

CONTROVERSY

Current perspective on live cell therapy

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Abstract

The practice of treating human illnesses with animal organs and extracts dates back more than 4,000 years to ancient antiquity. Even though cell therapy was approved in Switzerland in 1931 after Paul Niehans successfully treated a patient who had iatrogenic tetany after a total thyroidectomy and was on the verge of death, mainstream medicine still does not accept this kind of treatment. Nonetheless, the use of animal-derived stem cells in cell therapy has not decreased. Millions of patients have utilized it, according to records from the late 1900s, to treat a variety of illnesses that conventional medicine is unable to cure (Molnar 2006). Drug or hormone therapy is very different from cell therapy. The paradigm of biology and medical practice has now shifted to systems biology and systems medicine due to the enormous advancements made in cellular and biomolecular research. The goal of live cell therapy is to restore or regenerate malfunctioning organs and the various biological systems in the human body by using fetal precursor stem cells of animal lineage procured using "state of the art primary tissue cultures". The implantation of fetal precursor stem cells is a crucial component of the live cell therapy protocol, which is an individualized, integrative, eclectic, and holistic kind of medical treatment. This paper will give the current viewpoint on the procedure.

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The Live Cell Therapy Protocol

The use of animal-derived fetal and juvenile tissues for their inherent biological capacity for development to treat illness and restore vital physiological functions while enhancing overall health has long been referred to as "cell therapy". Paracelsus wrote, "Heart heals heart, kidneys heal kidney, and LIKE HEALS LIKE" in his book from the 16th century. (See Eknayan's review from 1996.). He truly made the scientific discovery of organospecificity, which forms the basis for modern stem cell transplantation.

Cell therapy was founded on pure empiricism. Due to the positive and often remarkable outcomes of this kind of treatment, cell therapy

has grown in popularity and is still sought after by patients today, including many well-known people and celebrities. The fetal precursor stem cells from close colony rabbits produced using the "state of the art primary tissue cultures" are used by the authors and scientists in this work (Abdul Halim, 2017 and 2022).

Live cell therapy is vastly different from drug or hormonal therapy. While conventional medicine has greatly benefited humanity, live cell therapy has allowed for the revival and regeneration of failing tissues and organs. This therapy plan is eclectic, integrative, and tailored to each patient individually. The implanted primary tissue cultures of fetal or very young

animal stem cells operate by way of the following therapeutic factors:

- i) The rapidly growing intrinsic biochemical substrates and enzymes found in fetal and very young tissues derived from animals.
- ii) The minerals and trace elements that make up these fetal tissues.
- iii) These fetal tissues' biological capacity for development, which promotes rapid tissue growth.
- iv) The ideal "epigenetic information" in the fetal xeno stem cells (derived from closed colony animals reared under strict veterinary supervision) which carries the potential to correct the unhealthy "methylozone" in the diseased microenvironment of the recipient patients.

Under electron microscope, we are aware that the transplanted cells break down order of magnitude all the way down to the nanoscale. However, these transportable particles supply the essential building blocks for the mending of cellular and subcellular abnormalities. The biological developmental capacity of these substances and elements cannot be quantified within scientific criteria, however they can now be analysed and studied in even greater detail with current molecular imaging technologies. (Xibo Ma et al.2012).

Cell therapists frequently observe that the results of a patient's multicellular/cellular implantation can vary from one multicellular/cellular implantation to the next. The physical relationships between each patient's macrocosm (electromagnetic, chemical, solar energy and cosmic radiation) and microcosm (elements, trace elements and elementary particles) environments should constantly be considered in the cell therapy protocol. Consequently, it is essential that cell therapy be applied as a component of a comprehensive and a customized treatment strategy at all times. A healthy physical environment, a healthy lifestyle, adequate sleep, preserving strong social ties, eating well, reducing or eliminating xenobiotics and adopting an optimistic outlook are all important components of the strategy. These physiological, psychological and emotional variables all contribute to pathophysiological alterations in the internal terrain of the body, which in turn promote disease through the

inflammatory process in the organ systems of the body.

According to Lipton (2011), Candace Pert (2003), P S Mueller et al. (2001), and Sathyanarayana Rao TS et al. (2009), the body's cells are strongly influenced by the thoughts in the patient. It cannot be ignored that the healing process can be accelerated by a positive therapeutic alliance between the patient and the attending physician and also social support. Medical care, nutrition, psychotherapy, and physical therapy must all be included in the treatment plan as needed.

The live cell therapy procedure offers the body the opportunity to simultaneously repair the illness and regenerate the declining essential functions of life. Thus, in addition to treating the body's malfunctioning organ systems, the goal should be to reduce or eradicate the underlying causes, which could include toxins, undetected infections, endocrine disruptors, vitamin and nutrient shortages, the consequences of mental stress, etc. The patient must faithfully follow the protocol, abstain from unnecessary medications, consume the right food and exercise, maintain a healthy lifestyle and leisure activities, and continue concurrent physical therapy and spiritual immersion in the manner of their choice (Scott Y. H. Kim, Lauren Schrock et al.). In summary, the goal of the live cell therapy procedure is to promote whole-body healing.

In the 20th century, the idea of cell therapy was hailed as a major development in medicine. (Schmid F, 1983; Niehans, P. 1960). The idea of systems biology/systems medicine, which has emerged from a current shift in the therapeutic thinking of medicine, is converging with the idea of live cell therapy, which has been utilized by live cell therapy practitioners for almost a century. (Mansoor Saqi M, 2016; Tretter F et al. 2019; Henrik Vogt et al. 2016; Kirschner M, 2016; Paul J Mills et al. 2017).

Cell therapy started on the basis of empirical experience of clinicians and not from the basic principles of immunotherapy. In 1931, Switzerland implemented stem cell xenotransplantation into clinical practice. This happened when Paul Niehans' treatment of a patient who had acute post-operative tetany after a total thyroidectomy was widely reported

to have had a remarkable rapid response. (Molnar 2006). Rejuvenation by cellular xenotransplantation has in reality been described in the early 1900s and reports of complications were surprisingly uncommon. (Deschamps JY et al., 2005). However the majority of conventional medical practitioners are not familiar and do not support cell therapy. Their stance is based on factors such as the alleged lack of basic research, the risk of disease transmission, the risk of irreversible allergic reactions, the difficulty of determining the results due to the lengthy latent period of therapy, the inability to conduct a double-blind test due to the lack of a suitable placebo preparation at the time, the unlawful and senseless expansion of the indications for cellular therapy to include incurable diseases, the absence of evidence from animal experiments and the uneasiness associated with injecting cell suspensions that are not precisely dose-controlled.

Up until 1987, doctors treated almost four million patients in Germany alone using frozen and lyophilized cells. When patients from the USSR and other European countries are taken into account, the projected figure might even surpass eight million. Russian and German were the languages of most publications on cell therapy. Cell therapy has been described as the safest form of biotherapy (Molnar 2006). The numerous publications on clinical and research-based studies of cellular xenotransplantation should be available to serious cell therapy researchers. Many of the ground-breaking studies are available only in non Anglophile scientific media (Schmid F., 1983; Schmid F., Stein J, 1967, Wolfram, K W.,1983).

To refute those who claim that no animal research has been done on xenotransplants, one merely needs to peruse publications and the PubMed database (Schmid F, Stein J, 1967; Schmid F. 1983). Numerous publications in non-Anglophile media exist on the topic. Actually, a lot of basic research has been conducted; however, more studies employing the research tools available today are necessary to provide a more precise description of live cell therapy in the fields of transplantology and regenerative medicine (Effie Apostolou, Helen Blau, et al. 2023; 2023; Schmid F, Stein J, 1967; Schmid F. 1983)

Why Do We Use Fetal Precursor Stem cell Xenotransplants?

Fetal precursor stem cells are currently known to be considerably safer than embryonic stem cells and to have a far higher potential for therapeutic use than adult stem cells (Knoepfler, Paul S. 2009; Molnar 2006; Abd Halim 2017). Animals raised in a controlled colony with stringent veterinary and genetic regulations possess xenogeneic fetal precursor stem cells with "zero age" and "ideal" epigenetic information, or methylene. Therefore, they have the ability to improve and rectify the unfavorable epigenetic information in the recipient patients' sick microenvironment. From the standpoint of biology implanted fetal precursor cells cannot alter the host organism's true genome (Samuel Lessard et al. 2015; Lawrence TC Ong et al. 2020).

Cell therapy is actually the implantation of any type of fetal xeno-transplant based on decades-old safety and efficacy evidence as well as documented clinical experience accumulated over many years. Stem cell transplantation follows Paracelsus's basic principle of organospecificity, or "LIKE CURES LIKE." Today, we have all the organ cells required for live cell therapy at our disposal—more than 250 distinct types of fetal precursor stem cells. The skill of the physician is in restoring the patient to optimal physiological status and choosing the appropriate fetal stem cell types for implantation, ultimately leading to healing the patient.

One of the main subjects of stem cell xenotransplantation is the mechanism of homing, often known as the Halsted Principle. The degree of organ dysfunction and the quantity of donated cells needed to treat the condition effectively seem to be correlated. This principle asserts that transplanted stem cells move to damaged organs or tissues where they are most needed (Schmid, 1983; Molnar, 2006; Zanjani, et al., 1993). Cell biologists today generally accept the homing principle, which has been known since 1908 in classical cell therapy. The "signal theory" was developed by Gunter Blobel, the 1999 Nobel Prize laureate in Physiology and Medicine. He was given credit for the discovery of "signal peptides," which function as "address peptide tags" to direct protein molecules and peptides to the correct

location. By merging traditional cell biological methodologies with molecular biology and biochemistry, he was able to successfully validate every part of his signal theory.. It is now widely accepted that the signal theory characterises cell biology (Blobel, 2018; Frenette et al., 1998; Quesenberry, 1998; Whetton and Graham, 2022; Ratajczak et al., 2016; Academic Press, 2016; Lapidot et al., 2005; Chute, 2006; Liesveld. et al., 2020; Li. et al, 2018). Blobel was credited with "ushering cell biology into the molecular age."

Over the last three decades cell xenotransplantation is getting more accepted as being safe and with the potential to be the treatment for a wide range of diseases currently untreatable in conventional medicine. Clinical trials with xenogeneic stem cells are now under way, an approach based on the premise that stem cells and precursor cells are characterized as being immunotolerant (Lin-Li Jiang et al. 2021; Zhong R, Platt JL, 2005; Poncelet AJ et al. 2009; Lanza R.P.et al, 1998; Burcin E et al, 2017; Gage FH, 1998; Chi-Ping Huang et al., 2021; Burcin E et al., 2012; Barboni B, Russo V et al. 2018; Ekser B, Ezzelarab M et al., 2012). But in reality cell therapists have been treating hormone dependent dysfunctions, neurodegenerative disorders such as Parkinson's disease, Amyotrophic lateral sclerosis, aging diseases and chromosomal disorders such as Down syndrome for more than the past 50 years (Niehans P. 1960; Wolfram, K W Culbert M L. 1983).

Fetal neural transplants have been repeatedly shown to cause functional recovery in animal models of neurodegenerative diseases, improve symptoms and reduce drug-induced side effects in patients with Parkinson's disease. From a practical and ethical perspective, obtaining human fetal tissue for neural transplantation is undoubtedly challenging (Ole Isacson O and colleagues, 1999). Obtaining these cells from fetuses of animal origin would have been easier thus avoiding these issues.

Although there has been much progress in human stem cell research, tissue engineering, regenerative medicine and blastocyst complementation, from the therapeutic standpoint human derived stem cell transplantation is far behind that of stem cell

xenotransplantation. Many researchers now believe that stem cell xenotransplantation provides the best short term solution to the organ shortage that restricts organ transplantation (Cooper,et al., Transplantation 101(8):p 1766-1769, 2017).

Cell therapy proponents have consistently argued for decades that their therapeutic approach is a safe form of biotherapy. Papers currently indicating that there is less chance than previously thought that xenotransplantation contains risks support this. However, if the cells are processed correctly, adhering to the 2003 Food and Drug Administration guideline and the ensuing World Health Organization consensus papers, such hazards can be effectively managed through donor selection or recipient management measures (Cooper, D. K. C. et al. 2017). The majority of fetal precursor stem cells used in modern medicine are produced using "state of the art primary tissue cultures," which are taken from close-colony rabbits. Asepsis is more easily maintained and the tissue culture process secures almost complete non immunogenicity of the cell transplants so that immunosuppression is not required (Molnar M.2006). It is possible to obtain all the 250 or more different types of precursor stem cells needed for regenerative medicine in unlimited quantities and without the use of genetic engineering.

Anaphylaxis and adverse effects?

Following the insertion of fetal precursor stem cell xenotransplants made using primary tissue cultures, cell therapists do not see anaphylactic shock. Even when using fetal and young tissue fragments of animal origin in the past, Neihans and subsequent cell therapy practitioners have not found this to be an issue. Moreover, immunosuppression is not applied. This is the actual situation that is seen in live cell therapy clinical settings. Most people assume that xenogeneic stem cell implantation must trigger a rejection reaction.. However, it didn't, and current immunology still doesn't have a good explanation for why (Neihans P. 1960; Molnar M. 2006).

The rate of problems following stem cell xenotransplantation is quite low. A few days following cell implantation, low grade fever and

rashes may occur infrequently. (Schmid F. 1983; Wolfram, K W et al 1983; Molnar 2006; Abdul Halim, 2017). We have seen that the therapeutic effects of the fetal stem cell xenotransplants remain complete despite inflammation at the implantation sites.

Transmission of Microorganisms and Xoonoses?

The experience of cell therapists using live cell therapy for over 50 years has demonstrated that the danger of transmitting an infectious microorganism to the recipient is minimal when donor selection and manufacturing procedures for fetal precursor cell transplants are done correctly. "By incorporating the requirements of "PHS Guidelines on Infectious Disease Issues in Xenotransplantation" of January 19, 2001 (Federal Register, Volume 66, No 19. Pages 8120-8121) it assures to the greatest degree afforded by modern science an absence of transmission of xoonoses by cell xenotransplants from the animal donor to the human recipient patient" (Molnar M, 2006).

Metastatic Implantation and Risks of Tumour Formation?

After the implantation of fetal precursor stem cell xenotransplants, metastatic implantation and tumour formation have not been observed. From the standpoint of cell biology, these cells are already predestined to develop into mature organ-specific cells. Unlike embryonic fetal stem cells, these cells do not have the capacity for teratogenicity or metastatic implantation (Murray MJ, Lessey BA. 1999; Cunningham JJ et al. 2012).

Does It Work?

Medical professionals do not require biochemical evidence to validate the beneficial outcomes of live cell therapy, since they have observed it experimentally in a significant number of treated cases. One of the most compelling and rewarding areas of pediatrics is the use of live cell therapy for Down syndrome (Schmid F. 1983; Molnar M, 2006; Abdul Halim, 2017). Treatment using live cells is not a panacea. In order to establish the best physiological state for optimum outcome of implantation of precursor stem cells, proper

patient preparation is essential. In the field of regenerative medicine, perhaps, the current research tools in genomes, transcriptomics, metabolomics, visual imaging studies, etc., will be able to clarify the mechanism of action and provide us with a more precise definition of live cell therapy. One simply needs to read the books produced by cell therapists, from Paul Niehans in the 1960s to more recent writings by cell therapists who are now in practice to comprehend the tremendous benefit of cell therapy in treating a range of chronic medical illnesses over time. These disorders include, but are not limited to:

- chromosomal and genetic disorders
- neurodegenerative disorders including Parkinson's disease, Pre Alzheimer disease
- hormone - dependent dysfunctions
- immunological dysfunctions including autoimmune disorders in general and AIDS
- end organ failures of all kinds
- iatrogenic medical disorders
- rejuvenation/revitalization and restoration of age dependent decrepid organ systems
- immunostimulation following completion of conventional oncological treatment

In 1981, Osband et al. used intramuscular injections of thymic extracts from five-day-old calves to treat ten out of seventeen children for Histiocytosis X, an immunosuppressive disorder. (Osband, M.E., Lipton, J.M. et al, 1981). Such a result would have been expected by any seasoned cell therapist. Immunodeficiency conditions like AIDS have been treated by cell therapists utilizing a combination of fetal stem cells from the thymus, spleen, mesenteric lymph nodes, mesenchyme, liver, and intestine. The author has personal experience with four AIDS cases, three of which have successfully recovered over a five-year period without anti-retroviral therapy (ART). (Halim, Abdul 2017).

Clinical trials?

The foundation for advancements in live cell therapy is the positive results seen in millions of patients over the course of more than a century following the implantation of fetal cells or tissues from animal sources. To clarify how the healing effects happen, fundamental scientific research was conducted (Schmid and Stein J, 1967; Bradford RW, Culbert M 1986). Randomised

control trials (RCTs) are useless for this form of individualised treatment which is a minor surgical form of treatment. Questions concerning the quantity and kind of fetal stem cells implanted, the time interval between implantations, the dietary supplements recommended, the detoxification protocol and compliance with the pre- and post-transplantation protocol cannot be satisfactorily answered. Furthermore, many who seek live cell therapy do so for conditions that conventional medicine is unable to treat or is no longer effective in treating. It is difficult to create appropriate clinical trial designs that consider the patient's entire condition when determining the best course of action for assessing the efficacy of live cell therapy.

Using live cells for treatment is not a panacea. However, this kind of therapy is safe as long as the fetal precursor stem cells are properly prepared. The patient will either have a favorable outcome after live cell therapy or there is no alteration in his or her clinical status.

Ethical concerns

There are no moral or religious concerns because fetal precursor stem cell xenotransplants are produced from rabbits without undergoing any genetic modification. The patient will be given information about the protocol, the advantages and disadvantages of therapy and will need to sign an informed consent form prior to beginning treatment.

Omics analyses related to cell transplantation.

Planning a personalized treatment plan and caring for patients with a wide range of medical disorders that are currently incurable in conventional medicine require an understanding of a person's genome as well as how their environment, lifestyle, diet, and other factors contribute to their diseased phenotypes.

Proteomics, metabolomics, transcriptomics and genomes are examples of "omics" sciences. scientific fields currently being researched. When combined, these methods can help provide a comprehensive understanding of the epigenomic and molecular components of cell transplantation.

Transcriptomics offer significant insights into the patterns of gene expression in the host tissue and the transplanted cells. It enables the identification of transplanted cells through the analysis of their gene expression profiles. Before transplanting, it allows researchers to evaluate the cell population's quality and purity. Certain patterns of gene expression that may function as biomarkers for the success or failure of cell transplantation can be found by transcriptomic analysis. These biomarkers have use in outcome prediction and monitoring. Through the evaluation of distinct gene expression profiles for both the recipient and donor cells, scientists can optimise transplantation protocols for specific patients.

Proteomics analysis provides valuable information about the protein composition of the transplanted cells and the host tissue. It aids in defining the protein profile of the transplantable cells. This entails figuring out which proteins, signaling molecules and surface indicators might affect the traits and behaviors of transplanted cells. Determining which proteins to look for can help with outcome prediction and transplant cell health monitoring. The integration of transplanted cells into the host tissue can be investigated using proteomics. It facilitates the identification of proteins engaged in cell signalling, adhesion, migration and interactions with the extracellular matrix.

Metabolomics research can identify specific metabolites that serve as markers for the success or failure of cell transplantation. It is possible to assess how successfully transplanted cells are integrating or supplying signaling responses into the host tissue by keeping an eye on these indicators.

Mass spectrometry-based omics analysis techniques for the identification of novel biomarkers will aid in the development of more precise pathophysiological diagnoses and in formulating stem cell prescriptions. These ought to facilitate better patient readiness for stem cell implantation and clinical outcome monitoring after stem cell therapy

Conclusion

Cell therapy employs tissue fragments from fetuses and young animals. Live cell therapy

appears to have significantly better theoretical and experimental underpinnings than many other modalities of cellular based treatment. A lot of the myths around live cell therapy are being debunked. The field of regenerative medicine and transplantology will benefit from additional study in order to better define stem cell transplantation utilizing both animal-derived fetal precursor stem cells and stem cells produced from humans.

References

- Abdul Halim AJ. Hope for Untreatable Medical Disorders with Live Cell Therapy. London: Troubador Publishing Ltd, 2017
- Abdul Halim Abdul Jalil, Muhammad Lokman Muhammad Isa. Live cell therapy: Past, present and future. *J Reprod Biotechnol Fertil* 2022 Vol 11:77-86
- Adamiak M, Suszynska M, Ahmad A L, Ahmed A I., Ratajczak, Ratajczak MZ. The Involvement of Hematopoietic-Specific PLC- β 2 in Homing and Engraftment of Hematopoietic Stem/Progenitor Cells. *Stem Cell Rev*. 2016; 12(6): 613–620
- Alain J Poncelet 1, Dufrane Denis, Pierre Gianello. Cellular xenotransplantation(Review). *Curr Opin Organ Transplant* 2009 Apr;14(2):168-74
- Barboni B, Russo V, Berardinelli P, et al., Placental Stem Cells from Domestic Animals: Translational Potential and Clinical Relevance. *Cell Transplant* 2018; 27: 93-116
- Blobel, 2018; Frenette et al., 1998; Quesenberry, 1998; Whetton and Graham, 2022; Ratajczak and Abdelbaset-Ismail, 2016; Academic Press, 2016; Lapidot and Dar, 2005; Chute, 2006; Liesveld. et al., 2020; Li. et al, 2018
- Blobel Laboratory Trainees. Günter Blobel: Pioneer of molecular cell biology (1936–2018). *J Cell Biol*. 2018; 217(4):1163-1167. doi: 10.1083/jcb.201803048
- Bradford RW, Culbert M (1986). The biochemical basis of live cell therapy. ISBN-10: 0934740038; ISBN-13: 978-0934740036
- Burcin Ekser, Ping Li, David K.C. Cooper, Xenotransplantation: Past, Present and Future. *Curr Opin Organ Transplant*. 2017 Dec; 22(6): 513–521
- Chi-Ping Huang 1, Chi-Yu Yang 2, Chih-Rong Shyr. Utilizing Xenogeneic Cells As a Therapeutic Agent for Treating Diseases. *Cell Transplant*. 2021 Jan-Dec;30:9636897211011995.
- Chute J. Stem cell homing. *Curr Opin Hematol*.(2006); 13(6):399-406.
- Chute J. Stem cell homing. *Curr Opin Hematol*.(2006); 13(6):399-406.
- Cooper, D. K. C., Pierson, R. N., Hering, B. J., Mohiuddin, M. M. et al., (2017). Regulation of Clinical Xenotransplantation-Time for a Reappraisal. *Transplantation*, 101(8), 1766-1769
- Deschamps JY, Roux FA, Sai P, Gouin E. History of xenotransplantation. *Xenotransplantation*. 2005; 12(2), 91–109. doi:10.1111/j.1399-3089.2004.00199
- Effie Apostolou, Helen Blau, Kenneth Chien, et al., Progress and challenges in stem cell biology. *Nature Cell Biology* volume 25, pages203–206 (2023)
- Eknoyan G. On the contributions of Paracelsus to nephrology. *Nephrol Dialysis Transplant*. 1996;11(7):1388-1394
- Ekser B, Ezzelarab M, Hara H, et al., Clinical xenotransplantation: the next medical revolution? *Lancet*. 2012;379:672–683.
- E Michael Molnar . Stem cell transplantation, Sunshine MD: Medical and Engineering Publishers. 2006
- Felix Tretter , Henriette Löffler-Stastka. Medical knowledge integration and "systems medicine": Needs, ambitions, limitations and options. *Med Hypotheses*. 2019 Dec;133:109386
- F H Gage. Cell therapy *Nature*. 1998 Apr 30;392(6679 Suppl):18-2)4
- Frenette P, Subbarao S, Mazo I, von Andrian U, Wagner D. Endothelial selectins and vascular cell adhesion molecule-1 promote hematopoietic progenitor homing to bone marrow. *Proc Nat Acad Sci*. 1998;95(24): 14423-14428.doi: 10.1073/ pnas.95.24.14423
- Henrik Vogt , Bjørn Hofmann , Linn Getz The new holism: P4 systems medicine and the medicalization of health and life itself. *Med Health Care Philos*. 2016 Jun;19(2):307-23
- Justine J Cunningham, Thomas M Ulbright, Martin F Pera & Leendert H J Looijenga. Lessons from human teratomas to guide development of safe stem cell therapies. *Nature Biotechnology* volume 30, pages849–857 (2012)
- Knoepfler, Paul S. (2009). "Deconstructing Stem Cell Tumorigenicity: A Roadmap to Safe Regenerative Medicine". *Stem Cells*. 27 (5): 1050–1056

- Lanza R.P. Cooper D.K.C. Chick W.L. Xenotransplantation. *Sci. Am.* 1997; 277: 54-59
- R P Lanza , D K Cooper. Xenotransplantation of cells and tissues: application to a range of diseases, from diabetes to Alzheimer's. *Mol Med Today.* 1998 Jan;4(1):39-45.
- Lapidot T, Dar A, Kollet O. How do stem cells find their way home? *Blood.* 2005; 106(6):1901-1910. doi: 10.1182/blood-2005-04-1417
- Lawrence T. C. Ong, Grant P. Parnell, Kelly Veale, et al., Regulation of the methylome in differentiation from adult stem cells may underpin vitamin D risk in Multiple sclerosis. *Genes & Immunity* volume 21 pages 335-347 (2020)
- Li D, Xue W, Li M, Dong M, Wang J, Wang X. et al. VCAM-1+ macrophages guide the homing of HSPCs to a vascular niche. *Nature.* 2018; 564(7734):119-124. doi: 10.1038/s41586-018-0709-7
- Liesveld J, Sharma N, Aljitawi O. Stem cell homing: From physiology to therapeutics. *Stem Cells.* 2020; 38(10):1241-1253. doi: 10.1002/stem.3242
- Lin-Li Jiang, Hui Li, Lei Liu. Xenogeneic Stem Cell Transplantation: Research Progress and Clinical Prospects. June 2021 *World Journal of Clinical Cases* 9(16):3826-3837
- Lipton B: The Biology of Belief, 13th (thirteenth) edition. Paperback. Amazon. 2011
- Mansoor Saqi , Johann Pellet et al. *Systems Medicine: The Future of Medical Genomics, Healthcare, and Wellness.* *Methods Mol Biol.* 2016:1386:43-60
- Marc Kirschner *Systems Medicine: Sketching the Landscape.* *Methods Mol Biol.* 2016:1386:3-15.
- Mansoor Saqi , Johann Pellet et al. *Systems Medicine: The Future of Medical Genomics, Healthcare, and Wellness.* *Methods Mol Biol.* 2016:1386:43-60
- Murray M J , B A Lessey. Embryo implantation and tumor metastasis: common pathways of invasion and angiogenesis. *Review. Semin Reprod Endocrinol.* 1999;17(3):275-90
- Niehans, P. *Introduction to Cell Therapy.* Pageant Books, Inc. New York, 1960
- Ole Isacson, Peyman Pakzaban & Wendy R. Galpern Transplanting Fetal Neural Xenogeneic cells in Parkinson's and Huntington's Disease Models.. *Cell Transplantation for Neurological Disorders. Toward Reconstruction of the Human Central Nervous System* Edited by: T. B. Freeman and H. Widner. ©Humana Press Inc., Totowa, NJ (1999)pp 189–210
- Osband, M.E., Lipton, J.M., Lavin, P., et al., (1981). Histiocytosis X: Demonstration of abnormal immunity, T-cell histamine H2-receptor deficiency and successful treatment with thymic extract. *New Engi. J. Med.*, 304, 146-15
- Paul J Mills , Sheila Patel , Tiffany Barsotti , et al., *J Evid Based Complementary Altern Med.* . 2017 Oct;22(4):527-530
- Quesenberry P, Becker P. Stem cell homing: Rolling, crawling, and nesting. *Proc Nat Acad Sci.* 1998;95(26): 15155-15157. doi: 10.1073/pnas.95.26.15155
- Samuel Lessard, Mélissa Beaudoin, Karim Benkirane, and Guillaume Lettre: Comparison of DNA methylation profiles in human fetal and adult red blood cell progenitors. *Genome Med.* 2015; 7(1): 1. doi: 10.1186/s13073-014-0122-
- Schmid F. *Cell therapy.* Thoune, Switzerland: Ott Publishers. 1983
- Schmid F, Stein J. *Cell research and cellular therapy.* Thoune, Switzerland: Ott Publishers. 1967
- Scott Y. H. Kim, MD, PhD, Lauren Schrock, MD, Renee M. Wilson, MA, Samuel A. Frank, MD, Robert G. Holloway, MD, MPH, Karl Kiebertz, MD, MPH, and Raymond G. De Vries, PhD *An Approach to Evaluating Therapeutic Misconception.* *IRB.* 2009 Sep-Oct; 31(5): 7–14).
- Whetton A, Graham G. Homing and mobilization in the stem cell niche. *Trends In Cell Biol.*1999;9(6):233-238. doi: 10.1016/s0962-8924(99) 01559-7
- Wolfram, K W Culbert M L. *Live Cell Therapy. My life with a medical breakthrough.* Constance Books (1 Jan. 1983)
- Xibo Ma et al. Development of new technologies for stem cell research. *J Biomed Biotechnol.* 2012
- Zanjani E, Ascensao J, Tavassoli M. Liver derived fetal hematopoietic stem cells selectively and preferentially home to the fetal bone marrow. *Blood.* 1993; 81(2): 399-404. doi: 10.1182/blood.v81.2.399.399
- Zhong R, Platt JL (November 2005). "Current status of animal-to-human transplantation". *Expert Opinion on Biological Therapy.* 2005 (11): 1415–1420