Biomedicine & Pharmacotherapy 182 (2025) 117750

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

The use of patient-derived xenografts and patient-derived organoids in the search for new therapeutic regimens for pancreatic carcinoma. A review

Emin Gayibov [a], Tomáš Sychra [a,b,d], Alžběta Spálenková [b,c], Pavel Souček [b,c,*,1], Martin Oliverius [a,d,**,2]

[a] 3rd Faculty of Medicine, Charles University, Prague, Czech Republic
[b] Centre of Toxicology and Health Safety, National Institute of Public Health, Prague, Czech Republic
[c] Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic
[d] Department of General Surgery, 3rd Faculty of Medicine, Charles University and University Hospital Královské Vinohrady, Prague, Czech Republic

ARTICLE INFO

Keywords:
Pancreatic neoplasms
Heterografts
Organoids
Models
Animal
Chemotherapy
Adjuvant

ABSTRACT

Patient-derived organoids (PDOs) and xenografts (PDXs) are powerful tools for personalized medicine in pancreatic cancer (PC) research. This study explores the complementary strengths of PDOs and PDXs in terms of practicality, genetic fidelity, cost, and labor considerations. Among other models like 2D cell cultures, spheroids, cancer-on-chip systems, cell line-derived xenografts (CDX), and genetically engineered mouse models (GEMMs), PDOs and PDXs uniquely balance genetic fidelity and personalized medicine potential, offering distinct advantages over the simplicity of 2D cultures and the advanced, but often resource-intensive, GEMMs and cancer-on-chip systems. PDOs excel in high-throughput drug screening due to their ease of use, lower cost, and shorter experimental timelines. However, they lack a complete tumor microenvironment. Conversely, PDXs offer a more complex microenvironment that closely reflects patient tumors, potentially leading to more clinically relevant results. Despite limitations in size, number of specimens, and engraftment success, PDXs demonstrate significant concordance with patient responses to treatment, highlighting their value in personalized medicine. Both models exhibit significant genetic fidelity, making them suitable for drug sensitivity testing. The choice between PDOs and PDXs depends on the research focus, resource availability, and desired level of microenvironment complexity. PDOs are advantageous for high-throughput screening of a diverse array of potential therapeutic agents due to their relative ease of culture and scalability. PDXs, on the other hand, offer a more physiologically relevant model, allowing for a comprehensive evaluation of drug efficacy and mechanisms of action.

1. Methodology

All the studies referred for this review have been searched via the National Library of Medicine-National Institute of Health (NLM-NIH), PubMed, with the keywords being patient-derived xenografts (PDXs) and organoids (PDOs), pancreatic cancer (PC), PDX and PDO comparison in PC treatment. A visual tool Connected Papers (www.connectedpapers.com) and reference manager software Mendeley (www.mendeley.com) were used for appropriate citation and access to similar papers regarding the use of PDX and PDO models in the treatment of PC. For this review, we specified the time range of referred studies as of the last 20 years, i.e., we disregarded the studies conducted before 2004. Our inclusion criteria comprised searches, which enable comparing PDX and PDO models in practical, genetic, cost-, and labor-related aspects with statistically significant data. We narrowed the literature search to include PDO and PDX models only for PC treatment, excluding the data

Abbreviations: CAF, cancer-associated fibroblasts; CDX, cell-derived xenograft; CNA, copy number alterations; GEMM, genetically engineered mouse model; NOD/SCID, non-obese diabetic/severe combined immunodeficiency; NU/NU, nude mouse; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PDO, patient-derived organoid; PDX, patient-derived xenograft; TME, tumor microenvironment.

* Correspondence to: Toxicogenomics Unit, National Institute of Public Health, Šrobárova 49/48, Prague 100 42, Czech Republic.
** Correspondence to: Department of General Surgery, 3rd Faculty of Medicine Charles University and University Hospital Královské Vinohrady, Šrobárova 1150/50, Prague 100 34, Czech Republic.
E-mail addresses: pavel.soucek@szu.cz (P. Souček), martin.oliverius@gmail.com (M. Oliverius).
[1] ORCID: 0000–0002-4294–6799
[2] ORCID: 0000–0002-8649–3824

https://doi.org/10.1016/j.biopha.2024.117750
Received 6 September 2024; Received in revised form 2 December 2024; Accepted 8 December 2024
Available online 16 December 2024

for other cancer types. There was no specific PC histopathological subtype as an inclusion criterion. Conclusion was made according to the comparison between these two models.

2. Background

Ranked as the sixth most common cause of cancer-related deaths, pancreatic cancer (PC) was a cause of 467,005 deaths worldwide in 2022 [1]. The PC mortality rate is estimated to surpass that of colorectal, prostate, and breast cancers by 2030 in the USA [2]. The current relative survival rate of PC including all races and ethnicities is 13 % in the USA, which places it the last in the list of cancers with lowest survival rates [3]. Being about 85 % of all PC diagnoses, the most common histological subtype of PC is pancreatic ductal adenocarcinoma (PDAC) [4]. The cancer usually progresses with vague symptoms only and often ends up with metastasis [5,6].

Drug combinations such as the commonly used FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin, and leucovorin), or gemcitabine alone or together with capecitabine are administered to patients suffering from the disease advancement, depending on their performance status [7–11]. Despite recent advancements in PC treatment, such as the 4.3-month increase in overall survival afforded by FOLFIRINOX-based therapy, non-resectable PC remains a disease with a dismal prognosis [10–14]. The efficacy of anticancer drugs is significantly limited due to frequent multi-drug resistance [15,16]. There is also an undeniable negative impact of conventional chemotherapy side effects, such as hematological toxicity, diarrhea, and loss of appetite on the life quality of patients [17]. There is no observed significant effect of adjuvant radiotherapy on prolonging the overall survival of PC patients [18,19].

Therefore, individualized treatment has been researched, including targeted therapies and combinations best suited for the patient. For this purpose, studies evaluating the utility of various models for the personalization of treatment have been published [14,20–23]. Among these, patient-derived xenografts (PDXs) and patient-derived organoids (PDOs) have emerged as valuable tools due to their ability to closely mimic the biological characteristics of patient tumors and their responses to therapy. These models allow researchers to test treatment strategies in a preclinical setting, providing insights that can guide clinical decisions. This review describes the full range of available models used for testing personalized treatments, with a particular focus on the advantages, drawbacks, and potential applications of PDXs and PDOs in translational research regarding PC treatment.

3. Alternative models for studying pancreatic cancer

Advancing our understanding of PC and developing effective treatments necessitate the use of various experimental models. Among the primary methods are 2D cell cultures, spheroids, cell-derived xenografts (CDX), tumor-on-chip technology and genetically engineered mouse models (GEMMs) (Fig. 1). Each of these models offers distinct advantages and limitations, contributing uniquely to the study of PC. Understanding their strengths and weaknesses is crucial for choosing the appropriate approach to study PC and for translating the results into clinical applications. These models are described in the following chapters and are summarized in Table 1.

3.1. 2D cell cultures

Many PC cell lines are already established and used because they are relatively homogeneous, cost-effective, less subject to regulations, and have easy manipulation and maintenance. While 2D cultures offer advantages like reproducibility and availability [14], they poorly mimic clinical PC due to the loss of tumor heterogeneity, limited disease complexity, and stromal or immune component absence [21,24,25]. Adaptation to plastic and genetic changes further reduce their resemblance to primary tissue. They poorly mimic clinical PC due to the loss of tumor heterogeneity, limited disease complexity, and stromal or immune component absence [21,24,25]. As a result, 2D culture models often have low predictive value for clinical outcomes, which can lead to the failure of promising therapies when tested in human trials. Despite these limitations, 2D cell cultures remain an invaluable tool in cancer research due to their accessibility, ease of use, and ability to provide rapid preliminary data, making them a practical choice for initial experimental screenings [26,27].

3.2. Spheroid models

Spheroid cultures are another model for studying PC. They serve as an intermediate model between 2D cultures and more advanced systems like PDOs, due to their ability to better replicate the tumor microenvironment compared to traditional 2D cultures [28]. These spheroids can be composed of multiple cell types, such as cancer cells, endothelial cells, pancreatic stellate cells, and monocytes [29], allowing them to more accurately mimic the heterocellular interactions found in PC. Spheroids grow in 3D structures that mimic in vivo tumor conditions, including cell interactions, hypoxia, and nutrient gradients, making them valuable for drug resistance studies [28,30]. Spheroids are

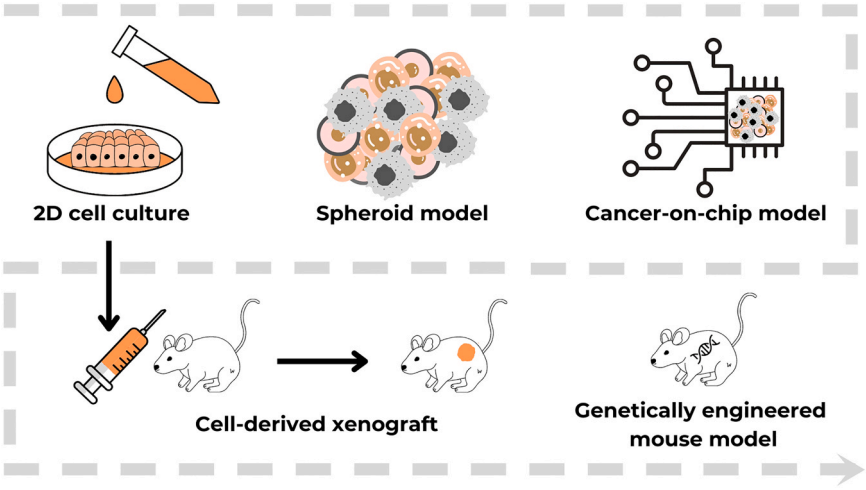

Fig. 1. Models other than patient-derived organoids and xenografts for studying pancreatic cancer and its treatment. The complexity increases in accordance with the gray dashed arrow.

Table 1
The summary of the models other than patient-derived organoids and xenografts for studying pancreatic cancer and its treatment.

Model	Advantages	Disadvantages	Reference
2D cell culture	homogeneous cost-effective less subject to regulations easy management sufficient availability	lack of full complexity and genetic fidelity loss of heterogeneity poor ability to reflect disease advancement and tissue complexity failure to retain the characteristics of the primary tumor	[14,21, 24–27]
Spheroid models	3D tumor-like environment with various cell types drug efficacy and resistance studies initial drug screening and mechanistic studies	lack of full complexity and genetic fidelity lack of key elements, such as the blood vessels and immune cells	[28–36]
Cancer-on-chip models	integration of PDOs with stromal components enhanced accuracy of drug response studies mimicking the intricate cellular interactions and desmoplastic stroma	lack of full complexity in terms of vascularization, tissues stiffness and spatial cell interactions potential negative effect of fabrication materials on drug response studies	[37–43]
Cell-derived xenograft	easy management short duration predictable and inexpensive initial drug screening	lack of full complexity lack of significant correspondence to the primary tumor restricts the study of interactions between cancer cells and the immune system	[22, 44–48]
Genetically engineered mouse models	detection of genetic aberrations in PC pathogenesis and its response to treatment	long duration needed to generate a particular mutant mouse off-target pathologies in other tissues	[49–53]

particularly valuable for drug testing, as their 3D structure replicates in vivo-like chemoresistance to agents such as gemcitabine. Their organization, with proliferative outer layers and hypoxic, necrotic cores, provides insights into drug penetration, efficacy, and resistance mechanisms [31,32].

While spheroids combine different cell types to mimic the TME, they lack the full complexity of living tumor interactions. Spheroids lack key elements like the blood vessel network for nutrient delivery, waste removal, and dynamic immune cell interactions critical for tumor progression and therapy response [33,34]. Although spheroids offer a more physiologically relevant environment than 2D cultures, they still lack the complexity and genetic fidelity of advanced models like PDOs. Nonetheless, spheroids are valuable for bridging the gap between the simpler *in vitro* models and more sophisticated *in vivo* or *ex vivo* approaches, offering a versatile platform for initial drug screening and mechanistic studies in PC research [31,35,36].

3.3. Cancer-on-chip models

Cancer-on-chip models represent a cutting-edge approach to replicating the complex tumor microenvironment of PC more accurately than traditional *in vitro* methods. These microfluidic devices allow for the integration of PDOs with stromal components, such as pancreatic stellate cells and immune cells, within a controlled, perfusable environment. This setup mimics the intricate cellular interactions and desmoplastic stroma of PDAC, providing a more physiologically relevant platform for drug testing [37–39].

Despite these advantages, cancer-on-chip models are not without limitations. While cancer-on-chip models do offer advanced features compared to traditional 2D cultures, they don't fully replicate the true 3D structure of a tumor. The chips typically allow for some degree of 3D organization and cell layering, but they may not perfectly mimic the full complexity and architecture of a tumor's 3D environment, particularly in terms of vascularization, tissue stiffness, and spatial cell interactions [40,41]. Moreover, the current devices often rely on commercially available cell lines for stromal components, which may not fully capture the patient-specific variations found in clinical samples. Additionally, the fabrication materials, such as polydimethylsiloxane, can absorb hydrophobic drugs, potentially affecting the accuracy of drug response studies [42,43].

3.4. Cell-derived xenografts

Frequently used methodology is the CDX - *in vivo* models in which human cancer cell lines are implanted into immunodeficient mice to study tumor growth and response to therapies. This approach is straightforward to manage and allows for the testing of multiple anticancer chemotherapeutics, within a short duration [22,44]. The use of immunodeficient mice in CDX models, however, limits the ability to study interactions between cancer cells and the immune system, making them less suitable for evaluating immunotherapies [45,46]. Despite these limitations, CDX models remain valuable in early-stage drug development for screening basic efficacy and toxicity of anticancer agents [26,47]. This method is also relatively predictable and cheaper than PDO and PDX models [22], which are the major focus of this paper. Unlike PDO and PDX models, which better mimic the tumor microenvironment and heterogeneity, CDX models lack the complexity needed to fully represent the biological behavior of patient-derived tumors [44, 48]. This also reduces their clinical translatability. Despite their limitations, CDX models are frequently used due to their cost-effectiveness and relative simplicity, making them a practical and efficient starting point for preclinical testing of new anticancer therapies.

3.5. Genetically engineered mouse models

GEMMs represent alternative methods to study various characteristics of PC and its response to different therapeutics [49]. Unlike 2D and CDX models, which are limited in their ability to capture genetic complexity and tumor-stromal interactions, GEMMs provide a more physiologically relevant *in vivo* system for studying the intricate genetic and molecular pathways involved in PC. GEMMs express oncogenes or dominant-negative tumor-suppressor genes in a non-physiological manner due to enhancer elements and ectopic promoters [50]. They can be utilized to understand how various genetic aberrations influence the PC response to the corresponding treatment.

Despite its advantages, this model still has some drawbacks. The long time needed to generate mutant mice carrying particular genetic alteration is disadvantageous. Another issue regarding the use of GEMM is whether the harbored tumor at the end of the treatment period has the same biological features as the initial tumor at the beginning of the study [49]. Studies involving GEMMs may also result in off-target pathologies in other tissues because the harboring mutant genes may be expressed in the whole pancreas thanks to pancreatic embryonic promoters such as p48 and Pdx-1 [51–53]. Although these challenges exist, GEMMs remain indispensable for advancing our understanding of PC genetics and for the development of targeted therapies that can be tailored to specific genetic profiles.

4. Pancreatic cancer patient-derived organoids

By definition, PDOs are 3D cell culture models made from resection and biopsies of human tumors [54]. Unlike 2D cultures, which are limited in cell diversity, PDOs allow for the co-culture of various cell

types, including stromal components, thereby offering a more accurate representation of tumor biology, and serve as an intermediate step between 2D cultures and xenografts [55]. This approach also enhances the understanding of intercellular interactions by co-culturing stromal components [14]. The development of PDOs aims to bridge the gap between the simplicity of 2D cell cultures and the physiological relevance of PDX models by allowing primary tumor cells to grow in a 3D environment without adhering to the dish bottom, thus better preserving the tumor characteristics [56]. Due to the favor of keeping the features of primary tumors, PDOs have been utilized as an alternative to conventional cell lines in many different studies involving cancer therapies [57]. Huch et al. developed a pioneer organoid made of continuously proliferating normal adult murine ductal cells, which laid the groundwork for further advancements in PDO technology [58]. Boj et al. sharpened this approach as they further established both normal and tumor-derived organoids of PDAC [59]. PDOs are already established for various gastrointestinal cancers, including colorectal, hepatocellular, or esophageal adenocarcinomas, and for surgically resected PC tissues, with a success rate of 80 % [59].

An organoid can root from a relatively small original cancer specimen of the patient, which must be noted as another advantage of working with PDOs (Fig. 2). This original tumorous tissue can also be taken from an already established PDX model to create a PDX-derived organoid (PDXO) [60]. PC organoids were also successfully derived from the paracentesis-taken ascites of patients diagnosed with PC and were successfully maintained for at least five passages by Choi et al., with an establishment rate of 48.7 % [61]. Successful PC PDO establishment by using the endoscopic ultrasound (EUS) fine needle biopsy sampling has also been reported, with 87 % success rate of PDO isolation, and 66 % growth rate for at least five lines [62].

4.1. *The genetics and the histology of pancreatic cancer patient-derived organoids*

Despite significant efforts to replicate the natural environment of tumors as closely as possible, the establishment of tumor organoids inevitably exposes tumor cells to changes in their microenvironment. These changes necessitate adaptation, which can drive genetic selection within the organoid model. Factors influencing this selection include the composition of the culture medium, the extracellular matrix used for scaffolding, oxygen levels, and interactions with tumor microenvironment components, such as immune cells or stromal elements. Additional factors, such as the mechanical properties of the matrix, nutrient availability, or even the process of passaging and long-term culture, may also contribute to genetic drift or selective pressures. The mechanisms underlying this genetic selection remain only partially understood, posing a critical challenge to ensuring the fidelity of organoid models to their original tumor tissues.

Considering genetic fidelity of PDOs, it was reported that 78 % of the established PDOs were able to hold the genetic hallmarks of the original pancreatic tumor tissue, according to the sequencing analyses for the *KRAS* gene and whole exome by Tiriac et al. [63]. To test the genomic stability and heterogeneity of the PC organoid lines, Usman et al. utilized the single-cell whole-genome sequencing. Results showed clonal populations with similar copy number profiles within the organoids. The proportion of these clones was shifted as the culture extended, pointing to the growth advantage of some clones. They also observed the sub-clonal genomic heterogeneity within each clonal population, indicating the genomic instability of the PC cells themselves [64].

Another study revealed a high degree of analogy in terms of genetics between the existing PDXs biobank and later established corresponding PDXOs. After analysis by the whole exome sequencing, 98.7 % median mutational correlation was revealed, pointing to the high mutational concordance of the PDX and PDXO pairs [65]. PC PDOs established from malignant ascites by Choi et al. also significantly reflected the genetic characteristics. Both the ascites and organoid samples revealed the presence of *KRAS G12V* mutation [61]. The studies referred in this paper regarding the genetic fidelity of the PC PDOs are summarized in Table 2. Furthermore, PC PDOs have been shown to recapitulate the histological features of the tissues from which they were derived. Boj et al., following the implantation of organoid cultures orthotopically, revealed that the implants were able to significantly harbor the histology of the original tissues from which the PDOs were generated [66]. Other studies also reported the significant recapitulation of the histological and genetic properties of primary tumors arising in the pancreas [67–69].

In conclusion, PDOs demonstrate a high degree of genetic fidelity to their original pancreatic tumor tissues, making them valuable models for studying cancer genetics and therapeutic responses. Despite some inherent genomic instability observed within the clonal populations, the strong mutational concordance between PDOs and their corresponding PDX models, as well as their ability to recapitulate histological features, underscores their potential as reliable and representative models for preclinical cancer research. Given their ability to closely mimic the patient's original tumor, PDOs hold great promise for advancing personalized cancer therapies and improving clinical outcomes. To investigate genetic changes in PDOs, further studies are needed to monitor PDOs over time during long-term cultivation in culture medium and extracellular matrix. For a more detailed examination, omic tools

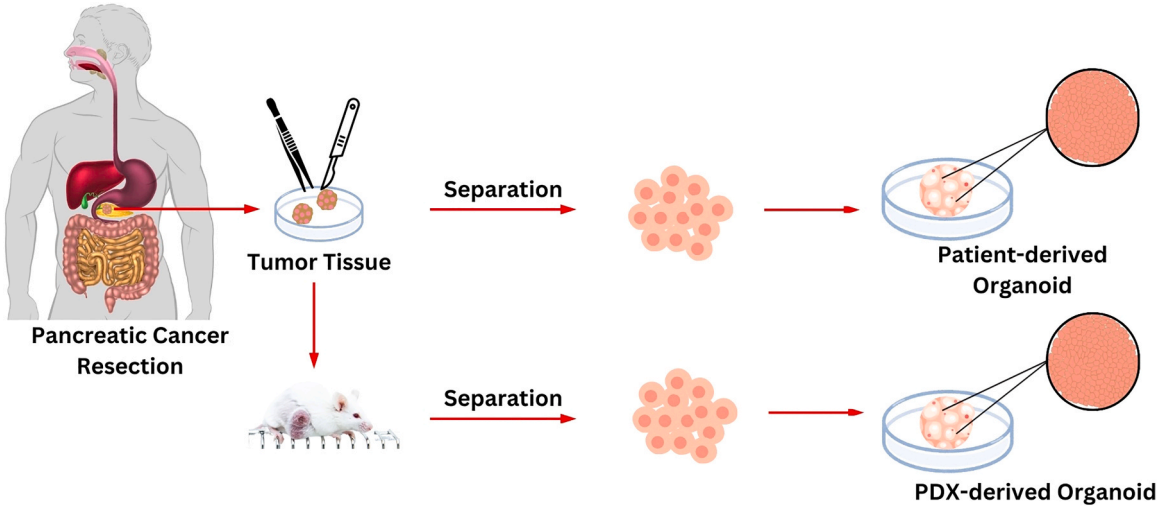

Fig. 2. Establishing pancreatic cancer patient-derived organoids and PDX-derived organoids.

Table 2
The summary of the studies referred in this paper regarding the genetic fidelity of the pancreatic cancer patient-derived organoids.

Study	Type of Study	Focus of Study	Observation	Reference
Choi et al.	organoid library establishment molecular profiling	PDOs from ascites or pleural fluid samples	the presence of *KRAS G12V* mutation in both the ascites and organoid samples	[61]
Tiriac et al.	molecular profiling and drug sensitivity testing	molecular and therapeutic profiling of PDOs for prediction of clinical response and prospective therapeutic selection	78 % of the established PDOs were able to hold the genetic fidelity according to the whole exome and *KRAS* sequencing	[63]
Usman et al.	molecular profiling	the genomic stability and heterogeneity of the PC organoid lines	similar copy number profiles within the organoids. Sub-clonal genomic heterogeneity within each clonal population, indicating the genomic instability of the PC cells themselves	[64]
Xu X et al.	organoid library establishment molecular profiling	degree of analogy between the biobank of PDXs and later established PDXOs	high mutational concordance of the PDX and PDXO pairs with a 98.7 % median mutational correlation	[65]

such as DNA and RNA sequencing, analysis of epigenetic profiles at both bulk and single-cell levels, as well as spatial omics analysis of organoid structures could be employed.

4.2. Pancreatic cancer patient-derived organoids for drug sensitivity profiling

One of the significant applications of PDOs in PC research is their use in dynamic chemotherapy sensitivity profiling, where they are utilized to evaluate the responsiveness of individual tumors to various chemotherapeutic agents, potentially reducing the reliance on animal models in drug screening. This approach allows for the personalized assessment of how individual tumors respond to different chemotherapeutic agents, potentially guiding the selection of the most effective treatment regimens for specific patients. By replicating the tumor's response in a controlled environment, PDOs can provide valuable insights that traditional 2D cell cultures might not fully capture. The ability to predict patient-specific responses to chemotherapy not only has the potential to enhance treatment outcomes but also to minimize unnecessary side effects by avoiding less effective therapies. Furthermore, the use of PDOs in drug-repurposing screens could significantly streamline the identification of new therapeutic options, expanding the arsenal of treatments available for PC.

The study done by Demyan et al. provided promising evidence supporting the use of PDOs for dynamic chemotherapy sensitivity profiling of PC. They successfully demonstrated the correlation between pathological responses to neoadjuvantly used chemotherapeutics in patients, notably oxaliplatin, and the response of corresponding PDOs to those drugs [54]. Profiling the response of PDOs to other anticancer drugs, including gemcitabine, paclitaxel, and 5-fluorouracil has also been reported [61,70,71]. These data show that the drug responses tested in these organoids correlate well with the patient's clinical responses [61], *in vivo* [70] and *in vitro* [71] responses of the tumor. It was also concluded that the PDO models analyzed by next-generation sequencing in combination with pharmacotyping may predict responses in PC patients and provide a solid reason for prioritizing therapeutic regimens [63].

PDOs are also suitable for an automated drug-repurposing screen. Hirt et al. were able to conduct this type of screening with 1172 FDA-approved compounds after creating a biobank of 31 genetically distinct lines of PDAC PDOs. Their study identified 26 compounds that effectively kill PDAC PDOs, of which 19 were among already approved drugs for other malignancies. The phenotypes of the utilized PDOs were also retained over multiple passages and after repetitive engraftment into mice subcutaneously [70].

Another study reported no significant change in the response to various different chemotherapeutics, including gemcitabine, paclitaxel, 5-fluorouracil, and oxaliplatin after conversion of the 3D PDAC PDOs into 2D cultures. Cell viability assays were utilized to investigate the sensitivity towards the mentioned drugs. As a result, the difference between the chemosensitivity of 2D and 3D PDAC cultures was not significant, except for the irinotecan active metabolite SN-38 ($p = 0.027$) [71]. Organoids derived from the paracentesis-taken ascitic fluid of PC patients by Choi et al., drug tested for sensitivity assays for 5-fluorouracil, oxaliplatin, irinotecan, gemcitabine, nab-paclitaxel, and erlotinib, recapitulated the clinical responses of real patients from whom the samples were taken [61]. Other studies also point to the promising benefits of PC PDO models for chemotherapy screening [67,69,72–75]. In one of these studies, Le Compte et al. utilized a panel of eight patient-derived PDAC PDOs to investigate individual tumor responses to standard-of-care chemotherapy. By employing artificial intelligence-driven, live-cell imaging analysis, they were able to identify patient-specific sensitivities to gemcitabine-paclitaxel and FOLFIRINOX. Notably, their single-organoid analysis revealed intra-tumor heterogeneity, detecting both drug-resistant and invasive organoid clones within individual patients [75]. This finding suggests that personalized treatment strategies based on organoid profiling could potentially improve clinical outcomes for PDAC patients. The studies referred in this paper regarding the usage of the PC PDOs for drug response profiling are summarized in Table 3.

In summary, these studies collectively highlight the potential of PDOs to personalize treatment regimens in PC and expand the repertoire of available therapies through drug repurposing and sensitivity screening. Their ability to closely mimic patient tumors makes them invaluable for optimizing individual treatments, offering a promising approach to improving clinical outcomes and advancing cancer research.

4.3. Patient-derived organoids on chip model

Moreover, PDOs can be utilized to create organoid-on-chip models, bridging the gap between traditional organoid cultures and advanced microfluidic systems for studying the tumor microenvironment. In a recent study, a tumor-chip device incorporating PDOs with stromal cells successfully replicated the PC TME, demonstrating that targeting the stroma within this model significantly enhanced the efficacy of chemotherapy agents [37]. Unlike monocultures, where stroma-depleting agents showed no effect on cancer cell viability, the tumor-chip model revealed that disrupting the stroma led to a marked increase in chemotherapy-induced cancer cell death. This suggests that cancer-on-chip models can be crucial for evaluating the impact of microenvironment-modulating therapies, potentially bridging the gap between preclinical studies and clinical applications.

Recent advancements also demonstrate that combining cancer-on-chip technology with PDOs can better replicate the tumor microenvironment's fibro-inflammatory responses and high molecular heterogeneity, which are typical in PC [39]. This integration allows for the development of personalized treatment strategies, as the microfluidic

Table 3
The summary of the studies referred in this paper regarding the usage of the pancreatic cancer patient-derived organoids for drug response profiling.

Study	Type of Study	Focus of Study	Observation	Reference
Demyan et al.	chemotherapy sensitivity profiling	the possibility of utilizing PDOs for dynamic chemotherapy sensitivity profiling	correlation between pathological responses to neoadjuvantly used chemotherapeutics in patients and the corresponding PDOs	[54]
Choi et al.	organoid library establishment chemotherapy sensitivity profiling	establishment of PDOs using ascitic or pleural fluid samples	organoids recapitulated the clinical responses of the original patients in drug sensitivity assays for various chemotherapeutics	[61]
Hirt et al.	chemotherapy sensitivity profiling	automated drug-repurposing screen via the PDOs	26 compounds that effectively kill PDAC PDOs were identified	[70]
Gassl et al.	chemotherapy sensitivity profiling	differences in response to various chemotherapeutics between the PDAC PDOs and corresponding 2D cultures	no significant difference between the chemosensitivity of 2D or 3D PDAC cultures, except for SN−38	[71]
Armstrong et al.	chemotherapy sensitivity profiling molecular profiling	PDO based high-throughput drug screening assay to assess treatment response to a variety of conventional and investigational treatments for PDAC	reproducible drug response curves distinct transcriptome signatures associated with response to the conventional chemotherapeutics	[73]
Le Compte et al.	chemotherapy sensitivity profiling	leveraging fully characterized PDAC organoid panel (N = 8) and artificial intelligence-driven, live-cell organoid image analysis with retrospective clinical patient response	patient-specific sensitivities to the standard of care therapies, gemcitabine-paclitaxel and FOLFIRINOX single-organoid analysis was able to detect resistant as well as invasive PDAC organoid clones	[75]
Hogenson et al.	chemotherapy sensitivity profiling	testing the influence of culture media on the phenotype of the corresponding PDOs	culture media significantly influence response of PDOs to chemotherapeutics	[85]

environment on a chip can more accurately reflect the complex cellular interactions and individualized drug responses in PC tumors. The ability to combine stromal components with PDOs in a perfusable environment not only mimics the desmoplastic stroma but also enhances the drug testing accuracy, potentially leading to more effective therapies.

4.4. Current limitations of pancreatic cancer patient-derived organoids

It is worth noting that there are still some important disadvantages brought by working with PDOs. This model still comprises an artificial environment for co-cultured cells, and it is still not completely understood how the genetic selection works for growth advantage of tumor cell clones [76]. Further exploration of genetic selection processes within PDOs, perhaps through techniques like single-cell sequencing and CRISPR-Cas9 is crucial to fully understand tumor evolution and improve the predictive value of these models. Single-cell sequencing technique allows researchers to analyze the genetic heterogeneity of individual cells within a PDO, providing insights into the clonal evolution of the tumor [77]. Using CRISPR-Cas9 can identify genes that are essential for organoid growth and drug resistance, and can provide mechanistic insights into the genetic basis of organoid behavior [78].

Many studies involving PDOs do not dive into the complexity of the tumor microenvironmental components. The usual lack of vascular and immune components and failure to accurately resemble the TME seen in the original PC specimen must be considered as drawbacks of working with PDOs [38,60,79]. This limitation may affect the accuracy of PDOs in predicting treatment responses *in vivo*, where these interactions play a critical role in tumor behavior and response to therapy. For example, a significant change in the proliferation ($p < 0.05$) and chemotherapy-induced cell death ($p < 0.05$) was observed upon co-culturing PDAC PDOs with cancer-associated fibroblasts, pointing to the fact the PDOs alone might disregard the effect of stromal components on the chemosensitivity [80]. One approach to address the limitations of PDOs in accurately representing the TME is by incorporating cancer-associated fibroblasts (CAFs) and other stromal cells [81,82]. These cells can recreate complex TME interactions, influencing tumor growth and drug resistance. As demonstrated by Go et al., co-culturing PDOs with CAFs at various densities resulted in a more physiologically relevant model [81]. Organoids, which typically grow individually in monoculture, formed tight, organ-like spheroids when co-cultured with CAFs, mimicking the in vivo tumor microenvironment. Other potential solutions include co-culturing with immune cells, such as T cells or macrophages, to simulate immune responses and understand tumor immune evasion strategies [83]. Additionally, mimicking the hypoxic and nutrient-limited conditions found in solid tumors can drive tumor adaptation and drug resistance mechanisms [84].

Additionally, preparing and maintaining organoids is not straightforward. The culture medium for PDOs must contain numerous growth factors and components such as Wnt, R-spondin, Noggin, and epidermal growth factor, which are essential for supporting the growth and differentiation of organoids [56]. These components are quite expensive and can significantly increase the cost of organoid culture management. Furthermore, the variability in the medium composition between different research groups can lead to inconsistencies in experimental outcomes. In fact, Hogenson et al. demonstrated a significant difference in response to chemotherapeutics, including 5-FU, gemcitabine, SN-38, docetaxel, and oxaliplatin by utilizing serum free PaTOM versus WNT culture media within same PC PDOs [85]. This highlights the challenge of standardizing culture conditions across laboratories. The development of these culture conditions requires considerable resource and expertise, making organoid culturing a complicated process harboring obstacles for widespread adoption in the settings of research and clinical settings. Optimizing culture medium conditions for PDOs involves a multi-faceted approach. Important considerations include selecting an appropriate base medium like ADMEF12 with B27 and N2 supplements, optimizing growth factor and Matrigel concentrations, maintaining low oxygen and high CO2 levels, and regularly exchanging the medium [86,87]. Regular monitoring of organoid growth and morphology is also crucial, along with adjusting culture conditions as needed.

5. Pancreatic cancer patient-derived xenografts

PDX models have emerged as a critical tool in cancer research, offering a more accurate and faithful representation of human tumor biology compared to traditional *in vitro* models or simpler xenograft systems. When compared to CDXs, the PDX model surpasses it in some aspects. It is consistent with the heterogeneous niche of cells, which correlates with the real situation of the tumor microenvironment, and it is one-step closer to making individualized therapy possible [22]. PDX models also maintain more accurately metabolic characteristics of primary tumors compared to CDXs as demonstrated by a particular study involving multiple metabolic pathways [88]. By maintaining the original architecture, cellular diversity, and genetic heterogeneity of patient tumors, PDX models provide researchers with a valuable platform for studying drug responses, tumor progression, and resistance mechanisms. Their ability to closely mimic the tumor microenvironment

makes them particularly useful for the development of personalized therapies and for exploring potential treatments for rare and difficult-to-study cancer subtypes. Furthermore, PDX models play a vital role in bridging the gap between preclinical research and clinical applications, allowing for more precise testing and validation of therapeutic strategies before they reach patients.

The usefulness of PDX models is well explained by Garcia et al., demonstrating that these models can be utilized for developing biomarkers, testing novel drugs, and comparing directly between patients and PDX models once in clinical trials [14]. It is anticipated that PDX models will be crucial in the search for therapies of uncommon cancer subtypes, which is another advantage. Using patient samples from rare cancers to create PDX models makes it possible to gather the samples required for further drug testing [23].

Given the critical role of the host environment in the success of PDX models, the choice of mice strain is crucial, particularly when considering the necessity for an immunodeficient host to prevent rejection of the human tumor tissue. Mice lacking an intact immune system are essential in the studies involving PDXs. Non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice are generally utilized for the PDX generation. NOD/SCID mice are created through a process of genetic engineering. The specific method involves transferring the SCID mutation, which causes severe combined immunodeficiency, from the C. B-17 strain onto the NOD background. This results in mice with defects in both innate and adaptive immunity, making them highly susceptible to engraftment with human cells and tissues [89]. NOD/SCID mice possess additional defects in their immunity, such as the absence of circulating complement components and low functionality of natural killer cells [89]. NOD/SCID mice come with several drawbacks, including a high incidence of thymoma with a relatively short lifespan [23]. Nude mouse (NU/NU) model is another alternative still widely utilized due to its relatively low cost, and lack of fur enabling easier observation of heterotopically implanted tumor growth [22]. This model arises from a mutation in the *Foxn1* gene, implementing itself in the immune system as the absence of a functional thymus, and thereby, a low number of T cells [46]. Other commonly used mice models for creating PDXs include NOD-SCID/IL2λ-receptor null (NSG) with a complete deficiency of IL-2 receptor subunit gamma (IL2Rγ), BALB/-cRag2 null/ IL2λ-receptor null (BRG), and Rag-2 null/Jak3 null (BRJ) mice. The latter two show lower macrophage-mediated phagocytosis of human cells [90–92]. The absence of a functional immune system in these conventional PDX models brings a limit to study interactions between the PC and immune system. The recent development of humanized mouse models can be a solution. Generation of this model involves the engraftment of immunocompromised mice with human immune cells [93,94]. Immunocompromised mice engrafted with human immune cells are used to analyze immune system interactions, which are absent in traditional PDX models.

In the context of PDX, the choice between heterotopic and orthotopic xenograft models is crucial, as each offers distinct advantages depending on the research goals. Orthotopic xenografts involve placing the tumor cells or tissue into the corresponding anatomical site in the mouse, such as implanting PC cells into the pancreas. Qiu W. et al. explain the procedure of orthotopic implantation of human PC tumors to immunodeficient mouse models. The orthotopically created PDXs share a similar tumor microenvironment with the original tumor hence they are thought to more closely mimic the natural tumorigenesis in the original PC than subcutaneous models [95]. They also induce muscle wasting resembling cancer cachexia syndrome and seem to be reliable for metastasis studies [96,97]. However, the work with orthotopically PDXs is more challenging as it requires better imaging and technique when compared to heterotopic transplantation [95]. It was also reported that the biomarker expression was significantly different in orthotopic PDX models of the PDAC samples compared to subcutaneously established ones, in terms of significant decrease in PEAK1 and increase in MST1R biomarkers [98].

A more frequently used method is the subcutaneous heterotopic transplantation of a human PC tumor to create a PDX model (Fig. 3). Heterotopic xenografts involve implanting human tumor cells or tissue into a different site in the mouse than the original tumor location, typically under the skin. This method is simpler and allows for easy monitoring and measurement of tumor growth, making it useful for initial drug screening and basic tumor biology studies. Sychra et. al. [22] were able to successfully engraft the tumor fragment subcutaneously within an average time interval of 54 minutes in the beginning, which later became 36 minutes with a success rate of 96 % in NOD/SCID strains and 85 % in NU/NU strains [22]. Liu et al. reported fewer mice using method of expanding PDX tissue of PDAC in mice through the incomplete resection of PDX tumors. After subcutaneously implanting in three male SCID mice, it took 57 days to expand the first passage, then 34 days to expand the second, and 42 days to expand the third passage of subcutaneously engrafted PDX tissue [99].

The success of PDX models is largely dependent on various factors, including the size of the tumor sample and the conditions under which the implantation is performed. An important factor for successful engraftment is the minimum tumor sample size, as the study shows that the size above 3.5 cm was statistically significant for the successful establishment of PDXs ($p = 0.001$) [100]. Successful tumor engraftment has also been significantly correlated with the prediction of recurrence and survival. It has been found that the engraftment rate of PC tumors was profoundly associated with both overall and recurrence-free survival, with $p < 0.001$ for both [101]. Pham et al. reported the significant correlation between the engraftment at the subcutaneous site with poorer patient overall survival in PDAC PDX models ($p = 0.0095$) [102]. Another factor determining the successful implantation is the prevention of lymphoproliferation, which is a common reason for the failure of engraftment. This can be achieved by single intraperitoneal injection of rituximab before the tumor implantation [101,103]. Table 4 summarizes the comparison regarding the success rates of PDXs across different mice strains in different studies.

PDX models are invaluable tools in cancer research, offering a highly accurate representation of human tumor biology and personalized therapy potential, though their success depends on various factors such as tumor sample size, implantation timing, choice of mouse strain, and the ability to replicate the tumor microenvironment. Their genetic fidelity, use in drug testing, and potential limitations will be discussed in the following chapters.

5.1. The genetic fidelity and the histology of pancreatic cancer patient-derived xenografts

Just as with PDO models, we must also question the genetic fidelity, histology, the ability to accurately capture the biological characteristics of the original tumors, and the suitability of PDX models for drug testing. PDX models are considered valuable tools in cancer research, but it is crucial to understand how well they preserve the properties of the original tumors and what limitations they may have. The study done by Xu W et al. reported a comparison of various aspects in successive generations of PDX models in NOD/SCID mice. It showed that all three PDX generations depicted similar histopathology to the primary PDAC tissue after staining with Hematoxylin & Eosin. They also concluded that PDX models preserve the morphology, structural aspects, and the degree of differentiation of the native PDAC samples [20]. Interestingly, the stromal proportion in PDAC PDXs was comparable with the proportion of stroma in the original patient tumors in another study [107].

Mattie et al. questioned the genetic stability of PDXs by doing copy number and mutation analysis. Copy number variation profiles of early and late xenograft passages were similar, with recurrent losses and gains on the similar specific chromosomal regions. Gene expression patterns of genes known to be frequently mutated in PC, including KRAS, CTNNB1, TP53, and SMAD4 were also highly stable for each individual model between early and late passage xenografts. The authors concluded that

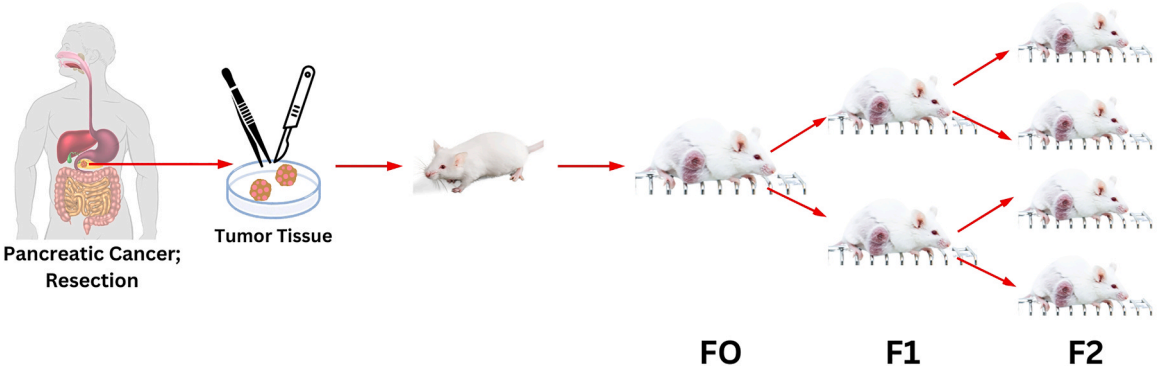

Fig. 3. Establishing a heterotopic patient-derived xenograft model for pancreatic carcinoma. F (0, 1, 2) – successive generations.

Table 4
Comparison regarding the success rates of PDXs across different mouse strains in different studies.

Histopathological subtype	Method of implantation	Mice strain	Generation	Engraftment rate (%)	Reference
Ductal adenocarcinoma	Orthotopic	NOD/SCID gamma	N/A	97.3	[104]
		NOD/SCID		57.1	
		RAG−1 deficient		0	
Multiple subtypes	Heterotopic subcutaneous	NOD/SCID	N/A	95.83	[22]
		NU/NU		85.45	
Ductal adenocarcinoma		NOD/SCID	F1	38.46	[20]
			F2	77.78	
			F3	71.43	
Multiple subtypes	Heterotopic subcutaneous	NU/NU	F1 to F3	93	[105]
Ductal adenocarcinoma	Orthotopic		N/A	55	[106]
	Heterotopic subcutaneous			69.9	
	Heterotopic intraperitoneal			57.6	

after extensive passaging, even though some difference exists between the original tumor specimens and respective xenografts, there is evidence for molecular profiles to remain stable [108]. Study done by Pham et al. also questioned the genetic fidelity of PDX models. They demonstrated the maintenance of gene expression profiles, copy number variants, and somatic mutations after serial passaging in the subsets of PDAC PDX models. The cohort had a median of 63 somatic mutations in PDXs compared to 49 mutations detected in the corresponding patient cohort. The median ratio of somatic mutations detected in the patient cohort that were found in their corresponding PDXs was 76 % [102]. The studies referred in this paper regarding the genetic fidelity of the PC PDXs are summarized in Table 5.

5.2. Pancreatic cancer patient-derived xenografts for drug sensitivity profiling

Given that one of the primary potential applications of PDX models in PC research is in drug sensitivity testing, it is essential to assess how effectively these models can replicate therapeutic responses observed in clinical settings. The study done by Rubio-Viqueira et al. tested the susceptibility of successive generations of PDXs to numerous anticancer agents, such as erlotinib, temsirolimus, and CI-1040. As the susceptibility of PDXs to the respective drugs did not change significantly, they concluded that the PDXs may serve as an *in vivo* platform to integrate the drug screening for PC [105]. Multiple drug profiling studies involving PC PDXs revealed a similar percentage of response to gemcitabine, which was between 40 % and 47 % [107,109,110]. The result of the study with sirolimus by utilizing the PC PDX model was significantly similar to the Phase II clinical trial of the same drug with response rates 24 % and 26 %, respectively [111].

Other studies have also demonstrated the potential clinical utility of PDX models in PC treatment research. Hidalgo et al. [112] successfully transplanted tumor tissue from 14 patients with refractory advanced PC into immunodeficient mice. These PDX models exhibited significant sensitivity to multiple chemotherapeutic agents, including irinotecan, bevacizumab, cetuximab, and irinotecan, highlighting the potential for personalized therapy. Similarly, Villarroel et al. [113] utilized PDX models to assess the efficacy of mitomycin C treatment, observing significant and long-lasting tumor response. However, a more nuanced picture emerged from a study by Witkiewicz et al. [114]. Despite testing over 500 single and combination drug regimens, they found that no single treatment was universally effective for the majority of PDAC PDX models. Moreover, each case exhibited unique sensitivity profiles that could not be predicted solely based on genetic analysis. This suggests that while PDX models offer valuable insights into tumor biology and drug response, relying solely on genetic analysis may not be sufficient to accurately predict therapeutic efficacy in all cases.

Another question is whether there is a difference in the therapeutic response of PDX models when implanted either orthotopically or heterotopically. When the response to the combination of 5-FU and oxaliplatin was compared between orthotopic and subcutaneous models of engraftment, a stronger response was revealed in the subcutaneous PDXs. Gemcitabine and nab-paclitaxel, however, showed a similar trend in both routes of implantation. The conclusion was that the transplantation route very likely affected the response of the PDX tumors to the treatment, but the resulting responses still demonstrated a similar trend between the two routes of implantation [107]. It has also been concluded that orthotopically established PDXs yields a more reliable model of tumor development as the implant is placed in the organ environment similar to that from which the original tumor sample was taken [115]. The studies referred in this paper regarding the usage of the PC PDXs for drug response profiling are summarized in Table 6. In conclusion, PDX models hold significant potential as a platform for drug response profiling in PC, with promising applications in predicting therapeutic outcomes and optimizing treatment strategies, especially when considering the influence of implantation methods.

Table 5
The summary of the studies referred in this paper regarding the genetic fidelity and the histology of the pancreatic cancer patient-derived xenografts.

Study	Type of Study	Focus of Study	Observation	Reference
Xu W et al.	animal models, xenografts	comparison of the differences among the generations of PDXs	all three PDX generations depicted a similar histopathology to the primary PDAC tissue PDX models preserve the morphology, structural aspects, and degree of differentiation of the PDAC samples	[20]
Hoover et al.	molecular profiling	an improved methodology for extracting high-quality RNA from formalin-fixed, paraffin-embedded cancer samples	significant difference in the biomarker expression in orthotopic PDX models of the PDAC samples compared to the subcutaneously established ones	[98]
Pham et al.	molecular profiling	the genetic fidelity of PDXs	maintenance of gene expression profiles, copy number variants, and somatic mutations after serial passaging in the subsets of PDAC PDX models	[102]
Behrens et al.	molecular profiling chemotherapy sensitivity profiling	establishing pancreatic carcinoma PDX models molecular characterization and the identification of responsiveness toward therapeutics	stromal proportion in PDAC PDX tumors was comparable with the proportion of stroma of the original tumors	[107]
Mattie et al.	molecular profiling	molecular characterization of PDXs	molecular profiles remain stable after extensive passaging, with subtle difference between the original tumor specimens and respective PDXs	[108]
Ben-David et al.	molecular profiling	monitoring the dynamics of copy number alterations in 1110 PDX samples across 24 cancer types	possible genetic differences occur once the tumor is engrafted and passaged across PDX generations	[119]

5.3. Current limitations of pancreatic cancer patient-derived xenografts

While PDX models are valuable tools in cancer research, offering a closer replication of human tumor biology, it is essential to recognize the limitations and challenges which can impact their effectiveness and application in both research and clinical settings. The significant time required to create this model, both orthotopically or heterotopically, however, may constitute a problem for patients suffering from advanced stages of PC. It clearly exceeds the period of time that would be useful for determining the best therapeutic modality [23]. Furthermore, a low success rate on one side and high cost on the other also limit the usage of PDX models in clinical trials [19]. Another drawback is seen when studying the process of metastasis and dissemination in immunocompromised mice models because the adaptive immune system has a crucial role in the selection of metastatic clones [116]. To overcome the limitations of traditional PDX models in studying tumor-immune interactions and metastasis, researchers have explored alternative approaches. Humanized mouse models, which incorporate human immune cells into immunodeficient mice, offer a more physiologically relevant environment for studying tumor-immune interactions [117]. However, the complexity and cost associated with generating and maintaining these models can be significant. Syngeneic tumor models, in which tumor cells from one mouse strain are implanted into another genetically identical mouse, on the other hand, provide a fully immunocompetent setting to study tumor-immune interactions [118]. While these approaches offer valuable insights, they still may not fully capture the complexity of human tumor biology.

Specimens to be implanted are also limited in number and size, and the engraftment success rate is under doubt, ranging between 20 % and 96 % across various laboratories [14,22,101,108]. Moreover, the potential for genetic drift over time raises concerns about the long-term reliability of PDX models for studying tumor biology and drug responses. Even though multiple studies conclude the relative genomic stability that the PDXs maintain, there is counter evidence of a significant change in copy number alterations in PDX models when compared with the corresponding primary tumors, pointing to possible genetic differences occurring once the tumor is engrafted and passaged. Ben-David et al. analyzed copy number alterations (CNAs) in 1110 PDX samples across 24 cancer types. They observed the particular CNAs acquired during PDX passaging differed from those acquired during tumor evolution in patients. Furthermore, several CNAs recurrently observed in primary tumors gradually disappeared in PDXs [119]. These findings highlight the importance of considering potential genetic differences between PDX models and primary tumors when interpreting preclinical data. Another factor to note is the 92 % genetic homology between mice and humans, still giving a considerable space for significant differences regarding ligands and receptors of both species as the ones with exactly the same function can differ in terms of their structures [120].

A unique problem with genomic characterization of PDX models is the presence of contaminating murine DNA, originating from stromal cells residing in the tumor itself, along with trace amounts of other murine tissues such as skin, hair, etc. that may be taken along with the tumor material during excision. Contamination with murine DNA further complicates the analysis, potentially leading to inaccurate results. This problem can be addressed by using a combination of cellular purification techniques and bioinformatics procedures [121]. Poirier et al. reported a thorough review of such purification methods [122]. Additionally, the absence of a functional immune system in these models limits their ability to study immune responses and the role of the immune system in cancer progression and treatment [45,46,90–92]. Lymphoproliferation and challenging techniques of orthotopic creation of PDXs are other concerns explained previously. PDXs may require further modification of implantation techniques and immunodeficient mice to increase the success rate. With regard to the implantation techniques, the success of PDX models can be improved by optimizing several factors, including the choice of implantation site [106], the careful selection of tissue fragment size [100], and the use of Matrigel, a basement membrane extract that provides a supportive extracellular matrix for tumor growth and enhances engraftment rates [102]. The specific genetic characteristics of the tumor can significantly influence the choice of mouse strain. Studies have demonstrated that the genomic stability and evolution of PDX models can vary depending on the tumor

Table 6
The summary of the studies referred in this paper regarding the usage of the pancreatic cancer patient-derived xenografts for drug response profiling.

Study	Type of Study	Focus of Study	Observation	Reference
Behrens et al.	molecular profiling chemotherapy sensitivity profiling	establishing pancreatic carcinoma PDX models molecular characterization and the identification of responsiveness toward therapeutics	implantation method very likely affected the response of the PDX tumor to the treatment, but the resulting responses still demonstrated a similar tendency	[107]
Rubio-Viqueira et al.	molecular profiling chemotherapy sensitivity testing	testing PDXs for major drug development–oriented applications in *in vivo* model	the susceptibility of successive generations of PDXs to erlotinib, temsirolimus, and CI−1040 did not change significantly	[105]
Hou et al.	chemotherapy sensitivity profiling molecular profiling	natural selection of tumor cell subclones and remodeling of tumor microenvironment cells by gemcitabine	gemcitabine sensitivity gene panel was established which can be further utilized to predict the gemcitabine sensitivity and patient prognosis	[109]
Garrido-Laguna et al.	chemotherapy sensitivity profiling	determining the efficacy of inhibiting the mammalian target of rapamycin in PC PDX models	24 % drug response rate of PDXs to sirolimus compared to 26 % in phase II clinical trials of sirolimus	[111]
Hidalgo et al.	chemotherapy sensitivity profiling	the use of the PDX as an investigational platform for therapeutic decision making and to guide PC treatment	PDXs established from 14 PC patients were treated with 63 drugs in 232 treatment regimens. A significant sensitivity to irinotecan, bevacizumab, and cetuximab was identified for 12 patients in their corresponding PDX models	[112]
Villarroel et al.	chemotherapy sensitivity profiling	the use of the PDX as an investigational platform to determine the efficacy of tumor response to mitomycin C treatment	mitomycin C treatment in a PDX generated from the patient's tumor, resulted in long-lasting (36 + months) tumor response. Inactivation of the PALB2 gene is a possible new target for personalizing cancer treatment	[113]
Witkiewicz et al.	molecular profiling chemotherapy sensitivity profiling	Testing the effectiveness and selectivity of the identified treatment responses by using PDX models	out of more than 500 single and combination drug regimens tested, no single treatment was effective for the majority of PDAC tumors, and each case had unique sensitivity profiles that could not be predicted using genetic analyses	[114]

type and its specific genetic alterations. For instance, a study by Ben-David et al. revealed that certain genetic alterations present in primary tumors may not be maintained in PDX models, highlighting the importance of considering the tumor's genetic landscape when selecting a suitable mouse strain [119].

In conclusion, while PDX models generally preserve the histological and genetic fidelity of the original tumors, making them valuable for cancer research, challenges such as genetic drift and murine DNA contamination must be addressed to fully realize their potential in preclinical studies.

Understanding the limitations of PDX models is crucial for accurately interpreting research findings and for optimizing their use in preclinical studies. While PDX models offer a valuable platform for replicating human tumor biology, researchers must be mindful of the challenges, such as time constraints, genetic stability, immune system limitations, and potential contamination, to ensure the validity and applicability of their results.

6. Conclusion

PDXs and PDOs have been utilized in various studies on individualized treatment and tested for chemosensitivity to anticancer drugs. Both models comprise relative advantages and disadvantages when being compared in genetic, practical, cost- and labor-related aspects, which should be considered according to the research intent, clinical utility, availability of funds, and time.

PDOs still comprise an artificial environment for co-cultured cells, and it is incompletely understood how the genetic selection for growth functions there. Lack of vasculature and immune components and failure to completely substitute the tumor microenvironment seen in the original PC specimen are also concerns of working with PDOs. On the other hand, PDXs bring limitations such as the number and size of specimens used, and the success rate of engraftment. The high cost and the technical expertise required to create and maintain PDX models further restrict their widespread use, especially in resource-limited settings. Their application to the study of PC metastasis and the role of immunomodulation is also limited, as in the case of PDOs. The comparison between the PDOs and PDXs in terms of multiple factors is summarized in Table 7.

PDO seems more convenient considering the lower effort and funds spent and shorter experiment duration. This is a reasonable approach given the time-demanding nature of the drug profiling. It can also be used as an alternative to PDXs in molecular profiling studies which already cost a lot. On the other hand, working with PDX seems to yield more clinically relevant results by being present as a stable disease that is transferable through generations. The significant heterogeneity of the primary tumor and the high concordance with patient response to treatment could compensate for the time-consuming and costly nature of PDXs. Both models have been shown to maintain genetic fidelity by multiple studies using molecular profiling, and both appear to provide applicable results in chemotherapy sensitivity profiling studies. Interchangeability between the two models is also suggested, as the high degree of similarities between PDXOs and parental PDXs in genomics, histopathology and pharmacology was confirmed [65]. The choice between PDOs and PDXs depends on the research focus, resource availability, and desired level of microenvironment complexity. PDOs are advantageous for high-throughput screening of a diverse array of potential therapeutic agents due to their relative ease of culture and scalability. Numerous studies support the future utility of PDOs in guiding treatment in prospective interventional trials for PC, as the drug sensitivity testing on PDOs has been shown to correlate with clinical responses to treatment in individual patients [54,61,123]. PDXs, on the other hand, offer a more physiologically relevant model, allowing for a comprehensive evaluation of drug efficacy and mechanisms of action. Indeed, numerous studies have demonstrated a strong correlation between drug sensitivity profiles observed in PDX models and the clinical responses of PC patients to corresponding therapies, highlighting the significant future potential of PDX models to accurately predict

Table 7
The summary of the comparison between patient-derived organoids and xenografts in pancreatic cancer treatment.

Model	Patient-derived organoids	Patient-derived xenografts
Cost	relatively low	high
Genetic fidelity	yes	yes
Utility in chemotherapy testing	yes	yes
Elapsed time until establishment	short	long
Tumor microenvironment	do not fully substitute	murine origin
Success Rate	relatively high	relatively low and inconsistent
Sustainability	relatively easy	demanding

therapeutic efficacy [111–113].

In the future, PDOs could be further improved by optimizing culture conditions and trying to better recapitulate the tumor microenvironment in patients. PDXs, on the other hand, may require further modification of implantation techniques and immunodeficient mice to increase the success rate, as well as the enrichment of their libraries to achieve further advances in precision cancer medicine. As both models continue to evolve, it is likely that PDOs and PDXs will become even more targeted and personalized, and they will play a crucial role in future clinical trials and personalized medicine.

Acknowledgements/funding

The work was supported by the Czech Medical Council project. No. AZV NW24–03–00024 to M.O. by the National Institute for Cancer Research – NICR (Programme EXCELES, ID Project No. LX22NPO5102) – Funded by the European Union – Next Generation EU to P.S. and by the Charles University, project GA UK No.: 308223.

Declaration of authorship

E.G. performed the research, prepared the first draft, and revised all subsequent versions of the paper. T.S., A.S, and P.S. read all paper versions and reviewed all versions of the paper, with A.S. contributing by writing some of the chapters. P.S. and M.O. supervised the study and drafted all paper versions. AI assistance was used for grammar checking and better English formulation.

CRediT authorship contribution statement

Emin Gayibov: Writing – original draft, Methodology. **Tomáš Sychra:** Writing – review & editing, Funding acquisition. **Alžběta Spálenková:** Writing – review & editing. **Pavel Souček:** Writing – review & editing, Supervision, Funding acquisition. **Martin Oliverius:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pavel Soucek reports financial support was provided by European Union. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Martin Oliverius reports financial support was provided by the Czech Medical Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Tomas Sychra reports financial support was provided by Charles University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R.L. Siegel, I. Soerjomataram, A. Jemal, Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 74 (3) (2024 May-Jun) 229–263, https://doi.org/10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.

[2] L. Rahib, B.D. Smith, R. Aizenberg, A.B. Rosenzweig, J.M. Fleshman, L. M. Matrisian, Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States, Cancer Res 74 (11) (2014 Jun 1) 2913–2921, https://doi.org/10.1158/0008-5472.CAN-14-0155. Erratum in: Cancer Res. 2014 Jul 15;74(14):4006. PMID: 24840647.

[3] R.L. Siegel, A.N. Giaquinto, A. Jemal, Cancer statistics, 2024, CA Cancer J. Clin. 74 (1) (2024 Jan-Feb) 12–49, https://doi.org/10.3322/caac.21820. Epub 2024 Jan 17. Erratum in: CA Cancer J Clin. 2024 Mar-Apr;74(2):203. doi: 10.3322/caac.21830. PMID: 38230766.

[4] P. Rawla, T. Sunkara, V. Gaduputi, Epidemiology of pancreatic cancer: global trends, etiology and risk factors, World J. Oncol. 10 (1) (2019 Feb) 10–27, https://doi.org/10.14740/wjon1166. Epub 2019 Feb 26. PMID: 30834048; PMCID: PMC6396775.

[5] Sara De Dosso, Alexander R. Siebenhüner, Thomas Winder, Alexander Meisel, Ralph Fritsch, Christoforos Astaras, Petr Szturz, Markus Borner, Treatment landscape of metastatic pancreatic cancer, Cancer Treat. Rev. 96 (2021) 102180.

[6] A. McGuigan, P. Kelly, R.C. Turkington, C. Jones, H.G. Coleman, R.S. McCain, Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes, World J. Gastroenterol. 24 (43) (2018 Nov 21) 4846–4861, https://doi.org/10.3748/wjg.v24.i43.4846. PMID: 30487695; PMCID: PMC6250924.

[7] T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, J. B. Bachet, Canadian cancer trials group and the unicancer-GI–PRODIGE Group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer, N. Engl. J. Med 379 (25) (2018 Dec 20) 2395–2406, https://doi.org/10.1056/NEJMoa1809775. PMID: 30575490.

[8] H. Oettle, P. Neuhaus, A. Hochhaus, J.T. Hartmann, K. Gellert, K. Ridwelski, M. Niedergethmann, C. Zülke, J. Fahlke, M.B. Arning, M. Sinn, A. Hinke, H. Riess, Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial, JAMA 310 (14) (2013 Oct 9) 1473–1481, https://doi.org/10.1001/jama.2013.279201. PMID: 24104372.

[9] J.P. Neoptolemos, D.D. Stocken, C. Bassi, P. Ghaneh, D. Cunningham, D. Goldstein, R. Padbury, M.J. Moore, S. Gallinger, C. Mariette, M.N. Wente, J. R. Izbicki, H. Friess, M.M. Lerch, C. Dervenis, A. Oláh, G. Butturini, R. Doi, P. A. Lind, D. Smith, J.W. Valle, D.H. Palmer, J.A. Buckels, J. Thompson, C. J. McKay, C.L. Rawcliffe, M.W. Büchler, European Study Group for Pancreatic Cancer, Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial, JAMA 304 (10) (2010 Sep 8) 1073–1081, doi: 10.1001/jama.2010.1275. PMID: 20823433.

[10] J.P. Neoptolemos, D.H. Palmer, P. Ghaneh, E.E. Psarelli, J.W. Valle, C. M. Halloran, O. Faluyi, D.A. O'Reilly, D. Cunningham, J. Wadsley, S. Darby, T. Meyer, R. Gillmore, A. Anthoney, P. Lind, B. Glimelius, S. Falk, J.R. Izbicki, G. W. Middleton, S. Cummins, P.J. Ross, H. Wasan, A. McDonald, T. Crosby, Y.T. Ma, K. Patel, D. Sherriff, R. Soomal, D. Borg, S. Sothi, P. Hammel, T. Hackert, R. Jackson, M.W. Büchler, European Study Group for Pancreatic Cancer, Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial, Lancet 389 (10073) (2017 Mar 11) 1011–1024, doi: 10.1016/S0140-6736(16)32409-6. Epub 2017 Jan 25. PMID: 28129987.

[11] M. Ducreux, A.S. Cuhna, C. Caramella, A. Hollebecque, P. Burtin, D. Goéré, T. Seufferlein, K. Haustermans, J.L. Van Laethem, T. Conroy, D. Arnold, ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (5) (2015 Sep) v56–v68, doi: 10.1093/annonc/mdv295. Erratum in: Ann Oncol. 2017 Jul 1;28(suppl_4): iv167-iv168. doi: 10.1093/annonc/mdx258. PMID: 26314780.

[12] T. Conroy, F. Desseigne, M. Ychou, O. Bouché, R. Guimbaud, Y. Bécouarn, A. Adenis, J.L. Raoul, S. Gourgou-Bourgade, C. de la Fouchardière, J. Bennouna, J.B. Bachet, F. Khemissa-Akouz, D. Péré-Vergé, C. Delbaldo, E. Assenat, B. Chauffert, P. Michel, C. Montoto-Grillot, M. Ducreux, Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, N. Engl. J. Med 364 (19) (2011 May 12) 1817–1825, doi: 10.1056/NEJMoa1011923. PMID: 21561347.

[13] D.D. Von Hoff, T. Ervin, F.P. Arena, E.G. Chiorean, J. Infante, M. Moore, T. Seay, S.A. Tjulandin, W.W. Ma, M.N. Saleh, M. Harris, M. Reni, S. Dowden, D. Laheru, N. Bahary, R.K. Ramanathan, J. Tabernero, M. Hidalgo, D. Goldstein, E. Van Cutsem, X. Wei, J. Iglesias, M.F. Renschler, Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine, N. Engl. J. Med 369 (18) (2013 Oct 31) 1691–1703, doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16. PMID: 24131140; PMCID: PMC4631139.

[14] P.L. Garcia, A.L. Miller, K.J. Yoon, Patient-derived xenograft models of pancreatic cancer: overview and comparison with other types of models, Cancers (Basel) 12 (5) (2020 May 22) 1327, https://doi.org/10.3390/cancers12051327. PMID: 32456018; PMCID: PMC7281668.

[15] G.L. Beatty, S. Eghbali, R. Kim, Deploying immunotherapy in pancreatic cancer: defining mechanisms of response and resistance, Am. Soc. Clin. Oncol. Educ. Book (37) (2017) 267–278, https://doi.org/10.1200/EDBK_175232. PMID: 28561678.

[16] C. Feig, A. Gopinathan, A. Neesse, D.S. Chan, N. Cook, D.A. Tuveson, The pancreas cancer microenvironment, Clin. Cancer Res 18 (16) (2012 Aug 15) 4266–4276, https://doi.org/10.1158/1078-0432.CCR-11-3114. PMID: 22896693; PMCID: PMC3442232.

[17] B. Zhang, F. Zhou, J. Hong, D.M. Ng, T. Yang, X. Zhou, J. Jin, F. Zhou, P. Chen, Y. Xu, The role of FOLFIRINOX in metastatic pancreatic cancer: a meta-analysis,

World J. Surg. Oncol. 19 (1) (2021 Jun 21) 182, https://doi.org/10.1186/s12957-021-02291-6. PMID: 34154596; PMCID: PMC8218408.
[18] M. Malla, F. Fekrmandi, N. Malik, H. Hatoum, S. George, R.M. Goldberg, S. Mukherjee, The evolving role of radiation in pancreatic cancer, Front Oncol. 12 (2023 Jan 11) 1060885, https://doi.org/10.3389/fonc.2022.1060885. PMID: 36713520; PMCID: PMC9875560.
[19] J.P. Neoptolemos, D.D. Stocken, H. Friess, C. Bassi, J.A. Dunn, H. Hickey, H. Beger, L. Fernandez-Cruz, C. Dervenis, F. Lacaine, M. Falconi, P. Pederzoli, A. Pap, D. Spooner, D.J. Kerr, M.W. Büchler, European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer, in: N Engl J Med, 350, 2004 Mar 18, pp. 1200–1210, doi: 10.1056/NEJMoa032295. Erratum in: N Engl J Med. 2004 Aug 12;351(7):726. PMID: 15028824.
[20] W. Xu, X.W. Yang, Z.Y. Zhao, B. Dong, X.Y. Guan, X.Y. Tian, H.G. Qian, C.Y. Hao, Establishment of pancreatic cancer patient-derived xenograft models and comparison of the differences among the generations, Am. J. Transl. Res 11 (5) (2019 May 15) 3128–3139. PMID: 31217882; PMCID: PMC6556656.
[21] Ergang Wang, Kun Xiang, Yun Zhang, Xiao-Fan Wang, Patient-derived organoids (PDOs) and PDO-derived xenografts (PDOXs): new opportunities in establishing faithful pre-clinical cancer models, ISSN 2667-0054, J. Natl. Cancer Cent. 2 (4) (2022) 263–276, https://doi.org/10.1016/j.jncc.2022.10.001.
[22] T. Sychra, R. Václavíková, A. Szabó, A. Spálenková, K. Šeborová, Balatka Š, T. Tesařová, K. Kočí, R. Gürlich, P. Souček, M. Oliverius, Introducing in vivo pancreatic cancer models for the study of new therapeutic regimens (English), Rozhl. Chir. 101 (12) (2022) 584–592, https://doi.org/10.33699/PIS.2022.101.12.584-592. PMID: 36759205.
[23] T. Goto, Patient-derived tumor xenograft models: toward the establishment of precision cancer medicine, J. Pers. Med. 10 (3) (2020 Jul 18) 64, https://doi.org/10.3390/jpm10030064. PMID: 32708458; PMCID: PMC7565668.
[24] E. Hessmann, S.M. Buchholz, I.E. Demir, S.K. Singh, T.M. Gress, V. Ellenrieder, A. Neesse, Microenvironmental determinants of pancreatic cancer, Physiol. Rev. 100 (4) (2020 Oct 1) 1707–1751, https://doi.org/10.1152/physrev.00042.2019. Epub 2020 Apr 16. PMID: 32297835.
[25] R.L. Barrett, E. Puré, Cancer-associated fibroblasts and their influence on tumor immunity and immunotherapy, Elife 9 (2020 Dec 28) e57243, https://doi.org/10.7554/eLife.57243. PMID: 33370234; PMCID: PMC7769568.
[26] T. Sychra, A. Spalenkova, S. Balatka, R. Vaclavikova, K. Seborova, M. Ehrlichova, J. Truksa, C. Sandoval-Acuña, V. Nemcova, A. Szabo, K. Koci, T. Tesarova, L. Chen, I. Ojima, M. Oliverius, P. Soucek, Third-generation taxanes SB-T-121605 and SB-T-121606 are effective in pancreatic ductal adenocarcinoma, iScience 27 (2) (2024 Jan 26) 109044, https://doi.org/10.1016/j.isci.2024.109044. PMID: 38357661; PMCID: PMC10865389.
[27] B. Zhao, C. Qin, Z. Li, et al., Multidrug resistance genes screening of pancreatic ductal adenocarcinoma based on sensitivity profile to chemotherapeutic drugs, Cancer Cell Int 22 (2022) 374, https://doi.org/10.1186/s12935-022-02785-7.
[28] P. Longati, X. Jia, J. Eimer, A. Wagman, M.R. Witt, S. Rehnmark, C. Verbeke, R. Toftgård, M. Löhr, R.L. Heuchel, 3D pancreatic carcinoma spheroids induce a matrix-rich, chemoresistant phenotype offering a better model for drug testing, BMC Cancer 13 (2013 Feb 27) 95, https://doi.org/10.1186/1471-2407-13-95. PMID: 23446043; PMCID: PMC3617005.
[29] G. Giustarini, G. Teng, A. Pavesi, G. Adriani, Characterization of 3D heterocellular spheroids of pancreatic ductal adenocarcinoma for the study of cell interactions in the tumor immune microenvironment, Front Oncol. 13 (2023 Jul 14) 1156769, https://doi.org/10.3389/fonc.2023.1156769. PMID: 37519820; PMCID: PMC10375712.
[30] A. Ivascu, M. Kubbies, Rapid generation of single-tumor spheroids for high-throughput cell function and toxicity analysis, J. Biomol. Screen 11 (8) (2006 Dec) 922–932, https://doi.org/10.1177/1087057106292763. Epub 2006 Sep 14. PMID: 16973921.
[31] I. Dufau, C. Frongia, F. Sicard, L. Dedieu, P. Cordelier, F. Ausseil, B. Ducommun, A. Valette, Multicellular tumor spheroid model to evaluate spatio-temporal dynamics effect of chemotherapeutics: application to the gemcitabine/CHK1 inhibitor combination in pancreatic cancer, BMC Cancer 12 (2012 Jan 13) 15, https://doi.org/10.1186/1471-2407-12-15. PMID: 22244109; PMCID: PMC3280152.
[32] F. Hirschhaeuser, H. Menne, C. Dittfeld, J. West, W. Mueller-Klieser, L.A. Kunz-Schughart, Multicellular tumor spheroids: an underestimated tool is catching up again, J. Biotechnol. 148 (1) (2010 Jul 1) 3–15, https://doi.org/10.1016/j.jbiotec.2010.01.012. Epub 2010 Jan 25. PMID: 20097238.
[33] K. Białkowska, P. Komorowski, M. Bryszewska, K. Miłowska, Spheroids as a type of three-dimensional cell cultures-examples of methods of preparation and the most important application, Int J. Mol. Sci. 21 (17) (2020 Aug 28) 6225, https://doi.org/10.3390/ijms21176225. PMID: 32872135; PMCID: PMC7503223.
[34] S.J. Han, S. Kwon, K.S. Kim, Challenges of applying multicellular tumor spheroids in preclinical phase, Cancer Cell Int 21 (1) (2021 Mar 4) 152, https://doi.org/10.1186/s12935-021-01853-8. PMID: 33663530; PMCID: PMC7934264.
[35] E. Ibello, F. Saracino, D. Delle Cave, S. Buonaiuto, F. Amoroso, G. Andolfi, M. Corona, O. Guardiola, V. Colonna, B. Sainz, Jr, L. Altucci, D. De Cesare, G. Cobellis, E. Lonardo, E.J. Patriarca, C. D'Aniello, G. Minchiotti, Three-dimensional environment sensitizes pancreatic cancer cells to the anti-proliferative effect of budesonide by reprogramming energy metabolism, J. Exp. Clin. Cancer Res 43 (1) (2024 Jun 14) 165, https://doi.org/10.1186/s13046-024-03072-1. PMID: 38877560; PMCID: PMC11177459.
[36] O. Firuzi, P.P. Che, B. El Hassouni, M. Buijs, S. Coppola, M. Löhr, N. Funel, R. Heuchel, I. Carnevale, T. Schmidt, G. Mantini, A. Avan, L. Saso, G.J. Peters, E. Giovannetti, Role of c-MET inhibitors in overcoming drug resistance in spheroid models of primary human pancreatic cancer and stellate cells, Cancers (Basel) 11 (5) (2019 May 8) 638, https://doi.org/10.3390/cancers11050638. PMID: 31072019; PMCID: PMC6562408.
[37] M.R. Haque, C.R. Wessel, D.D. Leary, et al., Patient-derived pancreatic cancer-on-a-chip recapitulates the tumor microenvironment, Micro Nanoeng. 8 (2022) 36, https://doi.org/10.1038/s41378-022-00370-6.
[38] Benjamin F.L. Lai, Rick X. Lu, Y. Hu, H.L. Davenport, W. Dou, E.Y. Wang, N. Radulovich, M.S. Tsao, Y. Sun, M. Radisic, Recapitulating pancreatic tumor microenvironment through synergistic use of patient organoids and organ-on-a-chip vasculature, Adv. Funct. Mater. 30 (48) (2020 Nov 25) 2000545, https://doi.org/10.1002/adfm.202000545. Epub 2020 Jun 8. PMID: 33692660; PMCID: PMC7939064.
[39] M.R. Haque, T.H. Rempert, T.A. Al-Hilal, C. Wang, A. Bhushan, F. Bishehsari, Organ-chip models: opportunities for precision medicine in pancreatic cancer, Cancers 13 (17) (2021 Sep 6) 4487, https://doi.org/10.3390/cancers13174487. PMID: 34503294; PMCID: PMC8430573.
[40] C. Bouquerel, A. Dubrova, I. Hofer, D.T.T. Phan, M. Bernheim, S. Ladaigue, C. Cavaniol, D. Maddalo, L. Cabel, F. Mechta-Grigoriou, C. Wilhelm, G. Zalcman, M.C. Parrini, S. Descroix, Bridging the gap between tumor-on-chip and clinics: a systematic review of 15 years of studies, Lab Chip 23 (18) (2023 Sep 13) 3906–3935, https://doi.org/10.1039/d3lc00531c. PMID: 37592893.
[41] C.M. Leung, P. de Haan, K. Ronaldson-Bouchard, et al., A guide to the organ-on-a-chip, Nat. Rev. Methods Prim. 2 (2022) 33, https://doi.org/10.1038/s43586-022-00118-6.
[42] S.B. Campbell, Q. Wu, J. Yazbeck, C. Liu, S. Okhovatian, M. Radisic, Beyond polydimethylsiloxane: alternative materials for fabrication of organ-on-a-chip devices and microphysiological systems, ACS Biomater. Sci. Eng. 7 (7) (2021 Jul 12) 2880–2899, https://doi.org/10.1021/acsbiomaterials.0c00640. Epub 2020 Sep 9. PMID: 34275293.
[43] B.J. Van Meer, H. de Vries, K.S.A. Firth, J. van Weerd, L.G.J. Tertoolen, H.B. J. Karperien, P. Jonkheijm, C. Denning, A.P. IJzerman, C.L. Mummery, Small molecule absorption by PDMS in the context of drug response bioassays, Biochem Biophys. Res Commun. 482 (2) (2017 Jan 8) 323–328, https://doi.org/10.1016/j.bbrc.2016.11.062. Epub 2016 Nov 14. PMID: 27856254; PMCID: PMC5240851.
[44] B.A. Ruggeri, F. Camp, S. Miknyoczki, Animal models of disease: pre-clinical animal models of cancer and their applications and utility in drug discovery, Biochem Pharm. 87 (1) (2014 Jan 1) 150–161, https://doi.org/10.1016/j.bcp.2013.06.020. Epub 2013 Jun 28. PMID: 23817077.
[45] I. Garrido-Laguna, M. Uson, N.V. Rajeshkumar, A.C. Tan, E. de Oliveira, C. Karikari, M.C. Villaroel, A. Salomon, G. Taylor, R. Sharma, R.H. Hruban, A. Maitra, D. Laheru, B. Rubio-Viqueira, A. Jimeno, M. Hidalgo, Tumor engraftment in nude mice and enrichment in stroma- related gene pathways predict poor survival and resistance to gemcitabine in patients with pancreatic cancer, Clin. Cancer Res 17 (17) (2011 Sep 1) 5793–5800, https://doi.org/10.1158/1078-0432.CCR-11-0341. Epub 2011 Jul 8. PMID: 21742805; PMCID: PMC3210576.
[46] C. Morton, P. Houghton, Establishment of human tumor xenografts in immunodeficient mice, Nat. Protoc. 2 (2007) 247–250, https://doi.org/10.1038/nprot.2007.25.
[47] Y. Lu, D. Xu, J. Peng, Z. Luo, C. Chen, Y. Chen, H. Chen, M. Zheng, P. Yin, Z. Wang, HNF1A inhibition induces the resistance of pancreatic cancer cells to gemcitabine by targeting ABCB1, EBioMedicine 44 (2019 Jun) 403–418, https://doi.org/10.1016/j.ebiom.2019.05.013. Epub 2019 May 15. PMID: 31103629; PMCID: PMC6606897.
[48] H. Tian, Y. Lyu, Y.G. Yang, Z. Hu, Humanized rodent models for cancer research, Front Oncol. 10 (2020 Sep 11) 1696, https://doi.org/10.3389/fonc.2020.01696. PMID: 33042811; PMCID: PMC7518015.
[49] A. Gopinathan, J.P. Morton, D.I. Jodrell, O.J. Sansom, GEMMs as preclinical models for testing pancreatic cancer therapies, Dis. Model Mech. 8 (10) (2015 Oct 1) 1185–1200, https://doi.org/10.1242/dmm.021055. PMID: 26438692; PMCID: PMC4610236.
[50] K.K. Frese, D.A. Tuveson, Maximizing mouse cancer models, Nat. Rev. Cancer 7 (9) (2007 Sep) 645–658, https://doi.org/10.1038/nrc2192. PMID: 17687385.
[51] S.R. Hingorani, L. Wang, A.S. Multani, C. Combs, T.B. Deramaudt, R.H. Hruban, A.K. Rustgi, S. Chang, D.A. Tuveson, Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice, Cancer Cell 7 (2005) 469–483, https://doi.org/10.1016/j.ccr.2005.04.023.
[52] C.B. Westphalen, K.P. Olive, Genetically engineered mouse models of pancreatic cancer, Cancer J. 18 (2012) 502–510, https://doi.org/10.1097/PPO.0b013e31827ab4c4.
[53] N.M. Gades, A. Ohash, L.D. Mills, M.A. Rowley, K.S. Predmore, R.J. Marler, F. J. Couch, Spontaneous vulvar papillomas in a colony of mice used for pancreatic cancer research, Comp. Med. 58 (2008) 271–275.
[54] L. Demyan, A.N. Habowski, D. Plenker, D.A. King, O.J. Standring, C. Tsang, St Surin, L. Rishi, A. Crawford, J.M. Boyd, J. Pasha, S.A. Patel, H. Galluzzo, Z. Metz, C. Gregersen, P.K. Fox, S. Valente, C. Abadali, S. Matadial-Ragoo, S. DePeralta, D.K. Deutsch, G.B. Herman, J.M. Talamini, M.A. Tuveson, D. A. Weiss, MJ. pancreatic cancer patient-derived organoids can predict response to neoadjuvant chemotherapy, Ann. Surg. 276 (3) (2022 Sep 1) 450–462, https://doi.org/10.1097/SLA.0000000000005558. Epub 2022 Jun 27. PMID: 35972511; PMCID: PMC10202108.
[55] E.R. Shamir, A.J. Ewald, Three-dimensional organotypic culture: experimental models of mammalian biology and disease, Nat. Rev. Mol. Cell Biol. 15 (10) (2014 Oct) 647–664, https://doi.org/10.1038/nrm3873. Epub 2014 Sep 17. PMID: 25237826; PMCID: PMC4352326.

[56] Evangelia Sereti, Irida Papapostolou, Konstantinos Dimas, Pancreatic cancer organoids: an emerging platform for precision medicine? Biomedicines 11 (3) (2023) 890, https://doi.org/10.3390/biomedicines11030890.
[57] D. Tuveson, H. Clevers, Cancer modeling meets human organoid technology, Science 364 (6444) (2019 Jun 7) 952–955, https://doi.org/10.1126/science.aaw6985. PMID: 31171691.
[58] M. Huch, P. Bonfanti, S.F. Boj, T. Sato, C.J. Loomans, M. van de Wetering, M. Sojoodi, V.S. Li, J. Schuijers, A. Gracanin, F. Ringnalda, H. Begthel, K. Hamer, J. Mulder, J.H. van Es, E. de Koning, R.G. Vries, H. Heimberg, H. Clevers, Unlimited in vitro expansion of adult bi-potent pancreas progenitors through the Lgr5/R-spondin axis, EMBO J. 32 (20) (2013 Oct 16) 2708–2721, https://doi.org/10.1038/emboj.2013.204. Epub 2013 Sep 17. PMID: 24045232; PMCID: PMC3801438.
[59] S.F. Boj, C.I. Hwang, L.A. Baker, I.I. Chio, D.D. Engle, V. Corbo, M. Jager, M. Ponz-Sarvise, H. Tiriac, M.S. Spector, A. Gracanin, T. Oni, K.H. Yu, R. van Boxtel, M. Huch, K.D. Rivera, J.P. Wilson, M.E. Feigin, D. Öhlund, A. Handly-Santana, C.M. Ardito-Abraham, M. Ludwig, E. Elyada, B. Alagesan, G. Biffi, G. N. Yordanov, B. Delcuze, B. Creighton, K. Wright, Y. Park, F.H. Morsink, I. Q. Molenaar, I.H. Borel Rinkes, E. Cuppen, Y. Hao, Y. Jin, I.J. Nijman, C. Iacobuzio-Donahue, S.D. Leach, D.J. Pappin, M. Hammell, D.S. Klimstra, O. Basturk, R.H. Hruban, G.J. Offerhaus, R.G. Vries, H. Clevers, D.A. Tuveson, Organoid models of human and mouse ductal pancreatic cancer, Cell 160 (1-2) (2015 Jan 15) 324–338, https://doi.org/10.1016/j.cell.2014.12.021. Epub 2014 Dec 31. PMID: 25557080; PMCID: PMC4334572.
[60] H. Xu, X. Lyu, M. Yi, W. Zhao, Y. Song, K. Wu, Organoid technology and applications in cancer research, J. Hematol. Oncol. 11 (1) (2018 Sep 15) 116, https://doi.org/10.1186/s13045-018-0662-9. PMID: 30219074; PMCID: PMC6139148.
[61] W. Choi, Y.H. Kim, S.M. Woo, Y. Yu, M.R. Lee, W.J. Lee, J.W. Chun, S.H. Sim, H. Chae, H. Shim, K.S. Lee, S.Y. Kong, Establishment of patient-derived organoids using ascitic or pleural fluid from cancer patients, Cancer Res Treat. 55 (4) (2023 Oct) 1077–1086, https://doi.org/10.4143/crt.2022.1630. Epub 2023 Jun 12. PMID: 37309112; PMCID: PMC10582554.
[62] H. Tiriac, J.C. Bucobo, D. Tzimas, S. Grewel, J.F. Lacomb, L.M. Rowehl, S. Nagula, M. Wu, J. Kim, A. Sasson, S. Vignesh, L. Martello, M. Munoz-Sagastibelza, J. Somma, D.A. Tuveson, E. Li, J.M. Buscaglia, Successful creation of pancreatic cancer organoids by means of EUS-guided fine-needle biopsy sampling for personalized cancer treatment, Gastrointest. Endosc. 87 (6) (2018 Jun) 1474–1480, https://doi.org/10.1016/j.gie.2017.12.032. Epub 2018 Jan 9. PMID: 29325707; PMCID: PMC6143289.
[63] H. Tiriac, P. Belleau, D.D. Engle, D. Plenker, A. Deschênes, T.D.D. Somerville, F.E. M. Froeling, R.A. Burkhart, R.E. Denroche, G.H. Jang, K. Miyabayashi, C. M. Young, H. Patel, M. Ma, J.F. LaComb, R.L.D. Palmaira, A.A. Javed, J.C. Huynh, M. Johnson, K. Arora, N. Robine, M. Shah, R. Sanghvi, A.B. Goetz, C.Y. Lowder, L. Martello, E. Driehuis, N. LeComte, G. Askan, C.A. Iacobuzio-Donahue, H. Clevers, L.D. Wood, R.H. Hruban, E. Thompson, A.J. Aguirre, B.M. Wolpin, A. Sasson, J. Kim, M. Wu, J.C. Bucobo, P. Allen, D.V. Sejpal, W. Nealon, J. D. Sullivan, J.M. Winter, P.A. Gimotty, J.L. Grem, D.J. DiMaio, J.M. Buscaglia, P. M. Grandgenett, J.R. Brody, O. Hollingsworth MA, Kane G.M. Notta, F. Kim, E. Crawford, J.M. Devoe, C. Ocean, A. Wolfgang, C.L. Yu, K.H. Li, E. Vakoc, C. R. Hubert, B. Fischer, S.E. Wilson, J.M. Moffitt, R. Knox, J. Krasnitz, A. Gallinger, S. Tuveson, DA. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer, Cancer Discov. 8 (9) (2018 Sep) 1112–1129, https://doi.org/10.1158/2159-8290.CD-18-0349. Epub 2018 May 31. PMID: 29853643; PMCID: PMC6125219.
[64] O.H. Usman, L. Zhang, G. Xie, et al., Genomic heterogeneity in pancreatic cancer organoids and its stability with culture, npj Genom. Med. 7 (2022) 71, https://doi.org/10.1038/s41525-022-00342-9.
[65] X. Xu, R. Kumari, J. Zhou, J. Chen, B. Mao, J. Wang, M. Zheng, X. Tu, X. An, X. Chen, L. Zhang, X. Tian, H. Wang, X. Dong, Z. Bao, S. Guo, X. Ouyang, L. Shang, F. Wang, X. Yan, R. Zhang, R.G.J. Vries, H. Clevers, Q.X. Li, A living biobank of matched pairs of patient-derived xenografts and organoids for cancer pharmacology, PLoS One 18 (1) (2023 Jan 5) e0279821, https://doi.org/10.1371/journal.pone.0279821. PMID: 36602988; PMCID: PMC9815646.
[66] S.F. Boj, C.I. Hwang, L.A. Baker, D.D. Engle, D.A. Tuveson, H. Clevers, Model organoids provide new research opportunities for ductal pancreatic cancer, Mol. Cell Oncol. 3 (1) (2015 Feb 23) e1014757, https://doi.org/10.1080/23723556.2015.1014757. PMID: 27308531; PMCID: PMC4845167.
[67] E. Driehuis, A. van Hoeck, K. Moore, S. Kolders, H.E. Francies, M.C. Gulersonmez, E.C.A. Stigter, B. Burgering, V. Geurts, A. Gracanin, G. Bounova, F.H. Morsink, R. Vries, S. Boj, J. van Es, G.J.A. Offerhaus, O. Kranenburg, M.J. Garnett, L. Wessels, E. Cuppen, L.A.A. Brosens, H. Clevers, Pancreatic cancer organoids recapitulate disease and allow personalized drug screening, Proc. Natl. Acad. Sci. USA 116 (52) (2019 Dec 26) 26580–26590, https://doi.org/10.1073/pnas.1911273116. Epub 2019 Dec 9. PMID: 31818951; PMCID: PMC6936689.
[68] K. Chen, Y. Ma, X. Zhong, J. Lan, D. Long, X. Tian, Y. Yang, Y. Yang, Single-cell transcriptome profiling of primary tumors and paired organoids of pancreatobiliary cancer, Cancer Lett. 582 (2024 Feb 1) 216586, https://doi.org/10.1016/j.canlet.2023.216586. Epub 2023 Dec 9. PMID: 38081505.
[69] Y. Zhang, C.W. Houchen, M. Li, Patient-derived organoid pharmacotyping guides precision medicine for pancreatic cancer, Clin. Cancer Res 28 (15) (2022 Aug 2) 3176–3178, https://doi.org/10.1158/1078-0432.CCR-22-1083. PMID: 35617521; PMCID: PMC9357115.
[70] C.K. Hirt, T.H. Booij, L. Grob, P. Simmler, N.C. Toussaint, D. Keller, D. Taube, V. Ludwig, A. Goryachkin, C. Pauli, D. Lenggenhager, D.J. Stekhoven, C. U. Stirnimann, K. Endhardt, F. Ringnalda, L. Villiger, A. Siebenhüner, S. Karkampouna, M. De Menna, J. Beshay, H. Klett, M. Kruithof-de Julio, J. Schüler, G. Schwank, Drug screening and genome editing in human pancreatic cancer organoids identifies drug-gene interactions and candidates for off-label treatment. Cell Genom. 2 (2) (2022 Feb) 100095 https://doi.org/10.1016/j.xgen.2022.100095. PMID: 35187519; PMCID: PMC7612395.
[71] V. Gassl, M.R. Aberle, B. Boonen, R.D.W. Vaes, S.W.M. Olde Damink, S.S. Rensen, Chemosensitivity of 3D pancreatic cancer organoids is not affected by transformation to 2d culture or switch to physiological culture medium, Cancers 14 (2022) 5617, https://doi.org/10.3390/cancers14225617.
[72] S. Hou, H. Tiriac, B.P. Sridharan, L. Scampavia, F. Madoux, J. Seldin, G.R. Souza, D. Watson, D. Tuveson, T.P. Spicer, Advanced development of primary pancreatic organoid tumor models for high-throughput phenotypic drug screening, SLAS Discov. 23 (6) (2018 Jul) 574–584, https://doi.org/10.1177/2472555218766842. Epub 2018 Apr 19. PMID: 29673279; PMCID: PMC6013403.
[73] A. Armstrong, M.R. Haque, S. Mirbagheri, U. Barlass, D.Z. Gilbert, J. Amin, A. Singh, A. Naqib, F. Bishehsari, Multiplex patient-based drug response assay in pancreatic ductal adenocarcinoma, Biomedicines 9 (7) (2021 Jun 23) 705, https://doi.org/10.3390/biomedicines9070705. PMID: 34201419; PMCID: PMC8301364.
[74] S. Watanabe, A. Yogo, T. Otsubo, H. Umehara, J. Oishi, T. Kodo, T. Masui, S. Takaishi, H. Seno, S. Uemoto, E. Hatano, Establishment of patient-derived organoids and a characterization-based drug discovery platform for treatment of pancreatic cancer, BMC Cancer 22 (1) (2022 May 3) 489, https://doi.org/10.1186/s12885-022-09619-9. PMID: 35505283; PMCID: PMC9063137.
[75] M. Le Compte, E.C. De La Hoz, S. Peeters, F.R. Fortes, C. Hermans, A. Domen, E. Smits, F. Lardon, T. Vandamme, A. Lin, S. Vanlanduit, G. Roeyen, S. Van Laere, H. Prenen, M. Peeters, C. Deben, Single-organoid analysis reveals clinically relevant treatment-resistant and invasive subclones in pancreatic cancer, NPJ Precis Oncol. 7 (1) (2023 Dec 8) 128, https://doi.org/10.1038/s41698-023-00480-y. PMID: 38066116; PMCID: PMC10709344.
[76] D. Behrens, W. Walther, I. Fichtner, Pancreatic cancer models for translational research, Pharmacol. Ther. 173 (2017) 146–158, https://doi.org/10.1016/j.pharmthera.2017.02.013.
[77] T.G. Krieger, S. Le Blanc, J. Jabs, F.W. Ten, N. Ishaque, K. Jechow, O. Debnath, C. S. Leonhardt, A. Giri, R. Eils, O. Strobel, C. Conrad, Single-cell analysis of patient-derived PDAC organoids reveals cell state heterogeneity and a conserved developmental hierarchy, Nat. Commun. 12 (1) (2021 Oct 5) 5826, https://doi.org/10.1038/s41467-021-26059-4. PMID: 34611171; PMCID: PMC8492851.
[78] M.H. Geurts, H. Clevers, CRISPR engineering in organoids for gene repair and disease modelling, Nat. Rev. Bioeng. 1 (2023) 32–45, https://doi.org/10.1038/s44222-022-00013-5.
[79] H. Aboulkheyr Es, L. Montazeri, A.R. Aref, M. Vosough, H. Baharvand, Personalized cancer medicine: an organoid approach, Trends Biotechnol. 36 (4) (2018 Apr) 358–371, https://doi.org/10.1016/j.tibtech.2017.12.005. Epub 2018 Jan 20. PMID: 29366522.
[80] S. Schuth, S. Le Blanc, T.G. Krieger, et al., Patient-specific modeling of stroma-mediated chemoresistance of pancreatic cancer using a three-dimensional organoid-fibroblast co-culture system, J. Exp. Clin. Cancer Res 41 (2022) 312, https://doi.org/10.1186/s13046-022-02519-7.
[81] Y.H. Go, W.H. Choi, W.J. Bae, S.I. Jung, C.H. Cho, S.A. Lee, J.S. Park, J.M. Ahn, S. W. Kim, K.J. Lee, D. Lee, J. Yoo, Modeling pancreatic cancer with patient-derived organoids integrating cancer-associated fibroblasts, Cancers (Basel) 14 (9) (2022 Apr 21) 2077, https://doi.org/10.3390/cancers14092077. PMID: 35565206; PMCID: PMC9103557.
[82] T. Kometani, K. Kamo, T. Kido, N. Hiraoka, T. Chibazakura, K. Unno, K. Sekine, Development of a novel co-culture system using human pancreatic cancer cells and human iPSC-derived stellate cells to mimic the characteristics of pancreatic ductal adenocarcinoma in vitro, Biochem Biophys. Res Commun. 658 (2023 May 28) 1–9, https://doi.org/10.1016/j.bbrc.2023.03.061. Epub 2023 Mar 24. PMID: 37004297.
[83] A. Lahusen, J. Cai, R. Schirmbeck, et al., A pancreatic cancer organoid-in-matrix platform shows distinct sensitivities to T cell killing, Sci. Rep. 14 (2024) 9377, https://doi.org/10.1038/s41598-024-60107-5.
[84] M. Geyer, D. Schreyer, L.M. Gaul, et al., A microfluidic-based PDAC organoid system reveals the impact of hypoxia in response to treatment, Cell Death Discov. 9 (2023) 20, https://doi.org/10.1038/s41420-023-01334-z.
[85] T.L. Hogenson, H. Xie, W.J. Phillips, M.D. Toruner, J.J. Li, I.P. Horn, D. J. Kennedy, L.L. Almada, D.L. Marks, R.M. Carr, M. Toruner, A.N. Sigafoos, A. N. Koenig-Kappes, R.L. Olson, E.J. Tolosa, C. Zhang, H. Li, J.D. Doles, J. Bleeker, M.T. Barrett, J.H. Boyum, B.R. Kipp, A. Mahipal, J.M. Hubbard, T.J. Scheffler Hanson, G.M. Petersen, S. Dasari, A.L. Oberg, M.J. Truty, R.P. Graham, M.J. Levy, M. Zhu, D.D. Billadeau, A.A. Adjei, N. Dusetti, J.L. Iovanna, T.S. Bekaii-Saab, W. W. Ma, M.E. Fernandez-Zapico, Culture media composition influences patient-derived organoid ability to predict therapeutic responses in gastrointestinal cancers, JCI Insight 7 (22) (2022 Nov 22) e158060, https://doi.org/10.1172/jci.insight.158060. PMID: 36256477; PMCID: PMC9746806.
[86] S.S. Wilson, M. Mayo, T. Melim, H. Knight, L. Patnaude, X. Wu, L. Phillips, S. Westmoreland, R. Dunstan, E. Fiebiger, S. Terrillon, Optimized culture conditions for improved growth and functional differentiation of mouse and human colon organoids, Front Immunol. 11 (2021 Feb 12) 547102, https://doi.org/10.3389/fimmu.2020.547102. PMID: 33643277; PMCID: PMC7906999.
[87] G. Kaushik, M.P. Ponnusamy, S.K. Batra, Concise review: current status of three-dimensional organoids as preclinical models, Stem Cells 36 (9) (2018 Sep) 1329–1340, https://doi.org/10.1002/stem.2852. Epub 2018 Jul 29. PMID: 29770526; PMCID: PMC6158106.

[88] S. Wen, X. Lin, W. Luo, Y. Pan, F. Liao, Z. Wang, B. Zhan, J. Feng, H. Huang, Metabolic difference between patient-derived xenograft model of pancreatic ductal adenocarcinoma and corresponding primary tumor, BMC Cancer 24 (1) (2024 Apr 17) 485, https://doi.org/10.1186/s12885-024-12193-x. PMID: 38632504; PMCID: PMC11022326.
[89] L.D. Shultz, P.A. Schweitzer, S.W. Christianson, B. Gott, I.B. Schweitzer, B. Tennent, S. McKenna, L. Mobraaten, T.V. Rajan, D.L. Greiner, et al., Multiple defects in innate and adaptive immunologic function in NOD/LtSz-scid mice, J. Immunol. 154 (1) (1995 Jan 1) 180–191. PMID: 7995938.
[90] Y. Zhou, J. Xia, S. Xu, T. She, Y. Zhang, Y. Sun, M. Wen, T. Jiang, Y. Xiong, J. Lei, Experimental mouse models for translational human cancer research, Front Immunol. 14 (2023 Mar 10) 1095388, https://doi.org/10.3389/fimmu.2023.1095388. PMID: 36969176; PMCID: PMC10036357.
[91] E. Traggiai, L. Chicha, L. Mazzucchelli, L. Bronz, J.C. Piffaretti, A. Lanzavecchia, M.G. Manz, Development of a human adaptive immune system in cord blood cell-transplanted mice, Science 304 (2004) 104–107, https://doi.org/10.1126/science.1093933.
[92] A. Ono, S. Hattori, R. Kariya, S. Iwanaga, M. Taura, H. Harada, S. Suzu, S. Okada, Comparative study of human hematopoietic cell engraftment into balb/c and c57bl/6 strain of rag-2/jak3 double-deficient mice, J. Biomed. Biotechnol. 2011 (2011) 539748, https://doi.org/10.1155/2011/539748.
[93] M.M. Cogels, R. Rouas, G.E. Ghanem, P. Martinive, A. Awada, D. Van Gestel, M. Krayem, Humanized mice as a valuable pre-clinical model for cancer immunotherapy research, Front Oncol. 11 (2021 Nov 18) 784947, https://doi.org/10.3389/fonc.2021.784947. PMID: 34869042; PMCID: PMC8636317.
[94] T. Martinov, K.M. McKenna, W.H. Tan, E.J. Collins, A.R. Kehret, J.D. Linton, T. M. Olsen, N. Shobaki, A. Rongvaux, Building the next generation of humanized hemato-lymphoid system mice, Front Immunol. 12 (2021 Feb 22) 643852, https://doi.org/10.3389/fimmu.2021.643852. PMID: 33692812; PMCID: PMC7938325.
[95] W. Qiu, G.H. Su, Development of orthotopic pancreatic tumor mouse models, Methods Mol. Biol. 980 (2013) 215–223, https://doi.org/10.1007/978-1-62703-287-2_11. PMID: 23359156; PMCID: PMC4049460.
[96] R.L. Nosacka, A.E. Delitto, D. Delitto, R. Patel, S.M. Judge, J.G. Trevino, A. R. Judge, Distinct cachexia profiles in response to human pancreatic tumours in mouse limb and respiratory muscle, J. Cachex-.-. Sarcopenia Muscle 11 (3) (2020 Jun) 820–837, https://doi.org/10.1002/jcsm.12550. Epub 2020 Feb 10. PMID: 32039571; PMCID: PMC7296265.
[97] K.L. Go, D. Delitto, S.M. Judge, et al., Orthotopic patient-derived pancreatic cancer xenografts engraft into the pancreatic parenchyma, metastasize, and induce muscle wasting to recapitulate the human disease, Pancreas 46 (6) (2017) 813–819.
[98] M. Hoover, Y. Adamian, M. Brown, et al., A novel method for RNA extraction from FFPE samples reveals significant differences in biomarker expression between orthotopic and subcutaneous pancreatic cancer patient-derived xenografts, Oncotarget 8 (4) (2017) 5885.
[99] Z. Liu, M.H.Y. Ahn, T. Kurokawa, et al., A fast, simple, and cost-effective method of expanding patient-derived xenograft mouse models of pancreatic ductal adenocarcinoma, J. Transl. Med 18 (2020) 255, https://doi.org/10.1186/s12967-020-02414-9.
[100] E. Jun, J. Jung, S.Y. Jeong, E.K. Choi, M.B. Kim, J.S. Lee, S.M. Hong, H.S. Seol, C. Hwang, R.M. Hoffman, I.K. Shim, S. Chang, S.C. Kim, Surgical and oncological factors affecting the successful engraftment of patient-derived xenografts in pancreatic ductal adenocarcinoma, Anticancer Res 36 (2) (2016 Feb) 517–521. PMID: 26851005.
[101] I.T. Lynch, A.M. Abdelrahman, R. Alva-Ruiz, A. Fogliati, R.P. Graham, R. Smoot, M.J. Truty, Cancer "avatar" models: patient-derived xenograft growth and recurrence and survival after surgical resection of pancreaticobiliary cancers, J. Am. Coll. Surg. 237 (3) (2023 Jun 16) 483–500, https://doi.org/10.1097/XCS.0000000000000786. Epub ahead of print. PMID: 37326316; PMCID: PMC10417234.
[102] N.A. Pham, N. Radulovich, E. Ibrahimov, et al., Patient-derived tumor xenograft and organoid models established from resected pancreatic, duodenal and biliary cancers, Sci. Rep. 11 (2021) 10619, https://doi.org/10.1038/s41598-021-90049-1.
[103] J.L. Leiting, M.C. Hernandez, L. Yang, et al., Rituximab decreases lymphoproliferative tumor formation in hepatopancreaticobiliary and gastrointestinal cancer patient-derived xenografts, Sci. Rep. 9 (2019) 5901.
[104] D.E. Magouliotis, K. Lafazanis, F. Koutsougianni, N. Sakellaridis, M. Ioannou, D. Zacharoulis, K. Dimas, Establishment of patient-derived orthotopic xenografts (PDX) as models for pancreatic ductal adenocarcinoma, Vivo 36 (3) (2022 May-Jun) 1114–1119, https://doi.org/10.21873/invivo.12809. PMID: 35478141; PMCID: PMC9087066.
[105] B. Rubio-Viqueira, A. Jimeno, G. Cusatis, X. Zhang, C. Iacobuzio-Donahue, C. Karikari, C. Shi, K. Danenberg, P.V. Danenberg, H. Kuramochi, K. Tanaka, S. Singh, H. Salimi-Moosavi, N. Bouraoud, M.L. Amador, S. Altiok, P. Kulesza, C. Yeo, W. Messersmith, J. Eshleman, R.H. Hruban, A. Maitra, M. Hidalgo, An in vivo platform for translational drug development in pancreatic cancer, Clin. Cancer Res 12 (15) (2006 Aug 1) 4652–4661, https://doi.org/10.1158/1078-0432.CCR-06-0113. PMID: 16899615.
[106] M. Rubio-Manzanares Dorado, L.M. Marín Gómez, D. Aparicio Sánchez, S. Pereira Arenas, J.M. Praena-Fernández, J.J. Borrero Martín, F. Farfán López, M.Á. Gómez Bravo, J. Muntané Relat, J. Padillo Ruiz, Translational pancreatic cancer research: a comparative study on patient-derived xenograft models, World J. Gastroenterol. 24 (7) (2018 Feb 21) 794–809, https://doi.org/10.3748/wjg.v24.i7.794. PMID: 29467550; PMCID: PMC5807938.
[107] D. Behrens, U. Pfohl, T. Conrad, M. Becker, B. Brzezicha, B. Büttner, S. Wagner, C. Hallas, R. Lawlor, V. Khazak, et al., Establishment and thorough characterization of xenograft (PDX) models derived from patients with pancreatic cancer for molecular analyses and chemosensitivity testing, Cancers 15 (2023) 5753, https://doi.org/10.3390/cancers15245753.
[108] M. Mattie, A. Christensen, M.S. Chang, W. Yeh, S. Said, Y. Shostak, L. Capo, A. Verlinsky, Z. An, I. Joseph, Y. Zhang, S. Kumar-Ganesan, K. Morrison, D. Stover, P. Challita-Eid, Molecular characterization of patient-derived human pancreatic tumor xenograft models for preclinical and translational development of cancer therapeutics, Neoplasia 15 (10) (2013 Oct) 1138–1150, https://doi.org/10.1593/neo.13922. PMID: 24204193; PMCID: PMC3819630.
[109] Z. Hou, J. Lin, Y. Ma, H. Fang, Y. Wu, Z. Chen, X. Lin, F. Lu, S. Wen, X. Yu, et al., Single-Cell RNA sequencing revealed subclonal heterogeneity and gene signatures of gemcitabine sensitivity in pancreatic cancer, Front. Pharmacol. 14 (2023) 1193791.
[110] O. Hoare, N. Fraunhoffer, A. Elkaoutari, O. Gayet, M. Bigonnet, J. Roques, R. Nicolle, C. McGuckin, N. Forraz, E. Sohier, et al., Exploring the complementarity of pancreatic ductal adenocarcinoma preclinical models, Cancers 13 (2021) 2473.
[111] I. Garrido-Laguna, A.C. Tan, M. Uson, M. Angenendt, W.W. Ma, M.C. Villaroel, M. Zhao, N.V. Rajeshkumar, A. Jimeno, R. Donehower, C. Iacobuzio-Donahue, M. Barrett, Rudek MA, B. Rubio-Viqueira, D. Laheru, M. Hidalgo, Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer, Br. J. Cancer 103 (5) (2010 Aug 24) 649–655, https://doi.org/10.1038/sj.bjc.6605819. Epub 2010 Jul 27. PMID: 20664591; PMCID: PMC2938261.
[112] M. Hidalgo, E. Bruckheimer, N.V. RajeshKumar, I. Garrido-Laguna, E. De Oliveira, B. Rubio-Viqueira, S. Strawn, M.J. Wick, J. Martell, D. Sidransky, A pilot clinical study of treatment guided by personalized tumor grafts in patients with advanced cancer, Mol. Cancer Ther. 10 (2011) 1311–1316, https://doi.org/10.1158/1535-7163.MCT-11-0233.
[113] M.C. Villarroel, N.V. RajeshKumar, I. Garrido-Laguna, A. De Jesus-Acosta, S. Jones, A. Maitra, R.H. Hruban, J.R. Eshleman, A. Klein, D. Laheru, et al., Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer, Mol. Cancer Ther. 10 (2010) 3–8, https://doi.org/10.1158/1535-7163.MCT-10-0893. Epub 2010 Dec 6. PMID: 21135251; PMCID: PMC3307340.
[114] A.K. Witkiewicz, U. Balaji, C. Eslinger, E. McMillan, W. Conway, B. Posner, G. B. Mills, E.M. O'Reilly, E.S. Knudsen, Integrated patient-derived models delineate individualized therapeutic vulnerabilities of pancreatic cancer, Cell Rep. 16 (2016) 2017–2031, doi: 10.1016/j.celrep.2016.07.023.
[115] C.R. Ireson, M.S. Alavijeh, A.M. Palmer, E.R. Fowler, H.J. Jones, The role of mouse tumour models in the discovery and development of anticancer drugs, Br. J. Cancer 121 (2) (2019 Jul) 101–108, https://doi.org/10.1038/s41416-019-0495-5. Epub 2019 Jun 24. PMID: 31231121; PMCID: PMC6738037.
[116] H. Gonzalez, C. Hagerling, Z. Werb, Roles of the immune system in cancer: from tumor initiation to metastatic progression, Genes Dev. 32 (19-20) (2018 Oct 1) 1267–1284, https://doi.org/10.1101/gad.314617.118. PMID: 30275043; PMCID: PMC6169832.
[117] L.D. Shultz, M.A. Brehm, J.V. Garcia-Martinez, D.L. Greiner, Humanized mice for immune system investigation: progress, promise and challenges, Nat. Rev. Immunol. 12 (11) (2012 Nov) 786–798, https://doi.org/10.1038/nri3311. Epub 2012 Oct 12. PMID: 23059428; PMCID: PMC3749872.
[118] B. Olson, Y. Li, Y. Lin, E.T. Liu, A. Patnaik, Mouse Models for Cancer Immunotherapy Research, Cancer Discov. 8 (11) (2018 Nov) 1358–1365, https://doi.org/10.1158/2159-8290.CD-18-0044. Epub 2018 Oct 11. PMID: 30309862; PMCID: PMC8725605.
[119] U. Ben-David, G. Ha, Y.Y. Tseng, N.F. Greenwald, C. Oh, J. Shih, J.M. McFarland, B. Wong, J.S. Boehm, R. Beroukhim, T.R. Golub, Patient-derived xenografts undergo mouse-specific tumor evolution, Nat. Genet 49 (11) (2017 Nov) 1567–1575, https://doi.org/10.1038/ng.3967. Epub 2017 Oct 9. PMID: 28991255; PMCID: PMC5659952.
[120] Ikumi Katano, Takeshi Takahashi, Ryoji Ito, Tsutomu Kamisako, Takuma Mizusawa, Yuyo Ka, Tomoyuki Ogura, Hiroshi Suemizu, Yutaka Kawakami, Mamoru Ito, Predominant development of mature and functional human NK cells in a novel human IL-2–Producing transgenic NOG mouse, J. Immunol. 194 (7) (2015) 3513–3525.
[121] M. Mattar, C.R. McCarthy, A.R. Kulick, B. Qeriqi, S. Guzman, E. de Stanchina, Establishing and maintaining an extensive library of patient-derived xenograft models, Front Oncol. 8 (2018 Feb 19) 19, https://doi.org/10.3389/fonc.2018.00019. PMID: 29515970; PMCID: PMC5825907.
[122] J.T. Poirier, Chapter 5 – Genetic profiling of tumors in PDX models, in: R. Uthamanthyl, P. Tinkey (Eds.), Patient Derived Tumor Xenograft Models, London: Academic Press, 2017, pp. 149–159.
[123] J.E. Grossman, L. Muthuswamy, L. Huang, D. Akshinthala, S. Perea, R. S. Gonzalez, L.L. Tsai, J. Cohen, B. Bockorny, A.J. Bullock, B. Schlechter, M.L. B. Peters, C. Conahan, S. Narasimhan, C. Lim, R.B. Davis, R. Besaw, M. S. Sawhney, D. Pleskow, T.M. Berzin, M. Smith, T.S. Kent, M. Callery, S. K. Muthuswamy, M. Hidalgo, Organoid sensitivity correlates with therapeutic response in patients with pancreatic cancer, Clin. Cancer Res 28 (4) (2022 Feb 15) 708–718, https://doi.org/10.1158/1078-0432.CCR-20-4116. PMID: 34789479; PMCID: PMC8866201.