In Depth Article

Mesenchymal Stem Cells (MSC) from the Wharton's Jelly of the Umbilical Cord: A New Therapeutic Opportunity.

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Introduction

Umbilical cord is an important source of stem cells, whether hematopoietic, and thus obtainable from placental blood, or mesenchymal, easily obtainable from the tissue of the cord itself. In this paper, we focus our attention on the mesenchymal stem cells present in the umbilical cord and which can be drawn from the Wharton's jelly, the matrix in which they are found (UCMSCs). Many studies conducted in recent years have shown that these cells have an enormous therapeutic potential for cell therapy. In particular, we want to focus on the potentials of this biological material, which can be easily obtained in the delivery room, and which entails no problems whatsoever, of either a medical, or, an ethical nature. Also worth noting, is the ease of obtaining this neonatal biological material, which is more primitive and uncontaminated than other sources of mesenchymal stem cells (MSC), such as those that can be drawn from bone marrow or fatty tissue. UCMSC, are also a low cost source for the community, since they would otherwise be disposed of as waste in the delivery room.

Umbilical cord blood collection.

Umbilical Cord Samples.

Mesenchymal Stem Cells

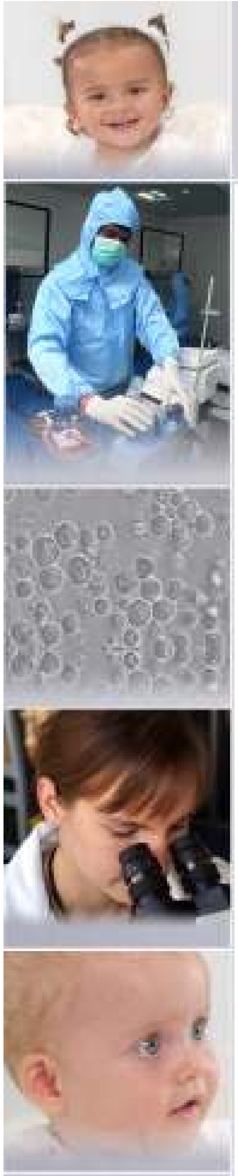
Mesenchymal stem cells (MSC) are a type of multipotent adult stem cell. MSCs are immature, and, like haematopoietic cells, which we find in umbilical cord blood, have a good capacity to renew themselves and differentiate continuously into specialized cells of the various human tissues. MSC's were originally described as early as the 1960's in animal experiments on embryo's, but it was not until the 1980's that the concept of common MSC's in adult tissues was confirmed. Source, and availability of MSC's has, however, taken some time to work out. While some MSC's can be found in many organs, those organs are not realistic targets for harvesting them without resulting organ damage. MSC's have also been sourced in bone marrow (1- 4 per 100,000 nucleated cells), or, in a smaller numbers, in the umbilical cord blood itself. They are also present, in much smaller concentrations in many adult human organs, and neonatally in foetal liver and amniotic fluid. Compared to these sources, however, MSC's can be found in more considerable numbers in Wharton's jelly, the matrix of the umbilical cord, and in the placental tissues. The added advantage of Wharton's Jelly is also that there is no risk in the harvesting procedure.

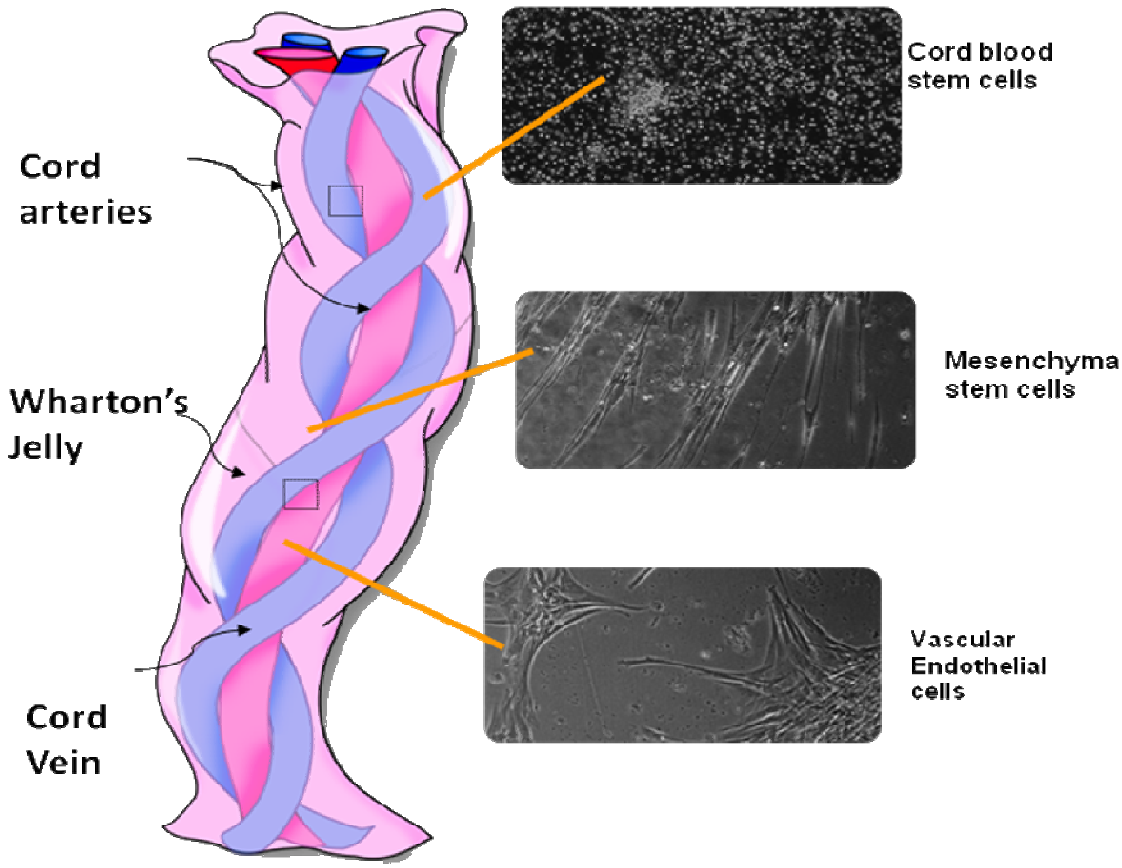
Pictured here are pieces of Wharton's Jelly.

MSCs can, like amniotic fluid cells, be easily expanded in vitro in the presence of serum alone, without the addition of growth factors, or in defined conditions without serum support at all.

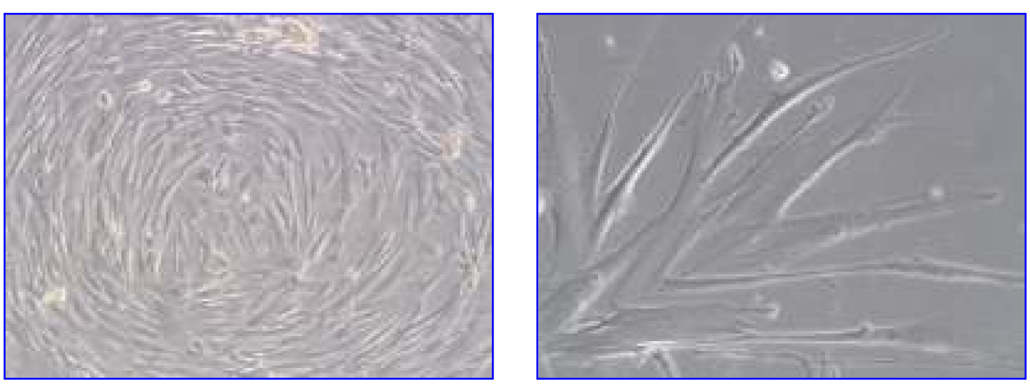
In bone marrow, MSCs play an essential role in the regulation of proliferation and differentiation of the myeloid cells and lymphoid cells, both B and T. For this reason they initially focussed the attention of researchers for their use in cases of allogeneic transplant of bone marrow with hematopoietic stem cells (HSC). MSCs, added to HSCs, have been used to support an immunosuppressive action that reduces the incidence and severity of graft-versus-host disease (GVHD) in some patients and makes it possible to use lower doses of pharmacological immunosuppressors. The use of MSCs, together with HSCs, has also shown a better engraftment and reconstitution of the bone marrow, including the T and B lymphoid lineages.

Experimentally, MSCs are identified by the expression of a number of surface markers, including STRO-1, SB-10, SH3, and SH4 anigens as well as Thy-1 (CD 90), TGF-β receptor type III endoglin (CD 105), Hyaluronic acid receptor CD-44, Integrin α1 subunit CD 29, CD 133, P75LNGFR and activated leucocytes-cell adhesion molecules (ALCAM CD 166).

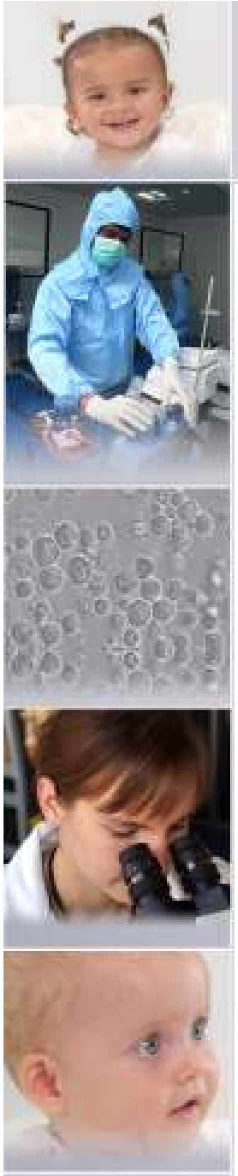




MSC are negative for the hematopoietic markers CD 34, CD 45 and CD 14. SH3, SH4 and STRO-1 antibodies recognize antigens that are present on mesenchymal cells but not on hematopoietic cells. However, these are not expressed exclusively to MSC and are found on other cell type. To date, there is no one single marker or combination of markers that has been shown to be specific and exclusive to MSCs therefore it remains a challenge to isolate MSC specifically from a mixed cell population but a combination of antibodies can be used to characterize MSC.



Pictured here are Mesenchymal Stem Cells growing from Umbilical Cord.



The potential of human MSC's for organ regeneration.

The promise of these extraordinary cells isolated from Wharton's jelly at the time of birth give rise, using particular culture media, to colonies of multipotent cells capable of generating, both in vitro and in vivo, numerous types of tissue cells (nerve, skin, blood, bone, cartilage, fat, muscle, skeleton, heart, kidney, endothelium, liver, and pancreas cells). This useful phenomenon of multi-differentiating capacity has been interpreted as an expression of the "plasticity" property of the MSC's. Therefore, in degenerating conditions, of certain pathological or tissue damage conditions, these cells could take differentiative routes other than their normal physiological ones. Such an interpretation appears to find confirmation in the positive clinical results obtained by various research centres with the administration of autologous (same patient as donor) MSCs in patients suffering from pathologies such as myocardial infarction, bone necrosis, bone fractures, meniscal tear, type 1 diabetes, acute necrosis of the brain, obstructive arteriopathy, and chronic toxic hepatopathy.

The reasons for MSC plasticity might be connected with the presence of a small subgroup of cells endowed with a much higher, more important differentiative potential. In recent years, McGuckin research group (Newcastle and Lyon) showed that it was possible to isolate, from Wharton's jelly, a more highly pluripotent group of cells which could differentiate reproducibly to the neural lineage including neurons, oligodendrocytes, and astrocytes.

Wharton's jelly is thus an important source of both mesenchymal stem cells and multi-pluripotent stem cells. Whether the lineage is the same for both groups is not yet known, but the usefulness of the Umbilical Cord was therefore proven. In degenerative diseases and in numerous pathologies, there is an accompanied loss of specialised cells in organs and tissues, resulting in functional failure. This can lead to a very high healthcare cost to deal with the ongoing symptoms and problems of the disease, with no ultimate underlying treatment available. The lower quality of life is also an issue, potentially leading to premature death. For this reason, developing new treatments capable not only of preventing, but also treating the pathology responsible for the tissue damage and also of restoring the structure and function of the damaged tissues and organs, is of great social importance.

Regenerative medicine is the term now given for what is considered the "final frontier" of research: to regenerate the damaged tissue in a way that guarantees restoration of the function of not one, but numerous specialized tissues such as: liver, pancreas, myocardium, prostate, bones, cartilage, endothelia, heart valves, bladder, auditory system, visual system, adrenal gland, skin, and more, through the transplant of cells, in order to provide new therapeutic treatments for pathologies or lesions that conventional medicine and pharmacological therapies are not able to treat effectively. Now that Wharton's Jelly has been found to contain "regenerating" MSC's, a vast therapeutic potential now opens up. The Umbilical Cord, which is normally discarded after birth, may now be considered useful for later in life, if it can be stored. Many researchers have now confirmed good levels of MSC's in Umbilical Cord. Many of the studies on umbilical cord stem cells have focused on tissues close to the blood supply, but research has also shown that different parts of the cord are useful for different sources of stem cells.

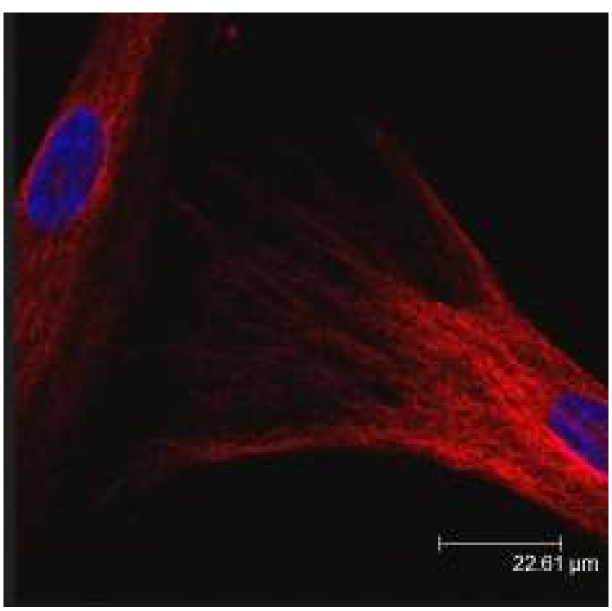
In cord blood, the frequency has been quoted as 2 per 200 million, but the frequency actually varies from child to child considerably. For Wharton's Jelly derived cells the frequency rises to 1 per 300 cells harvested.

Potential for storing Umbilical Cord.

Since availability of MSC's from different organs can be a problem, one of the most realistic sources in an adult human was considered to be Bone Marrow. Fat related adipose tissue was also considered to be a source. These sources do not require surgery that is considered to be life-threatening, but requiring a surgical procedure and a certain level of anaesthetic. Some pain can also be involved. Therefore, the potential to store your Umbilical Cord, which is taken at no risk to the child and stored for later life, was considered a true potential worth pursuing.

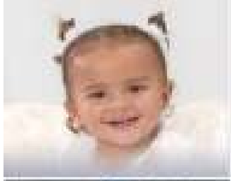
In 2007, The Cryo-Save group, Europe's largest stem cell bank, undertook an ambitious research and development plan to find a way to not only store the Wharton's Jelly, or just the MSC's but indeed the whole Umbilical Cord, in a way that would allow potential stem and progenitor cells resident in the cord to be maintained for later use. Working with leading research centres in Europe, including university hospitals, and the laboratory of their Scientific Director, they became the first in the world to offer a reproducible service to store Umbilical Cord.

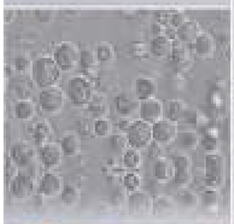
Storing a physical tissue, rather than storing individual separated cells, requires novel procedures for processing, freezing and thawing. It also has to be carried out in a way which complies with the European Directives for the use of cells and tissues. The procedure, allows multiple sections of cord to be frozen for later use, enhancing the availability of the cells for later potential therapies. Working with leading scientists, the team were able to produce a protocol which allows the tissue to be frozen and then thawed out whilst still allowing the stem cells to be harvested in high quality. The Scientific Director's team were able to show that the stem cells could go on to differentiate into bone, fat, cartilage, neural cells and liver amongst others. In doing so, Cryo-Save has been able to show that it can not only freeze the tissues of the Umbilical Cord, but also to unfreeze them and make them useful.

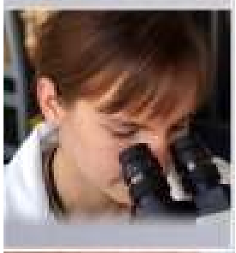


Left – Neural Cells growing from an original Umbilical Cord.

In a three year project, the study of the cells growing in laboratory culture demonstrated the useful-ness of Umbilical Cord. Now, Cryo-Save works with leading centres who are developing the cells for therapy, not least in heart and liver disease.







Cryo-Save's latest venture to support research and clinical development is with Professor Colin McGuckin and his team in Lyon at the Cell Therapy Research Institute. This group were the pioneers who first showed that Umbilical Cord Blood contained extremely early stem cells with some characteristics in common with embryonic stem cells, but without the ethical dilemmas and also were the pioneers who first made hepatic, neural and pancreatic tissues from cord blood. Following this they went on to develop similar tissues from the physical Umbilical Cord itself, which now, together with the Cryo-Save process allows, regenerative medicine to move to the next level. Professor McGuckin is also one of the founders of the Novus Sanguis charitable research consortium which was founded in 2008 to raise money to bring adult stem cells faster into the clinic via responsible regenerative medicine. Together with Cryo-Save they are now supporting the development of clinical networks to promote stem cell therapies.

The protocols for the isolation of MSCs from Wharton's's jelly have ended, as have the protocols for their in vitro culture and storage. The cell culture methods envisaged will permit basic scientific research on UCMSCs.

Our concept is for both the umbilical cord blood and the umbilical cord mesenchymal stem cells to be collected at birth and preserved in our laboratories to permit in the years to come a new approach for the prevention of degenerative diseases and future therapeutic applications. Whereas umbilical cord blood is already a familial and autologous therapeutic solution in oncology and hematology, MSCs are a valid alternative in cell therapy and regenerative medicine.

Conclusion.
Umbilical Cord is a rich source of a stem cell often called "Mesenchymal". The potential for this group of stem cells to differentiate into many different tissues such as bone, cartilage, fat, liver, neural, pancreatic and muscle has been shown, and the cells are also considered to have regenerating potential for certain degenerative conditions. Storing these cells is now considered possible from the Umbilical Cord by novel freezing technologies. The use of mesenchymal stem cells is also being proven through a worldwide network of clinical trials not least in heart, bowel, immune system and degenerative illnesses.

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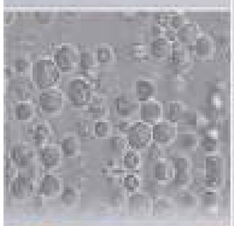

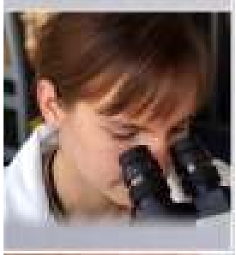

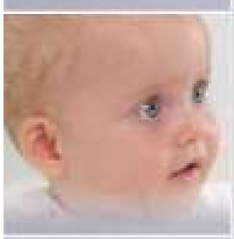

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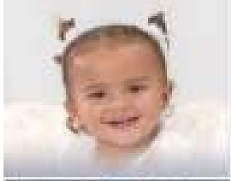

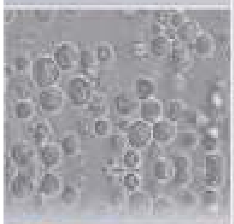

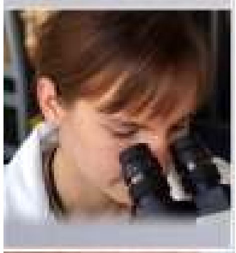

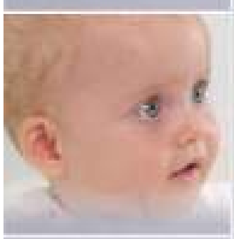

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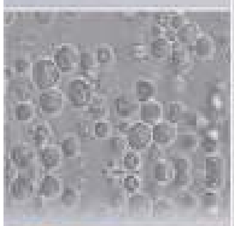

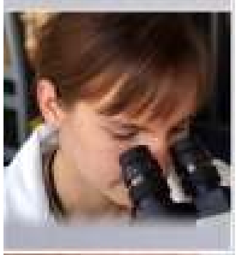

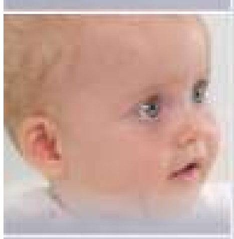

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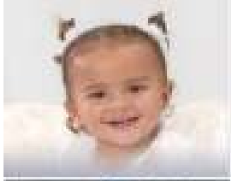

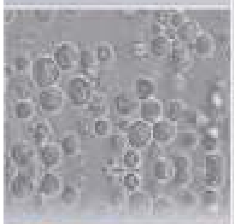
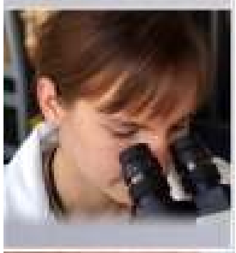
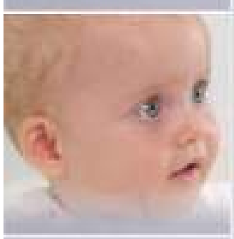

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