The Pharma Innovation Journal 2018; 7(6): 210-215

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(6): 210-215

www.thepharmajournal.com
Received: 01-04-2018
Accepted: 03-05-2018

Neeti Chana
Department of Drug Regulatory Affairs, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar Sec III, MB. Road, New Delhi, India

Neeti Chana
Department of Drug Regulatory Affairs, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar Sec III, MB. Road, New Delhi, India

Correspondence
Neeti Chana
Department of Drug Regulatory Affairs, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar Sec III, MB. Road, New Delhi, India

Cord cells transplantation: The source of regenerative medicine

Neeti Chana and Harvinder Popli

Abstract
The success of umbilical cord stem cell transplantation has seen many changes over the last 30 years. Over time medical line has witnessed successful allogeneic and autologous transplants for the malignant and non-malignant hematological and immunological diseases. These were pioneered by the cord stem cells, which became the future therapy and are known to us as "Regenerative medicines". There has been the establishment of private and public banks for cord blood and tissue preservation all across the globe. Successful preservation of cord cells had helped to develop minimally manipulated products for allogeneic hematopoietic reconstitution. About 345 clinical trials using mesenchymal stem cells from cord tissue are under process for discovering treatment methodologies for unlocking new possibilities. This paper captures information about cord blood banking, transplantation and current status of clinical research, to create awareness and knowledge among the readers about the subject

Keywords: Umbilical cord, cord blood, stem cells, cord blood transplant, cell banking, standards

Introduction
Stem Cells are the prime "undifferentiated, unspecialized, immature precursor cells" that live quiescently in every tissue compartment assisting the body to replace the old and regulating the growth of new cells by various processes [1]. They have the ability to self-renew and differentiate [2] into varied tissues of peculiar morphological and physiological characteristics. Due to this, they had gained popularity in tissue engineering and regenerative medicine becoming frontiers of medical science.

The Adult /Somatic stem cell found in the Bone Marrow, Blood, Cartilage, Fat (Adipose Tissue), Placenta and Liver, can produce hematopoietic and non-hematopoietic cells. But the technique is invasive and cells extracted may not be enough in quantity. Owing to the limitations of bone marrow transplant, science has found an alternative for treatment of hematological diseases – THE UMBILICAL CORD [3]. The stem cells extracted and seized from the birth cord are used for various hematological malignancies, both malignant and non-malignant in nature.

Such system of regenerative medicines can even be used for the exogenous creation of cells in a proper culture medium which can then be transferred to the body for repairing damaged tissue/organ [4]. Researchers have shown that adult stem cells including cord cells have enough capacity to expand under ex-vivo conditions. Through this process, it is easy to create cell lines for effective transplantation. Regenerative studies find great application in the dental field where tissues are cultured for treating periodontitis, craniofacial defects and even used to regenerate complete tooth [5]. The cord cells producing lowest immunogenicity has therefore increased the success rate of allogeneic transplants and other clinical practices [6]. The review article by S.J Forbes [7] highlight the examples of progress made in Diabetes, Arthritis and liver regeneration using the same concept. Already, there are products under clinical trials for ocular therapy [8] and some are being marketed for wound healing, cancers, and dermal grafts (Dermgraft®, Apligraf®, Matriderm® [9]).

History
Cord blood transplantation has its root embedded in 1982 when Biocyte Corporation emerged as the first Umbilical Cord Blood (UCB) company founded by Edward A. Boyse, Harvey Cantor, Bard J., Thomas L., Rockefeller R. It supported various grants with a view to study biology and cryopreservation techniques of the umbilical cord blood stem cells. The results established that the cells had the profound proliferative capacity – much higher than bone marrow and they can be cryopreserved for >20 yrs [10]. With the outcome of those studies, in

the year 1988, France, Fanconi Anaemia – an autosomal recessive disorder became the first disease to be treated using cryopreserved cord blood of unaffected sister sibling, that eventually proved potent for hematopoietic reconstitution after HLA matching [11].

The Umbilical Cord and Its Stem Cells

The umbilical cord or *funiculus umbilicalis* is a flexible and mechanically stable conduit between the growing fetus and the placenta enriching it with oxygen and nutrient vital for its growth. [12]

Stem cells isolated from the umbilical cord using different techniques like density gradient centrifugation, CD34 immuno-magnetic separation and fluorescence activated cell sorting, have shown that these cells exhibit CD 34^+ (a surface antigen) that differs extremely from bone marrow and peripheral blood stem cells not only in properties but also in numbers and composition [13,14]. This property had made cord stem cells valuable for cellular and microbiology studies [15]. The CD34+ antigen has empowered various clinical applications like immunotherapy, transplantation and even gene therapy as it plays role in early hematopoiesis [16].

Apart from the blood cells, the cord contains a substantial amount of Non-Hematopoietic cells namely – Endothelial progenitor cells (EPC), Mesenchymal Stromal cells (MSC), unrestricted somatic stem cells, multi-lineage progenitor cells, neural progenitor cells, unrestricted somatic stem cells, and very small embryonic stem cells [17]. Each of them owe different morphology, CD antigens markers (ranging from CD105, CD73, CD90 but lacking CD34, CD14, CD45, CD11b, CD79, HLA-DR) [18] and most importantly the property of differentiation into tissues (osteoblast, adipocytes [19], chondroblast, neuroglial cells, cardiomyocyte [20], pancreatic cells, hepatocytes [21]).

The pros and cons of UCB therapy

ADVANTAGES	DISADVANTAGES
Compared to bone marrow and peripheral blood, the UCB is easier to collect using the non-invasive technique.	A limited amount of blood (50-200 mL/ single cord unit) is received that at times not fulfill the volume needed for transplantation (more likely in adults).
With the help of cryopreservation, cord blood is available off shelf and can be used as and when needed.	The risk to the patient increases after treatment as the cells take time to engraft.**[22, 23]**
The chances of transmission of infectious diseases are less.	In case of relapse, the patient is again at risk because it is difficult
Graft vs. host diseases (GvHD) cases are less common even in allogeneic transplantation as proper screening and HLA matching is done before transplantation.[24]	to get the exact unit. An autologous transplantation can't be done for cancer using the cryopreserved unit of the patient because genetic mutations have already occurred. Therefore the chances of using own preserved cells are extremely less.

Overview of Collection and Storage Process

Once the decision to preserve the cord is taken by the family, the responsible cord bank gives a collection kit that contains a sterile bag and no. of syringes to ensure the procedure can be completed easily by obstetrics. At the same time, an informed consent giving details about the process, the tests and intended use of the cord is signed [25].The first step to bank the cord blood stem cells begin from hospitals where the cord blood is collected. Two methods are used to procure the cord blood:

1. In-utero collection by means of 60cc syringes
2. Ex-Utero collection in a sterile bag having EDTA/Citrate Phosphate Dextrose/Heparin (300cc)

The sterile bag is then marked with identification markers. The collected cord blood (having min. cell dosage $1.5x10^6$ - $5x10^6$ CD34+ cells/kg body weight) [26] along with the tissue, frozen at -196°F are shipped to storage laboratories within 24-48 hrs. under completely dry conditions (4℃ in the metal canister) to assure the cells' potency and viability [27]. The cord storage banks then account further processing – testing (ABO, Rh type, HLA, cell count and HIV-1, HIV-2, CMV), freezing and cryopreservation for at least 20 yrs [28, 29]. Many inventors had discovered the umbilical cord blood collection devices for decreasing contamination rate while transferring the blood transfer.

Table 2

Inventor	Original assignee	Patent no.	Date of patent	Patent name
Michael D. Grossman, *et al* [30]	Michael D. Grossman, *et al*	US 5915384A	Jun 29, 1999	Medical body fluid sampler device
Lisa J. Gruenburg [31]	Lisa J. Gruenburg	US 5690646A	Nov 25, 1997	Umbilical cord blood collection device and method
Nicholas J. Webb [32]	Cetus, L.C.	US5860989A	Jan. 19, 1999	Umbilical cord blood extractor
Hermann Knippscheer [33]	Cryo-Cell International, Inc.	US 5053025A	Oct 1, 1991	Method and apparatus for extracting fluid
Franciscus A. Kuypers *et al*. [33]	Childen's Hospital Medical Center of Northern California	WO 1997042872A1	Nov 20, 1997	Apparatus and method for collecting blood from an umbilical cord

Banking techniques

The possible applications of cord blood therapy have seen many advances since the first transplant that led to the development of public and private cord blood banks. The year 1992 saw a revolution when New York (US) established their first public bank to flourish and commercialize the use of stem cells from umbilical cord [13] and in the same year the first private bank – CryoCell international was formed.

The Public Banks

These non-profit, government-funded organizations collect and cryopreserve the cord blood without any charge from the donors. This level of open donation allows any patient worldwide use the unit stored without knowledge of the donor [35]. These banks have links with various national and international registries namely Bone Marrow Donors Worldwide (Netherlands), Netcord Foundation and National Marrow Donor Program (US) that help people access particular HLA matched unit [36].

The Private Banks

These are the profit-oriented banks collecting and preserving the cord blood as biological insurance for use by the child or close first and second-degree relative only. An appreciable amount of fee needs to be paid before the procedure begins but it ensures the cord use especially for people having potential family disease history [37, 38]. Private banks have become a hub of stem cells because of immense advertising and media strategies that even mislead parents about the therapies yet not discovered [39]**.** he private banks currently have an inventory of more than 10,00,000 units that can be useful for autologous or allogeneic transplantation [40]**.**

The process of banking the stem cell is tedious and need a combination of high precision techniques with highly skilled staff. Both the public and private banks are involved in the processing of cells for the ultimate transplantation.

The World's First Private-Public Bank

The Virgin Health Bank (UK) **[41]** the donor to store cord blood of their child both as a private sample and as a public sample for the use by family or the community. With the same view, many countries started the concept called community banking/ hybrid banking, which provides benefits like the highest probability of finding the matched cells from a large pool of cells stored, unlimited withdrawals without any restrictions, free access, financial and disaster relief.

Standards and Accreditations for Banking [42]

Standards are the guidelines designed to assure quality management system (QMS) at the institutional level to get the patient safety in return for the quality product. To assure conformance of cord blood product, these standards should be laid and accepted internationally so that each unit can be used as and when required across nations. Standards, mainly for cord blood, are driven internationally by organizations like FACT-NetCord (Foundation for the Accreditation of Cellular Therapy – NetCord) and AABB (American Association of Blood Banks). They foster advancement in cellular therapy and regenerative medicines. These standards are also compatibility to universally acknowledged ISO standards. The guidelines made for cord banks address basic issues like-collection, screening, and testing to determine donor eligibility, processing of unit, shipment, and release for transplantation.

Such accreditations give evidence that the cord bank exercises minimum level of quality standards ensuring excellent quality products, patient care, and laboratory practice. Today there are about 82 AABB accreditated and 67 FACT accreditated cord blood banks in the world (with 3-AABB and 1-FACT accreditated bank in India).

Table 3

THE WORLD'S TOP 10 CORD BLOOD BANKS					
Name	**Headquarter**	**Founded**	**Accreditations**	**Stored CB units**	**Private/ public**
Cord Blood Registry	California	1992	AABB, CLIAISO-9001:2008 FDA registered	More tha6,00,000	Private
Viacord	Massachusetts	1993	AABB, CLIA, FDA registered	More tha3,60,000	Private
Cryo-cell	Florida	1989	FACT,AABB, FDA, cGMP-cGTP compliant, ISO	More tha5,00,000	Private
China cord blood corporation	Beijing	1996	AABB	More tha5,00,000	Both
Cryo-save	Netherlands	2000	ISO	More tha2,50,000	Private
New York cord blood program	New York	1992	FACT-Netcord	More than 60,000	Public
CordVida	Brazil	2004	AABB	More than 10,500	Private
Americord	New York city	2008	AABB, FDA	---	Private
CryoHoldco	Latin America	2015	AABB	More than 300,000	Private
Vita34	Germany	1997	FACT	More than150,000	Both
INDIAN CORD BLOOD BANKS					
LifeCell	Chennai, Gurugram	2004	AABB, FDA, cGMP, ISO, DCGI	More than 200,000	Community banking
Cordlife	West Bengal	2001	AABB, CAP, ISO 9001:2000, DCGI, FDA	Near to 1 million	Private
StemCyte	Ahmedabad	1997	AABB, FDA, cGMP, ISO, DCGI, FACT	75,000-private units 35,000-public units	Both
Reliance	Mumbai	2002	AABB, DCGI, FDA Maharashtra, ISO 14001:2015,CAP	---	Both
Jeevan Foundation ***closed-2017***	Tamil Nadu	1995	AABB, ISO, NABH standards	6438	Public

Transplantation

To overcome the problem faced by single unit cord blood transplantation in adult patients, an alternative is well known as double unit cord blood transplantation using 2 units of partially matched HLA blood was performed for the first time in Europe (1999). Since then Eurocord registry has recorded massive increase in the number of transplants using double unit than single-unit cord blood for therapy [43]. This kind of transplantation not only gave better transplant results in adults with excess weight but eventually improved engraftment and survival rate **[44]**.

The National Bone Marrow Program (1999) and Center for cord blood (2005) was made by the US to enlist all the banks and their inventories that would be useful for transplantation

[45]. In the year 2009, transplants using cord blood crossed 20,000 in figures. The worlds cord blood inventory reached 3 million in the year 2013 marking huge success. According to 2015 update by *Health Resource and Service Administration* (HRSA), the total number of transplants performed in USA using umbilical cord blood and bone marrow accounts to 12,570 for autologous, 3840 for related allogeneic and 4918 for unrelated allogeneic with current cord blood registries – 444 from American Indians, more than 25000, 19000, 45000 and 102,000 respectively from Asian, black or African American, Latino and white-latino people, 253 from native Hawaiian or other Pacific Islander and nearly 23000 from other multiracial community. The Asian countries (Beijing, Tianjin, Seoul, Taipei, Ho Chi Minh, Bangkok, Tokyo) holds 56,854 cord blood inventories that have been used in about 437 transplants [46].

The Clinical Applications and Clinical Trials

From the last 50 years, cord blood which is best known for hematopoietic cells is being used in the treatment of about 80 kinds of hematological malignancies, metabolic disorders, and immunological problems. Apart from these, the stem cell therapy has shown a scope in treating inherited disorders (cartilage-hair, hypoplasia, osteoporosis), Breast cancers [47] (Ewing's sarcoma, metastatic breast cancer), Neuroblastoma and Renal cell carcinoma [48].

Table 4

<table>
<tr><th>Hematological disorders</th><th>Metabolic disorders</th><th>Immunological disorders</th></tr>
<tr><td>1. Hematological stem cell disorder (Aplastic anemia, Fanconi anemia)</td><td rowspan="8">Liposomal Storage Diseases:
Hurlers syndrome
Hunters syndrome
Wolman disease
Niemann-Pick disease
Krabbe Disease
Adrenoleukodystrophy
Beta-Glucuronidase deficiency
Sly syndrome</td><td rowspan="4">1. Phagocytic Disorders:
Omonn’s syndrome
Severe Combined Immune Deficiency
Ataxia-telangiectasia
Wiscott Aldrich Syndrome
X-linked Lymphoproliferative disorder</td></tr>
<tr><td>2. Acute leukemias (ALL, AML)</td></tr>
<tr><td>3. Chronic leukemias (CML, CLL)</td></tr>
<tr><td>4. Myeloproliferative disorders (Acute myelofibrosis, Polycythemia Vera)</td></tr>
<tr><td>5. Lymphoproliferative disorder (Reticular dysgenesis, Hodgkin’s and Non-Hodgkin’s disease)</td><td rowspan="4">2. Plasma Disorders (multiple myeloma, plasma cell leukemia)</td></tr>
<tr><td>6. Histiocytic disorder (Haemophagocytosis)</td></tr>
<tr><td>7. Myelodysplastic Syndrome (HbE Beta thalassemia, Sickle cell disease)</td></tr>
<tr><td>8. Inherited Platelet abnormalities (congenital thrombocytopenia)</td></tr>
</table>

A numerous number of US approved BLA’s for Hematopoietic Progenitor cells-cord blood products (HPC-CB) that are currently marketed as minimally manipulated unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution in patients with inherited, acquired or disorders from myeloblative treatment **[49]**.

Table 5

Product	Manufacturer	Approval date
Hemacord	New York Blood Center	NOV 10, 2011
Ducord	Duke University School of Medicine	APRIL 10, 2012
HPC, cord blood	Clinimmune Labs, University of Colorado Cord Blood Bank	MAY 24, 2012
Allocord	SSM Cardinal Glennon Children's Medical Center	MAY 30, 2013
Clevecord	Cleveland Cord Blood Center	JAN 1, 2016

A wide spectrum of non-hematopoietic conditions is being treated using the stem cells from the cord. Many of them are under investigational studies and some have been completed showing promising results providing optimism to those who have been suffering from these diseases.

Table 6

DISEASE	STATUS	CT IDENTIFIER & TRIAL COUNTRIES
Autism	All completed	Panama - NCT02192749
		China - NCT01343511
		US - NCT01638819
Cerebral Palsy	3 completed	US - NCT01988584
		China - NCT01929434
		Korea - NCT01193660
Spinal cord injur	1 recruiting	China - NCT02481440
Rheumatoid arthritis	1 active, not recruiting	Panama - NCT01985464
Alzheimer	1 completed 2 recruiting	Korea – NCT01297218, NCT03172117
Stroke	1 completed	US - NCT02397018
Systemic Lupus Erythematosus	1 active, not recruiting	US - NCT03171194
Crohn’s disease	1 recruiting	Korea - NCT02926300
Bronchopulmonary dysplasia	3 completed	Korea - NCT02023788
Duchenne muscular dystrophy	1 active, not recruiting	US - NCT02235844
Osteopetrosis	1 completed	US - NCT00730314
Diabetes – type II	2 completed	China - NCT01719640

		India - NCT00644241
Diabetes – type I	1 completed	US - NCT00873925
Periapical periodontitis	1 recruiting	Chile - NCT03102879
Skin diseases	1 completed	China - NCT02685722
	1 recruiting	China - NCT02668068
Liver failure	1 recruiting	China - NCT01844063

Future Applications

The genetic, immunological neurodegenerative and blood-related interventions are currently under the lens and many scientists feel that personalized regenerative medicines using stem cell can lead the way for therapy. The clinical trials on diseases like autism, cerebral palsy, AIDS and other cancerous conditions easily explain the futuristic potential of stem cell therapy. Seeing such rapid expansion, nearly every country is trying to make guidelines for ethical and safe research and viable commercialization of stem cell products (guideline for stem cell research by Indian Council of Medical Research and DBT- updated 2017). With such impact, the possibilities of using one's own cells to create biologically successful – substituted versions of tissues to restore the damaged organ in cases where no matched donor are available, has increased. Stem cells are helping hands of the doctors as they can elevate traditional therapy systems, supersede invasive procedures and also aid the patients by abolishing constant drug utilization thereby reducing the overall cost of therapy. The umbilical cord banks have seen the major up-gradation because of all new freezing **[50]** and thawing techniques, mergers of public and private banking techniques for increasing unit selection from a larger pool, increase in the initial amount of cells retrieved [51]. Recently many agents employing different mechanisms like Nicotinamide, mesenchymal stem cells, and intrabone marrow have been employed to create products (NAM-NK cells, NiCord®, Pneumostem®, Neurostem®) for immunological reconstitution that are under clinical trials [52].

References

1. Chagastelles PC, Nardi NB. Biology of stem cells: an overview. Kidney inter., Suppl. 2011; 1:63-67.
2. Avasthi S, Srivastava RN, Singh A, Srivastava M. Stem Cell: Past, Present and Future- A Review Article. Internet Journal of Medical Update. 2008; 3(1):22-30.
3. Broxmeyer HE, Douglas GW, Hangoc G, *et al*. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc. Natl. Acad. USA. 1989; 86(10):3828-3832.
4. Mao AS, Mooney DJ. Regenerative medicine: Current therapies and future directions. PNAS. 2015; 112(47):14452-9.
5. Nadig RR. Stem cell therapy-Hype or Hope? A review. J Conserv Dent. 2009; 12(4):131-138.
6. Roura S, Pujal JM *et al.* The role and potential of umbilical cord blood in an era of new therapies: a review. Stem Cell Research & Therapy. 2015; 6:123.
7. Forbes SJ. Recent advances in stem cells and regenerative medicine. Q J Med. 2014; 107 (4):251-252.
8. Gokuladhas K, Sivapriya N, Barath M, NewComer CH. Ocular progenitor cells and current applications in regenerative medicines-Review. Genes & Diseases 2017; 4 (2):88-99.
9. Colombo F, Sampogna G, Cocozza G, Guraya SY, Forgione A. Regenerative medicine: Clinical applications and future perspectives. Journal of Microscopy and Ultrastructure. 2017; 5(1):1-8.
10. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood. 2013; 122(4):491-498.
11. Gluckman E, Broxmeyer HA, Auerbach AD, *et al*. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med. 1989; 321(17):1174-1178.
12. Bosselmann S, Mielke G. Sonographic Assessment of the Umbilical Cord. Geburtshilfe und Frauenheilkunde. 2015; 75(8):808-818.
13. Verma V, Tabassum N, Yadav CB, Kumar M, Singh AK, *et al*. Cord Blood Banking: An Indian Perspective. Cell Mol Bio. 2016; 62(3):133-137.
14. Hordyjewska A, Popiolek L, Horecka A. Characteristics of hematopoietic stem cells of umbilical cord blood. Cytotechnology. 2015; 67:387-396.
15. Greaves MF, Brown J, Molgaard HV, *et al*. Molecular Features of CD34: A Hemopoietic Progenitor Cell-Associated Molecule. Leukemia. 1992; 6(1):31-36.
16. Sutherland DR, Keating A. The CD34 Antigen: Structure, Biology, and potential Clinical Applications. Journal of Hematotherapy. 1992; 1:115-129.
17. Matsumoto T, Mugishima H. Non-Hematopoietic Stem Cells in Umbilical Cord Blood. International Journal of Stem Cells. 2009; 2(2):83-89.
18. Weiss ML, Troyer DL. Stem Cells in the Umbilical Cord. Stem Cell Rev. 2006; 2(2):155-162.
19. Lindner U, Kramer J, Rohwedel J, Schlenke P. Mesenchymal stem or stromal cells towards a better understanding of their biology. Transfus Med Hemother 2010; 37:75-83.
20. Makino S, Fukuda K, Miyoshi S, *et al*. Cardiomyocytes can be generated from marrow stromal cells *in vitro*. J Clin Invest. 1999; 103:697-705.
21. Ong SY, Dai H, Leong KW. Inducing hepatic differentiation of human mesenchymal stem cells in pellet culture. Biomaterials. 2006; 27:4087-4097.
22. Park SK, Won JH. Usefulness of Umbilical Cord Blood Cells in Era of Hematopoiesis Research. International Journal of Stem Cells. 2009; 2(2):90-96.
23. Rodrigues CA, Sanz G, Brunstein CG, *et al*. Analysis of Risk Factors for Outcomes After Unrelated Cord Blood Transplantation in Adults With Lymphoid Malignancies: A Study by the Eurocord-Netcord and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Journal of Clinical Oncology. 2009; 27(2):256-263.
24. Thomson BG, Robertson KA, Gowan D *et al*. Analysis of engraftment, graft-host disease, and immune recovery following unrelated donor cord blood transplantation. Blood. 2000; 96(8):2703-2711.
25. Rahman J, Hasan K. The Era of Umbilical Cord Blood Transplantation and Banking. BSMMUJ. 2010; 3(1):47-53.
26. Berz D, McCormack EM, Winer ES, Colvin GA, Quesenberry PJ. Cryopreservation of Hematopoietic Stem Cells. Am J Hematol. 2007; 82(6):463-472.

27. Sivakumaran N, Rathnayaka IR *et al*. Umbilical Cord Blood Banking and its Therapeutic Uses. International Journal of Scientific Research and Innovative Technology. 2018; 5(1):160-172.
28. Sasidharan M, Surendran SA *et al*. Stem Cell Transplantation: Umbilical Cord. International Journal of Pharma Research & Review. 2015; 4(3):15-21.
29. M-Reboredo N, Diaz A, Castro A, Villaescusa RG. Collection, processing and cryopreservation of umbilical cord. Bone Marrow Transplantation. 2000; 26:1263-1270.
30. Michael D. Grossman *et al*. Medical Body Fluid Sampler Fluid, U.S. Patent US 5915384A, 1999.
31. Lisa J. Gruenberg. Umbilical Cord Blood Collection Device and Method, U.S. Patent US 5690646; 1997.
32. Nicholas J. Webb. Umbilical Cord Blood Extractor, U.S. Patent US 5860989, 1999.
33. H Knippscheer. Method and Apparatus for Extracting Fluid, U.S. Patent US 5053025, 1991.
34. FA Kuypers *et al*. Apparatus and Method for Collecting Blood from an Umbilical Cord, WO 1997042872A1; 1997.
35. Armson BA, Allan DS, Casper RF. Umbilical Cord Collection: Counselling, Collection, and Banking. J Obstet Gynaecol Can. 2015; 37(9):832-844.
36. Gluckman E, Ruggeri A, Rocha V, Baudoux E, Boo M, Kurtzberg J, Welte K, Navarrete C, van Walraven SM for Eurocord, Netcord, World Marrow Donor Association (WMDA) and National Marrow Donor Program (NMDP). Family-directed umbilical cord blood banking. Haematologica. 2011; 96(11):1700-1707.
37. Thornley I, Eapen M, Sung L, *et al*. Private Cord Blood Banking: Experiences And Views Of Pediatric Hematopoietic Cell Transplantation Physicians. Pediatrics. 2009; 123(3):1011-1017.
38. Fisk NM, Atun R. Public-private partnership in cord blood banking. BMJ. 2008; 336(7646).
39. Pandey D, Kaur S, Kamath A. Banking Umbilical Cord Blood (UCB) Stem Cells: Awareness, Attitude and Expectations of Potential Donors from One of the Largest Potential Repository (India). PLoS ONE. 2016; 11(5):0155782.
40. Butler MG, Menitove JE. Umbilical cord blood banking: an update. J Assist Reprod Genet DOI 10.1007/s10815-011-9577-x. 2011.
41. Mayor S. World's first public-private cord blood bank launched in UK. BMJ, 2007; 334(7588): 277.
42. Armitage S. Cord Blood Banking Standards: Autologous Versus Altruistic. Frontiers in Medicine. 2016; 2(94): 1-5
43. Sideri A, Neokleous N, *et al*. An overview of the progress on double umbilical cord blood transplantation. Haematologica. 2011; 96(8):1213-1220.
44. Majhail NS, Brunstein CG, Wagner JE. Double umbilical cord blood transplantation. Current Opinion in Immunology. 2006; 18(5): 571-575.
45. Fadel HE. Cord Blood Banking: Ethical Considerations. JIMA. 2010; 42(1):1-9.
46. Agarwal MB. Umbilical Cord Blood Transplantation: Newer Trends. JAPI. 2006; 54: 143-147.
47. Deepak A *et al*. Stem Cell Therapy for Breast Cancer: A Review. J Pharm. Sci. & Res. 2016; 8(6):533-535.
48. Bregni M, Herr W, Blaise D, The Solid Tumor Working Party of the EBMT. Allogeneic stem cell transplantation for renal cell carcinoma. Expert Rev Anticancer Ther. 2011; 11(6):901-11.
49. Sakai D, Schol J, Foldager CB, Sato M, Watanabe M. Regenerative technologies to bed side: Evolving the regulatory framework. JOT. 2017; 9:1-7.
50. Hanna J, Hubel A. Preservation of stem cells. Organogenesis. 2009; 5(3):134-137.
51. Ballen K. Umbilical Cord Blood Transplantation: Challenges and Future directions. Stem Cells Translational Medicine. 2017; 6:1312-1315.
52. Ballen K. Update on umbilical cord blood transplantation [version1; referees 2 approved] F1000Research. 2017, 6(F1000 Faculty Rev): 1556.