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Organoids: A New Frontier In Pharmacy? Exploring The Next Geration Of Greatness? Use Of M.L In Field Of Pharmacy, Baltimore Decleration & Ethical Empilcations Of Organoid And Their Unparalleled Scope?

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The field of organoids has witnessed remarkable advancements, emerging as a transformative tool in biomedical research. Organoids are three-dimensional, multicellular structures derived from stem cells that replicate the architecture and functionality of real organs. This review aims to comprehensively explore the origin, development, and applications of organoids, emphasizing their potential in drug discovery, regenerative medicine, and disease modeling.

A significant focus is placed on the concept of Organoid Intelligence (OI), envisioned as a form of genuine biological computing. OI integrates organ-on-chip systems with computational frameworks, offering revolutionary possibilities in biological computing and artificial intelligence. The paper delves into the application of machine learning (ML) in pharmacy, highlighting how ML algorithms enhance data analysis, predict drug efficacy, and personalize medicine in conjunction with organoid systems.

Additionally, the review examines the ethical dilemmas associated with OI, particularly in the context of the Baltimore Declaration. This declaration emphasizes the need for transparency' reproducibility, and ethical considerations in scientific research. By addressing the ethical challenges, this paper seeks to ensure the responsible development and application of OI technologies.

The convergence of organoids, OI, and ML promises to redefine the boundaries of computational biology and pharmaceutical sciences. This research review not only provides insights into the technological advancements but also underscores the importance of ethical and regulatory frameworks to guide the future of these innovations. Through a holistic approach, it aims to shed light on the transformative potential of organoids and their implications for science and society.

Key Words: Organoids, Drug Discovery, Personalized Medicine, Disease Modeling, Pharmacy Applications.

I. INTRODUCTION

It has always been difficult to study tissue and organ biology especially in mammal cells but the rapid progression and advancements in the field of stem cell culture have made it possible to derive in vitro 3D tissues called organoids. It also demonstrated vast potential that organoids have and that they can be used for developing organ models and have a wide range of applications in basic research, drug discovery, drug screening process and regenerative medicine. This has showed promise and potential for further development in other fields especially Bio-mechanical engineering, Bio-computing, Biotechnology and Pharmacy.

(Progress and potential in organoid research Giuliana Rossi) [1]

Now, O.I stands for Organoid Intelligence which was made possible due to rapid progression and advancement in field of Human Stem-cell is the latest and greatest frontier in new and emerging Biological Computing, O.I is meant to be established as a form of genuine computing. Latest developments have shown promising results hinting towards possibility to develop / replicate essential molecular and cellular aspects of cognition like learning and memory in-vitro and further. [1]

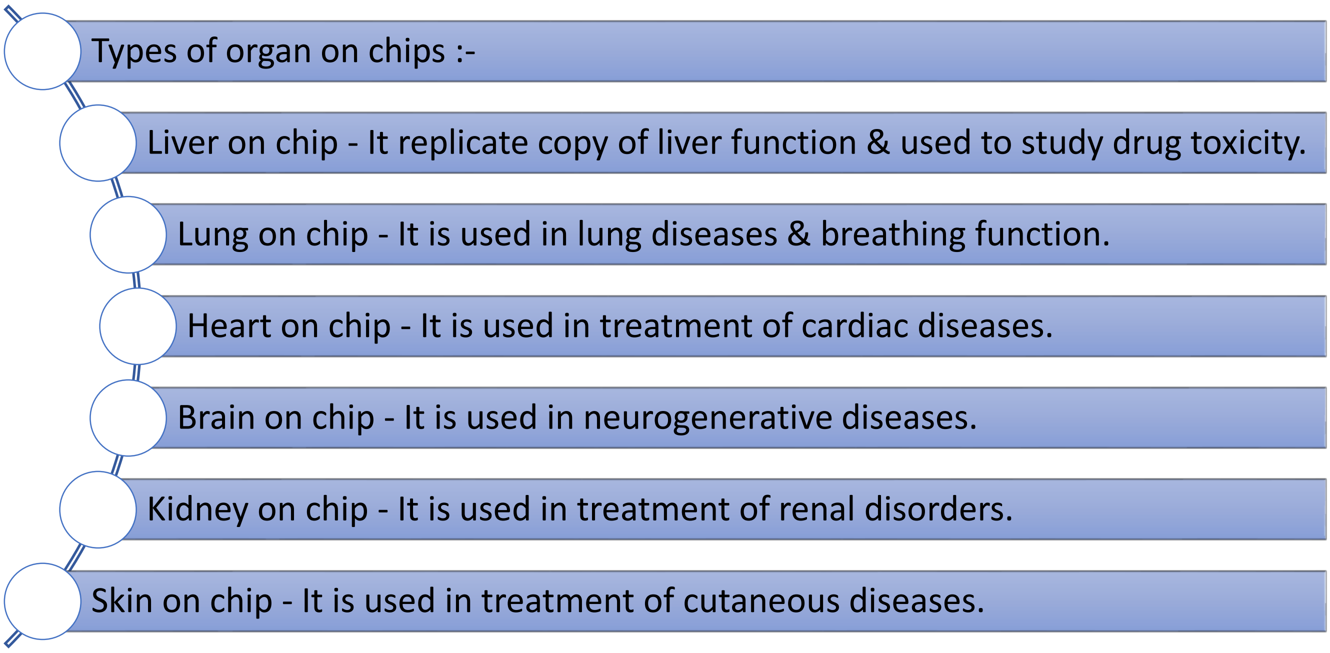

Figure 1: Types of Organs on Chip

Over the past few decades' synchronization between fields of Biology, Biotechnology, Stem Cell engineering and biomedical engineering have increased significantly and has let to formation of specifics organoid this has led to significant development and great new insight into this embryotic development like never before and if that was not enough have unleashed new potential in fields of regenerative medicine. Organoids are 3D structures and can mimic genetic structure hence allow us to custom tailor medicine for individual. Modern day boom in Organoid production is caused by Microfluidic technology. [2]

Machine Learning Models:

Trend of Machine learning started way before then people consider it. Trend of Machine learning started around 1950's coinciding with term "Artificial Intelligence "was a pivotal moment which changed the landscape of industry forever while reverting to topic of Machine Learning it can be broadly classified into 2 categories:

A) supervised machine learning
B) unsupervised machine learning

Now, in case of supervised machine learning we use labeled data and date is corresponded with target labels. In contrast unsupervised machine learning is focused on unsupervised and unlabeled data focusing on revealing patterns and structures. [2]

Machine learning in organoid model of human development:

Preliminary to Baltimore Deceleration:

Aim of First ever workshop for OI community was to address advancement is fields of Bioengineering and Stem cell culture and how they have increased complexity of already complex fields like "In-vivo-physiology and architecture" a platform famously known and referred to as MPS these developments unlock whole new horizon for modeling cognition as synthetic biological intelligence referred to ad O.I (Organoid Intelligence). It can be defined as interface between living tissue and computer technology where organoid is integrated into "organ on chip systems" and resulting data is interpreted. The very first Workshop was a pivotal point and served as establishing point for O.I as a recognized and emerging scientific discipline. The First workshop was held by John Hopkins University. [3]

Baltimore Declaration:

The very first Workshop for O.I was called upon between 22^{nd}-24^{th} February 2022 and its primary aim was to explore the potential of human brain braised culture to advance our understanding of human brain and it's functioning while unleashing a whole new generation of bio-computing hence they coined the Term Organoid-Intelligence (O.I) as it matches intention it's research and development approach aswell matches the name of very thing it seeks to replace A.I (ARTIFICIAL INTELLIGENCE) A.I is enablement of computers to replace thing which could be performed via human intelligence. [4]

M.L Assisted Neuro-Toxicity Prediction in Mid-Brain Toxicity:

We can consider organoids as extraordinarily complex multi-cellular proxies of human tissues which are currently rising the ranks as new novel tool to study neurodegenerative diseases such PD (Parkinson's Disease). P.D is a progressive neurodegenerative disease which cause degeneration of DAN'S (Midbrain dopaminergic neurons) meanwhile etiology of P.D itself is multifactorial after accumulation of sufficient evidence it can be suggested that combination and interaction of genetic risk variants, ageing, and environment leads to the development of PD. This was a necessity to highlight to identify which neurotoxin was the potential threat and causing the damage while prior to organoids major challenge was development of models that can replicate complexity of human brain but now stem cell derived organoids have solved that problem by showcasing there potential as promising disease models, by developing methods to automatically process HCI (high-content imaging) from organoids which was successfully demonstrated on organoids lead to refinement in pipeline for neurotoxin P.D organoid model. HMO's (Human midbrain organoids) to 6-OHDA to damage the dopaminergic system particularly ML) tools to analyze this in vitro toxicity assay. Using random forest (RF) classification, we assessed the neurotoxic effect of 6-OHDA on hMOs based on cellular features this allowed to develop better pipeline for treatment and predictions. It was concluded that DAN's within HMO'S showed signs of typical degradation. [5]

Organ Mimicking and its Application in pharmacy emphasis on Tumor on Chip:

Cancer is single handedly responsible for about 1/4[Th] of the death in world in present time chemotherapy is being used to treat cancer but drug resistance possesses a serious threat and this is where organoids and tumor on system comes to play. An Austrian research team developed a microfluidic chip model TOC to check efficacy of multifunctional lyposomes on target tumor. TOC itself consist of 3 sets of semicircular wells with varying cells this allows for us to facilitate for creation of tumor sphere for long term culture. Chip was used to evaluate tumor uptake rate and compared the obtained results with in vitro trials which revealed that TOC (TUMOR ON CHIP) were more accurate and even allowed to view 3d structures which allowed for more accurate and detailed sphere models. [6]

Table 1 : Literature Review

S. No.	Author	Paper	Year	Brief
1)	Giuliana Rossi	Progress and potential in organoid research	2018	Explains Emergence of organoids
2)	Huaiyu Shi)	Organoid intelligence: Integration of organoid technology and artificial intelligence in the new era of in vitro models'	2024	Talks about potential of organoid intelligence and organ on chips
3)	Itzy E. Morales Pantoja	First Organoid Intelligence (OI) workshop to form an OI community Itzy E. Morales Pantoja	2023	Steppingstone for Baltimore Declaration
4)	Thomas Hartung	The Baltimore declaration toward the exploration of organoid intelligence	2023	Baltimore declaration was a pivotal step in establishing O.I as next big thing in field of science
5)	Anna S. Monzel	Machine learning-assisted neurotoxicity prediction in human midbrain organoids	2020	Talks about establishing organoids as model for predicting neurotoxicity
6)	Yueyang Qu	Organ mimicking technologies and their applications in drug discovery	2023	Discusses about various implications of organ on chips
7)	Zakiya Gania	Strategies for Generating Human	2022	Discusses various drawbacks

		Pluripotent Stem Cell-Derived-Organoid Culture for Disease Modeling, Drug Screening, and Regenerative Therapy		
8)	Varvara G.	Advantages and Potential Benefits of Using Organoids in Nanotoxicology	2023	Discusses aspects of organoids and their potential advantage in field of Nanotoxicology
9)	Lena Smirnova	Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish	2023	Compares difference between O.I and Human intelligence
10)	Takanori Takebe	Organoids by design	2019	Discuses organoidgenesis and its mechanism
11)	Zixuan Zhao	Organoids	2022	Discusses problem in embryogenesis of organoid culture
12)	Chen Liu	Drug screening model meets cancer organoid technology, Translational Oncology	2020	Discusses about drug screening of cancer.
13)	Zahra Davoudi	Gut Organoid as a New Platform to Study Alginate and Chitosan Mediated PLGA Nanoparticles for Drug Delivery	2021	Discusses use of organoid especially epithelium organoid in study for nanoparticle drug delivery
14)	Mu Seog	A brain metastasis model for breast cancer using human embryonic stem cell-derived cerebral organoids	2022	Discusses role of BC-COS (Breast cancer cerebral organoids)
15)	Kim Hyung -Jun Park	Lung Organoid on a Chip: A New Ensemble Model for Preclinical Studies	2023	Discusses how Lung Organoid on a Chip works in diagnosis.
16	Geon Yoo	New Insights into the Clinical Implications of Yes-Associated Protein	2021	Discusses use of YAP in Lung Organoid

		in Lung Cancer: Roles in Drug Resistance, Tumor Immunity, Autophagy, and Organoid Development		
17	Giulia Spagnol	Patient Derived Organoids (PDOs), Extracellular Matrix (ECM), Tumor Microenvironment (TME) and Drug Screening: State of the Art and Clinical Implications of Ovarian Cancer Organoids in the Era of Precision Medicine	2023	Discussed how PDO's can be used to enhance preclinical drug delivery / trials
18	Lisa Liu	Patient-derived organoid (PDO) platforms to facilitate clinical decision making	2021	Discusses advancements in radiotherapy via use of organoids
19	Lena Smirnova	[Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish]	2023	Draws a comparison between Human Brain and O. I
20	Claudia Corrò	A brief history of organoids	2020	Brief History of Organoids

Drawbacks in PSCs Derived-Organoids Culture (Maturation):

In present time several methods are being used to produce psc derived organoids which include but are not limited to nephron filtration beating cardiac organoid, insulin-secreting organoid, or organoids with drug metabolism capability yet it is a challenge to produce functional organoids as the psc derived organoids are relatively immature in expression profile of fetal or progenitor cells rather than adult tissue cell types apart from that these cells lack in architectural and functional characteristics compared to their actual counterpart . [7]

Organoids Benefits in Toxicology studies:

It generally considered that Toxicology research covers an extensive research and field that generally consist of a broader perspective as pre-clinical studies requires an extensive study on toxicity of drug. Assessment of organoids heterogeneity is not performed sometimes hence research is generally considered to be qualitative in nature. Various studies have shown and characterized toxic effects in organoids quantitively relying on definition provided by Lancaster and Knoblich which consist of a quantitative description of structures and states of different cell types. One of key advantages of organoids is that when compared to preclinical models they have higher success rate as 90% of preclinical model fails. [8]

Human Brain vs Machine:

Human brain is slower at processing any arithmetic data when put against machines but when they are superior to machines, they surpass machines by miles and fields in which they are far superior to Machines are: -

- Processing complex information
- Decision making
- Abstract-reasoning
- Can do analysis or comprehend incomplete data sets

In 2013 it was observed

Table 2: Human brain VS Machine

HUMAN BRAIN	MACHINE
Processing capacity is 1 exaflop and analyses in 20 watts	Processing capacity is 1 exaflop (with 50 GPUS) and needs 10^{10} and take up to 4 weeks
Approximately 2500 terabytes storage capacity	Storage capacity can vary by machine, but significantly lower
It takes 40 min and 1 second (1% replication) for processing	It takes up to 4 weeks for full replication for processing
It is far more efficient	It is less efficient than human brain
Human brain can learn new information by just seeing it once, while artificial systems need to be trained hundreds of times with the same pieces of information to learn them.	To train "Alphago" it took 4 weeks and about 50 GPUS

This has led to high expectations from brain directed computing to replace silicon-based computing. [9]

Organoidgenesis:

The study and knowledge of organogenesis gave rise to organogenesis that's why nowadays organoids have become a comprehensive substitute for human organs. Organoidgenesis can mainly be divided into 8 stages:

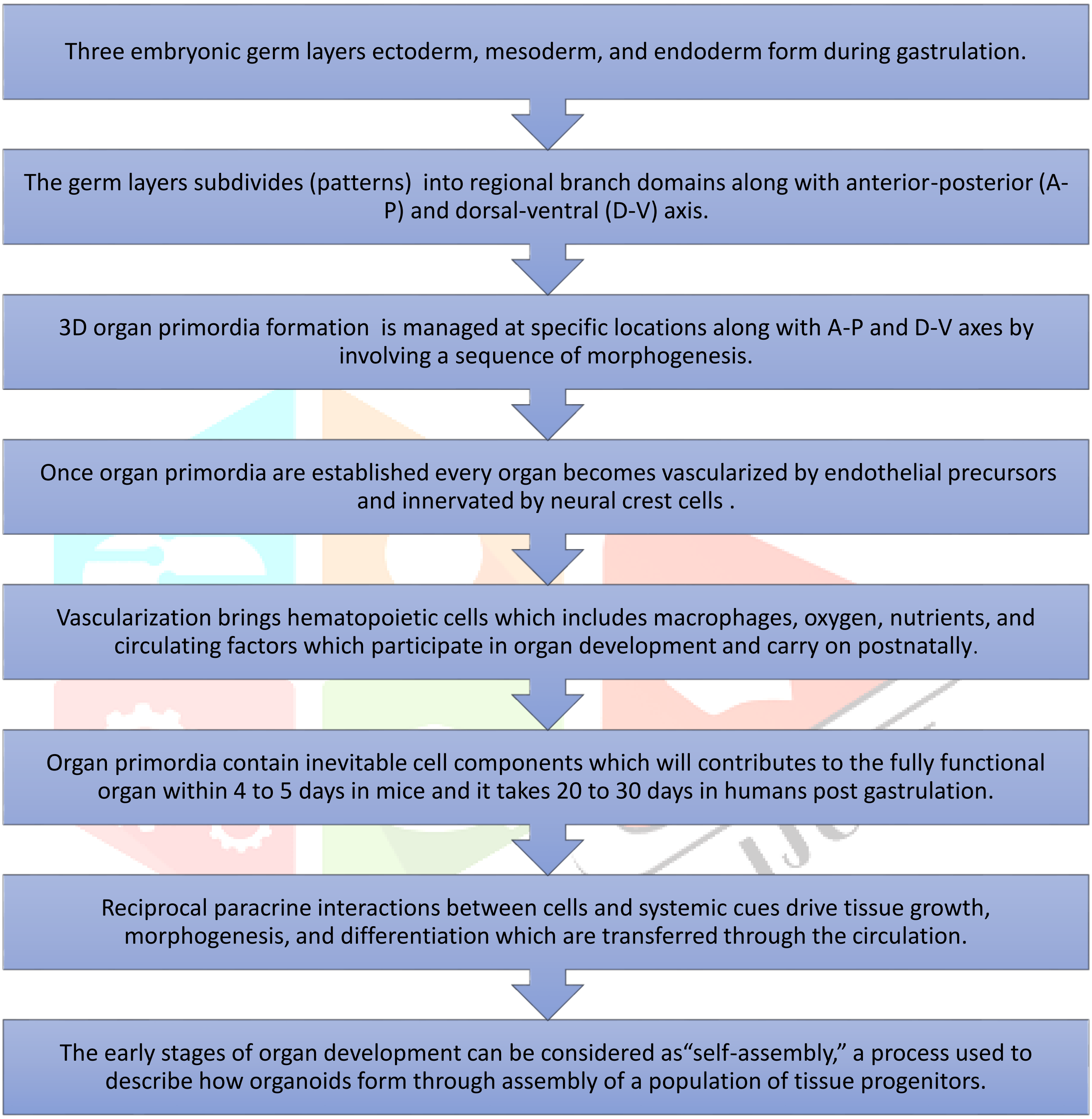

Figure 2: Organoidgenesis

Organoid Engineering:

It is a known fact that stem cell is critical in maintaining organ size, structure and function through cellular renewal, migration, differentiation, and apoptosis. Stem cells are confined in an in a fixed microenvironment defined as Stem cell Niche to regulate the very fate of organoid, stem cell niche is defined as A specific tissue microenvironment where stem cells both reside and receive stimuli that regulate cell fate. Now as organoid is a self-organized 3D tissue that can typically be derived from stem cell, and they replicate exact functionality and structure of a biological organ. Organoids can be derived from iPSC (induced pluripotent stem cells) or TDC's (tissue-derived cells) organoids cultures are used for a wide variety of applications and operations which includes i) Drug Discovery, ii) Personalized companion diagnostics, iii) cell Therapy.

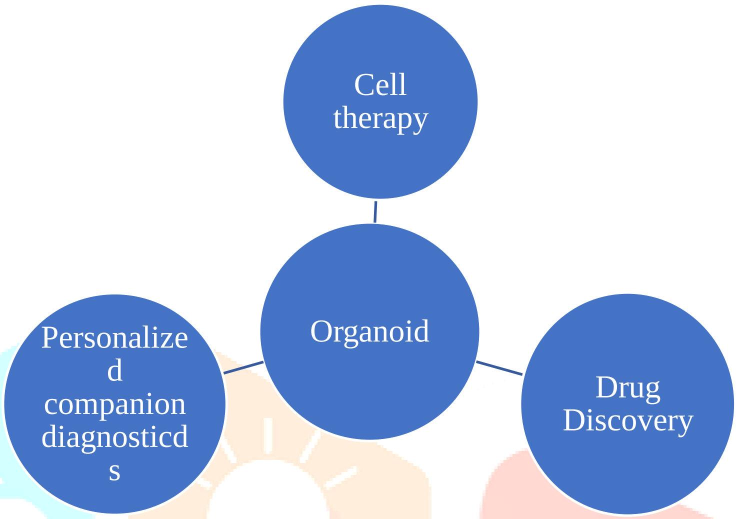

Figure 3 : Uses of Organoids

Even after this organoid are not perfect as they struggle to exhibit significant homogeneity instead, they showcase t significant heterogeneity and variable complexity in their cellular composition and can undergo poorly controlled morphogenesis in self-assembly process and often lack stromal vascular and immunological component Hence there is a great need to improve organoid culture. [11]

Cancer organoid on a chip for drug screening

A cultural tool of cancer organoids on a chip could be allowed to emulate the physiological environment of tumor cells as much as possible. The components of vascularized tissue, lymphatic vessels, and immune system can be produced by Organoid-on-a-chip system. It also simulated the characteristics of microcirculation in which, fluid outflow brought nutrients and drugs for tumor cells at the end of the capillary artery with net absorption of liquid at the venous end. A 3D microfluidic culture device provided by micro-physiological system (MPS) which is similar to the sophisticated living environment of lung cancer, which could complete drug screening in one step. The organoid cultured in MPS have better stemness than the traditional organoid grown in the matrix. The organoid-on-a-chip was costly , it was one of the most imitating devices for tumor microenvironment at present.

Organoids on a chip could automate the cultivation of tumor organoids and complete the drug screening of tumor organoids on a chip, which could save the human resources and reduce human operational error. Without monotonous manual procedures, human brain organoids on a micropillar array expanded its application in developmental biology, drug testing, and disease modeling. If any patient had multiple tumors or metastasis tumors, the chip could complete the culture of multi-site tumor organoids. Results of organoid drug screening in a chip was closer to the clinical tests than previous tumor models. In a lung cancer organoid chip, lung cancer cells invaded vascular channels and migrated to the distant liver, bone, or brain chip; metastatic diffusion could be detected, and the growth of metastatic lesions could be identified and studied. Comparable, Sun ghee Estelle Park et al. proposed that organoid-on-a-chip could emulated the microenvironment of tumor, carry out drug screening mechanically on a large scale, and realize the interaction of multiple organs and tissues.[12]

Gut Organoid potential as chitosan meditated PLGA nanoparticles for delivery:

IBD also referred to Crohn's Disease and Ulcerative Colitis, Involves chronic inflammation of intestines. Commonly used treatment used is 5-aminosalicylic acid (5-ASA) which can cause various side effects like due to its high dosage. To solve this issue rug encapsulation in nanoparticles like poly-lactic-co-glycolic acid (PLGA), offers a promising alternative by reducing side effects & enhancing targeted delivery. PLGA nanoparticles can be coated using polymers like alginate, which has a negative charge, or chitosan, which is positively charged, to improve targeting and uptake at inflamed sites. This study was conducted using murine-derived intestinal organoids as a model access to the transport of these directly charged PLGA nanoparticles organoids which mimicked intestinal epithelium were used to evaluate nanoparticles and drug efficiency. [13]

USE OF BCOS:

Implanting of breast cancer cells which are expressing eGFP on 70-day-old Cos produced BC-CO'S. Each CO with 2×104 cancer cells in 200 µL of CO medium in a single well of a 96-well U-bottom ULA plate were mixed and then centrifuged them at 1,000 rpm for 3 minutes for a short period of time. Culture plates were incubated for 12 hours in a 5% CO2 humidified atmosphere. After the aggregation and adhesion of cancer cells to the CO surface (forming a BC-CO), each BC-CO were transferred into a single well of a 24-well flat-bottom ULA plate containing 500 µL of CO medium, followed by incubation for an additional 24 hours for stabilization. Finally, moved the BC-COs into a 125 mL spinner flask containing CO medium and adapted cells were harvested using FACS. [14]

Lung-on-a-chip

Lung is an essential organ in the body that helps in constant breathing, with micro vessels flowing beneath the surface. The three-dimensional (3D) cell culture systems have many advantages compare to two-dimensional (2D) cell culture systems. They stimulate responses to stimuli, the expression of genes and proteins, and enhance cell function. Organ-on-a-chip models provide a more realistic emulation of the in vivo environment than the static trans-well condition, which lacks relevant mechanical properties. Mechanical stretching of epithelial cells can be generated by Lung-on-a-chip devices by producing negative pressure in the top channel and dynamic fluid flow in the bottom channel. A microfluidic device constructed on a co-culture system of epithelial and endothelial cells illustrate inflammation-induced thrombosis when it exposed to external stimuli, such as lipopolysaccharide. Lipopolysaccharide endotoxin indirectly stimulates intravascular thrombosis and that lung-on-a-chip models can be a novel methodology for in vitro analysis of potential drug candidates.

Main function of the lungs is exchange of gases between oxygen and carbon dioxide. This function of lungs can be monitored through the chip with a sensor system which measures hypoxia in real time along with the lung disease process.[15]

Role of Yap in Lung Organoid:

Organoids can efficiently recapitulate 3D structure and function of any organ many researchers and scientist and industrialist think that organoid abilities are most refined and significant in scientific advancements and show potential for various clinical applications. Organoids are generally Laminin-rich extracellular matrices, even though these matrices mimic the complexity extracellular TME yet their growth factor have not been accurately justified/defined and absence of immune cells and vasculatures is a major drawback it can be remedied through culturing of long organoids which have some immune cells and mesenchymal cells.

Long Organoid are formed from stem cell or progenitor cell and can be classified into 2 types

1.Airway organoids

2.Alveolar organoids

Airway Organoids	Alveolar Organoid
• Basal cell derived	• Type II pneumocytes Derived

YAP is a Mechano-sensitive Protein and plays a decisive role in cell proliferation and differentiation and multicellular asymmetric structure involves the self-organization.[16]

PDO's THE FUTURE OF PRE-CLINICAL PHASE:

PDO'S are instantly becoming the stepping stone in the fields of preclinical model for personalized medicine. In the previous decade there has been an astronomical increase interest to in tailoring personalized cancer therapy for each patient and whenever we refer to precision medicine we inherently or it is applied that we are referring to genomics. It has been proposed that functional precision medicine based on alteration has been proposed as a more robust alternative this was earlier described by Friedman. It can be considered that PDO's can provide an unpresented opportunity to enhance preclinical drug delivery. [17]

Advancements in radiotherapy via Organoids:

Recent advancements in field of radiotherapy have only been possible due to PDO's. Yao et al. had studied the ability of organoids to project drug response to chemoradiation rectal cancer. Results showed were impressive they showed 85% result accuracy which was highly matched to the patients. [18]

[Patient-derived organoid (PDO) platforms to facilitate clinical decision making, Lisa Liu]

Human Brain vs Machine:

Human brain when put against machines are slower at processing arithmetic data but when they surpass machines, they surpass machines by miles and fields in which they are far superior to Machines and surpass them are: -

- Processing complex information
- Decision making
- Abstract-reasoning
- Can do analysis or comprehend incomplete data sets

In 2013 it was observed that it took supercomputer about 40minutes and 1second to replicate 1% of Brains processing it is estimated Brain has capacity approximately of 2,500 Terabytes. For human brain to analyses 1exaflop it takes 20 watts while for computer it needs 10^{10} energy and can take up to 4 weeks to perform same task thus clearly signaling Brain is Far more efficient when compared to machines to put it in reference to train "Alphago" it took 4 weeks and about 50 GPUS. This has led to high expectations from brain directed computing to replace silicon-based computing. [19]

Brief History of Organoids:

It can be said that organoids were derived from cell aggregates. 3d culture system was established by the suspension culture to circumvent contact with plastic dish directly. This can be assured by using scaffold or scaffold-free technique. In year 1907 Henry Van Peters Wilson first described the very first attempt at an in-vitro organism which was followed by differential adhesion hypothesis given my Malcolm Steinberg in year 1964 as years progressed in 1987, scientists began to improve cell culture conditions by simulating the in vivo microenvironment.

Ethics:

Organoids are organ tissues models that theoretically can take biomedical research and clinical care into infinite depths for their merit and utility, however with this advancement, a major governance and ethical issues arise, such as emotional attachments, which hence requires adequate and informed consent. Some organs, such as brain organoids add complexity to structure.

The framework of "mindful innovation" proposed here stands on three pillars-exploration, engagement, and demarcation. Societal attitudes will play a pre-regulatory role in the way human-centric tissues & will handle any possible ethical implication. These should work effectively to address the entangled ethical problems in the study of neuropsychiatric disorders and therapies, bearing in mind that organoid technology rises to the challenge of presenting an extraordinary uniqueness to this work. [19] [20]

Conclusion:

From this we could withdraw that organoids will make a significant impact on various fields such as Pharmacy, Biotechnology and Biomedical engineering and it is also leading towards development of new Organoid Computing which can be the next big thing and can replace ai while not only being better than it but while being significantly better than it. Organoids also possess power enough to revolutionize the field of research especially cancer research as organoids have led to development of system on chips like lung on chips, epithelium on chip, brain on chip and Tumor on chip. These can be used to study organ systems in depth and tissues in depth and do not degrade making them easier to study while can also be used to do cancer research and making it easy as the chip can easily be paused in particular stage of cancer making it easy to inspect and showcase development of cancer while also increasing efficiency and need for in-silico analysis and can for a good alternate animal study

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