# EXOSOMES FROM UMBILICAL CORD STEM CELLS FOR AGING

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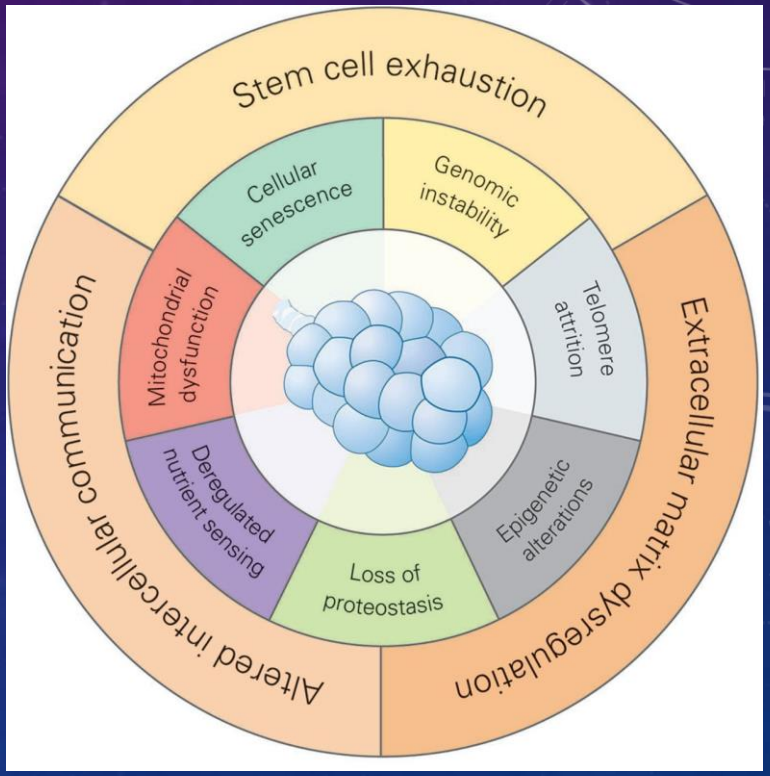
CO FOUNDER OF CLINICAL PEPTIDE SOCIETY

# 12 HALLMARKS OF AGING IN 2023

## (2013 HAD 9 HALLMARKS OF AGING)

LÓPEZ-OTÍN C, BLASCO MA, PARTRIDGE L, SERRANO M, KROEMER G. **HALLMARKS OF AGING: AN EXPANDING UNIVERSE.** *CELL.* 2023;186(2):243-278

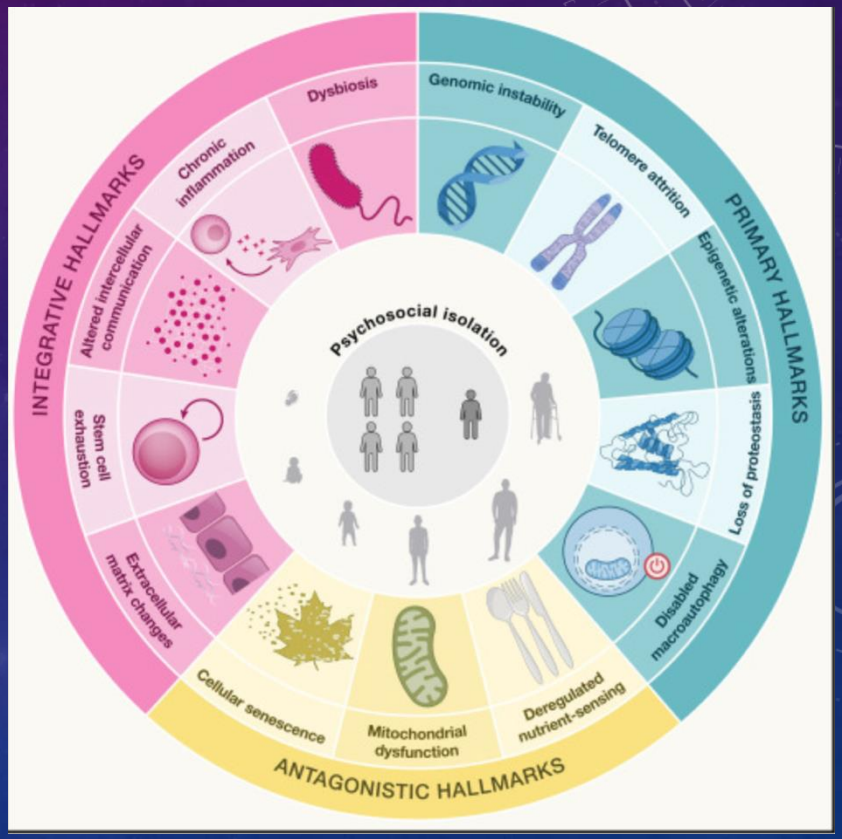
- Mitochondrial Dysfunction
- Genomic instability
- Shorten Telomeres
- Inefficient cell communication
- Stem Cell exhaustion
- Proteins become less functional
- Depletion of NAD
- Immune cell dysfunction
- Failed Autophagy
- Increase Senescence
- Chronic Inflammation
- Dysbiosis



# 14 HALLMARKS OF AGING IN 2025

KROEMER G, ET AL. "FROM GEROSCIENCE TO PRECISION GEROMEDICINE: UNDERSTANDING AND MANAGING AGING." *CELL.* 2025;188(8):2043-2062. DOI:10.1016/J.CELL.2025.03.011

1. Extracellular matrix changes
2. Psychosocial Isolation



# IF YOU HAVE TO PICK ONE THERAPY FOR AGING OR LONGEVITY WHAT WOULD IT BE?

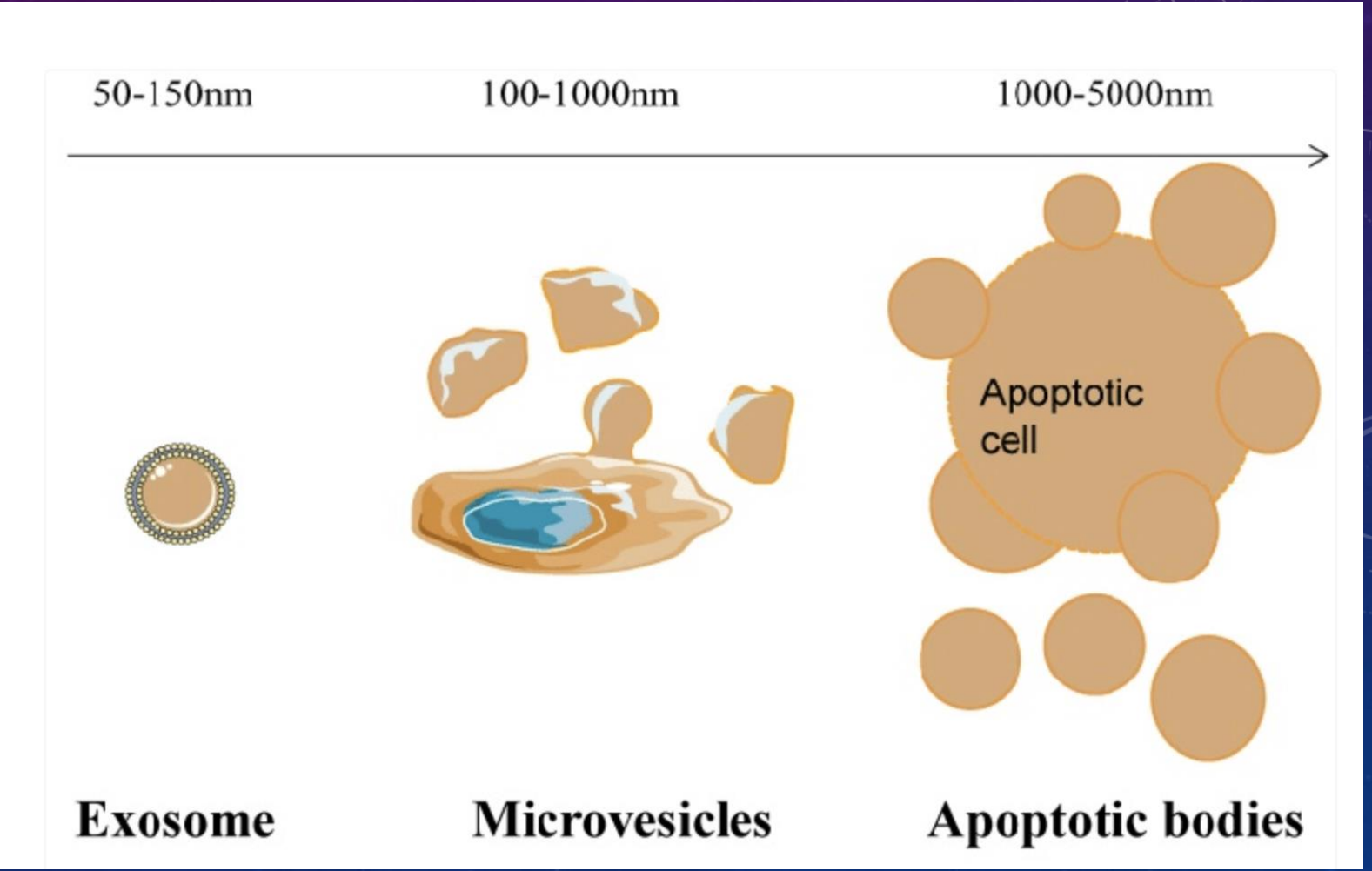
- Peptide Bio Regulators
- Peptides
- Therapeutic Plasma Exchange
- EBOO/ Ozone therapy
- Fasting
- Umbilical cord tissue MSC
- PRP
- Diet in Protein
- Cold Plunge / Sauna
- Umbilical cord tissue MSC exosomes
- Hyperbaric oxygen
- Supplements
- Meditation
- Exercise
- Senolytics
- Young Plasma

# EXOSOMES

- In 1983, exosomes were discovered in sheep reticulocytes but they were initially considered cellular waste
- Harding C, et. al. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. J Cell Biol. 1983;97(2):329–339.

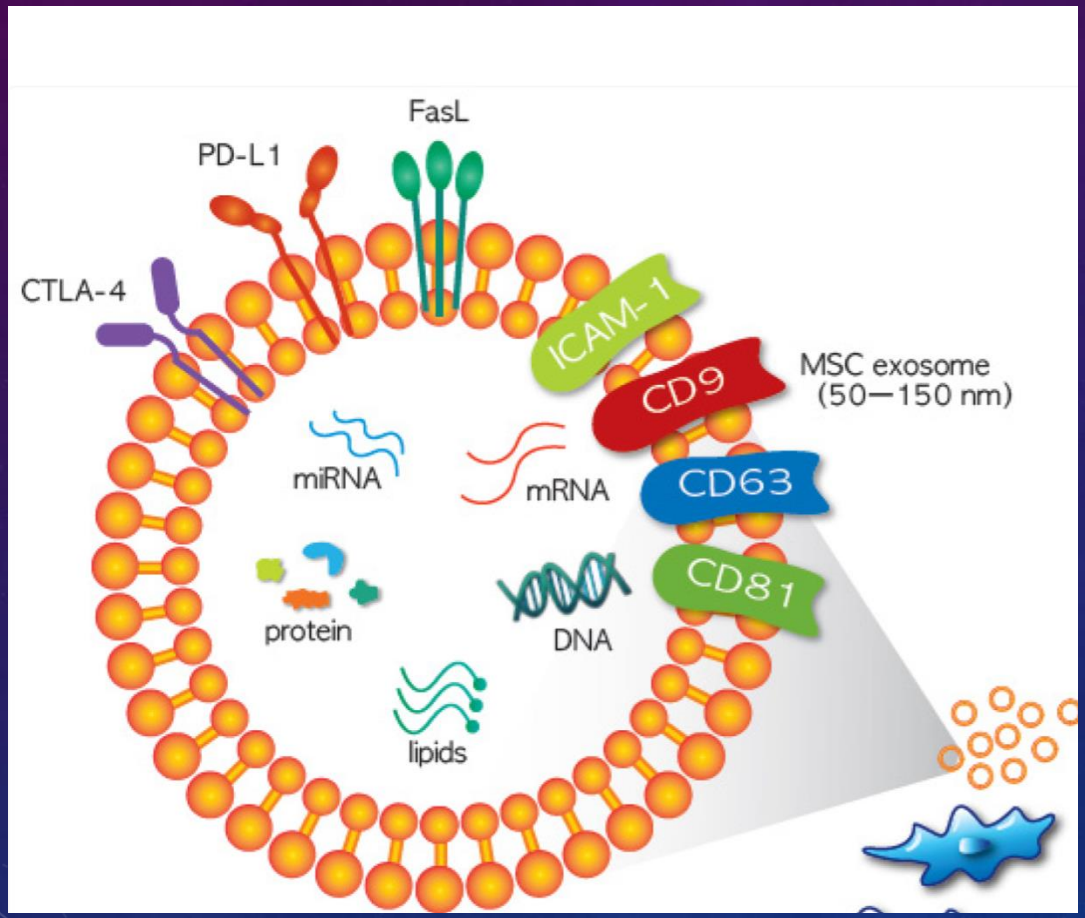
- Exosomes are secreted by a variety of cells and exist in almost all body fluids, including the blood, saliva, urine, cerebrospinal fluid, and milk.
- Simpson, Richard J, Kalra, et al. ExoCarta as a resource for exosomal research. J Extracellular Vesicles, 2012, 1 (1): 18374.

# EXTRACELLULAR VESICLES CAN BE DIVIDED INTO THREE TYPES



| Exosome | Microvesicles | Apoptotic bodies |
| --- | --- | --- |
| Size: 50-150nm | Size:100-1000nm | Size:1000-5000nm |
| Markers: CD81,CD63,CD9,HSP70, MCH-I,TSG101,LAMP1 | Markers: CD40,CD62,integrins | Markers: None |
| Source: Multivesicular endosomes | Source: Plasma membrane | Source: Apoptotic cell |

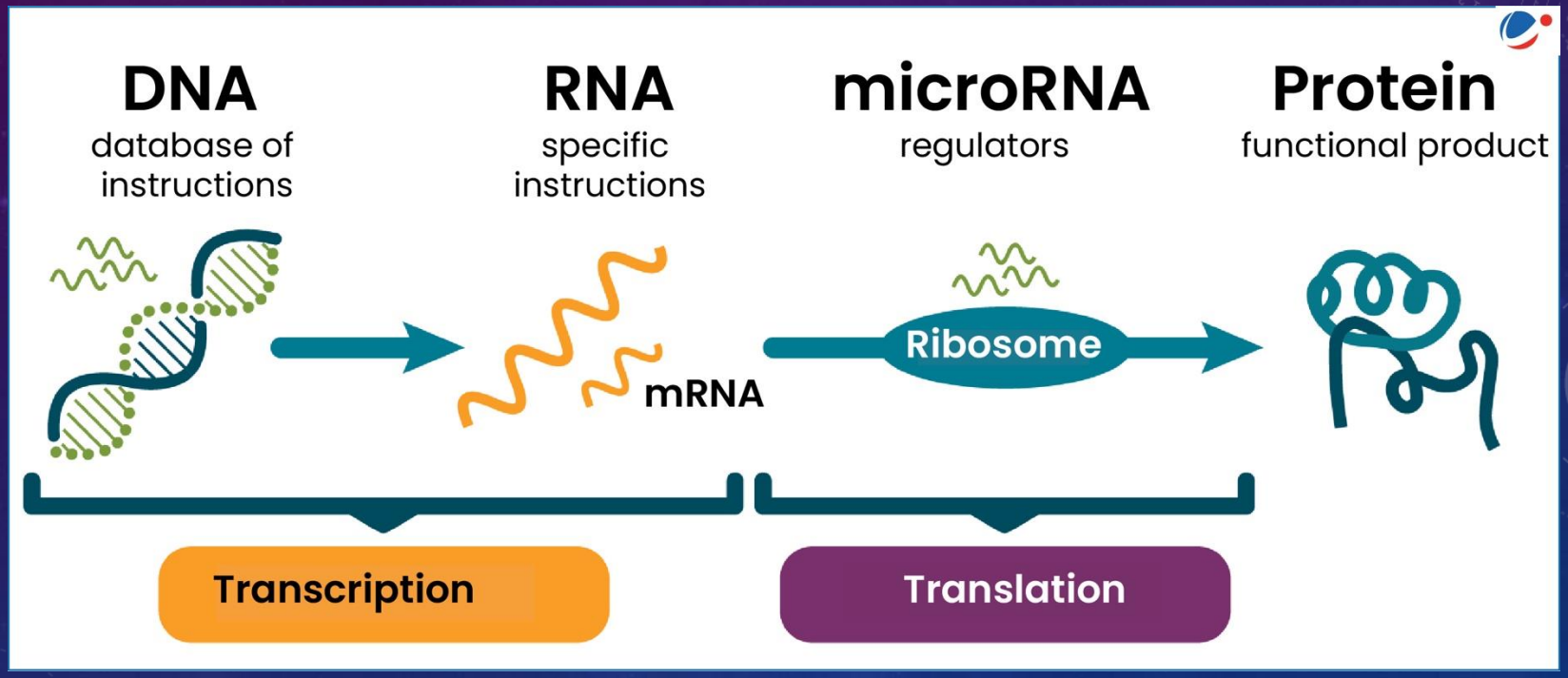
# EXOSOMES CONTAIN




CD9, CD63, CD81 are cell surface markers for exosomes

CD are transmembrane protein

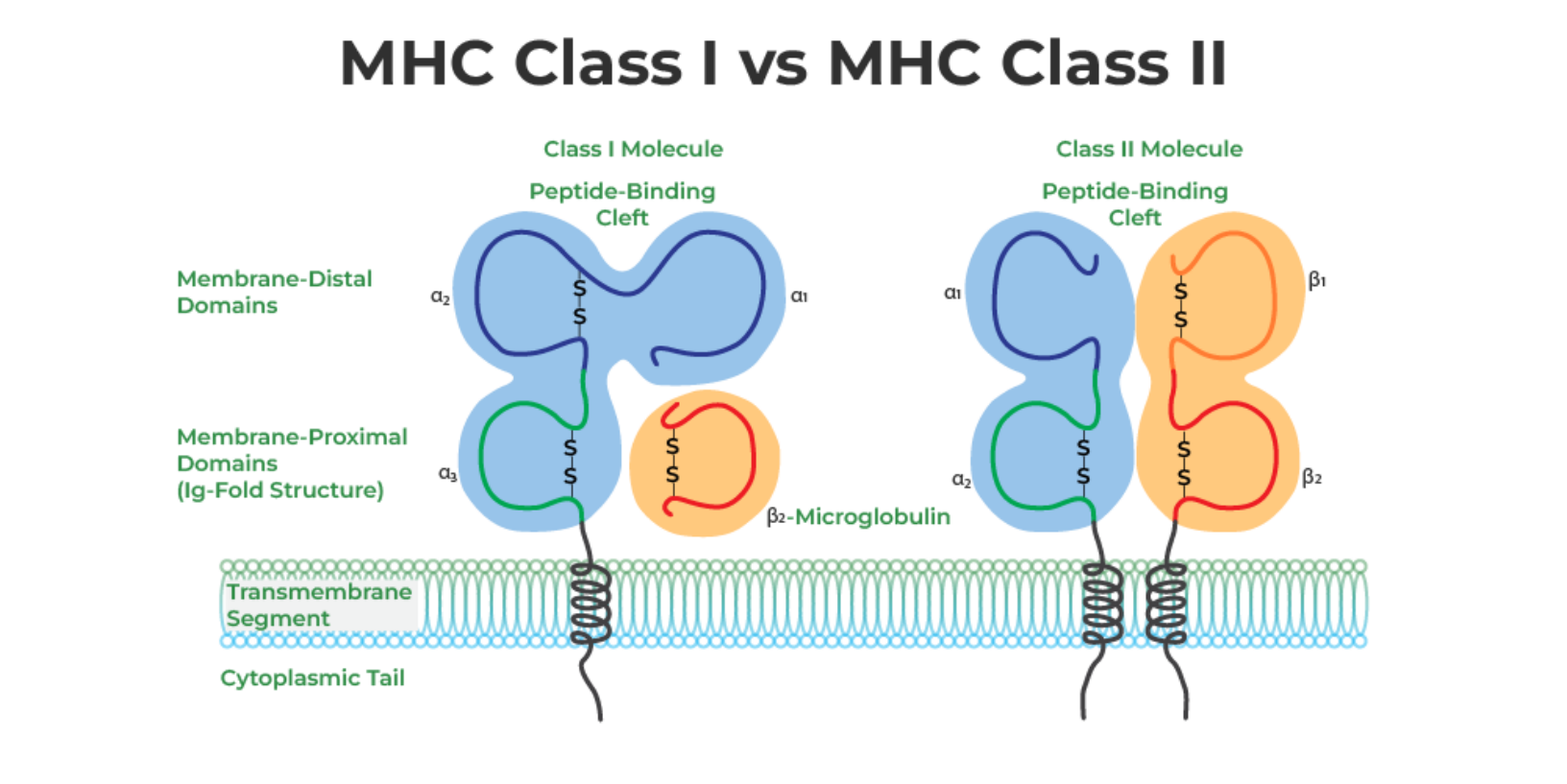
# MESSENGER RNA VS MICRO RNA



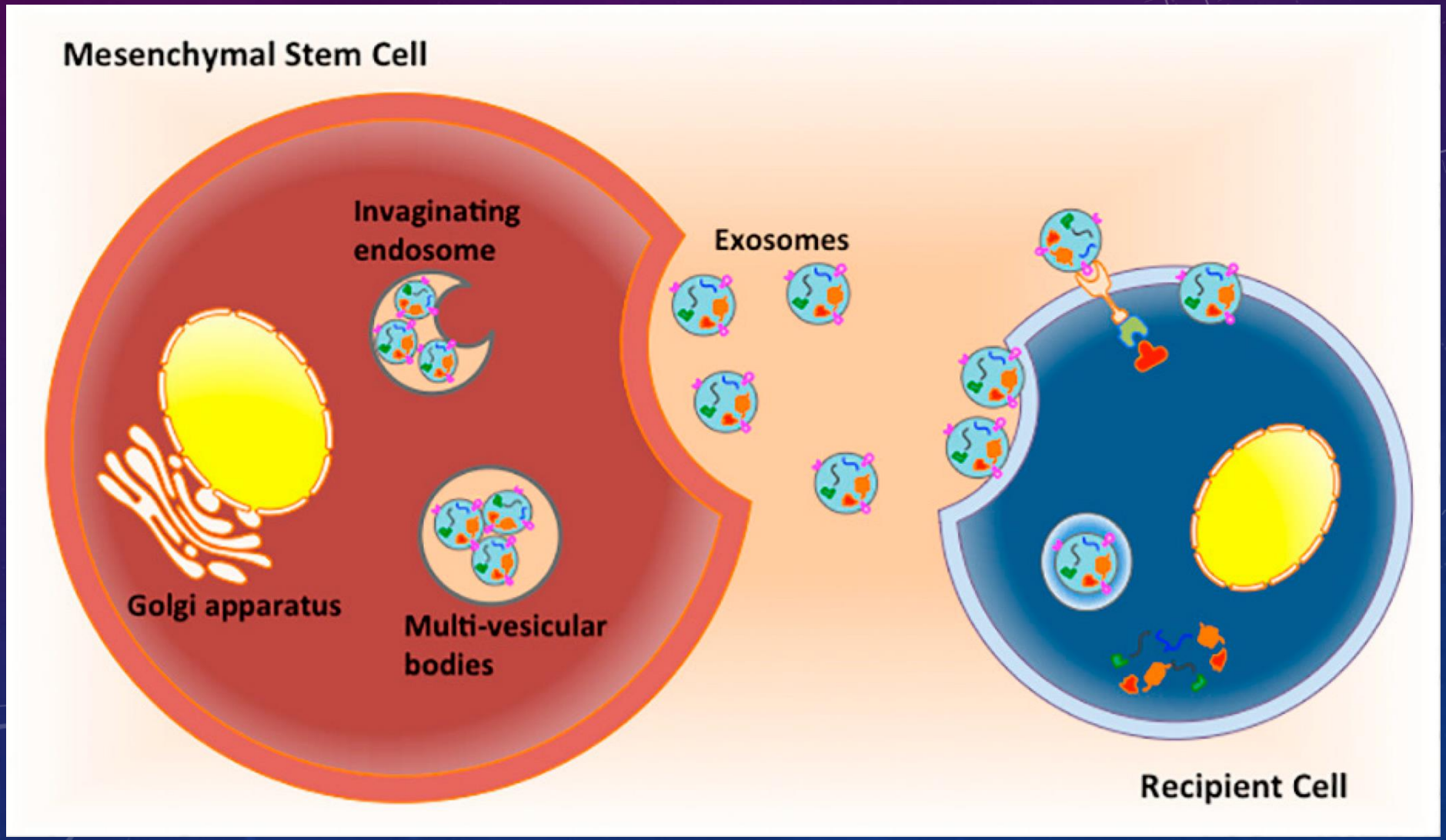
# EXOSOMES CONTAIN PHOSPHOLIPID BILYAER

- This phospholipid membrane protects the exosomes from toxins, oxidants, and enzymes
- Easily absorbed into other cells

# Exosomes contain no MHC complex (Secret handshake)

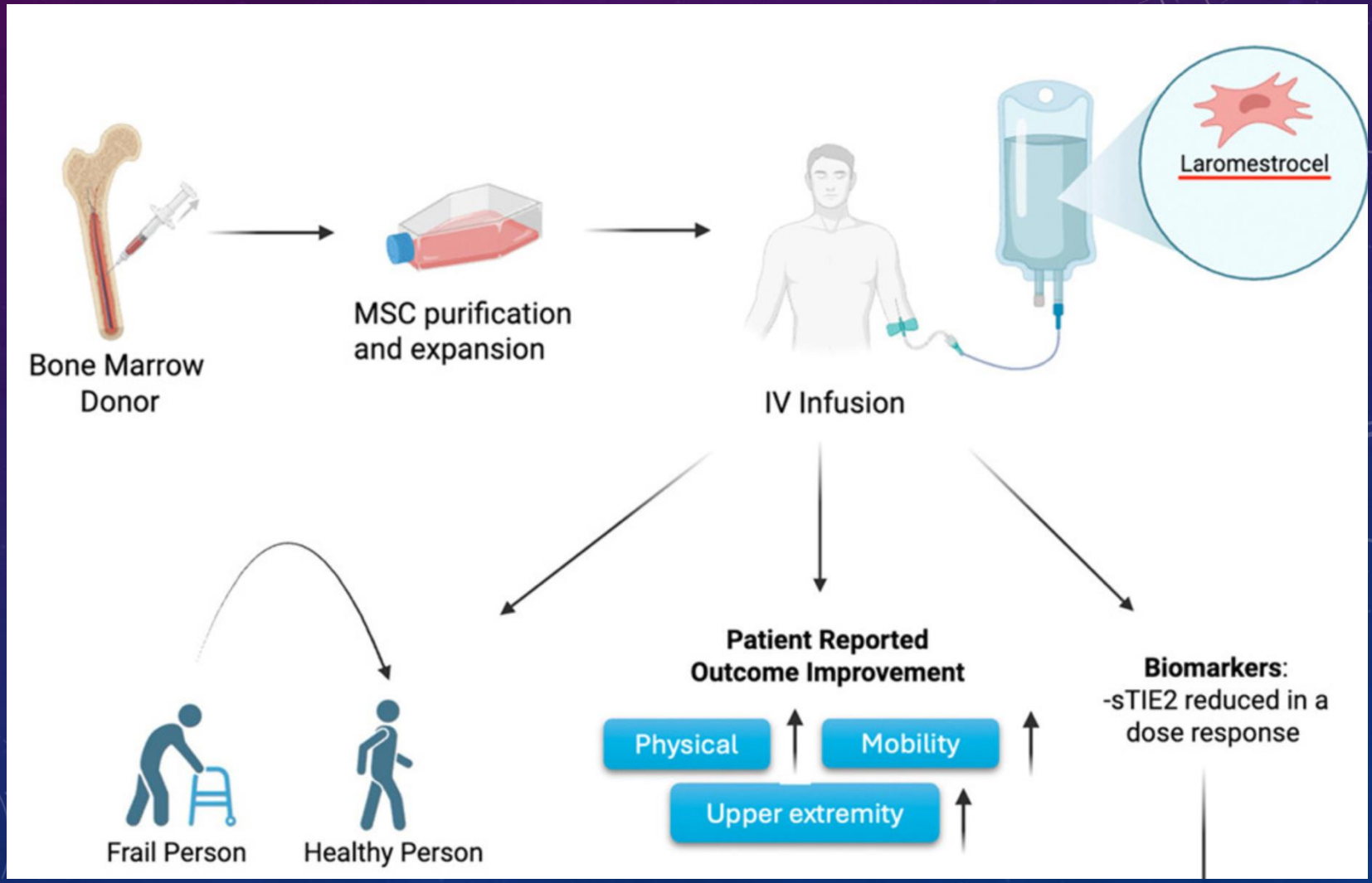


# STEM CELLS VS EXOSOMES



# RANDOMIZED PHASE 2 TRIAL ON MSC- 2026

RUIZ JG, OLIVA AA JR, RAMDAS KN, ET AL. RANDOMIZED PHASE 2B DOSE-ESCALATION TRIAL OF STEM CELL THERAPY WITH LAROMESTROCEL FOR AGING FRAILTY. *CELL STEM CELL*. 2026;33(3):393-404.E4. DOI:10.1016/J.STEM.2026.01.017. PMID: 41747733



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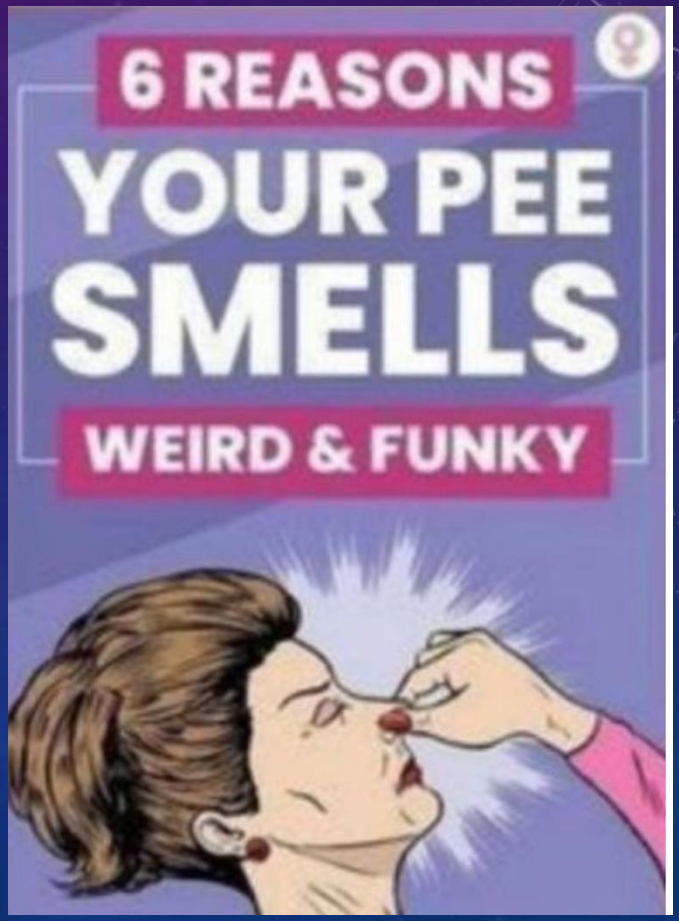
- 70 to 85 years old
- Single IV dose of placebo or 25, 50 100 or 200 million Bone Marrow Derived MSC

- The 200-million-cell group improved the 6-minute walk test by 63.4 meters compared with placebo
- It did not demonstrate lifespan extension.

# 6 REASONS WHY EXOSOMES ARE ATTRACTIVE IN AGING

LING M, TANG C, YANG X, ET AL. **INTEGRATED METABOLOMICS AND PHOSPHOPROTEOMICS REVEAL THE PROTECTIVE ROLE OF EXOSOMES FROM HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS IN NATURALLY AGING MOUSE LIVERS.** *EXP CELL RES.* 2023;427(1):113566.

- Exosomes modulate pathways associated with 6 Hallmarks of Aging.
- They don't reverse it



# #1 EXOSOMES ARE ATTRACTIVE IN AGING

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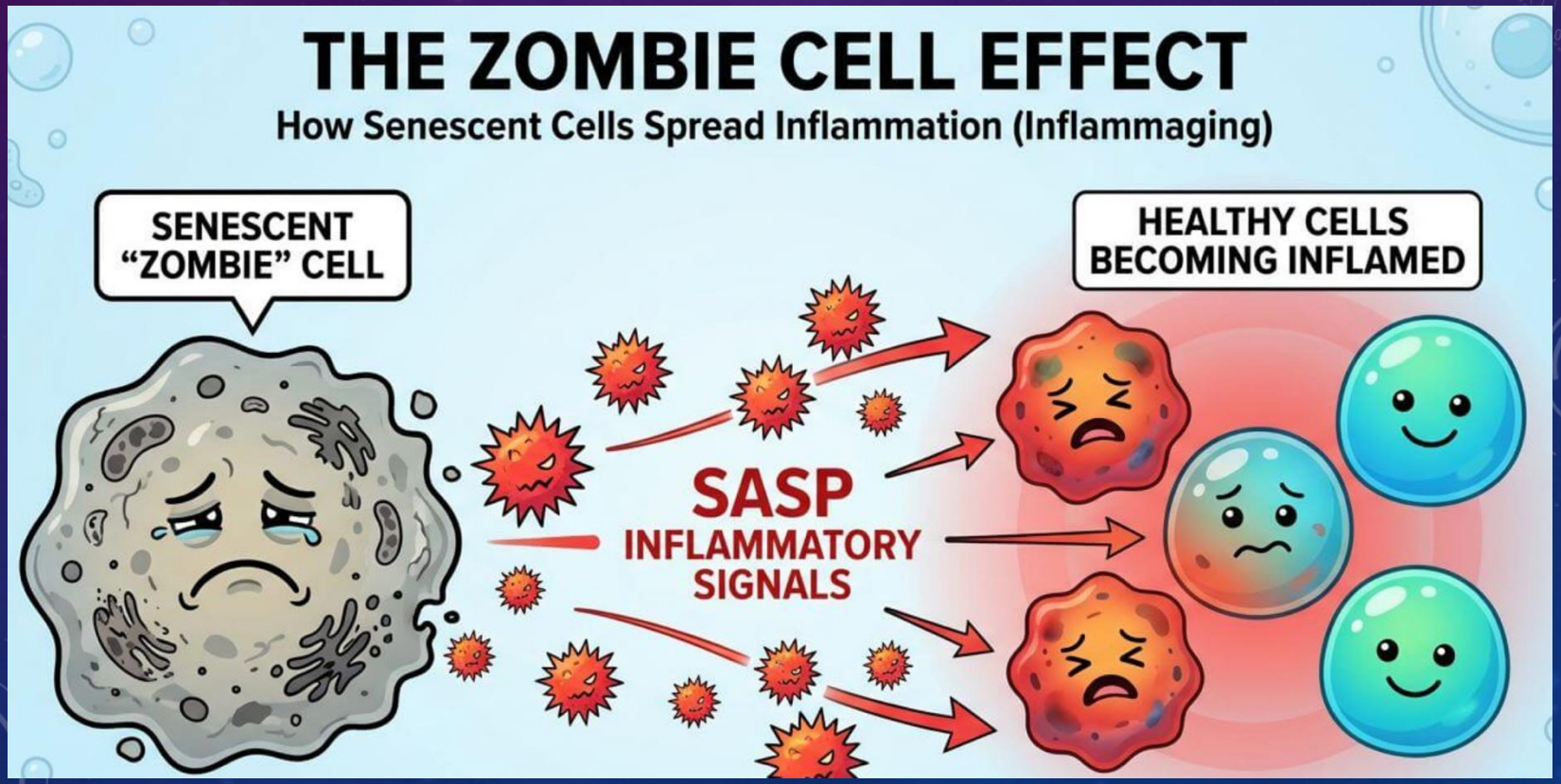
Decrease in SASP (senescent associated secretory phenotypes) cytokines



# #2 EXOSOMES ARE ATTRACTIVE IN AGING

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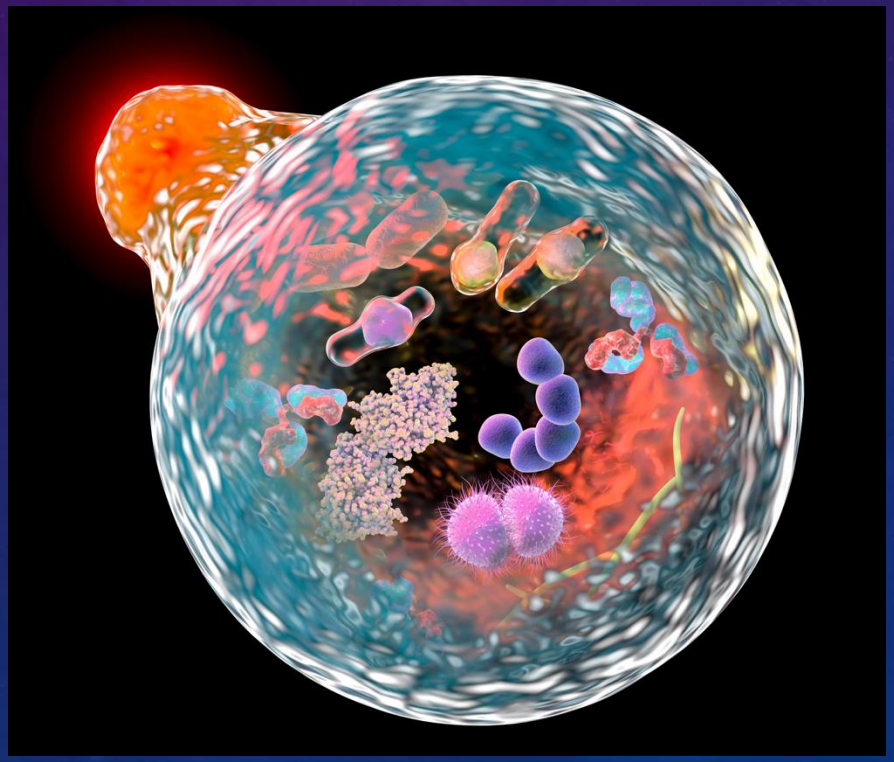
Increase in Autophagy PI3K/AKT/mTOR pathway

Breakdown and recycling old or damaged cells



# #3 EXOSOMES ARE ATTRACTIVE IN AGING

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Decrease in chronic inflammation

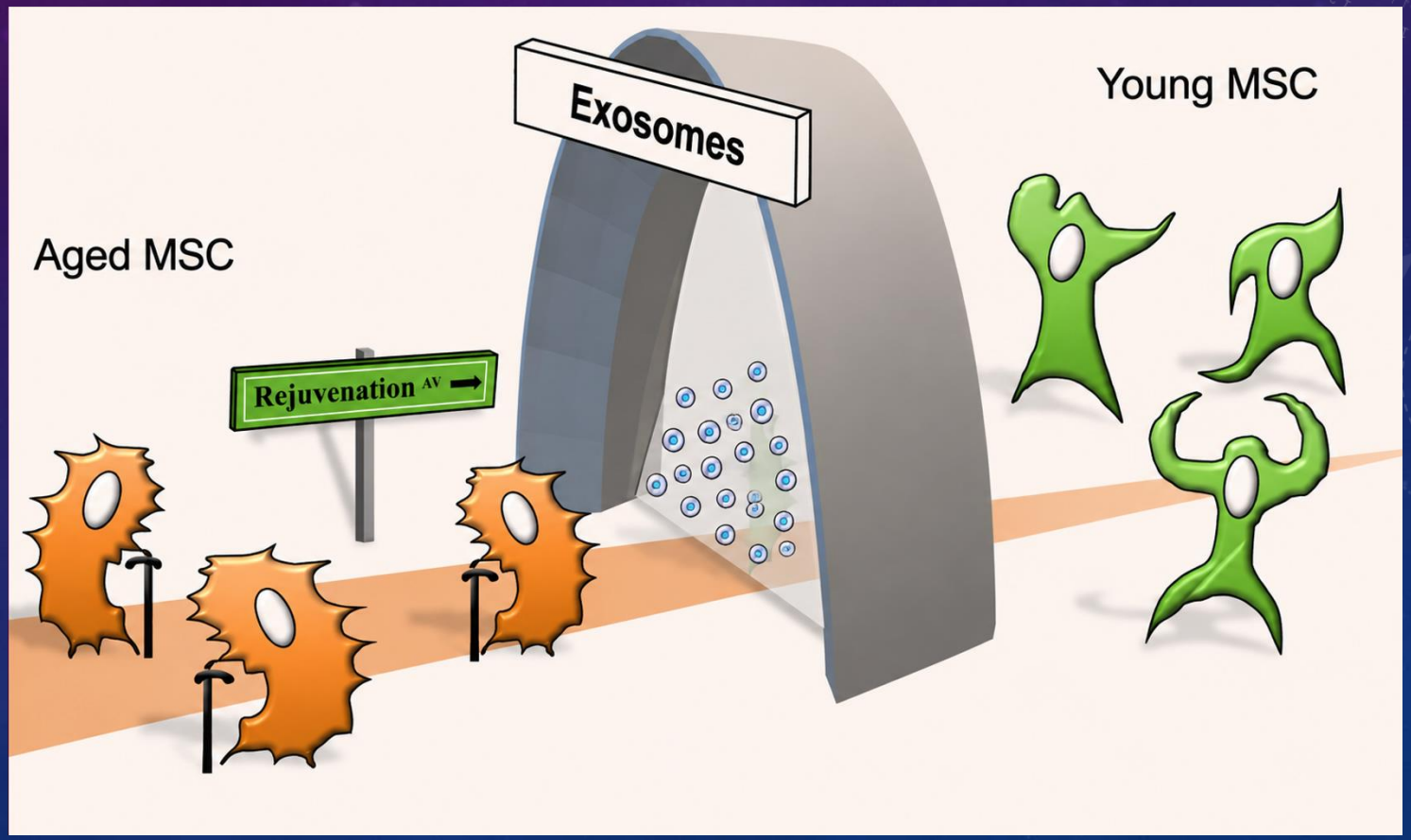
Reducing IL-6, TNF and IL-1 B

# #4 EXOSOMES ARE ATTRACTIVE IN AGING

LING M, TANG C, YANG X, ET AL. **INTEGRATED METABOLOMICS AND PHOSPHOPROTEOMICS REVEAL THE PROTECTIVE ROLE OF EXOSOMES FROM HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS IN NATURALLY AGING MOUSE LIVERS.** *EXP CELL RES.* 2023;427(1):113566.

Restore Stem Cell Exhaustion

Improve the function of existing aged tissue stem cells



# #5 EXOSOMES ARE ATTRACTIVE IN AGING

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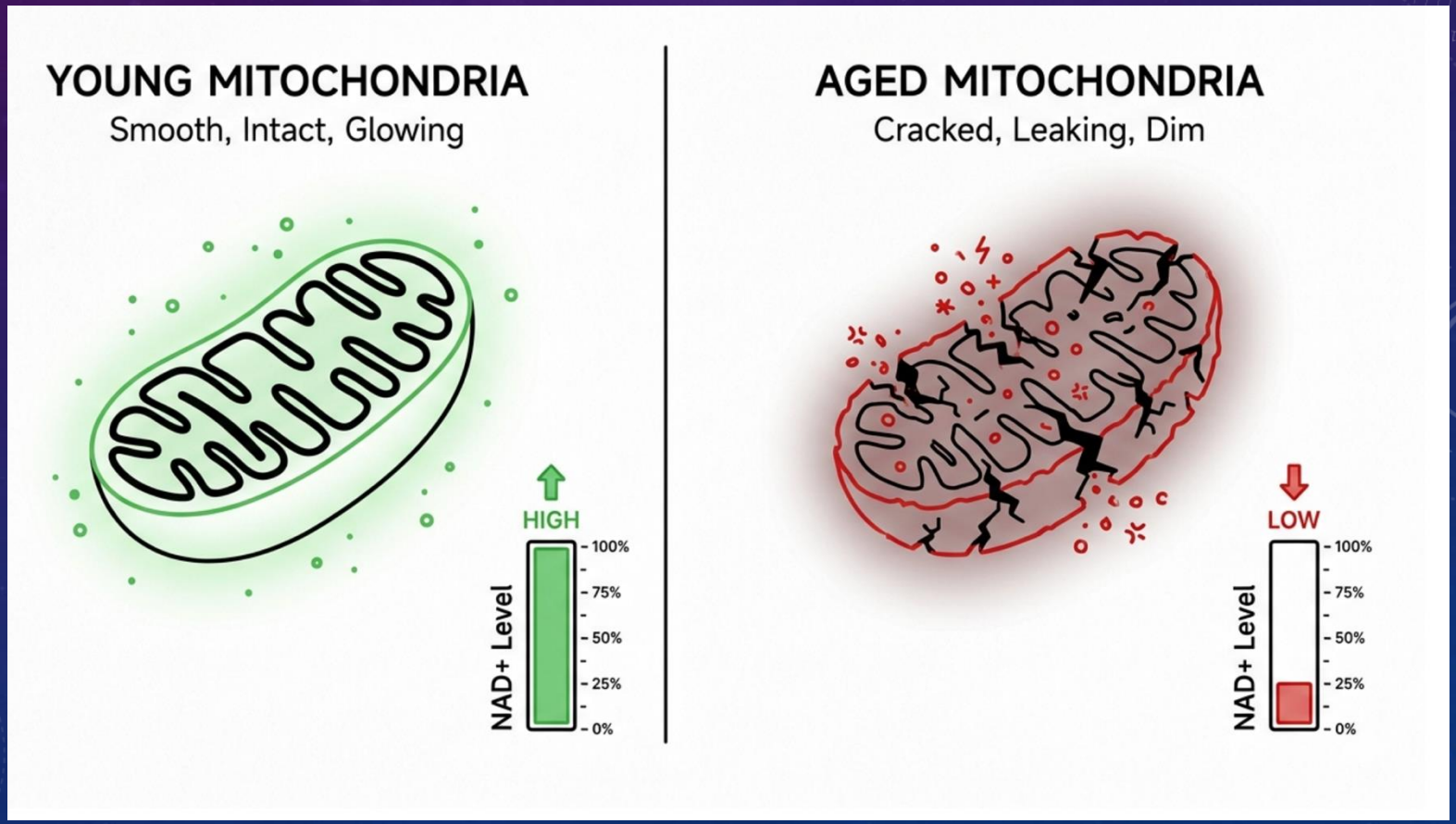
## Decrease Mitochondria Dysfunction

### Helps with Mitochondria repair and increase ATP production



# #6 EXOSOMES ARE ATTRACTIVE IN AGING

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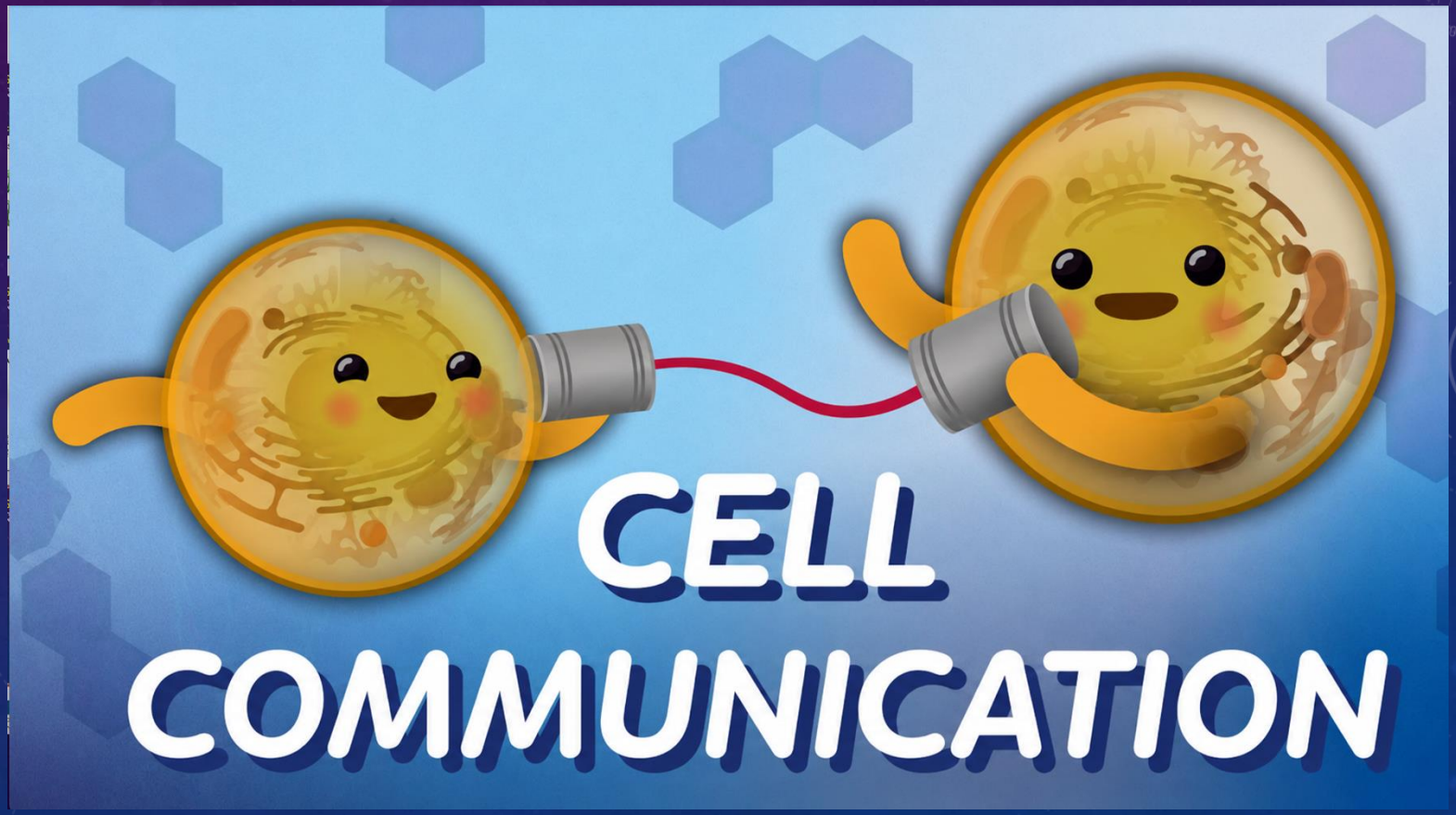
Improve Cell to Cell Communication

Restoring healthier signaling.



# CAN YOU REVERSE LIVER FIBROSIS WITH EXOSOMES?

J Extracell Vesicles. 2018 Apr 17;7(1):1461505. doi: 10.1080/20013078.2018.1461505. eCollection 2018.

## Therapeutic effects of serum extracellular vesicles in liver fibrosis

Li Chen [1], Ruju Chen [1], Sherri Kemper [1], Min Cong [2], Hong You [2], David R Brigstock [1 3]

Affiliations + expand

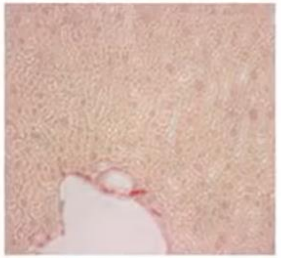
PMID: 29696080 PMCID: PMC5912192 DOI: 10.1080/20013078.2018.1461505

# Identify signatures for fibrosis in circulating exosomes

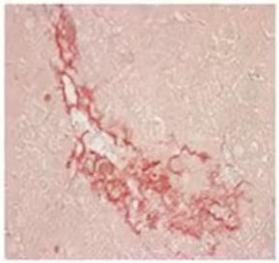
- 5 wk $CCl_4$ fibrosis model in mice
- Assess 940 microRNAs in circulating exosomes – *unbiased* analysis
- Confirm changes for selected miRs by RT-PCR

Collagen

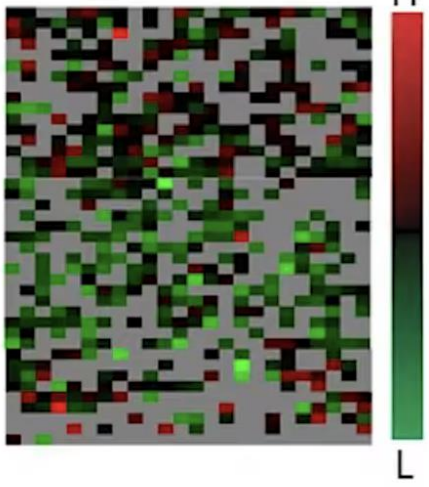
Ctrl



$CCl_4$

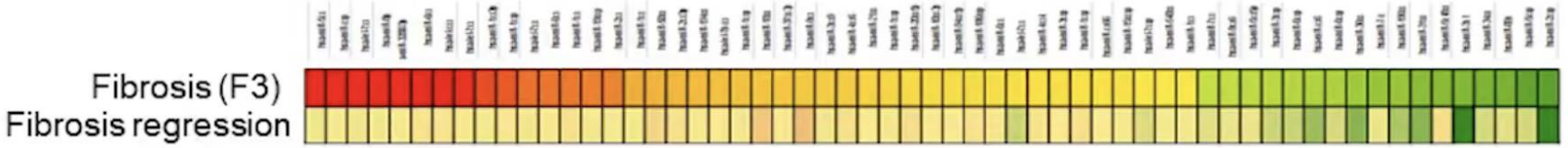


Heating map




| Upregulated | Downregulated |
|---|---|
| 1906 | **214** |
| 677-3p | 23b-3p |
| 541-3p | 106a-3p |
| 125b-1-3p | 200b-5p |
| 500-5p | 532-5p |
| 466j | 34c-3p |
| 544-3p | 151-3p |
| 1a-2-5p | 653-5p |
| 1194 | 687 |
| 700 | 483-5p |

- Clinical samples – Fibrosis progression / regression in HBV patients.

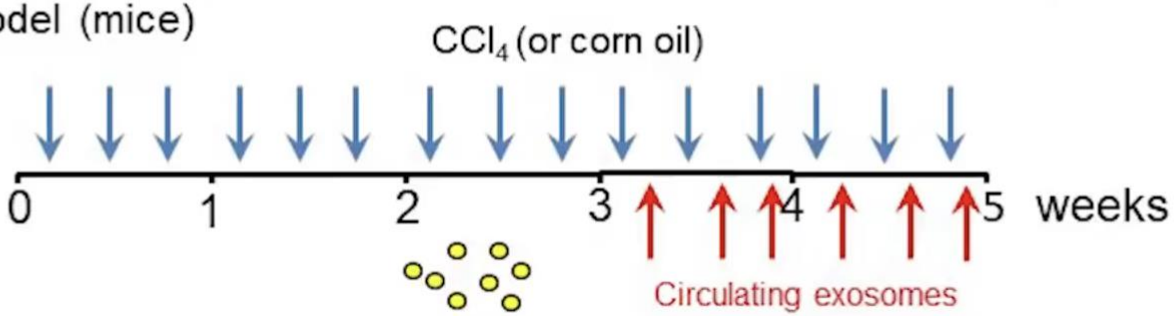



**Profiling of circulating exosomal miRNAs have potential for diagnosis of liver fibrosis.**

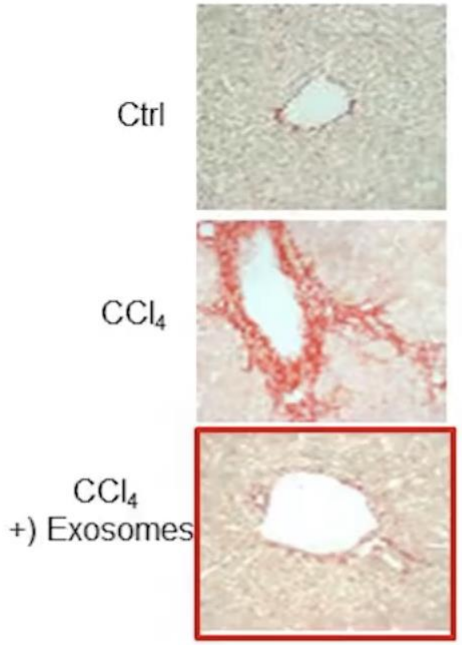
The reduction of miRs from baseline levels in fibrotic mice represent the loss of miRs that serve a protective function in healthy mice.

# Circulating exosomes are anti-fibrotic (chronic $CCl_4$ administration)

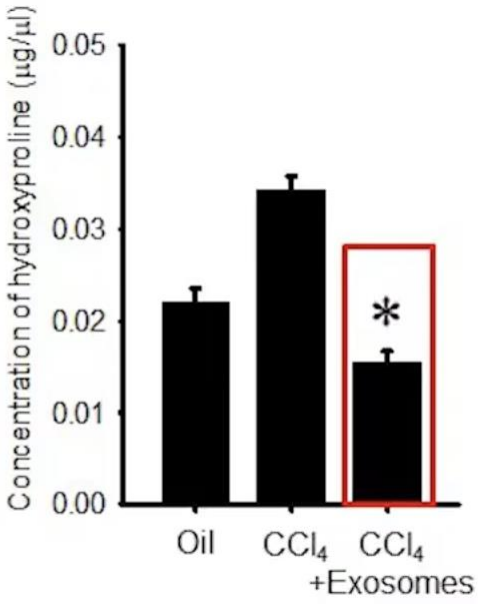
Experimental fibrosis model (mice)

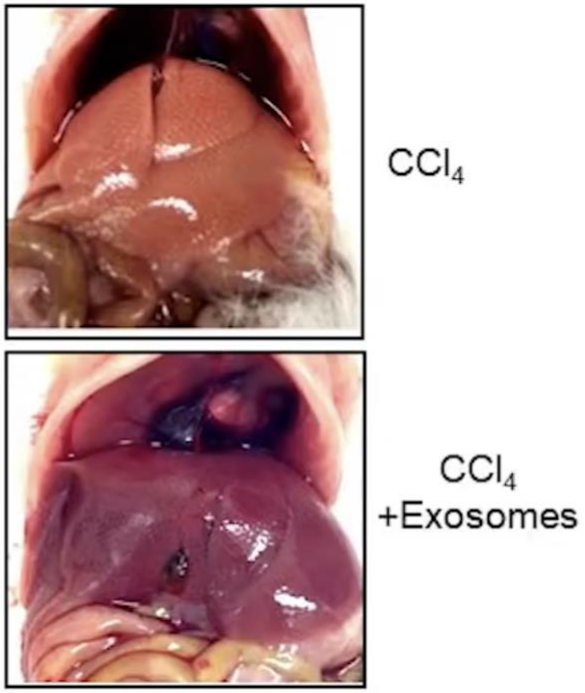



Sirius Red




Hydroxyproline assay

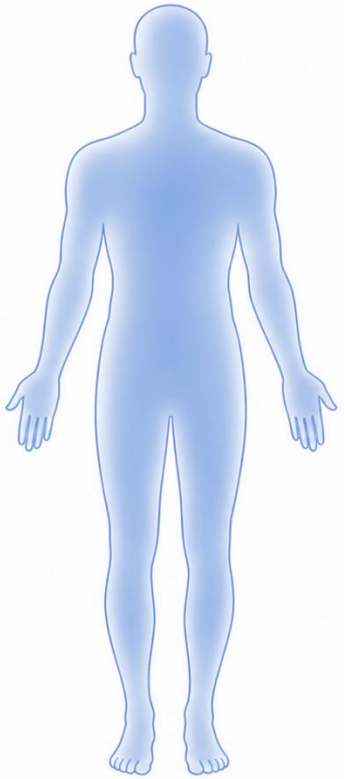


# REVERSING LIVER FIBROSIS IN MICE WITH HUMAN EXOSOMES

- Exosomes from normal healthy individuals are inherently anti-fibrogenic and contain microRNAs that have therapeutic actions in injured hepatocytes (produces fibrosis)

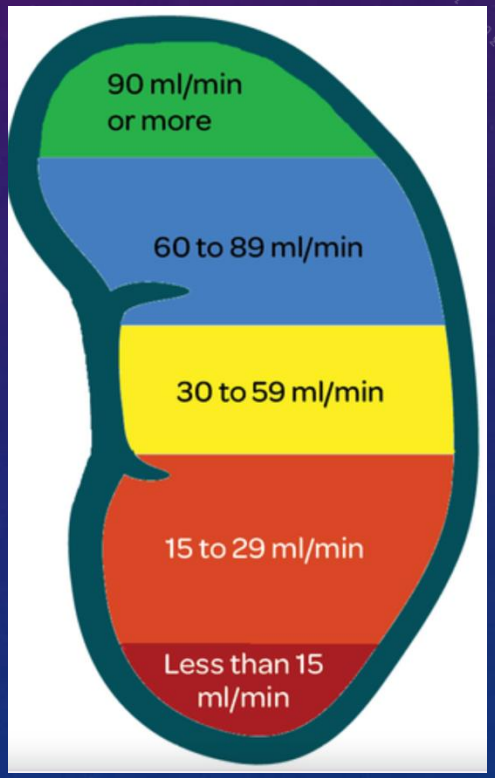
- Exosomes from healthy human subjects and contained higher miR-34c, -151-3p, -483-5p or -532-5p than exosomes from hepatic fibrosis patients.
- Chen L, et. al. Therapeutic effects of serum extracellular vesicles in liver fibrosis. J Extracell Vesicles. 2018 Apr 17;7(1):1461505.



# EXOSOMES FOR CHRONIC KIDNEY DISEASE

NASSAR W, ET AL. UMBILICAL CORD MESENCHYMAL STEM CELLS DERIVED EXTRACELLULAR VESICLES CAN SAFELY AMELIORATE THE PROGRESSION OF CHRONIC KIDNEY DISEASES. *BIOMATER RES.* 2016;20:21.

- 40 patients with stage III–IV CKD were randomized: treatment or placebo
- Exosomes 100 ug/kg
- Dose #1 – IV
- 1 week later
- Dose #2 – Intra-arterial of renal arteries



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## Kidney function results

| Parameter | Baseline | 12 weeks |
|---|---|---|
| eGFR | 31.05 ± 4.51 | 47.25 ± 5.14 mL/min |
| Creatinine | 3.44 ± 0.49 | 2.19 ± 0.25 mg/dL |

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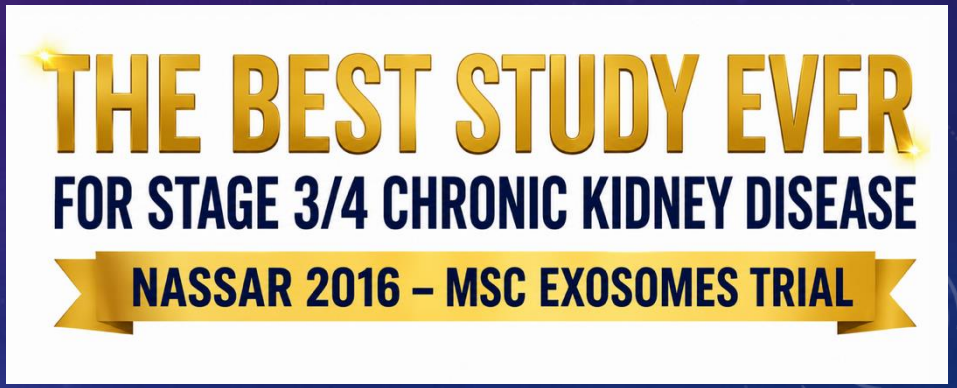
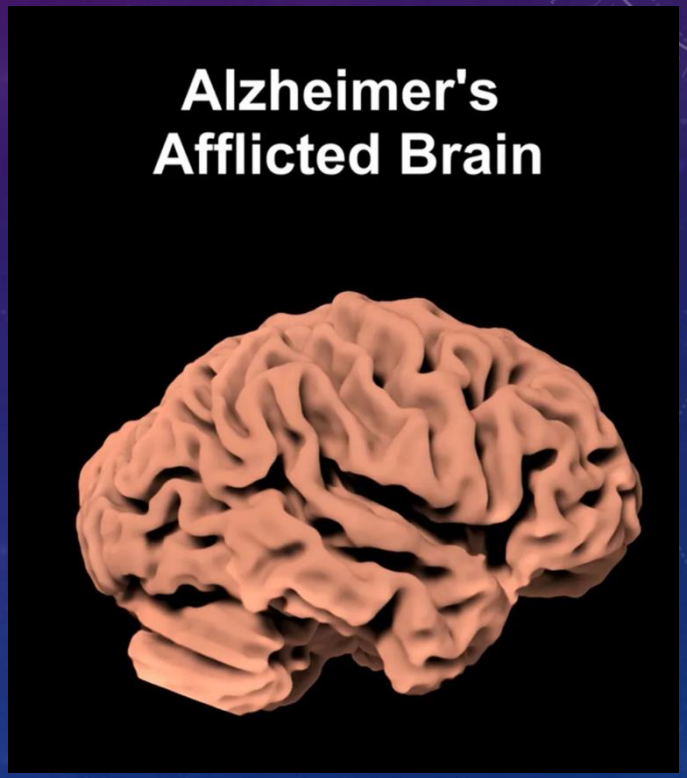
- Over 12 months, the treated patients showed improvements in **eGFR, serum creatinine, BUN and urine albumin/creatinine ratio**.
- **↓ TNF-α and ↑ IL-10/TGF-β1**, suggesting an immunomodulatory effect



# EXOSOMES FOR ALZHEIMER

XIE X, ET. AL., CLINICAL SAFETY AND EFFICACY OF ALLOGENIC HUMAN ADIPOSE MESENCHYMAL STROMAL CELLS-DERIVED EXOSOMES IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: A PHASE I/II CLINICAL TRIAL. GEN PSYCHIATR. 2023 OCT 11;36(5):E101143. DOI: 10.1136/GPSYCH-2023-101143.

- Phase I/II human trial studied allogeneic adipose-MSC-derived exosomes in patients with mild-to-moderate Alzheimer's disease.
- Intranasally twice weekly for 12 weeks



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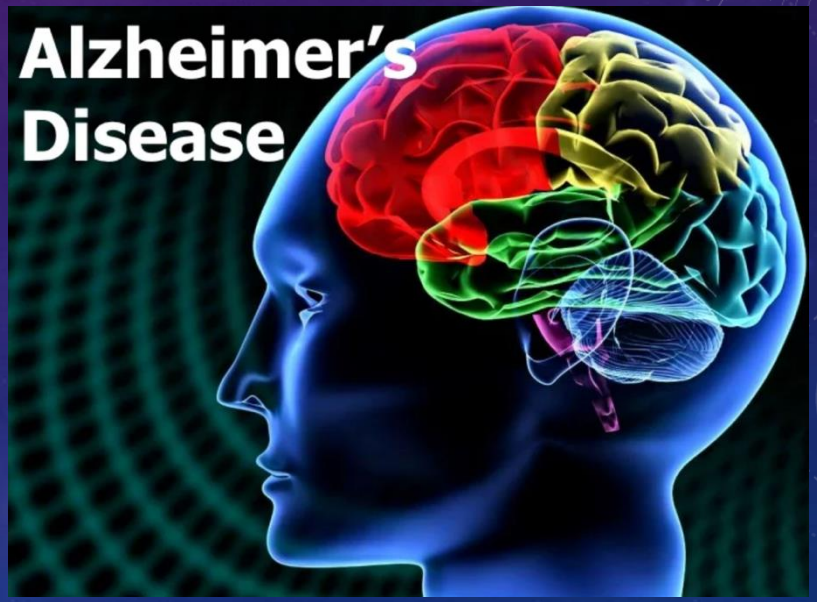
- N = 9
- Low dose N= 3 (2 x $10^8$)
- Med dose N= 3 (4 x $10^8$)
- High dose N=3 (8 x $10^8$)



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- Medium dose showed signals of improvement in ADAS-cog and MoCA
- N of 3 is too small to determine efficacy
- It was safe and well tolerated

# EXOSOMES FOR OSTEOARTHRITIS

BOLANDNAZAR NS, ET AL. SAFETY AND EFFICACY OF PLACENTAL MESENCHYMAL STROMAL CELLS-DERIVED EXTRACELLULAR VESICLES IN KNEE OSTEOARTHRITIS: A RANDOMIZED, TRIPLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL. *BMC MUSCULOSKELET DISORD.* 2024;25:856.

- Randomized, triple-blind, placebo-controlled clinical trial.
- N =29 (28 women)
- Mean age 55 years old
- One knee randomly assigned to Exosomes, other knee saline

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- One intra articular injection
- 5 ml of $3.5 \times 10^{10}$ particles
- Follow up at 2 and 6 months

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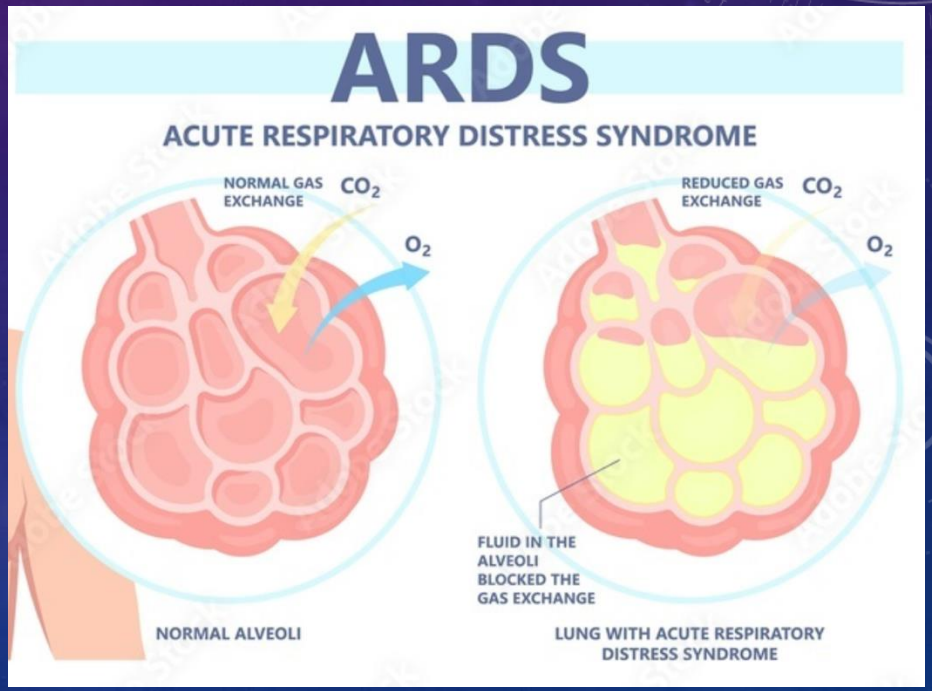
- Safe and well tolerated
- No significant improvement vs placebo in pain, WOMAC, function, or MRI cartilage outcomes

- Why did it fail?
- One injection vs multiple injection
- Small study
- Other studies may show a benefit with Exosomes for osteoarthritis.

# 2024 EXOSOMES FOR COVID-19/ARDS TRIAL

ZAMANIAN MH, ET AL. HUMAN PLACENTAL MESENCHYMAL STROMAL CELL-DERIVED SMALL EXTRACELLULAR VESICLES AS A TREATMENT FOR SEVERE COVID-19: A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL. *J EXTRACELL VESICLES.* 2024;13(7):E12492.

- Double blind randomized controlled trial in Iran
- N = 45
- 21 in Treatment group with Exosomes plus standard care
- 24 in Control group with placebo plus standard care



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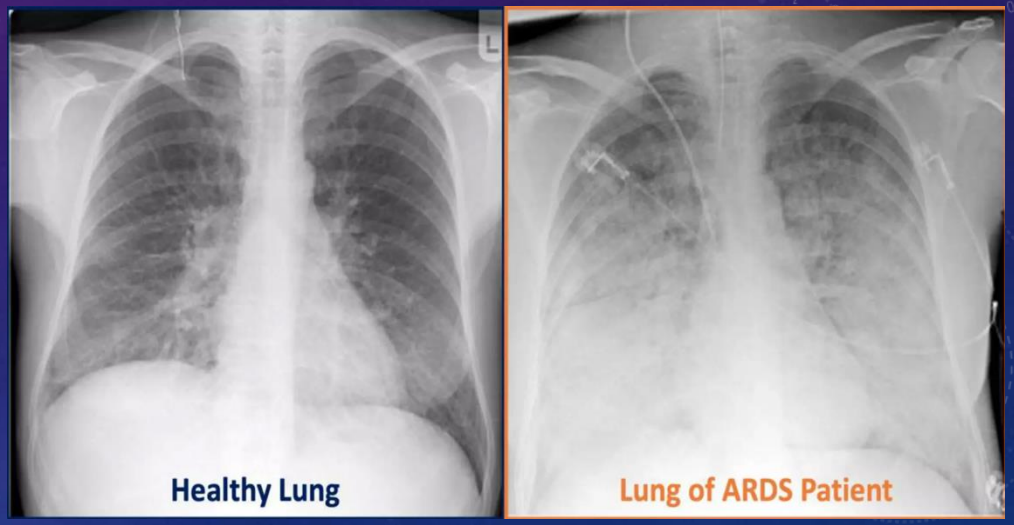
- Human placenta MSC Exosomes
- 1.5–2 × $10^9$ particles/kg IV
- 2 days of IV Exosomes over 30 minutes



# 2025 EXOSOMES FOR COVID-19/ARDS TRIAL

ZAMANIAN MH, ET AL. HUMAN PLACENTAL MESENCHYMAL STROMAL CELL-DERIVED SMALL EXTRACELLULAR VESICLES AS A TREATMENT FOR SEVERE COVID-19: A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL. *J EXTRACELL VESICLES.* 2024;13(7):E12492.

| OUTCOME | EXOSOME GROUP (n = 21) | PLACEBO GROUP (n = 24) |
|---|---|---|
| Deaths | 4/21 (19.0%) | 13/24 (54.2%) |
| Survival | 81.0% | 45.8% |

P = 0.015 Statistically significant

# 2025 EXOSOMES FOR COVID-19/ARDS TRIAL

ZAMANIAN MH, ET AL. HUMAN PLACENTAL MESENCHYMAL STROMAL CELL-DERIVED SMALL EXTRACELLULAR VESICLES AS A TREATMENT FOR SEVERE COVID-19: A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL. *J EXTRACELL VESICLES.* 2024;13(7):E12492.

| Group | Mean Time to Death (Days) Among Patients Who Died | Difference (Exosomes – Control) |
|---|---|---|
| Exosomes (n = 21) | 28 days | +17 days |
| Control / Placebo (n = 24) | 11 days | |

**Statistical Result: P < .001**

*Values represent mean time to death among patients who died.*

# EXOSOMES FROM HUMAN MESENCHYMAL STEM CELLS IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY

- IV Exosomes for women with Premature Ovarian Failure and hopefully will restore their menstruation
- N = 9

**ClinicalTrials.gov ID** NCT06072794

**Sponsor** Vitti Labs, LLC

**Information provided by** Vitti Labs, LLC (Responsible Party)

**Last Update Posted** 2024-09-19

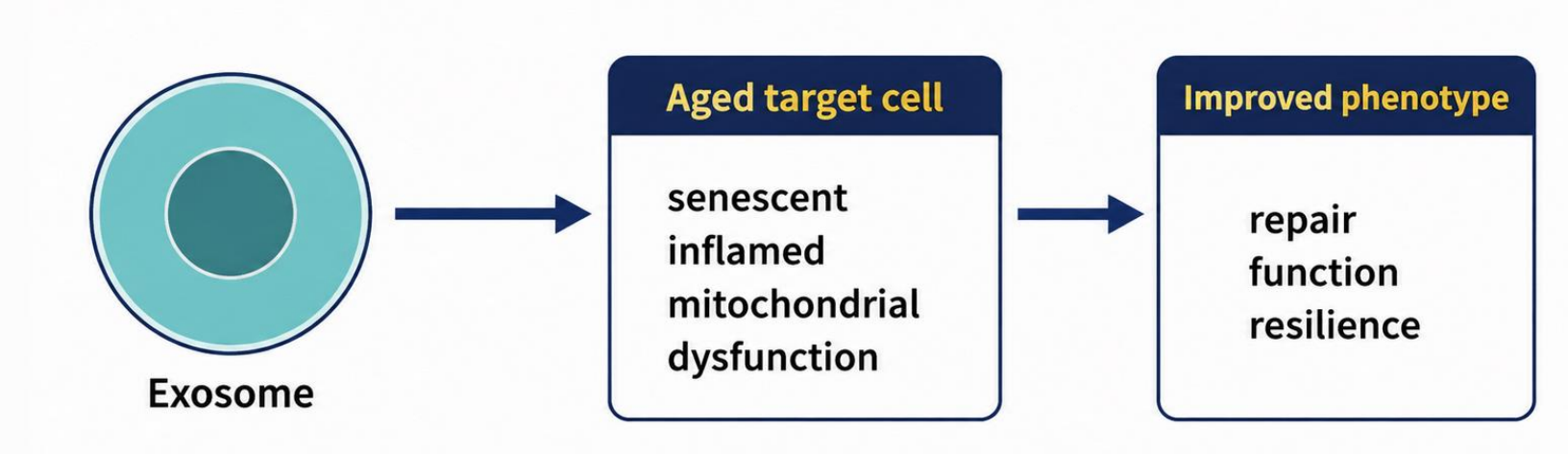
# FUTURE OR ONGOING TRIALS WITH EXOSOMES

| Study / Location | Indication / Population | NCT Number (ClinicalTrials.gov) |
|---|---|---|
| **MSC Exosome Therapy for COVID-19 ARDS (EXO-COV)** Shenzhen, China | Severe COVID-19 with ARDS (Adults) | **NCT04313647** |
| **Exosomes for Acute Respiratory Distress Syndrome (EXOD-ARDS)** Tainan, Taiwan | Acute Respiratory Distress Syndrome (ARDS) (Adults) | **NCT05029430** |
| **Exosomes in Sepsis-Associated ARDS** Guangzhou, China | Sepsis-Associated ARDS (Adults) | **NCT05413098** |
| **hUCMSC Exosomes in COVID-19 Pneumonia (Phase II)** Cleveland, Ohio, USA | Hospitalized COVID-19 Pneumonia (Adults) | **NCT04602104** |
| **MSC Exosomes for Lung Fibrosis (Post-ARDS)** Shanghai, China | Post-ARDS Pulmonary Fibrosis (Adults) | **NCT05894339** |
| **Inhaled Exosomes for COPD (Phase I/II)** Miami, Florida, USA | Chronic Obstructive Pulmonary Disease (COPD) (Adults) | **NCT05357681** |

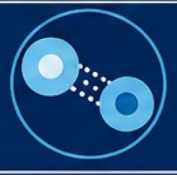
# FUTURE OR ONGOING TRIALS WITH EXOSOMES

| Indication / Condition | Exosome Therapy | Planned Sample Size (N) | NCT Number (ClinicalTrials.gov) |
|---|---|---|---|
| Hair Loss (Androgenetic Alopecia) | Umbilical Cord MSC (UC-MSC) Exosomes (topical) | 50 (Registry Trial) | NCT07203599 (Recruiting) |
| Skin Rejuvenation (Facial Aging) | Laser + Topical UC-MSC Exosomes | ~20 (Planned) | NCT07281690 (Recruiting) |
| Endometrial Repair (Intrauterine Adhesions / Endometrial Injury) | Intrauterine UC-MSC Exosomes (after hysteroscopic surgery) | 60 (Planned) | NCT07416578 (Active, Not Recruiting) |

# HOW EXOSOMES MAY IMPROVE HEALTHSPAN



# EXOSOMES ADDRESSING 6 OF 12 HALLMARKS OF AGING

| Hallmark of Aging | Key Benefit |
| --- | --- |
| 1. Cellular Senescence | Reduces senescence and chronic inflammation |
| 2. Mitochondrial Dysfunction | Increases ATP production and cellular energy |
| 3. Chronic Inflammation | Reduces chronic inflammation and tissue damage |
| 4. Impaired Autophagy | Improves autophagy and cellular cleanup |
| 5. Stem Cell Exhaustion | Restores tissue regeneration and repair capacity |
|  6. Altered Intercellular Communication | Improves tissue function and systemic homeostasis |