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Human hair regeneration using organoids and hair-on-chip technologies

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The hair follicle is a complex, dynamic mini organ that plays various important roles in facilitating the function of human skin. As human hair follicles do not naturally form after birth, there is a demand for methods to restore hair follicles in conditions involving permanent hair loss, such as scarring alopecia. However, robust therapeutics to regenerate hair follicles in humans have yet to be identified. Recent advances in the field of regenerative medicine show promise for human hair restoration. Regenerative medicine aims to restore lost tissues, such as hair follicles, by generating bioartificial substitutes. A myriad of biomaterials, scaffolds, and cell signalling modulators have been tested for hair regeneration. This includes strategies such as transplanting hair progenitor populations into skin to induce hair follicle neogenesis. Advanced manufacturing technologies such as 3D printing have also been employed to create bioprinted skin constructs with hair follicles, recapitulating hair-bearing human skin *in vitro*. Hair-on-a-chip models are also in development, which employ microfluidics and biomaterials to mimic the hair follicle microenvironment. Hair restoration has also been attempted through immunomodulatory methods, such as by employing Janus kinase inhibitors and mesenchymal stem cells for immunosuppression. Finally, human induced pluripotent stem cell-derived skin organoids have been established as a method to generate hair *in vitro*, creating various potential avenues for hair regenerative therapeutics. This Perspective reviews regenerative approaches to hair restoration, and emphasises the emerging role of engineered *in vitro* platforms in modelling human hair growth and enabling translational discovery.

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Introduction

Hair follicles (HFs) facilitate many of the skin's biological functions, including sensation, thermoregulation, and wound healing.[1,2] However, existing therapeutics for hair loss conditions lack efficacy.[3] Current treatments rely on lifelong preventative medications with variable results, or else necessitate the presence of existing patient HFs to allow for autologous hair transplantation.[4] There is therefore a demand for methods to restore HFs, to subsequently restore skin function.

One promising approach to restore HFs is regenerative medicine. This interdisciplinary field aims to create bioartificial substitutes for tissues using a combination of life sciences and engineering approaches, including cells, signalling factors, and scaffolds.[5] This review compares experimental methods of inducing HF neogenesis *via* regenerative medicine strategies. Emphasis is placed on maximising the functional and architectural quality of regenerated HFs, as well as the feasibility and suitability of the method's translation to the clinic. We also discuss potential future directions for hair regenerative therapeutics. Fig. 1 provides a schematic timeline of selected conceptual and technological milestones in HF regeneration.

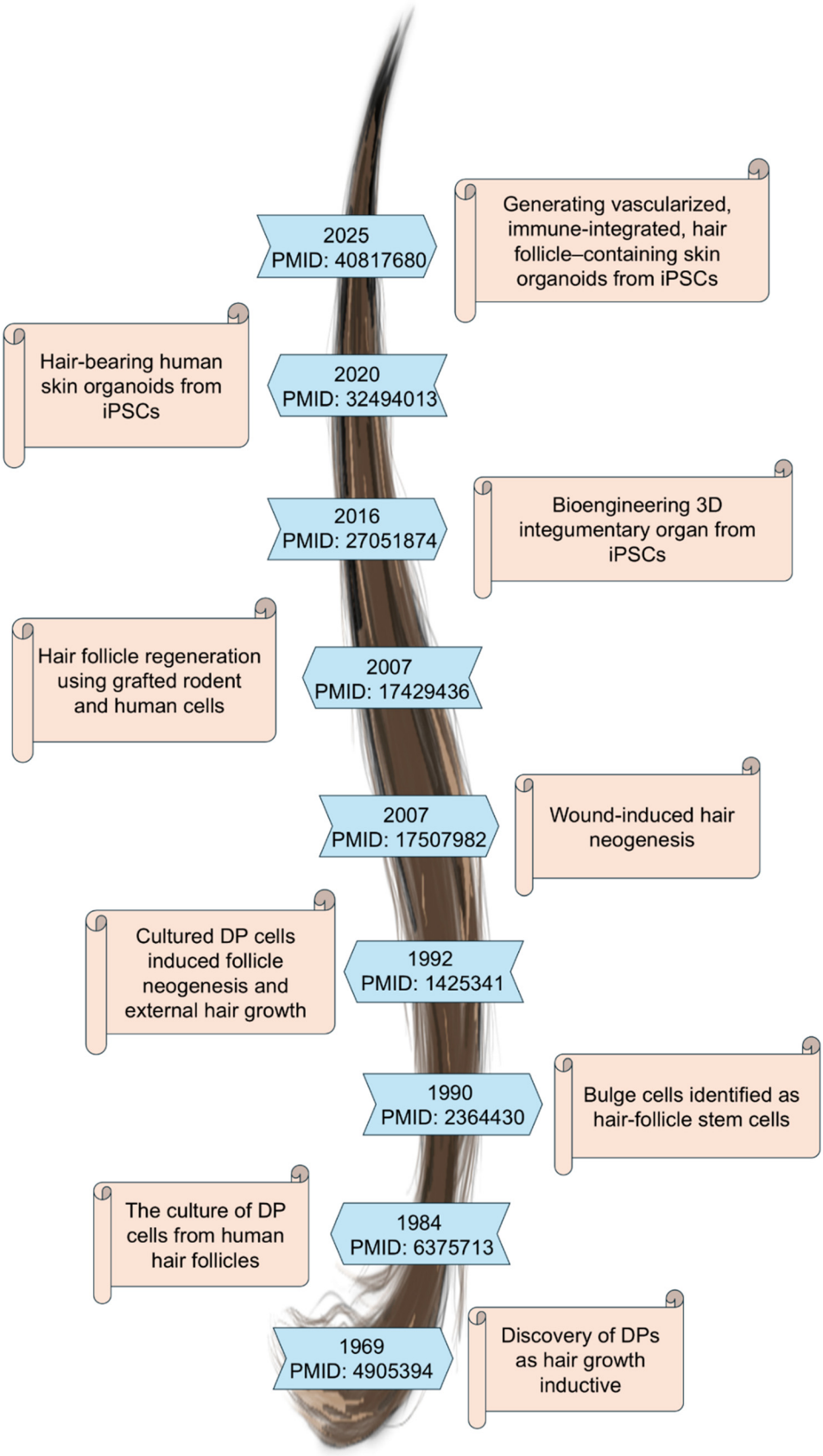

Fig. 1 Major milestones in hair-follicle regeneration research (1969–2025).

Hair follicle regenerative strategies

Hair loss is classified as scarring or non-scarring. Non-scarring hair loss is the most prevalent, encompassing conditions such as alopecia areata and androgenic alopecia, where the HF remains intact.[6] In scarring alopecia, however, there is permanent and irreversible HF destruction. This can be due to primary causes, such as inflammatory or autoimmune conditions, or secondary causes, such as skin wounds.[7]

Although regeneration of lost skin appendages has yet to be achieved in patients, exciting advances in regenerative medicine have recently shown the generation of HFs *in vitro*, which could pave the way for approaches in the clinic. An ideal regenerative medicine therapy for hair loss would be a scalable, xeno-free product, that restores lost hair aesthetically and biomimetically.[8] Such a therapy, however, has yet to be achieved.

Dermal progenitors-based therapies

Skin-derived precursor cells. Research into dermal progenitors led to the isolation of skin-derived precursor cells (SKPs), a multipotent progenitor population that derives from various niches including the dermal papilla (DP).[9] Murine SKPs have been shown to induce HF neogenesis when transplanted into mice, implying that they could be a clinically relevant population for HF regeneration.[9–11] However, there has been a lack of studies into human SKPs, as they quickly lose their stemness properties after *in vitro* expansion, and an optimal culture method has yet to be established.[12] Furthermore, the extensive research of murine HF-derived cells, which display very different properties to those of humans, may be impeding the translation of these studies into the clinic.[13]

One study showed that a combination of human epidermal stem cells and human SKPs, both derived from adult scalp skin, were capable of inducing hair formation when transplanted into nude mice[14] (Table 1). However, the lack of subsequent research into this cell population highlights the challenges in working with human SKPs for hair regeneration.

Dermal papilla cells. Like SKPs, human DP cells rapidly lose their hair-inductive properties when expanded in culture, impeding their translation into therapies.[15,16] This loss of function correlates with a loss of marker expression.[17] It has since been found that human DP cells cultured as spheroids, as opposed to 2D cultures, more closely resemble a true DP in terms of morphology and transcriptional signature.[18,19] Additionally, when sandwiched between foreskin epidermis and dermis and transplanted into immunocompromised mice, adult human DP spheroids were able to induce the formation of human HFs *de novo*.[19] The ability of DP cells to induce HF neogenesis in normally hairless foreskin highlights their potential for cell-based hair regenerative therapies. Enriching human DP cell aggregates with collagen further enhances their trichogenicity, as compared to standard spheroid culture.[20] With such great research interest and potential, it is little wonder that numerous biotechnology companies have proposed DP cell-based therapies for hair loss, with products currently at the preclinical stage.[21]

A common way to generate HF models experimentally is to incorporate DP cells into bilayer skin equivalents and allow them to self-organise into HFs. Vahav *et al.* incorporated human scalp-derived DP spheroids into a reconstructed human skin, composed of fibroblast-embedded collagen hydrogels on top of which keratinocytes were seeded.[22] It was found that the DP spheroids induced invagination of the keratinocytes into the collagen, leading to the eventual engulfment of the spheroid. Additionally, like *bona fide* HFs, the invaginating epidermis developed a K15-positive outer root sheath and a K10-positive inner root sheath.

Abreu *et al.* similarly seeded DP spheroid-keratinocyte aggregates into a dermal equivalent.[23] Laser ablation was used to create microchannels in the dermal equivalent, and keratinocytes were then seeded over the microchannels. It was found that the microchannels guided the infiltration of keratinocytes downwards to engulf the DP spheroid, and that the invaginating keratinocytes also developed a K15-positive outer root sheath and K10-positive inner root sheath. Although keratinocyte invagination is only an early step of HF morphogenesis, and no hair shaft was formed in either study, these studies demonstrate that DP spheroids can induce the formation of early hair-like structures in a tissue engineered skin equivalent.

Abaci *et al.* used 3D-printed moulds to manipulate the HF density and patterning of a human skin equivalent.[24] The 3D-printed moulds were used to create follicle-shaped microwells in a fibroblast-embedded collagen gel. DP cells were then seeded over the microwells, inducing spontaneous DP aggregate formation at the bottom of each microwell. Finally, keratinocytes were seeded over the constructs and allowed to fill the microwells. In addition to undergoing HF-specific keratinocyte differentiation, these constructs successfully developed hair shafts *ex vivo* after three weeks in culture.[24] This study is an important step towards generating a hair-bearing skin substitute, where HF density and patterning can be controlled to improve cosmetic outcomes. However, this skin equivalent still lacks the hair cycling and complex HF architecture present in *bona fide* human skin. Furthermore, a wound healing study could be performed, to assess the regenerative potential, safety, and translational readiness of the skin substitute for wound healing applications.

Tissue engineering and bioprinting

Biofabrication technologies have also been used to generate skin constructs with appendages.[25,26] In this context, 3D bioprinting allows for spatial precision and architectural

Table 1 An overview of pre-clinical regenerative strategies towards hair induction, their advantages and disadvantages, and respective key studies

Strategy	Overview	Advantages	Disadvantages	Study	Outcome	Ref.
Skin-derived precursor (SKP) cell transplantation	SKPs are a progenitor population from the dermis that have been shown to induce hair follicle (HF) formation on transplantation	SKPs can be isolated from patients for and expanded for autologous therapeutics, strong evidence in mouse studies	Lack of research into human SKP hair induction, no optimal culture method has been established, and hair-inductive capacity is lost during expansion	A mixture of human SKPs and human epidermal stem cells, both derived from adult scalp tissue, were encapsulated in Matrigel and transplanted into excisional wounds on the backs of nude mice	From 2×10^6 SKPs and 1×10^6 epidermal stem cells, around 33 ± 5 black hairs grew out of the nude mice's back skin after 15 days	14
Dermal papilla cell (DPC) transplantation	DPCs are a mesenchymal population at the base of the HF, which drives hair morphogenesis and cycling. DPCs can induce HF formation upon transplantation	DPCs can be cultured as spheroids and enriched with collagen to promote hair inductive capacity, and can be isolated from patients for autologous therapeutics	DPCs lose hair inductive capacity on expansion, lack specific markers for cell sorting, and the dermal papilla is difficult to digest to a single cell suspension	DPCs were seeded into the bottom of microwells within a fibroblast-collagen gel. Keratinocytes were then seeded over the top to fill the microwells. Overexpression of the *Lef-1* gene was performed in DPCs to restore DPC hair inductive gene signature	Human HFs formed *ex vivo* after 3 weeks. When constructs were vascularised and transplanted onto nude mice, hair growth was enhanced	24
Bioprinting hair-bearing skin constructs	3D printing techniques are used to print cells in bioink, recreating 3D tissues, including HFs	High spatial precision and architectural control of tissues, bioprinting can be performed *in situ*	Often produces only immature hair structures *ex vivo*, *in situ* HF bioprinting only shown with murine cells so far	Human DPCs and human keratinocytes were printed into a fibroblast-laden gel methacryloyl construct and cultured for 4 weeks	Keratinocytes engulfed the DPCs, forming early hair-like structures *in vitro*	34
Hair-on-a-chip models	A combination of biomaterials, microfluidics, and cell products, are used to recapitulate hair and its microenvironment	Can be used to maintain human HFs *ex vivo* for extended periods, culture array chips can be used to upscale HF production for transplantation, enhanced control over media perfusion	Limited research currently on utility for generating *de novo* HFs without any murine component, can be complex to fabricate	Spheroids containing DPCs, keratinocytes, and human umbilical vein endothelial cells, were co-cultured for 21 days, to determine optimal spheroid culture for hair-on-a--chip models	Spheroids expressed key HF markers and developed hair-like structures *in vitro*	40
Hair-bearing skin organoid culture	Skin organoids, generated from human pluripotent stem cells, can replicate the 3D architecture of human skin, including HFs	Skin organoids can be generated from iPSCs (autologous or HLA-matched), replicate the entire human skin including HFs, can be used to upscale production of hair inductive populations	Develops lanugo hairs rather than mature adult HFs, skin organoids are technical and time-consuming to generate	Human pluripotent stem cells were aggregated and stepwise modulation of TGFβ and FGF signalling pathways was performed. Skin organoids were cultured for around 120 days	Skin organoid HFs possessed pigmentation, sebaceous glands, but no medulla. Transplanted organoids developed outgrowing hair	60, 61

control of tissues, offering anatomically accurate and clinically relevant skin constructs. Bioprinting uses 3D printing principles to configure cells suspended in a bioink within three-dimensional space, to recreate tissue architecture. This technique allows for nuanced control of biophysical and biochemical tissue properties, high spatial control of cells, and a high level of reproducibility in the final product.[27] Bioprinting strategies have previously been employed to generate tissue-engineered skin substitutes of varying complexity.[28]

In 2013, Michael *et al.* generated a skin equivalent from human fibroblasts and keratinocytes using laser-assisted bioprinting.[29] Twenty layers of fibroblast-laden collagen and a subsequent twenty layers of keratinocyte-laden collagen were bioprinted onto a stabilisation matrix. When transplanted into nude mice with full thickness wounds, the skin equivalent integrated with the host skin and the keratinocyte layer differentiated to form a stratified epidermis, providing evidence that bioprinted skin constructs have viability *in vivo*. Another group used

extrusion-based bioprinting of fibroblasts and keratinocytes to generate a similar bilayer skin construct, with similar cell densities and morphology to human skin.[30] Recent studies have generated more complex and physiologically relevant constructs, such as by incorporating additional cell populations like immune cells, melanocytes, and adipocytes, and endothelial cells for a vascularised dermis.[31–33]

More recently, bioprinting techniques have been employed to generate more complex skin equivalents containing appendages. An extrusion-based bioprinting method with a customised coaxial nozzle was developed to bioprint HF-like structures into a pseudo-dermis.[34] The coaxial system possessed an inner nozzle and outer nozzle for dual material printing. To generate HFs, the inner nozzle was used to seed human DP cells and the outer nozzle seeded keratinocytes sequentially, into a fibroblast laden gelatine methacryloyl (GelMA) construct. The coaxial system allowed rapid, efficient printing, and the seeded keratinocytes successfully engulfed the DP aggregate. However, the bioprinted HF-like structure did not fully differentiate *in vitro*, and no transplantation experiment was performed.[34] Further *in vivo* experiments with this construct could determine if this construct has potential to develop mature HFs upon transplantation.

***In situ* bioprinted skin constructs.** Bioprinting can also be performed *in situ*, where cells are directly printed on a wound site. One study showed that *in situ* bioprinting can generate skin with appendages using murine cells.[35] A mixture of neonatal murine SKPs and epidermal stem cells were suspended in GelMA and printed *in situ* into full thickness mouse wounds. This allowed regeneration of skin containing HFs, sebaceous glands, and blood vessels, in addition to an epidermis and dermis.[35] *In situ* bioprinting technologies hold great clinical potential, due to their precision and the elimination of time needed for *in vitro* culture of skin constructs.[36] Furthermore, they can be tailored for anatomically relevant designs and to individual patient needs.

Hair-on-a-chip technologies. Another biofabrication strategy towards generating HFs *in vitro* is hair-on-a-chip studies. Organ-on-a-chip technology models specific organ structures in a miniaturized form, through a combination of cell sources, biomaterials, and microfluidics.[37] Until recently, research on HF chips has been limited, and skin-on-a-chip models often lacked skin appendages.[38] One study showed that HFs obtained from transplant patients could be maintained *ex vivo* in a chip-based bioreactor platform.[39] The dynamic perfused microchannel system here supported *ex vivo* hair elongation and increased the culture duration, highlighting the potential for maintaining HFs in culture for purposes such as drug screening. A more recent study co-cultured DP cells with keratinocytes and human umbilical vein endothelial cells (HUVECs), to optimize spheroids for a hair-on-a-chip model. From these spheroids, hair-like structures developed, and the spheroids were found to express key HF markers.[40] Subsequent hair-on-a-chip and transplantation studies could determine if this model can reconstitute mature, cycling HFs, a challenge not yet met by existing technologies.

Chip technologies have also been applied as a method to upscale HF culture for transplantation applications. A culture array chip was developed using a two-step moulding process, that allowed for large-scale preparation of HF germs from murine epithelial and mesenchymal populations.[41] This chip was fabricated using gas-permeable polydimethylsiloxane to facilitate HF germ oxygenation. The chip's microwell array allowed 5000 HF germs to be generated simultaneously, and upon transplantation into nude mice, these formed hair shafts that were capable of hair cycling. This chip was also successful in generating HF germs from human DP cells, HUVECs, and murine embryonic epithelial cells, demonstrating potential when using human hair-inductive populations (Fig. 2).[42] Furthermore, it was shown that the addition of HUVECs promoted hair shaft formation, highlighting the value of a vascular component for transplantation.

Immunomodulation for hair regeneration

The immune system plays a role in both HF morphogenesis and hair cycling, making up a key component of the HF niche.[43] The HF is considered an immune privileged site, as it is protected from the host immune system by a combination of mechanisms, including reduced antigen presentation, reduced immune cell recruitment, and active immunosuppression.[44] This immune privilege collapses in immune-mediated alopecias, such as alopecia areata and primary scarring alopecias.[45]

Mesenchymal stem cells. Mesenchymal stem cells (MSCs), which derive from the mesenchymal tissues, have an immunomodulatory effect that has shown promise for the treatment of alopecias.[46] One study using an *in vitro* model of alopecia areata showed that bone marrow-derived MSCs had an immunomodulatory effect on DP cells, and could induce the expression of molecules related to anagen re-entry.[47] These findings suggests that MSC therapy might be capable of restoring HF immune privilege and regenerating hair growth in patients with immune-mediated alopecias.[47]

JAK kinase inhibition. Another immunosuppressive therapy that shows promise for the treatment of immune-mediated alopecia is inhibition of Janus kinases (JAK), which are downstream signallers of the interferon gamma response.[45] Inhibition of JAK signalling using topical inhibitors has been shown to promote HF growth in both mouse and human skin, as well as enhance the hair inductivity of DP cells when injected with keratinocytes into nude mice.[48] JAK inhibition has recently been shown to have success in human patients. A retrospective cohort study showed that in adult patients with alopecia areata, the JAK

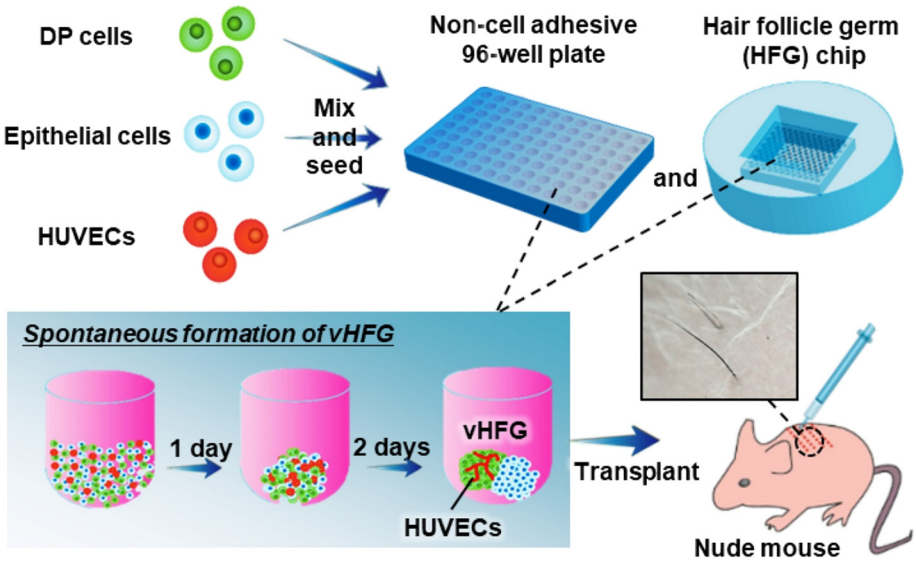

Fig. 2 Human dermal papilla (DP) cells, murine epithelial cells, and human umbilical vein endothelial cells (HUVECs) were combined and seeded in a 96-well plate and a hair follicle germ (HFG) chip. The HFG chip allowed for large-scale culture, with culture results comparable to the 96-well plate. After formation of vascularised hair follicles germs (vHFGs), these were transplanted into nude mice to produce outgrowing hair. From Kageyama *et al.* (2021),[42] used under CC BY 4.0 licence.

inhibitor tofacitinib induced a clinical response in 77% of patients.[49] However, long-term treatment with immunosuppressive agents such as JAK inhibitors may have negative effects, including decreasing immunosurveillance against infection and tumorigenesis.[50] Immunosuppressive treatments, therefore, need to be approached with caution.

Organoid and pluripotent stem cell models

iPSC-derived hair forming cells. Induced pluripotent stem cells (iPSCs) are derived from adult cells by converting them back to a pluripotent state.[51] Differentiating iPSCs into hair-inductive cells would provide a robust method to upscale hair-inductive cell culture with an autologous human cell source. Alternatively, iPSC lines could be banked and HLA-matched to recipients as needed.[52] iPSC-derived hair-inductive cells could also circumvent other barriers to hair regenerative therapeutics, including cell sorting difficulties due to lack of specific surface markers, the difficulty of enzymatically digesting the DP to single cells, and the labour-intensiveness of hair microdissection.[53,54]

Some success in deriving follicular cells from iPSCs has been achieved. In 2014, Yang *et al.* derived HF epithelial stem cells from human iPSCs, which successfully regenerated HF structures upon transplantation along with mouse neonatal dermal cells.[55] The xenogeneic dermal component here, however, limits therapeutic applicability, and only the epithelial HF component was generated from human iPSCs. Generating iPSC-derived DP cells with hair-inductive capacity would likely be more valuable for therapeutics, as this mesenchymal component is the key inductor of hair formation, and the main limiting factor for hair regenerative therapies.[56] Another group generated human iPSC-derived DP cells, but these had a very low yield of hair formation on transplantation as compared to DP cells derived from human embryonic stem cells.[57] Further refinement of the differentiation protocols used to convert human iPSCs into DP cells is needed, to ensure their trichogenicity is robust. Nonetheless, this research direction certainly holds promise for hair regenerative therapies in the future.

Hair-bearing skin organoids. Organoids are 3D multicellular cultures that replicate the architecture and physiology of an organ *in vitro*. They can be derived from pluripotent stem cells, such as embryonic stem cells or iPSCs, and the organoids produced undergo a maturation process that recapitulates human embryonic development.[58]

In 2018, Lee *et al.* generated mouse skin organoids from murine iPSCs.[59] These organoids possessed many mouse skin cell types and structures, including hair follicles.[59] This study served as proof-of-concept that skin organoids which recapitulate appendage-bearing skin can be generated from pluripotent stem cells.[59] In 2020, the same group developed human skin organoids using both human embryonic stem cells and iPSCs.[60] Human skin organoids were generated by aggregating pluripotent stem cells, then performing stepwise modulation of the BMP and TGFβ pathways. Over 120 days, the skin organoids developed a cyst-like configuration with an inner epidermis and an outer dermis, and hair placodes that matured into HFs with sebaceous glands, and melanocytes.[60] Additionally, when transplanted in nude mice, the skin organoids were able to reconstitute appendage-bearing skin with outgrowing HFs.

The human skin organoid protocol has limitations, in that the organoids underwent some off-target differentiation and formed cartilaginous structures, and no sweat glands

structures were observed. Furthermore, skin organoid formation was only successful in two of the four pluripotent stem cell lines tested in this study.[60] Recently, Shafiee *et al.* generated human skin organoids from iPSCs *via* direct embryoid body formation, to improve the success rate of skin organoid differentiation across iPSC lines.[61–64] The resultant skin organoids developed both pigmented HFs and eccrine sweat gland-like structures, representing another step towards the generation of a complete, functional human skin organ *in vitro*.[61]

Overall, the development of human skin organoids represents a significant milestone in human skin research, as it has established a physiologically relevant model that can be used to study embryonic skin development, perform drug testing and disease modelling, and potentially regenerate appendage-bearing skin in patients.

Regenerative medicine applications of human skin organoids. The human skin organoid represents a wealth of opportunities for regenerative medicine. Firstly, skin organoids could be applied as a platform to investigate the scarless, functional wound repair that is intrinsic to foetal skin. This would circumvent the need for a human foetus that has previously made these studies so difficult to perform. Scarless foetal skin wound healing is an expanding research area, with the aim of applying the findings to adult patients.[65] As the skin organoid resembles foetal skin in the second trimester, and scarless wound healing in humans is purported to occur up until 22 to 24 weeks gestation, it is very likely that skin organoids could also undergo this scarless wound repair mechanism. Skin organoids could therefore improve our understanding of appendage regeneration, the intrinsic cellular and extracellular differences within foetal skin contributing to scarless healing, and the associated signalling pathways.

Skin organoids could also be applied more directly to regenerative medicine, *via* harvesting components from it for transplantation. For instance, Ahmed *et al.* conducted a pilot study into the isolation of hair-inductive SKPs from skin organoids, for hair regenerative applications.[66] Skin organoid HFs could also potentially be harvested *via* microdissection. However, as these are lanugo hairs and not adult terminal hairs, they may not be suitable for direct transplantation into patients as a hair loss therapy. Investigating the effects of longer-term organoid culture and the influence of factors such as androgens could be a way to potentially mature skin organoid HFs and allow for their direct transplantation.

The use of skin organoid culture as a method to expand hair-inductive cell populations could overcome upscaling difficulties, which currently limit the translation of hair regenerative cell therapies into the clinic.[66] It may also be possible to use the naturally occurring skin structures of these organoids to generate appendage-bearing skin equivalents for grafting. This could be achieved *via* various tissue engineering approaches, including bioprinting skin organoid cell populations into planar grafts, culturing organoid cells in scaffolds, and possibly even directing cell signalling pathways to generate organoids large enough for direct engraftment. These regenerative medicine applications are still far away, with immense research endeavour needed to ensure their safety and efficacy. Nevertheless, skin organoids have opened many exciting possibilities for the future of dermatology.

Towards clinical hair follicle regeneration

Considerable progress has been made in generating HFs *in vitro*, particularly through methods recapitulating embryonic development. Over the next decade, the field will likely transition from developing HF models towards translating these systems into hair regenerative therapeutics. However, several key challenges must be addressed before HF regeneration becomes viable for the clinic.

Current pre-clinical strategies towards HF induction offer distinct advantages, yet also have limitations that hinder clinical translation (Table 1). Cell-based therapies, such as DP and SKP therapies, are limited by loss of hair inductive capacity on expansion, impacting scalability. Bioprinting methods generate HFs with excellent spatial patterning, but the HFs produced often remain immature. Skin organoids have excellent cellular complexity, but there is limited control over HF distribution and density, and no methods currently exist for the high-throughput isolation of hair-inductive units. Hair-on-a-chip methods allow precise control over the HF microenvironment leading to improved HF survival and reproducibility, but these have yet to be successful upon transplantation without the addition of a murine cellular component.

With these complimentary advantages and disadvantages, it is likely that hybrid platforms will emerge as pivotal within the next decade (Fig. 3). By integrating the biological fidelity of skin organoids, the spatial precision of bioprinting, and the microenvironmental control of hair-on-a-chip technologies, hybrid solutions could potentially overcome the limitations of individual platforms. For example, generating mouse skin organoids within a 3D spindle-shaped microfluidic device reduced cellular necrosis and improved spatial differentiation of epidermal and dermal layers, demonstrating the value of combining microfluidics with organoid culture.[67] We anticipate that hybrid platforms could similarly promote HF survival and quality, making hair regeneration in patients more achievable.

Several translational bottlenecks need to be navigated in order to achieve clinical HF regeneration. The transplanted material would require standardised culture methods and rigorously safety testing, in order to meet the relevant regulatory frameworks. If using an allogenic source, donor screening and infection control standards also need to be established. To promote transplant longevity, the addition of vascular and neural components could be considered, and the use of HLA-banking, autologous sources, or immune-

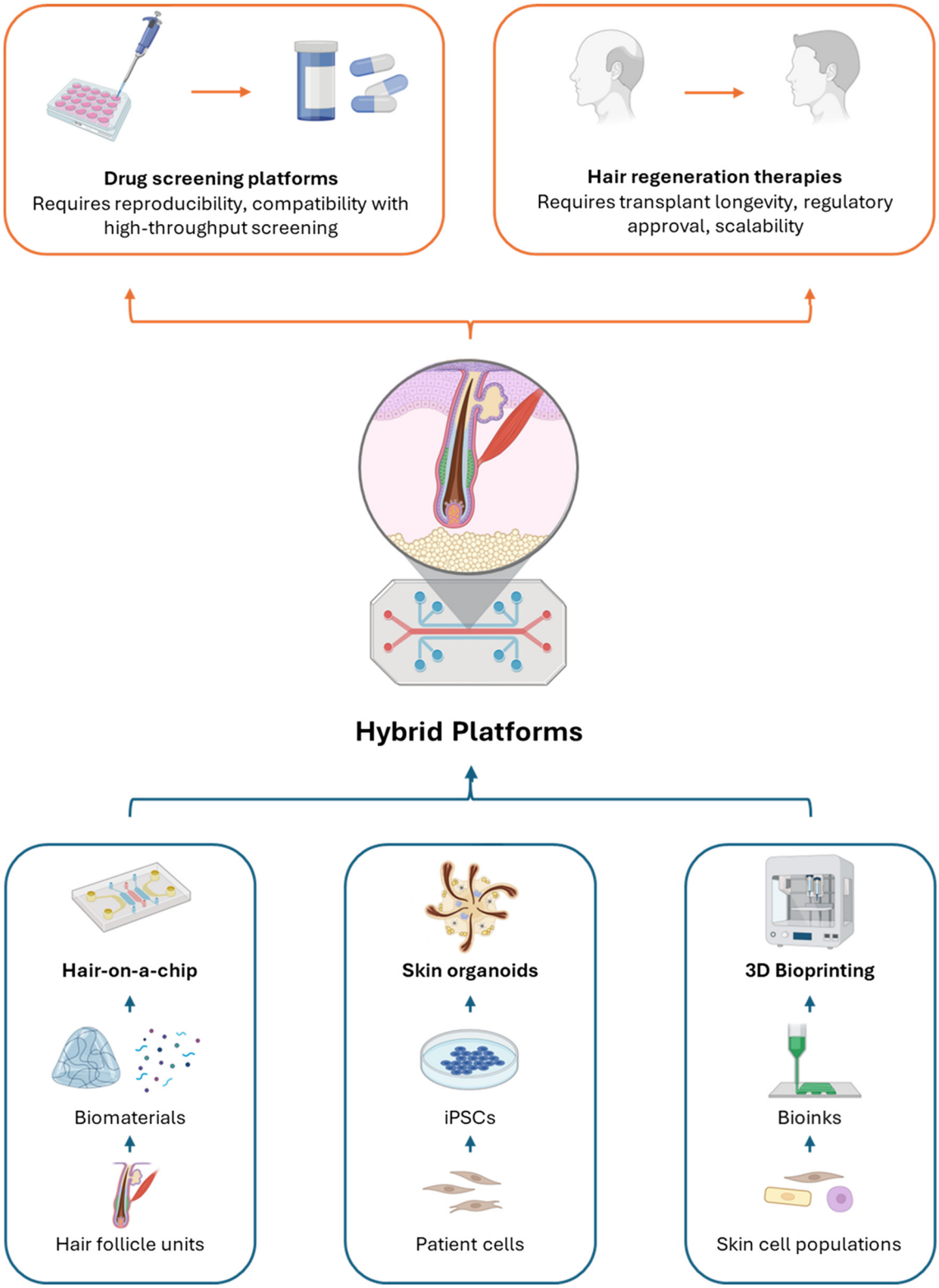

Fig. 3 Hybrid next-generation skin modelling platforms integrating organoids, 3D bioprinting, and microfluidics. By integrating the biological fidelity of skin organoids, the spatial precision of bioprinting, and the microenvironmental control of hair-on-a-chip technologies, hybrid solutions could potentially overcome the limitations of individual approaches, advancing physiologically relevant, scalable, and tunable human skin models for research and translational applications. Image created with https://BioRender.com.

evasive engineering may mitigate issues of immune rejection. Long-term clinical studies on transplant patients will also be required, to assess graft survival, functional aspects such as hair cycling, and aesthetic outcomes.

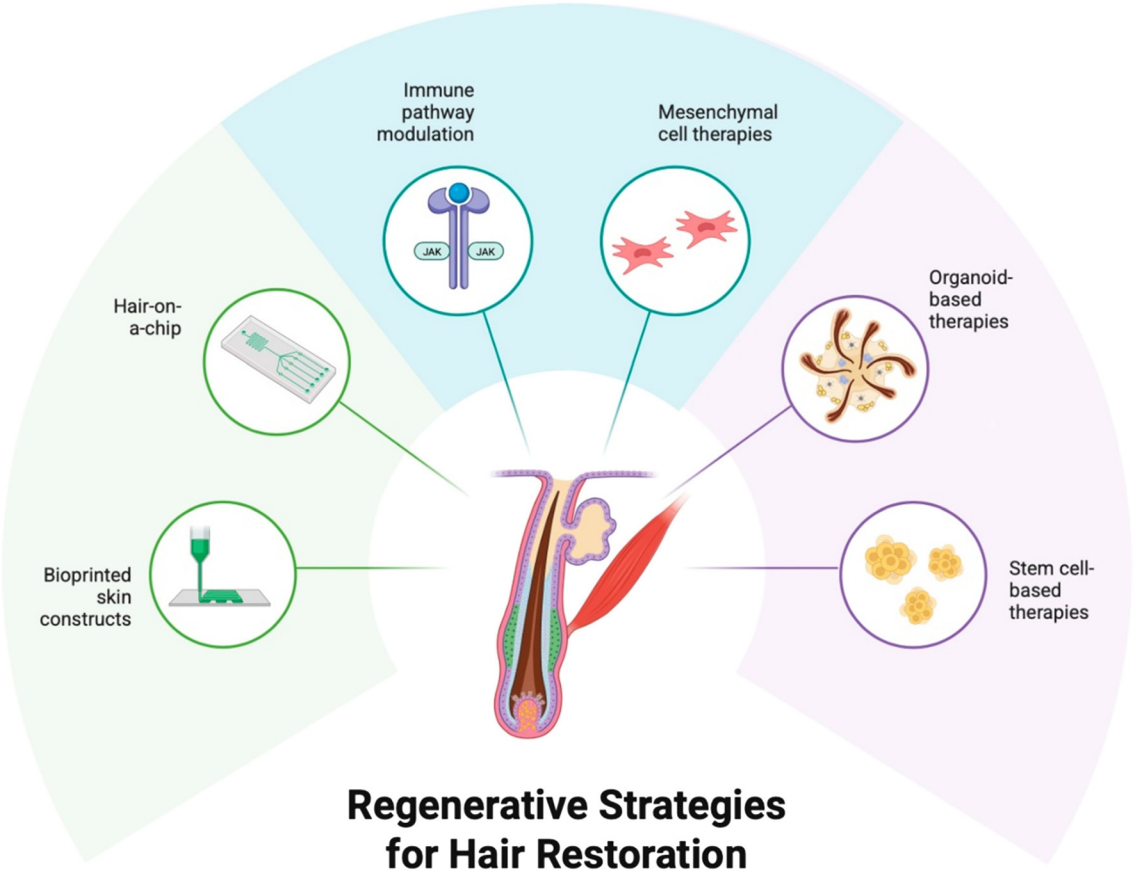

Fig. 4 Regenerative strategies to restore hair follicles. Image created with https://BioRender.com.

Another barrier towards translation is scalability. For both hair transplantation and drug screening, automated and high-throughput manufacturing pipelines are necessary to produce a sufficient number of HFs. Standardisation of culture protocols and workflows for both these translational applications is important, to ensure consistent HF quality both within and across batches. Without protocol standardisation and automated manufacturing, existing hair regenerative technologies are unlikely to progress beyond proof-of-concept studies towards translational applications.

Conclusion and future perspectives

Currently, no clinical therapies exist for regenerating fully functional, appendage bearing skin for patients. New developments in biofabrication, stem cell research, organoid culture, and other technologies hold promise for the future of functional skin regeneration (Fig. 4). However, these techniques are limited by risk of rejection, off-target differentiation, and low throughput. Ongoing research is needed into the safety of hair regenerative strategies, and technological developments such as robotics may improve throughput.[68] Overall, research is advancing towards a future where human skin can be regenerated with optimal cosmetic and functional outcomes.

Author contributions

Imaan A. Ahmed: writing – original draft, visualization, methodology, acquisition and analysis of data. Abbas Shafiee: conceptualization, supervision and validation, visualization, writing – review and editing. All authors read and approved the final manuscript. Schematic image created with https://BioRender.com.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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