HHS Public Access

Author manuscript

J Child Neurol. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

J Child Neurol. 2018 January ; 33(1): 73–81. doi:10.1177/0883073817739509.

Optic Pathway Gliomas in Neurofibromatosis Type 1

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Abstract

Neurofibromatosis type 1 (NF1) is one of the most common brain tumor predisposition syndromes, in which affected children are prone to develop low-grade gliomas. While NF1-associated gliomas can be found in several brain regions, the majority arise in the optic nerves, chiasm, tracks, and radiations (optic pathway gliomas; OPGs). Owing to their location, 35–50% of affected children present with reduced visual acuity. Unfortunately, despite tumor stabilization following chemotherapy, most children have improved vision. For this reasons, more effective therapies are being sought that reflect a deeper understanding of the *NF1* gene and the use of authenticated *Nf1* genetically-engineered mouse strains. The implementation of these models for drug discovery and validation has galvanized molecularly-targeted clinical trials in children with NF1-OPG. Future research focused on defining the cellular and molecular factors that underlie optic glioma development and progression also has the potential to provide personalized risk assessment strategies for this pediatric population.

Keywords

astrocytoma; pilocytic; precision medicine; RAS; vision; low-grade glioma

Neurofibromatosis type 1 (NF1) is the most common inheritable tumor predisposition syndrome, occurring in approximately 1 in 2,500–3,000 people worldwide[1, 2]. NF1 affects nearly every organ system in the body with broad clinical ramifications, such that children and adults with this condition may exhibit pigmentary abnormalities (café-au-lait macules, skinfold freckling, Lisch nodules), tumors of the peripheral and central nervous system (neurofibromas and gliomas), learning and attention problems, autism spectrum symptomatology, bone abnormalities (long bone dysplasias, scoliosis), seizures, sleep disturbances, vasculopathies (moyamoya syndrome, renal artery stenosis), and non-nervous system cancers (breast cancer, pheochromocytoma). Of the tumors involving the nervous system, peripheral nerve sheath tumors (cutaneous and plexiform neurofibromas) predominate, and 8–13% of those individuals harboring a plexiform neurofibroma will develop a malignant peripheral nerve sheath tumor[3].

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Conflicts: None to disclose.

Children and adults with NF1 are particularly prone to develop tumors of the central nervous system. In adults, high-grade gliomas may occur[4], whereas in children, the most commonly-encountered brain tumor is a low-grade glioma, a World Health Organization grade I tumor (pilocytic astrocytoma) with low mitotic rates and low proliferative indices. While these pilocytic astrocytomas can occur anywhere in the brain, they are most frequently detected in the optic pathway and brainstem. In this respect, nearly two-thirds of gliomas are found in the optic pathway, with brainstem (15–20%), cerebellum (~5%), cerebral hemispheres (~5%) and subcortical structures (~5%) accounting for the remaining locations[5].

Clinical Presentation and Natural History

Approximately 15–20% of children with NF1 will develop an optic pathway tumor[6, 7]; however, only 30–50% will be symptomatic from their glioma, and only one-third of affected children will require therapeutic intervention[6–8]. NF1-OPGs are most commonly seen in young children, with the majority occurring in children younger than seven years of age (mean 4.5 years)[9]. Rare cases of NF1-OPGs arising in adolescence or adulthood have also been reported[10].

NF1-OPGs can occur anywhere along the optic pathway including the nerves, chiasm, post-chiasmatic tracts, and radiations (Figure 1)[7, 11, 12]. Tumor location largely dictates the presenting signs and symptoms, with optic nerve gliomas often resulting in unilateral proptosis, visual acuity loss, visual field defect, strabismus, relative afferent pupillary defect, and optic disc edema (papilledema) or atrophy[13]. With chiasmal involvement, precocious puberty can be the main presenting symptom, but visual acuity loss and visual field defects can also occur[9, 14]. Rarely, OPGs involving the hypothalamus can exert enough mass effect to cause obstructive hydrocephalus and resultant headache and vomiting. Those occurring in the optic tracks and radiations most often present with visual acuity deficits, but may result in other neurological signs depending on the involvement of adjacent structures.

The behavior of NF1-OPGs can be unpredictable, requiring that all children with NF1 undergo routine surveillance (discussed below). Currently, there are no clear prognostic features, although patient sex, tumor location, and age of the patient have each been associated with an increased risk of clinical progression. As such, girls are more likely to lose vision and require treatment for OPG than boys, and girls with optic nerve gliomas are 5–10 times more likely to experience visual decline than their male counterparts[15, 16]. In addition, NF1-OPGs occurring in the post-chiasmatic optic pathway tend to exhibit more aggressive clinical behavior than those involving the optic nerve or chiasm[17]. Finally, tumors presenting before the age of 2 years and after 8–10 years of age are typically more aggressive than those presenting in children between 2–8 years of age[10, 17–19]. Advanced neuroimaging techniques using diffusion tensor imaging, routinely included on most magnetic resonance imaging (MRI) studies, have revealed that a decrease in the integrity of the white matter tracts of the optic radiations, as measured by fractional anisotropy, is associated with abnormal visual acuity in NF1-related OPG, and may be predictive of future visual acuity loss[20]. Further prospective studies investigating this association are ongoing.

Screening and Surveillance

Recommended screening for children with NF1 entails annual eye exams in all children less than ten years of age, and at least every two years until 18 years of age[9]. Age-appropriate assessments of visual acuity are critical for NF1-OPG surveillance[21, 22], since visual field testing is unreliable in young children and optic disc pallor does not predict vision outcome[9]. The most reliable information can be obtained when using Teller acuity cards (age 0–2 years), Lea figures (3–4 years of age), HOTV cards (4–6 years of age), and Snellen charts (≥6 years of age). Optic coherence tomography, a promising objective modality in NF1-associated OPG, measures retinal nerve fiber layer thickness (RNFL), a marker for visual loss in children with NF1. RNFL thickness correlates well with visual acuity, but sedation is required in young children to ensure full cooperation[9]. The use of this objective measure may circumvent some of the problems associated with accurately assessing vision, especially in children with NF1 and co-morbid attention and cognitive disabilities.

Recommended screening should be performed by an experienced pediatric ophthalmologist, and should include measurements of visual acuity, confrontational visual field evaluations, color vision testing, and assessments of pupils, eyelids, ocular motility, irises, and fundi[9]. All children with NF1 should undergo yearly measurements of weight and height plotted on standard growth charts to monitor for signs of precocious puberty[9].

Screening baseline MRI evaluations are not indicated for NF1-OPG, as the detection of these tumors rarely changes management in the absence of clinical symptoms or signs[23]. There may be, however, a role for neuroimaging screening in children in whom reliable visual assessment cannot be performed.

Once an OPG has been identified, the frequency of neuroimaging and visual assessment depends on the site of the tumor, degree of visual impairment and associated symptoms as well as evidence of progressive disease[9]. There is no consensus on the specific interval of neuroimaging and visual assessments, but most centers experienced in treating patients with NF1-associated OPG perform eye examinations and vision testing every three months for the first year after diagnosis, with increasing intervals thereafter[9]. MRI examinations may be performed at similar or less frequent intervals.

Similarly, there is little consensus as to what constitutes sufficient clinical progression to warrant treatment, further complicating patient care. Most institutions rely on a combination of clinical deterioration and radiological progression[24–27]. However, clinical deterioration can include the onset of new neurological symptoms or endocrinologic changes[24–27], a change in visual acuity[18], or visual field loss combined with impaired visual acuity[25]. Radiologic progression can include an increase in tumor size, or further extension into the optic pathway or hypothalamus, but should not be claimed based on a change in the enhancement pattern alone[9]. While no evidence-based data exist to date, the following findings have been proposed as criteria for clinical progression: (1) a two-line change in Snellen, HOTV matching, or Lea matching visual acuity compared with the previous examination or (2) a two-line decline in Teller visual acuity[9].

Pathophysiology

Like most solid tumors, NF1-OPGs are complex cellular ecosystems in which several different cell types participate in tumor initiation, evolution, and clinical progression (Figure 2). Among the critical cell types are neoplastic cellular elements (glioma stem cells and astrocytes) and non-neoplastic stromal cells (microglia, neurons and endothelial cells). The neoplastic cells are characterized by bi-allelic inactivation of the *NF1* tumor suppressor gene, resulting in loss of *NF1* protein (neurofibromin) expression. Whole genome sequencing of NF1-PA tumors confirmed genetic silencing of both *NF1* alleles through mutation, methylation, or genomic loss. In addition, 35–50% of the cells in these tumors retain one normal *NF1* gene (*NF1* heterozygosity), and represent the non-neoplastic stromal cells[28]. The majority of these *NF1* heterozygous mutant cells are immune system-like cells, called microglia, vitally important for normal brain function[29, 30], but in this context, are key contributors to brain tumor pathogenesis[31].

Since NF1-OPGs are rarely biopsied or surgically removed, human biological materials for mechanistic studies have been limited. Moreover, human low-grade glioma cells grow poorly *in vitro* and frequently undergo senescence[32], and none have been successfully maintained as patient-derived xenografts[33]. For these reasons[34], much of our understanding of the pathophysiology of NF1-associated low-grade gliomas derives from analyses of *Nf1* genetically-engineered mouse models. Based on the genetics of their human counterparts, mice heterozygous for a targeted germline inactivating mutation in the *Nf1* gene (*Nf1+/−* mice) have been engineered with a conditional *Nf1* allele ($Nf1^{flox}$) to enable somatic *Nf1* loss in neuroglial progenitor cells during embryonic development[35–37]. Analysis of the resulting *Nf1* mutant mice revealed that optic gliomas arise in >90% of mice by 3 months of age. Importantly, *Nf1+/−* cells are required for tumorigenesis[38], further underscoring the contribution of stromal cells to glioma formation.

Analogous to the majority of pediatric NF1-OPG, the murine tumors are located in the prechiasmatic optic nerves and chiasm. Additionally, similar to their human counterparts, the resulting *Nf1* optic gliomas have low proliferative indices (~1%), express glial fibrillary acidic protein (GFAP) and Olig2, and can be visualized by small-animal magnetic resonance imaging (MRI)[39, 40]. Relevant to NF1-OPG-associated vision loss in children, these tumors result in a time-dependent succession of events in the optic nerve, beginning with axonal injury at the site of the glioma, and then progressive retinal ganglion cell (RGC) apoptosis and loss, and culminating in reduced visual acuity[15, 41–43].

Further analysis of these mice and their derivative neoplastic cells revealed that tumor cell proliferation results from loss of neurofibromin negative regulation of the RAS proto-oncogene (Figure 3). As such, neurofibromin is structurally and functionally similar to a family of proteins, termed GTPase activating proteins (GAPs), which function to accelerate the conversion of active, GTP-bound RAS to its inactive GDP-bound form. Neurofibromin inactivation of RAS abrogates the growth-promoting signal initiated by RAS at the plasma membrane. Consistent with this mechanism of tumor growth regulation, increased RAS activation has been observed in both human NF1-PAs[44] and their murine counterparts[45]. Active RAS stimulates cell growth through a cascade of molecular intermediates whose

successive phosphorylation results in their activation. These signaling intermediates include AKT and MEK, which increase cell growth through activation of the mechanistic target of rapamycin (mTOR) complex[46] and ERK, respectively. Relevant to the design of human clinical trials, inhibition of AKT, mTOR, or MEK activity in *Nf1* mutant mice results in reduced tumor growth *in vivo*[47, 48], establishing the preclinical rationale for the use of these molecularly-targeted therapies in children with NF1-OPG (Table 1). However, it is worth noting that some of these therapies in mice require drug dosing that exceeds the maximal tolerated doses in children, and many do not result in durable stabilization of tumor growth[47, 49]. Moreover, cancer stem cells found in the murine tumors exhibit relative resistance to mTOR and MEK inhibition as a result of acquired adaptive responses[50], which may further limit the use of these pharmacologic agents for the treatment of children with NF1-OPG. Taken together, it is essential that future targeted therapies consider pediatric dosing and potential glioma resistance.

In addition to the neoplastic cells in the murine optic gliomas, a critical role for microglia in both tumor formation and maintenance has been established. Impairment of microglia infiltration by genetic reduction of an essential microglia chemotaxis receptor (CX3CR1) results in delayed tumor formation[51], while either genetic or pharmacologic silencing of microglia function is sufficient to reduce optic glioma proliferation *in vivo*[52–54]. Using advanced RNA-sequencing, one of the relevant growth factors produced by these tumor-associated microglia was discovered[55]. The chemokine CCL5 was demonstrated to be important for glioma maintenance, such that inhibiting its function with neutralizing antibodies dramatically attenuated glioma growth *in vivo*.

One of the most common morbidities associated with NF1-OPG is progressive vision loss. Analysis of *Nf1* mutant mice revealed that reduced neurofibromin expression in RGCs, the neurons that transmit visual information from the eye to the brain, results in increased programmed cell death by apoptosis. Neurofibromin regulation of RGC survival involves the generation of cyclic AMP (cAMP), such that *Nf1+/−* RGCs harbor reduced intracellular cAMP levels[56]. Elevating cAMP levels using an inhibitor of the enzyme responsible for cAMP degradation (phosphodiesterase-4 inhibitor; Rolipram) almost completely ameliorates the apoptosis and loss of RGCs associated with murine *Nf1* optic glioma. Moreover, the progressive axonal injury that culminates in RGC death and visual impairment results from microglia production of neurotoxins, including interleukin-1β[57]. This finding suggests that there might exist a therapeutic window between the elaboration of neurotoxins and irreversible RGC loss during which time pharmacologic intervention might prevent vision loss. Using *Nf1* optic glioma mice, the temporal course of tumorigenesis and retinal pathology was defined, identifying such a window before sufficient RGC apoptosis occurred (>50% RGC loss). Treatment of mice during this period resulted in preservation of RGC numbers two months following the cessation of therapy[43], suggesting that vision stabilization might be possible.

Treatment

When clinical progression occurs, the mainstay of treatment is chemotherapy (Table 1). Other treatment modalities commonly used in brain tumors, namely surgery and radiation,

are problematic in the setting of NF1-associated OPGs. Meaningful surgical resection of NF1-OPGs is usually impossible due to the location of these tumors. It is used, however, in the setting of large orbital tumors where there is no useful vision in the affected eye or to treat corneal exposure or proptosis. Hypothalamic and chiasmatic OPGs often require surgical debulking, and diagnostic biopsy should be considered in tumors arising in atypical locations[9, 58]. Radiation is not recommended in children with NF1, given the risk of secondary tumors (glioma and MPNSTs) in the setting of this tumor predisposition syndrome. In the NF1 population, there is an increased risk of moyamoya syndrome relative to the general population, a risk further heightened by radiation exposure to the large vessels of the Circle of Willis adjacent to the optic pathway[59]. Finally, the risk of late neurocognitive sequelae in children who have learning and attention differences should be considered before initiating radiation[9].

While chemotherapy is often used in symptomatic OPG, few children ever regain normal visual acuity following treatment[9] or experience improvements in vision[60, 61]. Some NF1 experts have raised the concern that chemotherapy may affect cognition in this vulnerable population[62, 63]; however, chemotherapy is usually effective at stabilizing disease or even shrinking NF1-OPGs. First-line OPG chemotherapy, initially proposed by Packer and colleagues, involves vincristine and carboplatin[64]. Second-line chemotherapy treatment options include vinblastine, which shows comparable efficacy to vincristine/carboplatin[65], vinorelbine[66], and temozolomide, an alkylating agent that should be used with caution in tumor-predisposition syndromes[67]. Bevacizumab has also been used to treat refractory NF1-OPG, and may improve visual outcome in some children, although the durability of these responses is unknown[68]. More recently, small molecule inhibitors have been used as investigational therapies for otherwise refractory tumors. Unfortunately, a phase II trial using sorafenib (a multi-kinase inhibitor) was stopped early due to an unexpected acceleration of tumor growth[69]. More promising is selumetinib, a MEK inhibitor that has shown growth inhibition in NF1-deficient GBM cell lines[70] and in NF1-associated plexiform neurofibromas[71]. A phase II clinical trial in low-grade glioma, including NF1-associated OPG is ongoing, but results are not yet available (NCT01089101).

Future directions

Using *Nf1* genetically-engineered mice, it now becomes possible to mechanistically define the factors that underlie tumor growth and associated vision loss. In this regard, the contribution of the germline *NF1* gene mutation and patient sex have been evaluated as potential actionable risk factors relevant to gliomagenesis and clinical progression. While conflicting data exist in the literature regarding the existence of genotype-phenotype correlations in children with NF1-OPG[72–74], proof-of-concept experiments were performed in which mice were generated with specific germline *NF1* gene mutations reported in children with NF1-OPG (R681X) and adults with spinal neurofibromas (G848R). Mice harboring the G848R mutation as their germline *Nf1* gene mutation did not develop optic gliomas, whereas those with the R681X mutation developed optic gliomas with greater volumes and proliferation indices than those harboring the engineered knockout allele as their germline *NF1* gene mutation[75]. These exciting early-phase data support a model in which the particular germline *NF1* gene mutation may have differential effects on

neurofibromin expression and function in stromal cells (e.g., microglia) that serve to increase tumor growth and associated retinal pathology[76]. Studies are ongoing to examine other germline *NF1* gene mutations, as well as create larger repositories of NF1 patient induced pluripotent stem cells for analysis.

Based on an analysis of children with NF1-OPG, girls with tumors located in the optic nerves were 5- to 10-fold more likely to require treatment for progressive vision loss[15, 16]. This interesting sexual dimorphism was further explored in *Nf1* mutant mice, where only female mice were found to have reduced visual acuity from their optic glioma, despite equal tumor volumes and proliferative indices in male and female mice[15]. Sexually-dimorphic differences can result from chromosomal influences (organizational) or gonadal sex hormones (activational) through the effects on gene expression or hormonal receptors, respectively. In *Nf1* mutant mice with optic glioma, there was no protective effect of male gonadal sex hormones. However, estrogen (estradiol) activation of microglia in female *Nf1* mutant mice was responsible for the progressive loss of RGCs and thinning of the retinal nerve fiber layer[57]. These findings demonstrate that inhibition of gonadal sex hormone-mediated microglia activation might attenuate vision loss, suggesting new potential drug treatments to reduce glioma-associated vision loss in children with NF1- OPG.

Collectively, these findings indicate that the biological behavior of these tumors is heavily influenced by a myriad of factors, which each might be actionable. As such, the ability to incorporate sex and the germline *NF1* gene mutation in combination with other factors, like asthma and genomic background[77–80], into predicable risk assessment models is likely to improve our ability to manage these children. In addition, some of these factors may yield actionable outcomes, including new therapeutic approaches. In this regard, we are in a unique position to effectively translate basic laboratory research findings into improved management strategies for NF1-OPG. The availability of numerous authenticated preclinical models, human induced pluripotent stem cell reagents[76], and a successful multi-institutional NF Clinical Trials Consortium[81] offer unprecedented opportunities to apply precision medicine approaches to this common brain tumor in children with NF1.

Acknowledgments

Acknowledgements of research support: D.H.G. is supported by a Research Program Award from the National Institute of Neurological Disorders and Stroke (1-R35-NS097211-01).

We authors thank Dr. Corina Anastasaki for creating the expert illustrations.

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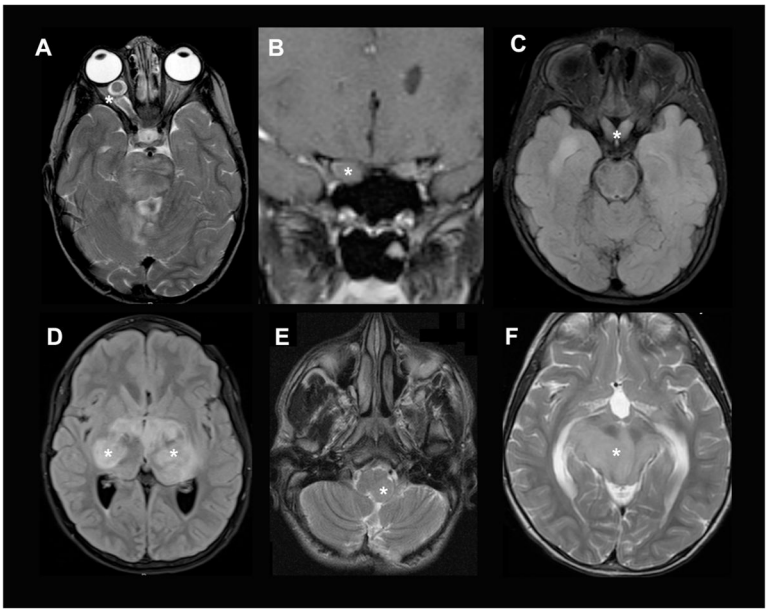

Figure 1. OPGs in children with NF1

Axial T2-weighted MR images of OPGs involving the (**A**) optic nerve, (**B**) optic chiasm, and (**C**) optic radiations. Asterisks denote the tumors.

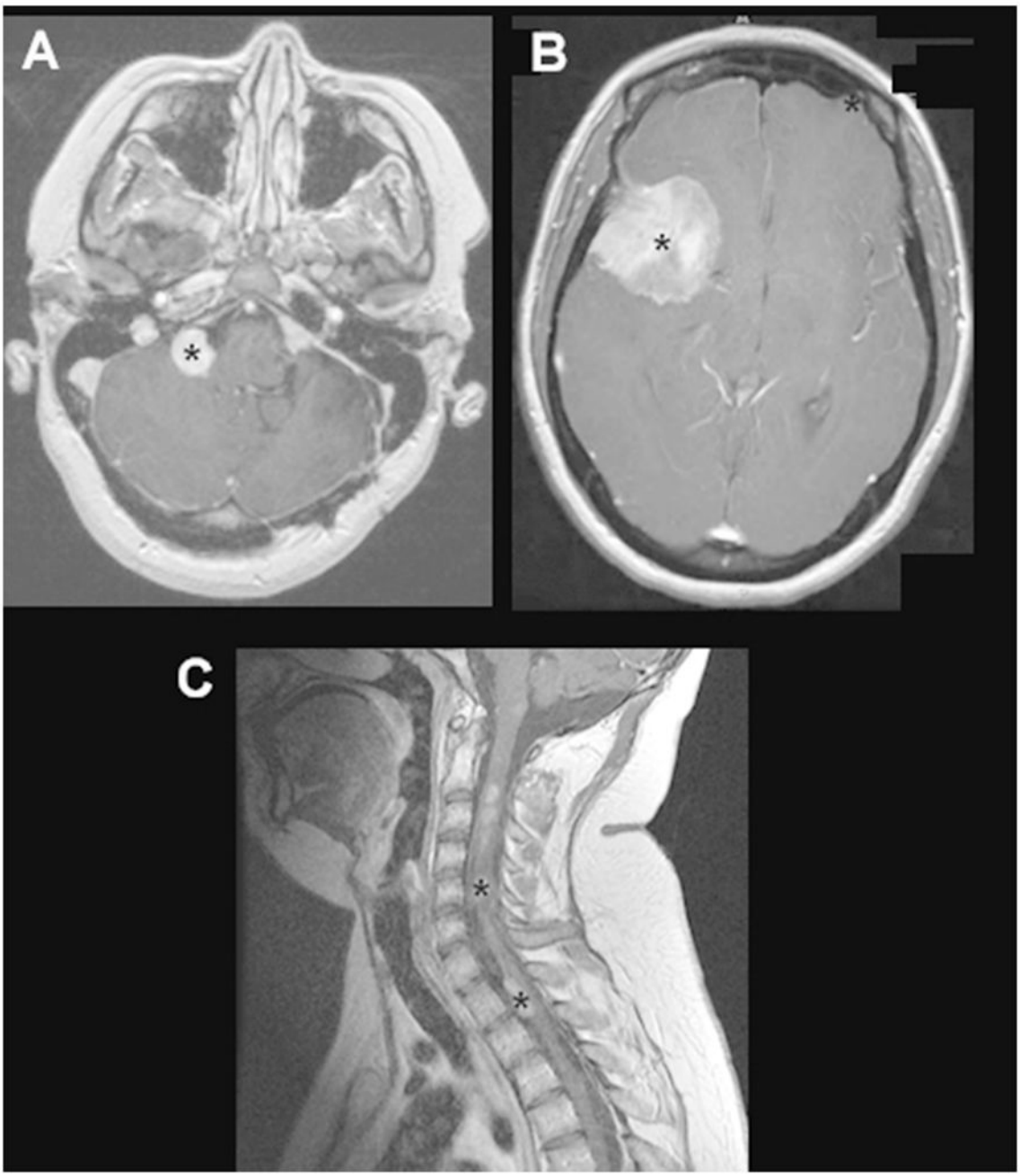

Figure 2. Ecosystem model for NF1-OPG therapeutic targeting

The complex interactions between numerous cell types in the optic glioma determine tumor formation, maintenance, and vision loss. Neoplastic glia (glioma stem cells and tumor astrocytes) lacking *NF1* gene expression produce chemokines that attract and activate microglia. These activated microglia elaborate growth factors that further promote tumor growth (*e.g.*, CCL5), as well as secrete neurotoxins (*e.g.*, IL-1β) that cause axonal injury, retinal ganglion cell death, and vision loss.

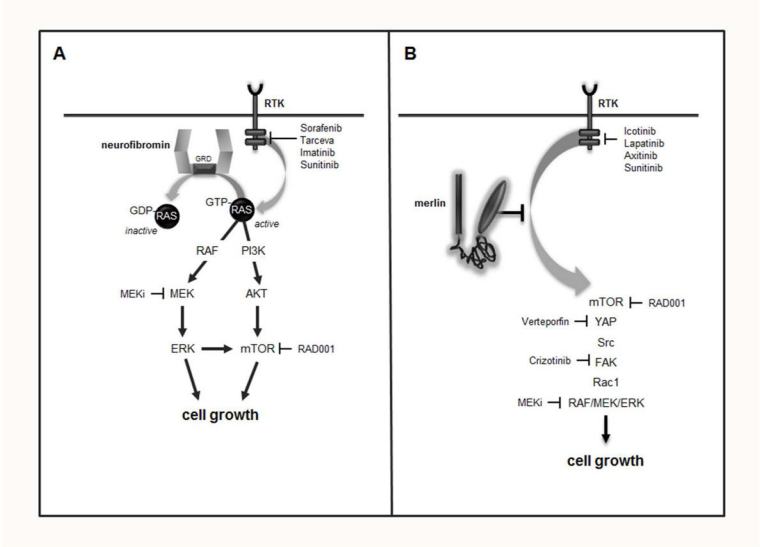

Figure 3. Neurofibromin regulation of cell biology in the central nervous system

The *NF1* protein, neurofibromin, functions as a GTPase-activating protein (GAP) for p21-RAS, accelerating its conversion from an active RAS-GTP bound molecule to an inactive RAS-GDP bound form. RAS can be activated by G protein-coupled receptors (GPCRs), including chemokine receptors, and by receptor tyrosine kinase (RTK) binding of growth factors, like epidermal growth factor. Active RAS controls multiple downstream signaling pathways, engaging MEK and AKT through kinase intermediates, to activate ERK and the mechanistic target of rapamycin (mTOR) complex, respectively. In addition, RAS activation suppresses cyclic AMP (cAMP) generation, important for central nervous system neuron survival.

Table 1

Treatments for NF1-OPG

Trial	Study number	Status	Sponsor	Phase	Ages	Disease status	Primary Outcome
Lenalidomide	NCT01553149	Active, not recruiting	NCI	II	0 to 21 years	Recurrent, Refractory, Progressive	Response Rate
Selumetinib	NCT01089101	Active, not recruiting	NCI	II	3 to 21 years	Recurrent, refractory	Response Rate
Vinblastine +/− Bevacizumab	NCT02840409	Active, recruiting	The Hospital for Sick Children	II	6 months to 18 years	Unresectable or Progressive	Response Rate
MEK 162	NCT02285439	Active	Children's Hospital Los Angeles	I/II	1 to 18 years	Recurrent, Refractory, Progressive	Response Rate
MEK 162	NCT01885195	Active, not recruiting	Array BioPharma	II	≥18 years	Recurrent or Progressive	Response Rate
RAD0001 (Everolimus)	NCT01158651	Active, not recruiting	University of Alabama at Birmingham	II	1 to 21 years	Chemotherapy refractory, radiologically progressive	Response Rate
Pomalidomide	NCT02415153	Active, not recruiting	NCI	I	3 to 20 years	Recurrent, Progressive, or Refractory	Maximum tolerated dose
Pegylated Interferon	NCT02343224	Active, recruiting	Emory University	II	3 to 18 years	Recurrent, refractory, Progressive	Response rate