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Transcriptomic-Guided Development of a Post-Procedure Formula to Prolong Skin Tone, Texture, and Wrinkle Appearance Benefits from Aesthetic Procedures

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1. Introduction

Aesthetic procedures have become increasingly popular to address a variety of skin concerns including aging. According to the American Society of Plastic Surgeons, minimally invasive skin resurfacing procedures experienced a 5% growth, accounting for nearly 14% of the total cosmetic minimally invasive procedures **[1]**. Procedures like non-ablative laser treatments are effective in addressing concerns like wrinkles, fine lines, hyperpigmentation, melasma, or solar lentigines, skin laxity, acne scarring, and skin texture **[2]**. These aesthetic procedures help to trigger the skin to regenerate by initiating a classic wound healing cascade, and its effects within the skin has been well studied **[3, 4, 5, 6]**.

Although minimally invasive procedures are effective, consumers seeking procedure treatments are in need of innovative products that not only boost the efficacy of the procedures but bridge the gap between clinical treatments and daily maintenance. This provides a holistic approach in delivering preventative and corrective benefits for skin rejuvenation. Current post-procedure formulas are designed primarily to soothe and protect the healing skin, so there remains an untapped opportunity to design a targeted formula that maximizes rejuvenation benefits based on the unique biological signature and specific needs of post-procedure skin.

It is well known that minimally invasive procedures alone demonstrates an inherent level of efficacy in providing skin and antiaging benefits. However, changes to the skin at a gene level after procedure treatment have not been widely studied. The hypothesis of this study is is to use transcriptomic analysis of skin treated with a fractional non-ablative laser to uncover the scientific changes to the skin after the treatment. With that knowledge, the effects of treatments can be maximized through the pairing with regenerative actives to bring about broader, faster, and improved skin benefits. Here, we present a customized post-procedure skincare formula with actives selected through transcriptomic-driven guidance to suit the distinct need of consumers undergoing aesthetic treatments. This revolutionizes formula development, enabling the delivery of top-tier performance for any skin needs.

2. Materials and Methods

Spatial Transcriptomics Analysis after Non Ablative Laser Resurfacing
Skin biopsies were collected from two participants who received Fraxel treatment at three time points: baseline (immediately before the first Fraxel laser treatment), 8 weeks after the first Fraxel session (immediately before the second treatment), and 20 weeks (12-weeks after the second Fraxel treatment). The study was approved by an Institutional Review Board, Allendale IRB (Old Lyme, CT, USA) and all procedures were performed with respect to the ethical principles stated in the Declaration of Helsinki. All samples were taken from the periauricular area at 3 timepoints: baseline, 8 weeks after the first session, and 20 weeks after the first session (12 weeks after the second session). Participants followed a simplified skincare routine throughout the study. Biopsies were fixed in 10% formalin, transferred to 70% ethanol, and paraffin-embedded for sectioning. Spatial transcriptomic profiling was performed on FFPE tissue sections using the Visium CytAssist platform (10x Genomics). Tissue preparation, probe hybridization, and library construction followed standard protocols. Sequencing was conducted on an Illumina NovaSeq, and data were processed and analyzed with Space Ranger and Loupe Browser software to generate spatial gene expression profiles.

Ex Vivo Microneedling Model
Fresh post-abdominoplasty normal human skin samples (n=2 lots (F/37/C) and (F/32/AA), 5-6 samples per treatment group per lot) were acquired from BioIVT Inc (Westbury, NY, USA). Tissue was defatted and cleaned of blood residue and subjected to treatment using a microneedling pen (36-pin needles, Dr. Pen A6 Cartridges Tips, Dr. Pen Inc., San Jose, CA, USA) with a needle length of 1.5 mm, as previously described [3]. Non-microneedled, untreated biopsies served as the experimental control. Biopsies subjected to microneedling were either untreated or received topical application of the regenerative active combination. Following a 6-day culture period, all biopsies were processed for histological and immunohistochemical analysis. Skin explants were processed for hematoxylin and eosin (H&E) staining and immunohistochemical staining against filaggrin (FLG) according to standard protocol (Novovita, Natick, MA, USA).

Oxidative Stress and Mitochondrial Response to UVA Exposure in Human Dermal Fibroblasts
Human primary dermal fibroblasts (Lot DFM093015A, P4, ZenBio, Durham, NC, USA) were plated in a 12-well plate in DMEM HG with FBS and Penicillin, Streptomycin, and Amphotericin B. Cells were left to attach for 72 hours at 37C and 5% CO2. Following 72 hours, growth medium was removed and replaced with treatment media containing the regenerative active combination for 48 hours in the following conditions, with 3 replicates per treatment group. To induce oxidative stress, media was removed and replaced with 1x dPBS and cells were exposed to 20J/cm2 UVA irradiation with a wavelength of 335-400nm using the Newport SOL-UV-6 solar simulator (Newport Corporation, Irvine, CA USA). The control group did not receive exposure to UVA. Following UVA exposure, the dPBS was removed and replaced with treatment medium. Cells were cultured for 6 hours. Following this time, media was removed and cells were harvested for qPCR. Cells were washed with 1x dPBS and lysed. RNA was extracted according to manufacturer instructions and quantified using the NanoDrop Spectrophotometer. qRT-PCR was performed in duplicate.

Measuring Mitochondrial Potential using TMRE Staining
Human dermal fibroblasts from aged donors (Lot 1616 and 2485, Cell Applications, San Diego, CA, USA) were plated in a 48-well glass-bottom dish (n=6 per treatment group per lot). Cells were left to adhere overnight. Following adhesion, media was removed and replaced with treatment medium. Cells were treated with the regenerative active combination for 7 days, where media was replaced every other day with the exception of weekends. Following the culture period, mitochondrial potential was measured using tetramethylrhodamine, ethyl ester (TMRE) staining to label active mitochondria. Media was removed and replaced with media containing 200nM of TMRE. Cells were incubated with the dye for 30 minutes at 37C/5% CO2.

Cells were then washed with 1X dPBS to reduce background when imaging. dPBS was added to each of the wells and imaged on the fluorescent microscope (Leica DM500, Wetzlar Germany).

Dermal Protein Release in Human Dermal Fibroblasts from Aged Donors
Human dermal fibroblasts from older aged donors (Lot 1616 and 2485, Cell Applications, San Diego, CA, USA) were plated in a 48-well culture dish (n=6 per treatment group per lot). Cells were left to adhere overnight. Following adhesion, media was removed and replaced with treatment medium. Cells were treated with the regenerative active combination for 7 days, where media was replaced every other day with the exception of weekends. Media supernatant was collected at each media change. An ELISA to quantify Pro-Collagen I (Catalogue #MK101, Takara Bio, Kusatsu, Shiga, Japan) release was conducted according to manufacturer protocol. Total protein content was determined by performing a Pierce Protein BCA (Catalogue #PI22660, Thermofisher Scientific, Waltham, MA, USA) according to manufacturer protocol. Total pro-collagen I release was normalized to total protein content for each sample.

Evaluation of Anti-Pigmentation Efficacy in Pigmented Reconstructed Epidermis Model
Human pigmented epidermis (ERP) was reconstructed according to the standard protocol [4]. All the tissue samples were incubated at 37 °C with 5% CO2 and saturated humidity.The ERP model was subjected to UV exposure, which was delivered using a 1600 W Xenon arc solar simulator (Newport SOL-UV-6, serial number 1003) equipped with a daily UV filter. During UV exposure, skin model samples were transferred to new 12-well plates containing fresh dPBS. The skin model samples were exposed to 7.5J/cm2 of daily UV then had fresh medium containing the regenerative active combination or solvent control replaced and cultured in an incubator with 5% CO2. The exposure started on Day 9 and was repeated four times from Day 9 to Day 14. At Day 15, the samples were harvested for analysis. Analysis included H&E, DOPA, and Fontana Masson staining in addition to select gene analysis. The quality of ERP models after treatment was controlled by tissue histology and melanocyte morphology via DOPA staining. The melanin present in the ERP model was quantified via Fontana Masson staining and image analysis. Slides were scanned using the Nanozoomer. For each epidermis sample, about 10-15 images were extracted via white light at a magnification of 20x. The area occupied by melanin is quantified with Histolab software. Statistical analysis, including graphic comparison and p-value significance calculated by Mann-Whitney U test was conducted using SPSS software.

Clinical Post-Procedure Laser Study
The study was monocentric, randomized, split-faced and double-blinded (approved by an Institutional Review Board, Adverra IRB, # Pro00073859 and all procedures were performed in accordance with the ethical principles stated in the Declaration of Helsinki). Prior to study start, all participants received necessary information and provided informed consent. Study eligibility was determined by physical examination and confirmation of all inclusion and exclusion criteria. Pariticipants with mild to severe crows feet wrinkle (grading of 2-5.6 on L'Oreal Atlas Scale), mild to severe dyschromia (grading of 3.5-8 on Griffith Scale), and mild to severe roughness (grading 3.5-8 on Griffith Scale) were included in the study. The study concluded with 35 participants with Fitzpatrick skin phototype II (n=6) and III (n=29), aged 52-62 years. No product related adverse events were reported throughout the study.

Non-ablative fractional laser treatment was performed using Sciton Halo® with a laser setting of 1470nm wavelength and 15mm scan line. A topical regimen was followed for 28 days following the laser resurfacing treatment in addition to follow-up visits including safety and tolerance evaluation on Day 0 (baseline), Day 1, Day 2, Day 3. Day 7, Day 14, and Day 28. Test materials consisted of a currently marketed over- the- counter (OTC) medical bench and the customized post-procedure formula containing the tested regenerative active combination. Participants applied 2mg/cm^2 of the test product to the assigned side of the face twice daily.

Auxiliary products, including a commercialized gentle facial cleanser (2x per day) and sunscreen were distributed to all participants to be used throughout the entire study. The clinical assessment of anti-aging efficacy was performed, in which grading was conducted on global wrinkles, fine lines, dyschromia, skin tone evenness, brightness, radiance, roughness, laxity, firmness, and overall healthy appearance on Day 0 (baseline), 7, 14, and 28 separately on each side of the face. Safety was assessed by recording any adverse events and tolerance, including local intolerances, erythema, peeling, pruritis, and dryness for the entirety of the study. Change from baseline was estimated using a linear mixed model, which included fixed effects for the baseline score, treatment, visit, and interaction of treatment group with visit and a random participant effect. Contrasts of least square mean estimations were used to calculate improvement versus baseline and comparisons between treatment groups. If model assumption was not met, Wilcoxon signed-rank tests were performed. Adjusted p-values were calculated using the Benjamini-Hochberg method.

Monotherapy Topical Clinical Study

The objective of the monotherapy clinical study was to understand changes from baseline to skin quality as a result of applying the formula without a laser treatment . To accomplish this objective, a 12-week monotherapy clinical study was conducted on 76 female participants with Fitzpatrick type I-VI (34% type I-II, 33% type III-IV, 33% type V-VI), aged 35-60 years. Participants presented with mild to moderate wrinkles, fine lines, uneven skin tone, dullness, rough skin texture, laxity, visible redness, and appearance of pores on the global face. Some participants presented suborn dark spots and/or post-acne marks. In this study, the post-procedure formula containing the tested regenerative active combination was applied twice daily with the use of regular cleanser and sunscreen. Clinical grading was performed on a 10 point modified Griffiths scale.

3. Results

Spatial Transcriptomics Reveals Gene Changes following Fraxel Laser Treatment

Following two sessions of Fraxel laser treatment, a total of 918 genes were found to be significantly differentially expressed at 20 weeks($P < 0.05$). To further elucidate the biological significance of these gene expression changes, we performed comprehensive enrichment analyses, including both oncological biological process (BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses. KEGG pathway analysis of the significantly upregulated genes revealed notable enrichment in several pathways: such as the tyrosine metabolism, chemokine signaling, melanogenesis, extracellular matrix (ECM)-receptor interaction, and tumor necrosis factor (TNF) signaling. These findings suggest increased activity in metabolic, inflammatory, pigmentation, and ECM-related processes following laser treatment. Conversely, Gene Ontology Biological Process (GO BP) analysis of the significantly downregulated genes demonstrated marked suppression of pathways related to epidermis development, cornification, and keratinization, indicating a reduction in epidermal differentiation and barrier formation processes. Collectively, these results provide insight into the molecular mechanisms underlying the skin's response to Fraxel laser treatment, implicating both enhanced regenerative and remodeling pathways as well as suppression of epidermal maturation.

Regenerative Active Combination Improves Skin Barrier Regeneration following Microneedling

Microneedling treatment of the skin creates microwounds that trigger a classic wound healing cascade. The effects of microneedling in ex vivo skin has been previously described [3]. This study evaluated the benefit of the regenerative active combination applied topically daily to microneedled tissue. Figure 1 demonstrates the histology and immunohistochemistry staining of the treated tissue. Hematoxylin and eosin (H&E) staining demonstrates healthy tissue morphology in untreated control tissue and the presence of micropunctures in the

microneedle-treated tissue (MNCTL and MN+Active Combination). Treatment with Regenerative Active Combination (MN+Active Combination) demonstrated improved tissue health compared to microneedling alone (MN Control).

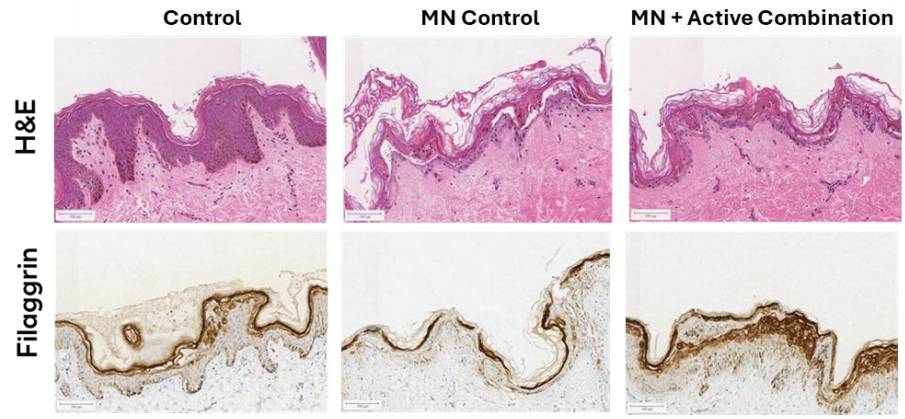

Figure 1. Representative histology and immunohistochemistry images of untreated control, microneedle control, and microneedled tissue treated with Regenerative Active Combination. Scale Bar = 100μm

Immunohistochemistry staining against filaggrin demonstrates expression in the stratum corneum and upper stratum granulosum in the untreated control. Microneedled control tissue (MN Control) demonstrated disruption of filaggrin expression localized to the microwounds. Treatment with the regenerative active combination following microneedling increased expression of filaggrin, indicating enhanced epidermal renewal and barrier restoration post microneedling disruption.

Regenerative Active Combination Mitigates Oxidative Stress and Promotes Mitochondrial Activity

The regenerative active combination was studied for its AOX benefits in fibroblasts exposed to UVA. Figure 2a demonstrates that the regenerative active combination provided antioxidative stress benefits to the cells. Following UV exposure, we observe a significant decrease in GSH-Px expression indicative of a stress response in the cells. Also observed is an increase in hemeoxygenase 1 (HO-1) expression, an enzyme whose metabolic products scavenge ROS and nitrogen reactive species to suppress inflammatory response in the tissue. We demonstrate that the pretreatment with the regenerative active combination provides a protective effect through maintaining expression levels of both GSH-Px and HO-1 comparable to untreated control.

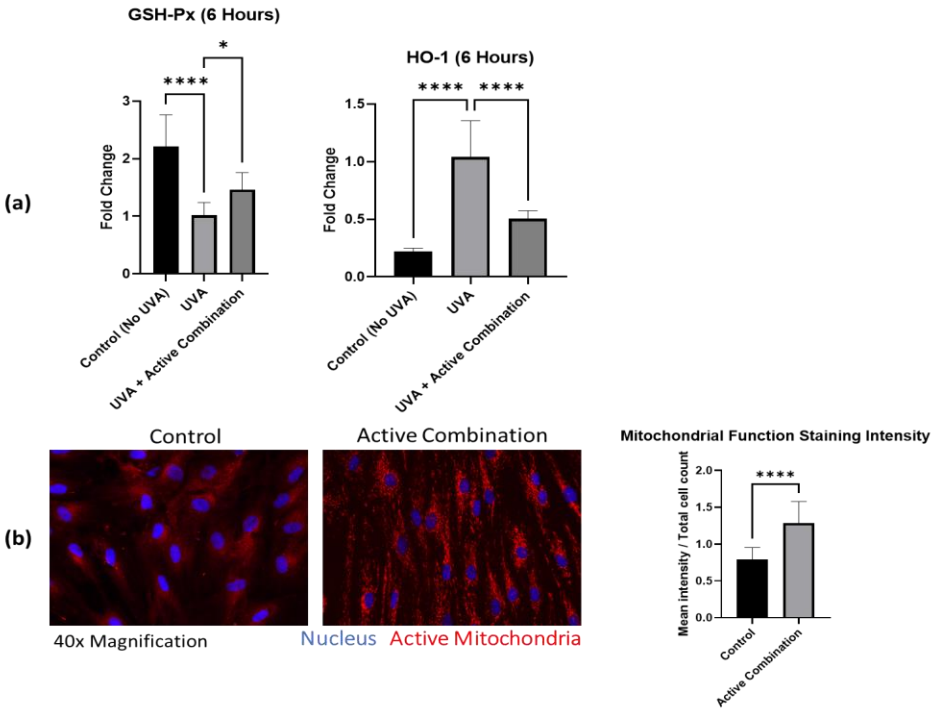

Figure 2. (a); Gene expression of key enzymes in oxidative stress markers GSH-Px and HO-1 response following UVA exposure. (b); Representative TMRE staining on aged fibroblasts treated with the regenerative active combination quantified to demonstrate significant increase in staining intensity normalized to total cell count. ****, p<0.0001.

Mitochondria are essential for skin health, producing energy (ATP) and regulating key cellular processes like calcium homeostasis, oxidative stress response, and apoptosis. Their energy production is crucial for the metabolically demanding process of wound healing, contributing to cellular signaling and matrix remodeling. After oxidative stress, cellular homeostasis is restored through ROS neutralization, which alters gene expression to activate repair mechanisms like glutathione peroxidase, or through apoptosis.The mitochondrial membrane potential is an essential component during the oxidative phosphorylation process and is a key marker for mitochondrial activity. This can be measured in cells using TMRE (tetramethylrhodamine, ethyl ester) dye. During the oxidative phosphorylation process, positively charged protons are transferred across the mitochondrial inner membrane creating a negative charge. TMRE, which is a positively charged dye, accumulates in the negatively charged mitochondria, with a higher intensity staining present in more active mitochondria. Figure 2b demonstrates the significant increase in TMRE staining normalized to cell count in fibroblasts from aged donors treated with the regenerative active combination. It is hypothesized that the antioxidant nature of these actives contributes to mitigate any oxidative stress in the cells and therefore can help promote proper mitochondrial function.

Regenerative Active Combination Mitigates Melanin Production in Basal and Stressed State Pigmented Reconstructed Skin Model

Hyperpigmentation is a frequent post aesthetic procedure complication, particularly after treatments like fractional lasers or strong chemical peels and in individuals with higher Fitzpatrick phototypes. Post-inflammatory hyperpigmentation (PIH) occurs as a response to skin inflammation or injury. Typically, when the skin is in an inflamed state, the released pro-inflammatory mediators (such as IL-1, IL-6, prostraglandins) stimulate melanocytes leading to melanin synthesis and transfer to surrounding keratinocytes *[7, 8]*. Management of hyperpigmentation requires a multifaceted approach, one strategy including the use of topical cosmetic agents to manage inflammation and prevent melanin synthesis or transfer.

Pigmented reconstructed epidermis was also exposed to a daily UV-radiation (DUVR) treatment to study potential anti-pigmentation benefits of the regenerative active combination following an external stressor. DUVR significantly increased melanin quantity compared to unexposed and untreated control tissue. Treatment with the regenerative active combination significantly decreased melanin quantity compared to the solvent control following DUVR exposure by 22% (Figure 3).

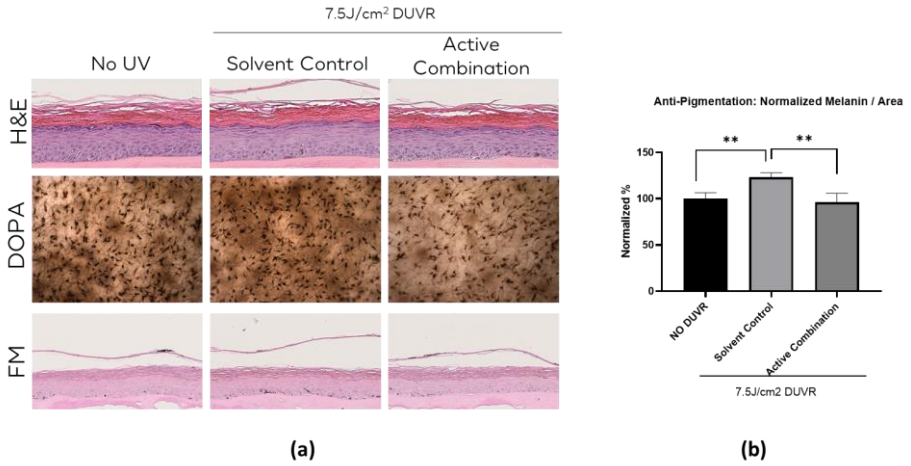

Figure 3. a) Histology (H&E), DOPA, Fontana-Masson (FM) staining following treatment with regenerative active combination after DUVR exposure; b) Quantification of melanin normalized to area following treatment with regenerative active combination after DUVR exposure. **, $p<0.01$.

Dermal Protein Synthesis Promotion from Regenerative Active Combination

Matrix remodeling is a key step in the wound healing process. Following stimulation of the aesthetic procedure, enhanced production and protection of dermal proteins such as collagen, elastin, and proteoglycans can help to maintain skin structure and provide antiaging benefits. Here, we studied the effects of the regenerative active combination on dermal regeneration, demonstrating that the active combination significantly upregulates pro-collagen I release by +137% compared to untreated control in fibroblasts from older age donor (data not shown).

Use of Post-Procedure Formula Containing Regenerative Active Combination following Non-Ablative Laser Treatment Augments Procedure Benefits

Following non-ablative laser treatment, the tested post-procedure formula containing the tested regenerative active combination has no reported adverse events or formula related complications. Clinical grading on Day 28 revealed the formula provided statistically significant improvement compared to the OTC Medical Bench on 9 key skin rejuvenation parameters (global wrinkles, skin firmness, skin laxity, overall healthy appearance, visual skin roughness, skin radiance, skin brightness, skin tone evenness, and overall skin dyschromia) as demonstrated in Figure 4. Representative participant images also reveal that the post-procedure formula containing the regenerative active combination improved global wrinkles, undereye wrinkles, wrinkles on the cheek, skin dyschromia, skin tone evenness, and overall healthy appearance on Day 28.

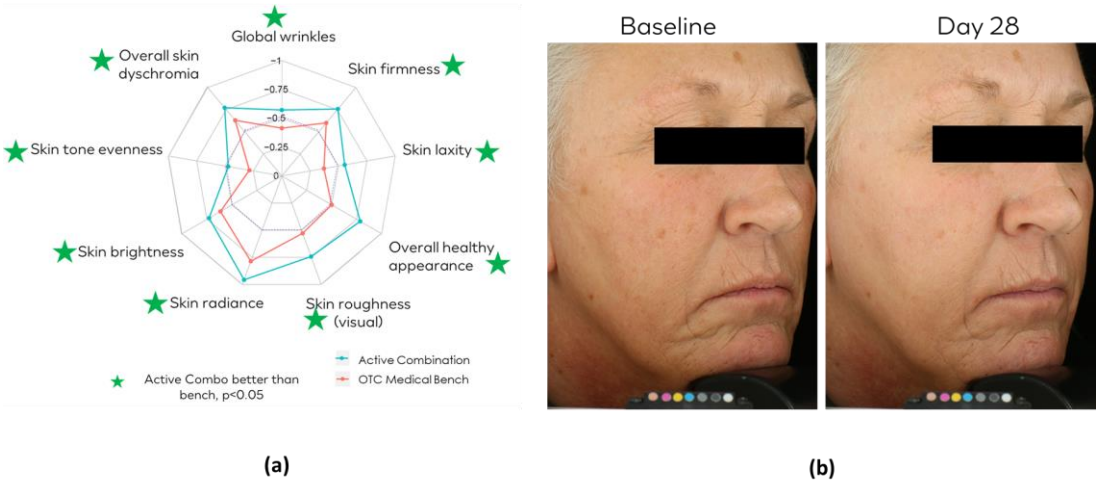

Figure 4. a) Spider plot demonstrating clinical grading on 9 dimensions related to anti-aging benefits based on clinical grading; b) representative participant image at baseline versus Day 28 demonstrating improvement in global wrinkles, skin firmness, and laxity.

Monotherapy Topical Clinical Study with Post-Procedure Formula Reveals Skin Rejuvenation Benefits

A clinical study of skin attributes, in which the formula containing the regenerative active combination was applied topically for 12 weeks, evaluates this formula for its skin benefits as a daily skincare routine. Clinical grading demonstrated statistically significant improvement in skin quality parameters as early as 4 weeks. At the conclusion of the study at week 12, parameters such as redness (-69.7%, p<0.0001), dark spots (-26.5%, p<0.0001), fine lines (-16.5%, p<0.0001) and wrinkles (-18%, p<0.0001), compared to baseline significantly improved (Figure 5).

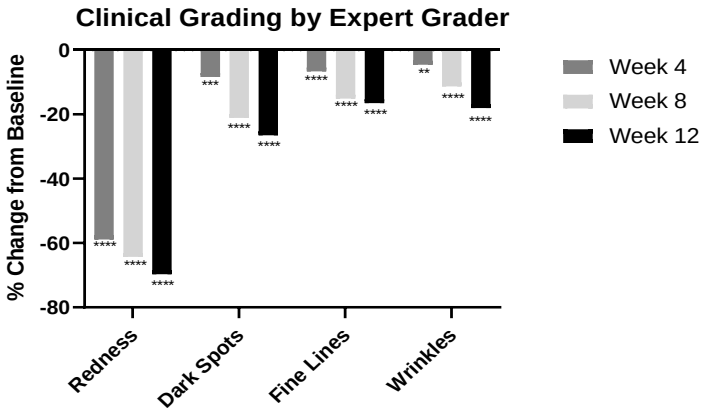

Figure 5. Expert grading at Week 4, Week 8, and Week 12 compared to baseline following treatment with the post-procedure formula, with significant improvement on redness, dark spots, fine linkes and wrinkles. **, p<0.01; ***, p<0.001;****, p<0.0001.

4. Discussion

Aesthetic procedures are very effective in addressing a multitude of skin concerns. However, while resurfacing procedures like laser treatments and microneedling deliver visible results, the treatments make the skin the skin go through a period of vulnerability during the healing and regenerative phases. To help address such concerns, current standard of care for skincare routines pre- and post-procedure typically includes gentle cleansers, moisturizers, and sunscreen. Ingredients that help to protect the skin barrier and minimize inflammation are also

commonly incorporated and the benefits such formulas in post-procedure skin have been studied **[9, 10, 11, 12]**. However, there lies a significant limitation in the development of optimal post-procedure formulas due to the limited understanding to the holistic gene changes following treatment. While clinical observation, histological studies, and select microarray panels have well documented alterations after procedure treatments, the intricate molecular dynamic shifts in the gene expression remains largely uncharacterized **[13, 14]**.

The current study revealed through spatial transcriptomic analysis of biopsies following treatment with fractional nonablative laser targeted genes related to metabolic, inflammatory, pigmentation, and barrier reformation processes. Integration of these learnings enabled the precise selection of actives best catered for post-procedure skin environment. The selected active combination demonstrated enhanced healing of the skin through improved mitochondrial function, enabling a dynamic response to oxidative stress, promoting pro-collagen I synthesis, and encouraging skin barrier repair. It also helped combat side effect of the laser procedure, particularly related to hyperpigmentation. These benefits translated to clinical studies, in which the regenerative active combination demonstrated statistically significant improvement in 9 dimensions of skin rejuvenation following non-ablative laser resurfacing and on key anti-aging parameters when used as a monotherapeutic treatment on uncompromised skin.

While the current study focused on nonablative laser resurfacing, the reported approach in this study is highly applicable to create customized skincare routines for skin rejuvenation treatments such as dermabrasion, ablative laser treatment, microneedling and chemical peels. With the rapid advancement of aesthetic procedures, understanding the distinct skin response following such treatments in conjunction with particular active combinations can greatly improve the standard of care for the patients seeking procedure routines. This also enables individualized skincare routines that can be potentially be translatable to treat compromised skin and post-UV exposed skin, or as a customized anti-aging skin routines based on with each individual’s unique skin biology profile.

5. Conclusion

Spatial transcriptomic analysis was introduced for the first time as a tool to optimize formula development and enhance aesthetic procedure benefits. This enabled the precise selection of actives to combat side effects and augment procedure outcomes, as demonstrated through in vitro benefits and improve in key anti-aging parameters in the clinical study. These benefits were also extended for daily use as a monotherapeutic, providing strong anti-aging benefits in the skin. This customized post-procedure skincare formula with actives selected through transcriptomic guidance suits the distinct needs of consumers undergoing aesthetic treatments to bring able better quality of post procedure skin care.

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