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Can organoids usher in cheap and effective cancer therapeutics?

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Dubbed as powerful ‘human modelling systems’, organoids are paving the way for personalised medicines and shaking up the global drug development scene. India, too, is joining the bandwagon. Let's explore the world of organoids and how it is pushing the boundaries of personalised medicine research and precision oncology.

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Dozens of science and technology development payloads returned to Earth from the International Space Station (ISS) as SpaceX’s 29th Commercial Resupply Services (CRS) mission, contracted by NASA, successfully concluded on December 22, 2023. More than 30 payloads sponsored by the ISS National Laboratory returned on this mission, many of which were life science investigations aimed at benefiting humanity by improving care for patients on Earth.

One among the payloads was an investigation from the University of California, San Diego (UCSD), which studied microgravity's effects on stem-cell derived brain organoids (lab grown replicas of human organs).

The brain organoids were employed as surrogates, where the lab-grown brain models derived from human stem cells served as windows into the human brain’s response to space-related stressors. The researchers believe that the results from this study could possibly lead to new ways to treat dementia, Alzheimer's, and other neurodegenerative conditions.

By definition, organoids are three?dimensional (3D) miniaturised versions of organs or tissues that are derived from stem cells and have the potential to self?organise and differentiate into 3D cell masses, recapitulating the morphology and functions of their in vivo counterparts. Organoid culture is an emerging 3D culture technology, and organoids derived from various organs and tissues, such as the eyes, brain, lung, heart, liver, and kidney, have been developed across the world by researchers for various medical purposes.

When compared with traditional bidimensional (2D) culture, organoid culture systems have the unique advantage of conserving parental gene expression and mutation characteristics, as well as long?term maintenance of the function and biological characteristics of the parental cells in vitro. All these features of organoids open up new opportunities for drug discovery, large?scale drug screening, and precision medicine.

Further, organoid technology has emerged as a rapidly growing field that has the potential to revolutionize the way diseases are studied and treated. This emerging technology has improved the chance of translatability of drugs for preclinical therapies and mimicking of the complexity of organs, proposing numerous approaches for human disease modelling, tissue engineering, drug development, diagnosis, and regenerative medicine.

Organoid technology stands out as having a major market, with a lot of scientific and business advancements in the fields of stem cells and tissue regeneration. A report by Future Market Insights predicts a 13 per cent CAGR for the global organoids industry between 2023 and 2033, driven by their increasing role in drug discovery, personalised medicine, and disease modelling. By 2033, the market is expected to reach $205.3 million, significantly expanding from its 2023 value of $60.4 million.

Why India is Bullish on Organoid Tech

Organoid technology in India may be at a nascent stage, but some significant developments are undeniably taking place. Several research institutions in the country are actively exploring organoids for various applications like drug discovery, disease modelling, and personalised medicine. Initiatives like the Department of Biotechnology's ‘Mission Innovation for Drug Discovery’ is further fuelling this research landscape.

Before we go ahead onto knowing some of those details on organoid-based research activities taking place in India, we need to know where organoid technology scores better than other drug testing technologies. Firstly, organoid technology provides researchers with a platform for conducting laboratory studies on living diseased tissue, which is impossible to accomplish in patients. It can create human modelling systems in a petri dish, which can be used to develop and test medications before they go through costly clinical trials.

Secondly, the ban on animal testing in various regions and the growing ethical concerns over animal source usage is contributing to the rise in organoid tech. The low translational efficiency of animal models to humans is drawing a lot of attention towards organoids and organ-on-chip. Few years back, a road-map was drawn by Indian Council for Medical Research (ICMR) regarding alternatives to animals in research in India and it also held a special session in January 2018 to discuss latest developments in new human-relevant model systems.

Sharing a few pertinent points about the advantages of organoid technology, **Dr Dwijit GuhaSarkar, Lead Scientist, Organoid Laboratory, Tata Translational Cancer Research Centre (TTCRC), Tata Medical Center, Kolkata,** says, “Animal models, though more physiologically and clinically relevant and being an in vivo (inside body) system, suffers from several limitations. The test (e.g., drug response) can be influenced by the animal system, which is often different from the human system. It is usually highly expensive, time consuming and definitely not scalable for high throughput screens. Whereas, Patient Derived Organoids (PDOs) are developed from human primary cells. While this is an ex vivo (outside body) system, it still recapitulates the 3D context of tissue microenvironment. PDOs also capture the individual differences (thus personalised model). Moreover, unlike animal models, organoids are scalable for high throughput drug screens within a turnaround time that is clinically relevant for personalised medicine. So, in short, this model system retains most of the advantages of both the conventional models.”

According to Dr GuhaSarkar, the pre-clinical testing of potential drug molecules will be much faster with organoid tech. He adds, “It will also be cost-effective as animal studies for large numbers of molecules is prohibitively expensive. Moreover, finding an alternative to animal use in research is ethically a better approach. Personalised medicine is a feasible idea with PDOs because of the clinically relevant turnaround time unlike animal studies.”

Another point to consider is that India's diverse and large population provides a readily available source of biomaterial for organoid generation. This facilitates personalised medicine research and allows for studying various disease models relevant to the Indian context. **Anushka Banerjee, Scientific Development and Communication Officer at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru,** says, “I believe, organoids provide a more physiologically-relevant environment in which we can study diseases and more importantly, accurate drug responses at the pre-clinical research stage, minimising late-stage development failures. This is complemented by genomic data analytics in relevant human – like models, that provides insights into underlying genetic causes and therefore, helps identify potential molecular drug targets and companion diagnostic biomarkers.”

Several laboratories across the country are now increasingly leaning towards organoids. One of the notable pioneers is IIT Madras, which joined hands with the prestigious Massachusetts Institute of Technology (MIT) on some exciting organoid-based research, specifically focusing on growing human brain tissue. The researchers have developed a 3D printed bioreactor that enables the growth of human brain tissues to study the tissue in its growth and developmental stage. The study will facilitate in accelerating the medical and therapeutic discoveries for diseases such as cancer and neurological disorders like Alzheimer’s and Parkinson’s.

Also, researchers at the National Centre for Cell Science (NCCS) in Pune, India, have developed patient-derived brain organoids from paediatric glioblastoma, a highly aggressive and often fatal childhood brain cancer. These organoids capture the unique genetic and biological features of each patient's tumour, offering a more personalised approach to understanding and treating the disease.

Not only are research studies happening at different institutions, but a few companies are also showing potential interest. In April 2023, InSphero AG announced that the company is making their patented Akura 96 and 384 Spheroid Microplates available to researchers in the Indian market by signing a distribution agreement with Bionova Supplies in biotechnology and scientific instruments.

Organoids, Genomics, and Cancer Therapeutics

While cancer remains a leading cause of death globally, hurdles remain in bringing new cancer therapies to patients, with up to 97 percent of drug candidates claimed to be failing in clinical trials. Hence, in this scenario, the synergy between organoid technology and genomics is revolutionising cancer therapy by offering a more precise and personalised approach. Researchers collectively opine that unlike traditional cell cultures, organoids have the ability to retain the intricate architecture and cell-cell interactions of their original tumours, mimicking their diverse genetic makeup and drug sensitivities. This allows researchers to study how different populations within a single tumour behave and respond to treatment, providing valuable insights into tumour evolution and resistance.

Organoids are giving a new lease of life to many rare cancers and its therapies that have no defined treatment pathways so far. Breakthroughs in understanding the cancer pathology and drug discovery using organoid in such cases go a long way. For example, in April 2023, scientists from the Princess Máxima Centre for Paediatric Oncology and the Hubrecht Institute in the Netherlands reported that organoids and CRISPR-Cas9 permitted them to acquire more knowledge into the tumours biology and biological ramifications of various changes to DNA in fibrolamellar carcinoma (FLC), a rare form of child’s liver cancer.

Dr Dwijit GuhaSarkar, being a scientist in the translational cancer research field, opines that in cancer, the most challenging issue is heterogeneity – the same type of cancer in different patients behave differently with respect to drug treatment. “Even within the same patient, tumour is not homogeneous and that is why, while some cancer cells are killed by a certain drug, other cancer cells can be resistant. These resistant cancer cells eventually cause recurrence, which often results in the patient's demise. PDOs are models that can recapitulate these genetic, epigenetic heterogeneity at a personalised level in the tissue culture system. Therefore, it is possible to find out what alternative drugs (already approved or new drugs) or new combinations of existing drugs can be effective for a particular patient's tumour which is otherwise resistant to the standard of care treatment”, adds Dr GuhaSarkar.

“Currently available alternative treatment approaches, such as monoclonal therapies or engineered cell (CAR-T) therapies are effective but extremely expensive and beyond the reach of most patients in India. PDO-based testing approaches can help identify alternative chemotherapeutic drugs that are indigenous developed or already approved for other treatments which can be repurposed without causing a significant financial burden to the patients”

While organoid technology might already be futuristic, the projected trend is pointing towards the convergence of organoids, genomics, and AI-based high-throughput screening (HTS). It is anticipated that the synergy of organoids, genomics, and AI-driven HTS holds immense promise for accelerating drug discovery and improving patient outcomes in fascinating ways. Progress in the field of AI/ML-based programmes has remarkably broadened the applications of 3D culture-based technologies, like many other fields, enabling handling of high throughput complex data analysis and drug response predicting model development.

Scientist Anushka Banerjee cannot agree more on this development. She says, “The organoid-genomics duo technologies have immense potential, especially in drug development for cancer research and treatment. Personalised medicine is the cornerstone of the future of drug development. The combination of genomics and organoid research allows us to analyse patient-specific, tumour microenvironment, which enables accurate testing of potential drug response, while providing insights into genetic changes that drive the disease in each individual and therefore, personalised targets – personalised therapy. This overall systems biology-led synergy can enhance the efficacy and specificity of cancer treatments.”

Sharing some valuable knowledge on the synergy, **Dr Vishnu Akhil Raj Kumar Yerra, Founder, Innovation Without Limits Garage, Raipur**, says, “Organoid patterns can be analysed from various perspectives. For instance, examining the physical response of organoids to drug exposure – including changes in temperature, density, and other physical parameters – is crucial. Additionally, the analysis extends to biochemical parameters, ranging from ions to biomolecules, and encompasses various imaging techniques like ultrasound, elastography, thermal scanning, X-rays, and MRI. Histopathology remains a fundamental, gold-standard technique, utilising various staining methods to highlight changes pre- and post-drug exposure. Compiling these diverse parameters into a comprehensive dataset, which varies with different drug concentrations, is a complex task. Developing an intricate mathematical framework that can effectively correlate these parameters with drug efficacy in disease treatment is crucial for advancing our understanding”.

Adds Dr Yerra, in the realm of biomolecules and organoid patterns associated with disease states, similarly complex architectures are required. These systems must be capable of processing varied variables and yielding meaningful insights into the organoid responses under different disease conditions. Thus, the integration of neural networks and artificial intelligence is vital for decoding and understanding the intricate patterns exhibited by organoids in response to drug treatments, patterns which are otherwise challenging to interpret.”

Leveraging Versatility of Organoids

Ever since scientists have found ways of culturing organ-specific tissue from stem cells it has ushered in numerous abilities to change the way diseases are studied and treated. These mini lab organs are proposing big dreams, revealing cancer's and many other diseases’ hidden codes, eventually rewriting the future of personalised medicine. Organoid technology is certainly bringing a paradigm shift in biomedical research and drug development and its versatility and precision is opening new avenues for understanding complex diseases and discovering potential therapeutic interventions.

While organoid technology comes with a huge set of advantages, it has its own limitations. Challenging culture requirements and a lack of commercially available cultivation media systems are limiting the experimental abilities. However, companies like Thermo Fisher are working towards addressing the limitations. In mid 2023, the company launched OncoPro Tumoroid Culture Medium Kit, which is their new off-the-shelf, modular tumoroid culture medium kit that is designed to make complex cancer models more accessible to researchers.

Therefore, to imagine a world where rare diseases have cures, complex health conditions are better understood, and cancer treatment is specifically tailored to each individual, the power of organoids needs to be leveraged. By fostering open collaboration and integrating expertise in these cutting-edge technologies, the potential to supercharge disease-centric research and transform biomedicine is absolutely possible.

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