Dysfunctional myocytes

Tissue Engineering and Gene Therapy in Heart Failure

Intermediate loss of myocyte numbers

Molecular/Gene Therapy

Cell Therapy

Stem Cells

Human studies

Animal studies

Tissue Engineering

Stems Cells

Bone marrow

Adipose tissue

Human studies

VEGF

bFGF
Cellular Cardiomyoplasty

- **Mesenchymal stem cells**
  - Cells possess multipotent capabilities, proliferate rapidly, induce angiogenesis, and differentiate into myogenic cells
  - Bone marrow
    - 2-3 mesenchymal cells per 100,000 cells
    - Low yield/painful

- **Human adipose tissue**
  - Multipotent stem cell population with high proliferate potential
  - **High number of mesenchymal stem cells (2–10%)**
  - Differentiate into endothelial cells, incorporate into vessels, and promote postischaemic neovascularization in nude mice
  - Reversed wall thinning in the scar area and improved cardiac function in rats with myocardial infarction

Adipose Derived Cells

- **Bone Marrow**
- **Adipose Tissue**

Graph showing stem cells per cc tissue with:
- **2000 ml of fat**
- **50 million nucleated cells/100 ml of fat**
Liquid FAT

Collagen/adipocytes debris

Washing media

Cells

Cells
Adipose Tissue-Derived Stem Cells

N=31 pigs

Adipose tissue-derived stem cells appear spindle-shaped under a phase contrast microscopy. After implantation, adipose tissue-derived stem cells engrafted the infarcted myocardium 30 days post-implantation.
New Blood Vessels after ADSC

Hoesch stain for nuclei (blue)

αSMA-smooth muscle markers

Nuclei

Antibodies for desmin (smc)

Overlay


Adipose tissue-derived stem cells-ADSC
Cellular Cardiomyoplasty

New cells co-staining GFP+ cells with endothelial and smooth muscle markers

Positively stained vessels with a diameter <10 mm (capillaries)

Stem cells - stained alpha-smooth muscle actin, and desmin

Adipose tissue-derived stem cells-ADSC

Animal

AutoQUANT derived 3D surface-rendered LVs

Baseline- control → 2 months- control

Baseline-ADSC → 2 months-ADSC

Improved LV
Cellular Cardiomyoplasty

Adipose tissue-derived stem cells-ADSC

Baseline
4 weeks after ADSC

Baseline
4 weeks after ADSC

2 Sample Cases-Pigs

The APOLLO trial (AdiPOse-derived stem ceLLs in the treatment of pts with ST-elevation myOcardial infarction)

PI: Prof. Patrick W. Serruys

• **Objective**
  - Feasibility and safety of IC early delivery of fresh ADRSCs in 48 pts aged 20 to 80 years with STEMI and LV dysfunction (LVEF 30-50%) after standard optimal care DESIGN

• **Design**
  - Prospective, **double-blind**, randomized, sequential dose escalation study (4 cohorts of 12 pts)
  - Exhaustive clinical & imaging protocol before and after liposuction and IC delivery of ADSCs within 24 hrs of primary PCI
  - Follow-up for 36 months to compare safety (MACE, HF, arrhythmias) and feasibility (assessing infarct size and LV performance)
The APOLLO trial (AdiPOse-derived stem cells in the treatment of pts with ST-elevation myocardial infarction)

63 year old, male

LVEF of 33% before ADSCs transfer

Invasive imaging (angio, IVUS, FFR/CFR, PV loops, etc) and IC cell delivery

Final results are pending
**PRECISE Trial**

(adiPose deRived stEm Cells In the treatment of patients with non revascularizable ischEmic myocardium)

**PI:** Francisco Fernandez-Aviles

- **N=36 total**
- **F/U 6 & 12 months**
  - MVO2
  - Holter 6, 18 months
  - Imaging 6, 12, 18, 24, 36 months
    - ETT, Echo, SPECT, MRI
  - Blood chemistry (BNP & others)
- **Design**
  - Prospective, double blind, randomized, parallel, placebo controlled, sequential dose escalation
- **Objective**
  - Safety/feasibility of ADSCs delivered into the myocardium using a NOGA mapping system
  - Severe CAD not eligible for revascularization

- **Must meet all Inclusion Criteria**
  - 20-75 y/o male/female
  - Angina class II-IV CCA
  - CAD not revascularization candidate
  - LVEF <45 with viability
    - SPECT, MIBI, LV angio or echo within 1 month of procedure
  - LV wall thickness > 8 mm at site of cell injection (echo)
  - BP >100, HR <110, O$_2$ SATs >95%
  - Ability to undergo liposuction

Intramyocardially ADRC
PRECISE Trial (adiPose deRived stEm Cells In the treatment of patients with non revascularizable ischemic myocardium)

- 3 cohorts
  - Cohort 1
    - N=3 placebo
    - N=9 (0.4 X 10^6 ADRCs)
  - Cohort 2
    - N=3 placebo
    - N=9 (0.8 X 10^6 ADRCs)
  - Cohort 3
    - N=3 placebo
    - N=9 (1.2 X 10^6 ADRCs)

Clinical Assessment
Stress tests
Holters
Imaging (Echo, MRI, SPECT)
Lab tests
PRECISE Trial

(adiPose deRived stEm Cells In the treatment of patients with non revascularizable ischemic myocardium)

Left Anterior Oblique

Lateral

NOGA Map-Guide

Intramycocardially ADRC//pending completion
Summary Points

Animal studies

• **Adipose tissue** - multi-potent stem cells
  – Ability to differentiate into vascular and cardiomyocytelineages
  – Ability to secrete several anti-apoptotic and angiotrophic growth factors
  – Improved global ejection fraction (~8-10%) and regional wall thickness, as well as improved myocardial perfusion

Human CAD studies

• **APOLLO trials**
  – First-in-man trial to evaluate the safety and feasibility of intracoronary ADRC infusion in the treatment of patient with *acute myocardial infarction*

• **PRECISE trials**
  – First-in-man trial to evaluate the safety and feasibility intramyocardially ADRC delivery in the treatment of *chronic refractory angina* not amenable for conventional treatment
Intracoronary Transplantation of Bone Marrow Progenitor Cells in Patients With Acute Myocardial Infarction

- **N=204 patients**
  - Placebo 103/Tx 101
  - DB/R/C/Multicenter

- **Methods:**
  - Acute ST-segment elevation MI successfully treated by PCI with stent implantation in the acute phase of the infarction
  - At 3 to 7 days after MI
    - Mononuclear cells were recovered from 50 mL bone marrow aspirate

- **4 months: Cath/LV other studies**

- **Substudy:**
  - 58 patients (BMC group, n30; placebo group, n28), coronary flow reserve (CFR) in the infarct artery and a reference vessel was assessed by intracoronary Doppler at the time of study therapy (4 days after acute myocardial infarction) and at the 4-month follow-up.

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JW 47 T2DM male yrs old
2 children
3 X’s all live in Texas
1 dog
LV Function & AMI

Comparison to Well Known Trials

- REPAIR-AMI-BMS + Stents
- ADMIRAL- Abcimimab + Stents NEJM 344:1895
- CADILLAC- Abcimimab + Stents NEJM 346:957

Absolute Change in % LV EF

P<0.014

NEJM 355:1210
LV Function & AMI

Infarct Zone Contractility

% Wall Thickening

Baseline 12 months

Placebo BMC Placebo BMC

P<0.001

Rolf AHA # 3419
Intracoronary BMC & Remodeling

No benefits for ESV in EF>56%
Only for <39%

Dill et al, 2007 REPAIR-AMI
### 2 years Clinical Follow Up

**REPAIR-AMI**

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Gene/Molecular Therapy

• **VEGF**
  - Vascular endothelial growth factor
  - Angiogenesis
    - ↑ Migration of endothelial cells
    - ↑ Mitosis of endothelial cells
    - Creation of blood vessel lumen
    - Creates lumen
    - Creates fenestrations
  - Chemotactic for macrophages and granulocytes
  - Vasodilation (indirectly by NO release)

• **bFGF** (basic fibroblastic growth factor)

  Wound healing
  Critical component of human embryonic stem cell
  Angiogenesis (forms new blood vessels)
No other coronaries
35 y/o male

bFGF given IC

1 year later
Whole Organ Decellularization

Research Animal

Decellularization Process
Skeleton remains/glycans

Progenitor Cells infused
8 days cells contract with pacing