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REVIEW

Porcine cancer models: potential tools to enhance cancer drug trials

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ABSTRACT

Introduction: The amount of time and money invested into cancer drug research, development, and clinical trials has continually increased over the past few decades. Despite record high cancer drug approval rates, cancer remains a leading cause of death. This suggests the need for more effective tools to help bring novel therapies to clinical practice in a timely manner.

Areas covered: In this review, current issues associated with clinical trials are discussed, specifically focusing on poor accrual rates and time for trial completion. In addition, details regarding preclinical studies required before advancing to clinical trials are discussed, including advantages and limitations of current preclinical animal cancer models and their relevance to human cancer trials. Finally, new translational porcine cancer models (Oncopig Cancer Model (OCM)) are presented as potential co-clinical trial models.

Expert opinion: In order to address issues impacting the poor success rate of oncology clinical trials, we propose the incorporation of the transformative OCM 'co-clinical trial' pathway into the cancer drug approval process. Due to the Oncopig's high homology to humans and similar tumor phenotypes, their utilization can provide improved preclinical prediction of both drug safety and efficacy prior to investing significant time and money in human clinical trials.

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Cancer Models; pigs; oncopig; clinical needs; oncology; translational Medicine

1. Introduction

Annually, investments into research and development in the pharmaceutical industry continue to increase, as does the cost of clinical trials [1,2]. The recent therapeutic successes of combination cancer therapies consisting of multiple drugs or biologics highlights the need for new preclinical evaluations to determine effectiveness of drug doses and locoregional delivery methods. Emerging knowledge of cancer drug targets and mechanisms, as well as innovations in genome editing to produce transgenic animal cancer models are being rapidly introduced into the drug discovery pathway. These advances, paired with the FDA's programs for expedited drug approvals, have increased the number of approved cancer drugs each year. Between 2012 and 2017, the FDA approved 58 drugs for cancer treatment, 95% of which were a part of one of the expedited approval programs [3]. Despite these successes, cancer still remains as a leading cause of mortality, with 18 million new cases and 9.6 million deaths in 2018 alone [4].

In order for new cancer drugs to pass FDA approval, these new chemical entities (NCE) are required to complete lengthy and expensive clinical trials to ensure their long-term safety, efficacy, and effectiveness in humans. This requires pharmaceutical companies to 'jump' from preclinical studies performed on suboptimal small animal models to investing significant time and money into clinical trials with a high probability of failure. In this review, we discuss issues with current animal cancer models and the clinical trial process, and how these limitations can hinder approval of new cancer drugs. The FDA follows the guidelines set forth by the International Committee on Harmonization for acceptable practices in drug development [5]. These guidelines require toxicity testing in two relevant animal species (Figure 1) [6]. Currently small animal rodent models, typically murine models, are used for initial *in vivo* testing of toxicity, pharmacodynamics, and pharmacokinetics of cancer drugs. Canines are commonly used as secondary relevant animal species for preclinical safety studies, and also play an important role in the clinical trial process through the NCI's Comparative Oncology program [7,8].

The left describes the Target Directed Drug Discovery path to preclinical murine studies. The right describes the Phenotypic Drug Discovery path to preclinical murine studies. Across the bottom illustrates that after the second preclinical study is successfully completed in a non-rodent species (i.e. dog or nonhuman primate) the drug is advanced to human clinical trials. The Porcine Trial depicted in the middle provides a second animal species in which the drug can be tested for safety, efficacy, and dosing in a model more predictive of responses in humans than models currently used prior to advancing to human clinical trials.

Here, we present an expert opinion regarding the use of porcine cancer models as translational, transformational tools to screen compounds prior to initiating human clinical trials. To date a number of porcine cancer models have been described in the literature (Table 1). These porcine cancer

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Article Highlights

- Cancer clinical trials are very expensive, time consuming, and have high failure rates
- For a drug to enter a clinical trial, it must first be tested for safety in a rodent model and non-rodent animal model
- Due to similarities between pigs and humans in terms of physiology, anatomy, drug metabolism, immunology, and genetics, pigs represent an ideal large animal cancer model for translational research
- The Oncopig Cancer Model (OCM) is a transgenic porcine model that develops clinically relevant site and cell-specific tumors resulting from inducible $KRAS^{G12D}$ and $TP53^{R167H}$ transgene expression
- Porcine trials can provide improved prediction of drug safety, efficacy, and dosing prior to advancing to human clinical trials, reducing the number of competing clinical trials and therefore the costs, accrual time, and failure rate of clinical trials
- Our expert opinion is that porcine cancer models can be utilized in co-clinical trial settings, in which pigs are enrolled in a clinical trial alongside human patients, serving the purpose of assessing drug safety and efficacy while reducing the number of human patients required for each trial

This box summarizes key points contained in the article.

models allows for evaluation of drug toxicity in a second animal model as required by the FDA, while simultaneously evaluating efficacy and dosing in a clinically relevant tumor model with similar metabolic rates as humans. Thus, porcine cancer models may be utilized to bridge the gap between preclinical studies and Phase I clinical trials, allowing for improved prediction of successful drug candidates for advancement to FDA clinical trials for FDA.

In addition to screening drugs prior to initiating human clinical trials, we also propose the use of porcine cancer models in what we refer to as 'co-clinical trials'. We define porcine co-clinical trials as trials in which both porcine and human patients are used to test a drug in the same trial. In such co-clinical trials, porcine treatment arms would be conducted in parallel with the human trial. Thus, the pig serves in dual roles: first as a second species to test drug toxicity and dosing following murine studies and second to assess efficacy in the trial phase. Such an approache could significantly reduce the time and money spent on drug approval by reducing the number of ineffective/toxic compounds advanced to human clinical trials, and by reducing the number of human patients required in porcine co-clinical trials, ultimately reducing accrual times by reducing the number of competing clinical trials and the number of patients required.

2. Clinical Trials

An accelerated cancer drug approval process could provide new affordable and innovative drugs for patients with reduced research and development (R&D) costs [15]. Aside from the heavy regulation and the need for drugs to be safe and effective, another factor bottlenecking approval of new drugs is time spent during clinical trials. From 2000 to 2015, the median duration of oncology phase 1 clinical trials was 3.3 years, followed by a median duration of 4.08 years for phase 2 clinical trials [16]. It is also important to note that the FDA has four expedited programs in place to help novel drugs make it into the market faster, but the drug must meet certain criteria of satisfying a serious clinical need [17]. For example, if a drug was labeled as a 'breakthrough,' the drug on average achieved FDA approval 2 years sooner than non-

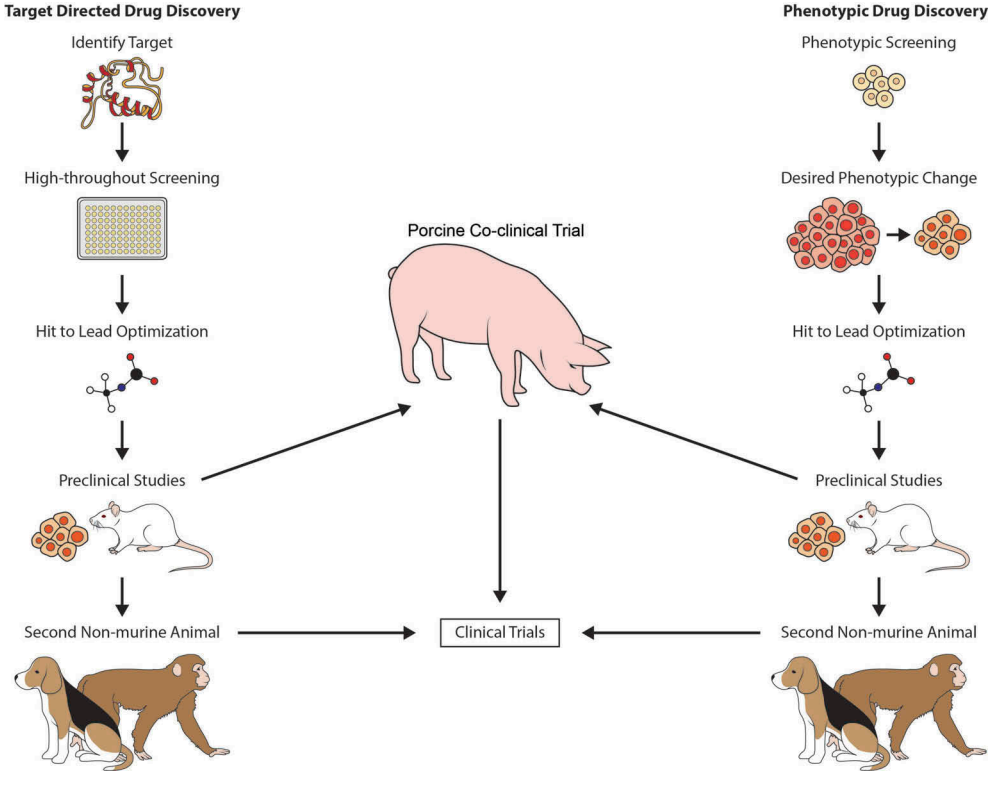

Figure 1. Target Directed and Phenotypic drug discovery pathways.

Table 1. Current porcine cancer models.

Model	Cancer Type	Advantages	Limitations	References
Oncopig	HCC *in vivo* ± alcohol induced cirrhosis Soft tissue Sarcomas Pancreatic	Clinically similar tumors inducible on command in specific locations Rapidly producible	Not every tumor type fully characterized Limited reagent availability	[94,97,98,101,103]
BRCA1 Knockout Yucatan	Breast Cancer	High targeting rate of BRCA1 KO Reproducible and effective	Death 18 days after birth – no long-term monitoring	[9]
$TP53^{R167\ H/R167\ H}$ Mutant	Lymphoma Renal Osteogenic	Ability to produce a wide range of Osteosarcomas	Random tumor location and timing	[10]
Adenomatous Polyposis Coli (APC) Mutant	Colorectal Adenocarcinomas	Creates varied polyp severity similar to human FAP with the same starting mutation	No invasive carcinomas modeled yet	[11,12]
Heterozygous TP53 Knockout	Osteosarcoma	Rapid disease onset Affected long bones of limbs, similar to human condition	Random location	[13]
Massachusetts General Hospital (MGH) herd	Myeloid Leukemias Lymphomas	Liquid tumor model	Difficult to reproduce May require immunosuppression Issues with inducing systemic growth	[14]

breakthrough drugs [3]. Aside from time concerns, advancing a drug through all three clinical trial phases costs around 40 USD million on average, with the cost of trials varying by medical specialty and individual phase [2,18]. Typically, phase 3 is the most expensive phase, oftentimes costing as much or even more then phases 1 and 2 combined [2]. This represents a substantial investment of time and money, with a high chance that the trial will fail due to poor accrual, toxicity, or poor efficacy [16,19].

2.1. Accrual Time

Accrual is defined as placing participants in clinical trials, and it is the most influential limiting factor resulting in the termination of a clinical trial [19]. An analysis of adult cancer clinical trials discovered that 38.7% percent of incomplete trials were ended due to poor accrual (stopped recruiting participants, or never began recruiting participants and will not start recruiting again) [19]. In order to obtain data that warrants a transition from a phase II to a phase III clinical trial, approximately 40 patients are typically enrolled for a single-arm study, and hundreds for a randomized control study containing multiple arms [20]. This requirement can be problematic since only 5% of cancer patients elect to participate in a clinical trial [21]. This issue is compounded by the large number of competing clinical trials targeting the same patient population. Furthermore, participants must meet a trial's outlined eligibility requirements, meaning that apart from having the targeted disease, participants need to fulfil other requirements based on age, gender, disease stage, and comorbid conditions in order to reduce variability. Apart from eligibility requirements, poor accruals also result from other factors such as organizational issues involving lack of promoting clinical trials, physician issues involving lack of knowledge about ongoing trials, and hesitance to discuss clinical trials with patients [22].

2.2. Toxicology and Drug Translation

In 2006, the CD28 super-antagonist drug TGN1412 was used in a first-in-human Phase I clinical trial to treat B cell leukemia after being deemed safe based on preclinical *in vivo* testing on cynomolgus and rhesus monkeys [23]. However, when administered to humans, all patients experienced adverse reactions including organ failure despite being given a dose 0.2% the quantity determined safe in non-human primates (NHPs) [23]. These types of clinical trial failures account for 18.1% of adult cancer clinical trial failures [19] and highlight the drawbacks of using current small animal and NHP models to assess toxicity and define maximum tolerated doses. Indeed, one of the main reasons the rate of drug attrition is so high, despite increasing amounts of funding, research, and development are because of Phase I clinical trial failures due to toxicities that were not observed in preclinical trials [19]. This high rate of clinical trial failures due to toxicity issues demonstrates our inability to accurately predict toxicity of new compounds in humans using currently available small animal cancer models [24,25]. This critical issue supports the need for preclinical cancer models that can improve predictability and translation of drug toxicity, effects, and dosages to human clinical trials.

One aspect of toxicity is bioactivation which relates to how drugs are metabolized. The Cytochrome P450 enzymes (CYP450) are a group of enzymes found primarily in the liver and small intestines that are ultimately responsible for the metabolism of the majority of drugs [26–28]. When drugs are converted into metabolites, the metabolites react with a target to produce the desired therapeutic effect, or cause toxicity [29]. Consequently, to satisfy the issue of drug toxicity and metabolism, an animal model with CYP450 levels and a metabolic rate similar to humans is required. Other aspects of toxicity can be related to the target of the drug [29]. For example, a drug can cause toxicity by interacting with targets that are related or unrelated to the intended target, or the drug can interact with the desired target resulting in a much

stronger effect than anticipated [30]. These issues are significant and contribute to the high rate of drug attrition [31].

3. Current Animal Models

Animal models are essential tools for drug discovery and approval. In order for new drugs to move through FDA approval, preclinical studies utilizing two relevant animal species (typically a murine model and a second non-murine animal cancer model) are required (Figure 1) [6]. This requires a new drug to be tested *in vitro* and *in vivo* for toxicity, bioavailability, and efficacy (i.e. ability to reduce tumor burden). In order to effectively address these requirements, a preclinical cancer model must be strategically chosen based on the relevance to the target human cancer (Table 2) as well has the three R's of animal research: Replace, Reduce, and Refine [32]. This section reviews the strengths and limitations of commonly used preclinical cancer models.

3.1. Mouse Models

Murine models have deep roots in the history of biomedical research, especially cancer research focused on defining oncogenic pathways and immune responses [33]. For example, in the 1970 s, mice with tumors transplanted between mice were extensively used to screen more than 10,000 compounds per year in hopes of identifying efficacious cancer drugs [34,35]. Today, mice are still the most commonly used animal since they provide an inbred genetic background with known genomic sequences, and provide access to widely available immunological and molecular probes. Due to their size, mice require minimal housing costs and smaller drug quantities for testing; thus, are relatively inexpensive, easy to maintain, and require less space.

Murine models provide additional value due to the availability of xenograft and genetically engineered mouse models (GEMMs) [36]. The value of GEMMs stems from the ability to edit genes to produce mice that reflect human genotypes. This provides the ability to research individual oncogenes and tumor suppressors [37], which led to the discovery of the tumor suppressor p53 [38–40]. More recently, murine models have been used to model mestastatic colorectal cancer which has the ability to progress to the liver via an orthotopic transplantation system [41]. The production of mice with relevant human mutations has supported novel drug discovery and investigations into precision medicine. This has even led to a precision medicine concept referred to as the 'Mouse Hospital' where mice are used in co-clinical trials [42]. Here, either GEMMs that contain a cancer patient's driver mutations or patient derived xenograft (PDX) models are created to test new therapies, new combinations of therapies, and observe their interactions at the same time as patients in the co-clinical trials [42]. There is currently a co-clinical trial platform that includes GEMMs, with one of the primary goals being to identify and overcome tumor resistance mechanisms. In that instance, real-time results from novel therapies and therapy combinations used in mice with cancer similar to humans are relayed from 'bench to bedside', ultimately aiding in the prediction of efficacy against the tumor [43]. This platform resulted in the launch of a clinical trial demonstrating a combination of As_2O_3 and retinoic acid was curative for retinoic acid-sensitive acute promyelocytic leukemia [43]. The versatility of mouse models is further demonstrated by the wide variety of techniques used to model tumors, such as genetic engineering and chemical induction, which has resulted in successful development of hepatocellular carcinoma and bladder cancer models [44,45].

Despite these advantages, mice have fundamental differences with humans such as their reduced size, lifespan, metabolism, and different organ anatomy and physiology that limits the their translatability to clinical practice. Murine cancers also differ from those observed in human clinical practice. For example, mice have longer telomeres and higher TERT activity compared to humans, meaning that murine cells can be immortalized more easily than human cells [46,47]. In addition, while xenografted tumor models have been extremely valuable for cancer research, these mouse models are immunodeficient, limiting their ability to model the impact of immune responses on tumor development, progression, and treatment [48,49], which is critical given the growing interest in immunotherapies. Lastly, the anatomical size of the mouse is a limitation regarding imaging and devices, making it difficult to monitor tumor response to new locoregional therapies *in vivo*. These limitations highlight the need for clinically relevant animal cancer models to transition results obtained in murine studies to human clinical practice, as evidenced by the fact that many drugs showing promise in murine studies fail to translate into successful human clinical trials [50].

3.2. Canine Models

Over the years, canine models have demonstrated their value for cancer drug evaluation, especially as a model for naturally occurring cancers. In 2016, 3 of the 4 small molecule cancer

Table 2. Attributes of animal models for preclinical human study components.

Model	Accrual	Animal and Utility Costs	Anatomy, Physiology and Metabolism
Mouse	Readily available from multiple sources	Inexpensive animal and maintenance	Large differences in size, physiology, and metabolism
Dog	Linked to incidence of spontaneous tumors	Clinical costs may vary greatly	Carnivore Many breeds with breed specific tumor incidences
Non-human primate	Long times based on animal availability and protocol approval	Expensive and high maintenance considerations	Low value for cancer studies Cannot induce tumors and onset of spontaneous tumors may take years
pig	Immediate relevant tumor formation Producible trial cohorts for clinically relevant tumors	Moderate animal and maintenance costs	Similar metabolic rate to humans Omnivore Used widely for surgical and interventional radiology

drugs approved by the FDA used dogs as their non-rodent model for testing safety and efficiency prior to advancing to human clinical trials [51]. Dogs represent ideal cancer models due to the many similar cancer disease characteristics they share with humans, such as spontaneous tumor development and similar responses to therapies [52–56]. Certain breeds are highly valuable for testing new therapies for rare cancer types [53,57,58] for which limited patients are available for human clinical trials. For example, osteosarcoma is observed 10 times more frequently in dogs than humans [55] providing a high number of canine osteosarcoma patients for testing new therapies that are critically needed for this deadly disease. Dogs also show strength over smaller models due to their size allowing for imaging techniques such as PET/CT scans and easily accessible tissue samples [59].

Limitations of dogs as cancer models stem from the fact that dogs are companion animals rather than experimental animals, and therefore cannot be subjected to the same experiments performed on small animal cancer models [60]. As with mice, dogs are often inbred, and therefore neither species reflects the diverse genetic backgrounds observed in human patients [5,61]. Furthermore, this also raises the question whether therapies shown to be effective in one breed will be successful in different breeds or translate to human clinical practice.

Canine cancer models are the basis of the NCI Comparative Oncology Program [7], where cancers that occur naturally in veterinary clinical patients are treated and studied as a clinical trial with the goal to translate and compare treatment responses to humans to aid in clinical trial success [8]. Since these cases are naturally occurring models, the clinical value is critically high sine the dog is receiving treatment can then help other similar dogs and human patients. Furthermore, patients may have additional attributes for a particular cancer that is difficult to replicate in the laboratory such as comorbidities, metastasis, and epigenetics [62]. The Comparative Oncology Program has proven invaluable due to its ability to determine specific treatment regimens for both client-owned dogs and human patients. The Comparative Oncology Program has 22 veterinary oncology clinics; however, since canine tumors develop spontaneously as observed in humans, the same limitations related to lengthy accrual times apply to canine clinical trials [63]. In addition, ethical considerations and the inability to experimentally induce tumors in dogs limits the benefits of canine tumor models.

3.3. Non-human Primate (NHP) Models

NHPs – comprised of cynomolgus macaques, common marmosets, and rhesus macaques are commonly used due to their close genetic similarity and biological phenotypes with humans [51,64] – represent another major non-rodent model used in the FDA cancer drug approval process [65]. While it is unquestionable that NHPs have been paramount in contributing to our scientific knowledge, there are significant limitations to consider before choosing NHPs as a relevant non-rodent cancer model. It is well documented that NHPs are not always reliable when translating results from experiments to treatments in patients [66–68]. While this is true for other currently used animal cancer models, it is particularly important given the other detriments associated with using NHPs, such as their high cost, difficult handling, housing, breeding, and acquisition, and the need for individuals highly experienced with NHPs. These problems result in small sample sizes for preclinical NHP efficacy and toxicology studies. In addition, although these animals share many similarities to humans [69,70], there is general agreement that efforts must be taken to apply the three R's [32] to NHP research. While the ban of chimpanzees and other great apes [71] has been initiated, the increased utilization of other large animal cancer models is also anticipated to reduce the use of NHPs in experimental cancer research.

3.4. Porcine Models

Pigs are relevant human disease models due to their anatomical, physiological, size, immunological, metabolic, and genetic to similarities with humans [72]. For example, pig organs such as the heart and liver closely resemble that of humans, which has allowed experimental surgeries and procedures to be piloted using pigs and spurred interest in their use as a source of organs for xenotransplantation [73–75]. Additionally, comparison of pig and human protein sequences has resulted in identification of 112 amino acid positions where the pig protein possesses the same variant implicated in a human disease [76]. This indicates that identical molecular mechanisms contribute to disease in both humans and pigs, increasing the likelihood that porcine cancer models will predict toxicity and efficacy in human patients across the spectrum of success metrics. Due to their significant role in agriculture there is a wealth of information on how to genetically select and breed pigs that has resulted in the development of diverse commercial breeds. In addition, their use in biomedical research and toxicology studies has resulted in the development of a number of genetically diverse, commercially available miniature pig breeds [77]. Furthermore, many clinically relevant methods for administering drugs can be utilized with pigs, such as oral, intravenous, subcutaneous, inhalation, and transdermal delivery [78]. However, porcine models do have limitations [79]. Like other large animals, pigs can be expensive to feed and house depending on location, and require extra labor to manage, especially when transportation is necessary. Secondly, the range of biomedical relevant antibodies and biologics specific to disease models commercially available is low compared to other prevalent models.

The use of pigs in biomedical research is well documented, with one notable discovery being the drug Heparin. Heparin is an anticoagulant discovered in the 1930 s that is still used today, and the only FDA approved source of heparin is derived from porcine intestinal mucosa [80]. More recently, minipigs have been utilized for monoclonal antibody and biologic testing [81], as a model for skin disease [82–84], and are becoming increasingly popular for toxicity studies [77]. To illustrate, porcine models have been instrumental in testing novel therapies like immune checkpoint blockades, bone marrow transplants, and other cellular therapies for hematological cancers [85]. The increased use of pigs for toxicity studies is due to the highly similar structure and expression of pig and human

CYP450 enzymes [86,87] as well as their highly similar basal metabolic rate [88,89]. This supports the case of using porcine models as a transitional model for bridging the gap between preclinical murine studies and human clinical trials. Pigs are also widely used in the development and testing of medical devices for a variety of clinical applications, including interventional radiology guided locoregional cancer therapies [90–92] since procedures for imagining techniques like ultrasound and CT scanning are established.

4. The Oncopig Cancer Model

There are also a number of genetically modified porcine cancer models currently available for preclinical research (Table 1). Therefore, while pigs are popular models for toxicology, surgery, and other medical procedures, their value as translational cancer models is becoming more broadly recognized [93]. In this section, we will focus on the Oncopig Cancer Model (OCM), an inducible transgenic pig model that develops site and cell specific tumors resulting from Cre recombinase induced expression of heterozygous $KRAS^{G12D}$ and $TP53^{R167\ H}$ transgenes [94]. The OCM is a highly relevant cancer model from a genomic perspective, as the $KRAS^{G12D}$ and $TP53^{R167\ H}$ transgenes are expressed by somatic cells in a heterozygous fashion, closely mimicking the human condition, and also represent two of the most common mutations found in human cancers [39,95,96]. Similar to humans, *TERT* is silenced in OCM somatic cells and is solely expressed in OCM cancer cells [97]. Induced OCM tumors have been shown to recapitulate histological, phenotypic, and genetic hallmarks as human tumors [94,97,98], including similar cytotoxic responses to chemotherapeutics used clinically [99]. The OCM provides the ability to create cohorts of relevant patients that can have their tumor development and treatment response monitored over clinically relevant timeframes, which is not possible in mice due to their short lifespan. The OCM thus represents an ideal large animal translational cancer model in which tumor induction can be controlled both spatially and temporally. By using the OCM in preclinical and co-clinical trial settings, accurate and translatable evidence for specific human cancers could be obtained in a cost-effective and timely manner. Since the OCM has been demonstrated to produce cancers that reflect their human counterparts with respect to staging, gene expression, and phenotype, their use could result in improved prediction of compound effectiveness, toxicity, and optimal dosing in humans. By performing porcine trials to test toxicity and efficacy of drugs showing promise in other animal cancer models, promising drug candidates can be screened before advancing to clinical trials and hence reducing the number of failed trials.

Successful development of OCM tumors that accurately reflect human tumor phenotypes and exhibit the hallmarks of human tumors has been demonstrated [94,97,98,100]. For example, hepatocytes isolated from Oncopig livers have been successfully transformed via *in vitro* exposure to Cre recombinase resulting in hepatocellular carcinoma (HCC) cells that present with similar phenotypic features and expression profiles as human HCC [97]. Oncopig HCC tumors have also been successfully developed *in vivo* [97], which, in addition to the successful development of alcohol-induced liver cirrhosis in Oncopigs [101], demonstrates the unique ability of the OCM to recapitulate clinically relevant tumor microenvironments. In addition to HCC, a number of other tumor types have been developed using the OCM platform, including soft-tissue sarcomas (STS) that replicate human STS transcription profiles [98]. In addition, the OCM has been utilized to induce *in vivo* pancreatic cancer that recapitulates histological hallmarks of human pancreatic cancer, including leukocyte infiltration and an analogous tumor microenvironment [102,103]. Lastly, the recent characterization of the OCM immune response and tumor microenvironment support the OCM as a relevant model to test immunotherapies [104]. Together, these results suggest the OCM represents an ideal translation model for cancer drug safety and efficacy testing.

The OCM can also be used as a tool to model tumor heterogeneity. Intratumor heterogeneity refers to the fact that within a single tumor, cells accumulate different mutations over time [105,106]. These mutations can confer selective growth advantages and represent one of the ways in which tumors evolve to become resistant to therapies [107]. Such mutations may lead to tumor recurrence if a small population of resistant cells are not eliminated with the chosen drug. Since the genomic mutation rate is similar between pigs and humans [76], the OCM represents an ideal model to assess the effect of intratumoral heterogeneity on novel and combination drug effectiveness. In addition, utilization of gene editing techniques such as CRISPR provides the opportunity to introduce different driver mutation profiles into Oncopig tumors, providing insights into the effects of driver mutations on drug effectiveness. Given the inherent benefits of the pig's similarities to humans combined with the ability to produce cohorts of Oncopig patients with clinically relevant inducible tumors, it is clear that the OCM provides an innovative translational tool for cancer drug trials.

5. Conclusion

Consistently, reviews criticizing the drug approval process and the pharmaceutical industry's productivity, relative to its R&D spending, express the need for transformative technologies and models to overcome an 'innovation drought.' One of the major issues is translating promising results from preclinical studies into safe and effective therapies for patients. Here, we propose porcine cancer models as a promising solution to the lack of clinically relevant large animal translational cancer models due to their similar size, physiology, anatomy, immunology, genetics, and metabolism to humans, as well as their ability to serve as a co-clinical trial model. By utilizing the porcine co-clinical trial approach, we anticipate that the number of failed and competing clinical trials may be reduced through the development of new tools to help identify potentially successful and unsuccessful therapies before advancing them to clinical trials. By doing so, we anticipate reduction of the overall time and money spent moving unpromising candidates through clinical trials, freeing up resources that can be allotted to testing of more promising novel drugs for more efficient translation into clinical practice.

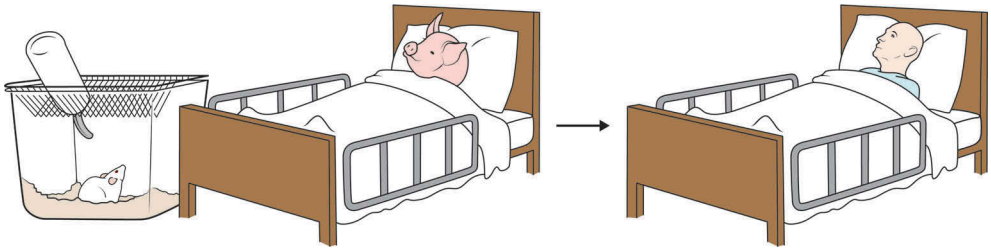

Figure 2. Transformative Porcine 'Co-Clinical Trial' Model.

6. Expert Opinion

Currently, there is a gap between preclinical safety studies and clinical trials, as current preclinical animal models in which to test safety and efficacy are suboptimal and often unpredictive of cancer drug efficacy in humans. Our goal is to offer a solution to improve success rates of oncology clinical trials by utilizing the porcine trial pathway, which represents an ideal translational infrastructure to bridge the gap between preclinical experiments and human clinical trials (Figure 2). After preclinical safety and efficacy studies are conducted in murine models, a drug would typically be tested in another species to assess toxicity but not efficacy. Utilizing porcine cancer models, a second trial can be launched to provide information regarding toxicity, dosing, and efficacy in a clinically relevant large animal cancer model. The first step in this process consists of defining the target cancer and patient population for the given drug. Once established, an appropriate cohort of pigs with the target tumor and relevant comorbid backgrounds can be developed at significantly reduced cost and accrual time compared to a human clinical trial. Thus, porcine cancer models can act as both an accurate second preclinical model for testing toxicity, as well as a clinically relevant tumor model to improve prediction of efficacy and optimal dosing prior to initiating human clinical trials.

Porcine cancer models may aid in reducing cost and accrual time associated with clinical trials in what we refer to as Porcine Co-Clinical Trials. In this model, pigs are enrolled in co-clinical trials in which both porcine and human patients undergo the same treatments in parallel. The Porcine Co-Clinical Trial Model leverages similar drug metabolism and cancer phenotypes between humans and pigs, and also supports interventional therapeutic device testing.

Moreover, porcine cancer models have the potential to further aid in reducing accrual times through incorporation into what we refer to as 'co-clinical trials.' Porcine co-clinical trials refer to trials in which both porcine and human patients are enrolled in the same trial at the same time. In such co-clinical trials, porcine treatment arms would be conducted in parallel with the human trial, possibly reducing the total number of human patients required for each trial. This could influence a human trial similar to how mouse co-clinical trials influence their human counterpart, in which the porcine patients provide useful information that allows the trial investigators to modify trial elements. Therefore, using these two approaches could possibly reduce clinical trial failure rates by reducing the number of ineffective/toxic compounds advancing to human clinical trials, reducing the number of clinical trials competing for the same patient population, and by reducing the number of human patients required in porcine co-clinical trials. In order to support this initiative, we are establishing a porcine electronic medical record system and baseline ranges for clinically relevant blood chemistries and tumor markers to support multi-institutional porcine co-clinical trial efforts.

In addition to being used to assess novel drugs, the similar size between pigs and humans makes them ideal for testing new drug delivery devices, such as those used in interventional radiology guided locoregional therapies, which significantly reduce systemic toxicities by delivering the drugs directly to the tumor. Pigs are already commonly used for testing and training of surgical and interventional procedures due to their similar size and anatomy with humans. This, combined with the use of porcine cancer models provides the unique opportunity to not only test safety of new delivery methods, but also efficacy and dosing using the same tools as in clinical practice. By applying the same porcine trial design, issues regarding device use and procedural challenges can be recognized and improved at significantly reduced cost and time compared to human clinical trials. Finally, the porcine co-clinical trial program can provide excellent translational value for testing device and drug combinations, which require a high number of trial arms to identify optimal doses and delivery timeframes. However, FDA guidelines regarding the use of pigs and other animal models in co-clinical trial settings are required before these approaches can be effectively implemented. In summation, porcine cancer models offer clinically relevant tumor models for testing novel cancer drugs, drug/device combinations, and drug delivery methods with results regarding safety, efficacy, and dosing translatable to clinical practice.

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Declaration of interest

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