The future of medicine could lie in organoid research

Organoids could have the power to revolutionize areas of biomedical research from disease modeling to drug development.

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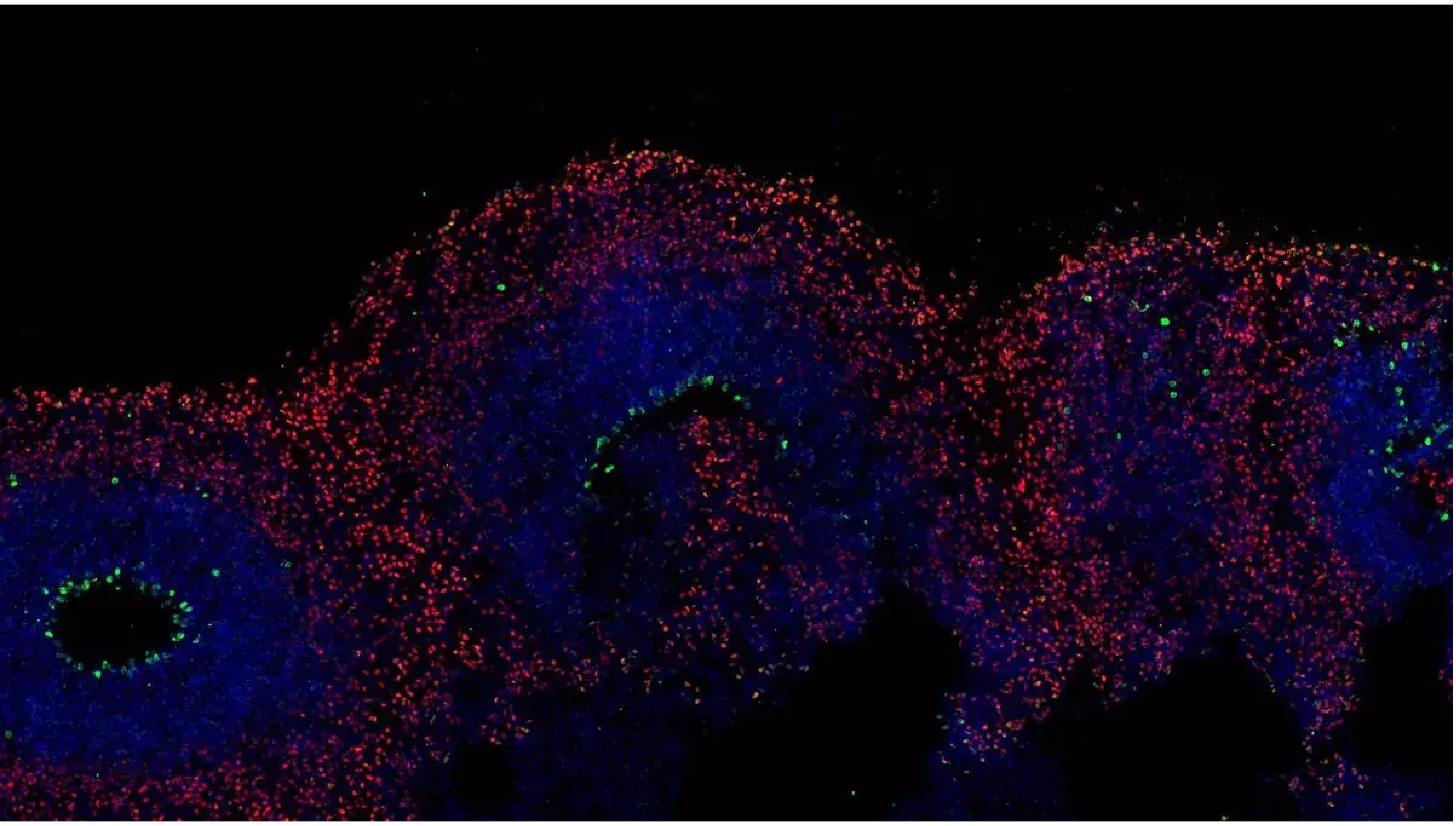


Patient-derived cerebral organoid, stained for cells in mitosis (green) and cortical neurons (red); all cells are counterstained in blue.

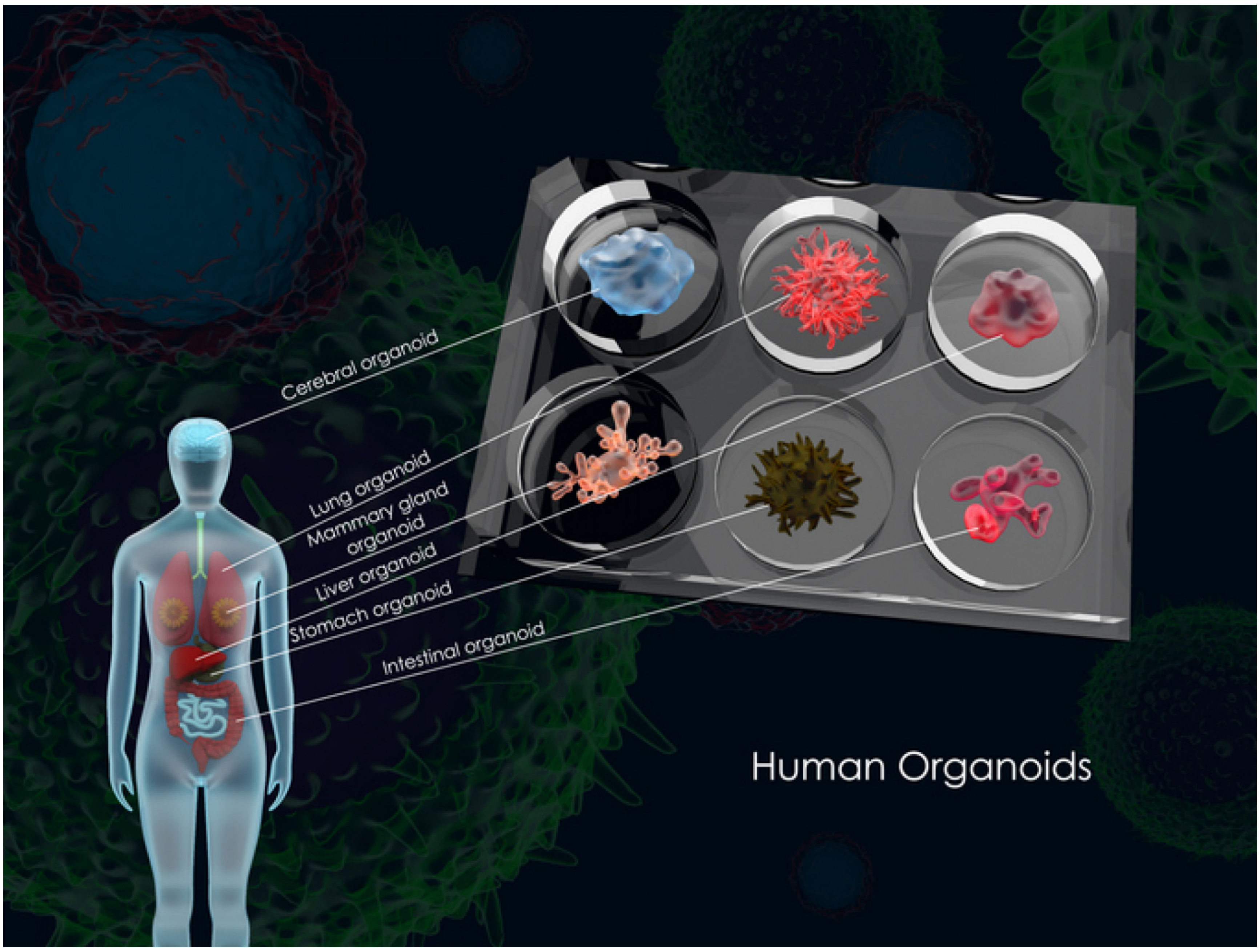
- One of the most exciting developments in biomedicine is in the field of organoids.
- These are miniature organs that can be used in medical testing and research.
- They provide much more accurate results than some other types of tests.

The field of biomedical sciences has come a long way since Alexander Fleming created the first antibiotic, Penicillin, in the 1920s.

One of the most exciting advances in modern biomedicine is the development of organoids, or mini-organs.

Organoids are intricate, miniature organs cultivated within the controlled environment of a laboratory dish. They are comprised of self-organized tissue, often derived from stem cells, and which mimic the key functional, structural, and biological complexity of a complete organ.

They are particularly helpful in disease research, as they allow researchers to better understand neurological disorders, genetic conditions, and complex diseases. Moreover, their role in drug development and toxicity testing holds the promise of safer and more effective pharmaceuticals in the future.

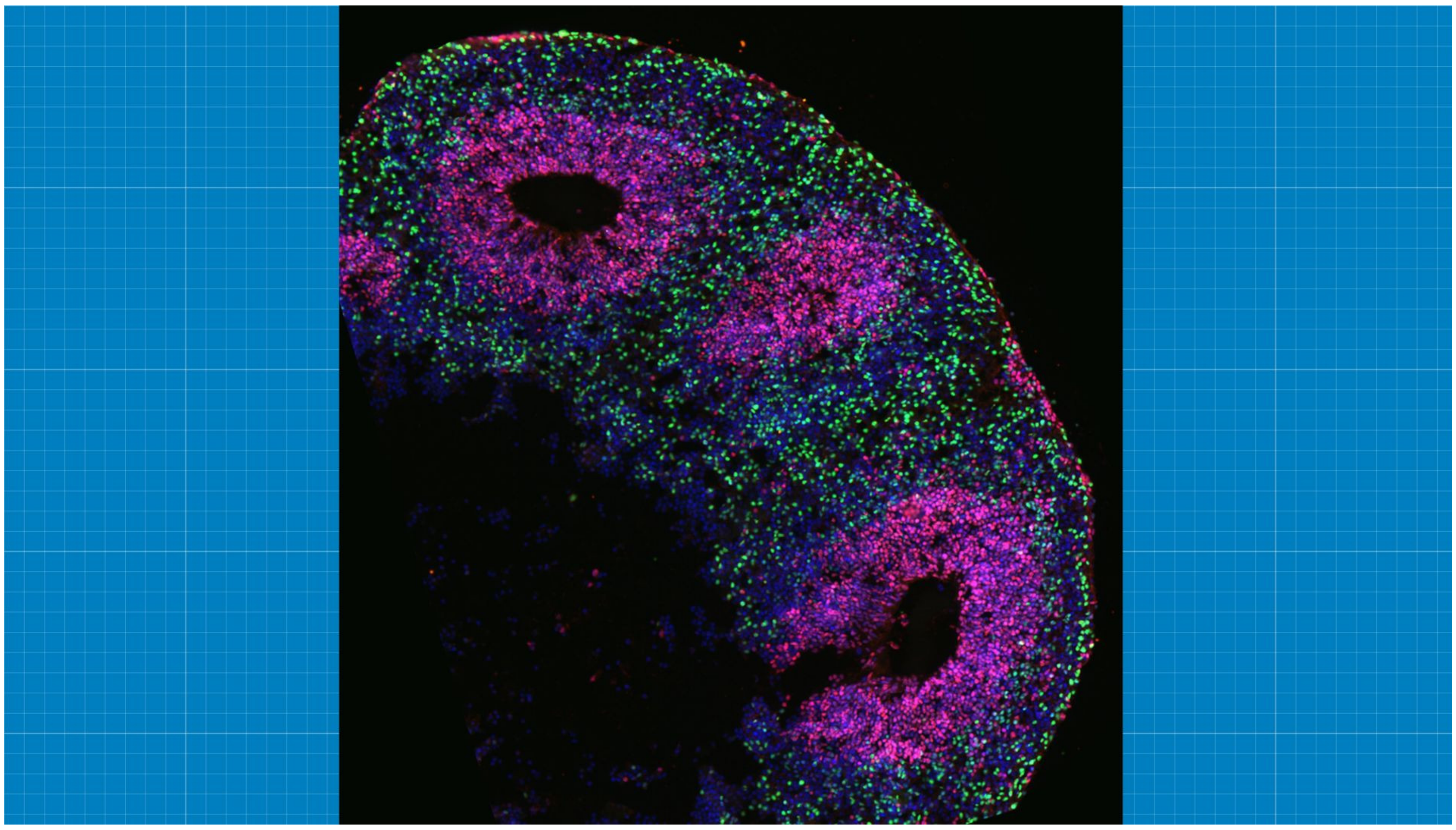


Organoids are helping researchers to better understand organ function and develop better pharmaceuticals. Meletios Verras

In this article, we explore the promise of organoids and take a look at some recent advances and insights from Dr. Nicolas Daviaud, who is working at the forefront of this field at the Tisch MS Research Center of New York.

What are organoids?

Organoids are three-dimensional structures cultivated in vitro (outside of the living organism) that replicate the architecture, cellular composition, and functionality of specific organs or tissues. They are created from stem cells or tissue-specific progenitor cells.



Cerebral organoid derived from a patient with MS after 42 days in culture, stained for stem cells (red) and cortical neurons (green), all cells are counterstained in blue. Dr. Nicolas Daviaud

Unlike traditional two-dimensional cell cultures, organoids offer a more accurate and physiologically relevant representation of organs and systems. This allows researchers to study the intricate interactions between different cell types, simulate disease conditions, and test potential therapies in a controlled laboratory environment.

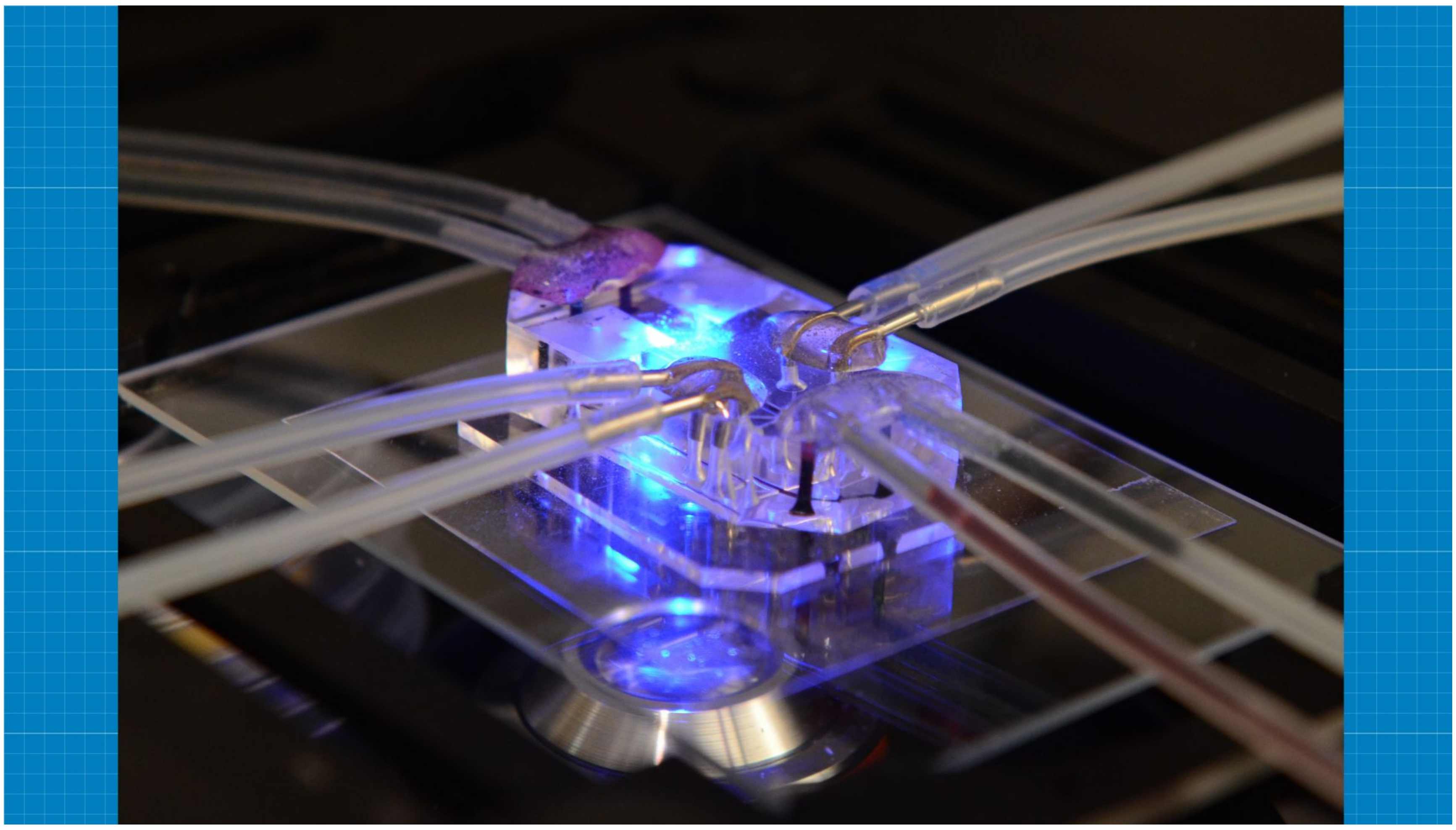
They also offer advantages over animal models.

In addition to not requiring any animal sacrifice, "Organoids display in-vivo-like properties, which allow researchers to study the development of tissues and organs, carry out realistic toxicity assessments, drug tests or genome editing strategies, and model human diseases," explained Dr. Daviaud.

He further added, "A high number can be grown at the same time, making them a useful tool to perform drug development and toxicity testing on human living tissue, which might be more accurate than animal models."

Organoids vs organ-on-a-chip

Another technology that is gaining momentum in this field of research is organ-on-a-chip.



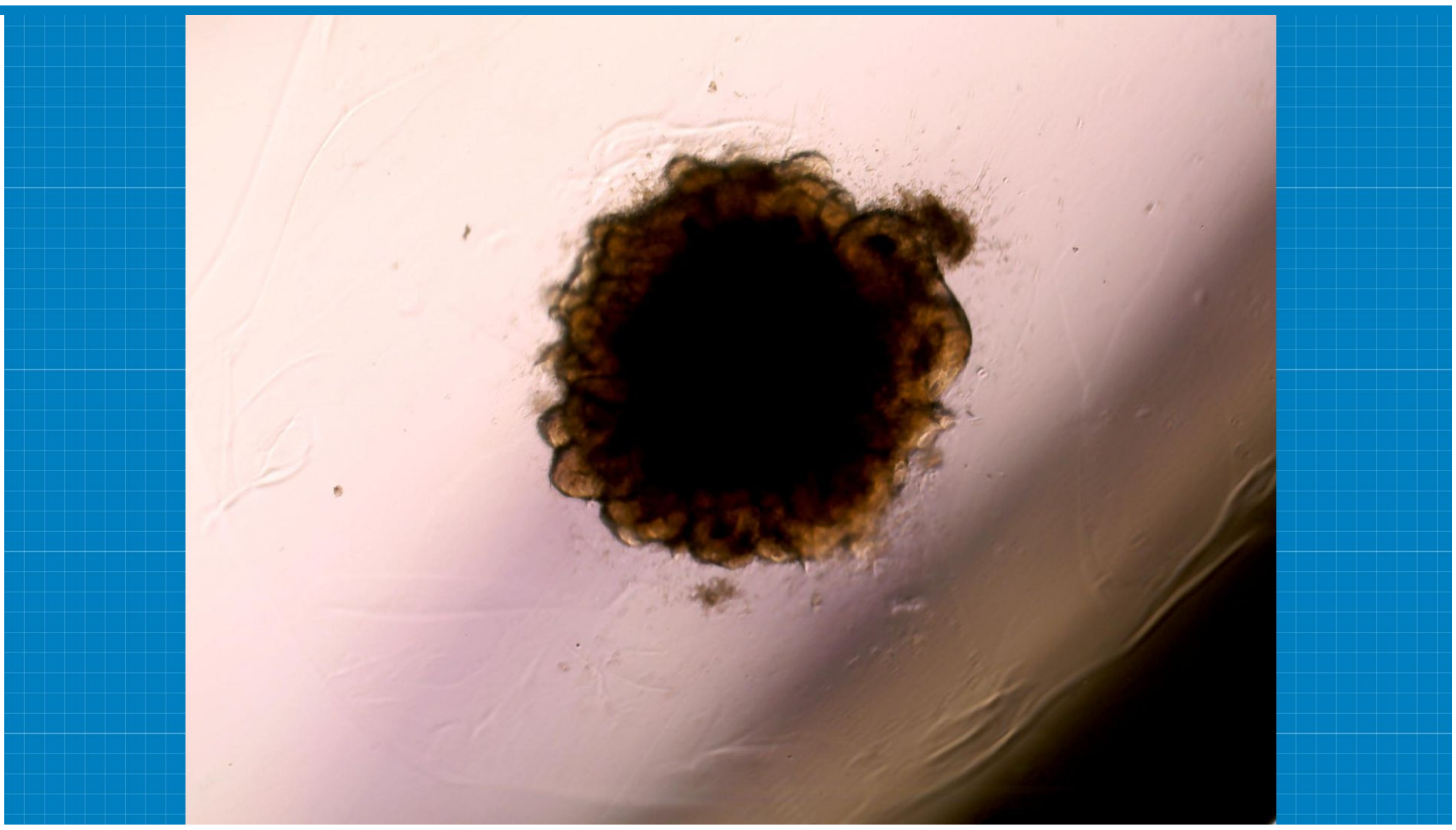
Lung on a chip. Wyss Institute for Biologically Inspired Engineering, Harvard University

Organ-on-a-chip refers to artificial, microfluidic devices that mimic the functions of organs on a smaller scale. These platforms recreate organ environments, enabling controlled studies of organ responses to various conditions and treatments.

So, what's the difference between organ-on-a-chip and organoids?

Organoids provide a more accurate representation of the overall complexity of organs compared to traditional cell cultures. They help study cellular interactions, disease mechanisms, and potential treatments within a controlled environment.

On the other hand, organ-on-a-chip technologies emphasize the precise simulation of specific organ functions, enabling meticulous drug testing and in-depth comprehension of organ-level reactions in a controlled setting.



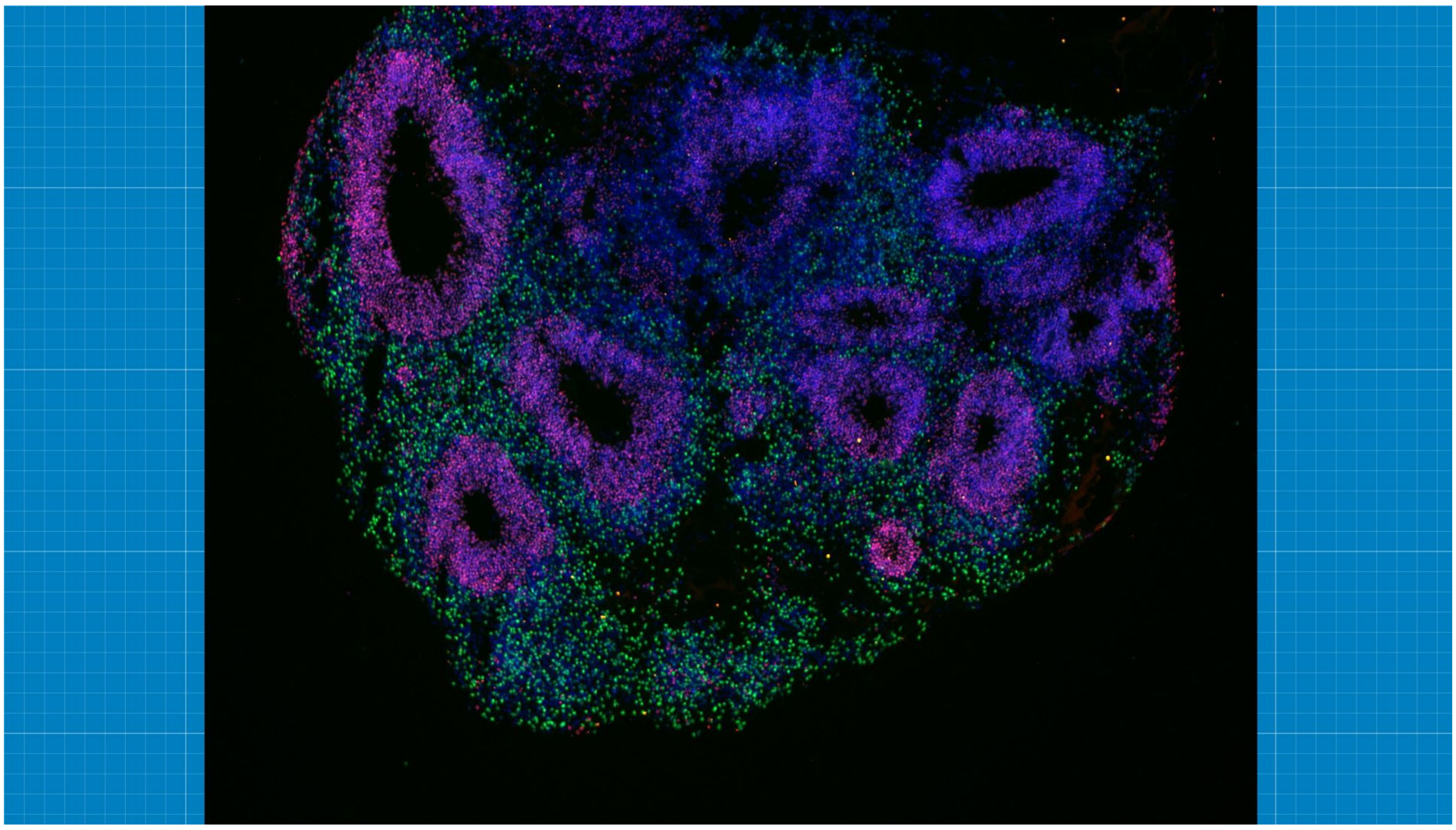
Patient-derived cerebral organoid after 30 days in culture showing many buds of neuroepithelial cells, which are going to form the cortical tissue. Nicolas Daviaud

In essence, both technologies contribute to advancing biomedical research by providing more accurate and relevant models for studying organs and tissues. The choice between organoids or organ-on-a-chip models often depends on the specific organ or tissue being investigated and the desired level of complexity in the experimental setup.

Organoids for MS research

With a foundational understanding of organoids and their significance, let's dive a bit deeper into their potential uses in disease research. Specifically, let's look at their role in understanding and tackling complex neurological disorders like multiple sclerosis (MS).

MS is a chronic autoimmune disorder where the immune system attacks the protective covering of the nerve fibers, leading to communication problems between the brain and the rest of the body. This results in a range of symptoms, including fatigue, difficulty walking, numbness or weakness, and vision problems.



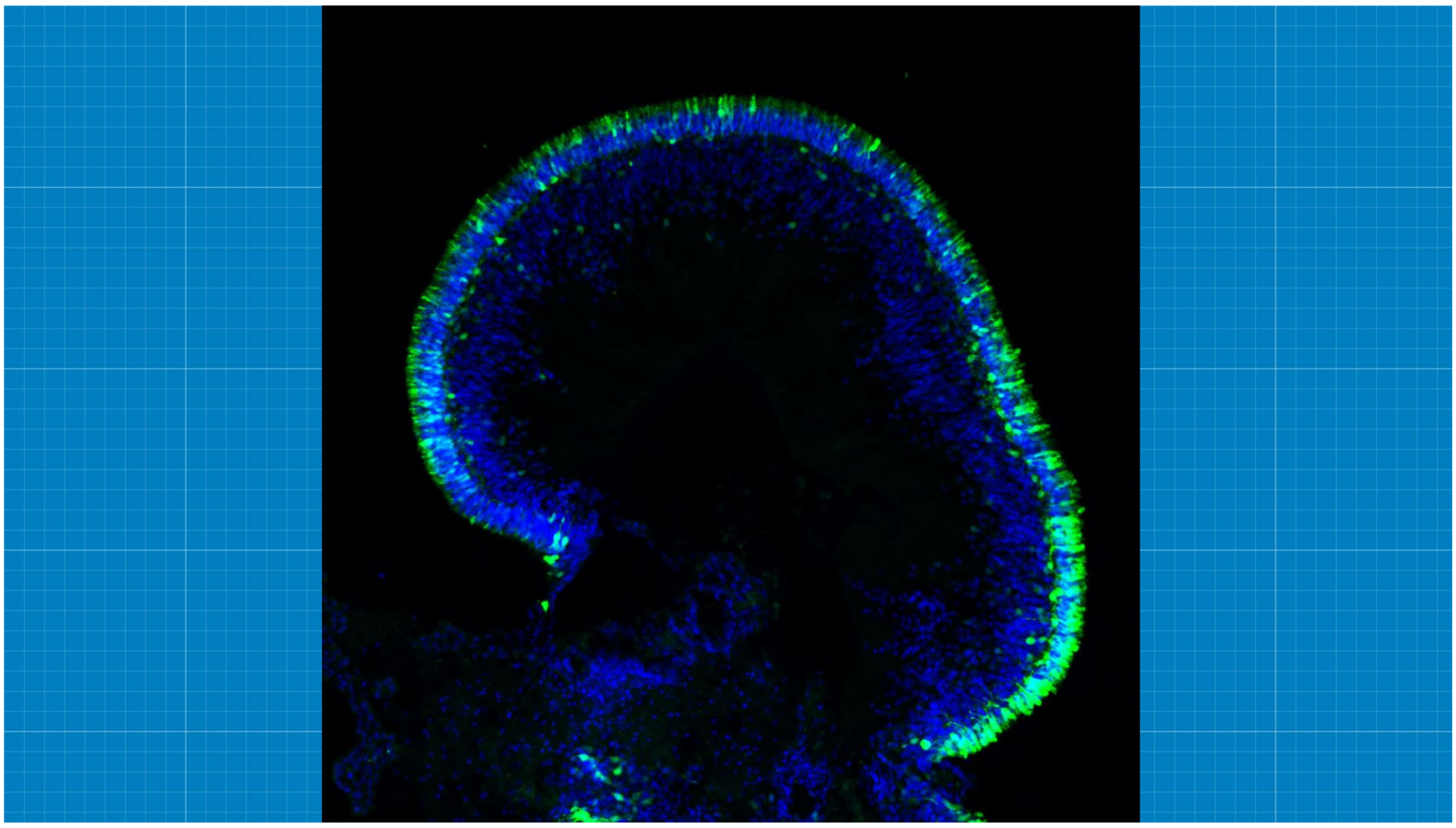
Patient-derived cerebral organoid after 42 days in culture, stained for stem cells (red) and cortical neurons (green), all cells are counterstained in blue. Dr. Nicolas Daviaud

Speaking of why he and his team chose to focus on MS, Dr. Daviaud said, "MS is a very complex disease to study, in large part due to the relative inaccessibility of the human brain and spinal cord tissue."

Generally, the progression of this disease is studied using animal models, especially rodents. However, this is not very practical. As Dr. Daviaud explained, "Rodents cannot naturally develop MS, so the use of rodents to model MS comes with some limitations, particularly when studying the genetic mechanisms associated with the disease."

Instead, the team uses organoids created from stem cells of healthy people, and those with different types of MS. They use induced Pluripotent Stem Cells (iPSCs), a type of Stem cell that can be generated from adult cells, like skin cells, and then "reprogrammed" to become various types of cells, in this case, brain cells.

These IPSC-derived brain cells organize themselves into structures that resemble parts of the human brain when grown in specific conditions, allowing researchers to study brain development and diseases in a more controlled setting.



An image of retinal organoids. NIH Image Gallery from Bethesda, Maryland, USA

"Organoids derived from patient-specific iPSCs address the limitations of animal models because they retain the genetic information of the donor, allowing analysis of the effect of genetics on the generation, proliferation, and differentiation of neural progenitors into glial cells and neurons," Dr. Daviaud pointed out.

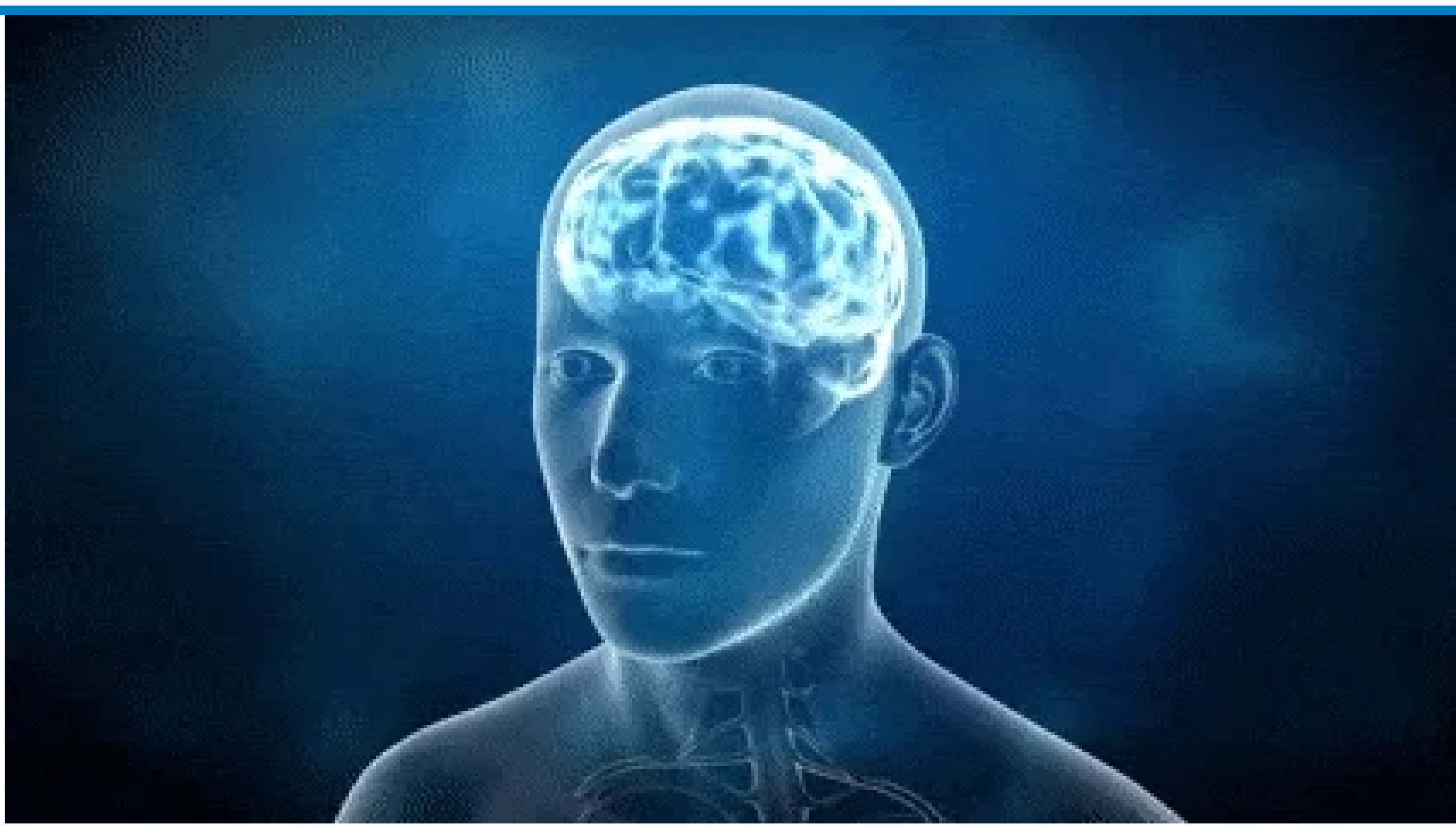
The organoid research showed that in MS, especially in primary progressive MS (PPMS), there was a decrease in cell growth and stem cell numbers, along with changes in the types of brain cells produced. These differences seemed to be linked to a protein called p21.

Their study demonstrated that a person's genetic makeup could affect how brain cells behave, giving insights into why MS exhibits different symptoms in different people. The findings also suggest that targeting the p21 protein could be a new approach to treating MS.

This work illustrates the potential of organoids to advance disease research.

Other advancements in organoid research

Organoids have also emerged as valuable tools in addressing challenges in the study of brain disorders.



via GIPHY

Dr. Daviaud pointed out that, "Cerebral organoids from different regions of the brain can be created and fused tc create an even more complex model of the human brain," he stated.

Recently, a study led by Madeline A. Lancaster from the Institute of Molecular Biotechnology of the Austrian Academy of Science (IMBA) used human stem cells to create organoids capable of imitating different brain regions.

The researchers then implanted the organoids in mice to observe how they could create nerve connections and influence muscle contractions in the spinal cord. They noticed that the organoids could develop connections that reach the mouse's spinal cord, causing muscle contractions.

Researchers can use this technique to study complex brain disorders and even replicate conditions like microcephaly, where abnormal development leads to a smaller head and brain size, along with accompanying developmental challenges, which is difficult to study using traditional models.

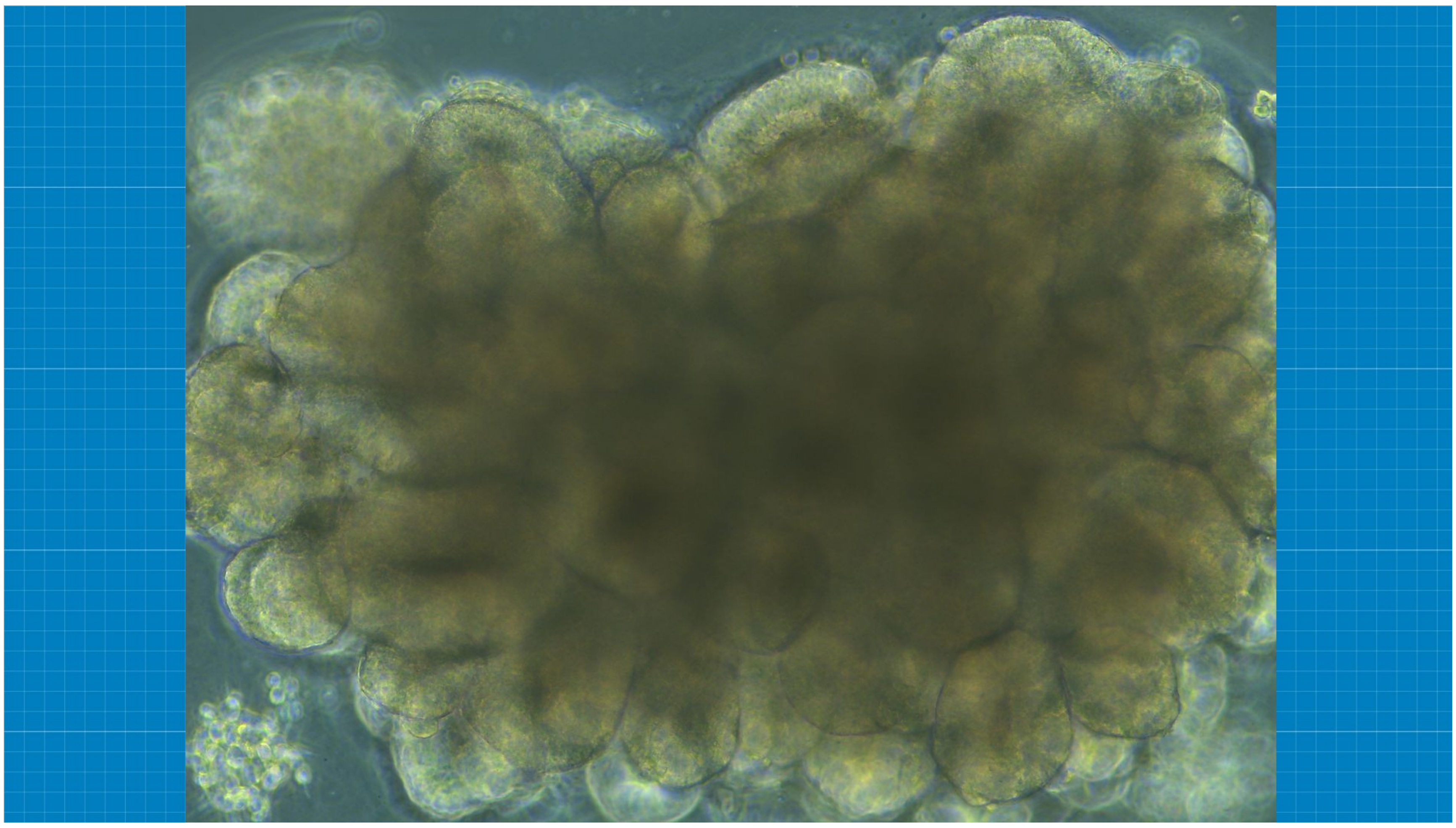
Other advances include heart organoids capable of beating and mimicking early heart development and structure, as shown in a study led by Zixuan Zhao from the National University of Singapore.

Zhao and team found that the organoids can be used to study genetic defects that can cause heart problems, similar to what has been observed in mice.

The uses of many other organoids are being explored, including the cultivation of lung organoids capable of mimicking the development of alveolar cells, which play a crucial role in facilitating efficient gas exchange in the lungs.

Additionally, researchers are exploring endometrial organoids that display responsiveness to reproductive hormones and retinal organoids designed to react to light stimulation.

Optimistic about these developments, Dr. Daviaud commented, "These new models will bring a better understanding of organ development and the disease related to those organs and will hopefully lead to new personalized treatments."



Cerebral organoid during development. *NIH Image Gallery from Bethesda, Maryland, USA*

Clinical trials and ethical considerations

Clinical trials of drugs developed out of organoid research are already underway.

"Numerous clinical trials using patient-derived cerebral organoids have already started, particularly on cancer. The goal of those clinical trials is to determine the consistency and accuracy of a patient-derived organoid to model a patient's cancer, but also to predict the clinical efficacy of anticancer drugs in order to predict the best chemotherapy regimen for each given patient," explained Dr. Daviaud.

Clinical trials derived from organoid research could eventually lead to personalized treatments based on individual genetics.

In one recent development, a team from The Tokyo Medical and Dental University achieved the world's first clinical transplantation of organoids into a patient with ulcerative colitis (UC), an inflammatory bowel disease.

Intestinal organoids of ulcerative colitis patients are delivered for transplantation by gastrointestinal endoscopists. Department of Gastroenterology and Hepatology, TMDU

These organoids were grown from healthy colonic mucosa, cultured for about a month to form spherical structures, and then transplanted into the patient's colon using colonoscopy.

There have, in the past, been ethical issues concerning organoid sourcing.

This was more of a concern when organoids were sourced from the embryonic pluripotent stem. These are derived from embryos at an early developmental stage.

However, this problem was solved when Shinya Yamanaka, a Japanese researcher and Nobel laureate, developed a protocol to create pluripotent stem cells from adult cells in 2006.

The Rise and Fall of Stem Cell Research

Dr. Daviaud addressed this significant achievement and added, "This protocol has since been improved, and pluripotent stem cells can now be created from cells isolated in blood, skin, or even urine."

"The use of iPSCs in organoid technology raises fewer ethical concerns, mostly related to the informed consent of tissue donors. Patients should be given explanations about how their cells will be used and stored so that they can give informed consent, and they should also be anonymized."

He also mentioned that ethical concerns raised by researchers led to the publication of guidelines for stem cell research and clinical translation by the International Society for Stem Cell Research (ISSCR). This ensures responsible and transparent practices while advancing organoid research.

Conclusion

Organoid research is progressing but is not without its challenges. As Dr. Daviaud aptly pointed out, "Despite the advantages of using organoids to study disorders, some challenges remain."

Transplanting human-derived “organoids” allows scientists to study brain disorders | 90 Seconds

For example, the absence of blood vessels and immune cells limits organoids from fully replicating complex interactions within the body. Nonetheless, innovation continues as researchers explore methods to incorporate these elements into organoids, particularly within cerebral models.

While organoids offer a controlled and detailed approach to replicating cellular and tissue dynamics, they cannot yet replace the complexity of interactions that occur within living organisms.

Looking forward, Dr. Daviaud optimistically concluded, "It is difficult to predict how organoids will influence precision medicine and tailored therapies, but it's clear they will play an increasingly important role in biomedical research."

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