MERAND PHARMACEUTICALS, INC.

microRNA Therapeutics for Treating Peripheral Arterial Disease (PAD) and other Cardiovascular Disorders

EXECUTIVE SUMMARY

Company ready to initiate First-in-Human, Phase 1, study with lead microRNA product MPMI-93 in patients with Peripheral Arterial Disease (PAD)

Has exclusive license for broad US and European patents covering all forms of modulation of miR-93 for PAD

Accomplishments to Date:

- **Raised $1.25M Series A and a $1.35M Convertible Note.**
- **Assembled highly experienced management team.**
- **Completed:**
  - successful pre-IND meeting and recent follow-up communication with FDA.
  - all toxicology studies needed to support the safety of MPMI-93, for intra-muscular (IM), administration and planned clinical investigation.
  - manufacturing and sterile fill finish of a sufficient quantity of clinical grade product

Currently raising $2.3M Series A1 to conduct first-in-human clinical study designed to demonstrate not only safety by also give an indication of bioactivity and provide information on the durability of the treatment.

THE CLINICAL PROBLEM

Peripheral Arterial Disease a $3.5B Market

BURDEN & MARKET

PAD is a highly prevalent disease with > 10 million patients in US and 200 million globally.

High annual health care cost, i.e. >$40,000/year for critical limb.

Cilostazol, had sales of $700M.
PAD has a CAGR of 6.5%.

RISK TO LEGS

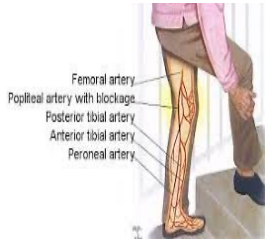
Claudication: Highly debilitating condition with 2/3 patients cannot walk more than 1 city block.

#1 Cause of amputation in adults.

RISK TO LIFE

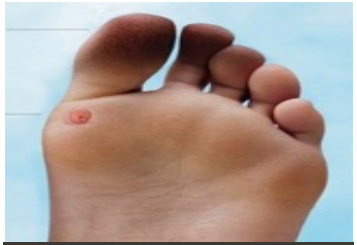
Patients with PAD suffer higher than expected rates of heart attack, stroke, and death even in presence of "optimal medical therapy."

NO DRUG HAS YET BEEN TESTED THAT HAS THE POTENTIAL TO TREAT LEGS & LIFE

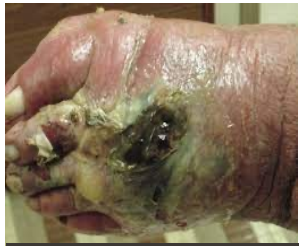


CLAUDICATION: Pain with Walking,

NUMBNESS Pain at Rest



ULCERS: Pain & Risk Limb Loss



GANGRENE

AMPUTATION

DEATH

BEYOND TREATING PATIENTS WITH PAD FOR ATHEROSCLEROSIS: AVAILABLE TREATMENTS FOR PAD ARE LIMITED

Cilostazol, last new therapeutic in PAD, was approved in 1999.

Medical treatments for PAD to reduce pain, leg symptoms, and limb loss do not exist.

Leg Bypass Surgery and Catheter-based revascularization in PAD are –

not designed for claudication;
not available to all;
not effective in many;
and can carry risk.

MPMI-93 represents a novel, disease modifying strategy to treat patients with PAD. First drug being tested that has the potential to treat legs and life in patients with PAD.

MERAND'S SOLUTION I of II: Biology of MPMi-93 in PAD

MicroRNA (miRNA) are small naturally-occurring RNAs that work in cell and condition specific manner to regulate multiple genes and pathways; especially in response to injury.

Data published in *Circulation 2013;127:1818-1828 & Circulation 2017;135:2403-2425*
Data slides are at the end of the presentation for review.

miR-93 was identified using an unbiased genetic, computational, and experimental approach. A loss of function of miR-93 reduced, and gain of function of miR-93 increased, blood vessel growth blood flow recovery in "challenging" mouse models of PAD. *Circulation 2013*

A feature that distinguished MPMI-93 from other agents that have been tested and failed in PAD studies, is that MPMi-93 (miR-93) *grows stable (not leaky)* blood vessels. *Circulation 2013*

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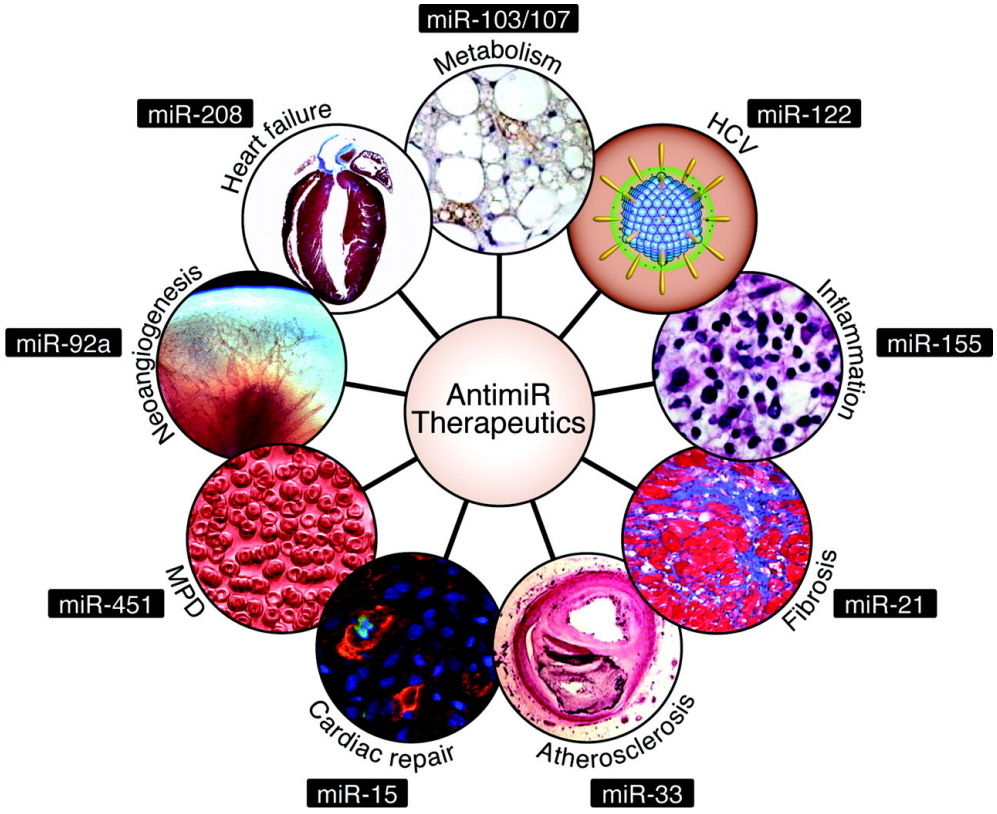
MPMI-93 promotes a shift in macrophages from a pro-inflammatory (M1-like) to a reparative (M-2) anti-inflammatory state that will

- exert a + paracrine effect on EC in ischemic to allow growth and less injury
- exert an effect that will limit the production of inflammatory cytokines that can assess the circulation and increase risk of MI and CVA. *Circulation 2017, and Annex BH and Cooke JP. New Directions in Therapeutic Angiogenesis and Arteriogenesis in PAD. Circ Res 2021;128:1944-1957*

Materials on efficacy and above rationale for miR-93 in PAD were submitted to the FDA and no additional efficacy studies were requested for the IND.

Why Develop a miR When Antagomers Dominate Current Drug Development

Antagomers are modified RNA and have long expression and prolonged action. Antagomers can even be delivered systemically which creates opportunities for off-target, off-tissue, toxicity.



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MERAND'S SOLUTION II of II: TAKE ADVANTAGE OF SAFETY OF IM DELIVERY OF UN-MODIFIED MICRO-RNA FOR INITIAL HUMAN STUDIES IN PATIENTS WITH PAD

1) De-risked the program: IND-enabling, pre-clinical toxicology studies in two species have been completed at Charles River Labs: No evidence of any toxicity.

2) Non-GLP toxicology studies using IM delivery at 50X therapeutic dose have been completed showing no change in miR-93 expression in kidney, liver, heart or plasma.

3) The FDA agreed that intra-muscular injection of the most symptomatic leg in our first-in-human study was safe, feasible, and was supported by data from prior PAD studies. *American Heart Journal 2007;153:874-80.*

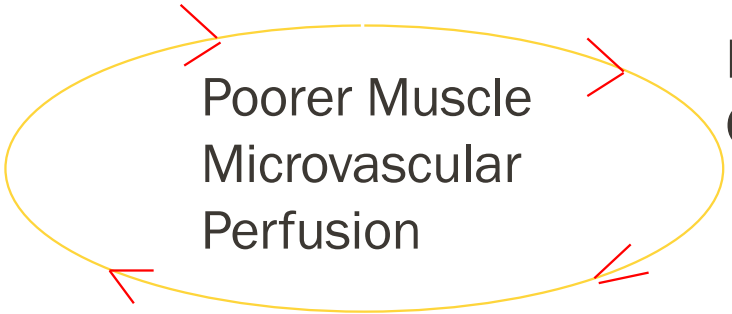
4) Moreover, the FDA agreed this delivery method afforded the opportunity to maximize delivery to the target limb while minimizing the risk of systemic exposure.

The Ischemic Leg Muscle is the Target Organ in PAD:

Reduced Perfusion Causes Muscle Ischemia and Leads to a Feed-Forward Pathway of Endothelial Injury causing >M1-like Macrophage Polarization & > ROS each of which worsens muscle microvascular perfusion and ischemia.

Inflammation Driven by > # M1-like macrophages

- Inhibits angiogenesis
- Increase injurious cytokines that access circulation



Increased Reactive Oxygen Species (ROS)

Greater Endothelial/Vascular Injury in Muscle

a) loss microvascular density
b) loss of vascular integrity i.e. greater vascular permeability

A few selected slides will show sites/effects from miR-93 delievry

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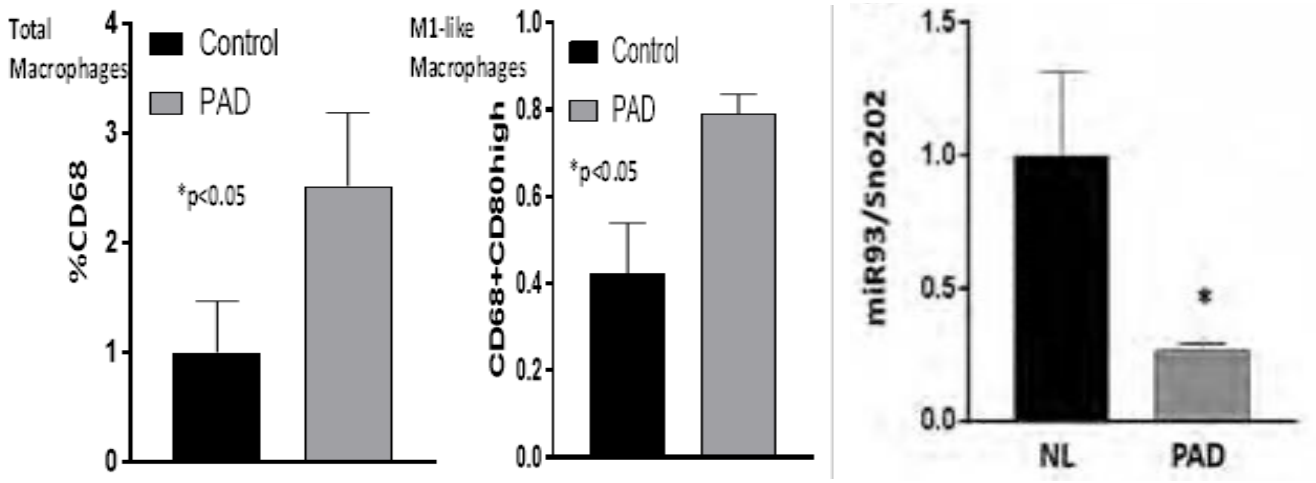
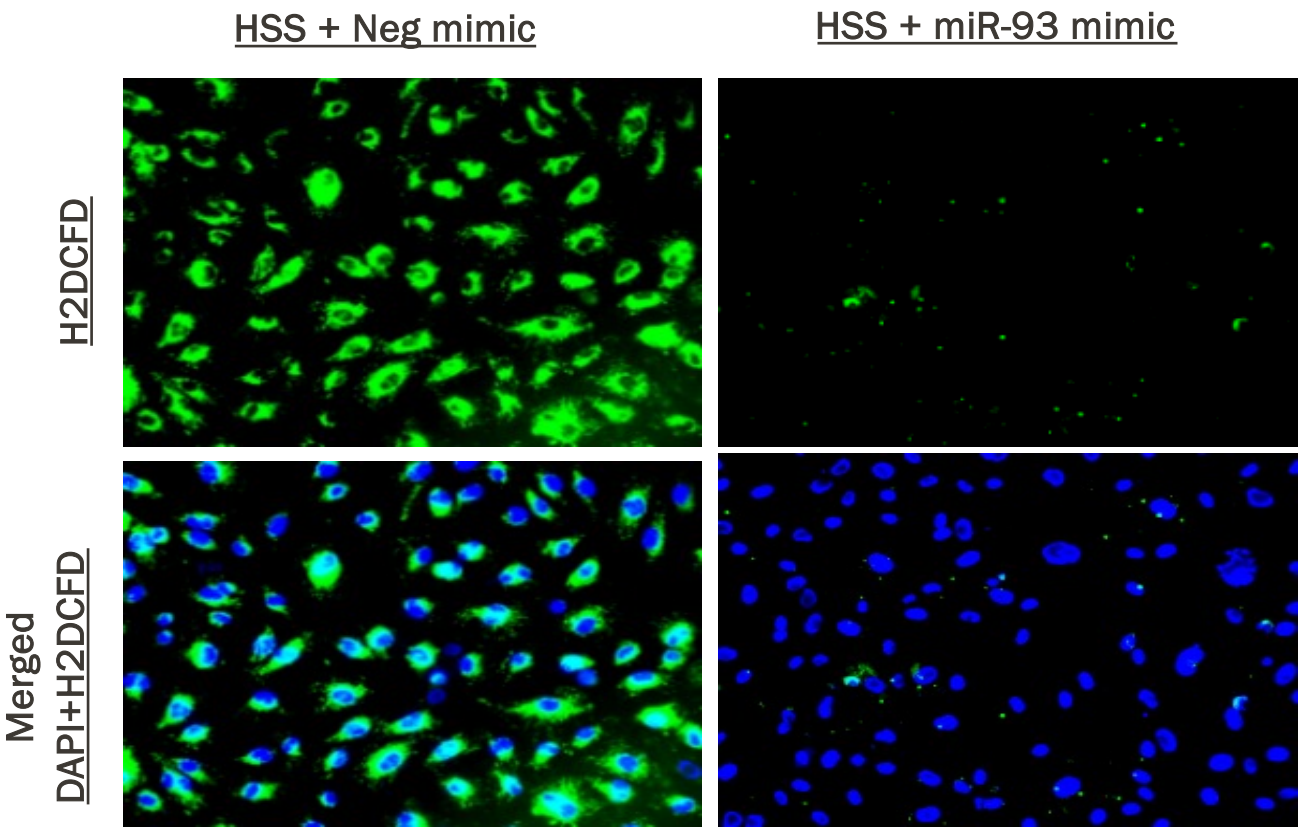
Data from human skeletal muscle biopsies shows patients with PAD have > macrophages, specifically >M1 CD86+/CD80^{high} macrophages and lower miR93 vs. non-PAD controls.

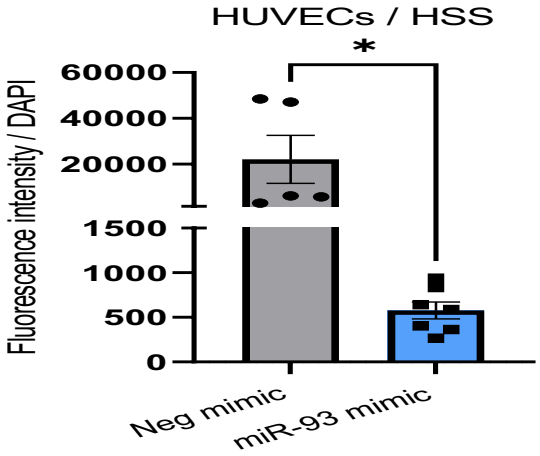


Compiled data taken in parts from
Circulation 2017;135:2403-2425
Circulation 2019;139:226-242.

M2 macrophage number was not different.
Data not shown

HUVEC under hypoxia/serum starvation (HSS): miR-93 vs. control is angiogenic* and nearly eliminates ROS





H2DCFD = 2',7'-dichlorodihydrofluorescein diacetate is a chemically reduced fluorescein and an indicator for reactive oxygen species (ROS) in cells,

* Angiogenic properties of miR-93 in EC under HSS published in Hazarika et al. Circulation 2013;127:1818-28.
Above ROS data is included in recently submitted manuscript.

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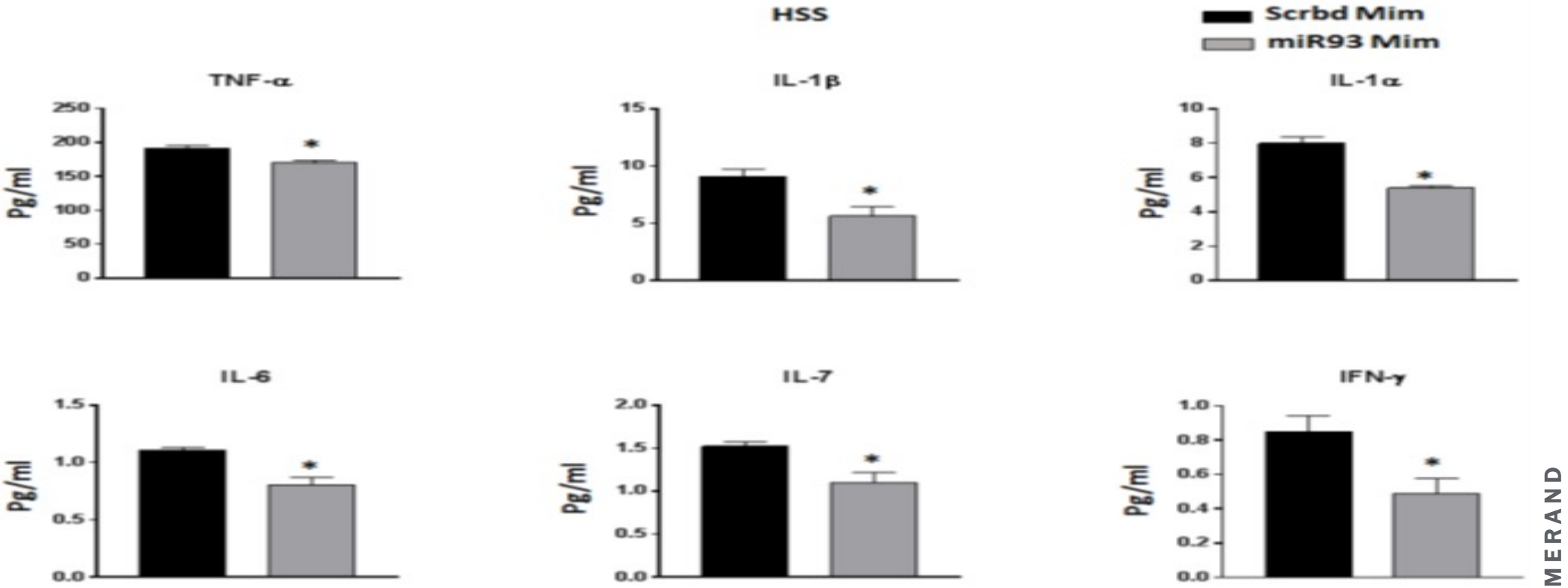
miR-93 Over-expression Reduces Pro Inflammatory Cytokine Production from Macrophages

Cytokine levels in conditioned media for Macrophages under HSS with miR-93 vs. scramble.



These and additional data in Circulation. 2017; 135:2403-25.

INTELLECTUAL PROPERTY

Broad Protection for Treating PAD

Title: Compositions and methods for treating peripheral arterial disease

Inventors at the University of Virginia: Brian Annex, Charles Farber, Surovi Hazarika

US 9,845,465 B2, issued 12/19/17

European Patent 2885008B, issued 11/7/2018

Covers the use of both miR-93 and pre-miR-93

Exclusively licensed from University of Virginia for all fields and all territories.

Title: Methods, Kits, Compositions for Reducing miR106B Activity

Inventor: Brian Annex

Assignee: Merand Pharmaceuticals, Inc.

Provision patent application US 63/148,940 filed on 2/12/2021

LEADERSHIP Internationally Recognized Physician/Scientist in PAD & Seasoned Biotech Execs

TONY GIORDANO, Ph.D
CEO

- Co-founded and/or served as President or Vice President of 7 different biotech companies:
- 2 sold to public companies.
- 3 currently active (1 recent IPO).
- Oversaw translation of 3 different products into clinical trials.
- Managed 2 companies focused on RNA technologies.
- Executed numerous licenses and partnerships with large pharmaceutical companies.

BRIAN H. ANNEX, M.D.
Chief Medical Officer

- Previous Chief of Cardiology at UVA now Chair, Department of Medicine at Medical College of Georgia.
- >$20 million dollars of NIH-funded research for PAD, alone ; >160 peer-reviewed publications H-index is 61.
- Leadership in >10 Phase I (first-in-human) as well as Phase II and Phase III human studies of PAD.
- Experience with FDA & regulatory groups.
- Consulting Editor: *Journal of Clinical Investigation.*
- Associate Editor: *Journal of the American College of Cardiology: Basic to Translational Science.*

CHUKE NWACHUKU, DrPH
Chief Development Officer

- Has held leadership and management roles at Bristol Myers Squibb, Astra Zeneca and Daiichi Sankyo.
- Scientific Project Officer for the ALLHAT clinical study, which resulted in global changes in how hypertension is managed.
- Had leadership role in proof-of-concept trial of a novel oral anticoagulant in PAD/CLI patients.
- Served on teams evaluating in-licensing opportunities, leading presentations/ recommendations to executive leadership.

LEADERSHIP Outstanding Clinical and Scientific Advisors

JOHN COOKE, M.D., Ph.D.

- Previously Stanford University Currently, Chair, Department of Cardiovascular Sciences, Houston Methodist Research Institute.
- Medical Director of RNA Therapeutics Program in the Houston Methodist DeBakey Heart and Vascular Center.
- 30 years of translational research experience in vascular diseases.
- Over 500 publications, 30 pending/granted patents.
- Serves on the Editorial Boards of Circulation, *Circulation Research and Cardiovascular Drugs and Therapy.*

RUSTY MONTGOMERY, Ph.D.

- Former Director of Research at Miragen, Inc. (a microRNA focused company).
- Oversaw all preclinical research from discovery to development.
- Managed Servier partnership and oversaw early-stage clinical development.
- Currently VP of Biology at BioAge Labs.

DOUG LOSORDO, M.D.

- Ex. VP, Global Head of R&D and Chief Medical Officer, KBP Biosciences.
- Prior Chief Medical Officer and Current Executive Vice President Cadadrius Biosciences --- www.caladrius.com a clinical-stage biopharmaceutical company with multiple technology platforms targeting select cardiovascular indications and autoimmune diseases.
- World leader in CD34+ cell therapy for ischemic heart and PAD.
- >220 publications, experience with NIH, FDA, RAC.
- Formerly Professor of Medicine at Northwestern and at Tufts.

MERAND'S $2.3M SERIES A1 WILL CREATE SUBSTANTIAL VALUE

Financing will fund clinical trial in PAD patients designed to show:

- Safety
- Biological activity of MPMI-93 through changes in macrophage polarization/inflammation
- Durability of response, i.e, how long will bioactivity continue following a single series of injections

Phase 1a: First-in-Human, Placebo Controlled, Double Blind Single Ascending Dose (SAD) Study in PAD Patients

- **Target Population:** Patients with severe PAD, ABI < 0.6, no planned surgery within 30 days.
- **Dose and Frequency Safety Study** 3 groups (6 active drug subjects + 2 placebo subjects/group)
  - Group 1: 15 mg/ml or placebo delivered in 10 intramuscular injections in most symptomatic limb
  - Group 2: 50 mg/ml or placebo delivered in 10 intramuscular injections in most symptomatic limb
  - Group 3: 200 mg/ml or placebo …in most symptomatic limb
- **Endpoints** (in drug vs. placebo)**:**
  - Safety: Freedom from serious adverse events, physical exam, and laboratory safety assessments
  - Changes in plasma miR-93 pre- to post-injection serial time points (drug vs. placebo).
  - Blood changes in polarization of circulating monocytes, pro and anti-inflammatory cytokines

Study Schedule Considering adding Day 28

Visit	1	2	3	4	5
Day	-30 to 0	1	4	7	14/EOS
Activity	Consent, Screening, Exam/Safety Lab Blood draw for biomarker	Dose, Serial Blood draw for changes miR-93, Blood draw for biomarker (pre) 24-hr PK & safety labs	Blood draw for biomarker (post dosing #1) Exam/Safety Lab	Blood draw for biomarker (post dosing #2)	Blood draw for biomarker (post dosing #3) Exam/Safety Lab

Rationale Behind Design of the Biomarker & Mechanism of Action Phase 1a Human Studies

PRE → POST ASSESSMENTS (aka pD from dosing)

IN MUSCLE

- Lower capillary density vs. non-PAD controls
- > # macrophages/area
- >M1-like (inflammatory):total macrophages
- <M2-like (anti-inflammatory):total macrophages
- >production of inflammatory cytokines (IIβ, IL6) that have been linked to MI and stroke
- #signals for increasing systemic inflammation
- <miR-93

IN MUSCLE

Assessment by biopsy is an option but <u>not part of initial plans as blood draws are better in safety study</u>

IN BLOOD → IN BLOOD

- >inflammatory and <anti-inflammatory cytokines
- >$CD14^{high}/CD16^{low}$ (classic monocytes directly linked to M1 in tissue)
- <$CD14^{low}/CD16^{high}$ (non-classic monocytes linked to M2 in tissue)

= indirect evidence others from publications

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FUTURE PLANS – Excellent Value Proposition

Series A/Note: $2.6 M

$1.25M Series A
- ✓ Confirm activity of MPNI-93 validated by DSI and independent lab
- ✓ Demonstrate lack of systemic exposure
- ✓ Establish manufacturing procedure
- ✓ Complete rat DRF toxicity study
- ✓ Conduct pre-IND meeting with FDA

$1.0M Convertible Note
- ✓ Develop GLP analytical methods
- ✓ Complete dog DRF study under GLP
- ✓ Manufacture GMP material

$0.35M Convertiible Note Extension
- ✓ Complete rat GLP toxicology study
- File IND

$2.3 M

- Phase 1a in PAD patients
  - Safety
  - Bioactivity
  - Durability of response

$10.2 M

- Manufacture additional GMP material
- Phase 1b/2a clinical study in PAD patients
- Advance 2nd generation asset through preclinical development

➢ Human POC for MPMI-93 in PAD
➢ IND filed for 2nd asset

Exit Opportunity

At POC Stage: $250-500M

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Thank you.

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