SCIENCE AND SOCIETY

Pluripotent stem cells progressing to the clinic

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Abstract | Basic experimental stem cell research has opened up the possibility of many diverse clinical applications; however, translation to clinical trials has been restricted to only a few diseases. To broaden this clinical scope, pluripotent stem cell derivatives provide a uniquely scalable source of functional differentiated cells that can potentially repair damaged or diseased tissues to treat a wide spectrum of diseases and injuries. However, gathering sound data on their distribution, longevity, function and mechanisms of action in host tissues is imperative to realizing their clinical benefit. The large-scale availability of treatments involving pluripotent stem cells remains some years away, because of the long and demanding regulatory pathway that is needed to ensure their safety.

Cell therapies are emerging as the next major development in human medicine[1–3] (BOX 1). The choice of stem cell type and application is determined by the accessibility of the cell type, its potential risks and the likelihood of its entering clinical trials. At present, the most prominent cell therapies involve bone marrow cells, mobilized blood stem cells (also known as mononucleocytes) and bone marrow stromal cells (often termed mesenchymal stem cells (MSCs)), all of which can be readily harvested from patients or donors for use in autologous or allogeneic therapies. To date, these cell types have shown good safety profiles in human clinical trials. Sources of immune-type MSCs include fat, placental and umbilical cord tissues. There is a body of evidence showing that MSCs can suppress inflammation and mobilize endogenous repair mechanisms through indirect effects on immune cells and tissue stem cell populations[4,5], which has led to their clinical testing for a range of conditions. However, other studies have shown that transplanted MSCs persist only briefly in the body[6,7], raising questions about their mechanisms of action.

In contrast to MSCs and other types of tissue-specific stem cells, pluripotent stem cells (PSCs) are derived either from cells of the pre-implantation human embryo, in which case they form embryonic stem cells (ES cells)[8,9], or from somatic cells that are induced to a primitive pluripotent state (termed induced PSCs (iPSCs)) by transduction of specific transcription factors[10–12].

PSCs are highly expandable (immortal) in culture *in vitro* and can be directed to form almost any cell type of the body. Their potential for regenerative medicine is therefore unique and extraordinary. ES cells are now in clinical trials for eye diseases, diabetes and heart disease, with some other applications registered for clinical trial approval[1,3,13]. To date, iPSCs have been used in one experimental procedure on an individual in Japan with macular degeneration and are expected to enter clinical trials in the near future.

In this Science and Society article, we discuss how basic experimental research can provide insight to guide the development of stem cell therapies, the current state of the art of potential clinical applications, and the steps required to go from bench to therapy. We also briefly discuss the responsibility of the scientific community in ensuring the safety of clinical translation.

Basic research informs clinical applications

Understanding the mechanism of action of any cell therapy is crucial to the success of clinical trials. Transplanted cells must mature, integrate and function following *in vivo* transplantation and correctly orchestrate these processes with the help of mature endogenous cells. In the absence of clearly demonstrated and coherent molecular or cellular models of how the transplanted cells contribute to tissue repair, it is difficult to predict the regenerative response or design strategies to achieve meaningful clinical outcomes. Thus, defining the specific properties of the cells that are produced, and their ability to develop into fully functional cell types *in situ*, will be crucial for achieving significant and sustained clinical benefits[14].

Unfortunately, there are many examples of clinical failures owing, in part, to the lack of demonstrated mechanisms of action for transplanted bone marrow cells, mononuclear blood cells and MSCs. By contrast, the mechanism of action of human PSCs is clearer and relies on their ability to be expanded and form functional derivatives that are suitable for transplantation. In early studies, mouse ES cells and iPSCs were shown to fully integrate into the developing mouse gastrula stage embryo and function normally in offspring, strongly suggesting that the human counterparts have the potential to regenerate diseased or injured human tissues[15,16].

Animal modelling

It is essential to carry out basic research on the integration and function of stem cell derivatives in tissues damaged by disease or injury in appropriate laboratory and animal models. If the cells cannot survive, integrate, proliferate and mature as complete functional units, it is unlikely that they will benefit patients.

Typically, mice or rats are used as animal models, because knockout or knock-in gene mutants that demonstrate disease phenotypes are frequently available in these species. Immune-incompetent mice tolerate human cell grafts, and humanized mice provide models that enable transplants to more closely resemble transplants performed in immune-competent humans.

However, cell therapies in rodent models do not always predict the response in more genetically heterogeneous human diseases[17]. Determining parameters that align closely in therapeutic response between rodent models and human disease are important for assessing therapeutic response[14]. For example, during spinal cord repair, respiratory function is more informative than the measurement of the poorly aligned corticospinal locomotion systems[18]. Even in the difficult condition of graft-versus-host disease (GVHD), mouse models are informative and have led to striking improvements in therapeutic success. The pathophysiology of acute and chronic GVHD is distinctly different in mice and humans; however, mouse experiments have led to safe and effective reconstitution of immune systems following transplantation[19].

Progress in clinical applications of PSCs

Early Phase I and Phase II clinical trials are testing the safety and therapeutic benefit of PSC derivatives, in five major areas of unmet clinical need (FIG. 1).

Spinal cord injury. Contusions to the spinal cord often leave some motor neurons intact but demyelinated, leading to paraplegia in these patients. Consequently, a target for cell therapy is the remyelination of neuronal axons across the site of injury, enabling motor neurons to begin functioning again to transmit messages to major muscle areas for both sensation and movement[20,21].

Most of the lessons of cell therapy for the repair of spinal cord injury come from studies on rats and mice that provide evidence for recovery of limb and tail movements following severe contusion injury. The recovery of movement in limbs that has been documented in rodents[22] has not yet been observed in the human — with one exception, which involved an injury in which the spinal cord was severed with a knife[1]. Human ES cell-derived oligodendrocyte precursor cells with remyelinating capacity, developed by the company Geron, showed strong evidence for safety and limb movement recovery following transplantation into the spinal cord in rodents. However, trial participants showed no evidence of motor recovery in their initial Phase I clinical study with the cell dose used[23] (FIG. 2). The company Asterias is now following up this initial clinical trial with the same cell type.

Neurodegeneration: Huntington disease. Basic research in neurodegenerative disorders of the central nervous system, which include Huntington disease, Parkinson disease and amyotrophic lateral sclerosis (ALS), continues to progress towards clinical trials.

Huntington disease is caused by the loss of medium spiny projection neurons (MSPNs), which are positive for the marker DARPP-32, in the striatum, which is a principal component of the basal ganglia of the brain responsible for voluntary movement. Fetal striatal tissue transplants have not, as yet, provided an effective long-term therapeutic option for Huntington disease, because the transplanted tissue develops the disease phenotype[24–26]. PSCs can be differentiated into MSPNs and are being investigated for clinical studies; however, transplants of PSC-derived cells may require inclusion of multiple populations of striatal interneurons and glial support cells to be effective[27].

Neurodegeneration: Parkinson disease. In Parkinson disease, the densely packed A9 dopaminergic neurons of the ventrolateral midbrain are lost. The exact cell type to transplant has been a concern, as dyskinesia has been observed in many clinical trial participants treated with fetal brain tissue transplants. When predominantly A9 dopaminergic neurons are transplanted into rodent dorsal striatum or mid-brain ablated with 6-hydroxydopamine, they extend fibres to form synapse connections with MSPNs and eventually mature and release dopamine, reducing Parkinson disease behaviour in animal models[26,28,29].

The Australian Therapeutic Goods Administration (TGA) has approved a Phase I clinical trial for Parkinson disease using human parthenogenetic embryonic stem cells (pES cells). Parthenogenetic

Glossary

Allogeneic therapies
Transplants using cells or tissues derived from a different person.

Autologous therapies
Immunologically compatible transplants using the patient's own cells or tissues.

A9 dopaminergic neurons
Mature dopamine-producing neurons of the midbrain substantia nigra, which are lost in Parkinson disease.

Choroid
Vascular layer of the eye between the retina and the sclera.

Cell-mediated immune rejection
Activation of the innate immune system in response to cells recognized as foreign, which can constitute a major barrier to successful organ transplantation and allogeneic cell therapies.

Dyskinesia
Repetitive, involuntary and purposeless movements.

Expandable (immortal) in culture
Capable of continuous cell replication and passage *in vitro* without senescence.

Graft-versus-host disease
(GVHD). When the immune cells of a foreign transplant attack the recipient's own tissues, causing serious life-threatening loss of organ or tissue function.

Housekeeping genes
Constitutive genes that are responsible for the maintenance of basic cell function and are normally expressed in all cells.

Humanized mice
Genetically modified mice with human immune cells that are tolerant to human grafts.

Immune-competent humans
Humans with natural uncompromised immunity.

Immune-incompetent mice
Mice that are genetically modified to prevent the development of an adaptive immune system.

Infarct
An area of tissue death or necrosis caused by lack of local oxygen due to blockage of blood supply.

Knock-in gene mutants
Cells or organisms with gene and regulatory DNA elements introduced into their genomes to enable expression of an introduced mutant gene.

Macula
An oval-shaped area near the centre of the retina of the eye, specialized for high-acuity vision.

Oligodendrocyte
Glial cell of the central nervous system (CNS) that is responsible for creating the myelin sheath surrounding the axons of CNS neurons, enabling transmission of electronic impulses.

Optogenetic
Light-directed identification and control of individual neurons, in living tissue, that have been genetically modified to express light-sensitive ion channels.

Pharmacogenetic
Drug-directed control of individual neurons that have been genetically modified to respond to specific drugs.

Teratomas
Tumours with organ and tissue components that are derivatives of more than one germ layer, typically formed *in vivo* from pluripotent stem cells.

Tissue stem cell
Undifferentiated stem cell in a tissue or organ that can self-renew and give rise to the major cell types of that tissue or organ. Tissue stem cells are also referred to as adult stem cells or somatic stem cells.

Ventricular arrhythmias
Severely abnormal heart rhythms that cause the majority of sudden deaths due to heart problems.

Box 1 | **Tissue stem cells emerge as a new paradigm in human medicine**

Bone marrow transplants, using bone marrow engrafting haematopoietic stem cells (HSCs), are well-established therapies for the treatment of blood diseases and cancers.

Bone marrow stromal cells, often termed mesenchymal stem cells (MSCs), are being studied in hundreds of clinical trials for a wide array of disease conditions, with some demonstrated clinical benefits for immune rejection, as in paediatric graft-versus-host disease (GVHD), bone repair and joint or lower back pain. Stromal cells from other tissues, such as placenta, umbilical cord and adipose tissue, are also in clinical trials for many of the same applications, with variable outcomes so far. Other applications of MSCs, such as therapy for myocardial infarct, diabetes, pulmonary diseases, neurological diseases, cartilage repair and liver disease, are less promising at the present time[1].

Neural stem cells from adult and fetal sources are being studied for many neurodegenerative disorders and diseases of the eye[1,3]. The neural stem cells are glial or neuron progenitors, and some have been immortalized and some engineered to overexpress neural growth factors such as glial derived neural growth factor (GDNF). Depending on the disorder, the neural stem cell type would be expected to, for example, insulate the myelin sheaths of neurons damaged in spinal cord injury, protect motor neurons in amyotrophic lateral sclerosis (ALS) or provide dopamine-secreting A9 dopaminergic neurons in Parkinson disease.

Limbal stem cells of the cornea have been approved for autologous therapies, in which the healthy limbal cells can be recovered from the patient's own eyes. The use of these cells as allogeneic transplants that involve donor cells (live or cadaveric sources) are also progressing well in clinical trials for the restoration of sight in cases of corneal burns[1].

Gene therapy using the research participant's own haematopoietic stem cells that are DNA-edited to replace a mutated gene with a normal copy is being used in clinical trials to successfully cure single-gene diseases such as thalassaemia, sickle cell disease, adrenoleukodystrophy and severe combined immunodeficiency[76,77].

Therapies that disrupt the function of crucial blood cell co-receptors for HIV infections, such as by mutating the chemokine receptor 5 gene (*CCR5*), or inhibiting its function using short inhibitory RNA technology, are being trialled as potential cures for AIDS[78,79]. The *CCR5* gene encodes a co-receptor that enables HIV to enter T cells and macrophages.

Probably the most advanced clinical trials for cell therapies at present are those using chimeric antigen receptor technologies (CAR-T) to increase the effectiveness of killer T cell destruction of acute lymphoblastic leukaemia (ALL), multiple myeloma and glioblastoma[80,81,82]. The research participant's own T cells are recovered and transfected with a tumour-recognition molecule, such as an antibody CD19 antigen, together with co-stimulatory and activating domains that mediate T cell lysis of tumour cells. The engineered CAR-T CD19 T cells are expanded *ex vivo* and re-infused back into the research participant. For ALL, clinical success has been reported to be as high as ~90% complete remission after 6 months.

embryos are formed by chemically activating the unfertilized human ovum. These embryos can form pES cells in culture but are unable to produce normal offspring because of numerous developmental and epigenetic defects[30]. The sponsor company, International Stem Cells, proposes to derive neural stem cells from pES cells for use in clinical trials for Parkinson disease, on the basis of preclinical safety studies with rats and two African Green monkeys[31,32]. Whether the probable clinical efficacy of this approach is sufficiently well supported by basic preclinical data is debatable.

To achieve sustained recovery of patients with Parkinson disease using cell transplants, important considerations include the purity, type and extent of mixing of dopaminergic and serotoninergic neurons[33]. The midbrain floorplate that contains A9 dopaminergic neurons is generated by activation of sonic hedgehog (SHH) signalling[34,35]. Generation of dopaminergic and serotoninergic neural cells recapitulates the natural developmental intermediate step. This is followed by the conversion of dopaminergic progenitors to midbrain A9 dopaminergic neurons in response to activation of WNT signalling[36]. This pathway seems to be crucial for the survival and proper function of the transplanted cells[26].

To predict the functionality of neuronal grafts in humans, it will be essential to demonstrate in rodent Parkinson disease models that drug-induced rotational movements, which are a characteristic phenotype of the condition, are corrected, and that cell grafts exhibit trans-synaptic connectivity. Optogenetic and pharmacogenetic techniques can provide important data on the degree of neural pathway connectivity and function of transplanted neurons[26]. Going forward, the many patients with Parkinson disease that have devices for deep-brain electrical stimulation embedded in their brains may provide ideal cases for testing cell therapy[37]. Cells for therapy can be transplanted at the same time as the device, and cell therapy and stimulation, together or independently, can be controlled, monitored and evaluated.

Neurodegeneration: amyotrophic lateral sclerosis. ALS is a fatal, progressive loss of neuromuscular capacity caused by the death of motor neurons. It is known that astrocytes are important support cells that maintain the health of motor neurons, but in motor neuron disease, they may become cytotoxic. Their shift to expression of pro-inflammatory and neurotoxic characteristics is symptomatic of the ALS cascade. Astrocytes may be derived from PSCs, and a Phase I–II clinical trial of a glial restricted progenitor derivative of ES cells has recently been approved[38]. Moreover, there is interest in using lentiviral glial-derived neural growth factor (GDNF)-secreting fetal-derived neural progenitors grafted into the spinal cord to prevent lethal failure of breathing in ALS[39].

In contrast to the known genetic form of ALS caused by mutation of the superoxide dismutase 1 (*SOD1*) gene[40], the spontaneous form of ALS is not well understood, and, consequently, the long-term recovery of motor neuron function is difficult to predict[41].

Loss of vision. The eye is the dominant organ for many of the first human clinical trials of PSC derivatives. PSCs are being used clinically for a range of eye diseases, including wet and dry age-related macular degeneration (AMD), Stargardt disease and myopic macular degeneration[42].

The most common form of blindness in people over the age of 60, dry AMD involves a progressive loss of the retinal epithelium monolayer from the macula, which results in damage to the photoreceptors. Central vision becomes blurred and is eventually lost. The wet form of AMD almost always begins with dry AMD, but it also involves abnormal blood vessel growth from the choroid, which leaks fluid or blood into the macula. Central vision becomes patchy and wavy and is progressively lost.

Stargardt disease is associated with mutations in the genes ATP binding cassette subfamily A member 4 (*ABCA4*), ELOVL fatty acid elongase 4 (*ELOVL4*) and prominin 1 (*PROM1*). It may involve formation of toxic bisretinoids and lipofuscin in the retinal pigmented epithelium (RPE) layer, causing loss of RPE and eventual blindness at a relatively early age. Myopic macular degeneration is associated with atrophy and cracks in the sub-retinal area that function as conduits for abnormal

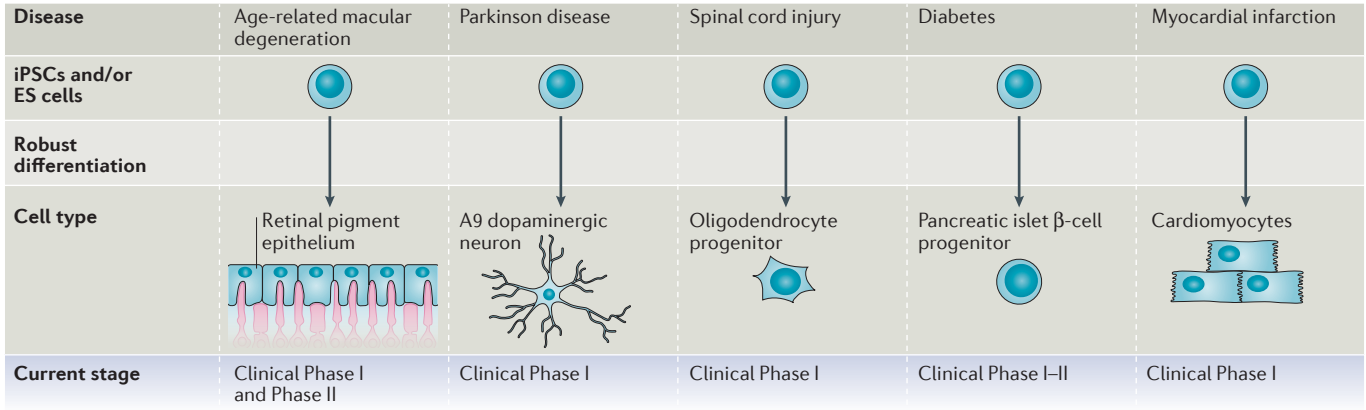

Figure 1 | **The leading applications for pluripotent stem cell derivatives.** Robust strategies have been developed to differentiate pluripotent stem cells into retinal pigment epithelium, A9 dopaminergic neurons, oligodendrocyte, pancreatic β-islet cells and cardiomyocytes. Clinical trials are underway for embryonic stem cell (ES cell) derivatives for age-related macular degeneration (AMD), type I diabetes, spinal cord injury, myocardial infarct and Parkinson disease (using parthenogenetic embryonic stem cells (pES cells)). Induced pluripotent stem cells (iPSCs) are in a clinical trial for AMD. Rigorously tested, abundant sources of these cell types are needed for preclinical research to generate data for regulatory approval for human studies. The cells also need to be manufactured in large quantities for clinical trials. These clinical studies in humans begin with regulatory approval for Phase I trials, which demonstrate safety. They are followed by Phase II studies showing proof of concept for cell therapy in human patients. Sometimes, Phase I–II studies are designed to demonstrate both safety and efficacy. Larger-scale Phase III clinical trials aim to demonstrate the statistical significance of the therapeutic benefit.

blood vessel growth (known as Fuchs spots), causing haemorrhage and scarring.

It is relatively easy to derive RPE from PSCs and, when transplanted into the Royal College of Surgeons rat model for AMD, these cells have been effective in maintaining vision[43]. RPE derived from human ES cells and iPSCs are capable of forming a monolayer between surviving rat host RPE layers and phagocytosing degenerating photoreceptor cells, which is necessary to maintain photoreceptor health[44,45].

Bioengineered polymer support scaffolds have been developed to obtain polarized monolayers of ES cell or iPSC-derived RPE that can attach to the Bruch's membrane underlying the RPE[46,47]. This culture system has proved to be very efficient and has led to effective coverage of the macula and maintenance of visual parameters in preclinical animal studies[48,49], and it is now entering clinical trials in the UK and California, USA. It will be interesting to compare how well vision is restored in trial participants who have received these monolayers of RPE on micro-thin matrices, versus those who have received ES cell- and iPSC-derived RPE cells applied either in suspension or as cultured flat sheets.

Reports of early Phase I clinical trials for sub-retinal injection of PSC-derived RPE cells in suspension have shown that the macula can be repopulated with new RPE, but coverage is often patchy[50]. Visual acuity is maintained in the transplanted eye but deteriorates in the 'control' uninjected eye in trial participants with dry AMD and Stargardt disease, as expected from preclinical experiments[44,50,51]. Concerns about immune rejection of RPE produced from ES cells and iPSCs have required that clinical trials for such transplants be accompanied by immune suppression. However, to date there is little evidence for rejection of PSC-derived RPE in the eye. Recently it was shown that in humanized mice, an immune response is mounted against iPSC-derived smooth muscle cells but not iPSC-derived RPE[52], suggesting that iPSC derivatives may vary in their immunogenicity.

In a clinical study in Japan, an individual with AMD who was transplanted with iPSC-derived RPE is apparently progressing satisfactorily, and her vision has stopped deteriorating; however, the experimental procedure was not performed on further individuals when serious spontaneous mutations were identified in the next person's iPSCs[53]. Japan now requires iPSCs to be used as allogeneic rather than autologous transplants.

Diabetes. Type I diabetes mellitus is generally a juvenile disease that is caused by autoimmune destruction of β-islet cells in the pancreas that secrete insulin, and patients depend on insulin injections for metabolic health and survival. Type II diabetes mellitus is more common, is usually characterized by insulin resistance and reduced insulin levels (although the patients are not insulin-dependent), and occurs in mature individuals, often associated with obesity. The derivation of pancreatic β-islet mature cell types and their progenitors from PSCs provides the opportunity for correction of type I diabetes, providing the transplanted cells can be adequately protected from cell-mediated immune rejection[54–57]. Through basic research, careful stepwise differentiation protocols have been developed to recapitulate the developmental pathway for functional progenitor β-cells[58]. These β-cell progenitors can be manufactured successfully[59] and, when enclosed in a suitable flat capsule a little smaller than a credit card, which prevents immune cell attack, they mature when transplanted and secrete insulin and other islet cell hormones[54]. This approach has been shown to control hyperglycaemia in diabetic rodents[54,57]. These cells are now in multicentre Phase I–II clinical trials by the company ViaCyte, as a subcutaneous encapsulated product to treat patients with type I diabetes[60].

Heart disease. Despite concerns and disappointments over cell therapeutic studies for the repair of the serious cardiac muscle damage that results from heart attacks[61,62], recent studies have shown that cardiac muscle derivatives of human ES cells can halt the deterioration of cardiac function and improve experimentally induced diminished heart function in rodent and monkey models[63,64]. Moreover, intramyocardial delivery of 1 billion human ES cell-derived cardiomyocytes in a monkey myocardial infarct model has shown extensive remuscularization of myocardial infarcts; however, non-fatal ventricular arrhythmias were observed[64].

ES cell-derived cardiomyocytes have been shown to perform better than mononucleated blood cells for repair of myocardial infarct[63]. A single patient who had a coronary bypass operation, at the same time was grafted in the infarct area with human ES cell-derived cardiomyocyte progenitors expressing the cardiac transcription factor insulin gene enhancer ISL1 and stage-specific embryonic antigen 1 (SSEA1), which are cell markers for cardiac progenitors. The cardiac progenitors were embedded in fibrin to enable a patch to be grafted to the damaged heart, enabling integration of the grafted cells into heart tissue[65]. No adverse events were associated with the graft, and the symptoms of heart disease improved after 3 months, although this may have been owing to revascularization resulting from the bypass surgery. Notably, contractility was observed in the previously akinetic heart patch area, and no arrhythmias were evident[65,66].

Essential steps for translation

The translation of a discovery into a product with potential for clinical evaluation involves preclinical development, which follows established processes that are guided by the appropriate regulatory body, such as the US Food and Drug Administration (FDA) (FIG. 3). Translation is a demanding process, in which both the safety and the efficacy of a candidate product are established by preclinical research, and usually involves both *in vitro* and *in vivo* animal model studies.

The FDA classifies PSC derivatives as human cellular and tissue products that are "more than minimally manipulated and used in a non-homologous manner" (this is known as '315s classification'). Thus, their approval requires a full multi-phase drug pipeline process (FIGS 2,3) consisting of extensive preclinical research that culminates in an Investigational New Drug (IND) application, which is necessary for commencing Phase I–III human clinical trials[67].

A primary bank of cells is needed for the preclinical studies. The generation of the bank of cells must meet the regulator's requirements, being produced under high security and sterility (that is, complying with good manufacturing practice (GMP)) conditions, which ensures that the preparations are free of potential pathogenic components. Any changes to the cell source or manufacturing procedure may require demonstration of bioequivalence using approved assays. The cell production company Lonza has generated GMP-qualified iPSCs, which are now available for clinical applications[68].

The safety of PSC-derived products needs to be fully addressed and must be demonstrated by ample preclinical data[69]. These data should include assays for chromosomal stability and for mutations in oncogenes and housekeeping genes, as well as in genes that are likely to affect cell function. At present, there is little agreement on what standards should be used for testing genetic mutations in therapeutic cell lines. However, the importance of such testing is exemplified by the ongoing trial for AMD in Japan, in which the presence of mutations in the iPSC lines has hampered the trial and led to changes in the approach, from using autologous cells to using allogeneic cells. *In vitro* culture conditions and passage number can contribute to an increased incidence of mutations in PSC lines[69,70].

Community access to PSC therapies

Although clinical trials are now evolving for PSC derivatives, it will take many years before they are available for patient use if they are successful. It is possible for clinicians to obtain approval for compassionate use that bypasses Phase II and III proof of concept, and also bypasses efficacy trials, in situations where no other life-saving treatment is available (FIG. 2). Fast-track, breakthrough therapy designation, accelerated approval and priority review are the other ways to hasten patient access to new cell therapies[67,71]. A new regulatory system was established in Japan that enables therapeutic cell products to enter the marketplace with provisional approval, thereby bypassing Phase II–III clinical trials. However, this system will require the eventual collection of data to demonstrate efficacy of the product[72]. This experiment with clinical trial regulation has attracted concerns in the scientific community as to the possibility of unleashing unproven therapies on large number of patients.

For ES cells, applications are most advanced in diseases of the eye, in particular for AMD and Stargardt disease (in Phase I and II trials). It could be expected that stem cell therapies may be available within

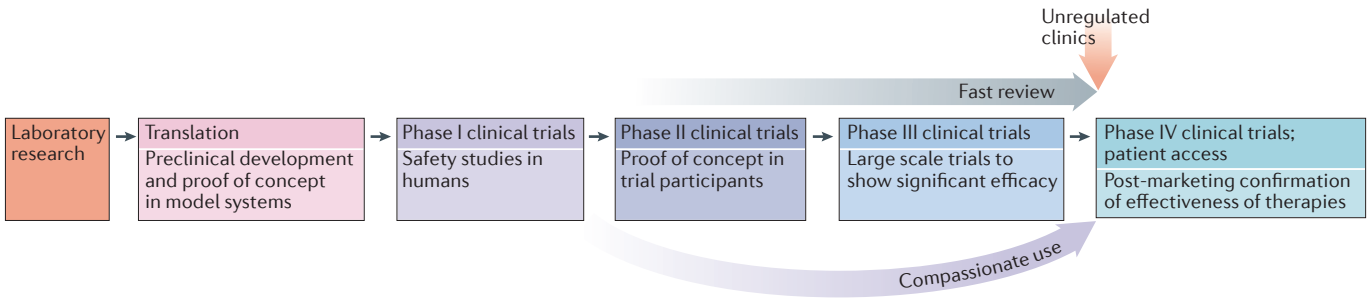

Figure 2 | **The bench to bedside pathway.** Discovery of a potential clinical product begins in basic research laboratories and then progresses to translation research, which establishes the product in proof-of-concept experiments conducted *in vitro* and *in vivo*, using suitable animal models of the target disease. Data on the delivery of cells, their biodistribution, the dose needed to achieve therapeutic benefit and the limit dose for toxicity, distribution and survival of the cells are needed in this preclinical development phase. The company or organization sponsoring the trial needs to apply for an Investigational New Drug (IND) or equivalent permit from the regulatory authority for first-in-human Phase I safety studies. The regulator (for example, the US Food and Drug Administration (FDA)) has a crucial role in the pathway to ensure that approved treatments are safe and effective. Phase I studies are safety studies done in a small number of subjects. Phase II studies provide the proof of concept in humans, using sufficient numbers of subjects to provide an indication of efficacy in addition to reassessing safety. Some studies are approved for Phase I–II if the data can be collected as a guide to efficacy. Phase III studies include a much larger number of participants to enable statistical assessment of clinical benefit and detection of any unusual risks associated with the treatment. Phase IV clinical studies are post-marketing trials in which data are collected on any adverse events and on patient responses to treatment. It is possible to apply to the regulator for fast review or compassionate use for patients in special circumstances. Clinics that use only autologous cells or products are not well-regulated and often present misleading information and substantial risk for patients. This could have consequences for the sustained development of all cell therapies, even those that are well-regulated and safe. Adapted with permission from REF. 67, Elsevier.

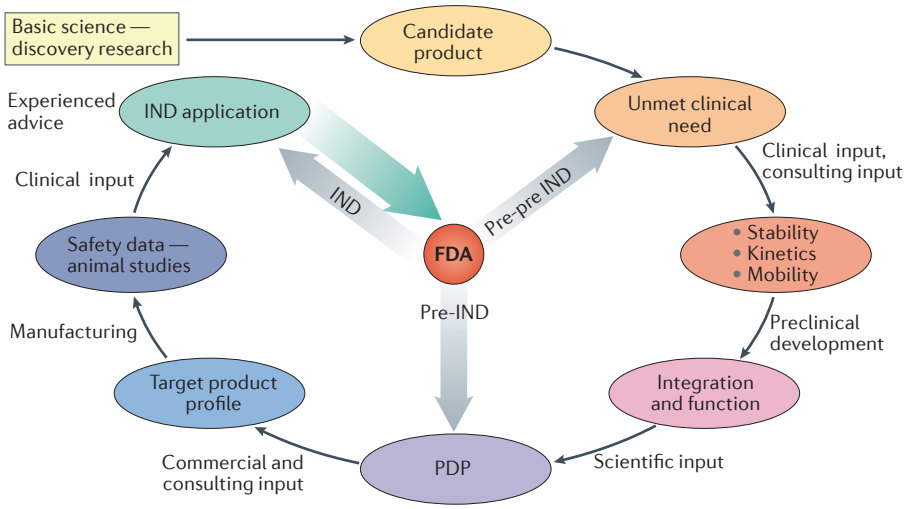

Figure 3 | **The translation pathway for product development and interactions with regulatory agencies.** The translation process begins with a basic discovery that has some potential for therapy in a disease or condition for which there is a significant unmet clinical need. The candidate product should have clinical support for its development. In the US, the sponsor company or organization should have a pre-pre-investigational new drug (IND) meeting with the Food and Drug Administration (FDA) to explore the pathway and data needed for IND registration. The preclinical development programme should involve regulatory expertise that is available in the sponsor company or as consulting services to the organization to ensure that the data needed for an IND is developed properly and completely. Scientific inputs are always needed in the process of translation to ensure, for example, that the cell integrates and functions properly in the targeted tissue. The product development plan (PDP) for the cell product needs to be established, and advice again obtained on the PDP at a pre-IND meeting with the FDA. Similarly, the target product profile needs to be presented to the regulator to initiate clinical trials and is essential for marketing the product[71]. This phase also needs the input of experienced professionals. The manufacturing process and bioassays of cell potency must be carefully designed to ensure adequate quantities of product are available for the preclinical and clinical trials. Clinical advice is essential in preparing the design of clinical trials and the parameters needed to test for proof of concept in animal studies and to assess safety and efficacy in selected human populations. Once the preclinical development data is obtained, the sponsor must seek IND approval from the governing regulatory body to commence clinical trials. This step involves a formal application, face-to-face interviews, and revisions of the application to the regulator's satisfaction.

3–6 years if the clinical trials deliver on expectations. Treatment for type I diabetes, now in initial Phase I–II trials, will take longer, as will ES cell therapies for heart disease, which are now in Phase I studies. Similarly, treatments for spinal cord injury may also become available if the clinical trials are positive. The latter are probably still 5 years or more away from registration for therapy, unless they are fast-tracked because the initial studies show a high degree of efficacy. Applications of iPSCs will probably first appear as treatments for eye diseases. Trials of therapies for Parkinson disease are also under consideration[73].

Challenges and risks of PSC therapies

The individuals and societies that make up the international stem cell community have a major responsibility for informing the general community about the progress of scientifically validated studies and alerting them of the dangers of unscientific and unregulated treatments.

The International Society for Stem Cell Research (ISSCR) has recently updated the Guidelines for Stem Cell Science and Clinical Translation[74] and has appointed a full-time Director of Public Policy to address issues that impinge directly on the safety of stem cell treatments. Other societies, including the US Institute of Medicine, have held workshops and produced reports that directly relate to the demand, quality, risks and dangers of unregulated stem cell therapies[75].

The identification of dangerous procedures and clinics would be helpful for patients, but legal issues can interfere in such listings. Unregulated clinical services continue to grow in the US, despite laws equating stem cell derivatives to drugs that must be subject to FDA regulation[72]. The situation outside the US may even be worse. It is essential that scientists are proactive in expressing their concern at this proliferation of untested and potentially dangerous procedures being offered to vulnerable patient populations throughout the world.

Conclusions and perspectives

Clearly, cell therapies have come of age as vehicles for medical intervention and are likely to become major tools in the future of regenerative medicine. To date, the incidence of teratomas seems to be well controlled in all of the major clinical trials, and few, if any, adverse events owing to the use of PSC derivatives have been reported. As yet, expectations for a broad base of clinical applications in regenerative medicine have not yet been met; thus, some of the initial hype has waned. The waning of hype is a positive development, as long as funding for rigorous stem cell science, and for basic, translational and clinical studies, is continued during this crucial period. Sound, well-designed, basic and translational studies need to continue to explore the potential therapeutic applications of these cells. The costs of the studies in the registration pipeline are very high as they reach clinical phases of testing, and only those showing robust clinical benefits will lead to therapies. Funding all of these studies will continue to be a major challenge.

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Competing interests statement
The authors declare competing interests: see Web version for details.