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Patient-Derived In Vitro and In Vivo Models of Cancer

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Abstract

Over the last two decades, cancer researchers have taken the promise offered by the Human Genome Project and have expanded its capacity to use sequencing to identify the genomic alterations that give rise to and sustain individual tumors. This expansion has allowed researchers to identify and target highly recurrent alterations in specific cancer contexts, such as EGFR mutations in non-small cell lung cancer (Lynch et al, N Engl J Med 350:2129–2139, 2004; Sharifnia et al., Proc Natl Acad Sci U S A 111:18661–18666, 2014), BCR-ABL translocations in chronic myeloid leukemia (Deininger, Pharmacol Rev 55:401–423. https://doi.org/10.1124/pr.55.3.4, 2003; Druker et al, N Engl J Med 344. 1038–1042, 2001; Druker et al, N Engl J Med 344:1031–1037. https://doi.org/10.1056/NEJM200104053441401, 2001), or HER2 amplifications in breast cancer (Slamon et al, N Engl J Med 344:783–792. https://doi.org/10.1056/NEJM200103153441101, 2001; Solca et al, Beyond trastuzumab: second-generation targeted therapies for HER-2-positive breast cancer. In: Sibilia M, Zielinski CC, Bartsch R, Grunt TW (eds) Drugs for HER-2-positive breast cancer. Springer, Basel, pp 91–107, 2011). Despite these advances in our capacity to identify the genetic alterations that drive tumor initiation, survival, and proliferation, our ability to target these alterations to provide effective treatment options for patients in need, particularly those with rare or advanced cancers, remains limited (Gould et al, Nat Med 21:431–439. https://doi.org/10.1038/nm.3853, 2015). Patient-derived models of cancer offer one potential mechanism to overcome this barrier between the bench and bedside. Through the development and testing of patient-derived models of cancer, functional genomics efforts can identify tumor-specific drug sensitivities and thereby provide a connection between tumor genetics and effective therapeutics for patients in need of treatment options.

Recognizing that cancer is a multifaceted set of disease states, the development of personalized models of cancer that can be used to compare treatment options, identify tumor-specific vulnerabilities, and guide clinical decision-making has tremendous potential for improving patient outcomes. This chapter will describe a representative set of patient-derived models of cancer, reviewing each of their strengths and weaknesses and highlighting how selecting a model to suit a specific question or context is critical. Each model comes with a unique set of pros and cons, making them more or less appropriate for each specific research or clinical question. As each model can be leveraged to gain new insights into cancer biology, the key to their deployment

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is to identify the most appropriate model for a specific context, while carefully considering the strengths and limitations of the selected model. When used appropriately, patient-derived models may prove to be the missing link needed to bring the promise of personalized oncology to fruition in the clinic.

Introduction: Why Are Patient-Derived Models Important and Useful?

Most cancer subtypes are complex and heterogeneous in histological presentation, genetic variation, and prognostic outcomes. For the most part, engineered models fail to recapitulate this diversity, and natural processes that underpin this diversity, ultimately creating models that fail to recreate the complexity of the disease states. Patient-derived cancer models were developed in order to more closely recapitulate patient tumors and allow us to capture the specifics of individual tumors. They can be loosely defined as any model of cancer that is developed from patient samples. Cancerous patient tissues and/or cells, as compared to genetically engineered cells or animal models, provide the benefit of having evolved in a patient and thereby having the full complement of genomic alterations acquired over time and driven by unique, environmental pressures present in that patient. Every tumor consists of a unique ratio of tumor cells, immune cells, fibroblasts, extracellular scaffolding, and endothelial cells, all of which interact both physically and molecularly. Unlike traditional two-dimensional cancer cell lines, modern patient-derived models of cancer seek to preserve elements of the genetic profile, cell-cell interactions, and physical components of a given tumor.

Patient-derived models of cancer provide tractable platforms with which researchers can test specific hypotheses. No model fully recapitulates the unique context of a patient’s tumor and, as a general rule, the greater the complexity of a model, the more limited is the number of ways one can perturb and/or evaluate it (Fig. 12.1). For example, two-dimensional cell line models can be plated in hundreds to thousands of replicates for high-throughput assays, but generating the equivalent number of mouse models is not practically feasible. Even the most complex cancer models do not fully recapitulate the native state of tumors, so when using these models, it is critical to account for the ways in which they do and do not faithfully represent the tumor from which they were derived. Additionally, evaluating agents that target tumor-extrinsic factors, such as the vasculature or immune system, is largely futile in simple systems that lack the complexity to evaluate multicellular (not to mention multisystem) therapeutic responses. Interpretation of the data generated in a specific model and any clinically relevant conclusions thereof are limited to the capacity of said model to recapitulate the tumor from which they were derived. Furthermore, limitations can be present in a variety of different elements within a model system as well as in how it is being assessed. In short, it is critical to recognize the strengths and weaknesses of each model, to evaluate the data generated in each model within the context of its specific capacity and limitations, and to design experiments and workflows accordingly [1].

For decades and at present, cancer modeling has been dominated by the use of two-dimensional cell lines as representations of different tumor types. For much of this time, the focus was warranted since site of origin and pathology were the best available methods

for determining diagnosis and treatment. There are many benefits to working with two-dimensional cell lines, since they provide a relatively stable and largely reproducible platform for experimentation and analysis. Unfortunately, they fail to recapitulate many tumor elements that are critical to therapeutic response, e.g., tumor-stromal interactions and microenvironment [2], restricting researchers' capacity to directly translate findings from these models into the clinic. Moreover, over time, cell lines evolve to their culture conditions, losing the heterogeneity and features of the cancer of which they were derived.

While patient-derived models can be powerful tools to study individual tumors, our capacity to use them to study the specific impact of a given gene alteration may be limited since models do not have naturally occurring isogenic controls and, rather, represent the accumulation of all of the alterations in a cell rather than an isolated few. Conversely, however, the genetic complexity of these models may be critical for gaining insight into the tumor's signaling or metabolism or other interactions that play critical role in its sensitivity to therapeutics. One could supplement a patient-derived model with engineered cell lines, e.g., those with targeted oncogenic mutations in genes such as a *KRAS G12D* [3] or deletions of tumor suppressors such as *PTEN* [4], which is beneficial when attempting to demonstrate the relationship between a specific alteration and a given phenotype. Recognizing that each tumor is the result of its own unique environment and the selective pressures to which it was exposed, patient-derived models provide a means to assess each tumor individually. When paired with genomics, this information may prove vital to elucidating the complex interplay between genomics and therapeutic response.

With the advent of rapid next-generation sequencing technologies, there has been a shift in the clinic from a singular focus on tissue of origin toward using molecular diagnostics to inform therapeutic strategies. This shift has allowed for the development and use of agents not focused on tumor type but on targeting the genetic events that drive and sustain individual tumors [5–12] and even agents that target recurrence [13]. While actionable mutations can be predictive of therapeutic response, their predictive power is often context-dependent. To better capture how inter-patient physiological and genetic variation contributes to therapeutic responses, it is imperative to both generate new cancer models and expand upon existing models to more accurately recapitulate what is observed in vivo on a molecular, genetic, histologic, and patient level. This will not only allow for discovery of novel interactions but will help in elucidating drug efficacy and possibly even stratifying patients with similar cancer profiles into new therapeutic groups. In order to continue developing agents that target these tumor-specific alterations, there is a need for the development and use of increasingly personalized and higher-fidelity models. In the next decade, diagnostic approaches that incorporate functional genomics have the potential to become a routine part of patient care, whereby direct assessments of drug sensitivity in patient-derived models could provide an avenue for rapid comparisons and personalization of therapeutics prescribed in the clinic [14–16]. Taken together with our increased capacity to sequence tumors to understand the genetic alterations driving and sustaining tumor growth, development, and treatment response, there has been an expeditious development of myriad patient-derived modeling platforms that allow investigators to assess the effects of different treatment modalities on various aspects of patient tumors (Fig. 12.2). *Combining physiologically relevant information from complimentary model systems could be the key to*

designing functional pipelines that allow for personalized therapeutic decision-making in the clinic.

Types of Models

This section will review several patient-derived models of cancer. It is key to note that each model has its own set of strengths and weaknesses and that their use is predicated on understanding and controlling for these system-specific considerations. For example, patient-derived xenografts in humanized mice may recapitulate more elements of the patient condition, but the feasibility, high cost, long timeline, and variable stability of these models limit the applications of their use. Conversely, patient-derived, two-dimensional tumor cell lines are relatively cheap and tractable but fail to reconstitute many of the elements of the tumor and its microenvironment that are targeted by therapeutics, thus limiting the scope and therefore the questions that can be asked with them.

Two-Dimensional Cancer Cell Lines

Two-dimensional cancer cell lines (CCLs) are a well-established model system for testing small molecules, such as the National Cancer Institute 60 (NCI60) project [17, 18]. Over the decades, thousands of commercially available cancer cell lines have been generated [19] and assessed using high-throughput drug and genetic screens. CCLs can also be established directly from dissociated patient tissue. While not always easy to establish, the strength of these models is in the ease of their propagation and culture. Hundreds to thousands of copies of these lines can be generated in very short timeframes, making them ideal for high-throughput screening. They have been used in pseudo-unselected trials for multiple compounds targeting similar pathways [20] and for pseudo-enrichment trials for drug efficacy in breast cancer [21, 22]. There have also been large-scale efforts by the Dependency Map Consortium (DepMap) to conduct RNAi and CRISPR screens in genomically characterized CCLs to identify cancer type-specific and pan-cancer dependencies [23–26] in conjunction with small molecule screening via the PRISM method that utilizes DNA barcoding to pool cell lines for high-efficiency drug screening [27]. Multiple other groups have also worked to generate publicly available pharmacogenomics datasets, such as the Cancer Cell Line Encyclopedia (CCLE) [28, 29], Genomics of Drug Sensitivity in Cancer (GDSC) [30, 31], and the Cancer Therapeutics Response Portal (CTRP) [32–34].

Established CCLs have been shown to be inconsistent across different laboratories, e.g., in a study of 27 cell lines all labeled as MCF7 (breast cancer), wide genetic variation and response to anticancer therapeutics were recorded [35], but this is an issue inherent in divergent evolution during propagation and variable maintenance practices, which is seen in other in vitro culture systems. As the most broadly used models of cancer, CCLs have been at the center of debates concerning consistency across different datasets, namely, the CCLE and the GDSC. Studies have shown that drug-gene interactions matched between CCLE and GDSC exhibited poor correlation and inconsistencies [36, 37], prompting other groups to join the debate on how best correct for experimental and methodological variation between the original drug screens and subsequent computational analysis [29, 38–43]. In response

to these issues, multiple patient-derived tumor modeling platforms, e.g., a customizable Functional Genomics Pipeline [44] and the National Cancer Institute's Patient-Derived Models Repository [45–47], have both implemented fidelity checks that use a combination of genomics and pathology to ensure model fidelity, and also produced datasets that explain the observed differences in drug sensitivity.

As patient-derived culture systems have been developed for the full gambit of tumor types, it is interesting to note that some tumor types, e.g., liver, are highly amenable to growth in two-dimensional culture while being resistant to growth in three dimensions. As such, two-dimensional culture of patient-derived models still has the potential to play a critical role in both precision oncology and cancer research at large. Besides known issues with inconsistent cell line nomenclature and contamination [48], a key outstanding question for the implementation of patient-derived models is how well they model tumor dynamics or recapitulate clinical cancer vulnerabilities. Despite many large-scale grants and clinical trials being fundamentally anchored by results from screens conducted in CCLs, these models tend to require further validation, as their simplicity, which is key to their broad use, also limits their fidelity. Moreover, cancer cell cultures grown in a monolayer lose their three-dimensional architecture and the resultant intercellular interactions. These changes induce changes in gene and protein expression. Thus, patient-derived models from heterogeneous cancers undergo in vitro selection, potentially altering their fidelity to the tumors from which they were derived.

Patient-Derived Organoids

Patient-derived organoids (PDOs) are generated via the dissociation and subsequent expansion of patient tumor samples. Unlike traditional two-dimensional cultures, PDOs are grown in the context of a matrix, e.g., laminin, to generate three-dimensional models of the tumors from which they were derived. Because these cells are grown in a three-dimensional matrix, the models retain some of the structural features and cellular diversity of the tumors from which they were derived (Table 12.1). By culturing PDOs in conditions that mimic the native environment, investigators are able to recapitulate elements of the primary tumor that are lost in two-dimensional culture, including preserving cell-cell and cell-extracellular matrix interactions.

The PDO system is a middle-ground approach between more complex models and two-dimensional cultures in that it has the capacity for layered complexity through the addition of other cell types (such as T cells) while still allowing investigators to generate thousands of replicates, which can be evaluated in shorter time frames and across more conditions than complex models. PDOs are also amenable to application in other model systems in which the tumor organoids serve as the base patient-derived model that is then made increasingly complex by the addition of alternative platforms, e.g., air interface models, tumor-immune co-cultures, and chorioallantoic membrane models. Furthermore, one can run concurrent-specific and high-throughput drug screens in mice and in three-dimensional culture (with or without co-cultures), respectively. When PDOs are used in co-cultures and other more complex models, one can assess the intricate interplay between tumors and

their micro-and macroenvironments, making them a useful tool for the development of both clinical and pre-clinical pipelines.

Air Interface Cultures

Cultures with an air-liquid interface (ALI) expose three-dimensional organoids to the air rather than encapsulating them in media and allow for long-term propagation of organoids. ALI organoids have been used to study differentiation programs [72], as well as paracrine signaling, and architecture of oncogenically transformed gastrointestinal tissues [73]. This model allows for in vitro profiling of primary tumor epithelium and immune and stromal components from patient biopsies, and it has been shown to accurately model the effects of immunotherapy on endogenous tumor-infiltrating lymphocytes [74]. Non-small cell lung cancer ALI cultures have been used to successfully screen aerosolized drugs, suggesting ALI cultures as a viable alternative to animal studies in regard to studying anticancer drug effects in the respiratory tract and inhalation delivery [75, 76]. These features make ALI models a good fit for studies assessing tumor-immune interactions, but the added complexity of the model increases the barrier to using them at large scale.

Chorioallontoic Membrane Models

Chorioallontoic membrane (CAM) models use the developing chicken embryo as the host into which patient-derived tumor models can be implanted in order to evaluate growth interactions with the vasculature and microenvironment. In contrast to the classic in vivo rodent PDX model, CAMs provide a more tractable and cheaper option that is naturally immunodeficient [78], provide an easily manipulated vascular environment, has relatively reduced maintenance requirements, and requires shorter experimental timelines [79]. CAMs have been used to evaluate nanoparticle drug delivery in ovarian cancer [80], in vivo perineural invasion of head and neck squamous cell carcinoma [81], cancer-associated autophagy programs [82], metastatic capacity of non-small cell lung and prostate cancer cells and screening for putative anti-metastatic drugs [83], and the effects of tumor cell invasion on vascular network structure and stability [83]. While CAMs are relatively tractable compared to PDXs, they are not as easily genetically manipulated, and many reagents, e.g., antibodies or cytokines, are incompatible with the avian model. Despite the aforementioned pitfalls of this model, CAMs can be used to provide insight to invasion studies, elucidate molecular and drug mechanisms, and drug pharmacokinetic and pharmacodynamic studies.

Tumor Slice Cultures

Tumor slice cultures (TSCs) are generated by isolating tumors from patients and creating ex vivo cultures that maintain the composition and orientation of the native tumor microenvironment and extracellular matrix. They are particularly well suited for assessment of the extent to which inter- and intra-tumoral heterogeneity affects the tumor response to therapies. In a TSC, the myriad cell types, vascular networks, and tissue organization from the original tumor are maintained and can be easily imaged and visualized. TSCs are also easily monitored over time, allowing researchers to examine the temporal dynamics of

perturbation at the cellular level, a feat that is increasingly complicated in murine models, which cannot be as readily imaged. For example, Minami et al. used real-time and serial imaging and immunohistochemical analysis of drug-treated TSCs from a mouse model of malignant glioma to inform the ways in which organotypic brain slice cultures could be used in testing anti-glioma drugs [84]. Since TSCs maintain the complexity and heterogeneity of the tumor from which they are derived and are rapidly culturable following biopsy, they have potential as personalized preclinical models to stratify individual patients for treatment on a diagnostic timeline. Patient tissue is the limiting reagent in this model, rendering TSCs a low-throughput model. Furthermore, using certain media conditions for each tumor may select for tumor growth over sustaining the growth of other cells (i.e., immune cell populations). Unlike PDXs or cell-based models, these cultures cannot be propagated, only remain viable for limited time windows, and develop abnormal growth kinetics and signaling after approximately 6 days in culture, depending on the tumor type and level of optimization of the culture conditions.

Over time, protocols for slice cultures have evolved to standardize TSC volume and surface area, permitting these models to be used for measuring metabolic activity across TSCs within and across patients, ultimately allowing for quantitative measurements of different biologic activities [85]. Vaira et al. showed that slices taken from human colon, lung, and prostate tumors maintained proliferative capacity and native morphology in culture, and demonstrated reduced proliferation upon treatment with targeted inhibition of Mdm2 and PI3K [86]. Merz et al. demonstrated that patient-derived glioblastoma TSCs recapitulated clinical responses to X-ray, spread-out Bragg-peak carbon irradiation, and temozolomide, suggesting their use in understanding therapeutic effects in glioblastoma and dissecting resistance mechanisms [87]. Similarly, Martin et al. showed that patient-derived TSCs of liver metastases of colorectal cancer could be screened with cetuximab, oxaliplatin, and pembrolizumab in order to identify patient-specific response to these standard of care regimens, suggesting a potential utility for TSCs in personalized oncology [88]. TSCs (ex vivo and from PDX) have also been shown to be a viable system for testing drug efficacy as shown in Table 12.2.

In addition to their potential use in evaluating tumor-specific drug sensitivities, TSCs have the capacity to stably model the tumor micro- and immune environment. Naipal et al. developed culture methods for breast cancer TSCs that maintained tumor and stromal cell morphological and viability characteristics for up to 7 days [93]. TSC treatment with FAC in decreasing dilutions revealed variation in sensitivity to the chemotherapeutic regimen due to morphological and proliferative capacities as well as prior exposure to neo-adjuvant therapy in vivo [93]. Jiang et al. showed that TSCs of pancreatic ductal adenocarcinoma (PDAC) maintained staining for the stromal component α-smooth muscle actin and infiltrating T cells and macrophages between day 1 and 6 of culture [89], while Misra et al. showed that these PDAC models stably preserve the tumor micro- and immune environment, and cancerous cells maintained their proliferative capacity and recapitulated the differentiation grade of the primary tumor, allowing for pharmacologic screening of heterogeneous patient-derived tissue [90]. Varying dose responses for 5-FU and FOLFOX were evaluated in patient-derived colorectal cancer TSCs, further underscoring the ability of TSCs to capture inter-patient heterogeneity in drug sensitivity [92]. Sivakumar et al. determined that the

immune cell composition in TSCs from syngeneic mouse models of pancreatic, breast, and colon cancer, melanoma, and a primary liver tumor sample remained stable over 7 days in culture and that TSCs from PDX models were valuable models for pharmacologic screening [91]. Taken together, TSC is a high-fidelity model that can be used to address drug sensitivity and mechanisms-of-action, metabolic studies, as well as monitor cell-cell molecular and physical interactions within a patient's tumor, but their use is limited to a relatively small scale and the short time interval for which these cultures remain viable.

Microfluidic Platforms

In microfluidic platforms, synthetic scaffolds made of glass or polymers provide substrate onto which three-dimensional models can be seeded. Three-dimensional microfluidic systems have been used to mimic vascular biology and physiological conditions by flowing fluid through chambers seeded with the cells of interest and monitoring phenotypes of interests [94]. In the cancer context, perfusable microfluidic systems have been shown to recapitulate expected drug toxicities in hepatoblastoma [95], triple-negative breast cancer [96], and head and neck cancer [97], to name a few. These platforms can also be customized to mimic in vivo tumor microenvironment by repopulating decellularized matrix [98], which is an ideal system for pharmacologic screening. Another use case for microfluidic platforms is to test candidate therapeutics against patient-derived single-cell suspensions, which can increase throughput from limited patient sample volume [99]. Lung adenocarcinoma PDX biopsies have been successfully screened with staurosporine in a microfluidic platform, indicating the potential of these systems to maintain physical interactions between cancers and their native tumor microenvironment [100].

Immune checkpoint blockade (ICB) treatment has been tested in murine- and patient-derived organotypic spheroids suspended in perfusable collagen hydrogels, which allows for monitoring of immune cell compositions and profiling of the secretome in response to ICB [101], though this model is restricted to tumor-infiltrating cells and does not address using appropriate immune cell ratios found in the parent patient tissue. Deng et al. showed that patient-derived tumor spheroids in a 3D microfluidic device treated with CDK4/6 inhibitors palbociclib and trilaciclib released increased T-helper 1 cytokines, supporting this model system as a future direction for studying the tumor immune microenvironment ex vivo [102]. Microfluidics have been used to identify factors that influence TCR-engineered T cell efficacy against cancerous hepatocytes [103, 104].

More complex microfluidic "organ-on-a-chip" (OOAC) systems can be used to assess how vascularization affects therapeutic efficacy and delivery in co-cultures of endothelial cells, fibroblasts, and tumor cells [105] and have been used to assess dynamics of nanoparticle intravasation from vessels into tumors [106]. Colorectal and breast cancer cells have been shown to grow around and utilize synthetic vasculature and display clinically relevant responses to anticancer therapies, suggesting that these vascularized micro-organs and micro-tumors could be a promising model for therapeutic testing of angiogenesis inhibitors [107]. However, tumor vasculature has been shown to have varying effects on drug delivery (and even anti-angiogenic medications) due to poorly executed neo-angiogenesis and remodeling [108], which may alter drug efficacy modeled in synthetic vasculature. A breast

cancer OOAC system successfully modeled ductal carcinoma in situ and mammary tissue layers that recapitulated clinical response to paclitaxel treatment [109]. In another OOAC study, cancer growth and invasion of non-small cell lung cancer was faithfully modeled, as were the effect of mechanical breathing on vascularization and cancer cell response to tyrosine kinase inhibitor rociletinib [110].

While these microfluidic platforms can be difficult and expensive to develop and maintain, the capacity to customize three-dimensional microfluidic platforms makes them ideal for modeling the complex interactions between cell populations and highlights them as a powerful tool for dissecting the molecular mechanisms underpinning treatment efficacy.

Patient-Derived Xenografts

Patient-derived xenografts (PDXs) are generated through the implantation of patient tumor tissue into mice, thus creating a mammalian model of the patient's tumor [111]. Once implanted, these tumors have the capacity to grow, establish a blood supply, and interact with the murine host, thereby providing a living mammalian system in which to run analyses. Once established, PDX models can be propagated; however, much like other patient derived models, they can lose their heterogeneity and be subject to further evolution in their new hosts over time as dominant clones take over and the tumor endures subsequent passaging. While early PDXs can retain elements of the tumor microenvironment, e.g., cancer-associated fibroblasts [112, 113], these elements can be lost over time as the tumors continue to evolve in their new environment. In a study of over a thousand PDXs across more than 18 tumor types, it was found that the selective environment of passaging xenografts in the mouse leads to the accumulation of copy number alterations, which puts evolutionary distance between the primary patient and the model [114]. This supports the notion that passage number may be a critical factor in retaining the complexity of PDX models and underscores the need to evaluate model fidelity not only at the time of development but also at the time of use to ensure that key components of the tumor are being recapitulated as expected.

Increased fidelity to the patient of origin may be obtained for some tumor types by altering the site of xenograft implantation. Traditionally, all PDXs regardless of tumor type have been implanted in the flank of their murine hosts, but through orthotopic implantation into the tissue of origin, researchers may produce a more accurate tumor model [115, 116]. By placing the PDX in a context that more closely resembles its native site of initiation, the model can provide contextual feedbacks specific to the site of origin, e.g., air interface in the lung or microbes in the gut. The type of mouse, e.g., athymic nude or NOD-SCID [111], used can also significantly alter the fidelity of these models and the types of questions that can be addressed. While PDXs have been traditionally generated in immune-compromised mice, in the last decade multiple groups have generated increasingly complex "humanized mice" that are engineered to express human genes (or mice transplanted with human monocytes) to allow for modeling of interactions between the tumor and the immune system [117]. Adding yet more complexity, other groups are advancing toward being able to generate personalized murine avatars that have patient-matched tumor and immune

components [118], though these models are not stable for extended periods, which limits their capacity to model long-term therapeutic responses.

There are several strengths associated with PDX models for drug testing. They represent the gold standard for preclinical models by providing a system where researchers can evaluate the impact of therapies or other perturbations on patient tumors while also evaluating their effects on other organs in a mammalian system. PDXs can be generated in genetically modified animals to evaluate the role of a specific host gene or protein upon tumor development, progression, or drug response [116]. PDX models can be used concurrently with clinical trials to evaluate the impact of drugs on anti-tumor efficacy and to generate a readout of potential toxicities in critical organs [119–121]. Though PDXs can be incredibly powerful in both model capacity and level of fidelity, it is impractical to generate sizeable cohorts of these models to exhaustively test larger drug libraries. Furthermore, their clinical use is limited by factors such as differences in surgical techniques, take rates (i.e., the fraction of tumors that successfully implant to generate a PDX, which is dependent upon multiple factors such as tumor type and implantation site), and timing (the time to generate a cohort of PDXs from a single patient tumor adequate for testing can be months or years depending on growth rates). One could use PDXs to address the efficacy and toxicity of drugs on a patient tumor and organ systems, and supplement this experiment with both genetically similar murine allografts and human xenografts to incorporate the immune system effects and increase the speed and power of the drug study. All together, these features limit the speed at which data from PDX models can be generated and used to identify treatment options for the patient from which they were derived but make them a useful tool for the development of preclinical data sets that can be used to support clinical trials (Box 12.1).

Conclusion

Patient-derived models of cancer have the potential to inform novel therapeutic options and elucidate the complex genetics and multifactorial intercellular interactions underlying cancer phenotypes. Depending on the specific research question, clinical context, or use case, and desired time frame, all patient-derived models have the potential to be the “correct” model, especially when more than one model is used in an orthogonal way or to approach different aspects of the same question. Key features to consider that were touched on in this chapter are time, cost, scale, and fidelity (Table 12.3). While genomics has rapidly expanded our understanding of tumorigenesis and tumor maintenance, the careful application of appropriate patient-derived models could provide a path to truly personalized oncology by providing platforms to understand the complex interplay between tumors, their environment, and therapeutic sensitivities.

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Box 12.1

While not directly derived from patient tissue, it is worth noting that the power of fly genetics allows researchers to design complex *Drosophila* (fly) avatars that represent the individual genetics of a given patient with >15 putative driver mutations. While fly avatars do not provide a mammalian environment, the genomic drivers present in a patient's cancer are modeled in *Drosophila* hindguts, which can then be screened with candidate therapeutics to assess drug toxicity and efficacy in vivo and to quantify animal survival rates in a clinically relevant timeline of 3 weeks [122, 123]. While the fidelity of these models to the initial patient tumor is much lower than that of PDXs, this avatar system is similar in that it can be read out in terms of survival, allowing researchers to gauge tumor-specific treatment efficacy as compared to generic toxicity. Unlike PDXs, these models can be generated and evaluated in clinically relevant time frames and on a sufficiently large scale to allow for broader testing of drug libraries, and ultimately, generating data that can be used to guide clinical decision-making [124].

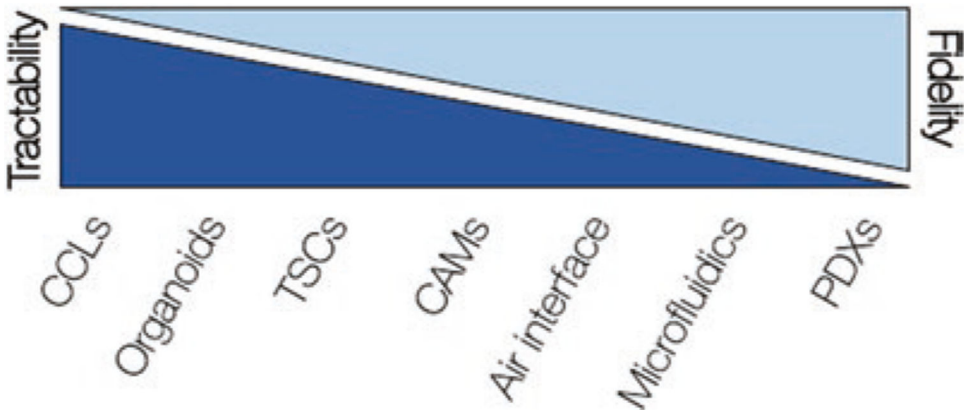

Fig. 12.1.

Relative relationship between ease of use in a laboratory setting and fidelity to the original patient across select patient-derived models of cancer. CCLs Cancer cell lines, TSCs tumor slice cultures, CAMs chorioallantoic membrane models, PDXs patient-derived xenografts

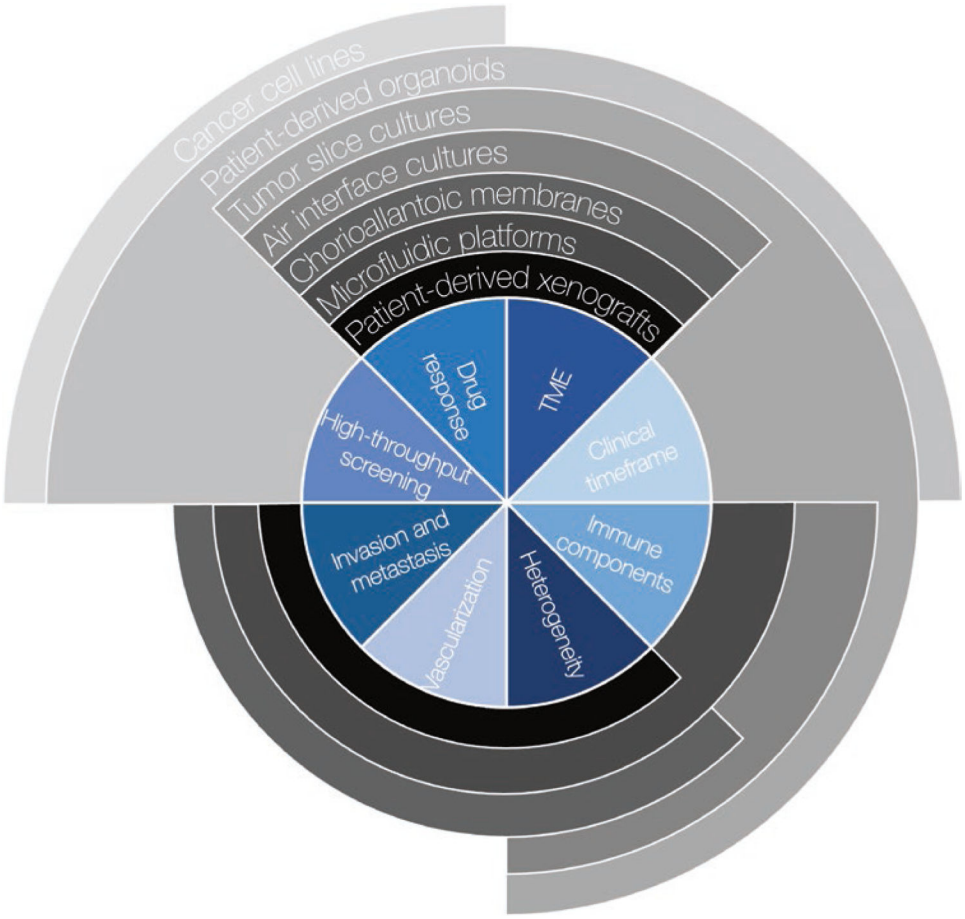

Fig. 12.2.

Relative capacity of select patient-derived models of cancer to recapitulate two elements directly related to patient care, high-throughput screening and assessment on a clinical timeframe, and a select six core elements of tumor architecture and proliferation: Ability to quantify response to drugs or other perturbations, tumor microenvironment (TME) factors like stromal cells or extrinsic growth factors, various immune components, intra-tumoral cellular and/or molecular heterogeneity, vascular organization and angiogenesis paradigms, and the ability to invade surrounding tissue or matrix and to metastasize

Table 12.1

Select publications demonstrating patient-derived organoid development for specific cancer types

Cancer type	References
Bladder	[49, 50]
Brain	[51, 52]
Breast	[53–55]
Colorectal	[56–61]
Gastric	[62]
Gastroesophageal	[61]
Kidney	[63]
Lung	[64, 65]
Ovarian	[66, 67]
Pancreatic	[68, 69]
Prostate	[70, 71]

Table 12.2

Select drug screening experiments in tumor slice culture models

Cancer type	Tumor source	Drugs tested	Reference
Pancreatic ductal adenocarcinoma	Patient	Staurosporine, cycloheximide	[89]
Pancreatic ductal adenocarcinoma	Patient	Rapamycin	[90]
Colon, triple-negative breast cancer	PDX PDX	Staurosporine Panels of FDA-approved drugs	[91]
Colorectal cancer	Patient	Cetuximab, oxaliplatin, and pembrolizumab	[88]
Colorectal cancer	Patient	5-fluorouracil (5-FU) and FOLFOX (5-FU and oxaliplatin)	[92]
Breast	Patient	FAC (5-FU, doxorubicin, 4-HC or preactivated cyclophosphamide)	[93]
Glioma	Mouse	Cisplatin, temozolomide, paclitaxel, tranilast	[84]
Colon, lung, prostate	Human	LY294002 (PI3K inhibitor), Nutlin-3	[86]

Table 12.3

Comparison of features of different patient-derived models of cancer

Model	Heterogeneity	Model complexity	Tumor microenvironment	Immune system components	Renewability	Screening capacity	Screening throughput
2-D cell lines	Little to none unless co-cultured	Large preexisting banks can be established from other models or directly form patients	None	None	Can be passaged and banked for future use	Single and combination agent	High
Organoids	Is lost over time, cellular diversity can be enforced through co-culture approaches	Establishment requires customization of culture conditions	TME can be engineered	None	Can be passaged and banked for future use	Single and combination agent	High
Air interface	Low to high	Complex experimental system that requires specialized equipment	TME from patient is maintained	Patient tumor-infiltrating immune cells are maintained	Can be passaged and banked for future use	ICB, single and combination agent	Low
CAM	Low to high	Easy to establish	TME from patient is maintained	Patient tumor-infiltrating immune cells are maintained	Can be regenerated with new eggs and cells from culture	Single and combination agent	Medium
TSC	High	Easy to establish	TME from patient is maintained	Patient tumor-infiltrating immune cells are maintained	Non-renewable	Single and combination agent	Low
Microfluidic co-cultures	Low to high	Complex experimental system that requires specialized equipment	TME is engineered	Immune complexity is engineered	Non-renewable	ICB, single and combination agent	Medium
PDX	High	Labor intensive to establish and grow out	TME from patient is partially maintained	None	Renewable as long as you have mice	ICB, CAR-T, single and combination agent	Low