Minireview

Regenerative and stem cell-based techniques for facial rejuvenation

J Sarah Crowley, Amy Liu and Marek Dobke

Department of Surgery, Division of Plastic Surgery, UC San Diego School of Medicine, San Diego, CA 92103-8890
Corresponding authors: Marek Dobke. Email: mdobke@health.ucsd.edu; Sarah Crowley, Email: Jiwonsarahcrowley@gmail.com; Amy Liu, Email: aml086@health.ucsd.edu

Impact statement

This review is focused on evaluation of methods of facial rejuvenation that have not yet been established as the "typical," mainstream surgical and non-surgical approaches. The ever-reaching goal to obtain the "fountain of youth" makes this a rapidly evolving field in the scope of regenerative medicine. However, these types of changes are frequently investigated and ahead of regulatory and credentialing bodies. Practitioners use products "off-label" on a not infrequent basis, and updated reviews such as this can help to inform clinicians about the evolving standards of care and risks prior to regulatory process completion, while helping patients to achieve their goals of obtaining youth and improving quality of life.

Abstract

This review discusses the most novel ideas and modalities being incorporated into facial rejuvenation. Recent innovative techniques include the use of regenerative stem cell techniques and regeneration supportive modalities such as nano-technology or gene therapies. This review aims to investigate approaches that are less well known and lacking established evidence in order to proactively study these techniques prior to them becoming popularized. These applications and relevant research were reviewed in the context of both surgical and non-surgical modalities in clinical practice. Future directions include the concept of "precision cosmetic medicine" utilizing gene editing and cellular therapies to tailor rejuvenation techniques based on each individual's genetic make-up and therefore needs.

Keywords: Stem cells, facial rejuvenation, genetics, fat grafting

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Introduction

Facial rejuvenation is a rapidly growing field as patients seek to obtain "the fountain of youth." Moreover, there has been a significant amount of dedicated research with attempts to delay or reverse aging on both a cellular and macroscale level. A thorough approach to facial rejuvenation necessitates a multi-modal approach that addresses all of the changes that occur with aging including damage to the skin, volume loss of all the tissues of the face including fat and bone, and tissue laxity. With careful evaluation of all of these facets, it is clear that a surgical facelift alone would not address the volume loss and skin damage.

With aging, there are recognized molecular and histologic skin changes including fibroblast senescence, flattened dermal-epidermal junctions leading to the appearance of atrophy, and decrease in Langerhans and dermal cells.[1] Additionally, the facial bone structure also changes with age; the orbital aperture increases in width and area, and the mandible becomes thinner.[2] One of the most effective and logical ways to achieve facial rejuvenation is through regenerative aesthetics, which utilizes the tissue's own natural potential to combat cell senescence and tissue atrophy through repairing of aging cells and the tissue matrix.

Regenerative interventions are defined as those leading towards renewal, restoration, and regrowth of damaged tissue.[3–5] Advances in molecular biology, genetics, and medical technology as well as empirical clinical experience provide a basis of interventions utilizing potential direct regenerative properties (e.g. stem cells) or those having indirect potential by modulating mesenchymal cells or

tissue milieu (e.g. gene/cellular therapy techniques, nanotechnology).[6] Additionally, with the advent of artificial intelligence (AI), we can utilize methods of imaging, molecular, and genetic studies to objectively evaluate patients prior to facial rejuvenation procedures.[7] Moreover, in the future, data-driven simulations can be utilized to predict tissue "needs" and predict outcomes.[7] This concept can be used in conjunction with the direct and already established use of stem cells.

With the combination of this multi-faceted approach, comes the idea of precision medicine for facial rejuvenation, whereby the goals are tailored to an individual's genetic make-up and needs. This review aims to provide an updated resource on the dynamic changing of approaches for facial rejuvenation to give patients and practitioners a thorough understanding to both surgical and non-surgical approaches to restoring youth.

Autologous fat and regenerative cell types

At the core of facial rejuvenation is the use of the regenerative properties of stem cells derived from autologous fat. The use of autologous fat for regenerative or reparative techniques was first described by Neuber in 1893 when he described harvesting a patient's arm fat in order to correct facial scarring contour deformities.[8] Since that time there have been numerous methods, and described applications for the use of fat grafting to the body, but one of the most popularized purposes today is for facial rejuvenation and contouring.[8–12]

Today, indications for fat grafting to the face for facial rejuvenation include sun damage, volume deficiency such as orbital, tear trough, and temporal hollowing, skin laxity, and rhytids.[8] In addition, fat grafting can be combined with other procedures such as facelifts, blepharoplasty, and laser resurfacing treatments to improve outcomes of facial rejuvenation through a multi-modal technique. Furthermore, fat grafts are biocompatible, clinically versatile, safe and provide a natural appearance.[3]

A well-described problem with fat grafting is the variable rates of fat grafting survival. This can range from 25 to 70%,[13,14] leading to great efforts to improve fat harvesting, processing, and grafting methods.[13,14] Coleman was one of the first to describe that the key to enhancing fat grafting survival was to inject in "miniscule amounts," thereby increasing the contact of the fat to surrounding vascular tissues.[15] Additionally, protocols developed by investigators from our group standardized the most efficacious ways for procurement, isolation, characterization, and evaluation of human mesenchymal cells.[16]

There are different theories for adipocyte survival. One theory proposes that dying adipocytes stimulate phagocytosis leading to transformation of these "wandering cells" into embryonic fat cells, mature cells, and connective tissue,[18] while another theory suggests that the final amount of fat survival depends on the number of viable adipocytes that were grafted.[17] Strategies have been attempted to improve fat grafting outcomes and survival through the discovery of regenerative stem cells. Given the complexity of stem cells and their interaction with the host environment, it may be that specific conditions, such as stem cell dose and timing, determine the anti-senescence (or pro-senescence) fate of fat grafts.[16]

Since Zuk et al. first identified regenerative stem cells in adipose tissue, the use of cell therapy for tissue regeneration has become a rapidly evolving field such that regenerative cells including fat cells, adipose-derived stem cells, stromal vascular fraction (SVF), nanofat, and platelet-rich plasma (PRP) have been described specifically for the use of facial rejuvenation.[4,18–20] Through the use of these different types of regenerative tissues, one's youth, beauty, and even function can be restored.

Aspirated adipose tissue is made up of adipocytes and progenitor cells, and it is now known that these preadipocyte progenitor and adipocyte-derived stem cells are attributed to the long-term survival of fat grafting.[13] Adipose-derived stem cells (ADSCs) are an alternate source (as opposed to mesenchymal cells derived from bone) of adult multipotent stem cells found within the perivascular adipose stroma.[4] These cells have the ability of self-renewal, differentiation into other mesoderm derivatives, and have paracrine properties, with ability of secreting growth factors and promoting angiogenesis and anti-apoptosis.[21] Due to ease of harvest and ability to harvest in large quantities, ADSCs have become a frequently used adult stem cell population for regenerative medicine and supplementation of fat grafts for facial contouring.[22]

Not only do these cells have the ability to differentiate, but studies have also shown the trophic abilities of these stem cells. It appears that fat processing and enrichment with autologous stem cells improves fat cell viability and clinical volume retention (Figure 1). Intravenous injection of ADSCs with fat grafting has helped to improve retention of the grafted fat as well as significantly higher adipogenesis gene expression and vasularity.[23,24] Additionally, SVF, which is the substance created after collagenase digestion of perivascularr adipose tissue and stroma, contains numerous types of progenitor stem cells including ADSCs, pericytes, endothelial progenitor cells, hematopoietic cells, and fibroblasts.[25] These cells within the SVF secrete growth factors and cytokines contributing to its regenerative properties through stimulating tissue growth and angiogenesis.[24] Cell-assisted lipotransfer is the use of SVF-enriched fat grafts, and studies using this technique have shown that there is improved fat retention of the grafted fat versus just fat grafting alone.[22,26–28] A unique form of SVF was studied in the form of a gel product that has been processed to have high concentrations of ADSCs and other SVF cells without the pro-inflammatory lipids, therefore, producing long-term higher volume retention and rejuvenation effects.[28]

Nano-therapy for facial rejuvenation

An emerging concept to facial rejuvenation is the use of both nanotechnology and genomics that will one day allow for precision tailored medicine.[29] Nanofat, a term first coined by Tonnard et al. in 2013, described mechanical emulsification followed by filtering of harvested fat, to create a substance without adipocytes but with multiple

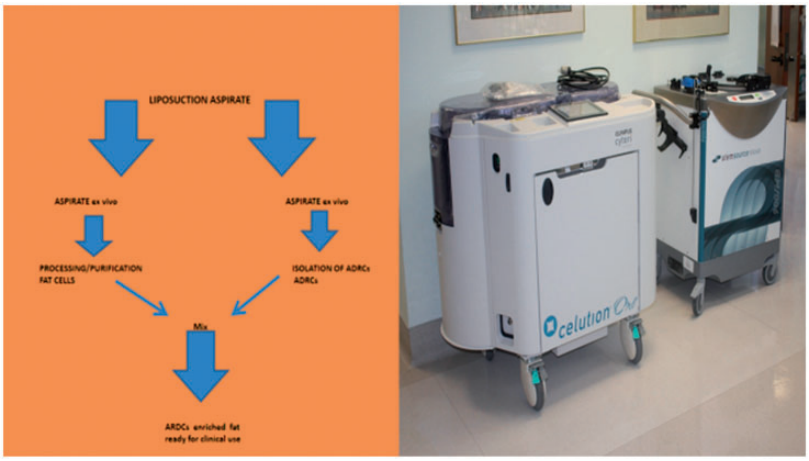

Figure 1. Partitioning and processing of procured fat allows enrichment of the injectate with autologous stem cells. The Celution System equipment allows separation of stem cells within an hour and administration of the stem cell bolus back into the prepared fat for administration during the same operative procedure, in a sterile closed system.

different types of mesenchymal cells and heavy in ADSCs.[29] The authors found that enzymatic digestion of fat to nanofat resulted in isolation of $1.975 \times 10^6/100\,mL$ viable stem cells within the SVF with particles smaller than 500 μm[29] compared to $3.075 \times 10^6/100\,mL$ cells within the lipoaspirate in the macrofat. Nanofat injections in the superficial subdermal level resulted in significant improvement in skin quality 3–6 months following injections.[29] Although the mechanism of actions are unclear, nanofat injections lead to enhanced collagen deposition, skin elasticity, angiogenesis, and thickening of the dermis leading to a growing interest for the use of in facial rejuvenation.[30–32] The use of nanofat has been described in the injectable tissue replacement and regeneration technique for facial rejuvenation which describes a method of replacing anatomic losses of fat with different sizes of autogenous fat grafts in order to substitute areas of bone, deep fat, superficial fat, and dermal/epithelial regeneration.[33] Additionally, while millifat is used for the deep fat compartments and areas of bone loss and microfat is used for superficial fat compartments, nanofat is used for the tear trough regions, intradermal injections, and microneedling.[33] The LipocubeNano™ is a mechanical isolation device (Lipocube Inc., London, UK) that maximizes the amount of matrix and optimizes the cell counts of nanofat.[11] It has allowed for a quicker and more efficient method of processing fat and lipoaspirate to create nanofat that not only has the ability to be injected through fine needles but also through microneedling devices.[28,29] The LipocubeNano™ has also transformed transdermal delivery through compounding with liposomal and/or exosomal transport vehicles in a unique biocreme form.[11,34,35]

The topical transdermal delivery of the nanofat in a biocreme form can be applied following fractional laser therapy. It has been shown to improve texture of the tissue rather than with just laser treatment alone.[34,35] The nanofat biocreme has shown a statistically significant improvement in nasolabial folds, wrinkles, and skin texture when used with a nonablative laser therapy.[34,35] Additionally, postauricular, post-treatment skin biopsies have shown an increase in elastic fibers and thickness of the epidermis.[34,35] These studies demonstrate that the use of nanofat microneedling and topical application, with or without fat grafting volumization, can improve the appearance of skin, one of the key facets to addressing the multiple dimensions required for a complete facial rejuvenation.

Cosmeuceticals are skin care products that "fits the niche between a drug and cosmetics" and include products such as moisturizer, sunscreens, and anti-aging products.[34,35] Nanotechnology has been incorporated into the use of cosmeuceuticals as it is believed that smaller particles such as nanoemulsions, nanocapsulses, nanopigments, liposome formulations, nanocrystals, to name a few, are more readily absorbed into the skin. These nanoparticles allow for improved stability of the cosmetic ingredients through encapsulating into nanoparticles.[34,35] Liposomes may encase retinols (promoting collagen synthesis, cell renewal, and reducing appearance of wrinkles) and increase their penetrability through skin layers.

The future development of nanopatterned substrates can provide structures that influence cell differentiation and subsequent tissue formation leading to devices for drugs, growth factors, gene delivery, and the creation of scaffolds for cell growth including regenerative cells. We will soon see this transition from the laboratory to clinical practice.[36] (Figure 2).

Gene therapy for facial rejuvenation

Research on combinatory chemical (e.g. dietary) or gene-based (e.g. "pharmacological" gene editing) interventions that possibly target multiple genes or pathways of aging (age slowing or reversing) will lead to an innovative method of the use of gene therapy for facial rejuvenation. In addition to the many environmental and external factors that affect aging, there are recognized genetic factors linked to aging such as epigenetic and transcriptional data.[37] The rate of aging is controlled by these genetic pathways eventually leading to the hallmarks of aging including genomic instability, telomere attrition, and cellular senescence.[38] A leading target for interventions to slow aging is inhibition

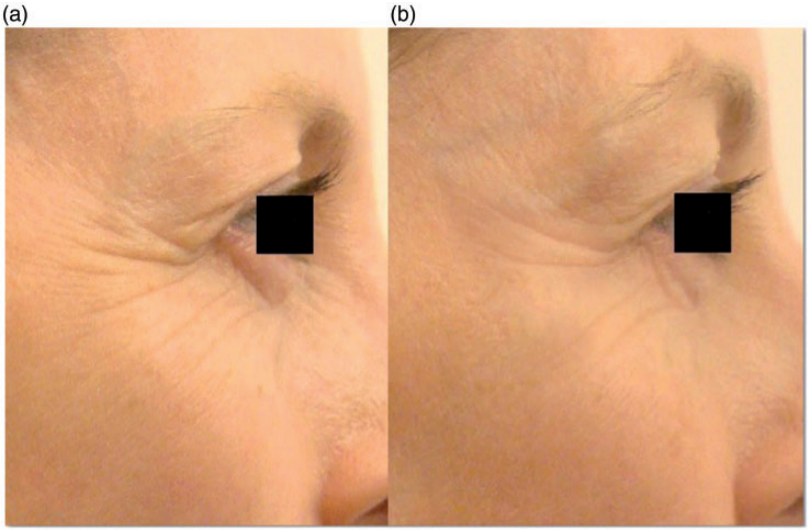

Figure 2. Notable skin and subcutaneous tissue volumization through hydration of lateral periorbital area resulting in wrinkle reduction after only two weeks of topical marine nano-collagen (tropocollagen) administration on water moist skin. Hydrophilic nano-collagen binds water (or other agents normally unable to penetrate the epidermal barrier) enabling dermal permeation across the skin (transepidermal and appendageal pathways) and its delivery to dermal layers below. Panel (a) 55 year old female with lateral orbital "crow feet" wrinkling before treatment by nano-collagen, and Panel (b) two weeks after, once a day, application of topical nano-collagen.

of the mechanistic target of rapamycin pathway which has been shown in model organisms to protect against age-related disease.[39,40] Other intervention strategies include gene augmentation, suppression, and/or editing. Particularly promising is CRISPR (clusters of regularly interspaced short palindromic repeats)-based technology allowing for genomic editing. In brief, CRISPR are specialized stretches of DNA associated with the protein Cas9 which is an enzyme capable of cutting strands of DNA (e.g. cancer cells or infectious microbes).[41] We are just steps away from the ability to edit the genome, not only by removing parts of DNA but also by inserting fragments of nucleic acid, such as in the case to reverse cell senescence.[41] No doubt that original, relatively straightforward autologous and personalized therapies will shift towards scalable and standardized "off the shelve" intervention approaches.[42,43]

It is expected that gene editing, including usage of technologies to slow down or reverse aging, will be done early in life. Additionally, since most common diseases and aging (at a cellular level) have a large epigenetic component, we have to think about genome modifications at an epigenetic level. However, the answer to addressing aging, rejuvenation, and lifespan may not necessarily come only from high tech labs and research. For example, dietary polyphenol curcumin, extract from turmeric, is increasingly recognized as anti-inflammatory, antioxidant, and anti-cellular senescence agent.[44] This "homeopathic" agent inhibits key instrinsic (telomere dependent also known as replicative senescence) and extrinsic (telomere independent also known as stress-induced premature senescence) aging determining processes.[45]

The application of gene editing technologies for facial rejuvenation has to be investigated not only in the context of efficacy but also safety. The recent literature does not indicate specific risks of curcumin related to its influence on stem cells and fibroblast proliferation, increased collagen deposition, or apoptosis.[46] However, since gene editing for combating senescence for cosmetic indications is so close to sensitive immune-oncological targets, research on emerging technologies safety has to be at the highest possible level.

Modulation of tissue homeostasis to optimize regeneration

Clinical key hallmarks of skin aging such as wrinkle formation, skin thinning, decreased resilience, increased laxity, dehydration, pigmentation changes, teleangiectasia can be reduced by many agents (cosmeceuticals) with or without regenerative mechanisms. However, some regenerative mechanisms involving methods of skin remodeling are particularly effective. The use of regenerative cells requires optimization of the environment for the most ideal outcome. For instance, the resulting substance after digestion and extraction of the ADSCs is known as SVF, which also has regenerative properties due to the numerous growth factors and cytokines that are secreted by the cells including ADSCs, pericytes, endothelial progenitor cells, hematopoietic cells, and fibroblasts, within the stroma.[25,47]

Vitamin C and PRP are examples of how modulation of tissue homeostasis may attune or enhance tissue regenerative capability. Vitamin C applied topically to the facial skin or transdermally through microneedling is highly efficient as a rejuvenation agent. It induces significant increase of collagen synthesis in the dermis in all age groups and exerts antioxidative, anti-inflammatory, and photoprotective properties.[48]

PRP is another form of autologous regenerative tissue that was first described by Marx et al. for its growth factor ability in bone grafts.[49] PRP contains a high concentration of platelets and is a source of proangiogenic factors, including platelet-derived growth factor and transforming

growth factor-beta.[50–52] Studies have shown that PRP increases the proliferation of ADSCs[13,50] and PRP has been increasing in popularity of use in microneedling procedures for facial rejuvenation, to reduce edema and ecchymosis following facelifts and for alopecia.[19,53–55] The use and efficacy of PRP in supplementing procedures ranging from fat grafting to dermal injections to topical application further underscores the increasing importance of maintaining tissue homeostasis in facial rejuvenation.[19] Not only can the addition of PRP contribute to the proliferation of ADSCs and promote wound healing through neoangiogenesis and collagen production stimulation, but use of PRP also shows significant effects on facial aesthetic outcomes (e.g. treatment of wrinkles, fat graft survival).[19,55,56] Platelet concentrates also contain growth factors and cytokines that enhance the persistence of grafted fat.[52,57]

However, studies comparing the use of multiple treatment modalities utilizing regenerative cells suggest that simply supplementing treatments with regenerative cells may potentiate, but may not optimize patient outcomes.[18,50] If one wants to attain optimal results, one must appreciate and understand tissue homeostasis and the effects of regenerative cell types in their therapeutic use. An insufficient understanding of tissue homeostasis potentially allows for risks of adverse complications such as inhibited, rather than promoted, wound healing.[58]

Another newer example of tissue modulation is the "Stem Cell Recruitment Facial," which is amniotic fluid (containing cytokines, extracellular matrix, proteins, and growth factors) that comes from a live C-section birth and involves microneedling with or without radiofrequency therapy in addition to topical and intradermal treatments of the amniotic fluid.[59]

With the growing number of commercialization of regenerative aesthetics, it is important for practitioners to be vigiliant and seek strong laboratory or clinical data rather than adopting the most recent opinions as evidence.[60]

Safety profile of the use of regenerative stem cells

Along with the many innovative and beneficial uses of regenerative stem cells, one must also be aware of any potential complications, side effects, and long-term potential dangers of the use of injecting stem cells. As mentioned above, fat reabsorption is a common and well-known problem following fat grafting. There has not been an established standardized way to fat graft, but previous consensus for fat harvesting for facial rejuvenation has been to harvest with minimal trauma with hand-held syringes, low negative pressure, processed with centrifugation at 3000 r/min for 3 min, and injection in microaliquots to increase vascular supply of the recipient bed.[61] Careful injection techniques using small microalqiuots can also help to decrease rates of fat necrosis and oil cysts.[62] Infections are uncommon and can be avoided by using meticulous sterile technique with minimization of air contamination which can also help with preserving fat grafting.[61] Inadvertant intravascular injection is a dreaded complication; risks can be reduced with thorough knowledge of anatomy, use of local vasoconstrictors, injection with a blunt-tipped cannula, low pressure and low volume injections (to avoid high pressure injection with retrograde flow), and aspiration prior to injection.[61] A large retrospective study that reviewed 1261 patients for full-face fat grafting found that only 4.9% of patients developed "moderate complications" including swelling, fibrosis, acne, headaches, and contour irregularities, without any severe complications.[63]

The overarching risk profile concern is the thromboembolic, immunological, and oncological safety issues with the use of injecting regenerative stem cells. A systematic review paper by Toyserkani et al. included 70 studies with 1400 patients treated with ADSCs and showed that risk of thromboembolic events was not statistically significant. Additionally, there were some development of antibodies to the injected cells, but with unknown consequences, one case of local breast cancer recurrence out of 121 patients across two studies within a one year follow-up, and no recurrence of prostate cancer in a 3–6-month follow-up in three studies.[64] The Food and Drug Administration agency (FDA) recognizes that cell-based regenerative medicine holds great potential to help treat patients in a wide variety of conditions, including both benign and malignant disease processes, but that it is critical to utilize these stem cell-based therapies in a safe, therapeutic, and efficacious way.[65] In November 2017, the FDA released a comprehensive framework of regulatory pathways that specifically addressing how to implement regenerative medicine.[65] Since then, more studies have been published on the oncological safety of the use of ADSCs, particularly in breast reconstruction. In mouse models, fat grafting in the setting of residual breast cancer did not increase tumor size, proliferation, histologic grade, or metastatic spread.[66] In fact, ADSCs have actually been found to have tumor-homing, and therefore, have tumor targeting capacity, which means that they could act as a carrier for anti-cancer drug delivery through nanotechnology.[67] More studies need to be conducted on long-term outcomes and safety of the use of stem cells but the future is promising. So far, clinical experience has not indicated that increasing the concentration of stem cells increases the risk of promoting growth of malignant stem cells this is a problem in the clinical setting.[68]

Future directions: Precision cosmetology and the science of facial aging

In addition to the many interventions to reverse the outward signs of aging, senolytic or the "prevention of aging" is a rapidly growing area of research. Many of these areas of interest started in the field of oncology pursuing approaches to induce senescence or destruction of cancer cells. Opposite strategies are aimed at the prevention or even reversal of senescence.[59,69,70] One of these strategies is to prevent senescent cells from releasing senescence—associated factors such as interleukins, chemokines, growth factors, enzymes and other molecules that can cause local inflammation and damage nearby cells.[69] And as described above, it is possible that PRP and amniotic

fluid products can promote modulation of tissue Conversely, it is possible that PRP and amniotic fluid can "simply" promote modulation of tissue regenerative capacity away from senescence (transgenic strategy) (Figures 3 and 4).[57,59,69]

Moreover, our review suggests that senescence messaging secretome of human adipose-derived stem cells might critically influence (negatively, e.g. bleomycin, positively, e.g. possibly retinoids) genotoxic/genostimulatory drug-based or mesenchymal stem cells therapies by imposing interference with tissue homeostasis, reduction of inflammation, metabolic enhancement and regeneration in autocrine and paracrine fashion.[70,71]

Ultimately, although autologous cell therapies have the advantage of becoming personalized approaches, they are inherently expensive and impractical. Since the condition of the autologous stem cells is dependent on the health of the individual donor, with increased age, one increases the risk of accumulation of damage and mutations in cells. Therefore, there is a need for the improvement of the standard fat transfer procedure to increase viability, survival of transplanted fat tissue, or healing of targeted areas for older individuals using autologous therapies.[72,73]

Figure 3. This scheme depicting facial rejuvenation by administration of stem cells from adipose tissue is deceptively simple. Extensive research is conducted to improve all aspects of the stem cell transplant journey, including cell procurement and preparation, optimization of stem cell activity, and controlling stem cell differentiation.

Allogenic and xenogeneic cell therapies have also emerged as potential alternatives to autologous products. Unlike autologous stem cells which are usually derived from a single patient that is usually older with multiple comorbidities, allogenic stem cells are manufactured from large batches of unrelated, younger, and healthier donor tissue that has shown minimal immune response, be expanded in quantities that maybe unattainable for the autologous source, undergo cryopreservation, and be readily available for delivery.[74] On the other hand, xenogenic cell therapies involve using cells from non-human sources such as porcine derivatives which have shown promising results in animal studies and clinical xenotransplantation in restoring lost tissue physiological function and repairing the wound.[75] Transformation of personalized autologous interventions into off-the-shelf allogeneic and xenogeneic cell therapies—that the recipient immune system is "blind to" and offers a single product for all, is what is postulated in cancer therapies, but should be expected in the future of cosmetic medicine as well.

Exosome-based therapies seem to show promise in this regard as they have begun to be researched as possible allogenic/xenogenic cell therapies.[76–78] Exosomes are small extracellular vesicles involved in intercellular communication that are made up of lipids, proteins, and RNA, and can differ functionally depending on their origin.[78] Current research in exosomes are encouraging in their potential applications for facial rejuvenation, ranging from wound healing, hair regeneration, and ameliorating skin photoaging through other topical and intradermal applications.[79–81] Genetically manipulated pluripotent stem cells offering

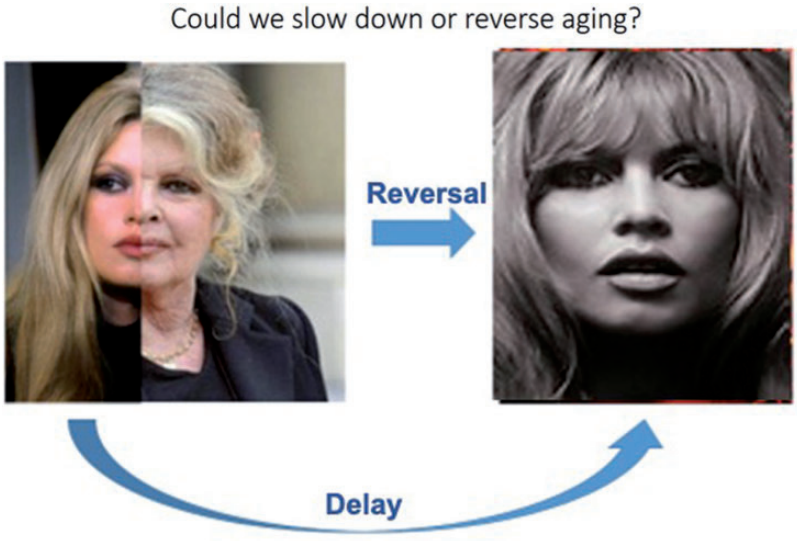

Figure 4. The promise of slowing down or reversing tissue senescence is an alluring prospect, and cutting edge research indicates that ablation or rejuvenation of senescent cells is possible. It may become the cornerstone for future facial rejuvenation techniques.

Figure 5. No doubt that the public will see increasing examples of proven and unproven "regenerative" modalities as products are marketed as safe and effective treatments for facial rejuvenation. Occasionally, sensationalist and irresponsible reporting by the media may reinforce and propagate such unfounded or exaggerated claims.

immune compatibility to all haplotypes could bring to realization true individualized cell rejuvenation therapy based on autologous material or off-the-shelf allogeneic material.[82]

Another key to realizing the potential of the human genome project for precision facial (and body) cosmetology is to use AI with its massive and quick processing power to analyze—to mine genomic and clinical data. A possible future practical application of AI in cosmetology is to untangle the interaction between facial skin, gut microbiome, and the efficacy of cosmeceuticals. Using microbiomic data may provide information about how one's skin will respond to not only externally applied agents but also to dietary changes.[83]

However, clinical testing should be ahead of commercial landscape as a core dimension, preventing decline in public trust in cosmetic medicine and surgery and growing disconnect between what patients want and need, and what they see and experience (Figure 5). Given the current research in the use of AI in imaging and diagnosis, one may imagine a future where cosmetic medicine may be made more accessible to patients by making that connection between what patients want and what they experience through the utilization of deep learning algorithms.

Additional AI such as machine learning has been used to help in objective surgical planning of preoperative and post-operative aesthetics as well as improve patient education. It has been helpful in the development of facial recognition technology, which has been used to classify facial beauty in patients relative to post-operative target features in order to set appropriate expectations before surgery.[84] Overall, with the emergence and development of AI, there is potential to recommend treatment modalities tailored to "the biology" of each patient in the future.[85]

AUTHORS' CONTRIBUTIONS

All authors participated in the literature review and writing of this mini-review manuscript. JSC, AL, and MD wrote the manuscript together and MD created figures.

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ORCID iD

J Sarah Crowley https://orcid.org/0000-0003-1837-3764

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