Contemporary Mouse Models in Glioma Research

William H. Hicks 1, Cylaina E. Bird 1, Jeffrey I. Traylor, MD 1, Diana D. Shi, MD 2, Tarek Y. El Ahmadi, MD 1, Timothy E. Richardson, DO, PhD 3, Samuel K. McBrayer, PhD 4,* and Kalil G. Abdullah, MD, MSc 1,5,*

1 Department of Neurological Surgery, University of Texas Southwestern Medical Center, Dallas, Texas (USA)
2 Department of Radiation Oncology, Brigham and Women’s Hospital and Dana-Farber Cancer Institute, Boston, MA, United States; Harvard Medical School, Boston, MA, United States
3 Department of Pathology and Glenn Biggs Institute for Alzheimer’s and Neurodegenerative Diseases, University of Texas Health San Antonio, San Antonio, Texas (USA)
4 Children’s Medical Center Research Institute, University of Texas Southwestern Medical Center, Dallas, Texas (USA)
5 Harrold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas (USA)
6 Peter O’Donnell Jr. Brain Institute, University of Texas Southwestern Medical Center, Dallas Texas (USA)
* Correspondence: samuel.mcbrayer@utsouthwestern.edu; kalil.abdullah@utsouthwestern.edu

Abstract: Despite advances in understanding of the molecular pathogenesis of glioma, outcomes remain dismal. Developing successful treatments for glioma requires faithful in vivo disease modeling and rigorous preclinical testing. Murine models, including xenografts, syngeneic, and genetically engineered models, are used to study gliomagenesis, identify methods of tumor progression, and test novel treatment strategies. Since the discovery of highly recurrent isocitrate dehydrogenase (IDH) mutations in lower-grade gliomas, there is increasing emphasis on effective modeling of IDH mutant brain tumors. Improvements in preclinical models that capture the phenotypic and molecular heterogeneity of gliomas are critical for the development of effective new therapies. Herein, we explore the current status, advancements, and challenges with contemporary murine glioma models.

Keywords: glioma; GEMM; isocitrate dehydrogenase; PDX; mouse model

1. Introduction

Diffuse gliomas are the most common primary tumor of the central nervous system (CNS) and are currently classified as lower-grade (WHO II and III) or glioblastoma (GBM; WHO grade IV) based on a combination of histologic and molecular features [1,2]. Lower-grade astrocytomas tend to be slower growing and are less aggressive than higher grade astrocytomas, with the diagnosis of GBM conferring a dismal prognosis [1]. Despite advances in treatment, patients with GBMs have a median survival of 15 months and a 5-year survival rate of <10% with maximal resection and concomitant chemotherapy and radiation [1]. The intractability of these tumors highlights the need for clinical testing of new therapies that display robust activity in accurate mouse models of glioma.

In vivo cancer modeling provides numerous advantages over in vitro modeling. Over 80% of the genes in the mouse genome have direct human orthologs, thereby leading to adoption of the mouse as the dominant model organism for cancer biology and cancer therapy studies [2]. Recent advances in genetic engineering have enabled the production of mouse models of glioma that increasingly mimic the microenvironmental and genomic characteristics of human brain tumors. The genetic landscape of glioma is characterized by alterations in genes encoding epidermal growth factor receptor (EGFR), phosphate and tensin homolog deleted on chromosome 10 (PTEN), neurofibromatosis 1 (NF1), RAS, TP53, and cyclin dependent kinase inhibitor 2 (CDKN2A/B) genes, among others, leading to cell proliferation and tumorigenesis [3,4]. Recently, mutations in iso-
citrate dehydrogenase 1 and 2 (IDH1/2) have been identified in the majority of lower-grade gliomas and a relatively small subset of GBMs [3,5]. As lower-grade gliomas invariable progress to secondary GBMs, evaluating the role of IDH directed therapy is important for patient care.

The genetic diversity, inter- and intra-tumoral heterogeneity, and extensive interaction with brain parenchyma displayed by gliomas lead to late clinical detection, resistance to treatment, and universal tumor recurrence following therapy. These characteristics highlight the need for efficient and representative preclinical mouse models of glioma [6,7]. In this review, the evolution, history, and current status of contemporary glioma mouse models is discussed.

2. Evolution of Cancer Mouse Models

Cancer mouse models evolved alongside advances in molecular and medical technology and vary in cost and immune status (Table 1).

Table 1. Comparison of preclinical animal model features

| Model | Tumor Source | Immune status | Cost | Labor/Time |
|-------|--------------|---------------|------|------------|
| CLX   | Human        | (-)           | $    | +          |
| PDX   | Human        | (-)           | $$   | ++         |
| Syngeneic | Mouse   | (+)           | $    | ++         |
| GEMM  | Mouse        | (+)           | $$$  | +++        |

CLX, cell-line xenograft; PDX, patient-derived xenograft; GEMM, genetically engineered mouse model

The first cancer animal model was the xenograft model. Historically, this model achieved tumor growth through heterotransplantation of human cancer cells into immune-privileged sites like the guinea pig eye or hamster cheek-pouch [8]. While effective as an animal culture of the tumor, these early models provided limited opportunity for study of tumor interaction with native tissue cell types and precluded orthotopic transplantation (into the organ of origin). This challenge was overcome in 1953, when cortisone-treated, irradiated rat xenograft models grew transplanted human tumors [9]. Rygaard and Paulson (1969) further established an immune-compromised host as a critical tool for effective tumor xenograft transplantation [10]. Engraftment rates were significantly improved by immune-compromised mice which led to widespread adoption of xenograft models in the cancer research field [11].

Around the time that the first xenograft models were established, syngeneic models were created to facilitate the identification of effective chemotherapies [14,15]. From the 1950s to 1970s, the National Cancer Institute conducted chemotherapeutic screening programs using syngeneic models of sarcoma 180, L1210 leukemia, B16 melanoma, and P388 leukemia, among others [12]. Syngeneic models are created through the use of carcinogens or genetic modification to induce tumorigenesis or by leveraging spontaneous tumor formation in the mouse [13,14]. Malignant transformation can be induced in vitro or in vivo. If primary cells are transformed in vitro, they can be introduced to an organism of the same species. C57BL/6, BALBc, and FVB/N are common mouse species used in syngeneic models and have been critical for the preclinical evaluation of experimental therapeutics [13,14]. Xenograft and syngeneic modeling approaches have been applied extensively to glioma research, as summarized below.

Genetically engineered mouse models (GEMMs) were first established when oncogenic viral DNA was detected in the adult mouse following transfection of the mouse embryo with simian virus 40 (SV40) [15]. In the 1980s, there was a rapid expansion of transgenic GEMMs with the creation of onco-mice [16-18]. These onco-mice have tumorigenic DNA, often known or proposed oncogenes, introduced into their genome to create a mouse predisposed to tumor formation. Subsequent models placed the oncogene under tissue specific promoters, like the pairing of the immunoglobulin enhancer to the
Myc gene to model B-cell lymphomas or the hormone inducible MMTV-Ras mouse to model breast cancer [17,19]. Gu et. al (1993) established the Cre-loxP system as a conditional gene targeted tool for genetic recombination [20]. A similar model was simultaneously developed utilizing the Fip-FRT system [21]. These molecular tools led to the development of conditional inducible mouse models of cancer and are discussed at greater lengths later in the review. As our genetic and molecular understanding of specific cancers, including glioma, continues to grow, individual genetically engineered mice can be bred to generate combinatorial genetic defects that better resemble the multi-allelic abnormalities in human cancer.

3. Xenograft models

Historically, orthotopic high grade glioma (HGG) xenograft models were created with patient-derived cell lines or established cell lines. In cell-line xenograft models (CLX), cells are implanted into the desired location in the mouse (Table 2). For glioma CLXs, immortalized glioma stem cell (GSC) lines commonly used for implantation include U87, U251, T98G and A172 [22,23]. CLXs are a quick and reproducible strategy for studying glioblastoma. However, they often result in well-circumscribed tumors that lack the characteristic infiltrative pattern that is observed in human gliomas [22,23]. Further, the selective pressures of cell culture reduce the subclonal heterogeneity of CLX and its ability to recapitulate the parent tumor [24]. Patient-derived xenografts models (PDX), on the other hand, involve direct xenotransplantation of human biopsy tissue (Table 3). PDX models have been shown to better recapitulate the vascular characteristics and blood brain barrier permeability of patient HGGs as compared to CLX model using the U87 cell line [22,23]. Thus, PDX models are better at recapitulating the stromal and extracellular characteristics of parent tumors than their CLX counterparts.

Several xenograft models have studied gliomagenesis [25-27]. In 1986, Kaye and colleagues were one of the first to create a model using this system by implanting a C6 glioma cell line (a rat glioma cell line) into neonatal and adult mice to demonstrate a reliable murine xenograft glioma model [26]. When creating a reliable xenograft model, the location of cancer stem cell implantation needs to be precise for development of a tumor that accurately recapitulates the human counterpart [27]. Iretenkauf et al. (2017) utilized a glioma xenograft model with nude mice and showed that the implantation location of GSCs can affect the developed tumor characteristics in the murine model [27].

### Table 2. Glioma CLX murine models

| Mouse species            | Brain tumor modeled | Source of genetic material | Reference |
|--------------------------|---------------------|----------------------------|-----------|
| BALB/c OlaHsd-Foxn1nu    | Glioma              | BT4C cells                 | [28]      |
| C57BL6/N                 | High Grade Glioma   | GL261 cells                | [29-36]   |
| CBA, BALB/c, AKR, C57 black, and RIII | High Grade Glioma | U87 and GL261 cells | [37] |
| CD-1, Nude, and NOD CRISPR Prkdc IL2Rynull | Glioma              | DAOY and T98G cells       | [38] |
| CIEA-NOG                 | GBM                 | Patient derived glioma cell lines | [39] |
| ICR                      | High Grade Glioma   | C6 rat glioma cells        | [40] |
| NOD/SCID                 | IDH1 Mutated Glioma | Patient derived IDH1/2 oligoastrocytoma | [41] |
|                          | GBM                 | TG1 human GBM cell line    | [42] |
| Tumor Type      | Cell Lines                                      | References |
|----------------|------------------------------------------------|------------|
| GBM            | T98 and U87 glioma cell lines                  | [43]       |
| Not reported   | U87 and U373 glioma cell lines                 | [44]       |
| GBM            | Ink4a/ARF-/- Id4 astrocyte cells               | [45]       |
| Malignant      | Commercial malignant cell lines                | [46]       |
| Astrocytoma    | BT70 malignant glioma cell line                | [47]       |
| High Grade Glioma | U87 human glioma cell line and C6 rat glioma cell line | [48]       |
| GBM            | LN229 and U87 human glioma cells               | [49]       |
| High Grade Glioma | E98 and E473 glioma cell lines                | [50]       |
| GBM            | Mouse GL261 cell line                         | [51]       |
| GBM            | Human U87 glioma and rat 9L gliosarcoma cell lines | [52]       |
| GBM            | Patient derived GBM cell lines                | [53-55]    |
| High Grade Glioma | Human glioma U87, U251, U373, A172, LN18, LN229, and D54 cell lines | [56]       |
| High Grade Glioma | HS683 cells                                   | [57]       |
| High Grade Glioma | LN229 cells                                   | [58,59]    |
| High Grade Glioma | SHG44 cells                                   | [60]       |
| High Grade Glioma | T98G and U373 cells                           | [61]       |
| High Grade Glioma | U87, U251 and D566 cells                      | [62]       |
| High Grade Glioma | U87 cells                                    | [63-85]    |
| GBM            | U87, LNZ308, LN229 cells                      | [86]       |
| High Grade Glioma | U87, U118, N10, U251, A172, and U373 cell lines | [87]       |
| High Grade Glioma | U251 cell line                              | [88,89]    |
| GBM            | U87 and LN229 cell line                      | [90]       |
| GBM            | LN229 cell line                              | [91]       |
| Glioma         | E102 and E106 glioma cell line                | [92]       |
| Glioma         | SNB-19 U87 glioma cell lines with co-transfecting COS-7 cells with pTet-On and treated with doxycycline | [93]       |
### Table 3. Glioma PDX murine models

| Mouse species | Brain tumor modeled | Source of genetic material | Reference |
|---------------|---------------------|---------------------------|-----------|
| C6B3F1        | High Grade Glioma   | Mouse Tu2449, Tu9648 and Tu251 mouse glioma cell lines | [103]     |
| eGFP NOD/SCID mice | Oligodendroglioma | Patient-derived tumor cells | [103]     |
| NOD-PrkdcSCID IL2Rγnull | Low Grade Glioma | Patient-derived low grade glioma tissue | [104]     |
| NOD-SCID      | Malignant Astrocytoma | Embryonic stem cells | [106]     |
|               | Glioma              | Patient-derived high grade glioma tissue | [107]     |
| NOG           | GBM                 | Patient-derived GBM cells | [108]     |
| Not reported  | Glioblastoma        | Patient-derived human GBMs | [109]     |
| NSG           | GBM                 | Patient-derived GBM neurospheres | [109]     |
|               | Glioma              | Patient-derived IDH mutant glioma tissue | [111]     |
|               | GBM                 | Patient-derived GBM tissue | [112,113] |
|               | High Grade Glioma   | Human astroglioma U373 and T98G and oligodendroglioma Hs663 cell line | [113]     |
|               | GBM                 | Patient-derived GBM tissue | [27,115]  |
| Nude/NOD/SCID | High Grade Glioma   | U87, U118, LN18, LN229 cell lines | [116]     |
| SCID          | IDH-Mutant Glioma   | Patient-derived glioma | [117]     |
3.1 Immunology research in xenograft models

Xenograft models have several benefits including low-cost and fast throughput [118]. A limitation of xenograft models is the required use of immune-deficient mice.

Immune-deficient mice used in xenograft models include nude mice, non-obese/diabetic mice (NOD), severe combined immunodeficient mice (SCID), and the combination NOD/SCID and NOD/SCID/interleukin 2 receptor \( \gamma \) null (NSG) mice. The nude (athymic) mouse has a depleted population of T lymphocytes acquired through mutations in FOXP1 [119]. Nude mice have increased NK cell and macrophage activity as well as intact B cells, dendritic cells, and granulocytes [120]. Thus, while unable to characterize the lymphocyte mediated response, nude mice models can provide information on other immune cell interactions with the tumor [120]. Another common mouse utilized is the SCID mouse which lacks mature B and T lymphocytes [121]. NSG mice carry significant reductions in natural killer cell function to reduce the innate and adaptive immune system for successful grafting of more sensitive tumors [123]. These immune-compromised mice are necessary for the successful engraftment of tumors without risk of short-term rejection. Loss of the immune microenvironment limits study of tumor interaction with the immune system and testing of immune modulating agents [124,125]. Recent studies show that humanized mouse models may help to overcome this challenge [124].

Humanized mouse models are used to generate a mouse with a competent human immune system to study immune responses to anti-cancer immunotherapies [125]. They are created with NSG or NOD/SCID mice undergoing whole body irradiation followed by injection of human CD34+ hematopoietic stem cells intravascularly [121,127]. After 12 weeks of age, engraftment of the human immune system success can be assessed with flow cytometry [125]. These humanized mice are then injected with patient derived tumor tissue to develop into humanized PDX models [125].

An alternate method to study immune systems in PDX models was proposed by Semenkow et al. (2017), who demonstrated that blocking T-cell co-activating signals with immune checkpoint inhibitors, abatacept and MR1, allowed for short term tumor development in orthotopic glioma murine models with intact immune systems [127]. Both models are expensive and time consuming but add to the current and future understanding of immune modulation on tumorigenesis and progression.

4. Syngeneic models

Syngeneic glioma rodent models have been generated via injection of the carcinogen ethyl nitrosourea into the placenta between the 15th and 18th day of murine pregnancy [22]. They can also be propagated with the use of immortalized cell lines, namely GL261 and CT-2A, that were derived after induction with the carcinogen 3-methylcholanthrene, forming a tumor that resembled a GBM [22,125,129]. Unlike xenograft models, syngeneic models utilize immune-competent animals. This allows the study of the interaction between the tumor and immune microenvironment and the possibility of testing immunotherapies for cancer treatment. Like other models that are based on cell line propagation, the syngeneic mouse model is subject to genetic drift with long term propagation [22]. In addition, given this model is created entirely from the animal system, it presents challenges in translating findings to human cancer. Gliomas grown through syngeneic induction present as well-circumscribed tumors without infiltration into the surrounding brain parenchyma, which is not the typical growth pattern appreciated in human astrocytoma [22]. Therefore, these models do not fully recapitulate the phenotypic characteristics of the tumor being studied [14,130].
5. Genetically engineered mouse models (GEMMs)

GEMMs involve manipulation of the mouse genome to induce tumor formation [120]. By causing the tumors to grow from endogenous mouse tissue, immune-competent mice can be utilized, a key advantage over xenograft models. The intact immune system and native tumor structure allows for the study of the tumor microenvironment, while the genetic level of control helps with evaluation of the molecular events leading to tumor formation, maintenance, and susceptibility to treatment [120]. Furthermore, GEMMs allow for the ability to activate relevant oncogenes at specific time points in tissue development, and they permit testing of potential therapeutic agents at various stages of tumorigenesis. This offers distinct advantages over PDX models, which are nearly universally derived from advanced tumors.

GEMMs are commonly made with inbred mouse strains. Mice commonly used for GEMMs include C57BL/6 mice, BALBc mice, and FVB/N mice. The C57BL/6 mouse strain, established in the 1920s to study immune responses to cancer, has an increased NK cell activity and high cell-mediated response, but a weak antibody-mediated response [130]. BALB/c mice in comparison to C57BL/6 mice have a better humoral immune reaction [132]. FVB/N mice (also known as friend virus B-type susceptibility), were created in the late 1970s from the 8th inbred generation of the National Institute of Health general purpose mouse [133]. In relation to BALB/c mice, FVB/N mice have been shown to respond with a greater Th2 bias, however, the immune status is poorly defined [134].

Historically, challenges with timing, sufficient tumor development, and inability to recapitulate the heterogenous intra-tumoral findings of gliomas made it difficult to utilize GEMMs for in vivo glioma modeling [120]. Advancements in these GEMMs have created several modeling systems that better recapitulate human gliomas. These systems include the replication competent avian-like sarcoma virus and the corresponding avian tumor virus A (RCAS-tVA), Cre-loxP system, and the sleeping beauty transposon (Table 4).

Table 4. Glioma murine GEMMs

| Mouse species                  | Brain tumor modeled | Source of genetic material          | Reference |
|-------------------------------|---------------------|-------------------------------------|-----------|
| C57BL/6 and Trp53-/-           | GBM                 | PDGFβ, p53 mutations                | [135]     |
| C57BL/6                       | Glioma              | Heterozygous TgGZT121, KRAS<sup>G12D</sup>, GFAP-CreER, PP-CreER, NG2-CreER, and Rosa26-tdTTomato mice crossed with PTEN, p53, Rb1, and NF1 mice | [136]     |
|                               | Glioma              | Crossing of NF1<sup>fl<sup>ox<sup>+</sup> mice with p53<sup>-/-</sup> mice and then crossed with wild type F1 C57Bl6 mice | [137]     |
| Crossed IDH1 and Nestin-Cre transgenic mice | IDH1 R132 Mutated Glioma | Nestin-Cre remodeling system | [140]     |
| FVB/N mice                    | Oligodendrocyte     | Ctv-a plasmid was transfected into an immortalized oligodendroglia cell line OLI-neu | [141]     |
| FVB/N, C57BL/6,               | GBM                 | KRas, Akt, Ink4a/Arf                | [142,143] |
| Mutations | Impact | Source |
|-----------|--------|--------|
| BALB/C, and 129 | GBM PDGFβ, Ink4a/ARF, PTEN mutations | [143] |
| Gtv-a Arf⁺ | High Grade Glioma Induction with RCAS-PDGF-B | [145] |
| INK4a⁺/+ and INK4a⁻/⁻ | GBM Introduced PTEN allele and p53 into MUT3 mice | [147] |
| MUT3 (Mice with mixed genetic background of C57BL/6, Sv129 and B6/CBA) | De novo GBM | |
| High Grade Glioma | KRas, p53, Ink4a/Arf mutations | [148] |
| GBM | EGFRvIII, Ink4a/ARF, PTEN mutations | [149] |
| GBM | PDGFβ mutation | [150] |
| RasB8 | High Grade Glioma | EGFRvIII and V₁₂ Ras mutation | [151] |
| Rosa26-SB11 | High Grade Astrocytoma | T2/onc mutagenic transposon | [152] |

5.1 Somatic gene delivery model

The RCAS-tVA system allows for oncogenes to be transferred to cells that express the tVA receptor using a cell-type specific promoter [22]. This model has the advantage of not proliferating in mammalian cells. Therefore, the interaction between induced tumor cells and healthy cells remains intact and can be evaluated [22,153]. Genetic mutations arising from single cells and cells selectively undergoing clonal expansion can be demonstrated by this model, including targeting neural specific cells [153]. Nestin positive cells (Ntv-a), glial fibrillary acidic protein (GFAP)-expressing cells (Gtv-a), and CNPase positive oligodendrocyte promoter (Ctv-a) mice models have been created to study glioma formation [152].

Holland and Varmus (1997) were the first to use an RCAS-tVA transgenic mouse model to demonstrate induction, proliferation, and migration of glial cells with β-FGF [153-155]. They also subsequently showed that EGFR mutations in murine glial cells induce lesions that are similar to human gliomas [156]. EGFR induced gliomas also occur in transgenic mice with a INK4a-ARF tumor suppressor locus disruption [156].

While the RCAS-tVA system is limited by the vector capacity of the RCAS virus, other viruses have been used for somatic gene transfer GEMM production, including adenoviruses and lentiviruses [22,154]. The advantage of these viruses in comparison to the RCAS virus is the ability to infect both dividing and non-dividing cells [152].

5.2 Conditional promoter specific model

The Cre-loxP system utilizes the Cre recombinase enzyme to induce recombination between two loxP recognition sites [22]. Conditional models breed a tissue specific transgenic Cre recombinase mouse with a mouse whose gene of interest has been flanked with loxP sites through a knock-in approach [156]. An inducible Cre-loxP system is created by placing Cre protein activity or gene expression under control of tamoxifen (Cre-ER) or tetracycline (Tet-On/Off) [157]. Cre-loxP systems are highly powerful and have been utilized to create mice that develop GBMs through the recombination of EGFRvIII mutations [22,157]. These genes can be placed under the control of brain specific promoters such as Nestin and GFAP for specific neural stem cell targeting [159,160].

Cre-loxP systems have been utilized to evaluate the relationship between NF1 and glioma formation. C57BL/6 mice with NF1 mutations inbred with C57BL/6 mice with TP53 mutations developed malignant glial neoplasms of the central and peripheral...
nervous system [160]. Zhu et al (2005) furthered this understanding demonstrating that mice with NFI and p53 mutations develop WHO grade II gliomas that progress to anaplastic astrocytoma and GBMs [137,161].

5.3 Transposon/Transposase models

The sleeping beauty system can identify genetic drivers in animal models [22]. These systems are thus important in understanding gliomagenesis [22]. Bender et al. (2010) utilized a T2/one transposon with a constitutively active sleeping beauty transposase to create a high-grade astrocytoma. The gliomas created displayed an invasive phenotype with positive GFAP and S100 staining, making this an effective system to model human glioma formation [152].

6. Special consideration for IDH1/2 mutations

IDH1/2 mutations are point mutations in the binding pocket of the IDH enzyme with arginine 132 or 172 being substituted with another amino acid (most commonly histidine). This enzyme normally converts isocitrate dehydrogenase to alpha-ketoglutarate (α-KG) [162]. The mutation causes conversion of α-KG into D-2-hydroxyglutarate (D-2-HG), a compound found in small intracellular quantities. Increased quantities of D-2-HG are thought to competitively inhibit α-KG dependent dioxygenases and cause cellular damage including hypermethylation of DNA and suppression of metabolic processes [163]. These mutations also upregulate vascular endothelial growth factor (VEGF) and produce hypoxia-inducible factor-alpha (HIF-1α) in high levels which promotes gliomagenesis and invasion [164]. Importantly, low grade gliomas with IDH mutations commonly progress to secondary GBMs. Thus, creating an IDH mutated animal model that accurately recapitulates parental tumors to study treatment and prevent progression to higher grade lesions is imperative.

Philip et. al (2018) utilized a RCAS-Ntva system to create IDH1 R132H glioma model with platelet derived growth factor receptor A amplification, loss of CDKN2A, alpha thalassemia/mental retardation syndrome x-linked (ATRX), and PTEN to display the transformation of immortal astrocytes to in vivo glioma development [165]. Heterotopic and orthotopic IDH1 mutant glioma xenografts are also utilized to model this disease state [22]. Borodovsky et al. (2015) utilized fresh patient tissue to create a flank derived IDH1 mutant tumor that was serially propagated [162]. Later, dissociated cells were implanted into nude mice orthotopically and displayed IDH1 mutant anaplastic astrocytoma formation leading to the creation of the JHH-273 murine model [162]. Murine GBM models have also been used to evaluate the effect of NAD+ depletion on IDH1 mutant tumors in SCID mice [166].

Validating and enhancing murine models of IDH mutant low-grade gliomas is important for pre-clinical testing of these new therapeutic strategies. A subcutaneous xenograft murine model with TS603 (a 1p/19q codeletion and IDH1 mutated anaplastic oligodendrogloma patient-derived cell line) has been utilized to test the effects of AGI-5198 (an IDH1-R132H mutant homodimer inhibitor) [166]. It was found that AGI-5198 was able to inhibit colony formation selectively in mutant IDH1 xenograft models and not in wildtype models, a potential benefit of this therapy [166]. Schumacher et al. (2014) utilized a humanized murine model to demonstrate that IDH1 has an immunogenic epitope that can be targeted with a mutation specific vaccination to induce interferon gamma producing T-cells against IDH1 mutant tumor cells [168,169]. There are currently on-going clinical trials to assess if these inhibitors and others will be effective treatment strategies for patients with low grade gliomas [169].

6. Conclusions

Glioma animal models offer an advantage over in vitro two-dimensional cultures as they better recapitulate the genetic, morphologic, and immunologic characteristics of parent tumors. Since the development of the first murine model 70 years ago, there have
been many advances including the creation of PDXs and GEMMs. These advances have allowed for the creation of reliable glioma models to study the genetic and molecular changes preceding gliomagenesis, immunologic reaction, and novel therapeutic reactions. The recent use of glioma murine models to study glioma tumor progression and IDH specific drug therapies provides an opportunity to accurately evaluate the safety and efficacy of compounds in the preclinical setting.

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