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*Editorial*

# INTESTINAL STEM CELLS (ISCS): ISCS-DERIVED ORGANOIDS FOR DISEASE MODELING AND THERAPY

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The intestine is a vital organ system that integrates immunological, metabolic, and neurological functions, serving as a central player in the communication between various organs, such as brain [1]. Despite its single-layered structure, it is remarkably resilient to ongoing mechanical, chemical, and biological challenges. The regeneration of intestinal epithelium, driven and regulated by intestinal stem cells (ISCs), is essential for maintaining both intestinal and overall body health [2]. Research indicated that the continuous depletion of ISCs significantly impaired intestinal function [3]. Therefore, a functional reservoir of ISCs is crucial for preserving intestinal homeostasis.

Several key factors significantly influence the regulation of ISCs function: the architecture of intestinal crypts, systemic signals [4], the mechanical stimulations such as shear stress and stretching [5], the niche provided by specialized epithelial and mesenchymal cells [6], dietary components [7], inflammatory signals from immune cells [8], and the effects of aging [9].

Recent advancements in ISCs research have underscored their pivotal role in intestinal regeneration. Progress in single-cell RNA sequencing and gene editing technologies [10] has enabled researchers to more accurately characterize the diversity and functions of ISCs populations, paving the way for new therapeutic options treating gastrointestinal diseases.

Intestinal organoids (IOs) are three-dimensional (3D) mini-guts cultivated from adult ISCs, possessing self-renewal and differentiation capabilities. The emerging of IOs represented a significant breakthrough in understanding the structure and functions of the native intestine [11]. IOs closely replicate the *in vivo* physiology of the original tissue, making them a unique and invaluable tool for studying the precise pathogenesis of gastrointestinal diseases, such as epithelial barrier dysfunction, abnormal immune responses, and microbiome disturbances. Advanced IOs technologies can be achieved through multi-omics approaches and co-culturing IOs with immune cells, mesenchymal cells, endothelial cells, and intestinal microbiota [12].

IOs are instrumental in investigating intestinal diseases like inflammatory bowel disease (IBD) and colorectal cancer, facilitating the discovery of biomarkers and the development of new therapeutic strategies. IOs derived from patient-specific ISCs are particularly valuable for assessing individual treatment responses, enabling more effective and personalized therapeutic approaches for maintaining intestinal health [13,14]. The transplantation of genetically modified IOs derived from patient biopsy samples based on existing therapies, offers a promising strategy for treating gastrointestinal diseases characterized by severe epithelial damage, such as ulcerative colitis (UC, one type of IBD). Hence, the integration of ISCs and IOs is paving the way for innovative advancements in regenerative medicine and disease modeling (Fig. 1).

The recent Food and Drug Administration (FDA) Modernization Act 2.0 has spurred increased industrial investment of research and development (R&D) in advanced *in vitro* 3D models, including organoids, spheroids, organ-on-chips, and 3D bioprinting [15]. This initiative reflects the FDA's endorsement of the reliability of organoid studies. One of the key future directions in development is the

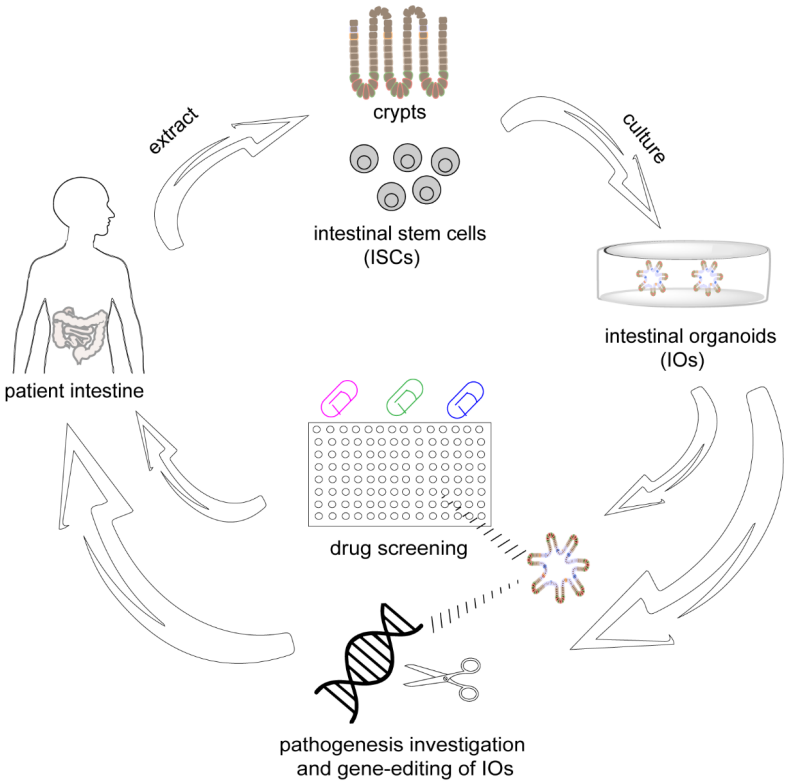


**Fig. 1. The potential applications of ISCs and IOs in gastrointestinal diseases.** Intestinal crypts or ISCs were extracted from the intestinal tissue of the patient's biopsy samples and cultured into IOs that maintained the pathologic status of the parents. This system was used for drug screening or investigating genetic pathogenesis and consequent gene editing. Finally, the drug-treated or gene-modified IOs were used in clinical trials. ISCs, intestinal stem cells; IOs, intestinal organoids.

integration of IOs with organ-on-chip technology. Using IOs in preclinical studies—such as drug screening, toxicity testing, and disease modeling—helps reduce reliance on animal testing while providing experimental results that closely mimic the physiological conditions of the human body.

Therefore, numerous hospitals, companies, and research institutions are dedicated to advancing IOs-related products and expanding their applications. Despite the progress made in understanding ISCs and IOs in recent years, several challenges remain to be addressed. These include increasing the biomimetic degree via co-culture of IOs with intestinal microenvironment (extracellular matrix, mesenchymal cells, enteric nervous system, etc.), developing new culture methodologies and enhancing engineering controls to improve the uniformity of each batch and the consistency of different batches. Resolving these issues will facilitate the transition of IOs from precise medicine into clinical trials.

## List of Abbreviations

ISCs, intestinal stem cells; IOs, intestinal organoids; IBD, inflammatory bowel disease; UC, ulcerative colitis; 3D, three-dimensional; FDA, Food and Drug Administration; R&D, research and development.

## Availability of Data and Materials

Not applicable.

## Author Contributions

PYW and DDZ contributed to the design of this work. DDZ drafted the work. PYW and DDZ revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest. PYW is serving the Editorial Board members of this journal. We declare that PYW had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MS.

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