

# Is the tissue-engineered intestine clinically viable?

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The clinical finding of malabsorption after massive resection of the small intestine is known as short-bowel syndrome. The remaining intestine undergoes compensatory hyperplasia, and for some patients this adaptation is adequate for sufficient nutrient absorption. For others, however, nutrients must be given parenterally to sustain life and to enable growth. Although parenteral nutrition provides adequate calories, patients on this therapy suffer from parenteral nutrition-associated liver disease and central venous catheter complications. The majority of patients who cannot be weaned from parenteral nutrition will require intestinal transplantation. Although the outcome following intestinal transplantation is improving, this procedure is still limited by donor availability and complications from immunosuppressive therapy.<sup>1</sup>

Tissue engineering uses cells, biomaterials (used as a scaffold to grow tissue on), and signaling molecules to generate new tissues.<sup>2</sup> Developments in tissue engineering technology have led to its application to many organ systems. Several tissue-engineered products are either in clinical use or are being investigated in clinical trials. For example, skin substitutes made by seeding human foreskin fibroblasts on biomaterials have been employed to treat patients with venous stasis ulcers and burn injuries.<sup>3</sup> Urinary bladder replacements made from autologous stem cells seeded on collagen and polyglycolic acid polymer constructs have been used to augment bladders for patients with myelomeningocele.<sup>4</sup>

The feasibility of the tissue-engineered intestine begins with the remarkable regenerative ability of the intestinal epithelium. When a synthetic material was used to patch a full-thickness defect created in the small intestine of a rodent, enteric cells at the interface between the patch and the native mucosa migrated into the bare area and formed organized epithelium.<sup>5</sup> This observation led to efforts to implant enteric cells attached to polymer materials into the omentum of a rodent. The implantation

of neonatal rodent intestinal organoid units (partially digested pieces of the intestine) attached to biodegradable polymer scaffolds into the rodent omentum produced cystic structures lined by epithelial cells.<sup>6</sup> Patches of such tissue-engineered structures were successfully anastomosed to the native small intestine of rodents.<sup>7</sup> After anastomosis, the rudimentary epithelium in the cystic structures developed into mature crypts and villi. When these tissue-engineered cysts were anastomosed to the side of the proximal small intestine in a rodent model of short-bowel syndrome, these animals lost less weight and recovered sooner than those that did not receive implanted tissue-engineered intestinal cysts.<sup>7</sup>

The successful regeneration of intestinal mucosa in rodents has highlighted the therapeutic potential of a tissue-engineered human intestine. Enteric cells could be procured from patients' intestinal biopsy samples to regenerate intestinal tissues. Such tissue-engineered treatments would avoid problems associated with intestinal transplantation, including donor availability and complications from immunosuppressive therapy. Before such a strategy can be brought into clinical practice, however, several considerable obstacles need to be overcome.<sup>8,9</sup> The first obstacle is the source of cells for tissue engineering. The current approach in rodents requires intestinal organoids that have been procured from neonatal animals; attempts to use organoids derived from older animals have failed to generate the rudimentary cysts. In the clinical setting, it would be difficult, and sometimes impossible, to obtain human neonatal intestinal organoids, especially for autologous stem cell transplantation. Furthermore, intestinal organoids cannot be cultured and grown to yield more organoids *in vitro*. Attempts to subdivide the organoids into single cells have also been unsuccessful in producing the rudimentary cysts after implantation, thereby preventing further characterization of the essential elements in the organoids necessary for the generation of

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crypts and villi. In the future, the requirement for organoids might be overcome by using stem cells to generate organoids. A recent study on markers of the intestinal epithelial stem cell might help define the stem cells that are needed for tissue engineering.<sup>10</sup>

The second obstacle is the need to recreate the peristaltic motion of the small intestine. Although tissues generated from intestinal organoids resemble the mucosa, functional smooth muscle layers and the neural plexus are absent. An example that highlights the clinical importance of the neuromuscular layer is small intestinal aganglionosis; in this disease, the mucosa is normal but the intestine fails to function because the enteric content cannot be propelled forward. The motility of enteric smooth muscle is primarily controlled by the myenteric plexus, which is a part of the enteric nervous system. These components of the small intestine would need to be generated as a part of the tissue-engineered intestine to produce peristalsis.

The third obstacle is scaling up the size of the tissue-engineered intestine to clinically useful dimensions. The current approach uses implantation of organoids that have been seeded on polymeric scaffolds that are wrapped within the omentum. The omentum provides the vascular supply to the organoids and enables integration of the absorbed nutrients with the host portal circulation. The omentum, however, is often removed or scarred in patients with short-bowel syndrome because of prior surgeries. Even when present, the surface area of the omentum is not large enough to generate the area of intestinal tissue needed for clinically significant results. An alternative means of providing vascular supply to the tissue-engineered intestine that would enable integration of the absorbed nutrients with the host circulation remains to be developed.

The fourth obstacle is regulatory approval and commercialization. Although cell-based therapy such as hematopoietic stem cell transplantation has been practiced for decades, the use of new types of stem cells, signaling molecules, and bioactive scaffolds for the tissue-engineered intestine will need to be scrutinized in clinical trials. The expense associated with such testing will require a sizeable market to attract the industry to bring the product to

commercialization. Although short-bowel syndrome is a costly problem to health-care systems, the number of patients with this syndrome is small when compared with the number of individuals with heart disease or cancer. This problem is compounded by the prolonged research time that is needed before such biologic devices could be brought into clinical practice, therefore, making the tissue-engineered intestine financially unattractive to the private investment sector. A substantial commitment from nonprofit organizations will be needed to fund such research efforts.

Despite these difficulties, the tissue-engineered intestine will be clinically viable, but it will require decades of research and development. Like many new technologies, the tissue-engineered intestine has gone through the initial phase of development, which generated a lot of excitement, and now the considerable limitations and the commercial reality of the project are being realized. Nevertheless, perseverance is worthwhile, as it is probable that a better understanding of intestinal regeneration gained through the research and development of the tissue-engineered intestine will ultimately enhance the lives of patients with short-bowel syndrome.

#### Competing interests

The author declared no competing interests

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