REVIEW ARTICLE

FRONTIERS IN MEDICINE

Stem Cells in the Treatment of Disease

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N Engl J Med 2019;380:1748-60.
DOI: 10.1056/NEJMra1716145

A slide show and an illustrated glossary are available at NEJM.org

Abbreviations Used.

AAV adeno-associated virus
CAR chimeric antigen receptor
ESC embryonic stem cell
iPSC induced pluripotent stem cell
MSC mesenchymal stem cell
MuSC muscle stem cell
PSC pluripotent stem cell (ESC and iPSC)
RPE retinal pigment epithelium

The derivation of induced pluripotent stem cells (iPSCs) has revolutionized stem-cell research (see the box for a list of the abbreviations used in this article). These cells, like embryonic stem cells (ESCs), can propagate in unlimited fashion and differentiate into essentially any specialized cell type. Unlike ESCs, iPSCs are generated from somatic cells, obviating ethical debates and providing patient-derived models of disease for studies of pathogenesis and drug screening and a source of cells for experimental transplantation therapies. Typically, iPSCs are generated by the transient over-expression of four transcription factors in readily accessible, fully differentiated cells, such as those of the blood, skin, or urine (Fig. 1). The resulting cells demonstrate the plasticity of cell fate,[1,2] re-express telomerase, and have restored telomere lengths and a "reset" epigenetic landscape, traits associated with immortalized cell lines.[3]

Progress in enlisting the regenerative potential of stem cells in adult tissues has thus far surmounted that of pluripotent stem cells (PSCs). The relatively restricted potency of these cells, hereafter referred to as adult stem cells (also called tissue-specific stem cells), may prove to be advantageous relative to ESCs and iPSCs for cell therapy in certain contexts: there is less concern regarding the tumorigenicity of these cells, and they are more likely than ESC- or iPSC-derived cell types to adopt a gene-expression pattern that is typical of adult cells. An alternative strategy to "adult" stem-cell delivery is the identification of drugs that target somatic, tissue-resident stem cells in situ to augment their regenerative function. Here, we describe advances in and challenges for the development of stem-cell–based therapies, focusing on the skin, heart, eye, skeletal muscle, neural tissue, pancreas, and blood (see slide show).

The Skin

An improved understanding of skin regeneration has been gained through attempts to restore skin in patients with the severe heritable blistering disease epidermolysis bullosa, which manifests as chronic erosions and ulcers in the skin and mucous membranes (Fig. 2). Epidermolysis bullosa is caused by mutations in genes that encode collagens and laminins, components of the extracellular matrix that are essential for maintaining the structural integrity of skin.[4]

De Luca and colleagues reported the engraftment of transgenic stem cells to generate 80% of the skin of a 7-year-old boy with epidermolysis bullosa.[5] This result was achieved by genetically engineering autologous tissue-specific stem cells derived from a biopsy specimen measuring 2×2 cm that was obtained from unaffected skin to express the normal laminin protein. Successful treatment of the boy was predicated on the discovery of a subset of self-renewing "adult" epidermal keratinocyte stem cells (holoclones) that could be grown in culture long term without loss of stem-cell properties. Other investigators have generated

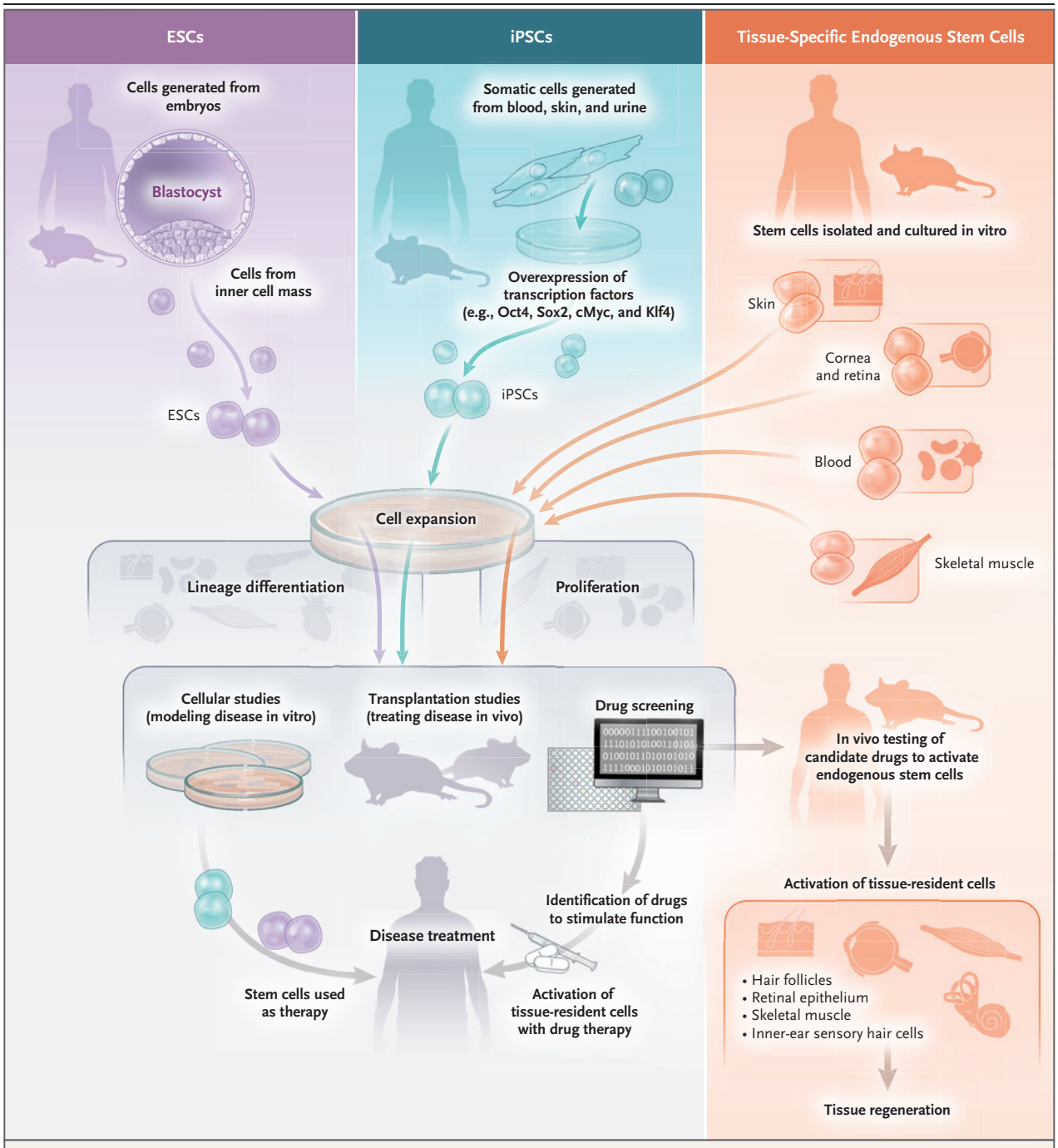
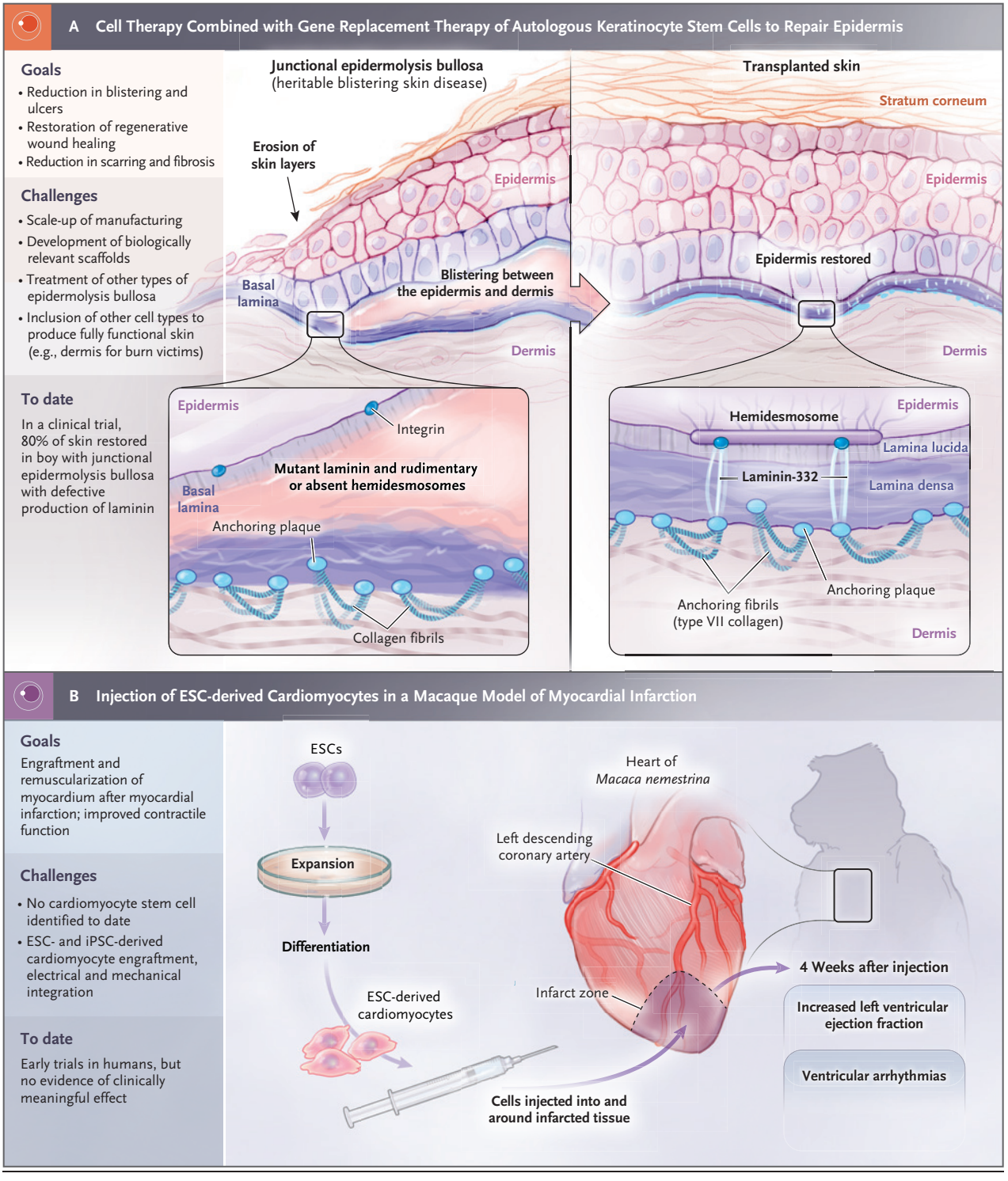


Figure 1. Types of Stem Cells.

Tissue-specific "adult" stem cells that are capable of both self-renewal and specialized tissue repair reside in certain tissues, such as the epidermis, limbal tissue of the eye, skeletal muscle, and blood. Pluripotent stem cells (PSCs) include embryonic stem cells (ESCs) that are derived from the blastocyst of the embryo and human induced pluripotent stem cells (iPSCs) that are created from readily accessible cells, such as those of the blood, skin, or urine, through the overexpression of four transcription factors in culture, rendering them immortal. Patient-specific human iPSCs can be extensively propagated in vitro and differentiated toward diverse cell states, such as cardiomyocytes or neurons, in order to model disease in culture, screen for drugs, and test for function in preclinical murine studies of disease, and to eventually use in clinical applications. Candidate drugs can also be used to stimulate the expansion and function of endogenous tissue-specific stem cells to augment tissue regeneration.



and transplanted similar, smaller skin grafts expressing collagen 7a to treat another epidermolysis bullosa subtype with the use of culture materials approved by the Food and Drug Administration.[6]

Although the transplantation of bone mar-

Figure 2 (facing page). Targeting the Skin and Cardiac Muscle.

The identification, isolation, and culture of a subset of self-renewing keratinocyte stem cells (holoclones) from a nonblistering region of the epidermis of a 7-year-old child with junctional epidermolysis bullosa caused by mutated *LAMB3,* which encodes a component of a laminin (laminin-332), was followed by transduction of these cells with a retrovirus that carried "replacement" LAMB3 (Panel A).[5] Sheets of transgenic epidermis were transplanted back to the patient, and the integrity of his skin improved markedly. A small unrandomized study[17] involving macaque monkeys was conducted in which human ESCs, differentiated into cardiomyocytes, were injected into and around the area of infarction. In a subset of those that received stem-cell therapy, increased left ventricular ejection fraction (LVEF) was observed 4 weeks after injection, but arrhythmias were also detected.

row, umbilical cord blood, mesenchymal stem cells (MSCs), and iPSC-derived keratinocytes has been reported,[7,8] autologous, epidermal tissue–specific stem-cell transplantation remains a benchmark,[5,6] having the advantage of providing a potentially unlimited source of nontumorigenic cells for prolonged treatment and even cure. Similar advances in the regeneration of the dermal skin layer are needed to improve treatments for burn victims.

THE HEART

Loss of heart muscle, most commonly through myocardial infarction, is life-threatening because the regenerative capacity of heart muscle is extremely limited. Assertions that the heart contains dedicated stem cells capable of extensive replacement of those lost have been challenged[9] and refuted by means of mouse lineage tracing.[10] Although carbon labeling in humans (through inadvertent exposure to fallout from nuclear-bomb testing) revealed that cardiomyocyte turnover does occur in the human adult heart,[11] the process is slow (not more than 1% per year),[12] in marked contrast with cardiomyocyte turnover in the hearts of murine neonates and zebrafish.[13,14] Nonetheless, because organ transplantation remains the sole therapeutic option for end-stage disease, various strategies of cell replacement have been embraced as potential alternatives (Fig. 2). Nearly 200 clinical trials involving stem cells have been undertaken, most commonly delivering autologous mononuclear and stromal cells derived from bone marrow. These cells are also known as "adult" MSCs — a misnomer, since they are not derived from mesenchyme and do not normally regenerate adult tissues (e.g., heart tissue). The consensus from several large-scale, randomized, placebo-controlled trials is that MSC delivery, although safe, does not provide long-term therapeutic benefit.[9,11]

In stark contrast with MSCs, human ESCs derived from cardiac progenitors and cardiomyocytes can engraft and remuscularize the myocardium when injected into rodents soon after infarct.[15,16] Studies involving the transplantation of ESC-derived cardiomyocytes into nonhuman primates after myocardial infarction have produced conflicting results: one study showed restoration of muscle, albeit accompanied by ventricular arrhythmias,[17] whereas another did not show remuscularization.[18] An 18-month phase 1 study reported safety and increased systolic function in patients with heart failure after the transplantation of ESC-derived cardiovascular progenitors embedded in a fibrin patch.[19]

Currently, the difficulties of using allogeneic ESC-derived or autologous iPSC-derived cardiovascular progenitors to treat cardiomyopathies seem daunting, given the challenges inherent in promoting electrical and mechanical integration of implanted engineered tissues. Moreover, ESC- and iPSC-derived cardiomyocytes are typically immature and engraft poorly. To surmount these challenges, investigators are developing methods to direct the differentiation of ventricular, atrial, and pacemaker cells,[20] bioengineer scaffolds to enhance the delivery and retention of engrafted cells,[21] and deliver combinations of cell types.[21,22]

Another use of patient-specific iPSCs is in vitro disease modeling. Although iPSC-derived cardiomyocytes are relatively immature, they manifest some features of cardiomyopathy, such as arrhythmias, channelopathies, hypertrophy, premature telomere shortening, and dilated cardiomyopathy[22-24] and are used to investigate mechanisms of pathogenesis and to screen drugs.

THE EYE

Ocular stem-cell therapy has been proposed as a means of treating disorders associated with loss of vision.[25] The retina, a light-sensitive nerve

layer lining the inner surface of the eye, relies on the integrity of the underlying retinal pigment epithelium (RPE). Age-related macular degeneration is characterized by a gradual loss of the RPE and consequent photoreceptor death in the macula (Fig. 3), resulting in patchy, wavy central vision and eventual blindness. No treatment currently exists for the "dry" form of the disease, which involves the deposit of drusen under the retina and degeneration that affects approximately 90% of persons with age-related macular degeneration. The delivery and engraftment of subretinal RPE stem cells pose numerous challenges, but the the results of early-phase clinical trials involving the use of iPSC- and ESC-derived RPE cells suggest that further evaluation of this approach is warranted.[25,26]

In the early stages of age-related macular degeneration, before photoreceptors are fully lost, dysfunctional RPE has been replaced and sight restored in animals by transplanting new RPE cells into the macula.[27] At later stages of age-related macular degeneration, cell therapy would require the transplantation of photoreceptor cells (or cells that could differentiate into photoreceptor cells), in addition to the RPE cells.

The unlimited proliferative capacity of ESCs and PSCs makes them an attractive source of RPE cells for the treatment of early-stage age-related macular degeneration. PSC-derived RPE has restored vision in studies of retinal degeneration in animals and has been tested in phase 1 clinical trials in the United States, China, Israel, the United Kingdom, South Korea, and Japan.[25,26] PSC-derived RPE cells are delivered as a cell suspension or seeded on bioengineered scaffolds that are then surgically implanted to permit precise positioning.[26] Transplantation of ESC–RPE cell suspensions has been associated with long-term macula pigmentation and, in some cases, with improved vision, albeit to a limited extent.[24,28] However, one trial of patient-specific autologous iPSC-derived RPE for the treatment of age-related macular degeneration was halted because potentially oncogenic mutations occurred during the expansion of iPSC cultures.[29-31]

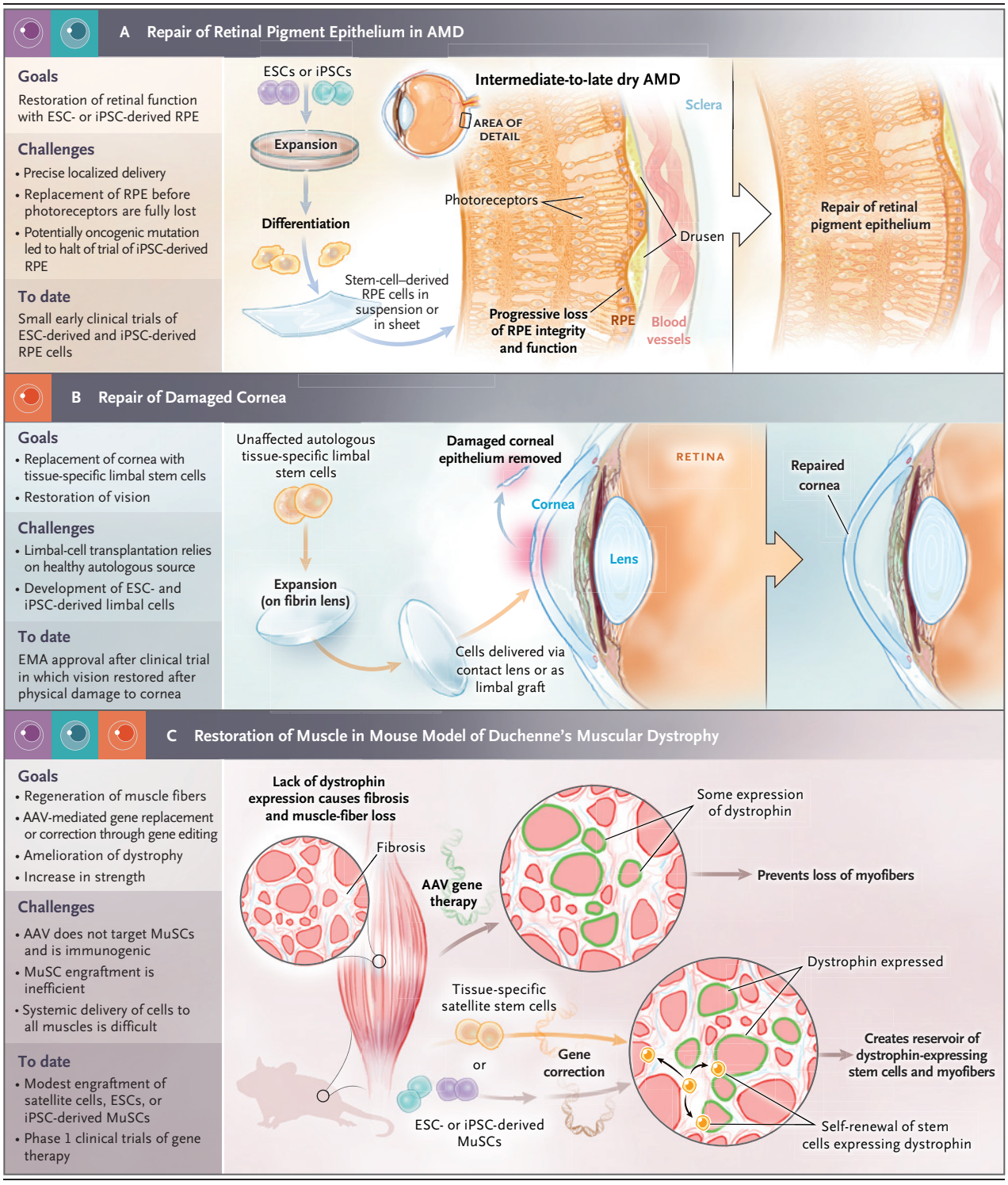
The transplantation of allogeneic RPE cells carries a risk of eliciting an immune response. An advantage of the eye is that it is relatively sequestered from the immune system, but the RPE is part of the blood–retina barrier and may be compromised in age-related macular degeneration. Therefore, immunosuppression may be needed, but only transiently, until the RPE is repaired. Stem-cell therapy for ocular indications is localized, is easily targeted, and requires relatively few cells. In addition to repair of the RPE, there has been progress in repair of the cornea and lens (Fig. 3).[25,32,33] In 2015, a preparation of "adult" tissue-specific limbal stem cells that can restore the cornea and sight after physical damage or chemical burn received marketing authorization from the European Medicines Agency.

Figure 3 (facing page). Targeting the Retina, the Cornea, and Muscle Tissue.

In a clinical trial, ESCs were differentiated into retinal pigment epithelial cells (RPEs) and delivered in a patch to treat age-related macular degeneration (AMD) (Panel A).[26] In a procedure involving the cornea, autologous tissue-specific stem cells were obtained from limbal tissue from a patient's healthy eye, cultivated on a fibrin substrate (contact lens) for transplantation to replace the opacified cornea of the contralateral eye damaged by chemical burn (Panel B).[33] In clinical trials to treat Duchenne's muscular dystrophy (Panel C), adeno-associated viral vectors (AAVs) containing a "replacement" gene were delivered systemically to patients. Results are pending (see ClinicalTrials.gov numbers, NCT03368742, NCT03375164, NCT03362502). An alternative approach to the treatment of Duchenne's muscular dystrophy that is currently under investigation in animal models entails delivery of either genetically corrected, tissue-specific satellite stem cells or iPSC- or ESC-derived muscle stem cells (MuSCs), which would replenish the stem-cell reservoir and restore dystrophin expression to myofibers. EMA denotes European Medicines Agency.

SKELETAL MUSCLE

The skeletal muscles make up 40% of the body mass. A progressive reduction in muscle mass and strength limits mobility with aging. In addition, genetic muscle-wasting disorders lead to a loss of voluntary movement, compromised quality of life, and premature death. Cell therapy represents a means of countering the muscle wasting caused by aging or disease (Fig. 2). The most common and severe inborn genetic disorder involving muscles, Duchenne's muscular dystrophy, is caused by mutations in *DMD*, the gene encoding dystrophin, a structural protein



crucial to membrane integrity during muscle contraction.[34] In 1992, the efficacy of transplantation of autologous, highly proliferative human myogenic progenitors known as myoblasts was examined in a clinical trial. Recipients had some restoration of dystrophin expression, but efficien-

cies were very low because myoblasts cannot replenish the stem-cell reservoir and engraft poorly.[35] Despite their lack of efficacy, myoblasts continue to be used in clinical trials.

Markers that identify and allow the prospective isolation of human "adult" muscle stem cells (MuSCs), or satellite cells, with robust regenerative potential have been described only in the past few years.[36-38] Circumscribed by a basal lamina in a niche juxtaposed to mature multinucleated myofibers, MuSCs are quiescent but can be triggered to self-renew and effect robust repair of damage over the long term. However, expansion of MuSCs in cell culture is difficult, owing to a drastic loss in stem-cell potential. This loss can be ameliorated by using an enriched culture medium[39] or hydrogels that have an elasticity that matches that of healthy muscle tissue.[40] Nevertheless, an insufficient supply of MuSCs limits their use in clinical applications. An alternative approach to muscle repair that has yet to be proven clinically is the stimulation of tissue-resident MuSCs in situ (Fig. 1), which would obviate the need for cell isolation, expansion, and delivery.[41,42] This form of repair has been modeled in mice.[39]

Gene therapy and gene editing are being tested for the purpose of replacing or restoring dystrophin in clinical trials (ClinicalTrials.gov numbers, NCT03368742, NCT03375164, and NCT03362502). With the use of adeno-associated viral (AAV) vectors, truncated yet functional versions of dystrophin have been expressed in skeletal muscles in animal studies.[43,44] One limitation of these studies is the elicitation of immunity; repeated administration of an AAV–gene-therapy vector may not be effective. This problem can be overcome in mice by inducing tolerance to dystrophin and to the AAV vector.[45] Another limitation is that existing vectors target mature muscle fibers but not the MuSCs that fuel growth and regeneration throughout life.[46]

An alternative to MuSCs is a systemically delivered pericyte subset — mesoangioblasts. In phase 1 and 2a trials, these cells were associated with few side effects, but assays of donor DNA in biopsy specimens from muscle supported the presence of only low levels of donor mesoangioblasts and low or no expression of donor-derived dystrophin.[47] Nonetheless, another clinical trial, which is expected to begin soon, will assess whether there is functional improvement.

Patient-derived iPSCs have yielded a theoretically unlimited supply of self-renewing, fetal-stage, therapeutic myogenic stem cells, allowing for gene replacement or correction before engraftment.[48-50] Moreover, because skeletal muscle is relatively inhospitable to tumor formation, it represents an attractive target tissue for PSC therapy.

NEURAL TISSUE

In most mammals, brain development is largely completed in utero. Limited neurogenesis continues throughout childhood and adult life but only in specific regions of the brain, primarily the dentate gyrus of the hippocampus and the subventricular zone of the striatum. Consequently, injury or disease that destroys neurons leads to permanent disability, prompting interest in PSCs as a source for cell-replacement therapies.

At the vanguard of such therapies is dopaminergic neuron replacement for Parkinson's disease, owing to decades of experience showing improvement in striatal dopaminergic and motor function and, in some patients, the long-term persistence of transplants of fetal-derived ventral midbrain tissues harboring dopamine-producing neuroblasts.[51,52] One concern is that the disease can propagate, albeit slowly, from the host to the graft, as indicated by the presence of Lewy bodies, the hallmark of Parkinson's disease, which suggests a prionlike mechanism.[51,52] Another is that dyskinesias develop in some patients who undergo fetal-tissue transplantation, a limitation that could potentially be overcome with the use of a more consistent cell source, such as PSCs, which can be selected for optimal viability, composition, and potency (Fig. 4). Preclinical studies indicate that PSC-derived dopaminergic neurons at a specific midbrain stage and of a particular subtype can function in rodent and primate models of Parkinson's disease.[53-56] Clinical trials involving transplantation of iPSC-derived dopaminergic neurons generated from persons who are homozygous at their histocompatibility loci, thereby

enabling partial matching to recipient tissue, are expected to begin soon.[57] A trial involving the use of ESC-derived dopaminergic neurons is also anticipated in the near future.[58]

Other neurologic indications for the use of stem cells are undergoing preclinical investigation. Among the most vexing challenges is spinal cord injury. Although the grafting of various forms of neural stem cells and oligodendrocyte progenitors has led to axonal growth and neural connectivity and offers promise of repair and recovery,[59] evidence of restored function has yet to be established in rigorous clinical trials.

THE PANCREAS

Type 1 insulin-dependent diabetes mellitus arises from autoimmune destruction of the insulin-producing beta cells of the pancreatic islet (Fig. 3). Relative insulin deficiency caused by beta-cell failure in patients with long-standing type 2 diabetes or diabetes that is secondary to injury or surgical excision represents another target for beta-cell replacement therapy. Because the native mammalian pancreas does not efficiently regenerate islets from endogenous tissue-specific stem cells,[60] replacement by PSCs is under investigation. Several groups of investigators have reported the differentiation of ESCs into glucose-responsive insulin-producing beta cells in vitro and after transplantation in animals.[61-66] After promising animal studies showing 2-year survival of encapsulated cells that mature into insulin-producing beta cells after transplantation, a phase 1–2 trial of ESC-derived endodermal progenitors (NCT02239354) is under way.[67] It remains unclear whether beta-cell progenitors alone or a mixture of progenitors of beta cells with progenitors of alpha, delta, and epsilon cells of the pancreatic islet is preferable.

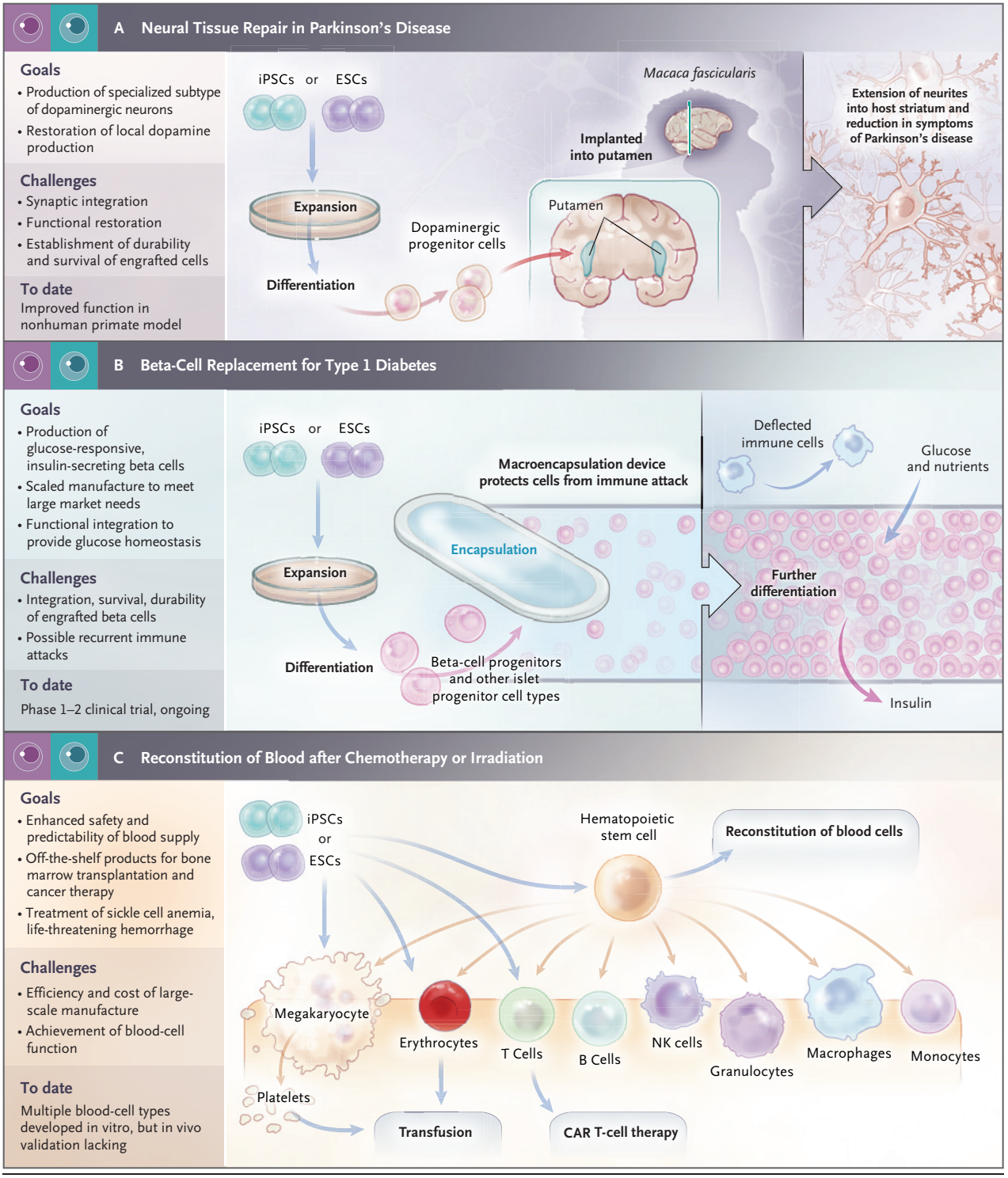
Persons with diabetes routinely monitor their own glucose levels multiple times per day to adjust their insulin regimen, but the beta cell is a natural monitor that could plausibly provide more precise and sensitive control of glucose levels. In patients with type 1 diabetes, unlike those with many other conditions, transplantation of autologous PSC-derived cells would be ill advised owing to autoimmune attack. Instead, strategies to counteract immune destruction and achieve immune tolerance are needed. To this end, blockade of T-cell costimulatory pathways shows promise.[65]

Because insulin is a circulating hormone, the transplanted cells do not need to be in the vicinity of the pancreas. Existing strategies for beta-cell delivery include encapsulation of either pancreatic endodermal progenitor cells or mature beta cells[67] and the subcutaneous placement of the capsule to allow ease of monitoring and recovery. Whether encapsulation can avert immune evasion and avoid inflammatory reactions that compromise graft function remains unknown.

THE BLOOD

Red cells, platelets, T cells, and hematopoietic stem cells have been among the most sought-after cell products to be derived from PSCs (Fig. 3). Although the generosity of volunteer blood donors provides red cells and platelets for transfusion, pathogens such as hepatitis C virus and Zika virus can contaminate the blood supply, compromising safety. Maintaining an adequate supply of platelets is notoriously challenging, given their short half-life and the requirement of room-temperature storage, which makes them susceptible to bacterial contamination.

In vitro manufacture of red cells and platelets offers an appealing source of pathogen-free products of a certain antigenic type at a defined dose. Several groups of investigators have found that quantities of red cells can be produced from PSCs in vitro. Given their embryonic origin, the resulting red cells are predisposed to produce embryonic and fetal forms of globin. They remain, for the most part, nucleated in vitro, yet once transplanted into murine hosts, the cells mature.[68-70] To meet the need for a predictable supply of platelets to counter life-threatening hemorrhages, investigators have focused on producing megakaryocyte populations from PSCs that can be expanded, cryopreserved, and differentiated into platelets in vitro.[71-73] A highly effective strategy for generating a scalable supply of megakaryocytes entails reversible immortalization of megakaryocyte precursors by means



of controlled ectopic expression of transgenes that serve to drive cell proliferation and arrest differentiation.[73] Subsequent reversal of transgene expression enables efficient synchronous differentiation into platelets.

Although yet to be proven clinically, a theo-

Figure 4 (facing page). Targeting the Brain, Replacing the Beta Cell, and Generating Blood Cells.

The injection of dopaminergic neuronal progenitor cells, derived from human iPSCs, into the putamen has been performed in *Macaca fascicularis*, also known as the long-tailed or crab-eating macaque, for the treatment of Parkinson's disease[54] (Panel A). The cells survived, and neurites extended into the host striatum. Neuronal progenitor cells derived from human embryonic stem cells have demonstrated similar behavior.[55] Embryonic stem cells have been differentiated in culture into glucose-responsive insulin-producing beta-cell progenitors that are then encapsulated to prevent immune destruction (ClinicalTrials.gov number, NCT02239354) (Panel B). Pluripotent stem cells (iPSCs or ESCs) have been used to generate a variety of blood cells in vitro and in mice (Panel C). EMA denotes European Medicines Agency and NK natural killer.

retical advantage of PSC-derived red cells and platelets is their relative safety; because they lack nuclei, they can be irradiated to reduce the risk of tumorigenicity. A hurdle for both red cells and platelets is that generation from PSCs remains inefficient and costly. Advances are needed to achieve commercial viability, including refinement of bioreactors and further elucidation of the biomechanical principles that promote megakaryocyte fragmentation into platelets.[74,75] Nonetheless, testing of PSC-derived platelets in humans is scheduled to commence this year.

Tumor-targeted T-cell therapies have garnered considerable excitement owing to their potential to induce remission in patients with previously intractable lymphoid cancers.[76] However, current methods require that patients undergo leukapheresis to isolate autologous T cells, which are then modified by ectopic expression of a chimeric antigen receptor (CAR) that targets the B-cell–specific CD19 antigen, before the cells are expanded in vitro for infusion into the patient. Such a cumbersome and labor-intensive manufacturing process has contributed to the prohibitively high costs of such therapies. In theory, PSC-derived T cells could provide an inexhaustible allogeneic supply for modification with CARs. To evade the immune response, further genetic engineering to eliminate major histocompatibility complex molecules in CAR T cells with the use of CRISPR–Cas9 (clustered regularly interspaced short palindromic repeats associated with Cas9 endonuclease) is required. A proof-of-principle demonstration of tumor-killing PSC-derived CAR T cells would raise the prospect of "off-the-shelf" tumor-directed T-cell therapies and almost certainly reduce costs.[77,78]

The derivation of engraftable hematopoietic stem cells represents the ultimate challenge for the engineering of blood lineages from PSCs. Despite the rise of allogeneic marrow registries with millions of donors and enhanced control of graft-versus-host disease with immunosuppressive drugs, allogeneic marrow transplantation remains a procedure that is associated with a high risk of death, limiting its use to the treatment of malignant or severe genetic disease. After decades of work, some groups have reported success in generating multipotential lymphoid–myeloid hematopoietic stem and progenitor cells from PSCs derived from mice, monkeys, and humans.[69,70,79,80] PSCs represent an appealing means of combining gene repair with cell-replacement therapy for inherited genetic bone marrow disorders such as sickle-cell anemia, but the potential for accrual of oncogenic mutations during propagation remains a concern.

PROSPECTS FOR THE FUTURE

The derivation of ESCs and iPSCs fueled expectations for cell-replacement therapy, but its greatest effect has been in basic research into the mechanisms of tissue differentiation and the pathophysiology of human disease. Dozens of disorders have been modeled in vitro with the use of patient-derived iPSCs,[22-24,81,82] and extensive screening to overcome disease phenotypes has yielded drug candidates.[83,84]

Relatively few clinical interventions have been tested to date, and proof of efficacy for tissue-replacement therapies remains an aspiration. A limitation of in vitro differentiation of ESCs is that the cells tend to be immature, although maturation sometimes occurs after transplantation in vivo.[16,53,60,68,69,85,86] Other challenges include the need for efficient scale-up and quality control for cell manufacture, especially given concern that oncogenic mutations plague cells in long-term culture.[87] Also required are a means of delivery that is minimally disruptive yet attains robust penetration, engraftment, and functional integration into host tissue. An additional challenge is the selection of patients most likely to benefit from the procedure (Table 1).

An audio interview with Dr. Blau is available at NEJM.org

Table 1. Challenges in the Clinical Use of Pluripotent Stem Cells.

Scale-up and quality control	Occurrence of oncogenic mutations during cell manufacture; viability of cells during transport and storage, especially when bioengineered scaffolds are used; cost-effective scale-up in bioreactors to overcome cumbersome labor-intensive production
Selection of biomarkers of differentiation	Functional assays for cell activity, gene expression profiles
Choice of preclinical animal model	Relevance of model to human disease; many diseases are not manifested in rodents, and surgical interventions to create them may not adequately recapitulate disorder
Preclinical assays	Targeted delivery that is minimally disruptive; achieves robust penetration, engraftment, and functional integration; maturation from fetal to adult stage; and persistence of biologic cell function
Expected mechanism of action	Does therapeutic effect occur through replacement of damaged tissue with stem cells or through paracrine mechanism?
Clinical trial considerations	Determination of patients most likely to benefit, which depends on nature of disease, assessment of time window of opportunity for intervention, and reliable measure of outcome
Unauthorized stem-cell clinics	Internet propagation of stem-cell therapies that are not efficacious or approved; these are both unethical and dangerous
Cost and availability of iPSC therapies	Autologous, patient-specific iPSC-derived cells would overcome need for lifelong immunosuppression, which is associated with increased risk of death, but are too costly given necessary quality control and too slow to meet acute needs (e.g., spinal cord injury and myocardial infarction); alternative strategy entails HLA-matched, quality-controlled, iPSC cell banks that are being pioneered in Japan

A more general concern is the rapidly growing direct-to-consumer marketplace (especially on the Internet) for stem-cell therapies whose effectiveness has not been proved through thorough medical review. This is a development that is both ethically dubious and downright dangerous for patient health and threatens to undermine the field of stem-cell research.

The ideal therapeutic scenario of patient-specific autologous iPSCs, which would obviate the need for lifelong immunosuppression, may never prove to be viable. The costs and time required for assuring quality control for each cell line, coupled with the need to treat acute disease, such as spinal cord injury or myocardial infarction, render individualized cell therapeutics impractical.[21] Continuous immunosuppression is associated with increased risks of illness and infection. Therefore, the widespread application of cell-replacement therapies must await the establishment of HLA-matched master cell banks that would serve as repositories for "universal" allogeneic donor cells or the invention of improved strategies for the generation of immunologic tolerance of engrafted tissues.[45] All of that being said, biotechnologies typically mature slowly and translate into reliable means of treatment over the course of decades. We remain confident that the hurdles facing PSC will be surmounted and that it will continue to influence the treatment of disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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