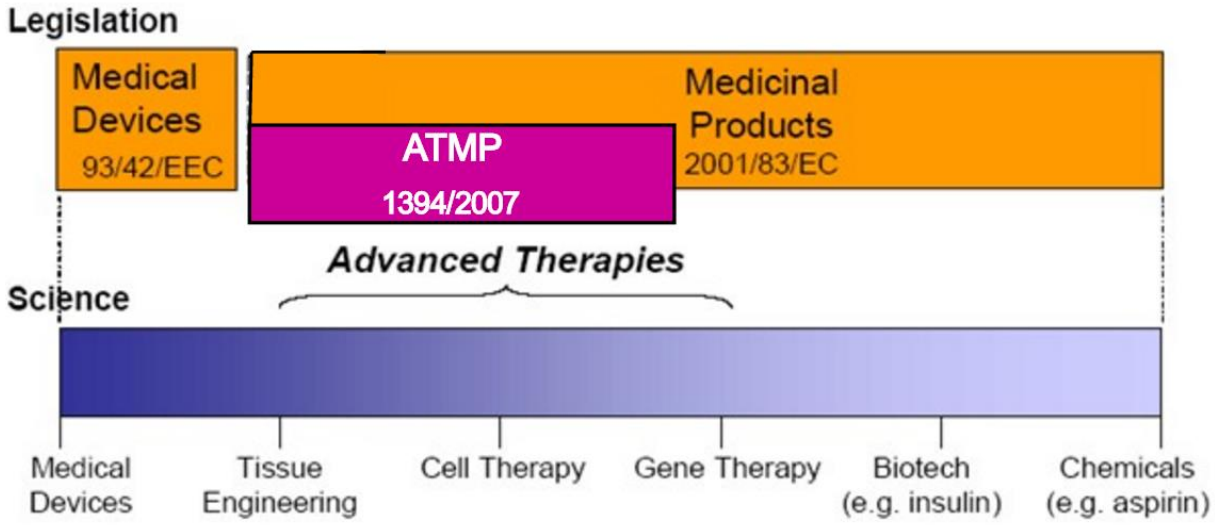
Stem Cell Therapy for Wound Healing in Diabetic Limb

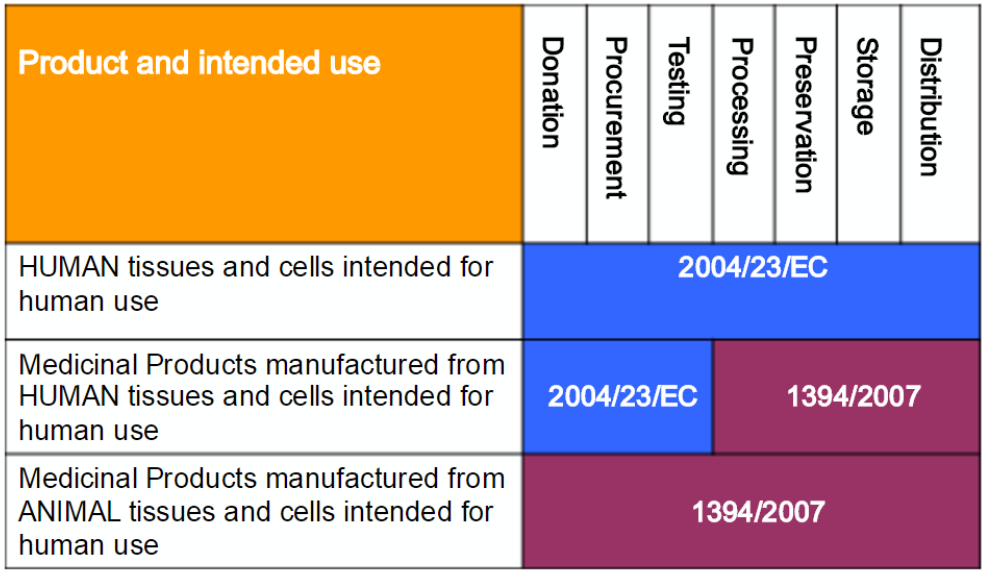
Tanom Bunaprasert M.D.
EC-ATMPs
(EC- Advanced Therapy Medicinal Products)
Chulalongkorn Hospital

Advanced Therapy Medicinal Products



Advanced Therapy Medicinal Products

Applicable regulatory framework for cell based (medical) products for human use.



Product and intended use	Donation	Procurement	Testing	Processing	Preservation	Storage	Distribution
HUMAN tissues and cells intended for human use	2004/23/EC						
Medicinal Products manufactured from HUMAN tissues and cells intended for human use	2004/23/EC			1394/2007			
Medicinal Products manufactured from ANIMAL tissues and cells intended for human use	1394/2007						

SIGNIFX
Quality and Regulatory in Life Sciences

Regulation is Risk-Based

- Cell therapy, gene therapy, and tissue-engineered products are complex living biologics, and are being developed in novel, evolving ways. Regulation of these products commonly reflects their novel, diverse nature.
- Regulations define criteria for product safety, identity, purity, potency, and clinical efficacy.
- FDA follows a science-driven, **risk-based approach** in evaluating whether and how these criteria have been met.
- Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.

FDA's Risk-Based Regulatory Framework for Cell and Gene Therapy Products

- Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
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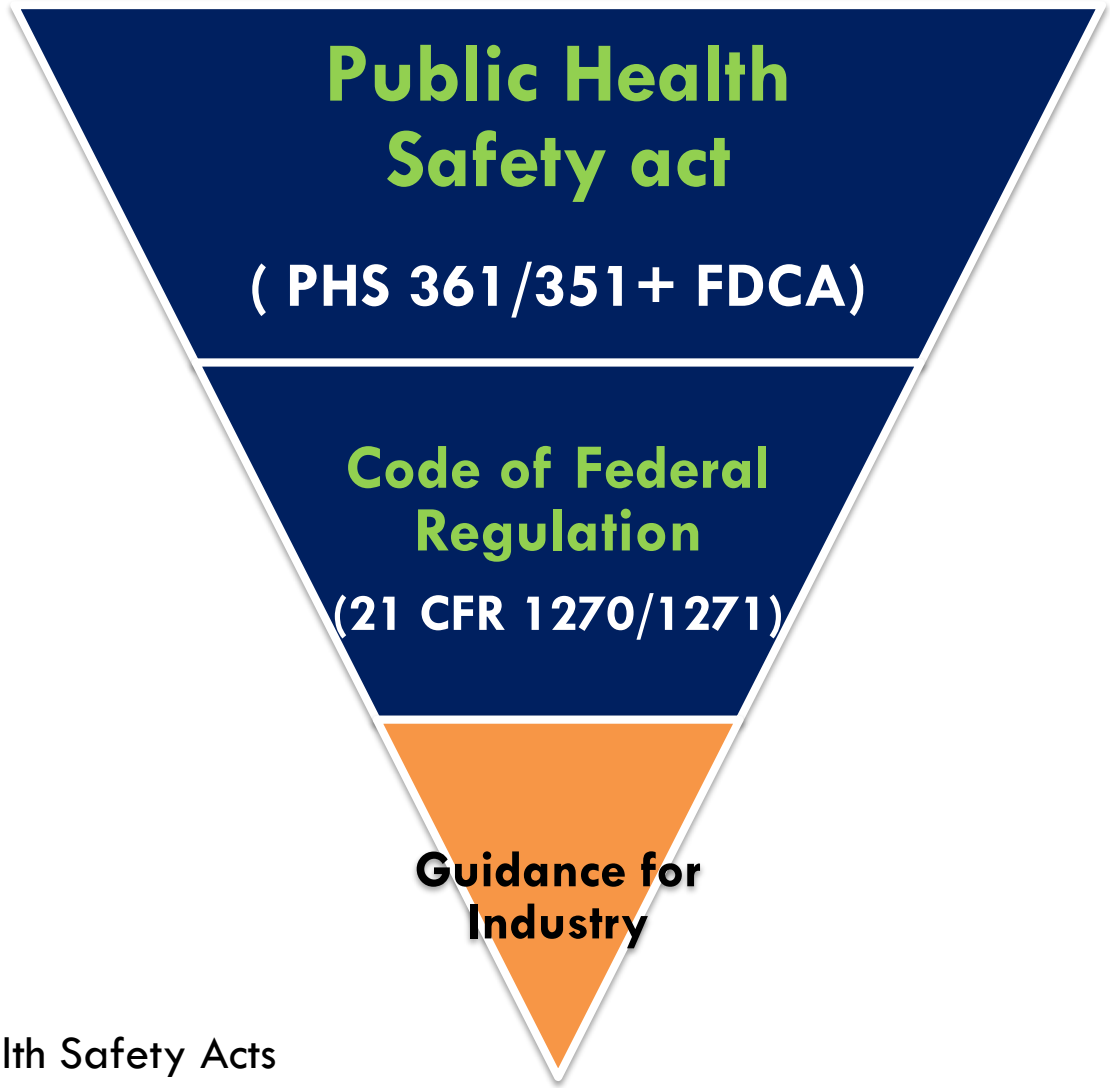
Lower Risk, "361" Products	Higher Risk, "351" Products
Comparatively simple, well-understood products, low-risk applications • Minimal manipulation, homologous use only, not combined with another article, no systemic effect (with some exceptions)	More complex, novel biologic products, higher-risk applications • Does not meet *all* criteria for a "361" product • Cells expanded *ex vivo*, gene-modified, activated, etc.
No requirement for clinical trials or pre-marketing approval	Require clinical trials to establish safety/efficacy prior to marketing approval
Must comply with Good Tissue Practices (GTPs), 21 CFR Part 1271	Must comply with Good Manufacturing Practices (GMPs) *and* GTPs

FDA Requirements - GMPs, GTPs, GCPs

Good Manufacturing Practices (GMPs)	Ensure consistent manufacture of safe, pure, potent products
Good Tissue Practices (GTPs)	Prevent infectious disease transmission Donor screening and testing
	Prevent cross-contamination, mixups Product recovery, processing, storage, labeling, distribution
Good Clinical Practices (GCPs)	Ethical, scientific quality standards Protect trial subjects rights, safety, confidentiality Assure credibility of clinical trial data

Authority of Laws

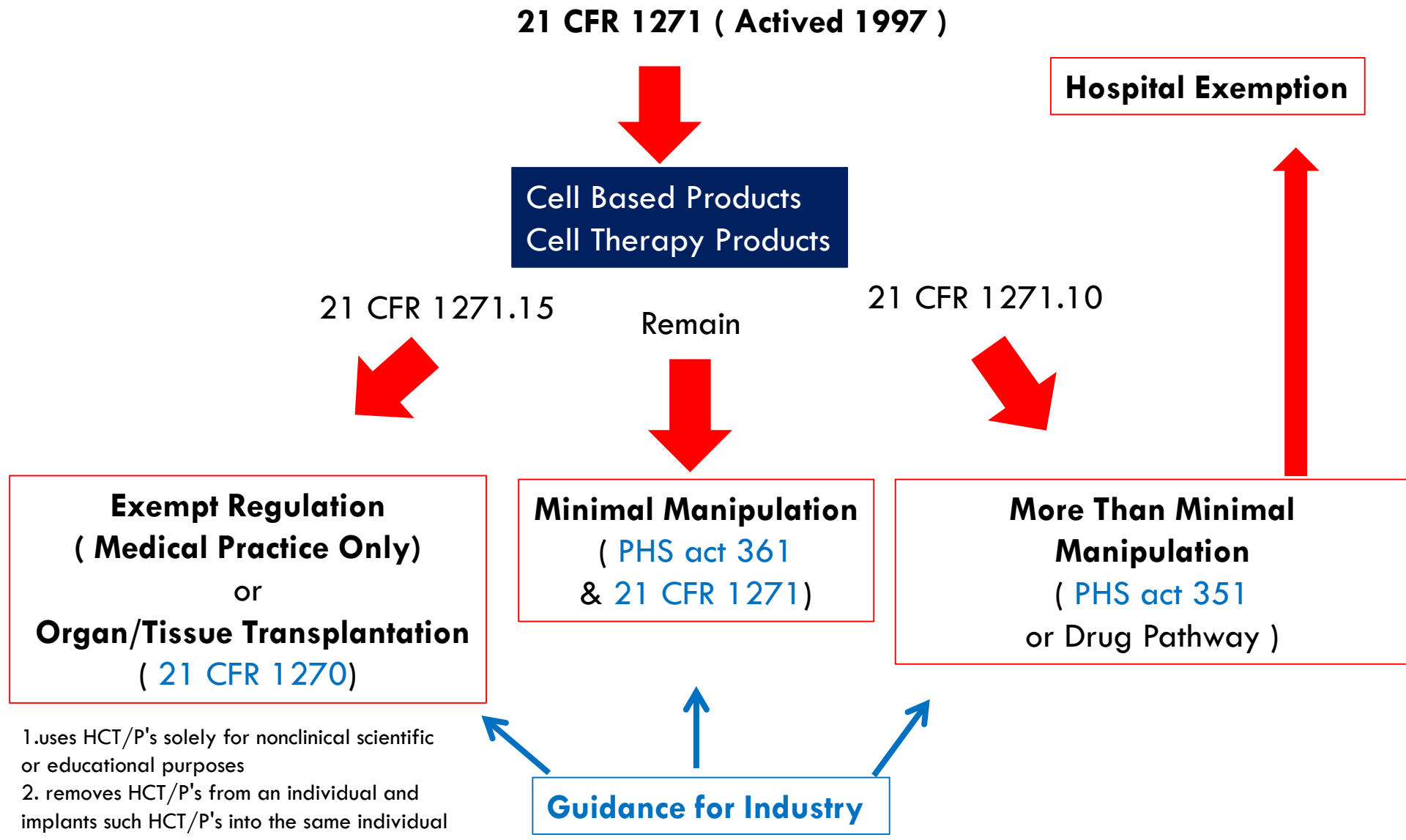


PHSA = Public Health Safety Acts
FDCA = Food Drug and Cosmetics Acts

Important !

Application of FDA Regulatory Requirements

	361 HCT/P	351 HCT/P	
	Tissue	Biologic Therapeutics	Device
Applicable Laws	361 PHS Act	361 PHS Act, 351 PHS Act, FD&C Act	FD&C Act
Applicable Regulations	21 CFR 1271	21 CFR 1271, 21 CFR 600's, 21 CFR 200's 21 CFR 300's	21 CFR 800's
Marketing Pathway	Premarket review not required	BLA	PMA, 510(k), HDE


21 CFR 1271 (Actived 1997)
Hospital Exemption
Cell Based Products
Cell Therapy Products
21 CFR 1271.15
Remain
21 CFR 1271.10
Exempt Regulation
(Medical Practice Only)
or
Organ/Tissue Transplantation
(21 CFR 1270)
Minimal Manipulation
(PHS act 361
& 21 CFR 1271)
More Than Minimal
Manipulation
(PHS act 351
or Drug Pathway)
1.uses HCT/P's solely for nonclinical scientific or educational purposes
2. removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure
Guidance for Industry

21CFR 1271.10 …… Identify ….. Minimal or More Than - Minimal Manipulation

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

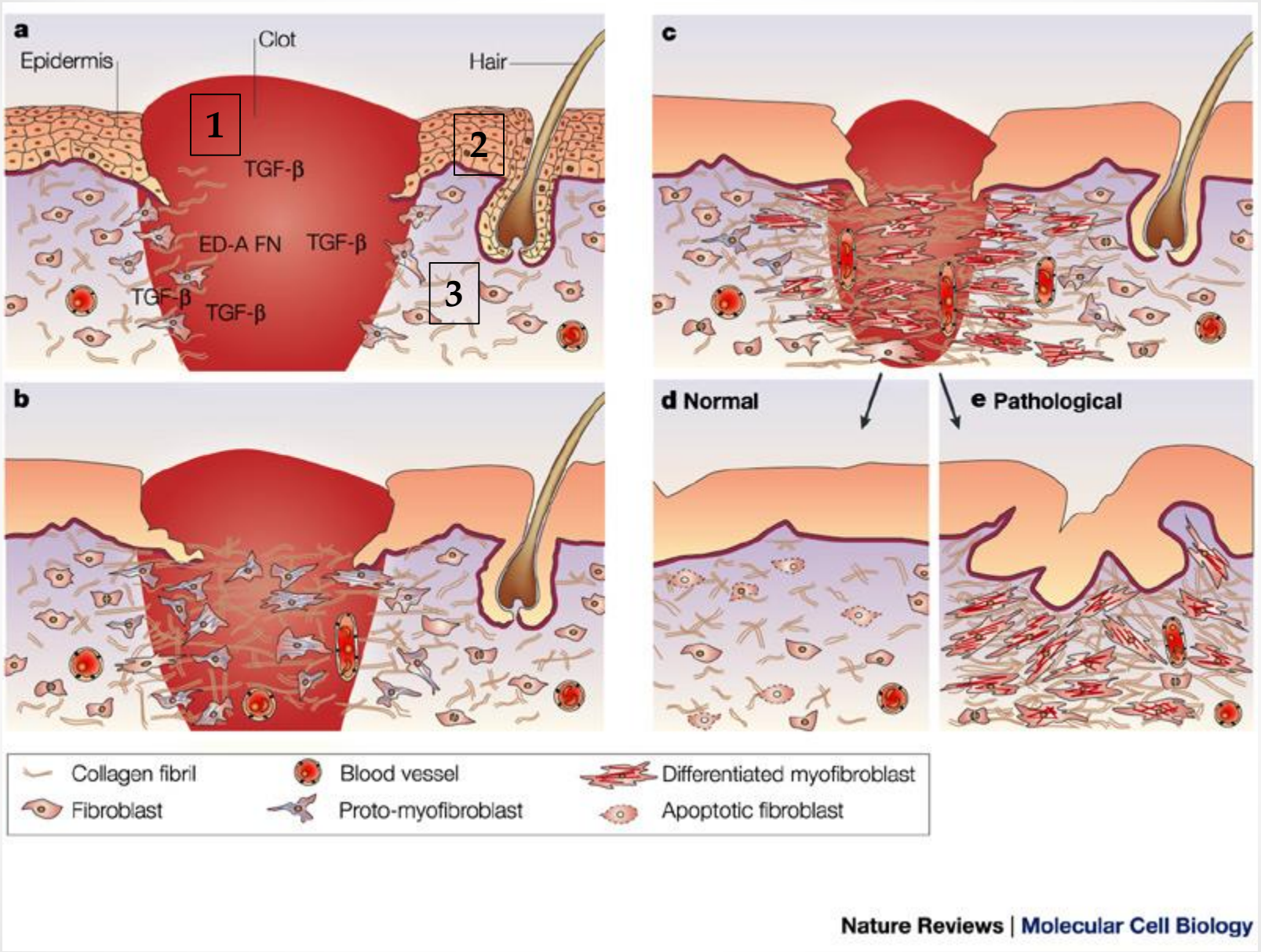
(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
(*a*) Is for autologous use;
(*b*) Is for allogeneic use in a first-degree or second-degree blood relative; or
(c) Is for reproductive use.
(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:
(1) You must register with FDA;
(2) You must submit to FDA a list of each HCT/P manufactured; and
(3) You must comply with the other requirements contained in this part.

Design Regeneration

Tissue Engineering Concepts

Tissue Engineered - Wound Healing



INTRODUCTION

Multicellular tissues exist in one of two types of cellular arrangements, epithelial or mesenchymal. Epithelial cells adhere tightly to each other at their lateral surfaces and to an organized extracellular matrix (ECM) at their basal domain, thereby producing a sheet of cells resting on a basal lamina with an apical surface. Mesenchymal cells, in contrast, are individual cells with a bipolar morphology that are held together as a tissue within a three-dimensional ECM (see Fig. 1.1). The conversion of epithelial cells into mesenchymal cells, an "epithelial-mesenchymal transition" (EMT), is central to many aspects of embryonic morphogenesis and adult tissue repair, as well as a number of disease states (Hay, 2005; Baum et al., 2008; Thiery et al., 2009). The reverse process whereby mesenchymal cells coalesce into an epithelium is a "mesenchymal-epithelial transition" (MET). Understanding the molecules that regulate this transition between epithelial and mesenchymal states offers important insights into how cells and tissues are organized.

Epithelial - Mesenchymal Transition (EMT)
Mesenchymal - Epithelial Transition (MET)

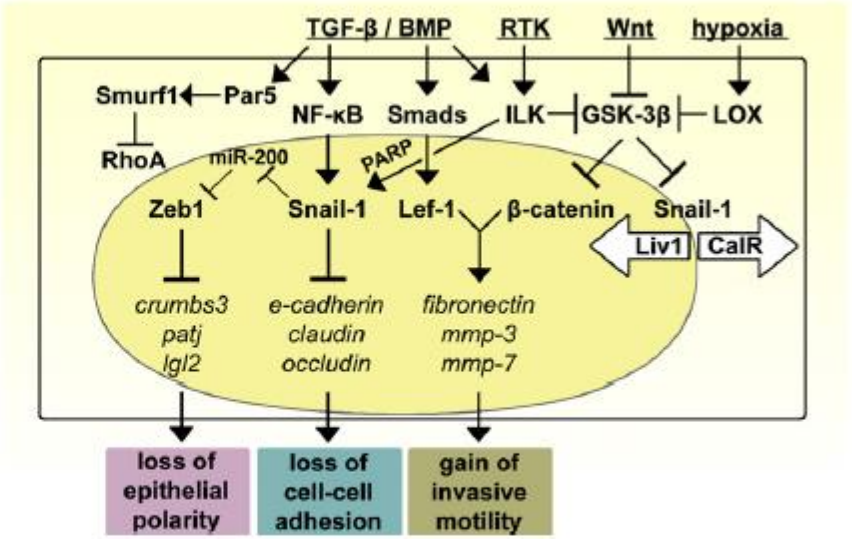


FIGURE 1.2

Induction of an EMT. This figure summarizes some of the important molecular pathways that bring about an EMT. Many of the signaling pathways converge on the activation of Snail-1 and nuclear β-catenin signaling to change gene expression, which results in the loss of epithelial cell polarity, the loss of cell-cell adhesion, and increased invasive cell motility.

DFU Problems = Surrounding (Wound Base) Problems
Which interfere wound closure

Poor wound base **reaction** = cell + signaling + supply

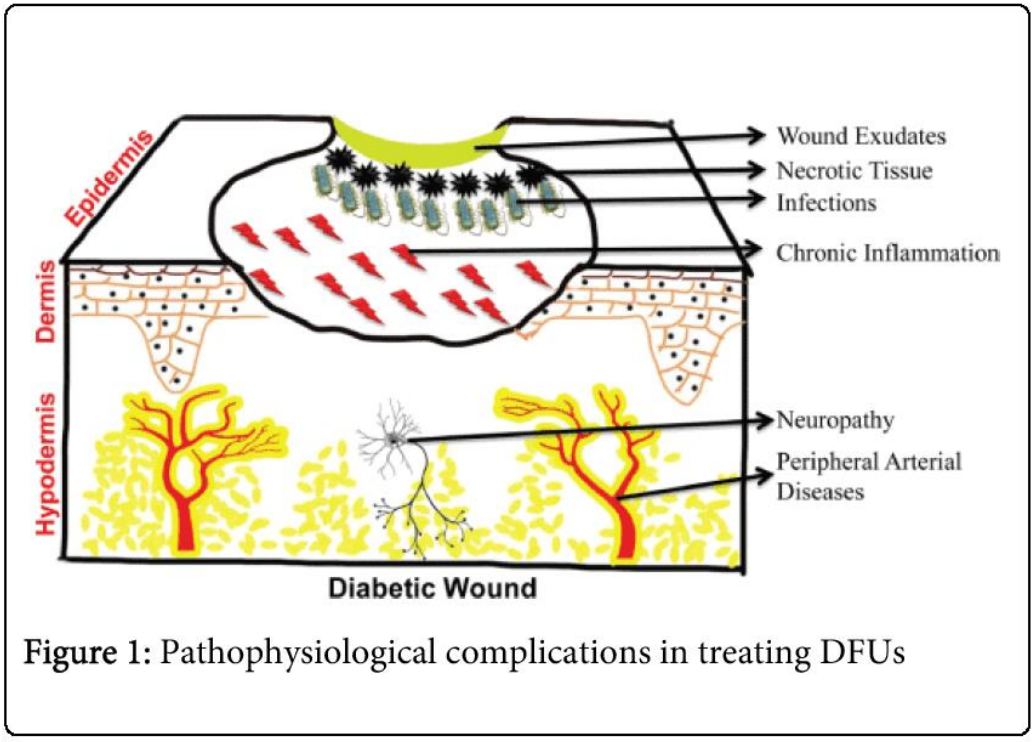
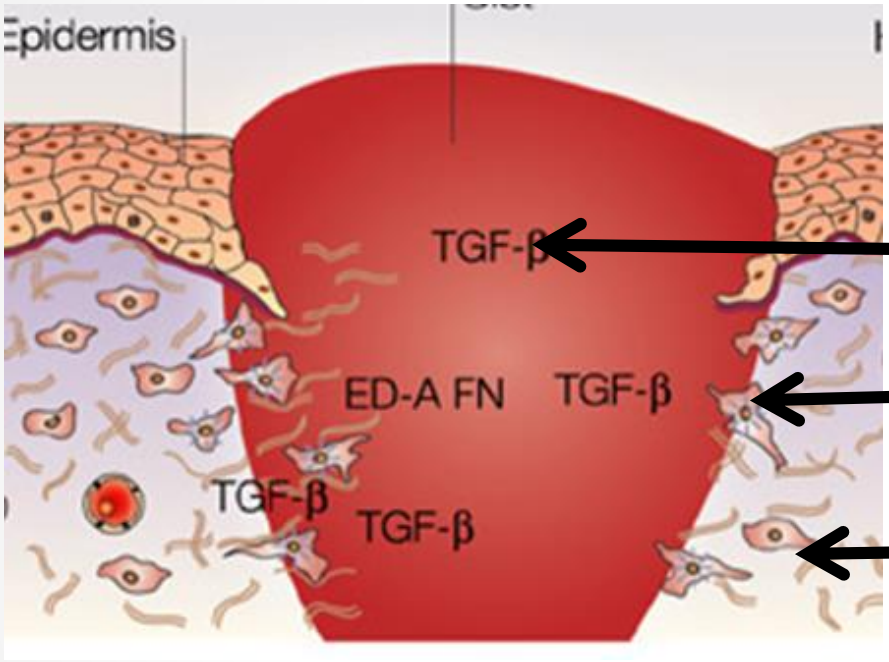


Figure 1: Pathophysiological complications in treating DFUs

Design Concepts

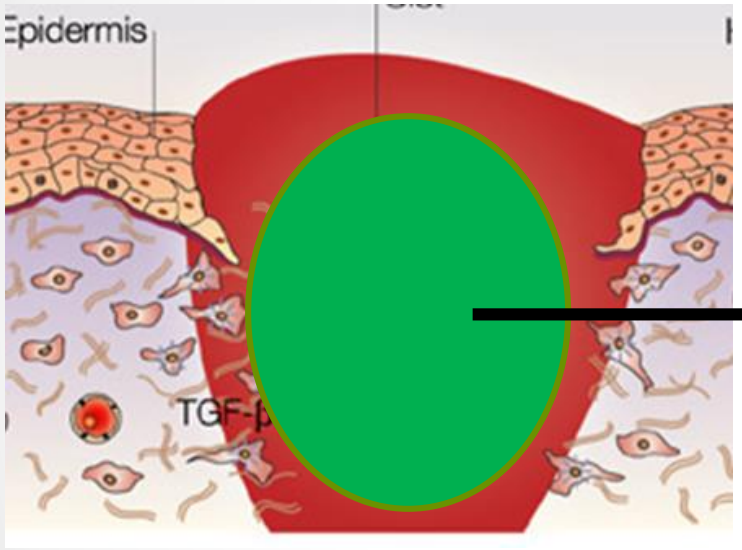


1.Defect Cavity (clot /debris)

2.Interface (Living/non Living)

3. Surrounding (Wound Base)

1 Tropical Products



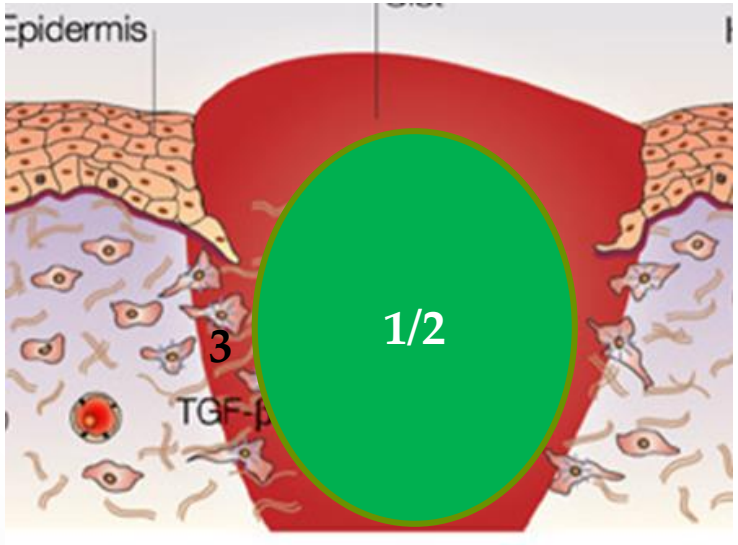
Device = Biomaterials

Drug- Device = Biomaterials + Drugs

Biologics – Device = Biomaterials + Biologics
(Tissue Engineered Products)

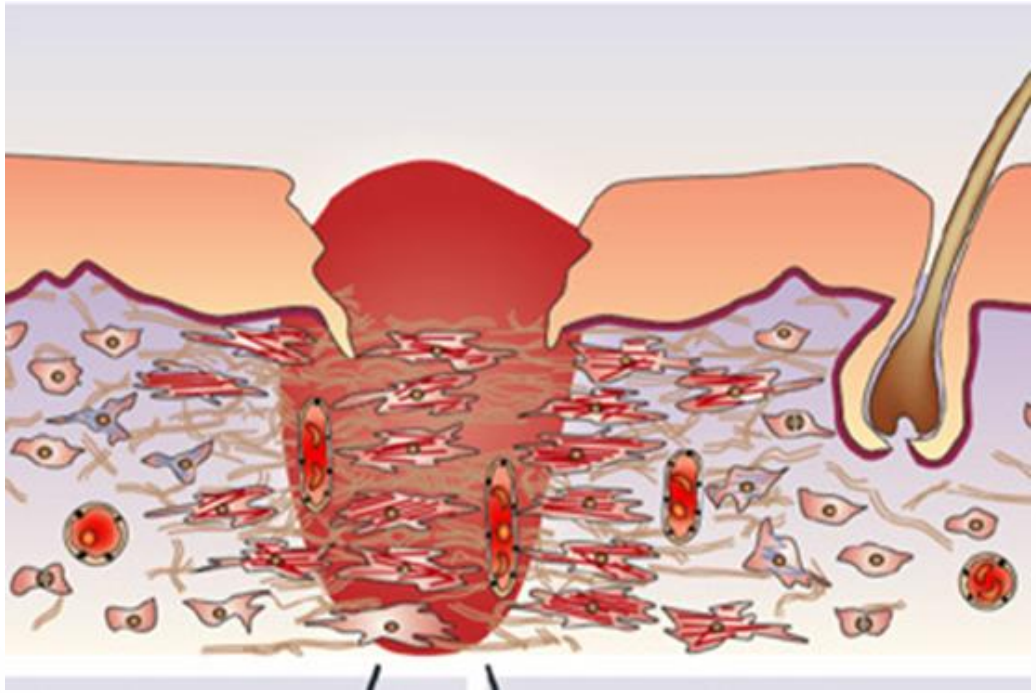
Mechanism of Defect Cavity Products

1. **Induced** New Tissue Formation in Defect **Cavity**
2. **Template** of New Tissue Formation in Defect **Cavity**
3. **Stimulation** of Wound **Interface**



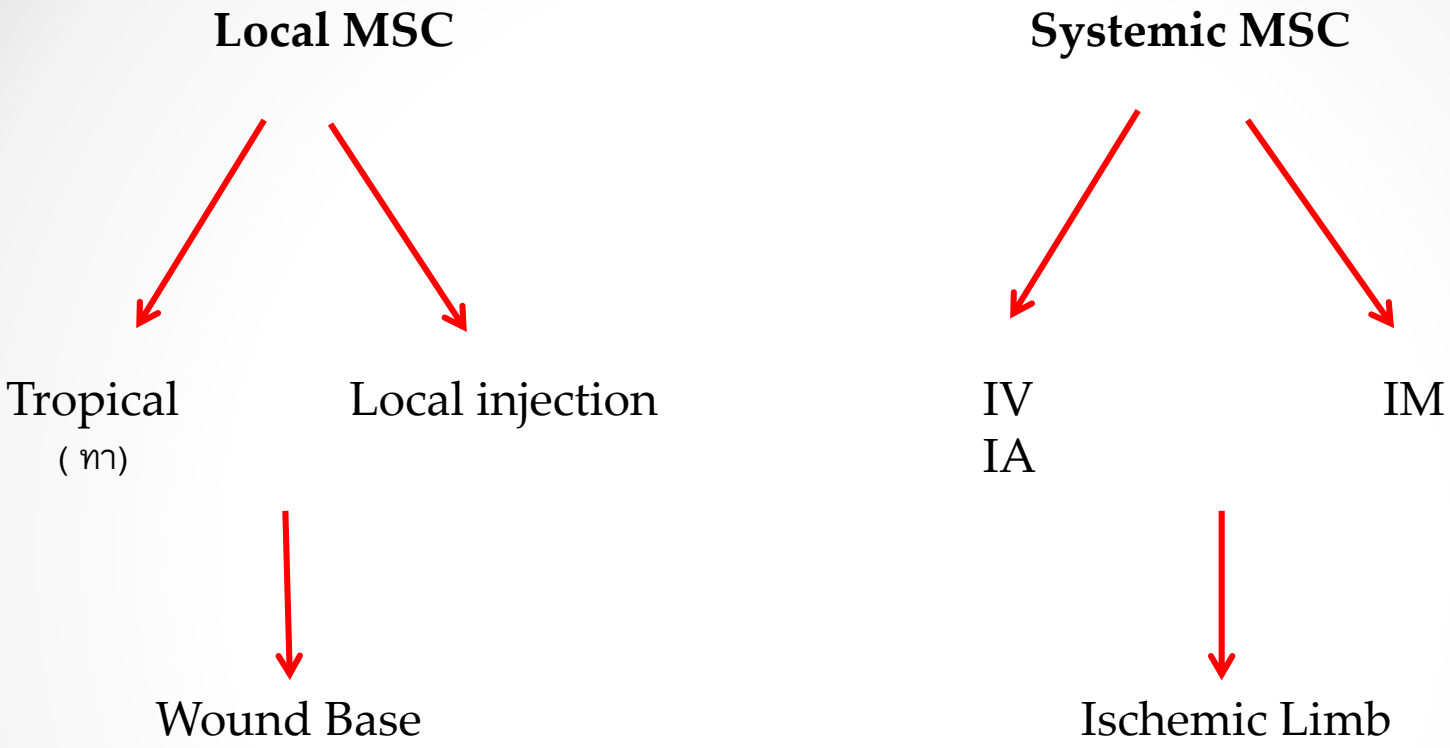
2. Surrounding (Wound Base) Products

1. **Bio-molecular Products** = Growth Factors / Signaling Molecules + Peptides
2. **Cellular Drug** = ADSC/MSC/Fibroblast/EPC



3. Systemic Products

- IV
- IM
- IA


Local MSC
Systemic MSC
Tropical
(ทา)
Local injection
IV
IA
IM
Wound Base
Ischemic Limb

ORIGINAL ARTICLE

Topical Administration of Allogeneic Mesenchymal Stromal Cells Seeded in a Collagen Scaffold Augments Wound Healing and Increases Angiogenesis in the Diabetic Rabbit Ulcer

Aonghus O'Loughlin,[1] Mangesh Kulkarni,[2] Michael Creane,[1] Erin E. Vaughan,[1] Emma Mooney,[1] Georgina Shaw,[1] Mary Murphy,[1] Peter Dockery,[3] Abhay Pandit,[2] and Timothy O'Brien[1]

There is a critical clinical need to develop therapies for nonhealing diabetic foot ulcers. Topically applied mesenchymal stromal cells (MSCs) provide a novel treatment to augment diabetic wound healing. A central pathological factor in nonhealing diabetic ulcers is an impaired blood supply. It was hypothesized that topically applied allogeneic MSCs would improve wound healing by augmenting angiogenesis. Allogeneic nondiabetic bone-marrow derived MSCs were seeded in a collagen scaffold. The cells were applied to a full-thickness cutaneous wound in the alloxan-induced diabetic rabbit ear ulcer model in a dose escalation fashion. Percentage wound closure and angiogenesis at 1 week was assessed using wound tracings and stereology, respectively. The topical application of 1,000,000 MSCs on a collagen scaffold demonstrated increased percentage wound closure when compared with lower doses. The collagen and collagen seeded with MSCs treatments result in increased angiogenesis when compared with untreated wounds. An improvement in wound healing as assessed by percentage wound closure was observed only at the highest cell dose. This cell-based therapy provides a novel therapeutic strategy for increasing wound closure and augmenting angiogenesis, which is a central pathophysiological deficit in the nonhealing diabetic foot ulcer. ***Diabetes*** **62:2588–2594, 2013**

of nonhealing diabetic ulcers is impaired angiogenesis in the wound.

There is a critical clinical need to develop novel treatments to improve healing of diabetic foot ulcers. Mesenchymal stromal cells (MSCs) provide a novel therapeutic treatment and have been shown to be beneficial in diabetic wound healing (3). The mechanisms underlying the beneficial effect of wound healing include paracrine secretion of growth factors and chemokines requisite for wound healing and the differentiation into keratinocytes and endothelial cells required for wound healing and angiogenesis. MSCs can be delivered in an allogeneic fashion and possess immunosuppressant and immunomodulatory properties (4).

To date, there have been encouraging results in preclinical models of diabetic wound healing. Treatment with MSCs resulted in increased wound closure, new granulation tissue formation, and increased blood vessel formation and cellularity (5–8). In addition, 10 humans have received autologous MSCs, resulting in augmented wound healing. There is one report of an effect related to dose with autologous MSCs seeded in a fibrin spray (9). Nonetheless, there have been no studies using allogeneic human MSC transplantation in the setting of diabetic cutaneous

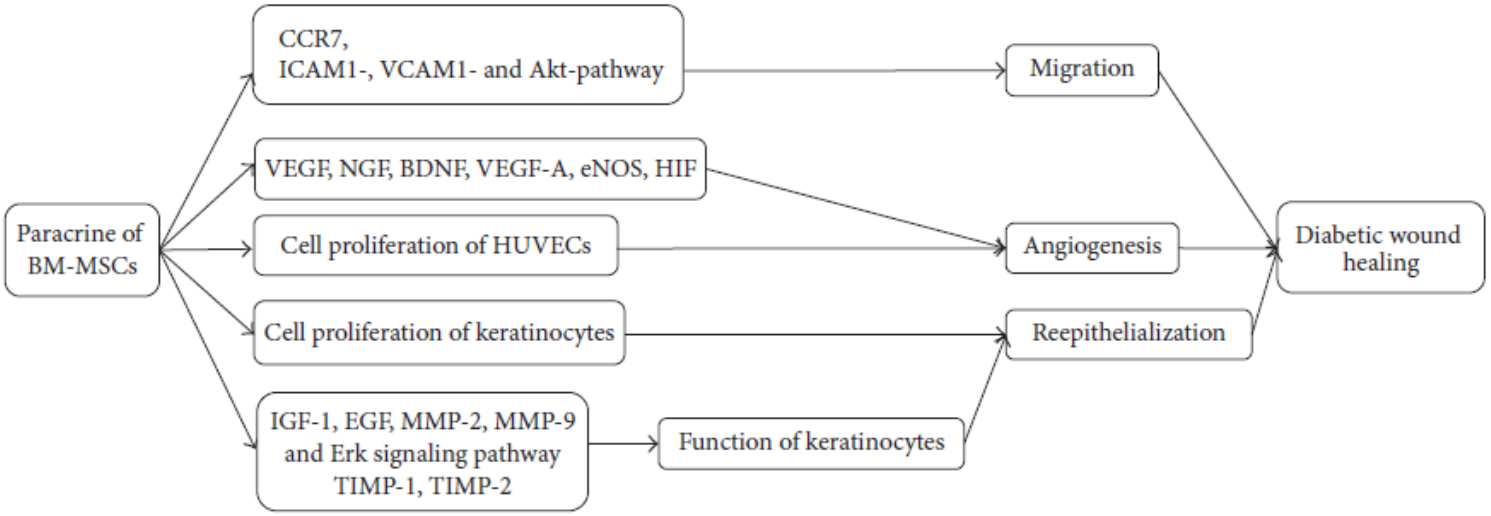


FIGURE 1: Mechanism of BM-MSCs for treatment of DFU. BM-MSCs can migrate and adhere via CCR7, ICAM1-, VCAM1-, and Akt-dependent mechanism and enhance angiogenesis through increasing VEGF, NGF, BDNF, VEGF-A, eNOS, and HIF. Cell proliferation of HUVECs and keratinocytes plays significant role in angiogenesis and reepithelialization, respectively. Keratinocyte function is improved by regulating IGF-1, EGF, MMP-2, MMP-9, TIMP-1, TIMP-2, and Erk signaling pathway. CCR7: C-C chemokine receptor type 7, ICAM1: intercellular adhesion molecule 1, VCAM1: vascular adhesion molecule 1, VEGF: vascular endothelial growth factor, NGF: nerve growth factor, BDNF: brain-derived neurotrophic factor, VEGF-A: vascular endothelial growth factor A, eNOS: endothelial nitric oxide synthase, HIF: hypoxia inducible factor, IGF-1: insulin-like growth factor 1, EGF: epidermal growth factor, MMP-2: matrix metalloproteinase-2, MMP-9: matrix metalloproteinase-9, TIMP-1: tissue inhibitor of metalloproteinase-1, and TIMP-2: tissue inhibitor of metalloproteinase-2.

2.2. Mechanism

2.2.1. Paracrine. BM-MSCs can enhance the migration, angiogenesis, and reepithelialization via paracrine to accelerate wound repair.

Allogeneic BM-MSCs can migrate and home to the wound area [22] through expressing C-C chemokine receptor type 7 (CCR7) [53] and adhere to endothelial cells (ECs) via intercellular adhesion molecule 1- (ICAM1-), vascular adhesion molecule 1- (VCAM1-), and Akt-dependent mechanism [54].

2.2.2. Mobilization of Autologous Stem Cells. Iwamoto and colleagues demonstrated that autologous stem cells mobilized from bone marrow by systemic injections of granulocyte colony-stimulating factor (GCSF) improved wound bed preparation and accelerated healing in mice [59]; albeit the presence of BM-MSCs in mobilized stem cells was not identified in this study, they were shown to be mobilized by GCSF in previous study [60]. In Tatsumi et al. study, GCSF

Shi et al. Stem Cell Research & Therapy (2016) 7:155
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Stem Cell Research & Therapy

RESEARCH Open Access

Localization of human adipose-derived stem cells and their effect in repair of diabetic foot ulcers in rats

Rongfeng Shi[1†], Yinpeng Jin[2†], Chuanwu Cao[1,3], Shilong Han[1,3], Xiaowen Shao[4], Lingyu Meng[2], Jie Cheng[1], Meiling Zhang[1], Jiayi Zheng[5], Jun Xu[6,7*] and Maoquan Li[1,3*]

Abstract

Background: Diabetic foot ulcer (DFU) is an intractable diabetic complication. Patients suffering from diabetes mellitus (DM) frequently present with infected DFUs. In this study, a wound healing model on diabetic rat foot was established to mimic the pathophysiology of clinical patients who suffer from DFUs. Our study aimed to explore the localization of human adipose-derived stem cells (hADSCs) and the role of these cells in the repair of foot ulcerated tissue in diabetic rats, and thus to estimate the possibilities of adipose-derived stem cells for diabetic wound therapy.

Method: Sprague–Dawley rats were used to establish diabetic models by streptozotocin injection. A full-thickness foot dorsal skin wound was created by a 5 mm skin biopsy punch and a Westcott scissor. These rats were randomly divided into two groups: the hADSC-treated group and the phosphate-buffered saline (PBS) control group. The hADSC or PBS treatment was delivered through the left femoral vein of rats. We evaluated the localization of hADSCs with fluorescence immunohistochemistry and the ulcer area and ulcerative histology were detected dynamically.

Result: The hADSCs had a positive effect on the full-thickness foot dorsal skin wound in diabetic rats with a significantly reduced ulcer area at day 15. More granulation tissue formation, angiogenesis, cellular proliferation, and higher levels of growth factors expression were also detected in wound beds.

Conclusions: Our data suggest that hADSC transplantation has the potential to promote foot wound healing in diabetic rats, and transplantation of exogenous stem cells may be suitable for clinical application in the treatment of DFU.

Keywords: Human adipose-derived stem cells, Diabetic foot ulcer, Tissue repair

Transfecting and tracing of transplanted hADSCs

Preparation of cell infection and lentiviral supernatants was performed as described previously [16]. Briefly, transient cotransfection of HEK293T cells were employed to produce the lentiviral vectors with four plasmids (Invitrogen). The vector-containing supernatants were harvested 48 and 72 hours after transfection, filtered, and then stored at –80 °C. hADSCs (passage 2) were infected with the lentivirus expressing ZsGreen at 70 % cell confluence [17]. Three days after transfection, the infection efficiency was detected using a fluorescence microscope (IX71; Olympus), and the cells were cultured successively. Twenty-four DFU model rats were injected with 5×10^6 ZsGreen-hASDCs via the femoral vein, and at 24 hours, day 3 (D3), day 7 (D7), and day 15 (D15) the distribution and engraftment of hADSCs in the wound bed were detected dynamically using fluorescence immunohistochemistry analysis with the antibodies specific against ZsGreen (Abcam Ltd, Cambridge, UK).

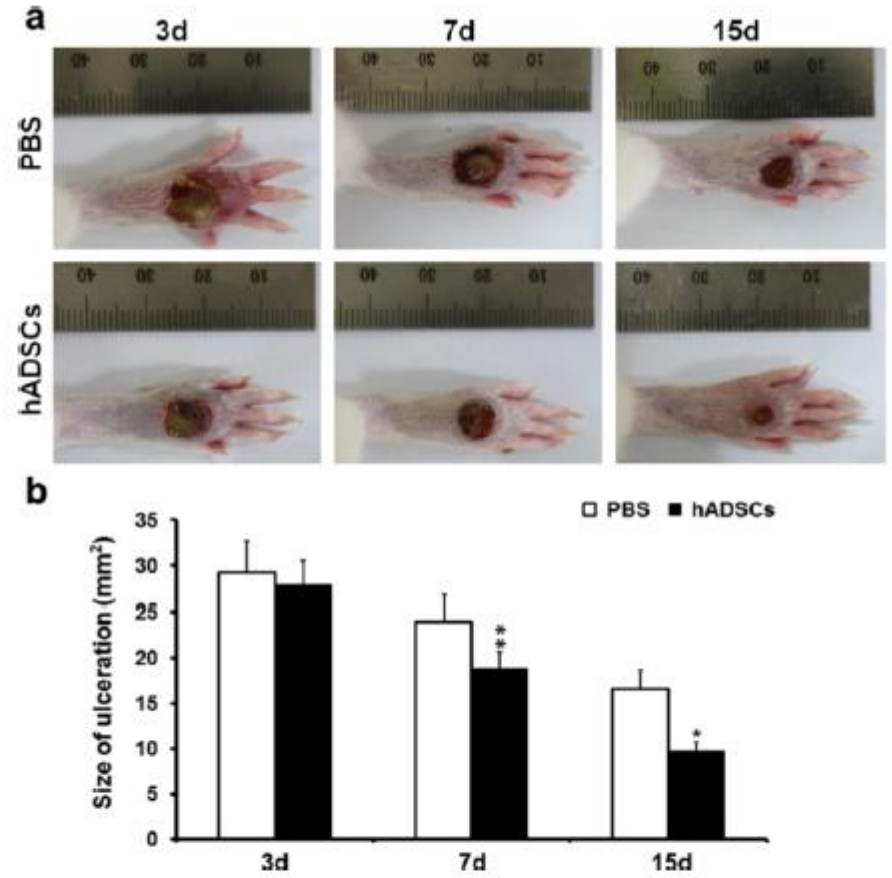

Fig. 2 Diabetic foot ulceration healing at different time points after treatment in the hADSC-treated and control groups. **a** Representative images of ulcerations on diabetic rat feet at D3, D7, and D15 after treatment with hADSCs and PBS. **b** Mean area of diabetic foot ulceration in hADSC-treated model rats during observation compared with control model rats at D3, D7, and D15 after treatment. Averaged data presented as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$. *d* days, *hADSC* human adipose-derived stem cell, *PBS* phosphate-buffered saline. Representative images and mean area of the foot ulcers in the euglycemic rats group were shown in additional file 1

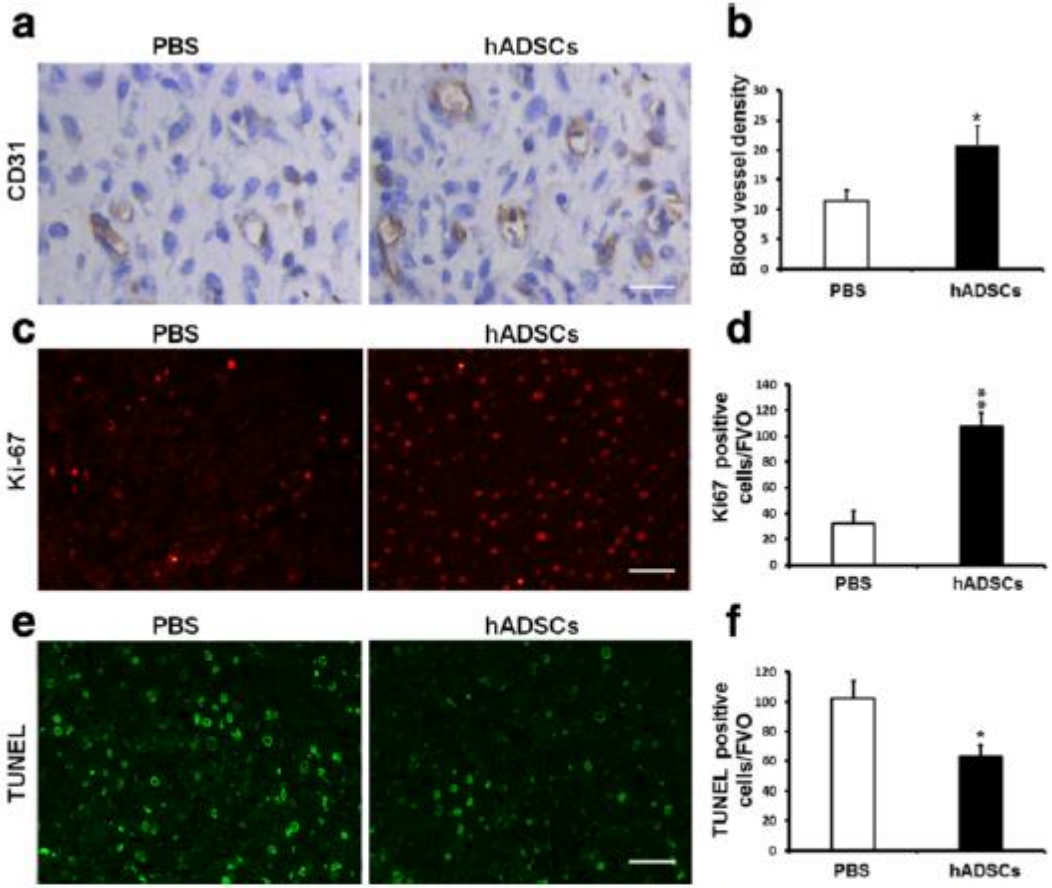

Fig. 4 Effects of hADSCs on angiogenesis, cell proliferation, and apoptosis of wounds at D15 after treatment. **a** Immunohistochemical staining of CD31 showed more blood vessel structures on the wound bed in model rats treated with hADSCs were clearly increased compared with control model rats. *Scale bar*, 50 μm. **b** Quantification of blood vessel density expressed as the average number of $CD31^+$ vessels per high-power field. **c** Cellular proliferation on the wound bed observed by Ki-67 immunofluorescence staining. The hADSC-treated group showed more positive cells than the PBS-treated group, indicating that hADSC treatment promoted cell proliferation in DFU healing. *Scale bar*, 100 μm. **d** Quantification analysis of the Ki-67 staining by digital image analysis. **e** Apoptotic cells detected by TUNEL assays. Few apoptotic cells were detected in the hADSC-treated group, suggesting that hADSC treatment reduced the apoptosis in the process of healing. *Scale bar*, 100 μm. **f** Quantification of TUNEL immunofluorescence staining by digital image analysis. Averaged data presented as mean ± SD. $^*P < 0.05$, $^{**}P < 0.01$. *hADSC* human adipose-derived stem cell, *PBS* phosphate-buffered saline, *TUNEL* terminal deoxynucleotidyl transferase dUTP nick end labeling

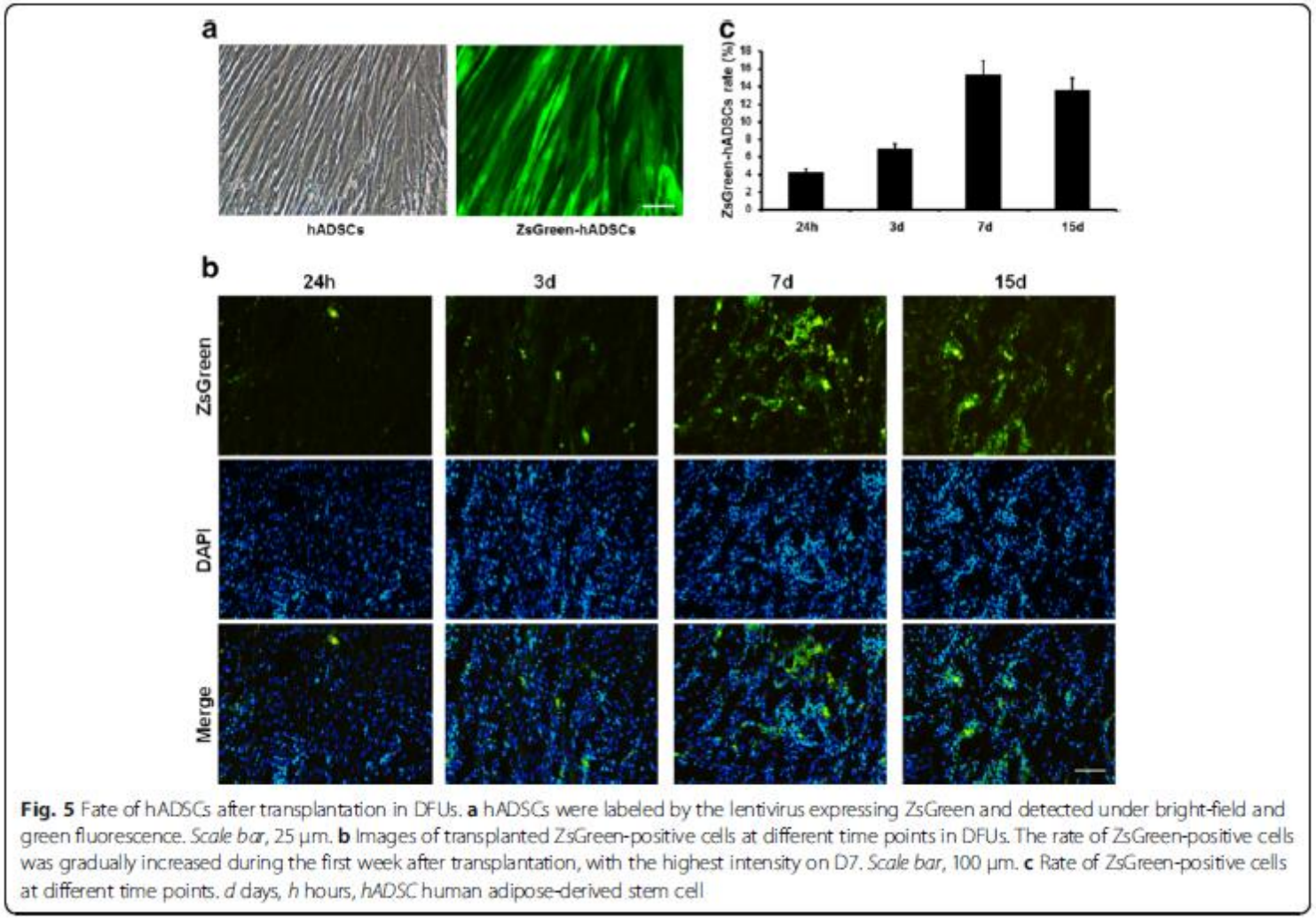

Fig. 5 Fate of hADSCs after transplantation in DFUs. **a** hADSCs were labeled by the lentivirus expressing ZsGreen and detected under bright-field and green fluorescence. *Scale bar*, 25 μm. **b** Images of transplanted ZsGreen-positive cells at different time points in DFUs. The rate of ZsGreen-positive cells was gradually increased during the first week after transplantation, with the highest intensity on D7. *Scale bar*, 100 μm. **c** Rate of ZsGreen-positive cells at different time points. *d* days, *h* hours, *hADSC* human adipose-derived stem cell

Clinical studies

Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Effectiveness of Autologous Stem Cell Therapy for the Treatment of Lower Extremity Ulcers

A Systematic Review and Meta-Analysis

Xupin Jiang, MD ,PhD, Hengshu Zhang, MD ,PhD, and Miao Teng, MD ,PhD

TABLE 1. Characteristics of the Included Studies

Study	Study Design	Country	Mean Age (Y)	Male (%)	Cause of Ulcers	DM (%)	Baseline Size of Ulcers (cm^2)	Stem Cell Type	Amount of Cells Transplanted	Delivery Method	Placebo	Follow-Up Duration (Weeks)	Adverse Events
Huang et al, 2005	R, SB, PC	China	71	64	CLI	100	2.6	G-CSF mobilized PBMNCs	3×10^9 per leg	i.m.	PGE1	12	No transplantation-related AE
Dash et al, 2009-Buerger*	R	India	40	NA	Buerger's disease	NA	4.9	BMMSCs	10^6 per cm^2	i.m.	No	12	No transplantation-related AE
Dash et al, 2009-DFU*	R	India	40	NA	DFU	100	5.7	BMMSCs	10^6 per cm^2	i.m.	No	12	No transplantation-related AE
Walter et al, 2011	R, DB, PC	Germany	64	73	CLI	50	3.1	BMMNCs	NA	i.a.	medium	12	No transplantation-related AE
Lu et al, 2011-BMMSCs†	R, DB, PC	China	63	39	CLI	100	4.5	BMMSCs	NA	i.m.	N.S.	6	No transplantation-related AE
Lu et al, 2011-BMMNCs†	R, DB, PC	China	65	42	CLI	100	4.4	BMMNCs	NA	i.m.	N.S.	6	No transplantation-related AE
Powell et al, 2011	R, DB, PC	USA	68	72	CLI	50	NA	BMTRCs	1.4×10^8 per leg	i.m.	electrolyte solution	48	No difference between 2 groups
Jain et al, 2011	R, DB, PC	India	56	65	44 DFU and 4 traumatic			92	56.6	BM derived cells	NA	i.m.	peripheral blood
12	No											transplantation-related AE	
Kirana et al, 2012-BMMNCs‡	R	Germany	68	75	CLI	100	9.6	BMMNCs	$>3 \times 10^7$	i.m. or i.a.	No	45	No transplantation-related AE
Kirana et al, 2012-BMTRCs‡	R	Germany	71	83	CLI	100	7.7	BMTRCs	$>5 \times 10^7$	i.m. or i.a.	No	45	No transplantation-related AE
Losordo et al, 2012-low dose§	R, DB, PC	USA	64	62	CLI	57	3.7	G-CSF mobilized PBMNCs	10^5 per kg BW	i.m.	NA	48	No transplantation-related AE
Losordo et al, 2012-high dose§	R, DB, PC	USA	68	73	CLI	62	7.2	G-CSF mobilized PBMNCs	10^6 per kg BW	i.m.	NA	48	No transplantation-related AE
Li et al, 2013	R, SB, PC	China	62	85	CLI	41	NA	BMMNCs	NA	i.m.	N.S.	24	No transplantation-related AE

Overall, autologous stem cell-based therapy was associated with better healing of lower extremity ulcers (12 comparisons, 290 patients, RR for partial healing = 3.07, 95% confidence interval [CI] = 1.14–8.24, $P = 0.03$; RR for complete healing = 2.26, 95% CI = 1.48–3.16, $P < 0.001$) with little heterogeneity ($I^2 = 0\%$). Moreover, autologous stem cell-based therapy was associated with a greater reduction in mean ulcer size (SMD = −0.63, 95% CI = −1.03 to −0.22, $P = 0.002$). Subgroup analyses indicated that stem cells from peripheral blood and bone marrow seemed to exert similar beneficial effects on the healing of ulcers. Stem cell therapy was not associated with any increased risks for adverse events.

Review Article

Mesenchymal Stem Cells Improve Healing of Diabetic Foot Ulcer

Yue Cao, Xiaokun Gang, Chenglin Sun, and Guixia Wang

Department of Endocrinology and Metabolism, The First Hospital of Jilin University, Changchun 130021, China

Correspondence should be addressed to Guixia Wang; gwang168@jlu.edu.cn

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Mesenchymal stem cells (MSCs), an ideal cell source for regenerative therapy with no ethical issues, play an important role in diabetic foot ulcer (DFU). Growing evidence has demonstrated that MSCs transplantation can accelerate wound closure, ameliorate clinical parameters, and avoid amputation. In this review, we clarify the mechanism of preclinical studies, as well as safety and efficacy of clinical trials in the treatment of DFU. Bone marrow-derived mesenchymal stem cells (BM-MSCs), compared with MSCs derived from other tissues, may be a suitable cell type that can provide easy, effective, and cost-efficient transplantation to treat DFU and protect patients from amputation.

Review Article

Mesenchymal Stem Cells Improve Healing of Diabetic Foot Ulcer

Yue Cao, Xiaokun Gang, Chenglin Sun, and Guixia Wang

Department of Endocrinology and Metabolism, The First Hospital of Jilin University, Changchun 130021, China

Correspondence should be addressed to Guixia Wang; gwang168@jlu.edu.cn

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Mesenchymal stem cells (MSCs), an ideal cell source for regenerative therapy with no ethical issues, play an important role in diabetic foot ulcer (DFU). Growing evidence has demonstrated that MSCs transplantation can accelerate wound closure, ameliorate clinical parameters, and avoid amputation. In this review, we clarify the mechanism of preclinical studies, as well as safety and efficacy of clinical trials in the treatment of DFU. Bone marrow-derived mesenchymal stem cells (BM-MSCs), compared with MSCs derived from other tissues, may be a suitable cell type that can provide easy, effective, and cost-efficient transplantation to treat DFU and protect patients from amputation.

2. BM-MSCs and DFU

2.1. Intrinsic Property. Bone marrow is one of the most common tissues from which MSCs can be acquired. BM-MSCs have no immunologic restriction and do not stimulate

3. Umbilical Cord Blood-Derived Mesenchymal Stem Cells (UCB-MSCs) and DFU

3.1. Intrinsic Property. UCB-MSCs have a similar morphology, cell surface antigens, and the potential of differentiation into BM-MSCs and umbilical cord-derived mesenchymal stem cells (UC-MSCs) [42, 52, 68]. Additionally, UCB-MSCs have several advantages, such as short doubling time [69], long viable time, and anti-inflammatory activity [42]. Thus,

4. MSCs Derived from Other Tissues

Up to date, preclinical studies on adipose-derived mesenchymal stem cells (AMSCs), umbilical cord-derived mesenchymal stem cells (UC-MSCs), placenta-derived mesenchymal stem cells (PMSCs), and human amniotic fluid-derived stem cells (AF-MSCs) for diabetic wound healing have been reported, but no clinical trials have been reported. However, human gingiva-derived mesenchymal stem cells (GMSCs) are only investigated in excisional wound model, and the data are quite limited.

4.1. AMSCs and Diabetic Wound Healing

4.1.1. Intrinsic Property. Adipose tissue derived from the mesenchyme is widely distributed and easily isolated. AMSCs have high colony frequency and represent an attractive alternative source of pluripotent cells, whose characteristics are similar to BM-MSCs [42, 74].

4.1.2. Mechanism. In diabetic rats with dorsal full-thickness skin wound, allogeneic AMSCs injected subcutaneously in the wound margin stimulated neoangiogenesis and increased tissue regeneration through paracrine and autocrine mechanisms [75]. The data showed that allogeneic AMSCs migrated to the wound margin and increased angiogenesis via the activation of endothelial activity and neoangiogenic capacities by increasing VEGF and von Willebrand factor (vWF). Simultaneously, as a proliferating cell nuclear antigen, Ki-67, was up-regulated to promote cellular proliferation. The proinflammatory reaction was reduced through the expression of EGF, VEGF, and prolyl 4-hydroxylase (rPH). Consistent with this notion, allogeneic AMSCs were harvested from the inguinal fat of normal rats secreted large amounts of several angiogenic growth factors including VEGF, hepatocyte growth factor (HGF), transforming growth factor beta 1 (TGF-β1), IGF-1, EGF, and keratinocyte growth factor (KGF) in vitro. In vivo, the transplantation of AMSCs sheets was created using cell-sheet technology accelerated wound healing and vascularization in full-thickness skin defects in Zucker diabetic fatty rats [76].

Additionally, direct injection of ASCs obtained from nondiabetic patients into full-thickness wound of diabetic mice model significantly increased the rate of wound closure [77]. In another study on diabetic mice, the new findings that silk fibroin patches cellularized with human adipose-derived MSCs (Ad-MSCs-SF) and silk fibroin patches decellularized with human adipose-derived MSCs (D-Ad-MSCs-SF) patches improved tissue regeneration and reduced the wound area through releasing angiogenic factors and collagen deposition stimulating molecules [78]. A decrease in the risk of transferring genetically mutated cells and the possibility of stimulating the immune system were the advantage of D-Ad-MSCs-SF patches, and decellularized patches could be prepared and stored for an extended period.

Table 1: Clinical trials of BM-MSCs and UCB-MSCs.

First author	Publication year	Cellular type	Object	Delivery method	Duration of observation	Clinical parameters
Dash	2009	Autologous BM-MSCs	24 patients with nonhealing ulcers of the lower limb (diabetic foot ulcers and Buerger disease)	Autologous cultured BM-derived MSCs along with standard wound dressing	12 weeks	Decrease in wound size, increase in pain-free walking distance, maintain normal liver and renal function, improve leg perfusion sufficiently
Amann	2009	Autologous BM-MSCs	51 patients with impending major amputation due to severe critical limb ischemia	Intramuscular transplantation	6 months	Improve leg perfusion sufficiently to reduce major amputations and permit durable limb salvage, reduce analgesics consumption, increase in pain-free walking distance
Vojtassak	2006	Autologous biograft composed of autologous skin fibroblasts on biodegradable collagen membrane (Coladerm) in combination with autologous BM-MSCs	Patients with diabetic foot	Directly to the wound and injected into the edges of the wound, finally covered with prepared autologous biograft, received two additional treatments with cultured MSC on days 7 and 17	29 days	Decrease in wound size and an increase in the vascularity of the dermis and in the dermal thickness of the wound bed
Lu	2011	Autologous BM-MSCs	41 type 2 diabetic patients with bilateral critical limb ischemia and foot ulcer	Intramuscular injection	24 weeks	Increase in pain-free walking distance, improve leg perfusion, ankle-brachial index (ABI), transcutaneous oxygen pressure (TcO_2), magnetic resonance angiography (MRA) analysis
Procházka	2010	Autologous BM-MSCs	96 patients with critical limb ischemia and foot ulcer	Inject into the ischemic limb along the posterior and anterior tibial artery	120 days	79% limb salvage in patients
Li	2013	Allogeneic UCB-MSCs	15 diabetic patients with foot disease	10 mL is injected intramuscularly into impaired lower limbs and 2 mL is delivered into the basilar portions of foot ulcers and the surrounding subcutaneous tissues	12 weeks	Weakness, numbness, pain, cold feeling, or intermittent limp, skin temperature, ABI, and transcutaneous oxygen pressure (TcO_2) are improved

BM-MSCs: bone marrow-derived mesenchymal stem cells and UCB-MSCs: umbilical cord blood-derived mesenchymal stem cells.

4.2. UC-MSCs and Diabetic Wound Healing

4.2.1. Intrinsic Properties. UC-MSCs are generally considered to be rich, safe, of short doubling time, and easy to collect [52]. Compared to BM-MSCs, it has been well documented that UC-MSCs have similar characteristics involving fibroblastic morphology, typical immunophenotypic markers, and multiple differentiation potential to BM-MSCs [79–82]. In addition, the trait of UC-MSCs has lower immunogenicity [83, 84].

4.2.2. Mechanism. In the study on DFU rats with UC-MSCs delivered through the left femoral artery, researchers found that UC-MSCs could specifically localize to the targeted area by detecting the expression of human leukocyte antigen type-I (HLA-1), a marker to track UC-MSCs in vivo.

Besides, UC-MSCs significantly reduced the size of foot ulcers and promoted epithelialization of ulcerated tissue via release of cytokeratin 19 from keratinocytes and formation of extracellular matrix [21]. In other studies of DFU rats, the data showed that administration of UC-MSCs contributed to improvement of vascular density [85, 86] and repair of wound and sensory functions [87] by the expression of VEGF, keratinocyte growth factor (KGF), platelet derived growth factor (PDGF), and brain-derived growth factor (BDGF).

4.3. PMSCs and Diabetic Wound Healing

4.3.1. Intrinsic Property. Placental tissue is readily available and can isolate a large number of MSCs for clinical application [88]. What is more, the morphology, size, surface phenotype, and immunosuppressive characteristics of PMSCs are similar to BM-MSCs, and the proliferation capability is better [39]. The best efficacy delivery is intraperitoneal injection [89].

4.3.2. Mechanism. In the research of diabetic Goto-Kakizaki (GK) rats, the experimental group showed that implanted PMSCs gathered to the wound tissue and differentiated into endothelial-like cells. Additionally, it has been found that PMSCs participate in angiogenesis in wound bed through secreting some proangiogenic molecules, such as VEGF, bFGF, and IGF-1, transforming growth factor-β (TGF-β) and hepatocyte growth factor (HGF) [90].

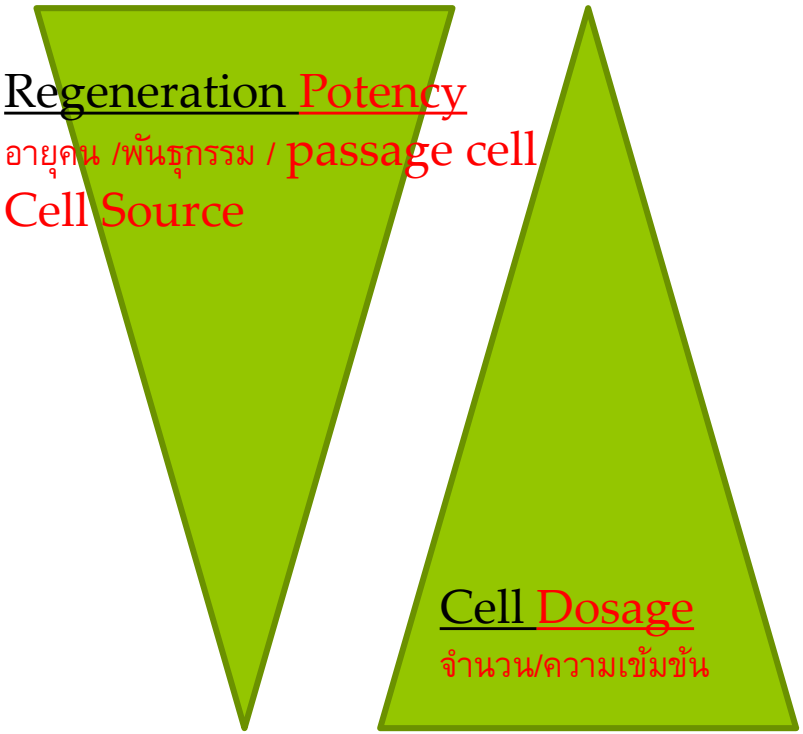
4.4. AF-MSCs and Diabetic Wound Healing. Large numbers of human AF-MSCs can be easily harvested from as little as 2 mL of amniotic fluid [91]. Human AF-MSCs remain stable and show high proliferative capacity, multilineage differentiation potential, immunomodulatory activity, and lack of significant immunogenicity [92].

The transplantation of human AF-MSCs has been shown to accelerate wound healing by secreting factors [93] to stimulate proliferation and migration of dermal fibroblasts. In full-thickness excisional wound of diabetic NOD/SCID mice, human AF-MSCs significantly accelerated wound closure through increasing the angiogenic factors, IGF-1, EGF, and interleukin-8 (IL-8), as well as enhancing reepithelialization by expressing keratinocyte-specific proteins and cytokeratin in the wound area [94]. Additionally, in a model of mouse with excisional wound, human AF-MSCs significantly enhanced wound healing via the TGF-beta/SMAD2 pathway [95], while human AF-MSCs accelerated wound closure through TGF-β/SMAD2 and PI3K/Akt pathways under the condition of hypoxia [96].

4.5. GMSCs and Wound Healing. Human GMSCs are homogenous, not tumorigenic [97], and easy to be isolated [98] and display stable phenotype. The most significant advantage of human GMSCs is without any ethical problems in clinical application [99]. Moreover, human GMSCs show a greater capacity of proliferation and migration than AMSCs [100] and BM-MSCs without growth factors [99].

In a murine excisional full-thickness skin wound model, systemic infusion of human GMSCs mitigated local inflammation mediated via suppression of inflammatory cells infiltration, production of IL-6 and TNF-α, and increasing expression of interleukin-10 (IL-10) [101]. This mechanism also existed in the hypoxic environment [102]. In addition, human GMSCs have elicited M2 polarization of macrophages, which may contribute to rapid reepithelialization, improvement of angiogenesis, and tissue remodeling of skin wound [101].

Healing Power



Total cell = 10 ล้าน / dose
Cell concentration = 1 ล้าน / ml – local
1 หมื่น / ml – iv drip
10 ล้าน / ml - IM

IV ระวัง Massive Pulmonary Emboli
Cardiovascular collapse

5. Are Autologous or Allogeneic MSCs More Appropriate?

It has been shown that autologous BM-MSCs are a major source and have obvious efficacy in cell therapy for patients suffering from DFU. Most recently, a study on the feasibility of autologous stem cell therapy in diabetic patients showed that AMSCs isolated from distal limbs of diabetic patients with critical ischemia was not satisfactory as an autologous AMSC source because of its improper phenotype and function [103]. In line with above evidence, the initial viability of the mouse MSCs extracted from the bone marrow of diabetic mice was poor in a normal glucose environment in vitro, but the expansion of that was subsequently improved [61].

Although allogeneic MSCs have had potent immunosuppressive properties, evidence also suggests that they elicit potential as a new therapeutic strategy for the treatment of DFU in animal models. Moreover, allogeneic UCB-MSCs have been successfully used to treat patients with DFU. With increasing number of clinical trials of allogeneic MSCs for acute and chronic diseases [104–107], a comprehensive understanding of the difference in immunological profile is essential.

Hence, the potential for autologous or allogeneic MSCs to be used to improve diabetic wound healing appears particularly promising. However, so far preclinical and clinical data are quite limited and further studies need to be explored for the feasibility of autologous and allogeneic MSCs therapy of DFU.

autologous

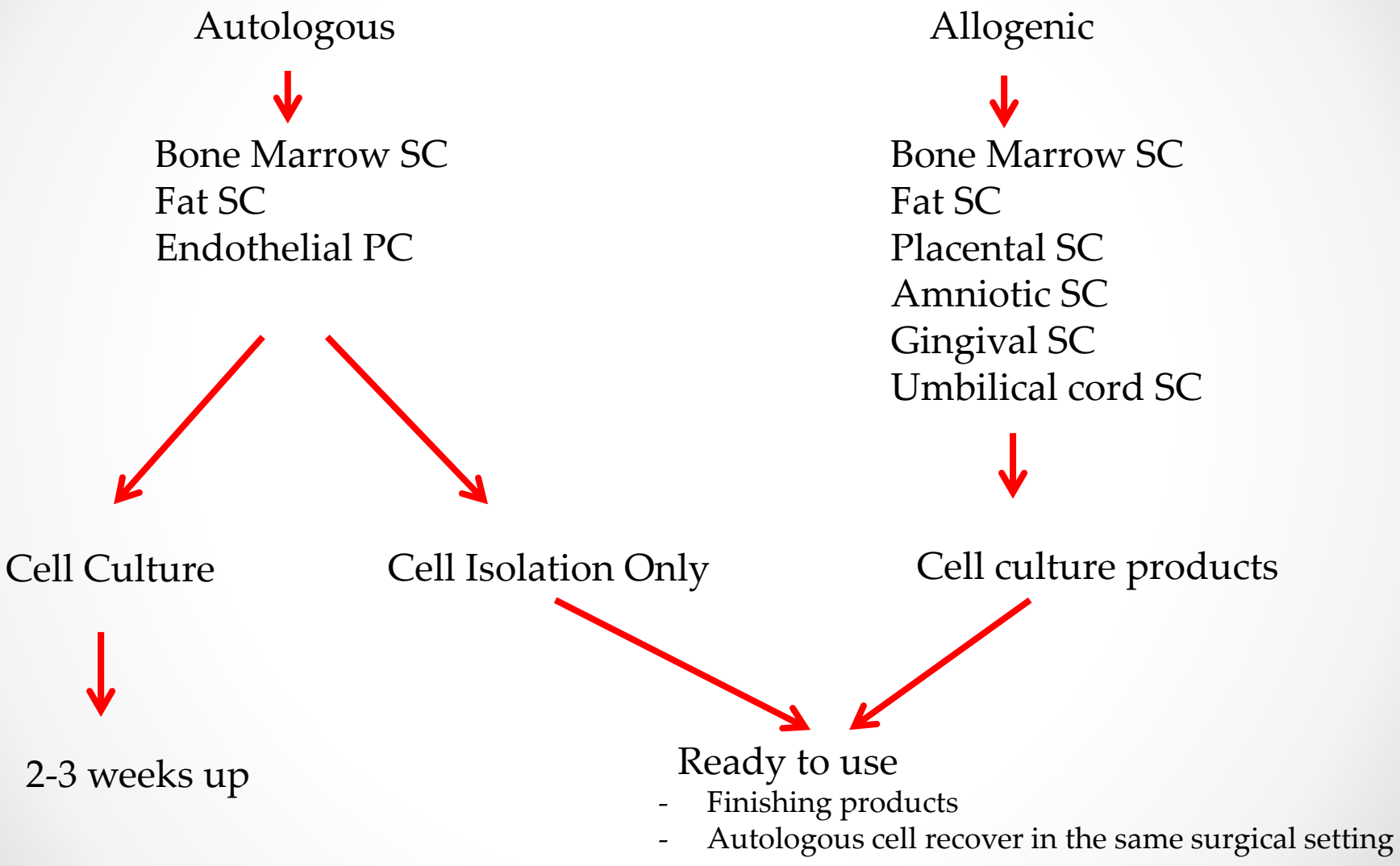
- คนไข้แก่มาก เหี่ยวทั้งตัว – แปลว่า stem cell ในตัวแย่ เอามาใช้ยาก
- คนไข้มีร่างกายแข็งแรง – แปลว่า stem cell ในตัวดี เอามาใช้ง่าย

Allogenic SC

- Cellular Drug
- Donor Eligibility
- Multiple Risks
- No Regulation in Thailand (International มี)

Culture Media Delivery Vehicle

มีผลกระทบมาก


Autologous
Bone Marrow SC
Fat SC
Endothelial PC
Allogenic
Bone Marrow SC
Fat SC
Placental SC
Amniotic SC
Gingival SC
Umbilical cord SC
Cell Culture
Cell Isolation Only
Cell culture products
2-3 weeks up
Ready to use
- Finishing products
- Autologous cell recover in the same surgical setting

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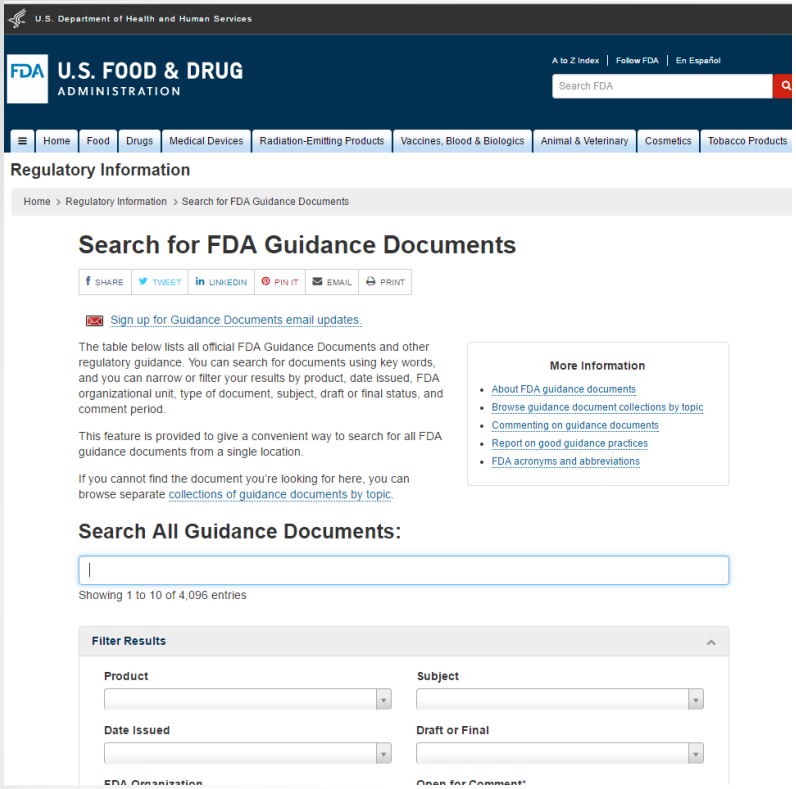

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Guidance for Industry

Potency Tests for Cellular and Gene Therapy Products

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Guidance for Industry

Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

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Contains Nonbinding Recommendations

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Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception

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Draft Guidance for Industry

DRAFT GUIDANCE

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Q3: Section 1271.15(b) refers to same surgical procedure. What types of procedures are considered the same surgical procedures?

A3: For the purposes of the exception in § 1271.15(b) and this guidance, procedures that involve an incision or instrumentation (e.g., incision or surgical technique) during which an HCT/P is removed from and implanted into the same patient within a single operation performed at the same establishment, are considered to be the same surgical procedures. Examples include autologous skin grafting and coronary artery bypass surgery involving autologous vein or artery grafting.

Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products

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Draft Guidance for Industry and Food and Drug Administration Staff

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1) The HCT/P is minimally manipulated;
2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4) Either:
    i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a) Is for autologous use;
        b) Is for allogeneic use in a first-degree or second-degree blood relative; or
        c) Is for reproductive use.


Thank You
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