eISSN 2005-5447
International Journal of Stem Cells Vol. 17, No. 2, 2024 https://doi.org/10.15283/ijsc24043

LETTER TO THE EDITOR

Standards for Organoids

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Organoids are three-dimensional structures derived from stem cells, which through self-organization can recapitulate the structure, function, and genetic traits of *in vivo* tissues and organs. Organoids have emerged as one of the most promising non-clinical experimental methods to replace animal testing and as an essential tool for basic and biomedical research. They can be generated from almost all patients, demonstrating exceptional potential in organ development, disease modeling, translational medicine, and personalized precision medicine. However, the highly variable procedures for manufacturing stem cell-derived organoids and the lack of reproducibility at endpoints remain challenges that must be addressed (1).

Once reproducible organoid-based assays are secured, inter-lab transferability will increase, enabling the widespread use of organoids in safety and efficacy evaluations of drugs and industrial chemicals, and further advancing the formal adoption of alternative testing methods. The FDA Modernization Act 2.0 in the United States, which has opened the door to non-animal testing for drug development, has caused a significant global impact, and the European Food Safety Authority has published a roadmap for validating New Approach Methodologies (NAMs). In South Korea, the Pharmaceutical Affairs Act (Article 2) (2) classifies organoids within the category of non-clinical tests. These global initiatives are expected to accelerate the regulatory acceptance of NAMs, yet organoid commercialization hinges on the attainment of reproducible research.

To align with the policies of regulatory bodies, ISO/TC 276 (Biotechnology) has been working on standardization of organoid-based alternative testing methods from the perspectives of bioprocessing and analytical methods, and the Organisation for Economic Co-operation and Development (OECD) from those of toxicity test guidelines for industrial chemicals. Scientists report (3) that culturing organoids to homogeneous sizes, along with well-defined extracelluar matrix and automation technologies, will be the turning points for standardizing mass production of high-quality organoids. Although it is difficult to address together, with the current level of knowledge, the lack of specificity in cell type composition, uncontrollable sizes and shapes, and functional deficiencies, discussions should be strong on critical assessment criteria at endpoints, including essential cell compositions of organs and optimized assessment methods (4).

To offset the variations, we should improve our capacity to compare the structure and cellular complexity of organoids against counterparts *in vivo*. The "Workshop on how to prepare the test guideline programme for emerging technologies" hosted by the OECD in 2022 highlighted the importance of developing documents to guide batteries of assays in recommendations for validating and approving emerging technologies such as organoids (5). That is, each element in a battery of assays should be technically validated – for instance, validated against biological relevance, clear descriptions of test methods, and blind testing, to ensure reproducibility over time and transferability to external laboratories.

Received: April 8, 2024, Revised: April 23, 2024,
Accepted: April 23, 2024, Published online: May 27, 2024
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In response to the recommendations from the the international organization and the requirements for standardization expressed by national stakeholders concerning organoids, the Ministry of Food and Drug Safety of South Korea, in partnership with Sungkyunkwan University, has inaugurated the Organoid Standards Initiative (OSI) and begun developing comprehensive guidelines in 2023 to facilitate standardized manufacturing and quality assessment of organoids. Organoid manufacturers, users, and regulatory bodies have joined in extensive discussions on the suitable quality of organoids, resulting in the publication of the 'Guidelines for manufacturing and application of organoids' series based on empirical, theoretical, and statistical evidence.

This issue of the *International Journal of Stem Cells* includes special reports based on the OSI guidelines. It features the latest information on standard organ-specific production and explores the future development directions: Ahn et al. (6), introduces cell type-specific culture strategies for organoids and presents quantitative and qualitative testing methods at endpoints; Lee et al. (7), discusses factors critical to organoid viability, including cell and organoid packing and transportation methods; Moon et al. (8), provides up-to-date information on culturing conditions and procedures for hepatotoxicity evaluation organoids, liver-specific functionalities, essential cell compositions, and test methods for quality evaluation criteria; Lee et al. (9), for heart; Kang et al. (10), for kidney; Lim et al. (11), for lung; Kwak et al. (12), for brain; and Lee et al. (13), for skin. In addition to the above guidelines, Son et al. (14) established the standardized manufacturing, maturation, and quality assessment protocols for human intestinal organoids through OSI activites. These guidelines provide journal readers with trustworthy insights for advancing the organ-specific production and guiding them towards excellence in research and applications.

Embrace the future of scientific innovation with the standardization of organoid production and quality evaluation at endpoints–a transformative leap that promises to lower false positives and negatives in toxicity testing and drug development, enhancing test sensitivity and specificity and increasing transferability, which will lead to regulatory acceptance. Our approach begins with redefining and enriching our collective wisdom in the form of reference standards. We are laying the cornerstone with quantitative and qualitative measures to assess organoid maturity–a starting point for groundbreaking progress in refined organoid production and quality assessment techniques. While these guidelines set the foundation, our vision extends beyond, anticipating the integration of computational modeling to bridge the gap between *in vivo* and *in vitro* findings, alongside *in silico* models to assess stability and effectiveness—frontiers we will explore through the OSI. Stay ahead with us; as organoid manufacturing technologies and analytical methods evolve, so too will our guidelines, ensuring you are always at the cutting edge of organoid research and application.

We extend our heartfelt gratitude to the visionary editors who have shown great interest in this special issue, to the chairs and members of the OSI subcommittees for their unwavering commitment, and to the Ministry of Food and Drug Safety for their invaluable contributions. This special issue stands as a beacon for progress towards advancing organoid standardization.

Keywords: Organoids, Standards, Stem cells, Guideline, Regulation, Quality

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Funding

The work was supported by the grant (23212MFDS265) from the Ministry of Food and Drug Safety in 2023.

Potential Conflict of Interest

There is no potential conflict of interest to declare.

References

1. Kim J. Lo and behold, the lab-grown organs have arrived! Int J Stem Cells 2022;15:1-2
2. Korean Law Information Center [Internet]. Sejong: Korea Ministry of Government Legislation [cited 2024 Mar 2]. Available from: https://www.law.go.kr/LSW/eng/engMain.do?eventGubun=060124
3. Clevers H, Lancaster M, Takebe T. Advances in organoid technology: Hans Clevers, Madeline Lancaster, and Takanori Takebe. Cell Stem Cell 2017;20:759-762
4. Garreta E, Kamm RD, Chuva de Sousa Lopes SM, et al. Rethinking organoid technology through bioengineering. Nat Mater 2021;20:145-155
5. OECD Environment Directorate Chemicals and Biotechnology Committee. Report on the WNT Workshop How to Prepare the Test Guidelines Programme for Emerging Technologies, Series on Testing and Assessment No. 378, ENV/CBC/MONO(2023)14 [Internet]. Paris: OECD; 2023 Jul 4 [cited 2024 Mar 9]. Available from: https://one.oecd.org/document/ENV/CBC/MONO(2023)14/en/pdf
6. Ahn SJ, Lee S, Kwon D, et al. Essential guidelines for manufacturing and application of organoids. Int J Stem Cells 2024;17:102-112
7. Lee S, Kwon D, Lee HB, et al. Guidelines for packaging, transport, and storage of source cells for organoids. Int J

Stem Cells 2024;17:113-119
8. Moon HR, Mun SJ, Kim TH, et al. Guidelines for manufacturing and application of organoids: liver. Int J Stem Cells 2024;17:120-129
9. Lee HA, Woo DH, Lim DS, et al. Guidelines for manufacturing and application of organoids: heart. Int J Stem Cells 2024;17:130-140
10. Kang HM, Kim DS, Kim YK, Shin K, Ahn SJ, Jung CR. Guidelines for manufacturing and application of organoids: kidney. Int J Stem Cells 2024;17:141-146
11. Lim K, Lee MO, Choi J, et al. Guidelines for manufacturing and application of organoids: lung. Int J Stem Cells 2024;17:147-157
12. Kwak T, Park SH, Lee S, et al. Guidelines for manufacturing and application of organoids: brain. Int J Stem Cells 2024;17:158-181
13. Lee S, Rim YA, Kim J, et al. Guidelines for manufacturing and application of organoids: skin. Int J Stem Cells 2024;17:182-193
14. Son MY, Lee H, Yang S, et al. Standardization and quality assessment for human intestinal organoids [Internet]. Frontiers in Cell and Developmental Biology; 2024. [cited 2024 May 2]. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2024.1383893