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# Potential of Tissue-Engineered Constructs for the Management of Short Bowel Syndrome in Regenerative Medicine

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## ABSTRACT

Short bowel syndrome is a life-threatening condition characterized by the intestine's inability to maintain homeostasis through enteral nutrition. Despite the use of conservative approaches, including parenteral nutrition, most patients fail to achieve complete enteral autonomy or correct electrolyte and nutrient deficiencies. Surgical interventions such as longitudinal intestinal lengthening and tailoring, serial transverse enteroplasty, and intestinal or multivisceral allotransplantation are associated with a high risk of complications owing to technical limitations and the requirement for immunosuppressive therapy. Tissue engineering is a promising alternative. Current strategies use various synthetic and biological extracellular matrices as scaffolds, including silk fibroin, collagen, gelatin, hydrogels, polyglycolic acid, and allogeneic intestinal submucosa. The cellular components of tissue-engineered constructs include embryonic, pluripotent, and mesenchymal stem cell lines, whose regenerative potential is enhanced by various adjuvants and growth factors. Given the biological properties of these cells and specifics of transplantation and post-transplant changes, mesenchymal stem cells are a promising cellular vehicle for morphofunctional restoration of the residual intestine. This study provides a comprehensive review of tissue-engineered constructs developed for intestinal reconstruction in short bowel syndrome.

**Keywords**: short bowel syndrome; intestinal transplantation; tissue engineering; cell-based therapy; literature review.

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# Потенциал тканеинженерных конструкций для коррекции синдрома короткой кишки в регенеративной медицине

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## АННОТАЦИЯ

Синдром короткой кишки — опасное для жизни состояние, проявляющееся неспособностью собственного кишечника поддерживать гомеостаз посредством энтерального питания. Несмотря на проведение различных консервативных мероприятий, включая парентеральное питание, в большинстве случаев не удаётся достичь полной энтеральной автономии и устранить дефицит электролитов и питательных веществ. Оперативные вмешательства, проводимые по показаниям, такие как удлинение и сужение кишки (LILT), последовательная поперечная энтеропластика (STEP), а также аллотрансплантация кишечника или его органокомплексов, сопряжены с высокий риском осложнений, обусловленных как техническими ограничениями, так и необходимостью проведения иммуносупрессивной терапии. Современным решением данной проблемы выступает тканевая инженерия. На сегодняшний день известны способы применения различных синтетических и биологических экстрацеллюлярных матриксов, в качестве скаффолда используют фиброин шёлка, коллаген, желатин, гидрогель, полигликолевые кислоты, аллогенную подслизистую основу кишечника. Клеточный компонент в тканеинженерных конструкциях представлен эмбриональными, плюрипотентными и мезенхимальными стволовыми линиями, чей регенераторный потенциал ряд авторов усиливает путём добавления различных адъювантов и факторов роста. Учитывая биологию данных клеток и особенности трансплантации и посттрансплантационные изменения, нельзя не отметить значительный потенциал мезенхимальных стволовых клеток как клеточного носителя для морфофункционального восстановления резидуального кишечника. Настоящая работа представляет собой обзор известных тканеинженерных конструкций, применяемых для восстановления кишечника при синдроме короткой кишки.

**Ключевые слова**: синдром короткой кишки; трансплантация кишечника; тканевая инженерия; клеточная инженерия; обзор литературы.

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ЭКО•ВЕКТОР

Intestinal tissue engineering is a promising field of medicine aimed at creating functional organs and tissues to replace damaged or lost structures [1]. One of its most relevant applications is the treatment of short bowel syndrome (SBS)—a severe condition requiring a comprehensive approach, including the development of tissue-engineered small intestine (TESI) [2].

SBS is characterized by the inability of the body to maintain adequate fluid, nutritional, energy, and micronutrient balance due to small intestine resection or congenital shortening. This leads to a reduction in the absorptive surface area, impaired nutrient absorption and utilization, and pronounced metabolic disturbances [3]. The most common causes of SBS are related to surgical interventions—intestinal resection with jejuno-colonic or ileo-colonic anastomosis due to mesenteric ischemic necrosis, inflammatory bowel disease, necrotizing enterocolitis, incomplete intestinal volvulus, or traumatic and radiation injuries [2]. Additional causes may include repeated surgeries and extensive trauma leading to significant loss of intestinal length [4].

Moreover, an increasing SBS incidence has been noted, which is attributed to improvements in diagnostic capabilities and a decline in mortality among premature infants with extremely low and very low birth weight, who often present with congenital intestinal malformations [5].

Currently, it is well established that SBS develops following the resection of more than 75% of the small intestine, which corresponds to a residual bowel length of less than 200 cm. A persistent severe clinical picture typically emerges when the remaining small intestine measures less than 120 cm in total length [6]. The clinical manifestations of intestinal failure may vary depending on the extent of bowel resection and presence of comorbidities. Patients with a residual small intestine of less than 10–25 cm develop ultra-SBS, which requires a distinct therapeutic strategy for maintaining nutritional status [7].

The clinical presentation of SBS includes diarrhea, abdominal pain, steatorrhea, dehydration, and signs of maldigestion and malnutrition. If not adequately compensated, patients may develop electrolyte, mineral, and fluid imbalances, which can lead to multiple-organ failure and even neurological deficits [6].

These data highlight the urgent need for novel therapeutic approaches, including tissue-engineering strategies. Traditional therapies, including parenteral nutrition (PN), may be insufficient to maintain adequate metabolic status in patients with SBS [8]. However, PN plays an essential role in correcting metabolic disturbances and may be required lifelong in patients with severe, decompensated intestinal failure. Notably, PN is associated with significant risks, including catheter-associated infections, sepsis, and catheter-induced thromboembolism [9].

Allotransplantation of the intestine or multivisceral organs is widely recognized as an SBS treatment; however, it requires lifelong immunosuppressive therapy, which is particularly critical in pediatric patients due owing to high complication risk [10].

Other surgical interventions for SBS include longitudinal intestinal lengthening and tailoring (LILT) and serial transverse enteroplasty (STEP). STEP, which was first introduced in 2002, has shown promising results in infants aged below 1 year. Repeat STEP has proven feasible and effective in restoring normal enteral nutrition in infants with SBS, underscoring the value of this approach [2]. In cases wherein SBS is complicated, for example, by intestinal fistula formation, the implementation of aggressive therapeutic strategies is required to prevent the development of severe intestinal failure [11].

Compared to STEP, LILT enables the creation of a longer intestinal lumen. According to a systematic review by Nagelkerke et al., LILT is preferable for pediatric patients, whereas STEP is considered a secondary option or is used in cases wherein LILT is technically unfeasible [12]. Nevertheless, no current approach offers a universal solution, indicating the need for more promising therapeutic strategies.

Tissue engineering is an emerging direction in the treatment of SBS. It involves the use of various extracellular matrix scaffolds combined with cell-based technologies to create a functional intestinal substitute capable of reducing rejection risk and improving patients' quality of life [13]. Recent studies have demonstrated that tissue-engineered constructs (TECs) may enable the recovery of full enteral autonomy in patients with severe intestinal failure [2, 14].

**Scaffolds for TECs**. In tissue engineering, particular attention is paid to developing synthetic or biological scaffolds capable of supporting the growth and proliferation of cell lines to form the desired tissue microarchitecture. It is crucial that synthetic scaffolds (e.g., polyglycolic acid [PGA] and polycaprolactone) and biological ones (collagen sponge, acellular dermal matrix, and intestinal submucosa) ensure biocompatibility and mechanical support and promote integration with surrounding tissues, which is critical for successful implantation [1].

Several studies have modified polylactide-based synthetic matrices and their copolymers, improving their mechanical and biological properties for use in tissue engineering, providing a more favorable environment for cell growth compared to biological scaffolds [15, 16].

Furthermore, silk fibroin is considered a promising biomaterial owing to its high mechanical strength and excellent biocompatibility [17]. Studies have shown that fibroin can be modified to enhance its antimicrobial properties and improve cellular adhesion [18]. Liu et al. developed a nanofibrous construct based on silk fibroin using coaxial electrospinning, incorporating recombinant human vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGF-β1) [19]. The resulting bioactive membrane, through controlled VEGF release, promotes angiogenesis and tissue regeneration, whereas the presence of TGF-β1 may further enhance this process by promoting cell differentiation and extracellular matrix formation, thereby providing

a synergistic effect for successful intestinal healing [20]. The addition of VEGF and platelet-derived growth factor has been found to significantly improve vascularization and maintain cell viability in tissue constructs [21]. Decomposed scaffold structures have been considered as basis for successful tissue engraftment and regeneration [22]. This underscores the potential for angiogenesis at the capillary level in the future intestinal segment; however, the issue of functional nutrient delivery remains unresolved [23].

Studies have shown that allogeneic decellularized collagen matrix-based biomaterials can mimic intestinal tissue, promoting regeneration without scarring or encapsulation and reducing inflammatory and fibrotic changes [8]. In contrast, biological matrices are derived from the decellularization of native organs, which preserves the macro- and microarchitecture of the extracellular matrix along with its mechanical properties, creating optimal conditions for cell colonization [22]. These matrices possess high biocompatibility and can be used to create functional tissues, making them promising candidates for regenerative medicine [24].

Various cross-linking agents and bioactive components can enhance the interaction between cells and collagen or chitosan matrices [16]. Owing to its unique properties such as controlled biodegradation and antimicrobial activity, chitosan may be used to create matrices with improved mechanical performance [25].

Modern technologies, including three-dimensional (3D) printing, open new avenues for fabricating complex matrix structures that more precisely mimic native tissues. Moreover, 3D printing enables micro- and nanoscale architectural control of the matrix, improving cell adhesion and proliferation [26]. Roegiers et al. developed an in vitro intestinal model based on gelatin-methacryloyl-aminoethyl methacrylate (GelMA-AEMA), which demonstrated permeability to nutrients and drugs [27]. The authors showed that hydrogel morphology significantly influences cellular response, as evidenced by comparisons between the formation of a functional intestinal epithelial monolayer on flat hydrogel films and on 3D hydrogel scaffolds that preserve morphological similarity to intestinal architecture [28]. The results exhibited that the developed constructs provided adequate permeability for a medium-sized marker molecule, supporting their potential application in biomedical research [29].

The combination of hydrogels with a culture of Caco-2/HT29-MTX cells showed high biocompatibility, enabling functional epithelial monolayer formation within 21 days on 2D hydrogel films [30]. This was confirmed by measurements of transepithelial electrical resistance and immunohistochemistry, indicating the successful establishment of barrier function [31]. Concurrently, 3D constructs failed to reach confluence within 35 days, underscoring the importance of selecting an appropriate scaffold architecture to achieve desired functional characteristics [28]. Thus, the findings confirm the morphofunctional similarity of novel gelatin methacrylate-based hydrogel systems to the residual intestine.

**Transplantation model**. The omentum and renal capsule are traditional transplantation sites of tissue-engineered constructs, as demonstrated by Zabolian et al. [32], who emphasized that the omentum is an ideal implantation site because of its high vascularization. This makes it suitable for successful intestinal anastomosis placement, including its application as a wrap around the anastomosis, combining advantages from surgery and tissue engineering. Moreover, exposure of the graft to the mesentery is feasible, as mesenteric vascularization more closely resembles native enterohepatic circulation [32]. This may provide more efficient nutrient absorption critical for assessing the function of TECs [33]. Thus, the choice of implantation site plays a key role in the success of tissue engineering and regenerative medicine.

**Cell Lines for TECs**. Regardless of the scaffold's origin, it can be seeded with various proliferative cell types [13]. Cell transplantation approaches have evolved from direct injection of cell suspensions into tissues or the vascular system. In 1993, the Vacanti Laboratory at Massachusetts General Hospital employed biodegradable polymer scaffolds seeded with cell clusters, which were subsequently implanted into host animals. These experimental methods demonstrated satisfactory cell viability, proliferation, and engraftment, particularly of enterocytes and fetal small intestinal cells [34].

Some studies have proposed using cell lines derived from human colorectal adenocarcinoma to culture villus-like structures that may further differentiate into enterocytes [35]. However, a major limitation of this approach is the high tumorigenic potential of such cell lines, restricting their use in intestinal regeneration [36]. Researchers turned to pluripotent embryonic stem cells (ESCs) as a promising avenue in cellular engineering to address this issue. ESCs are capable of self-organizing into 3D structures and organoids that exhibit native-like crypts and villi [35].

ESCs possess a high capacity for self-renewal and differentiation into various cell types. However, studies have shown that ESCs seeded onto decellularized matrices may not migrate into the scaffold or initiate lineage-specific differentiation, challenging their effectiveness in generating tissue structures [37]. Nevertheless, research has demonstrated the regenerative potential of TECs derived from ESCs. Konuma et al. reported the regeneration of intestinal segments through spontaneous integration of organoid structures into damaged areas, leading to distal intestine restoration [38]. Similar results have been achieved in other studies [39].

Notably, pluripotent stem cells possess unlimited proliferative capacity and can differentiate into cell types derived from all three germ layers [40]. This makes them ideal candidates for applications in regenerative medicine. In particular, it has been shown that pluripotent stem cells can be differentiated into tissues resembling embryonic intestine, exhibiting secretory and absorptive functions [41]. However, despite advancements in generating such tissues, considerable barriers to their clinical application remain [8]. For instance, tissues derived from pluripotent stem cells were found to

express mesenchymal markers such as FOXF1 and vimentin, indicating the presence of a mesenchymal layer. Nevertheless, these tissues lack vascular and neural components, which limits their functionality and viability upon transplantation. Moreover, their oncogenic potential and genomic instability and ethical and technical challenges remain major concerns [42]. These issues highlight the need for alternative approaches that preserve the mesenchyme alongside the epithelium, which may be particularly important for therapies aimed at replacing the small intestine.

Mesenchymal stromal cells (MSCs) are multipotent cells widely utilized in tissue engineering. They are capable of differentiating within the same germ layer, for example, into adipocytes, osteocytes, and chondrocytes, and are characterized by high proliferative potential and differentiation capacity [43]. MSCs possess immunomodulatory properties and contribute to tissue healing [44]. They are more readily available than ESCs, and their use in decellularized matrices may facilitate tissue structure formation [45].

In the context of small intestine tissue engineering, MSCs are valuable owing to their pleiotropic secretion of growth factors such as VEGF, IGF-1, HGF, and EGF [46]. These molecules play a key role in the regeneration of the smooth muscle layer and neuromuscular apparatus. Implantation of MSCs onto intestinal submucosal scaffolds, PGA, and type I collagen supports optimal cell differentiation and epithelial ingrowth [47]. Importantly, MSCs can be derived from readily accessible adipose tissue, offering greater practicality for clinical use [48]. In addition to promoting angiogenesis, these cells also exhibit immunomodulatory properties and protect against apoptosis, making them multifunctional in the field of tissue engineering [49].

**Organoids**. The methods developed by Evans et al. in the early 1990s have been adapted for the in vivo generation of TESI [50]. In this context, cells were isolated as organoid units—multicellular aggregates consisting of epithelial and mesenchymal components—opening new horizons for the creation of functional tissues [50]. Organoid units (OUs) are 3D structures that mimic an entire organ, including its high degree of complexity, organization, and functionality. OUs may be more effective for generating organ-specific structures compared to traditional approaches involving ESCs or MSCs [51]. Intestinal organoids have become valuable models for studying intestinal regeneration because of their ability to reproduce the cellular composition and architecture of the gut [52]. These organoids encompass a spectrum of intestinal cell types, including stem, Paneth, enteroendocrine, goblet, and transit-amplifying cells and enterocytes, providing a comprehensive platform for investigating regenerative processes [53].

Sugimoto et al. demonstrated the survival and regeneration of orthotopically transplanted organoid unit xenografts in vivo [54]. The authors used differentiated human colonic organoids generated using the CRISPR-Cas9 method. The cellular component was represented by colonic stem cells (CoSCs), and the recipients were mice of an experimental strain with induced immunodeficiency ($n$ = 178). CoSCs were orthotopically transplanted into a preformed defect in the colonic wall by injecting a suspension of 3–4-day-passaged cells into the mucosa, with subsequent exposure to cyanoacrylate glue. Post-transplantation, organized crypt-like structures formed, morphologically resembling the native colonic mucosa, with villi, crypts, and columnar epithelium.

Immunohistochemical analysis confirmed the presence of goblet, Paneth, and neuroendocrine cells through specific expression of GFP and LGR5 markers; approximately 80% of the cells were found to be of monoclonal origin. Although fully developed crypts, epithelium, and villi morphologically identical to residual native areas were histologically verified, assessment of mitotically active zones at the base of the crypts showed low expression of Ki67 and ethynyl deoxyuridine, indicating a relatively slow cellular regeneration. Nonetheless, we concluded that even xenogeneic organoid transplantation can lead to the formation of structures morphologically resembling native intestine, demonstrating a high degree of integration and functional activity. Moreover, patient-derived autologous organoids have been shown to regenerate epithelial cells in Crohn's disease, revealing that stem cell properties vary depending on disease activity [55].

In a study by Zakhem et al., a human tissue-engineered bowel (hTEB) based on a chitosan scaffold seeded with smooth muscle cells (SMCs) was used, followed by neo-innervation with human neuronal progenitor cells isolated and differentiated directly from the small intestine. In this context, hTEB transplantation was initially performed into the omentum of athymic rats with surgically induced SBS, followed by transplantation of the resulting construct (vascularized in vivo) directly into the intestine by creating two anastomoses on a bypassed intestinal loop. Zakhem et al. reported that the TECs explanted from the omentum on day 28 exhibited a physiological peristaltic response to equimolar solutions of potassium chloride and acetylcholine, which was inhibited by atropine and nifedipine, indicating the presence of functional neuromuscular synapses.

This approach demonstrated a significant increase in the intestinal absorptive surface area. This increase in absorptive surface area is critical as it is directly associated with improved ability of the intestine to absorb nutrients. The animals that received TECs began to regain body weight 1 week earlier than those in the control group, indicating more effective restoration of intestinal function. Specifically, by postoperative day 40, the animals with TECs reached 98.5% of their preoperative body weight, whereas those in the control group that did not undergo transplantation reached only 77% [56].

In earlier reports, Nakase et al. described the use of collagen scaffolds seeded with SMCs in a canine model for regenerating the muscular layer of the small intestine [57]. The study employed pure collagen matrices and constructs incorporating autologous SMCs isolated from the gastric wall. The authors noted that the scaffolds demonstrated

significant potential for intestinal regeneration; the implanted SMCs were morphologically verified within the lamina propria, forming an appropriate layer of smooth muscle.

Furthermore, the role of specific factors in promoting intestinal regeneration has been investigated. C3a has been shown to enhance the formation of intestinal organoids via C3aR1, implicating the complement system in the modulation of regenerative processes [58]. Exosomes derived from human adipose-derived mesenchymal stem cells have demonstrated cytoprotective effects by supporting intestinal stem cells in epithelial regeneration, indicating their therapeutic potential for intestinal repair [59].

Moreover, a recent study revealed the influence of microenvironmental factors, particularly hypoxia, on stem cell architecture and intestinal organoid differentiation [60].

An optimal cell product for matrix seeding is selected based on several factors, including cell availability, differentiation and migration capacity, and the intended therapeutic outcome [13]. Although ESCs have high potency, they may be less favorable because of difficulties in cultivation and directed differentiation. In contrast, CSCs and MSCs may offer more practical solutions owing to their accessibility and comparable capacity for tissue formation [37].

Thus, the optimal cellular component for developing prototypes of tissue-engineered constructs is predominantly represented by mesenchymal stem cells, owing to their unique properties and clinical applicability [45]. Notably, activated adipocytes, which can also serve as a source of MSCs, are capable of producing numerous angiogenic factors, further reinforcing their role in tissue engineering.

## CONCLUSION

In recent years, significant progress has been made in intestinal regeneration through the use of stem cells, organoids, and signaling pathway regulators, contributing to the restoration of intestinal tissues and functions. The application of organ-specific autologous cells in tissue engineering enables a personalized approach to SBS treatment. Utilizing these advanced strategies, individualized intestinal rehabilitation plans can be tailored to each patient. By improving synthetic and biological scaffolds, refining differentiation protocols for pluripotent and multipotent stem cells and organoid structures, and gaining a deeper understanding of the underlying molecular pathways, promising prospects can be achieved for the development of novel treatment approaches for SBS.

## ADDITIONAL INFORMATION

**Author contributions**: N.I.M.: investigation, data curation, writing—original draft, writing—review & editing; S.S.Yu.: data curation, writing—review & editing; L.A.I.: investigation, data curation, writing—review & editing; D.K.V.: data curation, writing—original draft, writing—review & editing; M.V.A.: writing—original draft, writing—review & editing; D.I.Kh.: writing—original draft, writing—review & editing. All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов**. Н.И.М. — проведение исследования, работа с данными, написание черновика, пересмотр и редактирование рукописи; С.С.Ю. — работа с данными, пересмотр и редактирование рукописи; Л.А.И. — проведение исследования, работа с данными, пересмотр и редактирование рукописи; Д.К.В. — работа с данными, написание черновика, пересмотр и редактирование рукописи. М.В.А. — написание черновика, редактирование рукописи. Д.И. Халилов — написание черновика, редактирование рукописи. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

**Этическая экспертиза**. Неприменимо.

**Источники финансирования**. Отсутствуют.

**Раскрытие интересов**. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

**Оригинальность**. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

**Доступ к данным**. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.

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**Рассмотрение и рецензирование**. Настоящая работа подана в журнал в инициативном порядке и рассмотрена в соответствии с процедурой fast-track. В рецензировании участвовали три внешних рецензента, член редакционной коллегии и научный редактор издания.

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