DR ALFRED GRECH,
DR STEPHEN WEST &
DR RAMON TONNA

CLINICAL TRANSLATION OF STEM CELL RESEARCH

ABSTRACT

Stem cells can be totipotent, pluripotent or multipotent and they can be sourced from various parts of the body. Stems cell research is in hyperdrive and this is responsible for its implementation into the clinical setting. Indeed, stem cell-based therapy has been applied successfully in cancer, hematopoietic and metabolic disorders. But stem cell therapy also has other potential indications in neurodegenerative diseases, stroke, cardiac infarction, arthritis, diabetes mellitus and hearing loss.

INTRODUCTION

HISTORY

Stem cell research started in mid-1800's. The early 1900's saw the discovery of how blood cells could be generated from other cells. It was Alexander Maksimov, a Russian histologist, who in 1908 proposed the term 'stem cell'. In 1968, a bone marrow transplant treated Severe Combined Immunodeficiency with success whilst in 1978 haemopoietic stem cells were isolated from human cord blood. The first human embryonic stem cell line was made by James Thomson and co-workers in 1998.[1] Embryonic-like stem cells derived from blood of the umbilical cord were discovered in 2005[2] and in 2007, stem cells were isolated from amniotic fluid.[3] In 2008, autologous adult mesenchymal stem cells were used to regenerate cartilage in the human knee.[4] In 2009 induced pluripotent stem cells (iPSCs) were derived from skin cells.[5]

DEFINITION

Most multicellular organisms have stem cells. Stem cells are non-specialized, basic cells which have the potency to differentiate into the wide range of adult cells.[6] Beside their ability to differentiate into multiple cell lineages, another characteristic is that they are able to renew themselves mitotically. Importantly, they function in organismal development, growth, maintenance and repair. These functions are being vigorously studied and researched. Indeed, stem cell research is in hyperdrive and promises to offer new revolutionary therapies for various diseases and injuries.

As pointed out, stem cells are unspecialized or undifferentiated. When they become specialized to a specific cell lineage they are differentiated. The process of differentiation is still being studied but it is known that for a cell to become differentiated it must receive signals both from its inside and its outside environment. The internal cues are orchestrated by the cell's genes, whilst the external signals include physical contact and chemical cues like bioactive molecules secreted by other cells in the surrounding micro-environment. These signals interrelate to cause epigenetic changes to the stem cell's DNA thus switching on and off genes which cause the structural and functional changes responsible for the specialization or differentiation of the stem cell.

POTENCY TYPES

A stem cell can be:

- **Totipotent** i.e. capable to give rise to all types of differentiated cells, including the supporting extra-embryonic structures of the placenta.
- **Pluripotent** i.e capable to give rise to all cell lineages of all the tissues of an organism, but not the placenta e.g. embryonic stem cells[7] and iPSCs.
- **Multipotent** i.e capable of forming a range of different cell lineage.
- **Unipotent** i.e capable of generating only one type of specialised cell lineage.

VARIETY OF STEM CELLS

An easy way to classify stem cells is to divide them into early stem cells and adult stem cells. Early stem cells, also called embryonic stem cells, are isolated from the inner cell mass of a blastocyst. Adult stem cells, also called mature stem cells, are found in various body tissues, placenta and the umbilical cord.

APPLICATIONS IN THE CLINICAL SETTING

Stem cells have anti-inflammatory, antifibrotic, antimicrobial, and regenerative capabilities and thus offer the innovative possibility to be utilized to treat damaged tissues and inflammation.

HEMATOPOIETIC DISORDERS

Autologous haemopoietic stem cells (HSCs) have been used for many years to treat malignant blood diseases like lymphomas and myelomas. However, HSCs when used alone may cause adverse rejection reactions like graft versus host disease and bleeding.[8] In clinical trials, it was found that adding mesenchymal stem cells (MSCs) can help prevent rejection. This is because MSCs have immune-suppressive properties. Another asset is that MSCs secrete cytokines that help haematopoiesis and thus aid in bone marrow recovery.[8,9]

LUNG DISEASES

MSCs are also showing great potential in the treatment of chronic lung diseases such as idiopathic pulmonary fibrosis (IPF), obstructive bronchiolitis[6] and chronic obstructive pulmonary disease (COPD). Several studies on various animal models of these diseases have shown that MSCs have protective and reparative effects and these acted as platforms to go into clinical trials. Indeed, several clinical trials are ongoing with encouraging early results.

Clinical trial with ClinicalTrials.gov Identifier: NCT02216630 is a multi-center study using stem cells from adipose tissue and then delivered intravenously to patients with COPD. Here the stem cells obtained via liposuction are not manipulated and not cultured. ClinicalTrials.gov Identifier: NCT02161744, ClinicalTrials.gov Identifier: NCT02161744, ClinicalTrials.gov Identifier: NCT02645305, and ClinicalTrials.gov Identifier: NCT01110252 are some other clinical trials on COPD patients.

Some clinical trials on IPF include those with ClinicalTrials.gov Identifier: NCT01919827, ClinicalTrials.gov Identifier: NCT02013700, and ClinicalTrials.gov Identifier: NCT01385644. Research is also entering the asthma arena. Already in 2019 Zhong et al.[10] have shown that human iPSC-MSCs given systematically protect mice from airway inflammation associated with chronic allergies and thus averting fibrosis. Moreover, a possible pathway mechanism (the TGF-β1/Smad pathway) was identified of how the stem cells might have worked. Clinical trial with ClinicalTrials.gov Identifier: NCT03137199 is a phase 1 investigation on 6 participants using allogeneic MSCs derived from their bone marrow and then given via an intravenous infusion. The estimated completion date of the trial is May 2021.

CANCER

An important revelation was that MSCs home towards tumour sites. This has led to cancer cyto-therapy, whereby allogeneic MSC are used to target the tumour by deregulating the tumour microenvironment. Naïve (unmodified) and genetically modified MSC (GM-MSC) are being tested. The latter are used to deliver anti-tumorigenic molecules, but successful results are inconsistent and variable.[11]

In a study in mice, in 2018, Kooreman et al.[12] showed that iPSCs can be employed in cancer vaccines to bring about anti-tumour immunity reactions. Indeed, they proposed to use these cells for various types of cancer, prophylactically and also therapeutically. Besides, they showed that this iPSC-based cancer vaccine can be personalised. Interestingly, in April 2019, Leaps by Bayer, the investment arm of the global life sciences company Bayer, and Khloris Biosciences, a biotechnology company have joined forces to develop these novel anti-cancer iPSCs-based vaccines, which potentially can prevent and cure cancer.

Research is also studying stem cell states in various cancer types. It is known that certain molecular dependencies occur in cancer stem cells, which are responsible for the cancer to form and progress and also to be resistant to therapy. Knowing these molecular dependencies could be an avenue in cancer treatment Lytle et al. (2019)[13] studied the stem cell state of pancreatic adenocarcinoma. They found an upregulation of RORγ (retinoic-acid-receptor-related orphan receptor gamma) which steer inflammation and the differentiation of T cells. Inhibiting it caused marked decrease in growth of the cancer which lead to improved survival. Thus they are proposing the use of autoimmune drugs as a new strategic treatment.

Another avenue of using stem cells is seen in the phase I clinical trial involving 53 participants who had a recurrence of their high-grade glioma. The trial started in March 2016 and is estimated to finish in June 2020. Its ClinicalTrials.gov Identifier is NCT02192359. Allogeneic neural stem cells which are genetically modified to express carboxylase were implanted into the tumour. These cells are expected to make the tumour cells respond more to irinotecan hydrochloride treatment than if the latter is given alone. Patients are then followed short term up to 3 and 6 months and long term annually for 15 years.

NEURODEGENERATIVE DISEASES

Over the past 30 years, neurodegenerative diseases have also been the focus of regenerative cell-based research. Specifically, in Parkinson's disease (PD), Grealish et al. (2014)[14] showed how to direct human embryonic stem cells into dopamine neurons. These neurons were then used as replacement cell-based therapy in a rat model of PD. It was found that there was acceptable restoration of motor function. This provided a preclinical platform for a clinical translation study.

Indeed, a clinical study (ClinicalTrials.gov Identifier: NCT02452723) using neural stem cells was started in July 2016. Its aim is to evaluate their safety in 12 PD patients. Its completion date is June 2020. Garitaonandia et al. (2018)[15] commented that human parthenogenetic-derived neural stem cells, ISC-hpNSC, were used in this study. Parthenogenetic stem cells are derived from human egg cells and act as embryonic cells. Under MRI-guided surgery, these cells were implanted bilaterally in the substantia nigra, putamen and caudate nucleus. It is expected that the preclinical results in the animal models are reflected in this human trial.

Clinical studies using stem cells are also underway in patients with Alzheimer's diseases. One such study is ClinicalTrials.gov Identifier: NCT02600130, which was started in August 2016 and is estimated to be completed in 2020. It is a Phase I, prospective, randomized, placebo-controlled, double-blinded study designed to test the safety and efficacy of Longeveron Mesenchymal Stem Cells for the treatment of subjects with clinically diagnosed Alzheimer's disease.

In another two clinical trials (ClinicalTrial.gov identifier NCT01297218 and NCT01696591) on patients with Alzheimer, Kim et al. (2015)[16] used MSCs derived from human umbilical cord blood and injected them stereotactically into the hippocampus bilaterally and the right precuneus. The studies were safe and well tolerated and served as platform for further trials to test effectiveness.

Another use of stem cells in neurological diseases is to screen drugs. Little et al. (2019)[17] derived neurons from iPSCs and are trying to use them as *in vitro* disease models of neurological diseases. Specifically, they propose to study the underlying disease mechanisms and screen drugs as potential treatments.

Several clinical trials have also been done for amyotrophic lateral sclerosis (ALS) therapy using stem cells. One such study carried out by Sykova et al. (2017)[18] used bone marrow-derived mesenchymal stem/stromal cells (BM-MSCs) in a nonrandomized, open-label clinical trial (phase I/IIa, EudraCT No. 2011-000362-35). The stem cells harvested were expanded and approximately 15 million cells were delivered to the cerebrospinal fluid through a lumbar puncture. The authors concluded that this intrathecal delivery of BM-MSCs in ALS patients was safe and reduced ALS progression.

SPINAL CORD INJURIES

Spinal cord injury is another candidate for stem cell therapy. Geron Corporation, a late-stage clinical biopharmaceutical company, was the first to start a clinical human trial using human embryonic stem cells directing them to become oligodendrocyte progenitors, which were then used to treat spinal cord injuries. However, they stopped this trial to focus on cancer treatments. Nevertheless, Asterius Biotherapeutics, another biotechnology company, took over the trial. Indeed, they carried out a phase 1 safety trial. The trial involved patients who suffered recent cervical spinal cord injuries leaving them paralysed from the neck down. The human embryonic cell-derived oligodendrocyte progenitor cells (OPCs) were implanted directly into the cervical spine seven days after the injury took place. They concluded that the trial proved the safety of the procedure and that they observed motor function improvements in the upper limbs. In 2017, Manley et al. published a paper on the results.[19]

STROKE

Allogeneic MSCs derived from adipose tissue were used in patients who suffered ischaemic stroke.[20] The cells were injected intravenously within a 2-week time frame after the stroke. Similarly, Hess et al. (2014),[21] in a phase II double blind trial gave intravenously MSCs 24-36 hours after the stroke. No clinical benefits were reported.

In 2016, Kalladka et al.[22] reported the results of their phase 1 study called PISCES, registered with ClinicalTrials.gov Identifier: NCT01151124. They used human neural stem cells in patients (males 60 years and over) suffering from chronic ischemic stroke. This study was carried out after promising improvement was observed in a similar study in rats. In the human study, single doses of 2, 5, 10 or 20 million human neural stem cells where implanted intracerebrally into the putamen. Brain images and clinical observation were carried out over two years. They reported that there were no adverse effects and patients showed improvement in their neurological functions. The patients will be followed for eight years.

Research is also ongoing in haemorrhagic strokes. Indeed, Huang et al. (2019)[7] derived MSCs from bone marrow and delivered them intraventricularly in haemorrhagic stroke animal models. They showed improvement in behaviour and brain damage. Besides they showed that this method is safe and that the stem cells were anti-inflammatory and encouraged neurogenesis. This is promising because external ventricular drain is used to ease intracranial pressure and on occasions to administer medications in patients with intracerebral haemorrhage.

INFLAMMATORY BOWEL DISEASES

Stems cells have anti-inflammatory and immune modulatory effects. These functions are being used as a therapeutic potential in a clinical trial (ClinicalTrials.gov Identifier: NCT03299413) which started in June 2017 and ending in January 2020. Here MSCs are being either injected into the inflamed large intestine or given parentally. It is hoped that there will be a reduction or eradication of the bowel inflammation. If this clinical trial gives positive results, stem cell-based therapy may become a part of the standard treatment algorithm, particularly for refractory IBD cases.

Gregoire et al. (2017)[23] in a review article states that 50% of 200 patients who had refractory fistulas because of Crohn's disease and were injected locally with MSCs had complete response. Similar promising results were also observed in patients with luminal Crohn's disease who received allogeneic MSCs administered systemically by an infusion.

CARDIAC INFARCTION AND HEART FAILURE

Research clinical entities are proposing stem cell transplantation as an option for severe heart failure when conventional or interventional treatments fail or if heart transplant is not feasible. There is still some debate as to what stem cell type is best to use. But various clinical research entities have used MSCs for patients with severe myocardial infarction. Autologous MSCs derived from bone marrow were not effective.[24] However, MSC transplants derived allogeneically showed some benefits.[25,26] Ascheim et al. (2014)[27] also showed some benefits in patients who had MI and who were treated with intramycocardial injections of MSCs.

Evidence is showing that generally when stem cells that have a phenotype that is similar to the phenotype of the cells of the recipient tissue are used, patients fair much better. In this context Assistance Publique-Hopitaux de Paris, a Parisian university hospital trust, have conducted a phase I clinical trial named ESCORT (Clinicaltrials.gov Identifier: NCT02057900).) They used human embryonic stem cells that were driven towards a cardiac phenotype fate *in vitro* before their transplantation. Since intramyocardial injections come with documented disadvantages, they carried out the stem cell transplant during coronary artery bypass or mitral valve surgical interventions. Specifically, a fibrin gel patch embedding the progenitor cells (8.2 million interquartile range (IQR): 5 to 10 million) was placed onto the epicardium of the infarcted area and then covered with an autologous pericardial flap. In 2018, Menasche et al.[28] published their outcome stating that the trial was safe and it provided a platform for efficacy studies.

As mentioned above, MSCs have been used in the treatment of MI. Several theories have been put forward on the mechanism of action of MSCs. One is that the MSCs transdifferentiate to cardiac muscle cells. An alternative proposal is that the MSCs secrete paracrine factors such as vascular growth factors which in turn promote angiogenesis and myocardial perfusion, suppress inflammation, and inhibit apoptosis (programmed cell death). Another theory is that they augment repair by stimulating the resident cardiac stem cells to do the above. This latter scenario is more favoured.

EYE DISEASE AND INJURY

Progress in stem-cell based therapy for eye disease and injury is notable. This is due to several factors: surgery is more accessible, assessment of progress is easy, and less stem cells are needed Moreover, the untreated eye can act as a control.

Trials on macular degeneration have been done, as it is a major cause of blindness. Cotrim et al. (2017)[29] concluded that intravitreal injections of CD34+ stem cells derived from bone marrow is safe and showed promising functional improvements.

RESEARCH CLINICAL ENTITIES ARE PROPOSING STEM CELL TRANSPLANTATION AS AN OPTION FOR SEVERE HEART FAILURE WHEN CONVENTIONAL OR INTERVENTIONAL TREATMENTS FAIL OR IF HEART TRANSPLANT IS NOT FEASIBLE. THERE IS STILL SOME DEBATE AS TO WHAT STEM CELL TYPE IS BEST TO USE. BUT VARIOUS CLINICAL RESEARCH ENTITIES HAVE USED MSCS FOR PATIENTS WITH SEVERE MYOCARDIAL INFARCTION.

Stem cells are also being successfully used to regenerate damaged corneal epithelia. Regeneration of the corneal epithelium usually involves stem cells located in the limbus. However, some eye injuries can result in limbal stem cell deficiency (LSCD). When LSCD is severe or total, limbal stem cell transplantation is the best treatment. But alternative stem cell sources are also being contemplated.

Stems cells are also being investigated in cataract research and treatment. Even though known risk factors (like smoking, age, diabetes mellitus and drugs) are associated with cataract development, little is known about the pathological molecular mechanisms. Patricia Murphy et al. (2018)[30] have used pluripotent stem cells and generated light-focusing micro-lenses. These micro-lenses potentially provide avenues to study the molecular mechanisms associated with the known risk factors and to screen drugs to treat or slow cataracts.

ARTHRITIS

MSCs have immuno-suppressive and healing properties which are being exploited to treat various bone disorders like rheumatoid arthritis (RA).[2] In March 2011 a clinical study (ClinicalTrials.gov Identifier: NCT03333681) was started to treat refractory RA. The study ended in 2013. The objectives of the study were the evaluation of safety and tolerability of using MSCs and to get preliminary statistics on their effectiveness. Specifically, patients with refractory RA received intravenously, allogeneic MSCs derived from adipose tissue, which were then expanded *in vitro*. In 2017 Alvaro-Gracia et al.[31] published their results and concluded that the intravenous infusion was safe and tolerable and that they observed clinical efficacy which justified further studies.

Shadmanfar et al. (2018)[32] also exploited MSCs, this time derived from bone marrow. These stem cells (40 million) were implanted intra-articularly in the knee joint of patients with RA. They observed clinical improvements but not after 12 months of the implantation. However, the procedure, besides being safe and tolerable, was also associated with decreased use of methotrexate and prednisolone.

Similarly, Emadelin et al. (2018)[33] implanted MSCs intra-articularly derived from bone marrow to treat osteoarthritis in the knee joint. They showed that these stem cells offered noteworthy pain relief for 6 months when compared to the placebo group.

SYSTEMIC SCLEROSIS, MULTIPLE SCLEROSIS, SYSTEMIC LUPUS ERYTHEMATOSUS

Autologous haemopoietic stem cells have been used in patients with life-threatening autoimmune diseases that were resistant to conservative therapy. The stems cells acted as immunosuppressants and brought about noticeable and encouraging remissions in a high percentage of patients. The commonest auto-immune conditions treated with Hematopoietic Stem Cell Transplantation are systemic sclerosis and multiple sclerosis.

Other diseases were also treated. For example, Burt et al. (2006)[34] conducted a non-randomized clinical trial (ClinicalTrials.gov Identifier: NCT00271934) using autologous HSCs and observed improvements in the enrolled patients with systemic lupus erythematosus who had visceral dysfunctions. Further to this, Huang et al. (2019)[35] showed the effectiveness of using autologous HSCs in patients with lupus nephritis that was refractory to conservative treatments.

DIABETES MELLITUS

Autologous stem cells (ASCs) are being used as stem cell therapy in DM, because their use eliminates the risk of rejection. However, the use of embryonic stem cells raises ethical issues and is associated with high rates of rejection. Thus, in 2007, Zhao et al.[36] isolated ASCs that could make insulin from peripheral blood. A clinical trial on type 1 diabetics found that most of the participants did not need insulin injections after transplanting HSCs.[37]

Currently, ViaCyte, a US biotech company, is conducting research on type 1 diabetes mellitus.[38] ViaCyte is trying to develop two products using stem cells to replace pancreatic beta islet cells. These stem-cell based products are devices that are envisaged to be implanted subcutaneously. The implants contain embryonic stem cells that differentiate into pancreatic progenitor cells which later change to mature insulin-secreting beta-cells that respond to glucose levels physiologically.

HEARING LOSS

The clinical trial with ClinicalTrials.gov Identifier: NCT02038972 was started in January 2013 and completed in January 2017. It involved 11 children (6 weeks to 6 years old) with acquired sensineuronal hearing loss. Its aim was to try to repair or to reverse the acquired sensorineural hearing loss using autologous human umbilical cord blood administered as a single infusion. In mouse and guinea pig models, administration of human umbilical cord blood (hUCB) confirmed the regrowth of the hair cells in the organ of Corti. In 2018, Baumgartner et al.[39] published a paper with the results. Specifically, they conclude that hUCB given intravenously was safe in the participating children and there was a statistically significant reduction in Auditory Brainstem Response (ABR)[28] threshold. Simply, an ABR is a test to determine the ability of the child to hear. Certain neurological 'markers' are registered when a child's hearing nerves respond to the sounds. Thus these markers roughly indicate the child's hearing level. Thus, a reduced ABR result in the trial is a positive and promising finding.

OTHER

Stems cells are also being utilized in basic developmental biology, helping researchers to understand cell types and tissues during the development of the embryo. Specifically, developmental biology studies how genes steer cell growth through differentiation of cells from the stem cell stage onwards. Thus, ultimately it can help to find new ways to be used in regenerative medicine.

Another role of stem cells is in drug development. In short, stem cells are being utilized to enable quick screening of drugs or chemicals, thus reducing testing on animals. Besides such testing using human stem cells addresses the fact that approximately 70% of drugs tested on animals fail during clinical trials, either because they have no effect or due to toxicity (mostly on the heart and liver). Moreover, stem cells can generate cell types that are hard to attain, like neurones, on which testing can be carried out. Another innovative stem cell application in this area is to harvest stem cells from individuals to help in designing personalized medicines. It is well known that there is great variation in drug liver metabolism probably due to differences in liver enzymes such as cytochrome P450 enzymes. iPSCs have the potential to remedy this. Indeed, with iPSC technology, patient-derived iPSCs can be utilized to generate liver cells (and other cell types) and these can then be used for toxicity testing. Thus it is clearly evident that stems cells have an important potential in the development of safer, cheaper, and better drugs.

Stem cells are also being researched in gene therapy. For example, theoretically, HSCs isolated from the blood, can be cultured and any defect corrected by gene editing. Subsequently, the patient receives chemotherapy which eradicates all resident HSCs; this is then followed by a transfusion of edited cells.

CONCLUSION

Stem cell research is catalysing a revolution in medicine. It has the potential to transform algorithms of conventional treatment, especially in many distressing and refractory diseases. The public is already increasingly turning to medical professionals asking for this novel treatment especially as anti-aging and cosmetic treatments. But misconceptions about stem cells as being miracle cells that can cure all ailments are flourishing. As discussed, encouraging results have been observed from

several clinical trials. But it is still early and further research through regulated clinical trials are needed to ascertain their efficacy and safety in medical applications. Moreover, before stem cell therapy is used clinically, one needs to fully understand the behaviour of stem cells upon transplantation and the mechanisms involved when they interact with the diseased or injured micro-environment.

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