Meeting report of the first conference of the International Placenta Stem Cell Society (IPLASS)

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Abstract

1. Introduction

For many years immunologists have been intrigued by the placenta due to the fact that this organ contributes to the maintenance of fetomaternal tolerance. Nevertheless, the mechanisms underlying maternal acceptance of the fetal allograft are not yet entirely understood and remain a major challenge.

In 1953 Medawar hypothesized that: i) there is a physical separation between the mother and the fetus; ii) the fetus is antigenically immature, and iii) that the mother possesses an immunological inertness [1]. Since that time, research advances have led to a revision, and in some instances, a retraction of these assumptions. New data have emerged that suggest that several mechanisms may contribute to the induction of maternal-fetal tolerance [2,3]. Considering the important role played by the placenta in modulating maternal immune responses, placental cells (*e.g.* cells isolated from amnion and chorionic fetal membranes) are likely to be ideal tools for cell based therapeutic applications.

With these concepts in mind, the keynote lecture of Dr. Diana W. Bianchi, and the first two sessions of the meeting were dedicated to cutting-edge research on mechanisms that contribute to or are correlated with fetomaternal tolerance and transplant immunology. The subsequent sessions focused on the biological and immunological properties of cell populations that can be isolated from different placental regions. The meeting participants also explored the characteristics of these cells that may make them valuable candidates for therapy. They also addressed research advances with a view to potential clinical applications.

1.1. Fetomaternal tolerance and transplant immunology

1.1.1. Fetal-maternal cell trafficking

During pregnancy, transplacental trafficking of cells from the fetus to the mother leads to a persistence of fetal cells in the maternal circulation and/or tissues without evidence of graft rejection or graft versus host disease (GVHD) [4].

A pioneer in the field of fetal-maternal stem cell trafficking, Dr. Diana W. Bianchi of the Mother Infant Research Institute at Tufts Medical Center, USA, graciously delivered the keynote speech

on “Fetal cells in the adult female following pregnancy: an under-appreciated source of progenitor cells.” This lecture highlighted her landmark findings of fetal cell microchimerism. The Bianchi laboratory was the first to demonstrate the long-term persistence of fetal $CD34^+$ $CD38^+$ nucleated cells in maternal blood [5]. Subsequently, using fluorescence *in situ* hybridization and Y-chromosome-specific probes, her laboratory showed that fetal cells also persist and trans-differentiate in maternal organs [6]. Most notably, the demonstration of a male thyroid follicle in a surgically-removed thyroid specimen from a post-partum woman suggested that fetal cells had stem cell-like properties [7] and could repair maternal organs. Although many autoimmune diseases are associated with fetal cell microchimerism, Dr. Bianchi's presentation focused on the naturally acquired pregnancy-associated progenitor cells that may have regenerative properties [8] Using a transgenic mouse model that expresses green fluorescent protein, she described her laboratory's efforts to understand the genes, cell surface antigens, and functions expressed by fetal cells in murine maternal organs [9]. Dr. Bianchi elegantly captured the intimate fetomaternal interactions at both a cellular and molecular level. She offered insightful research directions on how to advance scientific and clinical applications of these fetal cells.

1.1.2. Fetomaternal tolerance

Several mechanisms have been proposed to explain fetomaternal tolerance and immunomodulation. Among these mechanisms, regulatory T-cells (Tregs) can suppress maternal allo-responses targeted against the fetus [10].

In his presentation entitled “Regulatory T-cells in pregnancy,” Dr. Alexander G. Betz from the Medical Research Council in Cambridge, UK, and his colleagues explored the possibility of using Tregs from pregnancy for the therapy of autoimmune diseases. These cells show marked proliferation in pregnant women. They may even contribute to clinical improvement of autoimmune conditions in pregnant females. This response seems to be limited to the period of the pregnancy. Investigating the behavior of polyclonal Tregs can provide insights into potential clinical applications in autoimmune diseases.

Another mechanism involved in protecting the allogeneic fetus from maternal T-cells is the activity of the tryptophan catabolizing enzyme IDO (indoleamine 2,3 dioxygenase) [11]. Dr. Andrew L. Mellor of the Immunotherapy Center at the Medical College of Georgia, USA, addressed the potential use of IDO as an immunoregulatory drug in his speech “Indoleamine 2,3 dioxygenase (IDO): a pivotal counter-regulatory switch at sites of inflammation.” IDO has been shown to have a significant role in the regulation of T-cell mediated immune responses. Importantly, fetal tissues were actively rejected by maternal T cells only when fetal tissues were allogeneic. This revealed that IDO was essential in wild-type mice to protect fetal allografts [12]. Genetic ablation of IDO did not show the same results. This suggested that other mechanisms are involved in regulating maternal T-cell mediated responses [13]. In humans and mice, some dendritic cells (DCs) express IDO in response to inflammatory stimuli, which causes T-cell suppression [14]. This effect is also seen in some pathogens that lead to immunologic attenuation and reduced pathogen specific immunity. In mice, tumor growth promoters stimulate DCs to express IDO. Genetic ablation causes enhanced anti-pathogen and tumor response, especially when coupled with immunization strategies. Dr. Mellor will further investigate the role of IDO in T-cell and immune response regulation and its potential therapeutic applications.

Mesenchymal stem/stromal cells (MSCs) are multipotent, non-hematopoietic cells, capable of differentiation toward multiple cell lineages [15]. The relationship between MSCs from the fetus or mother and their role in fetomaternal tolerance was discussed by Dr. Sicco Scherjon of the Department of Immunohematology and Bloodbank at Leiden University Medical Center, Leiden, Netherlands, in his presentation "MSCs and the possible role in fetomaternal tolerance: a paradigm for transplantation tolerance." Growth characteristics of maternal and fetal MSCs do not differ [16]. The low immunogenicity of these cells was realized after engraftment in immune-competent sheep. These properties are partially explained by the fact that MSCs do not express HLA class II and co-stimulatory molecules in vitro, Both autologous and allogeneic MSCs inhibit the mixed lymphocyte reaction [17]. Using a trans-well technique, inhibition was shown to be both by cell-to-cell contact and the production of immunosuppressive cytokines by MSCs. Dr. Scherjon viewed this to be of potential therapeutic value in preventing solid organ rejection.

1.1.3. Transplantation tolerance

A major obstacle in transplantation is GVHD [18]. Dr. Kathryn J. Wood from the University of Oxford, UK, used her talk "Translating transplantation tolerance in the clinic: where are we, where do we go?" to address the current research progress in immunological tolerance in transplantation. Her emphasis was on cutting-edge approaches that allow deletion and immunoregulation to reduce or prevent immune response to donor antigens. In particular, Dr. Wood presented her series of investigations demonstrating the unique role of interferon-gamma (IFN-γ) in the functional activity of $CD25^{+}CD4^{+}$ Tregs [19]. These discoveries open the door for new immunological tolerance-based therapies in transplantation medicine.

1.1.4. MSCs and transplantation tolerance

Finding a suitable cell source, likely with low immunogenicity and immunomodulatory properties, is an important factor for successful transplantation outcome. In her presentation, "Immunomodulation by mesenchymal stem cells and clinical experiences," Dr. Cecilia Götherström from the Karolinska Institute, in Stockholm, Sweden, explored the possibility of using MSCs isolated from fetal tissues. Fetal MSCs have low immunogenicity and high differentiation potential in combination with a low in vivo oncogenic risk [20,21]. These cells do not induce an immune response and differ in many ways from adult cells that derive from bone marrow (BM). The differences include a higher capacity for expansion, and a higher differentiation ability; these cells more readily differentiate into bone [22]. This is believed to be due to the more primitive nature of the cells. They have longer telomeres, higher telomerase activity and exhibition of pluripotent embryonic markers, such as Nanog and Oct-4 (octamer-binding transcription factor 4) [20]. Fetal MSCs also have potential future applications. In prenatal transplantation for type III osteogenesis imperfecta, allogeneic fetal MSCs migrated from the intravascular space and demonstrated site-specific differentiation in bone and long-term persistence in an immunocompetent recipient across major histo-incompatibility barriers [23].

1.2. Recent pre-clinical and clinical studies using placenta-derived cells

1.2.1. Rationale and advances in pre-clinical studies

Human amniotic membrane (AM) has a long history of clinical utility. Experimental and clinical studies have demonstrated that AM transplantation promotes re-epithelialization, decreases inflammation and fibrosis, and modulates angiogenesis [24]. The applications of AM in surgery include treatment of skin wounds, burn injuries, chronic leg ulcers, head and neck surgery, and prevention of tissue adhesion in surgical procedures [24]. These ongoing applications are also enriched by studies aimed at expanding the use of AM-based therapy for other pathological conditions [25].

The use of the entire AM, was addressed by Dr. Susanne Wol-bank from the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Center in Vienna, Austria. In her presentation, "Suitability of amniotic membrane and cells thereof for tissue regeneration approaches", Dr. Wolbank discussed her evaluation of the differentiation potential of the entire AM *in toto* [26]. In vitro culture of AM under conditions that induce osteogenesis was shown by immunohistochemistry to result in mineralization and osteopontin expression by its sessile cells, coupled with a significant rise in calcium content and mRNA expression of multiple bone specific proteins. Taking into account these positive results, Dr. Wolbank concluded that stem cells within human AM can successfully differentiate along the osteogenic pathway, a finding she believes may enhance or replace current bone tissue engineering protocols.

The talk from Dr. Ornella Parolini from the Centro di Ricerca E. Menni, Fondazione Poliambulanza – Istituto Ospedaliero in Brescia, Italy, entitled, "Placenta generalities: structure and immunomodulatory properties- in vitro and in vivo studies", initiated an in-depth discussion regarding the structure of the placenta, and the biological and immunomodulatory properties of the different cell populations that can be isolated from placental tissues [2,3,25]. She addressed the use of placental cells for the treatment of different pathological conditions, mainly for those involving inflammatory and fibrotic mechanisms. In previous in vitro studies, Parolini's team demonstrated that AM-derived cells do not induce a T-cell response, actively suppress T-cell mediated immunity, and block differentiation and maturation of monocytes [27–29]. By in vivo studies, this group also showed that amniotic and chorionic cells can successfully engraft long-term in newborn swine and rat models. This indicates active tolerance of these cells [27]. After both allogeneic and xenogenic transplantation into mice with bleomycin-induced lung injury, fetal membrane-derived cells reduced lung fibrosis, despite the rare presence of donor cells in host lungs [30]. Successful outcomes were also obtained when fragments of the entire AM were applied as patches to treat rats with cardiac ischemia and rats with liver fibrosis induced by bile duct ligation [31,32]. In all of these applications, the beneficial effects observed seemed most likely related to bioactive molecules produced by placenta-derived cells that act by paracrine actions to promote the repair of host tissues.

It is therefore evident that the AM is an attractive, high-throughput source of stem cells, with features that encompass broad differentiation potential, important immunomodulatory properties and paracrine activities [25].

These concepts were reinforced by Dr. Ursula Manuelpillai of the Monash Institute of Medical Research, Monash University, Victoria, Australia, in her presentation entitled "Human amniotic epithelial cells (hAECs): a cellular therapy for inflammatory diseases?". Dr. Manuelpillai highlighted her group's recent findings in experimental mouse models of lung and liver fibrosis using bleomycin and carbon tetrachloride (CCl_4) treatments, respectively. In the lungs of

bleomycin-injured mice, a small percentage of injected hAECs persisted for longer periods compared to Wharton's jelly-derived MSCs. These cells produced surfactant proteins A-D following transplantation. This suggests hAECs differentiate into type II alveolar epithelium [33,34]. Overt immune responses to the xenotransplanted cells were not evident. Mice with lung and liver injuries that were treated with hAECs showed reduced apoptosis, inflammation, and fibrosis [34,35]. Dr. Manuelpillai believes that immunosuppressive mediators from the hAECs could modulate the activity of T-cells, DCs, and natural killer cells. Decreased fibrosis may be due to a reduction in pro-fibrotic cytokines, and induction of collagen degrading matrix metalloproteinases in the injured lungs and livers. hAEC treatment may also inhibit monocyte recruitment. In vitro studies showed that treatment with hAEC-conditioned medium did not stimulate proliferation of collagen depositing hepatic stellate cells, but enhanced apoptosis and altered cytokines secreted by these cells. She concluded that hAEC transplantation may be useful for targeting tissue inflammation, and in some instances, may also contribute to cell replacement.

Dr. Francesco Alviano and his colleagues of the Department of Histology, Embryology and Applied Biology at the University of Bologna, Italy, explored the use of AM-derived stem cells in treatment of diabetes mellitus. His speech was entitled “Amniotic membrane-derived stem cells and pancreatic islet-cell differentiation.” Dr. Alviano chose the AM as the source for these cells due to the ability of hAECs to express beta cell-markers, as well as the angiogenic and immunomodulatory properties of the AM-MSCs [36,37]. He compared the in vitro pancreatic differentiation of hAECs to that of human derived pancreatic cells. His group confirmed the pancreatic differentiation ability of hAECs. These cells exhibited increased glucagon and insulin expression. Preliminary studies in vivo using streptozotocin-diabetic rats showed that rats treated with hAECs and pancreatic-MSCs underwent a partial and transient correction of the altered phenotype.

Dr. Mark L. Weiss and colleagues in the Department of Anatomy and Physiology at Kansas State University, USA have been investigating the hypothesis that Wharton's jelly-derived MSCs may have clinical application in GVHD. In his presentation “Wharton's jelly mesenchymal stromal cells (WJCs) as immunoregulators in allogeneic transplantation,” Dr. Weiss outlined the status of current clinical trials that have used MSCs for treating or preventing GVHD. Dr. Weiss then outlined work that revealed plasticity in the immune properties of MSCs in response to cytokines such as INFγ (which has been called licensing of the MSCs), and suggested how this may apply in clinical treatment of GVHD. WJCs are MSCs that are obtained easily, safely and pain-free from donors of a consistent age, in contrast to BM derived- or adipose derived- MSCs that involve painful and invasive collection methods [38]. At first glance, WJCs and BM-derived MSCs have similar immune modulation properties and do not stimulate immune cell proliferation. Recent literature has revealed subtle differences in the in vitro immune modulation properties of WJCs with respect to MSCs derived from adipose tissue or from BM [39–42]. This literature suggests that WJCs and adipose-derived MSCs may be superior to BM-derived MSCs as therapy for GVHD. In conclusion, Dr. Weiss suggested that: licensed MSCs have superior therapeutic effects in animal models of GVHD. This should be considered when designing future clinical trials for GVHD.

Dr. Peter Ponsaerts's laboratory team in Experimental Hematology at the University of Antwerp, in Belgium, has previously studied the use of various autologous and allogeneic stem cell populations in animal models of neurotrauma, including spinal cord injury and experimental autoimmune encephalomyelitis. In course of their studies, they did not (yet) observe any

significant results to indicate potential in vivo benefits of stem cell transplantation for neurological diseases [43]. In his presentation entitled “Physiological comparison of autologous and allogeneic cell implantation in the central nervous system: defining and regulating immune cell activity against mesenchymal and neural stem cell grafts”, Dr. Ponsaerts further focused on optimizing the therapeutic procedures undertaken. Through culture and imaging studies, his group determined survival, differentiation, and immunogenicity of autologous and allogeneic cellular implants in the central nervous system of immunocompetent mice. These studies used murine BM-derived MSCs and embryonic brain-derived neural cells (NSC). While autologous transplantation of MSCs resulted in graft survival for at least four weeks, extensive microglial infiltration and astrocytic scar formation was observed [44]. In contrast, allogeneic transplantation of MSCs resulted in graft rejection two weeks post-transplantation [45,46]. Further autologous transplantation of NSC resulted in two week graft survival, followed by a progressive decrease in survival and increased infiltration by glial and astrocytic scar tissue [43]. Given the low survival percentage (less than 2%) of grafted autologous and allogeneic cells at week 2 post-grafting, the direct contribution of NSC to regeneration can be questioned. Potential benefits should be determined from the secreted factors and/or the reaction of endogenous stem cells towards the grafted cells. Interestingly, from this meeting, it appears that – in case of the use of placenta-derived cells – it seems to be easier to treat diseased mice using human cells instead of autologous or allogeneic cells. During the discussion of his presentation, it was therefore suggested that future experiments in regenerative medicine should use both human and autologous mouse or rat cells to demonstrate proof-of-principle, to compare results, and to understand the relative therapeutic efficacies.

To address whether placenta stem cell-based therapy may offer a neuro-restorative treatment, in the presentation, “Cell therapy for stroke: towards clinical application of Celgene human placenta-derived cells,” Dr. Cesar V. Borlongan of the Department of Neurosurgery and Brain Repair at the University of South Florida College of Medicine, USA, in collaboration with Celgene Cellular Therapeutics (New Jersey, USA), explored the safety and efficacy of human placenta-derived cell therapy products (PDACs®) in adult rat models of stroke [47,48]. His work is based on an intravenous transplantation model that occurs two days after transient occlusion of the middle cerebral artery (MCA). Results showed significant improvement in behavioral and neurological recovery from stroke. The response was seen to be dose dependent. Similar results were seen in cases of permanent MCA ligation. Significant improvement was seen with positive graft survival up to six months post-transplantation. It was also shown, due to absence of human specific vimentin staining, that graft survival was not essential for functional recovery in PDACs® transplanted stroke animals. Dr. Borlongan and his collaborators at Celgene Cellular Therapeutics also confirmed the safety of the intravenous cell transplants as evidenced by the lack of tumor or ectopic tissue formation in all PDACs® transplanted stroke models.

1.3. Clinical applications

In the presentation, “Placenta derived adherent stromal cells for the treatment of critical limb ischemia (CLI) - Lessons from first clinical trial,” Dr. Racheli Ofir from Pluristem Therapeutics Ltd. (Haifa, Israel), presented data derived from phase I clinical trials performed in parallel in the US and in Europe supporting the angiogenic and anti-inflammatory properties of placenta derived adherent stromal cells, indicated as PLX-PAD. These cells are derived from the human decidua and are expanded using Pluristem's 3D proprietary technology [49]. Based on the

accumulated in vitro and in vivo data, it was suggested that the anti-inflammatory and angiogenic properties of the PLX-PAD are mediated largely through paracrine effects. Pluristem has two ongoing phase I trials for the allogeneic use of these cells in critical limb ischemia (CLI) in patients who have exhausted all current therapies. The three-month follow-up data, including 21 patients afflicted with CLI, was presented. No immunologic reactions or other adverse effects related to the investigational product were observed in both trials, suggesting a promising safety profile. Furthermore, statistically significantly positive efficacy data was obtained using hemodynamic parameters, Ankle-Brachial Index, Toe-Brachial Index and Transcutaneous Oxygen Tension, as well as Quality of Life, pain and wound healing in patients treated in the trial. The data derived from these clinical trials suggests that allogeneic PLX-PAD administration to humans is safe and effective. This paves the way for further clinical studies.

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2. Conclusions

In summary, the first meeting of IPLASS was a celebration of novel conceptual and technical ideas directed towards advancing placenta stem cell research at multiple levels, from basic and translational to clinical investigation. Meanwhile, this meeting was also an occasion to point out the many unanswered issues on placental cells. These issues include the need for better definition of these cells in terms of their precise location in the placental tissues, their phenotype and stem cell potential, as well as the need to verify whether placental cells are better than those isolated from other sources in terms of therapeutic applicability. In this regard, only comparative studies using in parallel cells isolated from different sources in the same pre-clinical models will address this issue. The advantages of placenta with respect to other sources include the wide availability of discarded material, the possibility of banking placental cells and preparing “off-the-shelf” placenta-derived products (*e.g.* cells, fragment of AM).

However, the mechanisms whereby placental cell-based treatments exert therapeutic effects still remain poorly elucidated. In particular, it is increasingly accepted that improvement in tissue function observed after placental cell-based therapies are most likely due to paracrine action of these cells at the site of injury, rather than on their tissue-specific differentiation (*i.e.* regeneration of host tissues). The relative contributions of each of these two mechanisms, repair versus regeneration, as well as of the molecular pathways involved, remain to be determined.

Notably, seamless collaborative efforts between academic and industry-based scientists and regulatory authorities were apparent in most of the presentations. Altogether, this meeting achieved the IPLASS's goal of establishing a solid foundation for a “no-barrier” multi-disciplinary, multi-institutional, and multi-national scientific endeavor on which to build the future of placenta stem cell research and therapeutic applications.

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Abbreviations

AM	amniotic membrane
BM	bone marrow
CLI	critical limb ischemia
DCs	dendritic cells
GVHD	graft-versus-host disease
hAECs	human amniotic epithelial cells
IDO	indoleamine 2,3-dioxygenase
IFN-γ	interferon-gamma
IPLASS	international placenta stem cell society
MSCs	mesenchymal stem/stromal cells
MCA	middle cerebral artery

NSC	embryonic brain-derived neural cells
PDACs®	placenta-derived cell therapy products
PLX-PAD	placenta derived adherent stromal cells
Tregs	regulatory T-cells
WJCs	Wharton's jelly mesenchymal stromal cells

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Footnotes

Conflict of interest CVB is the Vice President-Elect of IPLASS, receives research funds from Celgene Cellular Therapeutics, and has patent applications relating to placenta cells. OP is the elected IPLASS President and has patent applications related to placental cells.

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References

[1] Medawar P. Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. Symp Soc Exp Biol. 1953;7:320–38.

[2] Parolini O, Alviano F, Bagnara GP, Bilic G, Buhring HJ, Evangelista M, et al. Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells. Stem Cells. 2008;26:300–11. [PubMed]

[3] Parolini O, Alviano F, Bergwerf I, Boraschi D, De Bari C, De Waele P, et al. Toward cell therapy using placenta-derived cells: disease mechanisms, cell biology, preclinical studies, and regulatory aspects at the round table. Stem Cells Dev. 2010;19:143–54. [PubMed]

[4] Bianchi DW, Fisk NM. Fetomaternal cell trafficking and the stem cell debate: gender matters. Jama. 2007;297:1489–91. [PubMed]

[5] Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl Acad Sci U S A. 1996;93:705–8.[PMC free article] [PubMed]

[6] Khosrotehrani K, Johnson KL, Cha DH, Salomon RN, Bianchi DW. Transfer of fetal cells with multilineage potential to maternal tissue. Jama. 2004;292:75–80. [PubMed]

[7] Srivatsa B, Srivatsa S, Johnson KL, Samura O, Lee SL, Bianchi DW. Microchimerism of presumed fetal origin in thyroid specimens from women: a case-control study. Lancet. 2001;358:2034–8. [PubMed]

[8] Bianchi DW. Fetomaternal cell traffic, pregnancy-associated progenitor cells, and autoimmune disease. Best Pract Res Clin Obstet Gynaecol. 2004;18:959–75. [PubMed]

[9] Fujiki Y, Johnson KL, Peter I, Tighiouart H, Bianchi DW. Fetal cells in the pregnant mouse are diverse and express a variety of progenitor and differentiated cell markers. Biol Reprod. 2009;81:26–32.[PMC free article] [PubMed]

[10] Aluvihare VR, Kallikourdis M, Betz AG. Tolerance, suppression and the fetal allograft. J Mol Med. 2005;83:88–96. [PubMed]

[11] Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med. 1999;189:1363–72. [PMC free article][PubMed]

[12] Mellor AL, Chandler P, Lee GK, Johnson T, Keskin DB, Lee J, et al. Indoleamine 2,3-dioxygenase, immunosuppression and pregnancy. J Reprod Immunol. 2002;57:143–50. [PubMed]

[13] Johnson BA, 3rd, Baban B, Mellor AL. Targeting the immunoregulatory indoleamine 2,3 dioxygenase pathway in immunotherapy. Immunotherapy. 2009;1:645–61. [PMC free article] [PubMed]

[14] Huang L, Baban B, Johnson BA, 3rd, Mellor AL. Dendritic cells, indoleamine 2,3 dioxygenase and acquired immune privilege. Int Rev Immunol. 2010;29:133–55. [PMC free article] [PubMed]

[15] Meirelles Lda S, Nardi NB. Methodology, biology and clinical applications of mesenchymal stem cells. Front Biosci. 2009;14:4281–98. [PubMed]

[16] In 't Anker PS, Scherjon SA, Kleijburg-van der Keur C, de Groot-Swings GM, Claas FH, Fibbe WE, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells. 2004;22:1338–45. [PubMed]

[17] Roelen DL, van der Mast BJ, in't Anker PS, Kleijburg C, Eikmans M, van Beelen E, et al. Differential immunomodulatory effects of fetal versus maternal multipotent stromal cells. Hum Immunol. 2009;70:16–23.[PubMed]

[18] Le Blanc K, Rasmusson I, Sundberg B, Gotherstrom C, Hassan M, Uzunel M, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet. 2004;363:1439–41. [PubMed]

[19] Wieckiewicz J, Goto R, Wood KJ. T regulatory cells and the control of alloimmunity: from characterisation to clinical application. Curr Opin Immunol. 2010;22:662–8. [PMC free article] [PubMed]

[20] Guillot PV, Gotherstrom C, Chan J, Kurata H, Fisk NM. Human first-trimester fetal MSC express pluripotency markers and grow faster and have longer telomeres than adult MSC. Stem Cells. 2007;25:646–54. [PubMed]

[21] Gotherstrom C, Lundqvist A, Duprez IR, Childs R, Berg L, le Blanc K. Fetal and adult multipotent mesenchymal stromal cells are killed by different pathways. Cytotherapy. 2011;13:269–78. [PubMed]

[22] Zhang ZY, Teoh SH, Chong MS, Schantz JT, Fisk NM, Choolani MA, et al. Superior osteogenic capacity for bone tissue engineering of fetal compared with perinatal and adult mesenchymal stem cells. Stem Cells. 2009;27:126–37. [PubMed]

[23] Le Blanc K, Gotherstrom C, Ringden O, Hassan M, McMahon R, Horwitz E, et al. Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation. 2005;79:1607–14. [PubMed]

[24] Parolini O, Soncini M, Evangelista M, Schmidt D. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine? Regen Med. 2009;4:275–91. [PubMed]

[25] Parolini O, Caruso M. Review: preclinical studies on placenta-derived cells and amniotic membrane: an update. Placenta. 2011;32(Suppl. 2):S186–95. [PubMed]

[26] Lindenmair A, Wolbank S, Stadler G, Meinl A, Peterbauer-Scherb A, Eibl J, et al. Osteogenic differentiation of intact human amniotic membrane. Biomaterials. 2010;31:8659–65. [PubMed]

[27] Bailo M, Soncini M, Vertua E, Signoroni PB, Sanzone S, Lombardi G, et al. Engraftment potential of human amnion and chorion cells derived from term placenta. Transplantation. 2004;78:1439–48. [PubMed]

[28] Magatti M, De Munari S, Vertua E, Gibelli L, Wengler GS, Parolini O. Human amnion mesenchyme harbors cells with allogeneic T-cell suppression and stimulation capabilities. Stem Cells. 2008;26:182–92.[PubMed]

[29] Magatti M, De Munari S, Vertua E, Nassauto C, Albertini A, Wengler GS, et al. Amniotic mesenchymal tissue cells inhibit dendritic cell differentiation of peripheral blood and amnion resident monocytes. Cell Transplant. 2009;18:899–914. [PubMed]

[30] Cargnoni A, Gibelli L, Tosini A, Signoroni PB, Nassuato C, Arienti D, et al. Transplantation of allogeneic and xenogeneic placenta-derived cells reduces bleomycin-induced lung fibrosis. Cell Transplant. 2009;18:405–22. [PubMed]

[31] Cargnoni A, Di Marcello M, Campagnol M, Nassuato C, Albertini A, Parolini O. Amniotic membrane patching promotes ischemic rat heart repair. Cell Transplant. 2009;18:1147–59. [PubMed]

[32] Sant'anna LB, Cargnoni A, Ressel L, Vanosi G, Parolini O. Amniotic Membrane application reduces liver fibrosis in a Bile Duct Ligation rat model. Cell Transplant. 2010 Aug 18; Epub ahead of print.[PubMed]

[33] Moodley Y, Atienza D, Manuelpillai U, Samuel CS, Tchongue J, Ilancheran S, et al. Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury. Am J Pathol. 2009;175:303–13. [PMC free article] [PubMed]

[34] Moodley Y, Ilancheran S, Samuel C, Vaghjiani V, Atienza D, Williams ED, et al. Human amnion epithelial cell transplantation abrogates lung fibrosis and augments repair. Am J Respir Crit Care Med. 2010;182:643–51. [PubMed]

[35] Manuelpillai U, Tchongue J, Lourensz D, Vaghjiani V, Samuel CS, Liu A, et al. Transplantation of human amnion epithelial cells reduces hepatic fibrosis in immunocompetent CCl-treated mice. Cell Transplant. 2010;19:1157–68. [PubMed]

[36] Miki T, Lehmann T, Cai H, Stolz DB, Strom SC. Stem cell characteristics of amniotic epithelial cells. Stem Cells. 2005;23:1549–59. [PubMed]

[37] Alviano F, Fossati V, Marchionni C, Arpinati M, Bonsi L, Franchina M, et al. Term Amniotic membrane is a high throughput source for multipotent Mesenchymal Stem Cells with the ability to differentiate into endothelial cells in vitro. BMC Dev Biol. 2007;7:11. [PMC free article] [PubMed]

[38] Weiss ML, Anderson C, Medicetty S, Seshareddy KB, Weiss RJ, VanderWerff I, et al. Immune properties of human umbilical cord Wharton's jelly-derived cells. Stem Cells. 2008;26:2865–74. [PubMed]

[39] Deuse T, Stubbendorff M, Tang-Quan K, Phillips N, Kay MA, Eiermann T, et al. Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells. Cell Transplant. 2010 Nov 5; Epub ahead of print. [PubMed]

[40] Najar M, Raicevic G, Boufker HI, Fayyad Kazan H, De Bruyn C, Meuleman N, et al. Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: Combined comparison of adipose tissue, Wharton's Jelly and bone marrow sources. Cell Immunol. 2010;264:171–9.[PubMed]

[41] Prasanna SJ, Gopalakrishnan D, Shankar SR, Vasandan AB. Pro-inflammatory cytokines, IFNgamma and TNFalpha, influence immune properties of human bone marrow and Wharton jelly mesenchymal stem cells differentially. PLoS One. 2010;5:e9016. [PMC free article] [PubMed]

[42] Yoo KH, Jang IK, Lee MW, Kim HE, Yang MS, Eom Y, et al. Comparison of immunomodulatory properties of mesenchymal stem cells derived from adult human tissues. Cell Immunol. 2009;259:150–6.[PubMed]

[43] Reekmans KP, Praet J, De Vocht N, Tambuyzer BR, Bergwerf I, Daans J, et al. Clinical potential of intravenous neural stem cell delivery for treatment of neuro-inflammatory disease in mice? Cell Transplant. 2010 Nov 19; Epub ahead of print. [PubMed]

[44] De Vocht N, Bergwerf I, Vanhoutte G, Daans J, De Visscher G, Chatterjee S, et al. Labeling of Luciferase/eGFP-Expressing bone marrow-derived stromal cells with fluorescent Micron-Sized Iron Oxide Particles improves Quantitative and Qualitative Multimodal imaging of cellular grafts in vivo. Mol Imaging Biol. 2011 Jan 19; Epub ahead of print. [PubMed]

[45] Tambuyzer BR, Bergwerf I, De Vocht N, Reekmans K, Daans J, Jorens PG, et al. Allogeneic stromal cell implantation in brain tissue leads to robust microglial activation. Immunol Cell Biol. 2009;87:267–73.[PubMed]

[46] Bergwerf I, Tambuyzer B, De Vocht N, Reekmans K, Praet J, Daans J, et al. Recognition of cellular implants by the brain's innate immune system. Immunol Cell Biol. 2011 Nov 23; Epub ahead of print.[PubMed]

[47] Borlongan CV. Cell therapy for stroke: remaining issues to address before embarking on clinical trials. Stroke. 2009;40:S146–8. [PMC free article] [PubMed]

[48] Yu SJ, Soncini M, Kaneko Y, Hess DC, Parolini O, Borlongan CV. Amnion: a potent graft source for cell therapy in stroke. Cell Transplant. 2009;18:111–8. [PubMed]

[49] Prather W. Pluristem therapeutics. Inc. Regen Med. 2008;3:117–22. [PubMed]