# *Lancet* Commission: Stem cells and regenerative medicine

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## Executive summary

In this Commission, we argue that a combination of poor quality science, unclear funding models, unrealistic hopes, and unscrupulous private clinics threatens regenerative medicine's social licence to operate. If regenerative medicine is to shift from mostly small-scale bespoke experimental interventions into routine clinical practice, substantial rethinking of the social contract that supports such research and clinical practice in the public arena will be required.

For decades, stem cell therapy was predominantly limited to bone marrow transplantation for haematological diseases and epidermis transplantation for large burns. Tissue engineering and gene therapy faced huge challenges on their way to clinical translation—a situation that began to change only at the end of the 1990s. The past 10 years have seen an exponential growth in experimental therapies, broadly defined as regenerative medicine, entering the clinical arena. Results vary from unequivocal clinical efficacy for previously incurable and devastating diseases to (more frequently) a modest or null effect. The reasons for these widely different outcomes are starting to emerge.

At this stage in their evolution, these experimental therapies (which include, but are not limited to, cell and gene therapy, tissue engineering, and new generation drugs) are necessarily financially expensive. Rigorous and costly clinical-grade procedures have to be followed in the development of medicinal products (involving cells, genetically manipulated cells, viral vectors, or biomaterials with or without cells), often produced in a very limited run. The cost of developing sufficiently high-quality trials means that only wealthier countries are able to fund them. Although public investments in this field are massive internationally, they do not carry guaranteed commercial returns. Compared with conventional drug development, such products follow a highly uncertain route to market. Furthermore, new therapies expose patients to risks, some of which are difficult to predict even with inbuilt safeguards.

Despite the relatively small number of clinical successes, optimism and excitement about the potential effect or implications of this field remain great. This enthusiasm has led to gaps between people's expectations that new therapies should be available, often inflated by media reports, and the realities of translating regenerative technologies into clinical practice. The same environment is also permissive of one-off compassionate applications and poorly regulated trials. Indeed, the number of poorly regulated clinics has grown; clinics that appeal to desperate patients and their families, who, in the absence of reliable clinical knowledge from trials, cannot be adequately informed to assess the risks and benefits.

These ethical and governance issues pose a challenge to scientists in engaging with the public, the press, and decision-making bodies in different national health systems. Political agendas might not coincide with the public good. In poorly regulated states, the authorisation of a novel therapy might be politically attractive, even when efficacy is unconfirmed, and the cost to taxpayers means other patients are deprived of established and effective therapies. These challenges are difficult to address and solve. We recommend a solution that lies in a coordinated strategy with four pillars: better science, better funding models, better governance, and better public and patient engagement.

## Introduction

In his Foreword to the Nuffield Council on Bioethics Report, *Emerging Biotechnologies: Technology, Choice and the Public Good*,[1] Michael Moran (chair of its Working Party on Emerging Biotechnologies) wrote: "When we began to look at the field of emerging biotechnologies… their sheer breadth became apparent and their differences perhaps more important than their similarities. The only cross-cutting issue common to all emerging biotechnologies is indeed that they are emerging. Therefore, we have focused precisely on this process of emergence, and on the conditions that shape it. We are concerned, above all, with how reflection on decisions concerning biotechnology innovation can produce outcomes better aligned with the public good."[1]

In the past 5 years since that report, biotechnology has already changed markedly, but the problem remains: when so much of what the near future holds emerges quickly and often unexpectedly, how do we make sound judgments about what is best for the public good? It is often difficult for policy to keep up. Policy makers might not always fully consider the social consequences, and might have different objectives from those doing the science. How do we ensure the knowledge gained from publicly funded research yields public benefit? With the palpable sense of (probably disproportionate) public excitement and expectation around stem cell therapies, it is the scope, rather than the scale, of the health benefits they promise that makes them relevant.

Because of this promise, a number of substantial challenges must be addressed if stem cell and regenerative medicine is to deliver sustainable, clinically significant, and equitable benefits. An urgent challenge could arise from the current combination of the political economy of hope invested in stem cell therapies,[2–4] the relative lack of

### Key messages and recommendations

**Key messages**

- Existing research is hampered by reduced funding for the best quality basic research, frequent absence of strong preclinical evidence, poor trial design, and poor and inconsistent reporting, particularly of non-randomised trials
- Evidence of the cost-effectiveness of regenerative medicine is exceedingly sparse and more is needed; the rarity of many conditions for which regenerative medicine is indicated means that uncertainty surrounding the expected effectiveness and cost-effectiveness will be ongoing and substantial
- Understanding expectations of patients and the broader public is key to maintaining public trust in cell and gene therapies; the current gap between public expectations and the realities of translating regenerative technologies threatens the social licence of regenerative medicine to operate
- Cell and gene therapies require a strong governance framework oriented towards the public interest; given the uncertainty and contested nature of the current social contract for these therapies, it is a mistake to think that the answer is more science with less regulation

**Recommendations**

- Preclinical work in animals should be done as rigorously as clinical experimentation; evaluation and reporting of trial results should be extremely detailed to allow appropriate moves to phase 2b and beyond
- Institutions should invest more to develop clinician scientists and reduce the burden of this double career, which would facilitate the transition from preclinical to clinical work; more academic good medical practice facilities should be created to make trials more affordable
- Research into how cell and gene therapies can become cost-effective and scalable should be a priority; the incorporation of wider societal benefits from new therapies within the appraisal framework should be considered in tandem with current work in this area more broadly
- An international register of cell and biological experimental interventions should be created, and sustainable funding secured for it, possibly within the European Medicines Agency and US Food and Drug Administration, but with a careful process of review to guarantee the scientific soundness of trials
- Policy should be developed by the International Committee of Medical Journal Editors so that trials reporting results of cell and biological therapies will not be published unless trials have been registered in the proposed international register
- The initial review for every experimental therapy should consider the relevant social and regulatory context
- Researchers and others involved in funding, publishing, and communicating stem cell research should integrate some responsibility for public dialogue into their research, engagement, and communication plans; such plans should include appropriate use of social media and internet forums

established therapies, and the persistence of a substantial cross-border market in untested and potentially ineffective therapies.[5] The great risk of the current situation is highlighted by the case of Vannoni in Italy, in which the Stamina Foundation initially succeeded in obtaining direct authorisation from the Italian Government to administer an unproven therapy to patients, thus bypassing the country's regulatory authorities.[6] The risk goes deeper than possible harm to individuals. When cases like this arise, the long-term credibility of stem cell research and scientific integrity are also at stake. A broad reflection on the ethics and governance of stem cell research and regenerative medicine should play an intrinsic part in their development, if their licence to operate is to be maintained. Within a global context, issues of ethics and inequalities might apply differently to Europe and the USA than in countries with emerging economies, with doctrinal and ideological dimensions, culturally specific meaning in different global locales, and cross-cultural differences that have hitherto unseen moral and ethical complexities holding an equivalent relevance.[7,8]

Fortunately, there is now general agreement of a need to discuss and scrutinise technologies upstream—that is, when they are still at a relatively early stage, rather than waiting until they are ready to be deployed.[9] As we discuss in this Commission's section on public engagement and trust, guidelines from the International Society of Stem Cell Research (ISSCR) and from the International Society of Cell Therapy (ISCT) now define the criteria for a correct and timely translation of stem cell research to clinics, and identify unproven therapies as a real danger for patients.[10–12] In principle, such upstream engagement fosters open dialogue among scientists and different public audiences. It brings uncertainties and risks, as well as potential benefits, of the new technologies out into the open and allows the results of these discussions to shape frameworks for anticipatory governance. In practice, however, the question of how technologies might be scrutinised upstream when their outcome can only be evaluated in patients should also be considered. This is indicative of the need for a reflexive science policy, rather than one constituted as a reflex regulatory response to developments in this field.[13]

Ethical and governance challenges will shift over time as stem cell and regenerative therapies move from the experimental to the routine. Early engagement can also influence choices about where to focus research and development efforts. Research funding for cell therapies is money that is not spent on other potential therapeutic advances. To ask whether the investment made in these therapies will provide a justifiable return in terms of future health benefits is legitimate. Although identification of promising lines of research is difficult early on, individuals with responsibility for allocating research funds have to do just this. When research does lead to a therapy becoming a routine part of clinical practice, issues of cost and access will become increasingly salient—once therapies are available, political and social pressures come to bear that are often not exerted when allocating research funding. Most regenerative medicine therapies, even once approved and established, will probably be considerably less cost-effective than other therapies funded in health-care systems. To fund these therapies would potentially result in other—more cost-effective—therapies having to be limited elsewhere, leading to foregone health, greater morbidity, and avoidable mortality for those patients who lose out. Yet, if successful, a cell, gene, or tissue engineering therapy could be economically viable as a

single intervention, rather than a costly life-long treatment. Ethical issues also arise in denying a truly life-saving therapy to a patient when it is considered too expensive.

Questions about access to treatment in all health-care systems are choices about priorities. The biggest question for the future will not, therefore, be concerned with whether regenerative medicine will be able to provide subtantial health benefits, but whether the cost of those benefits is worth paying. Provided efficacy is shown, high costs could be justified if the type of health benefits being provided are exceptional. For example, the severity of the diseases for which these treatments are used—or the importance in the long-term of substantially extending powers of bodily regeneration beyond those that are natural—might justify funding them versus currently more cost-effective therapies. But any such analysis needs to be reflexive: new abilities to repair the body might now seem extraordinary, but in the future might seem as unexceptional as blood transfusions do now. Identification of lines of research that promise effective treatments should be balanced with allowing researchers the freedom to pursue questions whose answers might not be known for many years, if ever.

To contextualise the ethical and economic challenges we describe in this Commission, and to understand the potential for therapeutic benefit, we will first describe the scientific underpinnings of key technologies involved, their origins, and possible trajectories in mainstream health care. Because these topics are already broad, cell and gene therapy in cancer research will not be covered here. As a huge and expanding area in its own right, its main goal is to destroy cancer tissue, rather than to regenerate diseased tissues.

## Cell and gene therapy

Cell and gene therapy can be broadly defined as medical procedures in which cells or genes represent the medicinal product (panel 1). As with any definition, this type of generic description cannot offer a complete insight and might also mask inaccuracies; we have, therefore, attempted to illustrate and expand upon this description through examples.

### Cell therapy: haemopoietic and epithelial stem cell transplantation

In cell therapy, cells are isolated from a donor and transplanted into a recipient (figure 1). The donor and the recipient can be the same (autologous transplantation) or a different individual (allogeneic transplantation). Attempts to mobilise a patient's own (endogenous) cells (usually with bioactive molecules such as growth factors, chemokines, or hormones) and direct them to where they might exert a beneficial effect in a given pathology (for example, coronary infarct) are also considered cell therapy, although they do not involve cell transplantation.

The first cell therapy in modern medical history was the intravenous transfusion of whole blood (rather than required cellular components, as is generally used today) from a donor to a recipient. This development became possible because of the identification of human blood groups by Carl Landsteiner in 1900, and during the First World War, blood transfusion became a consolidated medical practice necessary to restore blood volume after an acute haemorrhage (figure 2).[14–15] The next step in cell therapy came with bone marrow transplantation (BMT),[16] again historically linked with a world war, when civilians were exposed to potentially lethal doses of radiation from atomic bombs, and to subsequent use of nuclear radiation. The irradiation-induced damage to bone marrow ranged from aplasia to cancer. After many repeated attempts over a period of years, intravenous delivery of whole bone marrow

***Panel 1*: Definitions of regenerative medicine, cell and gene therapies, and tissue engineering**

**Regenerative medicine**

- An emerging medical endeavour aimed at regeneration via small molecule drugs, biological therapies, medical devices, or cells and genes
- Aims to replace or repair human cells, or regenerate tissue or organs to restore normal function

**Cell and gene therapy**

- Cell therapy is a developing medical technology based upon delivering cells as medicines for a growing variety of clinical indications
- Similarly, gene therapy is based on delivery of genes as medicines
- Delivery might be direct into patient tissues (in-vivo gene therapy) or cell mediated (ex-vivo gene therapy—a combination of cell and gene therapy)
- Gene therapy is not an exclusive domain of regenerative medicine; most ongoing gene therapy trials are for cancer treatments
- Although the terms cell and gene therapy have entered common language, with few exceptions, they are experimental therapies rather than standard or consolidated ones

**Tissue engineering**

- Implantation of artificial or reconstructed whole organs or tissues
- When these implants contain patient or donor cells, tissue engineering could be considered a special form of cell therapy

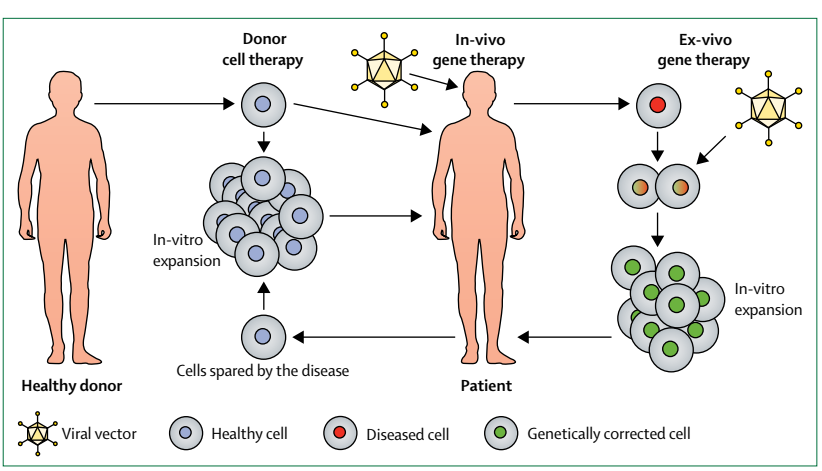


***Figure 1*: Cell and gene therapy**

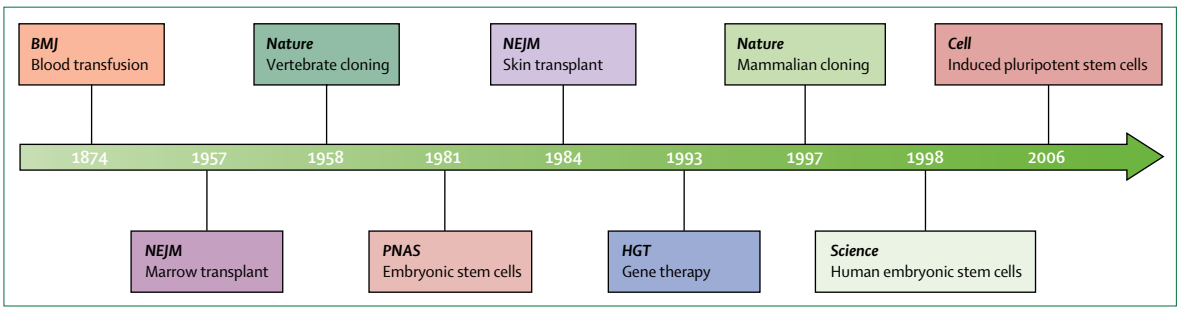


***Figure 2*: Landmark steps in regenerative medicine**[14–22]

*BMJ=British Medical Journal. NEJM=New England Journal of Medicine. PNAS=Proceedings of the National Academy of Sciences. HGT=Human Gene Therapy.*

finally resulted in transfer of long-term self-renewing stem cells from donor to patient with consequent reconstitution of all of the damaged blood cell types, and permanent therapeutic effects.[23]

Both blood and BMT require immunological matching of host and donor. Additionally, for BMT, immune suppression is required unless the donor and recipient are immunologically identical (ie, monozygotic twins, fully matched for both major and minor histocompatibility antigens). Mobilisation of stem cells in the donor's blood and the use of HLA-matched haemopoietic stem cells (HSC) from cord blood—stored in ad hoc banks—have further improved the simplicity and efficacy of BMT.[24,25] As well as donor-recipient blood transfusions, autologous transfusions can be made, for example, in which stored blood from a patient is used for their own transfusions required after undergoing major surgery.

Similarly, autologous BMT can be used in malignancies in which disease-free bone marrow is preserved before the massive myeloid ablation that occurs after radiotherapy. Bone marrow stem cells can also be collected and genetically corrected (via ex-vivo gene therapy), for later re-infusion into a patient. This procedure has been successfully applied not only for haematological diseases (for example, in congenital immune deficiencies) but also for degenerative diseases of the brain.[26–28]

Autologous cell therapy has also been used in clinics for large burns to the skin and to repair the cornea (figure 3).[29–31] This was made possible by the seminal discovery that stem cells from the epithelia can be clonally expanded in culture on a cell feeder layer where long term,[32] self-renewing cells form colonies termed holoclones. Indeed, epithelial stem cells from a patient can be used to generate large sheets that are transplanted onto the same patient to cover the surface previously burned. This treatment results in a long-lasting, life-saving persistence of almost normal epidermis, although no appendages can be generated.[33] In the case of the cornea, transplantation is hampered by donor shortage but autologous cell transplants have resulted in stable success rates of 70% and more. For this procedure, two interventions are necessary: one to biopsy the limbus (the border between cornea and conjunctiva where stem cells reside) and expand the cells in vitro; another to remove the scar and simultaneously transplant the in-vitro-generated new cornea. This therapy was the first cell therapy product to receive market authorisation in Europe.[34]

With the exception of blood and bone marrow, all other forms of cell therapy require donor cells to multiply in culture to acquire the large quantity of cells necessary for transplantation. Although commonly used in clinics today, cell culture exposes cells to potential damage, such as oxidative and mechanical stress, possibly resulting in mutations and chromosome abnormalities, senescence, and infection.[35–37] Cell therapy for the haemopoietic system and epithelia have seen a far higher percentage of clinical success, but new cell types are entering the clinical arena.

## Embryonic and induced pluripotent stem cells: the future?

Until now, almost all cell therapy clinical trials have been done with postnatal stem or progenitor cells (including cord blood), isolated from patient or donor tissue. However, in the future, an increasing number of trials will be done with differentiating or differentiated cells or tissues derived from embryonic stem cells (ESCs) or reprogrammed induced pluripotent stem cells (iPSCs). ESCs were originally studied by isolating them from the inner cell mass of mouse blastocysts, and adapting the cells to proliferate indefinitely in culture while maintaining pluripotency (the ability to generate many of the cell types of our body). Mouse ESCs were identified and characterised in the early 1980s; human ESC cell lines were derived in 1998.[38,39] ESCs opened a strong clinical opportunity, especially for diseases affecting tissues in which adult stem or progenitor cells have not been clearly identified, are inaccessible, or are difficult to expand in culture. Although ESCs show the potential to differentiate into virtually all our tissues, they also presented two key problems. Because ESCs are derived from an embryo, they are heterologous cells with respect to the patient and thus can be subject to immune rejection. Secondly, it is still difficult to induce differentiation into a desired

cell type with 100% efficiency. This inefficiency means that, after differentiation, a small fraction of undifferentiated cells might remain and continue to proliferate, forming tumours. Known as teratomas, these tumours consist of disorganised but partly differentiated tissues—such as bone, heart, or skin. Furthermore, as for any type of cell therapy, functional integration of the resulting cells differentiated from ESCs into the host tissue will remain a consequential, and major issue. Additionally, because human ESCs are derived from human embryos, they have stimulated ethical controversy,[40] which has delayed clinical translation of ESC research.

A groundbreaking development was the demonstration by Kazutoshi Takahashi and Shinya Yamanaka that it is possible to reprogramme an adult somatic cell to an embryonic-like state via the transfer of a limited number of genes into these cells.[41] Yamanaka's work was based on previous demonstrations that adult nuclei in frogs and in sheep (the famous Dolly) can give rise to a complete animal if reprogrammed upon transplantation inside an enucleated oocyte.[17] This research led to the creation of iPSCs, which behave in a very similar manner to ESCs. iPSCs can be derived from patients with specific mutations, thus allowing correction of the genetic defect ex vivo before transplantation in the same patient (figure 4).[42] Although iPSCs do not negate the risk of generating tumours, use of autologous iPSCs could help solve the immunological issues associated with transplantation of ESCs. Nonetheless, the idea of a heterologous use for iPSC is being developed. This opens the possibility of having banks (possibly HLA-specific) that would alleviate the logistics of procurement and reduce costs.[43] Additionally, iPSCs can be generated from patients with specific mutations, the effects and eventual genetic correction of which can now be studied in vitro. This is especially important for diseases that affect cells such as neurons that are otherwise very difficult to study in vitro, given the difficulty of obtaining biopsies from the patient.[44]

At the time of writing, fewer than ten trials that use ESCs are being run or are recruiting. These trials focus mainly on degenerative diseases of the retina, which is considered an immune-privileged organ. Although much preclinical research uses iPSCs, only one clinical trial has involved transplantation of such cells in patients; the trial started and was halted in Japan due to problems concerning the genetic stability of the cell lines used and the need to meet new regulatory legislation.[45] However, many other clinical trials of iPSCs are being planned, such as the reconfigured clinical trial in Japan to transplant retinal progenitors produced from third-party iPSCs.[46] Overall, the situation is not surprising given that fewer than ten years have elapsed since iPSCs were first described, even if the ethical issues in this case are different.[47]

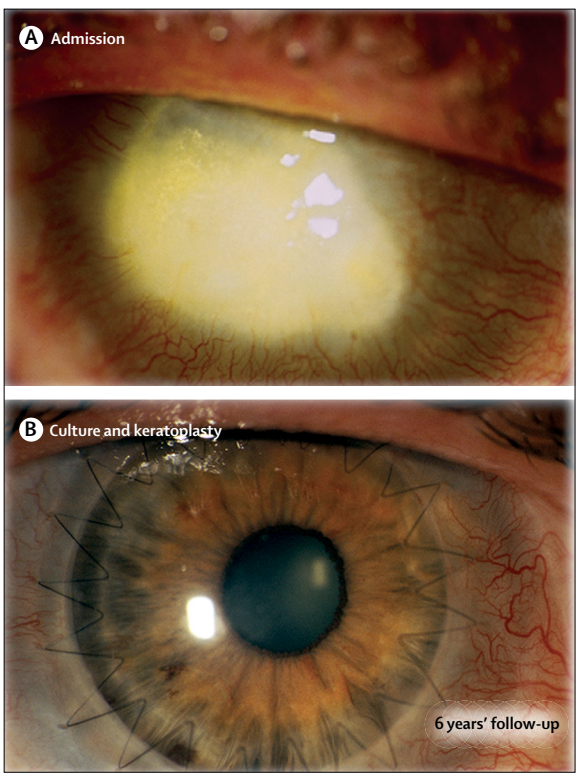


***Figure 3*: Corneal restoration**
(A) Left eye (at admission) of a 42 year-old patient who had total limbal stem cell deficiency due to acid burn. (B) Eye of the patient at the last follow-up, 6 years after graft.

Many studies have shown that organ-specific cells can be generated from different somatic cells, thus directly bypassing potential (eg, oncogenic) risks associated with pluripotency. Many differentiated cell types (eg, cardiac, endothelial, and liver cells) have been directly obtained from a variety of differentiated cells, using specific transcription factors, through a process called trans-differentiation.[48,49] Because this process involves going from one somatic specialised cell to a different type without transiting through an embryonic stage, it might be safer for patients and ultimately easier to translate into clinical treatments. However, the very preliminary evidence reported so far needs confirmation and robust evidence is needed to show that the converted cell is fully equivalent to a healthy, resident cell of a given tissue.

## Gene therapy: general concepts

Gene therapy aims to correct a genetic defect in a given cell type, to restore function, or to provide novel functions. Gene therapy was designed in the early 1980s as a strategy to provide cells of affected tissues or organs with a normal (wild-type) copy of the coding regions (cDNA) of the gene whose mutation had caused the disease. It was quickly understood that gene therapy could be used to provide cells with a novel function for a specific goal (eg, express

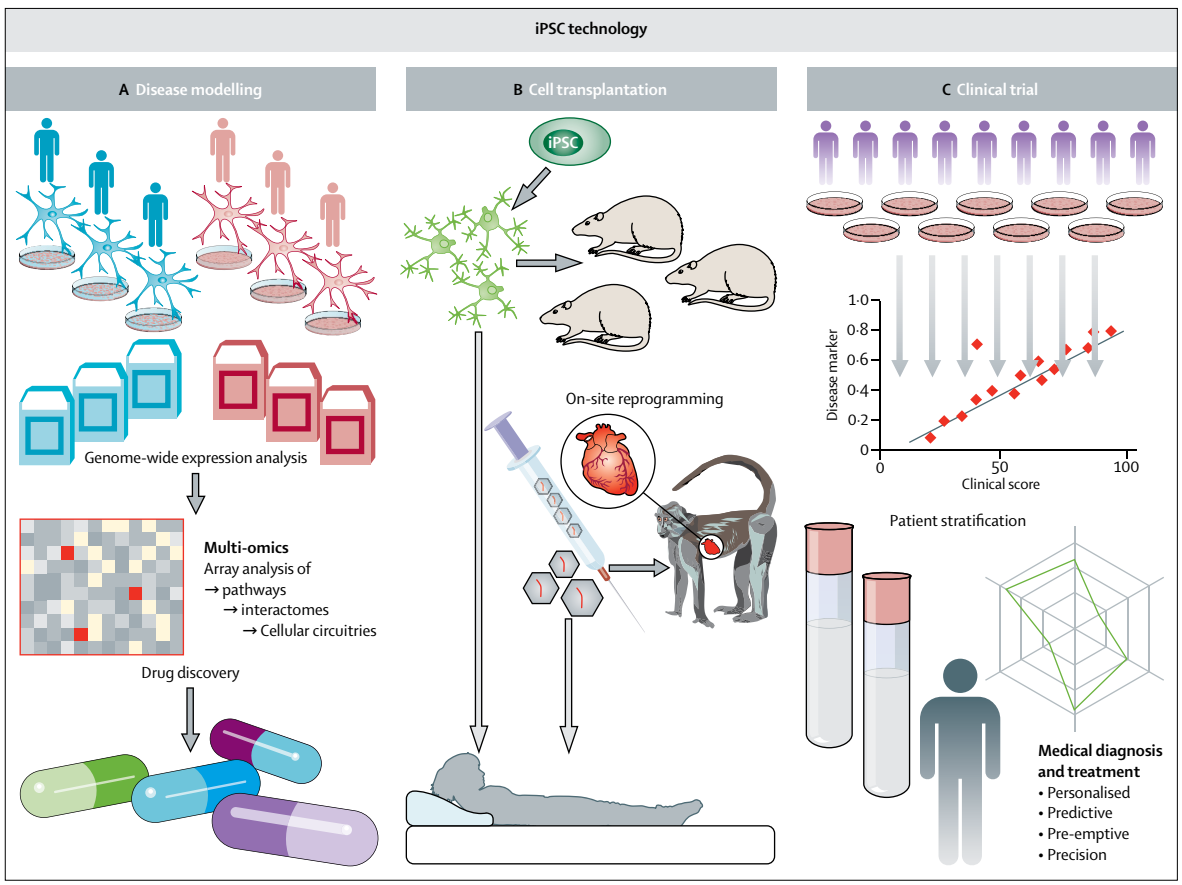


***Figure 4*: iPSC technology**
iPSC technology contributes to (A) disease modelling and drug screening, (B) cell transplantation, and (C) clinical trials. Reprinted with permission from Inoue and colleagues.[42] iPSC=induced pluripotent stem cells.

antigens that enhance immunogenicity of cancer cells or enhance lymphocytes with mechanisms to kill tumour cells more efficiently). This work on cancer is not considered regenerative medicine in the strictest sense and will, therefore, not be discussed in further detail.

Two possibilities have offered alternative options for correcting a gene defect in situ: genome editing[50–55] and correcting the mutated transcript. The transcript can be corrected by exon skipping using antisense oligomers, read-through of a premature termination codon using small molecules, or other small molecule-mediated modification of splicing.[56–59] These strategies have many features in common with conventional drug therapy, being based on either removal from the mature transcript of an exon harbouring a mutation, modification of splicing to induce exon inclusion, administration of drugs to induce a desired modification of splicing, or partial read-through of nonsense mutations[60,61] (allowing the production of a full length protein despite a premature stop codon). Drugs based on these strategies are rapidly progressing, particularly in the fields of Duchenne muscular dystrophy and spinal muscular atrophy.

Classically, gene therapy is divided into two main categories: in vivo, in which genes (or their products) are introduced directly into a patient's cells, and ex vivo, in which a patient's cells are grown in culture, genetically modified, and then reintroduced into the body (figure 1). Ex- vivo strategies are considered a form of cell therapy, illustrating the substantial overlaps that exist between cell and gene therapy. This is also reflected in the shared space both areas cohabit in scientific journals and conferences.

Since the early days of gene therapy development, it was apparent that delivery of genes into target cells would be a major hurdle. Genes—or more commonly their cDNA—are very large, highly hydrophilic, and electrically charged molecules that do not cross the cell membrane by themselves. The use of vectors to carry molecules into cells offered a solution to this problem. Viral vectors exploit the ability of viruses to enter our cells. A viral vector is a virus that has been modified to carry therapeutic cDNA rather than some of its own genes, while maintaining genes encoding its capsid and envelope that are vital for infection. Until now, they have been by far the most commonly used but they are not devoid of problems.

Non-viral vectors (such as liposomes) have also been tested but have consistently proved less effective than viral vectors. A new generation of nanoparticles now shows promise of becoming both efficacious and safe vectors; these vectors are mainly in the preclinical phase, although a few trials have already begun.[62,63]

Of the many viruses initially tested, the ones currently in use in patients are adenovirus and adeno-associated virus as non-integrating vectors, as well as retroviral vectors (both lentiviral and retroviral) that stably integrate into the host cell genome. Adenovirus and adeno-associated viruses are mainly used in vivo in patients.[64–66] Retroviral vectors are mainly used in ex-vivo gene therapy. Although adenovirus vectors can accommodate large cDNAs, they are highly immunogenic. For this reason they are mainly used in cancer gene therapy in which immunogenicity will enhance the host immune response—something to be avoided in the long-term correction of genetic defects, for which adeno-associated viruses are the vectors of choice. Adeno-associated viruses are far less immunogenic and are maintained over a long period of time (measurable in months) in non-dividing cells such as skeletal muscle. Because they are unavoidably lost from rapidly dividing cells, they are not usually used for haemopoietic and epithelial tissues. Additionally, adeno-associated viruses are small and only accommodate small cDNAs (up to 4–5 kB). Retroviruses and lentiviruses are also limited in the size of cDNA they can accommodate (up to about 5–6 kB)—importantly, these vectors integrate into the host cell genome, which ensures prolonged expression of the therapeutic gene, although this is accompanied by the risk of insertional mutagenesis.[67,68]

## Results and challenges of cell and gene therapy

Cell therapy has produced clinically extraordinary results, having saved hundreds of thousands of lives—especially those affected by congenital or acquired diseases of the haemopoietic and, to a lesser extent, epithelial tissues.[27,69–72] This success in such diseases is most likely because diseased host tissue can be ablated: bone marrow can be destroyed to various extents by radiation or cytotoxic agents, while skin or other epithelia can be surgically removed. These procedures create space for donor cells (either allogeneic or autologous) and favour their engraftment because they do not have to compete with resident diseased cells. In structurally more complex tissues such as the brain, heart, and skeletal muscles, where massive ablation of diseased tissue is clearly impossible, donor cell engraftment is lower and consequently, therapeutic efficacy is reduced.[73,74] Furthermore, at later stages of degenerative diseases, resident cells have already died and have been replaced by a thick, avascular fibrotic tissue, which makes engraftment of donor cells virtually impossible. Because of this, many current experimental strategies also aim to reduce fibrosis and enhance angiogenesis. A general consensus is emerging that all therapies, once proved safe, should be tested as soon as possible, ideally at diagnosis, before the onset of fibrosis.[75]

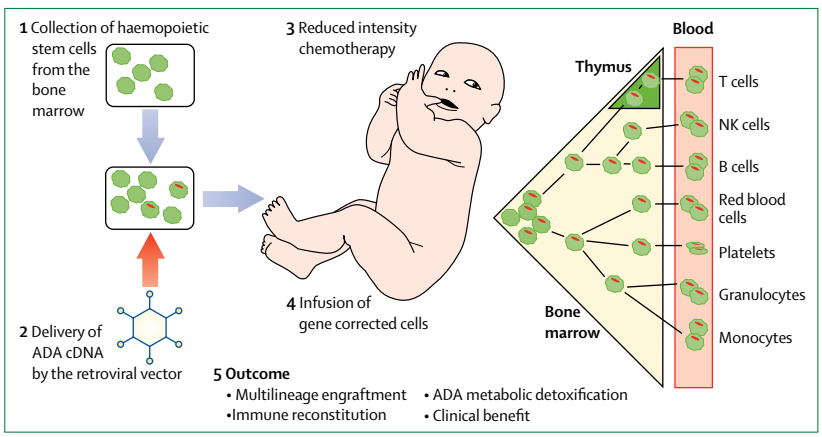


***Figure 5:*** **Gene therapy clinical trial for adenosine deaminase-severe combined immunodeficiency disorder**
CD34 positive cells are collected from the patient's bone marrow, transduced with a viral vector expressing adenosine deaminase, and, after mild myeloablation, are reinfused into the same patient. Adapted from Aiuiti and colleagues.[84] ADA=adenosine deaminase. NK=natural killers.

To date, congenital immune deficiencies represent the major success for gene therapy, including adenosine deaminase deficiency, severe combined immune deficiency, and Wiskott-Aldrich syndrome, and indeed the therapy for adenosine deaminase deficiency recently received market authorization.[76–83] With the exception of one major problem, described below, gene therapy has allowed long-term reconstitution of the immune system in children who were otherwise destined to succumb to infections. The experimental strategy was based on transplantation of autologous, genetically corrected CD34-positive haematopoietic stem cells (figure 5).[84] The same strategy was subsequently applied to β-thalassaemia[85] and more recently to X-linked adrenoleukodystrophy (ALD),[86] a demyelinating disease caused by a deficiency in the ALD protein, (an adenosine triphosphate-binding cassette transporter). Metachromatic leukodystrophy,[28,87] a lysosomal storage disease caused by deficiency of the enzyme aryl-sulphatase, has been similarly treated by transplantation of autologous, genetically corrected CD34-positive cells, which generated microglia that released a large amount of the missing enzyme. The enzyme released was also taken up from the extracellular space by neighbouring neurons, resulting in molecular and clinical correction of the disease. Another example of successful cell-mediated, ex-vivo gene therapy is treatment of junctional epidermolysis bullosa.[88] In this case, cDNA for the *LAMA5* gene was transferred using a retroviral vector into epidermal stem cells isolated from a patient. Sheets of corrected epidermal cells were then transplanted on the legs, using the same procedure first developed by Howard Green, where, although devoid of appendices, they reconstituted functional epidermis.[21]

Leber's congenital amaurosis, a rare inherited eye disease, was successfully treated through in-vivo gene therapy, with direct subretinal injection of

adeno-associated virus expressing the cDNA of the retinal pigment epithelium-specific 65 kDa gene.[89–91]

However, many cell therapies have had limited, variable, or transient efficacy. In the early 1990s, myoblast transplantation in Duchenne muscular dystrophy proved safe but not efficacious. This was due to very poor engraftment, with most cells dying immediately after transplantation and the surviving cells unable to migrate from the site of injection, so that the number of dystrophin-expressing cells was far too low to elicit any functional effect.[92] At a similar time, the transplantation of fetal dopaminergic neurons into patients with Parkinson's disease resulted in variable efficacy of different durations (mainly due to the paucity and heterogeneity of donor tissue, which made standardisation difficult).[93] Although long-term functional improvement was observed in some patients, too few could be treated. The field is eagerly awaiting ESC or iPSC-derived dopaminergic (autologous) neuroblasts that will be available in unlimited numbers.[94] However, Parkinson's disease might be privileged among neurodegenerative disorders because the tissue damage is restricted to a specific anatomical location (substantia nigra), in contrast with multiple sclerosis or amyotrophic lateral sclerosis, which have a widespread effect on far less accessible regions of the nervous system. The difficulty of targeting the nervous system, together with extreme financial pressure, was a reason for the announced closure of StemCells after the failure of a phase 2 trial.[95]

In the past 20 years, transplantation of different cell types in the infarcted heart has elicited generally very modest or no therapeutic effects,[96] and has even seen the death of a few patients. Death is thought to be due to uncontrollable fibrillation when skeletal myoblasts were transplanted, generating another excitable tissue, electrically uncoupled to resident myocardium.[97] Even if successful transplantation of cardiac stem-progenitor cells or in-vivo production of new cardiomyocytes was achieved (eg, by trans-differentiation of non-cardiac cells), newly generated cells would most likely be the size and the functional maturity of an embryonic, newly differentiated cardiomyocyte, far smaller than an adult one, and thus correct electrical coupling would remain a challenge.

Islet transplantation is an established (though non-optimal) therapy in diabetes, mid-way between cell and organ transplantation. The procedure needs substantial development,[98] both because of the need for constant immune suppression, and because long term correction of glycaemia is achieved in only a minority of patients. A large amount of preclinical work is ongoing and many trials have started or are ready to start for other diseases, for example with ESC-derived retinal progenitors for macular degeneration or other retinal diseases (see Trounson and McDonald[99] for a review).

Although the primary goal of cell transplantation is to replace lost or damaged tissue, intravenously injected cells seem to exert beneficial effects even if they do not replace lost tissue substantially.[100] These effects are ascribed to the purported production of growth factors or other bioactive molecules that ameliorate the survival of the residual tissue, for example by enhancing angiogenesis and, therefore, increasing the supply of oxygen to the affected area. However, this concept of a cell drugstore is highly controversial.[5,101] Many clinical trials have been done on the basis of this concept but results are still inconclusive and more rigorous evidence of real engraftment and functionality are needed to resolve this controversy.

Initial excitement about gene therapy was dampened by severe problems, including a few deaths, that delayed clinical success by almost 20 years. The stumbling blocks were represented mainly by the then poorly understood variability in immunogenicity and toxicity of different vectors across species, meaning that preclinical work was not always fully predictive of outcome in patients. Additionally, the erroneous initial belief that a good vector would work equally well in a variety of tissues affected by different diseases led to a number of strategic errors that time and experience eventually corrected. For example, adeno-associated virus-producing factor IX virtually cured haemophilia B in preclinical studies on mice and dogs but turned out to be immunogenic in patients, leading to the destruction of corrected liver cells.[102] This problem was partially solved by changing the serotype of the adeno-associated virus used to transduce human liver cells and allowing therapeutic concentrations of factor IX to be expressed long term.[103,104] Administration of a relatively high dose of an adenovirus expressing ornithine transcarbamylase, which was well tolerated in primates and in the first patient treated, led to a systemic inflammation and multiorgan failure in a second patient who died after 4 days.[105] This tragic event put a stop to the trial and stimulated new research aimed at delivering safer treatments in the future. Years later, five children participating in trials for a severe combined immune deficiency developed T-cell proliferative disease,[106,107] which led to the death of one child, despite the recovery of all the others from the otherwise invariably lethal disease. The event was due to activation of neighbouring proto-oncogenes by powerful enhancer elements in the vector and has subsequently been observed in other protocols using early-generation retroviral vectors. Since then, more sophisticated methods have been developed to reduce the risk of insertion near gene regulatory regions (by changing from retroviral to lentiviral backbones) and to limit the potential of transgene regulatory sequences to trans-activate target cell genes. These changes are unlikely to abolish the risk of this insertional mutagenesis completely, but trials suggest that the risk is very significantly reduced.[108,109]

The examples we report should not mask the fact that several dozen children born with incurable diseases are well, at home, and living a normal life thanks to the success of cell and gene therapy, without which they would not be alive. Never in the history of medicine has

progress occurred without a toll to pay—sadly, often through the lives of the first patients undergoing experimental therapy. Although risk should be reduced to a minimum, the only way to eliminate risk completely is to stop new experimental protocols and with it, medical progress; in this context, careful evaluation of the risk/benefit balance becomes crucial. Moreover, it would be unethical to use these therapies unless the disease was severe and no valid therapeutic option was available. For example, BMT with autologous, genetically corrected cells was initially only considered suitable for patients affected by congenital immune deficiencies who did not have an HLA-matched donor. Now gene therapy seems to be at least as efficacious and safe as standard BMT, and could become the therapy of choice for some conditions.

Another important consideration is not only the severity but also the duration of the disease. Metachromatic leukodystrophy and Duchenne muscular dystrophy are both lethal diseases but metachromatic leukodystrophy (in its most severe form) leads to death within the first years of life, and, thanks to better cardiac and respiratory assistance, patients with Duchenne muscular dystrophy now survive to around the age of 40 years and sometimes older. The risk of a new therapy is well justified in patients with metachromatic leukodystrophy who arguably have very few years ahead, but much less so for patients with Duchenne muscular dystrophy, who could live for decades and have time to wait for a less risky therapy.

## Modification of splicing: antisense oligonucleotides and small molecules

Targeting mutant RNA in Duchenne muscular dystrophy using splice-switching antisense oligonucleotides to restore the reading frame has been an exciting development. A further innovation is the use of antisense oligonucleotides to induce exon retention, which is ideal for severe type I spinal muscular atrophy.

Severe type I spinal muscular atrophy is a motor neuron disease affecting infants, who typically die by the age of 2 years. These infants never acquire the ability to sit. In a phase 1 clinical trial involving patients with severe type I spinal muscular atrophy, systemic delivery of SMN (the product of the mutated gene) with adeno-associated viral vector 9 was, on the whole, well tolerated with the exception of a transient transaminitis. Transaminitis is a relatively common issue in adeno-associated virus gene therapy trials, and and was controlled with corticosteroid administration. The adeno-associated virus gene therapy led to a dose response in terms of intervals free from the development of severe respiratory insufficiency. In a proportion of the children receiving the higher dose, adeno-associated virus 9 gene therapy led to remarkable acquisition of new milestones including sitting, standing, and walking.[110] Because antisense oligonucleotides are not capable of crossing the blood–brain barrier, treatment of patients with severe type I spinal muscular atrophy involved repeated intrathecal administration to maintain adequate concentrations of survival of motor neuron protein.

In the past six years, nusinersen, an antisense oligonucleotide, has been studied as part of a comprehensive programme of open label and randomised placebo-controlled studies in severe type I spinal muscular atrophy and for the milder variants (types 2 and 3). Published data on a phase 1 study in 28 patients with severe type I spinal muscular atrophy demonstrated the safety of four ascending doses. The pharmacokinetics indicated a prolonged CSF drug half-life (4–6 months), and clinical outcome data were encouraging.[111] Data from a more recent phase 2 study in infants with severe type I spinal muscular atrophy indicated safety and tolerability of nusinersen, with both respiratory and motor milestones showing statistically significant divergence from the natural history of the condition. Not only was the ventilation-free survival of treated infants significantly divergent from the natural history of the disease, but most of the treated infants improved their functional scores and acquired independent sitting—and in a few instances, also standing. The top line results of a randomised, placebo-controlled study for severe type I spinal muscular atrophy (ENDEAR study) were announced in a statement by the sponsors, Biogen and Ionis.[112] As the prespecified interim analysis showed a significant increase in the proportion of responders reaching motor milestones in nusinersen-treated patients versus those that received the sham procedure, the placebo-controlled part of the study was interrupted and all patients are transitioning to an open-label extension.[113,114]

In Duchenne muscular dystrophy, antisense oligonucleotides targeting mostly exonic splicing enhancers can induce exon skipping and restoration of the reading frame in patients with eligible out-of-frame deletions. This strategy to induce deleted but in-frame molecules mimics what happens naturally in the much milder Becker muscular dystrophy. Different formulations are in clinical trials in the field of Duchenne muscular dystrophy, the 2□OMethyl (2□OMe) backbone and the morpholino backbone, developed by two different groups. Since 2009, the results of several phase 1 and 2 studies have been published,[115] involving patients with Duchenne muscular dystrophy who can benefit from exon 51 skipping, which is potentially beneficial for the largest number of patients with Duchenne muscular dystrophy who carry deletions (about 13%). Targeting another nine exons would achieve correction in approximately 70% of boys carrying deletions. Indeed, phase 1 studies targeting exons 45 and 53 are now well underway. The outcome of several open-label studies and of two placebo-controlled studies of both compounds targeting exon 51 were encouraging.[116,117] Dystrophin was present in muscle biopsies of the

treated children, although the efficacy of the two compounds differed. Results showed statistically significant and clinically meaningful stabilisation of functional abilities in treated children (as measured by the 6 min walking test) once treatment was prolonged for several years. However, the outcome of a phase 3 study using an antisense oligonucleotide with a 2□OMe backbone that targeted exon 51 was inconclusive.[118] An important contributory factor for this disappointing result could be ascribed both to the relatively short duration of the study (48 weeks) and, more importantly, to the more advanced clinical features of the boys recruited into this phase 3 study, compared with previous trials. Because muscle mass is progressively lost in Duchenne muscular dystrophy, with time, less tissue can be rescued by antisense oligonucleotide therapy; therefore, the stage of the disease of the children recruited is of paramount importance, as is the duration of the clinical trial. Controlling these factors allows divergences in the clinical course to be observed between treated children and the placebo group. The safety profile of the 2□OMe antisense oligonucleotides targeting exon 51 was consistent with that of this class of compounds (skin reactions after repeated subcutaneous administration, reversible renal toxicity, and occasional thrombocytopenia) requiring careful clinical monitoring. In view of the unfavourable risk to benefit profile, and after the negative evaluation of this compound for market authorisation by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the sponsor (Biogen, Cambridge, MA, USA) interrupted the development of 2□OMe compounds for Duchenne muscular dystrophy.[115]

Meanwhile, the FDA accelerated approval for the morpholino antisense oligonucleotide, eteplirsen, developed by Sarepta to skip exon 51. This acceleration was based on the clinical trajectories of a group of children treated for more than 4 years compared with carefully matched untreated children. The FDA decision to grant market authorisation of this Sarepta antisense oligonucleotide compound has been criticised by some, mostly because of the small number of children treated and the low levels of dystrophin produced.[119]

Although novel larger studies targeting exon 51 and others are now underway, considerable research has also been devoted to future-generation antisense oligonucleotides with improved efficiency in targeting skeletal and cardiac muscles. Considerable improvement in efficacy and biodistribution has been achieved with the use of peptide-conjugated morpholino antisense oligonucleotides and of tricyclo DNA. The safety profile of these novel molecules will need to be assessed to determine whether they are ready to enter the clinic as they stand. At the same time, novel strategies (eg, TALEN, Zinc Finger and CRISPR-Cas9 nucleases) for permanently editing the genome (rather than continuously repairing the pre-mRNA) seem promising, but still face the common problem of delivery, especially into large tissues such as human muscle. No clinical trials with genome edited cells or with viral vectors expressing the necessary molecular machinery (CRISPR-Cas9) have been started so far; however, the correction of a genetic defect in a human embryo in vitro (not to be later implanted) was reported this year with great coverage in the press.[120]

## Tissue engineering

Tissue engineering combines the fields of cell biology and material science. Its major goal is the generation of tissues and organs that might be used for regeneration, replacement, or reconstruction, particularly in areas of unmet clinical need. The rapid development of the field has been driven by the plight of patients requiring healthy tissues and organs, but for whom conventional reconstruction is unsuitable; or where allotransplantation is limited by the availability of appropriate grafts of human origin, the need for immunosuppression, or technical considerations. Every day, around 13 people in the UK alone receive organ transplants. At the same time, around four people die or become too sick to receive a transplant while on the waiting list. The immunosuppression of those lucky enough to receive a graft also incurs considerable risks of multiple infections and an increased risk of cancer, and reduces life expectancy.[121] The development of safe and effective tissue-engineered alternatives would reduce mortality both by decreasing the number of patients on transplant waiting lists, and by eliminating the excess morbidity and mortality associated with immunosuppression.

The term tissue engineering was popularised by Langer and Vacanti,[122] and alludes to the combination of biomaterials, cells, and biologically active factors used to effect tissue formation. The process can involve de-novo growth in tissue culture (in vitro, ex vivo) or induction of tissue regeneration in vivo at sites or under conditions where it otherwise would not occur.

Biomaterials provide the 3D structure supporting cell engraftment and tissue growth. Ideally, they should not lead to an adverse immunological response from the host, should biodegrade in a suitable time period that permits sufficient cellular growth (while not producing harmful degradation products), and possess appropriate biomechanical properties compatible with their intended physiological function. To date, such materials have been divided into naturally derived materials, synthetic materials, and natural, acellular (biologic) scaffolds. Materials composed of naturally occurring macromolecules, in particular those that formulate the extracellular matrix, such as collagen, have been tested for tissue engineering purposes, but struggle to mimic the complexity of the composition of the extracellular matrix in vivo.

Synthetic materials have been considered, after their successful use in other areas of medicine. The polyester family of poly(L)-lactic acid (PLA), poly-glycolic acid (PGA), and poly-lactic-co-glycolic acid (PLGA) has long been used in sutures and orthopaedic fixatives, and has been widely applied to produce scaffolds. Degradation of these scaffolds occurs through hydrolysis and the degradation rate can be manipulated by altering material properties such as crystallinity, molecular weight, and porosity. The existing wide clinical application of polyesters supports their biocompatibility, although some studies[123] suggest problems can arise due to their propensity to disintegrate into small particles, or result in toxicity and inflammation associated with acidic degradation. When large volumes of tissue are engineered, vascular supply becomes a critical limiting factor with synthetic materials. Angiogenesis and cell migration and attachment into such materials have been shown to vary with properties such as porosity and surface moieties.

For many clinical tissue engineering purposes, the rich innate molecular and microarchitecture of extracellular matrix scaffolds can be superior to both simple naturally occurring and synthetic materials, at least in the short term. Such natural acellular matrices are derived from human or animal organs or tissues that have been treated to remove cells and other adversely immunogenic material, resulting in natural scaffolds that maintain their original architecture and at least 200 different biologically active (and potentially useful) molecules.

Organ and tissue decellularisation is believed to represent a potentially rich source of scaffolds for transplantation. For this reason, advancement towards the engineering of complex functional organs has attracted considerable public interest and funding internationally. If this strategy is successful, the approximate 40% of organs from human donors which (for medical or technical reasons) are not used for transplantation every year could be converted into valuable therapies. Additionally, since most extracellular matrix proteins are highly conserved, decellularised organs from animals could be engineered and humanised by seeding with human cells. Indeed, porcine and bovine tissue has been used for decades to treat patients, for example in heart valve replacements and tissue fillers. Antigens that have prevented the use of xenogenic organs, such as the highly pro-inflammatory galactosyl-(1,3)galactose (Gal), which causes hyperacute rejection, would probably be eliminated by the decellularisation process, and if not, genetically modified pigs that lack the Gal epitope are now available.

Internationally, a number of groups have used somatic cells to produce relatively simple organs serving as bodily conduits such as the trachea,[124] urethra,[125] and bladder,[126] with some encouraging results in compassionate use case reports, short case series, and early phase clinical trials. As well as mostly helping the patients receiving them, these early attempts at clinical translation have also served to highlight critical barriers to progress, such as vascularisation, biomechanical properties, and contractility. Overcoming these problems is essential before the definitive, larger scale clinical trials and commercialisation can be completed. By contrast to surgical meshes, which can be revascularised adequately after implantation, the presence of cells within these constructs requires an immediate blood supply to maintain cell survival due to the thickness of the tissue and corresponding diffusion distance. Loss of biomechanical properties has also caused problems for patients receiving both tissue engineered tracheas and bladders.[127,128]

One alternative solution would be the use of 3D printing of biocompatible materials, cells, and supporting components in complex 3D functional living tissues,[129] or 3D bioprinting of tissues and organs. While 3D bioprinting has already been used clinically for the generation and transplantation of acellular tracheal splints,[129] more complex tissues containing cells such as multilayered skin, bone, vascular grafts, heart tissue, and cartilaginous structures have been investigated both in vitro and in vivo. In the future, appropriately decorated cell-free polymers might be used for these engineered organs, with the expectation of host tissue and vascular ingrowth. Presently, however, tissue engineering solutions largely rely on the seeding of large numbers of cells, either with the ability to undergo multiple functional differentiation (stem or progenitor cells) or with mature cells (table).[125,130–133] As for cell therapy, ESCs and iPSCs might become a valuable resource in tissue engineering, as might directly converted adult cells.

Despite the promise of a potential replacement for conventional organ allotransplantation, early clinical experiences have highlighted major technical and biological hurdles, scientific and clinical controversy,[134] and commercial problems. Among these, the widely reported discharge of a distinguished surgeon from the Karolinska Institute and resignation of two Nobel committee members drew negative attention to the field of artificial organ transplantation. Such cases of individual misconduct, however, could equally have happened in any field of experimental medicine, with detrimental effect.[135] Even so, if the exciting potential of tissue engineering is to be fully realised, all the challenges we describe will need to be overcome.

Current research and practice of cell and gene therapy and tissue engineering would benefit from the enhancement and support of clinician scientists,[136] both in medicine and in surgery, who are also cell, molecular, or material biologists; academic good manufacturing practice (GMP) facilities to absorb and reduce costs; and a new generation of regulators who fully understand and, ideally, have been working in regenerative medicine.

| | Scaffold type | Size | Cells | Patients | Time (months) | Results |
|---|---|---|---|---|---|---|
| Bronchus[130] | Decellularised trachea | 7 cm | $1 \times 10^6$/mL epithelial cells; $1 \times 10^6$/mL chondrocytes | 1 | 4 | Normal mechanical properties and appearance of graft, improved quality of life, no immunosuppression |
| Trachea[131] | Decellularised trachea | 7 cm | $2{\cdot}5 \times 10^8$/mL epithelial cells; epithelial cell patches | 1 | 24 | Normal CT scan, appropriate growth, patient well |
| Pulmonary artery[132] | PCLA-PLA matrix with PGA fibres | 2 cm | $12 \times 10^6$/mL smooth muscle cells | 1 | 7 | Graft patent on angiography, no occlusion, no aneurysm, patient well |
| Bladder[133] | Collagen matrix or collagen-PGA matrix | 70–150 $cm^2$ | $50 \times 10^6/cm^3$ urothelial cells; $50 \times 10^6/cm^3$ smooth muscle cells | 7 | 46 | Volume and compliance increase, preservation of renal function, adequate structural architecture and phenotype |
| Urethra[125] | PGA-PLGA matrix | 5 cm | $1 \times 10^7$/mL epithelial cells; $1 \times 10^7$/mL smooth muscle cells; $1 \times 10^6$/mL chondrocytes | 4 | 71 | Maximum urinary flow rate 27·1 mL/s, no strictures, normal architecture (biopsy, 3 months) |

PLCA=poly-carpolactone. PLA=polylactic acid. PGA=polyglycolic acid. PLGA=poly-lacticglycolic acid.

***Table*: Clinical applications of tissue engineering**

## Small trials, difficult statistics, difficult regulation, and data reproducibility

With a few exceptions (eg, cell transplantation for heart infarct) the clinical work we have described has been done in small cohorts of patients who, for many diseases, show dramatically different progression and phenotypic heterogeneity, independent of the type of disease. This is due both to the rarity of these diseases and to safety reasons. Therefore, the costs of developing treatments are very high and the risk to which the patients will be exposed is relatively unknown. When risk is difficult to assess and quantify, regulation for safety concerns is problematic. Assessment of efficacy is also challenging because reliable outcome measures remain difficult to define. The net result of these factors is a situation in which—for cell therapy, gene therapy, and tissue engineering—there is a dearth of the type of data that have become expected for conventional pharmaceutical products before market authorisation is given, and even before research investment decisions are made.

This situation is vastly different from classic drug trials, which use large populations of randomised patients. In a very small number of cases (eg, immune congenital deficiencies), the clinical outcome is so striking (disease-free survival versus death) that statistics are not needed,[28,109,124] market authorisation is relatively simple to obtain, and data do not need careful meta-analysis other than patient follow-up. Glybera, an adeno-associated virus that produces protein phospholipase and is delivered through an intramuscular injection, represents another interesting case, particularly in relation to the regulatory landscape.[137] The product was designed for an extremely rare population of patients, who, missing this enzyme, undergo repeated attacks of acute pancreatitis. Market authorisation was initially denied because of insufficient statistical evidence (one patient had another attack of acute pancreatitis after treatment) but was later reconsidered. Conditional authorisation was granted using the trend, rather than statistical validity, as an indicator. But cases such as immune congenital deficiencies and, to a lesser extent, Glybera are exceptions. Often the effect is modest or very modest. Nevertheless, such outcomes suggest further protocol implementation might, in a stepwise progression, lead towards clear efficacy and improvement in patient health and quality of life. However, because the cost of these therapies is very high, the first challenge is to raise money for a trial that cannot promise, at best, more than a minimal effect.

Funding agencies might be reluctant to finance cell therapy projects but are also aware that, in not doing so, the particular strategy in question is killed, together with the possibility that, in time, it could have brought some real benefit. A solid, reliable and reproducible preclinical study in animal models (when available) in iPSC-derived patients' cells or organoids (3D cultures that mimic miniaturised developing organs to different extents)[138] will increase the chance of convincing investigators and, subsequently, funding bodies that a specific therapeutic strategy might yield a small but tangible effect.Nonetheless, funding agencies need to balance allocation of their limited budgets between research on expensive, high-risk, potentially revolutionary regenerative medicine interventions that could only be of benefit to small patient populations (at least in the short-term) against other less groundbreaking projects that might or might not have a larger population effect.

In defining reliable and objective endpoints that could produce a clear result, whether positive or negative, the problems of small cohorts and variability become pronounced: few patients will experience a detectable benefit, others will not, and some might even see their conditions worsen. In the age of personalised medicine,

these differences have theoretical explanations, but in practical terms, determining the reasons for such variability equates to looking for the proverbial needle in a haystack. In such cases, a logical course of action would be to do more trials with the aim of improving understanding of the heterogeneity in response.

But raising additional funds in an environment of such uncertainty is a major difficulty, despite the increasing funding that certain countries (eg, UK) allocate to this area. Additionally, a few further complicating issues need to be considered. The first is that journals and funding agencies naturally privilege both basic and clinical studies that show a clear positive result, creating a real risk of beautification of data, for example by arbitrarily excluding patients who produce negative results. Big Pharma offers countless examples of such practices in the process of bringing a drug to market, in which superior efficacy and safety is then claimed over pre-existing drugs.

Such reporting practices go on to affect academics, small companies, and large pharmaceutical industries for distinct reasons. One solution to the problem is to look to reproducibility of data by independent, unbiased investigators. In practice, however, this task is very difficult (if not impossible) in early phases: with the difficulties of getting such work funded and published, few researchers will spend time and money on confirming someone else's data. For more technically demanding methods, such as cell therapy, lack of the necessary specific expertise might lead to failure, simply because the product obtained when the protocol is reproduced is suboptimal. In the case of stem cells, for example, a suboptimal environment during extensive expansion in culture might lead to loss of the cells' regenerative features[139–141] and a mismatch in the quality of the product used by the original investigators.

To move from what is currently a catch-22 situation resulting in wasted time and resources—one that might lead to public distrust in medical research in this area—a partial solution would be a demonstration of willingness from funding bodies and journals to support confirmatory studies. In this scenario, coherent, reliable and concurring data would be publicly available before clinical studies move into phase 3.

## Health economics of regenerative medicine

The cell and gene therapy industry has sharply increased in the past 10 years, with dramatic rises in levels of investment, clinical efficacy, deals and partnerships, and government support. Worldwide, more than 300 companies are focused on cell or gene therapy, or both. Many of the major pharmaceutical companies, including GlaxoSmithKline (London, UK), Novartis (Basel, Switzerland), and Pfizer (New York, NY, US) have cell and gene programmes that they are actively pursuing, either in-house, or through partnerships with smaller academic or industrial pioneers. The large range of indications being targeted varies from diabetes, cardiovascular disease, and cancer (including haematological malignancies and solid tumour targets), to eye diseases, skin ulcers, and rare genetic diseases. For those treatments to be successful, careful navigation of clinical trial pathways is required, as well as overcoming remaining scientific, manufacturing, and regulatory hurdles.

All regenerative medicine today has benefited from the result of decades of basic research; as such, funding to the basic sciences must be protected, with substantial public and third-sector funding being invested in regenerative medicine. In 2010, an estimated 79% of all UK funding for regenerative medicine was for translation science, leaving just a fifth available for research aimed at commercialisation.

Still, taken as a whole, throughout the past 10 years, regenerative medicine has also received small but increasing investment from the private sector.[142] The preponderance of public and charitable investment is typical for emerging technologies, reflecting the situation that small, low capital private enterprises are not optimally suited to research and development and subsequent delivery of high-risk, high-cost technologies, with long time lines until benefit is seen and small market sizes.

Health economists accept that markets for health and health care do not typically satisfy criteria that define perfectly competitive, efficient markets. Additionally, when such markets or close approximations do exist in health care, and function well, they might still fail to deliver results that are in line with other desired societal objectives beyond efficiency. In particular, many societies choose to sacrifice some degree of efficiency in pursuit of other important societal objectives, notably equity. Balancing these two, often conflicting priorities typically leads to government intervention in the market place. In many systems, intervention comes in the form of the creation of single payer systems (such as the UK National Health Service) or highly regulated mandatory health insurance schemes (such as in Germany or France). The effect of these systems is to counter some of the market power enjoyed by many providers of health products and technologies (power that arises, for example, through the patent system). These systems also give rise to powerful bodies that have authority to determine which therapies are reimbursed through the payment system, with obvious potential consequences for regenerative and stem cell therapies.

Within this scenario the patent system arguably achieves the objective of encouraging innovation through the granting of temporary exclusivity, but its real effectiveness is open to debate. Owing to the length of time taken to secure market authorisation, the patent

term for a cell therapy product tends to be very short and poorly compensated by the grant of a supplementary protection certificate, which can provide no more than 5 years of patent-equivalent exclusivity. Consequently, considerable pressure is on patentees to recover development costs and reward investors within a shorter period of time than would be possible for the inventor of a new toaster or even a new small molecule drug. Perhaps unsurprisingly, therefore, the awarding of patents encourages what some regard as socially suboptimal pricing for treatments. The system gives patent owners a temporal monopoly, enabling them to levy royalty premiums on commodities in addition to any bare commodity profit. In maximising these benefits, patentees are not driven by the socially optimal level of supply, which might be greater. As a result, the gain of treatment accumulates more to the patentee in revenue than it does to the population in terms of health gain, at least for the short to medium term. Nevertheless, in the case of cell products, the returns might be so unrewarding as to deter investment in the first place. Indeed, when inventions are derived from fertilised human eggs, patents are unavailable in Europe. Patenting tends to accumulate around processes and equipment (especially important given the dominance of in-house, autologous treatments in which no cell product is ever placed on the market). Cell products benefit from a potentially far longer period of data exclusivity than the 11 years available to orthodox medicines, simply because of the impossibility of biosimilar cells ever arising: competitors must go back to square one and provide their own data to satisfy regulators, at considerable cost.

### Market power

In the context of regenerative medicine, payers must typically meet a range of objectives across whole populations. In many health-care markets, centralisation of the purchasing power in health care gives rise to a set of powerful organisations in the form of reimbursement authorities. These organisations are tasked with determining what goods and services should be provided within the publicly funded health-care systems to better meet societal objectives and to make efficient use of health-care budgets. In some cases, these organisations exert considerable influence on the market for goods, and have the power to offset the market power of monopolists. Treatments deemed ineligible for reimbursement will have limited opportunities in most markets. From the perspective of reimbursement agencies, regenerative medicine might not offer cost-effective therapy using existing reimbursement standards.

Reimbursement agencies frequently consider the cost-effectiveness of a therapy as part of the approvals process. Such criteria mean that when costs are high and expected benefit to patients is highly uncertain, as is typical for a nascent industry such as regenerative medicine, reimbursement is less likely. High costs at this stage in an industry's development are almost certainly unavoidable, arising as they do from the costs of research and development at the cutting edge of biology and technology, the limited scale of manufacturing, and the regulatory burden necessary to bring novel treatments from the laboratory to patients. From the perspective of the manufacturers, without confidence in reimbursement, they bear the risk of developing therapies at a great cost, but finding no market in which to sell them. In other areas of medicine that have faced similar challenges of high cost and uncertain patient benefit, three arguments are commonly put forward as to why reimbursement should cover therapies that are otherwise not cost-effective.

First, reimbursement agencies should consider paying a premium for innovation to encourage the development of new therapies. To the extent that products are patented, they will have no option: inventors are granted a temporary monopoly through patent protection and are then free to set a price. If price is determined such that a treatment is at the margin of cost-effectiveness then the producer gains all of the benefits of innovation because any health benefit that accrues from the new treatment is offset by health loss elsewhere in the system. The health system only gains from an innovation once the patent period has expired and other producers can enter the market, typically leading to a drop in prices through competition. Others have argued that this is insufficient, because the cost of a new therapy might be high in the present but, subject to reimbursement costs, would be reduced in the future through further innovation. The argument runs that if current innovation is not rewarded, then future innovation might not happen.

By asking health systems to pay for innovation now, manufacturers can shift the burden of risks associated with future research and development to the public purse. If future benefits from innovation are not realised, then the manufacturer has obtained the premium on the original innovation. On the other hand, if benefits are realised, then the manufacturer can set the price at the margin of cost-effectiveness and be rewarded, again, for the innovation. No doubt, in some cases they might also seek to argue for an additional innovation premium. From the health system perspective, allowing additional payment for innovation risks paying for benefit twice, and assuming the risk of developing future therapies. Because many therapies, particularly in regenerative medicine, are also developed through basic science research funded by the public, there is a substantial risk that the value of treatment in terms of health is not worth the expected lifetime cost.

The second line of argument is that some medical conditions should be considered under special rules for rare, or orphan, diseases. Orphan drug designation might apply if the treatment is being developed for a condition in which there are very few patients within a population. In these situations, a manufacturer would probably not invest resources in developing treatments because too few patients would need the treatment and the price required to obtain a return on investment would not be acceptable to payers. To address this, government intervention might be needed to induce manufacturers into the market. Such inducements could include enhanced patent protections, the creation of a favourable research environment through tax breaks or other forms of subsidy, or direct funding of early phase research. Although treatments developed for orphan designations (Orphan Medicinal Product Regulation, Regulation 847/2000) might not meet cost-effectiveness criteria, they might be approved for reimbursement. A reduction in efficiency might be considered an acceptable exchange for reasons of equity improvements. When regenerative medicine products meet the criteria for designated orphan treatments, reimbursement might be more likely.

The third argument in favour of paying a premium for treatments is that society in some way (especially affected patients and patients' associations), value these treatments more highly than other treatments; therefore, they are worthy of reimbursement despite being less cost-effective than other treatments when standard decision criteria are applied. This approach is exemplified by the end of life care criteria that the UK's National Institute for Health and Care Excellence (NICE) can apply in certain cases, such as when a treatment is not otherwise considered cost-effective but might provide some benefits to a select group of patients who are near the end of life. In this case, the argument is that society values a certain segment of the population as more worthy of treatment than other patients, and diverts resources to the favoured end of life group. The UK provides a second example of this through the Cancer Drugs Fund, a ring-fenced allotment of public funds that enables some patients to access otherwise cost-ineffective cancer therapies. The funding cannot be used to provide care for those with other conditions but who also do not have access to cost-ineffective therapies. Such approaches might be used to help achieve societal or political objectives that are not captured in the cost-effectiveness assessment process. However, evidence is emerging that suggests such approaches might be more likely to subvert societal preferences and is often in opposition to expert advice on allocation of resources. Those in the regenerative medicine field should probably exercise caution in pursuing such a strategy given the risk of backlash.

In some countries, notably the USA, public financing of care is more limited and where it does exist (Medicaid, Medicare), it is often not subject to value-based criteria for determining which goods should be provided. Market conditions are therefore more likely to be favourable for therapies early in development where higher costs are less of a barrier.

### Economic barriers to implementing regenerative medicine more widely

One of the greatest challenges facing regenerative medicine is how to transition from proof-of-concept models in the laboratory and early phase clinical trials to production on a scale that will drive down costs of treatment. Where possible, treatments will have to be developed with standardisation in mind. The more bespoke a treatment, the greater the likely cost. This is because treatments will need to be produced at a smaller scale, increasing production costs, and they might need to be accompanied by companion diagnostics to inform customisation. The use of automated production techniques and lower skilled staff will most likely be necessary to drive this process. Understanding whether and how it will be possible to produce at scale will be an important determinant of whether regenerative medicine moves from a boutique, expensive cottage industry to mass production that can take advantage of economies of scale.

One barrier to scalability is the availability of suitable manufacturing facilities. Again, the risk here to manufacturers is substantial. In view of the early stage of the industry, manufacturers might be reluctant to invest in manufacturing capacity—they might not yet know what sort of facilities will be needed, or on what scale. In the UK, the government and research funding bodies have recognised this problem, and money has been made available to further research in manufacturing technology and processes. For example, the Engineering and Physical Sciences Research Council have established a Centre for Innovative Manufacturing in Regenerative Medicine. The centre aims to foster collaboration between academics, clinicians, and industry to develop new ways of bringing regenerative medicines to market in cost-effective ways. In the short-term, public funding to support the development of manufacturing technologies will continue to be necessary, because governments are one of the few institutions capable of bearing the risk of failure. This investment of public money could lead to greater investment from private sector organisations in the longer term.

However, the emotional impact of devastating and presently incurable diseases might create a complex situation, where small companies and short-term investors might have their risk covered by payers, while becoming sole beneficiaries of the eventual profit. Moreover, they might exaggerate the potential benefit of a given treatment and lobby to get market authorisation. Once this is granted (examples of this already exist) they

***Panel 2*: Cost-effectiveness of treatments**

- Many of the therapies discussed in this Commission will probably have substantial costs when ultimately delivered to patients
- For many of the conditions being treated, these costs may be offset by potential savings over the longer term, by reducing the need for expensive health and social care
- Many treatments could also be life-saving, or lead to substantial improvements in population and individual health, or both
- Costs of regenerative medicine ought to be balanced against the cost savings and improvements in health.
- Regenerative treatments have great cost-effective potential for chronic and life-limiting illnesses, such as Duchene muscular dystrophy or Crohn's disease, with high, recurring costs of care and low health-related quality of life
- Therapies that improve such conditions could lead to substantial reductions in costs of other care, as well as substantial improvements in length of life, health, and wellbeing
- Any treatment—even a very expensive treatment—has the possibility to be cost-effective when the offset costs of continuing care and the gain in health are sufficiently large

For more on **NHS Economic Evaluations Database at the Centre for Reviews and Dissemination:** Crd.york.ac.uk

might fix an exorbitant price, in which the emotional support of patients is used to overcome any legitimate doubts of the reimbursement authorities.

### Considerations for the cost-effectiveness of regenerative medicine

Cell therapies and regenerative medicine, with their potential to improve the health of patients, represent a structural shift in health care by focusing on the underlying causes of disease by repairing, replacing, or regenerating damaged cells in the body. The potential exists to substantially reduce the burden of disease for some common conditions (eg, stroke, heart disease, progressive neurological conditions, autoimmune diseases, and trauma). As well as increasing life expectancy, regenerative medicine therapies could greatly improve the health-related quality of life of many patients with chronic diseases. Additionally, regenerative medicine could have a major effect on health services, substantially reducing demand for health care (panel 2). However, the potential health benefits and cost reductions to the health service should be balanced against the costs of regenerative medicine, which are also potentially huge, and which would be borne by the health services. Additionally, only a handful of rare diseases have been successfully treated so far, and there is no guarantee that more common, polygenic, or acquired disorders could also be successfully treated.

Although there is reason to believe the potential value for money of regenerative medicine, there is at the moment very little evidence to support this. Several studies[143–147] have calculated the cost of diseases that could potentially be eradicated or reduced using regenerative medicine (eg, heart disease, heart failure, diabetes, stroke, end-stage renal failure, Parkinson's disease, and spinal cord injury) producing figures of many millions of dollars, but the proportion of these costs that will be avoided because of regenerative medicine is unknown. Additionally, the potential cost savings are not balanced against the substantial costs of the regenerative medicine interventions.

Very few formal cost-effectiveness analyses of regenerative medicine interventions have been done—the kind of analyses that might be required by bodies such as NICE in England. For example, a review of the international NHS Economic Evaluations Database at the Centre for Reviews and Dissemination using the search term "regenerative medicine" found only three studies (last checked July, 2017). Even if regenerative medicine were cost-effective on the basis of the metrics commonly used by organisations such as NICE (eg, in terms of the incremental cost per quality-adjusted life-year gained), health services might not have sufficient budgets to afford them. Huge benefits might be reaped from regenerative medicine but at huge cost, and affordability might limit implementation, even if there is a good chance of cost savings down the line. For example, life-long costs for palliative therapies have been calculated for Duchenne muscular dystrophy in several European countries (figure 6).[148] The disease lasts decades, amounting to very high costs for the NHS. Even if economically convenient compared with life-long expensive palliative care, a huge amount of money would be needed in a relatively short time for regenerative medicine, rather than being distributed over many years or even decades.

While the market grows over the next few decades, thinking of ways that regenerative medicine products can be made more affordable and cost-effective will be useful so that patients can benefit. Options include limiting prices using some form of price regulation; improving manufacturing infrastructure to reduce the cost of goods; considering cost-effectiveness issues at the early development stage to avoid pursuing interventions that are unlikely to ever be good value for money; and greater use of patient access schemes to share risks between companies and health services.

In view of the personalised nature of regenerative medicine and high manufacturing costs, these therapies will probably need to be highly beneficial to patients (compared with current therapies) to be cost-effective. Alternatively, they might seek to target diseases for which treatment options are limited or unavailable, for which value for money might be easier to show.[149] With this in mind, developers ought to

undertake a realistic assessment of whether their technology will be reimbursed at a price sufficient to generate a competitive return. It should not be assumed that technologies that make it to market will automatically be adopted and paid for at a profitable rate.[150] One approach that has been considered for incentivising the production of technologies that meet population needs is value-based pricing. Here, prices are linked to the benefit a health-care programme delivers, rather than the price suggested by manufacturers.[151] Methods have advanced to assess the value of investing in research on innovative technologies, such as regenerative medicine.[152] Other novel approaches have been suggested with a view to identifying technologies that are good candidates for reimbursement. For example, the value-engineered translation framework is an approach that could be applied to regenerative medicine. This framework was designed to evaluate candidate therapies for their potential to achieve market reimbursement, on the basis of analyses of unmet need and the likelihood of clearing market access hurdles.[153]

## Regulation of stem cell therapies and regenerative medicine

Regulation of clinical research is well established. What is less clear is whether existing regulation is fit for purpose in relation to new technologies, and whether those tasked with applying regulations understand new technologies sufficiently. Scientific advancements in the field of regenerative medicine happen frequently and legislation and regulation developed in an earlier era might not be adequate to address new challenges posed as technology advances. The knowledge and technical capabilities of the research community will always be ahead of that of legislators and regulators, and the process of developing legislation and regulation will always be slow, subject as it is to wider public discussion and debate.

The core challenge for the ethics and regulation of cell therapies, as for other new technologies, is to appropriately balance the benefits against the risks. Doing so requires clarification of not only the types and the size of the benefits that cell therapies could create, but also of contextual factors such as how the benefits will be distributed throughout the population, and the opportunity costs of providing the benefit.

A robust and transparent system of laws and regulations is necessary and desirable. First, such regulations exist to protect patients from unnecessary risk. But they also provide a framework to give investigators, funding bodies, and commercial investors the confidence needed to invest in the research and development required to bring innovative products to market. When regulation is missing or weak, those who invest in and develop technologies are at risk of unfavourable, unforeseen changes in the regulatory environment.

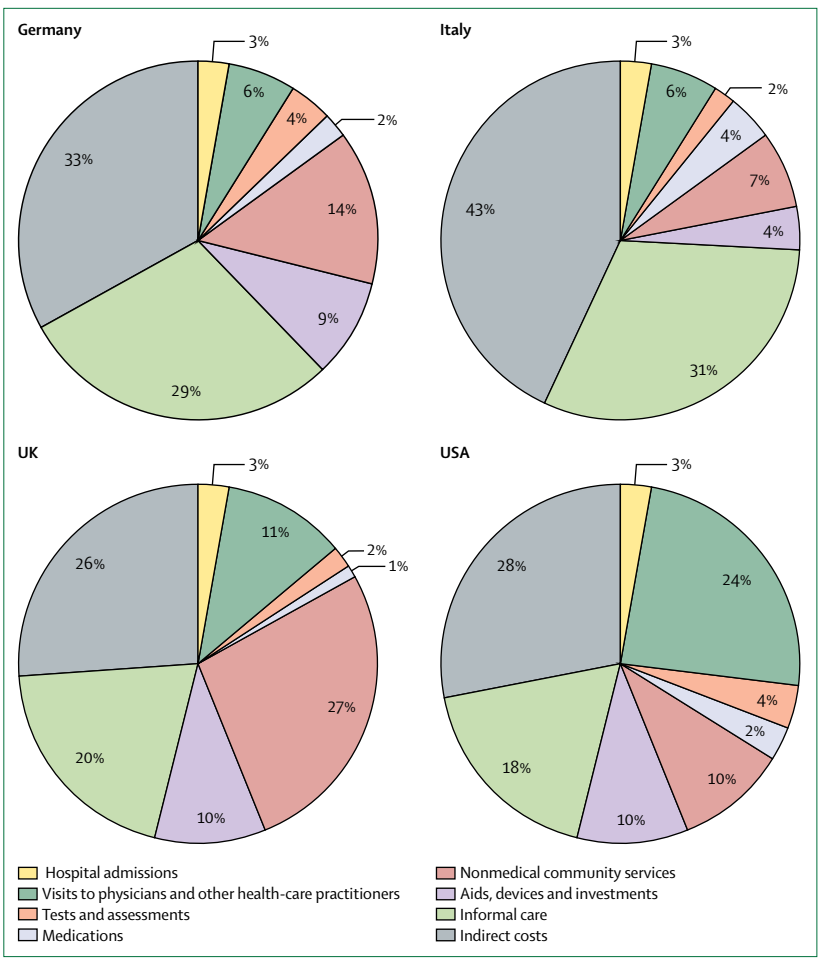


***Figure 6*: Annual costs of Duchenne muscular dystrophy**
The mean per-patient annual direct cost of illness as estimated in different countries. Adapted from Landfeldt and colleagues.[127]

Poor regulation, therefore, will discourage investment and ultimately be to the detriment of patients.

Compliance with regulation, however, does introduce costs to those developing new therapies. When a regulatory system works well, costs are the minimum needed to achieve regulatory objectives. When a system of regulation is overly burdensome and costly, this will unnecessarily deter investment—leading to potential losses both economically and in health gain of the population. In Europe, this effect could be particularly acute because regulation will exist at the national level as well as across nations. To address this problem, a new committee was created within the EMA—the Committee for Advanced Therapies (CAT)—whose members include working scientists who provide the requisite technical expertise. Still, navigating regulatory processes across multiple countries and jurisdictions will increase costs and introduce further risk to those looking to commercialise research.

The number of human regenerative medicine clinical trials remains small. As of June 2017, a search of

***Panel 3*: Balancing benefits and risks**

- Most cell therapy cases would require bone marrow aspirate, or a skin or muscle biopsy, which are minor surgeries that are essentially free of risk compared with huge potential benefit that might derive from their use
- A biopsy in the heart or an area of the brain should be considered more carefully because of the inherent risk of damaging one part of the body to fix another
- Additionally, improper cell manipulation could add another level of risk and long term expansion in culture; even under optimal conditions, cells are exposed to different kinds of stress (mechanic, oxidative) that could affect their safety as medicinal product
- Long term risks for transplanted cells (eg, tumour formation) have rarely been reported, with the longest follow-up of gene therapy of about 20 years

ClinicalTrials.gov (using the search term "regenerative medicine") identified 265 registered studies. Approximately half of these are open trials (those in set-up, or in recruitment stages), and half have been completed. A further 20 trials are listed as having "unknown status". By comparison, a similar search for adalimumab, a widely used biological therapy that shares certain characteristics with regenerative medicine, returns more than 500 trials.

If the same website is interrogated for "cell therapy", more than 36 328 trials are listed. As examples, 42 trials are listed for "muscular dystrophy" and 81 are listed for "cystic fibrosis". Many cell therapy trials do not describe the use of cells at all; of those remaining, many meet the characteristics of unproven cell therapies (eg, unclear rationale for efficacy, insufficient data from in-vitro studies, animal studies and safety studies in humans, inadequate information about patient consent and administration methods—see Srivastava and colleagues[11] for a discussion of the topic). Additionally, many of these trials lack supporting publications and therefore might well be categorised with the unregulated stem cell clinics market and cannot be considered to be on a par with rigorous trials by virtue of their presence on the database. This situation calls for the urgent creation of a novel register or subregister, where trials are peer reviewed and curated to guarantee a high clinical standard.

## Ethics

In examining the ethics of cell therapies, the health benefits and harms of such therapies should be the main focus, and a broad view could be taken of what could count as a health benefit or harm. Direct health benefits such as life extension or reduction in pain can be distinguished from indirect health benefits such as creating a regenerative medicine knowledge commons. Direct health benefits are relatively easier to measure, and often occur over a shorter term than indirect health benefits. Health risks and harms have also been interpreted broadly in this Commission, to encompass not only direct morbidity and mortality, but also to include indirect factors such as undermining of trust in the health-care system, violation of autonomy, and foregone benefits elsewhere in a health-care system.

### Balancing benefits against risks

As Hermansson and Hanson[154] argue, risk management problems can be modelled as having three main parties: those on whom the risk is imposed; those who control the risk; and those who benefit from the risk being taken. Risks are least ethically problematic when the same person fills all three roles—such as when an experienced and knowledgable mountaineer takes on a challenging ascent. Risks are most ethically problematic when those exposed to risk neither benefit from their risk exposure nor can control their exposure to the risk—such as when individuals are adversely affected by pollution from a poorly regulated factory. Judgments about the acceptability of risk also depend on the overall size of the benefit when compared with the risks (panel 3).

This analysis provides a useful baseline understanding of the diverse ethical profiles of cell therapies. Direct benefits and harms should typically be weighted more heavily than indirect risks and benefits, because it is less certain that indirect benefits and harms will occur, and also because in cases of direct harms, the risk is less typically shared by the broader community and more usually concentrated on particular individuals. For this reason, perhaps, the Declaration of Helsinki focuses on benefits and risks to individuals and groups involved in the research project, rather than the community more generally.[155]

We will trace out this analysis through different points on the translational continuum between phase 1 trials and routine medical practice. As therapies move along this continuum, direct risks will typically become more easily controllable, and as therapies shift from early phase to late phase trials and into routine clinical practice, there is an increasing expectation that the therapy will be directly beneficial to the individual patient (panel 4). A well functioning governance system would also ensure that the indirect risks (such as undermining of the social contract involved in research) are adequately controlled and indirect benefits are realised.

Risks of cell therapies can be controlled in two major ways: governance and individual consent. In a broad sense, governance is a framework of incentives, professional standards, regulations, norms, and social expectations oriented towards upholding rights and promoting the public interest. Informed consent supplements governance by allowing individuals to control their own risk on the basis of information

**_Panel 4_: Different translational stages have different risk profiles**

- Phase 1 clinical trials do not aim to benefit the individuals taking part in them. Information available about risks involved in trials might be too scant to make the risk easily appreciable by participants
- Phase 2 and 3 trials (for small and large cohorts of patients) aim to benefit individuals taking part along with the goal of generating new knowledge. Increased safety information from earlier trials makes risks more appreciable by participants
- Routine practice has the benefit to individual patients as its primary goal. The fact that a therapy has passed through the regulatory system and has been given marketing approval gives patients some confidence that the benefits of the therapy will generally be at least proportional to its risks. Increased information from clinical trials and from routine use of therapy makes it much easier for patients to be able to regulate their risk through informed consent
- Unregulated and uncontrolled stem cell therapies have a particularly problematic risk structure. In these cases, the risks of the therapy (both of medical harm, and financial loss) fall on patients, while the main beneficiaries are those who provide the therapies. Such therapies take advantage of lax regulatory environments of certain countries or simply act outside of any regulation. No mechanisms exist to ensure that information is accurate and complete, so neither regulation, nor informed consent, provides an adequate ability to balance the risks

**_Panel 5_: Paternalism**

- Paternalism is interfering with the liberty or autonomy of individuals to benefit them without their consent
- In cases in which the choices or actions that are beneficently interfered with are substantially non-autonomous, this is soft paternalism
- When the beneficent intervention interferes with choices or actions even when they are fully autonomous, informed, and voluntary, this is hard paternalism
- The distinction between hard and soft paternalism refers to the extent to which the choices or actions interfered with authentically embody the individual's autonomous will
- This question is separate from the coerciveness or otherwise of the means employed to interfere with these choices[137]
- Policy choices about paternalism thus need to take into account both the means by which paternalism is pursued, and also the extent to which the choices and actions interfered with are likely to fail to reflect a person's autonomous will[145]

provided to them. In the case of novel technologies, informed consent struggles to adequately protect individual interests outside of a strong governance framework. When the information available about risks and benefits is scanty or uncertain, it will be difficult for individuals to control their risks through informed consent alone.

Different systems can give either more or less control to the patient through individual consent, and will have difference tolerances for paternalism (panel 5). No system should allow individuals unfettered freedom to consent to any procedure no matter what the risks or benefits are. It is helpful to distinguish between cases in which access to a therapy that is reasonably believed to be against a patient's best interest is denied because of an assumption that something has been deficient in the patient's decision-making process (soft paternalism), and cases in which access to a therapy is denied simply on the grounds that it is contrary to a patient's interest (hard paternalism). Generally, hard paternalism is more difficult to justify—although ruling out certain medical interventions on hard paternalistic grounds, such as surgery without good medical reason or where an intervention would be futile, is an established medical practice.[156] Policy choices about paternalism need to take into account both the means by which paternalism is pursued, and also the extent to which the choices and actions interfered with are likely to fail to reflect a person's autonomous will.[157]

An individual's willingness to take a therapeutic risk will always be dependent on what that person anticipates might happen. When novel therapies involve patients who have no other options for treatment and are desperate, the hope of a cure can make them highly vulnerable to wishful thinking and—where money is involved—vulnerable to false promises. Both research and clinical practice face difficult problems in this respect, with complex and disputed judgments about the role that hope should serve in human life, and the conditions under which creating or sustaining false hope is ethically problematic. These life choices are important and cannot simply be taken away from patients.[158,159] But how best to reconcile the different values in play will vary according to local variation, with jurisdictions that place more weight on personal autonomy and responsibility giving the individual greater decision-making control than those that do not, and could mean tolerating false hope. A generic solution does not exist.

We next focus on two main areas of ethical contention: the source of cells to be used in cell therapies and access to cell therapies. In both cases, we address these questions with an eye to the translational continuum between bench science, clinical trials, and routine practice.

### The source of cells

The cells to be used for cell therapies either come from the same individual (autologous transplantation) or different individuals (allogeneic transplantation). When cell therapy requires donation from another individual, many of the ethical issues that are presented have extensive parallels with its early predecessors, bone marrow transplantation or organ transplantation, although a number of commentators have pointed to the gendered bioeconomies of tissue procurement in the context of ESCs.[160] Similar to these earlier interventions, allogeneic transplants can be taken either directly from patients' relatives or be mediated via an international donor bank or sold commercially. When the donor is a patient's relative, questions of risk, consent, and voluntariness emerge: potential donors might be considered by other family members to be morally obliged to undergo what could be a moderate or major medical intervention—a small tissue biopsy or an organ donation—and could face negative reactions if, for whatever reason, they refuse to donate.

This ethical complexity is reduced by the existence of donor banks, in which the patient is unlikely to know or meet the person who donates a tissue that could save his or her life. International donor banks exist for bone marrow and blood but at least for now, not for other tissues, ESCs, or iPSCs—although such banks have been considered as a real possibility once therapies using these cells become a reality. The development of autologous therapies or, more remotely, of a universal donor cell, could provide a resolution for these challenges.

The creation of international donor banks for ESCs or iPSCs raises a distinct set of policy questions and ethical concerns. For example, should these banks be purely non-commercial, or would it be ethically acceptable if a mixed economy of some private and some publicly funded banks emerged? Would models of ethics and governance designed for existing donor banks or biobanks be broadly adequate for ESC or iPSC donor banks? Donors might well not be able to foresee how their cells are going to be used in the future, and so questions will arise (as with biobanks) about the ethical validity of broad consent in donation.[161]

Ethical issues have been raised for example by the Catholic Church and other Christian groups about the use of embryonic stem cells in particular, on the basis that their use offends the sanctity of life. The concern relates to the Catholic doctrine[162] that human dignity and personhood arise at conception and not just at birth, as human rights law[163] suggests, and to the fact that the acquisition of ESCs requires the destruction of fertilised human eggs. On this basis, such cells are considered to already possess the moral status of a full human being and it would, therefore, be morally impermissible to use them for scientific research or therapeutic purposes. Similar debates have arisen in the context of the ethics of in-vitro fertilisation (IVF) and are not distinctive to the ethics of regenerative medicine. Environmental groups such as Greenpeace have a separate ideological objection: that, as living entities, the patenting of cells derived from human embryos should not be commercialised. Although ethical debates of this nature continue to strongly influence developments in the USA and certain European contexts, this issue will not be discussed in detail here.[164]

Several questions about the ownership and control of cell lines also arise: for example, is a cell line derived from me still my property? As Skloot describes,[165] the HeLa cell lines used to this day by many researchers were derived from cell samples from Henrietta Lacks in 1951. No consent was received at the time from Henrietta Lacks, and it was only 20 years later that family members became aware of the global usage of the cell line derived from her. The nature of their subsequent struggle for recognition revealed a wide gap between the regulatory concerns and the perceptions of her family about what should come back to them. The question of legal ownership of derived cell lines was further explored in the legal case Moore versus Regents of California (1990), in which John Moore petitioned (in the end unsuccessfully) for a share of the proceeds of a cell line that had been created from his spleen.[166] Both cases provide prescient examples of the ongoing tension between social innovation and social equality as Ruha Benjamin points out in her examination of stem cell initiatives in the USA.[167]

Under the current legal regimes within both the EU and the USA, autologous cells are regulated similarly to allogeneic cells. Both USA and EU regimes thus reject the principle that someone who donates their own cells for therapeutic modification should be able to decide whether and how those cells are to be returned to them. In the USA, the Code of Federal Regulations was modified in 2005 to bring autologous cells under its remit. A single word change was made: "Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into another human recipient", was changed to "…a human recipient". Although this change reflected questions about whether autologous cells should be considered as a medicinal product not just a practice, some people see this intervention as an expansion of the role of the state in the practice of medicine.[168] The situation within the EU is complex, and a gap exists between the legal position contained in the European Tissue and Cell Directive (2004/23) and its two satellite directives (2006/17 and 2006/86), collectively referred to as the "EUTCD", and the Advanced Therapy Medicinal Products Regulation (1394/2007; ATMP) and what has been adopted by regulators.

There is also diversity of regulatory regimes for stem cells in Europe within the limits set by the EUTCD and ATMP, and the complex landscape worldwide. Although a thorough and complete analysis of all countries where research on stem cells is happening would be beyond the scope of this Commission, we will provide a few examples. The clinical use of stem cells is tightly regulated in many countries (for example, by the EMA in the EU, by the FDA in the USA, and by the Ministry of Health, Labour and Welfare in Japan), or subject to less or no regulation in a number of others, including India, where at present only provisional guidelines exist, whose legal power is limited.[169] In China, the National Health and Family Planning Commission (NHFPC) has begun working with draft regulation for clinical research and applications that involve human stem cells,[170] which although officially considered formal is currently flexible. To control the activity of private clinics that offer stem cell therapies without abiding by any regulation, is, however, a challenge that applies to virtually any country.

Additionally, upstream of any therapeutic use, regulation of research on human ESCs varies substantially between countries, reflecting religious and cultural contexts, as well as socioeconomic conditions. Some European countries ban the in-country derivation of stem cell lines, for example, but permit use of imported human ESCs for research (Italy), other countries have no specific legislation associated with stem cell research at all (Ireland), some ban all ESC research (Lithuania), whereas others maintain a comprehensive and well established regulatory framework (UK, Spain).[171] In the USA, on March 9, 2009, President Barack Obama issued Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells. This order reversed a former prohibition on the support of human ESC research with federal funds. What will happen under President Trump is yet to be seen.[172] More generally, bioconservative political parties might, for purely ideological reasons, attempt to enforce more restrictive policies on ESC research, in the light of other indications of antiscientific attitudes.

### Access to therapies

Patients can access stem cell and regenerative therapies in four ways. First, and most straightforwardly, when a therapy has been tested and received marketing approval for the indication for which the clinical team intends to use it. Second, in the context of a clinical trial. Third, through permitted non-research access to a treatment that does not have marketing approval for that indication—including hospital exemption within the EU, and also off-label or compassionate use. Fourth and more crucially, through direct recruitment (usually through the internet) from commercial entities whose activity is not scrutinised or approved by any regulatory body.

### Access to cell therapies via clinical trials

Perhaps the most difficult questions surrounding access to experimental interventions are whether a maximum level of acceptable risk exists (even when validly consented to, raising again the issue of hard paternalism highlighted earlier) and what the response should be to severe adverse events in clinical trials. For example, under today's regulations, would BMT have emerged as a consolidated therapy? The first patients to be treated with BMT invariably died after transplantation, but the persistence of its pioneers in searching for the causes of its failure, their quest to improve understanding of transplant immunology, and the lack of pressure to move rapidly to market allowed this procedure to progressively develop into a safe and life-saving therapy. Subsequently, the few, though tragic, deaths that have since occurred in gene therapy trials led to their cessation and stimulated further research (for example on vector integration sites) that now ensure higher safety. Although increasing controls prohibitively raises costs and makes it difficult for academics to undertake even early phase (1 or 2a) trials, complete deregulation would legitimise the practices of stem cell clinics offering unproven therapies on the principle of free choice.

The next few years will probably bring a fresh iteration of the free to choose paradox, leading to clashes between medical and business motives pushing against the strict and expensive rules that the FDA and EMA currently defend. The key challenge for regulatory agencies will be to find a path that reconciles rigorous controls and economically affordable clinical protocols. Perhaps the most important issue for risk assessment is the relevance of the indirect benefits of this research for the creation of a knowledge commons.

For many of the conditions for which cell therapies are now being developed, enrolment in a clinical trial provides the only source of hope for patients. As such, selection of patients raises substantial ethical issues. Some diseases are so rare that essentially all eligible patients can be treated with no need for selection. However, the most common among the rare diseases (eg, haemophilia or cystic fibrosis) affect populations of patients who far exceed the number eligible for experimental trials, which are usually limited to a few patients, both for safety and economic reasons. Generally, most patients affected by serious diseases are inclined to accept the risks of experimental therapies in exchange for the hope, if not of a cure, then simply of a small improvement, a step towards treatment that could benefit other patients after them. Very often, selection is based on objective criteria (eg, age, type of mutation, severity, and availability of an HLA-compatible donor).

When more patients are eligible than the few who are normally enrolled, selection poses both medical and ethical issues. One argument is that the chance of

benefit is balanced by the unpredictability (within the limits of good preclinical work) of a first in man therapy. For those awaiting the next trial, however, the disease might progress to a stage at which they would no longer be eligible for the subsequent enrolment. No easy solution exists for this issue, and in many cases, the mere mention of stem cells is sufficient to tempt patients (or parents, in the case of children) to try unproven, experimental treatments. Although the results of any trial carry uncertainties, the use of such therapies also happens outside of the structure of a regulated health system, and comes at a high financial (out-of-pocket) cost. Such patient behaviour is fully understandable when the alternative is imminent, rapid disease progression towards an inevitably fatal end. Carefully designed and conducted clinical trials (which should not require a patient to bear any financial costs), however, must be differentiated from those in which private stem cell clinics are essentially taking advantage of patients' vulnerability.

### Permitted non-research use of therapies without marketing authorisation for that indication

US and EU regulatory agencies differ when it comes to access to therapies that have not received marketing approval. In the EU, the Medicinal Products Directive only applies to products that are placed on the market, and explicitly allows access to therapies that have not received marketing approval through the "hospital use" and "specials" exemptions.

Access to unlicensed medicinal products outside of a clinical trial has until very recently been more restricted in the USA. Such access was allowed only under the Expanded Access to Investigational Drugs for Treatment programme, which requires FDA approval and can be used only for products that are currently being tested somewhere in a clinical trial, and when it can be shown that expanded access would not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval. Since 2014, more than half of US states have passed "right to try" laws, which allow terminally ill patients to receive experimental therapies that have passed phase 1, without seeking FDA approval. These regulations attempt to balance considerations of safety and efficacy with the needs of patients who require urgent medical intervention and who have no other avenues available to them. When patients are in dire straits and when sufficient evidence indicates that the benefits are proportional to the risks for the individual patient, such exemptions do have a role. Furthermore, the idea of adaptive licensing should be explored more fully, in addition to the use of these exemptions.

## A social contract is needed

The mechanisms for regulating risk in research are only part of the framework for securing desired innovations in cell and gene therapies. We also need to revisit the social contract on which medical progress is based. We define social contract here to denote the construction of mutually beneficial alignments of interests to ensure that science develops in conjunction with social benefit rather than in opposition to it. Our definition goes beyond the private contract between patient and clinician or scientist, which is contained in rules of informed consent and malpractice liability. It incorporates the idea of the social licence, by which scientists are permitted to research. However, the social licence is more passive than the arrangement that is needed if cell and gene therapy is to be harnessed for mainstream use. Licences require the licensees (researchers) to behave in ways that prevent their permission to operate being withdrawn, but they raise only very limited expectations on licensors (the public). The path through which cell and gene therapies will transition from experimental therapy to mainstream practice is at an early stage. Therefore, a good governance framework would increase the sense of mutuality between the public and scientists and also enhance the sense of a common project that will take time to come to fruition. Scientists and wider society will need to commit to work together for a period if the benefits are to be secured. We use the term contract rather than licence to capture these needs for mutuality and endurance.

To sustain their licence to practise research in this area, scientists need to show that they can be trusted. This requires competence, addressed by our recommendations in respect of better science. It also involves openness, with scientists recognising the public stake in the future that therapies might make available, and acknowledging and addressing concerns raised. Trustworthiness is partly based on transparency, making the successes and failures accessible to researchers and the public (with appropriate respect for patient privacy). The social licence for research also requires accountability. The scientific community needs to accept responsibility for giving a publicly available, accurate account of the state of the science. Nevertheless, the continuation of social licence for research requires reassurance that scientists who disregard their public responsibilities can be held to account.

Issues of liability to individual patients for mishaps and misconduct are a subset of accountability. These will necessarily be addressed within specific regulatory systems and we cannot specify these in detail here. Informed consent will remain vital, but given the propensity to hype and the high probability that patients using emerging cell and gene therapies will have few options, there is a collective interest in raising the quality of information that patients receive. Although informed consent is mainly a private matter for patients, to improve the process, stewards for specific

registers to these therapies should provide accurate information about the uncertainties, success, and known risks of therapies that are included.

### Public engagement and trust

The way that research groups, their institutions, and funders undertake public engagement about medical research suggests that public engagement is perceived and executed in two ways. Most commonly, public engagement refers to activities that would just as easily be defined as dissemination and publicity, albeit now sometimes in a more interactive format at publication stage (such as podcasts, lay summaries, and lead author Q&As). But public engagement is a much more confused and patchy business. The benefits of targeted patient engagement exercises for patient participation in research have been well observed.[173] To adhere to the guidelines of the International Society for Stem Cell Research (ISSCR) and the International Society of Cell Therapy (ISCT), requesting that patients fully understand the risk to benefit balance and the nature of the trial in which they are participating, researchers need to engage quite extensively with potential trial participants.[10,11,174] Beyond targeted patient interactions and publicity initiatives, however, what researchers should do is unclear. The wider benefits and effectiveness of more general engagement programmes are reportedly mixed.[12] These reports are accompanied by concerns that extensive engagement would require substantial resources, and that in the absence of such resources, engagement can become tokenistic. This is not to say interest and concern is absent. When surveyed, medical researchers have given a range of ethical, moral, political, and pragmatic arguments for engaging the public in general and patients in particular.[175] As indicated throughout this Commission report, the case for public engagement in stem cell research is strong. The continued and unavoidable mismatches between public expectation and delivery of applications, the fact that regulatory conditions (whatever the level of complexity) can be easily ignored in countries in which no regulations exist, and private clinics attract desperate patients for large amounts of money—all create the conditions for public controversy. Regardless of different views on the usefulness and extent of public engagement, extensive outreach activities are only slowly becoming common in those countries and research areas where they are economically supported, never mind globally. The perception that public engagement options boil down to a choice between an ideal of an expensive, extensive deliberative programme on the one hand, or tokenistic activity of uncertain value on the other is creating a blind spot. Researchers can undertake activities themselves that are much more prosaic and straightforward at minimal cost. Stem cell research can be contextualised and informed by public discussions without extensive direct participation. A review of the public discourse—including media, political, interest group, and regulatory discussions—should form part of the early development of research programmes. A pre-emptive analysis (which might well include direct engagement, testimony, and consultation, but it is not limited to those) enables researchers to see where their questions overlap with the explicit and implicit questions posed in public discussions. Such analysis would open up the potential for increased public discourse to correct any misunderstandings about previous work in the field, the regulatory context of the research, its potential applications, and the probability that the current work will be realised in relation to patient and carer expectations.

## Conclusions

Individuals engaged in pure research justifiably bridle when unrealistic outcomes are presented as a tactic for swaying the use of limited public funds or of recruiting private funds for experimental and unproven procedures—whether that be for avian flu modelling, Ebola virus disease preparedness, or for patients in wheelchairs demanding the latest experimental treatment for Duchenne muscular dystrophy. But the problems of regulation are not limited to controlling irresponsibility of those lobbying to direct limited funding towards their work. Strict, though necessary, regulation often prevents academics and small companies to take risks associated with undertaking even phase 1 trials, let alone phase 2 and beyond. Regulatory bodies are aware of the problem and encourage researchers to interact very early to provide advice. Hopefully, through such guidance, costs associated with potentially unnecessary controls will be reduced as much as possible, without compromising on rigorous quality control of the medicinal product being developed.

Looking across the landscape of scientific discovery, we acknowledge that those who take risks in their work make some of our most important discoveries. When clinical experimentation explores unknown pathways, possibly even risking the lives of patients, regulation must be as stringent as possible.

The problem is only exacerbated for illnesses in which animal testing has only limited applicability, or might even be impossible. As a public health problem across the globe, Dengue fever, for example, grows alarmingly in part because vaccine testing is only possible with human participants. So, while we await yet more failed attempts at a vaccine, the disease spreads at frightening speed. Although regenerative medicine is not generally subjected to the pressures involved in response to infectious diseases, it does suffer from the same problems, in that the testing of experimental therapies relies on human participants. This reliance is only made more complex by the

personalisation of those therapies. In fact, because so many new developments are explored at the level of personalised medicine, the problem is, if anything, more acute.

Another problem is also looming: that of global governance. Although guidelines exist and are globally recommended, some places will always allow otherwise prohibited practices. Even with common efforts to expedite reviews and optimise regulation, there is simply no way to compete with an absence of regulation.[176]

So the question remains about what to do about desperate patients paying huge sums of money for unproven treatments.

We need to develop new ways of protecting those who "name and shame" poor, if not unethical science. Such whistle-blowers face legal and other threats from companies that do not meet regulators' conditions of strict oversight, and laws should be enforced where they exist. At the same time, exploration is essential for companies and academics to move the field forward, balancing risks, costs, and potential benefits as much as possible. How we proceed in this new global terrain might be the biggest challenge of all for researchers, doctors, patients, relatives, regulators, and society as a whole.

#### Contributors

All authors contributed to study design. GC wrote the section about cell therapy and revised the manuscript. MB co-wrote the section about tissue engineering. TB wrote the section about patient and public engagement and trust. PDC cowrote the section about tissue engineering. EC-S co-wrote the section about the definitions and sections about small trials, difficult statistics, difficult regulation and data reproducibility. SG co-wrote the section on ethics. JH co-wrote the section about regulation of stem cell therapies and regenerative medicine. CM co-wrote the definitions and sections about small trials, difficult statistics, difficult regulation and data reproducibility. JM co-wrote the section about regulation of stem cell therapies and regenerative medicine. SM co-wrote the section about health economics. FM wrote the section about antisense oligonucleotides. DN initiated the project and wrote the introduction. NO researched, compiled, and wrote the section about international regulations. AP coordinated, compiled, edited, and revised the manuscript. JR co-wrote the section about health economics. PS co-wrote the section about ethics. JS contributed to the section on public engagement and trust. AT wrote the section about gene therapy. JW co-wrote the section about ethics and the introduction.

#### Declaration of interests

AT is the founder and scientific director of Orchard Therapeutics; EC-S is currently employed by GlaxoSmithKline and holds shares in the company in that capacity, and contributed to this piece in an individual capacity before joining GlaxoSmithKline. All other authors declare no competing interests.

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