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Maximize the Appearance of Fuller and Thicker Hair with ProCelinyl™: A White Paper

ProCelinyl™ is a new and innovative ingredient that supports the hair follicle to improve the appearance of fuller and thicker hair. This white paper is a technical reference that outlines the studies undertaken by Revela to evaluate the efficacy and safety of ProCelinyl™.

Overview

Hair loss in women.

Millions of individuals are affected by hair loss. The National Alopecia Areata Foundation states that 147 million people worldwide are diagnosed or predisposed to alopecia areata. Moreover, this statistic does not consider all forms of hair loss and thinning. While most often associated as an issue for men, over 50% of women[1] experience some form of hair thinning or hair loss in their lifetime. More importantly, women encounter greater psychological comorbidity than men due to current and established societal norms. For those who identify as women, hair is heavily associated with sexuality and gender identity. Thus, women are more likely to experience a lower quality of life because of hair loss[2].

Current treatment options are limited for women.

Despite the devastating impact of hair loss on quality of life, current treatment options for women are limited due to serious side effects. Oral antiandrogens and topical minoxidil are amongst the most popular treatments for hair loss in both men and women. The Food and Drug Administration (FDA), a US government agency responsible for medical treatment regulation, has only approved minoxidil and finasteride for treatment of hair loss. With early diagnosis, these treatments can reduce the effects of hair loss. However, as hair loss progresses or if prescribed at later stages, minoxidil and finasteride are primarily only effective at slowing down hair shedding rather than stimulating new hair growth[3].

Finasteride can cause debilitating side effects making it an undesirable option for women. The FDA has deemed finasteride as pregnancy category X, meaning that it is medically inadvisable for use in females of childbearing age, unless they are using strict birth control measures. Several case studies and animal studies indicated fetal abnormalities with the use of finasteride and thus, the risks that pregnant women face when using this drug oftentimes outweigh its benefits[4-7].

Adverse side effects of minoxidil have also been reported to have higher incidence in women than men. For example, more women experience hypertrichosis (or excessive hair growth anywhere on the body) as a side effect of 5% minoxidil[8]. Extreme hair shedding and its category C FDA pregnancy rating also makes it difficult for some women to start minoxidil treatment[9-10]. Overall, the serious side effects experienced by women who opt for these treatments strongly underscore the need new treatment options.

No Innovation in the Hair Loss Industry

Current treatment options for hair thinning and hair loss not only cause adverse side effects, but they are extremely outdated. In fact, neither minoxidil nor finasteride were originally established as hair growth treatments but were found to induce hair growth as a side effect of treating different illnesses. While undergoing clinical trials in the 1960s as a medication

for high blood pressure and ulcers, minoxidil was found to cause hypertrichosis as an unintended side effect and was approved to treat hair loss in 1988[11]. Similarly, finasteride was first approved in 1992 as a treatment for prostate gland enlargement and was subsequently approved to treat male androgenic alopecia in 1997 after discovering it increased hair growth[12].

These outdated treatments have been the gold standards for decades, and until now, consumers have had to accept these as the recommended options. We started Revela to change that. Using our innovative, artificial intelligence (AI)- based ingredient discovery pipeline, we found ProCelinyl™, a patent - pending molecule that targets the dermal papilla in hair follicles. This white paper will review the technical advantages of ProCelinyl™ as a hair loss solution and present the data demonstrating its efficacy and safety.

The Discovery of ProCelinyl™: An AI-based approach

Machine learning in medicine and its shortcomings

Researchers readily use AI-based tools to aid traditional bench work. These tools can help process large amounts of data that would otherwise be too time consuming to analyze by hand. Modern medicine has also adopted ML and artificial intelligence (AI) in practices ranging from diagnosing disease to drug discovery. AI-based tools can help search through massive genomic and biochemical datasets to learn and predict new biological mechanisms and potential pharmaceuticals to treat disease.

At Revela, we use similar tools to find novel and effective ingredients in the wellness space, starting with hair loss. We were particularly interested in applying these tools to find ingredients that could target specific behaviors of a tissue or cell. For example, with hair loss we focused on ingredients that could support cell health and proliferation in the dermal papilla. However, the quality and relevance of an input dataset limits the predictive capability of AI models. Oftentimes, there are no clinically relevant, large - scale datasets available that probe particular cellular mechanisms in a manner primed for machine learning. Without these types of datasets, an AI cannot be trained to accurately predict molecules that can target the intended behaviors. Therefore, we created a new discovery pipeline that combines the power of empirical high throughput screening with *in silico* prediction via quantitative structure-activity relationship (QSAR) to find ProCelinyl™, our first novel ingredient in the hair thinning and wellness space (**Fig. 1**).

Revela's revolutionary discovery pipeline.

Our core technology is an ensemble of diverse machine learning models that predicts relationships between an ingredient's molecular structure and an induced functionally relevant response. These models include state-of-the-art graphical neural network architectures and gold-standard classical machine learning models. In our research, we focused on the dermal papilla as it plays a crucial role in the hair cycle.

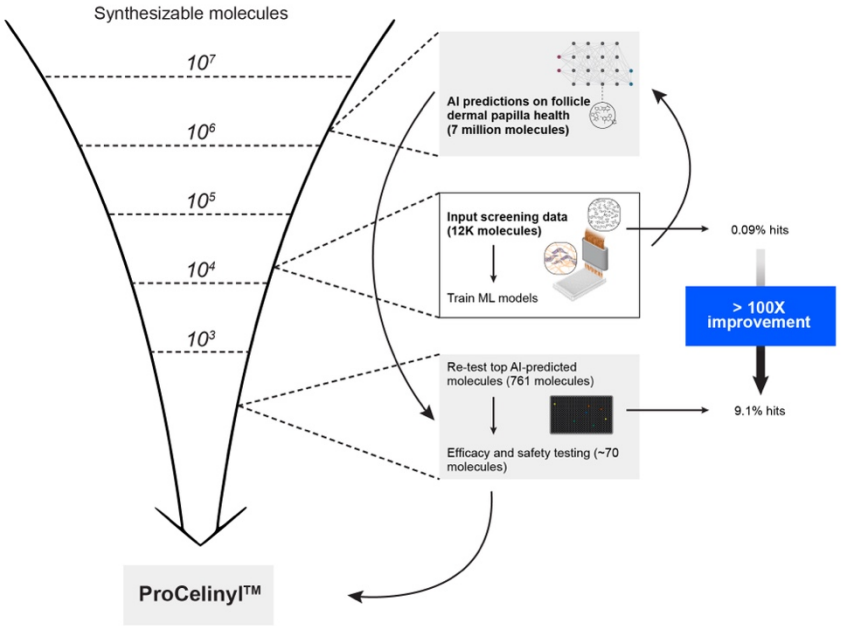

Figure 1. Revela's AI-guided molecular discovery pipeline for boosting dermal papilla cell health. To tackle the lack of high-quality data, we started with high-throughput screening to generate input data to train our AI. The AI was then used to screen a larger library and generate a new list of potential molecules to potentiate the follicle dermal papilla. The AI-predicted molecules were re-screened and additional efficacy and safety tests were applied until only one candidate - ProCelinyl™ - remained. The screening had a hit rate of 0.09% while our re-screen yielded a nearly 10% hit rate, yielding a >100x increase in efficiency in identifying top-performing molecules. AI: artificial intelligence, ML: machine learning.

A major problem we solved was the lack of high-quality data for the follicle dermal papilla. To address this, we generated our own high - quality data set by completing a traditional high-throughput screen of a 12K small molecule library, focusing on human follicle dermal papilla cells (hFDPCs) as the first step in our pipeline. The hit rate of this step was calculated to be 0.09%, a typical rate for a screen of this size. The initial screen generated enough data to allow our platform to be trained using ML parameters. It took the input dataset (data acquired from the screen) to optimize the desired output: finding ingredients that can support the health of the follicle dermal papilla.

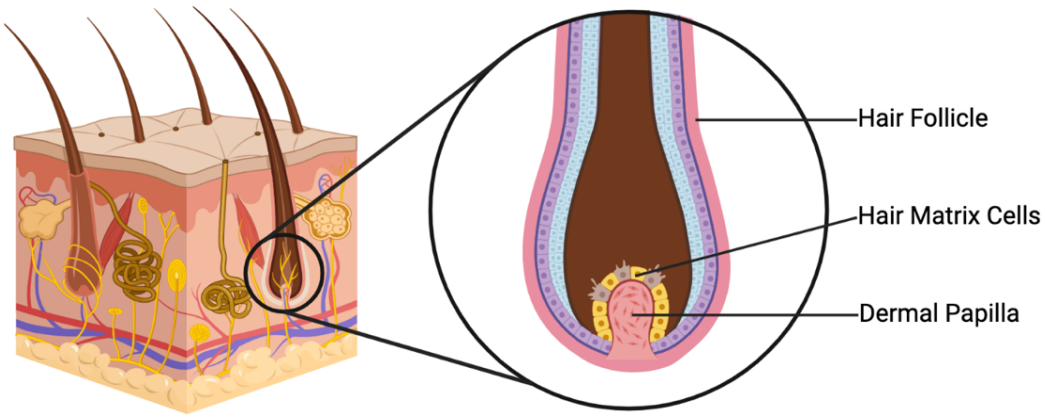

Figure 2. The dermal papilla is found at the bottom of the hair follicle where the hair bulb resides. The dermal papilla plays a crucial role in hair growth by acting as both a hub for cell signaling and a physical location for stem cells and hair matrix cells. The dermal papilla has been implicated in many forms of hair loss and is thus the target of our research efforts. *Created with biorender.com.*

Once the models were trained, they were used to screen a much larger library of over 5 million commercially - available ingredients for their predicted ability to support dermal follicle papilla health. Within the larger chemical space, the algorithm found a total of 761 candidates, including ProCelinyl™. We re-tested all 761 of these AI- predicted ingredients for their bio-functional activity and obtained a hit rate of nearly 10%. **Our AI- based ingredient screen increased hit recovery by >100x showing an improvement in speed, accuracy, and efficiency with our pipeline**. The efficacy and safety of the top predicted ingredients were validated in a series of follow-up *in vitro* and *ex vivo* assays prior to clinical testing.

ProCelinyl™ Supports the Dermal Papilla, a Key Player in Hair Loss:

The hair cycle and role of the dermal papilla.

Healthy hair undergoes cycles of growth, rest, and shedding. This is referred to as the hair cycle and it consists of three major stages: anagen, catagen, and telogen. There are also phases in which the hair transitions from one stage to the next, and another exogen phase, which refers to the shedding of hair - a completely normal phenomenon[13].Throughout the hair cycle, the follicle dermal papilla plays a pivotal role in regulating the growth and cycling of the hair by acting as an instructional hub for regenerative stem cells to reside and send signals for growth[14] (**Fig. 2**).

Anagen is the growth phase where cells in the hair matrix continuously grow and divide[15]. In this phase, the dermal papilla sends signals to follicular stem cells to grow and differentiate, initiating the growth of hair. Catagen is the middle phase where the hair is dynamically transitioning from growing to the rest phase (telogen). In this phase, cells in the dermal papilla slow down proliferation and epithelial cells start apoptosis in the hair bulb causing the bottom of the hair to form a club and move upwards in the follicle so it can be anchored during telogen[16].

Once the hair is in the telogen phase, the hair follicle becomes dormant, and minimal cellular activity occurs. The hair can then either move back into the anagen phase when the dermal papilla signals for stem cells to form a new, active follicle, or the hair can enter the exogen phase which means it sheds from the body. The hair follicle can undergo this cycle 10-30 times before starting to initiate exogen[17].

Changes in the dermal papilla contributes to hair loss.

Hair sheds regularly as a normal part of the hair cycle. In fact, according to the American Academy of Dermatologists, people shed between 50- 100 strands

of hair per day. However, hair loss and thinning occur when an abnormal amount of hair starts to shed. Changes in the dermal papilla can be a contributing factor to this hair loss as it affects the hair cycle and follicle regeneration[18]. Generally, hair loss is categorized by the point in the hair cycle in which the follicle is affected. The less common form is anagen effluvium. Medications or toxic chemicals (like chemotherapy) that affect a growing follicle in the anagen phase cause this type of hair loss[19]. Telogen effluvium is far more prevalent and includes female pattern hair loss (FPHL). In this type of hair loss, hair sheds abnormally because more hair follicles reach the telogen phase and fewer and fewer follicles can start anagen. A reduced number of cells in the dermal papilla can lead to both hair follicle miniaturization and decreased hair follicle regeneration, which both contribute to telogen effluvium[20]. This is oftentimes a result of stress and/or genetics, which can either be acute or chronic[21].

ProCelinyl™ improves the health of the follicle dermal papilla.

Because the reduction of cells in the dermal papilla plays such a critical role in hair loss, the follicle dermal papilla were the focus of our research efforts. Our in vitro tests show that ProCelinyl™ greatly improves the proliferation of hFDPCs (>50%) without eliciting negative side effects. Additionally, clinical trials show outstanding results in just 6 weeks as opposed to 3-4 months as seen with traditional hair loss treatments. It is important to reiterate the serious emotional and mental burden an individual can experience because of hair loss and thinning. With subpar standards of treatment, ProCelinyl's novel dermal papilla - supporting capabilities, paired with its ability to produce faster results makes it a defining ingredient that can change the landscape of effective hair loss solutions.

In Vitro ProCelinyl™ Experiments

In vitro studies show that ProCelinyl™ can target the dermal papilla.

The dermal papilla plays important roles in hair follicle morphogenesis and cycling and thus, was the target of our efficacy studies[22]. An assay using an ATP-based luminescence readout was developed to evaluate the proliferation of cultured hFDPCs and the effect of ProCelinyl™ on cell health. We observed a >50% increase in proliferation of hFDPCs treated with 5 µg/mL ProCelinyl™ in a 24-hour period relative to the vehicle control (i.e., 0.1% v/v DMSO) across several replicates and donors (**Fig. 3**). When compared to hesperetin, a known hair growth- promoting compound, at the same concentration (5 µg/mL), ProCelinyl™ significantly supported hFDPC activity. Not only is ProCelinyl™ effective at supporting the health of the dermal papilla, it also doesn't affect the surrounding skin. This is an important feature for minimizing the potential of side effects.

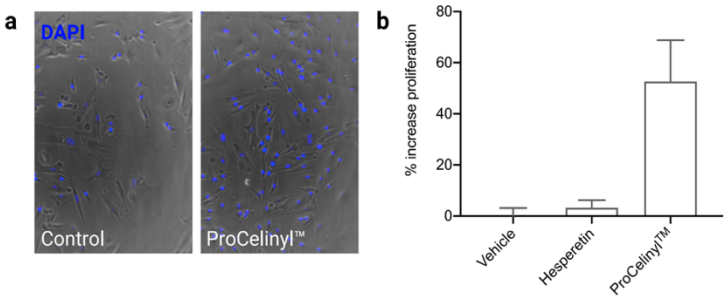

Figure 3. (a) Representative images of either vehicle (0.1% v/v DMSO) and ProCelinyl™ - treated hFDPC cultures after 24 hr. Cultures were counterstained with DAPI to visualize nuclei. (b) ProCelinyl™ showed >50% proliferation relative to the vehicle control and 10X more than hesperetin (a known hair growth-promoting compound) at the same concentration (5 µg/mL). Data represents mean ± s.d. and representative of at least 3 experimental replicates and at least n=2 donors.

We evaluated the specificity of ProCelinyl™ by culturing other relevant cell types found in the scalp, including adult human dermal microvascular endothelial cells (hDMECs), human dermal fibroblasts (hDFs), and human epidermal keratinocytes (hEKs) (**Fig. 4a**). ProCelinyl™ did not impact these other skin cells. ProCelinyl™ was also observed to have a dose-dependent response when treated with a progressively increasing concentration after 24 hours (**Fig. 4b**). The dose range spanned relevant concentrations amenable to formulating a hair serum.

ProCelinyl™ is nontoxic.

Rigorous safety assays were performed in accordance with the Organisation for Economic Cooperation and Development (OECD) cosmetic guidelines - an international body for chemical safety testing - to

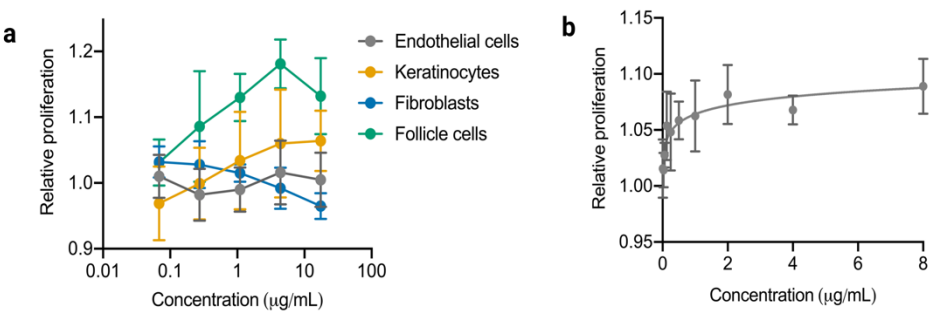

Figure 4. (a) Normalized proliferation of hDMECs, hDFs, hDKs, or hFDPCs treated with varying concentrations of ProCelinyl™ after 48 hr. (b) Normalized proliferation of hFDPCs treated with progressively increasing concentrations of ProCelinyl™ after 24hr. Data represents mean ± s.d. and representative of at least 3 experimental replicates and at least n=2 donors.

demonstrate that ProCelinyl™ is a safe ingredient. The first round of safety testing was to evaluate genotoxicity. No genotoxicity was observed using a well- established, bacteria- based assay known as the SOS-Chromotest[23] (**Fig. 5a**).

Next, human TK.6 lymphoblasts, a type of immature white blood cell, were used to further validate the nongenotoxic character of ProCelinyl™. This is a well - studied cell line that is heterozygous for the thymidine kinase gene (TK) and is readily used for gene alteration analyses. Forward changes in the genes manifest as micronuclei, small bodies outside the nucleus composed of damaged chromosome fragments and/or whole chromosomes and can be detected by flow cytometry[24].

While micronuclei (circled area) were observed in TK.6 cells treated with methyl methanesulfonate, a known genotoxic and alkylating agent, no differences in micronuclei formation (circled area) were observed relative to vehicle control (0.1% v/v DMSO) in TK.6 cells treated with ProCelinyl™, with or without S9 metabolic activation across all concentrations (**Fig. 5b**).

ProCelinyl™ exhibits a robust safety profile in line with pharmaceuticals.

With safety as one of our highest priorities, we wanted to ensure ProCelinyl™ was safe without a doubt. The safety assays we conducted were inspired by drug development safety protocols and go above and beyond the cosmetic standards for safety testing.

Our first step after confirming that ProCelinyl™ did not have any gene transforming properties was to test for reactive oxygen species (ROS) production and caspase 3/7 activation. ROS production and caspase 3/7 activation are early indicators of potential downstream cellular damage and apoptosis, respectively[25,26]. Cells treated with ProCelinyl™ did not have significant differences after 24 hours in either ROS production or Caspase 3/7 activation, as compared to vehicle control (0.1% v/v DMSO) across a 2-log concentration range (**Fig. 6**).

The gut is the largest interface between the internal and external environment and is therefore highly indicative of the state of the rest of the body[27]. Gut barrier failure can indicate more serious health issues like systemic inflammation and organ dysfunction or failure[28]. Because ProCelinyl™ is applied topically to the scalp at a maximum 0.02% v/v, there is likely only localized delivery to the follicles in the application area. However, a gut barrier experiment was performed to ensure ProCelinyl™ did not have any side effects to the gut if systemically present.

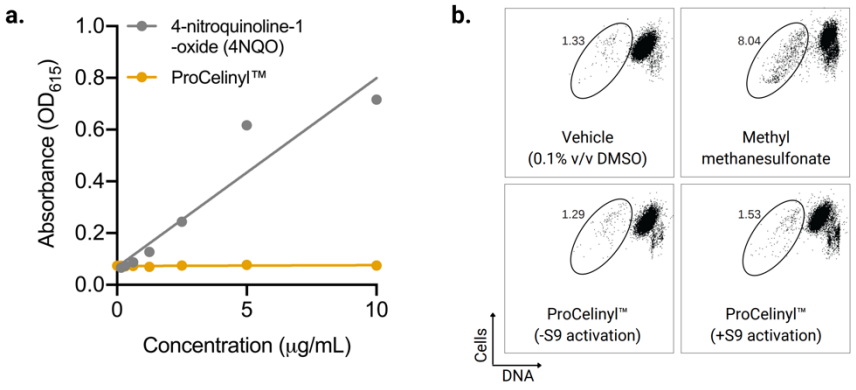

Figure 5. (a) The SOS-chromotest an assay that uses bacteria that produce β-galactosidase (an enzyme) which can be quantified via absorbance. This graph shows the normalized β-galactosidase activity using a known genotoxin (4NQO) as a positive control and ProCelinyl™ at varying concentrations. (b) Representative flow cytometry plots of TK.6 cells treated with a known genotoxin (methyl methanesulfonate) or ProCelinyl™. TK.6 cells were cultured with or without S9 metabolic activation for 24 hr. The circled region indicates micronuclei formation and thus, the darker the region, the more micronuclei are present. Data represents mean ± s.d. and representative of at least 2 experimental replicates.

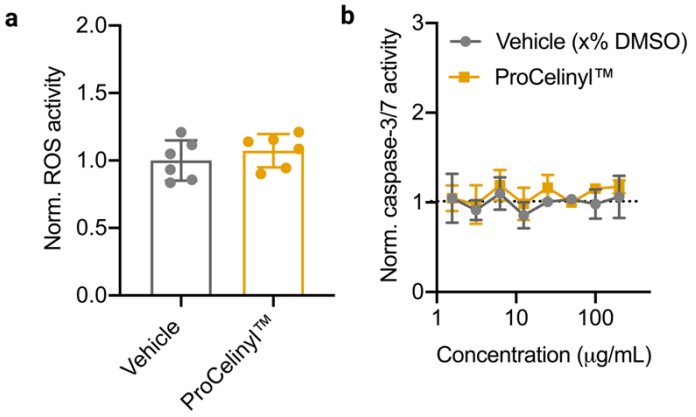

Figure 6. (a) Normalized reactive oxygen species (ROS) activity in hFDPCs treated with 5 µg/mL ProCelinyl™ relative to vehicle control (0.1% v/v DMSO) after 24 hr. (b) Normalized caspase 3/7 activity in HepG2 cells, a liver cell line commonly used to study apoptosis induced by small molecules. Cells were treated with either ProCelinyl™ or vehicle control containing correspondingly % v/v- matched amounts of DMSO. Dotted line at 1 represents no activity. Data represents mean ± s.d. and representative of at least 3 experimental replicates and at least n=2 donors.

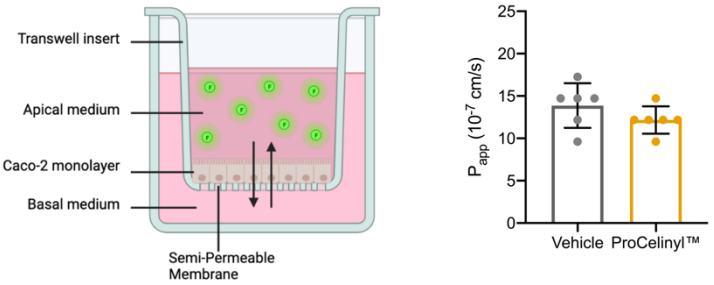

Figure 7. Apparent permeability of a Caco-2 monolayer dosed with DMSO and ProCelinyl™. Caco-2 cells are cultured in transwells until an intact monolayer is formed, then dosed with ProCelinyl™ in culture medium containing a fluorescent dye (Lucifer yellow). The dye is used as a quantifiable tracer to calculate apparent permeability. Data represents mean ± s.d. and representative of at least 6 experimental replicates.

Caco-2 cells were cultured in a monolayer on transwell inserts and dosed for 24 hours on the apical side with either the vehicle control (0.1% v/v DMSO) or ProCelinyl™. The apical side medium was also dosed with a fluorescent dye (Lucifer Yellow) to act as a quantifiable tracer for transfer occurring across the Caco-2 monolayer. No difference in apparent permeability (P_{app}) was observed between conditions and P_{app} stayed below the 10^{-6} range (the known experimental range for barrier breakage) suggesting that the barrier remained intact (**Fig. 7**).

ProCelinyl™ does not sensitize the skin and can be topically applied without irritation.

Skin irritation is one of the most common side effects associated with topical hair growth products like minoxidil. To ensure that such side effects do not occur with ProCelinyl™, several experiments to evaluate the skin-sensitizing potential of ProCelinyl™ were conducted. The first was a KeratinoSens - like assay where we ensured the Nrf2- ARE pathway, an early indicator of skin sensitization, was not activated[29,30]. To perform this assay, HEK293T cells were modified to emit a luciferin light signal when the Nrf2- ARE pathway was activated. No significant increase in luciferase signal was observed in cells treated with ProCelinyl™ when compared to cinnamic aldehyde, a known skin sensitizing agent (**Fig. 8**).

Skin inflammation can also cause unpleasant side effects like itching, burning, and cracking. Additionally, severe inflammation has the potential to contribute to hair loss by damaging the hair follicle[31]. Because ProCelinyl™ is applied topically, it is necessary to ensure inflammation does not occur as a side effect. The activation of dendritic cells (DCs) is

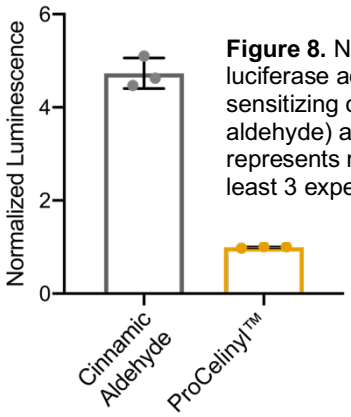

Figure 8. Normalized ARE-luciferase activity using a known sensitizing compound (cinnamic aldehyde) and ProCelinyl™. Data represents mean ± s.d. and at least 3 experimental replicates.

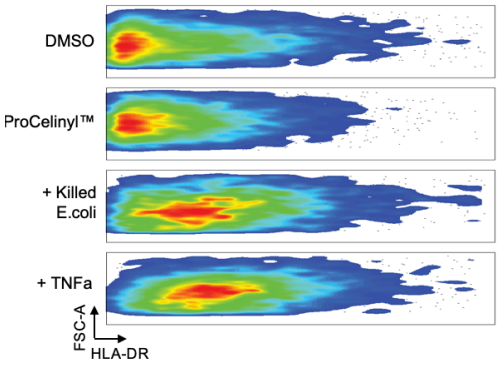

Figure 9. *In vitro* dendritic cell sensitization test. Monocyte-derived dendritic cells were treated with ProCelinyl™ and controls for 24 hr and then analyzed via flow cytometry. Representative plots showing change in HLA-DR expression.

known to cause significant downstream immunological responses like skin inflammation and irritation, and thus were used in our secondary skin- sensitization experiment[32].

For this assay, human immune cells from blood were differentiated into immature monocyte- derived DCs. These cells were then treated with ProCelinyl™ and bacteria (as a positive control). Flow cytometry was then used to analyze the expression of HLA-DR (**Fig. 9**), CD80, PDL-1, and CD141, markers associated with mo-DC activation[33] (**Fig. 10**). While the positive control led to increased expression of the these markers, no changes were observed after ProCelinyl™ treatment.

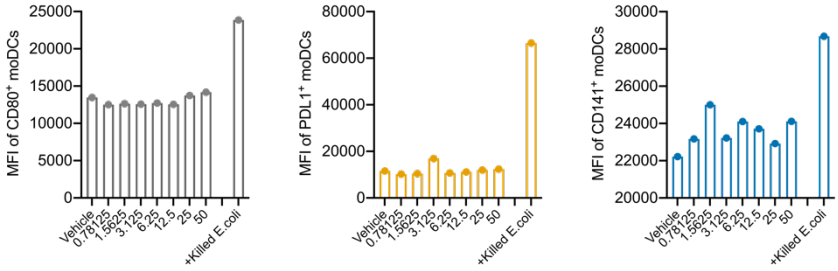

Figure 10. Representative flow cytometry plots for the expression of CD80, PDL-1, and CD141 as quantified via mean fluorescence intensity (MFI). Data represents mean ± s.d. and representative of at least 2 experimental replicates.

Ex vivo ProCelinyl™ Experiments

Ex vivo testing demonstrates that ProCelinyl™ is safe.

An ex vivo skin model (i.e., Genoskin) was used to further validate the safety of ProCelinyl™ by testing for Caspase-3, a marker of cell death. Leftover hair-containing skin tissue from cosmetic surgeries was biopsy-punched and prepared as ready-to-use models (**Fig. 11**). No visual differences were observed in Caspase-3 nor was there any difference in the average fluorescence of cells stained for Caspase-3 (**Fig. 12**).

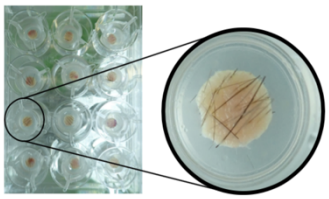

Figure 11. Hair-containing skin biopsies from facial cosmetic surgeries were prepared by Genoskin. The samples were preserved and cultured for *ex vivo* testing with vehicle control (distilled water) or ProCelinyl™ for 24 hrs, then processed for two-photon microscopy.

Clinical Trials

Clinical testing demonstrates that ProCelinyl™ can increase the appearance of fuller and thicker hair in just 6 weeks.

The ability of ProCelinyl™ to enhance the appearance of fuller hair was evaluated in a consumer perception clinical study. A total of 32 women volunteers experiencing hair loss or thinning between the ages of 27-65 completed the study. The subjects were instructed to apply the product to the hairline and scalp once every 2 days for 6 weeks (**Fig. 13**).

Typically, hair loss treatments take several months to start seeing results. Minoxidil takes a minimum of 8 weeks to 4 months of consistent use to start seeing results while finasteride has a similar timeline with results starting to appear in 3 months at the fastest[34]. However, with ProCelinyl™, **97% of the subjects saw improvements in their hairand 82% saw a decrease in hair shedding in just 6 weeks.** Additionally, no adverse effects were reported.

ProCelinyl™ is hypoallergenic.

To verify that ProCelinyl™ does not cause irritation, a repeated insult patch test (RIPT) was conducted. This 6-week study is the industry standard to test for skin sensitization in a clinical setting. A total

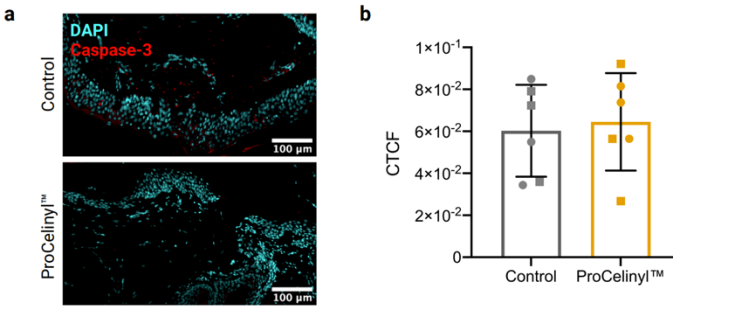

Figure 12. Representative images of *ex vivo* epithelial samples of epidermal tissue. The samples were preserved and cultured for *ex vivo* testing and vehicle control (distilled water) of ProCelinyl™ for 24hrs. Samples were stained for Caspase-3 (red) and with DAPI (cyan). (b) Average corrected fluorescence of cells stained for Caspase-3. Data representative of n=2 donors. Data in (b) compiled from two donors differentiated by a circle (donor 1) or a square (donor 2. Data represents mean ± s.d. and is representative of at least 3 experimental replicates.

of 218 male and female subjects, ranging in age from 18 to 70 years completed the study. Based on this test population, Revela's Hair Revival Serum containing ProCelinyl™ did not demonstrate a potential for eliciting dermal irritation or inducing sensitization.

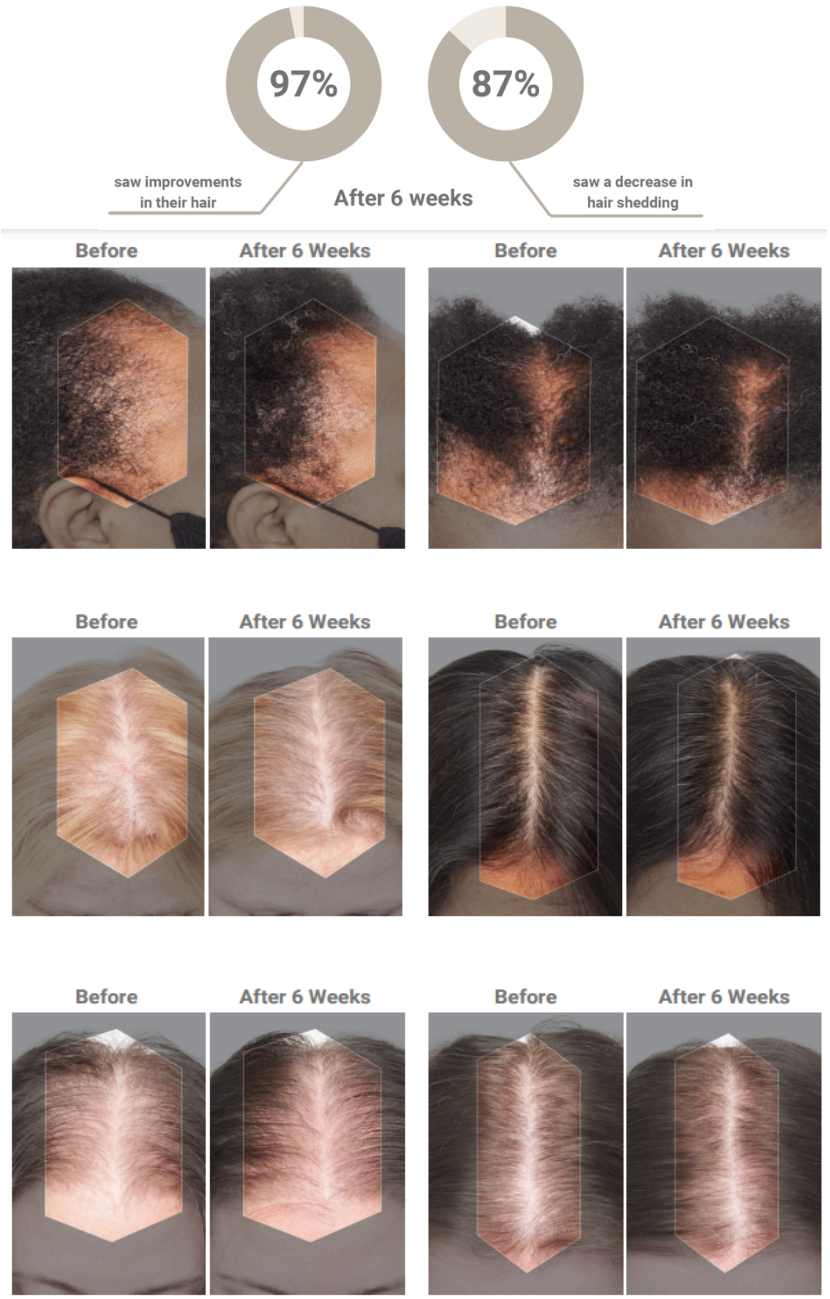

Figure 13. Before and after photos of the hairline from clinical trials. Subjects used ProCelinyl™ on the scalp and hairline once every 2 days for 6 weeks.

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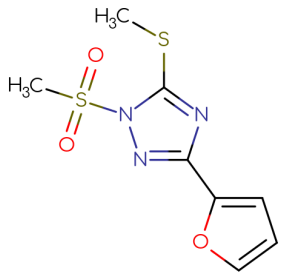
Summary

Technical information:

INCI Name: Furanyl Methylthio Methylsulfanyltriazole

Structure:



Dosage:

- 0.02% weight percent

Claims:

Efficacy:

- Improves *in vitro* follicle dermal papilla cell proliferation
- Increases the appearance of fuller and thicker hair in 6-8 weeks.

Safety:

- Nontoxic
- Specific for follicle dermal papilla cells
- No side effects
- Hypo-allergenic

Applications:

- Hair Revival Serum
- Oil-based Growth Concentrate
- Eyebrow Serum
- Eyelash-enhancing Products
- Beard-boosting Products