EXOSOMES: THE NEW FRONTIER IN STEM CELL TECHNOLOGY

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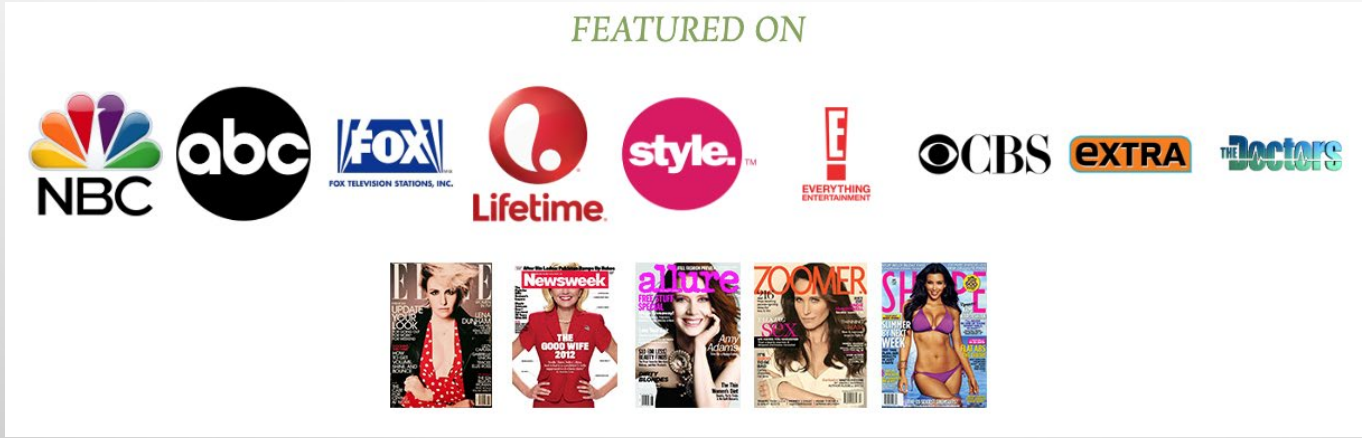

Associate Clinical Professor - UCLA

ABD AMERICAN BOARD OF DERMATOLOGY

AAD Fellow American Academy of Dermatology Excellence in Dermatology™

ASDS American Society for Dermatologic Surgery

ASLMS AMERICAN SOCIETY FOR LASER MEDICINE & SURGERY, Inc.

PAS PREMIERE AESTHETIC SOLUTIONS

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- EXOCELBIO: ADVISORY BOARD
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- AMP: ADVISORY BOARD

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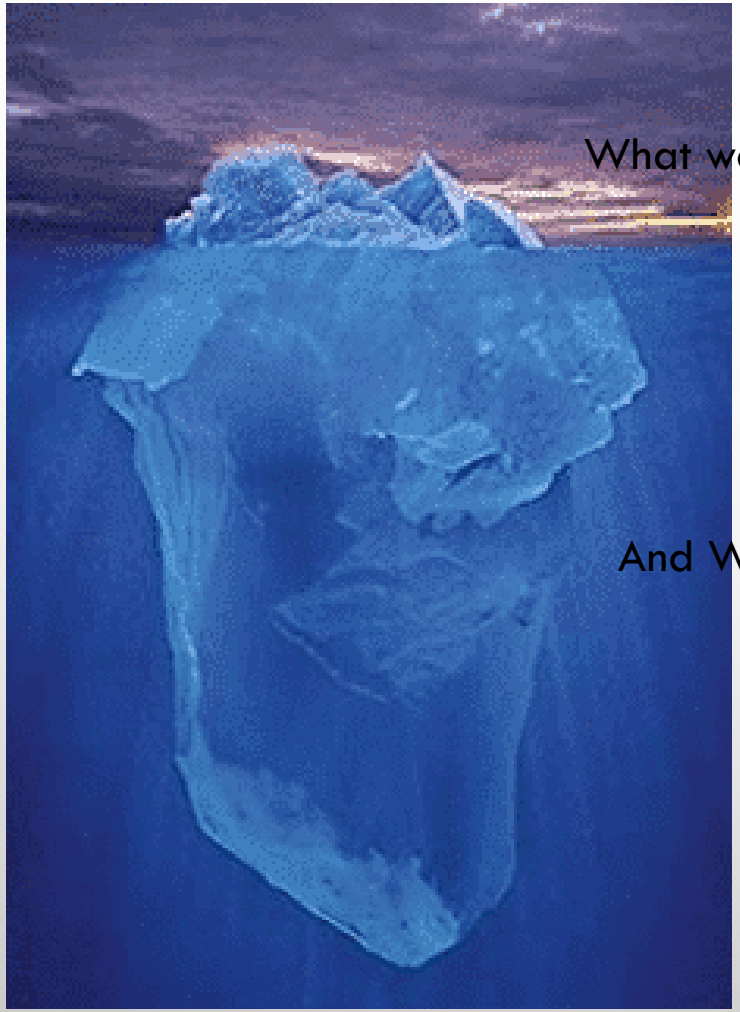

What we know about Exosomes

And What is yet to be discovered

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EXOSOMES AND SIBLINGS FOUND IN PLANTS

- JU ET AL. GRAPE EXOSOME-LIKE NANOPARTICLES INDUCE INTESTINAL STEM CELLS AND PROTECT MICE FROM DSS-INDUCED COLITIS. *MOL THER*. 2013 JUL21(7): 1345-57
  - GRAPE EXOSOMES PROTECT AGAINST DEXTRAN SULFATE SODIUM INDUCED COLITIS
  - GELN MODULATE INTESTINAL RENEWAL PROCESS AND REMODELING OF IT IN RESPONSE TO PATHOLOGICAL TRIGGERS

STEM CELL SOURCES

plant	adipose	neonatal	Mesenchymal bone marrow
• Communicate a different language, more AOX	• Highly inflammatory • Not medically monitored	• Inferior cell source • inflammatory	• Non-inflammatory • Medically monitored, dense, effective

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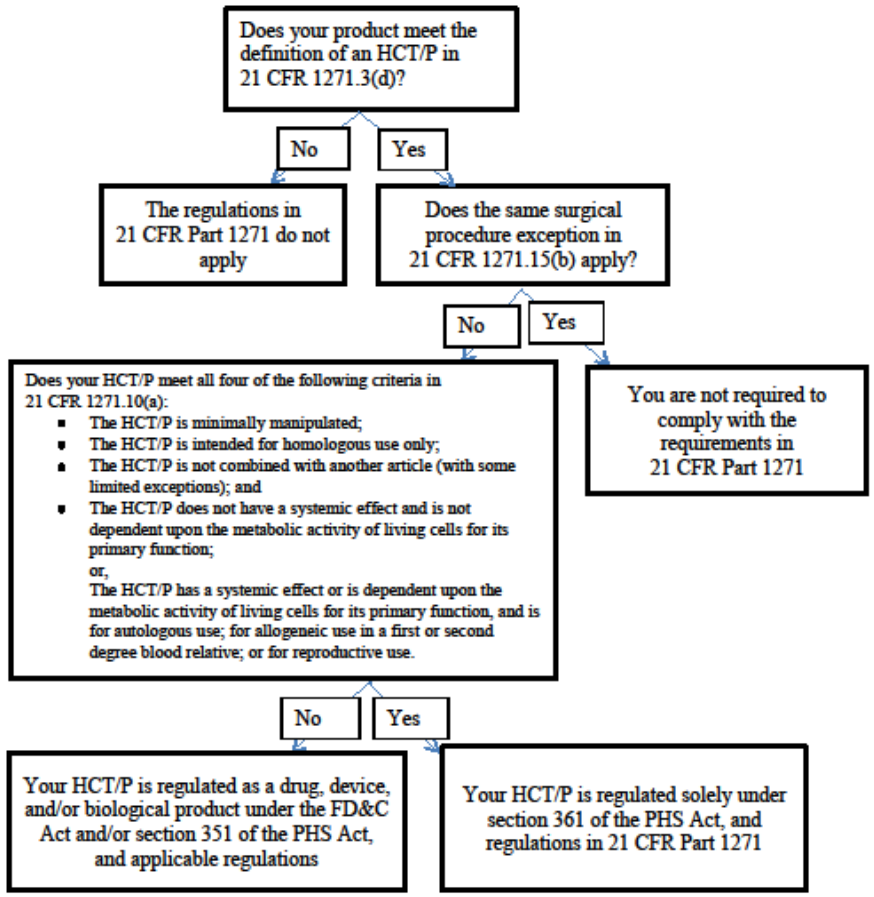
REGULATORY CONSIDERATIONS FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS: MINIMAL MANIPULATION AND HOMOLOGOUS USE: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF

Contains Nonbinding Recommendations

Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(b) and 1271.10(a)



STEM CELLS VS EXOSOMES

STEM CELLS

- LIVING CELLS
- MUST BE USED FRESH/CAREFULLY PRESERVED
- FOUND IN CERTAIN TISSUES
- PRODUCE “INFORMATION”
- LIMITED THERAPEUTIC POTENTIAL

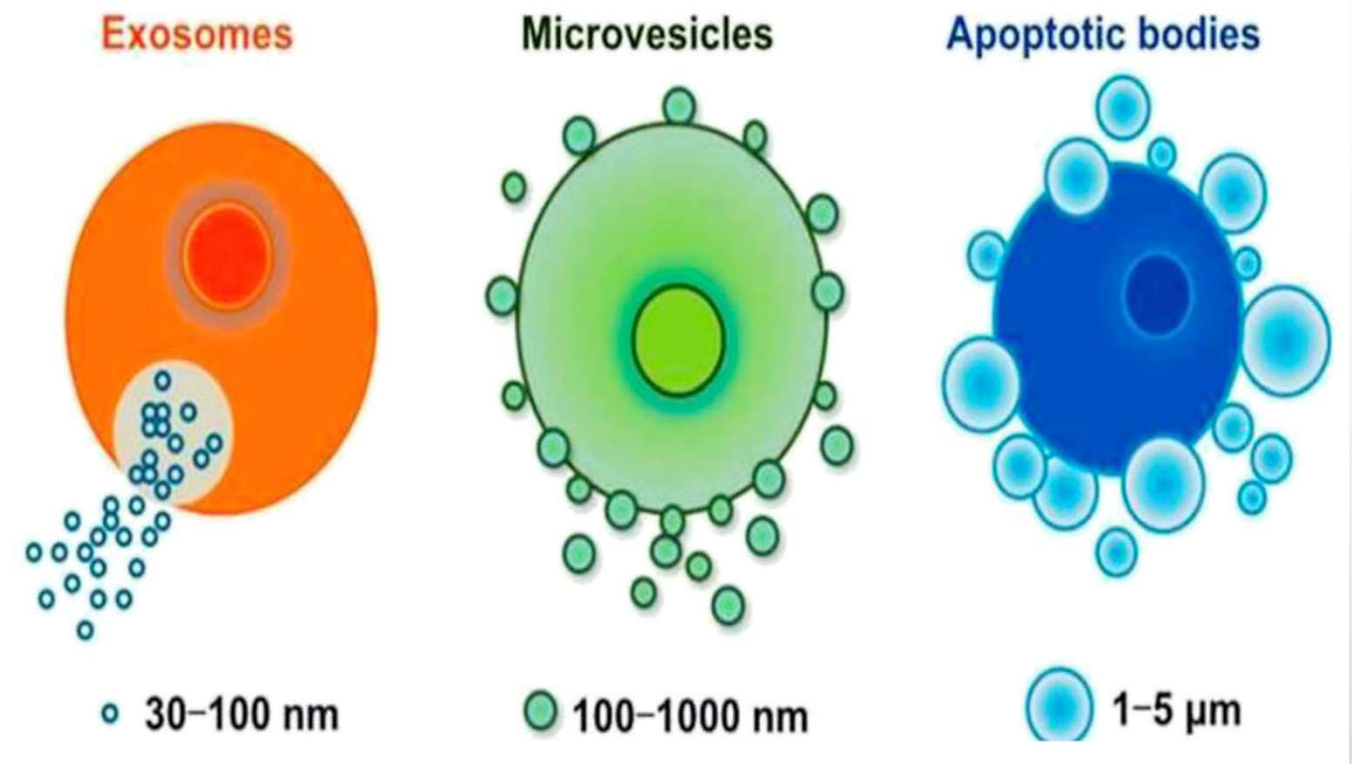
EXOSOMES

- ENDOGENOUS LIPID NANOPARTICLES CAN BE STERILIZED, STORED AND TRANSPORTED
- FOUND IN EVERY BODILY FLUID
- CARRY “INFORMATION”
- VAST THERAPEUTIC POTENTIAL
- NON-IMMUNOGENIC

SO WHAT IS AN EXOSOME AND WHAT DOES IT DO (BIOLOGICAL FUNCTIONS): MASSIVE BOOST IN REGENERATIVE POWER.

- EXTRACELLULAR VESICLES PRODUCED BY NEARLY ALL CELL TYPES, PRESENT IN ALL BIOLOGICAL FLUIDS
- PREVIOUSLY CALLED DEBRIS, PAPERS STARTED 1983, BUT "PLATELET DUST" AS EARLY AS 1967
- EXOSOMES ARE EXPELLED FROM CELL THROUGH EXOCYTOSIS, THEN TAKEN UP BY RECIPIENT CELL TO INDUCE VARIOUS BIOLOGICAL RESPONSES
- MANY FUNCTIONS, SOME NOT EVEN KNOWN YET:
  - ERADICATION OF OBSOLETE MOLECULES
  - ANGIOGENESIS
  - COAGULATION
  - DISSEMINATION OF ONOCEGENES FROM TUMOR CELLS?(CONCERN)
- RELEASED FROM STEM CELLS, RESPONSIBLE FOR CELL TO CELL COMMUNICATION BETWEEN:
  - FIBROBLASTS(MAKE COLLAGEN AND ELASTIN)
  - KERATINOCYTES (SKIN CELLS)
  - IMMUNE CELLS
  - TRANSFER GROWTH FACTORS, PROTEINS, GENETIC MATERIAL FOR TISSUE REPAIR
  - CONTAIN 3X AMOUNT OF GF COMPARED TO STEM CELLS-RESTORE AND REVITALIZE TARGET CELLS
  - MICRO-RNA STIMULATE FIBROBLAST GROWTH, COLLAGEN PRODUCTION AND SKIN REJUVENATION
  - ONCE EXOSOME RELEASED FROM STEM CELL—ATTRACTED TO CELLS WITH ACTIVE INFLAMMATION AND ARE ABSORBED, EXOSOMES THEN RELEASE "CARGO"

WHAT TYPES OF EXTRACELLULAR VESICLES ARE THERE:



Intercellular communication

- Proteins
- mRNA
- miRNA
- Lipids

- Proteins
- mRNA
- miRNA
- Lipids

- Cell organelles
- Proteins
- Nuclear fractions
- DNA

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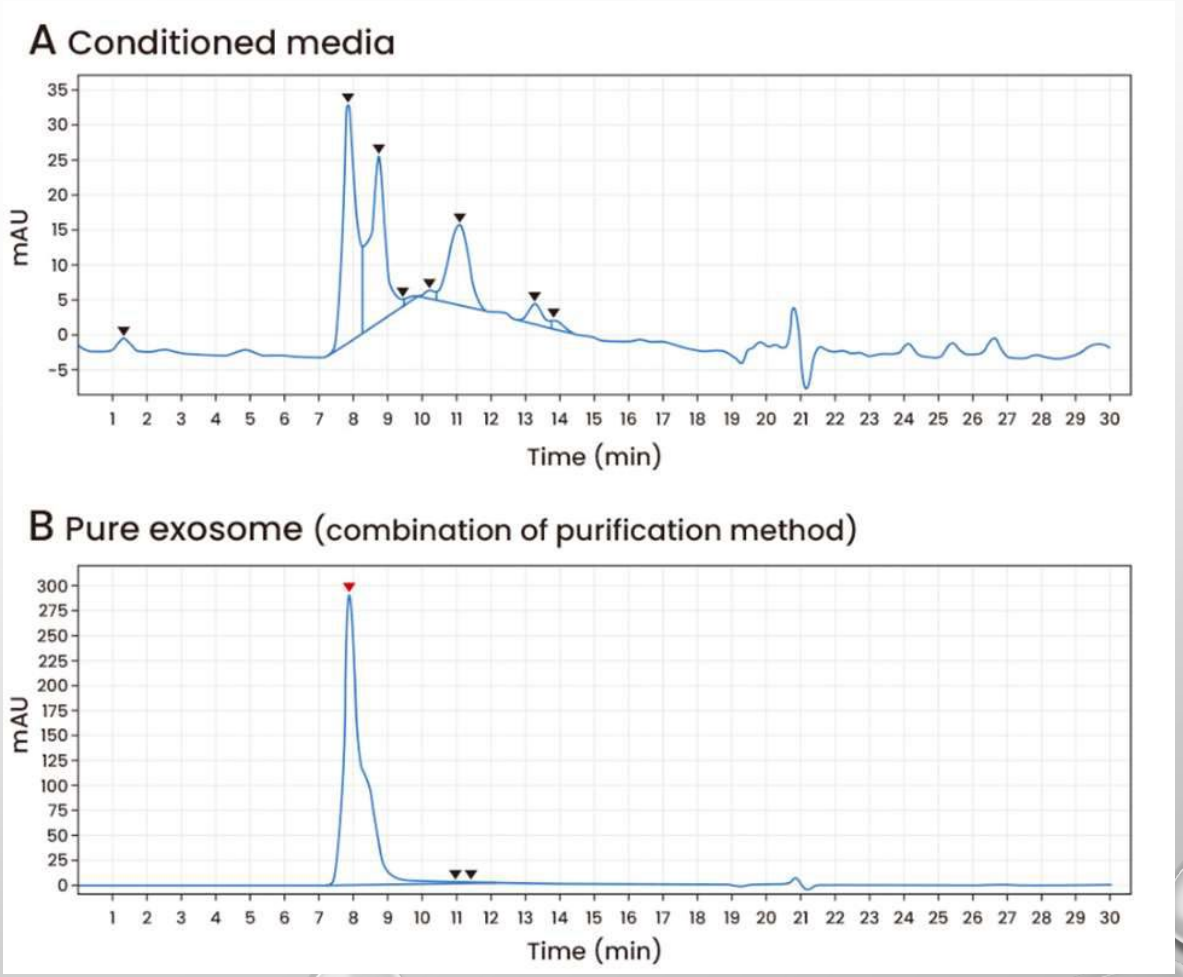
f Physiology and Biochemistry (2022) 78:573–580

CHALLENGES USING EXOSOMES

- CELL-LINE DEVELOPMENT-
  - SOPHISTICATED COMPOSITION, SMALL CELL SIZE AND HETEROGENOUS POPULATION
- SCALABILITY
- UPSTREAM CELL CULTURE
- DOWNSTREAM PURIFICATION PROCESSES
- CHARACTERIZATION AND QUALITY CONTROL
- STABILITY (SHELF-LIFE)
- REGULATORY CONSIDERATIONS
- TYPICALLY DERIVED FROM BONE MARROW OR PLACENTAL TISSUE



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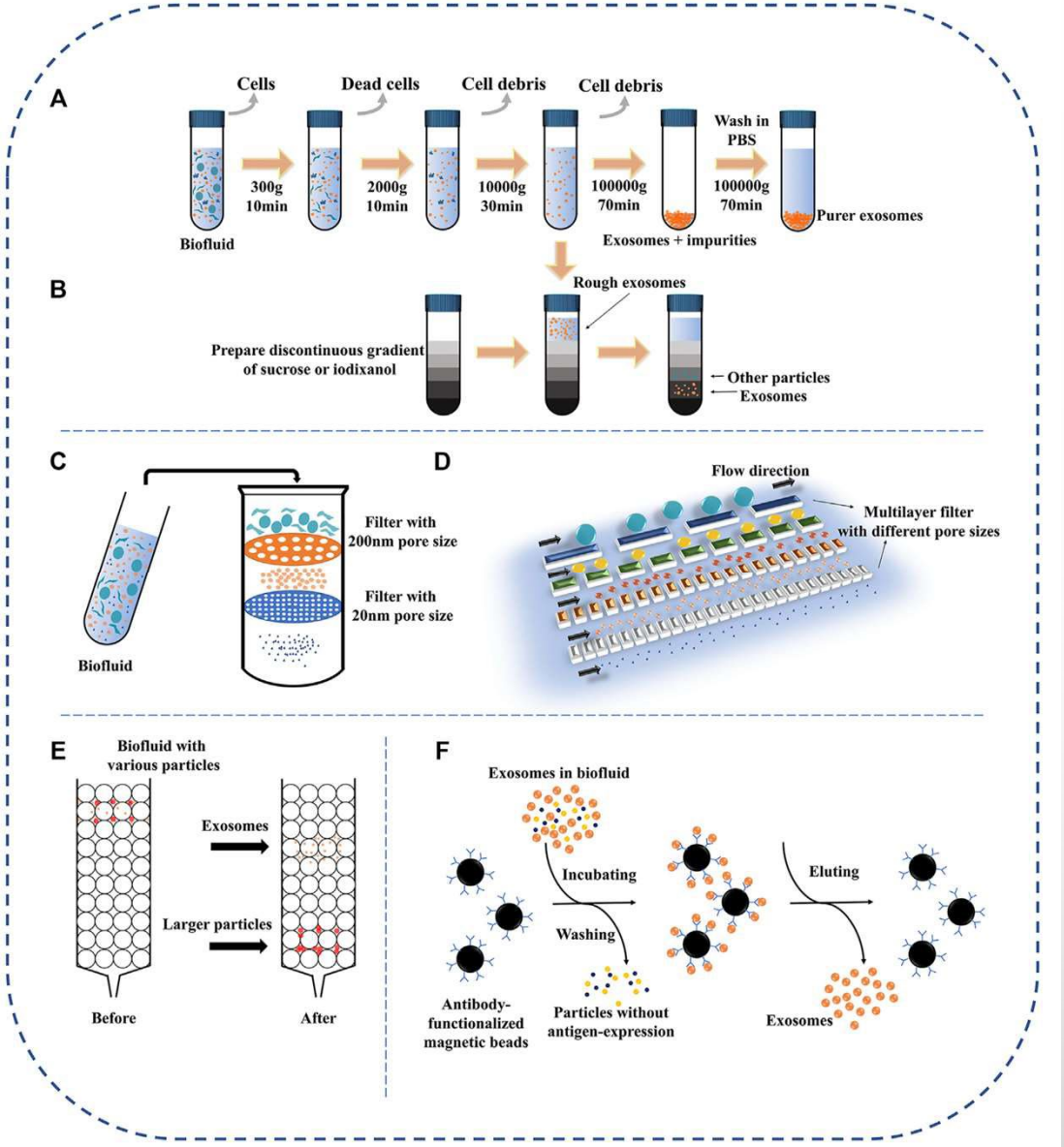
Taylor and Taylor.Exosomes/microvesicles: mediators of caner-associated immunosuppressive microenvironments.*Semin Immunopathol.2011*(33):441-54



How Exosomes are Made: Isolation Techniques”

*Ultracentrifugation: repeated can compromise integrity of EV’s

*Ultrafiltration:deforms large Evs

*Precipitation: final EV yield varied, contaminants

*Immunoaffinity capture: search ideal biomarker

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Chen et al.Review on Strategies and Technologies for Exosome Isolation and Purification. *Front Bioeng. Biotechnol.* 2022(9):811971.

EXOSOME CELL SOURCES

Umbilical Cord Mesenchymal Stem Cells-Exos

- Skin rejuvenation
- Human dermal fibroblast(HDF) migration and upregulation of collagen

Adipose Derived Stem Cells-Exos

- Cell proliferation and migration
- Decrease ROS production and DNA damage

Bone Marrow Derived Stem Cell-Exos

- Exosomes concentrate the natural function of a stem cell.
- most regenerative for skin

Human Trophoblast-Exos

- Superior regenerative capabilities
- Prolif and migration of HDF
- Increase collagen I and III, elastin
- Decr MMP1,3

Review Article

Update on Exosomes in Aesthetics

Nina Hartman, MD, Jameson Loyal, MD, and Sabrina Fabi, MD*

BACKGROUND In dermatology, exosomes have been leveraged given their roles in wound healing, cell migration, extracellular matrix reconstruction, and angiogenesis.

OBJECTIVE The purpose of this article is to review the literature investigating the use of exosomes in skin rejuvenation and hair regeneration.

MATERIALS AND METHODS The PubMed database was searched for studies published through October 2021.

RESULTS Early preclinical studies in aesthetics have demonstrated promising effects of exosomes on skin rejuvenation and hair growth in in vitro and murine models. Despite this, only 1 clinical study has been published to date, and there are no FDA-approved products on the market.

CONCLUSION Variation in purification techniques and practical issues surrounding isolation, storage, scalability, and reproducibility of an exosome product represent ongoing hindrances to the movement of exosomes into the clinical sphere.

- SKIN REJUVENATION AND PHOTOAGING
- SCARRING
- ALOPECIA
- HYPERPIGMENTATION

ol Surg 2022 Aug: 48(8): 862-5

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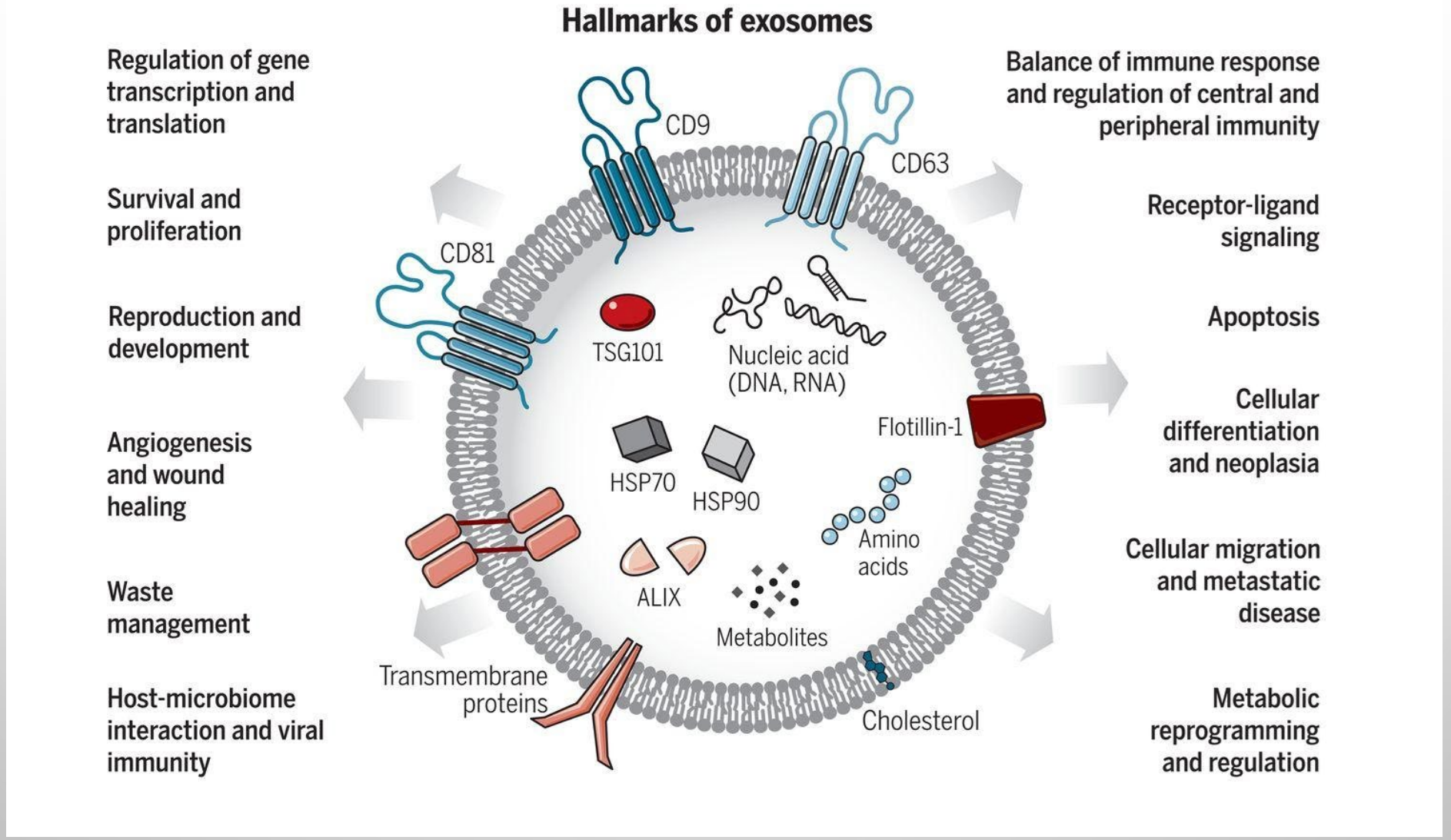
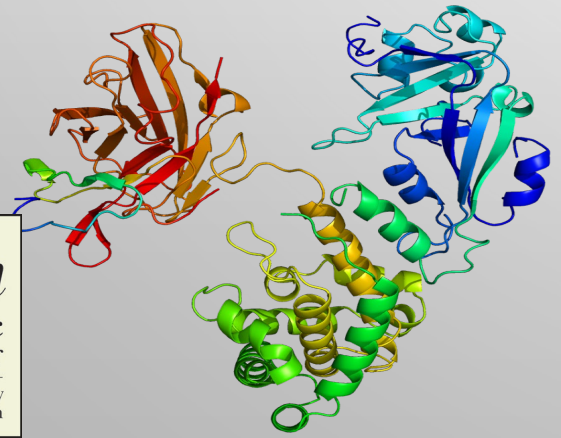


Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478):eaau6977. doi:10.1126/science.aau6977

COMPONENTS OF EXOSOMES

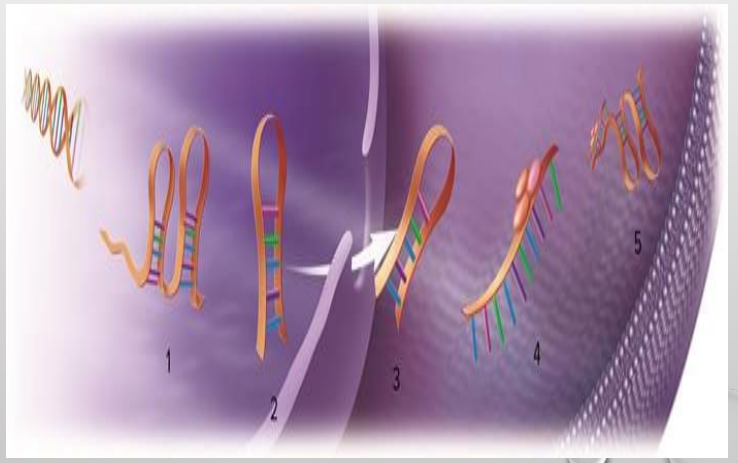
GROWTH FACTORS

- Stable protein bio-signals
- Manage inflammation and regeneration
- Used to enhance healing in aesthetic dermatological treatments



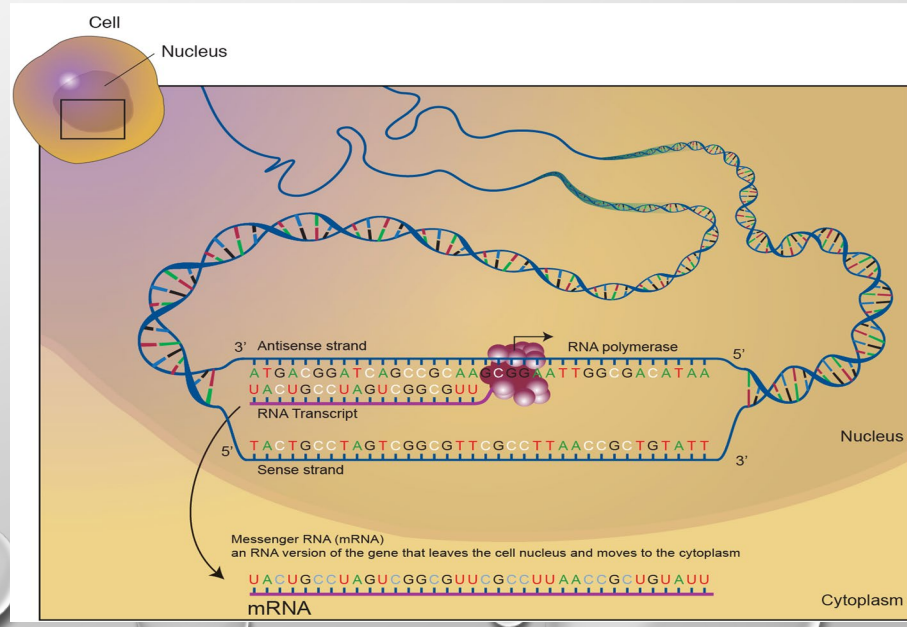
MICRO RNA

- REGULATE GENE EXPRESSION
- INTERACT WITH MESSENGER RNA



MESSENGER RNA

- MODERNA COVID VACCINE
- CANCER RESEARCH



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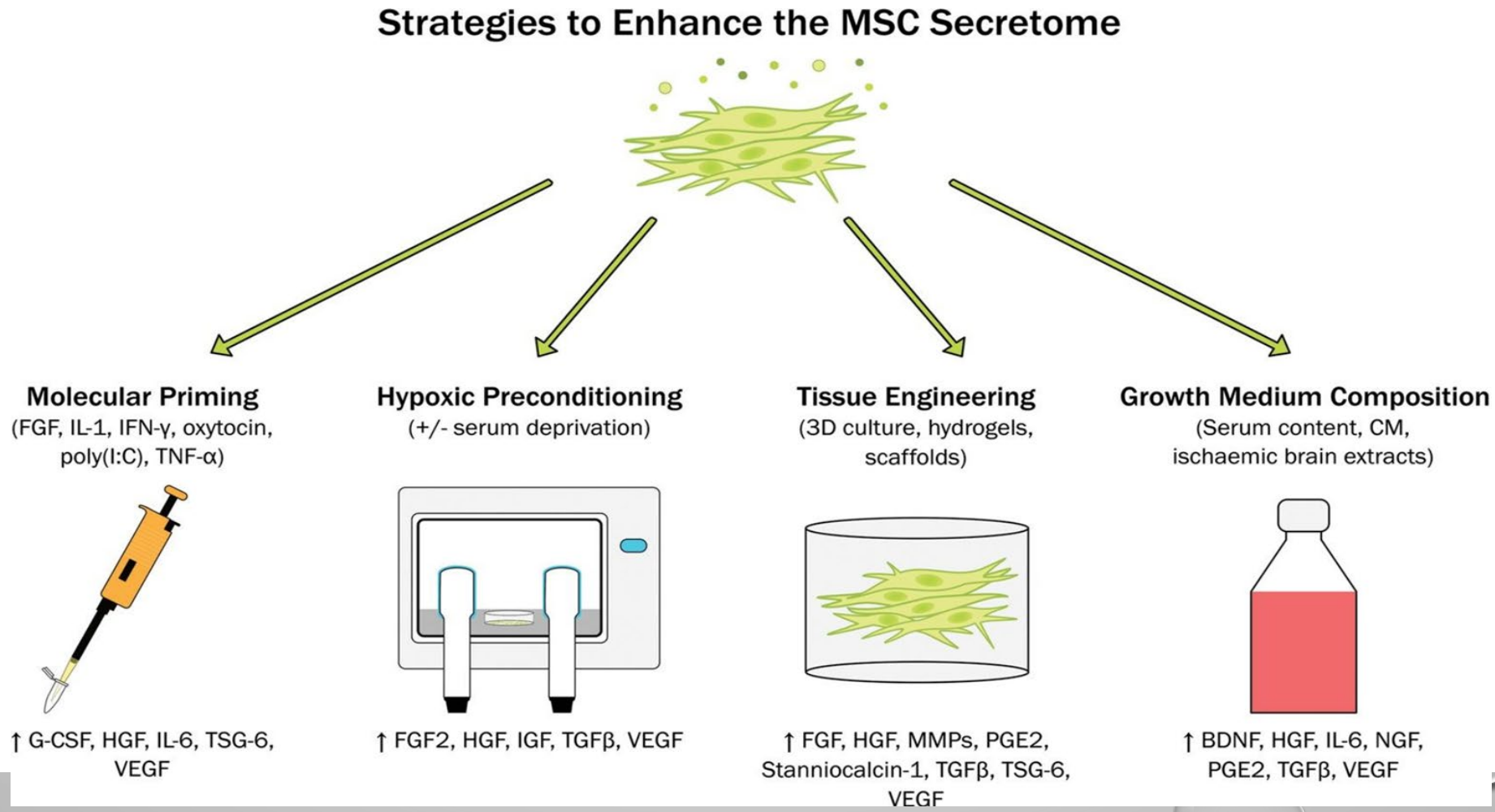
EXOSOMES CAN BE SEPARATELY ENGINEERED FOR SKIN –OR- HAIR SIGNALING



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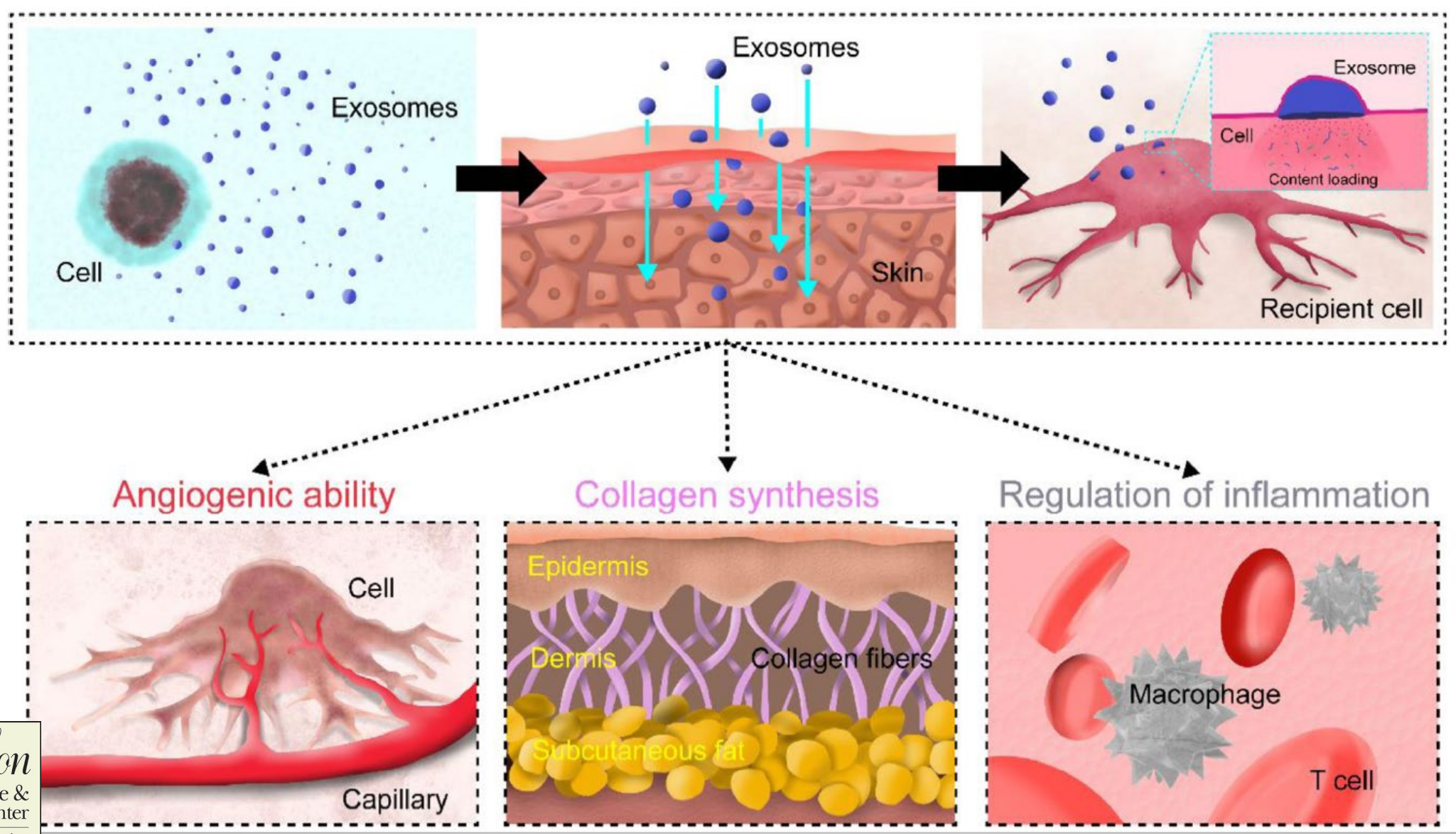
SKIN REGENERATIVE ABILITIES OF EXOSOMES



New: AnteAGE MDX Exosome Solution

- **<u>Bone Marrow Mesenchymal Exosomes:</u>** Physiologically balanced bio-signals released upon culture of Bone Marrow stem cells. Acting as the “command and control” over the processes of healing and inflammation

- **<u>Umbilical Mesenchymal Exosomes:</u>** Highly proliferative source of EVs. Combined with BM-MSCs to achieve unique loading of regenerative factors.

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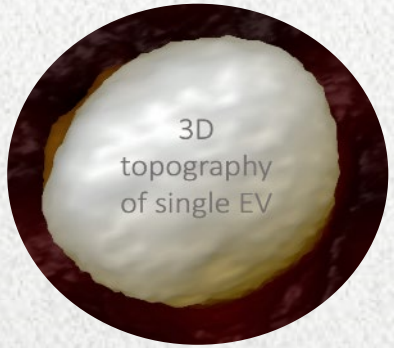
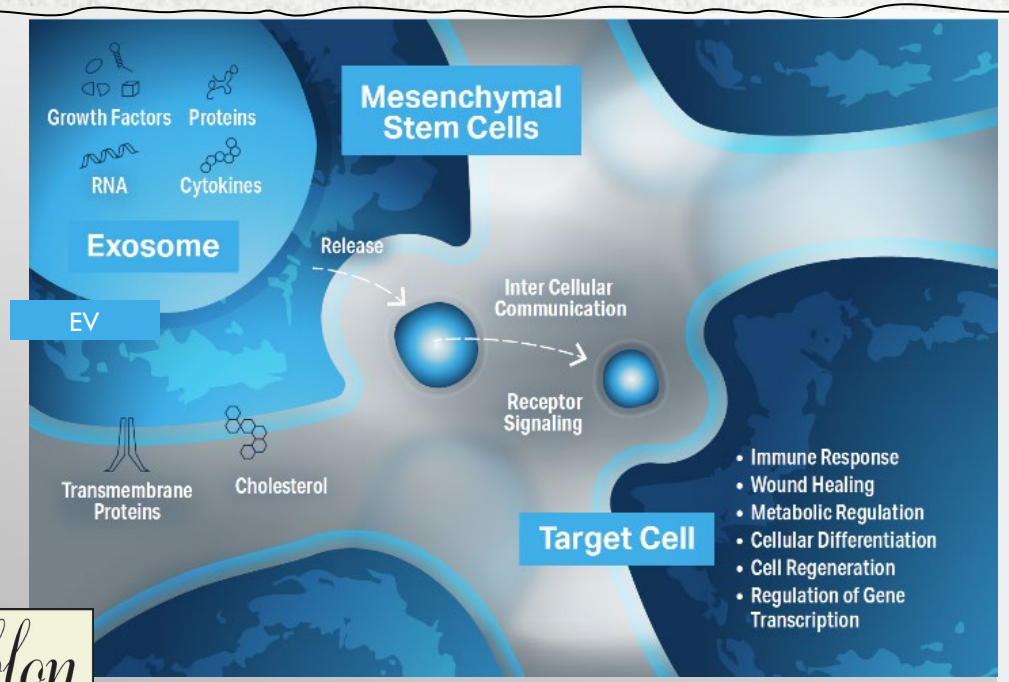
Combining BM and UC offers the best of both worlds.

UCMSC-EXOSOMES:
PRECISION GROWTH FACTORS & MRNA



EXTRACELLULAR VESICLES (EVS) ARE LIPID BILAYER MEMBRANE MICRO-VESICLES SECRETED BY VARIOUS TYPES OF CELLS SUCH AS STEM CELLS THAT CARRIES GROWTH FACTORS AND **CONTRIBUTE TO ANTI AGING.**



Mechanism of Action

- **EVs target and repair damaged tissue** at sites of inflammation to transfer their content resulting in phenotypic functional changes
- **EVs contain growth factors,** mRNA and microRNA, lipids and cell-signaling proteins to repair and regenerate cells
- They have a reliable and **robust safety profile** and are acellular. Meaning that have **no DNA** or cellular material.

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MANUFACTURING AND TESTING

- ✓ Fluorescent Assisted Cell Sorting (FACS)
- ✓ Positive for CD44, CD73, CD90, CD105, CD146
- ✓ Negative for Hematopoietic marker CD34, CD45, and endothelial marker CD31

Source the tissue

- ✓ High quality tissue with strict inclusion and exclusion criteria
- ✓ Single use of only the chorion

Test Source tissue

- ✓ Serology
- ✓ Sterility
- ✓ PCR

Sort and Select MSC's

Expand MSC's until Confluence

- ✓ Proprietary culture medium for optimized growth

Seed rolled, Bottled and grow

- ✓ Optimized medium for maximum efficacy

Collect EV's

- ✓ Ultra filter at 0.22 um

Adjust And Optimize

- ✓ In Vitro testing

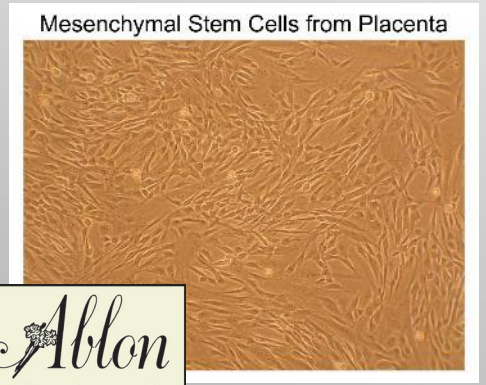
Characterize EV's

- ✓ NGS
- ✓ MUDPIT
- ✓ Nano Particle Analysis (Count whole EVs)

Release

- ✓ Serology
- ✓ Sterility
- ✓ PCR

9-Step Process



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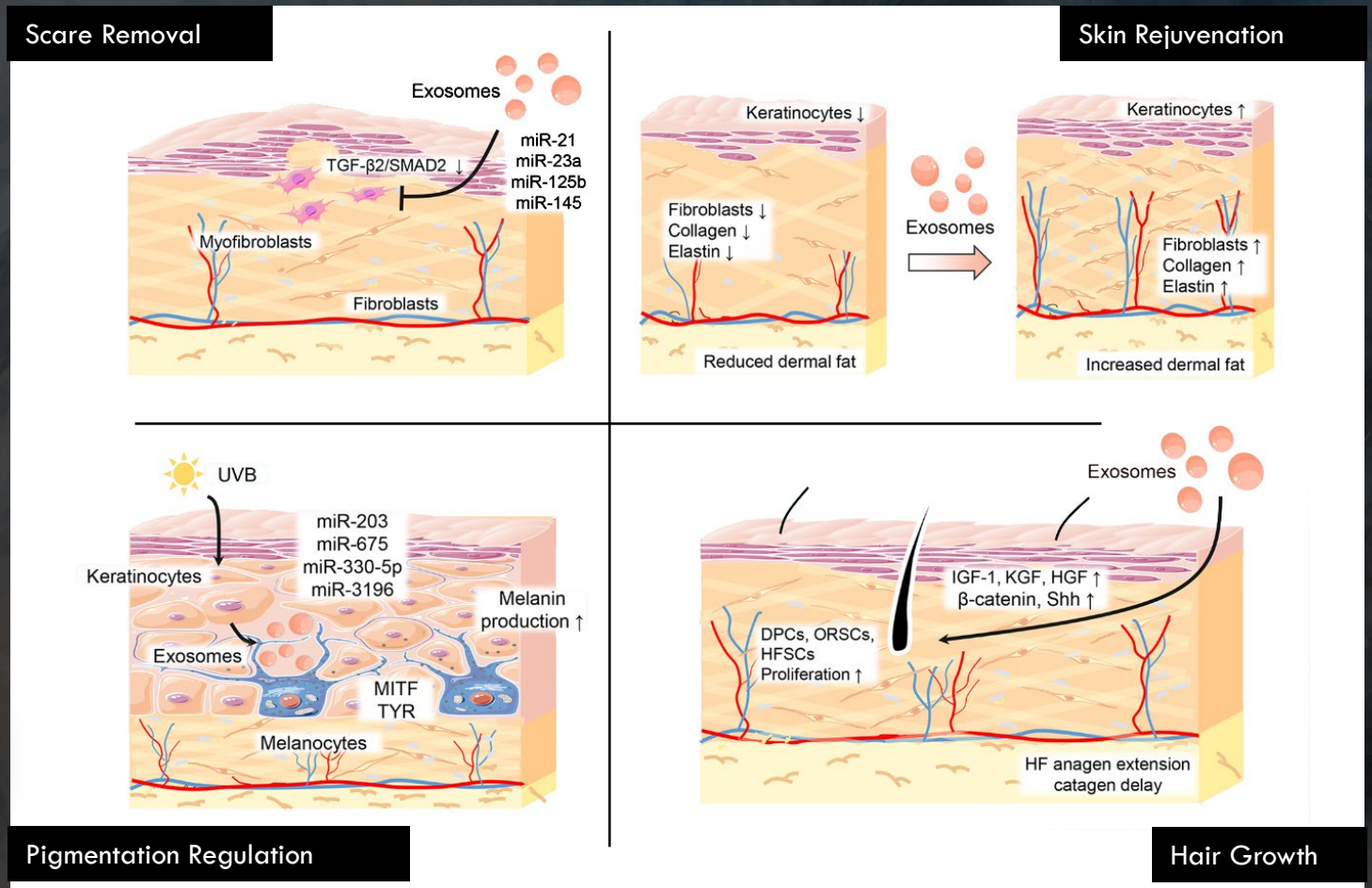
Index
ExoCel Bio
Third Parties

MRNA AND MIRNA ACTS AS A CATALYST FOR OUR OWN CELLS REGENERATION



Many studies demonstrate that miRNA down-regulate or up-regulate certain growth factors to help with skin and hair rejuvenation.

Reference: The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics, from Mingchen Xiong,Qi Zhang,Weijie Hu,Chongru Zhao,Wenchang Lv,Yi Yi,Yichen Wang,Hongbo Tang,Min Wu,Yiping Wu in Pharmacological Research April 2021

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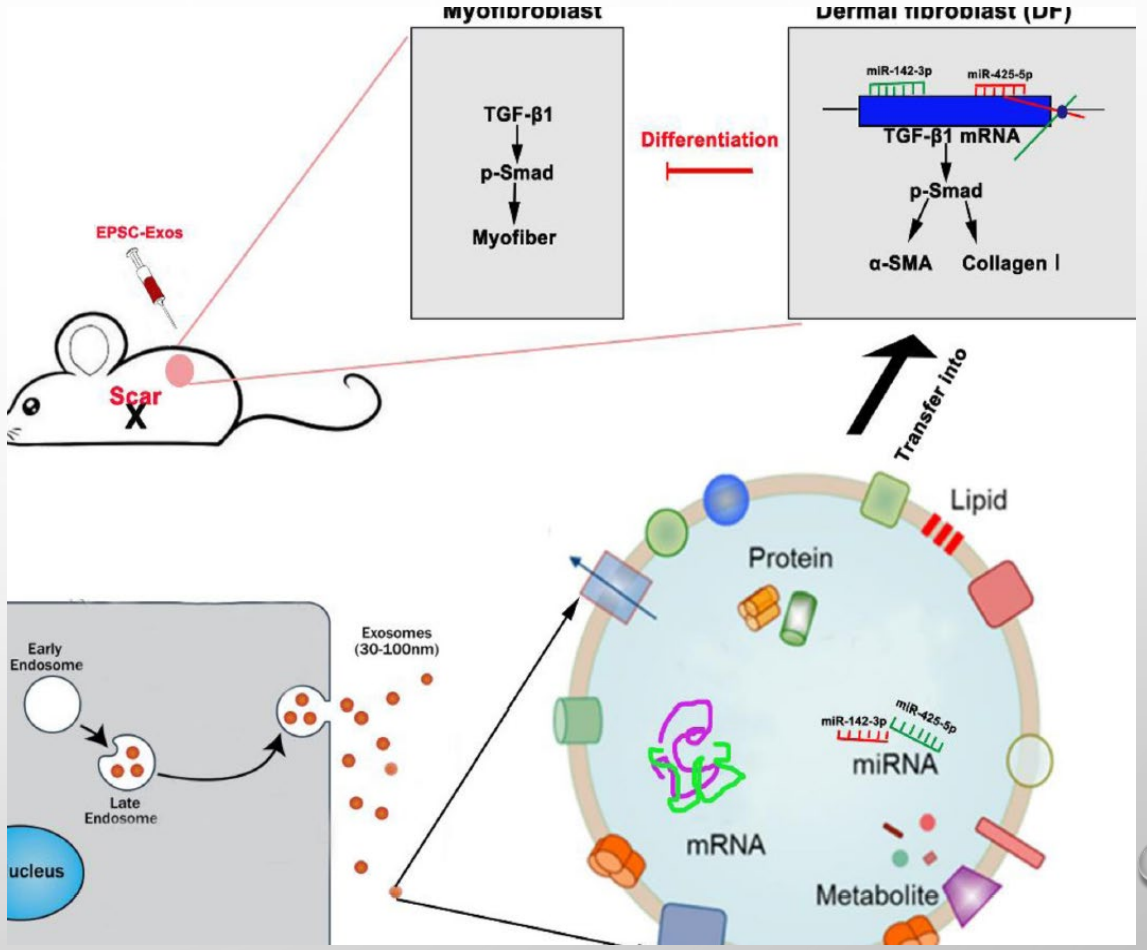
Exosomes promotes wound healing

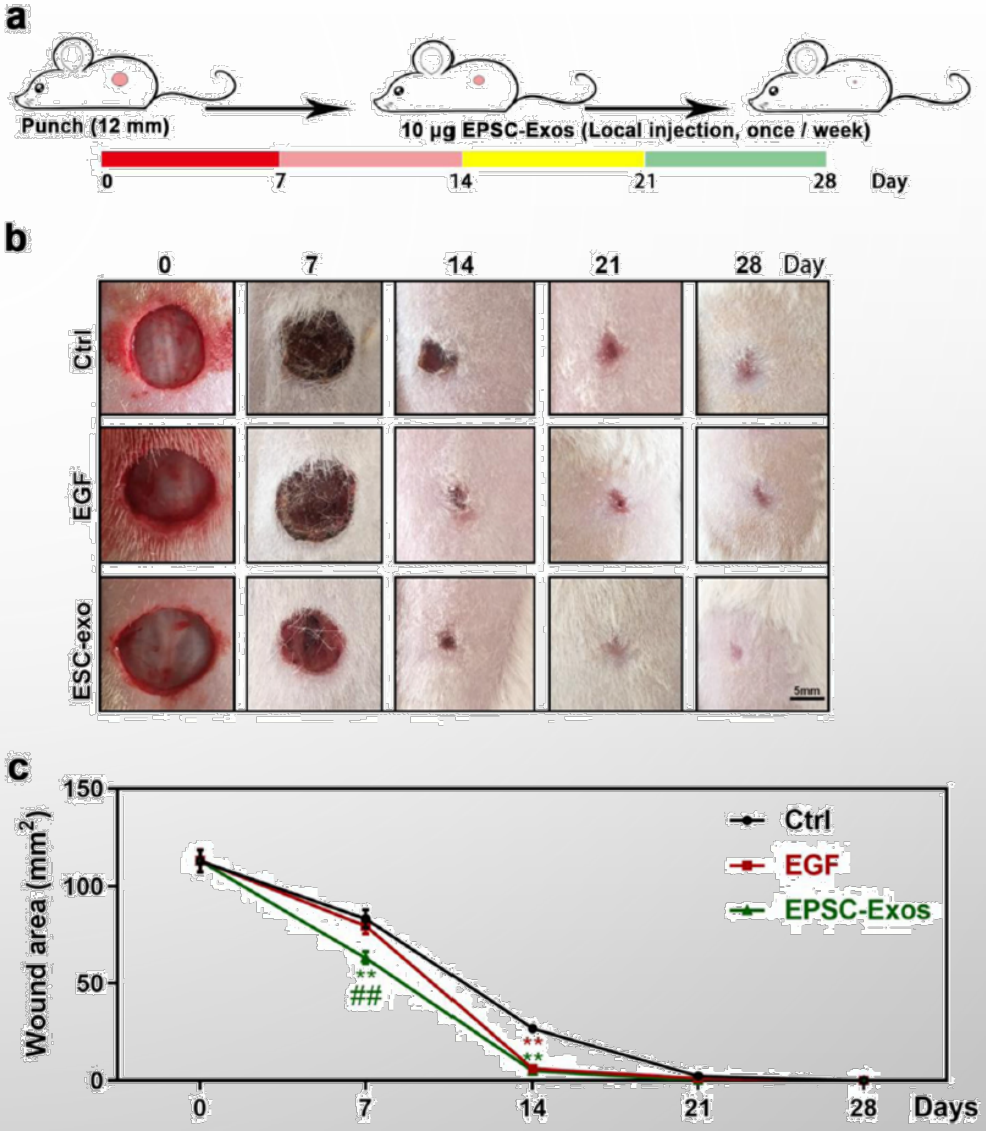
miRNAs 425-5p and 142-3p downregulate the transforming growth factor TGF-β1 expression and promoted wound healing and reduced scarring



Reference: Epidermal stem cell-derived exosomes promote skin regeneration by downregulating transforming growth factor-β1 in wound healing - Aug 2020

Exosomes promotes Collagen Distribution

Exosomes improve the regeneration level of skin appendages and collagen distribution



Reference: Epidermal stem cell-derived exosomes promote skin regeneration by downregulating transforming growth factor-β1 in wound healing - Aug 202

SKIN AND HAIR REJUVENATION THAT WORKS

Topical Aesthetic Post Procedure Companion

01 MSC's Exosomes — mRNA to instruct cell to repair.

02 Regenerative — Natural placental growth factors & cytokines

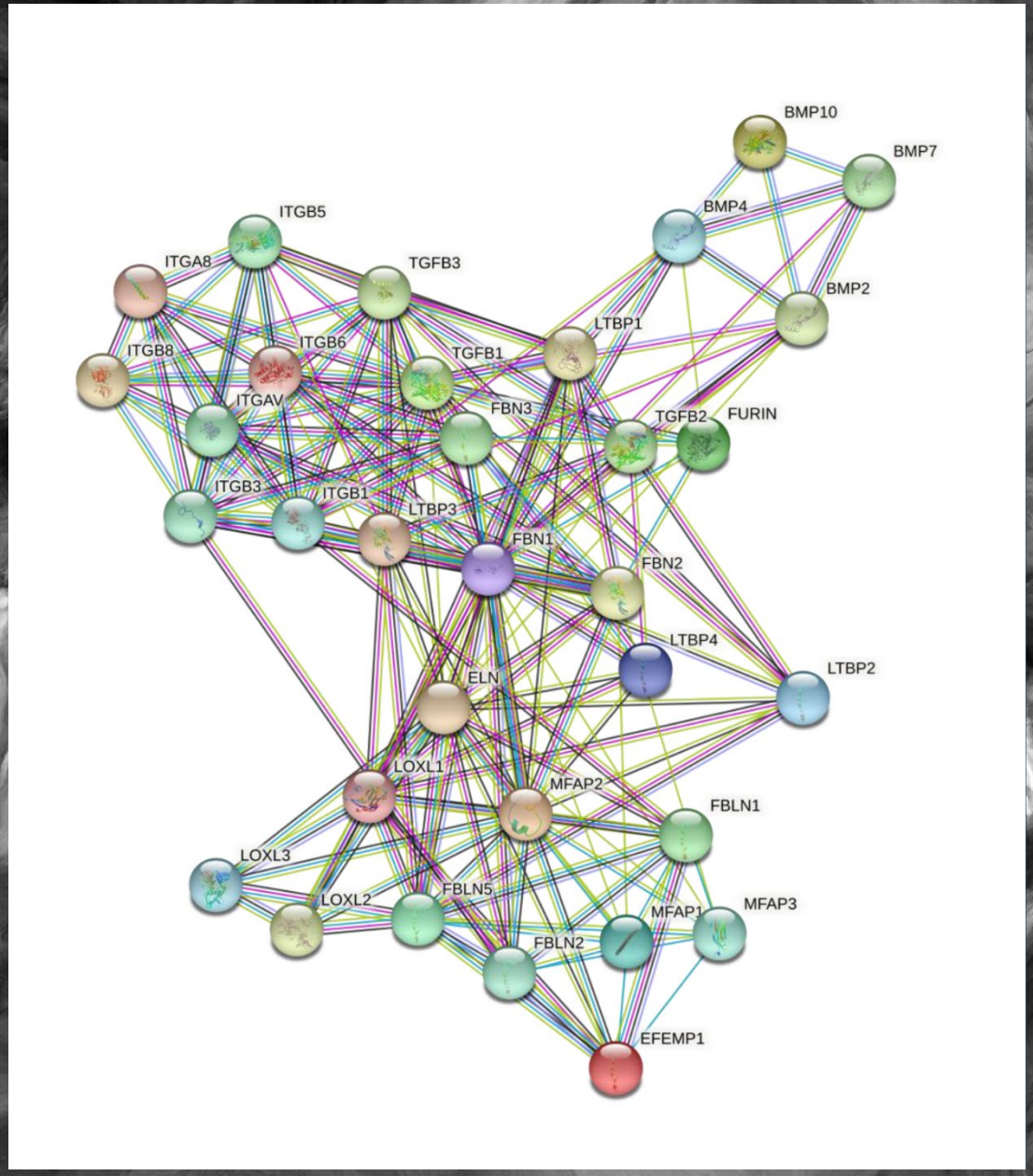
03 Anti-inflammatory — Reduce post procedure downtime and pain

Other Potential Research Use

- Anti-inflammatory response
- Aesthetic Subcutaneous Applications
- Ophthalmology
- Neurodegenerative Diseases
- Wounds Management
- Autoimmune diseases

EXOVEX™ IS PACKED WITH THOUSANDS OF BIO-ACTIVE MOLECULES

- **ANTI-AGING**
- 1544 PEPTIDE GROWTH FACTORS
- 24 MRNA + 33 MIRNA ASSOCIATED WITH ANGIOGENESIS
- 3 MRNA + 1 MIRNA ASSOCIATED WITH ANTI-APOPTOSIS
- **ANTI-WRINKLE**
- 56 MRNA + 5 MIRNA THAT CODE FOR COLLAGEN PRODUCTION
- 2 MRNA + 3 MIRNA THAT CODE FOR KERATIN PRODUCTION
- 3 MRNA THAT CODE FOR ELASTIN PRODUCTION
- 5 MRNA THAT CODE FOR FIBULIN
- **HAIR GROWTH**
- 8 MRNA + 1 MI RNA ASSOCIATED WITH FOLLICLE GROWTH



RF MICRONEEDLING

post Exovex Renew treatment with 12Billion

FACE

Cynosure LUX 1540nm (non-ablative fractionated laser) + one treatment of Exovex™ Reveal.

HAIR REJUVENATION CASE SERIES

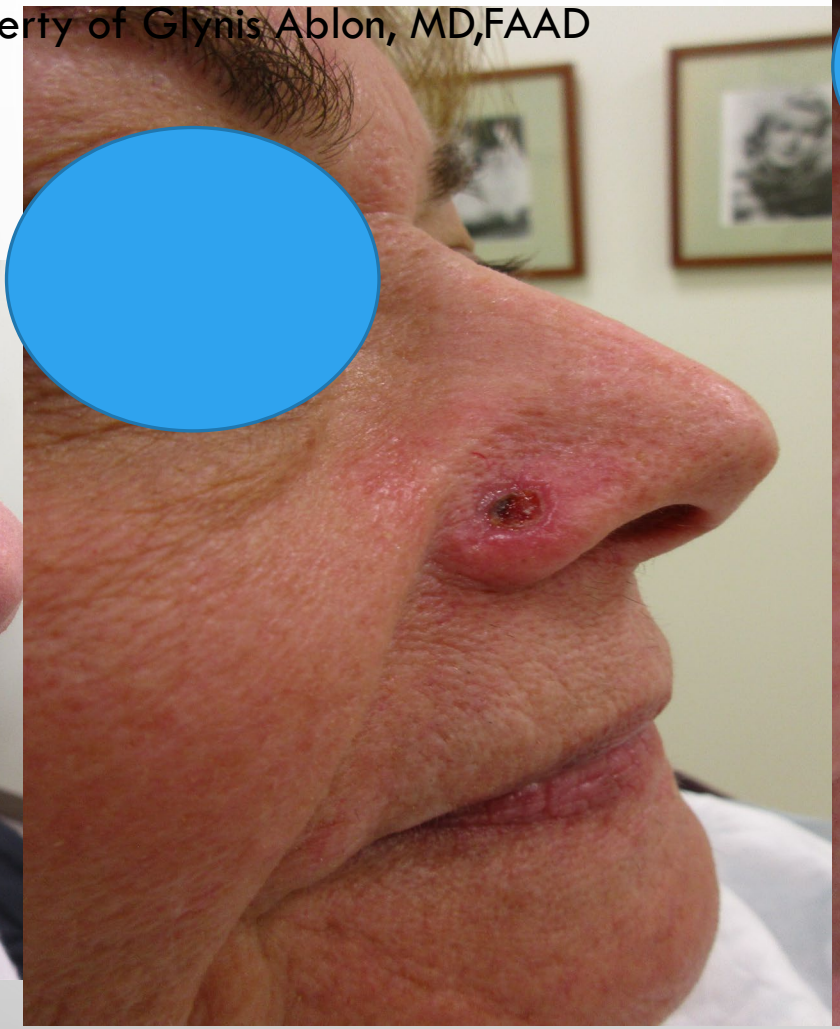
- EVALUATION OF HEALTHY HAIR APPEARANCE AND CONCENTRATION
- APPLICATION OF EXOVEX ON THE SCALP AFTER ENERGY BASED MICRONEEDLING
- BEFORE TREATMENT, AFTER 7 WEEKS, AFTER 14 WEEKS, AFTER 21 WEEKS, AND AFTER 7 MONTHS
- 20 PATIENTS
- INVESTIGATORS: DR. PEREDO
  DR. LEAVITT
  DR. SCHECHTER

HAIR

Before

After two **Exovex Reveal** 60 days apart

One week after excision
And exosome placement



2 weeks after excision and
2nd exosome placement

One month after excision and
2 exosome sessions

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SINGLE EXOSOME TREATMENT

PRE TREATMENT

3 MONTHS AFTER ONE SESSION

SINGLE EXOSOME TREATMENT

PRE TREATMENT

3 MONTHS AFTER ONE SESSION

BEFORE AND AFTER REGEN MED!!!

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CONCLUSION

- REGENERATIVE MEDICINE AND REGENERATIVE DERMATOLOGY IS RAPIDLY ADVANCING
- UNDERSTANDING THE MECHANISMS OF ACTION OF MESENCHYMAL STEM CELLS AND SOURCES IS KEY
- INTEGRATING REGENERATIVE DERMATOLOGY, ELEVATES YOUR PRACTICE
- DISCUSS ALL TREATMENT OPTIONS
- REMEMBER COMBINATION THERAPY ALWAYS WORKS BEST
- NEVER FORGET NUTRITION AND HORMONES CAN BE ADDED!
- PICK YOUR PATIENTS WISELY

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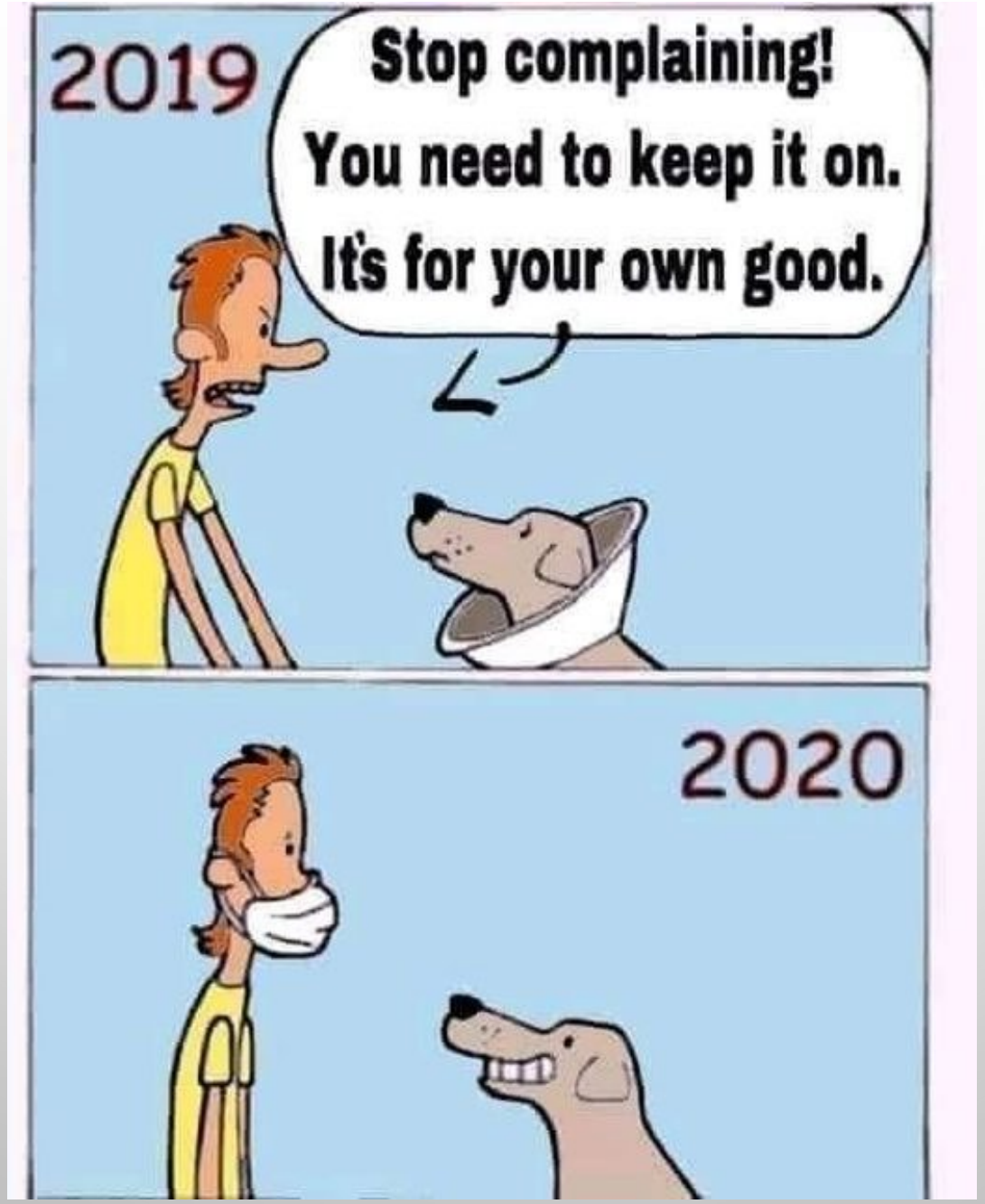
2019
Stop complaining!
You need to keep it on.
It's for your own good.
2020