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Pancreas 3D Organoids: Usage and Availability for Personalized Drug Screening

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1 Abstract

Background: Pancreatic organoids are a rapidly advancing field of research with new discoveries being made every day. A literature analysis was conducted to answer the question about the usage and availability for personalized drug screening of pancreatic 3D organoids, especially for the field of surgery.

Methods: A literature search in PubMed was conducted to identify relevant articles from the past 5 years using the keywords “pancreatic organoid”, “organ-on-a-chip” and “pancreatic chip”. Only English articles were included into this literature review, which was done in a non-systematic way. Articles were chosen without a predetermined protocol of inclusion and were based on the aim of the review.

Results: There are many promising innovations in the field of 3D cultures. personalized drug screening in particular holds great potential for surgical application, i.e a more personalised treatment approach could increase resectability of pancreatic cancer. Another area where organoids will have a major impact in the future is the personalised cultivation and evaluation of pancreatic islets with organoids. Ongoing research shows promising new advantages for islet transplantation in patients with type I diabetes mellitus.

Conclusions: Although there are already promising approaches further research has to show whether these advantages can also be applied to clinical practice. It is to believe that organoid systems will provide never seen possibilities to improve human live in the future.

Keywords: Pancreatic organoids[1], organoid[2], Organ-on-a-chip[3], PDAC[4]

2 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most lethal types of cancer and accounting for about 93% of all cancers arising from the pancreas(1,2). Although the survival rate increased during the last years, without surgery the 5-year survival is still below 10%(3). The only way to increase the cure rate to 20-25% is currently surgery combined with chemotherapy(4). Currently, the most commonly used chemotherapies are either gemcitabine and nab-paclitaxel or FOLFIRINOX, used singly or in combination. These treatment options can increase the survival rate of patients with early-stage pancreatic cancer but are not sufficient for late-stage cancer(5). Despite a high number of promising new drugs in preclinical trials, the molecular heterogeneity among PDAC patients limits their effectiveness(6). To identify which therapy could be most beneficial to every individual, and if surgery has any outstanding advantage, there needs to be a more personalized approach.

In recent years, patient-derived 3D organoids have exhibited advanced research. They can be replicated *ex vivo*, allowing the study of cancerous behavior to medical treatment and patient specific cancer properties. Organoids are progenitor cells with the phenotype matching the original tissue. Pancreas organoids can be initially cultured from resected patient tumor samples or even from fine needle aspiration. The tissue-derived stem cells can organize themselves into sphere-shaped organoids, which are mainly composed of epithelial cells. However, since pancreatic organoids are mainly composed of epithelial cells, they lack the tumor microenvironment (TME) of the body, which is primarily composed of fibroblasts and immune cells(7). Therefore, several different TME-modulating agents are being evaluated, trying to mimic the *in vivo* TME as precise as possible(8).

In a society in which autoimmune diseases are becoming more and more important better therapies and treatment approaches could be of crucial importance. One of the main problems of the endocrine pancreas is type 1 diabetes mellitus (T1DM), also called insulin dependent diabetes. T1DM is the result of immune mediated destruction of the beta cells in the endocrine pancreas(9). Traditional therapy is based on exogenous insulin, which has shown to be effective. Sadly, exogenous insulin mimics the normal beta cells poorly and hypoglycemic episodes are still a relevant risk factor(10). Allogenic islet transplantation has shown to be a safer alternative to external insulin therapy. However, one of the main issues in allogenic islet transplantation is the immune compatibility and the amount of suitable immune-matching donors. therefore, alternatives are being explored(11). Pancreatic organoids are thought to have a great impact on T1DM treatment in the upcoming years based on the work done with embryonic stem cells (ESC) and pluripotent stem cells (PSC)(10).

Within this review, the current literature is being presented and investigated. Especially publications from the last five years. In addition, the present state of organoid research will be discussed. The focus will be on the questions: i) what are the main advantages of organoids?, ii) how can we use pancreatic 3D organoids for personalized drug screening?, and iii) what are the greatest advantages for surgical use?

3 Methodology

A literature search in PubMed was conducted to identify relevant articles from the past 5 years using the keywords “pancreatic organoid”, “organ-on-a-chip” and “pancreatic chip”. Only

English articles were included into this literature review, which was done in a non-systematic way. Articles were chosen without a predetermined protocol of inclusion and were based on the aim of the review.

4 Culture Types

Since the first cell culture was established by Harrison in 1907(12) their development has progressed steadily. This enabled the proper investigation of the mechanisms of formation, function and the pathology of organs and their tissues. Until today 2D cell cultures are the most common cell culture method being used. In a 2D cell culture system, cells are grown as a monolayer in a culture flask or flat dish embedded into extracellular matrix (ECM). Furthermore, there is the suspension cell culture method, in which single cells or cell aggregates multiply in a nutrient fluid until further processing takes place. They do not represent the normal *in vivo* cell environment since they do not mimic the natural structures of tissues found in the body. Therefore, cell-to-cell and cell-to-ECM interactions are not comparable to those occurring *in vivo*. Because of this circumstance, predictive value of 2D culture is limited for drug discovery, testing or research outcome. Another disadvantage is the unlimited access to all ECM ingredients, which is not representative for tumour cells, i.e. *in vivo* cancer cells have variable access to these ingredients, due to the architecture of the tumour(13). Based on all these concerning disadvantages, there is a need for alternative culturing methods which would be better able to mimic the ECM. The development of 3D cultivation methods shows great potential for overcoming these challenges.

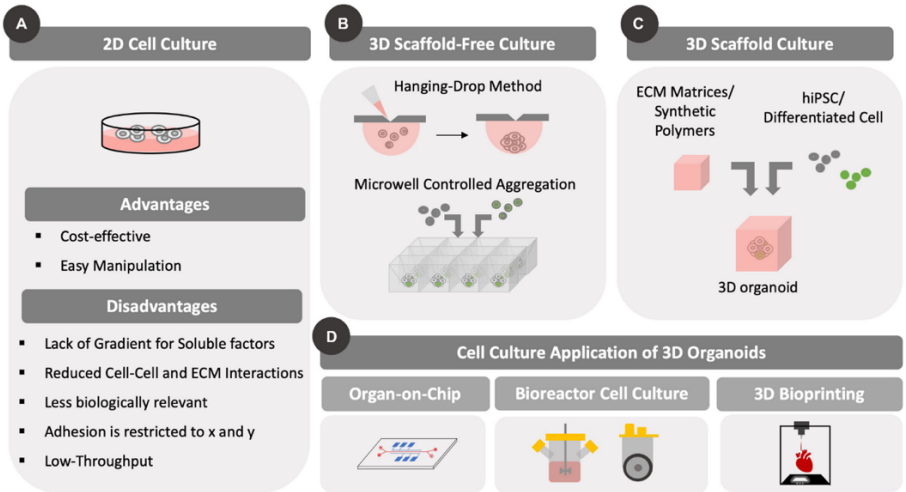

Figure 1: Different types of cell culture formats. Adapted from Gopal S et al. A) advantages and disadvantages of 2D culture. B) 3D cultures produced scaffold-free with the hanging drop method or microwell controlled Aggregation. C) cultures produced with scaffold like

extracellular matrix (ECM) matrices together with human induced pluripotent stem cells (hiPCS). D) different culture applications of 3D organoids(14).

3D cell culture is the next step in cancer research. It allows cells to grow in any direction and interact with the ECM resulting in growth that is not limited to the 2D culture medium structure of classical cultures (15). 3D culture methods can be differentiated in many ways. One of them is to divide them into scaffold 3D cell cultures, and scaffold free cell cultures. The main advantages of 3D cultures are that they form complex systems, show significantly better cell-to-cell and cell-to-ECM interaction, while also creating "niches". Cells can obtain signals from the surrounding environment, as it also happens *in vivo*. Another improvement is the maintained characteristics of the cell. In 3D environment, the cell can retain its unique morphology and mode of division, leading to a more diverse production of phenotypes. These exclusive properties allow a more intense study of healthy tissue-derived cultures for regenerative medicine, cancer research and drug testing, or testing of the effectiveness of cell response to radiation. In addition to that, 3D cell cultures reduce the amount of animal testing and is therefore more ethical(13,16). There are several types of 3D cultures. The simplest are aggregates, which are mainly a collection of cells. Aggregates can be cultured into spheroids. Spheroids are simple cell clusters obtained from cell line monocultures. They do not require a scaffold and can be cultured from various tissues to mimic *in vitro* behaviour to some degree. However, they do not form complex structures. Cells will be either located on the outside of the cluster, where they are well oxygenated, or buried on the inside, often resulting in hypoxia and eventually in cell necrosis(17).

The next step in 3D cultivation are organoids. The meaning of the term "organoid" has a lot of different definitions. In this article we will use the definition from Laura D Wood: that organoids are multicellular units which have been isolated from a tissue sample. These samples can be studied either directly or after passaging(18). Organoids are progenitor cells that can mimic physiological and pathological processes in the human body. It is possible to produce a variety of different organs as organoids, including small and large intestine, pancreas, kidney, brain, liver and many more. They reflect the anatomy of the cultured organs quite accurately by forming multicellular structures. In contrast to spheroids, organoids can be propagated for long term *ex vivo* study(19). Although cultivating organoids offers great potential, it is not an easy task. Organoids can be derived from a variety of cells, but they must be carefully isolated and supplied with the right nutrients and growth factors. These cells can be obtained from

embryonic stem cells from human or mouse embryos. They are first expended and, in the end, subsequentially differentiated in a multistep protocol in ECM. Together with natural ECM, the most widespread type is Matrigel purified from Engelbreth-Holm Swarm mouse sarcoma. In the end resulting in a fully differentiated organoid(16). Specific growth factors and differentiation modulators are added to the growth media for differentiation and controlled growth(20). Also, they can be gained from induced pluripotent stem cells (iPSC) or adult stem cells (ASC) taken from normal or cancerous tissue. Tissue derived stem cells are able to reorganise themselves into organoids, mostly composed of epithelial cells(21). The cell source, the culturing media and the ECM should be chosen according to the organ, and the result which is indented to be achieved. Compared to other organs such as the liver, the pancreas only has a very limited ability, or none at all, to regenerate, neither in homeostasis nor when injured. This circumstance complicates the production of pancreatic organoids(22), this is why iPSCs are often used to achieve good results. IPSCs are complex structures and do often contain other cell types like, endothelial, epithelial and mesenchymal cells. This favours the growth of organoids, with limited regeneration capacity(23).

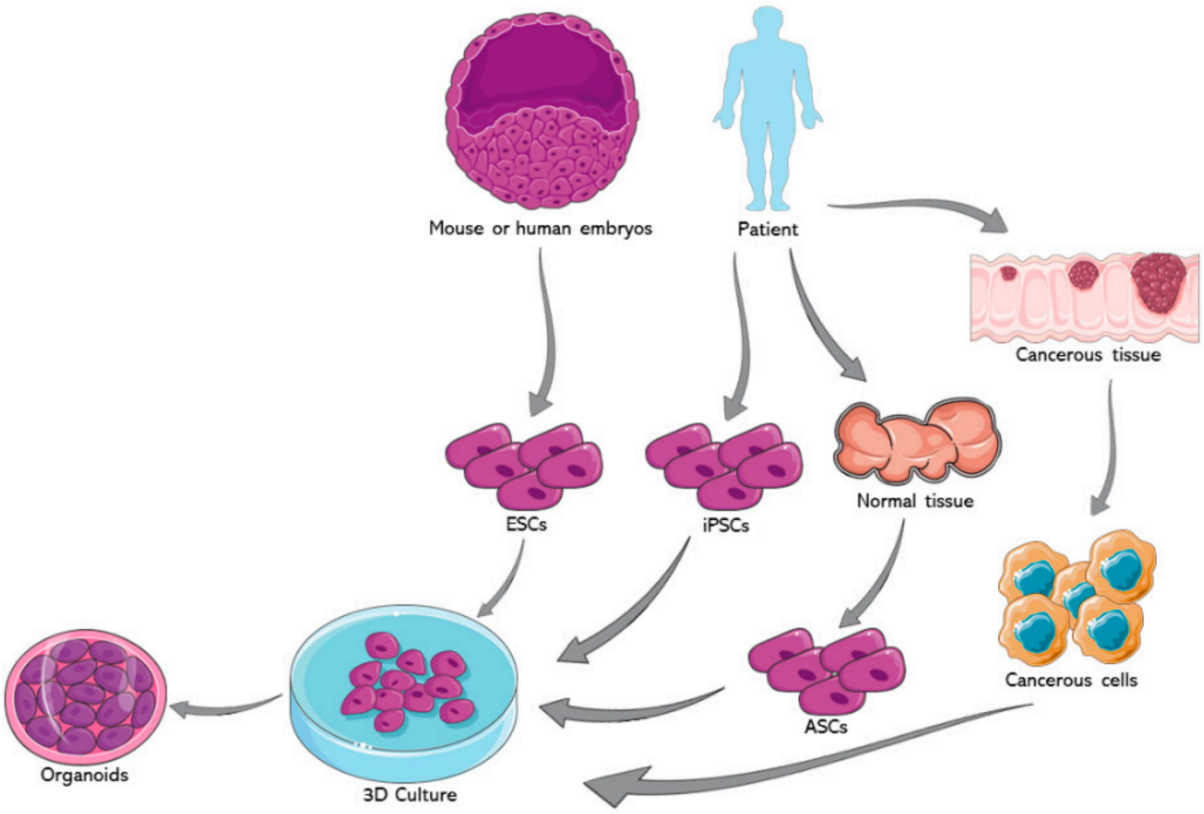

Figure 2: Generation of organoids from different types of stem cells. Adapted from Joseph Azar et al. Organoids can be generated from induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs) and patient-derived adult stem cells from normal and cancerous tissues (ASCs)(24).

Even though conventional organoid types are very similar to in vitro organs, it remains difficult to precisely control their development. Another limitation is the inability of conventional organoids to provide a complex TME. For this reason, organ-on-a-chip (OOAC) methods have been developed. These combine organoids with microfluidic systems to provide better interaction. As described by Qirui Wu et al.(25), OOAC cultures have the ability to mimic the physiologic organ much better than other culture types. By adding a microfluidic channel network, it is possible to influence important parameters of the culture such as concentration gradient and tissue-organ interactions. The design is different depending on the organ studied, but every device contains chambers for cells to grow while constantly being perfused by culture media. This does not only allow for better control, but also holds the ability to study the interaction of different organs in one culture by including elements of the immune, nervous and vascular system on to the chip; hence, producing a multi-organ-on-a-chip model(26).

The design of the organoid culture does depend on the function of the organ and therefore needs its unique system to mimic the TME. The pancreas consists of an exocrine part responsible to produce digestive enzymes, and an endocrine part which mainly deals with glucose regulation. The endocrine pancreas is organised in highly vascularised clusters called Islets of Langerhans. These islets hold several cells responsible to produce Insulin (β cells), Glucagon (α cells), somatostatins (δ cells) and pancreatic polypeptide (γ or PP cells)(27). On the other hand, the exocrine part of the pancreas is composed of a complex tubular network with serous acinar glands which accounts for up to 98% of the pancreatic tissue. These acinar cells are serous secretory cells producing digestive enzymes like pancreatic amylase, trypsin, chymotrypsin, carboxypolypeptidase, pancreatic lipase, cholesterol esterase and nucleases. These enzymes are secreted into the duodenal part of the digestive tract via the ductal system. The ducts are lined by pancreatic ductal cells which also secrete bicarbonate for neutralisation of stomach acidity(28).

Table 1: Comparison between different culture types.

	Patient-derived cell lines	Patient-derived xenografts	murine-derived organoids	Patient-derived organoids	Patient-derived 3D spheroids
Cost	€	€ € €	€ € €	€ €	€ €
Success rate	med	med	med	med	med
Speed	++	+	+	++	++
Reproducibility	++	+++	++	++	+
Predictive value	+	+++	++	+++	+
Throughput	med/high	low	low	med	med
Availability	+++	++	++	+	++
Comparability *	+	++	++	+++	++

** Comparability between culture and patient*

5 Organoid Applications

Organoids are a field of medicine holding a high potential for the future. There are a lot of different application possibilities for organoids under research now, which are opening many other options not yet discovered. There is a lot of potential, especially in the field of personalized medicine.

5.1 Personalized drug screening in pancreatic cancer

Pancreatic cancer, and especially PDAC, has a high heterogeneity causing the treatment to be quite broad, and with many side effects and limited results. And although a rather uncommon cancer type, PDACs prevalence is increasing by 0,5% to 1,0% annually. Moreover, there is narrow ability for effective screening, accounting both for a late diagnosis in advanced stages of disease and consequently why the majority of tumor are unresectable. Leaving only neoadjuvant chemotherapy as an option to treat and reduce the tumor size allowing surgical interventions. Therefore, effective treatment is very important(29). Successful personalized drug sensitivity testing is one option to optimize treatment strategies and reduce the tumor to a resectable size.

At the moment, the most effective approach for neoadjuvant treatment involves two different treatment regime combinations. The first one is FOLFIRINOX, which is a combination of four drugs: folinic acid (leucovorin), fluorouracil (5-FU), irinotecan (Camptosar) and oxalipatin (Eloxatin). The second one is a combination of gemcitabine and nab-paclitaxel. These two regimes have the potential to increase the resectability to 68%(30). Still, the resectability remains at a low level. Especially borderline resectable PDAC have a recurrence rate after neoadjuvant therapy followed by surgery of about 80%(31). There have been multiple targeted therapies under evaluation showing some positive results in the beginning. Sadly, none of them seem to show the desired results in further trials(32). This is partly explainable by the high heterogeneity of pancreatic cancer. At the same time, there are only few patients who benefit from these new therapies and too few have been included in trials to get desired results. Especially in patients with advanced stages, neoadjuvant treatment with broad spectrum drugs can be toxic for the recipient(33). To lower the risk factors and provide higher quality treatment, establishing patient's organoid together with drug testing could be a promising way. Unfortunately, patient-derived organoids have not yet arrived satisfactorily in everyday clinical practice. Susan Tsai et al(34). developed and characterized pancreatic cancer organoids and multicellular organotypic co-culture models with the aim of demonstrating the general applicability of organoid cultures in clinical practice. They were able to show that it is possible to reproduce human pancreatic cancer in such a way that they can be used for research purposes. Furthermore, the study shows that it is possible to create stromal and immune components by using primary organoid co-cultures which makes them even more significant for research and sensitivity testing. The biggest challenge is to produce organoids that reflect the *in vivo* TME as close as possible while at the same time being rapidly established to fit into a clinically relevant timeframe. Since PDAC is a very fast-growing tumor, speed is of utmost importance. Traditional sensitivity testing includes patient-derived-xenografts (PDX), which includes implanting tumor samples into mice either ectopically or orthotopically. These xenografts do recapitulate the TME better than 2D cultures(35), but the average time to establish them is at least 40 days until tests could be done, while getting results is being very time-consuming and costly. A study carried out by Frappart et al.(36), compared PDX tumor to PDX organoids together with patient derived organoids with a small-scale sensitivity testing. Concluding that organoids demonstrate the same feasibility for sensitivity testing as PDXs. Moreover, organoids are more cost-effective and faster in production. In addition, organoids have higher predictive value because they do not have unwanted interactions between xenograft and animal. Even though we urgently need new therapies, we also need the biomarker to guide the treatment.

Hervé Tiriac et al(37). generated a patient-derived organoid library which is able to summarize mutational spectrum and transcriptional subtypes of primary pancreatic cancer. Furthermore, they defined new oncogenes and continued analyses showed unique clusters, which could be used to improve treatment. A case study was performed which predicted improved response for patients due to organoid-based gene expression signatures. Finally, Tiriac et al. propose, that it is possible to predict clinical response by combined molecular and therapeutic profiling which could result in a more accurate therapy. Other research groups have also carried out similar projects and have come to similar results. It is possible to find concordance between patient derived organoids and thus enable a more targeted therapy(38).

Especially in the field of OOAC research, there is great potential for sensitivity testing and therefore for a more personalized treatment approach, i.e. several OOAC platforms have been developed in recent years with the objective of sensitivity testing. Fook Lun Lai et al(39). connected multiple cell types (patient-derived pancreatic organoids, human fibroblasts, and endothelial cells), placed on a flow controlled OOAC platform and ascertained drug sensitivity. Their results demonstrate that the value of a perfusable vascular network showed better reaction for drug screening comparing it to stiffened matrix. This presents the high value of those networks, and highlights another already mentioned advantage of OOACs, i.e., the ability to culture a variety of different cells on one platform. However, this is only one advantage of OOAC models. Zhang et al(40). introduced a scalable multiplexed drug-combination screening platform which uses 3D microtumor models. They produced a chip with a “Christmas tree mixer” structure with the ability to provide a large drug concentration range for screening. This high-throughput combination screening scheme has the potential to test nearly any number of drugs and their pairwise combination with multiple logarithmic mixing ratios. To test for efficacy and applicability of this chip, a 8-drug combination chip was implemented. The drug combination screening was performed with breast and pancreatic cancer cell lines. For pancreatic testing MIA PaCa-2 cell lines were used. Seven chemo-drugs and one media only as a positive control were screened, resulting in 172 different treatment settings. While testing cisplatin, docetaxel, doxorubicin, gemcitabine, irinotecan, oxaliplatin and fluorouracil as a single drug or in different combinations, they saw a few treatment combinations which showed higher effectiveness compared to a single drug therapy. Even though this study was based on MIA PaCa-2 cell lines, the relevance of OOAC can be inferred i.e., the possibility to test not only single drugs, but even interactions of several drugs, shows great potential. The next step would be testing with patient samples and adding more cell types like stroma cells for increased cell-to-cell interaction with the goal of achieving even greater *in vivo* similarities.

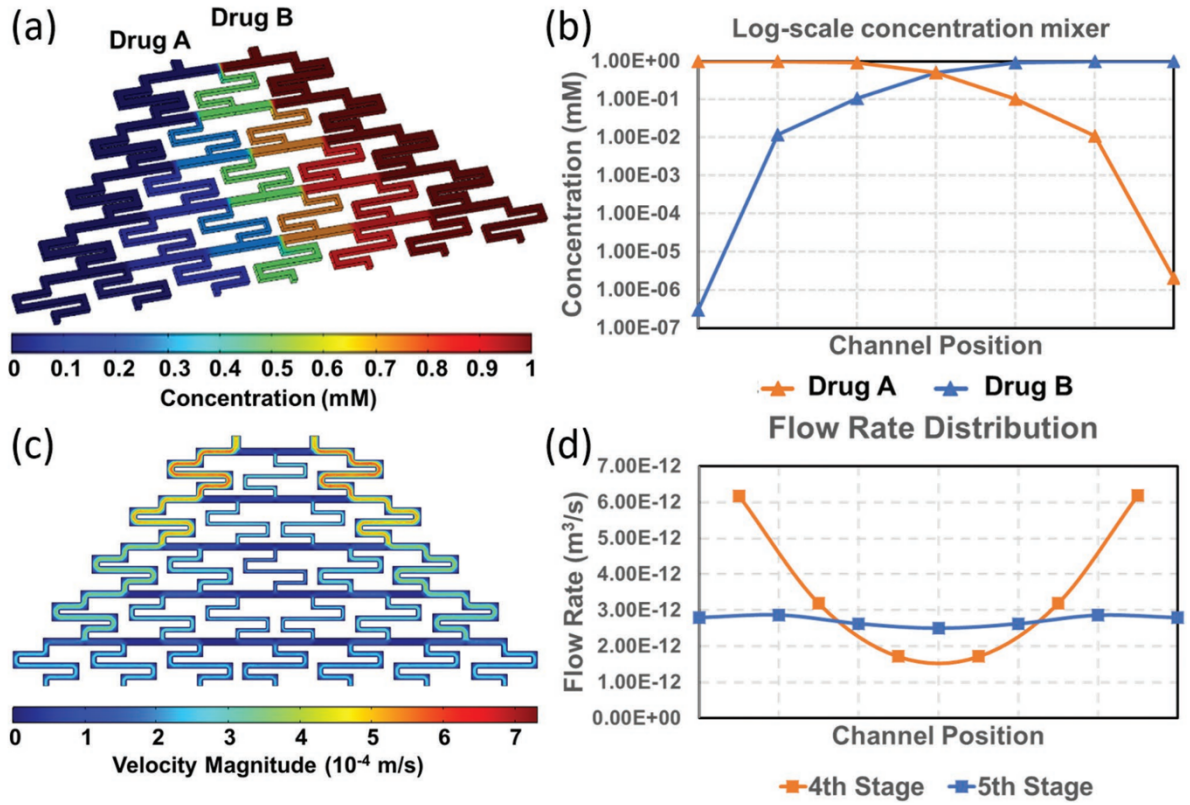

Figure 3: Concentration simulation of "Christmas tree mixer". Adapted from Zhang et al. COMSOL (a software for multiphysics-simulation) simulation results for logarithmic "Christmas tree mixer" a) Concentration simulation of the"Christmas tree mixer" using COMSOL. b) Display of the concentration of drug A and B at the end of the mixing process. c) Simulation of the velocity of the "Christmas tree mixer" with the use of COMSOL. d) Measurement of the flow rate at the two last channels (4th and 5th)(40).

For patients who went through surgery, postoperative chemotherapy is a determining factor for overall survival probability(41). Seppälä et al(42). established patient derived organoids from surgical specimens and endoscopic biopsies for high-throughput drug testing to explore if drug sensitivity testing could be done within a clinically meaningful timeframe. Single cells were placed in liquid Matrigel and supplied with feeding media. For sensitivity testing, single cells were placed on a 384-well assay plate in 10% Matrigel and tested for different chemotherapeutics. It was possible to obtain results rapidly within 18 days with a mean time of 49 days. The median time between surgery and initiation of chemotherapy was set to be 62 days according to a pancreatectomy database survey. What we can see from this, and other studies, is that there is also a possibility of using organoids in the postoperative phase and that the results obtained can still be used actively for therapy(43,44). The application of this method would create many new opportunities in the field of personalized drug screening. However, this Research area is still under development and there is still considerable work to be done before it can be used reliably in practice.

5.2 Usage of organoids in pancreatic cancer research

Although there is still much to discover, the use of organoids for cancer research is another very crucial area of application. In this area, the possibility of cultivating several cell types at the same time and examining them on one chip is particularly useful. It is, for example, possible to investigate the relationship between tumor cells and stroma, i.e. Haque et al(21). developed a patient derived organoid chip model with PDAC and bidirectional epithelium interaction, to test if TME modulating agents do have an enhancing effect on antitumor chemotherapy. Fine needle biopsies of PDAC were collected, and organoids were developed. A significant increased proliferation was observed after hematoxylin and eosin staining of organoid coculture with U937 and pancreatic stellate cells (stroma producing cells). This effect was also seen with MIA PaCa-2 cell lines (an epithelial pancreatic cell line) compared to monoculture. These results did suggest increased invasiveness of the primary cancer cells in coculture. As a next step, the cultures were transferred to the upper chamber of a two-chamber chip for further cultivation and evaluation, and the lower chamber was separated from the culture by a porous membrane and served as a continuous medium (Matrigel) supply. Since one of the objectives of the study was to investigate whether stroma therapy would enhance tumor therapy, a drug response study was conducted. Targeted therapy against PSCs (by ATRA) or macrophages (by Clodrosome) together with chemotherapy was performed. Comparing this therapy to single chemotherapy treatment, the results demonstrated clear evidence of increased effectivity of combination therapy and confirming the bidirectional interaction between stroma and tumor. Studies like this are groundbreaking in cancer research and further studies will make treatment even more effective, as they pave the way to a more personalized medicine. By introducing new results into practice, it might be possible to increase the informative value of organoids even more and, consequently, also the results of personalized drug screening regimes.

In the process of understanding the pathogenesis of the disease, the introduction of organoid biobanking is another step further. Organoids allow for an expansion of types and sample sizes that can be examined. Together with the longer durability of organoids, they are a great asset for research. There are more and more efforts to equip biobanks with organoids and to use their advantages for personalized drug screening and other fields of medicine(45).

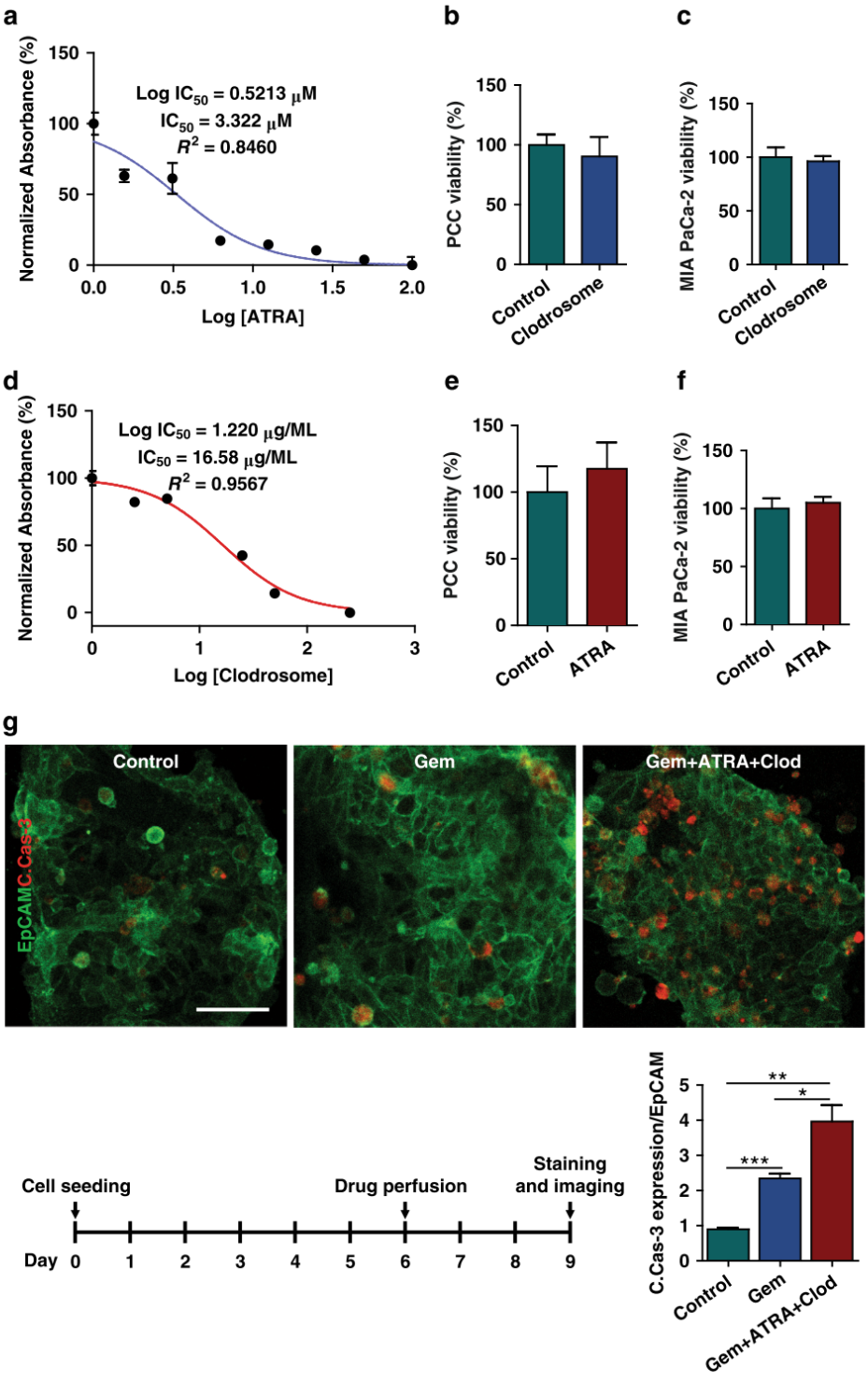

Figure 4: Effect of stroma depletion in chemotherapeutic response. Adapted from Haque MR et al. To show the utility of the multicellular PDO-based organ-chip system for drug screening, stroma-depleting agents were used along with gemcitabine(21).

5.3 Use of organoids in the treatment of diabetes mellitus

Another area of research which is getting more and more attention is the study of diabetes mellitus (DM). Mortality rates in lower-middle-income countries increased by 13% between 2000 and 2019(46). Therefore, sufficient treatment is more important than ever. The idea of

culturing pancreatic islets for transplantation has been around for a while. However, there have been some problems in producing these islets, i.e., they are more dependent on external factors, such as blood flow and interactions between cells, than other cell structures. Without these factors, cells are unable to maintain a good blood-glucose homeostasis. The introduction of 3D and OOAC models solve some of these issues. A comparative study between different types of spheroid production demonstrated that islet cell spheroids, generated either in locally fabricated silicon microwells or in Sphericalplate 5D, yielded highly functional insulin-producing constructs with minimal labor(47). Although providing better results than previous culturing methods, spheroids have limited application abilities. Due to their structure, spheroids are very susceptible to oxygen. When they reach a certain size, it is no longer possible to achieve sufficient oxygenation of the inner cells leading to necrosis, limiting the size and usability of such cultures.

Pancreas transplantation is one way to treat DM in the long term. However, it is a very complex and dangerous operation with many side effects and a high morbidity. Pancreatic islet transplantation is therefore a good alternative with lower morbidity levels(48). For islet transplantation several OOAC models have been designed, which could bring further perspectives in the field of personalized screening and treatment methods. Culturing pancreatic islets on microfluidic chips involves trapping sides, mostly micro-wells, where islets are immobilized and cultured under continuous flow. It has been shown that the size of the islets should be as consistent as possible, where smaller islets perform better than bigger ones(49). Before transplantation islets they need to be tested for potency. Enzyme-linked immunosorbent assay (ELISA) is still the predominant method used, which requires the separation of the cells, making this method very time and cost consuming. On-chip testing could therefore save a lot of time and money. Hori et al.(50) developed a compact fluidic system for the assessment of islet functionality called g-STAR. This novel system uses a micromesh sheet-embedded chip. Islets which are easily placed on the mesh are trapped and held in place. Microfluidic solution was pumped through the chip. The system was complemented by a sample fraction chip for fluid collection. The functional test with high and low glucose levels was performed with murine pancreatic islets to test the performance of the system. The results have indicated that the system successfully analyzes insulin secretion, which confirms that it is able to evaluate the quality of islets cheaply and quickly. Thanks to improved islet cell screening methods, pancreatic islet transplantation is becoming safer and personalized every day.

6 Discussion

3D culture systems are under research for quite some time, with new systems being released and new fields of applicability can be seen everywhere. But their biggest advantage is also holding their greatest challenge. With increasing cellular complexity culture systems are more error-prone than traditional cultures. The introduction of organ-on-a-chip devices increased the effectiveness of organoids by adding microfluidic systems to organoid cultures. What is important to remember, is that any culturing device needs to be appropriate for its specific purpose, since every organ needs its unique setup. Until now there is no device which is able to replace animal testing as a whole. Still a drawback of organoid systems is the lack of interorgan communication. right now, human organoids only mimic only one organ at a time and interaction between organs is still missing. However, research is currently underway to address these challenges as well, and promising novel multi-organ-on-a-chip devises will represent the body even more accurately in the future than previous systems(51). A major challenge in the treatment of pancreatic tumors is the low percentage of resectable tumors. The application of organoids can reduce this problem through high-throughput sensitivity testing methods enabling a more personalized medication. Even though PDAC has high heterogeneity, organoid sensitivity testing can lead to successful treatment results, subsequently resulting in tumor shrinkage. Which can eventually lead to resectability and thus holds great potential for surgical application.

Also, in the field of pancreatic islet transplantation, organoids could be used with great advantage for production and evaluation of islets. In particular, using organ-on-a-chip devices, it is possible to screen and produce islets in large numbers and with a more personalized approach, making islet transplantation a relevant alternative to transplantation of the entire pancreas.

7 Conclusion and recommendations

By reviewing the literature, it was possible to demonstrate the great advantages and potential which pancreatic 3D organoid culture systems hold especially in the field of personalized drug screening. It remains to be seen whether the advantages presented in the text will also be reflected in clinical practice. Further research is needed to answer these questions satisfactorily, but it is to believe that organoid systems will provide never seen possibilities to improve human live in the future.

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9 Attachments

This work is intended for publication in the "Lab on a Chip" journal.