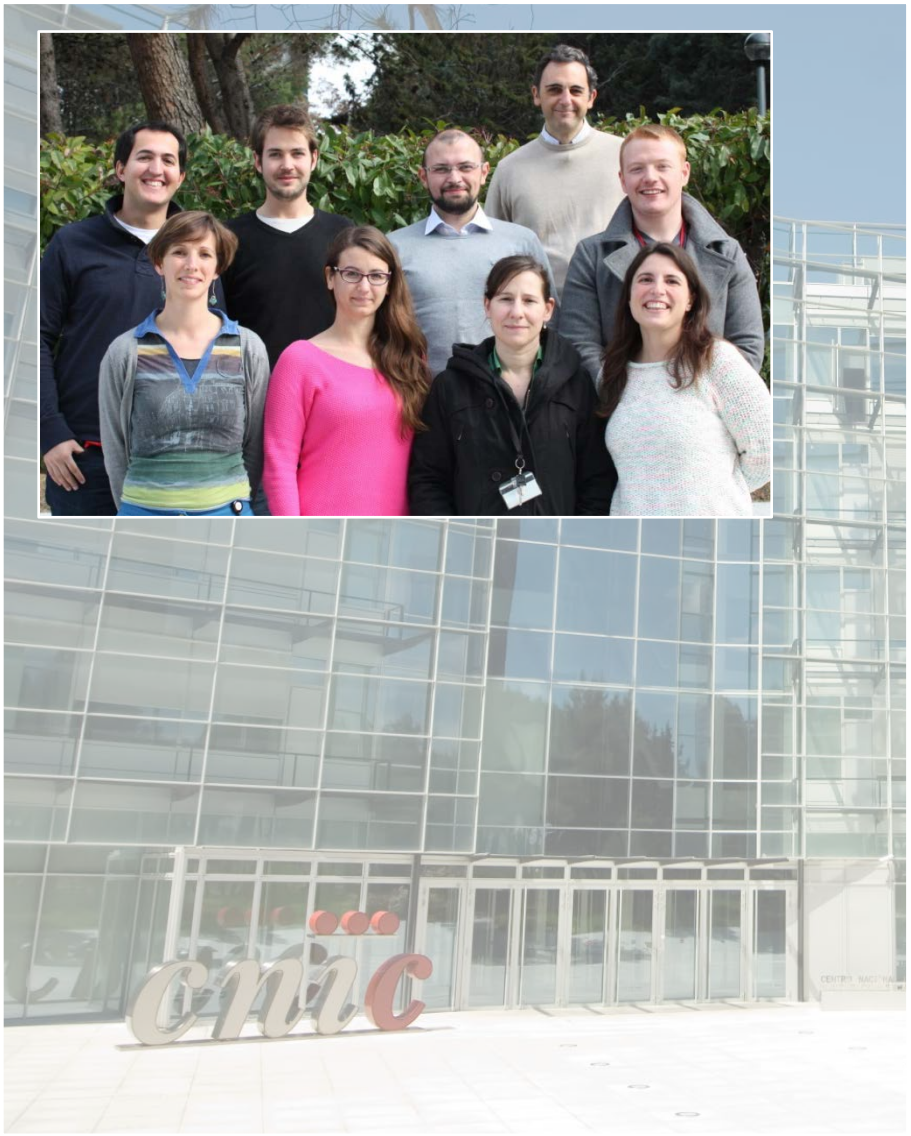
The Institution – CNIC



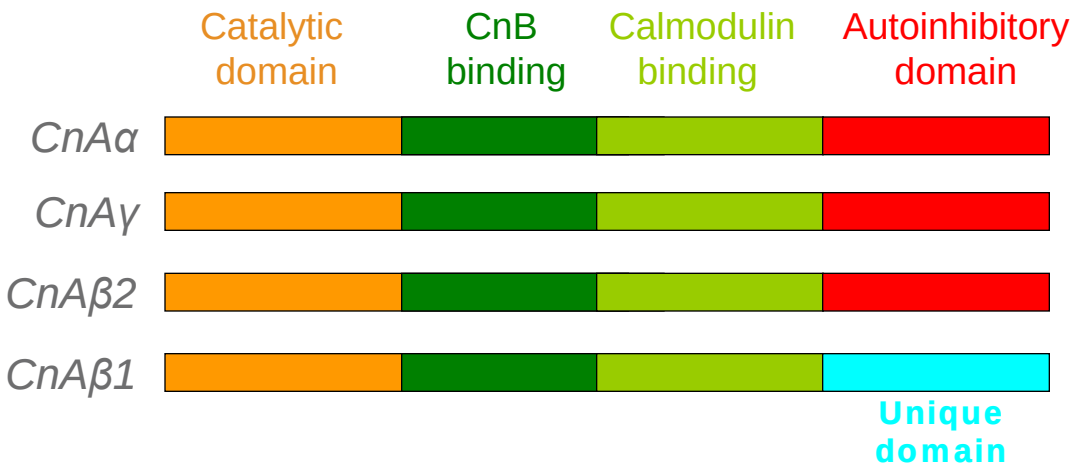
Lara-Pezzi Group:

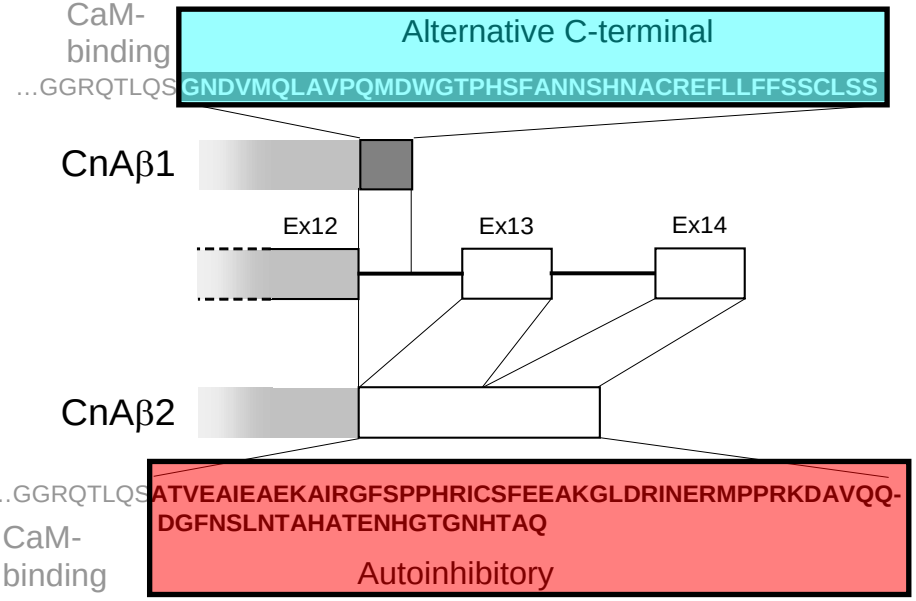
Postdoc:
Laura Padrón

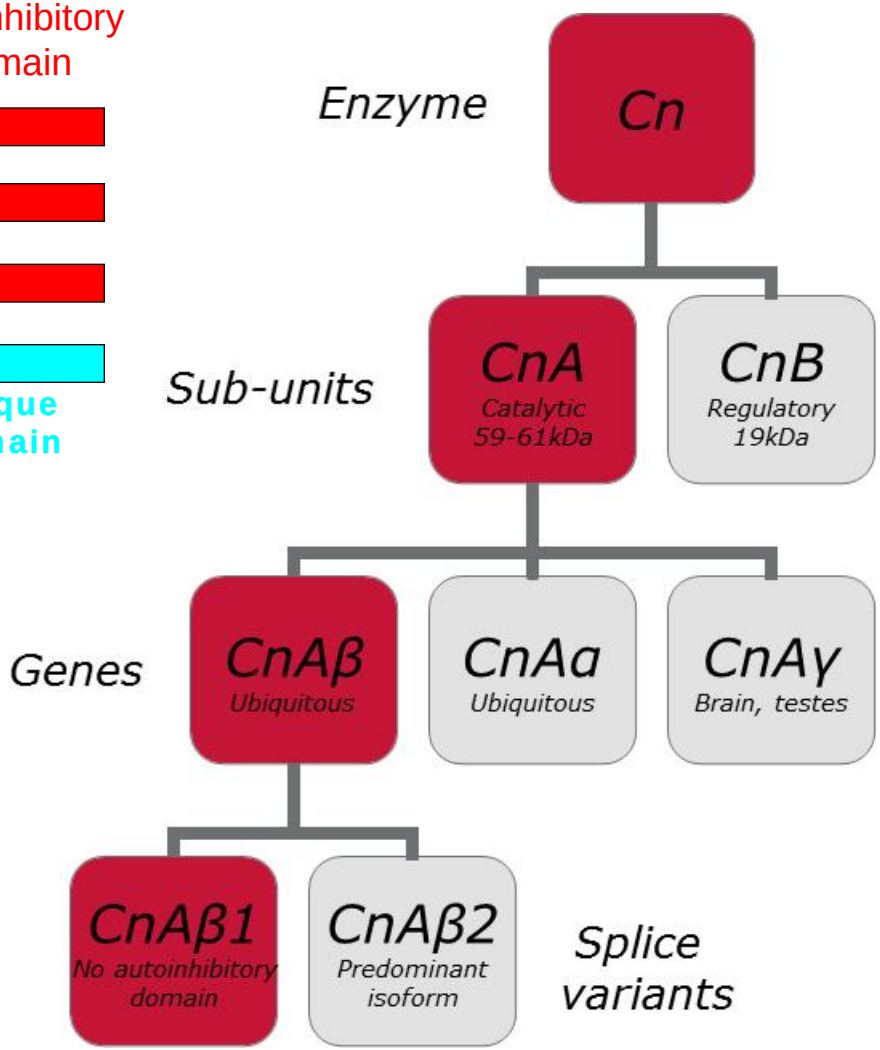
PhD Students:
Jesús Gómez Salinero
Alberto Gatto
Enda Clinton
Girolamo Giudice
Paula Ortiz
Javier Larrasa

Technicians:
María López Olañeta
María Villalba

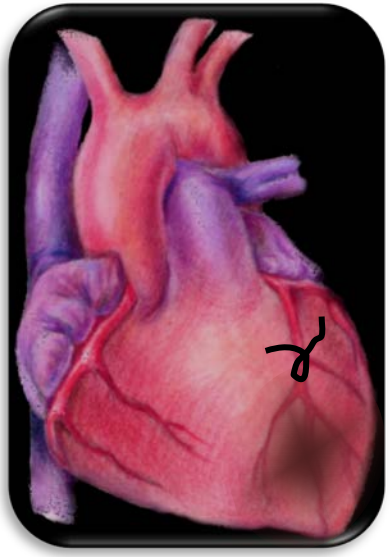
The Product – CnAβ1







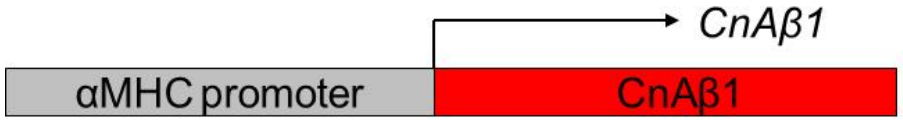
CnAβ1 improves cardiac function in infarcted mice

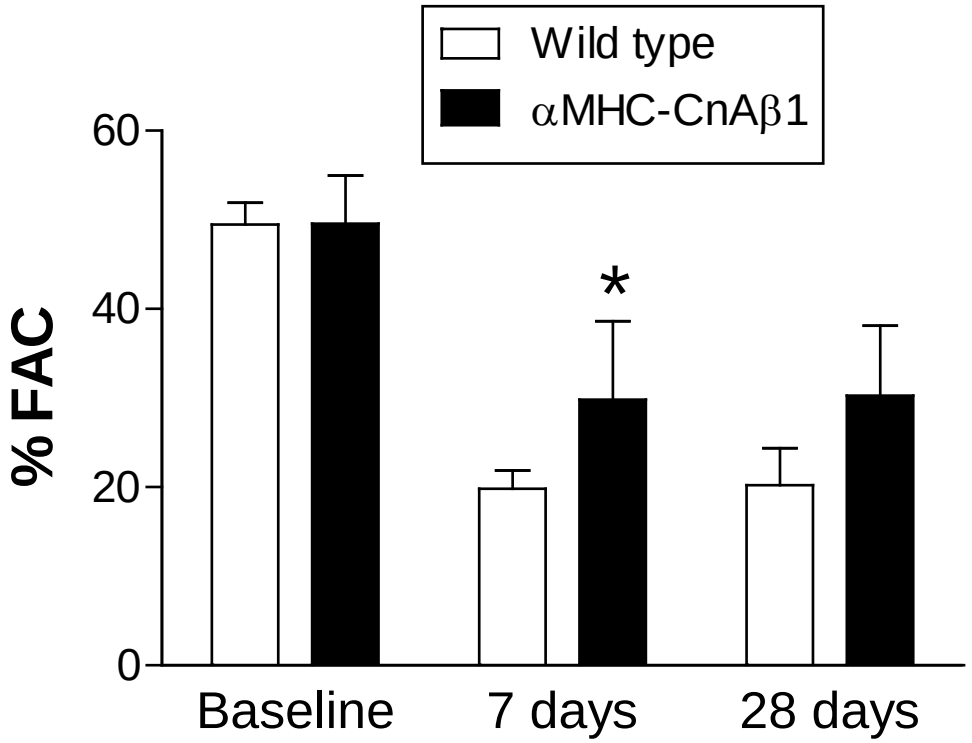


Left coronary artery ligation

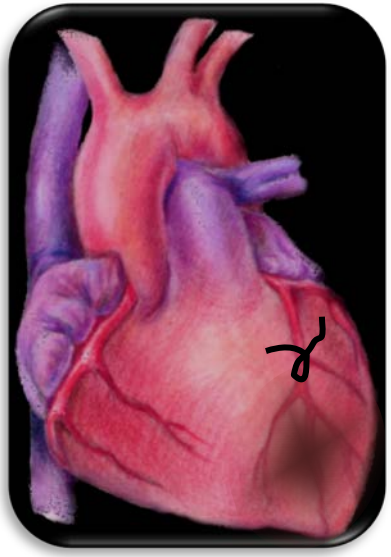
↓ 1 or 4 weeks

Echocardiography





CnAβ1 overexpression *after infarction*

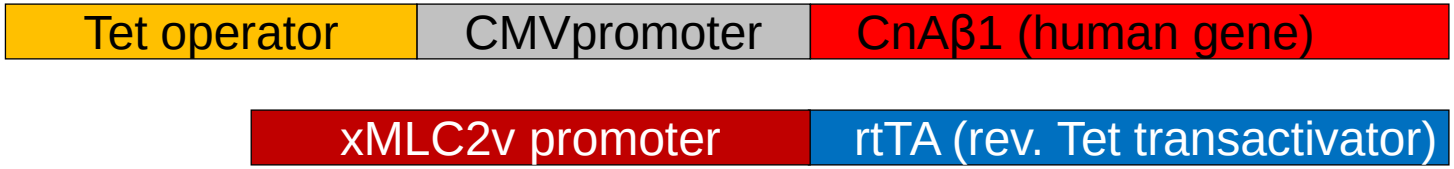


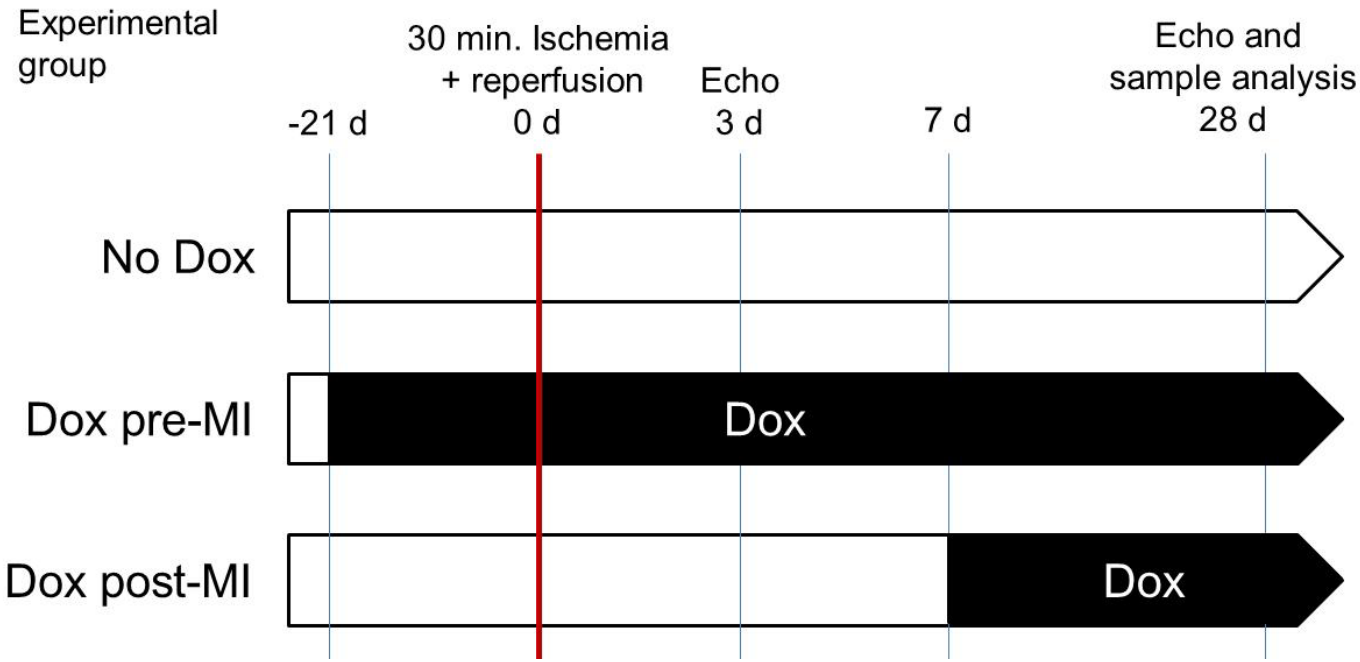
30’ Ischemia +
Reperfusion

↓ 3 or 28 days

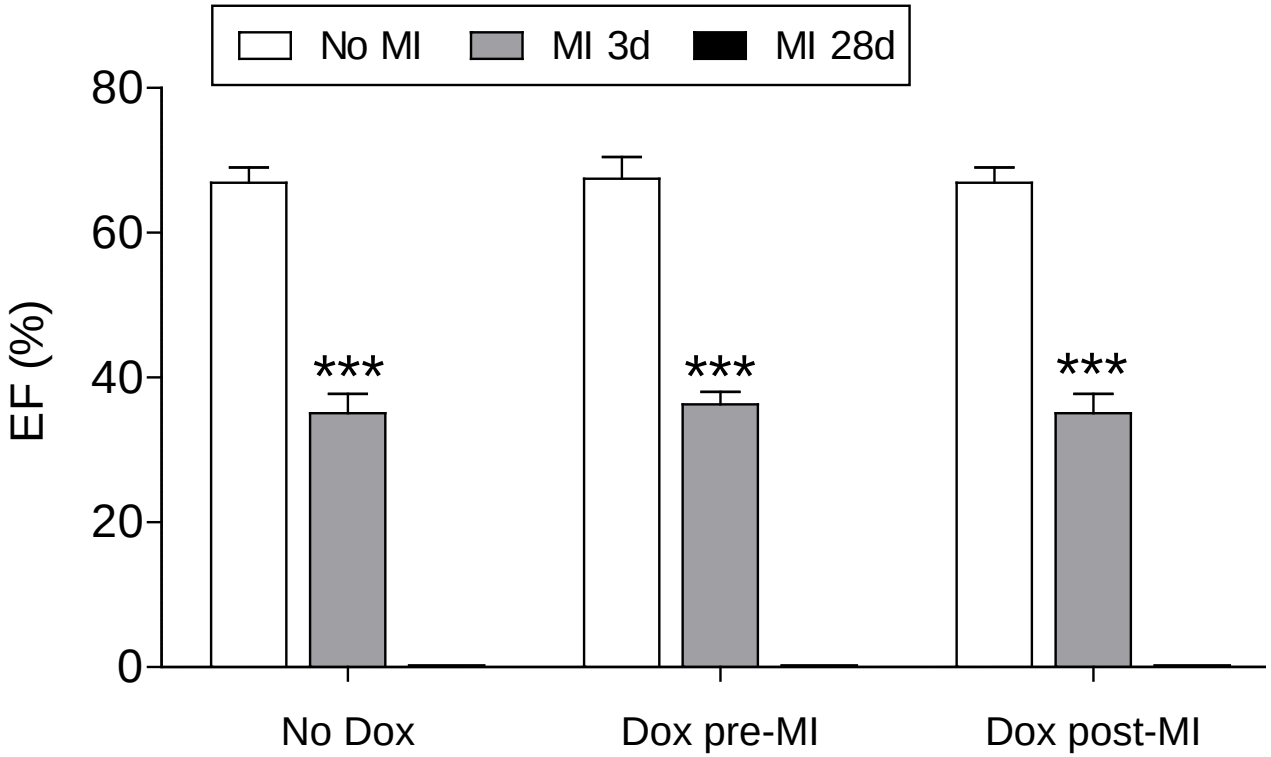
Echocardiography
qRT-PCR
Histology

CnAβ1 transgene + reverse Tet transactivator (***Tet-on***)





CnAβ1 overexpression *after infarction* improves cardiac function

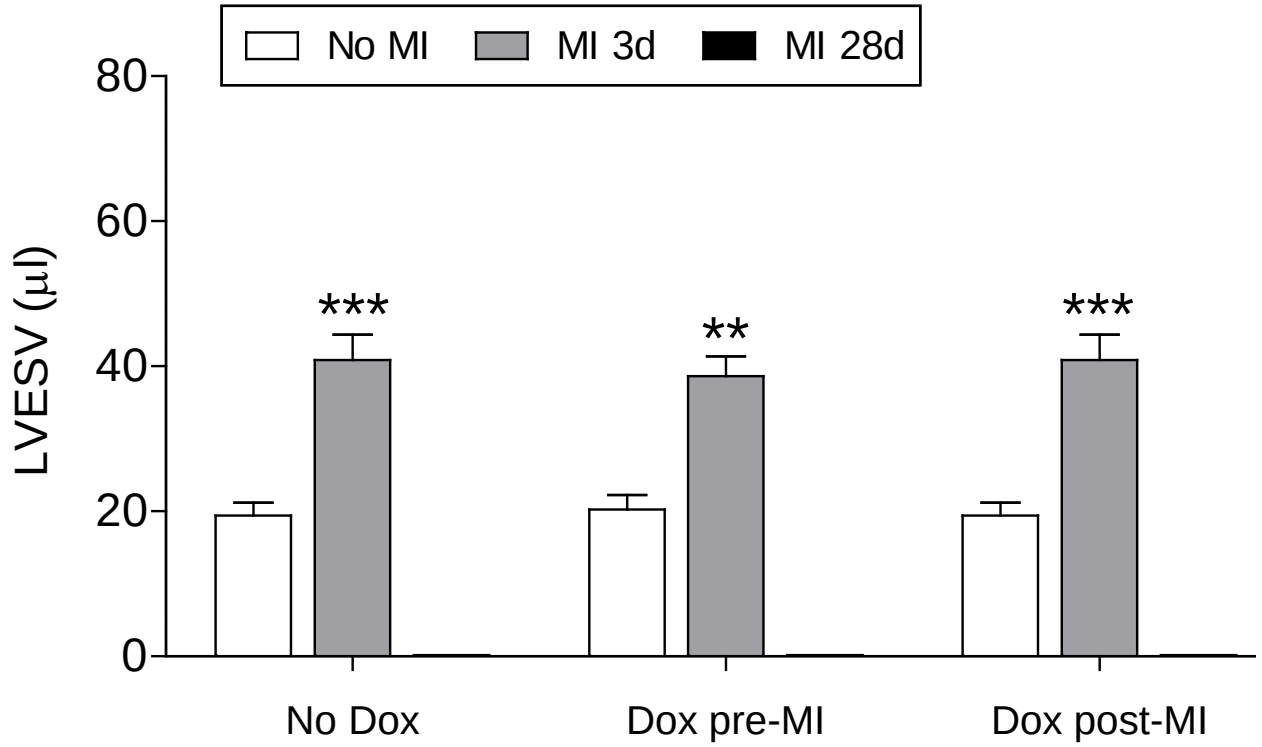


In control mice, Doxycycline had no effect

**p<0.05, **p<0.005, ***p<0.0005 vs No MI*
#p<0.05, ##p<0.005, ###p<0.0005 vs No Dox

López-Olañeta et al., Cardiovasc. Res. 2014

CnAβ1 overexpression *after infarction* improves cardiac function



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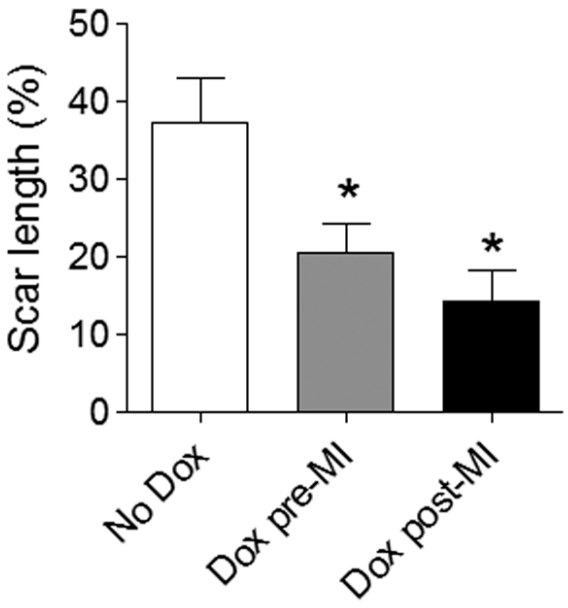
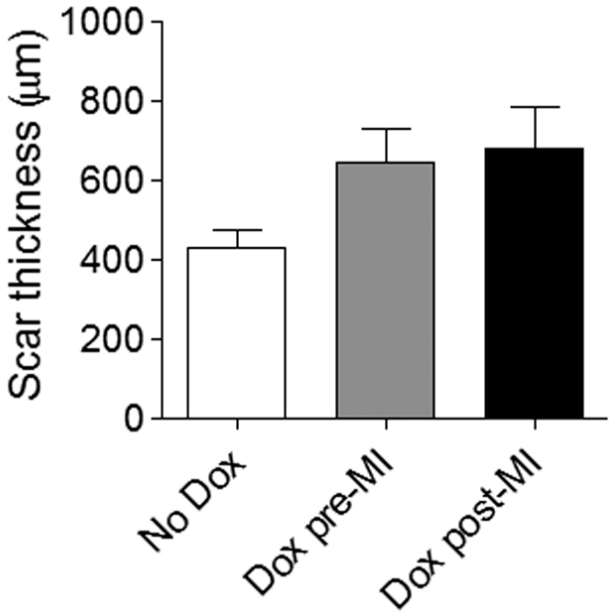
López-Olañeta et al., Cardiovasc. Res. 2014

CnAβ1 overexpression *after infarction* improves cardiac function

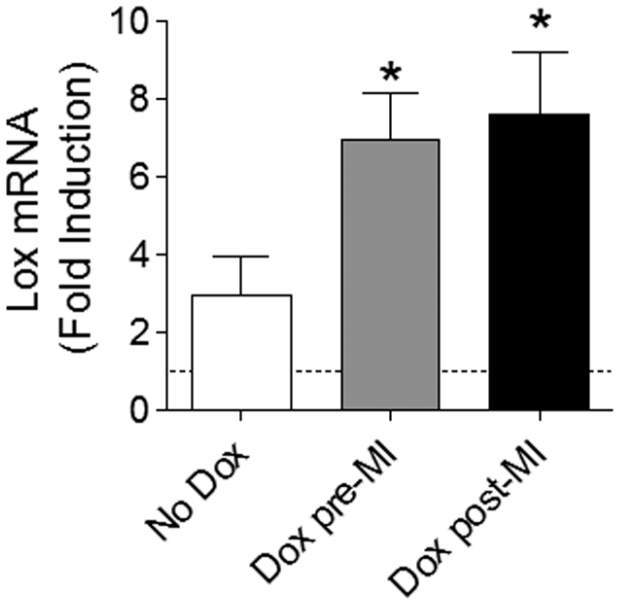
Scar length



Scar thickness



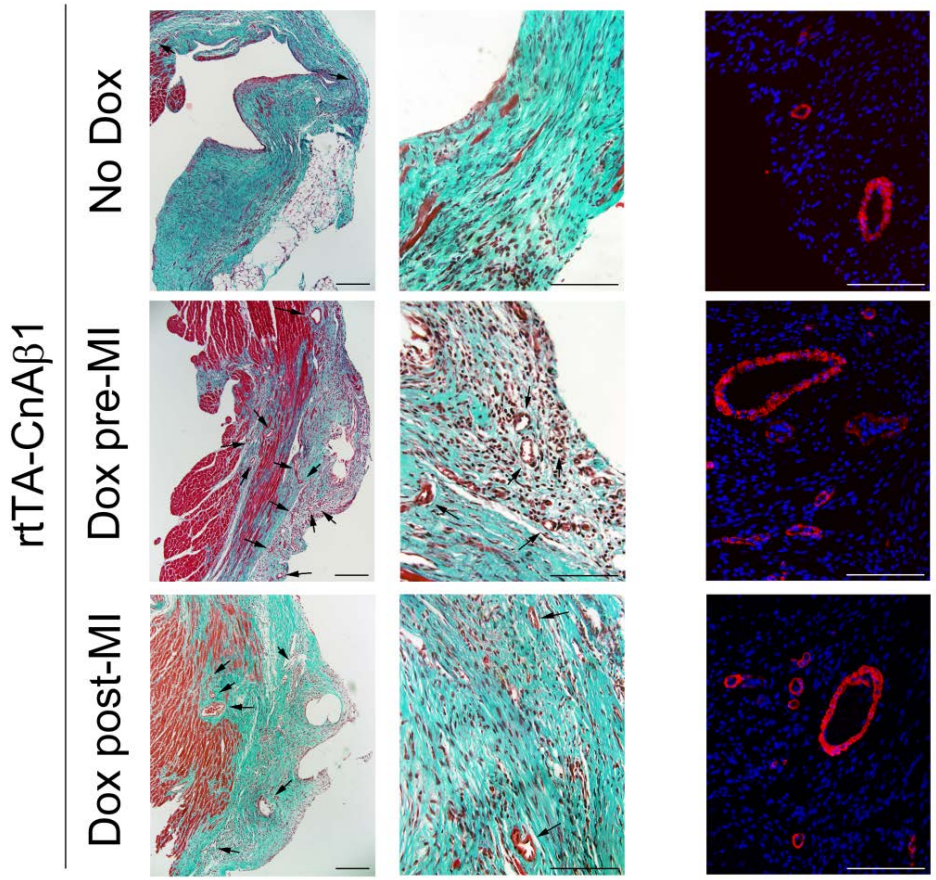
Lox

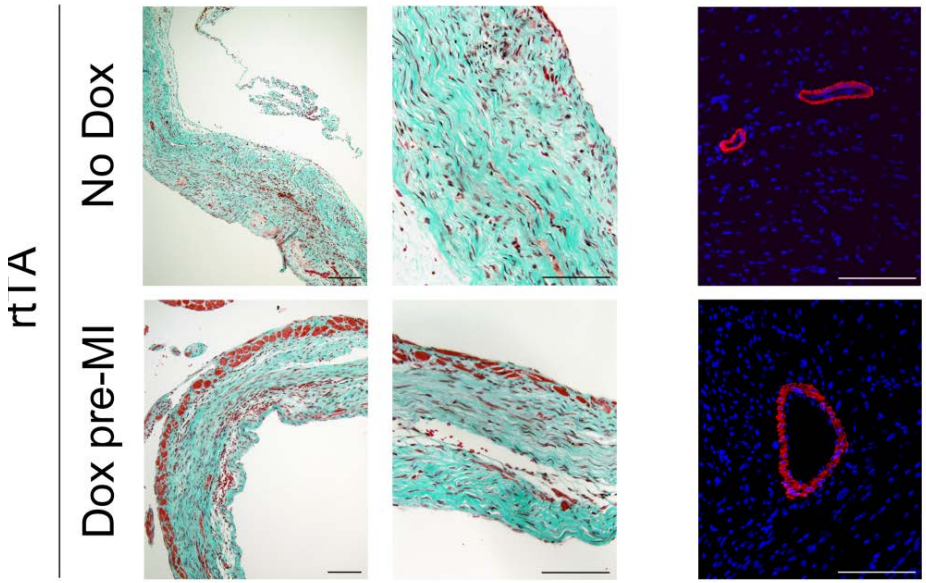


López-Olañeta et al., Cardiovasc. Res. 2014

**p<0.05 vs No Dox*

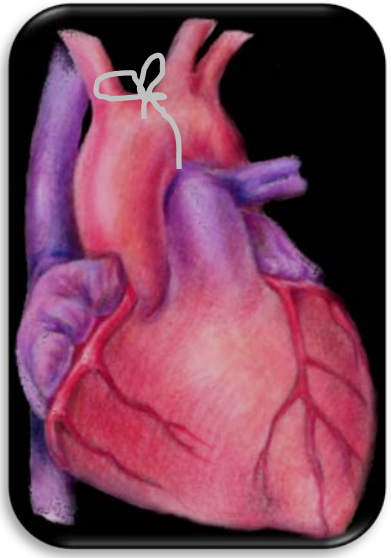
CnAβ1 overexpression *after infarction* improves cardiac function

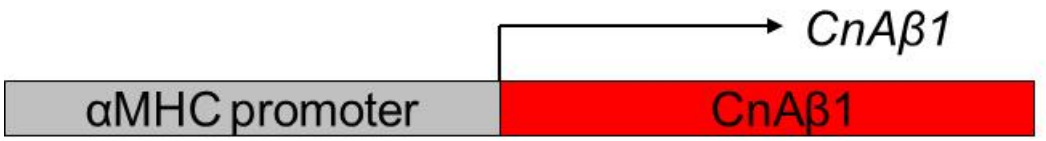




López-Olañeta et al., Cardiovasc. Res. 2014

CnAβ1 overexpression reduces cardiac hypertrophy

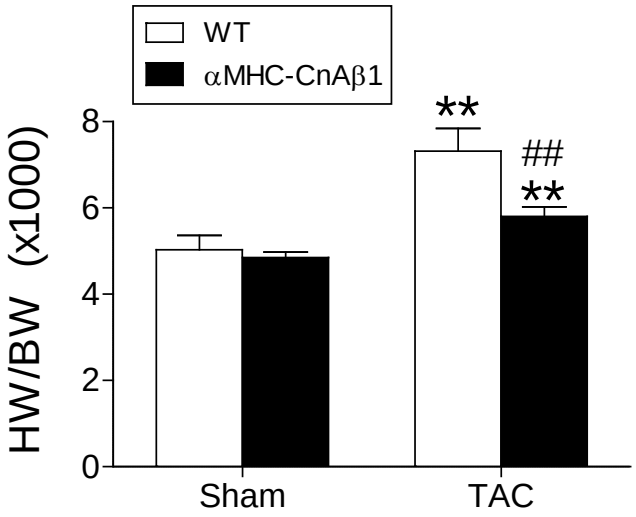


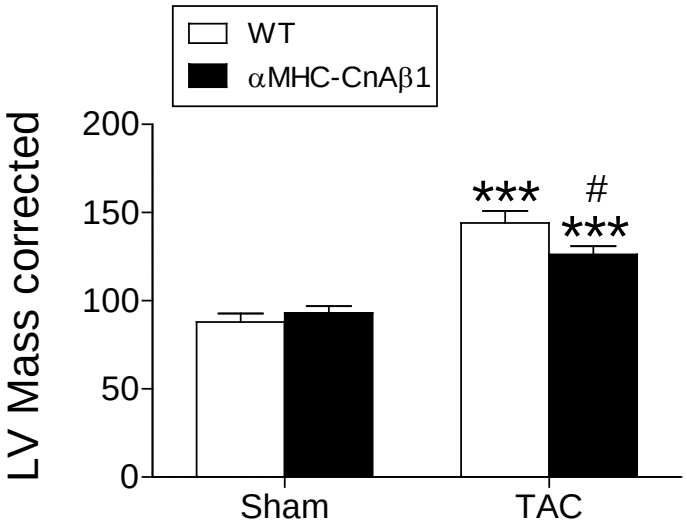


Transaortic banding

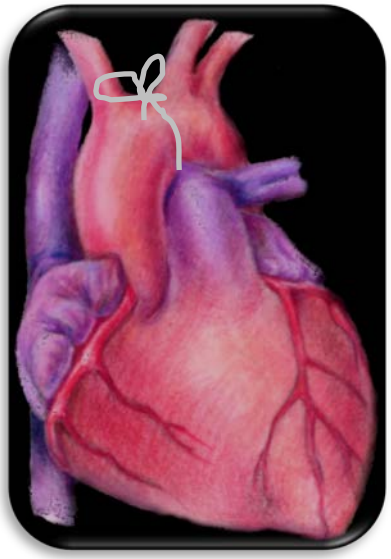
21 days

Echocardiography
qRT-PCR
Histology





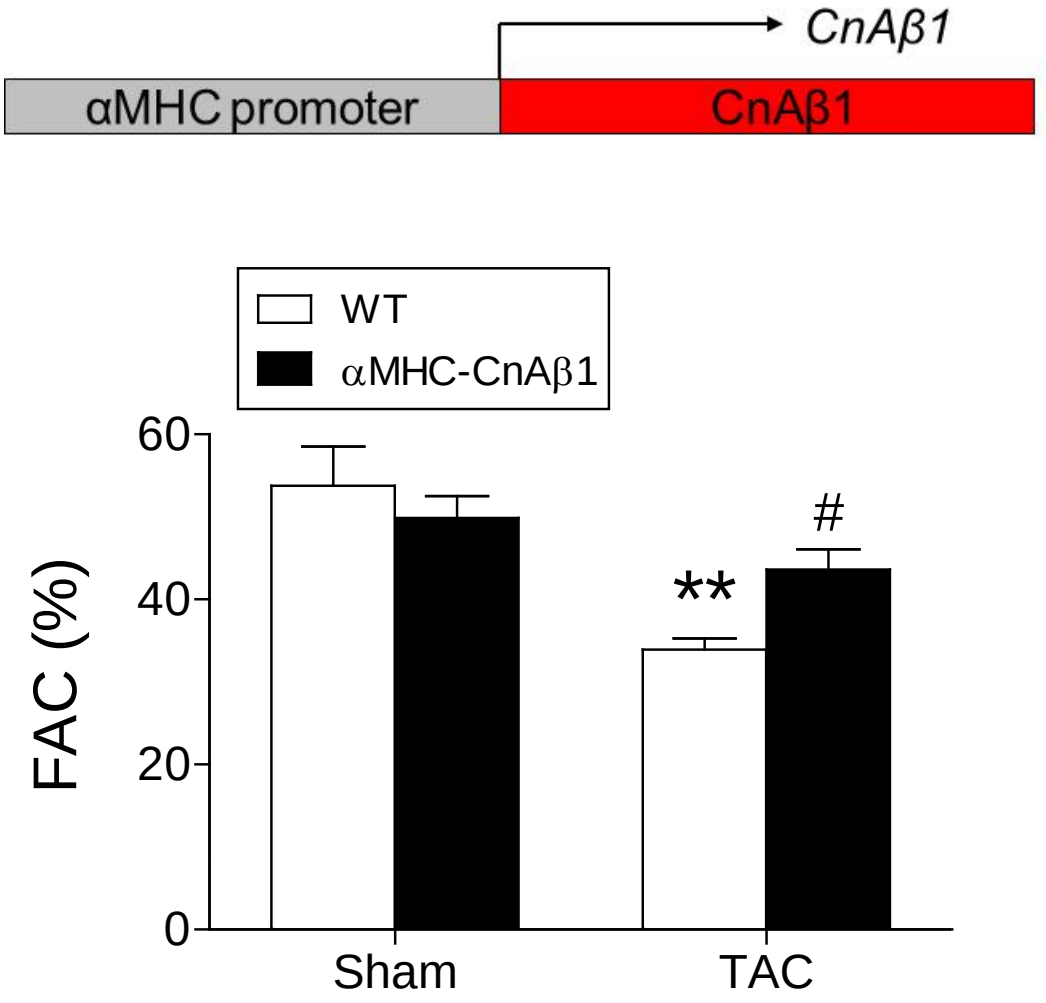
CnAβ1 overexpression improves function after aortic stenosis



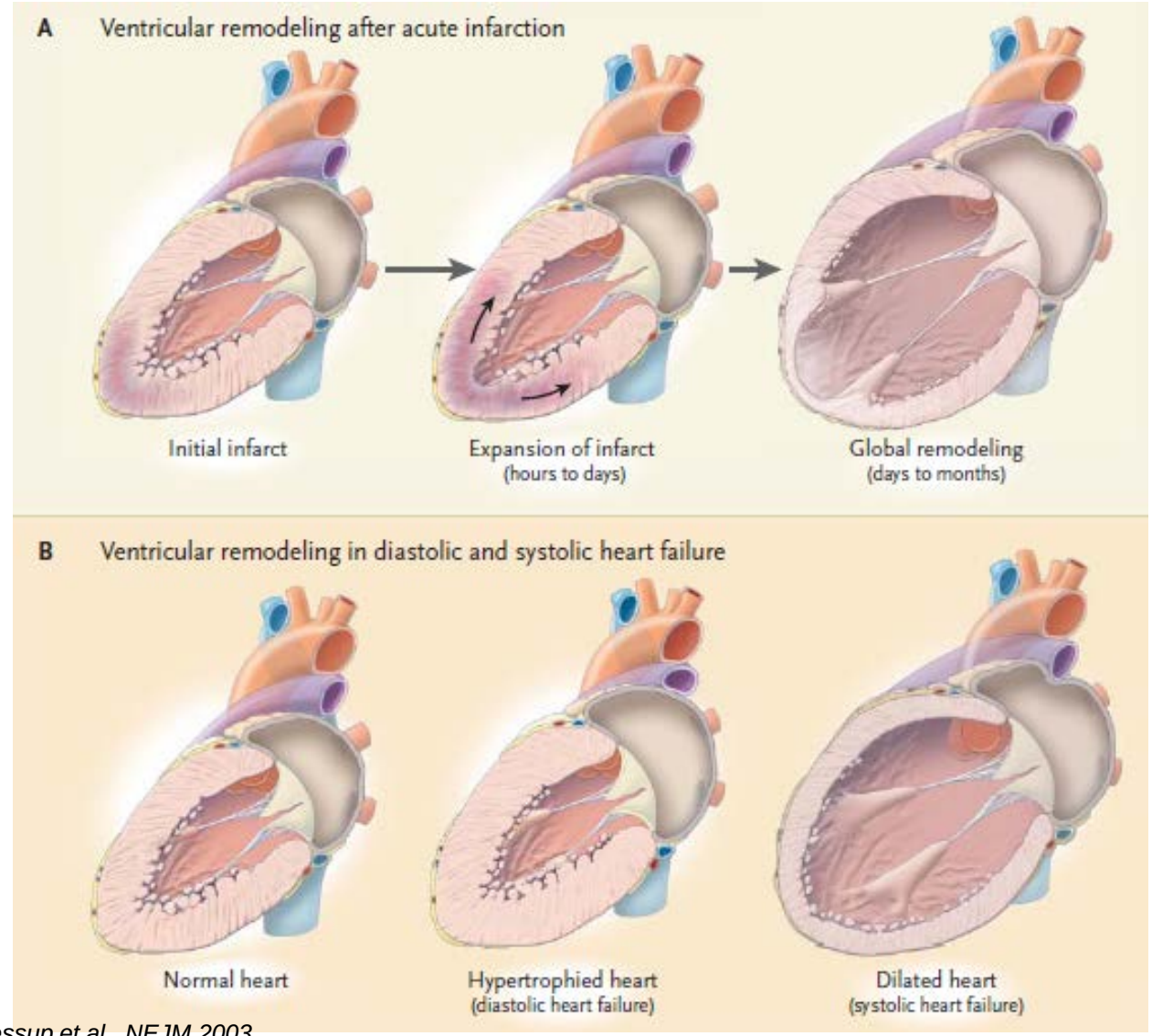
Transaortic banding

21 days

Echocardiography



Target Indications – Heart Remodelling and Failure



Jessup et al., NEJM 2003

HF has very high incidence, mainly among the elderly

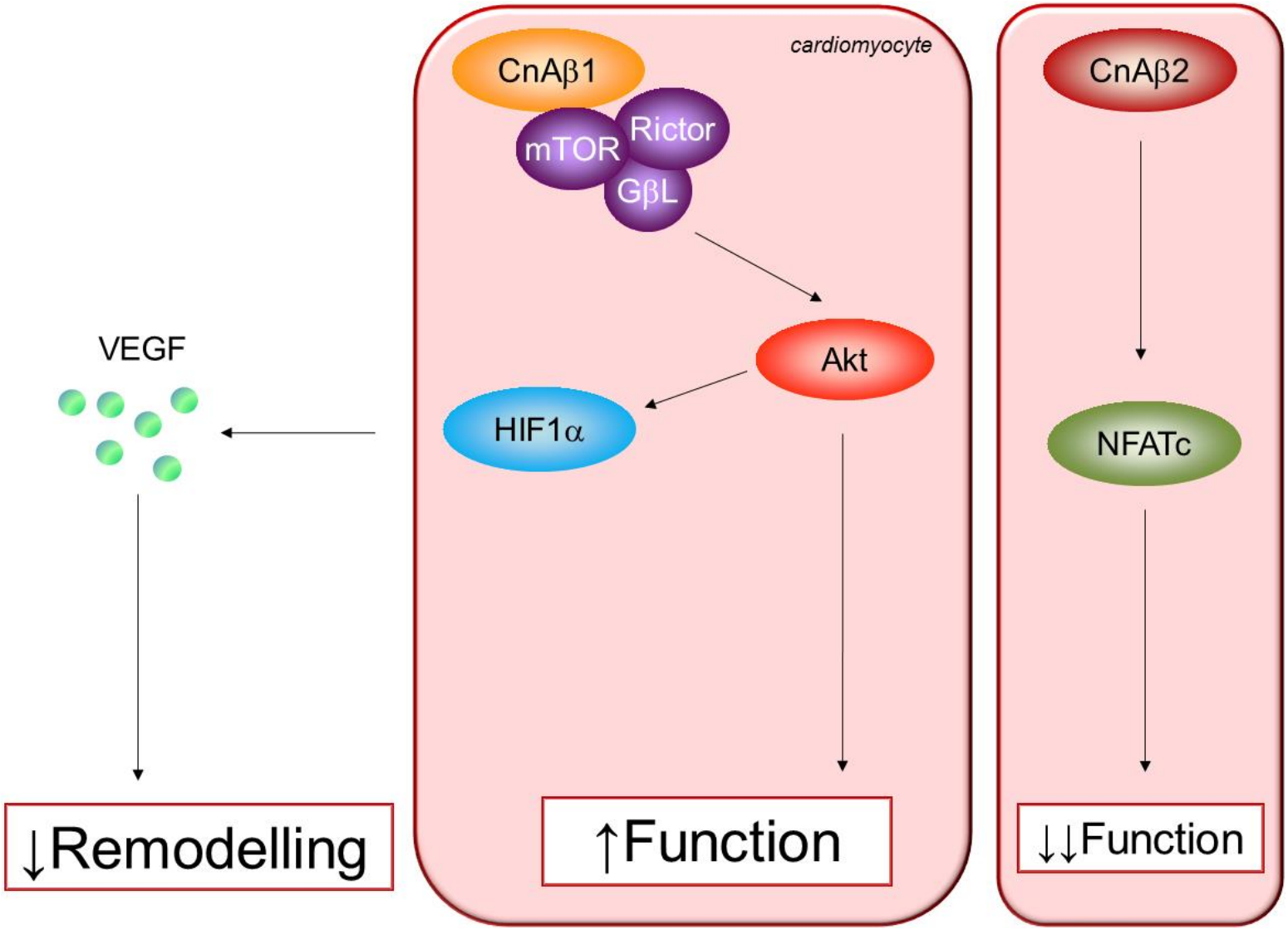
Despite current treatments, prognosis is still poor

Potential market:

EU – 3M people

US – 1.3 M people

Mechanisms of Action



Differential Features Facing the Market

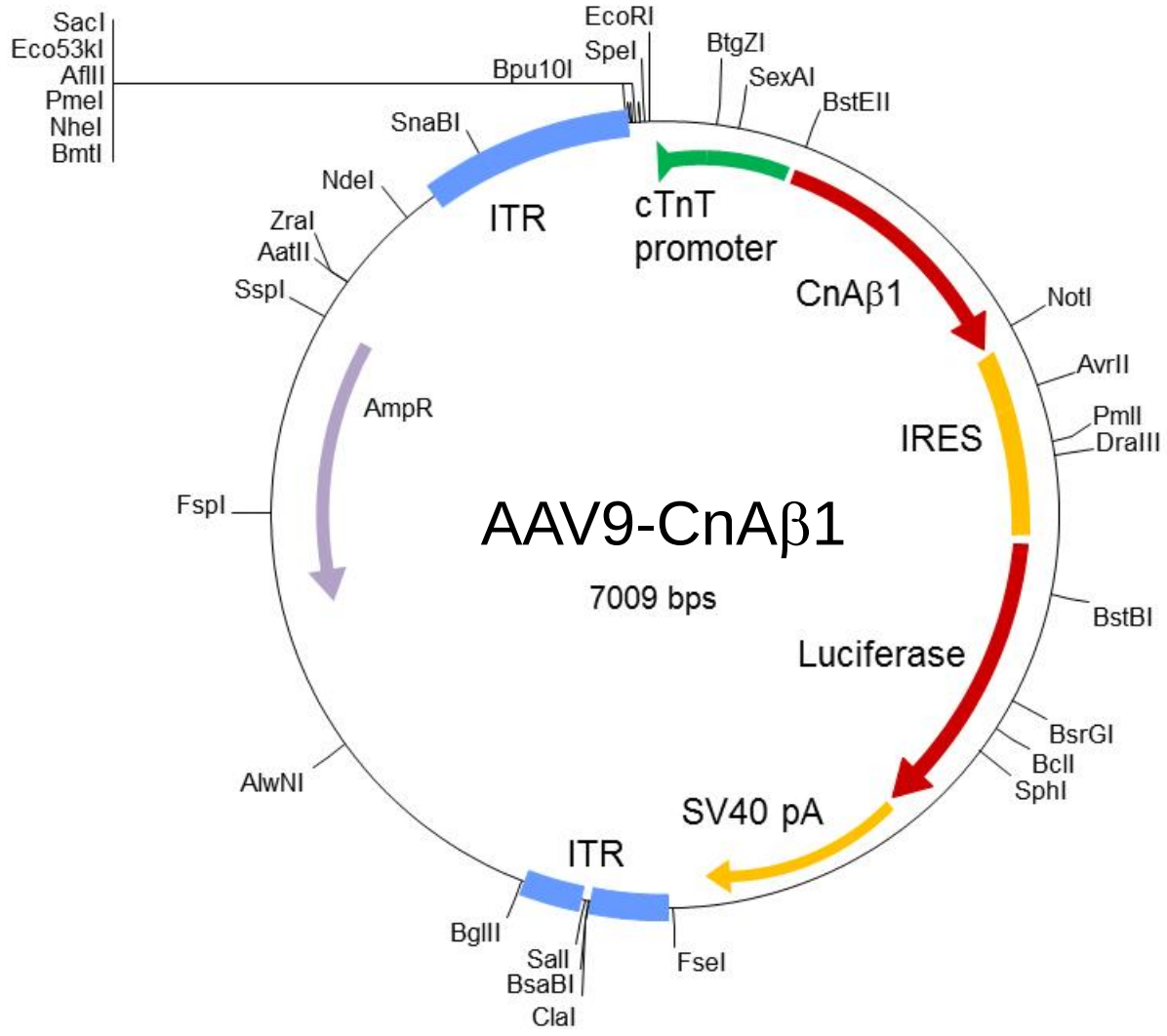
CnAβ1 is a natural product expressed at low levels in the heart
Chance of immune rejection is low. No immunomodulatory therapy required

Heart Failure is treated with complex pharmacological regimes
Some patients are refractory to this treatment; in others adherence is poor
Treatment with AAV9-CnAβ1 would require just 1 injection

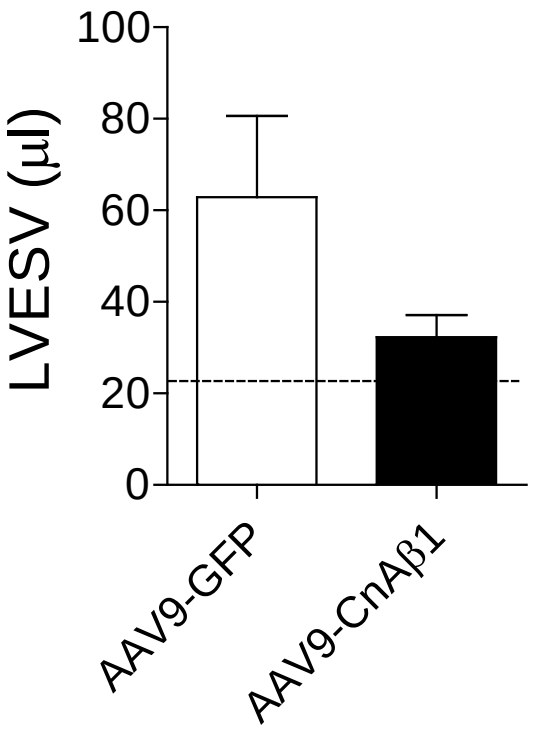
Gene therapy with AAV is safe and efficient

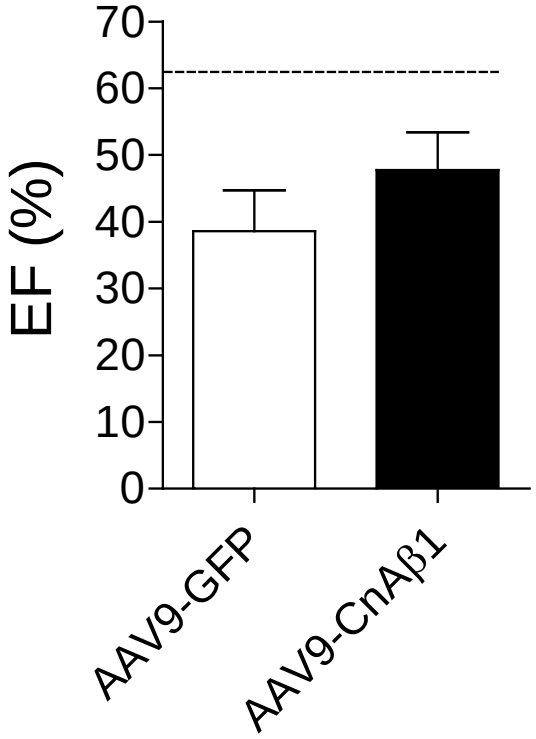
AAV9-CnAβ1 is cheaper than mechanical assist devices (LVADs)

Current Status of Development – AAV9-CnAβ1

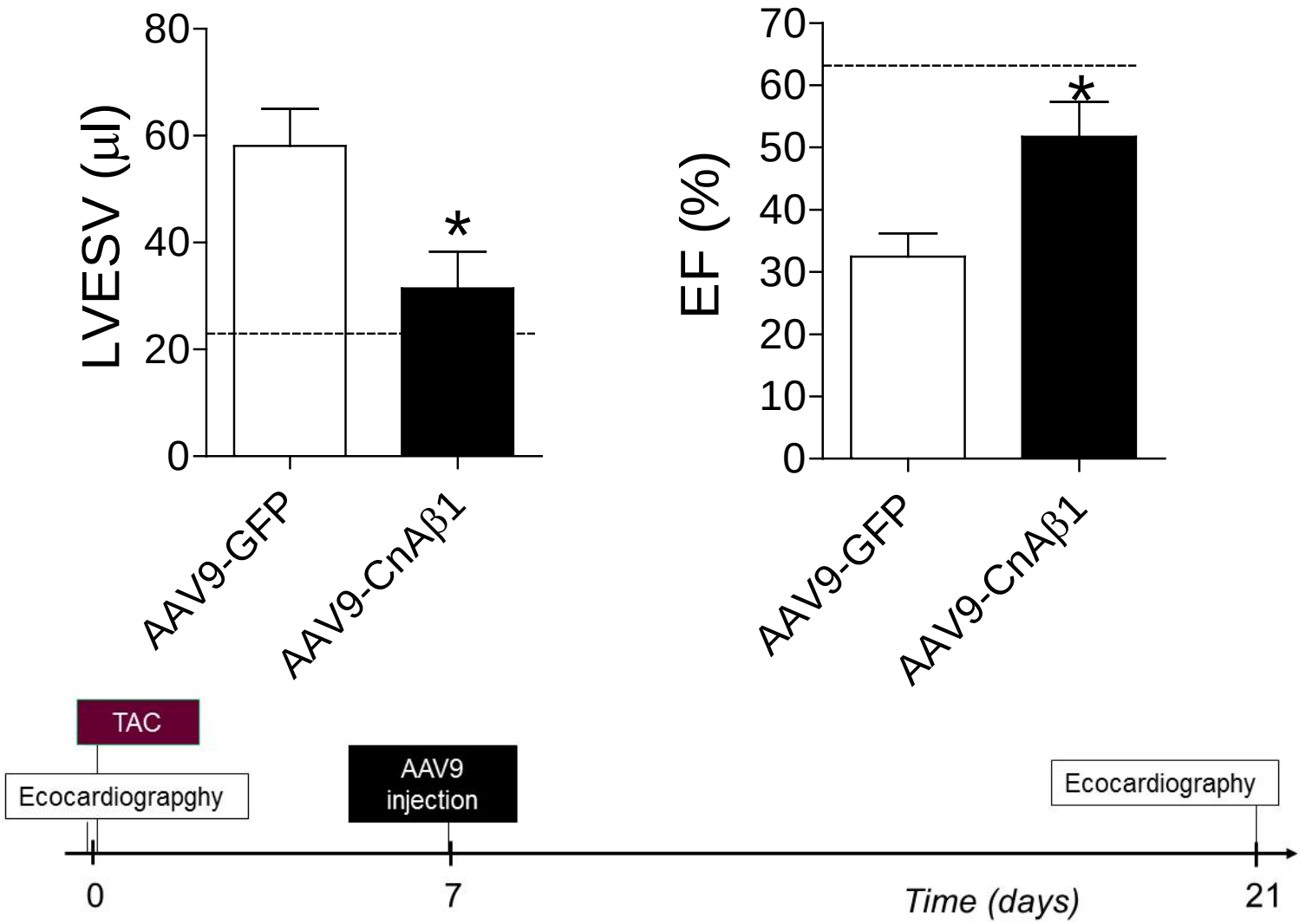


AAV9-CnAβ1 improves function after *myocardial infarction*

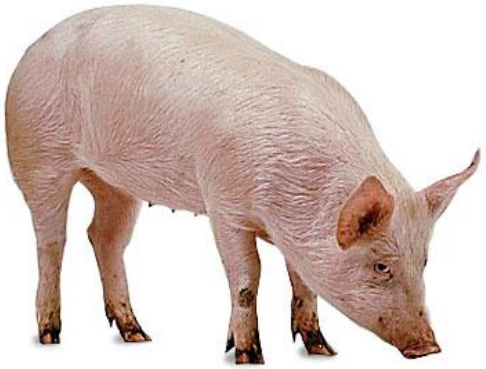


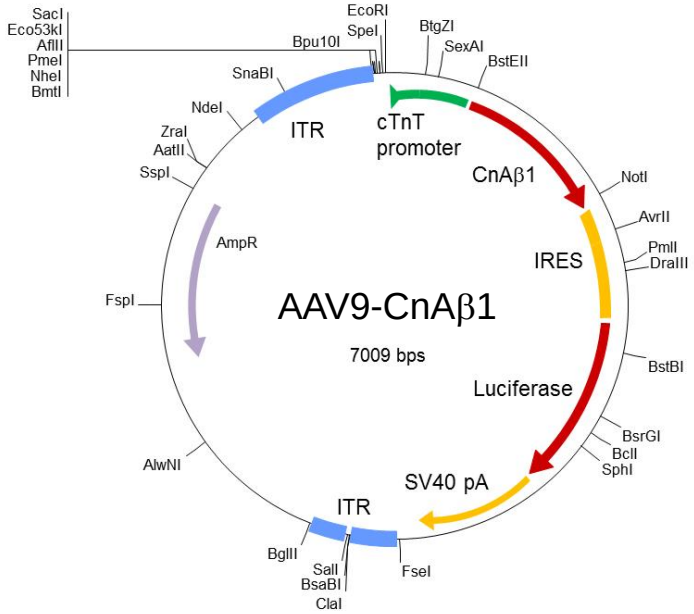


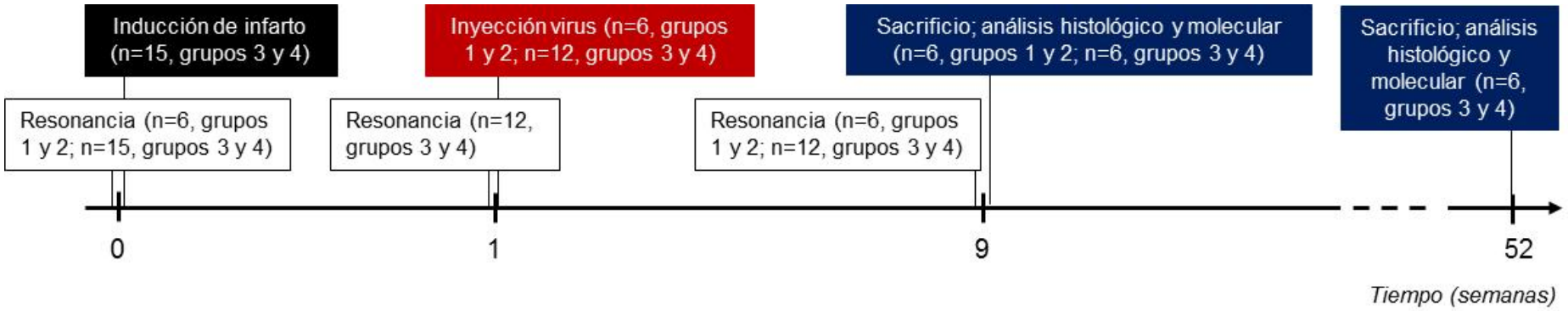
AAV9-CnAβ1 improves function after *aortic stenosis*



AAV9-CnAβ1 future developments







IPR Protection

EP12382329,6 (Date of application: 17/08/2012)
"*Methods of using the Calcineurin A variant CnAβ1 for the treatment of cardiac hypertrophy*"
Applicants: CNIC (90%), EMBL (10%). Inventors: Enrique Lara Pezzi, Nadia Rosenthal, et al.
PCT number: PCT/EP2013/067140 (date of application: 16/08/2013. PCT publication number: WO 2014/027087.

EP14155721.5 (Date of application: 19/02/2014)
"*AAV vectors for the treatment of ischemic and non-ischemic heart disease*"
Applicant: CNIC (100%). Inventors: Enrique Lara Pezzi, Borja Ibáñez et al.

Pitfalls and Risks

Some patients (30%) will present neutralizing antibodies against AAV9

Expression of CnAβ1 in other organs despite cardiac-specific promoter

Partnering Opportunities

Preclinical studies with AAV9-CnAβ1 in pig

Initial clinical studies

Partnering in future start-up company

Acknowledgements

CNIC

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María Villalba
Alberto Gatto
Enda Clinton
Girolamo Giudice
Paula Ortiz
Laura Padrón
Raquel San José

Fatima Sanchez-Cabo
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Borja Ibáñez & Group
Toño Enrique & Group
Mercedes Ricote & Group
Jesús Vázquez
Juan Bernal
Jesús J. Borreguero
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Homeostasis Programme
CDR Department
All technical Units

Imperial College London

Nadia Rosenthal
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Stuart Cook

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Pablo García-Pavía