organoids

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Editorial

The Next Generation of Organoids Will Be More Complex and Even Closer to Resembling Real Organs: An Interview with Prof. Dr. Hans Clevers

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In this issue, we are pleased and honored to have an interview with Professor Hans Clevers, who is the Advisory Board Member of *Organoids* [1].

Professor Clevers received his Ph.D degree from the University of Utrecht in 1985. He has received several scientific prizes, including The Academy Professor Prize of the Royal Netherlands Academy, the Ilse & Helmut Wachter award, the Keio Medical Science Prize, the Citation Laureate, the Pezcoller Foundation-AACR International Award, the Ammodo Science Award, the World Laureates Association Prize, and the 14th Weinman Award.

Currently, he is an advisor/guest researcher at the Hubrecht Institute (Utrecht, The Netherlands), and the head of Pharma Research and Early Development (pRED) at Roche (Basel, Switzerland).

Professor Clevers has authored more than 800 peer-reviewed scientific articles. Their main focus is on organoids, stem cells, and molecular genetics.

Here, in this interview, we are able to see his opinions on the field of organoids, as well as suggestions for our journal *Organoids*.

What motivated you to start working with MDPI on a journal specifically dedicated to organoid research?

Prof. Clevers: There are two reasons. Two ways of making organoids currently exist—one starts from pluripotent cells, IPS cells, or ES cells. This technology allows us to build organ-like structures, using principles from developmental biology. Our technology starts from existing tissues from children and adults, and these are different stem cells. The name of these cells are adult or tissue stem cells, and they are fully specialized. This technology started when we originally discovered gut stem cells, which we have successfully transformed into mini-guts, now referred to as intestinal organoids. Having devoted around 15 years to laboratory work on organoids, it is only natural that I would like to be involved with a journal that primarily focuses on this area. The second reason is that we have decided to publish papers only in open-access journals.

Which types of adult stem cells are you currently working with in order to produce organoids?

Prof. Clevers: We began with gut stem cells. After identifying the growth factor cocktail suitable for these cells, we applied it to numerous other tissues. Recently, we published a paper on conjunctiva organoids, and we have also utilized it for tear glands, the pancreas, and the liver. Currently, we are also actively working on lung and airway organoids.

Please let us know on which topics ***Organoids*** *should focus on in the future?*

Prof. Clevers: There are numerous possibilities in the field of adult stem cell-based organoids. There are various topics that journals can focus on: physiological epithelial functions such as trans-epithelial transport, hormone secretion, and the secretion of other glandular products, such as tears or digestive enzymes. Also, the properties of carcinomas and, of course, the use of human organoids in infectious disease research. Emerging fields include the interactions of organoids with the immune cells and neurons.

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The term "organoid" has been used in different ways by different publications in the past. What is your current definition of the term "organoid"?

Prof. Clevers: Organoids begin with stem cells, be it pluripotent stem cells or tissue stem cells. Organids from tissue stem cells can be grown directly from primary tissue, while retaining essential features and functions of the original tissue. These crucial attributes include cell type diversity and cellular functions. These organoids can be derived from various tissues, with epithelial stem cells playing a pivotal role. The protocols for growing these organoids are closely linked to the biology of epithelial stem cells. If one thinks about the specific functions of organs like the liver, lung, stomach, pancreas, or gut, the primary functions of these organs are consistently carried out by their epithelial cells. Additionally, carcinomas, by definition, originate from epithelial cells. Hence, tissue stem cell-derived organoid technology offers a valuable means to thoroughly study carcinomas.

You witnessed and crucially shaped the rise of the organoid field from the beginning, and contributed essentially to it. What do you think were the most important key developments/publications in the evolution of this research field? What impressed or surprised you most with regard to organoids?

Prof. Clevers: A significant surprise occurred at the beginning, when we attempted to grow adult tissues, as this had only done for a very limited number of tissues (e.g., the work of Howard Green on epidermis cultures). Many believed that the culturing of most primary tissues was essentially not possible, and that only cancer-derived tissue samples could be propagated in vitro. Another surprise arose when we began analyzing them, and realized that the organoids that Toshi Sato grew from gut stem cells contained a normal gut epithelium. I believe that even those working with induced pluripotent stem cells (IPS) were surprised by how accurately they could recreate development. Despite the current limitations, I am confident that this technology will continue to improve. Another surprising aspect to me has been the development of blastuloids, the growth of human embryo-like structures from stem cells, and similar advancements. I anticipate significant expansion in these areas in the coming years. Looking ahead to future developments, I expect that the next generation of organoids will be ever more complex, and even closer to resembling real organs.

As organoid research is coming of age, organoids are now moving towards applications in drug screening and personalized medicine. Could you give a few examples where organoids are already routinely used in hospitals or pharmacological research? Which will be the most important applications in the future?

Prof. Clevers: One benefit of organoids in clinical use would be transplantation. This is already underway in Japan for inflammatory bowel disease, in a program led by Mamoru Watanabe, and in Holland, the transplantation of salivary glands is being performed by a team led by Rob Coppes for individuals with dry mouth disease. I believe that human organoids can be used everywhere along the drug development process: from screening for novel compounds in organoid-based human disease models, to safety and toxicity studies. Another application is taking cells from patients for personalized approaches. This approach is currently being used for diseases such as cystic fibrosis, where a simple organoid-based test has been developed. Additionally, tumor-derived organoids hold promise for utilization for personalized medicine approaches.

In my impression, biofabrication is also undergoing rapid development, even if some things that form this area are still in their infancy. What can biofabrication/tissue engineering learn from the organoid field and vice versa? Do you think organoids are useful as building blocks for biofabrication, and maybe even superior to the bioprinting of single cells? Will it be possible to generate functional millimeter scale (or even larger) tissues using organoids? What are the major limitations regarding that, and which tissue will be the easiest or most useful tissue to start with?

Prof. Clevers: I believe two scientific disciplines will need to come together for biofabrication: materials science/engineering will have to collaborate with biologists, who understand how tissues are formed. In many countries, these two disciplines are often found in separate universities. However, in some places, there are attempts to bring together these two disciplines, which makes a lot of sense and is crucial for building in vitro organs.

What do you think about creating interfaces between neural organoids and computers/artificial intelligence, a very new field of research, which gained some public attention recently regarding "organoid intelligence"?

Prof. Clevers: There are speculations about the possibility of integrating organoid fragments into chips for use in computational electronics. What has already been done is transplanting human brain organoids into mouse brains, resulting in a connection that appears to contribute to the mice's behavior. However, it seems that we are still far from achieving a reproducible and productive integration of a biological brain into an artificial intelligence chip. While people fantasize about this possibility, for now, I would say it is probably still a concept better suited for science fiction.

Embryoids have been elected "Method of the Year 2023" by Nature Methods. Embryoids are fascinating, especially for developmental biologists, but are also ethically and legally problematic. Do you think that legislation is prepared for these developments? Do we need more ethical debate, also involving the public and politics?

Prof. Clevers: This is a question that always comes up in this field. Stem cells and embryo research are likely the areas of science that give rise to the overwhelming majority of ethical discussions. I've noticed that the ISSCR and their ethicists react promptly whenever new technology emerges. The normal progression of things typically involves the definition of guidelines originating from the scientific community, with input from ethicists. These guidelines invariably address safety concerns, as well as ethical acceptability. While the technology matures, (inter)national laws emerge. The rapid development embryoid and blastuloid technology will likely evoke a lot of activity around the formulation of additional guidelines, complimenting what already exists in the regulation of human stem cell and embryo research.

Conflicts of Interest: The authors declare no conflicts of interest.

Reference

1. Editorial Board of *Organoids*. Available online: https://www.mdpi.com/journal/organoids/editors (accessed on 4 February 2024).