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REVIEW

Tropomyosin receptor kinase B (TrkB) signalling: targeted therapy in neurogenic tumours

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Abstract

Tropomyosin receptor kinase B (TrkB), a transmembrane receptor protein, has been found to play a pivotal role in neural development. This protein is encoded by the neurotrophic receptor tyrosine kinase 2 (*NTRK2*) gene, and its abnormal activation caused by *NTRK2* overexpression or fusion can contribute to tumour initiation, progression, and resistance to therapeutics in multiple types of neurogenic tumours. Targeted therapies for this mechanism have been designed and developed in preclinical and clinical studies, including selective TrkB inhibitors and pan-TRK inhibitors. This review describes the gene structure, biological function, abnormal TrkB activation mechanism, and current-related targeted therapies in neurogenic tumours.

Keywords: TrkB; tyrosine kinase; NTRK; abnormal activation; gene fusion; neurogenic tumours; targeted therapy

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Introduction

The neurotrophic tropomyosin receptor kinases (TRKs) are a class of transmembrane tyrosine kinases that play an important role in neural development [1]. TrkA, TrkB, and TrkC are three members of the TRK family, encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes [2]. These TRKs are composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with kinase activity and high sequence homology [3]. The main differences between these TRKs are their binding ligands: TrkA binds with high affinity to the nerve growth factor [4], TrkB preferentially binds to the brain-derived neurotrophic factor (BDNF) [5] and neurotrophin-4/5 [6,7], and TrkC selectively pairs with neurotrophin-3 (NT3) [8]. In some cellular contexts, NT3 is also able to activate TrkA/B with less efficiency [9,10].

Of these three receptors, TrkB is expressed in tissues derived from the neural epithelium and neural crest cells and is therefore widely present in the central nervous system and peripheral nervous system (CNS and PNS). As the receptor for BDNF, TrkB plays an essential role in neuronal survival, proliferation, development, and synaptic plasticity and is further found to be essential in memory and cognition [11,12]. Studies have shown that mice with TrkB knockdown ultimately exhibit a significant reduction (>30%) in trigeminal ganglion neurons and facial motor nuclei compared with control mice [13], which indicates the importance of TrkB in normal neuronal development. In the last two decades, other studies have found the abnormal activation of TrkB in several types of neurogenic tumour, including neuroblastoma (NB) and glioma, which suggests an important oncogenic role and invites consideration as a potential therapeutic target [14].

Several drugs targeting TrkB have been developed recently, including selective TrkB inhibitors, pan-TRK inhibitors, and multi-tyrosinase inhibitors, and these have shown positive results in neurogenic tumours in preclinical and clinical studies. In this review, we summarise the dysregulation of TrkB activation in neurogenic tumours by comparison with the normal functions of TrkB in neural development.

TrkB expression and function in the normal nervous system

TrkB was first identified as a novel member of the Trk family in 1989 by Klein and *et al* [15]. Studies have demonstrated that TrkB gene (*NTRK*2) transcripts can be detected in embryos on day 9.5 and continue to be transcribed throughout the nervous system during embryonic development, as well as in adulthood [16]. *NTRK2* can encode two different classes of receptor; full-length TrkB (TrkB.FL) and three truncated forms (TrkB.T1, TrkB.T2, and TrkB-T-ShC), which lack the tyrosine kinase-signalling domain and cannot undergo autophosphorylation [17–19] (Figure 1). TrkB.FL expression is predominant in the embryonic stage and is highly expressed in most structures of the cerebrum including the cortical layers, the thalamus, and the hippocampus. In the PNS, it can be detected in neural crest-derived sympathetic neural networks and autonomic nervous system clusters. Proper expression of TrkB and its activation are critical for neuron and glial cell function [20], while downregulation is detected in brain regions involved by neurodegenerative diseases [21].

Further studies have been conducted to clarify the underlying mechanisms by which TrkB impacts on the nervous system. One study demonstrated that, when neurotrophins bind to TrkB, the receptor undergoes homodimerisation and autophosphorylation on tyrosine residues, which is required for its catalytic and signalling activities [22]. Three of the phosphorylated tyrosines (Y701, Y705, and Y706) were found to lie within the activation loop of the kinase domain and potentiate the tyrosine kinase activity of the receptor [23], while the other two phosphorylated tyrosines (Y515 and Y816) served as docking sites for proteins containing phosphorylated tyrosine binding (PTB) or Src homology 2 (SH2) domains [24]. Recruitment of the partner proteins and adaptors subsequently leads to the activation of downstream intracellular signalling pathways, including the PI3 kinase (PI3K) [25,26], Ras-mitogen-activated protein kinase (MAPK) [27,28], and protein kinase C (PKC) cascades [29] (Figure 2). The pivotal roles of these pathways in various cellular physiological processes indicate the profound impacts of TrkB activation. For instance, in cultured cerebellar granular neurons, TrkB-mediated activation of PKC and PI3K enhances cell survival [25,29] and contributes to epithelial resistance to anoikis, a form of programmed cell death that occurs in anchorage-dependent cells when they detach from the surrounding extracellular matrix [30]. In addition, the TrkB-mediated MAPK signalling pathway promotes the differentiation of cortical progenitor cells into neurons [31] and facilitates NIH 3T3 fibroblast proliferation and survival [32,33]. Furthermore, the BDNF/TrkB pathway has been demonstrated to transactivate EGFR, which is important for the proliferation and migration of embryonic cortical neurons [34]. In addition to the functions mentioned earlier, TrkB can be activated by ligands of the G protein-coupled receptor (GPCR) family of transmembrane receptors, mediating cell survival through the PI3K/AKT (protein kinase B) pathway [35]. Together, the precise regulation of TrkB signalling is critically important for normal neuronal cell function.

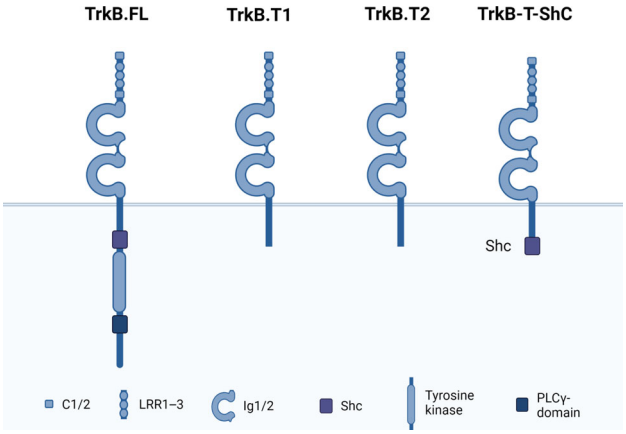

Figure 1. The structure and known splice variants of TrkB. *NTRK2* can encode two different classes of receptors: TrkB.FL and three truncated forms (TrkB.T1, TrkB.T2, and TrkB-T-ShC). C1/2, cysteine-rich clusters; LRR1–3, leucine-rich repeats; Ig1/2, immunoglobulin-like domains.

Abnormal TrkB activation in neurogenic tumours

Abnormal upregulation of TrkB was found to be essential in the pathogenesis of a range of neuro-related diseases, especially neurogenic tumours [36–38]. Three main abnormal activation pathways have been found, and a better understanding of the underlying mechanisms of the abnormal activation of TrkB would be beneficial for TrkB-targeted therapy development.

TrkB fusion

Currently, gene fusion is regarded as the most frequent oncogenic TRK activation pathway, resulting from intra- or inter-chromosomal rearrangements that juxtapose the 3′ region of the TRK gene with the 5′ sequence of the partner gene. With the progress of

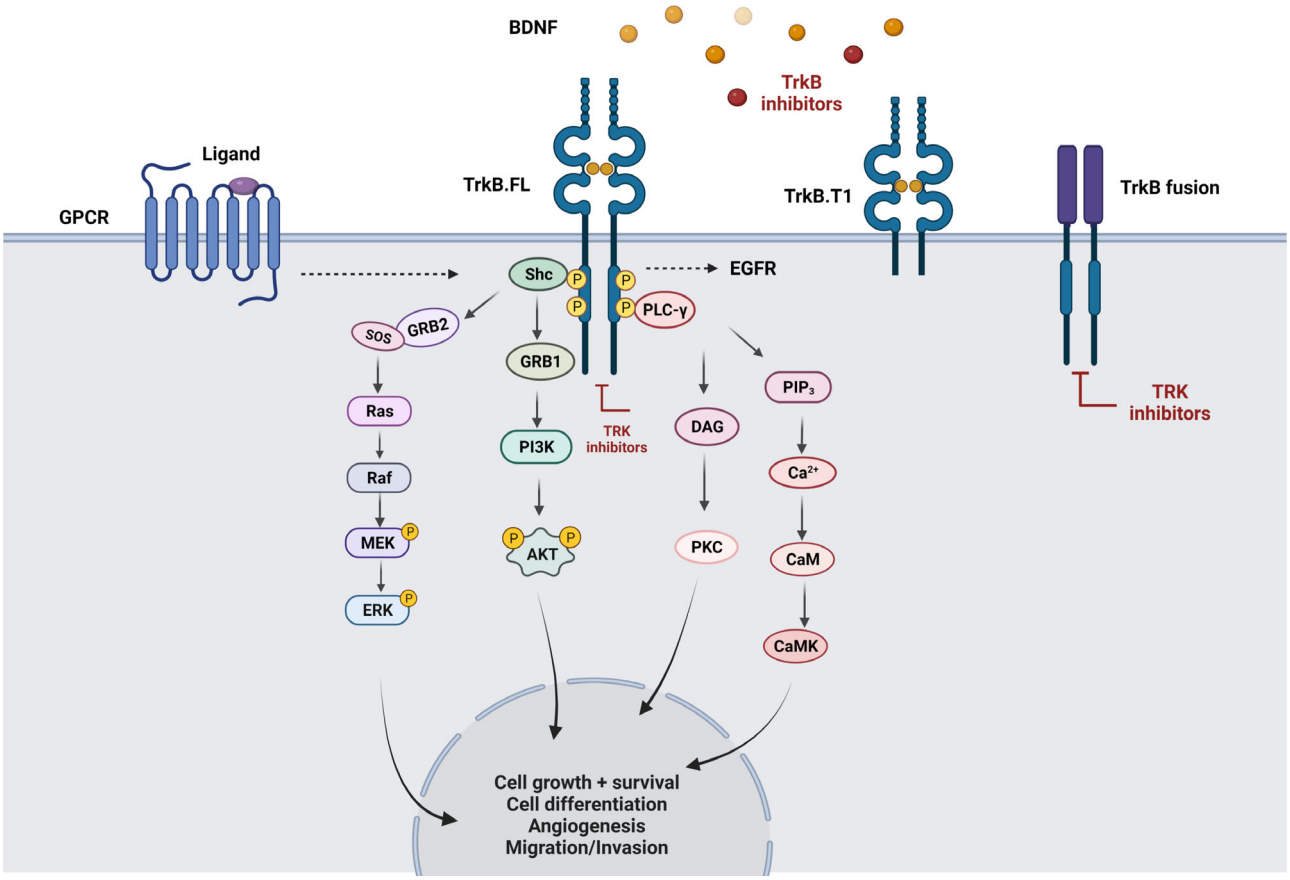

Figure 2. Schematic representation of TrkB signalling pathways. When BDNF binds to TrkB, the receptor undergoes homodimerisation resulting in the autophosphorylation of tyrosine residues. These residues serve as docking sites for cytoplasmic proteins such as ShC and PLCγ, whose recruitment leads to the activation of downstream mediators of the MAPK, PLCγ, and PI3 kinase pathways. Finally, these signals are transferred to the nucleus to mediate transcriptional programmes that regulate cellular functions such as growth, differentiation, and survival. Moreover, the BDNF/TrkB pathway can transactivate EGFR. TrkB can also be activated by ligands of the GPCR family of transmembrane receptors, mediating cell functions. Fusion proteins generated by intra- or inter-chromosomal rearrangement between the 3′ region of the TrkB gene and the 5′ region of the other gene can activate downstream signalling pathways.

detection technologies, TRK gene fusions have been found in a broad range of solid tumours, such as colon cancer, lung cancer, melanoma, and congenital infant fibrosarcoma [39]. Once gene fusion occurs, the transcript encodes a protein composed of the N-terminus of a partner gene with the C-terminus of TRK, including the tyrosine kinase domain [39]. The 5′ sequence of most partner genes encodes one or more dimerisation domains, such as zinc finger, coiled-coil domains, and tryptophan-aspartic acid repeats, which enables the fusion protein to be constitutively activated, independent of ligand binding [40,41]. However, the cause of TRK kinase activation in the absence of the dimerisation domain needs to be clarified.

It is noteworthy that TrkB fusions appear almost exclusively in neurogenic tumours. To date, only one case of TrkB fusion has been observed in lung adenocarcinoma (LUAD) (*TRIM24-NTRK2*) and head and neck squamous cell carcinoma (*PAN3-NTRK2*) [38]. In most cases, TrkB fusions occur at different frequencies in low- and high-grade gliomas. Among paediatric thigh-grade gliomas, *AGBL4* and *VCL* have been identified as the gene partners at a relative higher frequency (1–5%) in diffuse midline glioma, H3 K27-altered (H3 K27M-mt DMG), previously named diffuse intrinsic pontine glioma [38,42]. Other partners, such as *BCR*, *AFAP1*, *SQSTM1*, *NACC2*, and *QKI*, can appear at a low frequency (<1%) in glioblastoma (GBM), pilocytic astrocytoma, and other low-grade gliomas

Table 1. *NTRK2* fusions identified in neurogenic tumours by relative frequency

Tumour type	Fusion frequency	Fusion partner	Detection method	References
H3 K27M-mt DMG	4%	*AGBL4*	WGS	[38]
		VCL		[38]
GBM	0.26%	*GKAP*	RNA-seq	[48]
		KCTD8		[48]
		TBC1D2		[48]
		NOS1AP		
JPA	3.1%	*QKI*	WGS	[39]
		NACC2		[39]
LGG	0.22%	*SQSTM1*	RNA-seq	[43]
	0.43%	*AFAP1*		[43]
	0.26%	*VCAN*		[48]
Ganglioglioma	1.1%	*SLMAP*	RNA-seq	[44]
DNET	2.4%	*NAV1*		[44]

H3 K27M-mt DMG, diffuse midline glioma, H3 K27M-mutant; JPA, juvenile pilocytic astrocytoma; LGG, low-grade glioma; DNET, dysembryoplastic neuroepithelial tumour; WGS, whole genome sequencing; RNA-seq, RNA sequencing.

[14,43–48] (Table 1). As the accuracy and sensitivity of detection techniques have improved, it is believed that novel TrkB fusions will be detected in tumours of neural origin. Current techniques for detecting TRK fusions mainly include immunohistochemistry [45], fluorescence *in situ* hybridisation (FISH) [49], reverse transcription polymerase chain reaction (RT-PCR) [50], and next-generation sequencing (NGS) using DNA or RNA [51]. Given the low frequency of TrkB fusion in neuro-derived tumours, the inclusion of the *NTRK* gene in RNA-based NGS analysis is recommended with high specificity [51,52].

Ligand-dependent activation

Under normal circumstances, TrkB is activated mainly by ligand binding, and abnormalities of activation may also lead to dysregulation of TrkB signalling and thereby promote tumour development. This abnormal activation, primarily due to the overexpression of the ligand or receptor, was first identified in NB, a tumour originating from the neural crista-derived sympathetic system [53]. Generally, TrkB is significantly overexpressed in aggressive NB and frequently in association with *MYCN* oncogene amplification, which further indicates a poor prognosis for the patient [54]. It has been established that BDNF/TrkB signalling activates downstream pathways and promotes tumour progression in TrkB-expressing NB [54]. TrkB overexpression also protected NB cells from antitumour agent-induced apoptosis. It has been reported that BDNF/TrkB signalling increases the survival of NB cells treated with cisplatin, etoposide, and vinblastine in a dose-dependent manner by activating the AKT pathway [55–57]. In addition, TrkB overexpression is associated with the tumour autocrine HGF/C-Met loop, increasing angiogenesis and the invasive potential of NB, which contributes to the metastatic phenotype [58–60].

BDNF/TrkB overexpression is also detected in gliomas and has been associated with higher grade [61]. Additionally, GBMs have high BDNF and TrkB levels, and Trk-mediated activation of the PI3K and MAPK pathways enhances the viability of brain tumour stem cells from human GBMs, whereas its inhibition suppresses stem cell growth [62]. Moreover, BDNF and TrkB were found to be co-expressed in most cases of medulloblastoma (MB) [63,64] and associated with poor prognosis in patients with sonic hedgehog (SHH) subtype MB [65]. Furthermore, TrkB expression has also been detected in other neurogenic tumours, such as Ewing sarcoma [66,67]. However, how BDNF/TrkB signalling affects the progression of these tumours has not been clarified, and further research is needed.

TrkB gene mutations and splice variants

Previous studies have shown that TRK signalling can also be activated through gene mutations or splice variants in a ligand-independent way. Several somatic TrkB gene mutations have been detected in a variety of tumour types [68–73] (Table 2), including non-small cell lung cancer (NSCLC), acute myeloid leukaemia (AML), LUAD, melanoma [69], and colon adenocarcinoma [74,75]. However, no such mutation has been identified in neurogenic tumours to date. The TrkB splice variant, TrkB.T1, has long been identified in neurogenic tumours; it does not have tyrosine kinase activity, but its extracellular domain is completely homologous to the extracellular domain of TrkB.FL. Therefore, TrkB.T1, as a dominant-negative receptor, can bind to and create heterodimers with TrkB.FL, inhibiting TrkB.FL autophosphorylation and downstream signal activation [76]. An *in vitro* study showed that TrkB.T1 inhibits the growth of SY5Y NB cells [77]. This explains why TrkB.T1 is preferentially expressed in better-differentiated ganglioneuromas and ganglioneuroblastomas with favourable prognosis [54]. Moreover, TrkB.T1 can bind to the Rho guanine nucleotide dissociation inhibitor (Rho GDI) 1 and dissociate it in a BDNF-dependent manner. Then, Rho GDI binds to the small G protein RhoA, regulating the actin cytoskeleton and leading to the inhibition of glioma cell migration [78]. Therefore, overexpression of TrkB.T1 may be a new strategy for the treatment of

Table 2. *NTRK2* mutations in other tumour types

Location	Mutation	Identification	Effect	Tumour type
Extracellular domain	L138F	DNA-seq	Neutral	LUAD
	S167Y	NGS	Neutral	MPN
	A203T	NGS	GOF	MPN
	H245Y	NGS	Neutral	AML
Juxtamembrane domain	R458G	NGS	GOF	MPN
	P507L	DNA-seq	Neutral	Melanoma
Kinase domain	T695I	DNA-seq	LOF	Colorectal cancer
	D751N	DNA-seq	LOF	Colorectal cancer
	M713I	DNA-seq	LOF	NSCLC
	R715G	DNA-seq	LOF	NSCLC
	R734C	DNA-seq	LOF	NSCLC
	V752A	WES	LOF	Unspecified

DNA-seq, DNA sequencing; WES, whole exome sequencing; GOF, gain of function; LOF, loss of function; MPN, myeloproliferative neoplasm.

neurogenic tumours such as NB or glioma. However, a recent study showed that TrkB.T1 can be a predominant isoform in glioma and promote PDGF-induced gliomagenesis, accompanied by upregulation of the PI3K-related pathway [79]. These results suggest that the loss of intracellular kinase domains may play inverse roles in different neurogenic tumours, which indicates possibly more complex underlying mechanisms.

Targeted TrkB inhibition in neurogenic tumours

Because TrkB fusion is regarded as the most common oncogenic activation pathway, there are a number of therapies currently being tested, including selective TRK inhibitors and multi-tyrosinase inhibitors (Table 3 and Figure 3).

Selective TRK inhibitors targeting TrkB fusion

Due to the high homology of the intracellular domain of the TRK receptors and the oncogenic role of TrkA/C fusions, pan-TRK inhibitors have been developed and applied in the treatment of tumours containing TrkA/B/C fusions. To date, larotrectinib (LOXO-101), an inhibitor with a low nanomolar cellular potency against TrkA/B/C, is the only selective TRK inhibitor approved for clinical trials [80]. It was approved by the US Food and Drug Administration (FDA) in November 2018 to treat adult and paediatric patients with solid tumours containing *NTRK* gene fusions. Although larotrectinib has not been preclinically studied in neuro-derived tumours with TrkB fusion, it has been shown to inhibit TRK fusion activity in other tumours, such as LUAD with TrkA fusion (IC_{50}: 59 nM) and AML with TrkC fusion (IC_{50}: <10 nM) [81].

In an earlier clinical trial (NCT02122913, adults, phase 1), larotrectinib showed significant and durable antitumour activities in patients with TRK fusion-positive tumours, including metastatic CNS tumours, primary lung cancers, and peripheral-nerve sheath tumour [82,83]. The characteristic of successful penetration of the blood–brain barrier (BBB) provides the basis for later studies to recruit patients with primary CNS tumours with TRK fusion. In later reported trials (NCT02637687, children, phase 1/2 and NCT02576431, adults and children, phase 2), a total of 33 patients with various primary CNS and PNS tumours with *NTRK* gene fusion were enrolled, including 24 cases with TrkB fusion, 5 cases with TrkA fusion, and 4 cases with TrkC fusion [84]. In these clinical trials, the overall objective response rate for all patients was 79%, but only 30% for neurogenic tumours with a high incidence of neurological adverse reactions [84,85]. These results suggest that larotrectinib is active in patients with primary neurogenic tumours harbouring *NTRK* gene fusion, but the neural microenvironment, such as the interactions between microglia and glial cells, may affect the therapeutic effect [86–88].

Multi-tyrosinase inhibitors targeting TrkB fusion

In addition to selective drugs targeting TRK fusions, many multi-tyrosinase inhibitors have been applied in the last decade. Among them, the most clinically successful compound is entrectinib (RXDX-101), which is considered a first-generation TRK inhibitor together with larotrectinib. This compound inhibits the enzymatic activity of TrkA/B/C at low nanomolar concentrations, as well as potently inhibiting ROS1 and ALK [89]. In August 2019, it became the second TRK inhibitor to receive FDA approval to treat adult and paediatric patients with advanced solid tumours (age >12 years) harbouring *NTRK* and *ROS1* rearrangements [90]. In preclinical trials, entrectinib has shown the ability to inhibit the growth of TrkB-expressing NB cells compared to those without TrkB expression *in vitro* and *in vivo* [91]. In two phase 1 clinical trials (ALKA-372-001 and STARTRK-1), entrectinib exhibited good BBB penetration against tumours that metastasized to the brain [92]. The drug also showed a good tumour reduction effect in another patient with TrkA fusion-positive glioneuronal tumours [93]. However, in an integrated analysis of three phase 1–2 trials, the patient who had a TrkB fusion (2%) did not respond to entrectinib, and the most common serious treatment-related adverse events were nervous system

Table 3. Clinical trials for tumours with *NTRK* fusions

Drugs	Gene targets	NCT number	Phase	Neurogenic tumours	Status
First-generation pan-TRK inhibitors					
LOXO-101 (larotrectinib)	TrkA/B/C	NCT02122913	I	Adult solid tumours	Completed
		NCT04655404	I (early)	Children high-grade glioma	Recruiting
		NCT03834961	II	CNS neoplasm, solid neoplasm	Recruiting
		NCT04879121	II	Locally advanced malignant solid tumours and metastatic solid tumours	Recruiting
		NCT03213704	II	Advanced malignant solid neoplasm, malignant glioma, recurrent CNS neoplasms, childhood ependymoma and medulloblastoma, Ewing sarcoma, glioma, neuroblastoma, peripheral primitive neuroectodermal tumour, refractory CNS neoplasms	Recruiting
		NCT02576431	II	Primary brain tumours, pontine glioma	Recruiting
		NCT02637687	II	Neoplasms, CNS neoplasms	Recruiting
RXDX101 (entrectinib)	TrkA/B/C, ROS1, ALK	NCT02097810	I	Locally advanced solid tumours and metastatic solid tumours	Completed
		NCT02568267	II	Primary brain tumours, adult solid tumour	Recruiting
		NCT02650401	II	CNS tumours, NB, pons glioma, Ewing sarcoma, glioma, MB	Recruiting
Second-generation pan-TRK inhibitors					
LOXO-195 (selitrectinib)	TrkA/B/C	NCT03215511	I/II	Children and adult solid tumours	Active, not recruiting
TPX-0005 (repotrectinib)	TrkA/B/C, ROS1, ALK	NCT04094610	I/II	Locally advanced solid tumours, primary CNS tumours	Recruiting

disorders [94]. Therefore, further attention should be given to the therapeutic effect of this drug on tumours with TrkB fusion and its effect on the development and function of the nervous system in the ongoing phase 2 basket study (STARTRK-2) (Table 3).

Targeting drug resistance to TRK fusion inhibitors

When using the first-generation TRK inhibitors, acquired resistance emerges in some patients, which is mainly caused by secondary point mutations in the tyrosine kinase domains [92,95]. These mutations can occur in the solvent-front, gatekeeper residues, and the xDFG motif of the TRK enzyme. Several compounds have been developed to address this problem [96–99]. Among them, selitrectinib (LOXO-195) and repotrectinib (TPX-0005) have entered clinical trials and are regarded as second-generation TRK inhibitors. Selitrectinib is a constrained analogue of larotrectinib and is effective against resistance mutations that affect both the solvent front and the xDFG motif. To date, it has shown preliminary efficacy in two patients who developed acquired resistance mutations under treatment with larotrectinib [100]. Repotrectinib, like entrectinib, also showed considerable activity against TRK, ALK, and ROS1-rearranged tumours [101]. Repotrectinib can exhibit potent activity against secondary solvent-front mutations and has a good ability to penetrate the BBB.

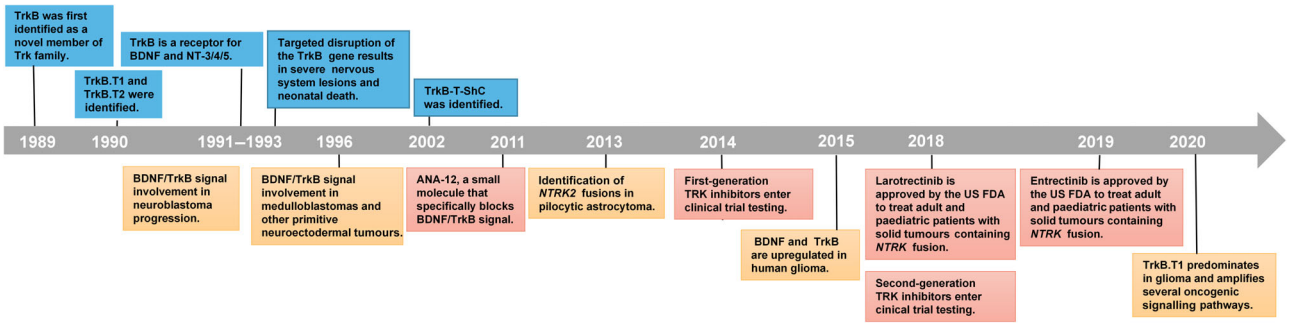

Figure 3. Timeline of key advances relating to TrkB and targeted therapy. Key events relating to the following fields of study are colour coded as follows: identification of TrkB receptor and ligands and their effect on neural development (blue), involvement of the TrkB pathway in neurogenic tumours (yellow), and progress in TrkB targeted therapy (red).

At present, there are no more clinical data on the treatment of neurogenic tumours with TRK fusion for these two drugs, and the related efficacy and safety need to be further clarified. Moreover, drug resistance can cause the activation of the bypass mechanism. This mechanism mainly restores MAPK signal transduction by activating parallel upstream receptor tyrosine kinases or downstream MAPK signal transduction nodes during drug therapy [102]. The specific molecules involved also need to be further explored.

Targeted BDNF/TrkB signal therapy

In addition to the development of inhibitors targeting TRK fusions, inhibitors of the BDNF/TrkB signalling pathway are also being explored. To date, researchers have developed a few small molecule compounds that selectively inhibit TrkB. Among them, ANA-12 is the only drug that has been characterised for anticancer effects in neuro-derived tumours [103]. It can directly and selectively bind to both low- and high-affinity sites on the extracellular domain of TrkB, blocking BDNF-induced cascade signalling without altering other TRK signals. In 2016, Thomaz *et al* utilised this small molecule compound and found pronounced inhibitory effects on paediatric SHH- and 3/4 group-MB cell viability and survival *in vitro* [104] and *in vivo* [105], accompanied by increased cell apoptosis and reduced ERK activity. In addition, MB cells treated with ANA-12 showed morphological alterations consistent with differentiation, elevated neural differentiation marker β-III tubulin levels, and reduced stemness marker Nestin expression. Pinheiro *et al* demonstrated that ANA-12 effectively and dose-dependently inhibits cell proliferation and survival in GBM [106]. In addition, a recent study showed that the combination of ANA-12 and AG 1478, a selective antagonist of EGFR, increased the inhibition of human GBM cell viability more significantly than either inhibitor alone [66].

Taken together, these results provide evidence that selective BDNF/TrkB signalling inhibitors alone or in combination with other receptor inhibitors can be a novel and promising strategy for dealing with BDNF/TrkB-mediated oncogenic events. Other selective TrkB inhibitors, such as cyclotraxin-b, which has anxiolytic properties [107], are also worthy of further exploration for their anticancer effects in neuro-derived tumours or other tumour types.

Conclusions and future perspectives

The TrkB receptor is widely expressed in the CNS and PNS, and its signal activation and conduction play a pivotal role in biological learning, memory, and movement. Dysregulation of receptor activation can lead to some psychiatric disorders and neurogenic tumours [108]. In this paper, we have summarised the abnormalities of TrkB in neural tumours, such as receptor fusion, ligand/receptor overexpression, and gene splicing. Although the relevant mechanisms have been widely explored, some issues still need to be further addressed. First, TrkB activation is often accompanied by other molecular abnormalities, including *MYCN* amplification in aggressive NB, EGFR expression in GBM, and *TP53* mutations in high-grade gliomas. In addition, some gene partners are recurrent in TrkB fusions such as *BCR* and *SPECC1L*. It is still unclear whether the co-existent mechanisms and particular fusion partners affect the response to drugs, which needs to be further elucidated in future clinical trials.

Some TRK inhibitors have been approved by several regulatory agencies for the treatment of TRK fusion-positive cancers based on positive results in early phase trials. However, because TRK receptors are intimately involved in the development and maintenance of the nervous system, some neurological adverse events can be observed in these treatments, such as hyperphagia, dizziness with or without ataxia, and withdrawal pain. In the clinic, these symptoms should be carefully monitored and managed with related pharmacological intervention (such as liraglutide, meclizine, non-steroidal anti-inflammatory agents) and/or dose modification [41]. In addition, the effectiveness and safety of existing targeted drugs for TRK fusion in neuro-derived tumours, especially for TrkB fusion, are lower than those of other tissue-derived tumours. This result suggests that the neuro-microenvironment may have an effect on targeted therapy, which needs to be further explored. Moreover, the exploration of TrkB gene mutations and splice variants in neuro-derived tumours also has a large gap, which requires more attention. Furthermore, since MAPK signal transduction can be restored during drug therapy, MAPK pathway-directed targeted therapy administered alone or in combination with TRK inhibition may represent a more reasonable treatment scheme in the future.

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Author contributions statement

All authors contributed to this review and reviewed the final manuscript.

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