CLINICAL SCIENCE OF EXOSOMES AND CURRENT STUDIES

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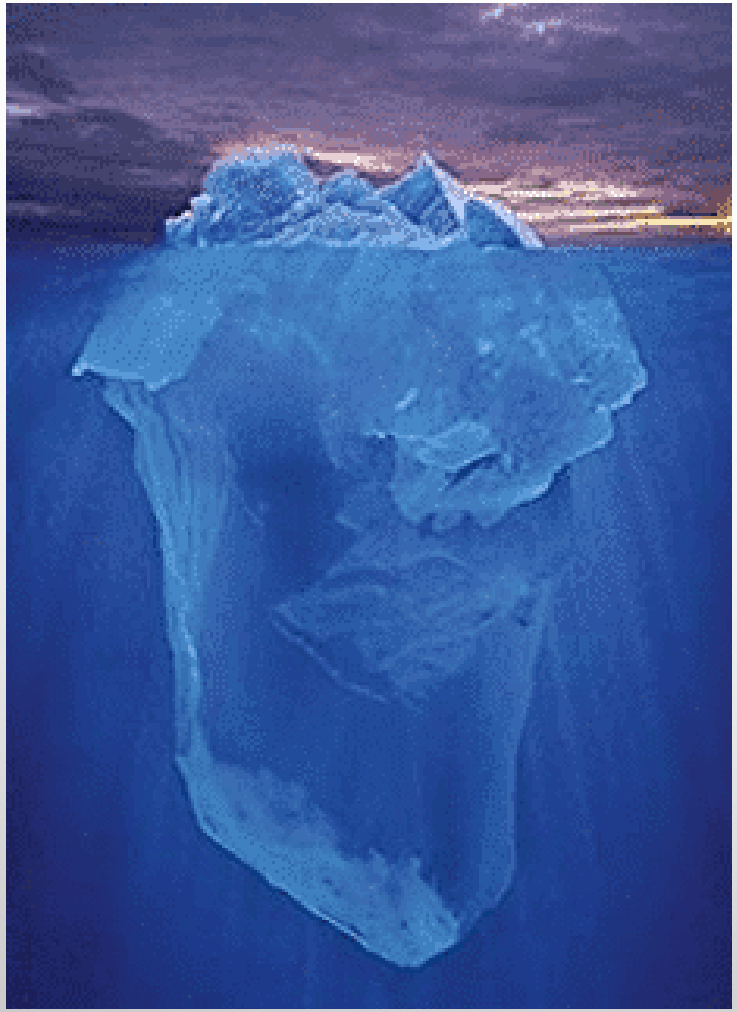


What we know about Exosomes

And what is yet to
be discovered

STEM CELLS VS EXOSOMES

STEM CELLS

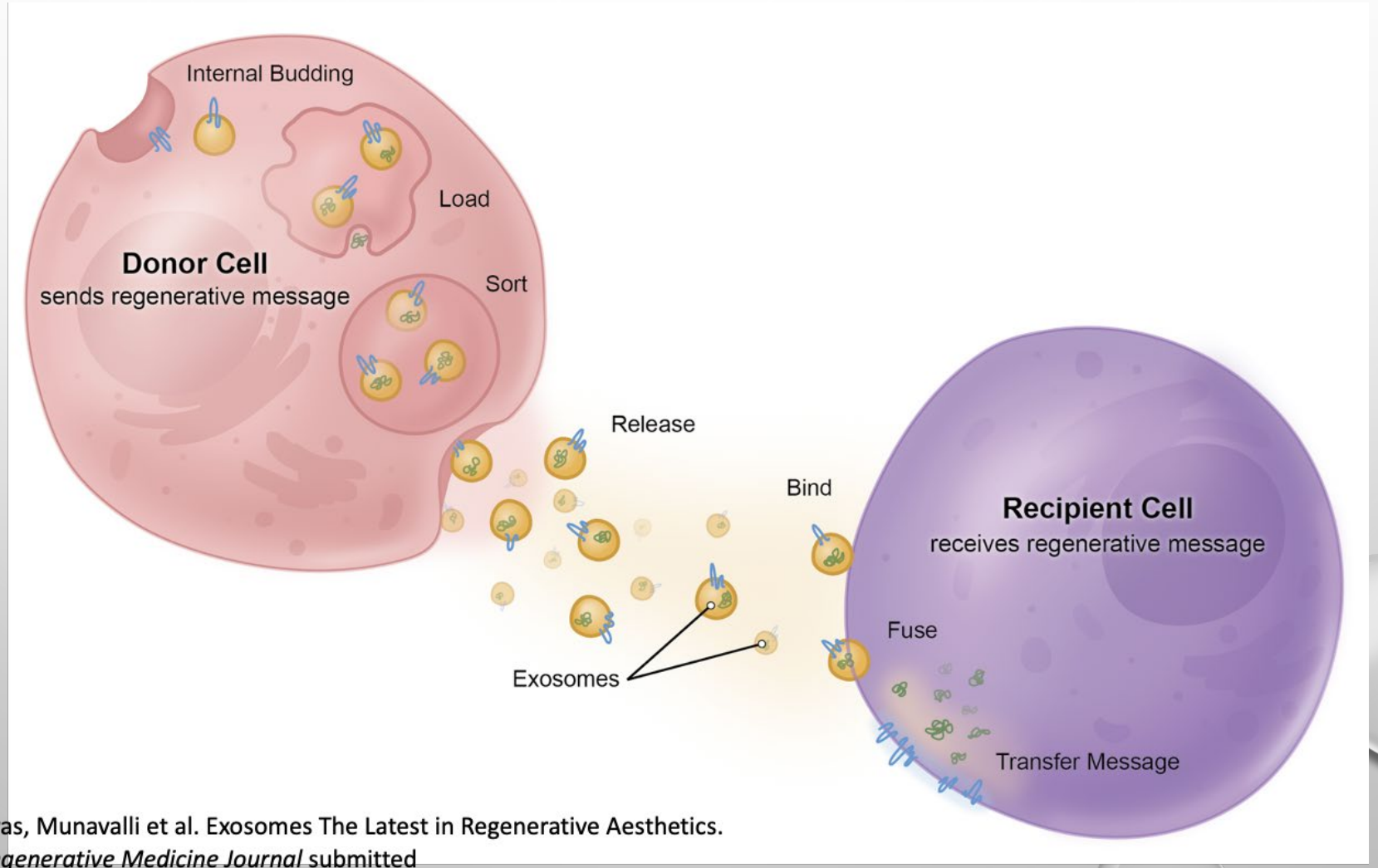
- LIVING CELLS
- MUST BE USED FRESH/CAREFULLY PRESERVED
- FOUND IN CERTAIN TISSUES
- PRODUCE “INFORMATION”
- LIMITED THERAPEUTIC POTENTIAL

EXOSOMES

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

EXOSOME SCIENCE AND REGENERATIVE AESTHETICS

Basics Of Exosome Technology



Vyas, Munavalli et al. Exosomes The Latest in Regenerative Aesthetics. *Regenerative Medicine Journal* submitted

•.J Cos Dermatol 2023 Oct;22(10):2628-2634.

A review of exosomes and their application in cutaneous medical aesthetics

Kehinde Raji Olumesi [1], David J Goldberg [1]

EXOSOME CELL SOURCES

Umbilical Cord Stem Cells

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

Adipose Derived Stem Cells

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

EXOSOME CELL SOURCES

Platelet Derived Stem Cells

- First Responders to Injury
- Myoblast Proliferation
- Chondrogenesis
- Aging Skin
- Hair

The Effects of ASC-Exosome on Frailty, Health Span, & Epigenetic Age

SCIENCE ADVANCES | RESEARCH ARTICLE

Oct 19, 2022

DISEASES AND DISORDERS

Small extracellular vesicles from young adipose-derived stem cells prevent frailty, improve health span, and decrease epigenetic age in old mice

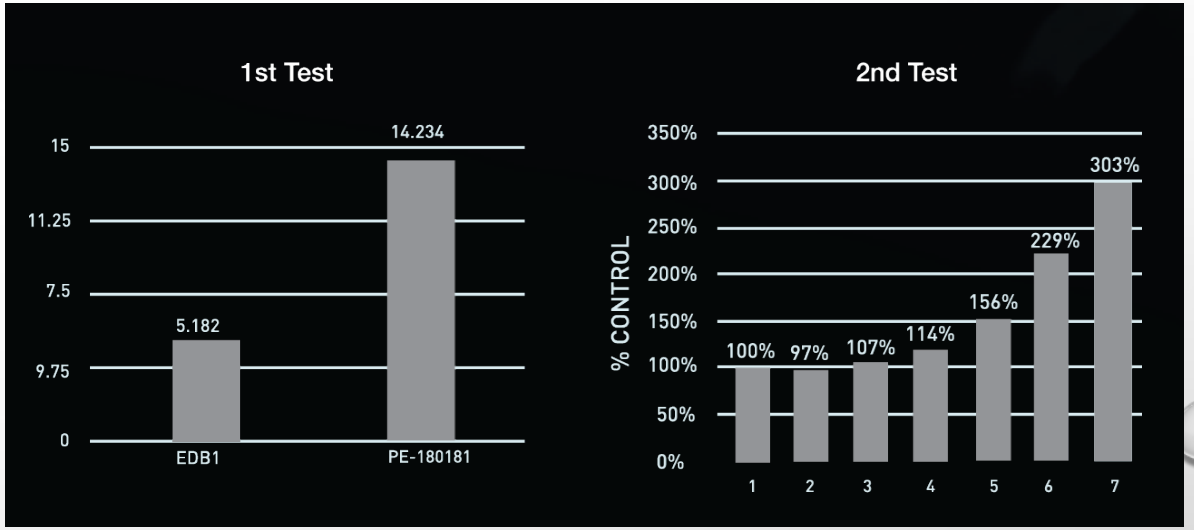
Jorge Sanz-Ros[1], Nekane Romero-García[1], Cristina Mas-Bargues[1], Daniel Monleón[2], Juozas Gordevicius[3], Robert T. Brooke[3], Mar Dromant[1], Ana Díaz[1], Aksinya Derevyanko[4], Ana Guío-Carrión[4], Aurora Román-Domínguez[1], Marta Inglés[5], María A. Blasco[4], Steve Horvath[6,7,8], Jose Viña[1], Consuelo Borrás[1]*

Aging is associated with an increased risk of frailty, disability, and mortality. Strategies to delay the degenerative changes associated with aging and frailty are particularly interesting. We treated old animals with small extracellular vesicles (sEVs) derived from adipose mesenchymal stem cells (ADSCs) of young animals, and we found an improvement in several parameters usually altered with aging, such as motor coordination, grip strength, fatigue resistance, fur regeneration, and renal function, as well as an important decrease in frailty. ADSC-sEVs induced proregenerative effects and a decrease in oxidative stress, inflammation, and senescence markers in muscle and kidney. Moreover, predicted epigenetic age was lower in tissues of old mice treated with ADSC-sEVs and their metabolome changed to a youth-like pattern. Last, we gained some insight into the microRNAs contained in sEVs that might be responsible for the observed effects. We propose that young sEV treatment can promote healthy aging.

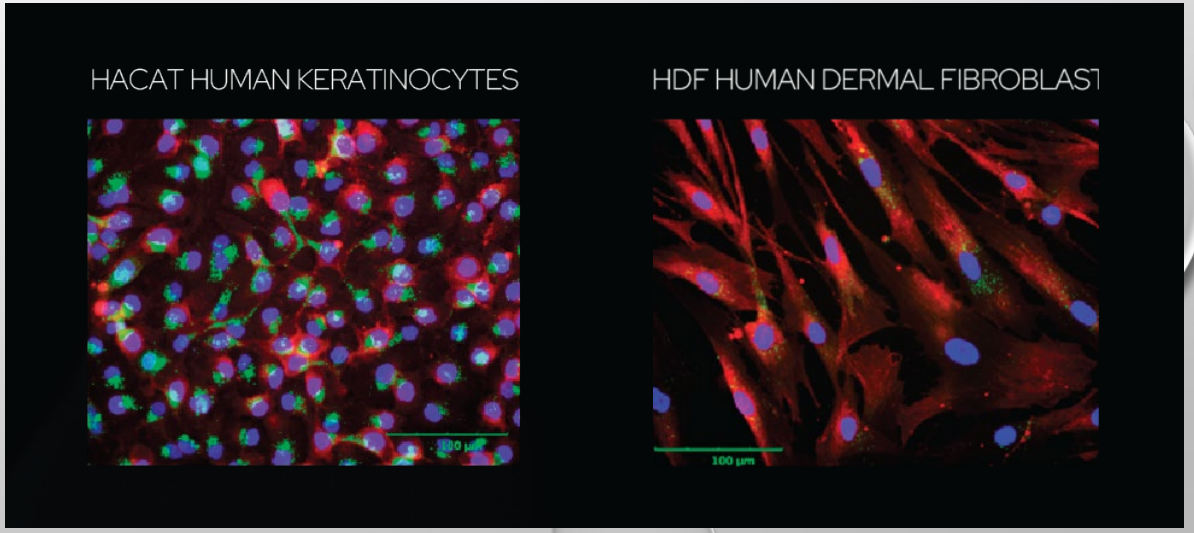
EXOSOME TECHNOLOGY

ELASTIN INCREASE

Increase the elastin amount of human dermal fibroblasts up to 300% in vitro.



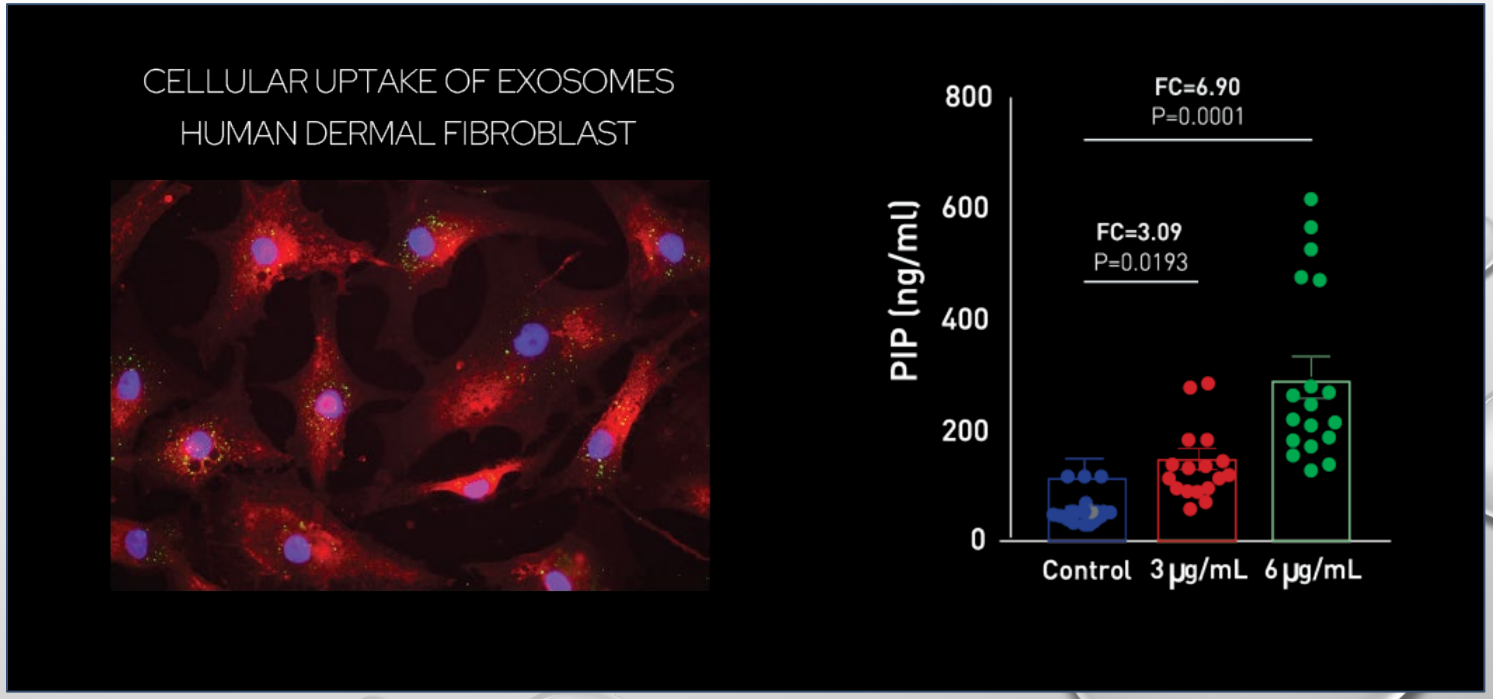
CELLULAR UPTAKE OF EXOSOMES



EXOSOME TECHNOLOGY

COLLAGEN INCREASE

After delivery of Exosome products into fibroblasts, neocollagenesis can increase up to 6 folds.



RESULTS

Courtesy of Dr. Chang Ro Lee, Lee Clinic

RESULTS

Exosome Regenerative Complex +

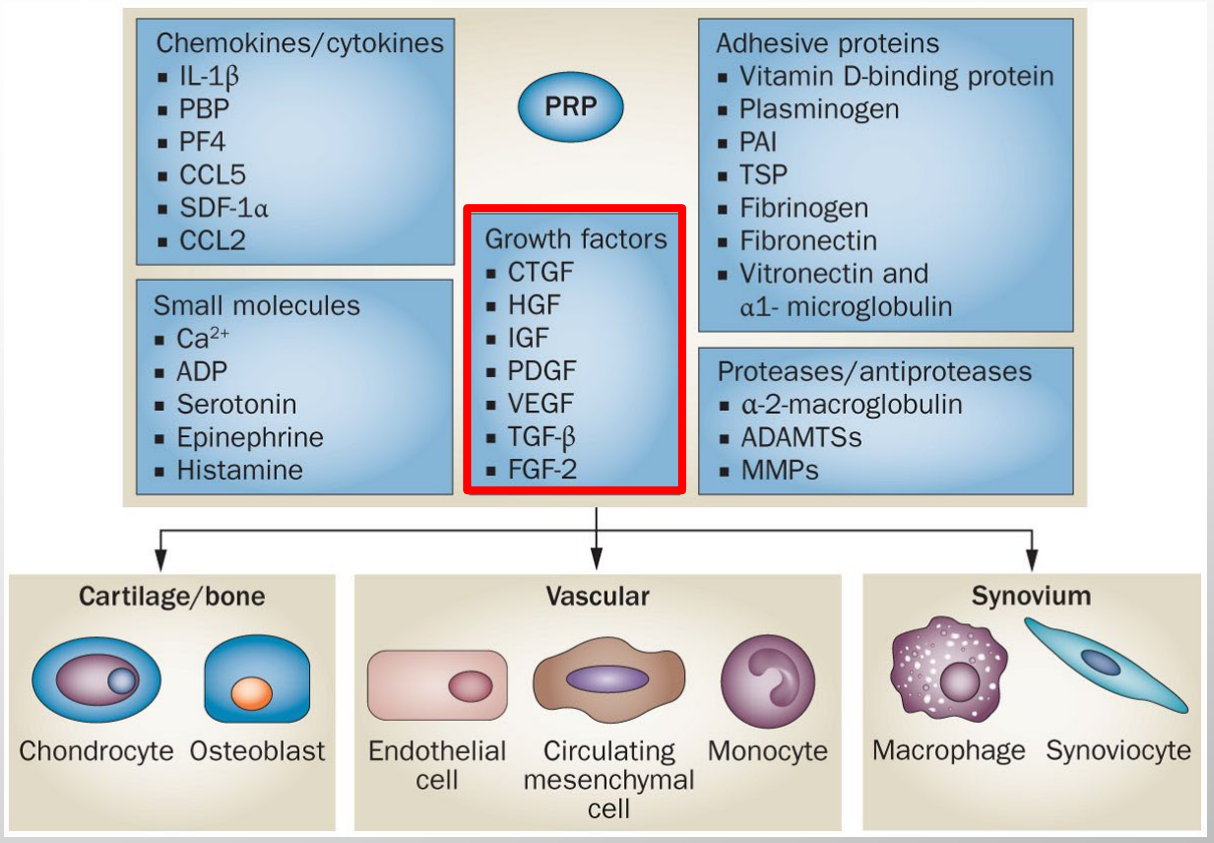
OUR STUDY

- RF-MICRONEEDLING
- EXOSOME TO ONE SIDE /PRP TO THE OTHER SIDE
- BIOPSIES FOR TYPE I/III COLLAGEN AND GAGS

- PLATELET RICH PLASMA

PRP COMPONENTS

- PLATELETS – RESERVOIR OF BIOACTIVE MOLECULES (GROWTH FACTORS & CYTOKINES) IMPORTANT FOR ANGIOGENESIS, CELLULAR MIGRATION, DIFFERENTIATION, AND PROLIFERATION



Andia, I et al. Platelet-rich plasma for managing pain and inflammation in osteoarthritis Nat. Rev. Rheumatol. 2013
Singh B, et al. Autologous Platelet-Rich Plasma for the Treatment of Pattern Hair Loss. Am J Clin Dermatol 2016

DRAWBACKS

- MYRIAD TECHNIQUES
- REQUIRES PHLEBOTOMY

EXOSOMES

ADIPOSE STEM CELL (ASC) EXOSOMES

- ASSOCIATED WITH SEVERAL SIGNALING PATHWAYS RELATED TO SKIN REGENERATION
- REBUILD SKIN BARRIER
- UNLIKE PRP, ASCE ARE MASS-PRODUCED
- HAVE LONG SHELF-LIFE

OUR STUDY

- OPEN-LABEL SPLIT FACE CLINICAL TRIAL ASSESSING THE SAFETY AND EFFICACY OF ADIPOSE **STEM CELL DERIVED EXOSOMES VS PRP POST RF MICRONEEDLING** IN THE COSMETIC IMPROVEMENT OF FACIAL PHOTOAGED SKIN

STUDY DESIGN

- 15 SUBJECTS FP I-IV BETWEEN AGES 44-68 YEARS OLD.
- SUBJECTS RECEIVED 3 RF MICRONEEDLING TREATMENTS TO THE FULL FACE SPACED AT 4-WEEK INTERVALS.
- POST TREATMENT, PRP APPLIED TO RIGHT SIDE AND EXOSOMES TO THE LEFT SIDE OF THE FACE.
- FOLLOWED FOR 6 MONTHS POST FINAL TREATMENT.
- 4 BIOPSIES TO THE RIGHT & LEFT INFRA-AURICULAR AREA AT:
  - BASELINE
  - AFTER FINAL TREATMENT (TX 3)
  - 3-MONTH FOLLOW-UP
  - 6-MONTH FOLLOW-UP
- INVESTIGATOR AND SUBJECT ASSESSMENTS REGARDING OVERALL SKIN APPEARANCE, WRINKLING, DYSCHROMIA, ERYTHEMA, AND TEXTURAL QUALITY.

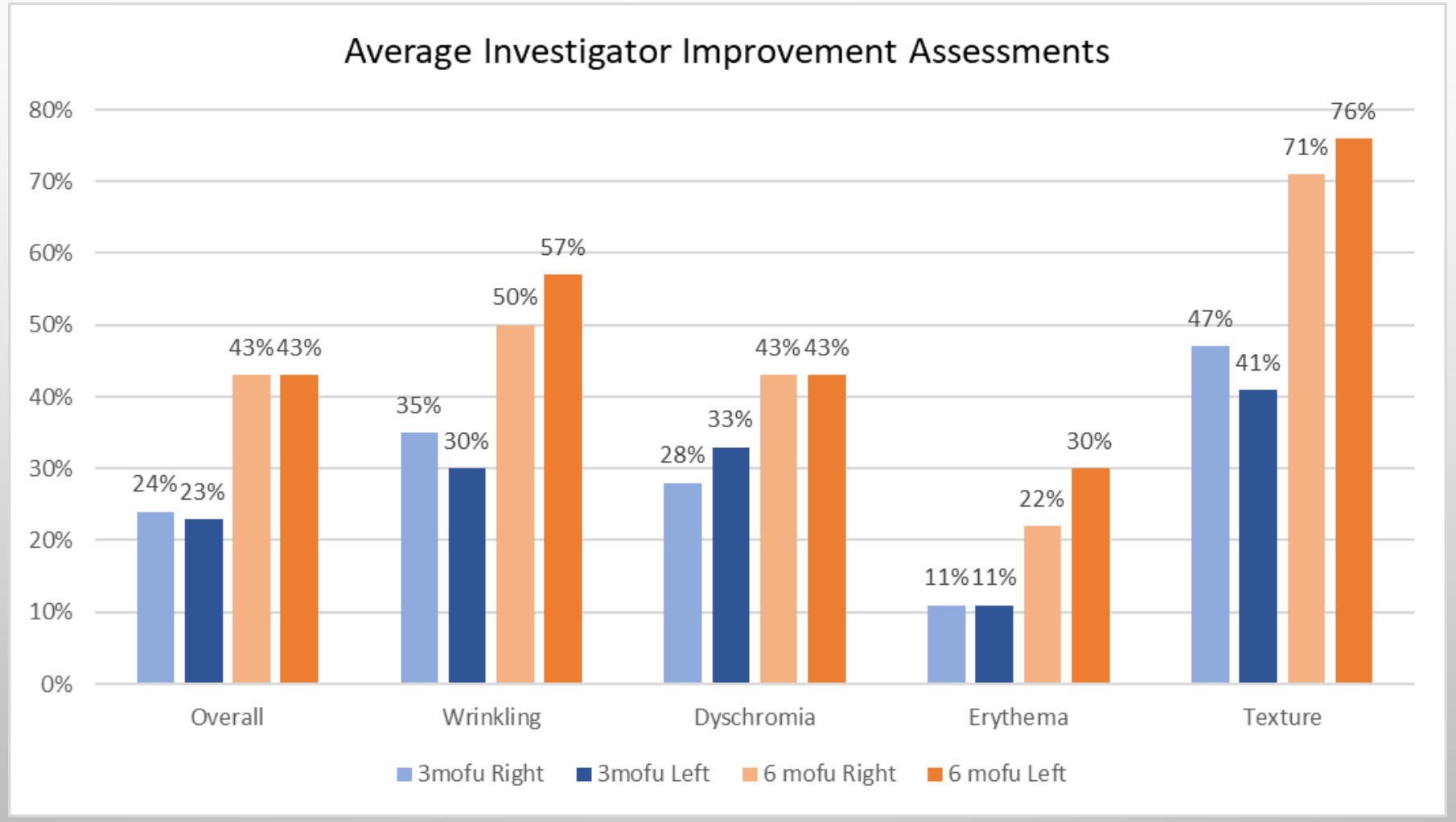
SUBJECT 06 – POST TX 1

SUBJECT 06 – POST TX 3

SUBJECT 06 – 3-MONTH FOLLOW-UP

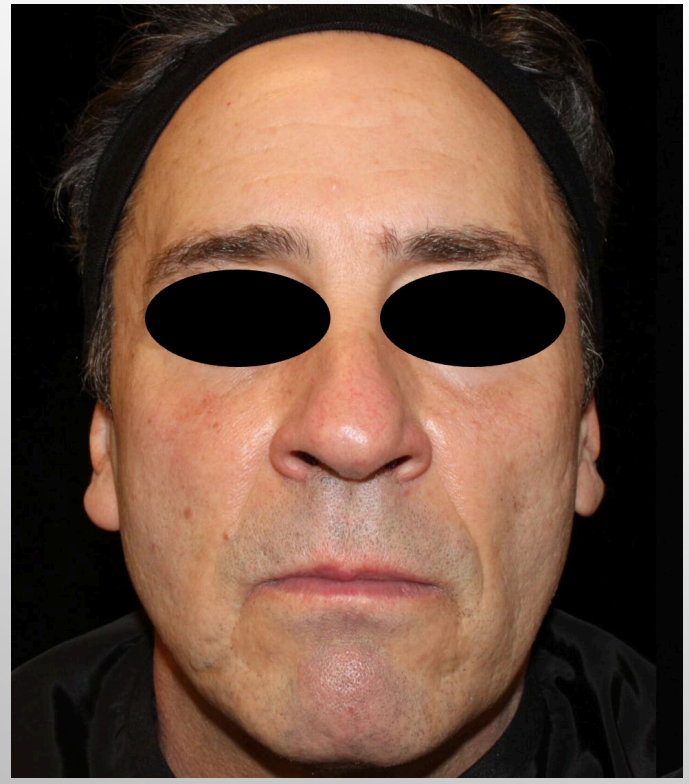
SUBJECT 06 – 6-MONTH FOLLOW-UP

3 AND 6-MONTH INVESTIGATOR IMPROVEMENT ASSESSMENTS

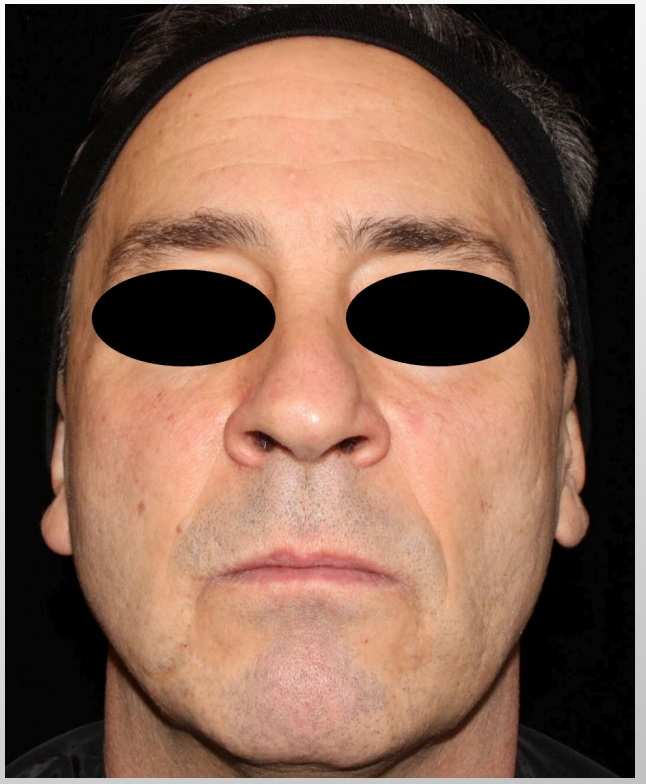


RF MICRONEEDLING: PRP TO R SIDE AND EXOSOMES TO L SIDE

BEFORE



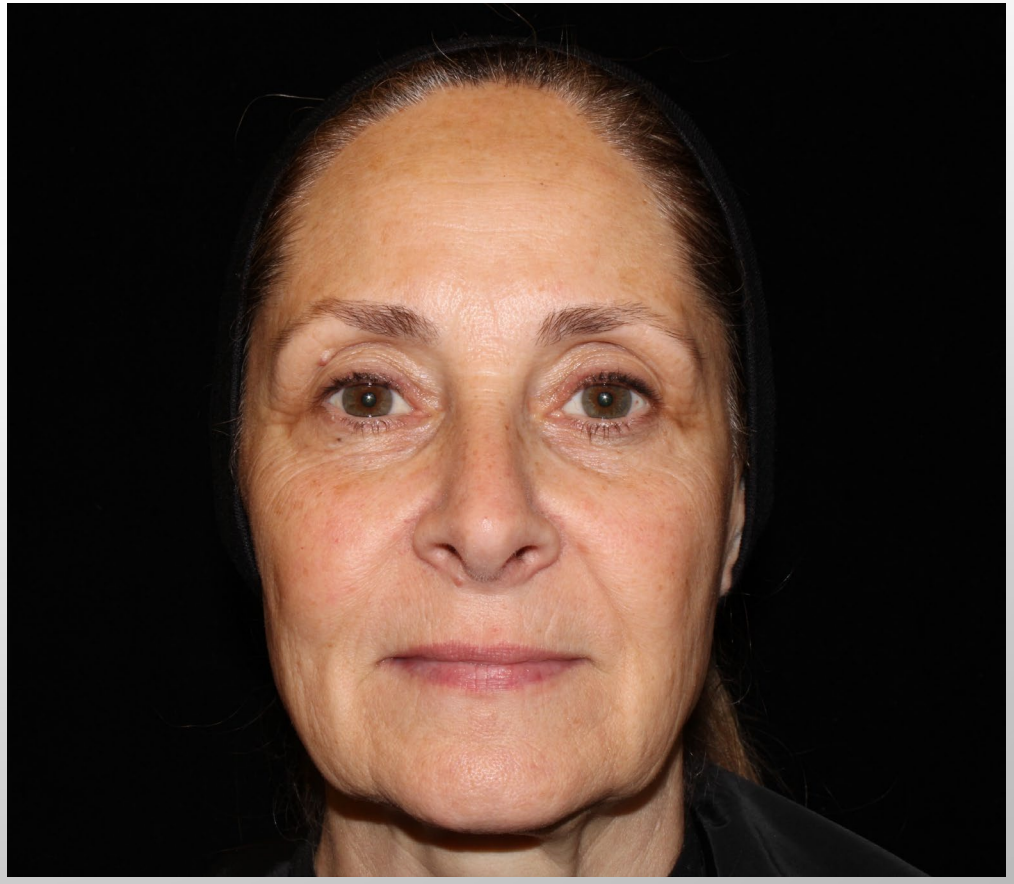
6 MONTHS LATER



RF MICRONEEDLING: PRP TO R SIDE AND EXOSOMES TO L SIDE

Baseline

6 Months after Treatment #3



BEFORE

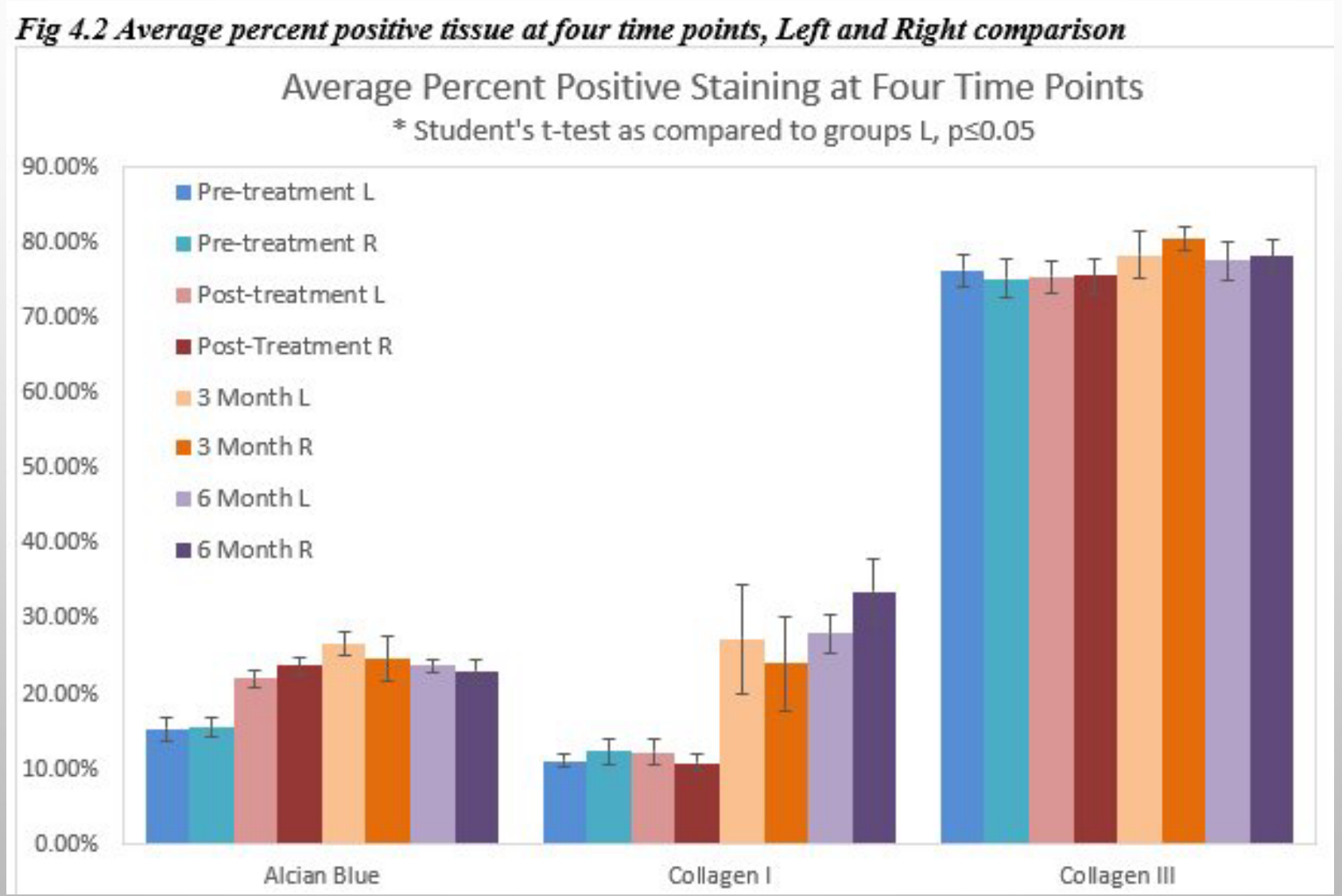
6 MONTHS LATER

Before

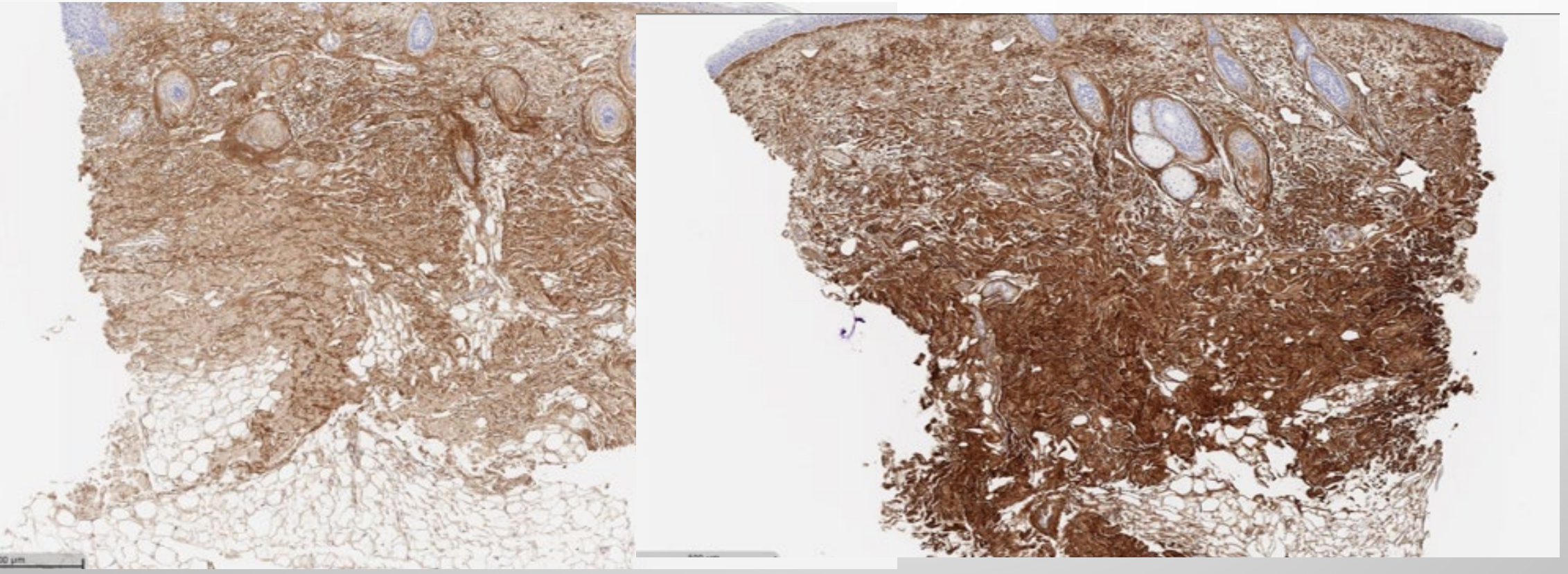
6 months later

AVERAGE % POSITIVE TISSUE AT 4 TIME POINTS

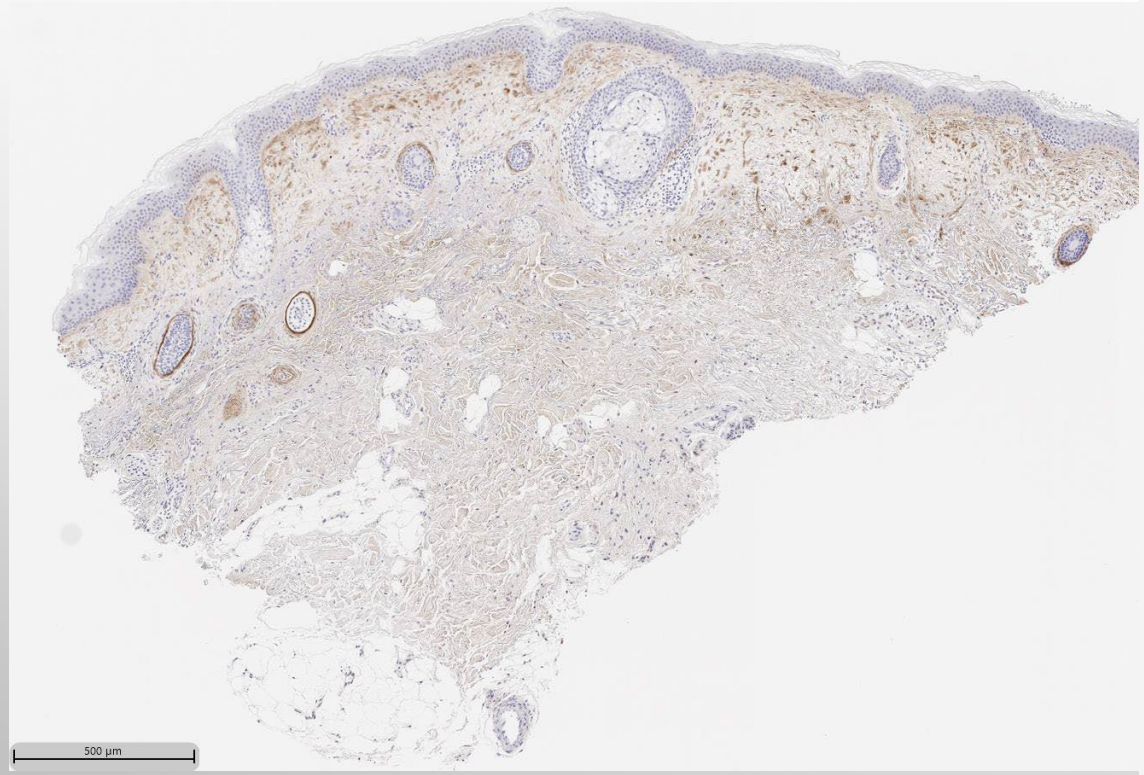
Fig 4.2 Average percent positive tissue at four time points, Left and Right comparison

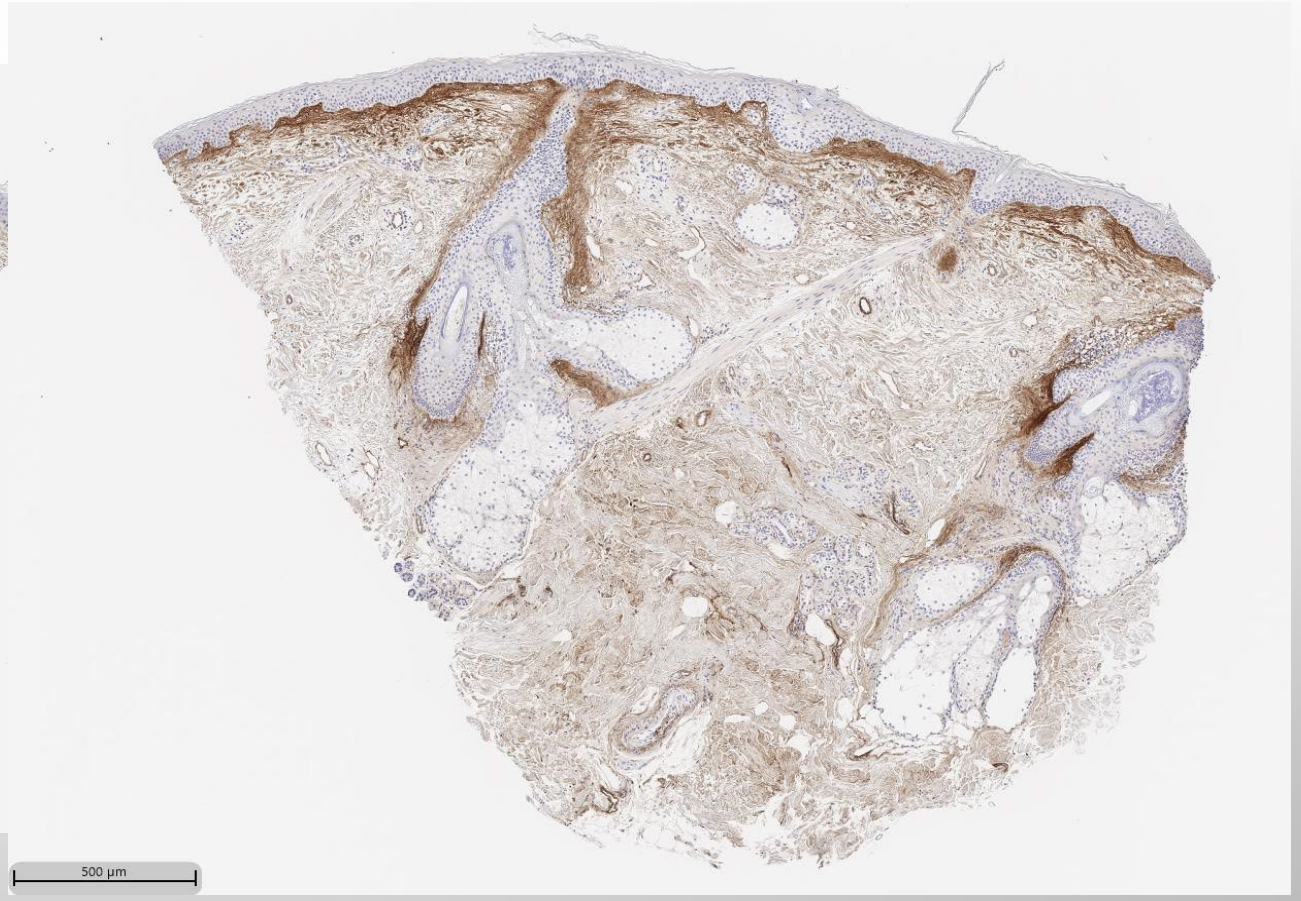


COLLAGEN IIII – PRE AND 6 MONTHS LATER

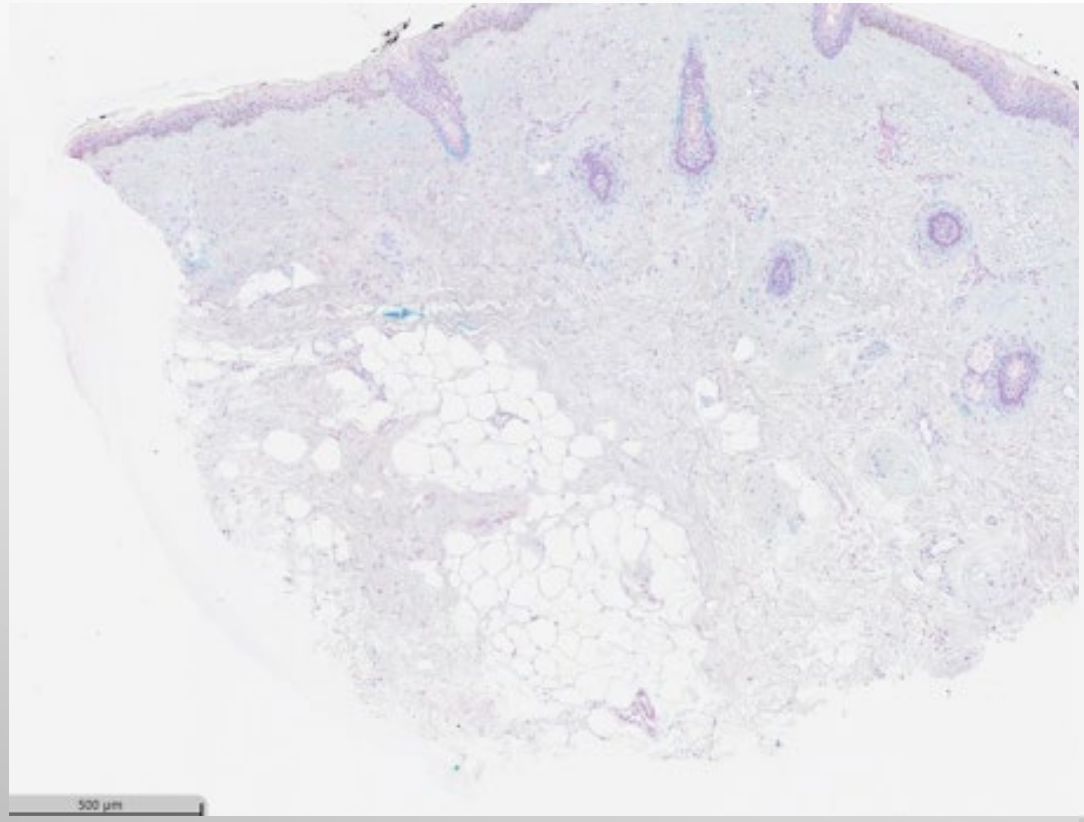


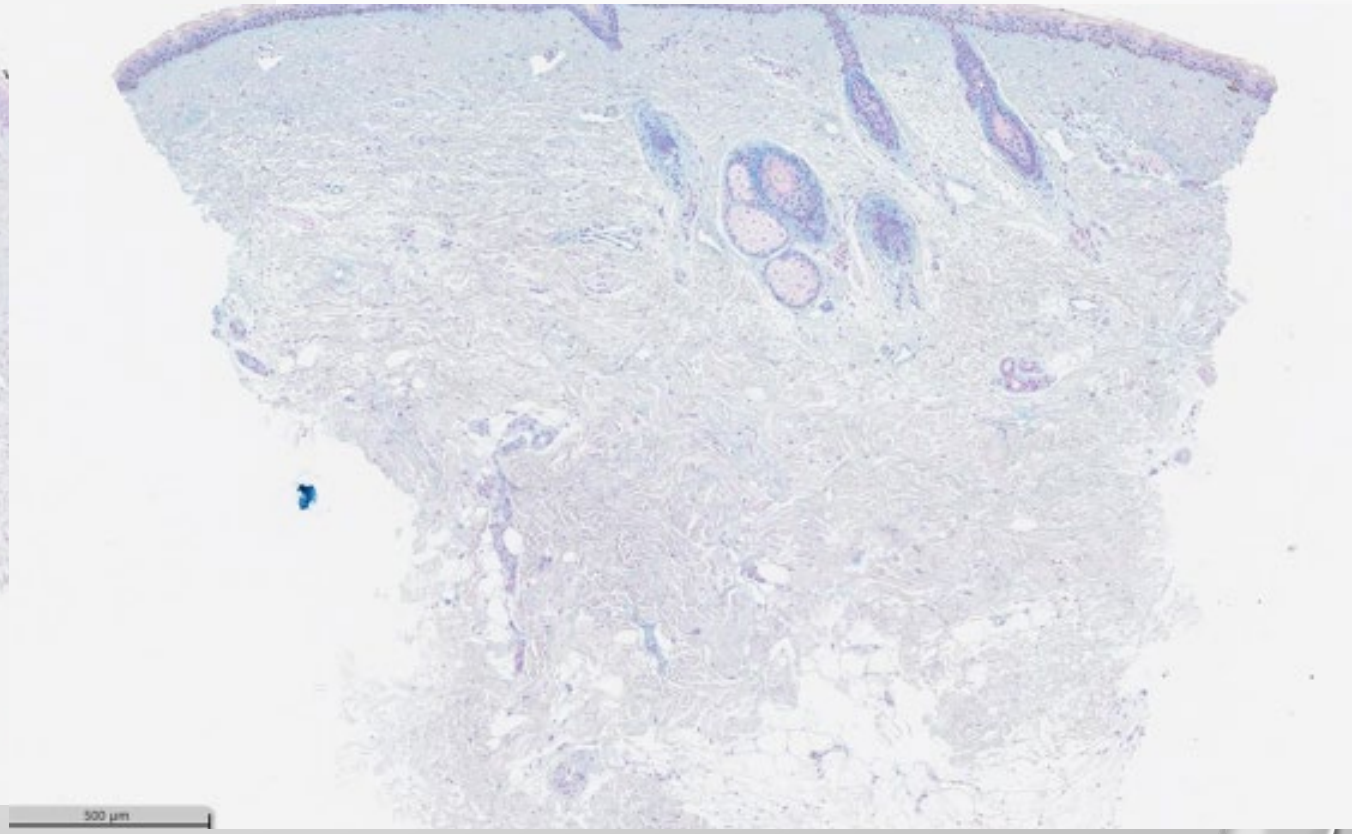
COLLAGEN I – PRE AND 6 MONTHS LATER





GAGS –PRE AND 6 MONTHS LATER





CONCLUSIONS

RESULTS SUMMARY

- EXOSOMES AND PRP INDICATED COMPARABLE HISTOLOGICAL RESULTS.
- EXOSOMES SHOWED SLIGHTLY BETTER RESULTS THAN PRP IN INVESTIGATOR VISUAL ASSESSMENTS.

ADVANTAGES OF EXOSOMES

- EXOSOMES ARE LESS INVASIVE AS THEY DO NOT REQUIRE BLOOD DRAW.
- CAN RESULT IN EQUAL OR IMPROVED EFFICACY THAN PRP.
- PRP IS HARVESTED FROM THE PATIENT'S OWN BLOOD, REFLECTING THEIR AGE, WHEREAS EXOSOMES ARE HARVESTED FROM HEALTHY DONORS AGED 18 TO 25 YEARS, POTENTIALLY OFFERING MORE ROBUST REGENERATIVE PROPERTIES.

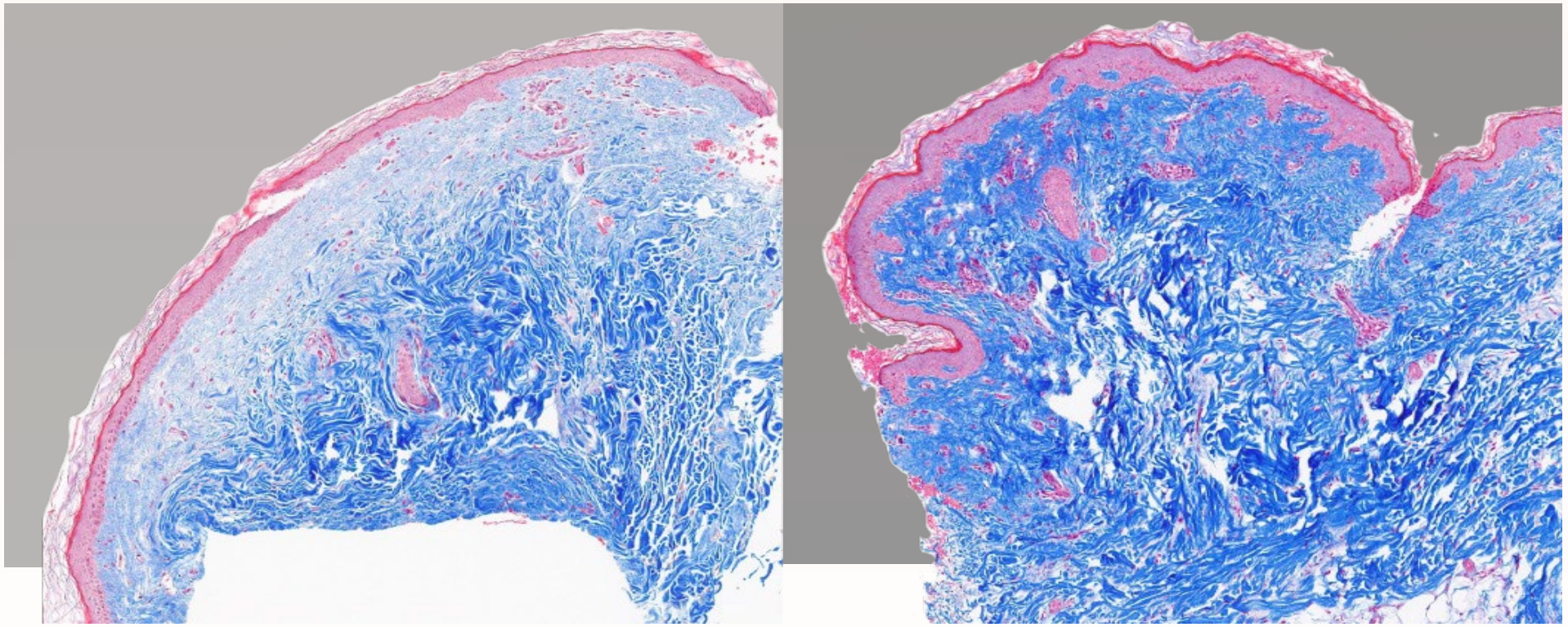
Platelet Derived Exosomes

Evaluate platelet-derived exosome formulation for skin renewal:

Collagen Improvement

Baseline

12 Weeks



Masson's Trichome

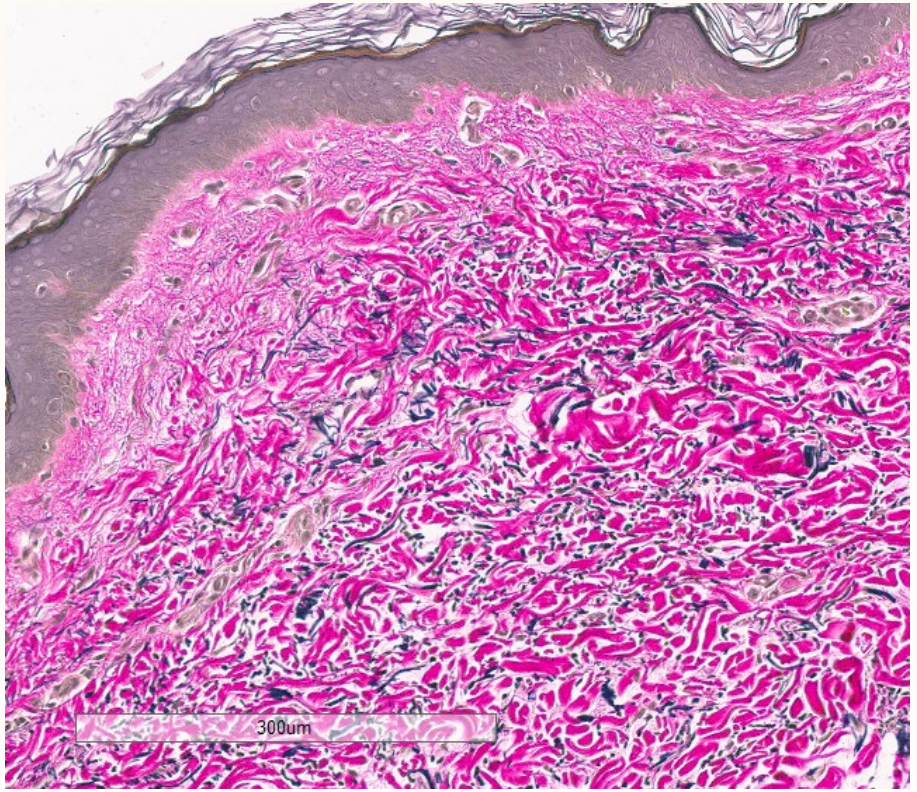
Data on file

80 yr old female

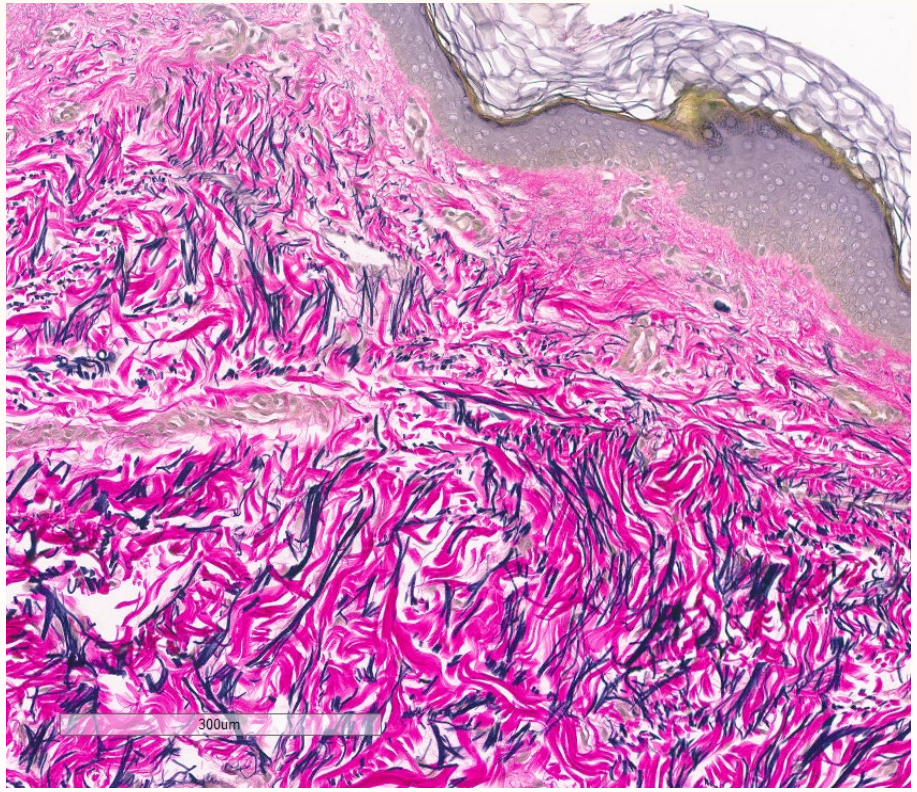
Data on file

Elastin Improvement

Baseline



12-weeks

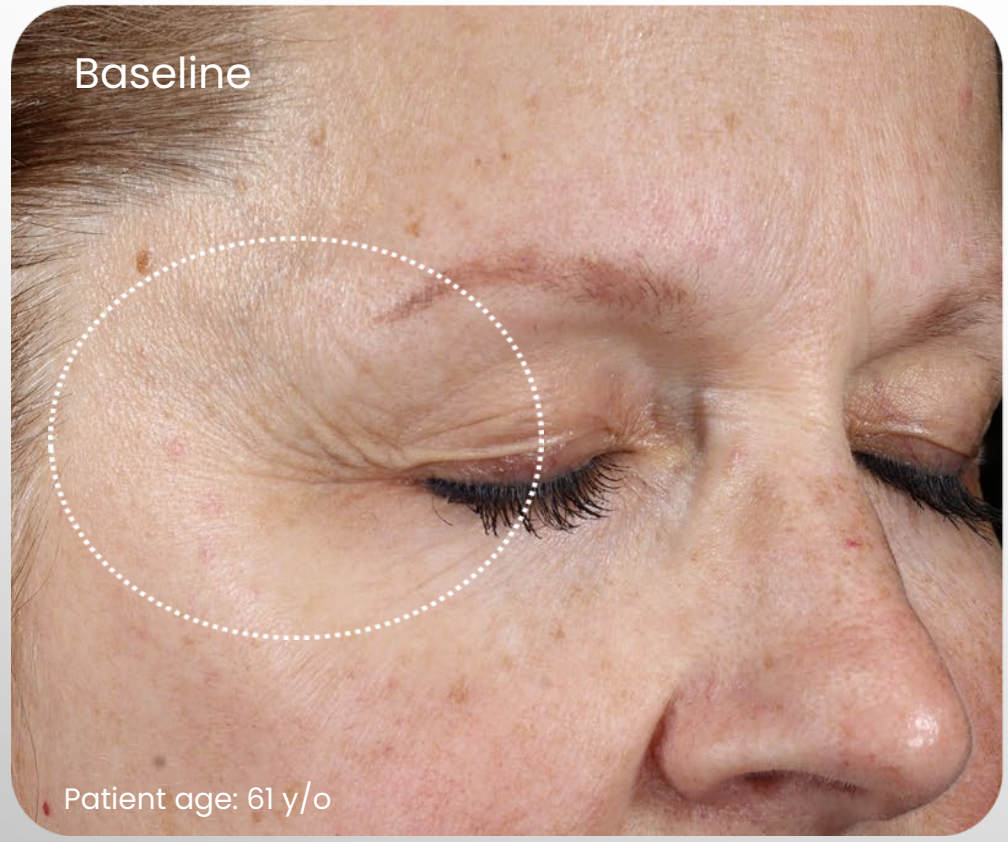


Verhoeff-van Gieson (elastin stain)

59 yr old Female

Data on file

Visible Reduction in Fine Lines & Wrinkles



Data on file

Visible Reduction in Redness

Data on file

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

Scientific Publications On Plants Stem Cells Producing Human Cell Signaling

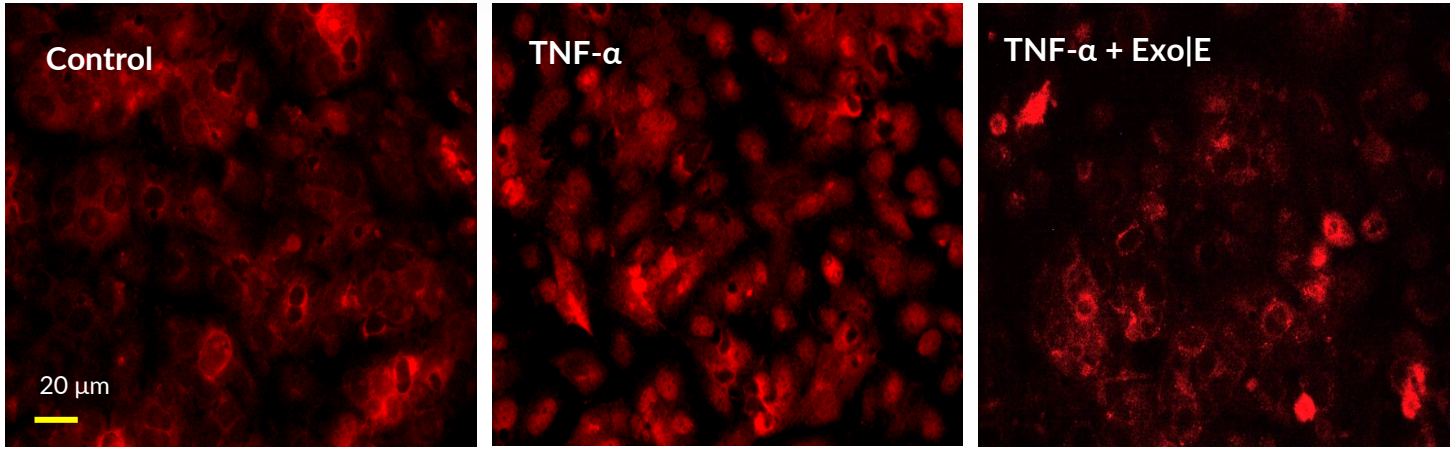
Talavera-Adame, D., Daniella Newman, Nathan Newman. Conventional and novel stem cell-based therapies for androgenic alopecia. *Stem Cells and Cloning: Advances and Applications*. 2017:10, 11-19.
2. Newman N, Rogowski N, Newman D, Talavera-Adame D. Autologous Adipose-Derived Stem Cell Treatment for Women with Genital Lichen Sclerosus. *J Gynecol Reprod Med*. 2018; 2(4): 1–4. 3. Talavera-Adame D, Sidhu H, Rogowski N, and Newman N. Comparative analysis of secretory factor profiles of human stromal vascular fraction by body region. *AJTM*. 2020; 4(2): 55-69.
4. Sidhu H, Talavera-Adame D, Newman N. Characterization of Primary and Immortalized Human Adipose Stem Cells Cultured in a Novel Serum-Free Xeno-Free Media. *AJTM*. 2021; 5(2): 85-111. (Image selected for cover of the journal)
5. Sidhu H, Talavera-Adame D, Newman N. Characterization of Human Adipose Stem Cells Growing in Optimized Serum-Free Xeno-Free Media. Convention Center at Los Angeles, CA, USA. *2019 Annual Meeting of the ISSCR*. June 26-29, 2019.
6. Talavera-Adame D, Sidhu H, Rogowski N, Newman N. Comparative Analysis of Secretory Factor Profiles of Human Stromal Vascular Fraction by Body Region. Convention Center at Los Angeles, CA, USA. Presented at the *2019 Annual Meeting of the ISSCR*. June 26–29, 2019.
7. Talavera-Adame D, Rajangam A, Sidhu H, Khan N, Newman N. Consortia Factors Induce Differentiation of Adipose Stem Cells to Hair Follicle Stem Cells. Convention Center at Los Angeles, CA, USA. Presented at the *2019 Annual Meeting of the ISSCR*. From June 26–29, 2019.
8. Sidhu HK, Talavera-Adame D, Newman N. Characterization of primary and immortalized human adipose stem cells cultured in a novel serum-free xeno-free media. Presented at the *2021 Annual Meeting of the ISSCR*. Virtually, from June 21–26, 2021.
9. Talavera-Adame D, Sidhu HK, Khan N, Zemach A, Palomares M, Newman N. Anti-inflammatory effects of adipose-stem-cell consortia factors as potential treatment for acute respiratory distress syndrome (ARDS) induced by cytokine storm syndrome. Presented at the *2021 Annual Meeting of the ISSCR*. Virtually, from June 21–26, 2021.

Publications Supporting Plant Derived Exosomes

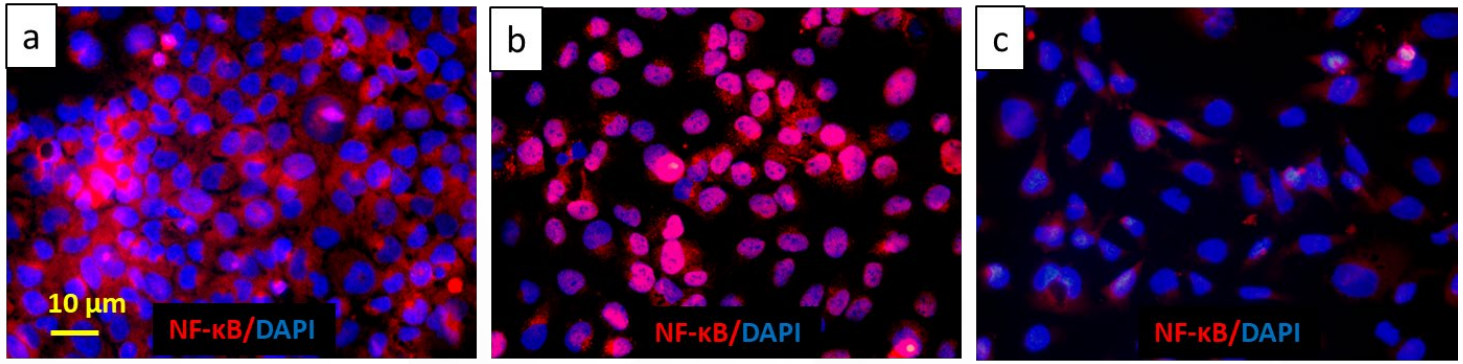
1. Plant-derived exosome-like nanoparticles: A concise review on its extraction methods, content, bioactivities, and potential as functional food ingredient, S Suharta et al. J Food Sci, 2021 Jul;86(7):2838-2850. doi: 10.1111/1750-3841.15787. Epub 2021 Jun 20\
2. Plant Exosome-like Nanovesicles: Emerging Therapeutics and Drug Delivery Nanoplatforms, Haseeb Anwar Dad et.al, Mol Ther, . 2021 Jan 6;29(1):13-31. doi: 10.1016/j.ymthe.2020.11.030. Epub 2020 Dec 3.
3. Plant-derived extracellular vesicles: a novel nanomedicine approach with advantages and challenges,Mohadeseh Nemati, et al, Cell Commun Signal. 2022 May 23;20(1):69. doi: 10.1186/s12964-022-00889-1.
4. The Emerging Role of Plant-Derived Exosomes-Like Nanoparticles in Immune Regulation and Periodontitis Treatment, Zeyu Zhang, et al, Front Immunol. 2022; 13: 896745. Published online 2022 Jun 10. doi: 10.3389/fimmu.2022.896745
5. Plant-Derived Extracellular Vesicles as Therapeutic Nanocarriers, Karamanidou T, Tsouknidas A. Int J Mol Sci. 2021 Dec 24;23(1):191

- **CONSORTIA FACTORS INDUCE DIFFERENTIATION OF ADIPOSE STEM CELLS TO HAIR FOLLICLE STEM CELLS, Dodanim Talavera-Adame, M.D. Ph.D., Alex Rajangam, Ph.D., Harpreet Sidhu, Ph.D, Nymul Khan, Ph.D., and Nathan Newman, M.D.* Abstract, ISSCR 2019.**
- **Consortia Factors- New Paradigm in Skin Care, Newman, N et al, In vitro Study,**

ANTI-INFLAMMATORY EFFECTS ON HUMAN CELLS



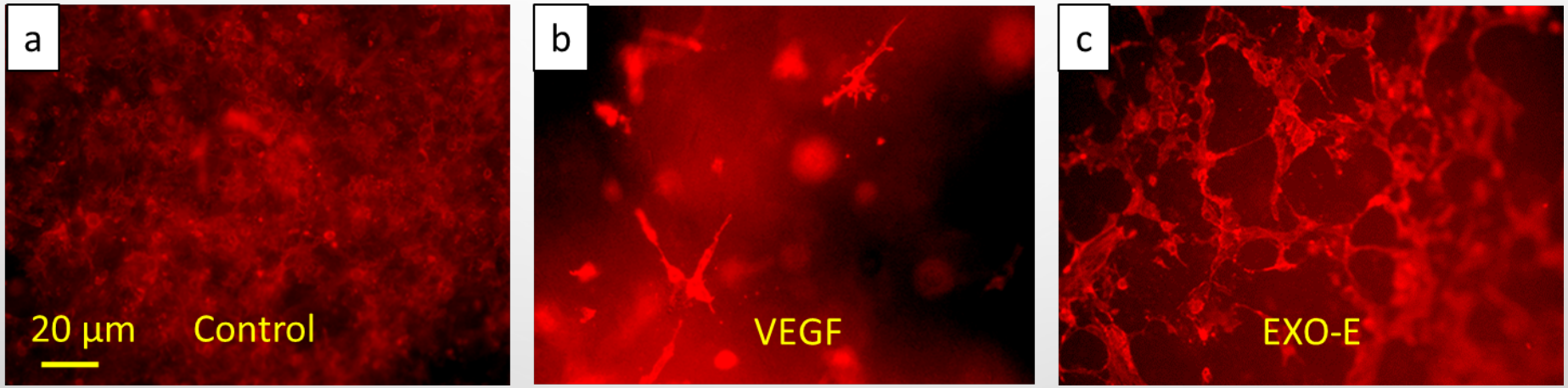
Human Dermal Microvascular Endothelial Cells plated in collagen-fibronectin gels with different treatments after 3 days stained with Phalloidin-Red Fluorescent Protein.



LPS = LipoPolySaccharides

NF-κB nuclear translocation in Human Dermal Microvascular Endothelial Cells (HMEC-1)

WOUND HEALING VIA ANGIOGENESIS



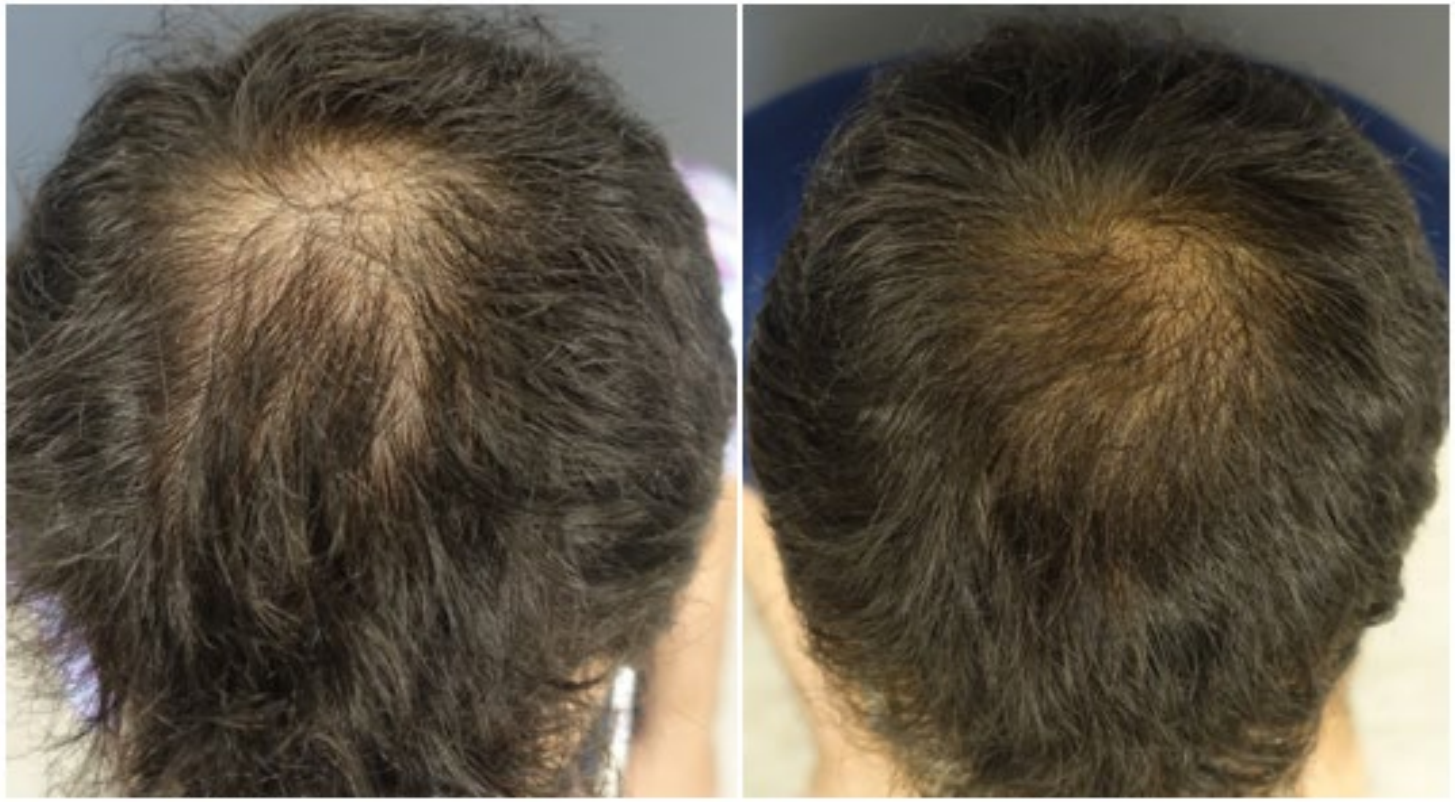
Human Dermal Microvascular Endothelial Cells plated in collagen-fibronectin gels with different treatments after 3 days.

RESULTS

ANTI-INFLAMMATORY EFFECTS OF EXO|E WITH ENERGY BASED TREATMENT

POST CO_2 Laser Resurfacing Treatment

Concern: Androgenic Alopecia | Applied Topically Twice A Day



BEFORE **AFTER 7 MONTHS**

EVALUATION OF WITH ULTRASOUND OR RF MICRONEEDLING TREATMENT FOR THE COSMETIC IMPROVEMENT OF HAIR AND SCALP HEALTH

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STUDY DESIGN

20 subjects, ages 23-79 with FP I-VI experiencing hair loss

10 subjects received RF Microneedling treatment to the scalp

10 subjects received Ultrasound treatment to the scalp

2x a day subjects instructed to apply hair serum at home

Treatment Protocol:

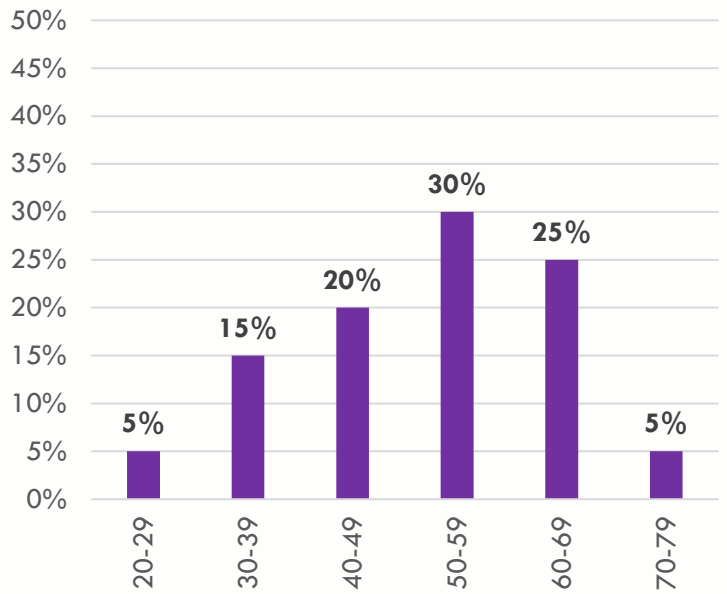
- 3 treatments spaced at 4-week intervals
- DE|RIVE hair serum applied to scalp post RF Microneedling and pre-Ultrasound treatment

Endpoints:

- Evaluate safety and efficacy of DE|RIVE hair serum

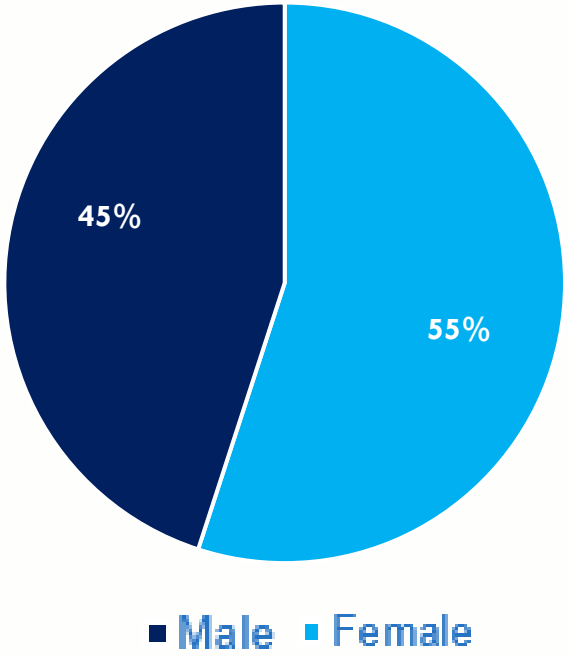
BASELINE DEMOGRAPHICS

Age



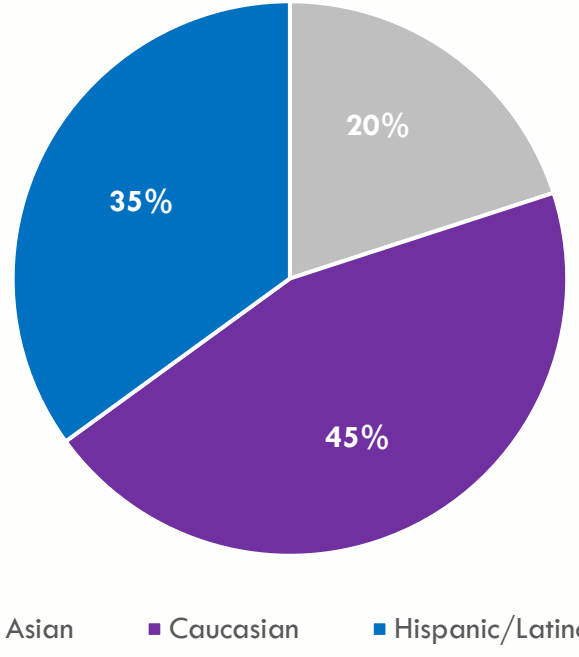
n=20

Gender



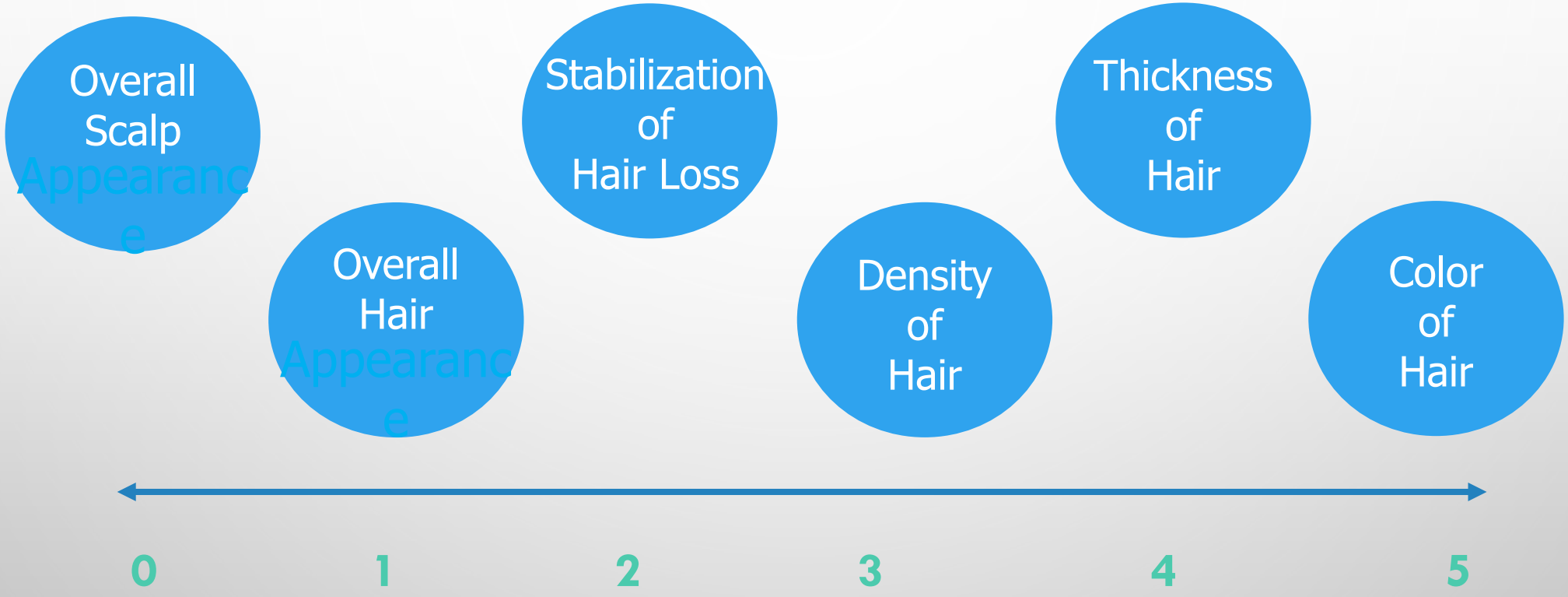
n=20

Race/Ethnicity



n=20

HAIR QUALITY ASSESSMENT – INVESTIGATOR

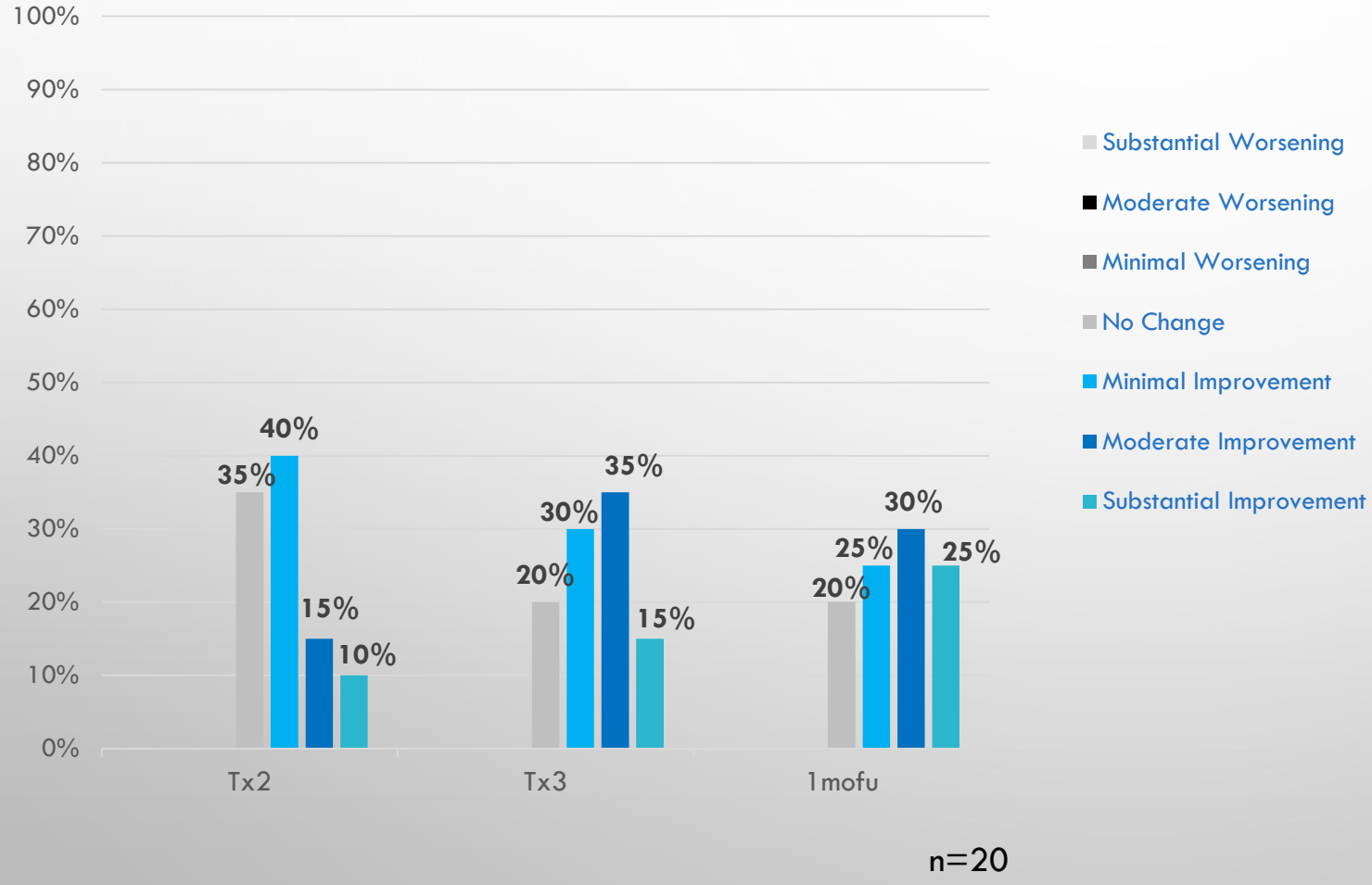


HAIR QUALITY ASSESSMENT - INVESTIGATOR

- **Overall Scalp Appearance:** Significant improvement, with fewer subjects being rated 2 and more 3 and 4
- **Overall Hair Appearance:** Noticeable improvement, with a shift towards higher ratings
- **Stabilization of Hair Loss:** Marked improvement, with a significant increase in subjects being rated 3
- **Density of Hair:** Improvement, with more subjects being rated 3 and 4
- **Thickness of Hair:** Improvement, with a higher percentage of subjects being rated 3 and 4
- **Color of Hair:** Some improvement

n=20

SUBJECT SATISFACTION



n=20

- Data indicates a clear trend of increasing improvement in hair and scalp health as self-reported by the subjects from Tx 2 to the 1-month follow-up
- Significant reductions in "no change" and "minimal improvement" ratings, coupled with the increases in "moderate improvement" and "substantial improvement" ratings.

RF MICRONEEDLING VS ULTRASOUND

COMPARATIVE SUMMARY

Investigator
Hair Quality Assessment

Generally, **Ultrasound** showed a more **pronounced shift** towards **higher ratings**

- Both treatments showed improvement, but Ultrasound had a more pronounced shift to higher ratings (3 and 4)
- **Overall Hair Appearance**: Both treatments showed improvement with Ultrasound showing a significant decrease in rating 2 and a higher percentage in rating 3
- **Stabilization of Hair Loss:** Both treatments led to improvement, but Ultrasound had a larger increase in higher ratings

COMPARATIVE SUMMARY

Investigator
Hair Quality Assessment

Generally, **Ultrasound** showed a more **pronounced shift** towards **higher ratings**

- **Density of Hair**: Both treatment showed improvement with Ultrasound demonstrating larger shift towards rating 3 and 4
- **Thickness of Hair:** Both showed improvement, but Ultrasound showed a more significant shift from rating 2 to higher ratings (3 and 4)
- **Color of Hair**: Both showed improvement with Ultrasound showing a more pronounced increase in higher ratings (4)

SCREENING

Ultrasound

3-month Follow-up

SCREENING

RF Microneedling

4-month Follow-up

- Both RF Microneedling and Ultrasound subjects experienced improvements in hair and scalp health.

- Results suggest that the combination of exosomes with Ultrasound treatment may maximize improvements.

CONCLUSION

- REGENERATIVE MEDICINE AND REGENERATIVE DERMATOLOGY IS RAPIDLY ADVANCING
- UNDERSTANDING THE MECHANISMS OF ACTION OF EXOSOMES AND SOURCES IS KEY
- VARYING SOURCES OF EXOSOMES AND EXOSOME LIKE SUBSTANCES
- LOOK FOR THE SCIENCE
- REMEMBER COMBINATION THERAPY ALWAYS WORKS BEST