

Translational Animal Models for Liver Cancer

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ABSTRACT

Animal models have become increasingly important in the study of hepatocellular carcinoma (HCC), as they serve as a critical bridge between laboratory-based discoveries and human clinical trials. Developing an ideal animal model for translational use is challenging, as the perfect model must be able to reproduce human disease genetically, anatomically, physiologically, and pathologically. This brief review provides an overview of the animal models currently available for translational liver cancer research, including rodent, rabbit, non-human primate, and pig models, with a focus on their respective benefits and shortcomings. While small animal models offer a solid starting point for investigation, large animal HCC models are becoming increasingly important for translation of preclinical results to clinical practice.

Key words: Animal models, hepatocellular carcinoma, translational research

INTRODUCTION

Hepatocellular carcinoma (HCC), or primary liver cancer, is the fifth most commonly diagnosed cancer and the second most common cause of cancer death in men worldwide, while it is the seventh most commonly diagnosed cancer and the sixth most common cause of cancer death in women.^[1,2] To better understand the natural history and treatment of this deadly disease, animal models have become increasingly important, as they serve as a critical bridge between laboratory-based discoveries and human clinical trials. Historically, animal liver cancer models have spanned rodents,^[3] rabbits,^[4] dogs,^[5] monkeys,^[6] and pigs.^[7] Over the past several decades, however, existing

animal models of liver cancer have been refined to more accurately represent the disease, and new animal models of HCC have been developed. Mammalian models currently utilized for investigation of HCC include mouse, rat, woodchuck, rabbit, and porcine platforms,^[8] all employed with the intent of allowing the accurate preclinical study of disease development, detection, treatment, and progression.^[8] This brief review provides an overview of the animal models currently available for translational liver cancer research, with a focus on their respective benefits and shortcomings.

The ideal animal model

Developing a robust animal model that is suitable for translational use is challenging, as the ideal model must be able to reproduce human disease genetically, anatomically, physiologically, and pathologically.^[9] A perfect animal model should harbor disease that arises from a relevant cell line which lends itself to propagation, characterization, storage, and study *in vitro*, which allows for benchtop molecular assays to be performed before or in parallel to animal experiments. It should mimic human disease on the molecular, cellular,

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and phenotypic basis, be reliable and predictable in tumor generation, proliferation, and growth kinetics, develop in a practical time frame, be readily imaged, allow for accurate assessment of treatment effects (i.e., no spontaneous tumor necrosis), and manifest survival differences in affected versus non-affected subjects. Furthermore, preclinical tumors should be generated in a background setting that replicates the clinical context in which the disease is found in humans (e.g., liver cirrhosis for HCC) to optimally recapitulate the tumor-host microenvironment on a molecular basis and to best reflect tumor and local host organ interactions. To this end, autochthonous tumor models those that spontaneously arise in the organ of interest rather than being transplanted (orthotopic model) confer potential advantages in studying the molecular basis of disease. Suitable animal models should be of adequate size to allow for utilization of tools employed in clinical practice. Finally, an ideal animal model should not be cost prohibitive or logistically impractical and should minimize pain and suffering experienced by the animals under study.

Rodent models

Mouse models

There are several methods for induction of murine liver cancer. These include chemical induction (through N-nitrosodiethylamine or diethylnitrosamine [DEN], aflatoxin B1, carbon tetrachloride, choline deficiency, or thioacetamide exposure), xenografting (e.g., human tumor cell lines or fragments implanted into immunodeficient animals), and genetic modification (e.g., hepatitis B and C virus transgenic mice expressing specific portions of the viral genome).^[3]

Small animals like mice offer advantages for cancer studies (Table 1). These include ease of handling, low procurement and maintenance costs, established methods for biologic and genetic manipulation, and the potential for high throughput. Two additional major advantages include rapid tumor induction, as mouse cell lines have very high rates of tumor growth, and easy surveillance of tumor growth by direct visualization, palpation, and measurement (Figure 1). For example, in the mouse xenograft model, the time span between tumor cell injection and tumor development is relatively short (days to weeks),^[10] which although efficient, does not mimic human HCC growth kinetics.^[11]

Even though mice provide versatile and flexible animal models, they have several limitations (Table 1).^[12] First, researchers need to consider that cellular origin and signaling pathways differ between mice and humans. For example, murine strains are highly inbred, essentially having 100% homozygosity at every locus.^[13,14] Murine cells also require fewer genetic mutations to develop tumorigenic phenotypes, making them easier to immortalize than human cells.^[15] In addition, unlike human cells, their signaling pathway requirements are reduced in Ras oncogene transformation,^[16] and in contrast to humans,

Table 1: Rodent tumor model advantages and disadvantages

Advantages	Drawbacks
Ease of handling	Genetic differences
Low procurement and maintenance costs	Small size precludes clinical device utilization and selective intra-arterial therapy
High throughput	Difficult to induce native HCC
Rapid tumor induction	Questionable translatability to human disease
Easy surveillance of tumor growth	
Established methods for biologic and genetic manipulation	

HCC: Hepatocellular carcinoma

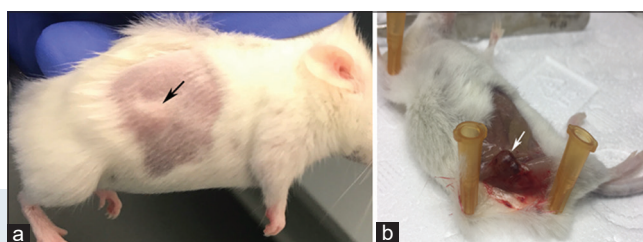


Figure 1: Photographs demonstrate mouse subcutaneous hepatocellular carcinoma xenograft (arrow) before (a) and following (b) euthanasia and tumor harvest.

Mus musculus demonstrate high levels of telomerase activity in normal somatic tissues.^[15,17] Another major drawback of employing mouse models is their small size, which precludes clinical device utilization and limits technical capability for interventions such as vascular catheterization for the study of transarterial therapy. Furthermore, without genetic modification, mice tend to develop sarcomas and lymphomas, whereas humans have a bias toward developing epithelial cancers, or carcinomas, with age.^[15] Specific to HCC research, mice are not susceptible to hepatitis viral infection. In addition, though mice develop liver steatosis when exposed to a diet high in fats or alcohol, the steatosis does not progress to a translational non-alcoholic steatohepatitis, cirrhosis, or HCC model. Finally, recent literature has uncovered meaningful issues with reproducibility of findings made in murine systems,^[18] and the direct translatability of findings made in mouse models to human clinical practice is questionable. To this end, while murine models are commonly used in preclinical drug research, many agents that show promise in mouse studies ultimately fail in human clinical trials.^[19]

Rat models

Among rat HCC models, the most frequently employed are the MCA-RH 7777 and N1-S1 cell lines derived from the Morris^[20] and Novikoff^[21] hepatoma models, respectively. The Morris hepatoma model was generated in Buffalo

rats following exposures to N-2-fluorenylphthalamic acid, which yielded a tumor used to develop the MCA-RH 7777 cell line.^[20] Tumor development using this line consists of intra-hepatic injection of syngeneic tumor cells in Buffalo rats, although the model is compatible with Sprague-Dawley rats as well.^[22] Advantages of this model include high inoculation rate and α -fetoprotein production, which allows for therapeutic monitoring. Shortcomings include lack of Buffalo rat availability, variability on imaging and histological exam,^[23] and aggressive metastatic behavior (although this may be useful in modeling multifocal HCC).^[24] The Novikoff hepatoma model originated from exposure of Sprague-Dawley rats to 4-dimethylaminoazobenzene yielding the N1-S1 cell line (isolated from ascitic fluid). N1-S1 tumors are also produced through intra-hepatic injection of syngeneic tumor cells. The advantage of this model includes the ability to generate concurrent liver cirrhosis through common bile duct ligation,^[25] while it is limited by suboptimal tumor induction rates,^[26] and potential for spontaneous regression.^[22]

Recently, a DEN-induced Wistar rat autochthonous HCC model was developed (Figure 2).^[27] Its benefits include recapitulation of the hepatocyte injury cirrhosis malignancy evolutionary cycle as is seen with human HCC, the presence of liver disease (which theoretically renders subjects susceptible to known complications associated with hepatic insufficiency), and tumor hypervascularity. In addition, the presence of cirrhosis and hepatic dysfunction narrows the therapeutic window for therapy compared to models without background liver disease,^[27] as is seen in the human condition. The main limitation of this model is the 3-month induction time required for proper tumor development.^[27]

In considering procedure based therapeutic interventions, transarterial treatments may be performed in rat HCC models,

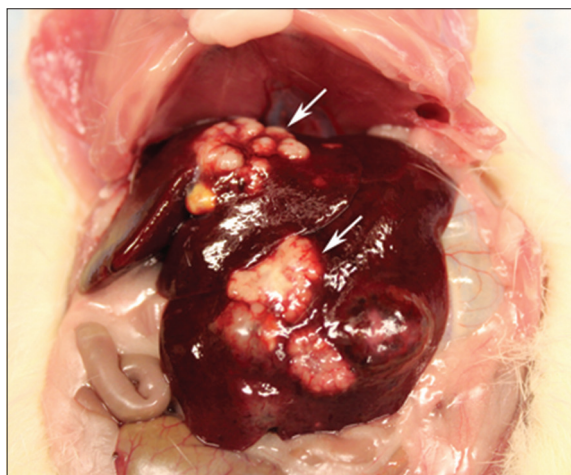


Figure 2: Photograph reveals multifocal disease (arrows) in diethylnitrosamine-induced Wistar rat autochthonous hepatocellular carcinoma model (image courtesy of Terence P. Gade M.D. Ph.D., Department of Radiology, University of Pennsylvania).

but most require a laparotomy and do not entail selective therapy. A segmental approach to transarterial therapy was described in the DEN-induced Wistar rat autochthonous HCC model but was associated with lengthy procedure times in undertaking selective arteriography.^[27]

Woodchuck models

From 1950 to 1970, the Woodchuck was introduced as a viral hepatitis model.^[28] Unlike human hepatitis virus, the inoculated Woodchuck hepatitis virus (WHV) does not incite cirrhosis in woodchucks.^[8] In addition, these animals are more challenging to handle and do not breed as efficiently as other laboratory rodents. However, WHV does result in spontaneous generation of HCC, allowing for utilization of this model for studying transarterial and percutaneous ablative therapy of primary HCC tumors in pre-clinical settings.^[29] More recent studies have demonstrated a similarity between woodchuck and human liver arterial anatomy, and that femoral arterial access can be achieved in the woodchuck for catheterization of the hepatic arterial system (as in human clinical practice), although this procedure is somewhat challenging due to the small caliber of the common femoral artery.^[30] The major drawback of this animal model is the prolonged time period (1–4 years) required to develop liver tumors of 1000 cm³,^[29] which is impractical within the desired time frame of scientific investigation.

Rabbit models

Developed in the 1930s by Rous and Beard,^[31] the VX2 tumor is an anaplastic squamous cell carcinoma which is induced in rabbits. Tumor development takes only 2–3 weeks, which makes the VX2 model an efficient model for the study of liver tumors. This model offers several advantages (Table 2), including reliability of tumor induction by orthotopic allografting, rapid growth, easy propagation in skeletal muscle, and ability to allograft donor tumors into multiple recipient rabbits.^[32] Many interventions can be accomplished utilizing the VX2 platform, including both transarterial and ablative therapies.^[33] Liver tumors grown from VX2 cell lines are well suited for investigating ablative therapies given sonographic visibility, and the innate hypervascularity of VX2 tumors coupled with the relatively more sizeable rabbit vasculature permits technically easier investigation of transarterial locoregional treatments for liver tumors (Figure 3). *In vitro* growth of VX2 cell lines allow cytotoxicity investigations, which may be correlated to results obtained *in vivo*.^[34] Limitations of the VX2 model (Table 2) includes squamous cell origin (dissimilar to HCC, which is an adenocarcinoma), unknown tumor biology, peripheral vascularization, varying tumor kinetics, and unknown genome organization. Another critical shortcoming of this model is spontaneous central tumor necrosis, which confounds the evaluation of therapeutic efficacy after pharmacological or interventional treatment. Since its introduction, progress has been made to

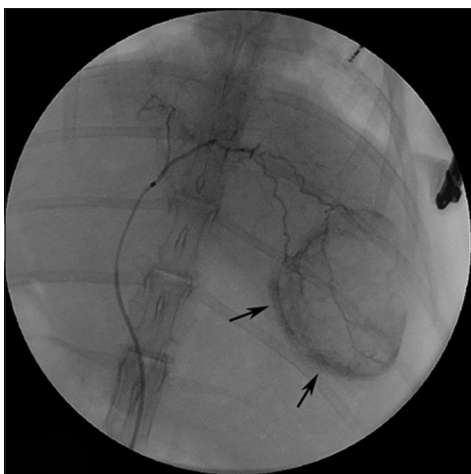


Figure 3: Fluoroscopic spot image from hepatic arteriogram during locoregional therapy of rabbit VX2 liver tumor. Left hepatic arteriogram demonstrates hypervascular left hepatic lobe tumor (arrow).

increase the viability of VX2 tumors by creating modified lines,^[35] potentially increasing the platform's general utility. The dissimilarity of VX2 tumor biology from human HCC also precludes definitive investigation of cytotoxic agents or targeted therapeutics, which represents a major drawback in this era of precision medicine.

Companion animal and non-human primate models

Canine cancer models have been used to study osteosarcoma, sarcoma, lung cancer, nasal and oral malignancy, and malignant non-Hodgkin's lymphoma given a high analogy to the corresponding human tumors.^[36] However, dogs tend to develop more lymphoid and sarcoma tumor types rather than carcinomas, and compared to humans, they have varying drug sensitivity. In addition, dogs are patients, not experimental animals, and therefore, cannot be systematically studied in the same way other animals can be. Thus, they are not widely used in the preclinical study of liver cancer. Non-human primates have genetic, anatomical, and physiological similarity to humans, offering advantages for studying cancer,^[37] rhesus macaques, cynomolgus macaques, and common marmosets have been shown to be susceptible to HCC induction.^[38] However, these animals have relatively small size, and metabolic studies have shown that non-human primates do not always simulate human cancer or disease.^[8] Pertaining to these animals, the ethical concerns of using companion animals and non-human primates for translational research could substantially limit the preclinical advancement of HCC models in these systems.

Pig models

Swine cancer models have shown to be a promising animal model (Table 3) due to their similarities to humans in size,

Table 2: Rabbit VX2 tumor model advantages and disadvantages

Advantages	Drawbacks
Reliable tumor induction by orthotopic allograft implantation	Physiologically different host
Rapid growth	Genetically dissimilar
Easy propagation in skeletal muscle	Varying tumor kinetics
Ability to graft donor tumors into multiple recipient rabbits	Spontaneous necrosis
Innate hypervascularity	Non-diseased liver
More sizeable vasculature than rodent models	

Table 3: Porcine model advantages and disadvantages

Advantages	Disadvantages
Similar size and anatomy allows utilization of same devices and instruments employed in clinical practice, enabling translation to human clinical trials	Larger housing requirements compared to small animals
Similar physiology allows for consistent pharmacokinetic analysis of drug metabolism	Longer generation intervals
Similar genetic background allows relevant investigation of molecular basis of disease and drug therapy	Lack of pig model of hepatitis infection
	Lower quality genome and fewer genomic tools compared to mice and humans

anatomy, pathophysiology, metabolism, genetics, epigenetics, and pathology.^[39] They are less expensive than non-human primate models, and they age 3–5 times faster than humans.^[40] This life cycle permits enough time to develop, characterize, and modulate cancer in a pig model.^[41]

For years, swine have served as a valuable resource for procedural training in surgery and interventional radiology. The size and anatomy of the pig liver, which is similar to that of humans, allows for utilization of instruments and devices employed in the care of patients, enabling easier application and translation to human clinical trials.^[42] Unlike other animal models, pigs also exhibit similar genetics and drug metabolism to humans,^[43] which allows for relevant investigation of the molecular basis of disease in addition to drug pharmacokinetics and therapeutic analyses. Until recently, pigs were most commonly used for practicing techniques rather than modeling disease; however, the establishment of porcine HCC models shows great promise in advancing diagnostic and therapeutic discoveries for liver cancer.

Drug-induced pig models have been created in which DEN was introduced intraperitoneally, weekly, for a period of 3–4 months.^[44,45] These models developed cirrhosis and, eventually, liver cancer over a 12–24 months period; however, this time frame is relatively impractical given the expense of housing animals for a protracted period, the unpredictability of spontaneous cancer formation, and the resultant delay in initiation of tumor-related scientific activities. In addition, tumors formed in the described model were small and numerous, which is more representative of advanced human liver cancer where the disease has already disseminated.^[8]

The recently developed oncopig cancer model (OCM) is a unique transgenic pig model that develops the inducible site and cell-specific tumors after Cre recombinase exposure.^[46] The OCM was designed to innately harbor mutations found in more than 50% of human cancers, *KRAS*^{G12D} and *TP53*^{R167H}, and the capability for rapid tumor induction in this model permits HCC study within a practical time frame.^[46] In the OCM, the innate *KRAS*^{G12D} and *TP53*^{R167H} germline mutations are heterozygous in nature, closely modeling human disease.^[46] OCM cohorts are developed through crossbreeding a transgene/major histocompatibility complex homozygous oncopig minnesota-mini composite sire with any number of domestic, mini-pig, or transgenic dams, allowing for the development of tumor-bearing pigs with a range of genetic backgrounds. This, coupled with the use of a maintenance diet, ensures manageable and clinically relevant animal subject sizes within study time periods. In initial investigations of the model, OCM HCC recapitulated human HCC histologic features, as well as transcriptional hallmarks of human HCC, including *TERT* reactivation, apoptosis evasion, angiogenesis activation, altered cell cycle regulation, and WNT signaling activation.^[47] Autologous injection of porcine HCC cells into the OCM yielded tumors histologically characterized as HCC.^[47] Importantly, liver cirrhosis can also be induced in swine models,^[48] allowing evaluation of HCC in its native host environment. Because medical comorbidities related to the cancer-host environment may impact therapeutic capability and serve as a competing cause of mortality as in the case of liver cancer and hepatic cirrhosis the ability to induce comorbidities in the oncopig (Figure 4)^[47] provides a unique opportunity to initiate tumors with and without comorbid illness to define combination-therapeutic approaches in a more controlled way that can be done in human patients. Finally, the OCM is immunocompetent, lending itself to the investigation of immunotherapies.^[42] Given these attributes, the OCM has potential to serve as a valuable transitional bridge between preclinical small animal murine studies and human clinical trials.

CONCLUSIONS

Animal models play a crucial role in serving as a bridge from preclinical HCC research to clinical care. Systematic

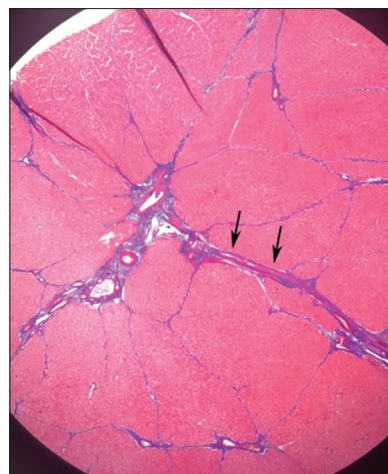


Figure 4: Trichrome stained oncopig liver histologic section after cirrhosis induction shows irregular hepatic lobules circumferentially surrounded by thick fibrous septa (arrows).

investigations in animal subjects may offer fundamental insights into mechanisms of disease development, as well as prevention, detection, treatment, and follow-up that can be applied to improve patient outcomes. While small animal models offer a solid starting point for investigation, the future will hold increasing importance for large animal HCC models as they become more widely used.

Declaration of patient consent

Not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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