Inflammatory Cytokine Secretion by Human Mesenchymal Stromal Cells is a Major Determinant of Cardiac Remodeling after Cell Therapy

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Disclosures

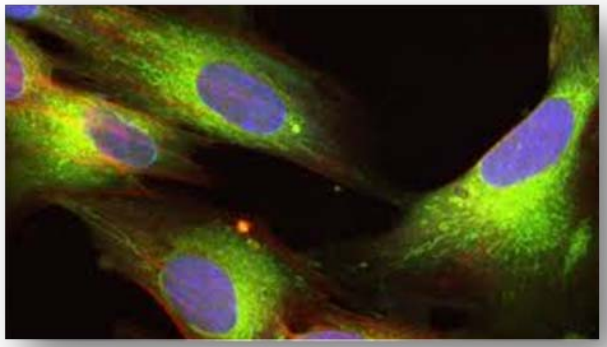
None

Mesenchymal Stromal Cells (MSCs) for Cardiovascular Repair

1. MSCs exist in the stromal fraction of many adult tissues.

2. MSCs are considered a promising cell source for heart repair.

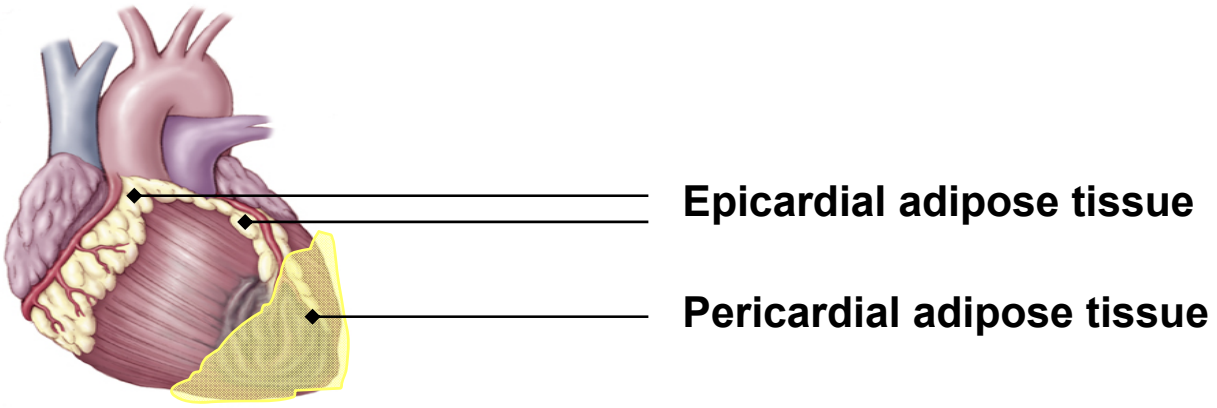
3. MSCs from different tissues share common features, but the source of MSCs might affect MSC properties and function.



Adipose Tissue as a Cell Source for Cardiovascular Regeneration and Repair

- **Adipose tissue** is considered an attractive source for MSCs with regenerative properties for heart repair.

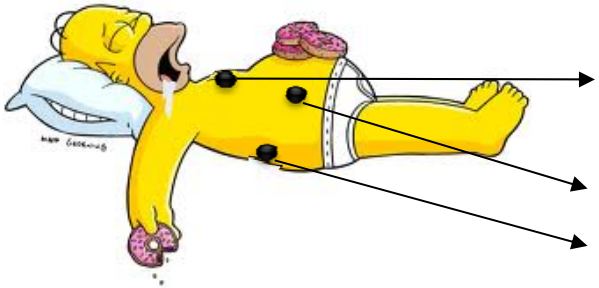
- **Cardiac adipose tissue** has been proposed as a source of progenitor cells and biological matrix for salvaging injured myocardium.



Aim

To test the hypothesis that, because of their proximity to the heart, human mesenchymal stromal cells (hMSCs) derived from **epicardial fat** would be **better** for infarct repair compared with **peripheral fat**-derived cells.

Methods

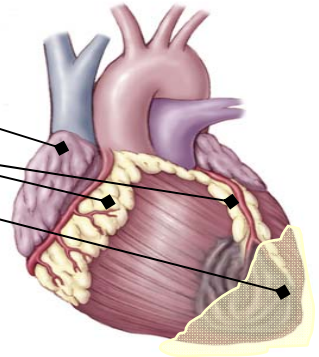


Medical procedures

- Open heart surgery
- Liposuction procedure
- Bone marrow biopsy

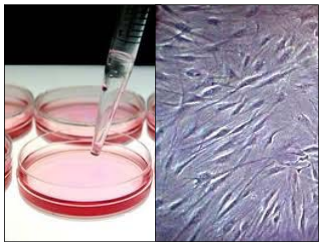
Tissue sources

- Right atrium
- Epicardial fat
- Pericardial fat
- Subcutaneous fat
- Bone marrow



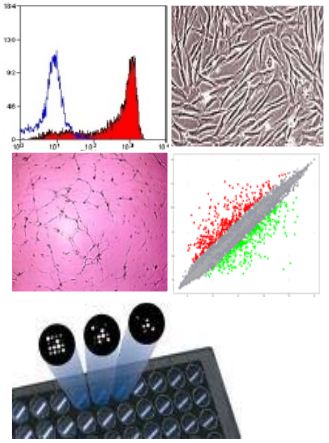
Enzymatic digestion

Cell culture



***In vitro* characteristics**

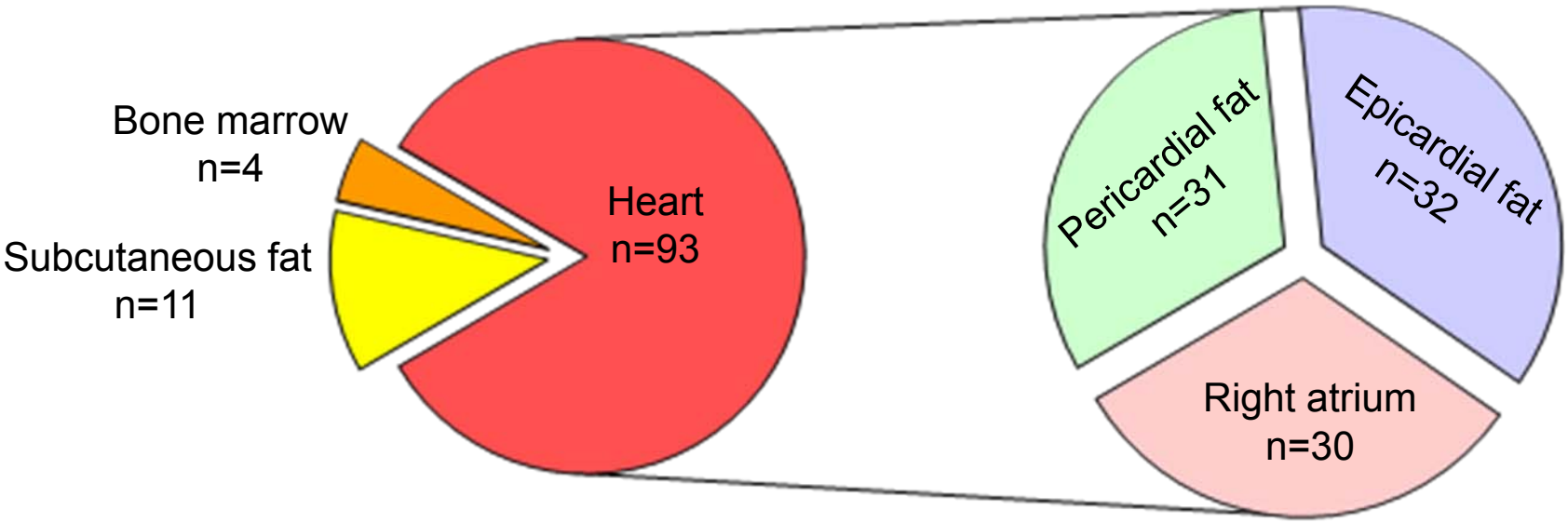
- Phenotype
- Cell proliferation
- Angiogenic potential
- Cytokine secretion
- Gene profile



***In vivo* study**

- Transplantation after MI in rats

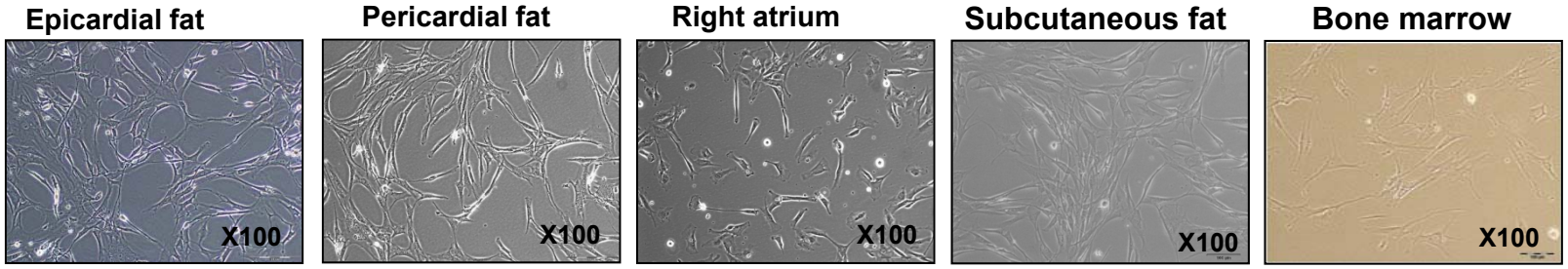
Source of Samples



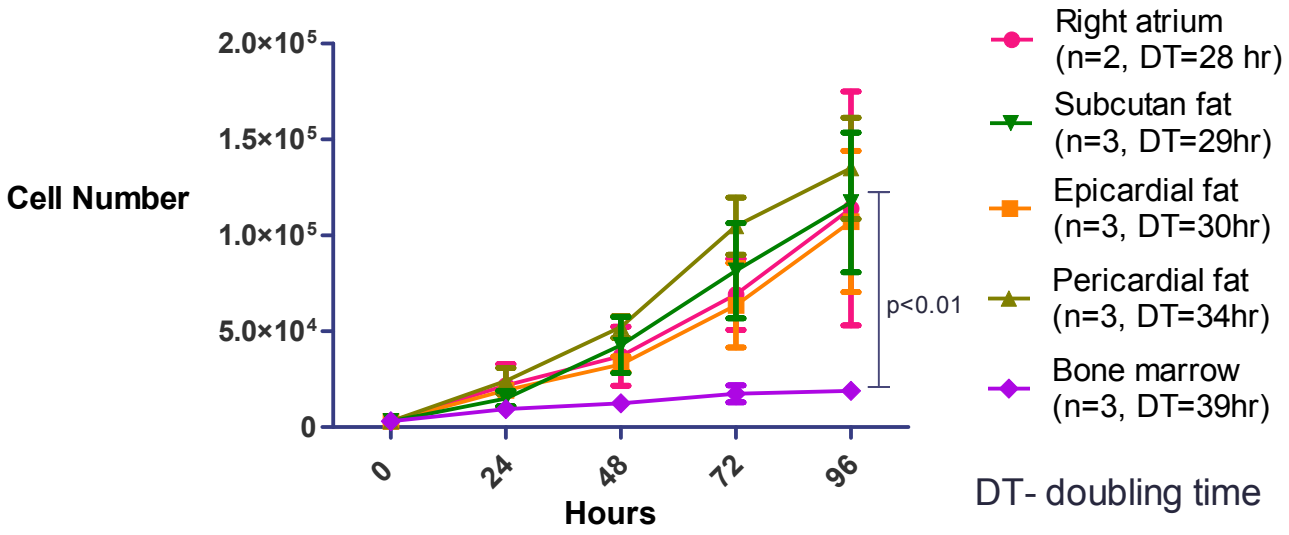
	Number of patients	Age	Gender
Open heart surgery	36	66 ± 1.6	21♂, 15♀
Liposuction procedure	11	52 ± 3.5	2♂, 9♀
Bone marrow biopsy	4	25.2 ± 0.6	4 ♂

Different Growth Rates of hMSCs from Different Sources

Morphology

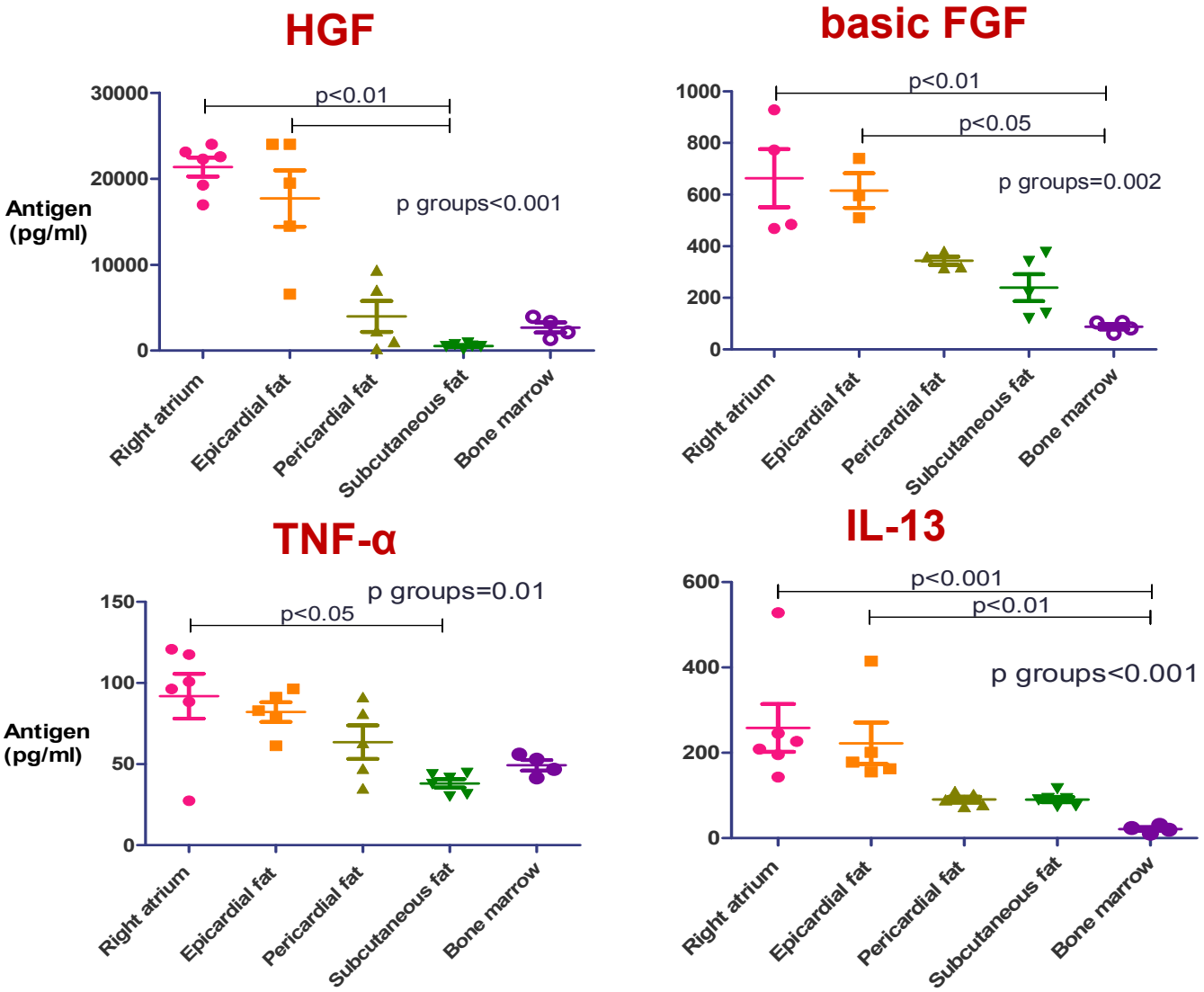


Cell Proliferation Based on XTT Reaction (passage 3)

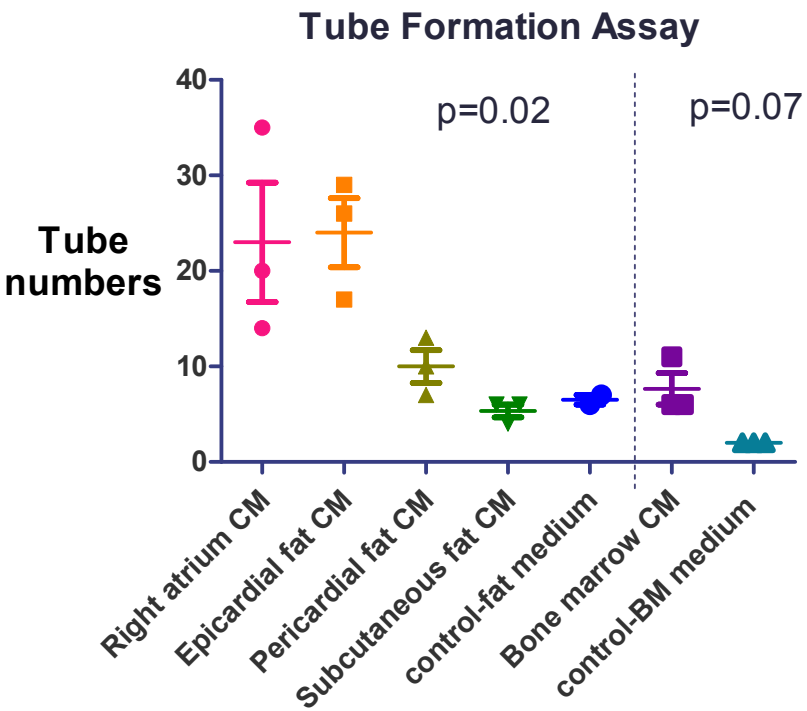


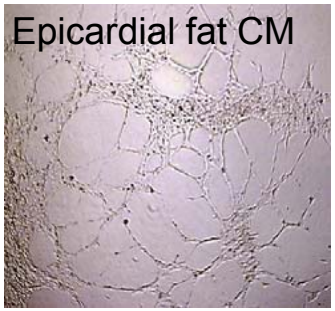
DT- doubling time

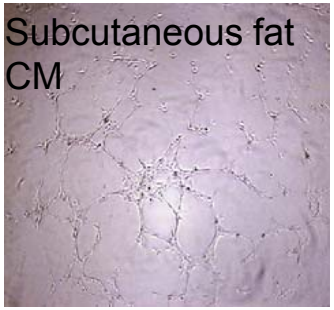
Variability in Cytokine Secretion by hMSCs from Different Sources

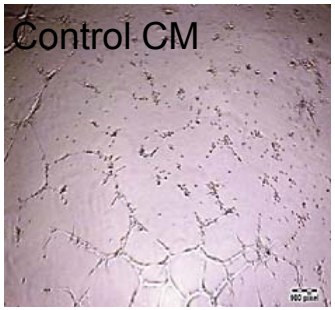


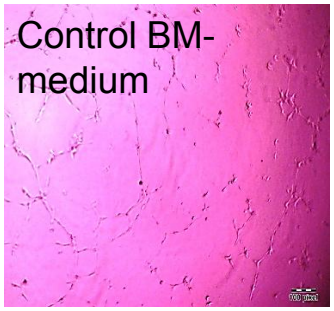
Angiogenic Potential by Tube Formation Assay





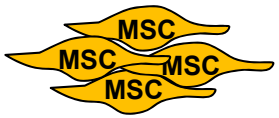






* CM-conditioned medium

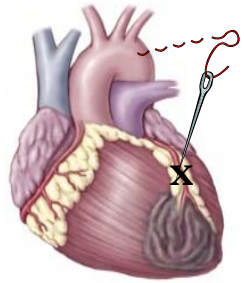
MSC Transplantation in a Rat Model of Myocardial Infarction (MI)



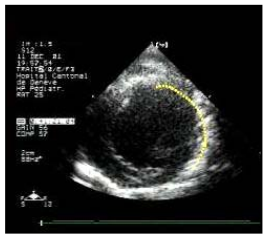
MSC isolation and expansion

1 6 7 34

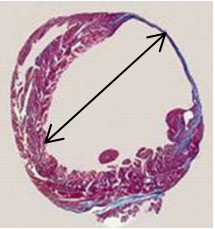
Coronary artery occlusion



1st echo examination **baseline**

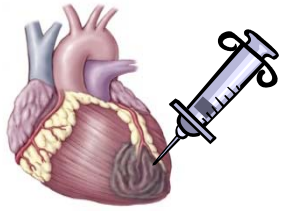


- 2nd echo examination
- Histology



2x10^6 MSCs transplantation into MI area (cells mixed with matrigel)

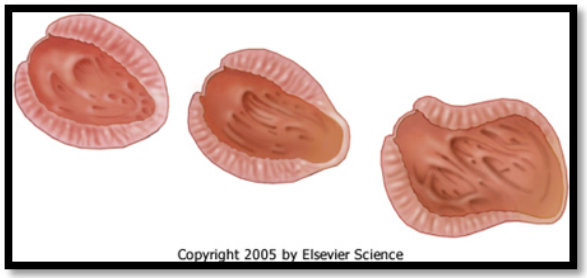
- Right atrium n=9
- Epicardial fat n=10
- Subcutaneous fat n=9
- Bone marrow n=8
- Matrigel n=11
- Saline n=10



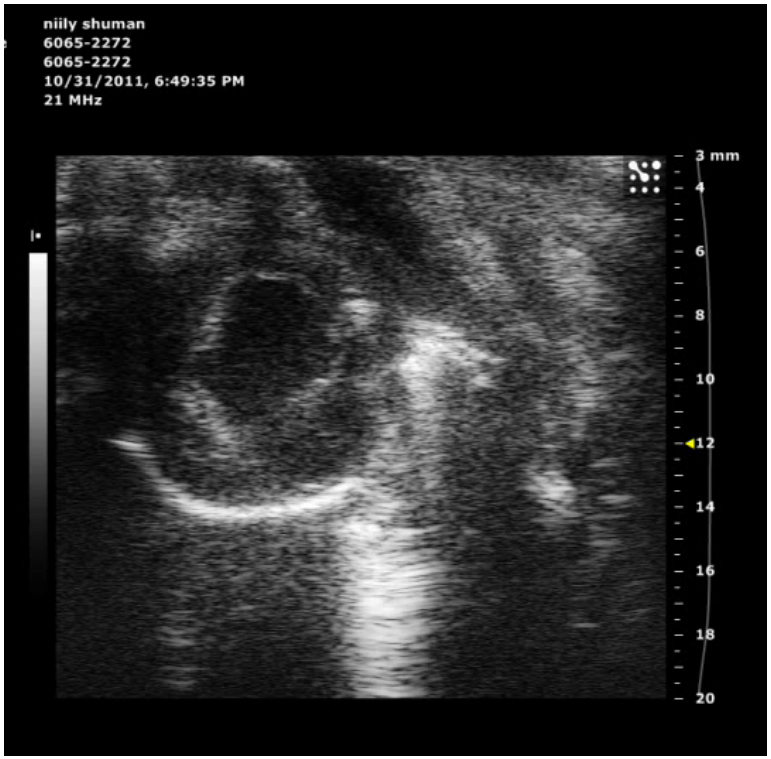
***In vivo* study**

Echocardiography Assessment of Cardiac Remodeling

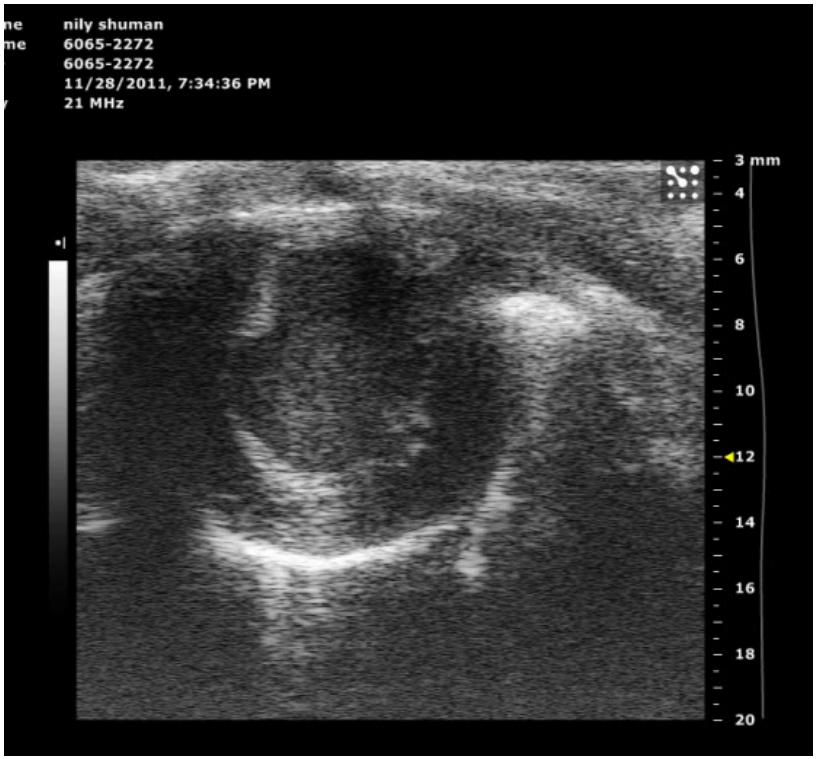
Ventricular remodeling



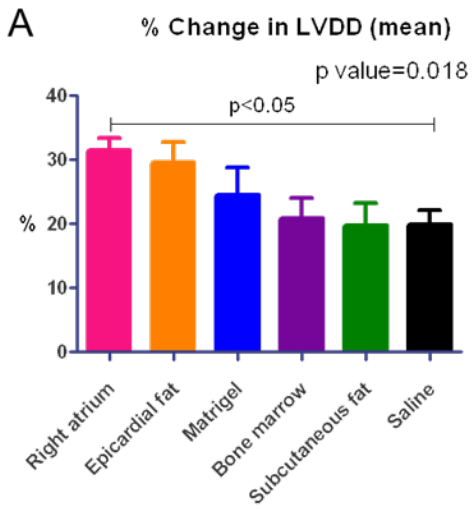
Baseline -6 days after MI
no treatment group

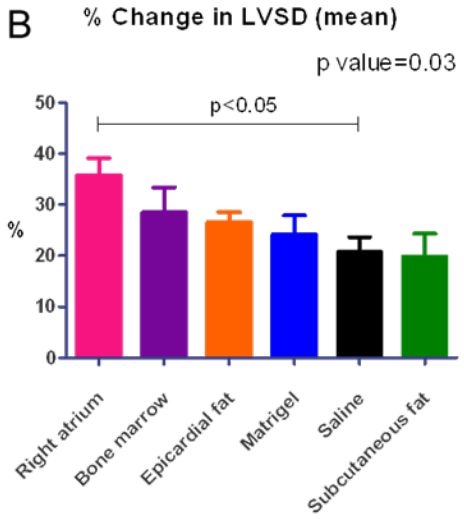


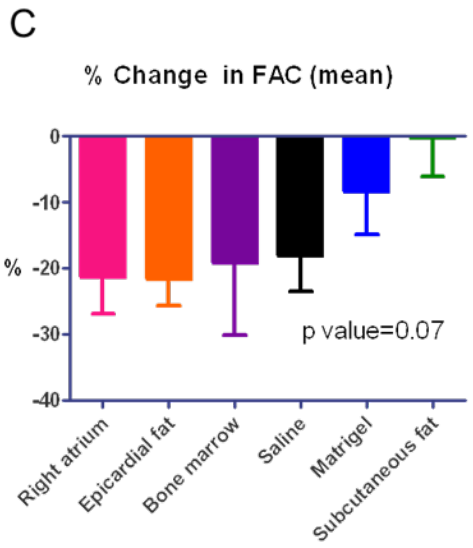
1 month follow-up
no treatment group



Subcutaneous Fat hMSC Transplantation Attenuates LV Dilatation and Dysfunction







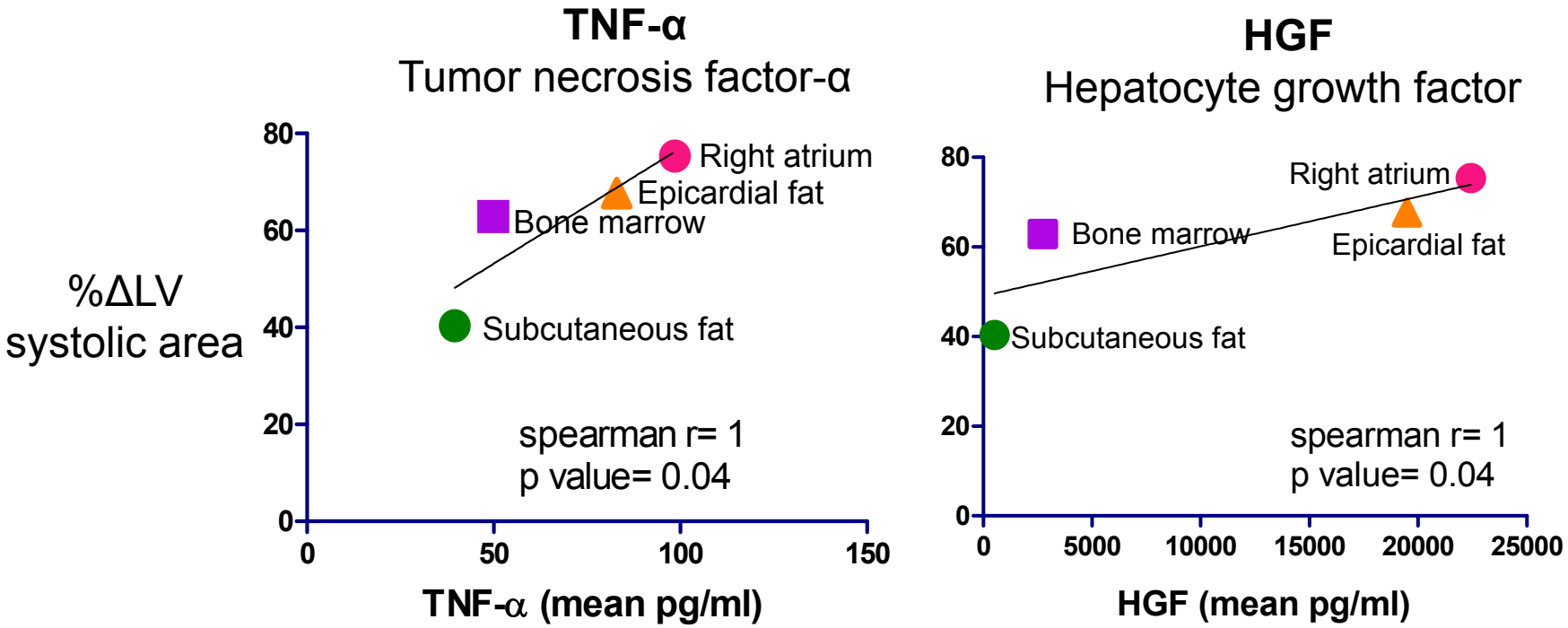
LVDD- left ventricle diastolic dimension
LVSD- left ventricle systolic dimension
FAC- fractional area change

$$\text{Change from baseline (\%)} = \frac{\text{follow-up- baseline}}{\text{baseline}} \times 100$$

$$\text{FAC(\%)} = \frac{\text{LV end diastolic area - LV end systolic area}}{\text{LV end-diastolic area}} \times 100$$

27 Days after Injection

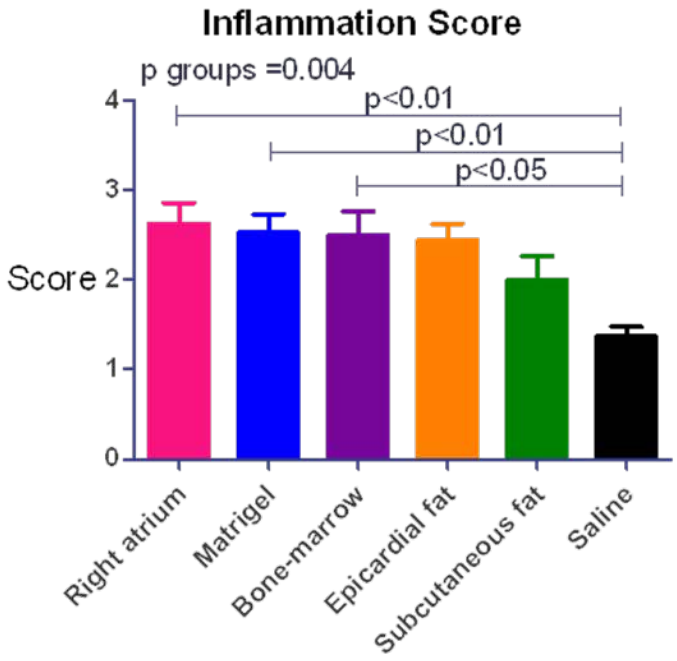
Correlation between hMSC TNF-α or HGF with LV Systolic Dilatation



- TNF-α and HGF secretion were measured *in vitro* and LV end systolic area was assessed after MSC transplantation in rats

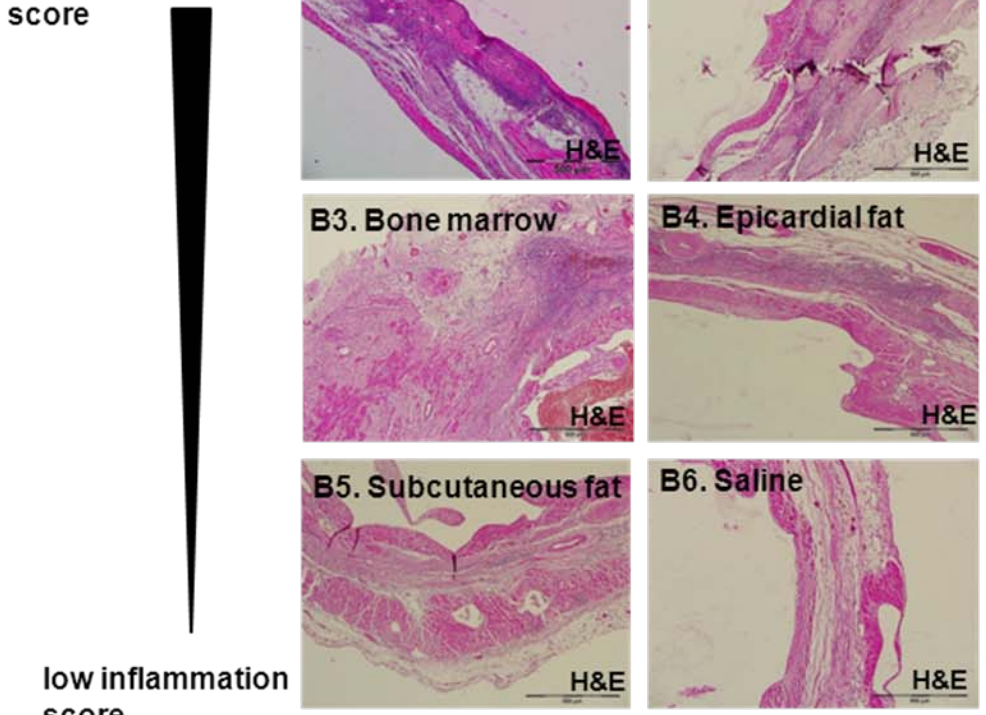
Inflammation in the Infarct, 27 Days after Transplantation

A



Score index
Infiltration of inflammatory cells was graded:
1- infiltrate of inflammatory cells not exceeding 1%
2- not exceeding 10%
3- not exceeding 50%
4- exceeding 50%

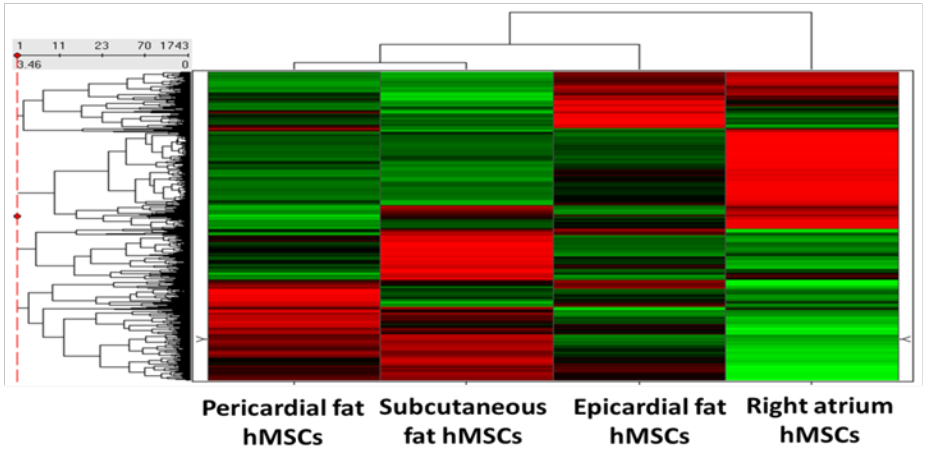
B

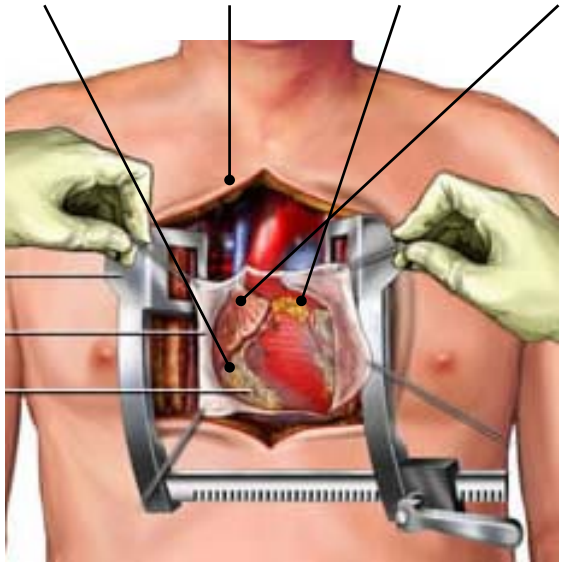


Gene Expression Profile of hMSCs from Different Sources

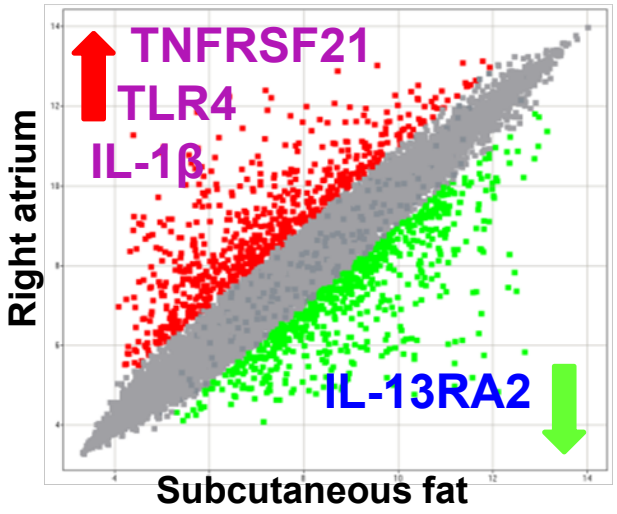
- 68 year-old male patient
- <u>History of:</u>
  Hyperlipidemia
  Hypertension
  Diabetes
  Ischemic heart disease
  Severe aortic stenosis
- Referred for coronary artery bypass surgery and aortic valve replacement.
- Subcutaneous fat hMSCs (from the chest) were used as reference cells for analysis.

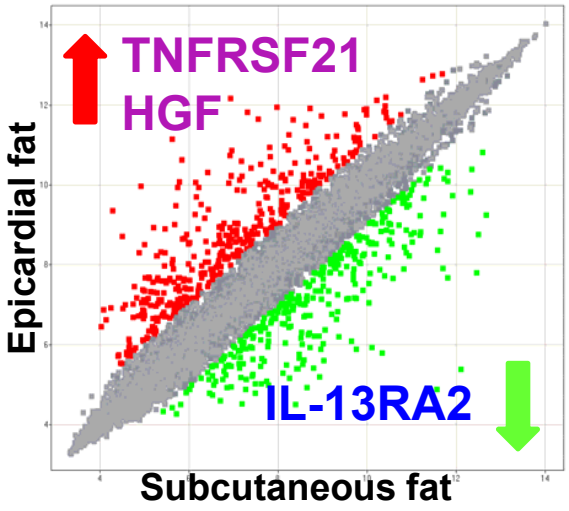
Gene Chip® Human Gene 1.0 ST Array

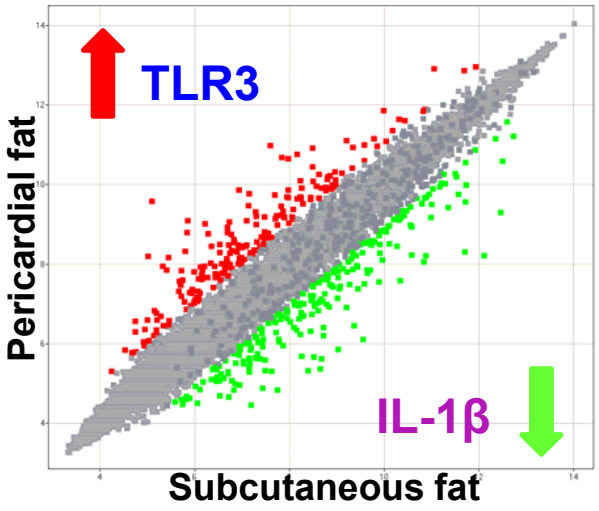




Variability in Gene Expression of hMSCs from Different Sources







Highly expressed genes

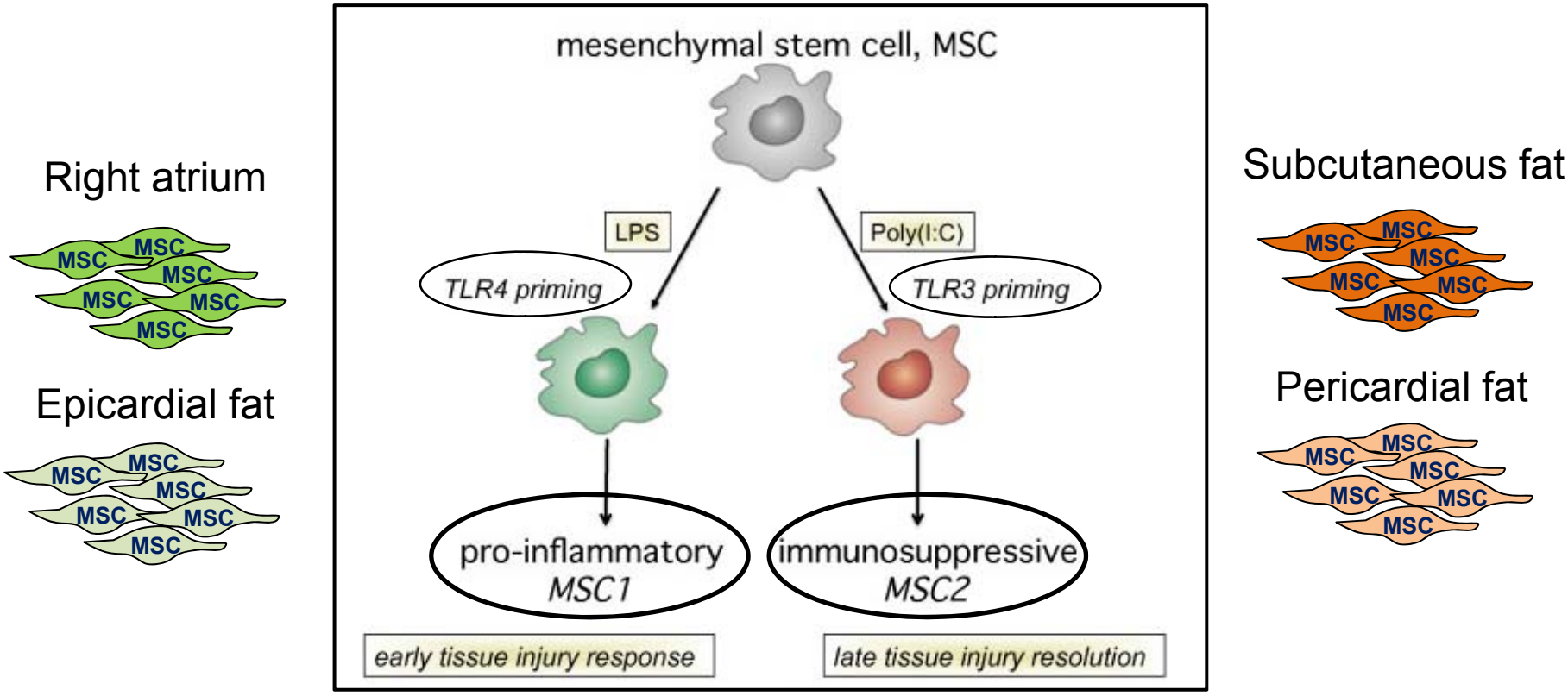
Similar expression to subcutaneous

Low expressed genes

Inflammatory genes

Anti-inflammatory genes

A New Mesenchymal Stem Cell (MSC) Paradigm: Polarization into a Pro-Inflammatory MSC1 or an Immunosuppressive MSC2 Phenotype



Ruth S. Waterman et al. April 2010. PLoS ONE.

Summary and Conclusions

1. The origin of hMSCs affects their reparative and immunomodulatory properties.

2. hMSCs from the right atrium and epicardial fat of IHD patients have pro-inflammatory properties (MSC1) and Impair recovery after myocardial infarction in rat.

3. Subcutaneous fat hMSCs have anti-inflammatory properties (MSC2) and attenuate cardiac remodeling and dysfunction after MI.

4. Our findings questioned the use of autologous cardiac MSCs from sick patients with ischemic heart disease.

Acknowledgments

Sheba Medical Center:

Cardiovascular Research Institute

Jonathan Leor, MD
Ayelet Itzhaki-Alfia, Ph.D.
Natalie Landa-Reuven, Ph.D.
David Kain
Radka Holbova
Natali Molotski, Ph.D.
Elad Asher, MD
Avishay Grupper, MD
Micha S. Feinberg, MD

Department of Cardiothorachic Surgery

Ehud Raanani, MD
Yigal Kassif, MD
Leonid Sternik, MD
Jacob Lavee, MD

Department of Plastic and Reconstructive surgery

Eyal Winkler, MD
Ariel Tessone, MD
Eran Millet, MD

Rigshospitalet Copenhagen:

The Heart Center

Jens Kastrup, MD
Mandana Haack-Sørensen, Ph.D.