

## **Lancet Commission: Stem Cells and Regenerative Medicine**

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## **Table of Contents**

|   |    |
|---|----|
| <i>Executive Summary</i>  | 2  |
| <i>Introduction</i>   | 5  |
| <i>Cell and Gene Therapy</i>  | 9  |
| <i>Modification of splicing: Antisense oligonucleotides and small molecules</i>           | 21 |
| <i>Tissue Engineering</i>   | 24 |
| <i>Small trials, difficult statistics, difficult regulation and data reproducibility.</i> | 28 |
| <i>Health economics of regenerative medicine</i>  | 31 |
| <i>Regulation of stem cell therapies and regenerative medicine</i>                        | 41 |
| <i>Ethics</i>   | 43 |
| <i>Public engagement and trust</i>  | 54 |
| <i>Conclusions</i>  | 56 |

## **Executive Summary**

This Commission argues 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, it will require significant rethinking of the social contract that supports such research and clinical practice in the public arena.

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. Recent 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 must 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. While there are massive public investments in this field internationally, they do not carry guaranteed commercial returns. Compared to conventional drug development, they follow a highly uncertain route to market. Moreover, 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, there remains great optimism and excitement about the potential impact of this field. This, in turn, 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 the clinical practice. The same environment is also permissive of one-off ‘compassionate’ applications and poorly controlled trials. Indeed, there is an international growth of poorly regulated 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 may not coincide with the public good. In poorly-regulated states, the authorization of a novel therapy may be politically attractive, even where efficacy is unconfirmed, and the burden for taxpayers could deprive other patients of established and effective therapies. These are difficult challenges to address and solve. The Commission recommends that the solution lies in a coordinated strategy with four pillars: *better science, better funding models, better governance, better public and patient engagement.*

## **Panel 1**

### **Key Messages and recommendations**

#### **Key messages**

- Current research is hampered by reduced funding for excellent basic research, frequent absence of strong pre-clinical 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 entails that there may be significant ongoing uncertainty surrounding the expected effectiveness and cost-effectiveness.
- Understanding patients' and broader publics' expectations is key for maintaining public trust in cell and gene therapies. The current gap between public expectations and the realities of translating regenerative technologies threatens regenerative medicine's social "licence 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**

1. Pre-clinical work in animals should be conducted as rigorously as clinical experimentation. Evaluation and reporting of trial results should be extremely detailed to allow appropriate moves to Phase IIb and beyond.
2. Institutions should invest more in the development of "Clinician Scientists" and reduce the burden of this "double career"; this would facilitate the transition from

pre-clinical to clinical work (1). Moreover more academic GMP facilities should be created to make trials affordable also for academics.

3. 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.
4. An international register of cell and biological experimental interventions should be created, and sustainable funding secured for it, possibly within the EMA and FDA, but with a careful process of review to guarantee the scientific soundness of trials.
5. Policy should be developed by the International Committee of Medical Journal Editors (ICJME) so that cell and biological therapies will not be published unless trials have been registered in the proposed international register.
6. The initial review for every experimental therapy should consider the relevant social and regulatory context.
7. 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.

## **Introduction**

In his *Foreword* to the Nuffield Council on Bioethics Report, *Emerging Biotechnologies: Technology, Choice, and the Public Good*, Michael Moran (who chaired 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.<sup>1</sup>*

In the few 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 may not always fully consider the social consequences, and may well have different objectives from those doing the science. How do we ensure the knowledge gained from publically 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 significant.

Because of this promise, there are a number of significant challenges that must be addressed if stem cell- and regenerative medicine is to deliver sustainable, significant and equitable benefits. The most urgent challenge may arise from the current combination of the ‘political economy of hope’ invested in stem cell therapies,<sup>2-4</sup> the relative lack of established therapies, and the persistence of a significant cross-border market in untested and probably inefficacious therapies.<sup>5</sup> The great risk of the current situation is highlighted by recent case of Vannoni in Italy, in which the Stamina Foundation succeeded in obtaining direct authorization from the Italian government, rather than through the country’s Regulatory Authorities.<sup>6</sup> The risk of this 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. It is vital, therefore, that a broad reflection on the ethics and governance of stem cell research and regenerative medicine plays an intrinsic role in their development, if their "licence to operate" is to be maintained. Within a global context, issues of ethics and inequalities may apply more strongly to Europe and the USA, 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.<sup>7,8</sup>

Fortunately, there is now general agreement of a need to discuss and scrutinize technologies 'upstream' – that is, when they are still at a relatively early stage, rather than waiting until they are ready to be deployed.<sup>9</sup> As discussed 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.<sup>10-12</sup> In principle, such upstream engagement fosters open dialogue amongst scientists and different publics. 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 - must 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.<sup>13</sup>

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. It is legitimate to ask whether the investment made in these therapies will provide a justifiable return in terms of

future health benefits. While it is difficult to identify promising lines of research early on, those with responsibility for allocating research funds must do just this. Where 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. It is possible that most regenerative medicine therapies, even once approved and established, may be significantly less cost effective than other therapies funded in healthcare systems, as is explored in more detail later. 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 because it is considered too expensive.

Questions about access to treatment in all healthcare systems are choices about priorities. The biggest question for the future will not, therefore, concern whether regenerative medicine will be able to provide significant health benefits, but whether the cost of those benefits is worth paying. Provided efficacy is demonstrated, it might be argued that a justification of high costs could be that there is something exceptional about the type of health benefits being provided. For example, the severity of the diseases for which these treatments are used – or the importance in the long-term of significantly extending powers of bodily regeneration beyond those that are 'natural' – might justify funding them over currently more cost effective therapies. But any such analysis must be reflexive: new abilities to repair the body may now seem extraordinary, but may come over time to seem as unexceptional as blood transfusions do now. There must be a balance between trying to identify lines of research that promise effective treatments, and allowing researchers the freedom to pursue questions where the answers may not show benefit for many years, if ever.



In order to contextualise the ethical and economic challenges described above and detailed further 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 healthcare. As 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 in the regeneration of a diseased one.

### **Cell and Gene Therapy**

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

#### **Cell therapy: haematopoietic 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 may be the same (autologous transplantation) or different individuals (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 may exert a beneficial effect in a given pathology (for example, coronary infarct) are also considered cell therapy, though 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 currently used) 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).<sup>14-22</sup> The next step in cell therapy came with bone marrow transplantation (BMT), again historically linked to 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 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.<sup>23</sup>

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 (i.e. monozygotic twins, fully matched for both major and minor histocompatibility antigens).

Mobilization of stem cells in the donor's blood and the use of HLA-matched hematopoietic stem cells (HSC) from cord blood - stored in "ad hoc" banks - have further improved the simplicity and efficacy of BMT.<sup>24, 25</sup>

As well as donor-recipient blood transfusions, autologous transfusions can be made, for example, where stored blood from a patient is used for his/her own transfusions required after undergoing major surgery.

Similarly, autologous BMT can be used both in malignancies, where 'disease-free' bone marrow is preserved before the massive myeloid ablation that occurs after radiotherapy. More recently, bone marrow stem cells can also be collected and genetically corrected (via *ex vivo* gene therapy – see below) and, for later re-infusion into a patient. Recently this procedure has been successfully applied not only to haematological diseases (for example, in

congenital immune deficiencies) but also to degenerative disease of the brain as detailed below.<sup>26-28</sup>

Autologous cell therapy has also been used in clinics for large burns to the skin and to repair the cornea as shown in Figure 3.<sup>29-31</sup> This was made possible by the seminal discovery that stem cells from the epithelia can be clonally expanded in culture on a 3T3-J2 feeder layer where long term,<sup>32</sup> self-renewing “holoclones” will appear. Indeed, epithelial stem cells generate large sheets that can be transplanted on the same patient to cover the surface previously burned. This treatment results in a long lasting, life-saving persistence of almost normal epidermis, though no appendages can be generated.<sup>33</sup> In the case of the cornea, transplantation from donors resulted in a high failure rate but autologous cell transplants resulted in stable success rates of 70% and above. 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 recently became the first cell therapy product to receive market authorization in Europe.<sup>34</sup>

With the exception of blood and bone marrow, all other forms of cell therapy require donor cells to multiply in culture in order to acquire the large quantity of cells necessary for transplantation. Though 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.<sup>35-37</sup> As explained below, cell therapy for the hematopoietic system and epithelia have seen a far higher percentage of clinical success, but new cell types have already entered the clinical arena.

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

Up until now, almost all cell therapy clinical trials have been conducted with post-natal stem/progenitor cells (including cord blood), isolated from patient or donor tissue. However,

in future, an increasing number of trials will be carried out with differentiating/differentiated cells or tissues derived from embryonic or reprogrammed ('induced pluripotent') stem cells (known as ESC and iPSC, respectively). ESC were originally isolated from the inner cell mass of mouse blastocysts, and adapted to proliferate indefinitely in culture while maintaining pluripotency (the ability to generate many of the cell types of our body). Mouse ESC were identified and characterised in the early nineteen-eighties while human ESC were derived only in 1998.<sup>38, 39</sup> ESC opened a strong clinical opportunity, especially for diseases affecting tissues where adult stem/progenitor cells have not been clearly identified or are inaccessible and/or difficult to expand in culture. However, although ESC show the unprecedented potential to differentiate into virtually all our tissues, they also presented two key problems. Because ESC are derived from an embryo, they are heterologous cells with respect to patient and thus may undergo immune rejection. Secondly, it is still difficult to induce differentiation into a desired cell type with 100% efficiency. This means that, after differentiation, they may still remain a small fraction of undifferentiated cells that continue to proliferate, and may form tumours. Known as teratomas, these consist of disorganised but partly differentiated tissues - such as bone, heart, or skin. Moreover, as for any type of cell therapy, functional integration into the host tissue will remain a consequential, and major issue.

Because human ESC are derived from human embryos, they have stimulated ethical controversy,<sup>40</sup> which, taken together with the scientific problems mentioned above, has delayed clinical translation of ESC research.

A more recent, ground breaking development was the demonstration by Shinya Yamanaka that it is possible to re-programme an adult somatic cell to an "embryonic-like" state via the transfer of a limited number of genes into these cells.<sup>41</sup> This innovation led to the creation of 'induced Pluripotent Stem cells (iPSC), which behave in a very similar manner to ESC, but with the advantage of being derived from a patient's own tissues, therefore allowing

autologous transplantation as well as creation of mature cell types with specific genetic defects (Figure 4).<sup>42</sup> Although iPSC do not negate the risk of generating tumours, their development has most likely solved the immunological issues. 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.<sup>43</sup> In addition, iPSC 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 cells like neurons that are otherwise impossible to study *in vitro*, given the difficulty of obtaining biopsies from the patient.<sup>44</sup>

Yamanaka's remarkable discovery of iPSC 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.<sup>17</sup>

At the time of writing, there are fewer than ten trials being run or recruiting which use ESC. These trials focus mainly on degenerative diseases of the retina, considered an immune-privileged organ. Currently, while there is much pre-clinical research utilizing iPSC, there has only been one clinical trial involving transplantation in patients, which 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.<sup>45</sup> However many other iPSC clinical trials are being planned, such as the reconfigured clinical trial in Japan to transplant retinal progenitors produced from third party iPSC.<sup>46</sup> Overall, the situation is not surprising given that less than ten years have elapsed since their discovery, even if the ethical issues in this case are different.<sup>47</sup>

Finally, many recent reports have shown that organ-specific cells could be generated from different somatic cells, thus directly bypassing potential (e.g. oncogenic) risks associated with pluripotency. Many differentiated cell types (e.g. 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.<sup>48, 49</sup> As this involves going from one

somatic specialized cell to a different type without transiting through an “embryonic” stage, it may 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 to show that the “converted” cell is functionally 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 (a) novel function(s). As for cell therapy, this is a broad definition. Gene therapy was designed in the early nineteen-nineties 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 it is also possible to provide cells with a novel function for a specific goal (e.g. express antigens that enhance immunogenicity of cancer cells, or provide lymphocytes with mechanisms to more efficiently kill tumour cells). Although this work on cancer and related clinical trials are representative of the majority of current gene therapy experimental interventions, they are not regenerative medicine in the strictest sense and will, therefore, not be discussed in further detail. More recently, two possibilities have offered alternative options for correcting a gene defect *in situ*. These are genome editing (for recent reviews see: <sup>50-55</sup>) and correcting the mutated transcript (exon skipping using antisense oligomers (AOs) or read through a premature termination codon or other small molecule-mediated modification of splicing).<sup>56-59</sup> 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<sup>60, 61</sup> (allowing the production of a full length protein despite a premature stop codon). Because of these features, these compounds are rapidly progressing, particularly in the fields of Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA).

Classically, gene therapy is divided in two main categories: *in vivo* - where 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 re-introduced into the body (Figure 1). The latter strategy is considered a form of cell therapy, which is an illustration of the significant overlaps that exist between cell and gene therapy. This is also reflected in the shared space both areas co-habit in scientific journals and conferences.

Since the early days of its development, it was apparent that the major hurdle for gene therapy would be the delivery of genes into target cells. Genes (or more commonly, their cDNA) are very large, highly hydrophilic and electrically charged molecules which by themselves do not cross the cell plasma membrane. 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. Until now, they have been by far the most commonly used, though they are not devoid of problems, as described below. Non-viral vectors (such as liposomes) have also been tested and long been implemented, but have consistently proved less effective. A new generation of nanoparticles now show promise of becoming both efficacious and safe vectors, though these are currently predominantly in the pre-clinical phase, with a few trials having already begun.<sup>62, 63</sup>

A viral vector is a virus that has been modified to carry therapeutic cDNA rather than some of its own genes (e.g. the disease-causing ones), while maintaining genes encoding for its capsid and envelope. Of the many viruses initially tested, the ones currently in use in patients are Adeno virus (AV) and Adeno-associated virus (AAV) as non-integrating vectors; as well as retroviral vectors (both lentiviral, LV and retroviral, RV) that stably integrate into the host cell genome. AV and AAV are predominantly used *in vivo* in patients.<sup>64-66</sup> Retroviral vectors are mainly employed in *ex vivo* gene therapy. While AV vectors accommodate large cDNAs, they are highly immunogenic. For this reason they are predominantly used in cancer

gene therapy where immunogenicity will enhance the host immune response – something to be avoided in the long term correction of genetic defects. In this case AAV are the vectors of choice. They are far less immunogenic, and are maintained over a long period of time (measurable in months) in non-dividing cells such as skeletal muscle. Since they are unavoidably lost from rapidly dividing cells, they are not usually used for hematopoietic and epithelial tissues. In addition, they are small and accommodate only small cDNAs (up to 4-5 kb). RV and LV, predominantly used for *ex vivo* gene therapy, also have limits in the size of cDNA they can accommodate (up to approximately 5-6 kb). Importantly, they integrate into the host cell genome, which ensures prolonged expression of the therapeutic gene, although this is accompanied by the risk of insertional mutagenesis, discussed below.<sup>67, 68</sup>

### **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 hematopoietic tissue.<sup>27, 69-72</sup> This is most likely because there is the option of ablating diseased host tissue: 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, since they do not have to compete with resident diseased cells. Moreover, blood is a fluid, and epithelia are 2D tissues, structurally less complex than organs such as the brain, heart, and skeletal muscles, where massive ablation of diseased tissue is clearly impossible. This results in much lower donor cell engraftment and consequently, in reduced therapeutic efficacy.<sup>73, 74</sup> 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 additionally aim to reduce fibrosis and enhance angiogenesis. A general consensus is



emerging that all these therapies, once proved safe, should be tested as soon as possible, ideally at diagnosis, before the onset of fibrosis.<sup>75</sup>

To date, congenital immune deficiencies represent the major success for gene therapy.<sup>76-82</sup> With the exception of one major problem, described below, they allowed long-term reconstitution of the immune system in children who were otherwise destined to succumb to infections. A scheme of the experimental strategy, based upon auto-transplantation of autologous, genetically corrected CD34+ hematopoietic stem cells, is shown in Figure 5.<sup>83</sup> The same strategy was subsequently applied to  $\beta$ -thalassemia,<sup>84</sup> and more recently to X-linked adrenoleukodystrophy,<sup>85</sup> a demyelinating disease caused by a deficiency in the ALD protein, (an adenosine triphosphate-binding cassette transporter) and to metachromatic leukodystrophy,<sup>28, 86</sup> a lysosomal storage disease, in which autologous, genetically corrected CD34+ cells were transplanted, generating microglia that overproduced and released a large amount of the missing enzyme (aryl-sulphatase). The enzyme released was also taken up from the extra-cellular space by neighbouring neurons, resulting in molecular and clinical correction of the disease. Another example of cell-mediated, *ex vivo* gene therapy is represented by junctional *epidermolysis bullosa*,<sup>87</sup> where the cDNA for Laminin 5 was transferred into the patient's epidermal stem cells with a retroviral vector. The corrected epidermal sheets were transplanted on the legs using the same procedure first developed by Howard Green, where, though devoid of appendices, they reconstituted functional epidermis.<sup>21</sup>

Through *in vivo* gene therapy, Leber's Congenital Amaurosis, a rare inherited eye disease, was successfully treated with direct sub-retinal injection of AAV expressing the cDNA of the RPE65 gene (Retinal pigment epithelium-specific 65 kDa protein).<sup>88-90</sup>

On the other hand, there are many examples of cell therapies which had limited, variable or transient efficacy. In the early nineteen-nineties, 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.<sup>91</sup> Almost contemporary with this, the transplant of foetal dopaminergic neurons into Parkinson's patients resulted in variable efficacy of different durations (mainly due to the paucity and heterogeneity of donor tissue that made standardization difficult).<sup>92</sup> Though long-term functional improvement was observed in some patients, too few patients could be treated. The field is eagerly awaiting ESC or iPSC-derived dopaminergic (autologous) neuroblasts which will be available in unlimited numbers.<sup>93</sup> It is important to note that Parkinson's may be privileged among neurodegenerative disorders as the tissue damage is restricted to a specific anatomical location (*substantia nigra*) – in comparison 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 has been, together with “extreme financial pressure”, a reason for the recent announced closure of StemCells Inc. after the failure of a Phase II trial.<sup>94</sup>

In the last twenty years, transplantation of different cell types in the infarcted heart has elicited generally very modest or no therapeutic effects,<sup>95</sup> and even seen the death of a few patients. This was due to uncontrollable fibrillation when skeletal myoblasts were transplanted, generating another excitable tissue, electrically uncoupled to resident myocardium.<sup>96</sup> Even if successful transplantation of cardiac stem-progenitor cells or *in vivo* production of new cardiomyocytes was achieved (e.g. 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 hampered in achieving correct electrical coupling.

Islet transplantation is an established (though non-optimal) therapy in diabetes, mid-way between cell and organ transplantation. It is still in need of significant development,<sup>97</sup> both due to the need for constant immune suppression, and because long term correction of glycaemia is achieved only in a minority of patients. A very large amount of preclinical work

is ongoing and many trials have started or are ready to start for other diseases, for example with embryonic stem cell-derived retina progenitors for macular degeneration or other retinal diseases. See<sup>98</sup> for a recent review.

While the primary goal of cell transplantation is replacement of lost or damaged tissue, it has recently been reported that intravenously injected cells appear to exert beneficial effects even if they do not replace lost tissue to any significant extent.<sup>99</sup> This is 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.<sup>100</sup> <sup>5</sup> Many clinical trials have been conducted based on this concept, but results are still inconclusive and more rigorous evidence of real “engraftment” and type of function should be provided to resolve this controversy.

With respect to gene therapy, initial excitement about this new frontier of medicine was dampened by severe problems, including a few deaths that delayed clinical success by almost twenty years, so that is only now finally becoming revived for many diseases. The stumbling blocks were represented mainly by the then poorly understood variability in immunogenicity and toxicity of different vectors across species, meaning that pre-clinical work was not always fully predictive of outcome in patients. In addition, 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, AAV- producing Factor IX (FIX) virtually cured Haemophilia B in pre-clinical work on mice and dogs but turned out to be immunogenic in patients, leading to destruction of corrected liver cells.<sup>101</sup> This problem was partially solved by changing the serotype of AAV used to transduce human liver cells and allowing therapeutic levels of FIX to be expressed long term.<sup>102, 103</sup> Administration of a relatively high dose of an AV expressing ornithine

transcarbamylase, well tolerated in primates and in the first patient treated, led to a systemic inflammation and multi-organ failure in a second patient who died after four days.<sup>104</sup> 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 (SCID) developed a T cell proliferative disease<sup>105, 106</sup> which led to the death of one of them, 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 methodologies 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 on-going trials suggest that the risk is very significantly reduced.<sup>107, 108</sup>

The examples reported above should not mask the fact that nowadays 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 still 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. While risk should be reduced to a minimum, the only way to completely eliminate risk 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 appears to be at least as efficacious and safe as standard BMT, and could become the therapy of choice for some conditions.

Another important consideration relates not only to the severity but also to the duration of the disease. Metachromatic Leukodystrophy and Duchenne Muscular Dystrophy are both lethal diseases but the first (in its most severe form) leads to death within the first years of life; while, thanks to better cardiac and respiratory assistance, the second now allows patients to survive to around age forty and sometimes more. The risk of a new therapy is well justified in Metachromatic Leukodystrophy patients who arguably have very few years ahead; but much less so in the second group, who may live for decades, and have time to wait for a less risky therapy. There is a more extensive discussion of this topic in the section on Ethics and Regulation below.

### **Modification of splicing: Antisense oligonucleotides and small molecules**

Targeting mutant RNA in Duchenne muscular dystrophy using antisense oligonucleotides (AONs) has been an exciting development of recent years. The use of splice switching AONs to induce restoration of the reading frame has been mostly developed for Duchenne Muscular Dystrophy. An exciting recent development is also that of the utilisation of AONs to induce exon retention, with Severe type I spinal muscular atrophy (SMA) being an ideal condition for this.

SMA 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 recent phase I clinical trial involving patients with SMA, systemic delivery of AAV9 were, on the whole, well tolerated with the exception of a transient transaminitis. This is a relatively common issue in AAV gene therapy trials, and 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, AAV9 gene therapy led to remarkable acquisition of new milestones including sitting, standing and

walking (Jerry Mendell, late breaking presentation, World Muscle Society 2016, Granada). Regarding AON therapies, as these compounds are not capable of crossing the blood brain barrier, this involved repeated intrathecal administration in SMA patients in order to maintain adequate SMN (Survival of Motor Neuron) protein level.

In the last few years, nusinersen, one such AON, has been studied as part of a comprehensive program of open label and randomised placebo controlled studies in SMA type 1 and for the milder variants SMA types 2 and 3. Published data on a phase 1 study in 28 SMA patients demonstrated safety of 4 ascending doses. The pharmacokinetics were indicative of a prolonged cerebro-spinal fluid drug half-life (4–6 months), and clinical outcome data was encouraging.<sup>109</sup> Data from a more recent phase 2 study in infants with type 1 SMA indicated safety and tolerability of nusinersen, with both respiratory and motor milestones demonstrating significant divergence from 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 the majority of treated infants improved their functional scores and acquired independent sitting - and in a few instances, also standing. Very recently, the top line results of a randomised, placebo controlled study in type 1 SMA (Endear study) were announced by the Sponsors Biogen and Ionis. As the prespecified interim analysis demonstrated a significant improvement in the proportion of nusinersen-treated motor milestones responders vs sham procedure control, the placebo controlled part of the study was interrupted and all patients are currently transitioning to an open label extension.

In DMD, AONs targeting mostly exonic splicing enhancers can induce exon skipping and restoration of the reading frame in boys 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 (BMD) condition. Different chemistries are currently in clinical trials in the DMD field, the 2'OMethyl (2'OMe) backbone, and the morpholino (PMO) backbone, developed by two different industrial partners (Prosensa/Biomarin and Sarepta

Therapeutics respectively). Since 2009, a number of phase I and phase II studies have been published, dealing with DMD patients who can benefit from exon 51 skipping, as this is potentially beneficial for the largest number of deleted DMD patients (~ 13%). Targeting another nine exons would achieve correction in approximately 70% of DMD boys carrying deletions. Indeed, phase I studies targeting exon 45 and 53 are now well underway. The outcome of several open-label studies and of two placebo-controlled studies of both chemistries targeting exon 51 were encouraging. They demonstrated the production of dystrophin in muscle biopsies of the children studied, although with differences in efficiency of the 2 chemistries. Encouraging clinical benefit was reported once treatment was prolonged for several years, with statistically significant and clinically meaningful stabilization of functional abilities in treated children (as measured by the six minute walking test) <sup>45-47</sup>. However, the outcome of a phase III study using a 2'OMe AON targeting exon 51 was inconclusive. 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 III study, compared to previous trials. Because in DMD there is a progressive loss of muscle mass (and hence less tissue) to be 'rescued' by the AON therapy, the stage of the disease in children recruited is of paramount importance, as is the duration of the clinical trial. This makes it possible to observe divergences in the clinical course between treated children and the placebo group. The 2'OMe AONs exon 51 safety profile was consistent that of this class of compounds (skin reactions following repeated sub-cutaneous administration; reversible renal toxicity, occasional thrombocytopenia) requiring careful clinical monitoring. In view of the unfavourable risk/benefit profile, and following the negative evaluation of this compound for market authorisation by both FDA and EMA, the sponsor (Biogen) has interrupted the development of 2'OMe compounds for DMD.<sup>110</sup>

A different outcome was seen in the recent FDA accelerated approval for the morpholino AON, developed by Sarepta to skip exon 51 (Exondys). This was based on the clinical trajectories of a group of children treated for more than 4 years compared to carefully

matched untreated children. An excellent safety profile of the PMO AON; and an unequivocal increase in dystrophin expression was demonstrated in the study, and in another ongoing phase III study, currently underway. The FDA decision to grant market authorisation of this Sarepta AON compound has been criticised by some, mostly due to the small number of children treated and the low levels of dystrophin produced.<sup>111</sup>

While novel larger studies targeting exons 51 and others are now underway, considerable research has also been devoted to future generation AONs with improved efficiency in targeting skeletal and cardiac muscles. Considerable improvement in efficacy and biodistribution has recently been achieved with the use of peptide-conjugated morpholino AONs and of tricyclos DNA. The safety profile of these more novel AONs will now need to be assessed to determine whether these molecules are ready to enter the clinic as they stand. At the same time, novel strategies (e.g. TALEN, Zinc Finger and CRISPR-Cas9 nucleases) for permanently editing the genome (rather than continuously repairing the pre-mRNA) appear promising, but still face the common problem of delivery, especially into large tissues such as human muscle.

## **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 4 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 (NHS Blood and Transplant Annual Review 2012-13).<sup>112</sup> 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 popularized by Langer and Vacanti,<sup>113</sup> 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 three-dimensional 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 (whilst 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, a-cellular (‘biologic’) scaffolds. Materials composed of naturally occurring macromolecules, in particular those that formulate the extracellular matrix (ECM) – such as collagen – have been tested for tissue engineering purposes, but struggle to mimic the complexity of the ECM composition *in vivo*.

Synthetic materials have been considered, following 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 suggest there can be problems 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, it is possible that the rich innate molecular and microarchitecture of extracellular matrix scaffolds may 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 which 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 the majority of ECM proteins are highly conserved, decellularised organs from animals and could also be engineered, and 'humanised' by seeding with human cells. In fact, for decades, porcine and bovine tissue has already been used 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 hyper-acute rejection are likely to 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 for tissue engineering relatively simple organs serving as bodily conduits such as the trachea,<sup>114</sup> urethra <sup>115</sup> and bladder,<sup>116</sup> with some encouraging results in 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 and thereby introduce organ tissue engineering as a routine therapeutic option. As opposed 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.<sup>117, 118</sup>

One alternative solution would be the use of three-dimensional (3D) printing of biocompatible materials, cells and supporting components in complex 3D functional living tissues, <sup>119</sup> or 3D bioprinting of tissues and organs. While 3D bioprinting has already been used clinically for the generation and transplantation of acellular tracheal splints,<sup>119</sup> 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 1).<sup>115, 120-123</sup> As for cell therapy, ESC and iPSC may become a valuable resource in tissue engineering as well as directly converted adult cells, as discussed above.

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,<sup>124</sup> 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 on 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.<sup>125</sup> Even so, if the exciting potential of tissue engineering is to be fully realised, all of the challenges described above 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 a) “clinician scientists”,<sup>126</sup> both in medicine and in surgery, who are also cell, molecular or material biologists; b) academic Good Manufacturing Practice (GMP) facilities to absorb and reduce costs; and c) a new generation of regulators who fully understand and, ideally, have been working in regenerative medicine (see Recommendation “Better science”).

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

With few exceptions (e.g. cell transplantation for heart infarct) the clinical work described above has been conducted on small cohorts of patients who, for many diseases, show dramatically different progression and phenotypic heterogeneity, independent of the type of disease. This is due to both 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, relatively unknown. When risk is difficult to assess and quantify, it makes regulation for safety concerns problematic. Efficacy also becomes challenging to assess 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 authorization is given, and even before research investment decisions are made.

This creates a vastly different scenario from classic drug trials, which use large populations of randomized patients. In a very small number of cases (e.g. immune congenital deficiencies) the clinical outcome is so striking (disease-free survival versus death) that statistics are not needed;<sup>28, 108, 114</sup> market authorization is relatively simple to obtain, and data do not need careful meta-analysis, other than patient follow up. Glybera represents another interesting case, particularly in relation to the regulatory landscape.<sup>127</sup> The product, an AAV producing protein phospholipase is delivered through an intra-muscular injection in an extremely rare population of patients – who, missing this enzyme, undergo repeated attacks of acute pancreatitis. Market authorization was initially denied because of insufficient statistical evidence (one patient had another attack of acute pancreatitis after treatment), but this was later reconsidered. Conditional authorisation was granted using the trend, rather than statistical validity, as an indicator. But cases like immune congenital deficiencies, and, to a lesser extent, Glybera, are exceptions. The rule is that often the effect is modest or very modest. Nevertheless, it suggests that further protocol implementation may, in a stepwise progression, lead towards clear efficacy and improvement in patient health and quality of life. However, since 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 may be reluctant to finance these 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 may have brought some real benefit. A solid, reliable and reproducible pre-clinical study in animal models (when available), in iPSC derived patients' cells, or organoids (3D cultures that to different extents mimic miniaturised developing organs)<sup>128</sup> will increase the chance of convincing investigators and, subsequently, funding bodies that a specific therapeutic strategy may yield a small but tangible effect.<sup>114</sup> Nonetheless, funding agencies

need to balance allocating their limited budgets between financing 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 may or may not have a larger population impact.

In defining reliable and objective end points 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 may even see their conditions worsen. In the age of personalized medicine, there are theoretical explanations for this, 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 aim to better understand heterogeneity in response.

But, raising additional funds in an environment of such uncertainty is currently a major difficulty, despite the increasing funding that certain countries (e.g. UK) allocate to this area (see below). Moreover, 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. This creates 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 is a very difficult (if not impossible) task 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. It is also important to underline that for more technically demanding

methodologies such as cell therapy, lack of the necessary specific expertise may lead to failure, simply because the medicinal product obtained when the protocol is reproduced is suboptimal. This is especially true in the case where stem cells are extensively expanded in culture, where a suboptimal environment may lead to loss of their regenerative features.<sup>129-131</sup> These factors can lead to a mismatch of 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 – and moreover – one which may lead to public distrust in medical research in this area, a suggested partial solution would be a demonstration of willingness from funding bodies and leading journals to support confirmatory studies. In this scenario, coherent, reliable and concurring data would be publically available before clinical studies move into Phase III.

### **Health economics of regenerative medicine**

The cell and gene therapy industry has sharply increased in recent times with dramatic rises in levels of investment, clinical efficacy, deals and partnerships, and government support. Worldwide, there are over 300 companies focused on cell and/or gene therapy. Many of the major big pharma players, 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 oncology indications (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, it is essential that funding to the basic sciences is protected (see Recommendation “Better science”) within the significant public and third-sector funding being invested in regenerative medicine. In 2010, it was estimated that 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, over the last 10 years regenerative medicine has also been receiving small but increasing investment from the private sector.<sup>132</sup> The preponderance of public and charitable investment is typical for emerging technologies. As alluded to in the previous section, it is also a reflection of the situation that small, low capital private enterprises are not optimally suited to R&D and subsequent technology delivery of high-risk, high-cost technologies, with long time horizons to benefit and small market sizes.

It is widely accepted by health economists that markets for health and healthcare do not typically satisfy criteria that define perfectly competitive, efficient, markets. In addition, where such markets or close approximations do exist in healthcare, and function well, they may 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 NHS) 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 five years of patent-equivalent exclusivity. There is, in consequence, considerable pressure 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 sub-optimal 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 may 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 over the short to medium term. Nevertheless, in the case of cell products, the returns may be so unrewarding as to deter investment in the first place. Indeed, where inventions are derived from fertilised human eggs, patents are unavailable in Europe anyway. 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). In contrast, cells enjoy potentially far longer exclusivity *outside* the patent system by virtue of the clinical data needed to secure an authorisation. Cell products benefit from a potentially far longer period of data exclusivity than the eleven 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 healthcare markets, centralisation of the purchasing power in healthcare 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 healthcare systems to better meet societal objectives and to make efficient use of healthcare 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 may not offer cost-effective forms of therapy using existing reimbursement standards.

Reimbursement agencies frequently consider the cost-effectiveness of a therapy – its value for money – as part of the approvals process. Such criteria mean that where costs are high and expected benefit to patients is highly uncertain – as is typical 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 for bringing novel treatments from the lab 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 (see Recommendation “Better funding models”).

The first is that 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, as 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, as the cost of a new therapy may be high in the present but subject to reimbursement costs would be reduced in future through further innovation. The argument runs that if current innovation is not rewarded, then future innovation may 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 realized, then the manufacturer has obtained the premium on the original innovation. On the other hand, if benefits are realized, 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 may also seek to argue for an additional innovation premium. From the health system perspective, allowing additional payment for innovation risks paying for benefit twice over, and assuming the risk of developing future therapies. As many therapies – particularly in regenerative medicine - are also developed through basic science research funded by the public, there is a significant risk that the value of treatment in terms of health displaced 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. Such treatments are known as orphan drugs (or treatments). Orphan drug designation may apply if the treatment is being developed for a condition in which there are very few patients within a population. In these situations it may be unlikely that a manufacturer would invest resources in developing treatments as too few patients would require the treatment and the price required to obtain a return on investment

would not be acceptable to payers. To address this, government intervention may be required in order to induce manufacturers into the market. Such inducements may take the form of 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) may not meet cost-effectiveness criteria, they may be approved for reimbursement. A reduction in efficiency may be considered an acceptable exchange for reasons of equity improvements. Where regenerative medicine products meet the criteria for designated orphan treatments, reimbursement may be more likely.

The third argument in favour of paying a premium for treatments is that society in some way, (especially affected patients and related 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 NICE can apply in certain cases. This occurs in situations where a treatment is not otherwise considered cost-effective but may provide some benefits to a select group of patients who are near the end of life. In this case the public argument is that society values a certain segment of the population as more worthy of treatment than other patients in need, 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 financing which 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 may be used to help achieve societal or political objectives that are not captured in the cost-effectiveness assessment process. However, increasing evidence is emerging that suggests such approaches may be more likely to subvert societal preferences and is often in opposition to expert advice on allocating resources. It might be that those in

the regenerative medicine field should exercise caution in pursuing such a strategy given the risk of backlash.

In some jurisdictions, notably the United States of America, 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 not as significant 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 lab and early phase clinical trials, to production on a scale that will drive down costs of treatment. Treatments will have to be developed with standardisation in mind where possible. The more bespoke a treatment is required to be, the greater the likely cost. This is because treatments will need to be produced at a smaller scale, increasing production costs, and they may 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, there is significant risk here to manufacturers. Given the early stage of the industry, manufacturers may be reluctant to invest in manufacturing capacity – they may not yet know what sort of facilities will be required, 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 in the development of 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, as governments are one of the few institutions capable of bearing the risk of failure. This investment of public money, may in the longer term, lead to greater investment from private sector organisations.

However, the emotional impact of devastating and presently incurable diseases may create a complex situation, where small companies and short term investors may have their risk covered by “payers”, while becoming sole beneficiaries of the eventual profit. Moreover, they may exaggerate the potential benefit of a given treatment and lobby to get market authorization. Once this is granted (examples of this already exist) they may fix an exorbitant price, in which the emotional support of patients is employed 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. As discussed above, the potential exists to significantly reduce the burden of disease for some common conditions, (e.g., 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. Moreover, regenerative medicine could have a major impact on health services, significantly reducing demand for health care (**See box. 2**). However, the potential health benefits and cost reductions to the health service must be balanced against the costs of regenerative medicine, which are also potentially huge, and which would be borne by the

health services. Moreover, so far only a handful of rare diseases have been successfully treated. While the cost of developing such therapies will remain to be covered before results are known, there is no guarantee that more common, polygenic or acquired disorders may also be successfully treated.

While there is reason to believe the *potential* value for money of regenerative medicine, there is at present very little *actual* evidence. Several studies calculate the current cost of diseases that could potentially be eradicated or reduced using regenerative medicine (e.g., heart disease, heart failure, diabetes, stroke, end stage renal failure, Parkinson's disease, spinal cord injury) producing figures of many millions of dollars,<sup>133-137</sup> but there is no evidence related to the proportion of these costs that will be avoided because of regenerative medicine. In addition, the potential cost savings are not balanced against the costs of the regenerative medicine interventions themselves, which will be substantial.

There are very few formal cost-effectiveness analyses of regenerative medicine interventions – 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 (Crd.york.ac.uk) using the search terms “regenerative medicine” OR “tissue engineering” OR “cell therapy” in any field found only eight studies (last checked June 2016).

Even if regenerative medicine was cost-effective based on the metrics commonly used by organisations such as NICE (e.g., in terms of the incremental cost per quality-adjusted life year gained), it is unclear whether health services would have sufficient budgets to be able to afford to implement them. Huge benefits might be reaped from regenerative medicine but at huge cost, and affordability may 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).<sup>138</sup> The

disease lasts decades, amounting to very high costs for the NHS. Even if economically convenient in comparison with life-long palliative – but expensive – therapies for regenerative medicine, a huge amount of money would be needed in a relatively short time, rather than being distributed over many years or even decades.

While the market grows over the next few decades, it is useful to think of ways that regenerative medicine products can be made more affordable and cost-effective so that patients can benefit. Options include limiting prices using some form of price regulation; improving manufacturing infrastructure to reduce 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.

Given 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) in order to be cost effective. Or else, they might seek to target diseases for which there are limited or no treatment options, where value for money may be easier to demonstrate.<sup>139</sup> 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 technologies that make it to market will automatically be adopted and paid for at a profitable rate.<sup>140</sup> 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.<sup>141</sup> There have also been recent advances in methods for value-of-information analysis to assess the value of investing in research on innovative technologies such as regenerative medicine.<sup>142</sup> Other novel approaches have been suggested with a view to identifying technologies that are good candidates for reimbursement. For example, the Value-Engineered Translation (VET) framework is an approach that could be



applied to regenerative medicine. VET was designed to evaluate candidate therapies for their potential to achieve market reimbursement, based on analyses of unmet need and the likelihood of clearing market access hurdles.<sup>143</sup>

### **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 may 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, then, is to appropriately balance the benefits against the risks. Doing so requires a clarification not only of 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 over the population, and the opportunity costs of providing the benefit.

A robust and transparent system of laws and regulations is necessary and desirable. First, it exists to protect patients from unnecessary risk. But it also provides a framework to give investigators, funding bodies and commercial investors the confidence required to invest in the research and development required to bring innovative products to market. Where regulation is missing or weak, those who invest in and develop technologies are at risk of

unfavourable, unforeseen changes in the regulatory environment. This will discourage investment and ultimately be to the detriment of patients.

Compliance with regulation does introduce costs to those developing new therapies. Where a regulatory system works well, costs are the minimum needed to achieve regulatory objectives. Where a system of regulation is overly burdensome and costly, this will unnecessarily deter investment – leading to potential losses both economically and in potential health gain of the population. In Europe, this may be particularly acute, as regulation will exist at national level as well as across nations. To address this problem a new committee was created within the European Medicinal Agency, 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.

Currently, the number of human regenerative medicine clinical trials remains small. The US National Institutes of Health maintain a database of clinical trials involving human participants, accessible online at [clinicaltrials.gov](http://clinicaltrials.gov). As of June 2016, a search of this database (using the search term ‘regenerative medicine’) identified 188 registered studies. Of these, 84 are open trials (those in set-up, or in recruitment stages), and 87 have been completed. A further 17 trials are listed as having ‘unknown status’. By comparison, for example, there are currently over 100 open trials of a single drug – adalimumab – a widely used biological therapy, the use of which shares certain characteristics with regenerative medicine (see below).

However, if the same website is interrogated for “cell therapy”, more than 31,000 (thirty one thousand) trials are listed. Taking as examples just the subsection of trials registered in the areas of “muscular dystrophy” or “cystic fibrosis”, 55 or 65 studies are listed,

respectively. Several of these do not really describe the use of cells at all; of those remaining, many meet the characteristics of unproven cell therapies (e.g. 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 et al, 2016 for a recent discussion of the topic).<sup>11</sup> In addition, almost all lack supporting publications. Many studies 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 website. This situation urgently calls for the creation of a novel register or sub-register, where trials are peer-reviewed and curated to guarantee a high clinical standard (see Recommendation “Better governance”). This issue is detailed below.

## **Ethics**

In examining the ethics of cell therapies, it is the health benefits and harms of such therapies that 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 health harms have also been interpreted broadly here, to encompass not only direct morbidity and mortality, but also to include indirect factors such as undermining of trust in the healthcare system, violation of autonomy, and foregone benefits elsewhere in a healthcare system.

## **Balancing benefits against risks**

As Hermansson and Hanso argue,<sup>144</sup> risk management problems can be modelled as having three main parties: (1) those on whom the risk is imposed; (2) those who control the risk, and (3) those who benefit from the risk being taken. Risks are least ethically problematic where the same person fills all three roles – as when an experienced and knowledgeable

mountaineer takes on a challenging ascent. Risks are most ethically problematic where the risk-exposed neither benefit from their risk exposure nor can control their exposure to the risk – as when individuals are adversely affected by pollution from a poorly regulated factory. Judgements about the acceptability of risk also depend on the overall size of the benefit when compared to the risks. **(See box. 3)**

This analysis provides a useful baseline understanding of the diverse ethical profiles of cell therapies. Direct benefits and harms should typically weigh more heavily than indirect risks and benefits, both because it is less certain that indirect benefits and harms will eventuate, 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. It is for this reason, perhaps, that the Declaration of Helsinki focuses on benefits and risks to individuals and groups involved in the research project, rather than the community more generally.<sup>145</sup>

We will trace out this analysis through different points on the translational continuum between Phase I trials and routine medical practice. As therapies move along this continuum, direct risks will typically become better 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. **(See box. 4)** As is discussed below, 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 realised.

There are two major ways in which the risks of cell therapies can be controlled: 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 provided to them. In cases of novel technologies, informed consent struggles to adequately

protect individual interests outside of a strong governance framework. Where the information available on 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 (**See Box. 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). In general, hard paternalism is more difficult to justify – though there is an established medical practice of ruling out certain medical interventions on hard paternalistic grounds, such as surgery without good medical reason or where an intervention would be futile.<sup>146</sup> 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.<sup>147</sup>

An individual's willingness to take a therapeutic risk will always be dependent on what that person anticipates might happen. Where 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 judgements about the role that hope should play in human life, and the conditions under which creating or sustaining 'false hope' is ethically problematic. These are important life choices that cannot simply be taken away from patients.<sup>148</sup> 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 others, and this may mean tolerating false hope. There is no generic solution.

In the rest of this section, we 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**

As discussed above, the cells to be used as the basis of cell therapies must 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 transplant or organ transplantation, although a number of commentators have pointed to the gendered bioeconomies of tissue procurement in the context of ESC.<sup>150</sup> As with these earlier interventions, allogeneic transplants can be taken either directly from a patient's relatives, or be mediated via an international donor bank or sold commercially. Where the donor is a patient's relative, questions of risk, consent and voluntariness emerge: potential donors may 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 very negative reactions if, for whatever reason, he or she refuses 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, ESC or induced pluripotent stem cells (iPSC), though this has been considered as a real possibility, once therapies using these cells become a reality. It is also possible that 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 ESC or iPSC raises a distinct set of policy questions and ethical concerns. For instance, whether they should 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.<sup>151</sup>

Ethical issues have been raised for example by the Catholic Church and other Christian groups in relation to 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 (see for example: the *donum vitae*, “Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation” (issued on February 22, 1987 by the Congregation for the Doctrine of the Faith) that human dignity and personhood arise at conception and not just (as human rights law suggests: Article 1 1948 UN Declaration on Human Rights) at birth,<sup>152, 153</sup> and to the fact that the acquisition of embryonic stem cells 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 IVF, and are not distinctive to the ethics of regenerative medicine. Environmentalists 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 US and certain European contexts, this issue will not be discussed in detail here.<sup>154</sup>

A number of questions about the ownership and control of cell-lines also arise: Is a cell-line derived from me still my property? These questions predate current regenerative medicine, and even the human genome project. In fact, they go back at least as far as the emergence of experimental cell lines. As Skloot describes,<sup>155</sup> the HeLa cell lines in current use by researchers derive 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 “Moore v. Regents of California: 249 Cal. Rep. 494 (1988), Cal.Lex. 2858. (1990)”, where John Moore petitioned (in the end unsuccessfully) for a share of the proceeds of a cell line that had been created from his spleen.<sup>156</sup> Both cases provide prescient examples of the likely on going tension between social innovation and social equality as Ruha Benjamin points out in her examination of stem cell initiatives in the US.<sup>157</sup>

Under the current legal regimes within both the EU and the US, autologous cells are regulated similarly to allogenic cells. Both US and EU regimes thus reject the principle that someone who donates his/her own cells for therapeutic modification should be able to decide whether and how those cells are to be returned to him/her. In the case of the US, the Code of Federal Regulations § 1271.3(d) was modified in 2005 to bring autologous cells under its remit. (A single word change was made: “[h]uman 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”. While this change reflected



questions about whether autologous cells should be considered as a medicinal product not just a practice, others see this intervention as an expansion of the role of the state in the practice of medicine.<sup>158</sup> The situation within the EU is complex, and there is some gap between the legal position contained in the European Tissue and Cell Directive (2004/23) and its two satellite directives (2006/17 & 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 European Union Tissues and Cells Directives (EUTCD) and Advanced Therapy Medicinal Products (ATMP), and a complex landscape worldwide. While a thorough and complete analysis of all countries where research on stem cells is on going would be beyond the scope of this Commission, we will provide a few examples. With respect to the clinical use of stem cells, this is tightly regulated in many countries (for example in the EU, US, Japan, through EMA, FDA and Ministry of Health, Labour and Welfare, respectively), or subject to less or no regulation in a number of others, including India, where at present there are only provisional guidelines whose legal power is limited.<sup>159</sup> In China the National Health and Family Planning Commission (NHFPC) has recently begun working with draft regulation for clinical research and applications that involve human stem cells,<sup>160</sup> which though considered formal is currently flexible. As discussed elsewhere, it is, however, nearly impossible to control the activity of private clinics that offer stem cell therapies without abiding by any regulation, a challenge which applies to virtually any country.

In addition, upstream of any therapeutic use, there is significant variation with respect to research on human embryonic stem cells, reflective of religious and cultural contexts, as well as socio-economic conditions. Some European countries ban the in-country derivation of stem cell lines, but permit use of imported human embryonic stem cell lines for research (Italy), others have no specific legislation relating to stem cells research at all (Ireland), some ban all ES cell research (Lithuania), while others maintain a comprehensive and well-established regulatory framework (UK, Spain).<sup>161</sup> In the case of the US, on March 9, 2009,

President Barack Obama issued Executive Order 13505: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells. This reversed a former prohibition on the supporting human ES research with federal funds. What will happen under the next President is yet to be seen. More generally, bioconservative political parties may, for purely ideological reasons, attempt to enforce more restrictive policies on ES research, in the light of other recent signs indicating anti-scientific attitudes.

### **Access to therapies**

There are four ways in which patient access to stem cell and regenerative therapies can be obtained. 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. This would include “specials” and the hospital exemption within the EU, and also off-label or compassionate use. Fourth and more critically, through direct recruitment (usually through the internet) from commercial entities whose activity is not scrutinized/approved by any regulatory body.

### **Access to cell therapies via clinical trials**

Perhaps the most difficult questions for access to experimental interventions are whether there should be a maximum level of acceptable risk (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, it is interesting to speculate whether under today’s regulations, BMT would have emerged as a consolidated therapy. The first patients to be treated invariably died after the transplant, but the persistence of its pioneers in searching for the causes of its failure, their quest to better understand 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. More recently, 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. While on the one hand increasing controls prohibitively raises costs to the point of making it very difficult for academics to conduct even early Phase (I or IIa) trials; on the other, complete deregulation would legitimise the practices of stem cell clinics offering unproven therapies on the principle of free choice.

The next few years are likely to bring a fresh iteration of the 'free to choose' paradigm, 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 from the point of view of 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. This means that selection of patients raises significant 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 (for example 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. In general, 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 may benefit other patients after them. Very often, selection is based on objective criteria (for example age, type of mutation, severity, and availability of an HLA-compatible donor).

In cases where more patients are eligible than the few who are normally enrolled, selection poses both medical and ethical issues. On the one hand it could be argued that the chance of benefit is balanced by the unpredictability (within the limits of good pre-clinical work: see Recommendation “Better science”) of a 'first in man' therapy. The problem is that for those awaiting the next trial, the disease may progress to a stage when they would no longer be eligible for the subsequent enrolment. There is no easy solution for this issue. This is exacerbated by the fact that, in nearly all cases, the mere mention of the words '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 happen outside of the structure of a regulated health system, and come 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. It is important to differentiate between carefully designed and conducted clinical trials (which should not require a patient to bear any financial costs) and those in which private stem cell clinics are essentially taking advantage of patients' vulnerability.

### **Permitted non-research usage of therapies that do not have marketing authorisation for that indication**

US and EU regulatory regimes 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 US. 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

where 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, laws, which allow terminally ill patients to receive experimental therapies that have passed Phase I, without seeking FDA approval.

These regulations attempt to balance considerations of safety and efficacy with meeting the needs of patients who require urgent medical intervention and who have no other avenues available to them.

Where patients are in dire straits and where there is sufficient evidence to indicate that the benefits are proportional to the risks for the individual patient, such exemptions do have a role to play. 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. The social contract is used 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. It goes beyond the private contract between patient and clinician/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). As we are at an early stage of the path through which cell and gene therapies will transition from experimental therapy to mainstream practice, a good governance framework needs to

increase the sense of mutuality between the public and scientists and also to enhance the sense there is a common project that will take time to come to fruition so that science and wider society need to commit to work in conjunction for a period if the benefits are to be secured. The use of the term 'contract' rather than 'licence' is used to capture these needs for mutuality and endurance.

To sustain their licence to practise research in this area, scientists need to demonstrate that they can be trusted. This requires competence, addressed by our recommendations in respect of better science. It also involves openness, recognising the public stake in the future that therapies may make available, acknowledging and addressing concerns that are 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. This takes a range of forms. The most important is the need for the scientific community 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 cannot be specified in detail. 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. While informed consent is primarily a private matter for patients, it could be better supported if the stewards of a register specific to these therapies used it to 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 conducted in two

ways.

Most commonly, it 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 (World Health organisation 2008).<sup>162</sup> 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/benefit balance and the nature of the trial they in which they are participating, researchers need to engage quite extensively with potential trial participants.<sup>10, 11, 163</sup> However, beyond targeted patient interactions and publicity initiatives, it is not clear what researchers should do. Reports of wider benefits and the effectiveness of more general engagement programmes have been found to be mixed, and accompanied by concerns that extensive engagement would require significant resources, and that in the absence of these it can become tokenistic.<sup>12</sup> This is not to say there's a lack of interest or concern. 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.<sup>164</sup> As indicated throughout this commission report, the case for 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 hopeless patients for large amounts of money – all create the conditions for public controversy. However, regardless of views held on the usefulness and desirable extent of public engagement, it is clear that extensive deliberative exercises are not becoming the norm even in those countries and research areas for which some funding for them is available, 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. There are much more prosaic and straightforward activities that researchers are able to undertake themselves at minimal cost. Stem cell research can be contextualized 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 may 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. This would open up the potential for increased public discourse and correctives to misapprehensions about previous work in the field, the regulatory context of the research, its potential applications and the likelihood that they will be realized in relation to patient and carer expectations.

## **Conclusions**

Those 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 to experimental and unproven procedures—whether that be for avian flu modelling, for Ebola preparedness, or for patients in wheelchairs demanding the latest experimental treatment for Duchenne muscular dystrophy. But the problems of regulation are not only limited to controlling irresponsibility on the part of those lobbying to direct limited funding towards their work. Strict, though necessary regulation often prevents or makes it extremely difficult for academics and small companies to take risks related to conducting even Phase I trials (see Recommendation “Better science”), let alone Phase II and beyond. Regulatory bodies are aware of the problem and encourage researchers to interact very early in order to provide advice. Through such guidance it is hoped, as far as possible, that costs related to potentially



unnecessary controls will be reduced, without compromising on rigorous quality control of the medicinal product under development.

Looking across the landscape of scientific discovery, it is acknowledged that those who take risks in their work make some of our most important discoveries. However, this is justifiably less the case where human lives are concerned. The absence of innovation in medicine is, therefore, just as much a problem in surgical innovation as it is in experimental stem cell therapies. When clinical experimentation explores unknown pathways, possibly even risking the life of patients, controls must be as stringent as possible.

The problem is only exacerbated with respect to illnesses in which animal testing has only limited applicability, or may even be impossible. As a public health problem across the globe, Dengue fever, for instance, grows alarmingly in part because vaccine testing is only possible with human subjects. So, while we await yet more failed attempts at a vaccine, the disease spreads at frightening speed.

Though 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 subjects. This is only made more complex by the personalization of those therapies. In fact, because so many new developments are explored at the level of personalized medicine, the problem is, if anything, more acute.

And there is another looming problem: that of global governance. Though guidelines exist and are globally recommended, there will always be places where otherwise prohibited practices are allowed. The fact is, even with common efforts to expedite reviews and optimize regulation, there is simply no way to compete with an absence of regulation. Renegade

surgeons sometimes boast of their enhanced outcomes based on the freshness of organs culled from places they dare not ask about.<sup>165</sup>

So the question of what to do about the desperate sufferer who mortgages a house for an experimental treatment that turns out to be little more than saline is one that we need to face boldly. Again, if one looks at transplantation practices, the reality could not be clearer. Of the roughly 9000 individuals awaiting transplants in the UK, some 1500 are of South Asian descent; yet there are only about 150 donors annually. For those who choose to go abroad, the choice can result in a grim outcome. Indeed, some 40% of those transplants will fail, or kill the patient outright, within a few years.

We must, therefore, be especially alert to the need to develop new ways of protecting those who name and shame poor, if not unethical science. This is important when set against the real legal and other threats they face from companies that do not meet regulator's conditions of strict oversight, and the enforcement of laws where they exist. At the same time, expedition is essential for companies and academics to remain competitive and move the field forward, balancing as much as possible, risks, costs and potential benefits. How we proceed in this new global terrain may be our biggest challenge of all.

**Box. 1****What do we mean by Regenerative Medicine and, more specifically, Cell and Gene Therapies and Tissue Engineering?**

Regenerative Medicine is an emerging medical endeavour aimed at regeneration via small molecule drugs, biologics, medical devices and/or cells and genes. It aims to replace or repair human cells and/or regenerate tissue or organs to restore normal function.

Cell Therapy is a developing medical technology based upon delivery of cells as medicines for a growing variety of the clinical indications. Likewise, gene therapy is based upon delivery of genes as medicines. Delivery may 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, as most ongoing gene therapy trials are for cancer treatments. Finally, tissue engineering is based upon 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. While the terms “cell or gene therapy” have entered common language, with few exceptions, they are experimental therapies rather than standard/consolidated ones.

**Box. 2 Cost-effectiveness of treatments**

Many of the therapies discussed here are likely to have significant costs when ultimately delivered to patients. But for many of the conditions being treated, these costs may be off-set by potential savings over the longer run, by reducing the need for expensive health and social care in the long-term. Many may also be life-saving, and/or lead to significant improvements in population and individual health. The costs of regenerative medicine ought to be balanced against the cost savings and improvements in health. Consider the potential for revolutionary treatments for chronic and life-limiting illnesses, such as Duchene muscular dystrophy or Crohn’s disease. Such illnesses are characterised by high, recurring costs of care

and low health-related quality of life. Therapies that improve such conditions could lead to significant reductions in costs of other care, as well as significant improvements in length of life, health and wellbeing. Any treatment – even a very expensive treatment – has the possibility to be cost-effective where the offset costs of continuing care and the gain in health are sufficiently large.

### **Box. 3 Balancing benefits and risks**

A bone marrow aspirate, a skin or muscle biopsy are minor surgeries and essentially free of risk in comparison with huge potential benefit that may derive from their use. This is the large majority of cases. 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. Moreover, improper cell manipulation may add another level of risk.

### **Box. 4: Different translational stages have different risk profiles**

- Phase I clinical trials do not aim to benefit the individuals taking part in them. Information available about risks involved in trials may be too scant to make the risk easily appreciable by participants.
- Phase II and III trials (for small and large cohorts of patients, respectively) 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 in general 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, whilst the main beneficiaries are those who provide the therapies. In addition, such therapies take advantage of lax regulatory environments of certain countries or simply act outside of any regulation. There are no mechanisms to ensure that information is accurate and complete, so neither regulation, nor informed consent, provides an adequate ability to balance the risks.

### **Box. 5: Paternalism**

Paternalism in general consists in interfering with the liberty or autonomy of individuals in order to benefit them without their consent. In cases where the choices or actions that are beneficently interfered with are substantially non-autonomous, this is *soft paternalism*. Where 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 is a separate question from the coerciveness or otherwise of the means employed to interfere with these choices.<sup>137</sup> 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.<sup>135</sup>

**Contributors:**

All authors contributed to study design. Giulio Cossu wrote the section on Cell Therapy and revised the manuscript. Martin Birchall co-wrote the section on Tissue Engineering. Tracey Brown wrote the section on patient and public engagement and trust. Paolo De Coppi co-wrote the section on Tissue Engineering. Emily Culme-Seymour co-wrote the section on the definitions and sections on Small trials, difficult statistics, difficult regulation and data reproducibility. Sahra Gibbon co-wrote the section on Ethics. Julian Hitchcock co-wrote the section on Regulation of stem cell therapies and regenerative medicine. Chris Mason co-wrote the definitions and sections on Small trials, difficult statistics, difficult regulation and data reproducibility. Jonathan Montgomery co-wrote the section on Regulation of stem cell therapies and regenerative medicine. Steve Morris co-wrote the section on health economics. Francesco Muntoni wrote the section on antisense oligonucleotides. David Napier initiated the project and wrote the Introduction. Nazanin Owji researched, compiled and wrote the section on international regulations. Aarathi Prasad co-ordinated, compiled, edited and revised the manuscript. Jeff Round co-wrote the section on health economics. Prince Saprai co-wrote the section on Ethics. Jack Stilgoe contributed to the section on public engagement and trust. Adrian Thrasher wrote the section on gene therapy. James Wilson co-wrote the section on Ethics and the introduction.

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No conflicts of interests have been declared by the authors with the exception of the following: Adrian Trasher is the founder and scientific director of Orchard Therapeutics; Emily Culme-Seymour is currently employed by GlaxoSmithKline and holds shares in the company in that capacity, and contributed to this piece in an individual capacity prior to joining GlaxoSmithKline.

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## Figure and Table legends

Figure 1: A simplified scheme of cell and gene therapy.

Figure 2: Landmark steps in regenerative medicine. Original papers <sup>14-22</sup> are listed in the Reference section

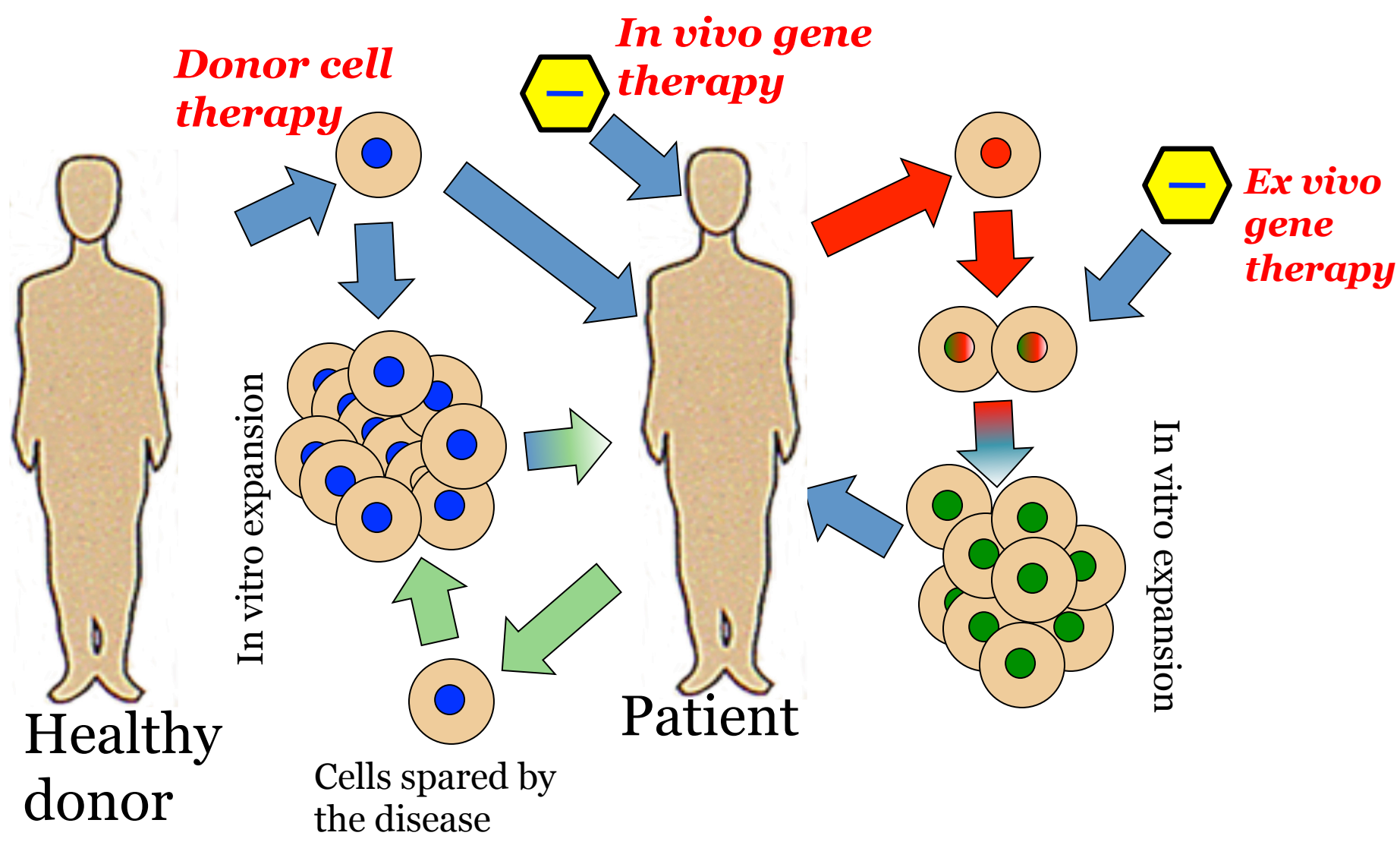
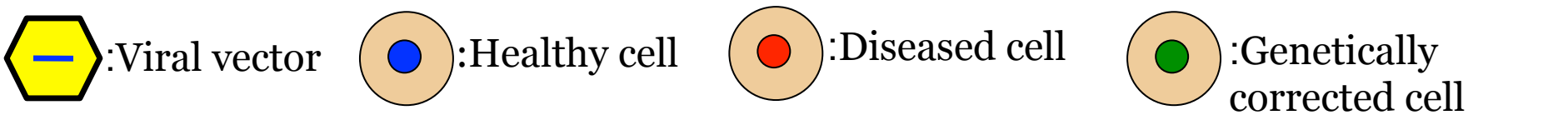
Figure 3: Corneal restoration. (A) Left eye (at admission) of a 42 year-old patient who had total limbal stem cell deficiency due to acid burn. (B) eye of the patient at the last follow-up, 6 years after graft. (Reprinted with permission from Regen. Med). <sup>29-31</sup>

Figure 4: iPSC technology contributes to disease modeling and drug screening (A), cell transplantation (B) and clinical trials (C) (Reprinted with permission from EMBO J.). <sup>42</sup>

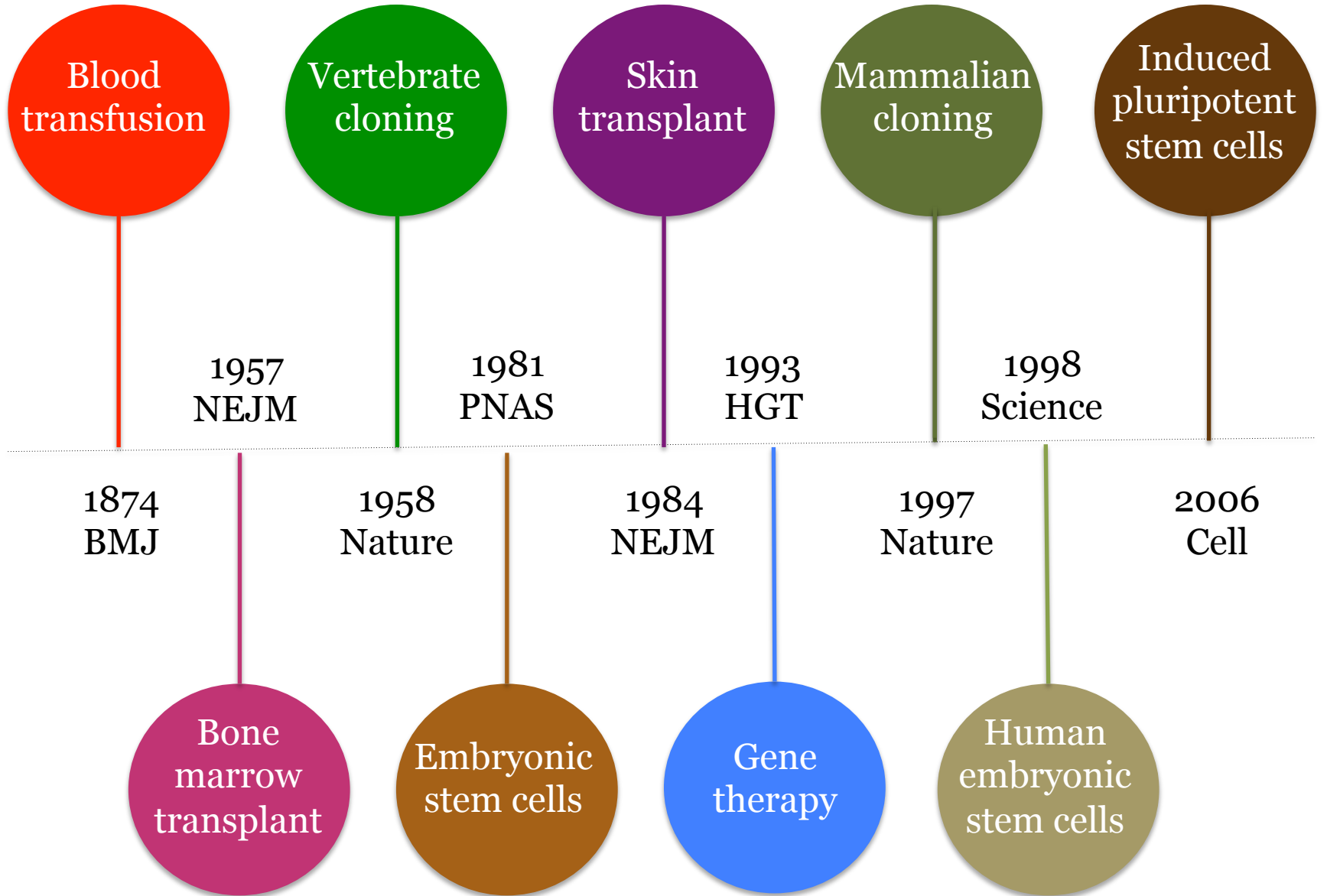
Figure 5: A scheme of the gene therapy clinical trial for ADA-SCID. CD34+ cells are collected from the patient's bone marrow, transduced with a viral vector expressing ADA and, after mild myeloablation, re-infused into the same patient. (Reprinted with permission from Immunologic Research). <sup>83</sup>

Figure 6. Annual costs of Duchenne Muscular Dystrophy (DMD). The mean per-patient annual direct cost of illness as estimated in different countries. (Reprinted from Neurology). <sup>138</sup>

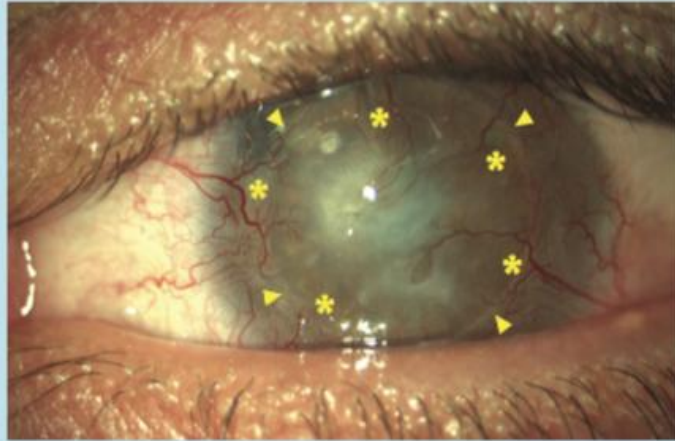
Table 1: Summary of clinical applications of tissue engineering (at the date of submission). PLCA: poly-carpolactone; PLA: poly-lactic acid; PGA: polyglycolic acid; PLGA: poly-lacticglycolic acid). <sup>115, 120-123</sup>







**(A) Admission**



**(B) Cultures + keratoplasty**

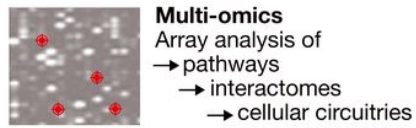
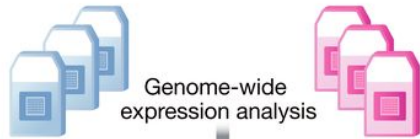
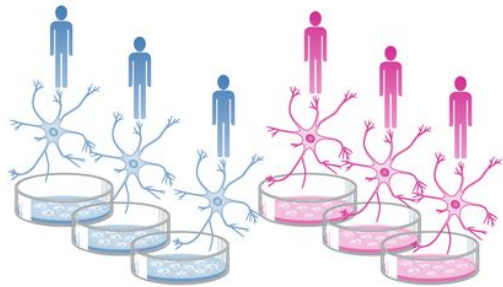


6 years follow-up

**iPSC TECHNOLOGY**

**A**

**Disease modeling**

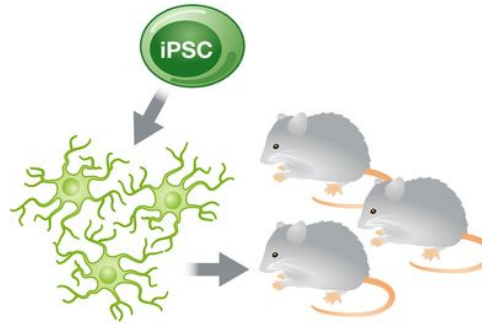


**Drug discovery**

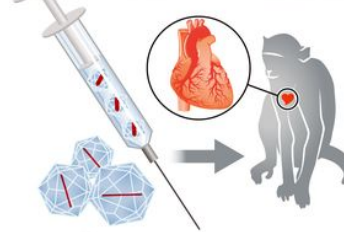


**B**

**Cell transplantation**

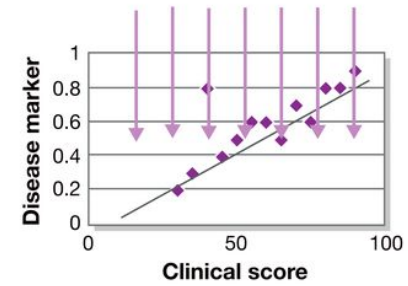
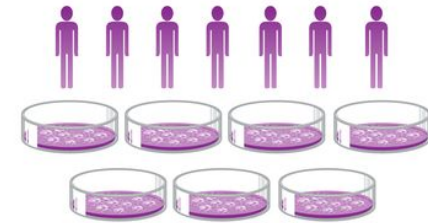


**Onsite reprogramming**

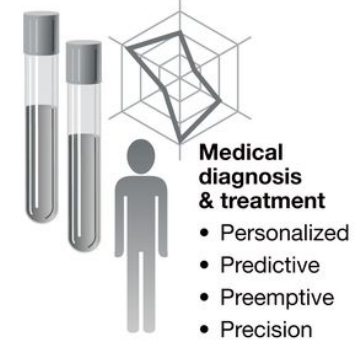


**C**

**Clinical trial**

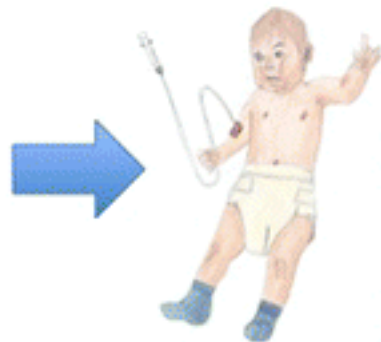
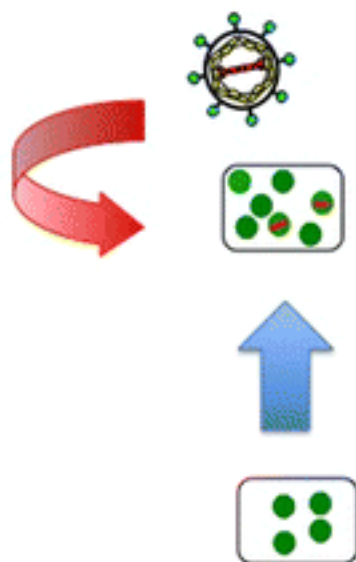


**Patient stratification**

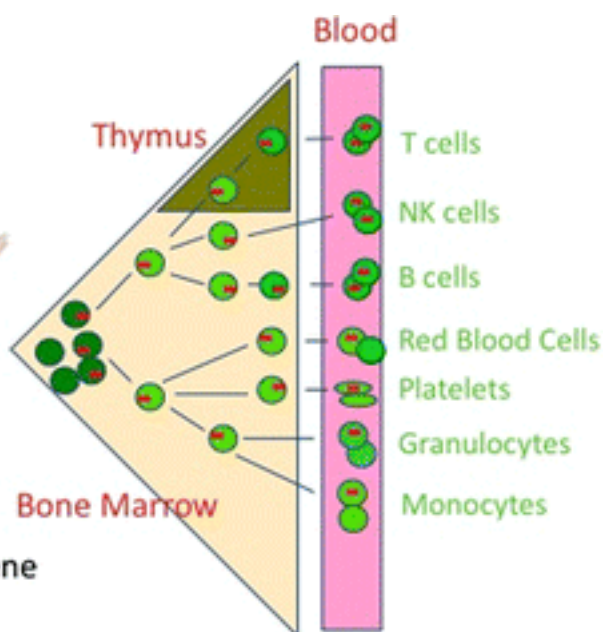


2. Delivery of ADA cDNA by the Retroviral vector

3. Reduced intensity chemotherapy

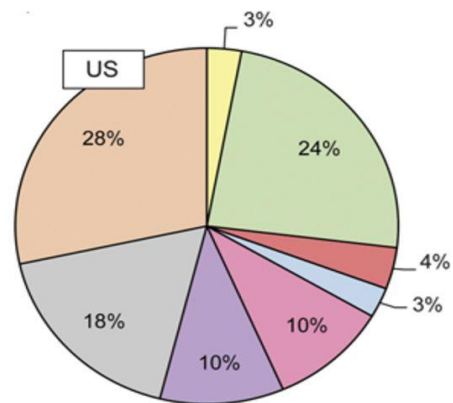
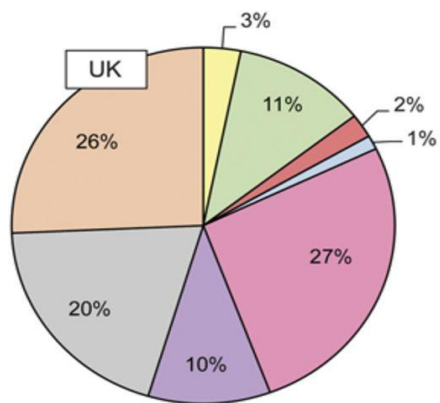
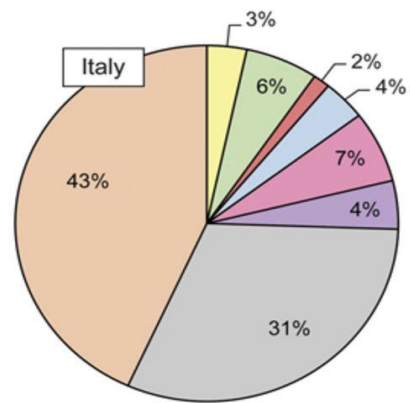
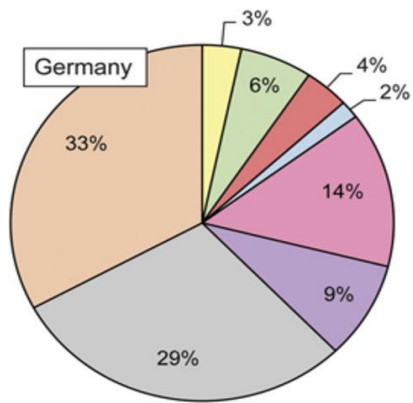


4. Infusion of gene corrected cells



1. Collection of hematopoietic stem cells from the bone marrow

5. Outcome:  
Multilineage engraftment  
Immune reconstitution  
ADA metabolic detoxifications  
Clinical benefit



- Hospital admissions
- Visits to physicians and other health care practitioners
- Tests and assessments
- Medications
- Nonmedical community services
- Aids, devices, and investments
- Informal care
- Indirect costs

| Organ            | Scaffold                               |                          | Cells               |                                     | Patient Number | Follow-up | Results  | Ref. |
|------------------|--|--------------------------|---------------------|-------------------------------------|----------------|-----------|--|------|
|                  | Type                                   | Size                     | Type                | Number                              |                |           |  |      |
| Bronchus         | Decellularised trachea                 | 7 cm                     | Epithelial cells    | 1*10 <sup>6</sup> /mL               | 1              | 4 months  | Normal mechanical properties and appearance of graft, improved quality of life, no immunosuppression           | 120  |
|                  |  |                          | Chondrocytes        | 1*10 <sup>6</sup> /mL               |                |           |  |      |
| Trachea (Whole)  | Decellularised trachea                 | 7 cm                     | Epithelial cells    | 2.5*10 <sup>8</sup>                 | 1              | 2 years   | Normal CT scan, appropriate growth, patient well   | 121  |
|                  |  |                          | Epithelial cells    | Patches                             |                |           |  |      |
| Pulmonary artery | PCLA-PLA matrix with PGA fibers        | 2 cm                     | Smooth muscle cells | 12*10 <sup>6</sup>                  | 1              | 7 months  | Graft patent on angiography, no occlusion, no aneurysm, patient well   | 122  |
| Bladder          | Collagen matrix or collagen-PGA matrix | 70 - 150 cm <sup>2</sup> | Urothelial cells    | 50*10 <sup>6</sup> /cm <sup>3</sup> | 7              | 46 months | Volume and compliance increase, preservation of renal function, adequate structural architecture and phenotype | 123  |
|                  |  |                          | Smooth muscle cells | 50*10 <sup>6</sup> /cm <sup>3</sup> |                |           |  |      |
| Urethra          | PGA-PLGA matrix                        | 5 cm                     | Epithelial cells    | 1*10 <sup>7</sup> /mL               | 4              | 71 months | Maximum urinary flow rate 27.1 mL/s, no strictures, normal architecture (biopsy, 3 months)                     | 115  |
|                  |  |                          | Smooth muscle cells | 1*10 <sup>7</sup> /mL               |                |           |  |      |
|                  |  |                          | Chondrocytes        | 1*10 <sup>6</sup> /mL               |                |           |  |      |