CRVB Centre for Research in Vascular Biology

UCC Coláiste na hOllscoile Corcaigh, Éire University College Cork, Ireland

Use of Low dose IGF1 for post-infarction myocardial repair

From bench to bedside

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HRB Health Research Board

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Torino Oct 2016

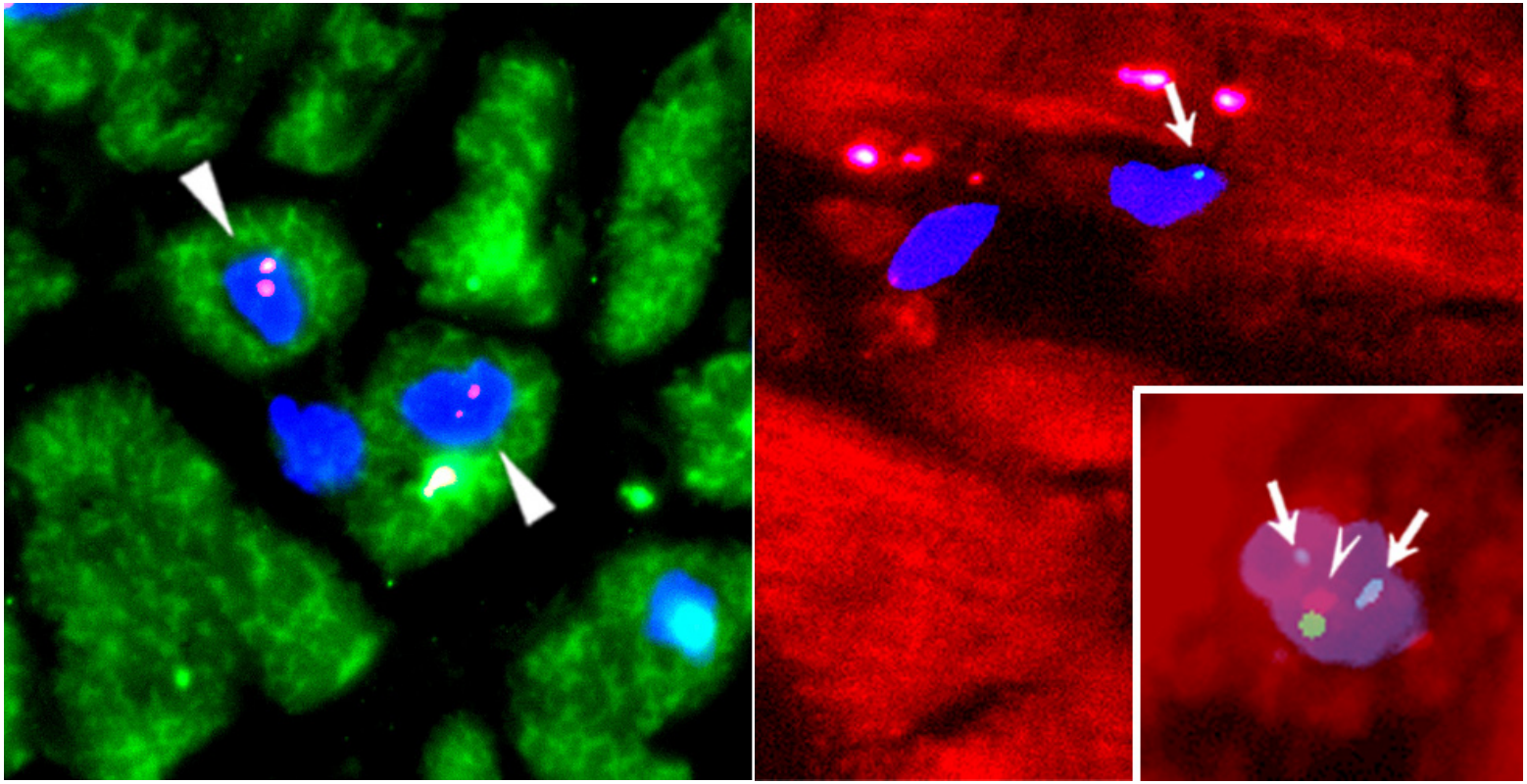
CELL THERAPY

CARDIAC REPAIR?

Limited Myocardial Chimerism in humans after BMT

1/5000 cardiomyocytes in heart from bone marrow

Deb Circ 2003

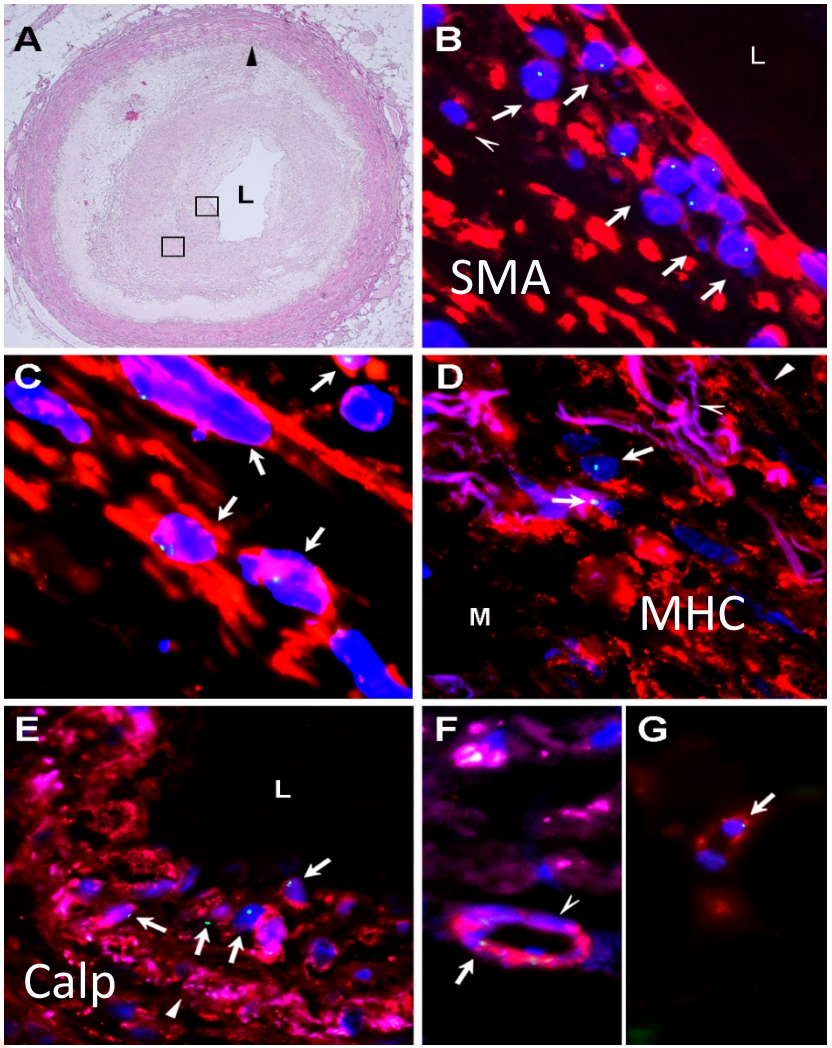


XX XX XY XX

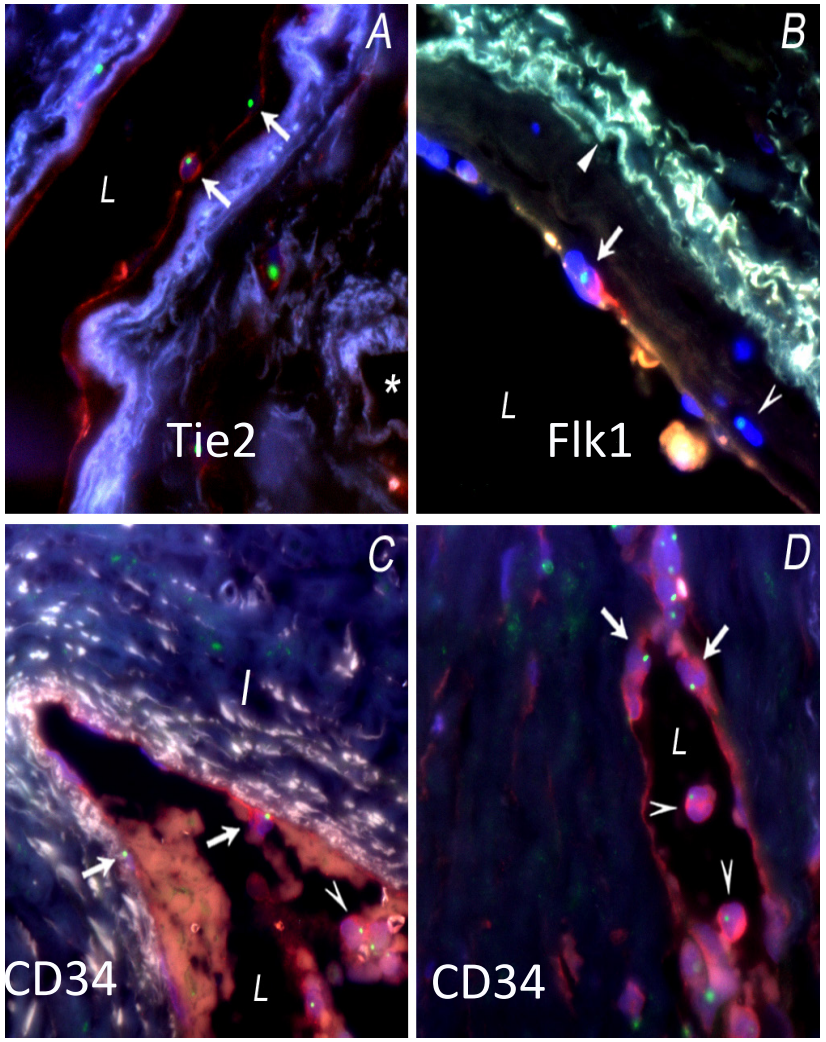
BM-derived EC and SMC chimerism 500 fold > cardiomyocytes

Caplice PNAS 2003
Simper Circ 2003

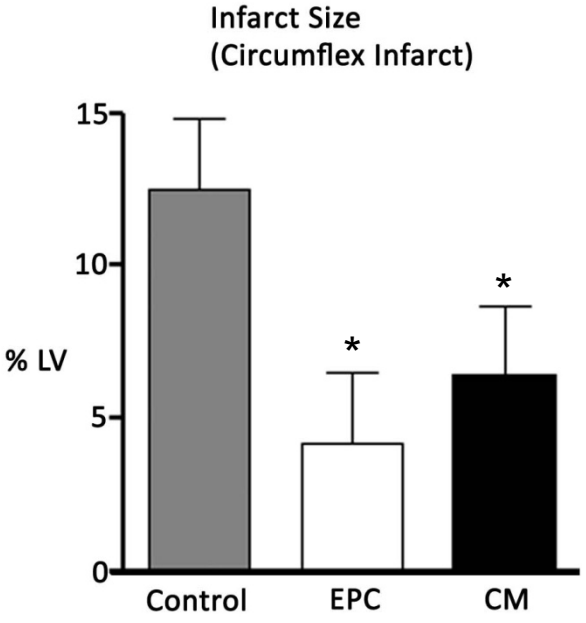
SMC Chimerism ~10%



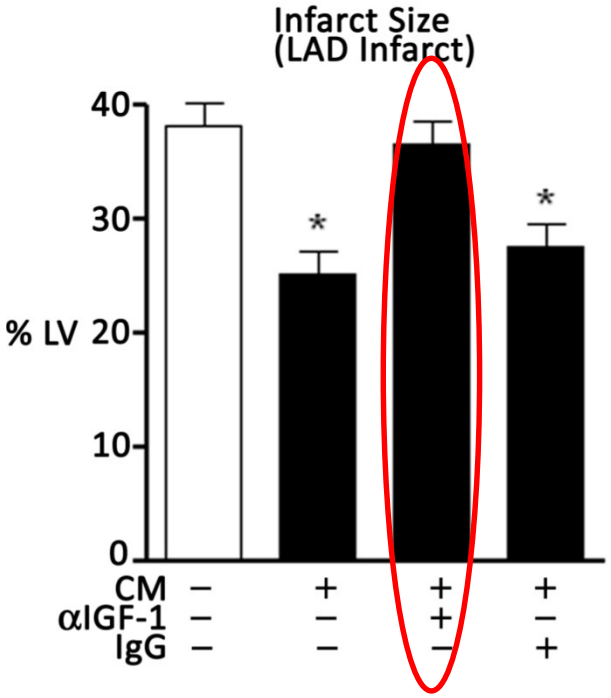
EC Chimerism ~ 15%

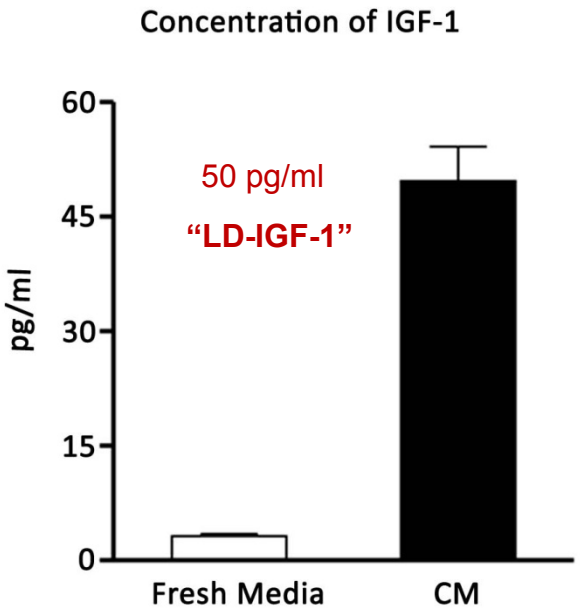


- We focused on endothelial progenitor cell (EPC) repair effects post acute infarction
- Identified EPC paracrine factors that were as potent as cells in cardiac repair
- Determined key factor(s) responsible for paracrine repair by use of inhibitors
- **Isolated low-dose IGF1 (LD-IGF1) as a candidate therapy post MI**



Doyle et al. Stem Cells Dev. 2008.





Hynes et EHJ 2012. Stem Cells Dev. 2008.

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IGF-1

- Previous trials had treated heart failure patients with microgram doses of human growth hormone (hGH) which mediates tissue effects of IGF-1

- RCTs showed no sustained benefit of hGH

- SIDE EFFECTS: Acute (vasovagal, hypoglycemia) and
- Chronic (arthralgia, edema, orthostatic hypotension, tachycardia)

- Consequently, interest in IGF-1 as a cardiac therapy abandoned

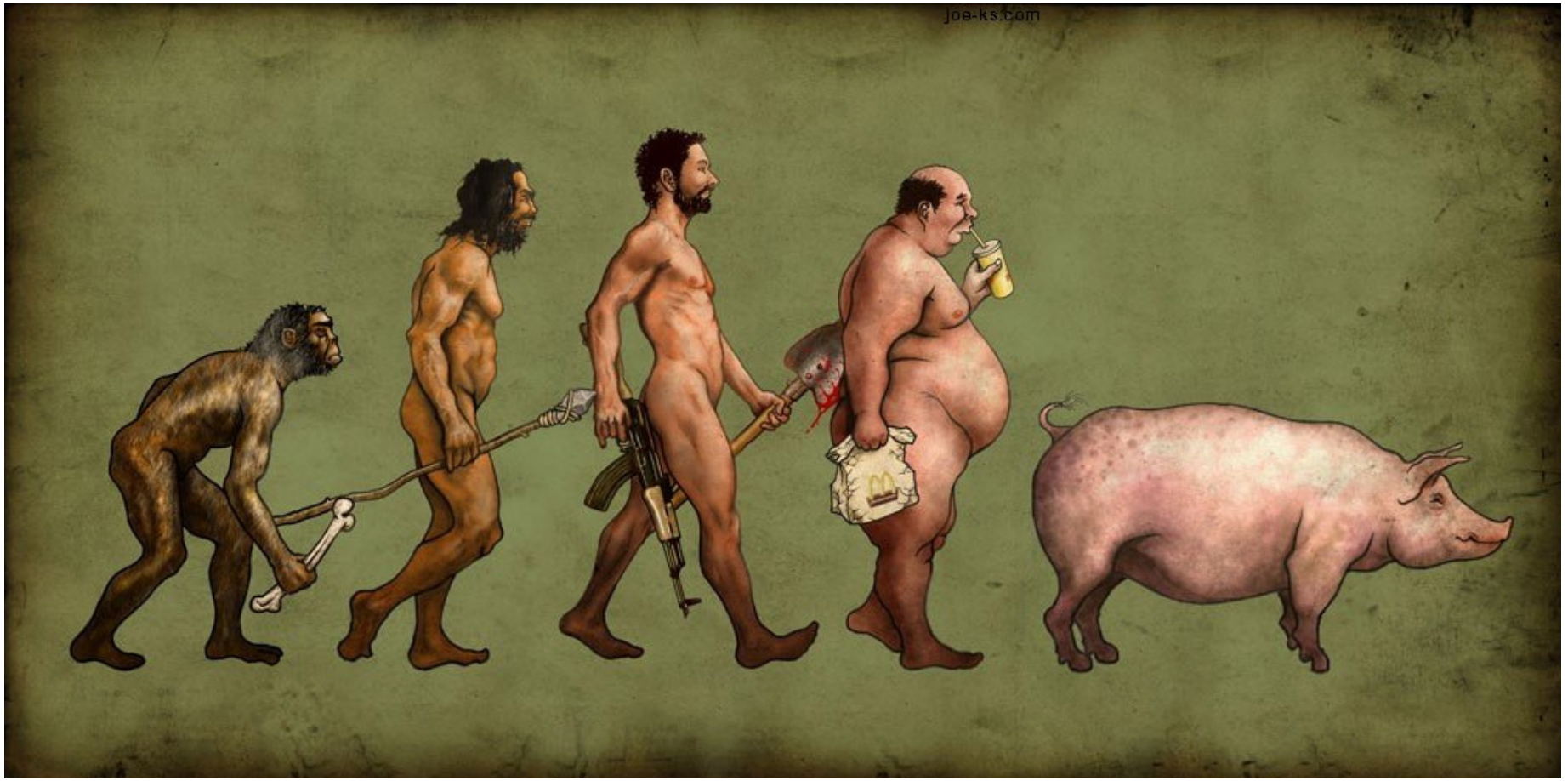
- **However, no RCT ever used IGF-1 in acute STEMI:**

  - **to target acute cardiomyocyte death in the context of infarction,**

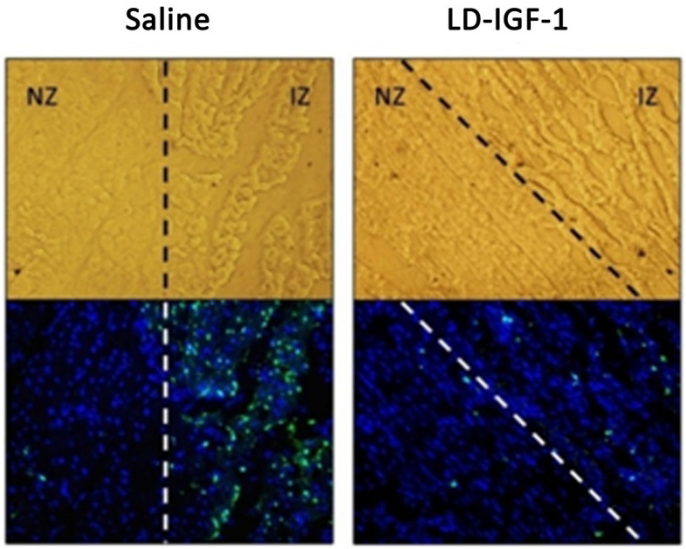
  - **at picogram concentration (less likely side-effects)**

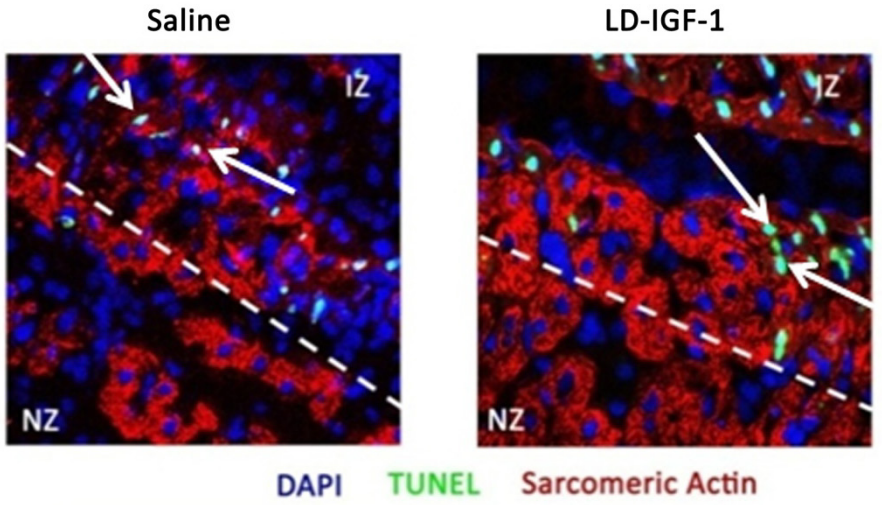
  - **Develop preclinical / clinical program using LD-IGF1 in STEMI**

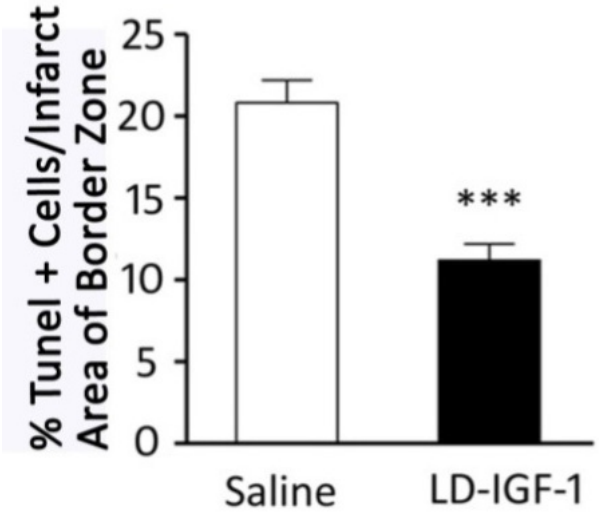
Porcine AMI model excellent for human disease

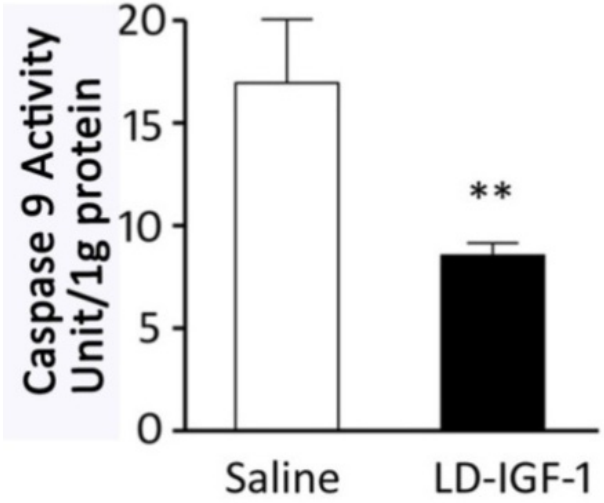


LD-IGF-1 reduces cell death at 24 Hours









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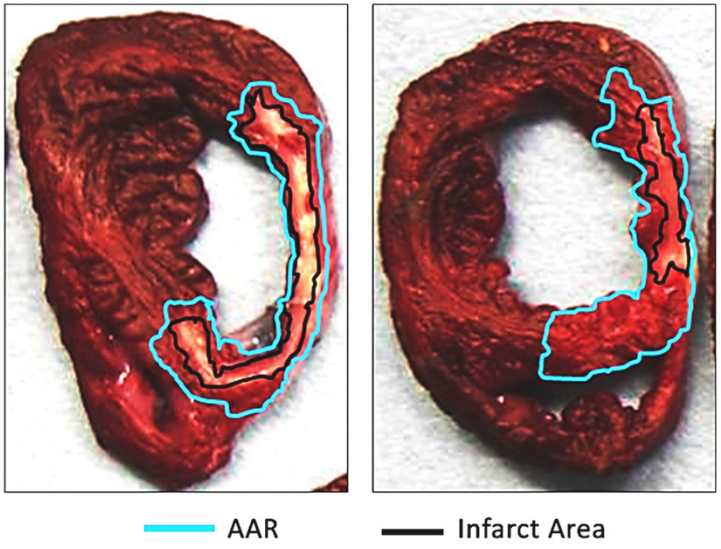
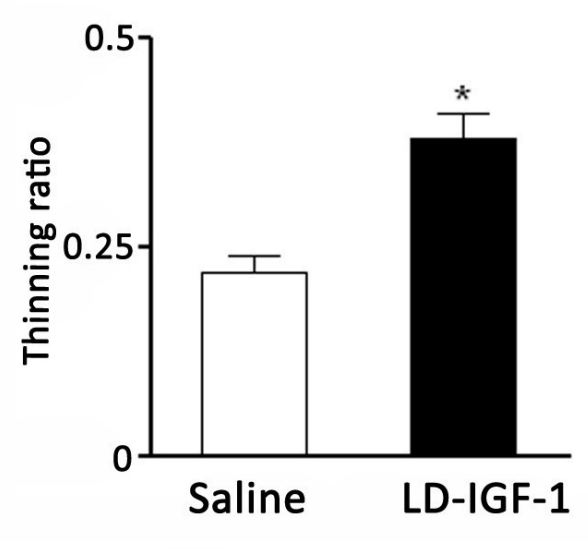
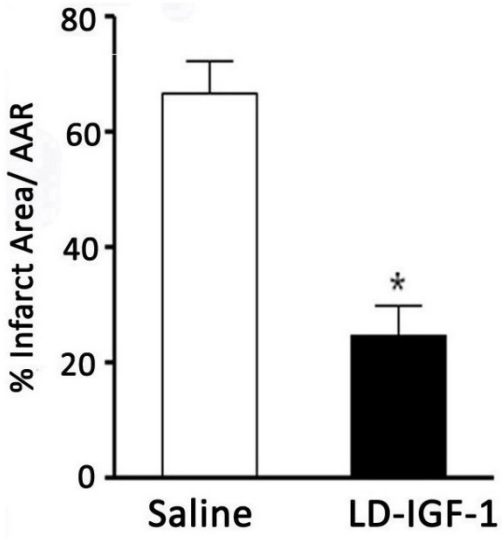
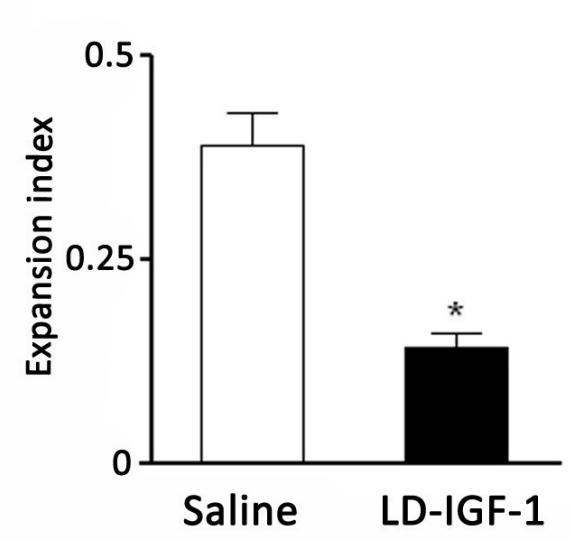
LD-IGF-1 Improves Infarct Remodelling at 2 months









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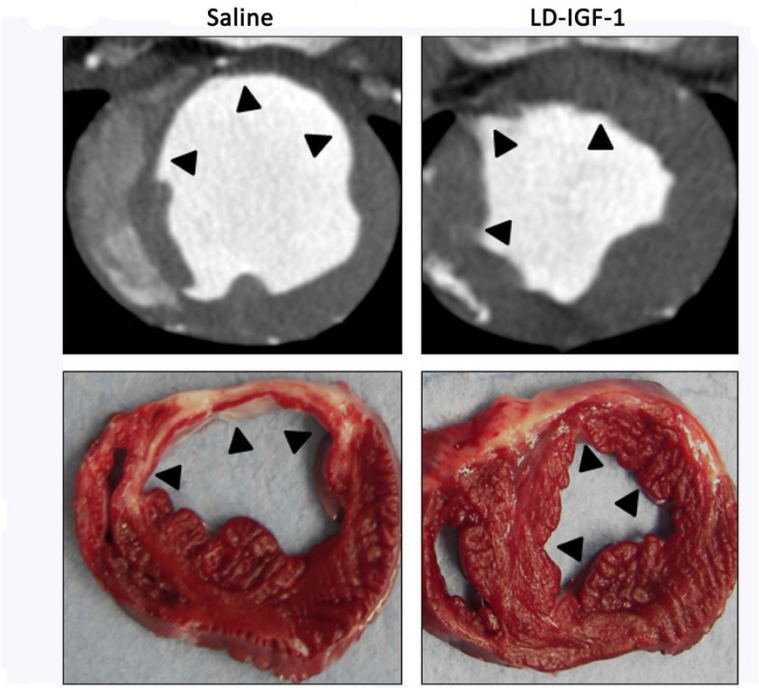
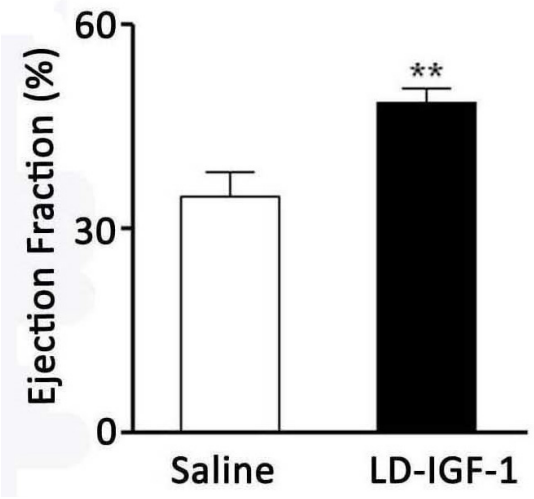
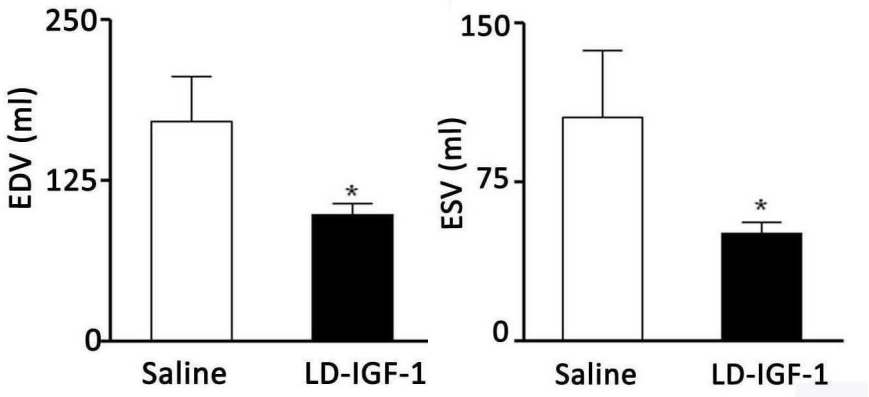
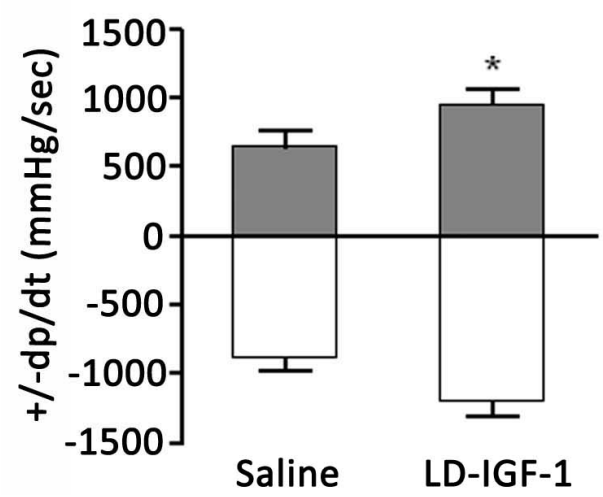
LD-IGF-1 reduces Global LV dilatation, improves ejection fraction, relaxation / contractility at 2 Months









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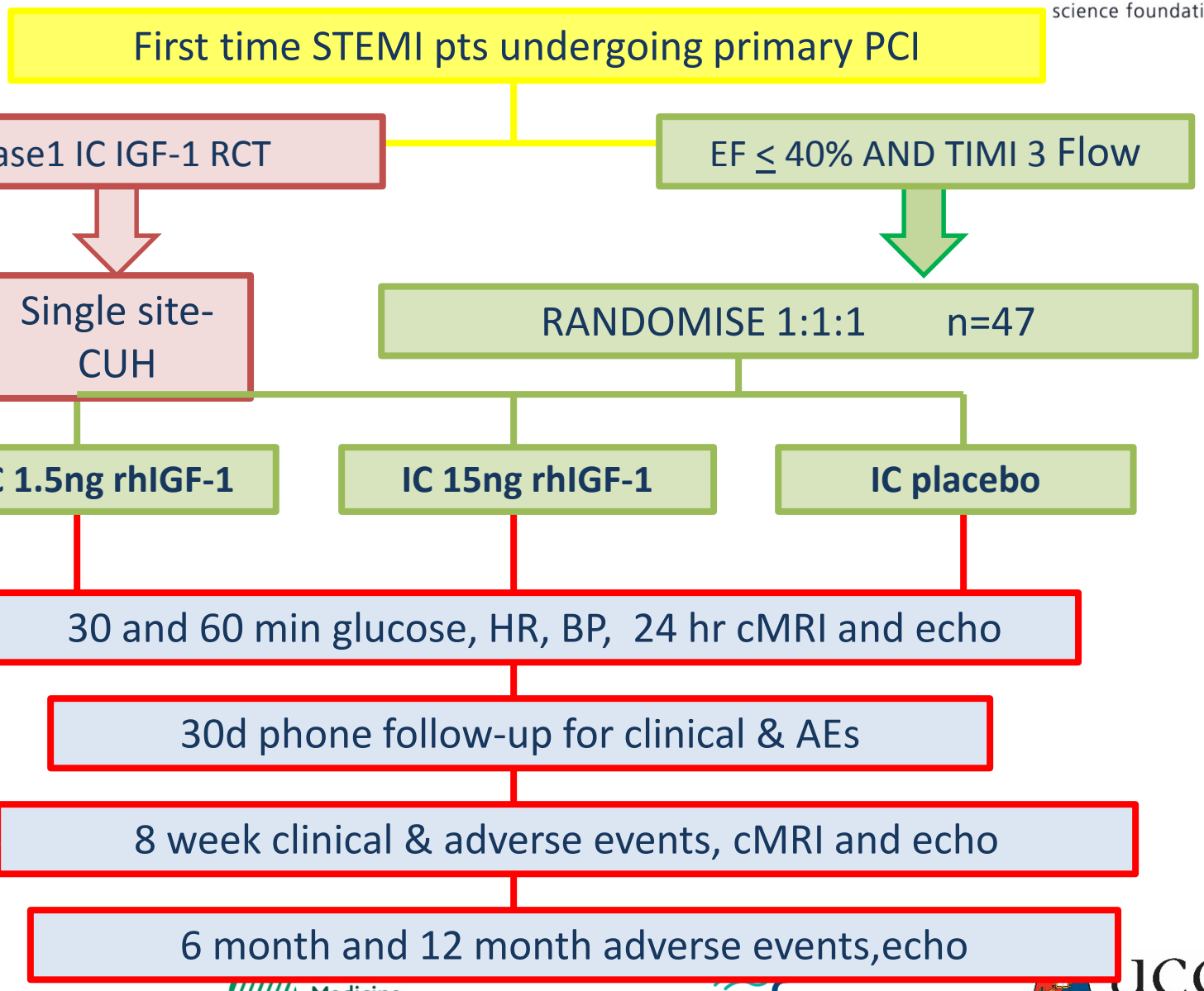
RESUS-AMI

- **R**andomised trial **E**valuating the **S**afety and efficacy of single low dose of intracoronary Ins**U**lin-like growth factor-1 following percutaneous coronary intervention for **S**T-elevation **A**cute **M**yocardial **I**nfarction
- Investigator initiated trial
- Double blinded, placebo controlled
- Three treatment groups, placebo, 1.5ng and 15 ng IGF-1. Enrollment target of 47 patients.
- Enrollment time over 42 months

RESUS-AMI


First time STEMI pts undergoing primary PCI
Phase1 IC IGF-1 RCT
EF ≤ 40% AND TIMI 3 Flow
Single site- CUH
RANDOMISE 1:1:1 n=47
IC 1.5ng rhIGF-1
IC 15ng rhIGF-1
IC placebo
Primary Safety EP: Serum glucose @ 30 and 60 minutes
30 and 60 min glucose, HR, BP, 24 hr cMRI and echo
30d phone follow-up for clinical & AEs
Primary Efficacy EP: % change in LVEF by cMRI at 8 weeks
8 week clinical & adverse events, cMRI and echo
6 month and 12 month adverse events,echo

Inclusion Criteria

- Presentation to PCI centre within 2-12 hrs of MI pain of at least 30mins duration
- 12 lead ECG shows ST ↑ or new LBBB
- Undergoing primary PCI for STEMI
- LVEF during PCI ≤ 40%
- TIMI 3 flow in IRA following reperfusion
- Age 18-75
- Negative pregnancy test in women of CBP
- Able to provide written informed consent based on competent mental status

Exclusion Criteria

- History of prior MI or CABG
- Valvular Heart Disease
- Prior hx : Heart failure, LVdysfn, Cardiomyopathy
- History of Atrial Fibrillation
- Active or prior malignancy
- Known Liver dysfunction
- Cardiogenic shock
- Estimated GFR <45ml/min/1.73msq
- Hx of hypoglycemia requiring hospitalization
- Hx of primary IGF1 deficiency or GH disorder incl acromegaly
- Contraindication to MRI (PM, ICD, magnet activated device, claustrophobia)
- Nursing mothers and known allergy to study drug

Safety Endpoints

- Primary
  - Serum glucose measurement at 30mins and 1 hour after study drug admin.
- Secondary
  - Incidence of hypotension or arrhythmias- time of study drug
  - Treatment-related adverse events
  - Incidence of abnormal clinical laboratory measurements through hospitalization for index event
  - Incidence of clinical events: CV and all cause death, re-infarction, unstable angina, TVR, worsening HF, CABG, stroke and arrhythmia through month 12.

Efficacy Endpoints

- Primary
  - Change in global LVEF at 8 weeks from baseline measurement by cardiac MRI
- Secondary
  - Change in LV mass, LV end-systolic and diastolic volumes, LV stroke volume and cardiac output at 8 weeks from baseline
  - Change in infarct size at 8 weeks from baseline
  - Change in regional LV wall motion and thickness at 8 weeks from baseline
  - NYHA and CCS functional class at 8 weeks, 6 and 12 months
  - Change in LVEF, LV volumes, RWMA at 6 and 12 months from baseline by echocardiography

RESUS-AMI-Current status

- Trial completed enrollment July 22 2016
- Prelim. Safety Endpoints: LD-IGF1 is safe when given IC during STEMI with no significant increase in adverse events in treatment versus placebo groups
- Primary and secondary efficacy endpoint analysis currently ongoing with additional mechanistic analysis being performed
- Data will be submitted in Dec 2016 for consideration as a late breaking trial at ACC conference March 2017 in Washington DC

Future

- If RESUS-AMI shows efficacy

Consider:

- RESUS-AMI 2 - multicentre trial Europe or USA
- LATE RESUS-AMI for 20% of patients that present after 12 hours of pain

Acknowledgements

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UCC / CUH Clinical Trial Staff

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- M De Voe (Monitor)

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- Darren Dahly

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- Molecular Medicine Ireland

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