WELCOME *To the*

2026 SYMPOSIUM

Biology of Intimal Hyperplasia and Strategies for Prevention

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Professor of Radiology
Associate Director of Center of
Regenerative Biotherapeutics
Mayo Clinic
Rochester, MN

Disclosures

Founder of Pavaj Vascular

Consultant for Humacyte, Medtronic, and Penumbra

Equity at Inova Vascular

NIH Grant HL098967 (PI), DK135407 (PI), DK138917 (PI), DK141802 (co-I), HL174785 (co-I), and HL179093 (co-I)

Outline

- Clinical and economic burden of hemodialysis AVF failure
- Pathophysiology of AVF failure
- Rationale and findings of Adipose Derived Mesenchymal Stem Cells in reducing vascular injury
- Nanoparticle Drug delivery platform

What is the Unmet Clinical Need?

- There are more than 4 Million patients with ESRD worldwide
- >820,000 patients in the US
- Expected to double in the next decade
- A well functioning vascular access is needed to perform hemodialysis
  - Catheter
  - AVF
  - AVG

Histopathology of venous stenosis

- Increased proliferation
- Matrix deposition
- Increased expression of SMC and inflammatory cells

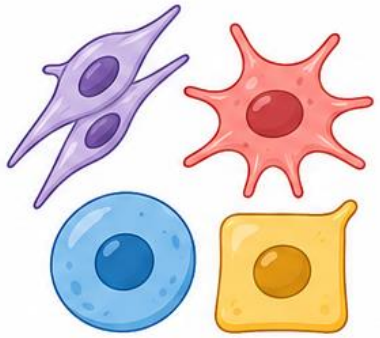
What information is needed to develop a CELL/Drug therapy to reduce venous stenosis?

- When do you give the cells/drug (Primary prevention or secondary)
- What location in the vessel wall (Endoluminal or periadventitial)
- What type of cellular product do you use (autologous vs. allogeneic)
- What is the source of the cells (Fat, BM, Blood, IPS, skin)
- GMP grade

From Cells to Mice to Pigs to Humans

A translational continuum to understand biology and improve human health

CELLS



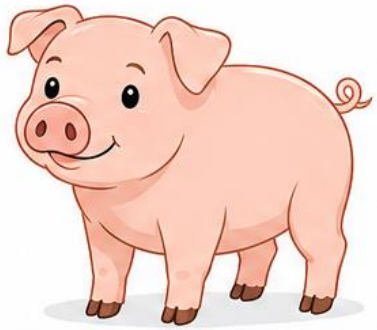
- In vitro models to dissect molecular mechanisms
- High-throughput screening and gene perturbation
- Identify pathways and targets

MICE



- In vivo models for rapid testing and mechanistic studies
- Genetic tools and controlled experiments
- Proof-of-concept and pathway validation

PIGS



- Large animal models with physiological similarities to humans
- Evaluate safety, efficacy, and dosing
- Bridge preclinical findings to clinical translation

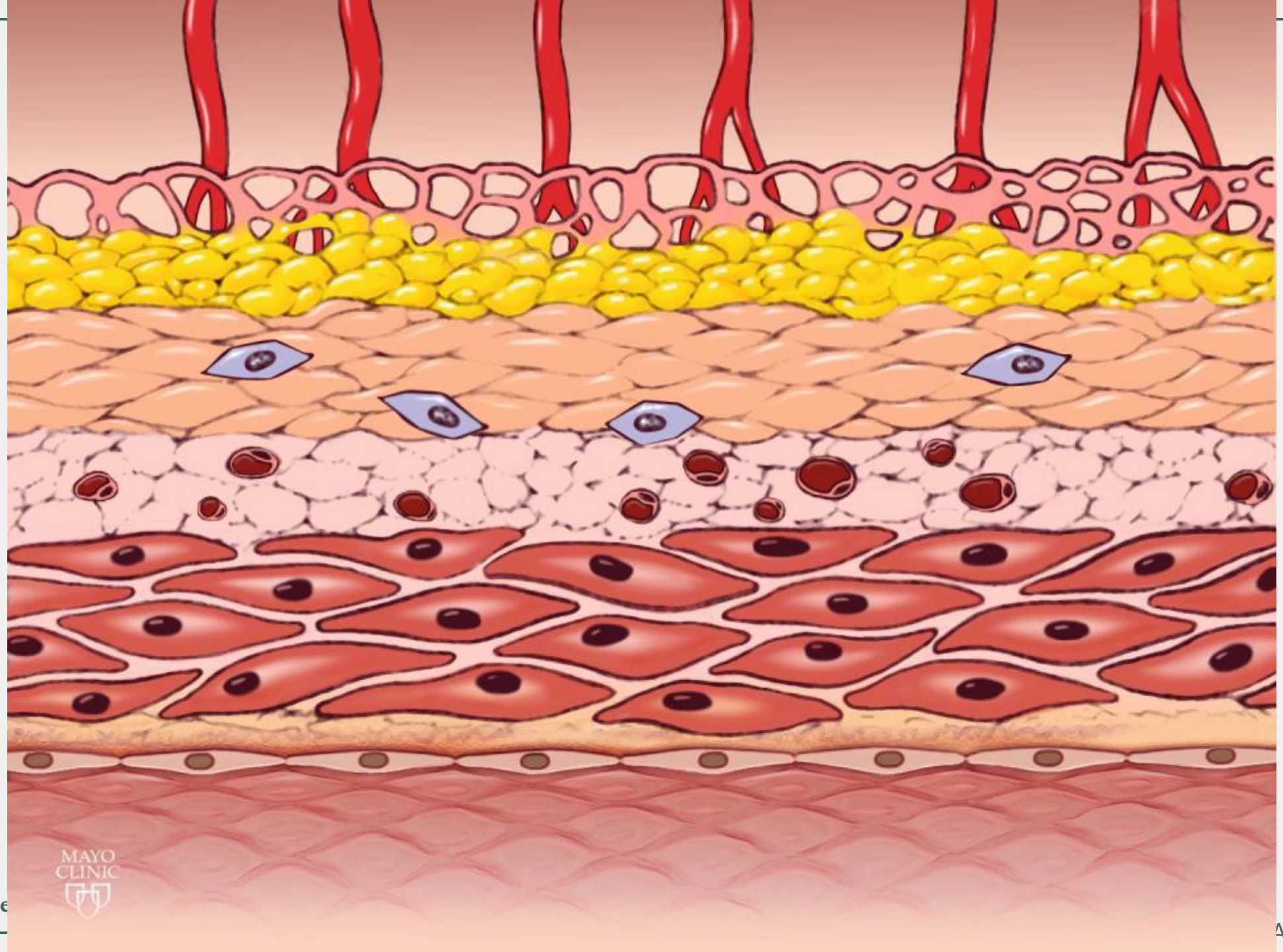
HUMANS



- Clinical studies and trials
- Evaluate safety and therapeutic benefit
- Improve human health and patient outcomes

Building knowledge at every step.

Advancing science from fundamental discovery to real-world impact.


MAYO
CLINIC

Adventitia is a therapeutic target:

OPEN

see commentary on page 234

Adventitial transduction of lentivirus-shRNA-VEGF-A in arteriovenous fistula reduces venous stenosis formation

Binxia Yang[1,5], Rajiv Janardhanan[1,5], Pawan Vohra[1], Eddie L. Greene[2], Santanu Bhattacharya[1], Sarah Withers[1], Bhaskar Roy[1], Evelyn C. Nieves Torres[1], Jaywant Mandrekar[3], Edward B. Leof[4], Debabrata Mukhopadhyay[4] and Sanjay Misra[1,4]

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PLOS ONE

Adventitial Delivery of Lentivirus-shRNA-ADAMTS-1 Reduces Venous Stenosis Formation in Arteriovenous Fistula

Evelyn C. Nieves Torres[1☯], Binxia Yang[1☯], Rajiv Janardhanan[1], Akshaar Brahmbhatt[1], Ed Leof[2], Debabrata Mukhopadhyay[2], Sanjay Misra[1,2]*

1 Vascular and Interventional Radiology Translational Laboratory, Department of Radiology, Mayo Clinic, Rochester, Minnesota, United States of America, **2** Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota, United States of America

LABORATORY INVESTIGATION

The Role of Repeat Administration of Adventitial Delivery of Lentivirus-shRNA-*Vegf-A* in Arteriovenous Fistula to Prevent Venous Stenosis Formation

Rajiv Janardhanan, PhD, Binxia Yang, MD, PhD, Sreenivasulu Kilari, PhD, Edward B. Leof, PhD, Debabrata Mukhopadhyay, PhD, and Sanjay Misra, MD

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PLOS ONE

The Role of *Iex-1* in the Pathogenesis of Venous Neointimal Hyperplasia Associated with Hemodialysis Arteriovenous Fistula

Akshaar Brahmbhatt[1], Evelyn NievesTorres[1], Binxia Yang[1], William D. Edwards[2], Prabir Roy Chaudhury[3], Min Kyun Lee[4], Hyunjoon Kong[4], Debabrata Mukhopadhyay[5], Rajiv Kumar[5,6], Sanjay Misra[1,5]*

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NDT Advance Access published September 11, 2008

Nephrol Dial Transplant (2008) 1 of 12
doi: 10.1093/ndt/gfn433

NDT Nephrology Dialysis Transplantation

Original Article

Adventitial transplantation of blood outgrowth endothelial cells in porcine haemodialysis grafts alleviates hypoxia and decreases neointimal proliferation through a matrix metalloproteinase-9-mediated pathway—a pilot study

Deborah Hughes[1], Alex A. Fu[2], Alessandra Puggioni[3], James F. Glockner[2], Bilal Anwer[4], Antonio M. McGuire[5], Debabrata Mukhopadhyay[6] and Sanjay Misra[1,2,3]

[1]Division of Cardiovascular Diseases and Internal Medicine, [2]Department of Radiology, [3]Division of Vascular Surgery, Mayo Clinic, Rochester, [4]University of Minnesota Medical School, Minneapolis, [5]Mayo Medical School, Mayo Clinic, Rochester and [6]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, USA

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Radiology

Tracking and Therapeutic Value of Human Adipose Tissue–derived Mesenchymal Stem Cell Transplantation in Reducing Venous Neointimal Hyperplasia Associated with Arteriovenous Fistula[1]

ORIGINAL RESEARCH ■ MOLECULAR IMAGING

BASIC RESEARCH www.jasn.org

Therapeutic Effect of Adipose Derived Mesenchymal Stem Cell Transplantation in Reducing Restenosis in a Murine Angioplasty Model

Chuanqi Cai,[1,2] Sreenivasulu Kilari,[2] Chenglei Zhao,[2,3] Michael L. Simeon,[2] Avanish Misra,[2] Yiqing Li,[1] Andre J. van Wijnen,[4,5] Debabrata Mukhopadhyay,[6] and Sanjay Misra[2,5,7]

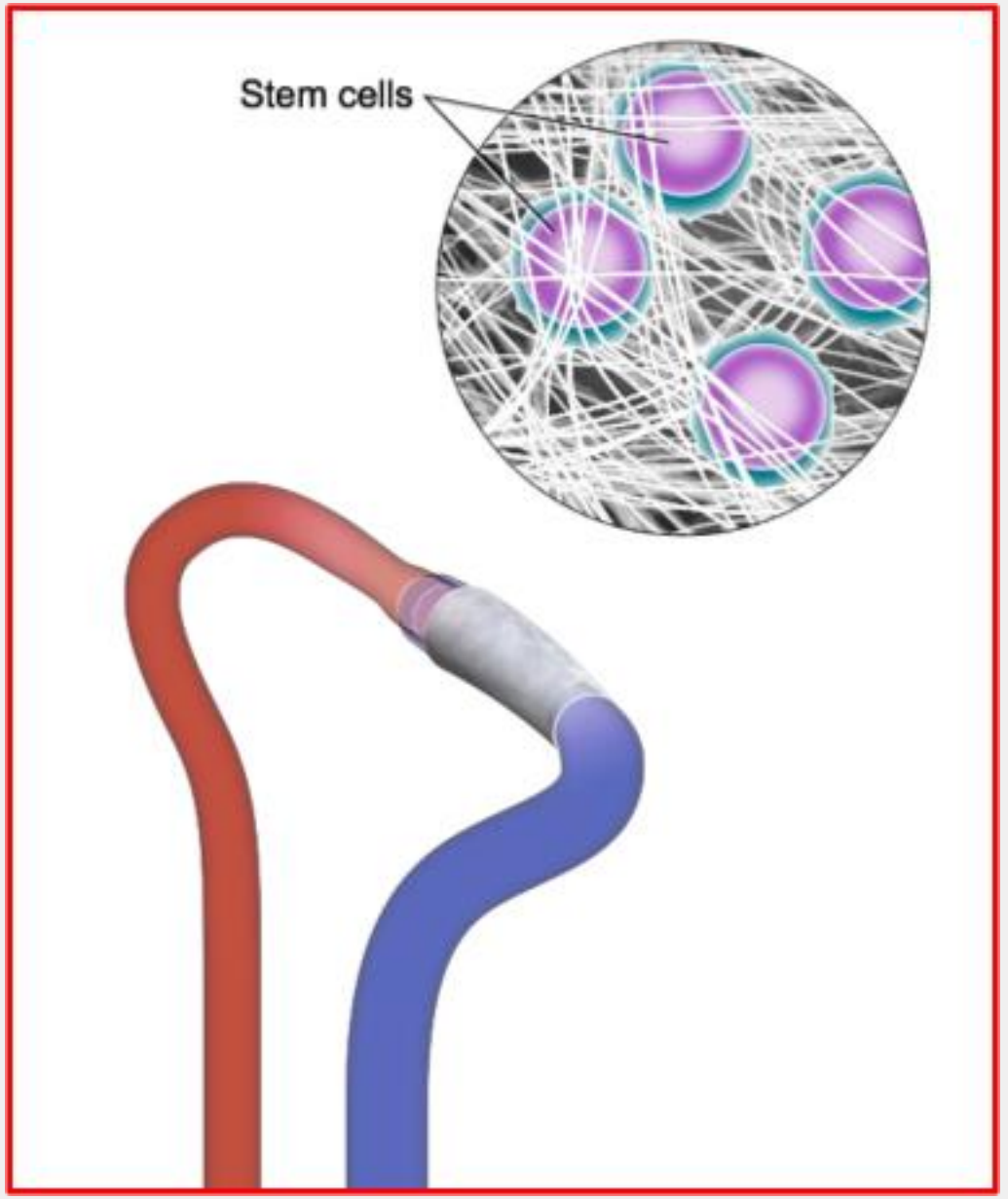
[1]Department of Vascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Vascular and Interventional Radiology Translational Laboratory, Department of Radiology, Mayo Clinic, Rochester, Minnesota
[3]Department of Vascular Surgery, The Second Xiangya Hospital, Central South University, Changsha, China
[4]Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota
[5]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota
[6]Department of Biochemistry and Molecular Biology, Mayo Clinic, Jacksonville, Florida
[7]Department of Radiology, Vascular and Interventional Radiology, Mayo Clinic, Rochester, Minnesota

Radiology

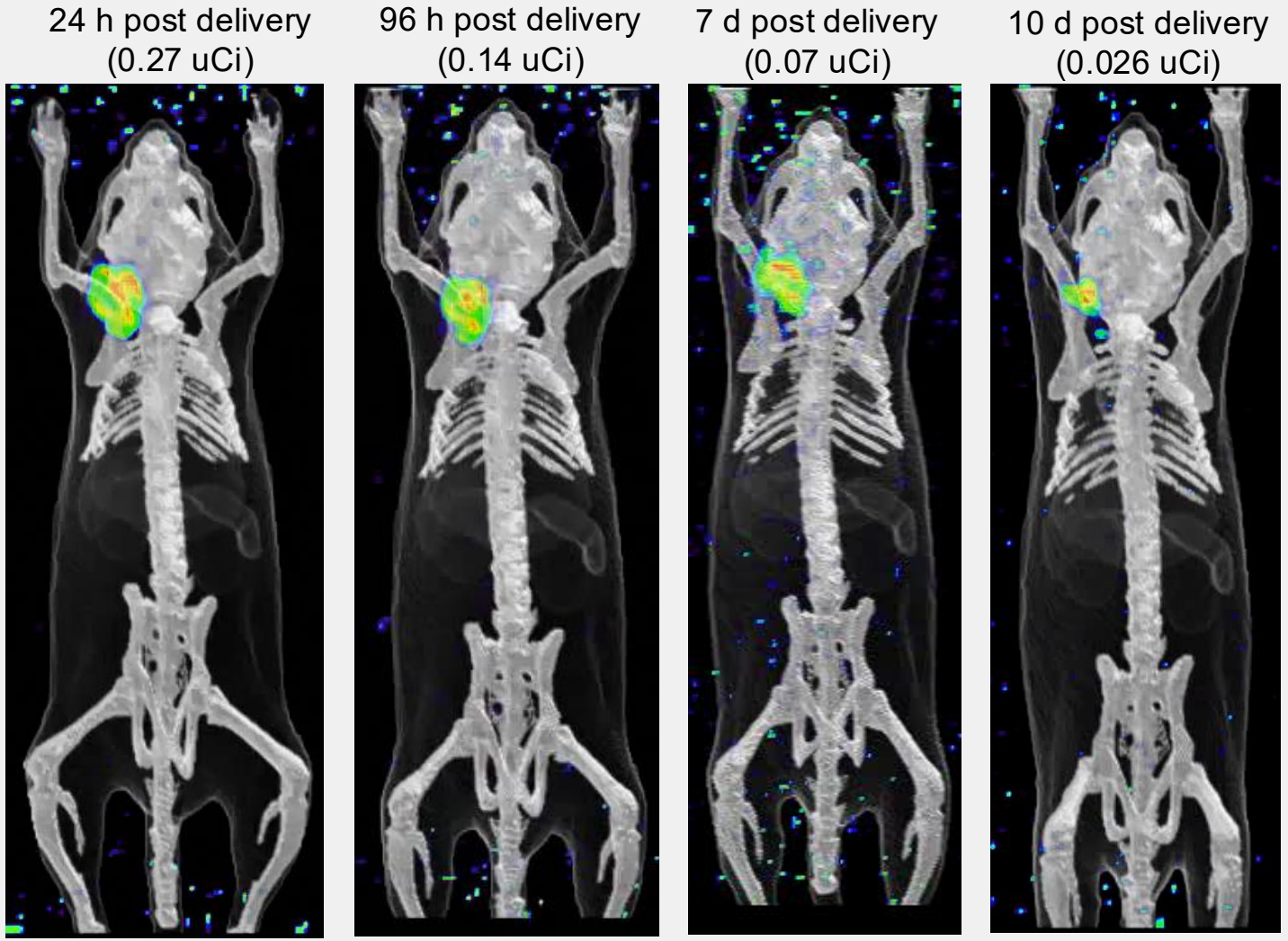
Tracking and Therapeutic Value of Human Adipose Tissue–derived Mesenchymal Stem Cell Transplantation in Reducing Venous Neointimal Hyperplasia Associated with Arteriovenous Fistula[1]

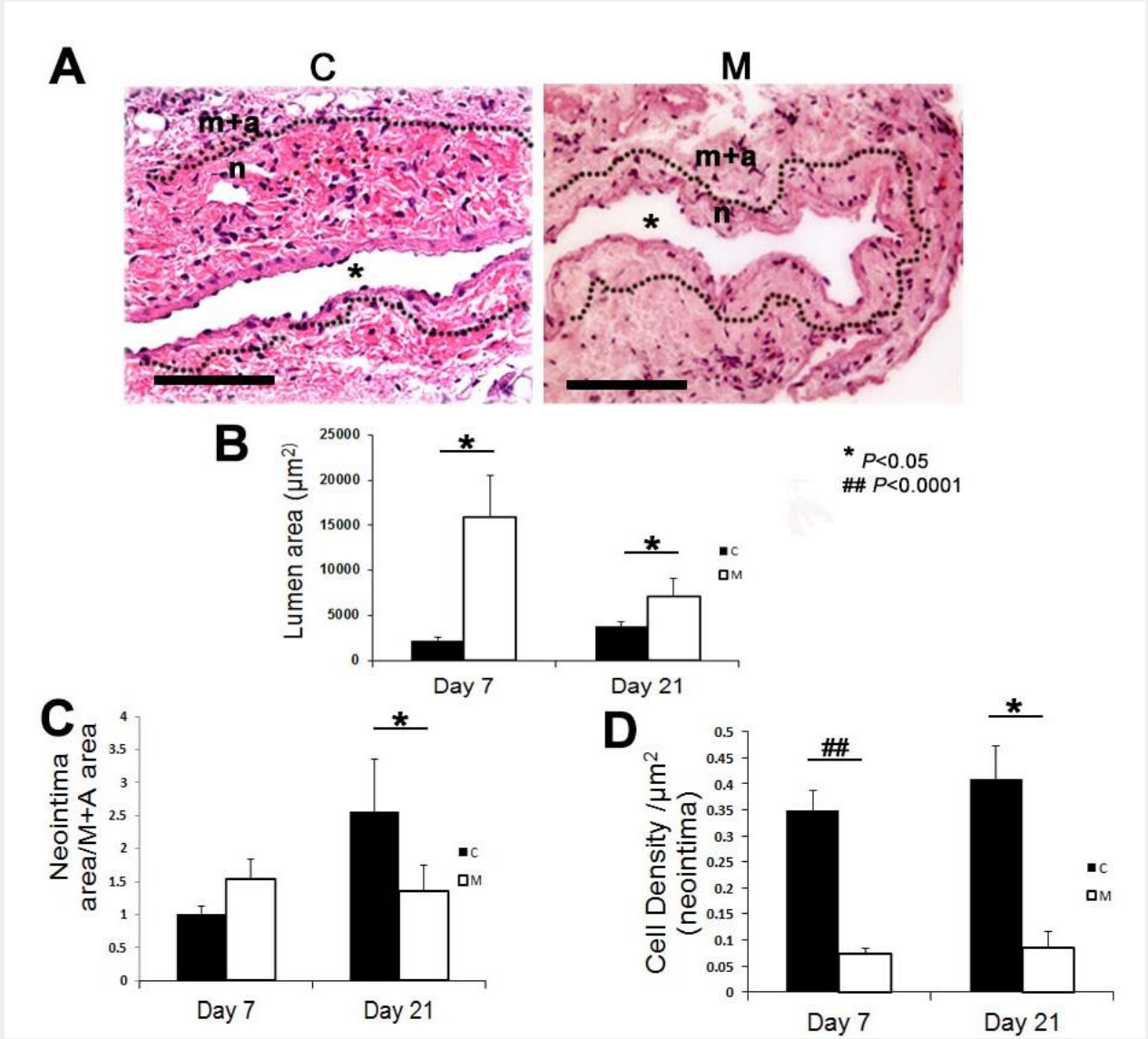
ORIGINAL RESEARCH ■ MOLECULAR IMAGING

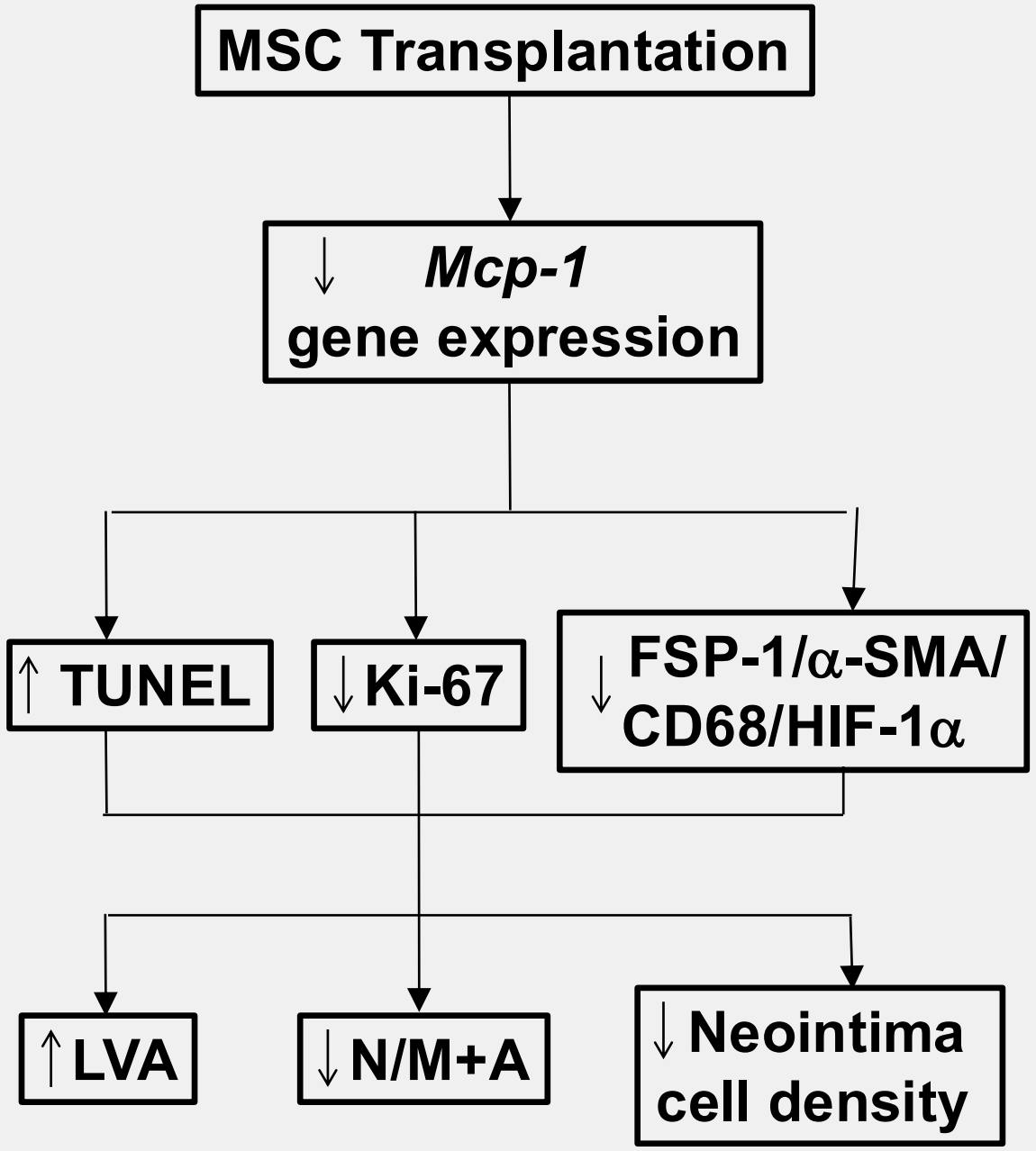
Radiology. 2016 May;279(2):513-22. doi: 10.1148/radiol.2015150947. Epub 2015 Nov 19.

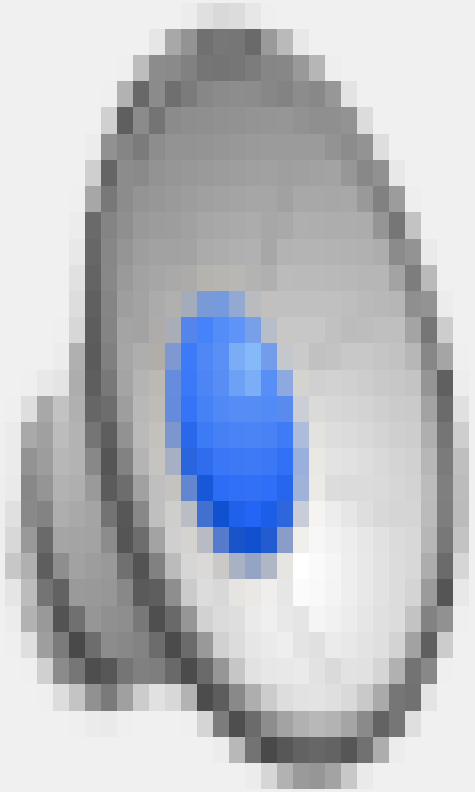


Imaging MSCs in Arteriovenous Fistula model



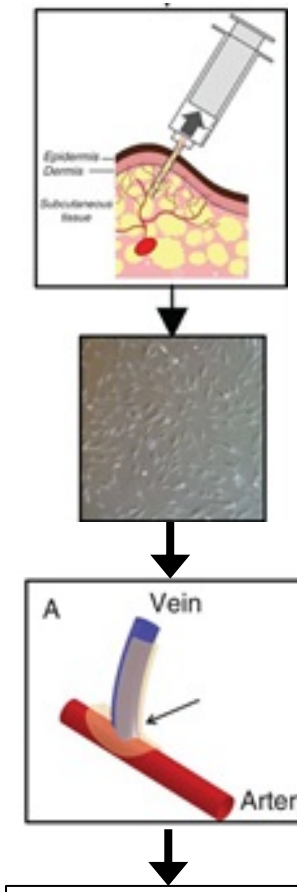

A
C
M
m+a
n
*
B
Lumen area (μm²)
25000
20000
15000
10000
5000
0
Day 7
Day 21
C
D
* P<0.05
P<0.0001
Neointima area/M+A area
Cell Density /μm² (neointima)
##


MSC Transplantation
↓ Mcp-1 gene expression
↑ TUNEL
↓ Ki-67
↓ FSP-1/α-SMA/ CD68/HIF-1α
↑ LVA
↓ N/M+A
↓ Neointima cell density



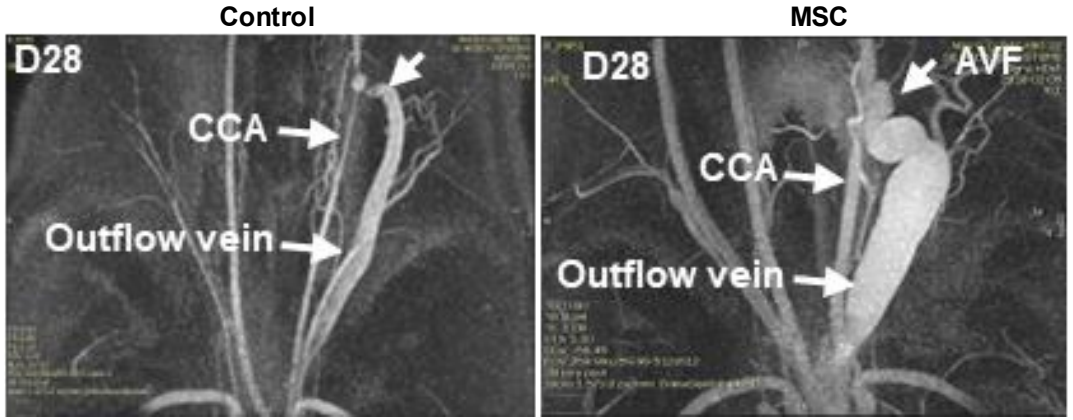
Large animal porcine model: Mimic clinical settings

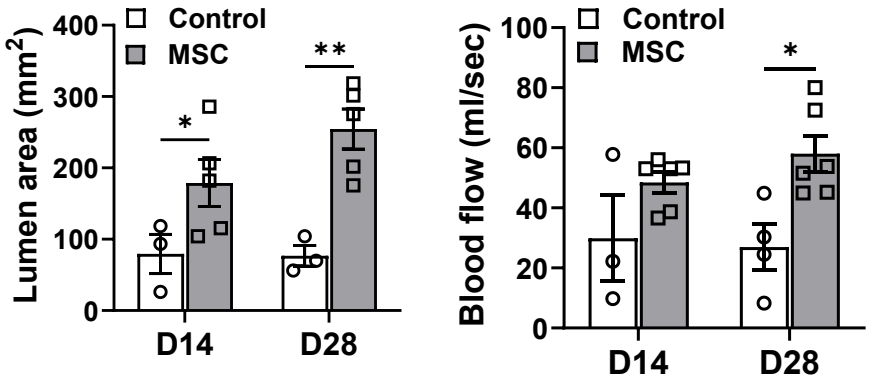
Autologous / allogeneic MSCs

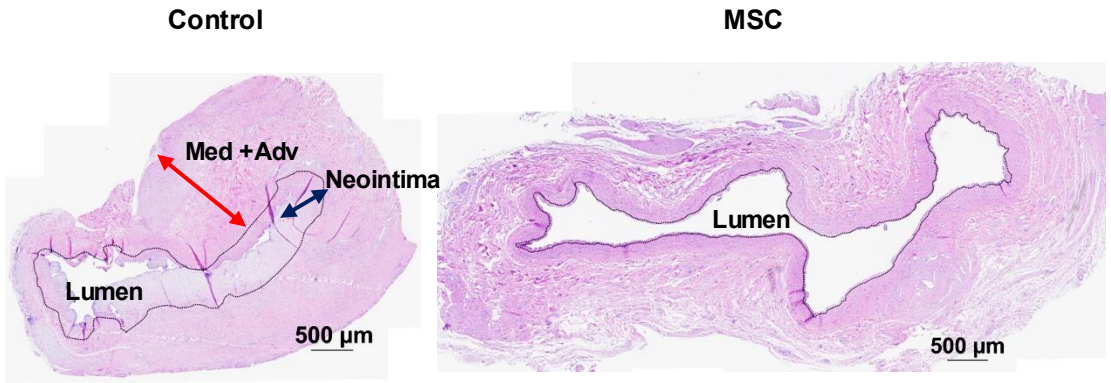


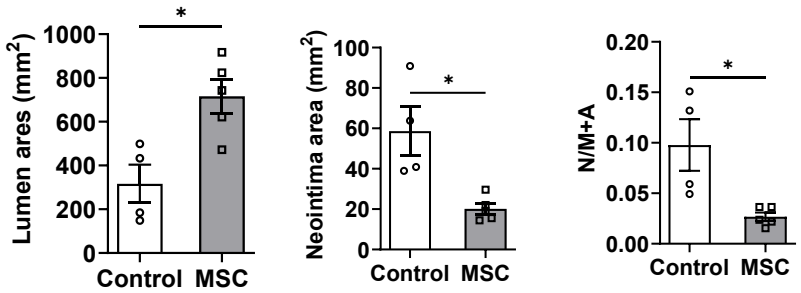
MRI/MRA: D14 and 28
Histology: D28

MRI/MRA at D28









MSC improves AVF function in porcine AVF model

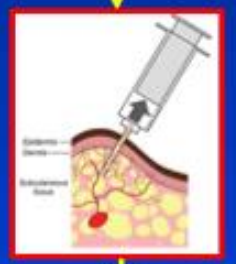
AMSC HD AVF Trial:

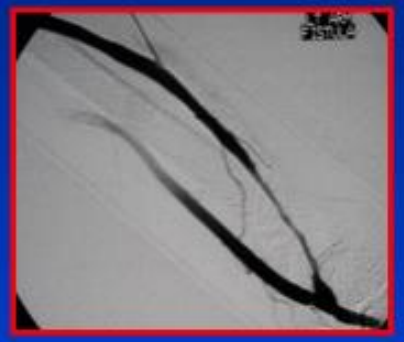
Clinicaltrials.gov:
NCT02808208

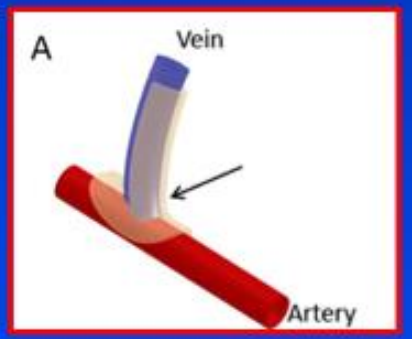
Vein mapping ? AVF

No cells

AMSC







Arteriovenous Fistula

U/S 1, 2, 3, 6, and 12-Months

- Maturation, Primary patency, Blood flow

Inclusion Criteria:



- Pre-dialysis or dialysis patients
- Age 18-85 years old
- New planned AVF- either BCF or RCF
- Two stage fistulas not allowed
- Dose of stem cells is based on surface area

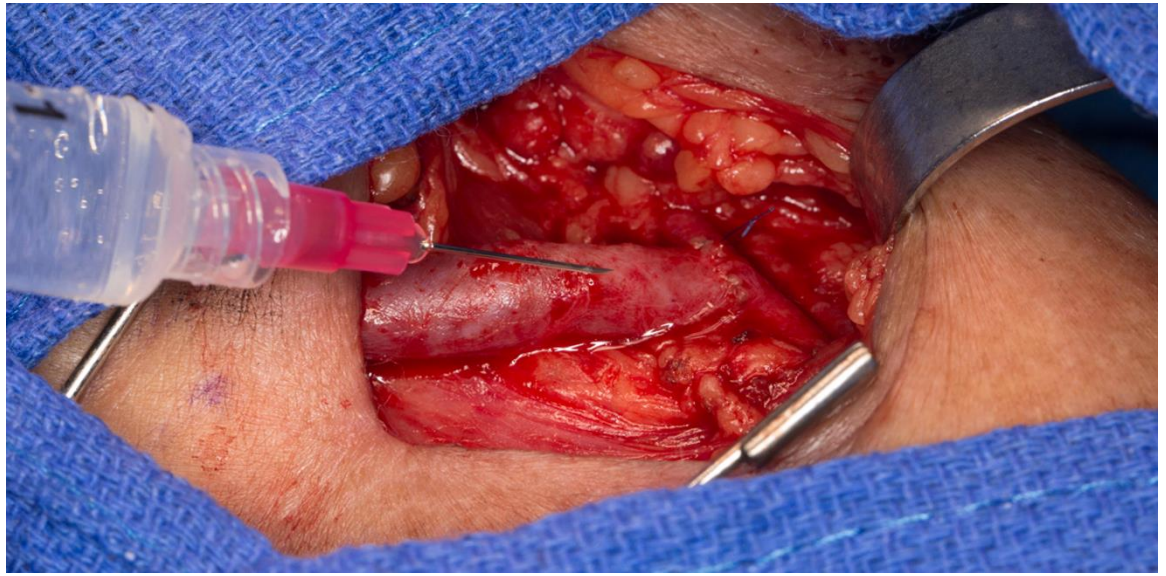
of outflow vein=[(2π)(radius in cm)(5cm) x (500,000 cells per cm2]

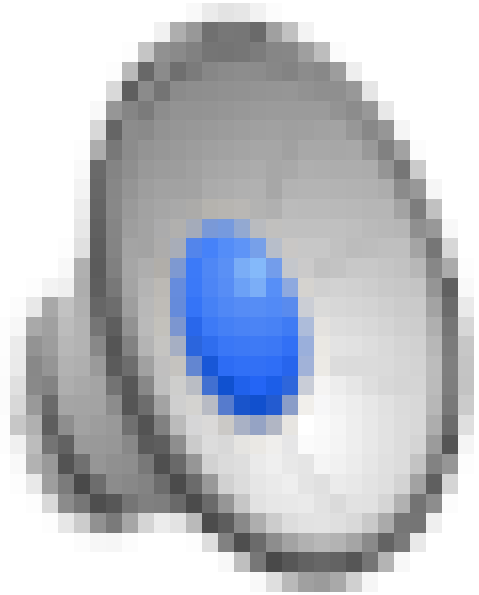
- Cells are CD73(+), CD90(+), CD105 (+), CD44(+), HLA-ABC(+)

July 25, 2017







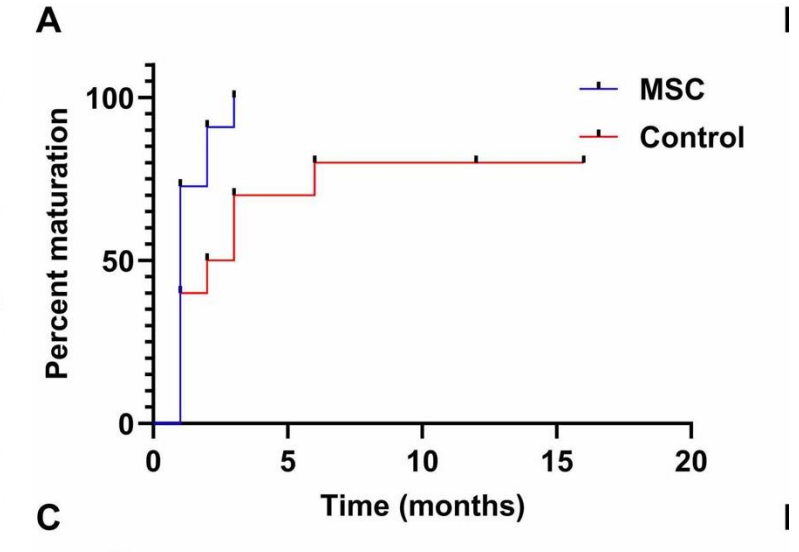


Phase 1 randomized controlled trial: periadventitial delivery of Autologous MSCs to AVF outflow vein

Characteristic	BCF control *N* = 6	BCF MSC *N* = 4	*P* value	RCF control *N* = 4	RCF MSC *N* = 7	*P* value
Female, *n* (%)	3 (50.0)	1 (25.0)	0.45	0 (0)	2	0.26
Age, mean years (SD)	73.3 (8.4)	61.8 (14.5)	0.11	71.3 (9.2)	64.1 (11.5)	0.70
Tobacco smoker, *n* (%)	3 (50.0)	2 (50.0)	1.00	3 (75.0)	4 (57.1)	0.57
Diabetes mellitus, *n* (%)	6 (100.0)	2 (50.0)	0.07	2 (50.0)	7 (100.0)	0.05*
CAD, *n* (%)	4 (66.7)	2 (50.0)	0.62	3 (75.0)	6 (85.7)	0.67
HLD, *n* (%)	6 (100.0)	2 (50.0)	0.07	4 (100.0)	7 (100.0)	1.00
Hypertension, *n* (%)	6 (100.0)	4 (100.0)	1.00	3 (75.0)	7 (100.0)	0.19
Peripheral arterial disease, *n* (%)	0 (0.0)	2 (50.0)	0.07	1 (25.0)	1 (14.3)	0.67

AVF maturation: Ready for dialysis

AVF vein	BCF	RCF
Diameter	≥6 mm	≥4 mm
Blood flow	≥600 ml/min	≥500 ml/min



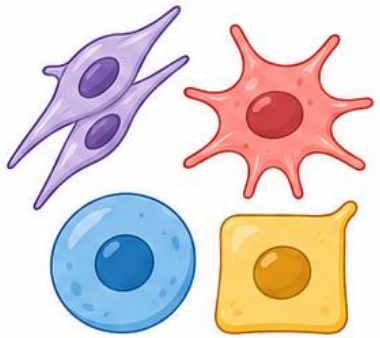
PTA interventions following MSC transplantation

MSC (n=11)	Control (n=10)
12 PTA (3 patients)	17 PTA (7 patients)

From Cells to Mice to Pigs to Humans

A translational continuum to understand biology and improve human health

CELLS



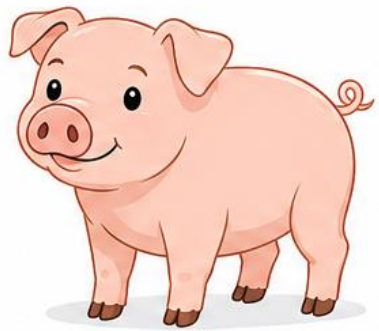
- In vitro models to dissect molecular mechanisms
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PIGS



- Large animal models with physiological similarities to humans
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HUMANS



- Clinical studies and trials
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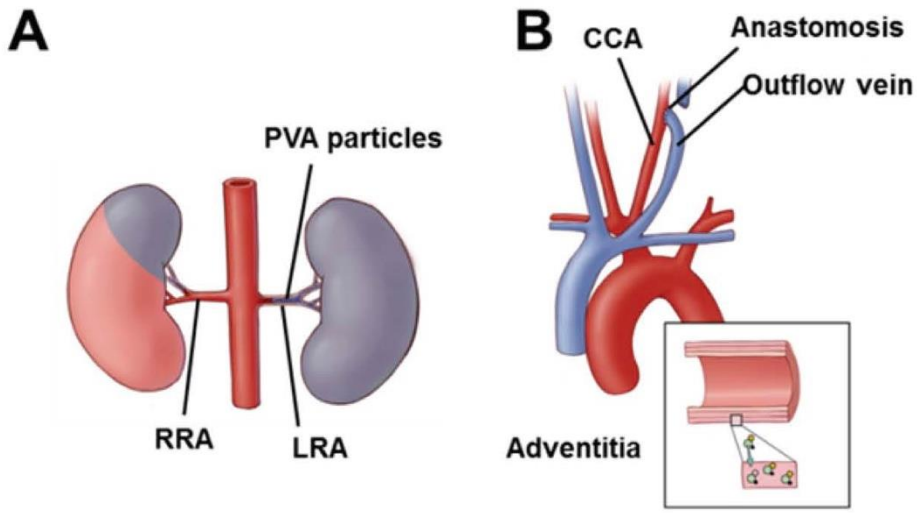
Building knowledge at every step.

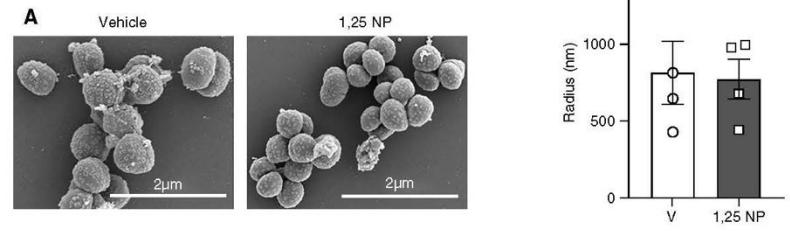
Advancing science from fundamental discovery to real-world impact.

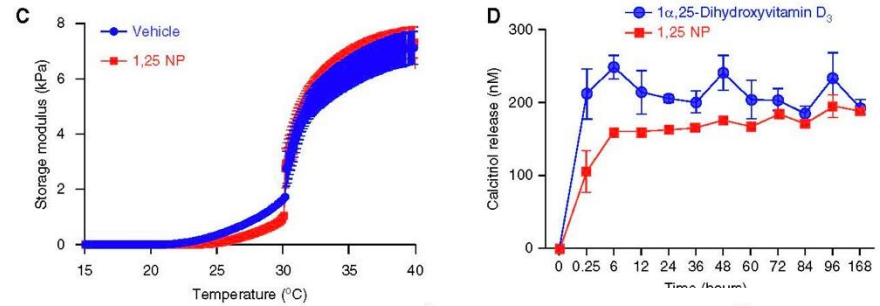
1α,25-Dihydroxyvitamin D_3 Encapsulated in Nanoparticles Prevents Venous Neointimal Hyperplasia and Stenosis in Porcine Arteriovenous Fistulas

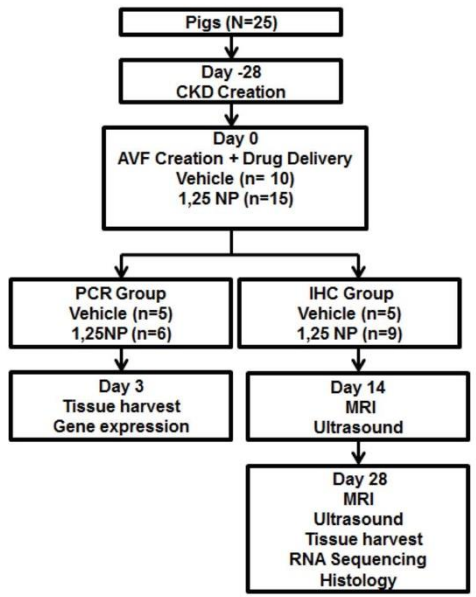
Avishek K. Singh,[1] Chuanqi Cai,[1] Sreenivasulu Kilari,[1] Chenglei Zhao,[1] Michael L. Simeon,[1] Edwin Takahashi,[1] Elazer R. Edelman,[2,3] Hyunjoon (Joon) Kong,[4] Thanila Macedo,[1] Ravinder J. Singh,[5] Matthew W. Urban,[1] Rajiv Kumar,[6] and Sanjay Misra[1]

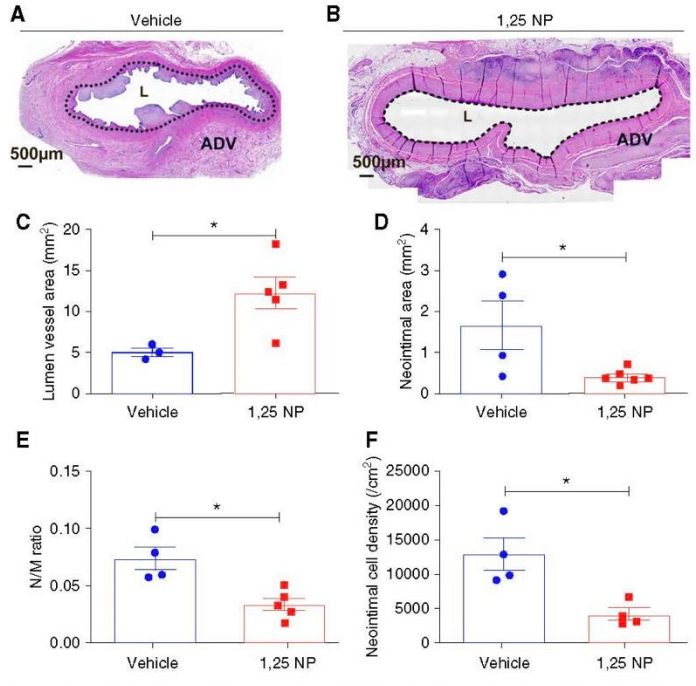
Due to the number of contributing authors, the affiliations are listed at the end of this article.

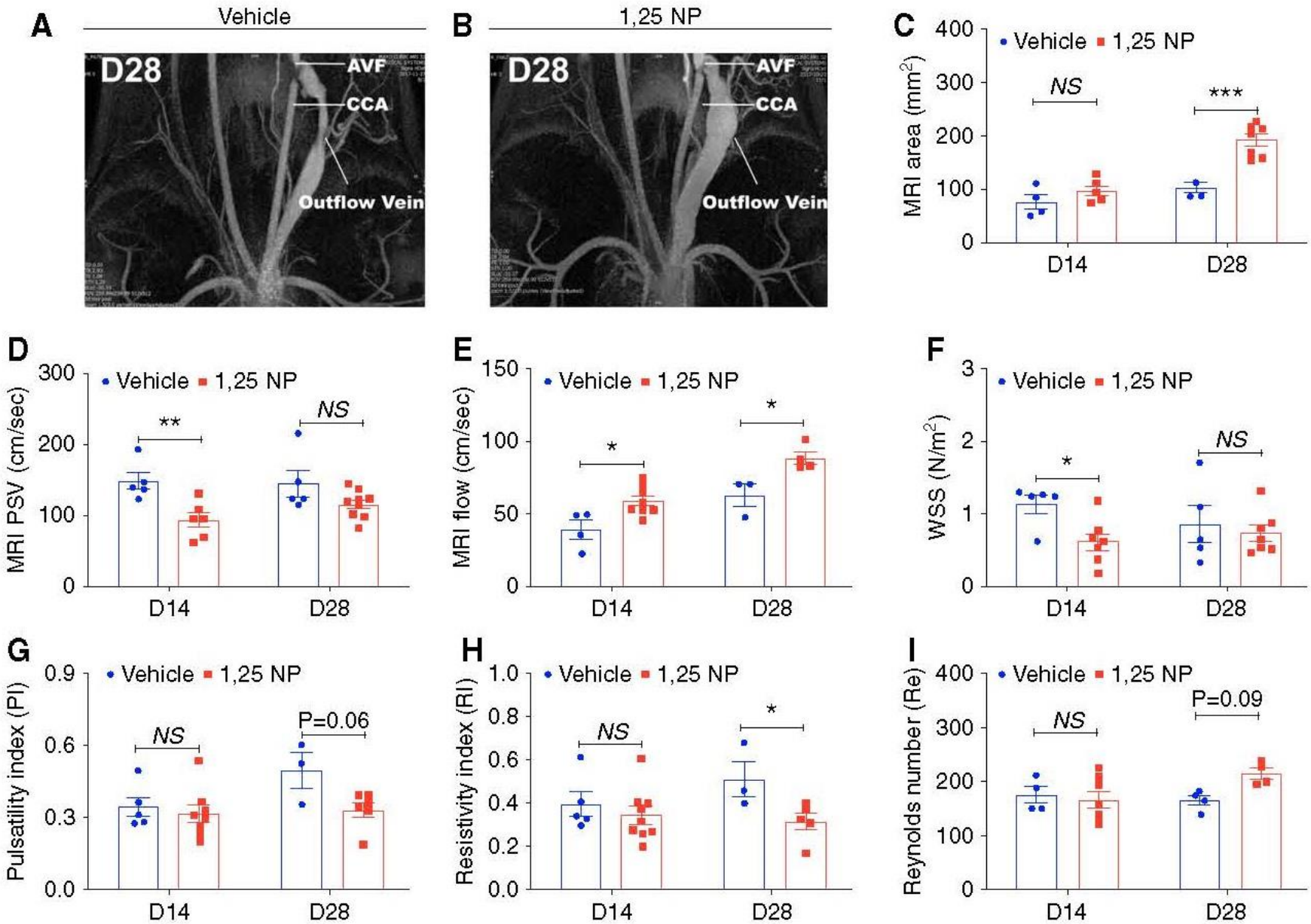


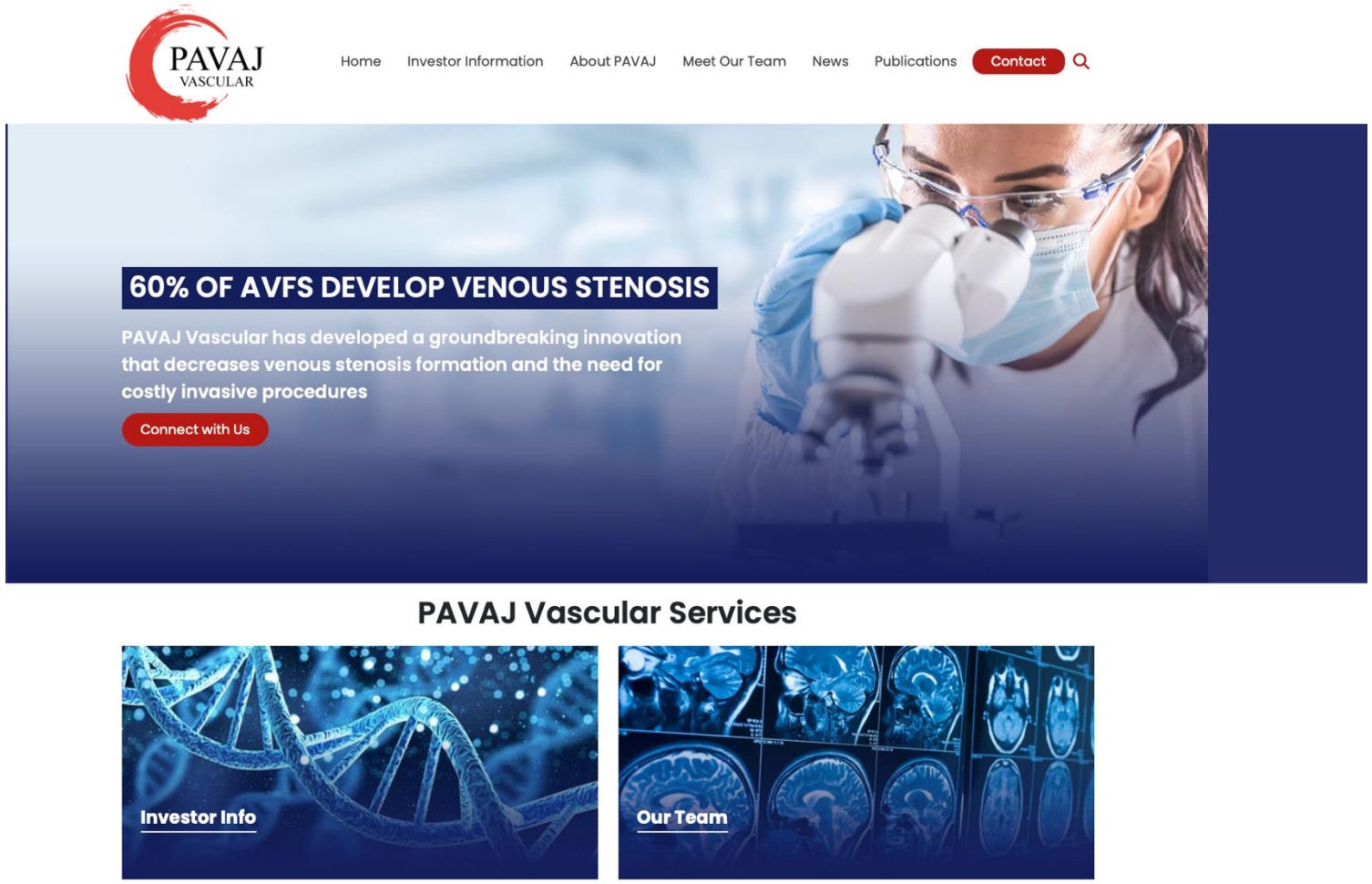









A
Vehicle
D28
AVF
CCA
Outflow Vein
B
1,25 NP
D28
AVF
CCA
Outflow Vein
C
Vehicle
1,25 NP
MRI area (mm2)
400
300
200
100
0
NS
***
D14
D28
D
Vehicle
1,25 NP
MRI PSV (cm/sec)
300
200
100
0
**
NS
D14
D28
E
Vehicle
1,25 NP
MRI flow (cm/sec)
150
100
50
0
*
*
D14
D28
F
Vehicle
1,25 NP
WSS (N/m2)
3
2
1
0
*
NS
D14
D28
G
Vehicle
1,25 NP
Pulsatility index (PI)
0.9
0.6
0.3
0.0
NS
P=0.06
D14
D28
H
Vehicle
1,25 NP
Resistivity index (RI)
1.0
0.8
0.6
0.4
0.2
0.0
NS
*
D14
D28
I
Vehicle
1,25 NP
Reynolds number (Re)
400
300
200
100
0
NS
P=0.09
D14
D28



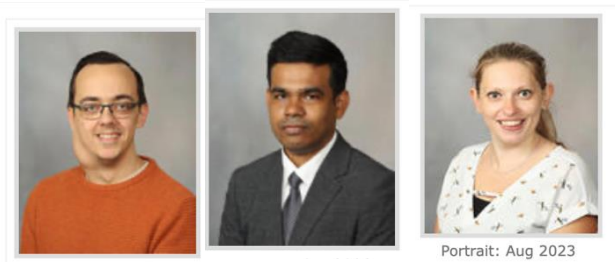
Pavaj Vascular:

- Company formed June 2021
- Licensed Technology from Mayo from 1,25 NP drug delivery Aug 2021
- Friends and family round
- NIH Direct SBIR Phase 2 Phase grant
- >40 Batches of NPs formed
- GMP manufacturing underway
- IND Filing Q3 2026
- FIH studies planned for Q1 2027

https://pavajvascular.com/meet-our-team/

Vascular and Interventional Radiology Translational Lab











OUR GLOBAL COLLABORATIONS

Partnering Across Continents to Advance Innovation and Patient Care



Stronger Together.
Better Outcomes.

Through our global collaborations, we share knowledge, advance research, and improve lives around the world.


NIH
National Heart, Lung,
and Blood Institute


NIH
NIDDK


American
Heart
Association®
life is why™


MAYO
CLINIC


SIR Foundation
Advancing interventional radiology through research


Regenerative Medicine
Minnesota
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