REVIEW ARTICLE

# Malignant peripheral nerve sheath tumor: models, biology, and translation

Bandarigoda N. Somatilaka[1], Ali Sadek[1], Renee M. McKay[1] and Lu Q. Le[1,2,3,4,5]✉

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Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive, invasive cancer that comprise around 10% of all soft tissue sarcomas and develop in about 8–13% of patients with Neurofibromatosis Type 1. They are associated with poor prognosis and are the leading cause of mortality in NF1 patients. MPNSTs can also develop sporadically or following exposure to radiation. There is currently no effective targeted therapy to treat MPNSTs and surgical removal remains the mainstay treatment. Unfortunately, surgery is not always possible due to the size and location of the tumor, thus, a better understanding of MPNST initiation and development is required to design novel therapeutics. Here, we provide an overview of MPNST biology and genetics, discuss findings regarding the developmental origin of MPNST, and summarize the various model systems employed to study MPNST. Finally, we discuss current management strategies for MPNST, as well as recent developments in translating basic research findings into potential therapies.

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## NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis 1 (NF1) is an autosomal dominant disorder caused by mutations in the *NF1* gene that encodes the tumor suppressor neurofibromin. The *NF1* gene has one of the highest rates of spontaneous mutation in the human genome owing to its large size, which spans over 300 kilobases, and contains 60 exons, including several alternatively spliced exons. Approximately half of *NF1* mutations are de novo events while the rest are inherited. The incidence of NF1 is 1 in every 3000 live births making it one of the most common single gene inherited conditions [1].

Neurofibromin functions as a RAS GTPase Activating Protein (RAS-GAP), acting as an off-switch to all RAS proteins [2, 3] and is expressed in multiple cell types, particularly those of neural crest origin, including neurons, cells of the nervous system, and early melanocytes [4]. Therefore, almost all individuals with NF1 develop neurocutaneous pathologies of the skin, central nervous system, and peripheral nervous system. Loss of the second copy of *NF1*, referred to as loss of heterozygosity (LOH), is observed in some of these pathologies but not all.

The clinical manifestations of NF1 are wide-ranging and highly variable. They can be broadly divided into tumor and non-tumor manifestations. Major non-tumor manifestations of NF1 include pigmentary lesions (café-au-lait spots, axillary and inguinal freckling, and Lisch nodules), skeletal abnormalities (scoliosis, dysplasia of the long bone, pseudarthrosis of the tibia, macrocephaly, and short stature), vascular disorders (vasculopathy, pulmonary stenosis, and hypertension), learning disabilities, and social/behavioral disorders [4, 5]. Tumor manifestations include mostly benign neoplasms, but malignant tumors can also develop.

## NF1-ASSOCIATED NEOPLASMS

Due to the high rate of LOH, individuals with NF1 are at increased risk for developing various types of benign and malignant neoplasms [6, 7]. One of the most common central nervous system tumors found in both children and adult NF1 patients is glioma [8]. Symptomatic optic pathway gliomas (OPGs) are more often found in young children, are usually indolent, and typically regress with age. Chemotherapy is used to treat OPG patients when there is confirmed decline in vision or evidence of hypothalamic involvement [8, 9]. Gliomas in adults can be more aggressive and are typically located in other areas of the brain. Other neoplasms that can arise in NF1 patients are glioblastomas, pilocytic astrocytomas, gastrointestinal stromal tumors, pheochromocytomas, and juvenile myelomonocytic leukemia [10].

The hallmark tumor of NF1, however, is the neurofibroma. Neurofibromas fall into two main subtypes: cutaneous and plexiform. They arise from biallelic loss of *NF1* in the Schwann cell lineage. Dermal or cutaneous neurofibromas (cNF) are benign tumors that can project above the surface of the skin or reside within the skin. They are present in >99% of NF1 patients and first appear in the preadolescent years. They continue to increase in number throughout life; in some cases, the number of cNF can be exceptionally high, resulting not only in physical discomfort, but also cosmetic disfigurement and emotional distress [4, 11, 12]. As medical treatments to date have been ineffective, surgical removal remains the only approach to manage cNF [12].

Unlike cNF, plexiform neurofibroma (pNF) is usually congenital and develops in more than 50% of NF1 patients. These tumors arise from nerve plexuses and develop within peripheral nerves

[1]Department of Dermatology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9069, USA. [2]Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9069, USA. [3]UTSW Comprehensive Neurofibromatosis Clinic, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9069, USA. [4]Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9069, USA. [5]O'Donnell Brain Institute, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390-9069, USA. ✉email: lu.le@utsouthwestern.edu

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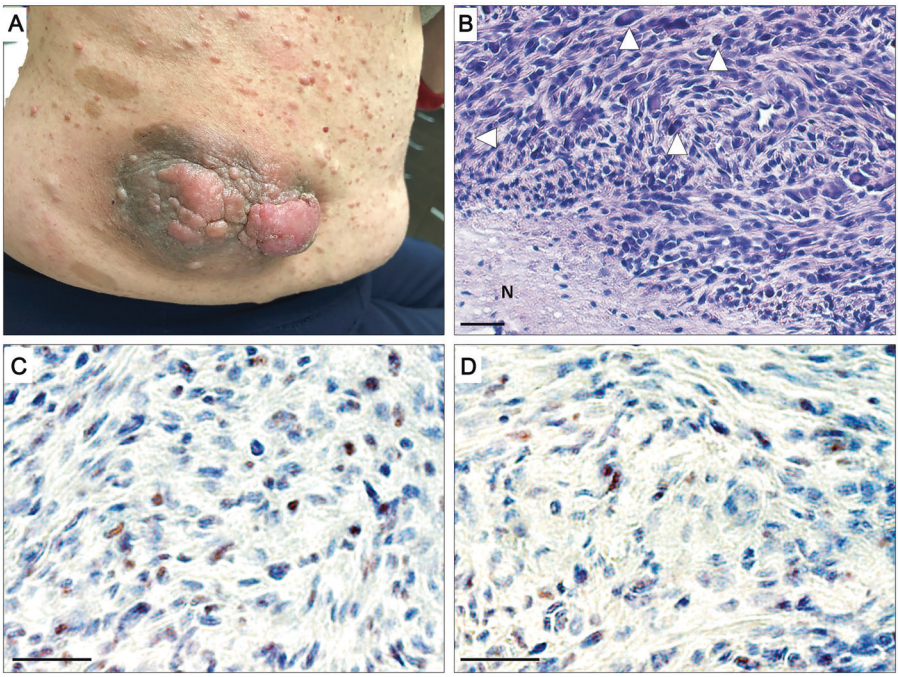


**Fig. 1 Morphology and histology of MPNST. A** Photo of MPNST on the right flank of an NF1 patient. Also note the cutaneous neurofibroma tumors and café-au-lait macules surrounding the MPNST. **B** Hematoxylin and eosin-stained paraffin section of the tumor in (**A**). N; necrotic pseudopalisade. White arrowheads mark mitotic cells. **C** Ki67 and **D** pH3 mark proliferating cells in the MPNST. Scale bar: 50 μm.

and their perineural sheaths. pNFs can grow very large, affecting entire sections of the body and impinging on vital organs. Therefore, these pNFs can cause disfigurement and pain and impair function of the affected area. Due to their large and infiltrative nature, surgical removal of pNF can be difficult [4, 5, 7, 13]. In 2020, the FDA approved the first molecularly targeted therapy for symptomatic, inoperable pNF: selumetinib, a MEK inhibitor [14]. While this news was welcomed in the NF1 field, selumetinib is not a "cure all": findings in both mice and humans have demonstrated that selumetinib does not completely eradicate the tumor, and once treatment is stopped tumors begin to grow again [14–16]. Importantly, about 8–13% of individuals with NF1 will go on to develop malignant peripheral nerve sheath tumors (MPNST) (Fig. 1A), aggressive tumors that arise due to malignant transformation of pNF [17].

## MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST)

MPNST is a rare malignancy accounting for about 10% of all soft tissue sarcomas [18]. The estimated incidence of MPNST is 1.46 per 1,000,000 individuals [19]. The 8–13% of individuals with *NF1* mutations that develop MPNST constitute nearly 50% of all MPNST cases. Of the remaining cases, 45% of MPNSTs occur sporadically with unidentified genetic anomalies, and the rest are associated with radiotherapy. For NF1-associated MPNST, the transition from pNF to MPNST is difficult to detect radiologically or by biopsy due to the intralesional heterogeneity of these tumors. MPNSTs are associated with poor survival outcomes, and in fact are the leading cause of mortality in NF1 patients [20]. These poor outcomes can be due to delayed diagnosis but are mostly due to poor therapeutic success. While complete surgical resection is the primary treatment for MPNST it is often hindered by the large size of tumors, early metastasis, their proximity to complex nerve networks, and a low rate of negative resection margins [21, 22]. Chemotherapy and ionizing radiation are also sometimes used for unresectable and high-risk MPNSTs. There is currently no FDA-approved drug for MPNST treatment although a number of clinical trials are underway. These are discussed at the end of this review (section *9*).

Histologically, MPNSTs are diagnosed by the presence of features such as perivascular hypercellularity, fascicles, uniform spindle cells with hyperchromatic nuclei, high mitotic indices, and necrosis (Fig. 1B) [23, 24]. A recently identified tumor within the transition of pNF to MPNST is called atypical neurofibromatosis neoplasms of uncertain biological potential (ANNUBP). ANNUBPs exhibit features that are not commonly seen in pNF, including loss of neurofibroma architecture, high cellularity, and high mitotic activity [24]. ANNUBPs are thought to be premalignant tumors that represent a transitional step in pNF progression to MPNST. Moreover, the pNF microenvironment, which contains perineural cells, fibroblasts, endothelial cells, neurons, and cells of hematopoietic origin, may influence their malignant transformation [25, 26].

## DEVELOPMENTAL ORIGIN OF MPNST

### Malignant tumors arising from peripheral nerve tissues

- *NF1-associated MPNST:* The developmental origin of MPNST is a burning question in the field. By definition, MPNST is a malignant tumor that comes from *any cell* in the peripheral nerve, and, in NF1-associated MPNST, it is thought that MPNSTs arise from pNFs following progression to ANNUBP. However, the cell(s) of origin within pNF that gives rise to ANNUBP and then to MPNST remains unknown. One possibility is that neoplastic *NF1*-null Schwann cells undergo further mutation that drives progression to MPNST. Another possibility is the existence of a special, stem cell-like population that is responsible for MPNST initiation (see below). Alternatively, the neurofibroma may act like an "incubator" for other stem cell populations within the tumor microenvironment (TME) that makes them susceptible to tumorigenic progression to MPNST. These cells could be

pericytes, fibroblasts, endothelial cells, etc. There is also the possibility that all of the above mechanisms contribute to MPNST development.

- *Sporadic MPNST:* In the case of sporadic MPNST, even less is known about the cell of origin and there is a relative paucity of preclinical models. Sporadic MPNSTs typically have a later age of onset and are smaller in size than NF1-associated MPNSTs, which likely accounts for the better prognosis for patients with sporadic MPNST [27]. Bottillo et al. reported that *NF1* mutation is present in about 41% of sporadic MPNSTs they analyzed [28]. While the histology of NF1-associated and sporadic MPNSTs is similar, it is believed that these MPNSTs arise via different mechanisms, with sporadic MPNSTs thought to arise de novo, rather than progressing from a pNF [29].

### Cancer stem cells in MPNST

The cancer stem cell theory posits that cancer growth is due to a small population of relatively quiescent cells with stem-like properties that sustain the cancer and are resistant to therapies that target rapidly dividing cells [30]. The identification of a cancer stem cell population was first reported by Lapidot et al. in the context of acute myeloid leukemia [31]. This was soon extended to solid tumors, including brain, breast, and lung cancers [32–34]. In 2011, Spyra et al. reported the identification of MPNST cancer stem cells using an established MPNST cell line [35]. These cells had increased expression of stem cell markers including CD133, Oct4, and Nestin, and decreased markers of differentiation such as NCAM and CD90. Additionally, these cells induced tumor formation more readily than the parental cells when injected into nude mice [35]. More recently, Sun et al. used in vivo MPNST models to identify a quiescent stem cell-like cell population that is required for MPNST initiation [36]. They used two different *Nestin*-promoter transgenes—one driving thymidine kinase (TK) and one driving diphtheria toxin receptor—to eliminate these cells in mouse models of MPNST and found that tumor initiation and development was significantly impeded. They also observed a role for these cells in tumor regrowth following chemotherapy. Importantly, the stem cell gene signature of these cells was observed in the cognate human tumors from which the xenograft mice were derived supporting the clinical relevance of these findings. The identification of cancer stem cells has implications not only for therapeutic strategies but may also shed light on the mechanisms underlying the transition from pNF to MPNST.

## THE GENETICS OF MPNST

### NF1-associated MPNST

Although individuals with NF1 are heterozygous for *NF1* gene mutation, benign and malignant tumor formation is caused by LOH of the remaining wild-type *NF1* allele in somatic cells [37]. Only 8–13% of NF1 patients develop MPNST suggesting *NF1* deficiency is necessary but not sufficient to induce malignancy. As such, cooperating mutations in other genes that drive malignant progression must be acquired. With the advent of next-generation sequencing, a number of these cooperating mutations have been identified [38, 39]. Not surprisingly, mutations in tumor suppressors, as well as mutations that cause upregulation of oncogenic genes have been found. For example, loss/inactivation of the tumor suppressor genes (TSGs) *CDKN2A* and *PTEN* (Phosphatase and tensin homolog deleted from chromosome 10) is frequently observed in MPNST [38–40]. Mutation or deletion of the TSG *CDKN2A*, which encodes the cell cycle inhibitors *p16INK4A* and *p14ARF*, is found in about 50% of neoplasms including ANNUBP that ultimately progress into MPNST, thus implicating it as a key driver of progression to MPNST [41, 42]. PTEN is an inhibitor of the PI3K and mTOR pathways (Fig. 2), and loss of PTEN function results in upregulation of these pathways which are involved in cell proliferation and survival. Another TSG shown to be involved in MPNST is TP53, although there have been conflicting reports on the frequency of mutation observed [43, 44]. A summary of studies reporting on TP53 mutation in MPNST is provided in a review by Lemberg et al. [39].

Epigenetic dysregulation is also involved in NF1-associated MPNST: inactivating mutations in *SUZ12* or *EED*, two components of the polycomb repressive complex 2 (PRC2) have been shown to be associated with MPNST formation [45, 46]. (See section "Epigenetic regulation of MPNST development" below).

### Genetic instability in MPNST

Genetic instability is a hallmark of most cancers and a driver of malignancy and aggressiveness, and includes nucleotide sequence mutations and microsatellite instability, as well as larger genetic changes such as chromosomal gains, losses, and rearrangements leading to DNA copy number alterations (CNA). A number of studies have demonstrated that, like other malignancies, MPNST display significant genetic instability [47]. Recurrent losses have been observed for many chromosomal regions including 1p, 9p, 11, 12p, 14q, and 22q while gains, which are observed more frequently than losses, include chromosome 7, 8q, 9q, 13q, 15q, and 17q [48–51]. Many of the regions of chromosomal loss and gain are large, making it difficult to pinpoint the gene(s) within these regions that is involved in tumorigenesis. However, some of the relevant genes have been identified and we discuss these in section "Gene amplifications in MPNST development".

While the exact causes of this genetic instability have yet to be completely elucidated, longitudinal genomic analyses suggest that there is a non-random stepwise progression. Peacock et al. found *MET* and *HGF* copy number gains in MPNST but not in pNF that increased during disease progression and following treatment with chemotherapy and radiation [52]. They also found that additional genomic gains and losses occurred over time leading to even greater genetic complexity that supports MPNST progression. Pemov et al. used comprehensive multiplatform genomics analyses to distinguish genetic changes that occur in the transition from pNF to atypical neurofibroma (ANF; now reclassified as ANNUBP) to MPNST [53]. They found that MPNST has much greater genetic instability and complexity compared to pNF or ANNUBP, with a greater number of CNAs resulting in overexpression of 178 oncogenes and loss of 144 TSGs. They also identified loss of CDKN2A and SMARCA2 as key drivers of the transition from PNF to ANNUBP.

Szymanski et al. took advantage of this feature of MPNST to design a cell-free whole genome sequencing test that can distinguish MPNST from pNF based on CNAs, microdeletions, etc. [54]. This liquid biopsy method could one day be used clinically as an early, non-invasive detection and monitoring test.

The fact that MPNSTs have greater genetic instability than pNFs has implications for treatment planning. As radiotherapy and chemotherapy tend to increase genetic instability and can cause de novo genetic mutations to arise, it would perhaps be advisable to perform clinical trials on patients whose MPNST have not yet been treated: potential therapies might have a better chance of success in untreated MPNSTs rather than following chemotherapy and radiation therapy when the tumors have likely accumulated even more mutations [52] making them more aggressive and treatment resistant (discussed further in section "Conclusion and future perspective").

### Gene amplifications in MPNST development

The chromosomal gains observed in MPNST result in amplification of many genes, although copy number variation can also occur in a gene-specific manner. Some of the amplified genes that play an important role in MPNST pathogenesis have been identified. For example, amplification of several receptor tyrosine kinases (RTKs) has been observed in MPNST, including *MET, c-kit*, platelet-derived

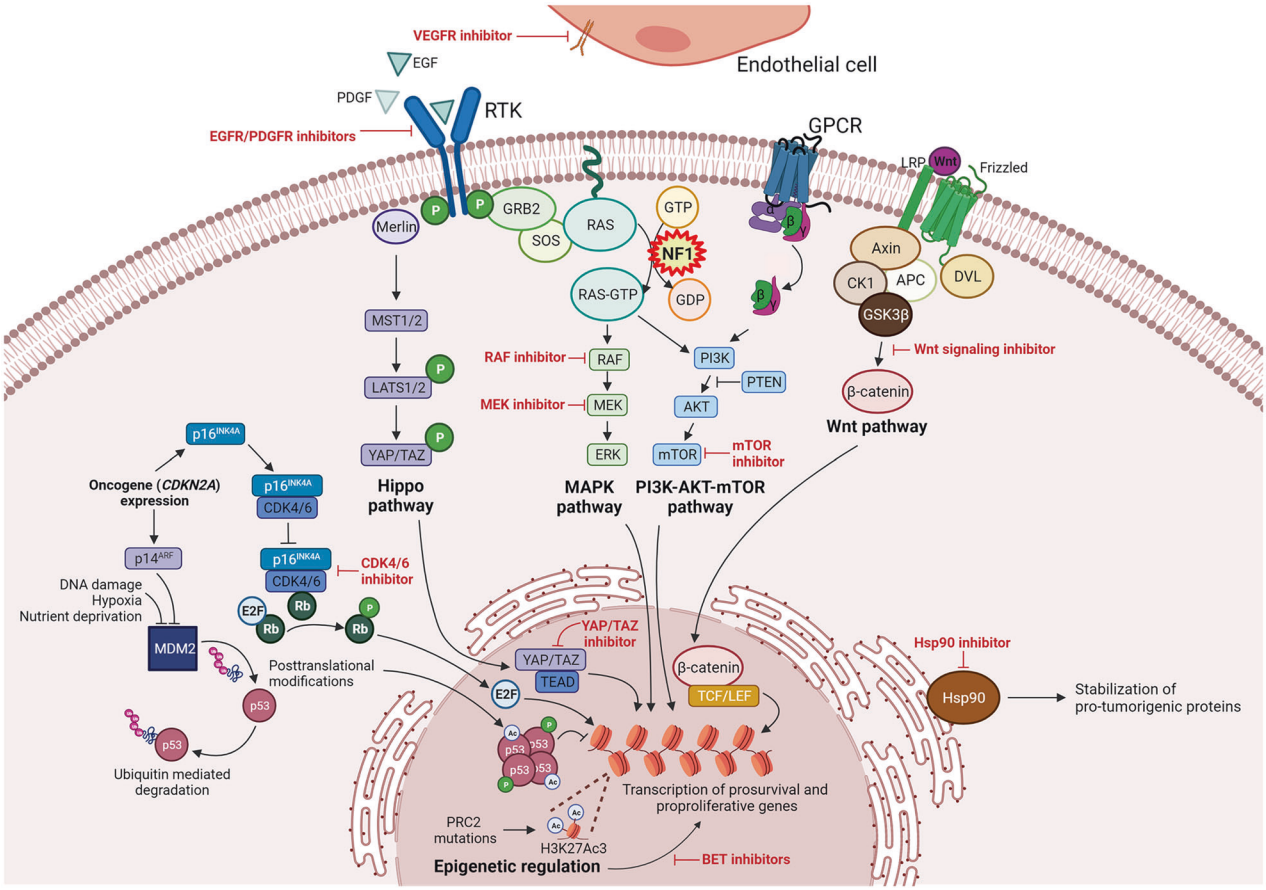


**Fig. 2 Key cellular pathways underpinning MPNST development.** Created with BioRender.com.

growth factor (*PDGFRA)*, and epidermal growth factor receptor (*EGFR)* [55–57], and subsequent studies have demonstrated their relevance to MPNST pathogenesis. (i) In 2008, Mantripragada et al. reported amplification of both *MET* (also known as *Hepatic Growth Factor Receptor* (*HGFR*)), as well as its ligand, *HGF* [57] in human MPNST samples compared to neurofibromas. In 2018, Peacock et al. reported that mice with *Nf1* ablation and *MET* overexpression driven by *Plp-Cre* developed MPNSTs in the absence of other mutations indicating that, in the context of *Nf1* loss, MET activation is sufficient for malignant transform [52]. (ii) Holtkamp et al. showed that *c-KIT* is amplified in MPNST [56], and treatment of MPNST cell lines with imatinib, a c-kit inhibitor, slowed cell growth [58]. (iii) Ki et al. used a zebrafish model to show that overexpression of *PDGFR* in *Nf1/p53* mutant fish increased the rate and penetrance of MPNST development [59]. *(iv)* Wu et al. reported that the $Nf1^{fl/fl}$;*DhhCre* mouse model of neurofibroma develops MPNST when *EGFR* is overexpressed [60].

Genes encoding other types of proteins besides RTKs have also been found to be amplified in MPNST. In 2011, Yang et al. reported *c-MYC* as an amplified gene in MPNST [61], and more recently, Dehner et al. analyzed expression of genes located on chromosome arm 8q, a frequent location of chromosomal gain in MPNST, and determined that *c-MYC* and *Rad21* are more highly expressed in MPNST, compared to pNF, and likely to be involved in tumorigenesis [51]. *c-MYC* encodes a basic-loop-helix transcription factor and has been found to be amplified in a variety of cancers [62]. It regulates a number of key cellular processes that can be hijacked for cancer growth, including cell proliferation, metabolism, and differentiation. *Rad21* encodes a DNA double-strand break repair protein, and the role of its upregulation in MPNST remains to be determined.

The identification of additional genes with amplified expression that play a role in MPNST pathogenesis should provide new therapeutic opportunities.

## Epigenetic regulation of MPNST development

In 2014, Patel et al. used a mouse model of MPNST [63] to screen for epigenetic changes and discovered that bromodomain-containing 4 (BRD4), a member of the bromodomain and extraterminal (BET) family and an epigenetic regulator, is highly upregulated in these tumors [64]. They then targeted BRD4 with the BRD4 inhibitor JQ1 and found that it inhibited cell growth and caused tumor regression. Subsequently, 3 independent groups performed genome sequencing analyses on human MPNST and found recurring mutations in *SUZ12* and *EED*, components of PRC2 [65–67]. PRC2 is a histone methyltransferase complex that represses gene transcription [68]; when the complex is inactivated, H3K27 becomes acetylated (rather than methylated) (Fig. 3). These acetylated histones become targets for BRD4 binding, which then recruits transcription factors that activate transcription of oncogenic factors [69]. De Raedt et al. also used the BRD4 inhibitor JQ1, together with a MEK inhibitor, to show that this combination therapy reduced MPNST growth in *Nf1/p53/Suz12* mice [65]. These findings nominate BRD4 as a prime therapeutic target that could potentially be effective in most MPNSTs regardless of their underlying secondary genetic mutations (Fig. 3).

## Non-NF1-associated MPNST

Compared with NF1-associated MPNST, less is known about the molecular underpinnings that drive development of sporadic MPNST. However, some findings include: (i) Similar to NF1-associated MPNSTs, mutations in PRC2 components have been

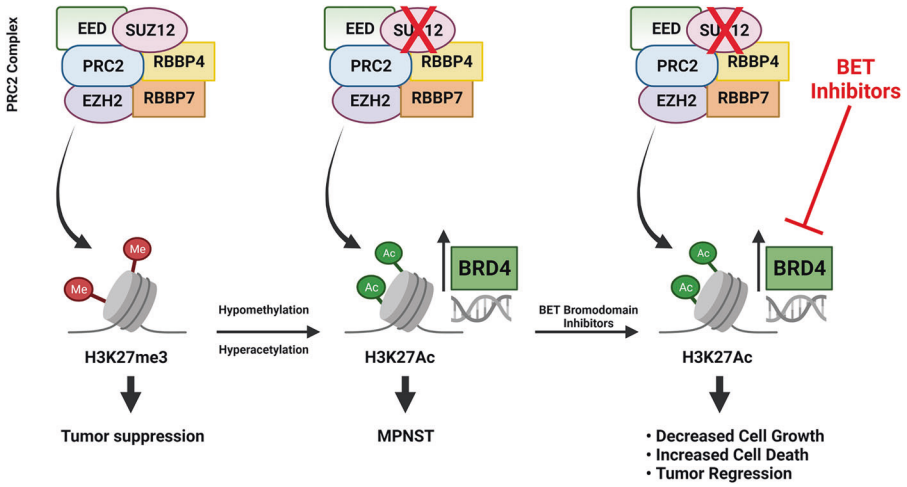


**Fig. 3 Epigenetic regulation in MPNST.** BRD4 bromodomain-containing protein 4, EED embryonic ectoderm development, EZH2 enhancer of zeste homolog 2, PRC2 polycomb repressive complex 2, RBBP4/7 retinoblastoma binding protein 4/7, SUZ12 suppressor of zeste 12. Created with BioRender.com.

found in non-hereditary MPNSTs, with over 90% of sporadic MPNSTs harboring mutations in either *SUZ12* or *EED* [66, 67]. (ii) B-RAF is a serine/threonine protein kinase that phosphorylates and activates mitogen-activated protein kinase (MAPK), and mutations in *BRAF* have been found in a number of cancers [70]. Using an immunohistochemical assay, Hirbe et al. observed the oncogenic $BRAF^{V600E}$ mutation, in which the valine at position 600 is replaced with glutamic acid, present in sporadic NF1 [71]. Their finding that over 90% of cells in $BRAF^{V600E}$-positive MPNSTs are $BRAF^{V600E}$-immunoreactive, while no benign neurofibromas were positive indicates that $BRAF^{V600E}$ is likely a driver mutation in sporadic MPNST. (iii) TP53 mutations have also been identified in sporadic MPNSTs [44]. (*iv*) Recently, Longo et al. established a cell line from a patient sporadic MPNST and found that while some of the mutations found in NF1-associated MPNSTs were present (e.g., *CDKN2A*, *PTEN*, and *TP53*), there were also mutations not typically found, including *DNMT1, NUMA1*, and *NTRK1* [72].

In 2020, plans for more in-depth analyses using whole genome sequencing, RNA sequencing, and DNA methylation profiling to assess MPNSTs were outlined by the Genomics of MPNST (GeM) Consortium, which consists of 10 participating institutions [73]. These analyses should provide important insights into the genetic similarities and differences in sporadic versus NF1-associated MPNST.

## MODELING MPNST

A number of model systems have been deployed to study MPNST including cell culture models, Drosophila and zebrafish models, genetically engineered mouse models (GEMMs), and xenograft models using patient-derived MPNST cells. Studies using these model systems have contributed immensely to our understanding of MPNST biology. Each system is discussed briefly below.

### Cell culture/ in vitro models

Molecular characterization of cells obtained from primary, metastatic, and recurrent MPNSTs that are either NF1-associated or sporadic have been extensively characterized [29, 74–80] (Table 1). Tumor cell lines isolated from human patients with malignant schwannomas have been studied to understand the mechanism of action of neurofibromin [81]. Several human-derived cell lines have been used to study the role of tyrosine kinase receptors such as stem cell factor/KIT complex [55, 74, 82], EGFR [83, 84], PDGFR [55, 85] and HGFR [86] in MPNST. Other studies include investigating how growth factors [87, 88], steroid hormones [89, 90] and micro-RNAs [90] are involved in MPNST pathology. A number of human MPNST cell lines have been surveyed to identify oncogene mutations driving MPNST in addition to *NF1* [76]. Xenograft models using human MPNST cell lines are extensively used to explore the efficacy of chemotherapy [58, 91–94] and viral therapy [95, 96] as potential treatment strategies for MPNST.

Immortalized human Schwann cells have been used to test candidate oncogenes and tumor suppressors that are involved in malignant transformation of Schwann cells [97, 98]. These Schwann cells, obtained from nerves of healthy human individuals and NF1 patients, along with neurofibromas were immortalized using lentiviral transduction of human *TERT* and mouse *Cdk4* transgenes [99].

Another important model system in this category is the in vitro 3-D organotypic model, whereby the different components that comprise the tumor—neoplastic Schwann cells, fibroblasts, endothelial cells, mast cells, etc.—are grown on a matrix, and give rise to tumors [100, 101]. This system therefore more closely replicates the complexity of the actual in vivo tumor environment. Advantages of the 3-D model include the ability to test the requirement for different cellular components and the requirement of particular genes in those cells for tumor development, as well as drug screening/testing in a more biologically relevant system than 2-D culture.

### *Nf1*-mutant fly models

The Drosophila Nf1 protein is highly conserved, with an amino acid sequence similarity of 60% to human neurofibromin [102]. *Nf1*-mutant fly models exhibit similar behavioral phenotypes to mammalian models [103–108], therefore, Drosophila provides a powerful genetic system to investigate the signaling events upstream and downstream of *Nf1*. While *Nf1*-mutant flies have growth defects [102, 106, 109], impaired learning [103–106], defective neuropeptide signaling [110], improper circadian rhythm activity [111] and excessive behavior [107, 108, 112], only the latter two phenotypes have been shown to be associated with increased Ras-MAPK signaling [111]. The other phenotypes have been linked to decreased signaling in the cAMP-Protein Kinase A pathway [102, 113].

### Zebrafish models of MPNST

*Nf1*-mutant zebrafish models have also been deployed to investigate the biology of MPNST and as a system for preclinical

**Table 1.** Human MPNST cell lines and xenograft models derived from them.

| Cell line | Origin | Recipient mouse species | | | | | Route of administration | | | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Nude | SCID | NSG | NOD/SCID | NIH III | SC | IP | IN | TV | |
| S462 | NF1 MPNST | x | | | | | x | | x | | [29, 35, 55, 78, 239–241] |
| S462.TY | NF1 MPNST | x | | | | | x | | | | [77, 242] |
| sNF02.2 | Metastatic lung of NF1 MPNST | | | | | | | | | | [29, 76, 77, 243] |
| sNF94.3 | NF1 MPNST | | x | | | | | | x | | [29, 243] |
| sNF96.2 | NF1 MPNST | | x | | | | x | | | | [29, 76, 77, 89, 243] |
| ST88-14 | NF1 MPNST | x | x | x | | x | x | x | | | [29, 55, 74–78, 81, 83, 240, 241, 244–248] |
| T265 | NF1 MPNST | x | x | x | | x | | x | | | [29, 74–77, 240, 247, 249] |
| ST88-3 | NF1 MPNST | | | | | | | | | | [75, 77, 81, 83, 244] |
| 90-8 | NF1 MPNST | | | | | | | | | | [29, 43, 75, 81, 83, 246, 250] |
| FMS-1 | NF1 MPNST | x | x | | x | | x | | | | [84] |
| MPNST642 | NF1 MPNST | | x | | | | x | | | | [29, 240] |
| MPNST724 | MPNST | | x | | | | x | | | | [29, 240, 251] |
| NMS-2 | NF1 MPNST | x | | | | | x | | | | [29, 91] |
| NMS-2PC | Metastatic retroperitoneal lesion of NF1 MPNST | x | | | x | | x | | | | [29, 91] |
| YST-1 | Sporadic MPNST | x | | | | | x | | | | [75, 78, 80, 252] |
| STS26T | Metastatic left scapula of sporadic MPNST | x | x | x | | x | x | x | x | x | [29, 74–78, 240, 241, 246, 247, 253] |
| Hs-Sch-2 | Sporadic MPNST | x | | | x | | x | | | | [29, 78, 254] |

*IN* intraneural, *IP* intraperitoneal, *SC* subcutaneous, *TV* tail vein.

drug screening. One of the earliest efforts in zebrafish involved determining how p53 contributes to MPNST development in zebrafish carrying mutations in ribosomal protein (RP) encoding genes. This work demonstrated that a threshold amount of RPs is required for p53 protein production in vivo and disruption of this regulation leads to MPNST tumorigenesis [114]. Extension of this work reported that MPNSTs that arise in zebrafish as a result of mutations in either *rp* genes or in *p53* are highly aneuploid, suggesting that zebrafish is a useful tool to study aneuploidy in human cancer. A major contribution to developing zebrafish models of MPNST came from Thomas Look and colleagues. Using targeted mutagenesis strategies, they generated zebrafish containing stable germline mutations in *nf1a* and *nf1b*, orthologues of *Nf1*. Ablating *p53* in an $nf1a^{+/-}$; $nf1b^{-/-}$ background resulted in accelerated onset and increased penetrance of MPNSTs in adult fish. This was also the first animal model displaying the characteristic pigmentation lesions of NF1 [115]. These fish have been used to identify drivers of *NF1/p53* deficient MPNSTs and for in vivo evaluation of candidate drugs as potential treatments for MPNST [116, 117]. Another zebrafish model containing a large deletion in chromosome 1, where the *rps6* RP gene is located, and in the heterozygous condition also gave rise to tumors with histological features consistent with MPNSTs [118]. A recent study identified the membrane-bound glycoprotein RECK as a tumor suppressor for zebrafish MPNST in *rp*- and *p53*-mutant zebrafish backgrounds [119]. Developing better zebrafish models for MPNST was a recommendation from the "MPNST State of the Science: Outlining a Research Agenda for the Future" conference at the National Institutes of Health, 2016 [120].

## Mouse models of MPNST

As for many other diseases, GEMMs of MPNST have been a workhorse for investigating the underlying biology of MPNST development and for preclinical drug testing (Table 2). Mouse models have employed 4 common mechanisms to initiate MPNST growth: (1) Spontaneous LOH of TSGs; (2) Using nervous system-specific promoters for overexpression of candidate oncogenes; (3) Spatiotemporal conditional activation/mutation of oncogenes; and (4) Adenoviral or lentiviral expression of shRNAs to knock down relevant genes.

Unlike humans, mice heterozygous for loss of *Nf1* ($Nf1^{+/-}$) do not develop peripheral nerve sheath tumors or other characteristic symptoms of human NF1 [121, 122]. However, combining *Nf1* heterozygosity with *Ink4a* and *Arf* deficiency gives rise to MPNST with low penetrance [123]. Alternatively, inactivating mutations of the TSG *Trp53* are associated with MPNST [43, 124]. The first and most studied MPNST model is the $Nf1^{+/-}$; $Trp53^{+/-}$ cis mouse (cisNP), where inactivating mutations in *Nf1* and *Trp53* are placed in a cis configuration, as both genes are linked on mouse chromosome 11 [125, 126]. As in the mouse, these two genes are also closely linked in humans. Spontaneous loss of the wild-type alleles of these genes initiates tumorigenesis resulting in a variety of sarcomas, including MPNST [125–127]. The cisNP mouse model was used to identify Ras pathway components that might be optimal therapeutic targets [128, 129] and to test a variety of new therapies [130–132]. This model has also been used to identify other candidate genes whose mutations potentiate *Nf1* inactivation to tumorigenesis [65]. A drawback of the cisNP model is that these tumors do not develop through a process that involves

**Table 2.** Mouse models of MPNST.

| Mouse model | Method of mutation | Promoter | Overexpressed genes | Penetrance (%) | References |
|---|---|---|---|---|---|
| *Nf1*$^{+/-}$; *Trp53*$^{+/-}$ | Germline | | | 81 | [125, 126] |
| *Nf1*$^{+/-}$; *Arf*$^{-/-}$; *Ink4a*$^{-/-}$ | Germline | | | 26 | [123] |
| *Nf1*$^{flox/flox}$; *Pten*$^{flox/flox}$ | cko in Dhh$^{+}$ cells | | | 92 | [135] |
| *Nf1*$^{flox/flox}$; *Pten*$^{flox/+}$ | cko in Dhh$^{+}$ cells | | | 42 | [135] |
| *Nf1*$^{flox/+}$; *Pten*$^{flox/flox}$ | cko in Dhh$^{+}$ cells | | | 82 | [135] |
| *Nf1*$^{flox/flox}$; *Arf*$^{flox/flox}$ | cko in Postn$^{+}$ neural crest-derived progenitor Schwann cells | | | 100 | [136] |
| *Nf1*$^{flox/flox}$; *Pten*$^{flox/+}$ | cko in Postn$^{+}$ neural crest-derived progenitor Schwann cells | | | 60 | [136] |
| *Nf1*$^{flox/flox}$ | cko in Dhh$^{+}$ cells | CNP | *EGFR* | 33 | [60] |
| *Nf1*$^{flox/flox}$; *Arf*$^{flox/flox}$; *Ink4a*$^{flox/flox}$ | cko in the sciatic nerve with Adenovirus-Cre injections | | | 100 | [140] |
| *Nf1*$^{flox/-}$; *Arf*$^{flox/flox}$; *Ink4a*$^{flox/flox}$ | cko in the sciatic nerve with Adenovirus-Cre injections | | | 75 | [141] |
| *Nf1*$^{flox/flox}$; *Nf1/p53* shRNA | cKO in Periostin$^{+}$ cells followed by lentivirus-mediated knockdown | | | 56 | [143] |
| *Nf1*$^{flox/-}$; *Nf1/p53* shRNA | cKO in GFAP$^{+}$ cells followed by lentivirus-mediated knockdown | | | 73 | [143] |
| ($P_0$)GGFβ3 | Schwann cell-specific overexpression | P0 | *GGFβ3* | 71 | [133] |
| *Trp53*$^{+/-}$ | Germline, Schwann cell-specific overexpression of GGFβ3 | P0 | *GGFβ3* | 95 | [134] |
| *Pten*$^{flox/+}$ | cKO in GFAP$^{+}$ cells | | *Kras-G12D* | 100 | [137] |
| *Pten*$^{flox/flox}$ | cko in Dhh$^{+}$ cells followed by overexpression of EGFR | CNP | *EGFR* | 100 | [138] |
| *Trp53*$^{+/-}$ | Germline, Schwann cell-specific overexpression of EGFR | CNP | *EGFR* | 19 | [139] |

*cko* conditional knockout, *CNP* 2–3-cyclic nucleotide 3-phosphodiesterase, *Dhh* Desert hedgehog, *EGFR* epidermal growth factor receptor, *GGFβ3* glial growth factor β3, *Postn* periostin.

progression from benign pNF to ANNUBP to MPNST as seen in human NF1 patients.

A transgenic mouse model that overexpresses the growth factor neuregulin-1 in myelinating Schwann cells develops neurofibroma and peripheral ganglion-associated MPNST. Further analysis of this mouse model showed abnormalities in p16$^{INK4A}$–cyclin D/CDK4–Rb and p19$^{ARF}$–Mdm–p53 signaling pathways and chromosomal alterations that account for multiple mutations in neoplasia-associated genes analogous to their human counterparts [133, 134]. Although this mouse model has sustained neurofibromin expression, it successfully recapitulates neurofibroma to MPNST progression.

The Cre-loxP system has been used to conditionally inactivate *Nf1* in combination with *Pten*, and *Cdkn2a*, respectively, in Schwann cells resulting in peripheral tumors that progress into MPNST [135, 136]. Conditional knockout of *Nf1* with Schwann cell-specific overexpression of EGFR promotes MPNST in a JAK2/STAT3-dependent manner [60]. Using *hGFAP-Cre* to inactivate a single copy of the *Pten* gene with conditional overexpression of K-Ras results in cutaneous and plexiform neurofibroma with complete penetrance. These tumors develop into *Nf1*-independent MPNST over time [137]. Complete Schwann cell-specific inactivation of *Pten* with overexpression of EGFR promotes onset of peripheral tumors that progress into sporadic MPNST [138]. Transgenic mice heterozygous for a *Trp53* null allele and overexpressing EGFR in Schwann cells show significantly increased neurofibroma and MPNST formation [139]. Injection of adenovirus-Cre into mice carrying floxed alleles of *Nf1* and *Cdkn2a* causes MPNST through localized loss of *Nf1*, *p16*$^{INK4A}$, and *p19*$^{ARF}$ [140]. Furthermore, using adenovirus-Cre injections to generate MPNST in *Nf1*$^{flox/flox}$; *Ink4a/Arf* $^{flox/flox}$, and *Nf1*$^{flox/-}$;*Ink4a/Arf* $^{flox/flox}$ mice revealed that haploinsufficiency of *Nf1* in hematopoietic stem cells accelerates MPNST onset [141]. CRISPR-Cas9 genome editing has also been used to inactivate *Nf1* and *Trp53* via adenovirus delivery to the sciatic nerve of wild-type mice resulting in MPNST development [142].

It is hypothesized that in human patients with NF1, MPNSTs arise from *Nf1*-deficient cells following acquisition of secondary genetic mutations. To model this sequence of genetic events in mice, Hirbe et al. coupled embryonic Schwann cell precursor-specific *Nf1* inactivation with lentivirus-mediated somatic *p53* knockdown in adult mice. These mice develop low-grade MPNST with partial penetrance [143].

Although robust pNF models have existed for over 20 years, the benign neurofibroma to MPNST transition has only recently been modeled in mice: in 2019, Rhodes et al. reported that conditional deletion of the tumor suppressor *Arf* together with *Nf1* in the neural crest-derived Schwann cell lineage in mice leads to development of tumors that resemble human ANNUBP and progress to MPNST [136]. In-depth studies of this mouse model of pNF to MPNST transition should provide a deeper understanding of tumor progression mechanisms and will be useful for preclinical therapeutic testing. Validated models of MPNST metastasis are also needed.

### Patient-derived xenograft (PDX) models of MPNST

While preclinical mouse models are an important system for elucidating molecular mechanisms, identifying therapeutic targets, and testing novel drugs, it is not unusual for drugs that showed promise in preclinical models to fail in human clinical trials [144]. Additionally, patient-derived tumor cells passaged in culture lack the presence of the TME leading to the question of

whether they can accurately predict drug response in patients. PDX models overcome these deficiencies by implanting patient tumor tissue into immune-deficient host mice, so that the tumor cells grow within an in vivo environment. Bhola et al. developed and characterized a human NF1-MPNST explant grown subcutaneously in NOD-SCID mice to evaluate the effect of rapamycin treatment [145]. Another study implanted tumor fragments from schwannomas, neurofibromas, and a neurofibrosarcoma into nude mice to assess the effectiveness of a potent, fungal-derived inhibitor of angiogenesis, AGM-1470, in suppressing the vascularization and growth of human Schwann cell tumors [146]. After injection into the sciatic nerve of nude mice and propagation in multiple mouse-to-mouse passages, the orthoxenograft models were standardized and validated and used for preclinical drug testing [147]. Genomic and transcriptomic datasets resulting from 55 tumor samples derived from 23 individuals are currently available with clinical annotation in NF Data Portal and at http://synapse.org/jhubiobank [148]. Thus, PDX models are an important translational tool [149, 150].

**Human induced pluripotent stem cell model to study MPNST**

The advent of somatic cell reprogramming using the "Yamanaka factors" to reprogram mouse embryonic fibroblasts [151] and its subsequent application to human cells [152] has revolutionized the study of disease. This technique has been leveraged by the NF1 field: *NF1*-mutant human induced Pluripotent Stem Cells (hiPSCs) have been generated from pNF cells from NF1 patients as a model system to study pNF and test potential treatments [153]. Wild-type hiPSCs in which CRISPR is used to introduce patient-based *NF1* mutations are being used to study the effect of particular mutations on cellular phenotypes [154, 155], Likewise, *NF1* mutations introduced using CRISPR together with mutations in other potential genes of interest is underway to study the mechanisms by which pNF transitions to ANNUBP and ultimately to MPNST [155–157].

## BIOLOGY OF MPNST

MPNSTs are complex, heterogeneous tumors, and no two MPNSTs are the same. Genetic analyses aimed at elucidating the molecular mechanisms driving MPNST development have identified key signaling pathways that play a role in MPNST development.

### Key signal transduction pathways underpinning MPNST development

*RAS/MAPK pathway*. Dysregulation of the MAPK pathway - also known as the Ras-Raf-MEK-ERK pathway—has been shown to play a role in many different cancer types, and it is a key RAS effector pathway in neurofibromatosis: In NF1, mutation/loss of *NF1* increases GTP-bound RAS, which in turn activates the MAPK pathway. This involves a cascade of kinase activity in which RAS activates RAF, RAF activates MEK, and MEK activates ERK, ultimately transducing signals to regulate gene expression that alters cell growth, proliferation, survival, and differentiation (Fig. 2). The MAPK pathway has been shown to be upregulated in a majority of MPNSTs [158]. As discussed in section "Non-NF1 associated MPNST", activating mutations in *BRAF* have also been identified in MPNST, and are found more frequently in sporadic MPNST than NF1-associated MPNST [40, 71]. While the MEK inhibitor selumetinib is the first and only FDA-approved targeted therapy for pNF [14], the efficacy of this drug as a monotherapy has not been tested for MPNST (see section "Targeting key cellular pathways driving MPNST development" for further discussion).

*PI3K/AKT/mTOR pathway*. Another key RAS effector signaling pathway is the *PI3K/AKT/mTOR* pathway. Studies have shown that the mTOR pathway becomes constitutively activated when *NF1* is mutated and RAS is upregulated [159, 160]. When activated, phosphatidylinositol 3 kinase (PI3K) phosphorylates AKT which in turn phosphorylates and inactivates tuberous sclerosis complex 2 a negative regulator of mechanistic target of rapamycin (mTOR), thus activating mTOR, a serine threonine kinase. Two distinct complexes contain mTOR: (1) mTORC1, which contains mTOR, raptor (regulatory protein associated with mTOR), and mLST8 (mammalian lethal with Sec13 protein 8), and (2) mTORC2, which contains mTOR, mLST8, rictor (rapamycin insensitive companion of mTOR), and deptor (DEP domain-containing mTOR interacting protein). These two complexes act as transmitters of external signals such as nutrient availability, growth factor stimulation, hypoxia, etc. to effect changes in cell proliferation, growth, metabolism, and autophagy (reviewed in [161]. Endo et al. found that between 47–63% of MPNSTs were positive for mTOR pathway activation (as measured by p-AKT, p-mTOR, p-S6RP, p-p70S6K, and p-4E-BP1), and that positivity for both p-AKT and p-mTOR was associated with aggressive behavior and worse prognosis [162]. Additionally, PTEN, a TSG and negative regulator of the mTOR pathway, was shown to be down-regulated in some MPNSTs due to promoter methylation [163]. This pathway is therefore a prime target for therapeutic inhibition (see section "Targeting key cellular pathways driving MPNST development").

*Hippo pathway*. The HIPPO pathway, which was initially discovered in Drosophila and is evolutionary conserved, is dysregulated in a variety of cancers. The pathway involves a cascade of kinases including mammalian sterile kinase-20 1/2 (MST1/2) kinases, which when activated phosphorylate the large tumor suppressor 1/2 (LATS1/2) kinases. These in turn phosphorylate Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), keeping them sequestered in the cytoplasm via binding to the 14-3-3 protein. When the pathway is inhibited, YAP and TAZ are not phosphorylated and they translocate into the nucleus, interact with the transcription factors TEAD1-4 (TEA domain family member), and regulate transcription of genes involved in cell proliferation, cell differentiation, and apoptosis (Fig. 2) (reviewed in [164]. In 2011, Yang et al. performed an array comparative genomic hybridization analysis on 51 human MPNST samples and found CNAs in components of the HIPPO pathway [61]. Subsequently, Wu et al. found a YAP gene signature to be highly enriched in a gene set enrichment analysis of two different MPNST cohorts, and also observed strong nuclear YAP and TAZ expression in patient MPNST samples compared to benign neurofibromas [165]. They also showed that *Lats1* deletion in mice driven by *Dhh-Cre* results in MPNST-like tumor development [165]. In 2019, Isfort et al. also reported strong nuclear expression of YAP and TAZ in human MPNSTs [166]. Together, these data demonstrate a role for the HIPPO pathway in MPNST development and provide additional therapeutic targets.

*Wnt pathway*. The Wnt signaling pathway has also been shown to play a role in many types of cancer [167]. In the canonical Wnt pathway, signaling begins with binding of Wnt ligands to Frizzled receptors, ultimately leading to stabilization of β-catenin, which translocates to the nucleus, binds with the transcription factors, T cell factor-lymphoid enhancer factor, and regulates gene transcription. In the absence of Wnt signaling, β-catenin is phosphorylated by glycogen synthase kinase 3β and casein kinase 1, targeting it for ubiquitination and degradation. In 2013, Watson et al. performed a forward genetic screen in mice using the Sleeping Beauty transposon system to induce oncogenic changes in Schwann cell precursor cells and Schwann cells to drive tumor formation [98]. The screen identified several genes of the canonical Wnt pathway as drivers of neurofibroma and MPNST, and these tumors exhibited strong nuclear β-catenin staining. The upregulation of these genes in human MPNST samples confirmed the activation of the Wnt pathway. Further, activation of the Wnt pathway in immortalized human Schwann cells caused them to

display oncogenic properties, although these cells did not form tumors when injected into mice. Interestingly, Watson et al. also identified *Wnt5a*, a ligand for the non-canonical Wnt signaling pathway, as being upregulated in MPNST samples using a gene expression microarray [98]. That same year, Luscan et al. similarly reported upregulation of the *Wnt5a* ligand in MPNST cell lines and patient MPNSTs [168]. More recently, Thomson et al. reported that knockdown of *Wnt5a* in MPNST cells surprisingly increased tumor growth, and these cells express genes involved in immune regulation and extracellular remodeling [169]. These data suggest that *Wnt5a* acts as a tumor suppressor in MPNST, likely via effects on the TME.

### Roles of the TME and NF1 heterogeneity in MPNST development

In addition to the neoplastic Schwann cells, MPNSTs contain a complex TME that includes fibroblasts, endothelial cells, mast cells, pericytes, etc. A critical role for the TME in neurofibroma has been well established in mouse models. In 2002, Zhu et al. used conditional mouse knockouts to show that loss of *Nf1* in Schwann cells is necessary but not sufficient for neurofibroma development: $Nf1^{fl/-}$;*Krox20-cre* mice but not $Nf1^{fl/fl}$;*Krox20-cre* mice developed pNF, demonstrating a requirement for *Nf1* heterozygosity in the cells of the TME [170]. Interestingly, they observed invasion of $Nf1^{+/-}$ mast cells into the tumors. Subsequently, Yang et al. reported that transplantation of $Nf1^{+/-}$ bone marrow into lethally irradiated $Nf1^{fl/fl}$;*Krox20-cre* mice resulted in pNF formation, and demonstrated genetically and pharmacologically that the $Nf1^{+/-}$ tumor-infiltrating bone marrow cells were mast cells, further supporting the role of $Nf1^{+/-}$ mast cells in neurofibroma initiation and progression [171]. On the other hand, *Dhh-Cre;* $Nf1^{fl/fl}$ mice [172] and *Plp-CreERT;* $Nf1^{fl/fl}$ mice induced with tamoxifen on postnatal day 1 develop pNF suggesting that *Nf1*-heterozygosity is not always required. In the case of the *Plp-CreERT;* $Nf1^{fl/fl}$ model, some mice go on to develop MPNST [26].

The role of the TME in MPNST development is less clear. In 2017, Dodd et al. reported that $Nf1^{+/-}$ hematopoietic stem cells accelerated development of MPNST in their GEM model, which was generated by injection of adenovirus-Cre into the sciatic nerve of $Nf1^{fl/-}$; $Ink4a/Arf^{fl/fl}$ mice [141]. However, in 2018, Brosseau et al. reported that while an *Nf1*-heterozygous TME is required for neurofibroma formation, it may be inhibitory for malignant progression [26]. Using *Plp-CreERT2;* $Nf1^{fl/fl}$ mice and *Plp-CreERT2;* $Nf1^{fl/-}$ mice, which are *Nf1*-null only in Schwann cells or *Nf1*-null in Schwann cells and *Nf1*-heterozygous in all other cells, respectively, they show that an *Nf1*-heterozygous microenvironment impairs MPNST development [26]. This finding aligns with the fact that NF1 patients (who are *NF1*-heterozygous in all cells of the body) rarely develop cancers that develop in patients with sporadic *NF1* mutation, such as lung, ovarian, and melanoma, suggesting that the *NF1*-heterozygous TME somehow impairs development of certain tumor types. Further studies need to be done to better understand the role of the TME in MPNST development.

## CURRENT MANAGEMENT OF MPNST

### Surgical management of MPNST

Current management of MPNST is similar to that of soft tissue sarcomas, relying on local control measures in both adult and pediatric populations [173–175]. Diagnosis of MPNST is based primarily on clinical suspicion. A patient with a known history of NF1 or who shows the characteristic symptoms and presents with a tumor that rapidly increases in size and causes neurologic symptoms and/or pain is suspected to have a MPNST [21, 174, 176].

Magnetic Resonance Imaging (MRI) is often used to locate the site and determine the size and invasiveness of neurofibroma tumors, as the imaging enhances the contrast between tumor and adjacent tissues. However, MRI and/or computerized tomography (CT) imaging do not reliably determine malignant transformation [173, 177–179]. Positron emission tomography with the glucose analog $^{18}$fluorodeoxyglucose (FDG-PET) can detect increased metabolism in malignant tumors allowing for successful discrimination of MPNST from pNF. FDG-PET also allows for estimation of the grade of the malignant tumor in a heterogeneous lesion [177, 180, 181]. Currently, quantitative FDG-PET imaging used in conjunction with CT or MRI offers the best ability to distinguish between benign tumors and MPNST [182, 183].

Once the diagnosis of MPNST is made, surgical resection of the tumor is the only curative therapy available. For surgery to be successful, the tumor should be completely removed with wide (2 cm) negative margins [173, 174, 184]. Patients who have had incomplete excision of tumors show significantly increased risk of local and distant recurrence compared to those who have had complete tumor resection [185]. However, complete resection of the tumor is not always possible due to the location/and or size of the tumor and avoiding postoperative morbidity can be challenging [185–187]. Therefore, for high-grade tumors (>5 cm) for which complete resection cannot be achieved, adjuvant radiotherapy is recommended [19, 173, 184, 186, 188].

### Radiation therapy

As part of a multimodality approach to treating these aggressive tumors, radiation therapy can also be administered locally, either preoperatively or postoperatively. However, there are some potential risks: Preoperative radiotherapy can cause short-term wound healing issues while postoperative radiotherapy can affect long-term function, and result in fibrosis and edema in soft tissue sarcomas [173, 186, 189, 190]. Therefore, careful clinical consideration is required to decide between preoperative and postoperative radiotherapy. Some studies have demonstrated that postoperative radiotherapy is effective in preventing local recurrence of tumors without providing an overall survival advantage [188, 190] while others concluded that postoperative radiotherapy increases both 5-year disease-free and overall survival of MPNST patients [191, 192]. Additionally, radiation therapy can increase the mutational burden of the tumor, thereby making it even more aggressive, and can also induce secondary malignancies [193, 194].

### Medical management

Currently there is no consensus on the use of chemotherapy for treatment of MPNST [184, 195]. The available data regarding the use of chemotherapy against MPNST is mostly derived from histologically unselected populations of soft tissue sarcomas [173, 196, 197]. A recent phase II clinical trial conducted by the Sarcoma Alliance for Research (SARC) reported that NF1-associated MPNST patients respond poorly to chemotherapy compared to those with sporadic MPNST in terms of tumor size reduction. However, both groups achieved disease stabilization after 4 rounds of chemotherapy [198]. Similarly, another study with European pediatric MPNST patients reported that *NF1*-dependent MPNST show inferior responses to chemotherapy relative to sporadic MPNST [199]. Therefore, the use of chemotherapy must be an individualized decision based on the medical condition of the patient and the estimated risk of tumor recurrence. As there are no successful curative therapies for patients with recurrent, unresectable, or metastatic disease, these patients could benefit from enrolling in clinical trials.

## TRANSLATING CURRENT RESEARCH IN THE LABORATORY INTO FUTURE THERAPIES FOR MPNST

Based on information gleaned from genomic analyses of MPNST that have identified key pathways and genes involved in MPNST

development, as well as preclinical studies, a number of clinical trials have been performed or are underway to test candidate therapies.

**Targeting key cellular pathways driving MPNST development**

*Targeting RTK signaling*. Growth factors like EGFR, Vascular Endothelial Growth Factor (VEGF), and PDGFR, as well as hormones, cytokines, neurotrophic factors, and other extracellular signaling molecules like the proto-oncogene c-KIT can bind to the RTK family of cell-surface receptors. These ligands regulate normal cellular processes including survival, proliferation, differentiation, and migration. Dysregulation of RTK signaling due to a variety of genetic and epigenetic alterations is a common cause of cell transformation, cancer development, and metastasis. Mutations that activate RTKs or components of downstream pathways such as MAPK, PI3K/AKT, and JAK/STAT have been identified in multiple cancers [200–203]. However, while direct inhibition of RTKs and inhibition of downstream pathways such as MAP kinase and PI3K/AKT pathways show moderate efficacy against MPNST in preclinical models, small-molecule inhibitors such as imatinib and dasatinib, that target the PDGFR pathway and c-KIT, respectively, have not yielded significant outcomes in clinical trials against MPNST [56, 98, 204, 205].

As discussed in section "Gene amplifications in MPNST development", amplification of RTKs is frequently observed in MPNST. RTKs regulate a variety of key cellular processes making them a prime therapeutic target. In addition to amplification of these RTKs, expression of their respective ligands has also been found to be upregulated. Holtkamp et al. found that the EGFR ligands transforming growth factor alpha and EGF are also expressed at higher levels in MPNSTs than in neurofibromas [55]. Also, growth of MPNST in the cisNP mouse model has been shown to be stimulated by EGF and delayed by EGFR inhibitors [55, 60, 206, 207]. Despite this, a phase II trial of erlotinib, an EGFR inhibitor, in metastatic or unresectable MPNST showed no obvious benefit [208]. The VEGF inhibitor bevacizumab in combination with the mTORC1 inhibitor everolimus also failed to show promise in a phase II MPNST study [209].

*Targeting RAS or RAS-activated signaling pathways*. The majority of MPNST are associated with inactivating mutations in the *NF1* gene. Neurofibromin binds to the GTP-bound active form of RAS through its GAP-related domain and enhances RAS's intrinsic GTPase activity, ultimately functioning as an off-switch to all RAS proteins [2, 3, 210]. As discussed, inactivating mutations of *NF1* therefore activate multiple effector pathways including the RAS/RAF/MEK/ERK cascade [3, 211, 212]. RAS-GTP itself has been considered undruggable as its topology is not amenable to high-affinity small-molecule inhibition. However, a recent breakthrough has led to the development of direct RAS inhibitors that specifically target the glycine to cysteine mutation at residue 12 (G12C) in KRAS that is observed primarily in lung cancer [213]. As a result, $RAS^{G12C}$-specific inhibitors have entered phase I/II clinical trials against a variety of solid tumors that have a $KRAS^{G12C}$ mutation, but do not include MPNST [3].

RAS proteins are post-translationally modified facilitating their membrane association. One such modification is farnesylation. Farnesyl transferase enzymes that catalyze this modification have been targeted therapeutically in *NF1*-deficient Schwann cells and *NF1*-dependent MPNST cells [214, 215]. However, this strategy has been unsuccessful in clinical trials for pNF [216, 217].

An alternative to direct inhibition of RAS is to target signaling pathways downstream of activated RAS [46, 218]. Sorafenib, an orally administered, small-molecule RAF kinase and tyrosine kinase inhibitor has been shown to inhibit MAPK signaling and cell growth, and to induce G1 cell-cycle arrest in MPNST cell lines in a *B-raf*-dependent fashion [219]. However, in a multicenter phase II trial, sorafenib showed no significant response, with overall survival of treated MPNST patients similar to controls [220]. A pharmacological MEK inhibitor, PD0325901, has been effective in controlling tumor growth in a neurofibroma mouse model and patient-derived MPNST xenografts [221], while another MEK inhibitor, selumetinib, has shown successful outcomes for symptomatic, unresectable pNF in phase I and II clinical trials [14, 16]. Selumetinib is now approved by the FDA for treatment of NF1-associated pNF, although it is unclear if MEK inhibition will be useful in the context of MPNST [222]. However, a promising report from Nagabushan et al. showed a sustained complete response with selumetinib monotherapy in an adolescent patient with recurrent MPNST [223].

As described earlier, the mTOR signaling pathway is also activated downstream of Ras [129], and expression of p-AKT, p-mTOR, and p-S6RP are associated with poor prognosis in MPNST patients [162]. However, while mTOR inhibitors in vitro and in xenografts have demonstrated tumor growth suppression, clinical trials have shown modest effect on pNF [162, 224, 225]. A direct mTOR kinase inhibitor that inhibits both mTORC1 and mTORC2 showed more promising results in NF1-dependent MPNST cell lines, sporadic MPNST cell lines, and pNF-derived primary Schwann cells [226]. Combined mTOR and MAPK inhibition has shown synergistic effects in vitro and in vivo [227]. The combination of mTORC1 inhibitor sirolimus and MEK inhibitor selumetinib is currently being tested against MPNST in a phase II clinical trial (NCT03433183). MAPK-interacting kinases (MNKs), which converge on the mTORC1 effector eIF4E, have been therapeutic targets in *NF1*-deficient malignancies. Genetic and chemical inhibition of MNKs in *NF1*-deficient in vitro and in vivo models has been shown to kill the cancer cells through effects on eIF4E [130]. Also, co-inhibition of MNKs and MEK cause dramatic tumor regression in the cisNP mouse model of MPNST [130]. Therefore, combined MNK and MEK suppression represents a promising therapeutic strategy for Ras-driven tumors. Combination of mTOR inhibition with other signaling inhibitors has also been tested against MPNST. For example, dual inhibition of the mTOR pathway and the molecular chaperone hsp90 effectively abrogated the cellular stress response and caused cell death and tumor regression in the cisNP mouse MPNST model [131]. Despite this promising outcome, the Hsp90 inhibitor ganetespib, in combination with the mTOR inhibitor sirolimus has not shown success in MPNST patients in a phase I/II clinical trial [228]. Additionally, inhibition of the mTOR pathway with sapanisertib, along with histone deacetylase (HDAC) inhibition was shown to be selectively toxic to Ras-driven tumors, including human MPNST xenografts and the cisNP mouse model [229]. Moreover, the multi-kinase inhibitor PLX3397 in combination with rapamycin inhibited MPNST growth in xenografts [58] and is currently being tested in a phase II clinical trial (NCT02584647).

*Targeting cyclin-dependent kinases (CDKs)*. Loss-of-function mutations in the *CDKN2A* and the *CDKN2B* genes, which encode CDK inhibitors, are a feature of ANFs and some MPNST. As these mutations lead to increased CDK4 or CDK6 activity, it is hypothesized that these tumors may become sensitive to CDK4/6 inhibitors. As such, CDK4/6 inhibition using ribociclib, an FDA-approved drug against breast cancer, in combination with doxorubicin is currently in phase II trial for MPNST (NCT03009201) [230].

**Targeting epigenetic regulation associated with loss of Polycomb Repressor Complex 2 (PRC2) function**

Due to the diversity of secondary mutational hits that drive MPNST formation, no two MPNSTs are the same molecularly, a factor that likely contributes to treatment failure. A potentially more effective therapeutic strategy would be one that targets all MPNSTs regardless of this diversity. As discussed in section "Epigenetic regulation of MPNST development", mutations in epigenetic

regulators have been identified in a high percentage of MPNST [65–67], and one approach would be to target these epigenetic alterations. Loss of function mutations in *EED* and *SUZ12*, essential components of PRC2, are often observed in MPNST, and most MPNST show decreased H3K27-di- and tri-methylation, which is mediated by EZH2, the enzymatic component of the PRC2 complex. BRD4 is involved in activation of Ras-mediated transcription through H3K27 acetylation, which is enhanced by loss of methylation at the same site. As a result, loss of PRC2 function sensitizes MPNST cells to BRD4 inhibition, providing a potential strategy to be further validated in preclinical models of MPNST and tested in clinical trials [65, 78, 231]. Unfortunately, a phase II study testing CPI-0610, a BET protein inhibitor (NCT02986919), on patients with MPNST was withdrawn due to lack of enrollment. This treatment strategy warrants further clinical investigation.

### Synthetic lethality strategy for treating MPNST

Synthetic lethality occurs when mutation in or suppression of two genes causes cell death, while mutation/suppression of one of these genes does not. This concept has been harnessed for genetic and drug screening of cancer cells, whereby mutation in a particular cancer gene may be associated with a therapeutic vulnerability that can be targeted, thus killing these cells. As non-cancer cells do not have this cancer gene mutation, they will be spared. Genetic screens using RNAi libraries or CRISPR/Cas9 libraries can be performed to identify gene products whose loss would result in cell death when combined with *NF1* deficiency [157, 232, 233]. For example, a recent siRNA kinome screen by Guo et al. identified Polo-like Kinase 1 (PLK1) as a target in *NF1*-null MPNST cell lines [232]. They also showed that treatment of a mouse MPNST xenograft with the PLK1 inhibitor, volasertib, inhibited tumor growth. While CRISPR forward genetic screens have been reported for a number of cancer cell lines (reviewed in [234]), this type of screen has yet to be reported for *NF1*-deficient cells or MPNST cells. It is likely, however, that such screens are currently underway [233], and likely that they will identify novel therapeutic candidates.

### Small-molecule screening to identify novel therapies and new therapeutic targets

High-throughput drug screening is an important tool for drug discovery, identifying chemical leads that can preferentially target tumor cells while sparing non-tumor cells, and small-molecule drug screens can also identify synthetic lethal combinations. In the last decade, multiple such screens have been carried out to identify drugs that can target MPNST. For example, a medium throughput synthetic lethal screen using *Nf1*-null mouse embryonic fibroblasts identified cantharidin, a protein phosphatase 2 (PP2A) inhibitor, as well as nifedipine, a calcium antagonist as toxic against these cells but not *Nf1*-wild-type controls [235]. Cantharidin was also effective against human MPNST cells.

In 2011, Wood et al. carried out a screen using an *NF1*-null MPNST cell line, and identified UC1, a small-molecule drug that killed these cells but not an $NF1^{+/+}$ MPNST cell line [236]. Due to the concern that cultured cell lines can undergo genetic drift with passaging over time thereby having altered biology compared to the original cells, Chau et al. used primary cells isolated from a mouse MPNST model and expanded at low passage for their screen [63]. They identified "compound 21" (Cpd21), which inhibited cell growth in the original MPNST cells, as well as tumor cells from several other MPNST models. Extending their analyses to human MPNST cells, they found the drug was also effective against these cells, while growth of wild-type Schwann cells was not affected at similar doses.

In 2017, Kolberg et al. screened 299 clinical and investigational compounds for efficacy against several different MPNST cell lines [78]. They identified gemcitabine, a chemotherapeutic agent that has been in use clinically for more than two decades to treat many types of cancer, and inhibitors of polo-like kinase (PLK1), a cell-cycle regulator. As discussed earlier, this finding was reproduced by Guo et al. who also identified PLK1 in both an siRNA kinome screen and a screen using ~2000 known chemical compounds [232]. In 2018, Kahen et al. reported a drug screen in which they also tested FDA-approved drugs alone or in combination against MPNST cell lines, and found that drug combinations targeting both the MEK and mTOR pathways were the most effective against *NF1*-null MPNSTs [237].

Following up on their finding that BRD4 levels are upregulated in MPNST, and that Brd4 or BET inhibition causes apoptotic cell death due to upregulation of Bim [64], Cooper et al. demonstrated synthetic lethality when Brd4 depletion was combined with BET inhibition to overcome resistance to BET inhibitors both in vitro and in vivo [238].

## CONCLUSION AND FUTURE PERSPECTIVES

There is currently no targeted therapy for MPNST treatment and surgery remains the mainstay treatment. A concerted effort must be made to expand clinical trials and improve enrollment, and to identify novel therapeutic targets and compounds. While potentially interesting compounds have been identified in small-molecule drug screens, they do not always show efficacy in preclinical mouse models, and if they do, this success does not always translate to the clinic. Most drugs identified in these screens have yet to show efficacy in clinical trials. This may be in part due to the cell types used for the screens: using human cells for screening rather than mouse could potentially improve the success rate. Additionally, using CRISPR gene editing of human iPSCs to engineer specific patient-based mutations could provide a platform for identifying more effective drugs. Still, these screens hold the promise of identifying novel compounds for drug development, as well as identifying candidates for combination therapy, which is more likely to maximize efficacy and minimize toxicity resulting in a more successful treatment strategy.

Another potential reason for MPNST clinical trial failures is the patient population that is enrolled. Currently, MPNST patients who are enrolled in a drug trial will typically have first exhausted all available treatment options, including radiation therapy and multiple rounds of non-specific chemotherapy with different DNA-damaging agents. As these treatments are not curative, and the tumors usually return and/or continue to grow, these patients may then be enrolled in a clinical trial. This is likely the wrong strategy, as MPNSTs are already genetically unstable and the above treatments (radiation and chemotherapy) can cause additional mutations, making the MPNSTs even more aggressive and changing the tumor molecularly from what it was at initial diagnosis. This may also be a reason for the failure of many clinical trials. Thus, it is possible that if MPNST patients were enrolled in a clinical trial at the time of diagnosis (if determined to be a non-surgical candidate), then clinical trial outcomes might be improved. Of course, this approach would require a major paradigm shift in current treatment regimens, and how, or more accurately "when" we perform clinical trials for MPNST in the future.

## REFERENCES

1. Holt GR. Von Recklinghausen's neurofibromatosis. Otolaryngol Clin N Am. 1987;20:179–93.
2. Bos JL, Rehmann H, Wittinghofer A. GEFs and GAPs: critical elements in the control of small G proteins. Cell. 2007;129:865–77.
3. Stalnecker CA, Der CJ. RAS, wanted dead or alive: advances in targeting RAS mutant cancers. Sci Signal. 2020;13:eaay6013.
4. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. J Am Acad Dermatol. 2009;61:1–14.

5. Rad E, Tee AR. Neurofibromatosis type 1: fundamental insights into cell signalling and cancer. Semin Cell Dev Biol. 2016;52:39–46.
6. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Prim. 2017;3:17004.
7. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol. 2007;6:340–51.
8. Albers AC, Gutmann DH. Gliomas in patients with neurofibromatosis type 1. Expert Rev Neurother. 2009;9:535–9.
9. Fisher MJ, Loguidice M, Gutmann DH, Listernick R, Ferner RE, Ullrich NJ, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro Oncol. 2012;14:790–7.
10. Rosenbaum T, Wimmer K. Neurofibromatosis type 1 (NF1) and associated tumors. Klin Padiatr. 2014;226:309–15.
11. Muir D, Neubauer D, Lim IT, Yachnis AT, Wallace MR. Tumorigenic properties of neurofibromin-deficient neurofibroma Schwann cells. Am J Pathol. 2001;158:501–13.
12. Chamseddin BH, Le LQ. Management of cutaneous neurofibroma: current therapy and future directions. Neurooncol Adv. 2020;2:i107–i116.
13. Theos A, Korf BR.American College of Physicians, American Physiological Society.Pathophysiology of neurofibromatosis type 1. Ann Intern Med. 2006;144:842–9.
14. Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382:1430–42.
15. Chen Z, Liu C, Patel AJ, Liao CP, Wang Y, Le LQ. Cells of origin in the embryonic nerve roots for NF1-associated plexiform neurofibroma. Cancer Cell. 2014;26:695–706.
16. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Engl J Med. 2016;375:2550–60.
17. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet. 2002;39:311–4.
18. Fuchs B, Spinner RJ, Rock MG. Malignant peripheral nerve sheath tumors: an update. J Surg Orthop Adv. 2005;14:168–74.
19. Bates JE, Peterson CR, Dhakal S, Giampoli EJ, Constine LS. Malignant peripheral nerve sheath tumors (MPNST): a SEER analysis of incidence across the age spectrum and therapeutic interventions in the pediatric population. Pediatr Blood Cancer. 2014;61:1955–60.
20. Kim A, Stewart DR, Reilly KM, Viskochil D, Miettinen MM, Widemann BC. Malignant peripheral nerve sheath tumors state of the science: leveraging clinical and biological insights into effective therapies. Sarcoma. 2017;2017:7429697.
21. Farid M, Demicco EG, Garcia R, Ahn L, Merola PR, Cioffi A, et al. Malignant peripheral nerve sheath tumors. Oncologist. 2014;19:193–201.
22. LaFemina J, Qin LX, Moraco NH, Antonescu CR, Fields RC, Crago AM, et al. Oncologic outcomes of sporadic, neurofibromatosis-associated, and radiation-induced malignant peripheral nerve sheath tumors. Ann Surg Oncol. 2013;20:66–72.
23. Pekmezci M, Reuss DE, Hirbe AC, Dahiya S, Gutmann DH, von Deimling A, et al. Morphologic and immunohistochemical features of malignant peripheral nerve sheath tumors and cellular schwannomas. Mod Pathol. 2015;28:187–200.
24. Miettinen MM, Antonescu CR, Fletcher CDM, Kim A, Lazar AJ, Quezado MM, et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1-a consensus overview. Hum Pathol. 2017;67:1–10.
25. Longo JF, Weber SM, Turner-Ivey BP, Carroll SL. Recent advances in the diagnosis and pathogenesis of neurofibromatosis type 1 (NF1)-associated peripheral nervous system neoplasms. Adv Anat Pathol. 2018;25:353–68.
26. Brosseau JP, Liao CP, Wang Y, Ramani V, Vandergriff T, Lee M, et al. NF1 heterozygosity fosters de novo tumorigenesis but impairs malignant transformation. Nat Commun. 2018;9:5014.
27. Kolberg M, Holand M, Agesen TH, Brekke HR, Liestol K, Hall KS, et al. Survival meta-analyses for >1800 malignant peripheral nerve sheath tumor patients with and without neurofibromatosis type 1. Neuro Oncol. 2013;15:135–47.
28. Bottillo I, Ahlquist T, Brekke H, Danielsen SA, van den Berg E, Mertens F, et al. Germline and somatic NF1 mutations in sporadic and NF1-associated malignant peripheral nerve sheath tumours. J Pathol. 2009;217:693–701.
29. Pemov A, Li H, Presley W, Wallace MR, Miller DT. Genetics of human malignant peripheral nerve sheath tumors. Neurooncol Adv. 2020;2:i50–i61.
30. Ebben JD, Treisman DM, Zorniak M, Kutty RG, Clark PA, Kuo JS. The cancer stem cell paradigm: a new understanding of tumor development and treatment. Expert Opin Ther Targets. 2010;14:621–32.
31. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994;367:645–8.
32. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA. 2003;100:3983–8.
33. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, et al. Identification of a cancer stem cell in human brain tumors. Cancer Res. 2003;63:5821–8.
34. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, et al. Identification of bronchioalveolar stem cells in normal lung and lung cancer. Cell. 2005;121:823–35.
35. Spyra M, Kluwe L, Hagel C, Nguyen R, Panse J, Kurtz A, et al. Cancer stem cell-like cells derived from malignant peripheral nerve sheath tumors. PLoS ONE. 2011;6:e21099.
36. Sun D, Xie XP, Zhang X, Wang Z, Sait SF, Iyer SV, et al. Stem-like cells drive NF1-associated MPNST functional heterogeneity and tumor progression. Cell Stem Cell. 2021;28:1397–1410 e1394.
37. Laycock-van Spyk S, Thomas N, Cooper DN, Upadhyaya M. Neurofibromatosis type 1-associated tumours: their somatic mutational spectrum and pathogenesis. Hum Genomics. 2011;5:623–90.
38. Brohl AS, Kahen E, Yoder SJ, Teer JK, Reed DR. The genomic landscape of malignant peripheral nerve sheath tumors: diverse drivers of Ras pathway activation. Sci Rep. 2017;7:14992.
39. Lemberg KM, Wang J, Pratilas CA. From genes to -omics: the evolving molecular landscape of malignant peripheral nerve sheath tumor. Genes. 2020;11:691.
40. Kaplan HG, Rostad S, Ross JS, Ali SM, Millis SZ. Genomic profiling in patients with malignant peripheral nerve sheath tumors reveals multiple pathways with targetable mutations. J Natl Compr Canc Netw. 2018;16:967–74.
41. Beert E, Brems H, Daniels B, De Wever I, Van Calenbergh F, Schoenaers J, et al. Atypical neurofibromas in neurofibromatosis type 1 are premalignant tumors. Genes Chromosomes Cancer. 2011;50:1021–32.
42. Chaney KE, Perrino MR, Kershner LJ, Patel AV, Wu J, Choi K, et al. Cdkn2a loss in a model of neurofibroma demonstrates stepwise tumor progression to atypical neurofibroma and MPNST. Cancer Res. 2020;80:4720–30.
43. Legius E, Dierick H, Wu R, Hall BK, Marynen P, Cassiman JJ, et al. TP53 mutations are frequent in malignant NF1 tumors. Genes Chromosomes Cancer. 1994;10:250–5.
44. Verdijk RM, den Bakker MA, Dubbink HJ, Hop WC, Dinjens WN, Kros JM. TP53 mutation analysis of malignant peripheral nerve sheath tumors. J Neuropathol Exp Neurol. 2010;69:16–26.
45. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol. 2011;178:1932–9.
46. Carroll SL. Molecular mechanisms promoting the pathogenesis of Schwann cell neoplasms. Acta Neuropathol. 2012;123:321–48.
47. Carroll SL. The challenge of cancer genomics in rare nervous system neoplasms: malignant peripheral nerve sheath tumors as a paradigm for cross-species comparative oncogenomics. Am J Pathol. 2016;186:464–77.
48. Mertens F, Rydholm A, Bauer HF, Limon J, Nedoszytko B, Szadowska A, et al. Cytogenetic findings in malignant peripheral nerve sheath tumors. Int J Cancer. 1995;61:793–8.
49. Berner JM, Sorlie T, Mertens F, Henriksen J, Saeter G, Mandahl N, et al. Chromosome band 9p21 is frequently altered in malignant peripheral nerve sheath tumors: studies of CDKN2A and other genes of the pRB pathway. Genes Chromosomes Cancer. 1999;26:151–60.
50. Schmidt H, Taubert H, Wurl P, Bache M, Bartel F, Holzhausen HJ, et al. Cytogenetic characterization of six malignant peripheral nerve sheath tumors: comparison of karyotyping and comparative genomic hybridization. Cancer Genet Cytogenet. 2001;128:14–23.
51. Dehner C, Moon CI, Zhang X, Zhou Z, Miller C, Xu H, et al. Chromosome 8 gain is associated with high-grade transformation in MPNST. JCI Insight. 2021;6:e146351.
52. Peacock JD, Pridgeon MG, Tovar EA, Essenburg CJ, Bowman M, Madaj Z, et al. Genomic status of MET potentiates sensitivity to MET and MEK inhibition in NF1-related malignant peripheral nerve sheath tumors. Cancer Res. 2018;78:3672–87.
53. Pemov A, Hansen NF, Sindiri S, Patidar R, Higham CS, Dombi E, et al. Low mutation burden and frequent loss of CDKN2A/B and SMARCA2, but not PRC2, define premalignant neurofibromatosis type 1-associated atypical neurofibromas. Neuro Oncol. 2019;21:981–92.
54. Szymanski JJ, Sundby RT, Jones PA, Srihari D, Earland N, Harris PK, et al. Cell-free DNA ultra-low-pass whole genome sequencing to distinguish malignant peripheral nerve sheath tumor (MPNST) from its benign precursor lesion: a cross-sectional study. PLoS Med. 2021;18:e1003734.
55. Holtkamp N, Malzer E, Zietsch J, Okuducu AF, Mucha J, Mawrin C, et al. EGFR and erbB2 in malignant peripheral nerve sheath tumors and implications for targeted therapy. Neuro Oncol. 2008;10:946–57.
56. Holtkamp N, Okuducu AF, Mucha J, Afanasieva A, Hartmann C, Atallah I, et al. Mutation and expression of PDGFRA and KIT in malignant peripheral nerve sheath tumors, and its implications for imatinib sensitivity. Carcinogenesis. 2006;27:664–71.

57. Mantripragada KK, Spurlock G, Kluwe L, Chuzhanova N, Ferner RE, Frayling IM, et al. High-resolution DNA copy number profiling of malignant peripheral nerve sheath tumors using targeted microarray-based comparative genomic hybridization. Clin Cancer Res. 2008;14:1015–24.
58. Patwardhan PP, Surriga O, Beckman MJ, de Stanchina E, Dematteo RP, Tap WD, et al. Sustained inhibition of receptor tyrosine kinases and macrophage depletion by PLX3397 and rapamycin as a potential new approach for the treatment of MPNSTs. Clin Cancer Res. 2014;20:3146–58.
59. Ki DH, He S, Rodig S, Look AT. Overexpression of PDGFRA cooperates with loss of NF1 and p53 to accelerate the molecular pathogenesis of malignant peripheral nerve sheath tumors. Oncogene. 2017;36:1058–68.
60. Wu J, Patmore DM, Jousma E, Eaves DW, Breving K, Patel AV, et al. EGFR-STAT3 signaling promotes formation of malignant peripheral nerve sheath tumors. Oncogene. 2014;33:173–80.
61. Yang J, Ylipaa A, Sun Y, Zheng H, Chen K, Nykter M, et al. Genomic and molecular characterization of malignant peripheral nerve sheath tumor identifies the IGF1R pathway as a primary target for treatment. Clin Cancer Res. 2011;17:7563–73.
62. Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010;463:899–905.
63. Chau V, Lim SK, Mo W, Liu C, Patel AJ, McKay RM, et al. Preclinical therapeutic efficacy of a novel pharmacologic inducer of apoptosis in malignant peripheral nerve sheath tumors. Cancer Res. 2014;74:586–97.
64. Patel AJ, Liao CP, Chen Z, Liu C, Wang Y, Le LQ. BET bromodomain inhibition triggers apoptosis of NF1-associated malignant peripheral nerve sheath tumors through Bim induction. Cell Rep. 2014;6:81–92.
65. De Raedt T, Beert E, Pasmant E, Luscan A, Brems H, Ortonne N, et al. PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies. Nature. 2014;514:247–51.
66. Lee W, Teckie S, Wiesner T, Ran L, Prieto Granada CN, Lin M, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Genet. 2014;46:1227–32.
67. Zhang M, Wang Y, Jones S, Sausen M, McMahon K, Sharma R, et al. Somatic mutations of SUZ12 in malignant peripheral nerve sheath tumors. Nat Genet. 2014;46:1170–2.
68. Morey L, Helin K. Polycomb group protein-mediated repression of transcription. Trends Biochem Sci. 2010;35:323–32.
69. Harachi M, Masui K, Cavenee WK, Mischel PS, Shibata N. Protein acetylation at the interface of genetics, epigenetics and environment in cancer. Metabolites. 2021;11:216.
70. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949–54.
71. Hirbe AC, Pekmezci M, Dahiya S, Apicelli AJ, Van Tine BA, Perry A, et al. BRAFV600E mutation in sporadic and neurofibromatosis type 1-related malignant peripheral nerve sheath tumors. Neuro Oncol. 2014;16:466–7.
72. Longo JF, Brosius SN, Znoyko I, Alers VA, Jenkins DP, Wilson RC, et al. Establishment and genomic characterization of a sporadic malignant peripheral nerve sheath tumor cell line. Sci Rep. 2021;11:5690.
73. Miller DT, Cortes-Ciriano I, Pillay N, Hirbe AC, Snuderl M, Bui MM, et al. Genomics of MPNST (GeM) Consortium: rationale and study design for multi-omic characterization of NF1-associated and sporadic MPNSTs. Genes. 2020;11:387.
74. Badache A, De Vries GH. Neurofibrosarcoma-derived Schwann cells overexpress platelet-derived growth factor (PDGF) receptors and are induced to proliferate by PDGF BB. J Cell Physiol. 1998;177:334–42.
75. Miller SJ, Rangwala F, Williams J, Ackerman P, Kong S, Jegga AG, et al. Large-scale molecular comparison of human schwann cells to malignant peripheral nerve sheath tumor cell lines and tissues. Cancer Res. 2006;66:2584–91.
76. Sun D, Tainsky MA, Haddad R. Oncogene mutation survey in MPNST cell lines enhances the dominant role of hyperactive Ras in NF1 associated pro-survival and malignancy. Transl Oncogenomics. 2012;5:1–7.
77. Guo J, Grovola MR, Xie H, Coggins GE, Duggan P, Hasan R, et al. Comprehensive pharmacological profiling of neurofibromatosis cell lines. Am J Cancer Res. 2017;7:923–34.
78. Kolberg M, Bruun J, Murumagi A, Mpindi JP, Bergsland CH, Holand M, et al. Drug sensitivity and resistance testing identifies PLK1 inhibitors and gemcitabine as potent drugs for malignant peripheral nerve sheath tumors. Mol Oncol. 2017;11:1156–71.
79. Fang Y, Elahi A, Denley RC, Rao PH, Brennan MF, Jhanwar SC. Molecular characterization of permanent cell lines from primary, metastatic and recurrent malignant peripheral nerve sheath tumors (MPNST) with underlying neurofibromatosis-1. Anticancer Res. 2009;29:1255–62.
80. Jia LQ, Osada M, Ishioka C, Gamo M, Ikawa S, Suzuki T, et al. Screening the p53 status of human cell lines using a yeast functional assay. Mol Carcinog. 1997;19:243–53.
81. DeClue JE, Papageorge AG, Fletcher JA, Diehl SR, Ratner N, Vass WC, et al. Abnormal regulation of mammalian p21ras contributes to malignant tumor growth in von Recklinghausen (type 1) neurofibromatosis. Cell. 1992;69:265–73.
82. Ryan JJ, Klein KA, Neuberger TJ, Leftwich JA, Westin EH, Kauma S, et al. Role for the stem cell factor/KIT complex in Schwann cell neoplasia and mast cell proliferation associated with neurofibromatosis. J Neurosci Res. 1994;37:415–32.
83. DeClue JE, Heffelfinger S, Benvenuto G, Ling B, Li S, Rui W, et al. Epidermal growth factor receptor expression in neurofibromatosis type 1-related tumors and NF1 animal models. J Clin Investig. 2000;105:1233–41.
84. Hakozaki M, Hojo H, Sato M, Tajino T, Yamada H, Kikuchi S, et al. Establishment and characterization of a novel human malignant peripheral nerve sheath tumor cell line, FMS-1, that overexpresses epidermal growth factor receptor and cyclooxygenase-2. Virchows Arch. 2009;455:517–26.
85. Dang I, DeVries GH. Schwann cell lines derived from malignant peripheral nerve sheath tumors respond abnormally to platelet-derived growth factor-BB. J Neurosci Res. 2005;79:318–28.
86. Torres KE, Zhu QS, Bill K, Lopez G, Ghadimi MP, Xie X, et al. Activated MET is a molecular prognosticator and potential therapeutic target for malignant peripheral nerve sheath tumors. Clin Cancer Res. 2011;17:3943–55.
87. Eckert JM, Byer SJ, Clodfelder-Miller BJ, Carroll SL. Neuregulin-1 beta and neuregulin-1 alpha differentially affect the migration and invasion of malignant peripheral nerve sheath tumor cells. Glia. 2009;57:1501–20.
88. Demestre M, Terzi MY, Mautner V, Vajkoczy P, Kurtz A, Pina AL. Effects of pigment epithelium derived factor (PEDF) on malignant peripheral nerve sheath tumours (MPNSTs). J Neurooncol. 2013;115:391–9.
89. Perrin GQ, Li H, Fishbein L, Thomson SA, Hwang MS, Scarborough MT, et al. An orthotopic xenograft model of intraneural NF1 MPNST suggests a potential association between steroid hormones and tumor cell proliferation. Lab Invest. 2007;87:1092–102.
90. Byer SJ, Eckert JM, Brossier NM, Clodfelder-Miller BJ, Turk AN, Carroll AJ, et al. Tamoxifen inhibits malignant peripheral nerve sheath tumor growth in an estrogen receptor-independent manner. Neuro Oncol. 2011;13:28–41.
91. Imaizumi S, Motoyama T, Ogose A, Hotta T, Takahashi HE. Characterization and chemosensitivity of two human malignant peripheral nerve sheath tumour cell lines derived from a patient with neurofibromatosis type 1. Virchows Arch. 1998;433:435–41.
92. Hirokawa Y, Nakajima H, Hanemann CO, Kurtz A, Frahm S, Mautner V, et al. Signal therapy of NF1-deficient tumor xenograft in mice by the anti-PAK1 drug FK228. Cancer Biol Ther. 2005;4:379–81.
93. Ohishi J, Aoki M, Nabeshima K, Suzumiya J, Takeuchi T, Ogose A, et al. Imatinib mesylate inhibits cell growth of malignant peripheral nerve sheath tumors in vitro and in vivo through suppression of PDGFR-beta. BMC Cancer. 2013;13:224.
94. Wang W, Lin W, Hong B, Li X, Zhang M, Zhang L, et al. Effect of triptolide on malignant peripheral nerve sheath tumours in vitro and in vivo. J Int Med Res. 2012;40:2284–94.
95. Deyle DR, Escobar DZ, Peng KW, Babovic-Vuksanovic D. Oncolytic measles virus as a novel therapy for malignant peripheral nerve sheath tumors. Gene. 2015;565:140–5.
96. Maldonado AR, Klanke C, Jegga AG, Aronow BJ, Mahller YY, Cripe TP, et al. Molecular engineering and validation of an oncolytic herpes simplex virus type 1 transcriptionally targeted to midkine-positive tumors. J Gene Med. 2010;12:613–23.
97. Rahrmann EP, Watson AL, Keng VW, Choi K, Moriarity BS, Beckmann DA, et al. Forward genetic screen for malignant peripheral nerve sheath tumor formation identifies new genes and pathways driving tumorigenesis. Nat Genet. 2013;45:756–66.
98. Watson AL, Rahrmann EP, Moriarity BS, Choi K, Conboy CB, Greeley AD, et al. Canonical Wnt/beta-catenin signaling drives human schwann cell transformation, progression, and tumor maintenance. Cancer Discov. 2013;3:674–89.
99. Li H, Chang LJ, Neubauer DR, Muir DF, Wallace MR. Immortalization of human normal and NF1 neurofibroma Schwann cells. Lab Investig. 2016;96:1105–15.
100. Kraniak JM, Chalasani A, Wallace MR, Mattingly RR. Development of 3D culture models of plexiform neurofibroma and initial application for phenotypic characterization and drug screening. Exp Neurol. 2018;299:289–98.
101. Moll C, Reboredo J, Schwarz T, Appelt A, Schurlein S, Walles H, et al. Tissue engineering of a human 3D in vitro tumor test system. J Vis Exp. 2013;78:50460.
102. The I, Hannigan GE, Cowley GS, Reginald S, Zhong Y, Gusella JF, et al. Rescue of a Drosophila NF1 mutant phenotype by protein kinase A. Science. 1997;276:791–4.
103. Guo HF, Tong J, Hannan F, Luo L, Zhong Y. A neurofibromatosis-1-regulated pathway is required for learning in Drosophila. Nature. 2000;403:895–8.
104. Ho IS, Hannan F, Guo HF, Hakker I, Zhong Y. Distinct functional domains of neurofibromatosis type 1 regulate immediate versus long-term memory formation. J Neurosci. 2007;27:6852–7.

105. Buchanan ME, Davis RL. A distinct set of Drosophila brain neurons required for neurofibromatosis type 1-dependent learning and memory. J Neurosci. 2010;30:10135–43.
106. Gouzi JY, Moressis A, Walker JA, Apostolopoulou AA, Palmer RH, Bernards A, et al. The receptor tyrosine kinase Alk controls neurofibromin functions in Drosophila growth and learning. PLoS Genet. 2011;7:e1002281.
107. van der Voet M, Harich B, Franke B, Schenck A. ADHD-associated dopamine transporter, latrophilin and neurofibromin share a dopamine-related locomotor signature in Drosophila. Mol Psychiatry. 2016;21:565–73.
108. King LB, Koch M, Murphy KR, Velazquez Y, Ja WW, Tomchik SM. Neurofibromin loss of function drives excessive grooming in Drosophila. G3. 2016;6:1083–93.
109. Walker JA, Gouzi JY, Long JB, Huang S, Maher RC, Xia H, et al. Genetic and functional studies implicate synaptic overgrowth and ring gland cAMP/PKA signaling defects in the Drosophila melanogaster neurofibromatosis-1 growth deficiency. PLoS Genet. 2013;9:e1003958.
110. Guo HF, The I, Hannan F, Bernards A, Zhong Y. Requirement of Drosophila NF1 for activation of adenylyl cyclase by PACAP38-like neuropeptides. Science. 1997;276:795–8.
111. Williams JA, Su HS, Bernards A, Field J, Sehgal A. A circadian output in Drosophila mediated by neurofibromatosis-1 and Ras/MAPK. Science. 2001;293:2251–6.
112. King LB, Boto T, Botero V, Aviles AM, Jomsky BM, Joseph C, et al. Developmental loss of neurofibromin across distributed neuronal circuits drives excessive grooming in Drosophila. PLoS Genet. 2020;16:e1008920.
113. Tong J, Hannan F, Zhu Y, Bernards A, Zhong Y. Neurofibromin regulates G protein-stimulated adenylyl cyclase activity. Nat Neurosci. 2002;5:95–96.
114. MacInnes AW, Amsterdam A, Whittaker CA, Hopkins N, Lees JA. Loss of p53 synthesis in zebrafish tumors with ribosomal protein gene mutations. Proc Natl Acad Sci USA. 2008;105:10408–13.
115. Shin J, Padmanabhan A, de Groh ED, Lee JS, Haidar S, Dahlberg S, et al. Zebrafish neurofibromatosis type 1 genes have redundant functions in tumorigenesis and embryonic development. Dis Model Mech. 2012;5:881–94.
116. Ki DH, Oppel F, Durbin AD, Look AT. Mechanisms underlying synergy between DNA topoisomerase I-targeted drugs and mTOR kinase inhibitors in NF1-associated malignant peripheral nerve sheath tumors. Oncogene. 2019;38:6585–98.
117. Oppel F, Tao T, Shi H, Ross KN, Zimmerman MW, He S, et al. Loss of atrx cooperates with p53-deficiency to promote the development of sarcomas and other malignancies. PLoS Genet. 2019;15:e1008039.
118. Astone M, Pizzi M, Peron M, Domenichini A, Guzzardo V, Tochterle S, et al. A GFP-tagged gross deletion on chromosome 1 causes malignant peripheral nerve sheath tumors and carcinomas in Zebrafish. PLoS ONE. 2015;10:e0145178.
119. Kumari R, Silic MR, Jones-Hall YL, Nin-Velez A, Yang JY, Mittal SK, et al. Identification of RECK as an evolutionarily conserved tumor suppressor gene for zebrafish malignant peripheral nerve sheath tumors. Oncotarget. 2018;9:23494–504.
120. Reilly KM, Kim A, Blakely J, Ferner RE, Gutmann DH, Legius E, et al. Neurofibromatosis type 1-associated MPNST state of the science: outlining a research agenda for the future. J Natl Cancer Inst. 2017;109.
121. Jacks T, Shih TS, Schmitt EM, Bronson RT, Bernards A, Weinberg RA. Tumour predisposition in mice heterozygous for a targeted mutation in Nf1. Nat Genet. 1994;7:353–61.
122. Brannan CI, Perkins AS, Vogel KS, Ratner N, Nordlund ML, Reid SW, et al. Targeted disruption of the neurofibromatosis type-1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues. Genes Dev. 1994;8:1019–29.
123. Joseph NM, Mosher JT, Buchstaller J, Snider P, McKeever PE, Lim M, et al. The loss of Nf1 transiently promotes self-renewal but not tumorigenesis by neural crest stem cells. Cancer Cell. 2008;13:129–40.
124. Greenblatt MS, Bennett WP, Hollstein M, Harris CC. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis. Cancer Res. 1994;54:4855–78.
125. Vogel KS, Klesse LJ, Velasco-Miguel S, Meyers K, Rushing EJ, Parada LF. Mouse tumor model for neurofibromatosis type 1. Science. 1999;286:2176–9.
126. Cichowski K, Shih TS, Schmitt E, Santiago S, Reilly K, McLaughlin ME, et al. Mouse models of tumor development in neurofibromatosis type 1. Science. 1999;286:2172–6.
127. Reilly KM, Tuskan RG, Christy E, Loisel DA, Ledger J, Bronson RT, et al. Susceptibility to astrocytoma in mice mutant for Nf1 and Trp53 is linked to chromosome 11 and subject to epigenetic effects. Proc Natl Acad Sci USA. 2004;101:13008–13.
128. Johannessen CM, Johnson BW, Williams SM, Chan AW, Reczek EE, Lynch RC, et al. TORC1 is essential for NF1-associated malignancies. Curr Biol. 2008;18:56–62.
129. Malone CF, Fromm JA, Maertens O, DeRaedt T, Ingraham R, Cichowski K. Defining key signaling nodes and therapeutic biomarkers in NF1-mutant cancers. Cancer Discov. 2014;4:1062–73.
130. Lock R, Ingraham R, Maertens O, Miller AL, Weledji N, Legius E, et al. Cotargeting MNK and MEK kinases induces the regression of NF1-mutant cancers. J Clin Investig. 2016;126:2181–90.
131. De Raedt T, Walton Z, Yecies JL, Li D, Chen Y, Malone CF, et al. Exploiting cancer cell vulnerabilities to develop a combination therapy for ras-driven tumors. Cancer Cell. 2011;20:400–13.
132. Mo W, Chen J, Patel A, Zhang L, Chau V, Li Y, et al. CXCR4/CXCL12 mediate autocrine cell- cycle progression in NF1-associated malignant peripheral nerve sheath tumors. Cell. 2013;152:1077–90.
133. Huijbregts RP, Roth KA, Schmidt RE, Carroll SL. Hypertrophic neuropathies and malignant peripheral nerve sheath tumors in transgenic mice overexpressing glial growth factor beta3 in myelinating Schwann cells. J Neurosci. 2003;23:7269–80.
134. Kazmi SJ, Byer SJ, Eckert JM, Turk AN, Huijbregts RP, Brossier NM, et al. Transgenic mice overexpressing neuregulin-1 model neurofibroma-malignant peripheral nerve sheath tumor progression and implicate specific chromosomal copy number variations in tumorigenesis. Am J Pathol. 2013;182:646–67.
135. Keng VW, Rahrmann EP, Watson AL, Tschida BR, Moertel CL, Jessen WJ, et al. PTEN and NF1 inactivation in Schwann cells produces a severe phenotype in the peripheral nervous system that promotes the development and malignant progression of peripheral nerve sheath tumors. Cancer Res. 2012;72:3405–13.
136. Rhodes SD, He Y, Smith A, Jiang L, Lu Q, Mund J, et al. Cdkn2a (Arf) loss drives NF1-associated atypical neurofibroma and malignant transformation. Hum Mol Genet. 2019;28:2752–62.
137. Gregorian C, Nakashima J, Dry SM, Nghiemphu PL, Smith KB, Ao Y, et al. PTEN dosage is essential for neurofibroma development and malignant transformation. Proc Natl Acad Sci USA. 2009;106:19479–84.
138. Keng VW, Watson AL, Rahrmann EP, Li H, Tschida BR, Moriarity BS, et al. Conditional inactivation of Pten with EGFR overexpression in Schwann cells models sporadic MPNST. Sarcoma. 2012;2012:620834.
139. Rahrmann EP, Moriarity BS, Otto GM, Watson AL, Choi K, Collins MH, et al. Trp53 haploinsufficiency modifies EGFR-driven peripheral nerve sheath tumorigenesis. Am J Pathol. 2014;184:2082–98.
140. Dodd RD, Mito JK, Eward WC, Chitalia R, Sachdeva M, Ma Y, et al. NF1 deletion generates multiple subtypes of soft-tissue sarcoma that respond to MEK inhibition. Mol Cancer Ther. 2013;12:1906–17.
141. Dodd RD, Lee CL, Overton T, Huang W, Eward WC, Luo L, et al. NF1(+/-) hematopoietic cells accelerate malignant peripheral nerve sheath tumor development without altering chemotherapy response. Cancer Res. 2017;77:4486–97.
142. Huang J, Chen M, Whitley MJ, Kuo HC, Xu ES, Walens A, et al. Generation and comparison of CRISPR-Cas9 and Cre-mediated genetically engineered mouse models of sarcoma. Nat Commun. 2017;8:15999.
143. Hirbe AC, Dahiya S, Friedmann-Morvinski D, Verma IM, Clapp DW, Gutmann DH. Spatially- and temporally-controlled postnatal p53 knockdown cooperates with embryonic Schwann cell precursor Nf1 gene loss to promote malignant peripheral nerve sheath tumor formation. Oncotarget. 2016;7:7403–14.
144. Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. Am J Transl Res. 2014;6:114–8.
145. Bhola P, Banerjee S, Mukherjee J, Balasubramanium A, Arun V, Karim Z, et al. Preclinical in vivo evaluation of rapamycin in human malignant peripheral nerve sheath explant xenograft. Int J Cancer. 2010;126:563–71.
146. Takamiya Y, Friedlander RM, Brem H, Malick A, Martuza RL. Inhibition of angiogenesis and growth of human nerve-sheath tumors by AGM-1470. J Neurosurg. 1993;78:470–6.
147. Castellsague J, Gel B, Fernandez-Rodriguez J, Llatjos R, Blanco I, Benavente Y, et al. Comprehensive establishment and characterization of orthoxenograft mouse models of malignant peripheral nerve sheath tumors for personalized medicine. EMBO Mol Med. 2015;7:608–27.
148. Pollard K, Banerjee J, Doan X, Wang J, Guo X, Allaway R, et al. A clinically and genomically annotated nerve sheath tumor biospecimen repository. Sci Data. 2020;7:184.
149. Inoue A, Deem AK, Kopetz S, Heffernan TP, Draetta GF, Carugo A. Current and future horizons of patient-derived xenograft models in colorectal cancer translational research. Cancers. 2019;11:1321.
150. Yoshida GJ. Applications of patient-derived tumor xenograft models and tumor organoids. J Hematol Oncol. 2020;13:4.
151. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663–76.

152. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861–72.
153. Carrio M, Mazuelas H, Richaud-Patin Y, Gel B, Terribas E, Rosas I, et al. Reprogramming captures the genetic and tumorigenic properties of neurofibromatosis type 1 plexiform neurofibromas. Stem Cell Rep. 2019;12:411–26.
154. Anastasaki C, Wegscheid ML, Hartigan K, Papke JB, Kopp ND, Chen J, et al. Human iPSC-derived neurons and cerebral organoids establish differential effects of germline NF1 gene mutations. Stem Cell Rep. 2020;14:541–50.
155. Wegscheid ML, Anastasaki C, Gutmann DH. Human stem cell modeling in neurofibromatosis type 1 (NF1). Exp Neurol. 2018;299:270–80.
156. Mo J, Anastasaki C, Chen Z, Shipman T, Papke J, Yin K, et al. Humanized neurofibroma model from induced pluripotent stem cells delineates tumor pathogenesis and developmental origins. J Clin Investig. 2021;131:e139807.
157. Williams KB, Largaespada DA. New model systems and the development of targeted therapies for the treatment of neurofibromatosis type 1-associated malignant peripheral nerve sheath tumors. Genes 2020;11:477.
158. Zou C, Smith KD, Liu J, Lahat G, Myers S, Wang WL, et al. Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. Ann Surg. 2009;249:1014–22.
159. Dasgupta B, Yi Y, Chen DY, Weber JD, Gutmann DH. Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated human and mouse brain tumors. Cancer Res. 2005;65:2755–60.
160. Johannessen CM, Reczek EE, James MF, Brems H, Legius E, Cichowski K. The NF1 tumor suppressor critically regulates TSC2 and mTOR. Proc Natl Acad Sci USA. 2005;102:8573–8.
161. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168:960–76.
162. Endo M, Yamamoto H, Setsu N, Kohashi K, Takahashi Y, Ishii T, et al. Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant peripheral nerve sheath tumors. Clin Cancer Res. 2013;19:450–61.
163. Bradtmoller M, Hartmann C, Zietsch J, Jaschke S, Mautner VF, Kurtz A, et al. Impaired Pten expression in human malignant peripheral nerve sheath tumours. PLoS ONE. 2012;7:e47595.
164. Misra JR, Irvine KD. The Hippo signaling network and its biological functions. Annu Rev Genet. 2018;52:65–87.
165. Wu LMN, Deng Y, Wang J, Zhao C, Wang J, Rao R, et al. Programming of Schwann cells by Lats1/2-TAZ/YAP signaling drives malignant peripheral nerve sheath tumorigenesis. Cancer Cell. 2018;33:292–308 e297.
166. Isfort I, Elges S, Cyra M, Berthold R, Renner M, Mechtersheimer G, et al. Prevalence of the Hippo effectors YAP1/TAZ in tumors of soft tissue and bone. Sci Rep. 2019;9:19704.
167. Katoh M. Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). Int J Oncol. 2017;51:1357–69.
168. Luscan A, Shackleford G, Masliah-Planchon J, Laurendeau I, Ortonne N, Varin J, et al. The activation of the WNT signaling pathway is a Hallmark in neurofibromatosis type 1 tumorigenesis. Clin Cancer Res. 2014;20:358–71.
169. Thomson CS, Pundavela J, Perrino MR, Coover RA, Choi K, Chaney KE, et al. WNT5A inhibition alters the malignant peripheral nerve sheath tumor microenvironment and enhances tumor growth. Oncogene. 2021;40:4229–41.
170. Zhu Y, Ghosh P, Charnay P, Burns DK, Parada LF. Neurofibromas in NF1: Schwann cell origin and role of tumor environment. Science. 2002;296:920–2.
171. Yang FC, Ingram DA, Chen S, Zhu Y, Yuan J, Li X, et al. Nf1-dependent tumors require a microenvironment containing Nf1+/— and c-kit-dependent bone marrow. Cell. 2008;135:437–48.
172. Wu J, Williams JP, Rizvi TA, Kordich JJ, Witte D, Meijer D, et al. Plexiform and dermal neurofibromas and pigmentation are caused by Nf1 loss in desert hedgehog-expressing cells. Cancer Cell. 2008;13:105–16.
173. Scaife CL, Pisters PW. Combined-modality treatment of localized soft tissue sarcomas of the extremities. Surg Oncol Clin N Am. 2003;12:355–68.
174. Gupta G, Mammis A, Maniker A. Malignant peripheral nerve sheath tumors. Neurosurg Clin N Am. 2008;19:533–43. v
175. Martin E, Coert JH, Flucke UE, Slooff WM, van de Sande MAJ, van Noesel MM, et al. Neurofibromatosis-associated malignant peripheral nerve sheath tumors in children have a worse prognosis: a nationwide cohort study. Pediatr Blood Cancer. 2020;67:e28138.
176. Garozzo D. Peripheral nerve tumors in neurofibromatosis 1: an overview on management and indications for surgical treatment in our experience. Neurol India. 2019;67:S38–S44.
177. Ferner RE, Golding JF, Smith M, Calonje E, Jan W, Sanjayanathan V, et al. [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study. Ann Oncol. 2008;19:390–4.
178. Mautner VF, Friedrich RE, von Deimling A, Hagel C, Korf B, Knofel MT, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis type 1: MRI supports the diagnosis of malignant plexiform neurofibroma. Neuroradiology. 2003;45:618–25.
179. Suratwala SJ, Kondra K, Cronin M, Leone V. Malignant peripheral nerve sheath tumor of the sciatic nerve presenting with leg pain in the setting of lumbar scoliosis and spinal stenosis. Spine Deform. 2020;8:333–8.
180. Ferner RE, Lucas JD, O'Doherty MJ, Hughes RA, Smith MA, Cronin BF, et al. Evaluation of (18)fluorodeoxyglucose positron emission tomography ((18)FDG PET) in the detection of malignant peripheral nerve sheath tumours arising from within plexiform neurofibromas in neurofibromatosis 1. J Neurol Neurosurg Psychiatry. 2000;68:353–7.
181. Widemann BC, Italiano A. Biology and management of undifferentiated pleomorphic sarcoma, myxofibrosarcoma, and malignant peripheral nerve sheath tumors: state of the art and perspectives. J Clin Oncol. 2018;36:160–7.
182. Tovmassian D, Abdul Razak M, London K. The Role of [(18)F]FDG-PET/CT in predicting malignant transformation of plexiform neurofibromas in neurofibromatosis-1. Int J Surg Oncol. 2016;2016:6162182.
183. Ahlawat S, Blakeley JO, Langmead S, Belzberg AJ, Fayad LM. Current status and recommendations for imaging in neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis. Skelet Radio. 2020;49:199–219.
184. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. Cancer Res. 2002;62:1573–7.
185. Dunn GP, Spiliopoulos K, Plotkin SR, Hornicek FJ, Harmon DC, Delaney TF, et al. Role of resection of malignant peripheral nerve sheath tumors in patients with neurofibromatosis type 1. J Neurosurg. 2013;118:142–8.
186. Gachiani J, Kim D, Nelson A, Kline D. Surgical management of malignant peripheral nerve sheath tumors. Neurosurg Focus. 2007;22:E13.
187. Levi AD, Ross AL, Cuartas E, Qadir R, Temple HT. The surgical management of symptomatic peripheral nerve sheath tumors. Neurosurgery. 2010;66:833–40.
188. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16:197–203.
189. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359:2235–41.
190. Kahn J, Gillespie A, Tsokos M, Ondos J, Dombi E, Camphausen K, et al. Radiation therapy in management of sporadic and neurofibromatosis type 1-associated malignant peripheral nerve sheath tumors. Front Oncol. 2014;4:324.
191. Arshi A, Tajudeen BA, St John M. Malignant peripheral nerve sheath tumors of the head and neck: Demographics, clinicopathologic features, management, and treatment outcomes. Oral Oncol. 2015;51:1088–94.
192. Kar M, Deo SV, Shukla NK, Malik A, DattaGupta S, Mohanti BK, et al. Malignant peripheral nerve sheath tumors (MPNST)—clinicopathological study and treatment outcome of twenty-four cases. World J Surg Oncol. 2006;4:55.
193. Bhatia S, Chen Y, Wong FL, Hageman L, Smith K, Korf B, et al. Subsequent neoplasms after a primary tumor in individuals with neurofibromatosis type 1. J Clin Oncol. 2019;37:3050–8.
194. Nakamura JL, Phong C, Pinarbasi E, Kogan SC, Vandenberg S, Horvai AE, et al. Dose-dependent effects of focal fractionated irradiation on secondary malignant neoplasms in Nf1 mutant mice. Cancer Res. 2011;71:106–15.
195. Chou D, Bilsky MH, Luzzati A, Fisher CG, Gokaslan ZL, Rhines LD, et al. Malignant peripheral nerve sheath tumors of the spine: results of surgical management from a multicenter study. J Neurosurg Spine. 2017;26:291–8.
196. Ferrari A, Miceli R, Rey A, Oberlin O, Orbach D, Brennan B, et al. Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: results of a pooled analysis from United States and European groups. Eur J Cancer. 2011;47:724–31.
197. Tierney JF. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997;350:1647–54.
198. Higham CS, Steinberg SM, Dombi E, Perry A, Helman LJ, Schuetze SM, et al. SARC006: Phase II trial of chemotherapy in sporadic and neurofibromatosis type 1 associated chemotherapy-naive malignant peripheral nerve sheath tumors. Sarcoma. 2017;2017:8685638.
199. Carli M, Ferrari A, Mattke A, Zanetti I, Casanova M, Bisogno G, et al. Pediatric malignant peripheral nerve sheath tumor: the Italian and German soft tissue sarcoma cooperative group. J Clin Oncol. 2005;23:8422–30.
200. Hubbard SR, Miller WT. Receptor tyrosine kinases: mechanisms of activation and signaling. Curr Opin Cell Biol. 2007;19:117–23.

201. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141:1117–34.
202. Butti R, Das S, Gunasekaran VP, Yadav AS, Kumar D, Kundu GC. Receptor tyrosine kinases (RTKs) in breast cancer: signaling, therapeutic implications and challenges. Mol Cancer. 2018;17:34.
203. Regad T, Targeting RTK. Signaling pathways in cancer. Cancers. 2015;7:1758–84.
204. Chugh R, Wathen JK, Maki RG, Benjamin RS, Patel SR, Meyers PA, et al. Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. J Clin Oncol. 2009;27:3148–53.
205. Schuetze SM, Wathen JK, Lucas DR, Choy E, Samuels BL, Staddon AP, et al. SARC009: Phase 2 study of dasatinib in patients with previously treated, high-grade, advanced sarcoma. Cancer. 2016;122:868–74.
206. Li H, Velasco-Miguel S, Vass WC, Parada LF, DeClue JE. Epidermal growth factor receptor signaling pathways are associated with tumorigenesis in the Nf1:p53 mouse tumor model. Cancer Res. 2002;62:4507–13.
207. Tabone-Eglinger S, Bahleda R, Cote JF, Terrier P, Vidaud D, Cayre A, et al. Frequent EGFR positivity and overexpression in high-grade areas of human MPNSTs. Sarcoma. 2008;2008:849156.
208. Albritton KH, Rankin C, Coffin CM, Ratner N, Budd GT, Schuetze SM, et al. Phase II study of erlotinib in metastatic or unresectable malignant peripheral nerve sheath tumors (MPNST). J Clin Oncol. 2006;24:9518–9518.
209. Widemann BC, Lu Y, Reinke D, Okuno SH, Meyer CF, Cote GM, et al. Targeting sporadic and neurofibromatosis type 1 (NF1) related refractory malignant peripheral nerve sheath tumors (MPNST) in a phase II study of everolimus in combination with Bevacizumab (SARC016). Sarcoma. 2019;2019:7656747.
210. Ohba Y, Mochizuki N, Yamashita S, Chan AM, Schrader JW, Hattori S, et al. Regulatory proteins of R-Ras, TC21/R-Ras2, and M-Ras/R-Ras3. J Biol Chem. 2000;275:20020–6.
211. Cox AD, Der CJ. Ras history: the saga continues. Small GTPases. 2010;1:2–27.
212. Ratner N, Miller SJ. A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. Nat Rev Cancer. 2015;15:290–301.
213. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503:548–51.
214. Kim HA, Ling B, Ratner N. Nf1-deficient mouse Schwann cells are angiogenic and invasive and can be induced to hyperproliferate: reversion of some phenotypes by an inhibitor of farnesyl protein transferase. Mol Cell Biol. 1997;17:862–72.
215. Wojtkowiak JW, Fouad F, LaLonde DT, Kleinman MD, Gibbs RA, Reiners JJ Jr, et al. Induction of apoptosis in neurofibromatosis type 1 malignant peripheral nerve sheath tumor cell lines by a combination of novel farnesyl transferase inhibitors and lovastatin. J Pharmacol Exp Ther. 2008;326:1–11.
216. Widemann BC, Salzer WL, Arceci RJ, Blaney SM, Fox E, End D, et al. Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. J Clin Oncol. 2006;24:507–16.
217. Widemann BC, Dombi E, Gillespie A, Wolters PL, Belasco J, Goldman S, et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol. 2014;16:707–18.
218. Morrison DK. MAP kinase pathways. Cold Spring Harb Perspect Biol. 2012;4:a011254.
219. Ambrosini G, Cheema HS, Seelman S, Teed A, Sambol EB, Singer S, et al. Sorafenib inhibits growth and mitogen-activated protein kinase signaling in malignant peripheral nerve sheath cells. Mol Cancer Ther. 2008;7:890–6.
220. Maki RG, D'Adamo DR, Keohan ML, Saulle M, Schuetze SM, Undevia SD, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27:3133–40.
221. Jessen WJ, Miller SJ, Jousma E, Wu J, Rizvi TA, Brundage ME, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J Clin Investig. 2013;123:340–7.
222. Markham A, Keam SJ. Selumetinib: first approval. Drugs. 2020;80:931–7.
223. Nagabushan S, Lau LMS, Barahona P, Wong M, Sherstyuk A, Marshall GM, et al. Efficacy of MEK inhibition in a recurrent malignant peripheral nerve sheath tumor. NPJ Precis Oncol. 2021;5:9.
224. Johansson G, Mahller YY, Collins MH, Kim MO, Nobukuni T, Perentesis J, et al. Effective in vivo targeting of the mammalian target of rapamycin pathway in malignant peripheral nerve sheath tumors. Mol Cancer Ther. 2008;7:1237–45.
225. Weiss B, Widemann BC, Wolters P, Dombi E, Vinks A, Cantor A, et al. Sirolimus for progressive neurofibromatosis type 1-associated plexiform neurofibromas: a neurofibromatosis Clinical Trials Consortium phase II study. Neuro Oncol. 2015;17:596–603.
226. Varin J, Poulain L, Hivelin M, Nusbaum P, Hubas A, Laurendeau I, et al. Dual mTORC1/2 inhibition induces anti-proliferative effect in NF1-associated plexiform neurofibroma and malignant peripheral nerve sheath tumor cells. Oncotarget. 2016;7:35753–67.
227. Watson AL, Anderson LK, Greeley AD, Keng VW, Rahrmann EP, Halfond AL, et al. Co-targeting the MAPK and PI3K/AKT/mTOR pathways in two genetically engineered mouse models of schwann cell tumors reduces tumor grade and multiplicity. Oncotarget. 2014;5:1502–14.
228. Kim A, Lu Y, Okuno SH, Reinke D, Maertens O, Perentesis J, et al. Targeting refractory sarcomas and malignant peripheral nerve sheath tumors in a phase I/II study of sirolimus in combination with Ganetespib (SARC023). Sarcoma. 2020;2020:5784876.
229. Malone CF, Emerson C, Ingraham R, Barbosa W, Guerra S, Yoon H, et al. mTOR and HDAC inhibitors converge on the TXNIP/thioredoxin pathway to cause catastrophic oxidative stress and regression of RAS-driven tumors. Cancer Discov. 2017;7:1450–63.
230. Kohlmeyer JL, Kaemmer CA, Pulliam C, Maharjan CK, Samayoa AM, Major HJ, et al. RABL6A Is an essential driver of MPNSTs that negatively regulates the RB1 pathway and sensitizes tumor cells to CDK4/6 inhibitors. Clin Cancer Res. 2020;26:2997–3011.
231. Cleven AH, Sannaa GA, Briaire-de Bruijn I, Ingram DR, van de Rijn M, Rubin BP, et al. Loss of H3K27 tri-methylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival. Mod Pathol. 2016;29:582–90.
232. Guo J, Chaney KE, Choi K, Witek G, Patel AV, Xie H, et al. Polo-like kinase 1 as a therapeutic target for malignant peripheral nerve sheath tumors (MPNST) and schwannomas. Am J Cancer Res. 2020;10:856–69.
233. Williams KB, Williams RL, Rathe SK, Hawkinson J, Largaespada DA. Abstract A37: Synthetic lethality as a tool to reveal novel vulnerabilities in NF1-associated tumorigenesis. Mol Cancer Therapeutics. 2017;16:A37–A37.
234. Castells-Roca L, Tejero E, Rodriguez-Santiago B, Surralles J. CRISPR screens in synthetic lethality and combinatorial therapies for cancer. Cancers. 2021;13:1591.
235. Semenova G, Stepanova DS, Deyev SM, Chernoff J. Medium throughput biochemical compound screening identifies novel agents for pharmacotherapy of neurofibromatosis type 1. Biochimie. 2017;135:1–5.
236. Wood M, Rawe M, Johansson G, Pang S, Soderquist RS, Patel AV, et al. Discovery of a small molecule targeting IRA2 deletion in budding yeast and neurofibromin loss in malignant peripheral nerve sheath tumor cells. Mol Cancer Ther. 2011;10:1740–50.
237. Kahen EJ, Brohl A, Yu D, Welch D, Cubitt CL, Lee JK, et al. Neurofibromin level directs RAS pathway signaling and mediates sensitivity to targeted agents in malignant peripheral nerve sheath tumors. Oncotarget. 2018;9:22571–85.
238. Cooper JM, Patel AJ, Chen Z, Liao CP, Chen K, Mo J, et al. Overcoming BET inhibitor resistance in malignant peripheral nerve sheath tumors. Clin Cancer Res. 2019;25:3404–16.
239. Mashour GA, Drissel SN, Frahm S, Farassati F, Martuza RL, Mautner VF, et al. Differential modulation of malignant peripheral nerve sheath tumor growth by omega-3 and omega-6 fatty acids. Oncogene. 2005;24:2367–74.
240. Lopez G, Torres K, Liu J, Hernandez B, Young E, Belousov R, et al. Autophagic survival in resistance to histone deacetylase inhibitors: novel strategies to treat malignant peripheral nerve sheath tumors. Cancer Res. 2011;71:185–96.
241. Reuss DE, Mucha J, Hagenlocher C, Ehemann V, Kluwe L, Mautner V, et al. Sensitivity of malignant peripheral nerve sheath tumor cells to TRAIL is augmented by loss of NF1 through modulation of MYC/MAD and is potentiated by curcumin through induction of ROS. PLoS ONE. 2013;8:e57152.
242. Mahller YY, Vaikunth SS, Ripberger MC, Baird WH, Saeki Y, Cancelas JA, et al. Tissue inhibitor of metalloproteinase-3 via oncolytic herpesvirus inhibits tumor growth and vascular progenitors. Cancer Res. 2008;68:1170–9.
243. Li Y, Rao PK, Wen R, Song Y, Muir D, Wallace P, et al. Notch and Schwann cell transformation. Oncogene. 2004;23:1146–52.
244. Glover TW, Stein CK, Legius E, Andersen LB, Brereton A, Johnson S. Molecular and cytogenetic analysis of tumors in von Recklinghausen neurofibromatosis. Genes Chromosomes Cancer. 1991;3:62–70.
245. Yan N, Ricca C, Fletcher J, Glover T, Seizinger BR, Manne V. Farnesyltransferase inhibitors block the neurofibromatosis type I (NF1) malignant phenotype. Cancer Res. 1995;55:3569–75.
246. Mattingly RR, Kraniak JM, Dilworth JT, Mathieu P, Bealmear B, Nowak JE, et al. The mitogen-activated protein kinase/extracellular signal-regulated kinase kinase inhibitor PD184352 (CI-1040) selectively induces apoptosis in malignant schwannoma cell lines. J Pharmacol Exp Ther. 2006;316:456–65.
247. Koelsche C, Renner M, Hartmann W, Brandt R, Lehner B, Waldburger N, et al. TERT promoter hotspot mutations are recurrent in myxoid liposarcomas but rare in other soft tissue sarcoma entities. J Exp Clin Cancer Res. 2014;33:33.
248. Teicher BA, Polley E, Kunkel M, Evans D, Silvers T, Delosh R, et al. Sarcoma cell line screen of oncology drugs and investigational agents identifies patterns

associated with gene and microRNA expression. Mol Cancer Ther. 2015;14:2452–62.
249. Lee PR, Cohen JE, Tendi EA, Farrer R, GH DEV, Becker KG, et al. Transcriptional profiling in an MPNST-derived cell line and normal human Schwann cells. Neuron Glia Biol. 2004;1:135–47.
250. Yi C, Troutman S, Fera D, Stemmer-Rachamimov A, Avila JL, Christian N, et al. A tight junction-associated Merlin-angiomotin complex mediates Merlin's regulation of mitogenic signaling and tumor suppressive functions. Cancer Cell. 2011;19:527–40.
251. Subramanian S, Thayanithy V, West RB, Lee CH, Beck AH, Zhu S, et al. Genome-wide transcriptome analyses reveal p53 inactivation mediated loss of miR-34a expression in malignant peripheral nerve sheath tumours. J Pathol. 2010;220:58–70.
252. Nagashima Y, Ohaki Y, Tanaka Y, Sumino K, Funabiki T, Okuyama T, et al. Establishment of an epithelioid malignant schwannoma cell line (YST-1). Virchows Arch B Cell Pathol Incl Mol Pathol. 1990;59:321–7.
253. Dahlberg WK, Little JB, Fletcher JA, Suit HD, Okunieff P. Radiosensitivity in vitro of human soft tissue sarcoma cell lines and skin fibroblasts derived from the same patients. Int J Radiat Biol. 1993;63:191–8.
254. Sonobe H, Takeuchi T, Furihata M, Taguchi T, Kawai A, Ohjimi Y, et al. A new human malignant peripheral nerve sheath tumour-cell line, HS-sch-2, harbouring p53 point mutation. Int J Oncol. 2000;17:347–52.

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## COMPETING INTERESTS

The authors declare no competing interests.

## CONSENT TO PUBLISH

There are no enrolled patients in this review and all authors provided consent for publication.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Lu Q. Le.

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