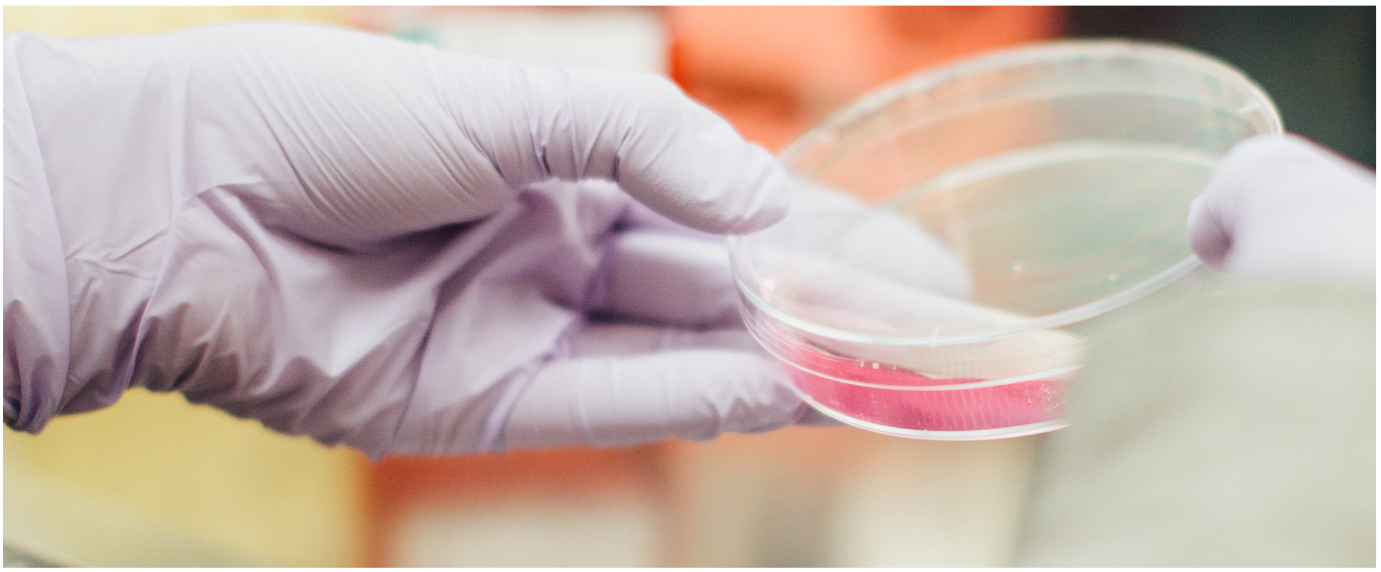
News and Analysis

Organoids in gastroenterology: a One Health approach

Phoebe Tarver
Year 4, iMSc Epidemiology, Veterinary Science, University of Bristol
Email: xv19729@bristol.ac.uk



Abstract

This article presents a summary of the use of patient-derived organoids (PDOs) as a novel research tool for gastroenterology, with a focus on inflammatory bowel disease, in human and veterinary medicine. In addition, it aims to highlight their advantages and limitations over current research models from an ethical perspective. Finally, to draw attention to their potential for contribution to the concept of One Health and the importance of collaboration between human and veterinary medicine resources.

Abbreviations

GI – gastrointestinal
IBD – inflammatory bowel disease
PDO – patient-derived organoid

Introduction

Patient-derived organoids (PDOs) are three-dimensional structures generated from stem cells with the ability to self-organise and resemble in vivo organs.[1] They can re-create components of anatomy and recapitulate basic tissue-level functions of their physiological equivalents, to obtain a bioartificial organ.[2] PDOs play an important role in modelling the pathogenesis mechanisms of diseases, individuals' drug sensitivities (giving rise to personalised medicine), toxicology studies, and much more.[2] Only recently are PDOs finding their applications in veterinary medicine. This article reviews the current use of canine PDOs in comparative gastroenterology and the importance of a One Health approach; a concept recognising the interrelations of human and animal health and proposes a multi-disciplinary approach to tackling problems common to both species.[3]

Organoids in gastroenterology

Gastroenterological research has historically used two-dimensional models of the human gastrointestinal (GI) system using a monolayer of cells to imitate in vivo organ functionality. Gnotobiotics have also been used to replicate the human GI system within mice, involving bacterial colonisation of the gut and subsequent euthanasia.[4] In addition to the ethical issues this method raises, it is evident that mice are a poor model in biomedical research. Around 90% of drugs developed using mouse models have failed in clinical trials,[5] indicating the need for better models. The canine GI system closely resembles that of humans, with a functional and taxonomic overlap of around 60% compared to 10–20% overlap between mice and humans.[6] Furthermore, dogs develop analogous GI diseases such as colorectal cancer and inflammatory bowel disease (IBD) and show similar clinical signs to humans, making them superior models to mice.[4] The practicality and cost of obtaining canine intestinal tissue is feasible as veterinary surgeons have access to these during GI surgery and often take samples for histological use. Canine PDOs provide a more representative model of the human GI system[7] compared to previously mentioned methods, whilst reducing the number of animals used in research. Canine PDOs achieve the 'reduction' and 'replacement' aspects of the 3Rs, an ethical framework for preserving welfare of research animals. 'Refinement' aims to refine tests to alleviate animal stress during research, 'replacement' encourages use of research methods not involving animals, and 'reduction' aims to reduce the number of animals used per experiment.[8]

A recent study

Inflammatory bowel disease is characterised by chronic inflammation of the GI tract[9] and is highly prevalent in both humans in the UK (0.81%)[10] and dogs (approximately 0.9–2.0%).[11] The aetiology of the

disease is currently unknown,[12] and treatment in both species is largely symptomatic.[13,14]

A 2019 study[4] using healthy and diseased dogs (presenting with IBD), created PDOs through collection of adult intestinal stem cells from samples of canine GI tissue. Culture of these cells and visualisation with microscopy demonstrated successful differentiation into crypt epithelial cells.

In IBD, inflammation is mediated through PGE2 which acts through receptors EP1, EP2, EP3, and EP4, in both humans and canines.[4,15] The latest NSAID class 'piprants' target the EP4 receptor and aim to reduce common GI side effects that occur with NSAID drugs, important for IBD patient.[16] The results of this study showed that the EP4 receptor was successfully expressed in the canine PDOs generated, thus deeming this model fit for development of piprant drugs. A limitation to this particular study is that immune and mesenchymal cells, usually detected in abundance in native gut tissue, were absent, supporting the already known fact that the methodologies for generating PDOs require further development to obtain full physiologic functionality.[17] One may question the robustness of these results due to these inaccuracies of the PDO, however, it is clear that canine PDO models provide much improved representation of human tissue than our current mouse models.[6] The use of PDOs for research into IBD treatments could benefit the health of both animal and human patients and facilitate more collaboration between human and veterinary clinicians and researchers.[18]

Conclusion

PDOs present the unique ability to investigate disease processes and develop innovative therapies on highly representative tissue of both humans and animals. They offer a sustainable solution to use of animals in research as fewer animals are needed, overcoming some of the ethical issues involved in research animals. The anatomical similarities shared between humans and canines, coupled with parallels in disease prevalence such as IBD, opens the door for collaboration between human and veterinary fields with PDOs providing an interface for this to happen. Overall, PDOs provide a highly efficient method of biomedical research, transferable across sectors, and collaboration in this way has the potential to accelerate advances in research for the benefit of both disciplines.[19]

Copyright

This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view a copy of the license, visit https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode. The copyright of all articles belongs to the author(s), and a citation should be made when any article is quoted, used or referred to in another work. All articles included in the INSPIRE Student Health Sciences Research Journal are written and reviewed by students, and the Editorial Board is composed of students. Thus, this journal has been created for educational purposes and all content is available for reuse by the authors in other formats, including peer-reviewed journals.

References

1. Stoeklé H-C, Ivasilevitch A, Marignac G, et al. Creation and use of organoids in biomedical research and healthcare: The bioethical and metabioethical issues. Cell Adhesion & Migration. 2021;15(1):285–94.
2. Bose S, Clevers H, Shen X. Promises and challenges of organoid-guided precision medicine. Med. 2021;2(9):1011–26.
3. Mackenzie JS, Jeggo M. The One Health approach—why is it so important? Tropical Medicine and Infectious Disease. 2019;4(2):88.
4. Ericsson AC. A brief history of animal modeling. Mo Med. 2013;110(3):201–5.
5. Chandra L, Borcherding DC, Kingsbury D, et al. Derivation of adult canine intestinal organoids for translational research in gastroenterology. BMC Biology. 2019;17(1).
6. Coelho LP, Kultima JR, Costea PI, et al. Similarity of the dog and human gut microbiomes in gene content and response to Diet. Microbiome. 2018;6(1).
7. Meneses A, Schneeberger K, Kruitwagen H, et al. Intestinal organoids—current and future applications. Veterinary Sciences. 2016;3(4):31.
8. Hubrecht RC, Carter E. The 3Rs and humane experimental technique: Implementing change. Animals. 2019;9(10):754.
9. What is inflammatory bowel disease (IBD)? Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2022 [cited 2023Feb25]. Available from: https://www.cdc.gov/ibd/what-is-IBD.htm#:~:text=What%20Is%20IBD%3F,damage%20to%20the%20GI%20tract
10. IBD statistics 2022: Crohn's and ulcerative colitis. Ampersand Health. 2022 [cited 2023Feb25]. Available from: https://ampersandhealth.co.uk/myibdcare/resources/ibd-statistics-2022-crohns-and-ulcerative-colitis/#:~:text=What%20percentage%20of%20people%20get,IBD%20affects%20the%20elderly%20population
11. Dandrieux JR, Mansfield CS. Chronic enteropathy in canines: Prevalence, impact and management strategies. Veterinary Medicine: Research and Reports. 2019Dec6;Volume 10:203–14.
12. Yan Y. Pathogenesis of inflammatory bowel diseases. Inflammatory Bowel Disease – Advances in Pathogenesis and Management. 2012;
13. Sethi S. Inflammatory bowel disease: Causes, symptoms, and treatments. Medical News Today. MediLexicon International; 2020 [cited 2023Feb25]. Available from: https://www.medicalnewstoday.com/articles/316395
14. Llera R. Inflammatory bowel disease in dogs: VCA Animal Hospital. Vca. [cited 2023Feb25]. Available from: https://vcahospitals.com/know-your-pet/inflammatory-bowel-disease-in-dogs
15. Shi J, Johansson J, Woodling NS, et al. The prostaglandin E2 e-prostanoid 4 receptor exerts anti-inflammatory effects in brain innate immunity. The Journal of Immunology. 2010;184(12):7207–18.
16. Kirkby Shaw K, Rausch-Derra LC, Rhodes L. Grapiprant: An ep 4 prostaglandin receptor antagonist and novel therapy for pain and inflammation. Veterinary Medicine and Science. 2015;2(1):3–9. doi:10.1002/vms3.13
17. Hofer M, Lutolf MP. Engineering organoids. Nature Reviews Materials. 2021;6(5):402–20.
18. Sreedharan S, Nanni S. Introducing one health to medical and veterinary students. The Lancet Planetary Health. 2019;3(5).
19. Csukovich G, Pratscher B, Burgener IA. The world of organoids: Gastrointestinal disease modelling in the age of 3R and one health with specific relevance to dogs and cats. Animals. 2022;12(18):2461.

Phoebe Tarver

I am a fourth year veterinary student currently completing my intercalated Master's in Epidemiology. My interests include oncology and veterinary epidemiology. I hope to pursue research throughout my career alongside clinical work and look forward to seeing how the field of One Health can contribute to both veterinary and human biomedical research in the future.