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Oncopigs: an inducible transgenic large animal cancer model to address pre-clinical assessments

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ABSTRACT

Cancer research progress has been markedly hampered by the lack of clinically relevant systems in which to study the effects of mutational interactions on cancer phenotypes. To address this, we developed an inducible transgenic Oncopig®, a unique genotypically, anatomically, metabolically, and physiologically relevant large animal model that develops inducible site and cell specific tumors for preclinical study of human cancer. The Oncopig® harbors mutations found in >50% of human cancers- $KRAS^{G12D}$ and $TP53^{R167H}$- and results in tumors that recapitulate the phenotype and physiology of human cancers. As in human disease, TERT is solely expressed in Oncopig® cancer cells, and innate Oncopig® $KRAS^{G12D}$ and $TP53^{R167H}$ driver mutations are heterozygous in nature. The Oncopig® size allows utilization of the same interventional tools, such as radiological, imaging and surgical devices all employed in human clinical practice. The Oncopig® is also an ideal model for investigation of drug toxicity, as its basal metabolic rate and xenosensor pregnane X receptor homology and functionality (responsible for the metabolism of half of all prescription drugs) are also very similar to humans. In addition, we have demonstrated the ability to genetically engineer Oncopig® cell lines to facilitate the controlled addition of gene mutations in induced tumors for improved preclinical investigation of the impact of cancer phenotypes on diagnostic and therapeutic approaches. Therefore, the Oncopig Cancer Model® fulfills current unmet clinical modeling, needs as the only FDA cleared large animal cancer model, that supports device, drug and diagnostic safety, risk and efficacy studies. (238 words)

Keywords: Oncopig®, large-animal, pre-clinical, safety, and efficacy

Introduction

BUILDING BLOCKS FOR PORCINE CANCER MODELS

The global incidence of cancer is rapidly rising, and despite an improved understanding of cancer molecular biology, immune landscapes, and advancements in cytotoxic, biologic, and immunologic anti-cancer therapeutics, cancer remains a leading cause of death worldwide[1]. Cancer is caused by the accumulation of a series of gene mutations called driver mutations that confer selective growth advantages to tumor cells. As cancer therapies move toward personalized medicine, predictive modeling of the role driver mutations play in tumorigenesis and therapeutic susceptibility will become essential[2-8]. The development of next-generation sequencing technology has made the evaluation of mutated genes possible in clinical practice, allowing for identification of driver mutations underlying cancer development in individual patients. This, combined with recent advances in gene editing technologies such as CRISPR-Cas9 enables development of personalized tumor models for prediction of treatment responses for mutational profiles observed clinically. Pigs represent an ideal animal model for development of personalized tumor models due to their similar size, anatomy, physiology, metabolism, immunity, and genetics compared to humans. Such models would support new initiatives in precision medicine, provide approaches to create disease site tumor models with designated spatial and temporal clinical outcomes, and create standardized tumor models analogous to human tumors to enable therapeutic studies[6,9-11]. In this review, we discuss the process of utilizing genomic sequencing approaches, gene editing technologies, and transgenic porcine cancer models to develop clinically relevant, personalized large animal cancer models for use in co-clinical trials, improving translation into the clinic to ultimately de risk clinical failure and potentially accelerate clinical trials.

While human clinical trials are the benchmark for testing cancer diagnostics and therapies; regulatory, enrollment, and financial challenges of trial inception are significant. Advances in cancer care are therefore dependent upon the use of preclinical *in vivo* model systems to test new treatments. However, currently the majority of preclinical efficacy studies are done in mice, yet 90% or more of the drugs fail in the clinic, indicating therapeutic success in rodent models does not translate to improved patient outcomes in clinical trials[12] and underscores the deficiencies of these models to recapitulate the complexity of human tumor biology and clinical responses[13-16].

Murine models provide a critical first step in assessing a therapeutic path towards clinical utility; particularly with respect to drug toxicity[3]. However, rodent models are not amenable to clinically relevant imaging and surgical or local regional therapeutic studies[17,18]. Mice differ vastly from humans with respect to size (300x smaller), organ and tissue structures, and systemic immune physiology (only 10% overlap)[13]. In contrast to mice, pigs share many similarities with humans in terms of anatomy, physiology, immunology, and genetics, including requiring multiple genetic changes to develop cancer. In addition, both their basal metabolic rate and their xenosensor pregnane X receptor[19] that regulates CYP3A expression—responsible for the metabolism of half of all prescription drugs—are very similar to humans. Pigs therefore represent a relevant preclinical model to study clinical imaging, surgical techniques, and therapeutic approaches.

TECHNOLOGY PLATFORM: MODELING ONCOLOGY ON DEMAND

The Oncopig® is a novel, malleable, genetically defined, and highly relevant inducible cancer model that allows preclinical investigation, clinical outcome comparisons, and assessment of standard, novel, and experimental drugs, devices, and techniques unachievable with current preclinical models[9,20-23]. Beyond these pig/human similarities described above, the Oncopig® allows for the induction of highly relevant tumors and comorbidities (i.e. cirrhosis, obesity, cardiovascular disease) which can be key to successful qualification of therapeutic safety and

efficacy. Each of the Oncopig® has a transgene construct inserted into the genome that allows for expression of $KRAS^{G12D}$ and $TP53^{R167H}$ driver mutations commonly observed in human tumors (**Figure 1**). There is a stop sequence located upstream of the genes that prevents the genes from being expressed. This allows the pigs to be bred and raised like normal animals, and why tumors can be specifically induced in precise organs and sites on demand. The stop sequence is flanked by loxP sites so exposure to an adenoviral vector encoding for Cre recombinase (AdCre) triggers a recombination event removing the STOP sequence and allowing the driver mutations to be expressed, thus triggering oncogenesis.

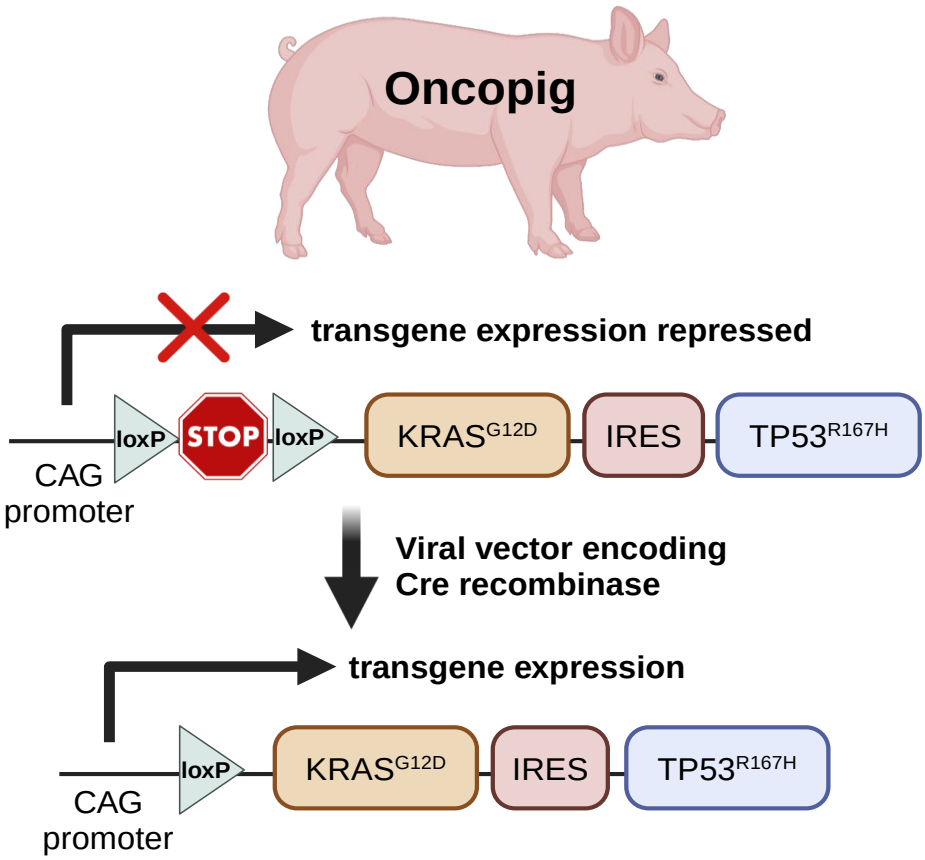

Figure 1. Cre activation of oncogenic transgene expression. Figure was created using BioRender.

Using this approach, we are able to inject AdCre in defined locations (i.e. specific organs and specific locations within those organs) within the Oncopig® to induce tumors on demand. This approach allows us to use a single animal to induce a wide range of different tumor types for downstream applications. Induction of multiple tumors in a single organ, as well as multiple tumors across multiple organs has been demonstrated in a single animal.

To date, several protocols involving direct AdCre injection to induce multiple Oncopig® models (**Figure 2**) with non-specific tumor histology have been developed, including liver, pancreas, kidney, bladder, lung, and colon cancer models. While tumor induction in every organ system has not been tested, we have successfully developed tumor induction protocols for every organ attempted to date. The Oncopig Cancer Model® presents an FDA cleared inducible transgenic pig tumor model that supports site/tissue specific tumors induced via injection of AdCre or Oncopig® cancer cell lines. When utilizing standardized protocols for tumor induction, an 85+% induction success rate is observed in 100% of animals with predictable tumor growth (average tumor size 0.5-3cm in approx. 1-2 weeks post induction). Tumors are readily imageable for visualization and/or targeting using clinically relevant imaging approaches (ultrasound, CT, MRI, endoscopy, and fluoroscopy).

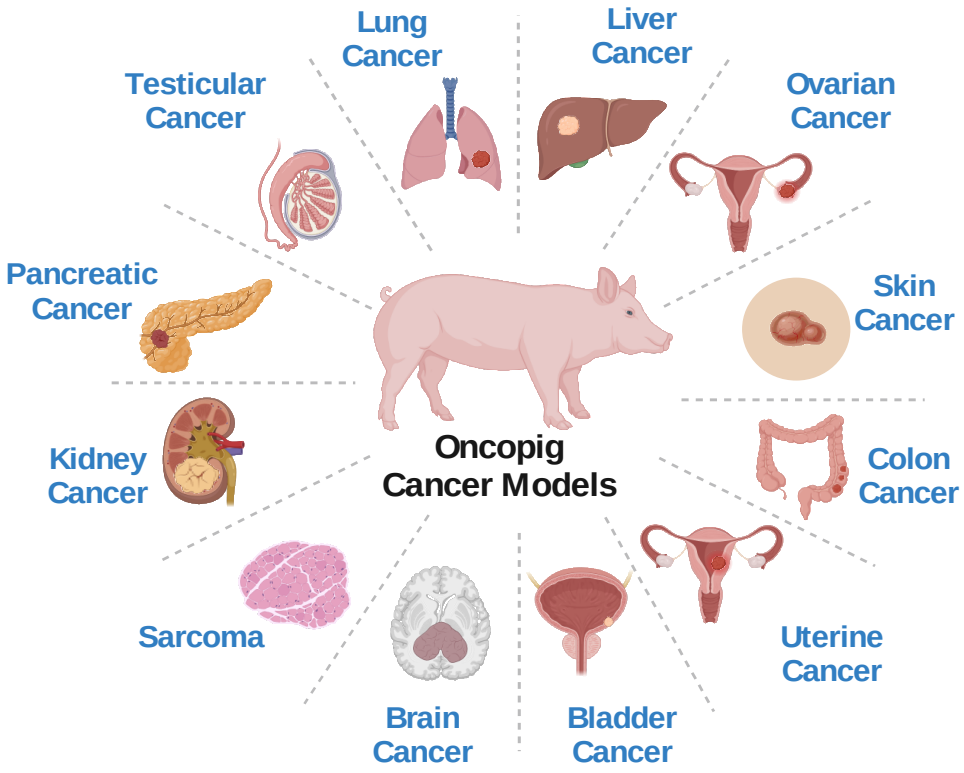

Figure 2. Oncopig® Cancer Models. Figure was created using BioRender.

All non-specific histology models are developed using one of two approaches: 1) image-guided biopsy collection of target organ, incubation of biopsy with AdCre suspended in PBS, injection of AdCre-biopsy mixed with gelfoam into target organ, or 2) direct injection of AdCre into the target organ. Across all organ systems, tumors form within 1-2 weeks and reach a size range of 0.5-3cm in that timeframe. Spontaneous tumor regression as a result of T-cell mediated tumor cell killing is observed across all models, with tumor regression rates varying from a few weeks to months. This spontaneous regression can be eliminated through immunosuppression to facilitate use for long-term follow-up studies.

Focus has been on: 1) development of tumor induction methods through alteration of molecular pathways commonly disrupted in human cancers (*precision medicine*); 2) development of approaches to induce tumors at defined disease sites (*spatial and temporal*); and 3) creation of standardized tumor models analogous to human tumors to support preclinical therapeutic studies (*translational relevance*). Combined, these Sus Clinicals technology platforms permit development of: 1) clinically relevant cell lines and tumors with defined driver mutational profiles (the what); 2) tumors with precise knowledge of induction times (the when); and 3) tumors in defined locations and comorbid microenvironments (the where). These technology platforms therefore facilitate generation of consistent tumors and microenvironments for on-demand preclinical testing in a predictive large animal model, helping established medical device, diagnostic, and pharma companies optimize their innovation portfolios and move their most promising technologies to successful market launch[24-27].

PROVIDING SOLUTIONS TO UNMET CLINICAL NEEDS

Since the Oncopig® is a highly specific and reproducible model for tumor induction, it provides a tool for multiple applications in addressing unmet clinical needs for devices, drugs and diagnostic applications. Hence, potentially drastically reducing development time, while reducing risks and improving safety for trial subjects and patients (**Figure 3** and **Table 1**). Furthermore, the Oncopig® utilizes the same metabolic processes that result in clinical pathogenesis supporting the testing of new

pharmacological and biological therapeutics. Advantages of these models include rapid formation of tumors of clinically relevant sizes for device testing. Use cases for the Oncopig® cancer models with non-specific tumor histology are broad and include use for preclinical evaluation of devices spanning interventional radiology, surgery, and endoscopy, including ablation and/or therapeutic delivery devices. Applications for interventional radiology include testing new imaging approaches for tumor detection and targeting, evaluation of new biopsy approaches, and testing arterially-directed or percutaneous device-based therapeutic approaches. Applications for the surgical field include evaluation of microdissection tools, robotic surgical equipment, laparoscopy approaches, and evaluation of new devices for tumor sampling, resection, and treatment. Applications for endoscopy fields including testing new endoscope-based imaging, biopsy, and treatment approaches. These models are also widely applicable for evaluation of novel next-generation external imaging devices, including novel CT/MRI approaches, augmented reality/virtual reality tools, and guidance software. Radiation studies are also feasible using the Oncopig® model, including both external and internally-delivered radiation therapies. Finally, these models can also be incorporated in training programs utilizing phantoms or healthy pigs to provide a more accurate "real world" experience by facilitating targeting of tumor masses in living animals.

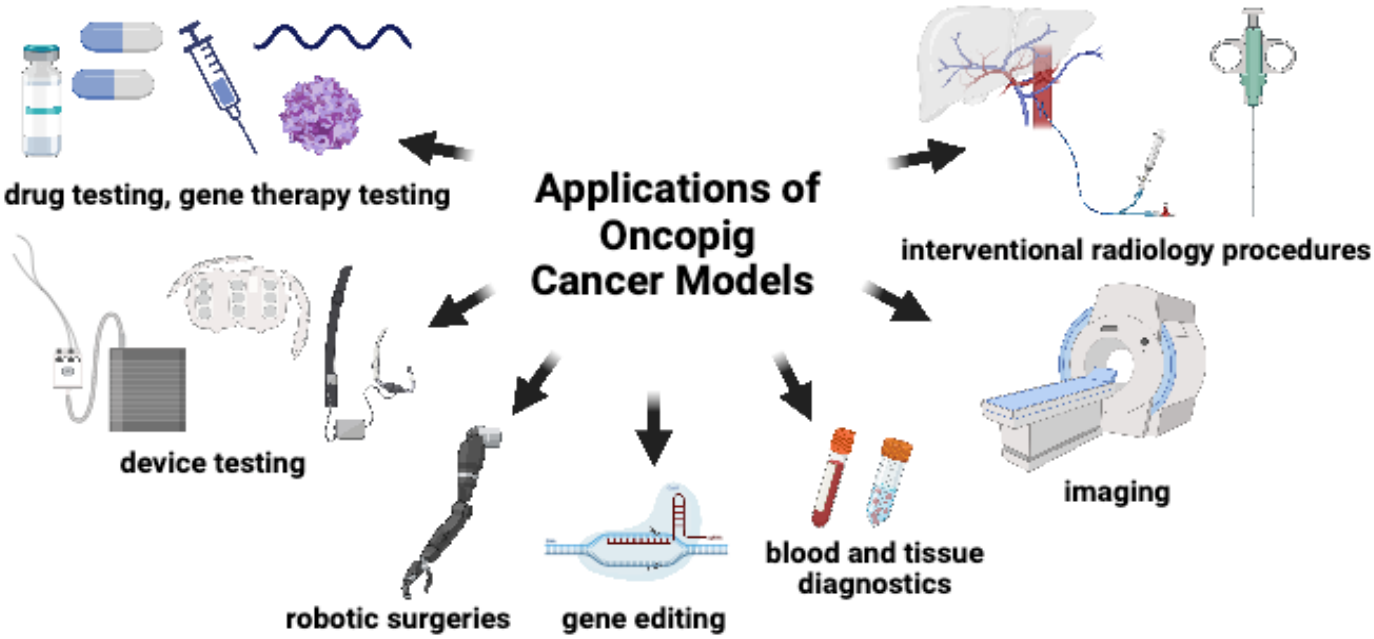

Figure 3. Applications of Oncopig® Cancer Models. Figure was created using BioRender.

Table 1. Applications of Oncopig® and Porcine Cancer Models

Tumor Location	Applications
Sarcoma	*In vivo* induction[9,20] and immune responses[36]; transcriptional microenvironments[39]; and nuclear drug targets[50]
Intramuscular	Histology and imaging[20]
Intratesticular	Histology and imaging[20]
Liver	autologous Oncopig® hepatocellular model[51,52]; genome editing[37]; drug metabolism[25]; hyperthermia and ultrasound treatment[53]; local regional therapies-molecular and immune[54]; microenvironments[55]; precision medicine editing[37]; genome editing tumor cells[40]; drug eluting beads[28,29]; micro-ablation[30]; radioembolization[35]; staging liver microenvironment[56,57]; radiologic modalities[58]; biomarkers[59]; glass microsphere therapeutics[60]; image guided ultrasound thermal ablation[53,61,62]; radiological staging[56]; robotic surgery[63]
Lung	*In vivo* modeling via endovascular Cre induction or *ex vivo* biopsy Cre induction[64]; microwave ablation[32]
Bladder	Cre injection into bladder[65], drug screening[66]
Uterine	Histological and marker development[62]
Ovarian	Histological and marker development[62]
Skin	Cre-inducible melanoma model[67]
Kidney	Micro-ablation[30,31,33]; transcatheter probe development[68]
Colorectal	Drug delivery[69]; site-specific electroporation[70]; biomarkers[71,72]; esophageal microparticle treatment[69]
Pancreatic	Endovascular injection of Cre[73,74]; Cre induction through duct[75]; staging[73]

The promise of liquid biopsies to advance precision medicine strategies requires a large animal model to support collection of adequate samples over an extended time course. One major challenge associated with translating targeted therapeutics into clinical practice is the extensive use of CT and MRI for hepatocellular carcinoma (HCC) diagnosis, which results in a lack of routine clinical biopsy collections for biological profiling[28,29]. Therefore, while studies have demonstrated molecular and metabolic profiling can provide novel insights into HCC development, aggressiveness, and treatment response[30-32], the lack of routine clinical HCC biopsy collection has significantly limited our knowledge of HCC tumor biology and slowed progression of HCC precision medicine approaches[33-35]. To address this unmet clinical need, testing and validation of minimally invasive profiling techniques—such as liquid biopsy approaches to detect driver mutations in cell free DNA (cfDNA) are critically needed. Liquid biopsy is based on the analysis of cfDNA fragments originating from cells as a result of cell death due to normal cell turnover, and as part of the immune response when tissue damage or a disease like cancer is present. Temporal profiling of cfDNA carrying cancer-specific information such as the presence/

absence of driver mutations has the potential to improve treatment stratification, prognosis, and treatment response monitoring, especially for cancers like HCC that are not routinely biopsied. Therefore, the combination of improved minimally invasive approaches to profile HCC tumor biology and development of preclinical models for targeted therapeutic testing has the potential to significantly improve clinical HCC outcomes.

OUTLOOKS AND FUTURE PERSPECTIVES FOR PORCINE BIOMEDICAL MODELS

Progress has clearly been achieved in the utility of the pig as a large animal biomedical model[6,9,21,36,37]. The justification for using genetically modify animals (GMO) to develop a disease on demand reflects the Principles of 3Rs (Replacement, Reduction and Refinement). The use of such a GMO animal replaces the need for intensive and painful chemical/radiation exposures to induce tumors; significantly reduces the need for large numbers of animals to ensure proper cohorts for pre-clinical trials; and refines pre-clinical modeling due to the fact that the Oncopig® provides a single animal in which to conduct safety, risk and efficacy studies. The coming years yet still require focused attention with respect to full utility for drug, diagnostic and device development. Following are areas in which we have identified that require the broader research community. The amount of time and money invested into cancer therapeutic research, development, and clinical trials has continually increased over the past few decades. Despite record high cancer therapeutic approval rates, cancer remains a leading cause of death worldwide. This necessitates more effective tools to translate novel therapies into clinical practice. Current issues associated with clinical trials specifically focus on poor accrual rates and time for trial completion. In addition, preclinical studies are required before advancing to clinical trials. The translational Oncopig Cancer Model® provides a notable enhancement to current preclinical models. To address issues impacting the poor success rate of oncology clinical trials, we are incorporating the transformative Oncopig® platform into the cancer diagnostic and therapeutic approval process. Due to the Oncopig®'s high homology to humans and similar tumor phenotypes, their utility provides improved preclinical indication for both therapeutic safety and efficacy prior to investing significant time and money in human clinical trials.

In addition, because treated and untreated tumors can simultaneously exist in an individual animal, each Oncopig® can feasibly serve as its own internal control, thereby allowing the Oncopig® platform to accelerate development, safety, and efficacy testing of new clinical products and procedures. The *hypothesis* behind the Oncopig® was that genetic alteration of pathways commonly disrupted in human cancers could provide a standardized disease site porcine tumor model, analogous to human tumors, which supports therapeutic investigation. Certainly, evidence provided in this mini-review supports that hypothesis. However, further efforts are essential for full exploitation of this technology platform as a tool for addressing cancer therapies. For example, although AdCre has provided a robust induction signal more specific induction vectors with tissue-specific Cre expression should be developed. Further, utilizing viral vectors that co-express Cre recombinase and CRISPR genome editing components would support both induction of transgene expression and the ability for additional defined oncogenic mutations. Delivery of induction signals and genome editing components will require approaches for defined delivery to cells over extended time periods. This is due to the inherent need for cells to be dividing so that recombination and nuclear division and repair mechanisms are functioning. Thus, in low mitogenic tissues, delivery vehicles (loaded patches or nanoparticles with defined signal release) need to be developed.

Disadvantages of these models include formation of tumors with non-specific tumor histology (due to lack of cell-specific targeting of the AdCre vector) and spontaneous regression observed over the course of several weeks to months due to T cell mediated tumor cell killing. This spontaneous

tumor regression is eliminated using cyclosporine a dosing to facilitate long-term efficacy studies. The development of next-generation sequencing technology has made the evaluation of mutated genes possible in clinical practice, allowing for identification of driver mutations underlying cancer development in individual patients[26,38,39]. This, combined with recent advances in gene editing technologies such as CRISPR-Cas9 enables development of personalized tumor models for prediction of treatment responses for mutational profiles observed clinically[37,40].

While human clinical trials are the benchmark for testing cancer diagnostics and therapies, regulatory, enrollment, and financial challenges of trial inception are significant[5,23]. Advances in cancer care are therefore dependent upon the use of preclinical *in vivo* model systems to test new treatments. However, therapeutic success in preclinical rodent glioblastoma multiforme (GBM) models does not translate to improved patient outcomes in clinical trials and underscore the deficiencies of these models to recapitulate the complexity of human GBM biology and clinical responses[13,14]. In addition, rodent models are not amenable to clinically relevant imaging, surgical, or LRT studies and differ vastly from humans with respect to brain size (300x smaller), structure (negligible white matter and gyral formation), and systemic immune physiology (only 10% overlap)[13]. Therefore, development of a large animal model that more closely reflects human brain size, structure, physiology, and systemic immunity is imperative[41]. In contrast to mice, the pig brain is only 5-10x smaller than humans and has extremely similar white matter composition, gyral structure, and immune systems (80% overlap)[14,20,41-43]. However, despite the increased clinical relevance compared to rodents, to date developed porcine xenografts GBM models have required immunosuppression to facilitate tumor induction[42,44,45]. In addition, while progress has been made on porcine GBM model development using lentiviral vector-based induction of cancer driver mutations, these models have significant limitations, including need for BSL2 containment, demonstrated capability limited to spinal cord, development of motor deficits within 3-weeks, and limited control of driver mutational profiles and tumor heterogeneity[46]. Therefore, generation of novel immunocompetent porcine GBM models as described in this proposal has the potential to accelerate translation of GBM diagnostic imaging and therapeutic approaches spanning surgical techniques, LRTs, and precision medicine into clinical practice, resulting in improvements in patient outcomes and quality of life not possible with current rodent models. Technological approaches to address lack of inbred breeds.

Critical to the full utility of using Oncopigs® is to: (1) mitigate the inflammatory anti-tumor immune response and prevent tumor regression; (2) develop vectors to enhance *in vivo* somatic cell genome editing; (3) development of rare cancer models; and (4) development of Oncopig® strains with inherent co-morbidities (crossbreeding Oncopigs® with inherent comorbidities, e.g. obesity, diabetes, metabolic syndrome or atherosclerosis) or through induction via diet[47,48]. Finally, the use of transgenic pigs requires FDA regulatory clearance for use across the United States; thus, recognition by health regulatory agencies of the Oncopig® and other transgenic pigs value as a pre-clinical model[49] is a critical next step, and building upon the foundational work with Oncopigs® to establish mini-pig lines for broader applications.

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