Mesenchymal stromal cells: promising cell therapy candidates

Mesenchymal stromal cells (MSC) are increasingly moving into the spotlight as the beacon of hope for somatic cell therapies. The biomedical research community is currently carrying out more than 300 clinical trials to investigate their suitability for a broad range of indications.

Prof. Dr. Hubert Schrezenmeier, professor of transfusion medicine and medical director at the Institute for Clinical Transfusion Medicine and Immunogenetics (IKT) in Ulm, is involved in four clinical trials that are being carried out in cooperation with Ulm University Hospital. Schrezenmeier believes that the broad range of applications makes the fibroblast-like MSC excellent candidates for cell therapy.

MSC – what does it stand for?

Around four to five years ago, MSC was an acronym for mesenchymal stem cells. However, current knowledge suggests that the term mesenchymal stromal cells is more appropriate for two reasons: the cells’ differentiation ability is not as good as previously thought and their self-renewal capacity has not yet been proven. The term mesenchymal stromal cells (MSC) encompasses cells found in more than a dozen different human tissues and organs, such as bone marrow, adipose tissue and umbilical cord blood. It is difficult to differentiate MSC from other cells as a specific MSC marker has not yet been identified. The accepted professional procedure is therefore to classify cells as MSC if they show the following properties: they adhere to plastic, can differentiate into osteoblasts, adipocytes and chondrocytes under standard culture conditions, and express certain surface antigens and not others.

Schrezenmeier and his team have developed a production process for GMP-grade MSC as part of several EU projects. Schrezenmeier is not concerned about the cell heterogeneity. “When the cells are kept in culture for two to three weeks, they develop as a uniform population or subpopulation that is free from lymphocytes, haematopoietic cells and endothelial cells,” says Schrezenmeier explaining that according to current knowledge MSC are characterized by in vivo, but not ex vivo, heterogeneity.

Immunomodulation and regeneration
MSC have the potential to suppress the immune system and to differentiate into chondrocytes (cartilage cells), osteoblasts (bone cells), adipocytes (fat cells) and potentially also other cell types. They are also thought to be able to stimulate the differentiation and proliferation of organ stem cells. This potential makes them good candidates for various applications, including for example the immunomodulatory therapy of autoimmune diseases (i.e. diseases characterized by excessive inflammatory reactions such as Crohn’s disease and rheumatoid arthritis). Graft-versus-host disease (GVHD), a condition that can occur after an allogeneic stem cell transplant, is one of the best studied diseases and there are a large number of clinical trials investigating the prevention and treatment of the disease. Schrezenmeier explains that a number of studies have already documented the clinical efficacy of MSC for the prevention of GVHD.
Great bone formation potential

Numerous clinical trials investigating the use of MSC for controlling problems of organ transplantation, cardiac diseases and liver cirrhosis are also being carried out. Schrezenmeier believes that the greatest potential of MSC lies in the formation of bone. Several dozen clinical trials are currently being carried out to investigate the use of MSC for the treatment of bone and cartilage defects.

There are no other therapies besides MSC currently available for some of the indications under investigation. In addition, MSC can also be used alongside other cell therapies, for example they can be cotransplanted with haematopoietic stem cell transplants.

As far as regenerative therapies are concerned, MSC occupy a special place because they are easily accessible (they can easily be isolated from bone marrow and adipose tissue, for example), are easy to cultivate and can be used for a broad range of applications. However, it will take several more years before comparative phase 3 trials will have documented the efficacy of MSC in treating regenerative indications.

No risks discovered yet

Ongoing or completed clinical trials have not yet detected any adverse side effects, any acute infusion-dependent toxicity or autonomous proliferation of the cells (tumorigenicity). However, MSC therapy has been discredited by two publications that had carried out in vitro studies and claimed to have discovered that MSC underwent transdifferentiation into epithelial tumours. The two papers have since been withdrawn as the original data had become unusable due to laboratory contamination.

Schrezenmeier’s team has been granted permission to carry out four different clinical phase II trials focusing on the use of MSC for the regeneration of bone in different indications. The required preparations are currently being produced for use in three clinical trials. It is expected that the recruitment of around 30 patients for one of the trials will be completed by the end of the year, and
the recruitment of the patients for the other two trials by mid-2015.

The field of MSC research has a long way yet to go. Working with his colleagues from Ulm – Karin Scharffetter-Kochanek (Department of Dermatology at the University of Ulm) and Anita Ignatius (Institute of Orthopaedic Research and Biomechanics) – in an EU-funded project, Schrezenmeier discovered a previously unknown physiological function of MSC in mice. The researchers found that the application of MSC accelerated the wound-healing process and reduced tissue fibrosis (Qi, et. al.). This finding substantiates the assumption that MSC have a paracrine function.

Issues of persistence, biodistribution and dosage still need to be addressed

The mechanisms with which MSC affect their environment are not yet understood in detail. A number of EU projects are investigating these fundamental aspects with regard to the therapeutic application of MSC. It has been shown that the biodistribution of MSC depends on the way the cells are applied. When applied intravenously, almost 90 percent of the cells initially make their way to the lungs; after a few days, the cells home in on different organs, mainly the liver, spleen and bone marrow. Small numbers are also found in the brain. Schrezenmeier believes that the fact that the cells are initially trapped in the lungs is not necessarily a therapeutic disadvantage and uses a myocard regeneration model to explain that MSC factors such as TSG-6 exert their regenerative effect on the heart even from their remote location in the lungs.

In the clinical trials that he has carried out, Scherzenmeier has applied MSC directly into the lesion site. Preclinical investigations that studied the biodistribution of MSC have shown that the cells did not migrate beyond the lesion. Questions relating to the persistence of MSC in the body are currently
difficult to answer as previous and ongoing clinical MSC trials do not involve a marker substance. Such substances are avoided in order to reduce the number of manipulation steps that can compromise the risk profile of MSC-based medicinal products.

Little information is yet available about the dose of MSC required for treating the indications investigated. GVHD trials involving the systemic administration of MSC found that a dose of two million cells per kg body weight was best. Trials with several hundred patients undergoing GVHD therapy have not revealed any adverse effects. That said, further trials will have to be carried out in order to assess the most effective MSC dose.

GMP-compliant production made in Ulm

Over the last four years, Schrezenmeier and his team have carried out EU-funded projects in which they focused on the production of GMP-grade MSC for clinical application. In 2013, the researchers were given the go-ahead from the relevant authorities for the procedure they had developed. Three different MSC sources (bone marrow, adipose tissue and umbilical cord blood) were investigated; umbilical cord blood proved to be too complicated for pharmaceutical implementation. Since there was more preclinical data available from bone marrow-derived MSC, and no production-relevant differences from adipose tissue-derived MSC were known, the consortium decided to use bone marrow as the MSC source.
Since MSC are a relatively infrequent type of cells – only one in 10,000 to 100,000 cells in the bone marrow is an MSC – they need to be expanded outside the body in order to generate clinically effective doses. Biphasic MSC proliferation comprises 17 population duplications. To begin with, 4,000 cells are seeded on an area of one square centimetre; around 50,000 cells per square centimetre are needed to produce a dense cell lawn. Since MSC can only grow effectively by adhering to a matrix, sufficient matrix area needs to be provided, and this is quite a complex process. 200 million cells are required for a clinical dose, which requires a cultivation area of two square metres. There is sufficient room to grow such a large number of cells in the six GMP units in the buildings located on the Ulm University Eselsberg campus, where stackable cell culture chambers are used for growing cells.

Thrombocyte lysate is a good growth medium

The researchers from Ulm have since found out that blood platelet lysate is an excellent medium for growing MSC. In this area too, much has been achieved over the last four years: it used to be standard laboratory practice to grow MSC in culture media supplemented with foetal bovine serum. MSC did not grow well in other media. However, foetal bovine serum is not suitable for GMP production due to the risk of contamination with infectious agents. Thus, information that MSC grow well in thrombocyte lysate – a substitute for foetal bovine serum that is approved for application in human patients – was excellent news, in particular as the lysate is produced in the Blood Donation Centre in Ulm.

“In the end, we ran a quality assessment on a relatively standardized substance of human origin for the production of MSC. Although not all of its molecular constituents are known in detail, we nevertheless decided to use thrombocyte lysate, mainly for practical reasons. Many aspects support the suitability of thrombocyte lysate for the applications envisaged,” says Schrezenmeier. However, he is nevertheless very interested in finding out what exactly promotes the growth of MSC.

The production of clinical MSC doses is very costly, which immediately raises the question as to how such therapies can be financed. With ongoing clinical trials in mind, Schrezenmeier does not see the cost-benefit ratio as at all disadvantageous, particularly in cases where these cells would be used for treating common indications, for example fractures of long bones that do not heal (femur or tibia fractures; accident victims) or avascular or aseptic necroses (painful bone diseases of the femoral head).

Further reading:


