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Opinion
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The Advantages of Topical a Cell Delivered Concert with Minimal Depth FUE Procedures: A Single Case Study

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Opinion

Minimal depth follicular unit extractions (FUEs) are defined as those in which the punch depth is restricted to 1.8-3.0 mm below the scalp surface, corresponding anatomically with the reticular dermis–subcutaneous adipose boundary and superseding the depth of the average hair follicle (HF) by as much as 2.4mm [1]. Conceivable advantages inherent to the minimal depth FUE approach arise from the retention of follicle-adjacent and -associated tissues in an undisturbed state, ready to interact with post-surgical topical treatments. In particular, regenerative cell populations, including epidermal stem cells within the bulge region and mesenchymal stem cells in the dermal papilla, remain intact. Given the appropriate stimulation, such cell populations should be capable of efficiently regenerating a HF at the graft site in its entirety. Herein, we propose that topical application of A Cell, a porcine-derived extracellular matrix (ECM) product, to minimal depth FUE graft sites activates stem cell populations in those areas to establish a new HF. Indeed, a myriad of research findings support the idea that ECM-directed cues can determine stem cell activity and differentiated fate. For example, skeletal myoblasts cultured on skeletal muscle ECM display accelerated growth and differentiation compared to controls [2,3]. Conversely, mesenchymal stem cells cultured on a matrix of endothelial cell origin exhibit a vascular cell phenotype upon differentiation [4]. Additional research findings suggest that stem cells require the cell-generated physical forces supplied by matrix adhesive proteins to induce differentiation [5]. Moreover, ECM constituents, namely hyaluronic acid (HA), may further influence cell behavior in the wound response cascade via activation of anti-apoptotic pathways [6]. Clinically, ECM coatings and patches have been used to improve cell performance in bioartificial kidneys and initiate full epithelialization of severe, chronic wounds in as few as 13 days, respectively [7,8].

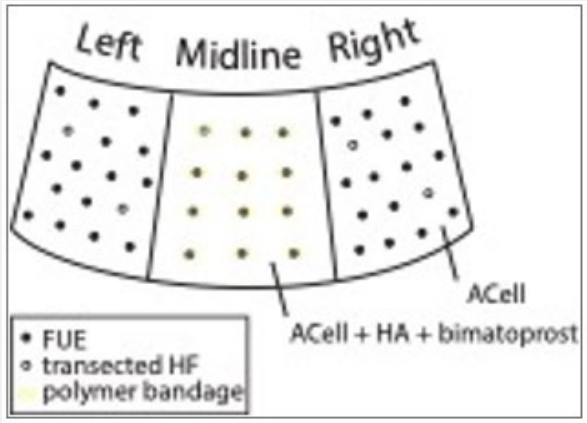

Figure 1: Schematic outlining donor scalp treatment zones. Left of midline (negative control), 17 FUs were extracted using a sharp 1.15mm diameter punch with stop depth set to 2.5mm. Of those, 1 single hair FU and 2 hairs within a multi-hair FU were intentionally transected. All sites were left to heal without further treatment. Right of midline (positive control), 17 FUs were extracted in an identical manner. Two of the single hair FUs were intentionally transected. All extraction sites lying right of midline were treated with A Cell powder. Within the midline region, 12 FUs were extracted with a sharp 1.15 mm punch, stop depth set to 2.1mm; one of the 12 was intentionally transected. Extraction sites were treated immediately with a single drop of an ECM suspension (10 mg mL-1 A Cell in HA) and sealed with a HA-PEG photo-bandage.

In the following case study, minimal depth FUE sites created in the occipital scalp of a 29-year-old Caucasian male (Norwood Class 3A) were treated with granularized ECM (MatriStem

MicroMatrix, A Cell), alone or as a suspension in HA. Hair regrowth was evaluated at 3 months and compared to the negative control region of the scalp where no treatment was applied. In each region, intentional HF transections were made in order to assess the extent to which ECM therapy may be considered effective. Donor scalp treatment zones, HF extraction counts, and HF transection details are provided in Figure 1. In the midline occipital scalp, a hydrogel sealant was created over the ECM/HA treatment using a liquid bandage formulated with a water-soluble, poly (ethylene glycol)-based photopolymer system dispersed in a mixture of HA gel and normal saline. Upon exposure to high intensity visible light (Smart Lite Max LED Curing Light, Dentsply), the bandage polymerized into a breathable hydrogel sealant that confined the serosanguinous exudate to the extraction site. The seal provided by the bandage was broken as the HF elongated, and 1 week after the procedure, intact bandages were removed entirely. Extraction sites were then treated with a single drop of bimatoprost 0.03% ophthalmic solution, a prostaglandin up-regulator, once daily every Monday through Friday over the course of one month.

Hair regrowth in the extraction sites was evaluated in the midline region at 3 months post-surgery and in the midline adjacent regions at 6 months post-surgery. No follicle re-growth was observed on the control side of the scalp, but 24% of extraction sites on the right side of the scalp contained a single follicle, none of which corresponded to sites of intentional graft transection. In the mid-occipital region, where follicles were harvested using a slightly shorter punch and extraction sites were treated with ECM, HA gel, and bimatoprost, 42% of extraction sites, including the intentional transection, exhibited hair re-growth. Interestingly, the completely transected graft grew with multiple hairs and is shown within the circle in the top left corner of Figure 2.

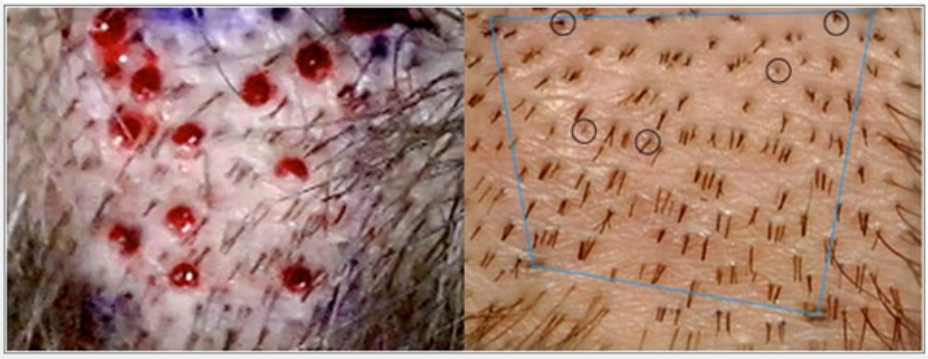

Figure 2: Photograph of the mid-occipital extraction sites immediately following surgery and 3 months after the procedure was completed. Freshly made extractions are presented in the image on the left, and the healed sites are pictured on the right. Sites where follicles were regenerated are circled.

In this study, wound healing was excellent in all three regions; there was no visible difference in the healing between control and ECM-treated extractions sites at the macroscopic level. Nevertheless, the rate of hair regeneration in extraction sites varied with respect to incision depth and extraction site treatment protocol. Hair regeneration was lowest in the negative control region, where, similar to the positive control region, incision depth was set to 2.5 mm. Thus, one may conclude that treatment of extraction sites with ACell had a positive effect on hair regeneration since hair regeneration was observed in 24% of sites in the positive control region at 6 months.

The mid-occipital region of the patient's scalp is depicted at each stage of evaluation in Figure 3; the follicular grouping within the dark blue circle serves as the reference point for each diagram. In this study, wound healing was excellent in all three regions; there was no visible difference in the healing between control and ECM-treated extractions sites at the macroscopic level. Nevertheless, the rate of hair regeneration in extraction sites varied with respect to incision depth and extraction site treatment protocol. Hair regeneration was lowest in the negative control region, where, similar to the positive control region, incision depth was set to 2.5mm. Thus, one may conclude that treatment of extraction sites with A Cell had a positive effect on hair regeneration since hair regeneration was observed in 24% of sites in the positive control region at 6 months. The dominant factor responsible for the nearly twofold improvement in hair regenerative percentage observed at midline (42%), however, is complicated by the combined use of a shorter depth stop and an augmented topical treatment relative to controls. In the midline region, the punch stop was set to 2.1mm, placing the maximum depth of the superior margin of the punch approximately 1.45mm (versus 1.85mm for the 2.5mm stop) below the scalp surface and increasing the likelihood of stem cells in the bulge region remaining undisturbed. Superior margin depth (S) was calculated via rearrangement of trigonometric relationships using the equation S = depth stop – punch diameter/tan (hair exit angle), where the hair exit angle range for this particular patient was 50°-60°. For reference, CK 15+ stem cells reside along the bulge region of the HF at skin depths ranging from 1.0mm to 1.8mm [1]. Moreover, since stem cells from adjacent FUs have the capacity to migrate along chemical gradients as part of the wound healing cascade [9,10] treating the excision sites with HA-doped A Cell may have established a stronger stem cell recruitment signal than

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that established by A Cell alone. Consequently, the HF regenerative potential of the topical combination treatment used on midline incisions may have surpassed the impact the A Cell treatment alone even if the extractions had both been conducted with the 2.5 mm stop. Based on this case report, A Cell has a positive impact on hair follicle regeneration when used in combination with minimal depth FUE procedures, and a follow-up, controlled study is warranted to evaluate the potential for ECM products to induce follicle neogenesis. The reduced percentage of follicle regeneration at deeper extraction depths, presumably from compromises to the local population of CK 15+ stem cells, would fully substantiate the theory that stem cells originating from the extraction site rather than from an adjacent location are the primary contributor to follicle regeneration had both depths received identical topical treatments. Given the discrepancy in treatments, the source of stem cells leading to follicle neogenesis should be studied traced, ideally in a systematic experimental process that incorporates HA gel, bimatoprost ophthalmic solution, and a wound sealant with a granular ECM product.

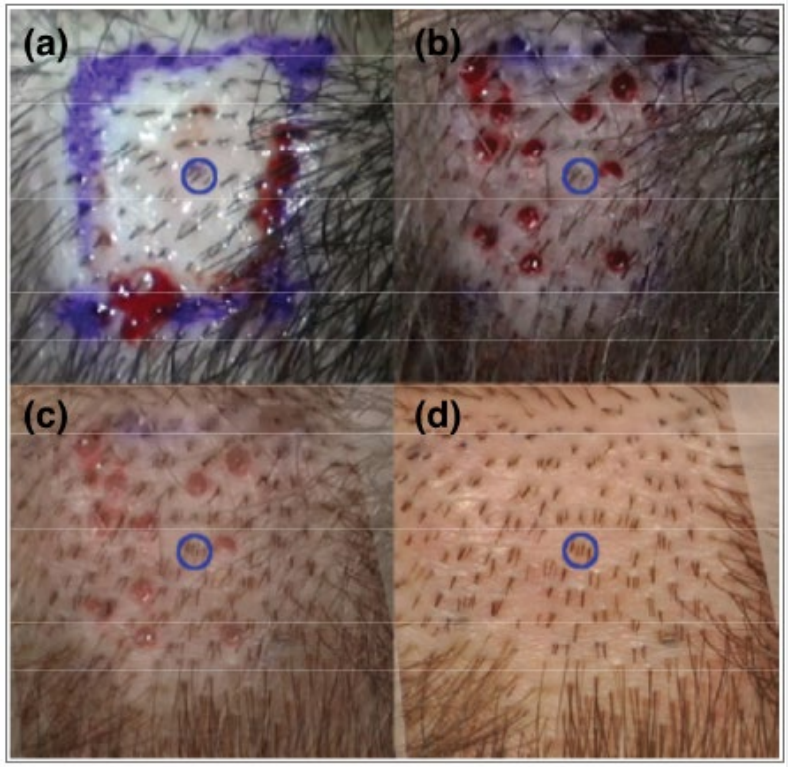

Figure 3: The mid-occipital scalp region
a) prior to FU harvesting,
b) immediately following the extraction of 12 FUs,
c) 1week post-surgery, and
d) 3-months post-surgery.
The follicular grouping within the dark blue circle served as a reference point for comparing changes in the area over time.

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