

The future of stem cell therapy in hernia and abdominal wall repair

A. H. Petter-Puchner · R. H. Fortelny ·
S. Gruber-Blum · H. Redl · U. Dietz

Received: 21 December 2013 / Accepted: 10 July 2014 / Published online: 14 August 2014
© Springer-Verlag France 2014

Abstract

Introduction Stem cell therapies have been proposed in pre-clinical trials as new treatment options in abdominal wall repair.

Materials and Methods This work lists sources of feasible cell lines and the current status of literature and provides a cautious outlook into future developments. Special attention was paid to translational issues and practicability in a complex field.

Conclusion Cell-based therapies will play a role in the clinical setting in the future. Regulatory and ethical issues need to be addressed as well as the proof of cost-effectiveness.

Introduction

Overview

For over two decades, stem cell therapy (SCT) has fuelled the hopes and aspirations of researchers and health care

professionals in regenerative medicine. The magical aura of pluripotency seemed as a promise for the cure of a broad spectrum of diseases, as different as cancer or wound healing [1, 20, 26]. What began as an optimistic journey into the age of cell-based therapies turned in a rocky and twisted road built around ethical, practical and biological uncertainties which have not been overcome to date [4, 9, 31, 32, 36]. SCT entered the realm of abdominal wall repair fuelled by the hope that cell-based therapies could specifically target the underlying pathophysiology of herniosis. In this context, the herniologist (scientist, surgeon or both) is obliged to ask the question if the attempt to implement SCT in a field of comparably low inherent complexity really is a clinical necessity? The necessity to develop new treatment options for challenging procedures in hernia surgery (closure of open abdomen, wound infections, obesity-related issues) is evident [5, 12]. If SCT could be a solution for the remaining hardships in abdominal wall repair cannot be answered today. The body of evidence is weak; experience for the most part is limited to experimental settings and it is hard to predict the course SCT will take in general and in abdominal wall repair in particular. In consequence, this manuscript is not so much a review in a classical sense but more an overview of recent proceedings and an outlook on future possibilities. Based on own research, the authors feel confident that some aspects of SCT will play a role in the treatment of abdominal wall defects.

Classification of stem cells based on their origin (source)

Clarification: Cell potency describes the ability to differentiate into other cell types. Only cells of the morula are totipotent and can become any tissue, whereas pluri-

A. H. Petter-Puchner (✉) · S. Gruber-Blum · H. Redl
Cluster for Tissue Regeneration, Ludwig Boltzmann Institute for
Experimental and Clinical Traumatology, Donaueschingenstr 13,
1200 Vienna, Austria
e-mail: alexander.petter@trauma.lbg.ac.at

A. H. Petter-Puchner · R. H. Fortelny · S. Gruber-Blum
Department of Visceral, General and Oncologic Surgery,
Wilhelminenspital, Vienna, Austria

R. H. Fortelny
Paracelsus Medizinische Privatuniversität, Strubergasse 21,
5020 Salzburg, Austria

U. Dietz
Department of General, Visceral, Vascular and Pediatric
Surgery, University Hospital Wuerzburg, Wuerzburg, Germany

Table 1 Provides an overview of different approaches to cell based abdominal wall therapies and refers to related literature

Stem cell types	Human embryonic cells	Foetal stem cells	Autologous bone marrow stem cells	Stromal vascular fraction	Adipose tissue derived stem cells	Induced stem cells
Abbreviation	HESCs	FSCs	BMSCs	SVF	ASCs	iSCs
Origin	Human embryos fertilized in vitro	Allograft Cord blood Bone marrow Placenta Amnion Amniotic fluid	Autologous	Autologous Digestion of adipose tissue (collagenase)	Expansion of SVF cells adhering to culture plates	Somatic cells
Advantages	Omnipotency	High degree of multipotency	Technically easy access to the cell pool	Heterogenous mesenchymal cell population Stem cells: 3 % High expression of VEGF and bFGF	Decreased oxygen demand Inducing Neovascularisation	Potentially unrestricted pool of somatic cells Predifferentiation
Disadvantages	Ethical concern, Teratogenicity	Availability (tissue banks)	Acceptance of patients (invasive harvesting)	ECM cocktail makes it difficult to assess SC impact to therapeutic success	Longer purification and culturing process than with SVF	Immunogenicity
Potential use in abdominal wall repair	Functional reconstruction	Antiadhesive barrier, improved implant integration	Antiadhesive in combination with alloplastics	Bedside processing, good use of fat tissue for scaffold seeding	Scaffold seeding	Implant/seeding of differentiated cells
Abdominal wall literature	–	Petter-Puchner et al. [37]	Dolce et al. [8]; Zhao et al. [47]	Wolf et al. [45]	Altmann et al. [2]	–

multipotency suggest the potential to differentiate in a limited number of tissues. Pluripotent cells are more versatile and describe the characteristics of embryonic stem cells, multipotent cells are typically found in many adult tissues, e.g., adipose tissue. Oligo- and unipotency is found further down the pathway of differentiation. Lymphoid stem cells are oligopotent (can only differentiate into few cell types; currently it is unclear if truly unipotent cells really exist—even hepatocytes as most differentiated cells known to date are at least bipotent).

An overview of the following chapter is provided in Table 1.

Human embryonic stem cells

Human embryonic stem cells (HESCs) are generated by the transfer of pluripotent cells from a preimplantation-stage embryo to the cell culture. The use of embryos created during in vitro fertilization and HESCs in regenerative medicine has evoked unparalleled emotions based on ethical and religious beliefs and has led to substantial discussions about the necessity and legitimization of limits and

prohibitions in biomedical sciences. Much of the fierceness was based on the initial hopes that embryonic stem cells could serve as universal cure. Today we know that pluripotent stem cells can be derived by other means than sacrificing embryos and that there are also practical reasons to abandon this approach [43, 46]. Embryonic stem cells seem to be related with a higher risk of cancerogenicity and unpredictable differentiation in the hosts organism [17, 43]. Trials using embryonic stem cells for the repair of abdominal wall defects have not been published to the best of our knowledge.

Fetal stem cells

Fetal stem cells (FSCs) represent an intermediate stage between embryonic and adult cell lines. FSCs can be derived from various sources during gestation, such as cord blood, bone marrow or from extraembryonic tissues like placenta or amniotic fluid [8, 16, 34]. FSCs have preserved a high degree of multipotency and seem to be capable to adopt the pluripotent status of embryonic stem cells when exposed to adequate stimulation. In 2011, Petter-Puchner

et al. published a paper on vital human amnion for prevention of adhesions to a polypropylene mesh and enhancing implant integration in experimental IPOM in the rat [37]. Viability was verified prior to implant. The results were excellent with the amnion preventing adhesions efficiently and promoting rapid tissue integration. Amnion was fixed to the mesh with fibrin sealant only and was applied after the mesh was sutured to the abdominal wall. The handling characteristics were outstanding and although the positive effects can not only be contributed to the fetal stem cells contained in the amnion, the potential lies at hand. For this trial, human vital amnion was used, processed under “good manufacturing practice (GMP)” conditions as a side product in an umbilical cord blood bank. In consequence, clinical use was a realistic endeavor and further experiments to evaluate the safety and efficacy of FSCs and amnion in abdominal wall repair seem worthwhile. The major benefits of FSCs are the possibility to obtain them without ethical problems and the practicability to use them already incorporated in a biologic scaffold material (=amnion). However, this approach can hardly be autologous as preservation of amnion or umbilical cord blood is not routinely performed in most countries. Therefore, it remains unclear if immunologic or teratogenic complications could arise. In the preclinical trial, no such adverse effects were observed in a short observation period.

Autologous bone marrow stem (stromal) cells

Bone marrow is a long known and prominent source for hematopoietic and mesenchymal stem cells used in various fields of medicine. The key advantage of mesenchymal bone marrow stem cells (BMSCs) over embryonic or FSCs lay clear at hand-comparably easy access to the cell pool at any timepoint of life, allowing an autologous approach. Two studies must be mentioned in this chapter [8, 47]. In a work published by Dolce from Todd Heniford's group, the effect of BMSC coating on integration and adhesion prevention was tested with three different prosthetic materials [8]. In combination with a polyglactin implant, significantly enhanced adhesion prevention was found. The short observation period of 2 weeks restricts any conclusion and it should be noted that the final stage of adhesions could only be assessed at a later time point when physiological fibrinolysis and enzymatic degradation of adhesions by collagenases are terminated.

The working group around Zhao from China demonstrated the positive effects of BMSCs on the integration of a decellularized dermal collagen matrix in a rabbit model of incisional hernia [47]. In comparison to decellularized collagen alone, cell seeded implants prevented re-herniation and bulging. Integration and cell ingrowth into

collagen was markedly improved over the control group. The observation period of 2 months provided first insights on the behavior of BMSC seeded grafts in a chronic time frame. Time will tell if the clinical benefits of BMSCs in abdominal wall repair can outweigh the practical and ethical obstacles to obtain these cell lines and process them. It is an interesting side mark that McFarlin et al. showed beneficial effects of BMSCs which have been administered systemically in a model of wound healing [30]. The potential of BMSCs to differentiate and display various characteristics (including undesirable ones) cannot be predicted or be safely guided today.

Stromal vascular fraction

The stromal vascular fraction (SVF) is gained by digesting adipose tissue that has been minced into small pieces and digested by collagenases [19].

The cell pellet obtained contains a heterogenous mesodermal cell population consisting of both adipose and hematopoietic stem cells and progenitor cells as well as other cells [3, 49]. The percentage of adipose stem cells and progenitor cells in the SVF is approximately as high as three percent which is a lot more than what can be yielded from bone marrow without expansion [13]. SVF can be used in a wide range of applications in regenerative medicine [25, 27].

SVF injected between dermal tissue and subcutaneous tissue of random skin flaps promotes higher blood flow perfusion and capillary density of flap tissues than a control group. Also, a higher expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) can be found in the SVF group by ELISA. This could mean that the SVF is capable to secrete these two factors and thus increase flap survival [40].

In combination with platelet-rich fibrin, the SVF leads to a higher vessel density in soft tissue augmentation, a significantly reduced resorption rate and enhanced engraftment [28]. SVF is defined as Adipose derived stem cells (ASCs), before they adhere to plastic surfaces in the cell culture. This characteristic leads to possible advantages of SVF, such as avoiding the risk of infection during lengthy cultivation or washing out of growth factors present in the extracellular matrix (ECM). First attempts to use these components of the extracellular matrix for improving implant integration have been published recently with promising results [45].

Adipose tissue derived stem cells

ASCs are gained through culturing of the so-called stromal vascular fraction (SVF; see above) in plastic cell culture flasks, where elongated cells begin to adhere. The selection

of these adherent cells allows the definition of “adipose stromal/stem cells” or “adipose mesenchymal stromal/stem cells”.

ASCs attracted interest due to many useful characteristics like the potential to differentiate along multiple lineage pathways, the easy method of harvesting and the practical way of clinical application [48]. Cell types that can be gained by cultivating ASCs under different conditions are adipocytes, osteoblasts, chondrocytes, myocytes, and neuronal cells. [15, 28, 49]. ASCs have a decreased need for oxygen for surviving and proliferation compared to mature adipocytes and they display better properties under mechanical distress offering a better choice for reconstructing big defects with poor oxygen supply, such as chronic defects in open abdomen [3, 44]. The ability of ASCs to secrete various factors for neo-vascularization is a big advantage, as the need for formation of new vessels is a limiting factor for autologous tissue transfer as well as for reconstruction using scaffolds of critical size [39]. This ability is substance of recent research [38]. An induction of vascular tube formation of endothelial cells in a fibrin matrix by ASCs has been shown [18].

In this context, we refer to the pioneering work of the study group around Butler from Houston, TX [2]. The authors showed that ASCs led to an improved integration of a porcine acellular dermal matrix. The issue of boosting the performance of biologic hernia implants using stem cell seeding will be picked up in the discussion section.

Induced stem cells

The reversal (metaplasia) of somatic cells to a pluripotent stage is a physiologically observed phenomenon, for example, in the repair of tissue injury in the gastrointestinal tract [9]. Induced stem cells (iSCs) are most often created for therapeutic purposes by somatic cell nuclear transfer (the nucleus of an egg cell is brought into another somatic cell). This is a potent technique, most prominently investigated and exploited in attempts of cloning endangered animal species [35, 42] among others. The idea to epigenetically reprogram a given somatic cell and come up with a multi(toti) potent iSC is tempting. Ethical issues need to be addressed as egg cells are not autologously available to all patients. However, concerns have been raised that iSCs are acting antigenic and could be rejected by the host. The reasons for this are only partly understood but seem to be substantially hindering to the rise of this intriguing approach [10].

“Other than stem cell” approaches: fibroblasts, myoblasts, tenocytes, extracellular matrix (plasma)

Among others, a seemingly practical approach to mesh coating is the concept of seeding implants with autologous

fibroblasts. A study of Lai et al. published in 2003 on a rat study of small intestine submucosa seeded with fibroblasts was arguably among the first publications on the issue of abdominal wall repair using stem cells techniques ever [24]. More recent publications could demonstrate the improvement of biocompatibility of synthetic mesh materials after incubation with autologous plasma as source of autologous multipotent cells [14, 25]. This is another example of ECM-based therapies. Song et al. brought forward the concept of seeding small intestine submucosa with tenocytes and demonstrated promising results in terms of mechanical endurance [41]. Myoblasts were used by De Coppi et al. as another potential source of autologous cell therapy in experimental research [7, 14, 25]. Satellite progenitor cells are another pool of potentially useful cells but robust data are missing [29]. The studies mentioned in this paragraph are united by the use of autologous cell pools and interesting findings on the feasibility to attach and seed them on acellular matrices [6]. However, more robust preclinical sequels to rather small pilot studies are often missing.

Discussion

As it is the aim of this work to give an overview of stem cell research in hernia and abdominal wall repair, this chapter will focus on three specific issues relevant to surgeons rather than offering a broad, encyclopedic discussion on SCT in general. First, which stem cell lines could possibly play a role in the field in the near future? Second, how will these cells contribute to the clinical benefit? Third, what are the expectations and limitations of stem cells improving existing implant materials?

It seems evident that any kind of SCT in abdominal wall surgery must be easily accessible in terms of obtaining, processing and re-implanting the pluripotent cells. In our mind, these considerations will determine future preferences for the cell sources. The desired outcome, viable and functional collagen (and muscle at best) lie clear at hand and relativise the question whether ASCs, fibroblasts or hamatopoetic SCs should be addressed. Currently, these demands clearly point to ASCs and SVF. Especially, SVF allows a rapid procedure from harvesting to re-implanting within a few hours. The time factor does not only cut costs, reduce risks of infections in the culture but also facilitates any regulatory issue related to long-term preservation. BMSCs are among the best investigated options in SCT, but, in our opinion, the invasiveness of obtaining the cells (with regard to pain and possible complications) was only justified if the superiority of a treatment with BMSCs for an abdominal wall repair-related indication could be proven. This, indeed, is purely speculative, rendering BMSCs

as an unpractical approach. Although most will agree that an autologous approach should be preferred to an allogenic transplant for the same reasons as well as to reduce possible immunologic complications, it must be noted that human vital amnion containing fetal stem cells is truly an amazing matrix to work with in hernia repair [33, 37]. Chronic data on adverse effects of amnion and fetal stem cells are currently missing, but this option should not be discarded right away. A recent study by Fatimah et al. revealed that human amnion cells differentiate to epidermal cells when cultured at an air–liquid interface. This finding is not only interesting for the treatment of acute wounds but could also open new possibilities in the management of chronic wounds, such as closure of open abdomen, in which the use of amnion layered scaffolds was a tempting perspective [11]. In summary, we strongly believe that adipose tissue will be the most accessible source for SCT in abdominal wall repair and that umbilical cord blood and amnion banks could regain more attention in this context.

Which clinical benefits can be expected from SCT in abdominal wall repair? Current data point to enhanced tissue integration of implants and adhesion prevention. The aim of restoring function has recently moved in the background because it is unclear how the desired differentiation can be achieved in a reproducible manner. It is evident that the improvement of implant integration could play a key role for the fast incorporation of three-dimensional scaffolds in the treatment of large, complex defects. These defects are more common in the pelvic floor after abdominoperineal resections of rectal carcinomas than in hernia repair [21, 22]. For both indications, it is unwise to use SCT as shortcut to close contaminated defects hastily. Poor wound conditions at the defect site (infection, little vascularization, immunologic deficiencies) cannot be “levelled” by any (biologic or synthetic) material or cell therapy. Concerning adhesion prevention, the technical difficulties to reliably attach stem cells to a scaffold material must be underlined. The desired neo-peritonealisation occurs foremost by diffusion of mesothelial cells from the visceral side, eliciting vascularization and fibroblastic ingrowth from the parietal side [45]. This fragile equilibrium can easily be disturbed by immunologic responses to the cell/scaffold compound, resulting in a foreign body reaction and causing adhesions. In contrast, if stem cells detach from their matrix prematurely, their possible impact is annihilated. In our hands, fibrin sealant proved as excellent agent to firmly place human vital amnion containing fetal stem cells over a polypropylene meshes and fixation sutures. Embedding stem cells in porous, three-dimensional scaffolds is another feasible option, requiring new implant designs.

When considering recent discussions and current trends, the authors express their belief that SCT cannot serve to

compensate shortcomings of existing devices. This is especially true for obvious attempts to tune the integration of various collagen matrices. SCT will only provide the full array of benefits if all components are carefully selected to work in synergy. This matters specifically in patients in which a collagen disease (“herniosis”) might be responsible for the hernia [23]. It is simply not known if autologous cell therapies could offer any benefit in these patients or if they just contributed to the production of insufficient collagen at the defect site. Any approach to implement SCT as marketing tool or as justification to abandon evidence-based principles of abdominal wall repair will be doomed to fail and cause serious damage to the reputation of these techniques. This is even more important in a field where the standard of care is already extremely high. Finally, it must be emphasized that even the most intriguing concepts (e.g., systemic administration of cells) will have to pass ever more demanding regulatory restrictions, such as the advanced therapy medicinal product (ATMP), issued by the European medicines agency [30].

Conclusion

SCT will play a role in abdominal wall repair to enhance tissue integration and prevent adhesion formation. May be restoring function could become a later goal. Feasible approaches include autologous cell harvesting from adipose tissue and fetal stem cells as an autologous or allogenic option. New implant materials are needed to comply with the specific demands. SCT must not be abused as salvage maneuver for critical devices or techniques. With all respect for progressiveness and SCT triggered enthusiasm, the criteria of evidence-based medicine must be obeyed for the sake of our patients.

Acknowledgments The authors report that they have no disclosures or financial interests in conducting and publishing this review.

References

1. Adas G, Kemik O, Eryasar B et al (2013) Treatment of ischemic colonic anastomoses with systemic transplanted bone marrow derived mesenchymal stem cells. *Eur Rev Med Pharmacol Sci* 17:2275–2285
2. Altman AM, Abdul Khalek FJ, Alt EU, Butler CE (2010) Adipose tissue-derived stem cells enhance bioprosthetic mesh repair of ventral hernias. *Plast Reconstr Surg* 126:845–854. doi:10.1097/PRS.0b013e3181e6044f
3. Astori G, Vignati F, Bardelli S et al (2007) “In vitro” and multicolor phenotypic characterization of cell subpopulations identified in fresh human adipose tissue stromal vascular fraction and in the derived mesenchymal stem cells. *J Transl Med* 5:55. doi:10.1186/1479-5876-5-55

4. Bryan N, Ahswin H, Smart N et al (2013) The in vivo evaluation of tissue-based biomaterials in a rat full-thickness abdominal wall defect model. *J Biomed Mater Res Part B Appl Biomater*. doi:[10.1002/jbm.b.33050](https://doi.org/10.1002/jbm.b.33050)
5. Chatterjee A, Krishnan NM, Rosen JM (2013) Complex ventral hernia repair using components separation with or without biologic mesh: a cost-utility analysis. *Ann Plast Surg*. doi:[10.1097/SAP.0b013e31829fd306](https://doi.org/10.1097/SAP.0b013e31829fd306)
6. Davis RP, Nemes C, Varga E et al (2013) Generation of induced pluripotent stem cells from human foetal fibroblasts using the Sleeping Beauty transposon gene delivery system. *Differentiation* 86:30–37. doi:[10.1016/j.diff.2013.06.002](https://doi.org/10.1016/j.diff.2013.06.002)
7. De Coppi P, Bellini S, Conconi MT (2006) Myoblast-acellular skeletal muscle matrix constructs guarantee a long-term repair of experimental full-thickness abdominal wall defects. *Tissue Eng Jul* 12(7):1929–1936
8. Dolce CJ, Stefanidis D, Keller JE et al (2010) Pushing the envelope in biomaterial research: initial results of prosthetic coating with stem cells in a rat model. *Surg Endosc* 24:2687–2693. doi:[10.1007/s00464-010-1026-x](https://doi.org/10.1007/s00464-010-1026-x)
9. Ethics Committee of American Society for Reproductive Medicine (2013) Donating embryos for human embryonic stem cell (hESC) research: a committee opinion. *Fertil Steril* 100:935–939. doi:[10.1016/j.fertnstert.2013.08.038](https://doi.org/10.1016/j.fertnstert.2013.08.038)
10. Fairchild P (2013) Interview: immunogenicity: the elephant in the room for regenerative medicine? Interviewed by Alexandra Hemsley. *Regen Med* 8:23–26. doi:[10.2217/rme.12.110](https://doi.org/10.2217/rme.12.110)
11. Fatimah SS, Chua K, Tan GC et al (2013) Organotypic culture of human amnion cells in air-liquid interface as a potential substitute for skin regeneration. *Cytherapy* 15:1030–1041. doi:[10.1016/j.jcyt.2013.05.003](https://doi.org/10.1016/j.jcyt.2013.05.003)
12. Fortelny RH, Hofmann A, Gruber-Blum S et al (2013) Delayed closure of open abdomen in septic patients is facilitated by combined negative pressure wound therapy and dynamic fascial suture. *Surg Endosc*. doi:[10.1007/s00464-013-3251-6](https://doi.org/10.1007/s00464-013-3251-6)
13. Fraser JK, Zhu M, Wulur I, Alfonso Z (2008) Adipose-derived stem cells. *Methods Mol Biol* 449:59–67. doi:[10.1007/978-1-60327-169-1_4](https://doi.org/10.1007/978-1-60327-169-1_4)
14. Gerullis H, Georgas E, Eimer C et al (2013) Coating with autologous plasma improves biocompatibility of mesh grafts in vitro: development stage of a surgical innovation. *Biomed Res Int* 2013:536814. doi:[10.1155/2013/536814](https://doi.org/10.1155/2013/536814)
15. Gimble JM, Bunnell BA, Guilak F (2012) Human adipose-derived cells: an update on the transition to clinical translation. *Regen Med* 7:225–235. doi:[10.2217/rme.11.119](https://doi.org/10.2217/rme.11.119)
16. Grumezescu AM, Holban AM, Andronesu E et al (2013) Anionic polymers and 10 nm Fe₃O₄@UA wound dressings support human foetal stem cells normal development and exhibit great antimicrobial properties. *Int J Pharm*. doi:[10.1016/j.ijpharm.2013.08.026](https://doi.org/10.1016/j.ijpharm.2013.08.026)
17. Herbets CA, Kwa MSG, Hermesen HPH (2011) Risk factors in the development of stem cell therapy. *J Transl Med* 9:29. doi:[10.1186/1479-5876-9-29](https://doi.org/10.1186/1479-5876-9-29)
18. Holthoner W, Hohenegger K, Husa A-M (2012) Adipose-derived stem cells induce vascular tube formation of outgrowth endothelial cells in a fibrin matrix. *J Tissue Eng Regen Med*. doi:[10.1002/term.1620](https://doi.org/10.1002/term.1620)
19. Katz AJ, Llull R, Hedrick MH, Futrell JW (1999) Emerging approaches to the tissue engineering of fat. *Clin Plast Surg* 26:587–603
20. Keeney M, Deveza L, Yang F (2013) Programming stem cells for therapeutic angiogenesis using biodegradable polymeric nanoparticles. *J Vis Exp* e50736. doi:[10.3791/50736](https://doi.org/10.3791/50736)
21. Killeen S, Devaney A, Mannion M et al (2013) Omental pedicle flaps following proctectomy: a systematic review. *Colorectal Dis* 15:e634–e645. doi:[10.1111/codi.12394](https://doi.org/10.1111/codi.12394)
22. Killeen S, Mannion M, Devaney A, Winter DC (2013) Omentoplasty to assist perineal defect closure following laparoscopic abdominoperineal resection. *Colorectal Dis* 15:e623–e626. doi:[10.1111/codi.12426](https://doi.org/10.1111/codi.12426)
23. Klinge U, Junge K, Mertens PR (2004) Herniosis: a biological approach. *Hernia* Dec 8(4):300–301
24. Lai JY, Chang PY, Lin JN (2003) Body wall repair using small intestinal submucosa seeded with cells. *J Pediatr Surg* 38(12):1752–1755 PubMed PMID: 14666459
25. Lee VK, Singh G, Trasatti JP et al (2013) Design and fabrication of human skin by 3d bioprinting. *Tissue Eng Part C Methods*. doi:[10.1089/ten.TEC.2013.0335](https://doi.org/10.1089/ten.TEC.2013.0335)
26. Lee WYW, Zhang T, Lau CPY et al (2013) Immortalized human fetal bone marrow-derived mesenchymal stromal cell expressing suicide gene for anti-tumor therapy in vitro and in vivo. *Cytherapy* 15:1484–1497. doi:[10.1016/j.jcyt.2013.06.010](https://doi.org/10.1016/j.jcyt.2013.06.010)
27. Li L-Q, Gao J-H, Lu F et al (2012) Experimental study of the effect of adipose stromal vascular fraction cells with VEGF on the neovascularization of free fat transplantation. *Zhonghua Zheng Xing Wai Ke Za Zhi* 28:122–126
28. Liu B, Tan X-Y, Liu Y-P et al (2013) The adjuvant use of stromal vascular fraction and platelet-rich fibrin for autologous adipose tissue transplantation. *Tissue Eng Part C Methods* 19:1–14. doi:[10.1089/ten.TEC.2012.0126](https://doi.org/10.1089/ten.TEC.2012.0126)
29. Logan MS, Propst JT, Nottingham JM et al (2010) Human satellite progenitor cells for use in myofascial repair: isolation and characterization. *Ann Plast Surg* 64(6):794–799. doi:[10.1097/SAP.0b013e3181b025cb](https://doi.org/10.1097/SAP.0b013e3181b025cb)
30. McFarlin K, Gao X, Liu YB, Dulchavsky DS et al (2006) Bone marrow-derived mesenchymal stromal cells accelerate wound healing in the rat. *Wound Repair Regen* 14(4):471–478
31. Mertes H (2013) A moratorium on breeding better babies. *J Med Ethics*. doi:[10.1136/medethics-2013-101560](https://doi.org/10.1136/medethics-2013-101560)
32. Niemansburg SL, Teraa M, Hesam H et al (2013) Stem cell trials for cardiovascular medicine: ethical rationale. *Tissue Eng Part A*. doi:[10.1089/ten.TEA.2013.0332](https://doi.org/10.1089/ten.TEA.2013.0332)
33. Niknejad H, Paeini-Vayghan G, Tehrani FA et al (2013) Side dependent effects of the human amnion on angiogenesis. *Placenta* 34:340–345. doi:[10.1016/j.placenta.2013.02.001](https://doi.org/10.1016/j.placenta.2013.02.001)
34. Nirmal RS, Nair PD (2013) Significance of soluble growth factors in the chondrogenic response of human umbilical cord matrix stem cells in a porous three dimensional scaffold. *Eur Cell Mater* 26:234–251
35. Perota A, Lagutina I, Duchi R et al (2013) 215 live piglets generated by somatic cell nuclear transfer following targeting of a porcine enhanced green fluorescent protein line mediated by zinc-finger nucleases to establish cloned hygromycin-resistant primary cell lines suitable for cre-mediated recombinase-mediated cassette exchange. *Reprod Fertil Dev* 26:221–222. doi:[10.1071/RDv26n1Ab215](https://doi.org/10.1071/RDv26n1Ab215)
36. Petter-Puchner AH, Dietz UA (2013) Biological implants in abdominal wall repair. *Br J Surg* 100:987–988. doi:[10.1002/bjs.9156](https://doi.org/10.1002/bjs.9156)
37. Petter-Puchner AH, Fortelny RH, Mika K et al (2010) Human vital amniotic membrane reduces adhesions in experimental intraperitoneal onlay mesh repair. *Surg Endosc* 25:2125–2131. doi:[10.1007/s00464-010-1507-y](https://doi.org/10.1007/s00464-010-1507-y)
38. Rada T, Reis RL, Gomes ME (2009) Adipose tissue-derived stem cells and their application in bone and cartilage tissue engineering. *Tissue Eng Part B Rev* 15:113–125. doi:[10.1089/ten.teb.2008.0423](https://doi.org/10.1089/ten.teb.2008.0423)
39. Rehman J, Traktuev D, Li J et al (2004) Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation* 109:1292–1298. doi:[10.1161/01.CIR.0000121425.42966.F1](https://doi.org/10.1161/01.CIR.0000121425.42966.F1)
40. Sheng L, Yang M, Li H et al (2011) Transplantation of adipose stromal cells promotes neovascularization of random skin flaps. *Tohoku J Exp Med* 224:229–234

41. Song Z, Peng Z, Liu Z, Yang J, Tang R, Gu Y (2013) Reconstruction of abdominal wall musculofascial defects with small intestinal submucosa scaffolds seeded with tenocytes in rats. *Tissue Eng Part A* 19(13–14):1543–1553
42. Stroud T, Xiang T, Romo S, Kjelland ME (2013) 38 rocky mountain bighorn sheep (*ovis canadensis canadensis*) embryos produced using somatic cell nuclear transfer. *Reprod Fertil Dev* 26:133. doi:[10.1071/RDv26n1Ab38](https://doi.org/10.1071/RDv26n1Ab38)
43. Sykova E, Forostyak S (2013) Stem cells in regenerative medicine. *Laser Ther* 22:87–92. doi:[10.3136/islsm.22.87](https://doi.org/10.3136/islsm.22.87)
44. Von Heimburg D, Hemmrich K, Zachariah S et al (2005) Oxygen consumption in undifferentiated versus differentiated adipogenic mesenchymal precursor cells. *Respir Physiol Neurobiol* 146:107–116. doi:[10.1016/j.resp.2004.12.013](https://doi.org/10.1016/j.resp.2004.12.013)
45. Wolf MT, Carruthers CA, Dearth CL et al (2013) Polypropylene surgical mesh coated with extracellular matrix mitigates the host foreign body response. *J Biomed Mater Res A*. doi:[10.1002/jbm.a.34671](https://doi.org/10.1002/jbm.a.34671)
46. Zhang WY, de Almeida PE (2008) A tool for monitoring pluripotency in stem cell research. *StemBook*. Teratoma Formation, Cambridge
47. Zhao Y, Zhang Z, Wang J et al (2012) Abdominal hernia repair with a decellularized dermal scaffold seeded with autologous bone marrow-derived mesenchymal stem cells. *Artif Organs* 36:247–255. doi:[10.1111/j.1525-1594.2011.01343.x](https://doi.org/10.1111/j.1525-1594.2011.01343.x)
48. Zuk PA, Zhu M, Mizuno H et al (2001) Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 7:211–228. doi:[10.1089/107632701300062859](https://doi.org/10.1089/107632701300062859)
49. Zuk PA, Zhu M, Ashjian P et al (2002) Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 13:4279–4295. doi:[10.1091/mbc.E02-02-0105](https://doi.org/10.1091/mbc.E02-02-0105)