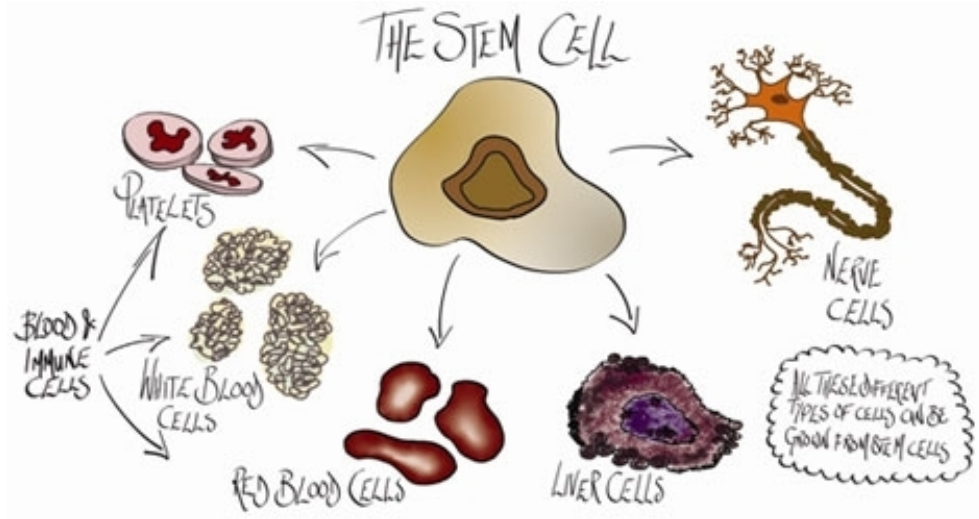
70TH ESCVS CONGRESS & 7TH IMAD MEETING

20 I 23 JUNE 2022

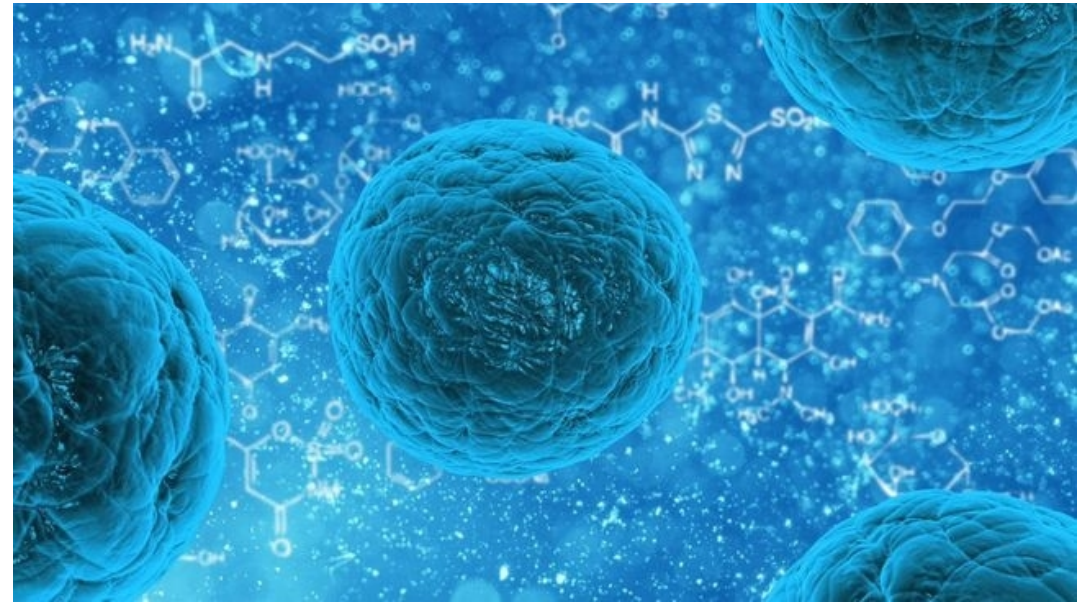
Liège I Théâtre de Liège I Belgium

Stem cell therapies for aorta

A.Tulga ULUS

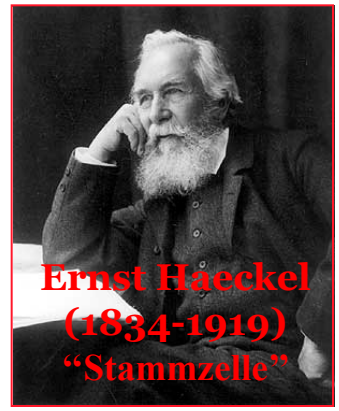


- ✓ Regenerative medicine,
- ✓ Experimental and
- ✓ Clinical studies
- ✓ Conclusion

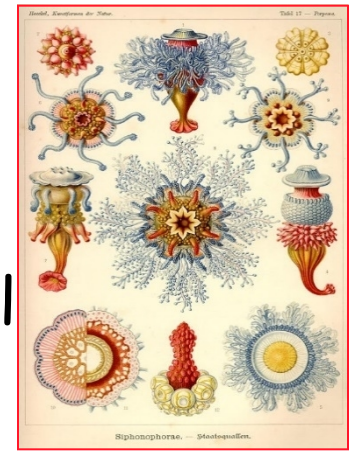


I have no conflict of interest

Since the 19th century, scientists from all over the world have studied stem cells, from plants, to mice, to patients in search of a cure for their diseases.



1868 The term "stem cell" appears in scientific literature, when German biologist Ernst Haeckel uses the phrase stem cell



Süreyya Tahsin Aygün (1895-1981)
First regenerative medicine interventions; cell culture, myocardial regenartion.

stem cell

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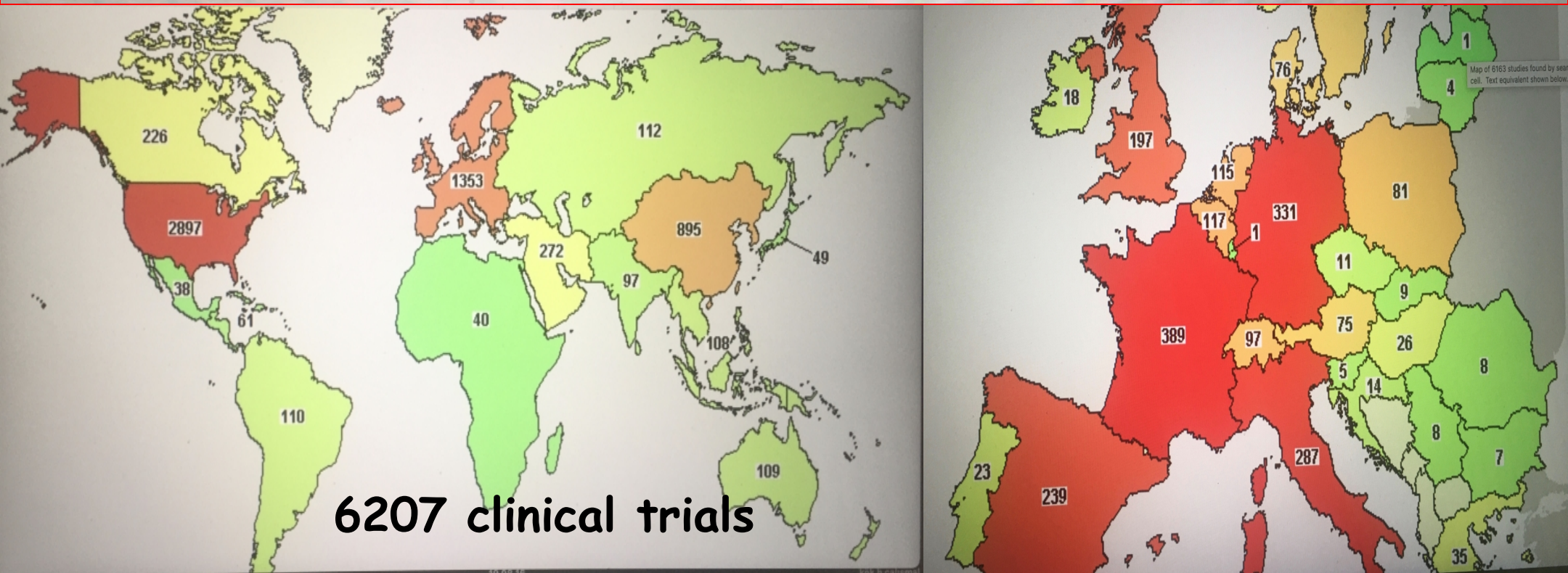
495,909 results

Page 1 of 49,591

1980 2023



6207 clinical trials

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stem cell, aneurysm

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RESULTS BY YEAR

349 results

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1982

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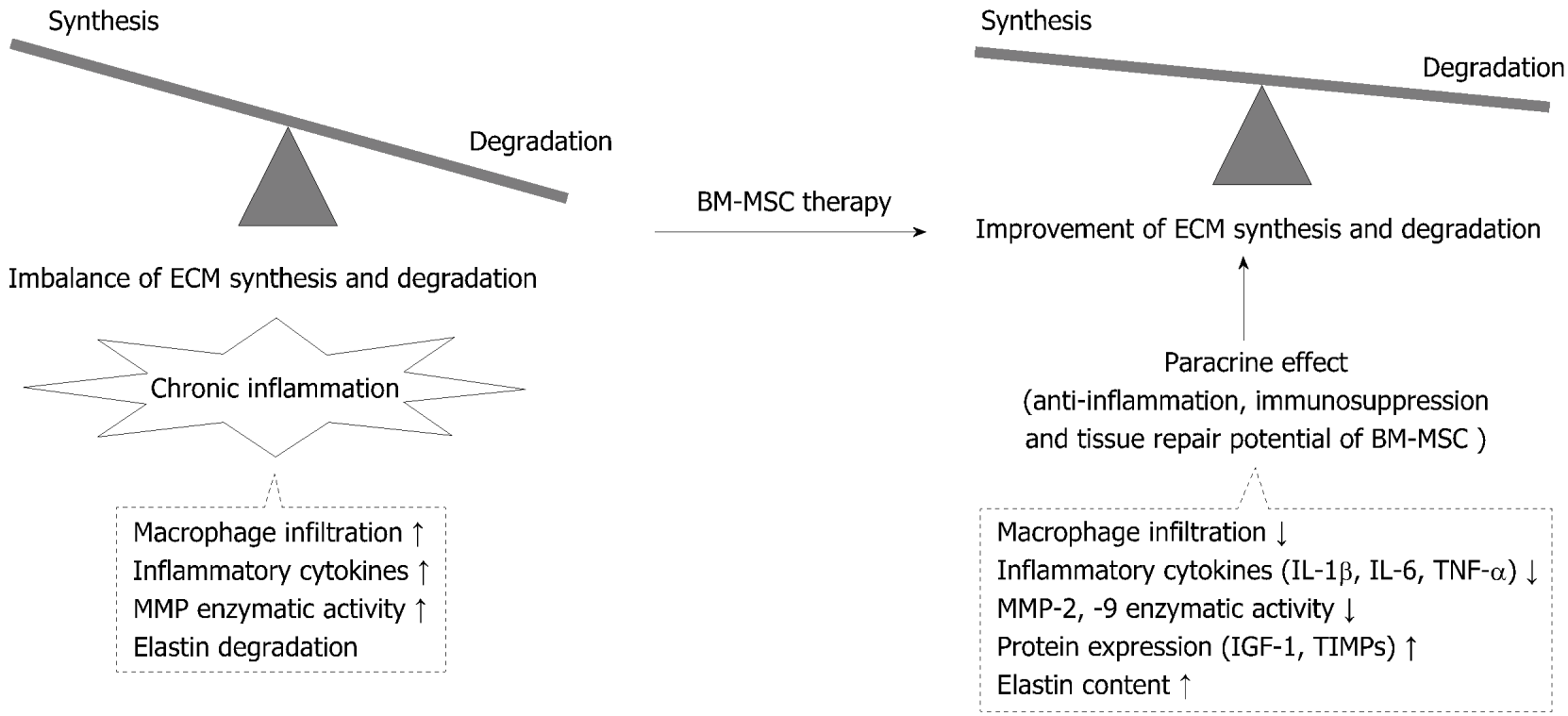
13 clinical trials

Aortic aneurysm is caused by an imbalance between synthesis and degradation of extracellular matrices such as collagen and elastin in the aortic wall.

Therefore, control of inflammation may be an alternative strategy for treatment of AA.



MSCs have not only the potential anti-inflammatory and immunosuppressive properties, they can be recruited into damaged tissue.

Migration mechanism of MSCs; stimulation by the inflammatory cytokines…

MSCs are known to accumulate in damaged tissue sites.

It has been reported that the migration of MSCs is accelerated through up-regulation of pro-MMP-2 and membrane-type 1-MMP complex by stimulation of the **inflammatory cytokines**.

Preclinical studies

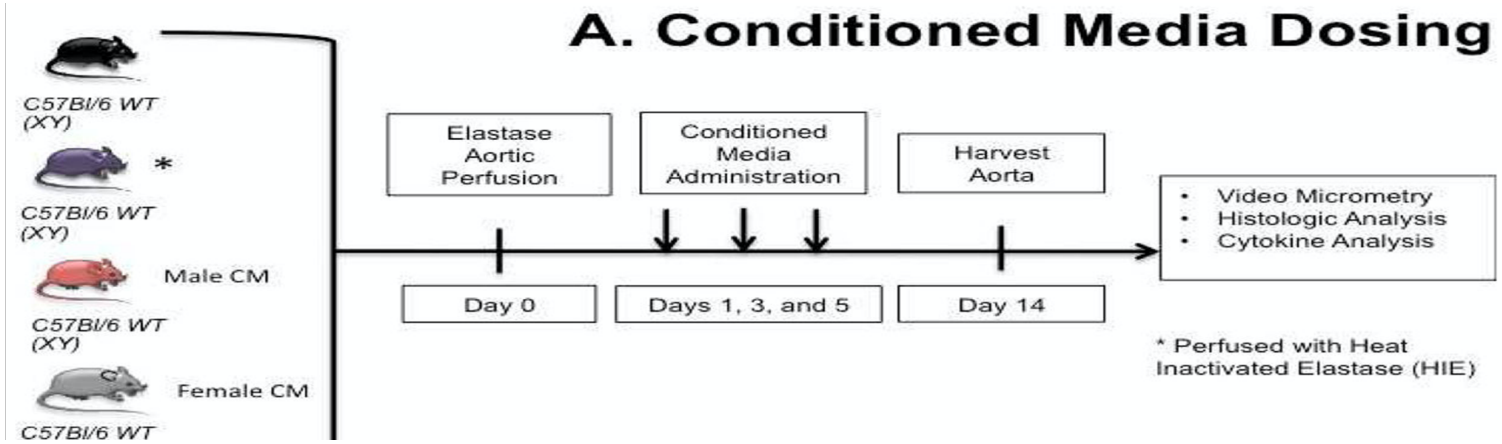
J Surg Res. 2015 November ; 199(1): 249–258. doi:10.1016/j.jss.2015.04.025.

Attenuation of Aortic Aneurysms with Stem Cells from Different Genders

John P. Davis, MD[1], Morgan Salmon, PhD[1], Nicolas H. Pope, MD[1], Guanyi Lu, MD, PhD[1], Gang Su, MD[1], Ashish K. Sharma, MBBS, PhD[1], Gorav Ailawadi, MD[1], and Gilbert R. Upchurch Jr., MD[1]

murine AAA model

Given the decreased rate of AAA in women, it is hypothesized that **female MSC** would attenuate AAA growth more than male MSC.



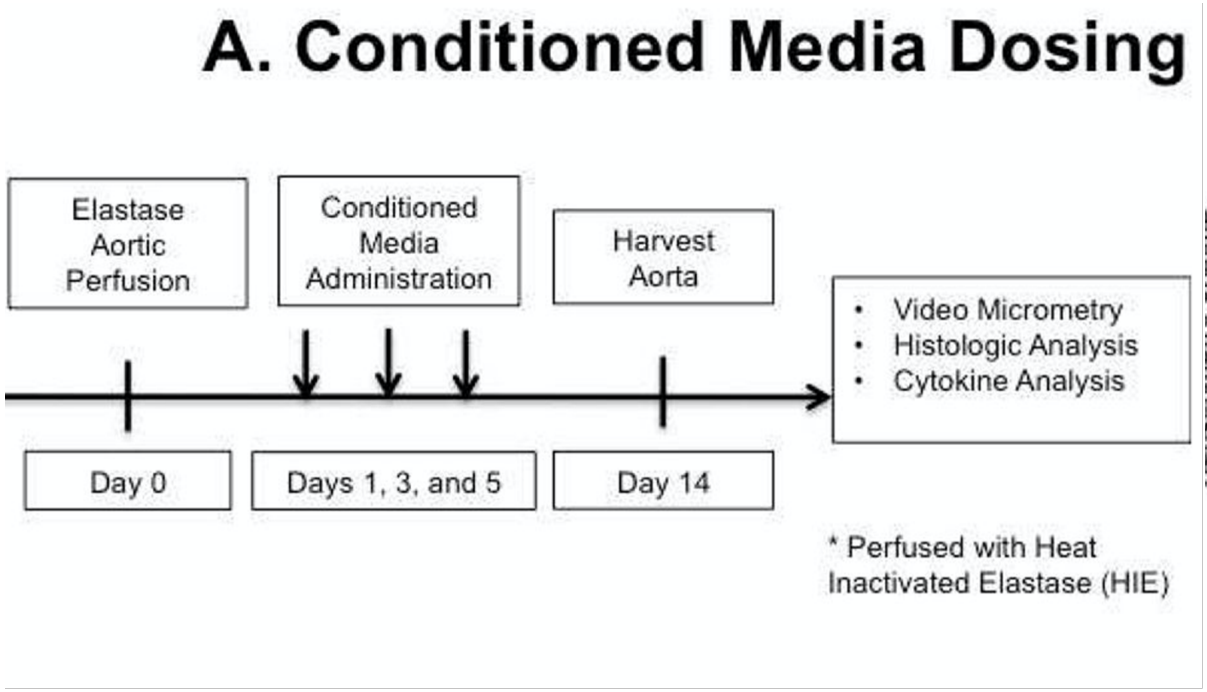
-Aortas of male mice were perfused with pancreatic elastase to induce AAA formation.

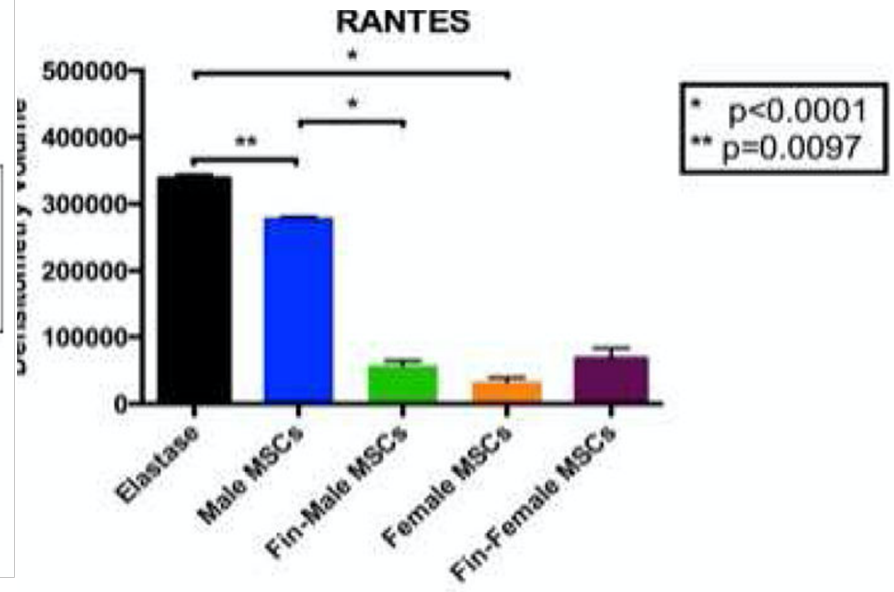
-Bone marrow-derived MSC from male and female mice were dosed via tail vein.

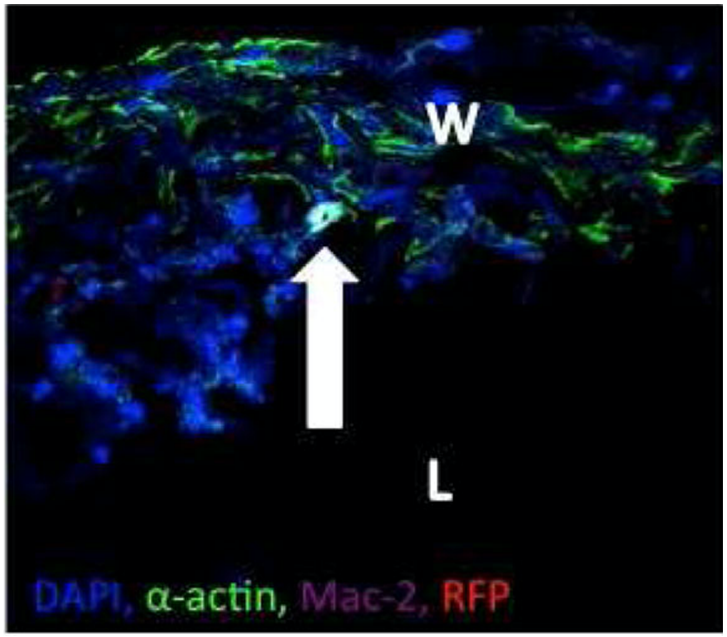
Mean aortic dilation in the elastase group was 121±5.2%, while male MSC inhibited AAA growth (87.8±6.9%, P=0.008) compared to elastase.

Female MSC showed the most marked attenuation of AAA growth (75.2±8.3% P= 0.0004).

Pro-inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and macrophage chemotactic protein-1 (MCP-1) were only **decreased in tissues treated with female MSC** (p=0.017, p=0.001, and p<0.0001, respectively when compared to elastase).







Confocal microscopy revealing integration of MSC into the aortic wall (arrow) on day 14

Conclusion

- **These data exhibit that female MSC more strongly attenuate AAA growth in the murine model.**

- **Furthermore, female MSC and male MSC inhibit proinflammatory cytokines at varying levels.**

STEM CELLS AND DEVELOPMENT
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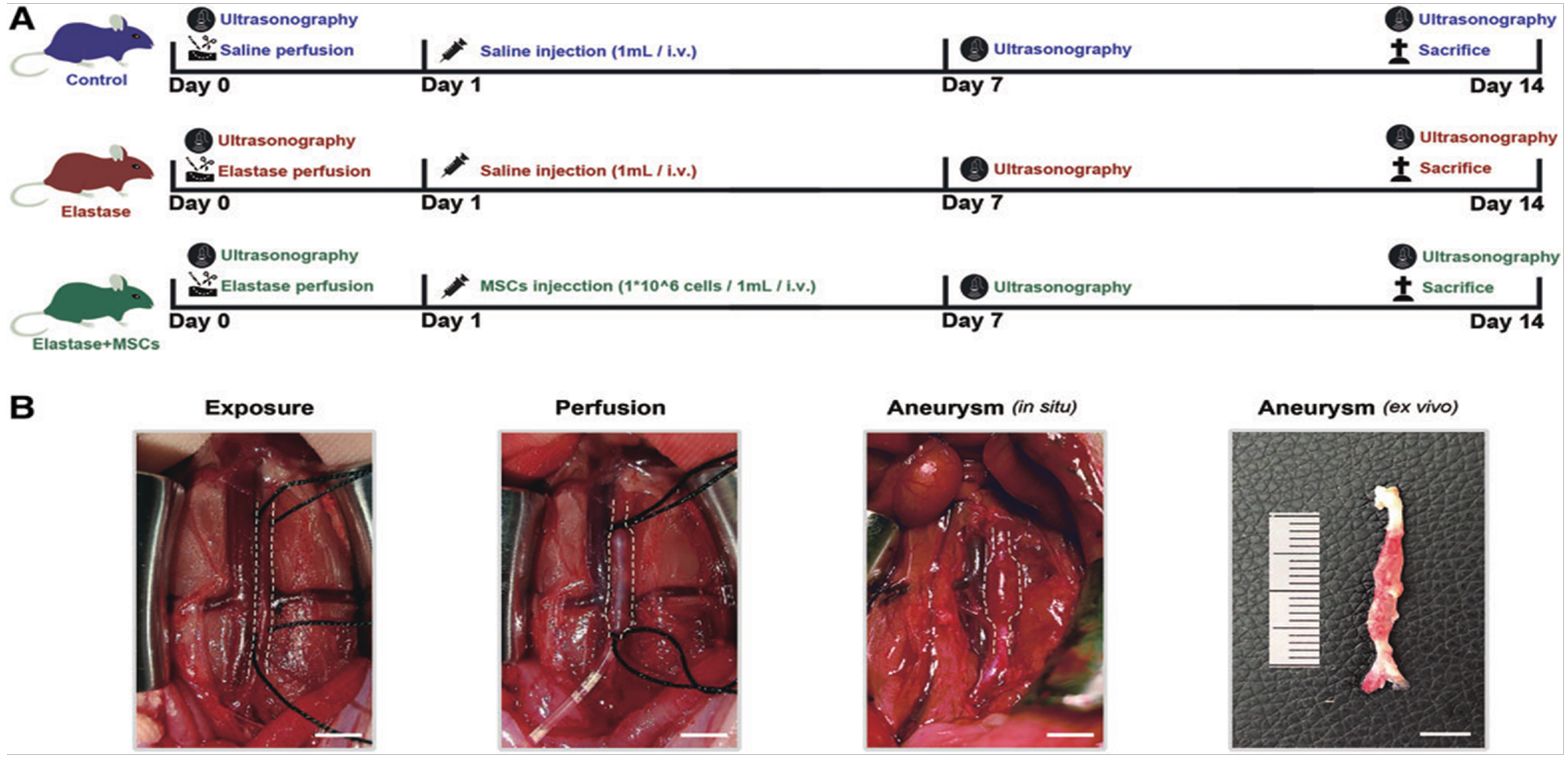
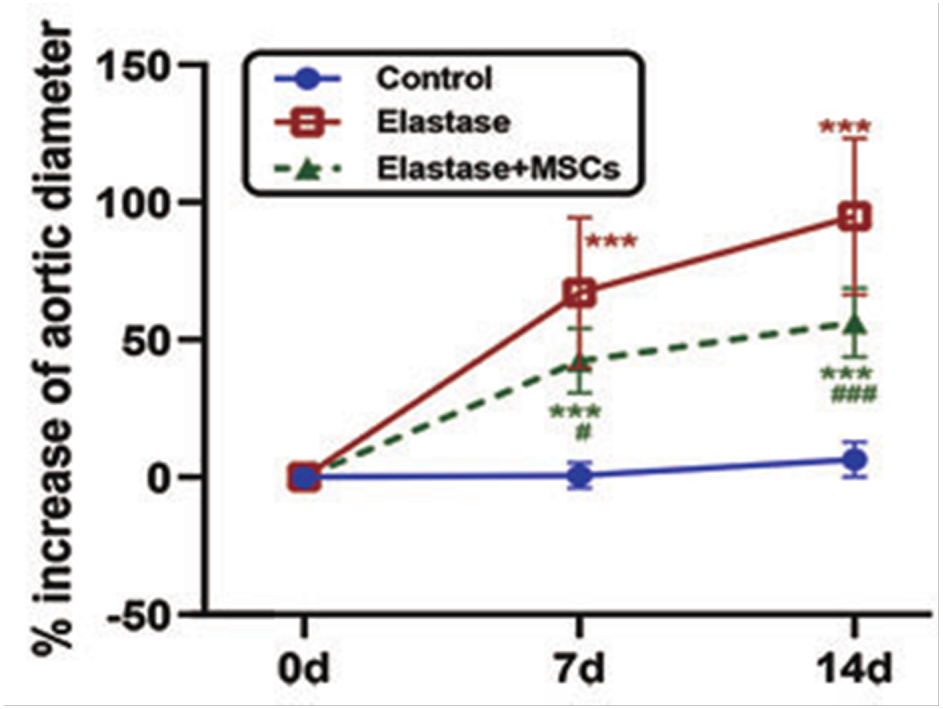
Mary Ann Liebert, Inc.
DOI: 10.1089/scd.2020.0058

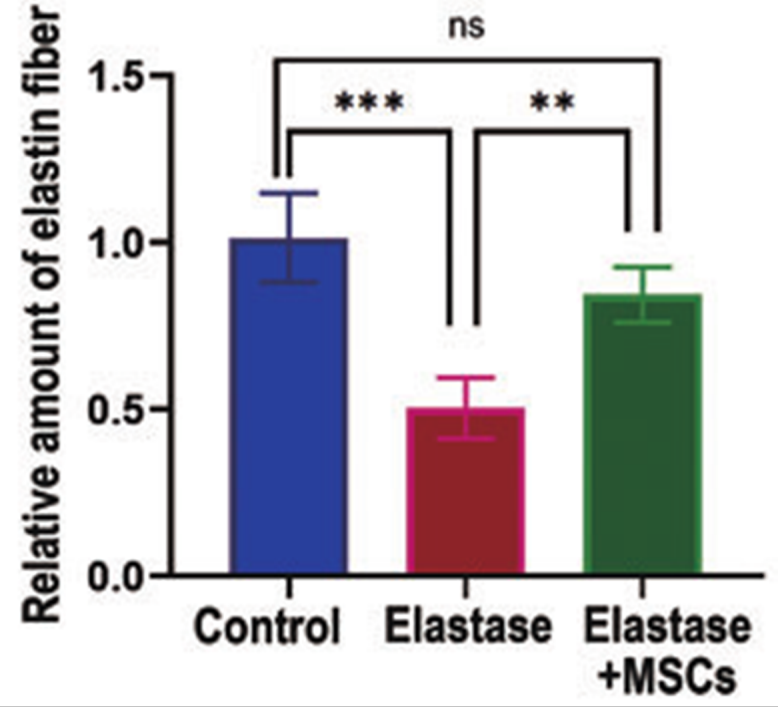
Human Umbilical Cord Mesenchymal Stem Cells Attenuate Abdominal Aortic Aneurysm Progression in Sprague-Dawley Rats: Implication of Vascular Smooth Muscle Cell Phenotypic Modulation

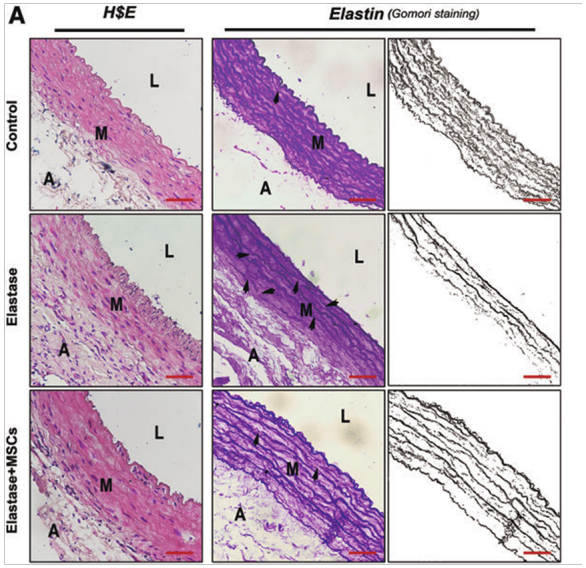
Hao Wen,[1–3] Mingjing Wang,[4] Shiqiang Gong,[4] Xintong Li,[1–3] Jinze Meng,[4] Jie Wen,[5] Yifei Wang,[4] Shuqing Zhang,[4] and Shijie Xin[1–3]



investigate the therapeutic efficacy of human umbilical cord mesenchymal stem cells (UC-MSCs) in elastase-induced AAA model







UC-MSCs reduce elastin degradation and fragmentation.

Li *et al. Stem Cell Research & Therapy* (2022) 13:81
https://doi.org/10.1186/s13287-022-02755-w

Therapeutic efficacy of mesenchymal stem cells for abdominal aortic aneurysm: a meta-analysis of preclinical studies

Xintong Li[1,2†], Hao Wen[3†], Junyuan Lv[4], Boyang Luan[3], Jinze Meng[5], Shiqiang Gong[5], Jie Wen[6] and Shijie Xin[1,2*]

Meta-analysis of 18 studies demonstrated that MSCs intervention has significant therapeutic effects on suppressing aortic diameter enlargement compared with the control group.

Meta analysis with random effects model showed that MSCs intervention significantly reduced the final value of maximum diameter compared with the control group ($P < 0.05$).

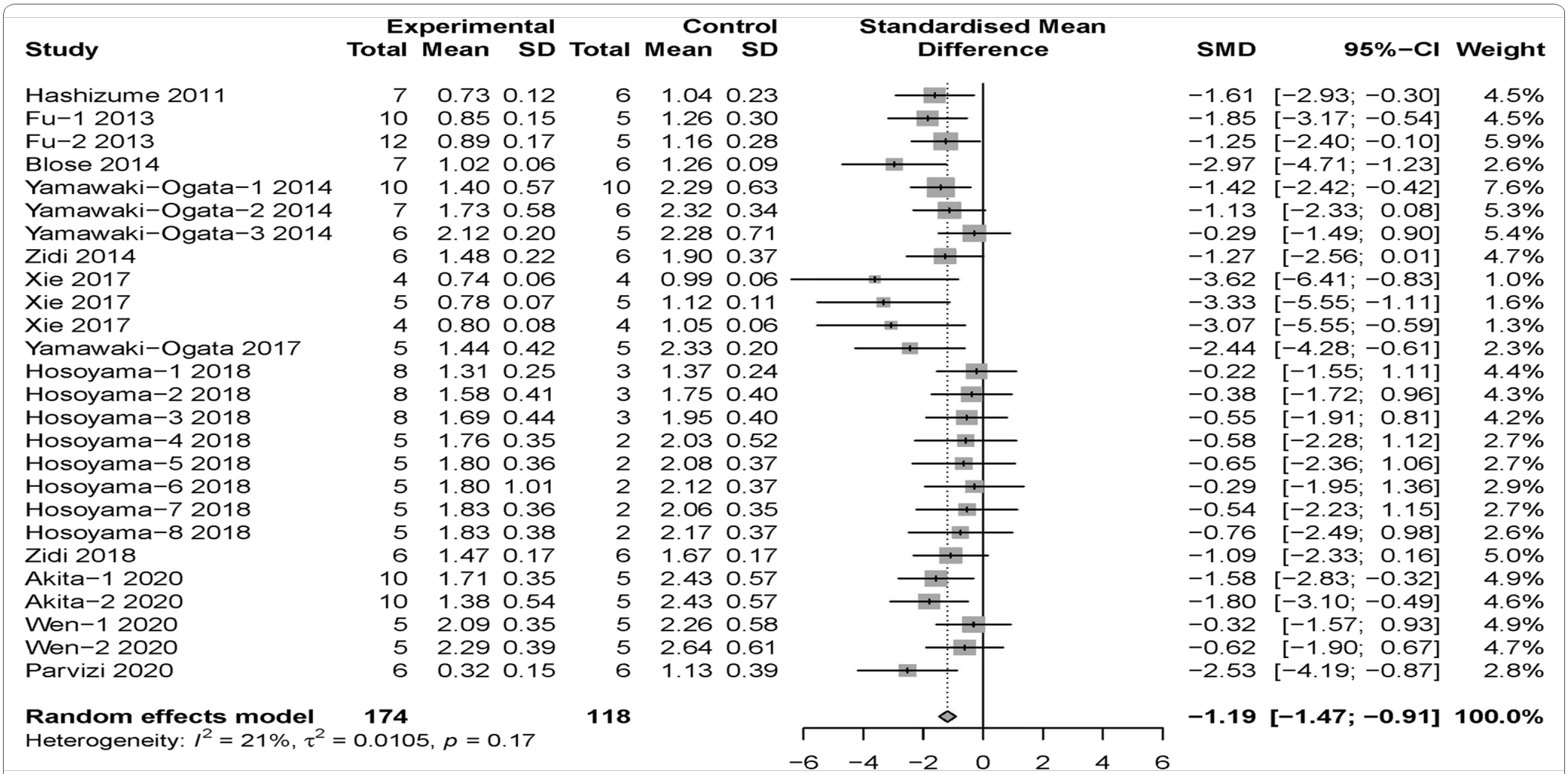


Fig. 3 The forest plot: the therapeutic effects of MSCs for maximum aortic diameter in AAA models, compared with control group

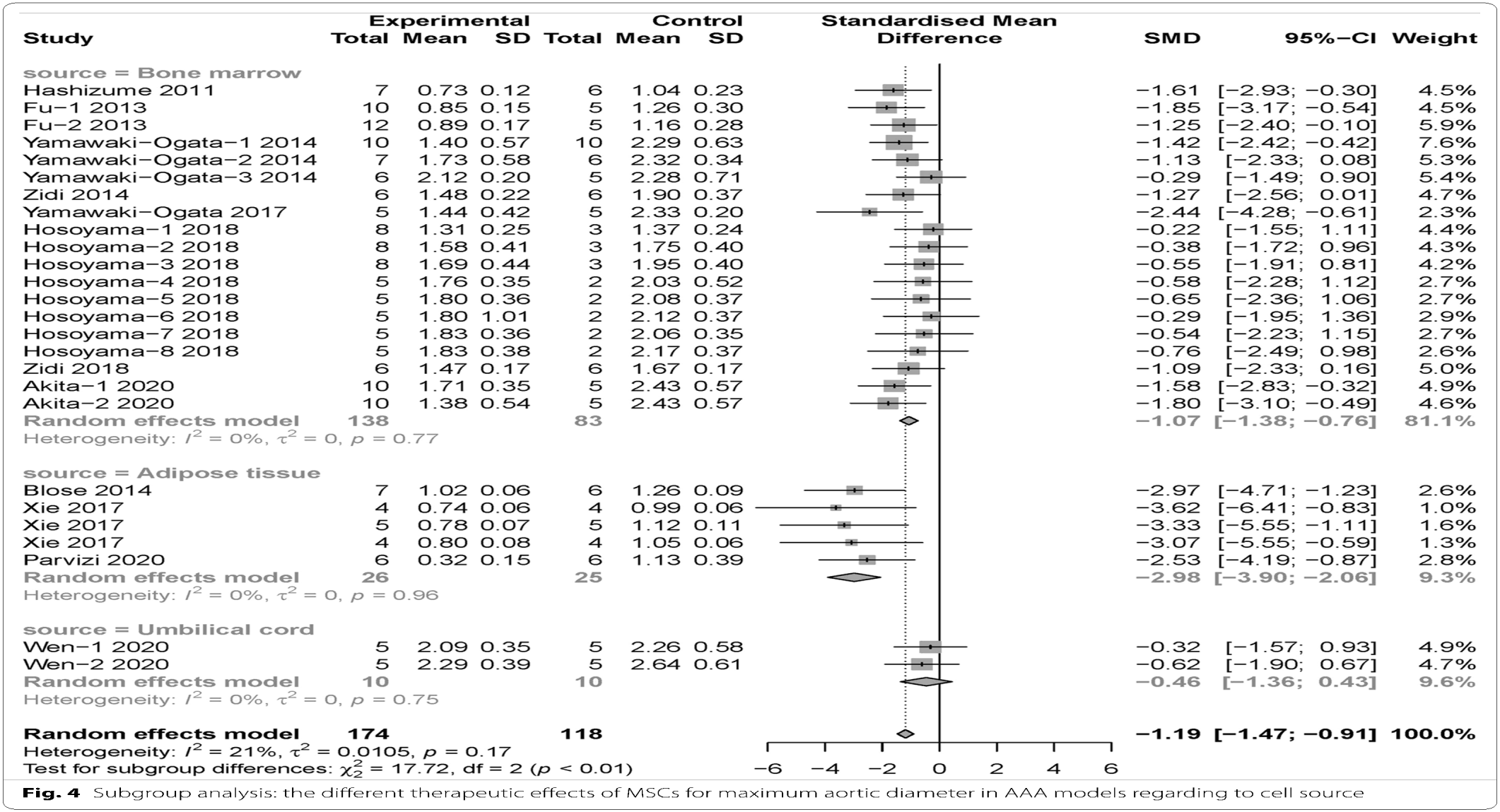


Fig. 4 Subgroup analysis: the different therapeutic effects of MSCs for maximum aortic diameter in AAA models regarding to cell source

Adipose derived MSCs showed better therapeutic efficacy in AAA than other cell types regarding to maximum aortic diameter.

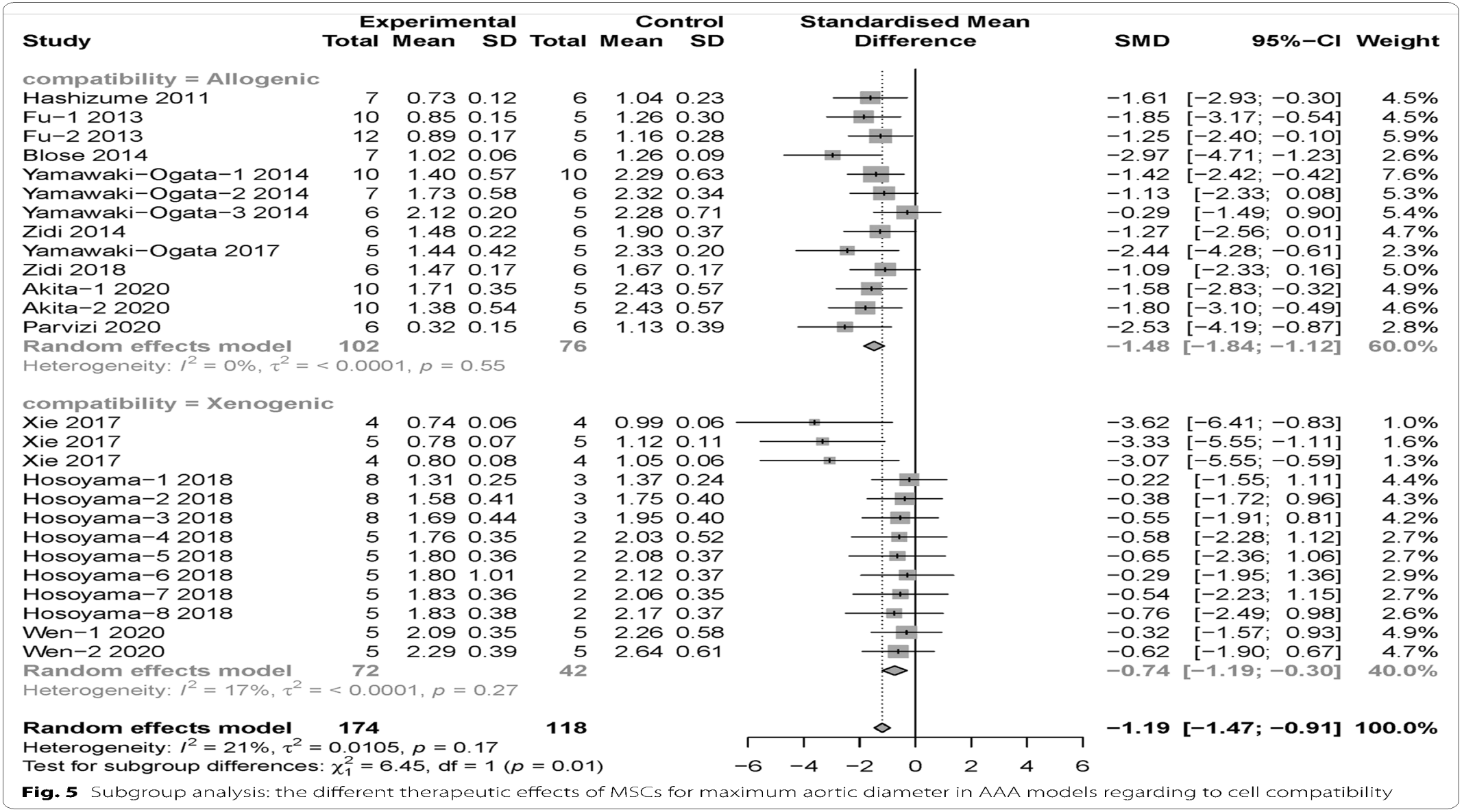


Fig. 5 Subgroup analysis: the different therapeutic effects of MSCs for maximum aortic diameter in AAA models regarding to cell compatibility

Significant improvement of allogeneic MSCs compared to xenogeneic MSCs in terms of maximum aortic diameter reduction.

Although IV-administration is the least invasive and simple procedure, the targeting ability is lower and injected MSCs are trapped in other tissues such as lung, spleen, liver and kidney.

In contrast, the implantation of cell-sheet and the direct injection into aortic wall make it possible to target AA.

Conclusion:

Results suggested that MSC intervention is effective in AAA by suppressing aortic diameter enlargement, reducing elastin degradation, and modulating local immunoinflammatory reactions.

It remains unclear

-cell numbers,
-frequency and
-administration timing

of SCs are required for AA treatment.

Clinial Trials

Stem Cells in Thoracic Aortic Aneurysms and Dissections: Potential Contributors to Aortic Repair

(Ann Thorac Surg 2012 93:1524–33)

Ying H. Shen, MD, PhD, Xiaoqing Hu, MD, Sili Zou, MD, Darrell Wu, MD, Joseph S. Coselli, MD, and Scott A. LeMaire, MD

Texas Heart Institute at St. Luke's Episcopal Hospital; and Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, and Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas

Both c-kit+ cells and CD34+ cells have been shown to play a critical role in tissue repair in the cardiovascular system; differentiate into endothelial cells, SMCs, and cardiomyocytes.

Characteristics	Control (n = 5)	TAA (n = 12)	TAD (n = 18)	*p* Values
Age (y)	61.9 ± 4.4	66.0 ± 5.5	62.5 ± 5.5	0.2
Men	3 (60%)	5 (42%)	13 (72%)	0.3
Hypertension	4 (80%)	10 (83%)	18 (100%)	0.2
COPD	1 (20%)	4 (33%)	6 (33%)	0.8
Diabetes	2 (40%)	2 (17%)	1 (6%)	0.1
Stroke	3 (60%)	1 (8%)	2 (11%)	0.02
Coronary artery disease	0	2 (17%)	3 (17%)	0.6
Peripheral artery disease	0	2 (17%)	2 (11%)	0.6
Smoking history	1 (20%)	11 (92%)	11 (61%)	0.02
Lipid-lowering medication	3 (60%)	6 (50%)	6 (33%)	0.5
Aneurysm diameter at sample site (cm)	NA	5.8 ± 1.2	6.2 ± 1.4	0.4

[a] Age and aortic diameter were compared using one-way analysis of variance. All other variables were compared using χ^2.

COPD = chronic obstructive pulmonary disease; NA = not applicable; TAA = thoracic aortic aneurysm; TAD = thoracic aortic dissection.

This study demonstrates that “STRO-1+, c-kit+, and CD34+” **cells are abundant in human TAA and TAD tissues**, and that can differentiate into SMCs, fibroblasts, or macrophages within the diseased aortic wall.

These findings suggest the potential for SCs to participate in both **reparative and destructive aortic remodeling processes**.

Rationale and Design of the ARREST Trial Investigating Mesenchymal Stem Cells in the Treatment of Small AAA

Short Title: Rationale for the ARREST Trial

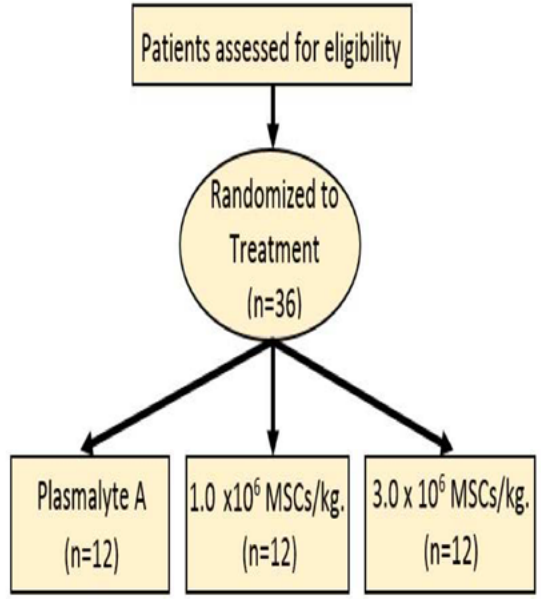
S. Keisin Wang, MD, Linden A. Green, PhD, Ashley R. Gutwein, MD, Natalie A. Drucker, MD, Raghu L. Motaganahalli, MD, Andres Fajardo, MD, Clifford C. Babbey BS, and Michael P. Murphy, MD

IU Health Center for Aortic Disease
Indiana University School of Medicine, Division of Vascular Surgery, Indianapolis IN

Ann Vasc Surg
2018 Feb;47:230-237.
doi: 10.1016/j.avsg.2017.08.044.

Design of ARREST Trial

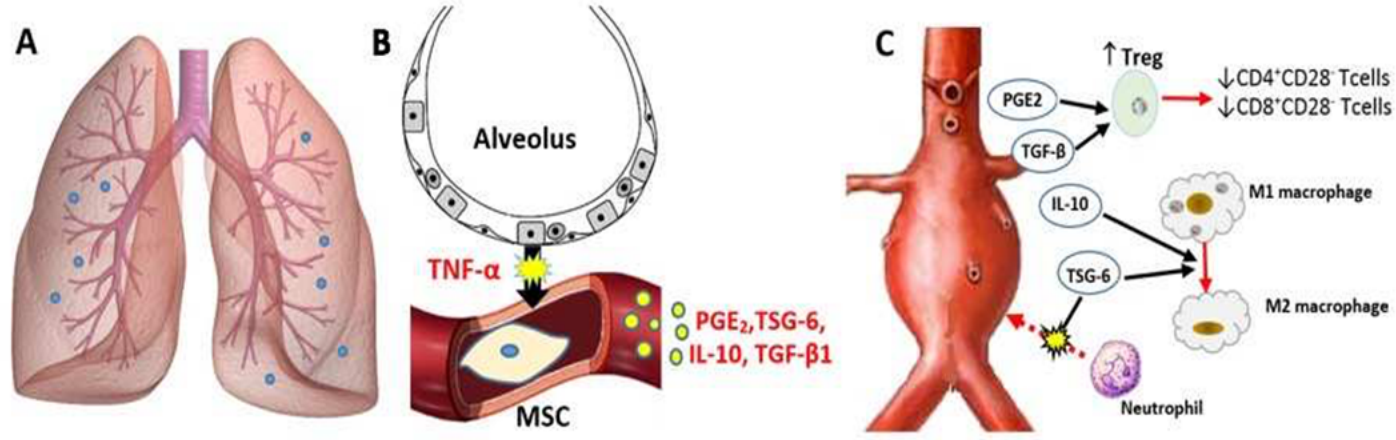
Phase I investigation into the safety of MSC infusion for patients with small AAA and the cells' effects on modulation of AAA related inflammation.



ARREST is a Phase I, single-center, double-blind, randomized controlled trial investigating infusion both dilute and concentrated MSCs compared to placebo in 36 small AAA (35-45 mm) patients.

Subjects will be followed by study personnel for 12 months to ascertain incidence of adverse events, immune cell phenotype expression, peripheral cytokine profile, and peri-aortic inflammation.

Maximum transverse aortic diameter will be assessed regularly for 5 years by a combination of CT and duplex sonography.



Abstract 295: The Stem Cell Therapy to Prevent Expansion of Abdominal Aortic Aneurysm (STOP-AAA) Trial: Rationale and Design

Michael P Murphy and The Investigators of the Cardiovascular Cell Therapy Rsch Network

Originally published 17 Mar 2018 | https://doi.org/10.1161/atvb.34.suppl_1.295 |
Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;34:A295

Methods

A randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of autologous bone marrow derived MSCs in suppressing expansion of small AAA (35- 50mm).

40 patients will be randomized in a 1:1 fashion to receive systemic administration of placebo or 3 doses of 2x106 MSC/kg. at baseline, 24, and 52 weeks.

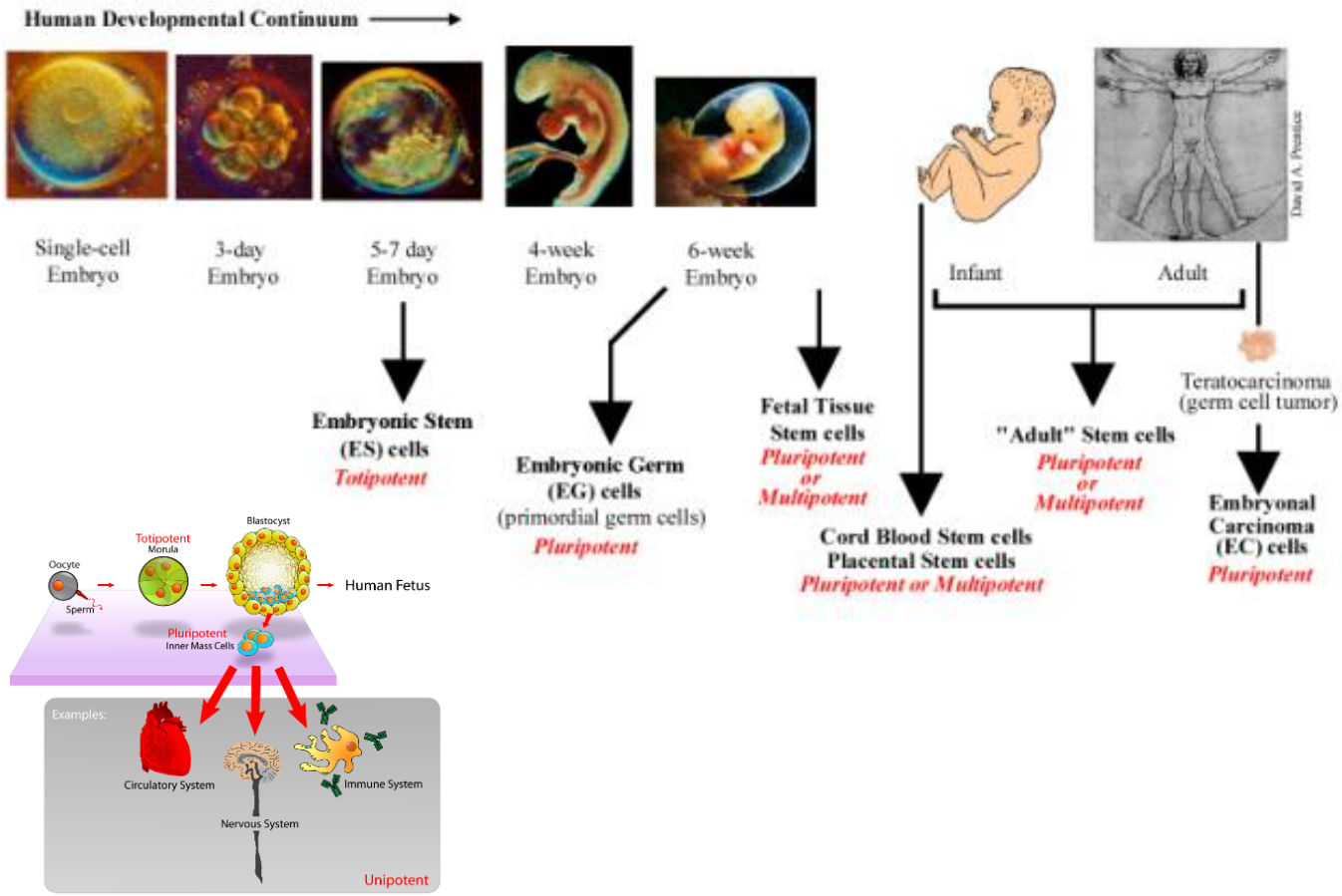
The primary endpoint will be change in AAA diameter at 18 months as measured by a single blinded observer using contrast enhanced helical computed tomographic angiography (CTA).

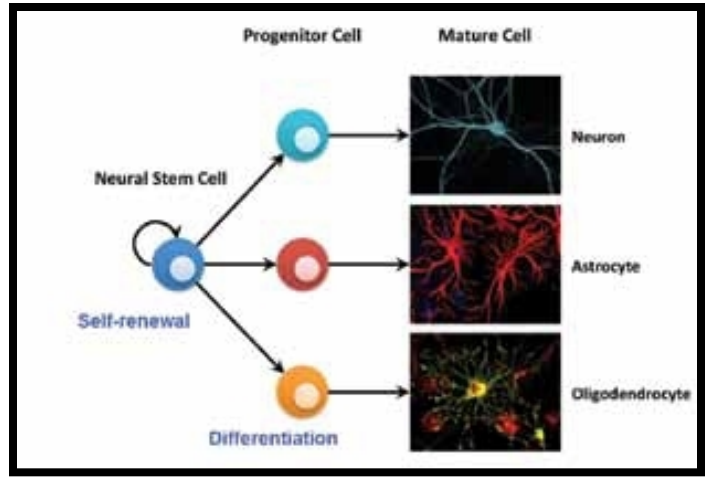
The STOP-AAA will be the first in man study to assess the efficacy of autologous bone marrow derived MSCs to suppress AAA expansion.

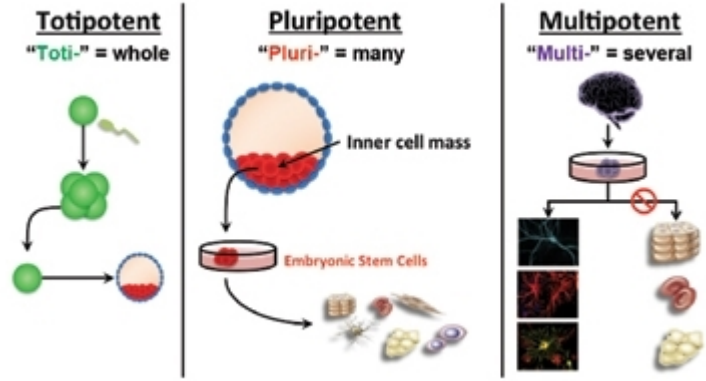
CONCLUSION

Treatment of AA using SCs has been demonstrated to be effective, and promises to be a new non-surgical therapeutic strategy.

Stem Cells







Stem Cells types

- **Totipotent (total):**
  - Total potential to differentiate into any adult cell type
  - Total potential to form specialized tissue needed for embryonic development
- **Pluripotent (plural):**
  - Potential to form most or all 220 differentiated adult cell types
- **Multipotent (multiple):**
  - Limited potential
  - Forms only multiple adult cell types