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Abstract:

Buerger's disease or Thromboangiitis Obliterans (TAO) is a nonatherosclerotic segmental vascular disease which affects small and medium arteries and veins in the upper and lower extremities. Based on pathological findings, TAO can be considered as a distinct form of vasculitis that is most prevalent in young male smokers. There is no definitive cure for this disease as therapeutic modalities are limited in number and efficacy. Surgical bypass has limited utility and 24% of patients will ultimately require amputation. Recently, studies have shown that therapeutic angiogenesis and immunomodulatory approaches through the delivery of stem cells to target tissues are potential options for ischemic lesion treatment. In this review, we summarize the current knowledge of TAO treatment and provide an overview of stem cell-based treatment modalities.

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Review

Stem Cell Therapy for Thromboangiitis Obliterans (Buerger's Disease)

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Abstract: Buerger's disease or Thromboangiitis Obliterans (TAO) is a nonatherosclerotic segmental vascular disease which affects small and medium arteries and veins in the upper and lower extremities. Based on pathological findings, TAO can be considered as a distinct form of vasculitis that is most prevalent in young male smokers. There is no definitive cure for this disease as therapeutic modalities are limited in number and efficacy. Surgical bypass has limited utility and 24% of patients will ultimately require amputation. Recently, studies have shown that therapeutic angiogenesis and immunomodulatory approaches through the delivery of stem cells to target tissues are potential options for ischemic lesion treatment. In this review, we summarize the current knowledge of TAO treatment and provide an overview of stem cell-based treatment modalities.

Keywords: thromboangiitis obliterans; inflammation; angiogenesis; immunomodulation; pluripotent stem cell; mesenchymal stem cell

1. Introduction

Thromboangiitis Obliterans (TAO), commonly described as nonatherosclerotic segmented occlusive vascular disease, is caused by inflammation of the peripheral blood vessels leading to impaired blood circulation, coagulation, and critical limb ischemia (CLI) [1]. TAO was first medically described by the Austrian-Belgian surgeon Alexander von Winiwarter in 1879 and later named as Buerger's disease after Leo Buerger for his contributions to the pathological understanding of this disease. While TAO has a global distribution, it is most prevalent in Middle and Far Eastern nationalities, which may be due to the differences in diagnostic criteria. Overall, the prevalence of TAO in Western Europe ranges between 0.5 to 5.6 percent. However, in Eastern countries such as Korea and Japan, the prevalence of TAO represents up to 16 to 66 percent of patients with some form of peripheral arterial diseases (PAD). Interestingly, TAO makes up to 80 percent of the PAD in Ashkenazi Jews in Israel [1,2]. Although the precise etiology still remains unknown [1], it predominantly affects young male and female smokers [3–6]. Subjection to tobacco product usage especially in form of smoking, as well as chewing tobacco, is well known to be associated with majority of the onset, maintenance, and progression of TAO. In addition, almost 60 percent of patients afflicted with TAO also have concurrent severe periodontal disease or chronic anaerobic

oral infections. Anaerobic bacterial DNA fragments have been found in both TAO's arterial lesions and periodontal lesions within TAO patients, which indicated association between periodontal disease and development of TAO [7]. Still, around 5% of cases may be caused by other non-smoking related factors such as frostbite, extremity trauma, or even sympathomimetic drug abuse [4,5,8,9].

TAO is a rare form of vasculitis which is distinguished from other types by cellular inflammatory thrombus formation with relative sparing of the vessel wall. TAO has also shown to contain elevated level of pro- and anti-inflammatory cytokines and autoantibodies [10–12]. While the precise pathophysiology behind TAO is controversial, it is believed to be due to an IL-33-mediated immune response resulting in vascular abnormalities [10,13]. In keeping with its inflammatory nature, in various studies, TAO patients have been shown to have increased cellular immunity to type I and III collagen, higher titers of anti-endothelial cell antibodies, anticardiolipin antibodies, and prothrombin gene mutation [14–17]. TAO has clinical manifestations in both the arms and legs, differentiating it from atherosclerotic PAD that typically only involves the legs. The progression of TAO may be broken down into three phases. First is the acute phase, characterized with inflammatory thrombus and high levels of polymorphonuclear neutrophils occluding the vessel lumen while sparing the wall. Then comes the subacute phase with progression of occlusion. Lastly, the chronic phase is when the inflammation has died down while vascular fibrosis takes place. TAO can be differentiated from atherosclerosis or other vascular disease via the preservation of internal elastic lamina. [18] Also, TAO and CLI have different pathophysiologies. TAO is a vasculitis that does not affect large vessels as seen in the case of CLI.

The diagnosis of TAO is done via confirmation of 5 clinical criteria, as there is neither a specific test nor serologic markers for diagnosing TAO. Specifically, the 5 clinical criteria include: (1) smoking history; (2) onset of disease before age of 50; (3) infrapopliteal arterial occlusions; (4) either upper limb involvement or phlebitis migrans; and (5) absence of atherosclerotic risk factors other than smoking [2]. On imaging studies, Martorell's sign, corkscrew collaterals, is also commonly observed, though it is not pathognomonic for TAO [19]. The clinical pathogenesis of TAO begins with lower extremity pain during physical activity which progresses to pain while resting. Previous study has shown that 100 percent of the TAO patients had lower extremities involvement while upper extremity complications were seen in 44 percent of the time [20]. Additionally, patients may experience Raynaud's phenomena. Many patients also develop ischemic ulcerations that eventually progress to gangrene [3–5]. Clinical presentations are typically due to the occlusive nature, complications such as coldness, numbness, Raynaud's phenomena, claudication, pain and ulceration of fingers and toes, and phlebitis migrans are fairly common [21].

Despite considerable advances in treatment options, TAO is still associated with high morbidity [22]. While pharmacological approaches and surgical intervention remain generally palliative, novel therapeutic approaches such as gene and stem cell therapy to promote angiogenesis have been considered promising for the treatment of TAO [23–26]. The chief aim of this paper is to provide an overview of the current treatment modalities of TAO and outline approaches using stem cell therapy that may provide new therapeutic solutions to halt the pathogenesis of TAO.

2. Conventional Approaches

If TAO patients are left untreated, the disease is likely to progress to amputation. All patients with TAO are advised to stop smoking and avoid second-hand smoke exposure. From a study looking at 110 patients, 43% of patients underwent 108 amputation procedures. All of these amputations were done to patients who continued to smoke after the TAO diagnosis [27]. However, cessation does not completely prevent disease development and progression [28]. Proper foot care is essential to monitor for and treat ischemic ulceration. Often emollient skin cream is helpful to prevent fissure formation.

2.1. Pharmacologic Treatment

Pharmacological treatment of TAO is focused on anticoagulation (Aspirin), vasodilators (calcium channel blockers), systemic anti-inflammatory drugs (prostacyclins analogs) and analgesics. [29,30] Previous studies have demonstrated that iloprost is effective for analgesia and improved wound healing potential.

These properties are superior with intravenous infusion. Additionally, thrombolytic therapy with streptokinase and urokinase have demonstrated utility for the treatment of toe and foot gangrene [31]. It has been also reported treatment with bosentan (endothelin receptor antagonists) could improve healing of the ulcers [32]. Calcium-channel blockers like nifedipine can increase distal blood flow due to peripheral vasodilation and improve circulation to the distal ischemic limb. They also can be beneficial in combination with antibiotics and iloprost [3,33].

2.2. Surgical Procedures

Surgical modalities such as revascularization offer limited efficacy for the treatment of TAO patients with clinical symptoms such as rest pain, claudication, ulceration, and gangrene. Unfortunately, revascularization is rarely possible since there is poor outflow, because of the absence of distal vascular targets, and thus results of surgical intervention are poor. In addition, according to one study, there was a 53% graft failure rate, which was mainly due to complications of anastomosis to a diseased artery, disease progression as patients continued to smoke, and vein graft stenosis. Furthermore, failure of secondary revascularization procedure increased the risk of both persistent disabling claudication and amputation [34]. Endovascular treatment modalities have demonstrated utility lessening the progression of TAO [35]. In the setting of multi-level occlusion the stent puncture technique can help overcome vascular access challenges. [36]. Further, sympathectomy may be useful in relieving pain and promoting the healing of ulcers in some patients; however, these effects were not consistent [34]. Spinal cord stimulation may also be used for relief or treat pain in these patients [37].

3. Gene Therapy

In 1998, a benchmark publication demonstrated that vascular endothelial growth factor (VEGF) gene transfer shows utility in the treatment of TAO. Isner et al. revealed the feasibility of intramuscular gene transfer of naked plasmid DNA encoding—VEGF165 in six patients affected by TAO. Following this gene transfer, patients began to show marked improvement in healing of ischemic ulcers associated with increased blood flow in affected limbs. Patients also showed improvement in ankle-brachial index (ABI) in addition to demonstrating new vessel growth with magnetic resonance angiography (MRA) and serial contrast angiography [23]. Furthermore, phase I clinical trial data demonstrated the safety of intramuscular injections of plasmid DNA expressing two isoforms of hepatocyte growth factor (HGF) (VM202) for patients with CLI, a PAD with similar morbidities as TAO. Following plasmid DNA injection, the median ABI and transcutaneous oxygen pressure (tcPO2) values showed a positive shift, and patients responded clinically with a reduction in reported pain profile [38]. To demonstrate clinical efficacy of intramuscular plasmid injections, Belch and colleagues have evaluated intramuscular injections of non-viral 1 (NV1) fibroblast growth factor (FGF) in a phase 3 clinical trial in CLI patients. In this study, patients who were not considered suitable for revascularization were randomized to treatment with NV1FGF (naked DNA plasmid with gene encoding FGF1) or placebo. In a one-year follow-up study, the NV1FGF treated group didn't show a significant improvement in major amputation rates and mortality over the placebo group [39]. While advancements in gene therapy show hope for future therapeutic options, stem cell therapy may also play an important role in improving the quality of life in patients affected by TAO.

4. Stem Cell-Based Approaches

Clinical trials have evaluated the potential benefits of stem cell therapy in CLI, which has similar clinical symptoms as TAO [40,41]. Reported benefits include more rapid angiogenesis, reduced inflammation, increased temperature and perfusion of the ischemic limb, and overall increased healing rates as observed by the size of the wound. Clinically, patients have lower rates of surgical amputation and report lower rates of claudication. These treatment approaches are based on the stem cells' ability to stimulate immunomodulation [10,42] and formation of new blood vessel formation (angiogenesis) and vessel growth (vasculogenesis) [25,43,44]. It has been recently reported that cell therapy using mononuclear stem cells (MNCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and pluripotent stem cells

(PSCs) may have useful roles in prevention of the progression of disease and reduction in major amputation rates [25,43].

4.1. Mononuclear Stem Cells (MNC)

MNCs isolated from bone marrow (BM-MNC) and peripheral blood (PB-MNC) have widely been used for cardiovascular disease applications [45]. Both BM-MNC and PB-MNC consist of heterogenous populations of hematopoietic stem cells, MSC, and EPC, and their cellular compositions vary depending on the purification procedure. The MNC-based cell therapy is popular because of the ease with which they are harvested, and the implantation can be done in short turnaround time [46].

Research studies on bone marrow mononuclear cells (BM-MNC) implantation have shown that cell therapy could increase tissue angiogenesis, neovascularization, and collateral vessel formation in both experimental models and clinical trials. (Table 1) The first clinical therapeutic effect of cell transplantation in angiogenesis process was shown by Tateishi-Yuyama et al. who evaluated therapeutic angiogenesis for patients with severe peripheral vascular disease and limb ischemia by autologous implantation of BM-MNC. Their results revealed that use of BM-MNC is a safe and effective method to achieve therapeutic angiogenesis [47]. A more recent double-blind randomized placebo-controlled study containing 20 patients demonstrated significant improvement in rest pain, increase in ABI, and ankle pressure. The safety and efficacy of utilizing BM-MNC therapy was tested for patients who were not appropriate surgical candidates [48]. In a study by Idei et al., long term clinical outcomes of BMMNC transplantation was assayed in patients with CLI including peripheral arterial disease (PAD) and TAO. Reduction of long-term major amputation risk was observed in patients with PAD who were treated with autologous BM-MNC. In TAO patients, ABI and TcPO2 were markedly enhanced at 1 month after cell therapy and these effects remain at a high level during the 3-year follow-up [49]. In long-term clinical trial, involving 115 patients, using autologous BM-MNC injected have been shown to have equivocal safety and efficacy to conventional revascularization therapies in extending the amputation-free interval in chronic limb ischemia. 6 months post BM-MNC injection resulted in improved pain-free walking time, rest pain, and tissue oxygen pressure that were not observed in PB-MNC. The improvement in the ischemic pain scale, ulcer size, and pain-free walking time was maintained over the course of 2 years of follow-ups [50].

Moriya et al. have shown that treatment with PB-MNCs improves ischemic symptoms and amputation rates in TAO [57]. It has been demonstrated that some factors such as granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating factor (GM-CSF), VEGF, and estrogen induce EPC mobilization from BM into PB, and the mobilized EPC then localize to the neovascularization site and contribute to the repair of damaged vessels [58]. In a phase I/IIa clinical trial, cell therapy outcome was evaluated in patients with PAD or TAO. It has been reported that following intramuscular injection of PB-MNC containing G-CSF-mobilized CD34+ stem cells, ischemic signs and symptoms involving Wong-Baker FACES pain rating scale (WBS), toe brachial pressure index (TBPI), TcPO2, total or pain-free walking distance, and size of ulcer improved in all patients. Furthermore, no mortality or major amputations were observed in this clinical study [59].

Table 1. Stem cell therapy clinical studies in TAO patients.

Study	Year	Patients (n)	Cell Source	Cell Route	Follow up	Main Results	Ref.
Kim et al.	2006	27	BM-MSC	Fenestration of the tibia bone	19.1 ± 3.5 months (range 12.4 ± 25 months)	Improved angiogenesis	[24]
Heo et al.	2016	37	BM-MSC	IM	11.9 ± 7.2 months	Improvement of TBPI and healing of ischemic wounds, pain relief	[41]
Idei et al.	2011	26	BM-MSC	IM	4.8 years	Increase in ABI, $TcPO_2$ In 3 years follow up	[49]
Kim et al.	2006	4	UCB-MSC	IM	1 and 4 months	Disappearance of ischemic rest pain, healing of necrotic skin lesions, increase in number and size of capillaries	[51]
Lee at al.	2012	15 male CLI patients including TAO	ADSC	IM	6 months	Improved angiogenesis	[43]
Ra et al.	2017	17	ADSC	IM	2 years	Increase in TWD, PFWD and decrease in rest pain	[52]
Baran et al.	2019	25 males and 3 females	PB-MNC	IM	139.6 ± 10.5 months	Improved angiogenesis and increase in quality of life	[53]
Aoyama et al.	2017	6	PB-MNC	IM	3 months	Decrease in major amputation	[54]
Guo et al.	2018	40	BM-MNC	IM	10 years	Decreased ulcer size and pain, increase in TBA and TCPO2, and 85.3% amputation-free survival	[55]
Kondo et al.	2018	108	BM-MNC	IM	10 years	87.9% major amputation-free and 80.9% amputation-free	[56]

BM-MSC, bone marrow mesenchymal stem cell; UC-MSCs, umbilical cord blood derived mesenchymal stem cells; ADSCs, adipose tissue derived mesenchymal stem cells; TBPI, toe brachial pressure index; $TcPO_2$, transcutaneous partial oxygen pressure; ABI, ankle-brachial index. TWD, total walking distance; PFWD, pain free walking distance; IM, Intramuscular.

4.2. Endothelial Progenitor Cells (EPC)

The stimulation of angiogenesis is critical to reversing the pathogenesis of TAO. Several factors are involved in the angiogenic process. It has been shown that growth factors, angiogenic genes, and stem cells including EPCs, are involved in modulation of angiogenesis [60]. It has been hypothesized that stem cell therapy for ischemic limbs could promote vascular angiogenesis by supplying EPCs, cytokines, and angiogenic factors. EPCs refer to the cell population that carries the ability for differentiation into endothelial cells. CD34+ or CD133+ (AC133+) MNC-enriched EPC can be derived from adult bone marrow (BM) or peripheral blood (PB) [61]. Human cord blood–derived CD133 progenitors implanted into the ischemic hind limbs of mice are capable of being incorporated into the capillary networks and improved neovascularization and vessel perfusion [62]. The safety and efficacy of therapeutic angiogenesis using EPC was evaluated with twenty-eight patients with CLI who were not suitable for surgical or endovascular revascularization. Apheresis was performed to obtain the necessary EPC and they were implanted into the ischemic limb. No safety concerns arose, while tissue perfusion improved and patients obtained a high amputation-free rate [63].

4.3. Mesenchymal Stem Cells (MSC)

MSC are multipotent stem cells and can be derived from various sources such as bone marrow, liver, adipose tissue, blood, and liver [64,65]. Thus, the availability and plasticity of MSC make them attractive agents of cellular based therapies. As a multipotent stem cell, MSC can be predominantly differentiated into cells of musculoskeletal and fat lineages and also to endothelial lineage [66]. Besides differentiating into cells of the endothelial lineage, MSC have further contributed to immunomodulatory and angiogenic response by secreting paracrine factors and cytokines such as VEGF, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF), interleukin-10 (IL-10) [42,65]. Investigations have been performed examining the potential of MSC derived from bone marrow (BM-MSC), umbilical cord blood (UC-MSC), and adipose tissue (ADSC).

BM-MSC have widely been used to treat wounds and/or ischemic tissue due to their immunomodulatory and angiogenic effect [42,45,65]. In a recent study, Martin-Rufino et al. investigated the efficacy of sequential intravenous allogeneic MSC administration in treating TAO instead of usual local intramuscular injections [10]. The idea was to illicit a systemic anti-inflammatory effect in the vasculature and thus to modulate the immune response. In this single patient clinical study, the patient with TAO and at risk of amputation was treated with four sequential intravenous infusions of allogeneic BM-MSC, a total of 3.4×10^8 cells, from a healthy donor. The infusion of BM-MSC passed the safety issue and showed no allograft rejection. Six months after the infusions the result showed significantly healed foot ulcer accompanied with reduced rest pain. Furthermore, the infusion resulted in the improvement of Walking Impairment Questionnaire scores and quality of life and the patient did not need any amputation sixteen months after the infusion. The success of this therapy can be attributed to the immunomodulatory activity BM-MSC against IL-33 mediated inflammation in TAO [10,13].

Studies have revealed that paracrine factors secreted by UC-MSC stimulate angiogenesis. A preclinical study has shown that UC-MSC therapy is better than BM-MSC transplantation in improving angiogenesis in an ischemic limb disease (ILD) mouse model. UC-MSC cells can secrete high levels of HGF and upon stimulation with TNFα also produce higher amounts of VEGF compared to the BM-MSC, which are key elements for angiogenesis process during ischemia [67]. Kim et al. have also demonstrated UC-MSC transplantation can produce effective outcomes in TAO. Cell therapy improves ischemic symptoms including alleviation of ischemic rest pain, healing of necrotic skin lesions associated with an increase in the size and density of capillaries [51].

Studies have been recently reported that adipose tissue derived-MSCs (ADSC) can be differentiated into endothelial cells and enhance micro-vascularity and blood flow in CLI animal models. The mechanism by which ADSC induce therapeutic angiogenesis is through the secretion of angiogenic factors such as VEGF [68–71]. In a pre-clinical study, by Moon et al., ADSC were extracted from digested human adipose tissue and transplanted into three different sites of the athymic nude murine hindlimb

one to seven days after femoral artery ligation. The transplanted group demonstrated increased blood flow and restored tissue function in ischemic limbs, directly correlated with the number of ADSC administered. The results suggest that ADSC may stand as an easily attainable source for MSC-based treatment of ischemic tissue injury [72]. Lee et al. determined the safety and efficacy of multiple intramuscular transplantations of ADSC are safe and effective demonstrating improved pain rating scales and pain-free walking distances and limb amputation rates. The collateral vascular network formation was also detected in the affected arteries using angiography [43,52]. A seven-patient phase I trial using adipose-derived stroma cells strongly improved revascularization and tissue perfusion in CLI. CLI is considered to be the end stage of PAD that often has no therapeutic options. The seven enrolled patients with non-vascularizable CLI showed improved ulcer evolution, wound healing, and increased transcutaneous oxygen pressure [73].

4.4. Pluripotent Stem Cells (PSC)

Pluripotent stem cells have the ability to self-renew infinitely and can be any cells of the body. These PSC can be derived either from inner cell mass of the blastocyst to become embryonic stem cells (ESC), or from somatic cells by expressing specific transcription factors (e.g., Oct4, Sox-2, Klf-4 and c-myc) to form induced pluripotent stem cells (iPSC) [74,75]. The use of iPSCs are advantageous as they avoid ethical concerns associated with ESC. Both ESC and iPSC have already been used to derive vascular cells such as endothelial (EC) and vascular smooth muscle cells (VSMC) to induce neovascularization. In two separate studies Cho et al. [76] and Huang et al. [77] demonstrated efficacy of ESC-derived endothelial cells in inducing neovascularization in animal model of CLI. While intramuscular (IM) injection of ESC-EC by Cho et al. resulted in improved blood perfusion and limb salvage, the study by Huang et al. compared various routes of cell delivery and found systemic route to be more efficient in improving blood perfusion and neovascularization than IM [76,77]. In another study, Yamahara et al, used a combination of ESC-derived EC and VSMC to treat ischemic limb [78]. The result showed formation of mature vasculature compared to EC or SMC alone. These initial studies have led to the generation of clinical grade ESC-EC product developed using good manufacturing practice for use in perfusing ischemic limb in patients [79].

Similar to ESC, iPSC have been used to derive functional EC. An initial study by Rufaihah et al. showed the efficacy of these cells in improving blood perfusion and neovascularization in an animal model of limb ischemia [80]. In order to further establish PSC as a functional source of EC, Lai et al. compared EC derived from various sources including bone marrow (BM-EC), ESC, and iPSC in their ability to improve neovascularization and secretion of paracrine factors [81]. The ESC- and iPSC-EC outperformed BM-EC in their ability to secrete paracrine factors and have similar in vivo efficiency in inducing neovascularization as compared to EC derived from human umbilical vein. These data further support the feasibility of using human PSC-EC in developing novel cell therapies for patients with CLI and TAO.

5. Pre-Clinical Insights into Cellular Dysfunction in Vascular Diseases

However, despite all the medical advances in stem cell-based therapy, the cessation of smoking and nicotine exposure is still paramount as both stressors can affect the success of stem cell therapy. In preclinical mice studies, prolonged nicotine exposure between 3–6 months has been shown to decrease EPC numbers, and the ability of EPC to proliferate and migrate. In a 6-month long-term nicotine exposure study in mice model, the mice subjected to systemic nicotine via drinking water demonstrated significant decrease in EPC numbers, and their ability to proliferate and migrate. A potential mechanism was found to be the significantly decreased nicotinic acetylcholine receptor subunit expression, thus decreasing cholinergic angiogenic pathways. This suggests that continued nicotine use during and after EPC cell therapy may lead to decreased therapeutic efficacy [82]. High nicotinic concentration, 1.5 mg/mL, increased rate of apoptosis, while changing cellular structure and motility of human UC-MSC [83]. Previous long-term exposure to nicotine may already have

profound effect on the MSC's overall efficacy as therapeutic agent. A study of MSC derived from smokers were shown to have impaired angiogenesis via possible involvement of activin A when compared to MSC from non-smoker counterparts [84]. Human adipose-derived MSC, when cultured in cigarette smoke-infused media, showed decrease in proliferation and migration capacity, and decrease in IL-6 and IL-8, which are markers of inflammation involved in the wound healing process [85]. A similar study with Human iPSC-EC also confirmed an increase in apoptosis rate along with elevated reactive oxygen species generation when exposed to nicotine from e-liquids of electronic cigarettes. There was no significant difference between traditional and E-cigarettes' effects on the effector cell population, which emphasized that the harms of nicotine may be independent of route of exposure [86]. An in vitro mouse ESC study has furthermore shown decreased cellular proliferation with less than 48 h of high nicotinic exposure; however, interestingly at lower concentration nicotine had the reversed effect with elevated proliferation. Another mechanistic pathway study revealed nicotine exposure to be disruptive on the Wnt pathway [87]. From the listed preclinical studies, the effect of nicotine on stem cells and their efficacy appears to be profound. Thus, it is still strongly advisable to encourage TAO patients to completely eliminate nicotine from their daily habits.

6. Future Application of Biomaterial-Based Approaches as Therapies for TAO

So far, a number of clinical trials using stem cells and genes have assessed the safety of the therapeutics with limited success in functional recovery. In recent years pre-clinical proangiogenic and immunomodulatory research has shown increased interest in the development of biomaterial-based approaches to enhance the therapeutic efficacy of such modalities as delivery vehicles [88,89]. For example, in one of the studies an injectable biomaterial was developed using elastin-like polypeptide to deliver proangiogenic endothelial nitric oxide synthase (eNOS) and anti-inflammatory cytokine IL-10 plasmid DNAs. The biomaterial delivery vehicle contained an injectable ELP scaffold encapsulating IL-10 and hollow spheres with eNOS in them. This design allowed spatiotemporal release of IL-10 and eNOS and resulted in an enhanced angiogenesis and reduced inflammation in mouse model of CLI. The therapeutics also improved functional recovery in these animals [90]. In another study, Thomas et al. developed tunable collagen microgels that improved the MSC encapsulation efficiency with enhanced proangiogenic and immunomodulatory function. These MSC embedded within microgels improved vascularization with reduced inflammation in vivo in mouse model of CLI [91,92]. Moreover, recently we encapsulated human iPSC-derived vascular smooth muscle cells (hiPSC-VSMC) in biomimetic collagen scaffold to treat both acute and diabetic wounds. Our study reported an enhanced level of proangiogenic paracrine secretion and anti-inflammatory IL-10 release from the cells. The hiPSC-VSMC containing scaffolds showed improved wound closure, vascularization, and immunomodulation [93,94]. These studies and several other have now shown promising results in delivering stem cells and genes using biomaterials. The utilization of biomaterials to promote vascularization and immunomodulation via delivery of cells and gene thus will be a significant advancement for the field of Buerger's disease.

7. Conclusions

In the past two decades, stem cell-based therapy has demonstrated clinical efficacy in the form of therapeutic angiogenesis in peripheral vascular disease. Use of cell therapy for induction of angiogenesis as well as immunomodulation in the animal model has slowly progressed into human clinical trials. While the angiogenic and immunomodulatory potentials of stem cell-based therapy have been demonstrated in human clinical trials of both CLI and TAO, there are still many challenges. The factors that would determine the success of these cell therapies in near future are (i) understanding the mechanism and therapeutic potentials of cell-based therapy; (ii) establishing a large-scale and renewable source of autologous cells; (iii) developing biomaterial strategies to improve cell potency in vivo; (iv) deciding optimal dose, efficient route of administration, and frequency of application; and further encouraging cessation of nicotine exposure during therapeutic intervention. Ultimately, we will also need to understand how the in vivo tissue microenvironment affects the therapeutic activity.

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References

1. Olin, J.W. Thromboangiitis obliterans (Buerger's disease). *N. Engl. J. Med.* **2000**, *343*, 864–869. [CrossRef]
2. Matsushita, M.; Nishikimi, N.; Sakurai, T.; Nimura, Y. Decrease in prevalence of Buerger's disease in Japan. *Surgery* **1998**, *124*, 498–502. [CrossRef]
3. Vijayakumar, A.; Tiwari, R.; Prabhuswamy, V.K. Thromboangiitis Obliterans (Buerger's Disease)—Current Practices. *Int. J. Inflamm.* **2013**, *2013*, 156905. [CrossRef] [PubMed]
4. Hagen, B.; Lohse, S. Clinical and radiologic aspects of buerger's disease. *Cardiovasc. Interv. Radiol.* **1984**, *7*, 283–293. [CrossRef] [PubMed]
5. Juergens, J. Thromboangiitis obliterans (Buerger's disease, TAO). *Peripher. Vasc. Dis.* **1980**, 467–491.
6. Joviliano, E.; Dellalibera-Joviliano, R.; Dalio, M.; Évora, P.; Piccinato, C. Etiopathogenesis, clinical diagnosis and treatment of thromboangiitis obliterans—Current practices. *Int. J. Angiol.* **2009**, *18*, 119–125. [CrossRef] [PubMed]
7. Iwai, T.; Inoue, Y.; Umeda, M.; Huang, Y.; Kurihara, N.; Koike, M.; Ishikawa, I. Oral bacteria in the occluded arteries of patients with Buerger disease. *J. Vasc. Surg.* **2005**, *42*, 107–115. [CrossRef] [PubMed]
8. Hill, G.L. A rational basis for management of patients with the Buerger syndrome. *Br. J. Surg.* **1974**, *61*, 476–481. [CrossRef]
9. Busch, K. Buerger's disease (thromboangiitis obliterans): Clinical features and assessment by colour duplex ultrasound. *Australas. J. Ultrasound Med.* **2011**, *14*, 18–22. [CrossRef]
10. Martin-Rufino, J.D.; Lozano, F.S.; Redondo, A.M.; Villarón, E.M.; Rueda, R.; Fernandez-Samos, R.; Sanchez-Guijo, F. Sequential intravenous allogeneic mesenchymal stromal cells as a potential treatment for thromboangiitis obliterans (Buerger's disease). *Stem Cell Res. Ther.* **2018**, *9*, 150. [CrossRef]
11. Klein-Weigel, P.F.; Richter, J.G. Thromboangiitis obliterans (Buerger's disease). *Vasa* **2014**, *43*, 337–346. [CrossRef] [PubMed]
12. Klein-Weigel, P.; Volz, T.S.; Zange, L.; Richter, J. Buerger's disease: Providing integrated care. *J. Multidiscip. Health* **2016**, *9*, 511–518. [CrossRef] [PubMed]
13. Sun, X.-L.; Law, B.Y.-K.; Dias, I.R.D.S.R.; Mok, S.W.F.; He, Y.-Z.; Wong, V.K.-W. Pathogenesis of thromboangiitis obliterans: Gene polymorphism and immunoregulation of human vascular endothelial cells. *Atherosclerosis* **2017**, *265*, 258–265. [CrossRef] [PubMed]
14. Adar, R.; Mozes, M.; Shoshan, S.; Sofer, B.; Zinger, H.; Dayan, M.; Mozes, E.; Papa, M.Z.; Halpern, Z. Cellular Sensitivity to Collagen in Thromboangiitis Obliterans. *N. Engl. J. Med.* **1983**, *308*, 1113–1116. [CrossRef]
15. Eichhorn, J.; Sima, D.; Lindschau, C.; Turowski, A.; Schmidt, H.; Schneider, W.; Haller, H.; Luft, F.C. Antiendothelial cell antibodies in thromboangiitis obliterans. *Am. J. Med Sci.* **1998**, *315*, 17–23. [CrossRef]
16. Avcu, F.; Akar, E.; Demirkiliç, U.; Yilmaz, E.; Akar, N.; Yalçin, A. The role of prothrombotic mutations in patients with Buerger's disease. *Thromb. Res.* **2000**, *100*, 143–147. [CrossRef]
17. Maslowski, L.; McBane, R.; Alexewicz, P.; Wysokinski, W.E. Antiphospholipid antibodies in thromboangiitis obliterans. *Vasc. Med.* **2002**, *7*, 259–264. [CrossRef] [PubMed]
18. Piazza, G.; Creager, M.A. Thromboangiitis obliterans. *Circulation* **2010**, *121*, 1858–1861. [CrossRef]
19. Olin, J.; Young, J.; Graor, R.; Ruschhaupt, W.; Bartholomew, J. The changing clinical spectrum of thromboangiitis obliterans (Buerger's disease). *Circulation* **1990**, *82* (Suppl. 5), Iv3–Iv8.
20. Małecki, R.; Zdrojowy, K.; Adamiec, R. Thromboangiitis obliterans in the 21st century—A new face of disease. *Atheroscler.* **2009**, *206*, 328–334. [CrossRef] [PubMed]
21. Hida, N.; Ohta, T. Current Status of Patients with Buerger Disease in Japan. *Ann. Vasc. Dis.* **2013**, *6*, 617–623. [CrossRef]
22. Cooper, L.T.; Tse, T.S.; Mikhail, M.A.; McBane, R.D.; Stanson, A.W.; Ballman, K.V. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). *J. Am. Coll. Cardiol.* **2004**, *44*, 2410–2411. [CrossRef] [PubMed]

23. Isner, J.M.; Baumgartner, I.; Rauh, G.; Schainfeld, R.; Blair, R.; Manor, O.; Razvi, S.; Symes, J.F. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: Preliminary clinical results. *J. Vasc. Surg.* **1998**, *28*, 964–975. [CrossRef]
24. Kim, D.I.; Kim, M.J.; Joh, J.H.; Shin, S.W.; Do, Y.S.; Moon, J.Y.; Kim, N.R.; Lim, J.E.; Kim, A.K.; Eo, H.S. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. *Stem Cells* **2006**, *24*, 1194–1200. [CrossRef]
25. Durdu, S.; Akar, A.R.; Arat, M.; Sancak, T.; Eren, N.T.; Ozyurda, U. Autologous bone-marrow mononuclear cell implantation for patients with Rutherford grade II-III thromboangiitis obliterans. *J. Vasc. Surg.* **2006**, *44*, 732–739. [CrossRef] [PubMed]
26. Kajiguchi, M.; Kondo, T.; Izawa, H.; Kobayashi, M.; Yamamoto, K.; Shintani, S.; Numaguchi, Y.; Naoe, T.; Takamatsu, J.; Komori, K.; et al. Safety and Efficacy of Autologous Progenitor Cell Transplantation for Therapeutic Angiogenesis in Patients With Critical Limb Ischemia. *Circ. J.* **2007**, *71*, 196–201. [CrossRef]
27. Ohta, T.; Ishioashi, H.; Hosaka, M.; Sugimoto, I. Clinical and social consequences of buerger disease. *J. Vasc. Surg.* **2004**, *39*, 176–180. [CrossRef]
28. Lawrence, P.F.; Lund, O.I.; Jimenez, J.C.; Muttalib, R. Substitution of smokeless tobacco for cigarettes in Buerger's disease does not prevent limb loss. *J. Vasc. Surg.* **2008**, *48*, 210–212. [CrossRef]
29. Bozkurt, A.K.; Cengiz, K.; Arslan, C.; Mine, D.Y.; Oner, S.; Deniz, D.B.; Ufuk, D. A Stable Prostacyclin Analogue (Iloprost) in the Treatment of Buerger's Disease: A Prospective Analysis of 150 Patients. *Ann. Thorac. Cardiovasc. Surg.* **2013**, *19*, 120–125. [CrossRef] [PubMed]
30. Cacione, D.G.; Macedo, C.R.; Baptista-Silva, J.C.C. Pharmacological treatment for Buerger's disease. *Cochrane Database Syst. Rev.* **2016**, *2016*, CD011033. [CrossRef]
31. Hussein, E. Intra-arterial streptokinase as adjuvant therapy for complicated Buerger's disease: Early trials. *Int. Surg.* **1993**, *78*, 54–58.
32. De Haro, J.; Bleda, S.; Acin, F. An open-label study on long-term outcomes of bosentan for treating ulcers in thromboangiitis obliterans (Buerger's disease). *Int. J. Cardiol.* **2014**, *177*, 529–531. [CrossRef]
33. Jorge, V.C.; Araújo, A.C.; Noronha, C.; Panarra, A.; Riso, N.; Riscado, M.V. Buerger's disease (Thromboangiitis obliterans): A diagnostic challenge. *BMJ Case Rep.* **2011**, *2011*, 0820114621. [CrossRef] [PubMed]
34. Sasajima, T.; Kubo, Y.; Inaba, M.; Goh, K.; Azuma, N. Role of infrainguinal bypass in Buerger's disease: An eighteen-year experience. *Eur. J. Vasc. Endovasc. Surg.* **1997**, *13*, 186–192. [CrossRef]
35. Ryu, S.-W.; Jeon, H.-J.; Cho, S.-S.; Choi, R.-M.; Yoon, J.-S.; Ko, H.-S.; Lee, J.-D. Treatment of digit ulcers in a patient with Buerger's disease by using cervical spinal cord stimulation-a case report. *Korean J. Anesthesiol.* **2013**, *65*, 167–171. [CrossRef]
36. Lee, J.-H.; Ko, Y.-G.; Choi, D. Endovascular Treatment of Multilevel Chronic Total Occlusion Using a Stent Puncture Technique in Buerger's Disease. *Korean Circ. J.* **2016**, *46*, 417–420. [CrossRef] [PubMed]
37. Donas, K.P.; Schulte, S.; Ktenidis, K.; Horsch, S. The role of epidural spinal cord stimulation in the treatment of Buerger's disease. *J. Vasc. Surg.* **2005**, *41*, 830–836. [CrossRef]
38. Henry, T.D.; Hirsch, A.T.; Goldman, J.; Wang, Y.L.; Lips, D.L.; McMillan, W.D.; Duval, S.; Biggs, T.A.; Keo, H.H. Safety of a non-viral plasmid-encoding dual isoforms of hepatocyte growth factor in critical limb ischemia patients: A phase I study. *Gene Ther.* **2011**, *18*, 788–794. [CrossRef]
39. Belch, J.J.F.; Hiatt, W.R.; Baumgartner, I.; Driver, I.V.; Nikol, S.; Norgren, L.; Van Belle, E. Effect of fibroblast growth factor NV1FGF on amputation and death: A randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet* **2011**, *377*, 1929–1937. [CrossRef]
40. Lee, K.-B.; Kang, E.-S.; Kim, A.-K.; Kim, M.-H.; Do, Y.-S.; Park, K.-B.; Park, H.-S.; Um, S.H.; Cho, S.-W.; Kim, D.-I. Stem Cell Therapy in Patients with Thromboangiitis Obliterans: Assessment of the Long-Term Clinical Outcome and Analysis of the Prognostic Factors. *Int. J. Stem Cells* **2011**, *4*, 88–98. [CrossRef] [PubMed]
41. Heo, S.-H.; Park, Y.-S.; Kang, E.-S.; Park, K.-B.; Do, Y.-S.; Kang, K.-S.; Kim, D.-I. Early Results of Clinical Application of Autologous Whole Bone Marrow Stem Cell Transplantation for Critical Limb Ischemia with Buerger's Disease. *Sci. Rep.* **2016**, *6*, 19690. [CrossRef]
42. Gao, F.; Chiu, S.M.; Motan, D.A.L.; Zhang, Z.; Chen, L.; Ji, H.-L.; Tse, H.-F.; Fu, Q.-L.; Lian, Q. Mesenchymal stem cells and immunomodulation: Current status and future prospects. *Cell Death Dis.* **2016**, *7*, e2062. [CrossRef]
43. Lee, H.C.; An, S.G.; Lee, H.W.; Park, J.-S.; Cha, K.S.; Hong, T.J.; Park, J.H.; Lee, S.Y.; Kim, S.-P.; Kim, Y.D.; et al. Safety and Effect of Adipose Tissue-Derived Stem Cell Implantation in Patients with Critical Limb Ischemia. *Circ. J.* **2012**, *76*, 1750–1760. [CrossRef] [PubMed]

44. Miyamoto, K.; Nishigami, K.; Nagaya, N.; Akutsu, K.; Chiku, M.; Kamei, M.; Soma, T.; Miyata, S.; Higashi, M.; Tanaka, R.; et al. Unblinded Pilot Study of Autologous Transplantation of Bone Marrow Mononuclear Cells in Patients With Thromboangiitis Obliterans. *Circulation* **2006**, *114*, 2679–2684. [CrossRef] [PubMed]
45. Brenes, R.A.; Bear, M.; Jadlowiec, C.; Goodwin, M.; Hashim, P.W.; Protack, C.D.; Ziegler, K.R.; Li, X.; Model, L.S.; Lv, W.; et al. Cell-based interventions for therapeutic angiogenesis: Review of potential cell sources. *Vascular* **2012**, *20*, 360–368. [CrossRef]
46. Goumans, M.-J.; Maring, J.A.; Smits, A.M. A straightforward guide to the basic science behind cardiovascular cell-based therapies. *Heart* **2014**, *100*, 1153–1157. [CrossRef]
47. Tateishi-Yuyama, E.; Matsubara, H.; Murohara, T.; Ikeda, U.; Shintani, S.; Masaki, H.; Amano, K.; Kishimoto, Y.; Yoshimoto, K.; Akashi, H.; et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: A pilot study and a randomised controlled trial. *Lancet* **2002**, *360*, 427–435. [CrossRef]
48. Gupta, P.K.; Chullikana, A.; Parakh, R.; Desai, S.; Das, A.; Gottipamula, S.; Krishnamurthy, S.; Anthony, N.; Pherwani, A.; Majumdar, A.S. A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia. *J. Transl. Med.* **2013**, *11*, 143. [CrossRef]
49. Idei, N.; Soga, J.; Hata, T.; Fujii, Y.; Fujimura, N.; Mikami, S.; Maruhashi, T.; Nishioka, K.; Hidaka, T.; Kihara, Y.; et al. Autologous Bone-Marrow Mononuclear Cell Implantation Reduces Long-Term Major Amputation Risk in Patients With Critical Limb Ischemia. *Circ. Cardiovasc. Interv.* **2011**, *4*, 15–25. [CrossRef]
50. Matoba, S.; Tatsumi, T.; Murohara, T.; Imaizumi, T.; Katsuda, Y.; Ito, M.; Saito, Y.; Uemura, S.; Suzuki, H.; Fukumoto, S.; et al. Long-term clinical outcome after intramuscular implantation of bone marrow mononuclear cells (Therapeutic Angiogenesis by Cell Transplantation [TACT] trial) in patients with chronic limb ischemia. *Am. Hear. J.* **2008**, *156*, 1010–1018. [CrossRef]
51. Kim, S.W.; Han, H.; Chae, G.T.; Lee, S.H.; Bo, S.; Yoon, J.H.; Lee, Y.S.; Lee, K.S.; Park, H.K.; Kang, K.S. Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model. *Stem Cells* **2006**, *24*, 1620–1626. [CrossRef]
52. Ra, J.C.; Jeong, E.C.; Kang, S.K.; Lee, S.J.; Choi, K.H. A Prospective, Nonrandomized, no Placebo-Controlled, Phase I/II Clinical Trial Assessing the Safety and Efficacy of Intramuscular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells in Patients with Severe Buerger's Disease. *Cell Med.* **2017**, *9*, 87–102. [CrossRef] [PubMed]
53. Baran, Ç.; Durdu, S.; Özçınar, E.; Çakıcı, M.; Hasde, A.I.; Şırlak, M.; Akar, R.; Inan, B. Long-term follow-up of patients with Buerger's disease after autologous stem cell therapy. *Anatol. J. Cardiol.* **2018**, *21*, 155–162. [CrossRef]
54. Aoyama, N.; Nishinari, M.; Ohtani, S.; Kanai, A.; Noda, C.; Hirata, M.; Miyamoto, A.; Watanabe, M.; Minamino, T.; Izumi, T.; et al. Clinical features and predictors of patients with critical limb ischemia who responded to autologous mononuclear cell transplantation for therapeutic angiogenesis. *Hear. Vessel.* **2017**, *32*, 1099–1108. [CrossRef]
55. Guo, J.; Guo, L.; Cui, S.; Tong, Z.; Dardik, A.; Gu, Y. Autologous bone marrow-derived mononuclear cell therapy in Chinese patients with critical limb ischemia due to thromboangiitis obliterans: 10-year results. *Stem Cell Res. Ther.* **2018**, *9*, 1–8. [CrossRef]
56. Kondo, K.; Yanishi, K.; Hayashida, R.; Shintani, S.; Shibata, R.; Murotani, K.; Ando, M.; Mizuno, M.; Fujiwara, T.; Murohara, T.; et al. Long-Term Clinical Outcomes Survey of Bone Marrow-Derived Cell Therapy in Critical Limb Ischemia in Japan. *Circ. J.* **2018**, *82*, 1168–1178. [CrossRef]
57. Moriya, J.; Minamino, T.; Tateno, K.; Shimizu, N.; Kuwabara, Y.; Sato, Y.; Saito, Y.; Komuro, I. Long-Term Outcome of Therapeutic Neovascularization Using Peripheral Blood Mononuclear Cells for Limb Ischemia. *Circ. Cardiovasc. Interv.* **2009**, *2*, 245–254. [CrossRef]
58. Imanishi, T.; Tsujioka, H.; Akasaka, T. Endothelial Progenitor Cells Dysfunction and Senescence: Contribution to Oxidative Stress. *Curr. Cardiol. Rev.* **2008**, *4*, 275–286. [CrossRef]
59. Kawamoto, A.; Katayama, M.; Handa, N.; Kinoshita, M.; Takano, H.; Horii, M.; Sadamoto, K.; Yokoyama, A.; Yamanaka, T.; Onodera, R.; et al. Intramuscular Transplantation of G-CSF-Mobilized CD34+Cells in Patients With Critical Limb Ischemia: A Phase I/IIa, Multicenter, Single-Blinded, Dose-Escalation Clinical Trial. *Stem Cells* **2009**, *27*, 2857–2864. [CrossRef] [PubMed]
60. Huang, N.F.; Li, S. Mesenchymal stem cells for vascular regeneration. *Regen. Med.* **2008**, *3*, 877–892. [CrossRef]

61. Friedrich, E.B.; Walenta, K.; Scharlau, J.; Nickenig, G.; Werner, N. CD34−/CD133+/VEGFR-2+ endothelial progenitor cell subpopulation with potent vasoregenerative capacities. *Circ. Res.* **2006**, *98*, e20–e25. [CrossRef]
62. Yang, C.; Zhang, Z.H.; Li, Z.; Yang, R.C.; Qian, G.Q.; Han, Z. Enhancement of neovascularization with cord blood CD133+ cell-derived endothelial progenitor cell transplantation. *Thromb. Haemost.* **2004**, *91*, 1202–1212. [CrossRef]
63. Lara-Hernandez, R.; Lozano, P.; Blanes, P.; Torreguitart-Mirada, N.; Galmés, A.; Besalduch, J. Safety and Efficacy of Therapeutic Angiogenesis as a Novel Treatment in Patients with Critical Limb Ischemia. *Ann. Vasc. Surg.* **2010**, *24*, 287–294. [CrossRef]
64. Pittenger, M.F.; Mackay, A.M.; Beck, S.C.; Jaiswal, R.K.; Douglas, R.; Mosca, J.D.; Moorman, M.A.; Simonetti, D.W.; Craig, S.; Marshak, D.R. Multilineage Potential of Adult Human Mesenchymal Stem Cells. *Science* **1999**, *284*, 143–147. [CrossRef]
65. Galipeau, J.; Sensébé, L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. *Cell Stem Cell* **2018**, *22*, 824–833. [CrossRef]
66. Zomer, H.D.; Vidane, A.S.; Gonçalves, N.N.; Martins, D.D.S.; Ambrósio, C.E. 662. Mesenchymal and Induced Pluripotent Stem Cells: General Insights and Clinical Perspectives. *Mol. Ther.* **2015**, *23*, S263. [CrossRef]
67. Shetty, P.; Thakur, A.M.; Ravindran, G.; Viswanathan, C. Directed therapeutic angiogenesis by mesenchymal stem cells from umbilical cord matrix in preclinical model of ischemic limb disease. *Stem Cell Stud.* **2011**, *1*, 16. [CrossRef]
68. Kondo, K.; Shintani, S.; Shibata, R.; Murakami, H.; Murakami, R.; Imaizumi, M.; Kitagawa, Y.; Murohara, T. Implantation of Adipose-Derived Regenerative Cells Enhances Ischemia-Induced Angiogenesis. *Arter. Thromb. Vasc. Biol.* **2009**, *29*, 61–66. [CrossRef] [PubMed]
69. Sumi, M.; Sata, M.; Toya, N.; Yanaga, K.; Ohki, T.; Nagai, R. Transplantation of adipose stromal cells, but not mature adipocytes, augments ischemia-induced angiogenesis. *Life Sci.* **2007**, *80*, 559–565. [CrossRef]
70. Traktuev, D.O.; Merfeld-Clauss, S.; Li, J.; Kolonin, M.G.; Pasqualini, R.; Pasqualini, R.; Johnstone, B.H.; March, K.L. A Population of Multipotent CD34-Positive Adipose Stromal Cells Share Pericyte and Mesenchymal Surface Markers, Reside in a Periendothelial Location, and Stabilize Endothelial Networks. *Circ. Res.* **2008**, *102*, 77–85. [CrossRef] [PubMed]
71. Nakagami, H.; Maeda, K.; Morishita, R.; Iguchi, S.; Nishikawa, T.; Takami, Y.; Kikuchi, Y.; Saito, Y.; Tamai, K.; Ogihara, T.; et al. Novel Autologous Cell Therapy in Ischemic Limb Disease Through Growth Factor Secretion by Cultured Adipose Tissue–Derived Stromal Cells. *Arter. Thromb. Vasc. Biol.* **2005**, *25*, 2542–2547. [CrossRef]
72. Moon, M.H.; Kim, S.Y.; Kim, Y.J.; Kim, S.J.; Lee, J.B.; Bae, Y.C.; Sung, S.M.; Jung, J.S. Human Adipose Tissue-Derived Mesenchymal Stem Cells Improve Postnatal Neovascularization in a Mouse Model of Hindlimb Ischemia. *Cell. Physiol. Biochem.* **2006**, *17*, 279–290. [CrossRef]
73. Bura, A.; Planat-Benard, V.; Bourin, P.; Silvestre, J.-S.; Gross, F.; Grolleau, J.-L.; Saint-Lebese, B.; Peyrafitte, J.-A.; Fleury, S.; Gadelorge, M.; et al. Phase I trial: The use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia. *Cytotherapy* **2014**, *16*, 245–257. [CrossRef]
74. Thomson, J.A.; Itskovitz-Eldor, J.; Shapiro, S.S.; Waknitz, M.A.; Swiergiel, J.J.; Marshall, V.S.; Jones, J.M. Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* **1998**, *282*, 1145–1147. [CrossRef]
75. Takahashi, K.; Tanabe, K.; Ohnuki, M.; Narita, M.; Ichisaka, T.; Tomoda, K.; Yamanaka, S. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell* **2007**, *131*, 861–872. [CrossRef] [PubMed]
76. Cho, S.-W.; Moon, S.-H.; Lee, S.-H.; Kang, S.-W.; Kim, J.; Lim, J.M.; Kim, H.-S.; Kim, B.-S.; Chung, H.-M. Improvement of Postnatal Neovascularization by Human Embryonic Stem Cell–Derived Endothelial-Like Cell Transplantation in a Mouse Model of Hindlimb Ischemia. *Circulation* **2007**, *116*, 2409–2419. [CrossRef]
77. Huang, N.F.; Niiyama, H.; Peter, C.; De, A.; Natkunam, Y.; Fleissner, F.; Li, Z.; Rollins, M.D.; Wu, J.C.; Gambhir, S.S.; et al. Embryonic stem cell-derived endothelial cells engraft into the ischemic hindlimb and restore perfusion. *Arter. Thromb. Vasc. Biol.* **2010**, *30*, 984–991. [CrossRef]
78. Yamahara, K.; Sone, M.; Itoh, H.; Yamashita, J.K.; Yurugi-Kobayashi, T.; Homma, K.; Chao, T.-H.; Miyashita, K.; Park, K.; Oyamada, N.; et al. Correction: Augmentation of Neovascularization in Hindlimb Ischemia by Combined Transplantation of Human Embryonic Stem Cells-Derived Endothelial and Mural Cells. *PLoS ONE* **2009**, *4*, 1666. [CrossRef]
79. Macaskill, M.G.; Saif, J.; Condie, A.; Jansen, M.A.; MacGillivray, T.J.; Tavares, A.A.; Fleisinger, L.; Spencer, H.L.; Besnier, M.; Martin, E.; et al. Robust Revascularization in Models of Limb Ischemia Using a Clinically Translatable Human Stem Cell-Derived Endothelial Cell Product. *Mol. Ther.* **2018**, *26*, 1669–1684. [CrossRef]

80. Rufaihah, A.J.; Huang, N.F.; Jamé, S.; Lee, J.C.; Nguyen, H.N.; Byers, B.; De, A.; Okogbaa, J.; Rollins, M.; Reijo-Pera, R.; et al. Endothelial Cells Derived From Human iPSCS Increase Capillary Density and Improve Perfusion in a Mouse Model of Peripheral Arterial Disease. *Arter. Thromb. Vasc. Biol.* **2011**, *31*, e72–e79. [CrossRef] [PubMed]
81. Lai, W.-H.; Ho, J.C.Y.; Chan, Y.-C.; Ng, J.H.L.; Au, K.-W.; Wong, L.-Y.; Siu, C.-W.; Tse, H.-F. Attenuation of Hind-Limb Ischemia in Mice with Endothelial-Like Cells Derived from Different Sources of Human Stem Cells. *PLoS ONE* **2013**, *8*, e57876. [CrossRef] [PubMed]
82. Li, W.; Du, D.-Y.; Liu, Y.; Jiang, F.; Zhang, P.; Li, Y.-T. Long-term nicotine exposure induces dysfunction of mouse endothelial progenitor cells. *Exp. Ther. Med.* **2016**, *13*, 85–90. [CrossRef]
83. Zeng, H.-L.; Qin, Y.-L.; Chen, H.-Z.; Bu, Q.-Q.; Li, Y.; Zhong, Q.; Han, X.-A.; Chen, J.; Yu, P.-X.; Liu, G.-X. Effects of Nicotine on Proliferation and Survival in Human Umbilical Cord Mesenchymal Stem Cells. *J. Biochem. Mol. Toxicol.* **2014**, *28*, 181–189. [CrossRef] [PubMed]
84. Barwinska, D.; Traktuev, D.O.; Merfeld-Clauss, S.; Cook, T.G.; Lu, H.; Petrache, I.; March, K.L. Cigarette Smoking Impairs Adipose Stromal Cell Vasculogenic Activity and Abrogates Potency to Ameliorate Ischemia. *Stem Cells* **2018**, *36*, 856–867. [CrossRef] [PubMed]
85. Wahl, E.A.; Schenck, T.L.; Machens, H.-G.; Egaña, J.T. Acute stimulation of mesenchymal stem cells with cigarette smoke extract affects their migration, differentiation and paracrine potential. *Sci. Rep.* **2016**, *6*, 22957. [CrossRef]
86. Lee, W.H.; Ong, S.-G.; Zhou, Y.; Tian, L.; Bae, H.R.; Baker, N.; Whitlatch, A.; Mohammadi, L.; Guo, H.; Nadeau, K.C.; et al. Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell–Derived Endothelial Cells. *J. Am. Coll. Cardiol.* **2019**, *73*, 2722–2737. [CrossRef]
87. Qu, Q.; Zhang, F.; Zhang, X.; Yin, W. Bidirectional Regulation of Mouse Embryonic Stem Cell Proliferation by Nicotine Is Mediated Through Wnt Signaling Pathway. *Dose-Response* **2017**, *15*, 1559325817739760. [CrossRef]
88. Thomas, D.; O'Brien, T.; Pandit, A. Tissue Engineering: Toward Customized Extracellular Niche Engineering: Progress in Cell-Entrapment Technologies. *Adv. Mater.* **2018**, *30*, 1703948. [CrossRef]
89. Veith, A.P.; Henderson, K.; Spencer, A.; Sligar, A.D.; Baker, A.B. Therapeutic strategies for enhancing angiogenesis in wound healing. *Adv. Drug Deliv. Rev.* **2019**, *146*, 97–125. [CrossRef]
90. Dash, B.C.; Thomas, D.; Monaghan, M.; Carroll, O.; Chen, X.; Woodhouse, K.; O'Brien, T.; Pandit, A. An injectable elastin-based gene delivery platform for dose-dependent modulation of angiogenesis and inflammation for critical limb ischemia. *Biomaterials* **2015**, *65*, 126–139. [CrossRef]
91. Thomas, D.; Marsico, G.; Isa, I.L.M.; Thirumaran, A.; Chen, X.; Lukasz, B.; Fontana, G.; Rodriguez, B.; Marchetti-Deschmann, M.; O'Brien, T.; et al. Temporal changes guided by mesenchymal stem cells on a 3D microgel platform enhance angiogenesis in vivo at a low-cell dose. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 19033–19044. [CrossRef] [PubMed]
92. Thomas, D.; Fontana, G.; Chen, X.; Sanz-Nogués, C.; Zeugolis, D.I.; Dockery, P.; O'Brien, T.; Pandit, A. A shape-controlled tuneable microgel platform to modulate angiogenic paracrine responses in stem cells. *Biomaterials* **2014**, *35*, 8757–8766. [CrossRef]
93. Gorecka, J.; Gao, X.; Fereydooni, A.; Dash, B.C.; Luo, J.; Lee, S.R.; Taniguchi, R.; Hsia, H.C.; Qyang, Y.; Dardik, A. Induced pluripotent stem cell-derived smooth muscle cells increase angiogenesis and accelerate diabetic wound healing. *Regen. Med.* **2020**, *15*, 1277–1293. [CrossRef]
94. Dash, B.C.; Setia, O.; Gorecka, J.; Peyvandi, H.; Duan, K.; Lopes, L.; Berthiaume, F.; Berthiaume, F.; Dardik, A.; Hsia, H.C. A Dense Fibrillar Collagen Scaffold Differentially Modulates Secretory Function of iPSC-Derived Vascular Smooth Muscle Cells to Promote Wound Healing. *Cells* **2020**, *9*, 966. [CrossRef]