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Review article

Growth factors and their peptide mimetics for treatment of traumatic brain injury

Emily Atkinson [a,b], Rachael Dickman [a,*]

[a] School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, UK
[b] UCL Centre for Nerve Engineering, University College London, 29-39 Brunswick Square, London WC1N 1AX, UK

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of disability in adults, caused by a physical insult damaging the brain. Growth factor-based therapies have the potential to reduce the effects of secondary injury and improve outcomes by providing neuroprotection against glutamate excitotoxicity, oxidative damage, hypoxia, and ischemia, as well as promoting neurite outgrowth and the formation of new blood vessels. Despite promising evidence in preclinical studies, few neurotrophic factors have been tested in clinical trials for TBI. Translation to the clinic is not trivial and is limited by the short *in vivo* half-life of the protein, the inability to cross the blood–brain barrier and human delivery systems. Synthetic peptide mimetics have the potential to be used in place of recombinant growth factors, activating the same downstream signalling pathways, with a decrease in size and more favourable pharmacokinetic properties. In this review, we will discuss growth factors with the potential to modulate damage caused by secondary injury mechanisms following a traumatic brain injury that have been trialled in other indications including spinal cord injury, stroke and neurodegenerative diseases. Peptide mimetics of nerve growth factor (NGF), hepatocyte growth factor (HGF), glial cell line-derived growth factor (GDNF), brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) will be highlighted, most of which have not yet been tested in preclinical or clinical models of TBI.

1. Introduction

1.1. Traumatic brain injury

Traumatic Brain Injury (TBI) can be defined as a severe head injury resulting from an external force that disrupts normal brain function. In the UK, TBI is the most common cause of death and disability in those under 40 and is also an international health concern with approximately 69 million individuals suffering a TBI each year worldwide.[1] Over three million individuals who have suffered a TBI experience further complications including neurological dysfunction and long-term disability, leading to high socioeconomic costs.[2] The main causes of injury include falls, motor vehicle crashes, contact sports, firearm-related incidents and war-related injuries. Following the injury, the severity is classified using

Abbreviations: 6-OHDA, 6-hydroxydopamine; AD, Alzhiemer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; BBB, blood–brain barrier; BDNF, brain derived growth factor; CAM, cell adhesion molecules; CDNF, cerebral dopaminergic neurotrophic factor; CNS, central nervous system; CREB, cAMP response element-binding protein; DNSP, dopamine neuron stimulating peptide; EPO, erythropoietin; ERK, extracellular signal-regulated kinase; Fc, fragment crystallisable; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FN3, fibronectin type III; GDNF, glial cell line-derived neurotrophic factor; GFL, GDNF family ligands; GFR, GDNF family receptor; HGF, hepatocyte growth factor; hGH, human growth hormone; IGF, insulin-like growth factor; K_d, dissociation constant; LPS, lipopolysaccharide; MAPK, MEK, mitogen-activated protein kinase; Met, mesenchymal-epithelial transition factor; mTor, mammalian target of rapamycin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NCAM, neural cell adhesion molecule; NCT, national clinical trial; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; Np, neuroplastin; NR2B, *N*-methyl D-aspartate receptor subtype 2B; NT-3, neurotrophin-3; $p75^{NTR}$, pan-neurotrophin receptor; PD, Parkinson's disease; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PDNF, Parasite-derived neurotrophic factor; PI3K, phosphoninositide-3 kinase; PLC-γ1, phospholipase C-γ; RaPID, random non-standard peptide integrated discovery; Ras, (from) rat sarcoma virus; RET, rearranged upon translation receptor; SCI, spinal cord injury; STaMPtide, single-chain tandem macrocyclic peptide; STAT, signal transducer and activator of transcription; TBI, traumatic brain injury; TGF, transforming growth factor; Trk, tropomyosin kinase receptor; VEGF, vascular endothelial growth factor.

* Corresponding author.
E-mail addresses: emily.atkinson.20@ucl.ac.uk (E. Atkinson), rachael.dickman.13@ucl.ac.uk (R. Dickman).

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the Glasgow Coma Scale, based on the patient's ability to speak, move their body, and make eye movements, dictating the level of monitoring and treatment required.[3]

Treatment options are currently limited and focus on symptom moderation. The lack of treatment options available has directed research into alternative therapeutic strategies in regenerative medicine, including the use of neuroprotective growth factors and their mimetics. A limited number of growth factors have been tested in clinical trials for TBI including nerve growth factor (NGF), however many other relevant growth factors have been tested in other central nervous system (CNS) disorders with related pathologies, including spinal cord injury (SCI), stroke, Parkinson's Disease (PD) and Alzheimer's Disease (AD). Many growth factors do not meet the clinical trial endpoint due to unfavourable pharmacological properties, with peptide growth factor mimetics a favourable alternative. This review highlights promising growth factors and their mimetics with potential applications in the treatment of secondary injury following a TBI; including nerve growth factor (NGF), hepatocyte growth factor (HGF), glial cell-line derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF).

1.2. TBI pathology

Although often discussed as a single entity, TBI has a heterogeneous, complex pathology which can be divided into two injury mechanisms: primary and secondary injury.[4] Primary injury is the direct result of the head injury which can trigger almost immediate non-specific cell death, cerebral oedema, and vascular disruption due to the dissipation of energy within the brain matter. The secondary injury is the body's physiological response to the primary injury, progressing in the subsequent minutes to months or even up to years and impacting otherwise undamaged cells (Fig. 1). The delay prior to the secondary injury provides a window of opportunity for administration of a neuroprotective therapeutic. This would have potential to prevent further cell death and injury exacerbation from the biochemical events that follow.[5] Examples of secondary injury which can be targeted with growth factor therapeutics include blood–brain barrier disturbance, oxidative stress, inflammation, mitochondrial dysfunction, induced cell death and glutamate excitotoxicity, and have been reviewed elsewhere.[6–7]

1.3. Current treatment options

Treatment for TBI is focused on symptom moderation and patient stabilisation but is contingent on the severity of the injury.[7] Those sustaining a mild injury or concussion are advised to recover at home following a medical check-up, whereas those with a moderate to severe injury may require intense and ongoing medical support. Emergency care after a moderate to severe brain injury is centred around stabilising the patient to ensure the brain receives sufficient oxygen and blood flow. Pain should be carefully managed with small doses of opioids, to avoid an increase in intracranial pressure,[10] which is carefully monitored. In some cases, surgical intervention to open a hole in the skull is required to relieve pressure and drain excess fluid. High intracranial pressure can lead to reduced cerebral perfusion, increasing the likelihood of ischemia and therefore cell death.[11] In addition, removing blood clots and segments of the skull may help the healing process and further rehabilitation is often required. Depending on the individual, drugs can also be offered including anticonvulsants to treat seizures, diuretics to prevent fluid build-up and anti-coagulants to prevent blood clots, however limited options are available to treat secondary injury.[12] The current treatment options are suboptimal and there is a need for more advanced neuroprotective therapies on the market to prevent further damage during the secondary injury caused by TBI. Promising areas of research include stem cell therapies, gene therapies, and growth factor therapies.[13–16] This review will focus on the current preclinical and clinical research on growth factors and their mimetics with potential applications in TBI, though few growth factor mimetics have been tested for this indication to date. We aim to demonstrate that growth factors and mimetics which display neuroregenerative potential or neuroprotective effects on secondary injury, particularly in *in vivo* models of stroke, SCI, ALS, PD or AD, should also be investigated as TBI therapeutics.

2. Growth factors

Growth factors are endogenous signalling proteins secreted by cells for regeneration and tissue repair and are therefore perfect candidates for regenerative medicine. The immature brain requires a plethora of growth factors for development but these factors are either not expressed or expressed in much lower concentrations in the adult brain. It has also been shown that after injury, particular growth factors and receptors are transiently upregulated and the introduction of growth

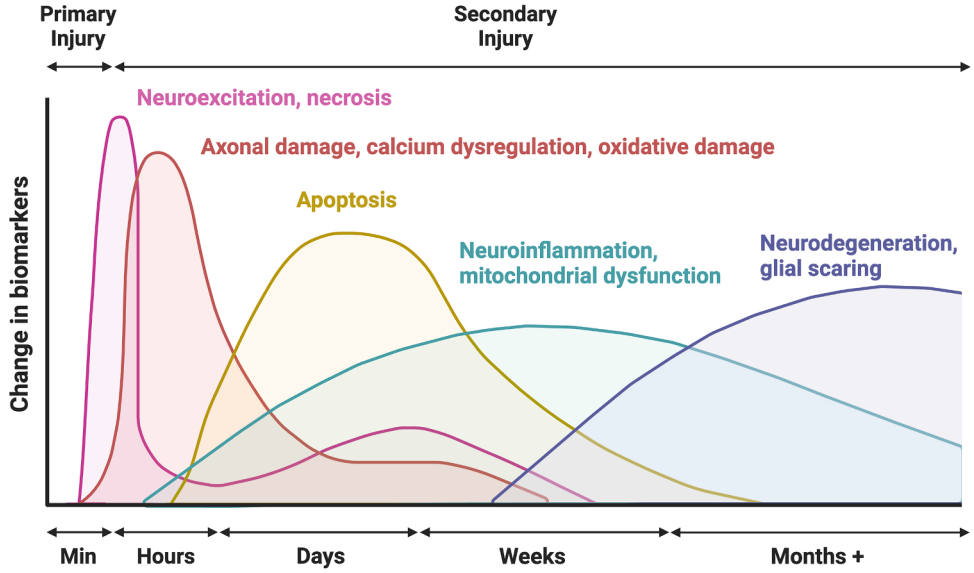

Fig. 1. Mechanisms of secondary injury. Figure adapted from Buhlman et al[8] and Bramlett et al.[9]

factors may be beneficial to assist in neuroregeneration (see Sections 2.1.1.-2.1.6.). Successful growth factor therapies with FDA approval are currently on the market for bone regeneration,[17] and chronic diabetic wounds,[18] and neurotrophic keratitis (clinical trials NCT04293549, NCT03836859, NCT02101281, NCT03019627), demonstrating their clinical potential. Recombinant growth factors have been exploited in both preclinical and clinical trials for both TBI and neurodegenerative diseases, but despite promising preclinical results, this has not translated to clinical success.[19–22]

2.1. GFs identified with the potential to treat TBI

A broad range of growth factors are suitable for the treatment of TBI due to the complex and multistep pathology. As aforementioned, neuroprotective therapy may be administered during the window following the primary injury to prevent further cell death, however very few neurotrophic factors have reached clinical trials for this indication. Some of the first growth factors tested in human clinical trials for TBI include recombinant human growth hormone (hGH, NCT00766038), erythropoietin (EPO, NCT00987454) and nerve growth factor (NGF, NCT01212679). Both hGH and EPO were delivered subcutaneously in phase II and III clinical trials respectively, and NGF was delivered intranasally to bypass the blood brain barrier (BBB). Furthermore, other growth factors have been clinically trialled in other indications with relevant pathologies, such as ischemic stroke, SCI, amyotrophic lateral sclerosis (ALS), PD and AD. It is predicted that these growth factors and

Table 1
Summary of exogenous growth factors delivered to the CNS in clinical trials with the potential to modulate secondary injury following TBI.

Growth Factor	Properties Beneficial to Secondary Injury	Disease Application	Delivery Method	Clinical Trial	End Date	Outcome
NGF	Anti-inflammatory Neuroprotective Pro-angiogenic Upregulates Antioxidants [37–39]	Traumatic Brain Injury	Intranasal	Phase II NCT01212679	2017	Not reported.
		Acute Ischemic Stroke	Intranasal	Phase IV NCT03686163	2020	Not reported.
HGF	Neuroprotective Anti-inflammatory Anti-fibrotic	Amyotrophic Lateral Sclerosis	Intrathecal injection (HGF minus five residues)	Phase I UMIN000007062	2019	No serious adverse effects, yet to assess the efficacy.
	Anti-apoptotic Pro-angiogenic Reduce glial scarring [49,50,52]	Spinal Cord Injury	Intrathecal injection (KP-100IT)	Phase I/II NCT0293334	2020	No serious adverse effects. Improvement in motor score.
				Phase III NCT04475224	2023	Recruiting.
GDNF	Neuroprotective Neuroregenerative Mitogenic [62,85–87]	Parkinson's Disease	Intracerebroventricular infusion	Phase I NCT00006488	2003	No improvement in symptoms and adverse side effects observed.[88]
			Intraputaminal infusion	Phase II NCT03652363	2003	Improvements in motor functions with GDNF and placebo.[89]
			Intraputaminal infusion	Phase II	2006	Improvements in motor functions with GDNF and placebo.[90]
			Intraputaminal infusion	Phase II	2007	Improvements in motor functions with GDNF and placebo.[59,91]
			Intraputaminal infusion	Phase II NCT03652363	2019	No significant change in motor scores. Elevated levels of dopamine after 8 weeks. GDNF recipients had continued improvement in motor function with ongoing treatment.[92]
CDNF	Reduces haemorrhagic lesions Reduces peri-focal edema Antioxidant Anti-inflammatory Neuroprotective [93]	Parkinson's Disease	Intraputaminal infusion	Phase I/II NCT03295786	2023	Safe and well tolerated. Early signs of efficacy.
BDNF	Neuroprotective Anti-inflammatory [70]	Amyotrophic Lateral Sclerosis	Intrathecal infusion	Phase I/II/III	1999	Pilot study demonstrated BDNF increased survival and prevented the loss of pulmonary function in ALS patients.[46,94] Phase III failed to meet primary endpoints with no significant differences to the placebo.[66]
PDGF-B	Anti-inflammatory Neuroprotective Inhibits endoplasmic reticulum stress Inhibits autophagy [75,95,96]	Parkinson's Disease	Intracerebroventricular infusion	Phase I/IIa NCT00866502	2015	Confirmed safety. Improvement in motor function in experimental and placebo groups.[76]
				NCT01807338	–	Follow up study to assess safety and tolerability three years on from NCT00866502. No results reported.
				NCT02408562	–	Follow up study from NCT00866502 to assess repeated dosing. Terminated due to supply issues with the delivery pump.
FGF1	Anti-apoptotic Mitogenic (fibroblasts) Pro-angiogenic Neuroprotective Neuroregenerative [83,97]	Spinal Cord Injury	Novel biodegradable device containing FGF-1 implanted into the spinal cord	Phase I NCT02490501	2020	Results not reported.
		Parkinson's Disease	Intranasal	Phase I NCT05493462	–	Results not reported.

their mimetics could also be beneficial in the treatment of TBI (Table 1).

Ischemic stroke is caused by a lack of blood supply leading to a hypoxic environment in the brain, causing metabolic changes, cell damage and death. Biochemical events include inflammation, increased extracellular calcium levels, excitotoxicity, impairment of the blood–-brain barrier and free-radical mediated toxicity, all of which are also linked to the pathology of a TBI.[23–24] Ischemic stroke and secondary injury following TBI are also intrinsically linked as TBI has been identified as a risk factor for stroke, therefore growth factors considered for neuroprotection and regeneration in stroke could also be considered for TBI.[25] This includes NGF which has recently been tested in clinical trials for both TBI and ischemic stroke.

Growth factors in clinical trials for SCI (HGF and FGF) and their mimetics will be also explored. SCI is the result of instantaneous physical damage to the spinal cord resulting in death and damage to cells of the CNS. The resulting cascade of events results in further damage including ischemia, oxidative stress, inflammation, glutamate excitotoxicity and activation of apoptotic pathways.[26] These mechanisms of secondary injury also occur following TBI and therefore, growth factors with therapeutic potential for SCI may also be considered for the treatment of TBI.

Growth factors in clinical trials for the most common neurodegenerative diseases, PD, AD and ALS, have also been considered, including HGF, GDNF, CDNF, BDNF, FGF and PDGF. Glutamate excitotoxicity, neuroinflammation and oxidative stress are implicated in both neurodegenerative disease and secondary injury following TBI. It is predicted that reactive oxygen species mediate glutamate excitotoxicity and inflammation, therefore growth factors that can protect against these types of cell-mediated death in neurodegeneration models may also be beneficial in TBI models.[27–28] Furthermore, in patients with TBI there is a clinical correlation with neurodegenerative disease.[29]

Other growth factors have demonstrated potential for the treatment of TBI in preclinical and/or clinical settings, such as hGH, EPO, vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF), which have been reviewed elsewhere.[30] This review will discuss growth factors that have been delivered locally to the CNS in clinical trials for the listed indications, including via local injection to the brain or spinal cord and intranasal delivery. This comprises NGF, HGF, GDNF, BDNF, PDGF and FGF (Fig. 2).

2.1.1. *Nerve growth factor (NGF)*

NGF was the first neurotrophic factor discovered in the 1950s and is fundamental for the development of neurons in both the peripheral and central nervous systems. NGF is the only growth factor discussed in this review that has been delivered in a clinical trial directly for the treatment of TBI.[31] The neurotrophin elicits neuroprotective and pro-survival properties in response to binding to tropomyosin kinase receptor A (TrkA), stimulating canonical signalling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide-3 kinase (PI3K), protein kinase B (Akt) and the phospholipase C-γ (PLC- γ1) pathway. With a lower affinity, NGF also binds to the p75 pan-neurotrophin receptor ($p75^{NTR}$) which can activate further signalling pathways, including Jun kinase and nuclear factor kappa light chain enhancer of activated B cells (NF-κB) cascades which induce apoptosis in the absence of TrkA.[32]

Several case studies reported positive outcomes following the delivery of recombinant NGF following traumatic brain injuries in children.[33–34] In one example, murine NGF was delivered to one child intranasally, following a severe TBI post-cardiac arrest. The patient received four cycles of intranasal NGF (0.1 mg/kg, twice a day for 10 days) and showed improvements in cognitive and motor functions with no side effects reported. Preliminary findings from this study demonstrate NGF is a safe and promising neurotrophic factor for rescuing neurons and improving motor function following brain damage.[33] More recently, a clinical trial was completed whereby 20 μg/day NGF was delivered to patients intranasally, beginning 24–72 h post-TBI and continued for 2 weeks (Phase II, NCT01212679, 2017), though results have not yet been reported.

In the presence of NGF, astrocytes are directed towards a neuroprotective and anti-inflammatory phenotype,[35] which could potentially reduce the negative effects associated with excessive glial scarring following TBI. Furthermore, NGF is pro-angiogenic, increasing the

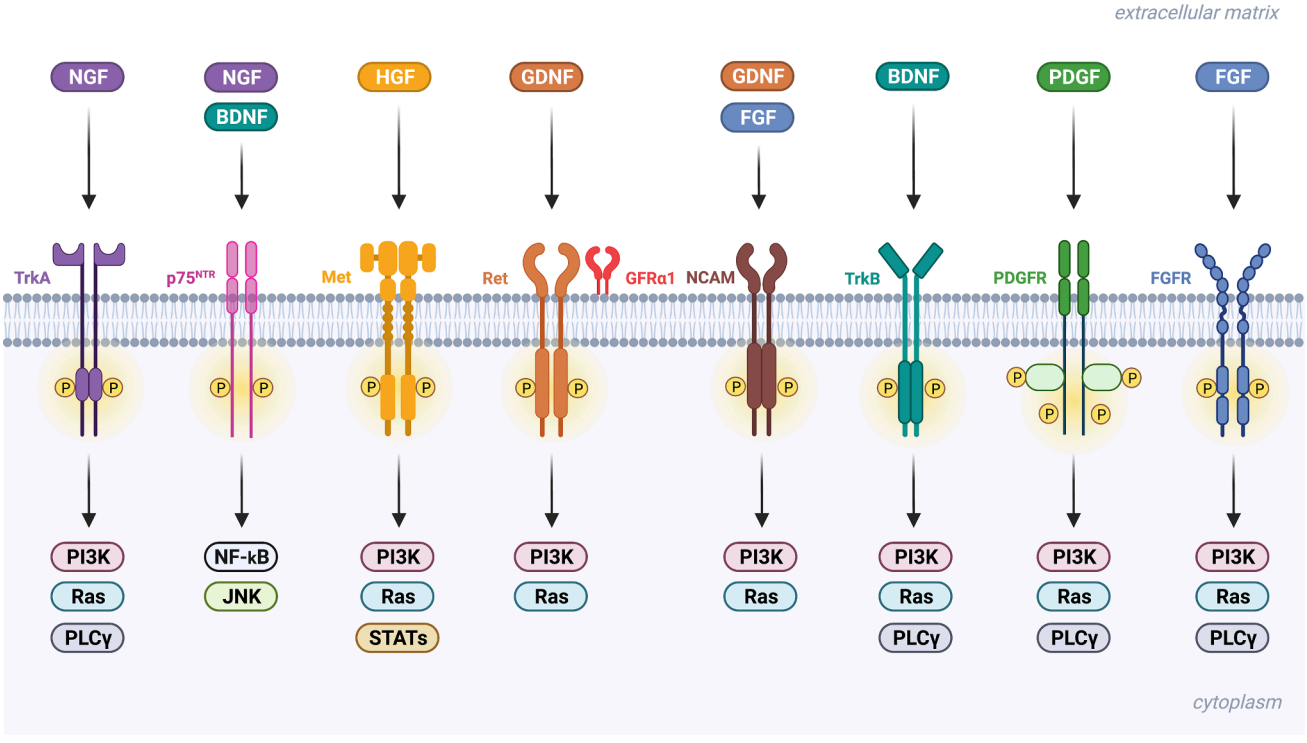

Fig. 2. Summary of growth factors and signalling pathways activated for treatment of secondary injury in TBI.

production of vascular endothelial growth factor (VEGF) and promoting endothelial cell proliferation and migration.[36–37] The formation of new blood vessels may be important to reduce hypoxia following ruptures caused by TBI. A detailed overview of clinical uses and neuroprotective mechanisms of NGF, including for TBI and other CNS disorders, has been published recently.[38–39]

2.1.2. Hepatocyte growth factor

Hepatocyte growth factor (HGF), also known as scatter factor, is a 728 amino acid protein that exerts biological activity upon binding to the tyrosine kinase mesenchymal-epithelial transition factor (Met) receptor.[40] HGF was initially isolated as a liver mitogen and motility factor for epithelial cells but is also a neurotrophic factor of interest for its role within the CNS. The Met receptor is not only expressed on endothelial and epithelial cells but also on neural precursors and neurons, and is essential in the development of the nervous system.[41] Upon HGF binding to the Met receptor, downstream signalling pathways are activated, including the PI3K–Akt pathway, MAPK cascades and signal transducer and activator or transcription molecules (STATs) which all lead to cell proliferation, survival and migration.[42] The role of HGF in promoting neuron survival in neurodegenerative disease and brain injury has been recently reviewed, with evidence that HGF exerts anti-apoptotic, anti-fibrotic, anti-inflammatory, pro-angiogenic, and immune-modulatory actions and therefore would be a candidate for TBI treatment.[43]

The Met receptor is upregulated the day after a SCI, however there is not an equivalent HGF increase until a later time point.[44] HGF treatment has been extensively studied in preclinical models of SCI, demonstrating therapeutic potential in both rodent and non-human primate SCI models whereby improvement in functional motor recovery was observed due to neuroprotection of the corticospinal fibres and myelination.[45] Due to the efficacy demonstrated in the preclinical results, HGF was advanced to clinical trials, with Phase III currently recruiting participants, following a Phase I/II study which demonstrated the safety and efficacy of the therapy (NCT02193334).[46] Researchers leading this clinical trial have reviewed the application of HGF for acute spinal cord injury from preclinical to clinical trials.[47] Furthermore, in a separate study, recombinant human HGF with a five-residue deletion (KP-100) was recently evaluated in phase I clinical trial for ALS (UMIN000007062) where it was considered safe for further investigation, with no severe side effects reported.[48]

As HGF has shown safety in clinical trials for ALS and efficacy in clinical trials for SCI, it can be predicted that HGF could also be an appropriate treatment for TBI. In the preclinical non-human primate SCI study discussed, functional recovery was observed due to significant neuroprotection following secondary injury, as less cell death occurred compared with the control.[45] The neurotrophic effects and corresponding signalling pathways of HGF in the treatment of SCI, including anti-inflammatory, anti-fibrotic, anti-apoptotic effects, and angiogenic properties, have been reviewed.[49] In addition, HGF reduces astrocytic scar formation and promotes axonal growth by blocking the secretion of transforming growth factor (TGF) β1 and TGFβ2 from activated astrocytes.[50] This may be an important mechanism for TBI, as glial scarring forms a mechanical barrier and prevents tissue regeneration and therefore may inhibit recovery.[51] Another common result of TBI is ischemia and apoptosis. In rat models of cerebral ischemia, HGF reduced the infarction volume in a dose-dependent manner.[52]

2.1.3. Glial cell line-derived neurotrophic factor

Glial cell line-derived neurotrophic factor (GDNF) comprises 134 amino acids and was originally isolated from a rat glioma cell line as a potent neurotrophic factor, facilitating the survival of dopaminergic neurons.[53] It was later shown to have a profound impact on other populations of neurons, both in the CNS and peripheral nervous system.[54] GDNF exerts its neuroprotective properties by binding to co-receptor GDNF family receptor alpha 1 (GFRα-1) to form a complex which binds to the rearranged during transfection (RET) receptor. The resulting downstream intracellular signalling pathways include PI3K and MAPK/extracellular signal-regulated kinase (ERK) pathways. These pathways promote cell survival and prevent apoptosis by regulating caspase 3, caspase 9, proapoptotic factors and B-cell lymphoma 2 activation, as well as influence cell differentiation, migration, proliferation, chemotaxis, synaptic plasticity and neurite outgrowth.[55–56]

Following preclinical studies demonstrating the neuroprotective role of GDNF on dopaminergic neurons,[57] several clinical trials across the last decade have investigated whether the local administration of exogenous GDNF to the brain could improve symptoms for patients with PD, with variable success.[58] In the most recent completed clinical trial (Bristol 3), GDNF was directly infused into the brains of patients with late-stage PD monthly (NCT03652363). Though the study resulted in a decrease in Unified Parkinson's Disease Rating Score (UPDRS III), suggesting an improvement in motor abilities, this was not significant compared with the placebo. Further, elevated levels of dopamine were present in the putamen of patients receiving GDNF after 8 weeks, suggesting GDNF has a biological impact on dopaminergic neurons and still remains a promising, viable treatment option for the treatment of PD.[59] In addition, another GDNF-family growth factor, cerebral dopamine neurotrophic factor (CDNF), has been shown to provide neuroprotection from endoplasmic reticulum stress, dissolve intracellular α-synuclein aggregates and regulate unfolded protein response to stress *in vitro*, and has recently completed a phase I clinical trial that demonstrated safety and early efficacy following intraputaminal infusion for patients with advanced PD (NCT03295786).[60–61]

Though a lot of research has focussed on GDNF leading to dopaminergic cell survival in the context of PD, it is known to have potent neurotrophic functions on a variety of other neurons, and therefore has the potential to protect neurons in the brain from secondary damage following TBI.[56] Most notably, GDNF prevents excitatory neuronal death by reducing the calcium influx mediated by the (*N*-methyl-D-aspartate)-receptor (NMDA),[62] and therefore has the potential to reduce cell death caused by glutamate excitotoxicity in TBI.

2.1.4. Brain-derived neurotrophic factor

Brain-derived Neurotrophic factor (BDNF) is a protein containing 116 amino acids, originally found to support chick embryo dorsal root ganglia survival.[63] BDNF has essential roles in neuronal survival and differentiation during development and synaptic plasticity in the developed brain. The growth factor exerts neuroprotective properties by binding to the tropomyosin-related kinase-B receptor (TrkB) with a K_d = ~9.9 nM, leading to signalling down the MAPK/ERK pathway supporting synaptic plasticity and neuronal function, and the PI3K/mTOR pathway promoting neuronal survival.[64] When present at high concentrations, BDNF also binds to $p75^{NTR}$ with a K_d = ~1.0 nM, which is associated with apoptosis via c-Jun *N*-terminal kinases signalling and neuroprotection through NF-kB activation.[65]

Early clinical trials from the 1990s demonstrated the therapeutic potential of BDNF to aid survival in 1,135 patients with ALS. Results from phase I and II of the study suggested BDNF increased survival and prevented the loss of pulmonary function, however in phase III this was not statistically significant from the placebo condition. Nevertheless, a subset of patients with early respiratory impairment showed statistically significant benefits, demonstrating the potential for BDNF in certain conditions with alternative delivery methods and higher doses of BDNF.[66] Furthermore, there is an ongoing first-in-human trial investigating the safety of a gene therapy designed to deliver the BDNF gene to the brain (NCT05040217). Twelve participants with either AD or mild cognitive impairment will undergo a one-time procedure, and it is predicted that the increase in BDNF will prevent cell loss. BDNF for the treatment of AD and its pharmaceutical potential has been recently reviewed.[67]

Within a couple of hours following TBI, mRNA expression levels for BDNF transiently increase, however begin to decrease from 24 h post-injury.[68–69] It is suggested that BDNF is upregulated to attenuate the

secondary injury due to its neuroprotective properties and therefore could be delivered exogenously to maximise this effect. BDNF treatment following brain injuries has been reviewed,[70–71] with preclinical studies specifically highlighting the beneficial anti-inflammatory properties that are important following injury.

2.1.5. Platelet-derived growth factor

The PDGF family of growth factors contain five disulfide-linked dimers, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD, acting on two tyrosine kinase receptors, PDGF receptor α (PDBFR-α) and PDGF receptor β (PDGFR-β).[72–73] PDGFR-α binds to the A-, B-, and C-chains of PDGF, whereas PDGFR-β binds specifically to the PDGF-BB and DD-chains, both stimulating downstream signalling pathways including PI3K and Ras.[74] PDGF family signalling is known to play a role in neurogenesis, cell survival, cell differentiation and blood vessel formation in the CNS.[75]

A recombinant PDGF solution (sNN0031) was delivered to patients with moderate PD in a first-in-human phase I/IIa clinical trial via intracerebroventricular administration using a novel delivery device (NCT00866502). The study confirmed that sNN0031 was safe and after a 3-month follow-up, patients receiving the highest dose showed improvement in dopamine transporter binding, whereas the signal declined in those receiving lower doses and in the placebo condition. All patients, including those in the placebo condition, showed an improvement in their motor function. All but one patient reported adverse effects, though these were associated with the delivery pump, rather than the growth factor.[76] A follow-up study on the tolerability and safety of sNN0031 was completed three years on (NCT01807338), however no results were reported. A further phase I/II study was planned to study the tolerability of repeat intracerebroventricular administration of sNN0031 in patients with PD, however this was terminated due to supply issues with the infusion system (NCT02408562). Further studies are needed to determine whether clinical improvement from the first study was related to PDGF.

Relating to secondary injury following TBI, PDGF-B/PDGFR-β signalling has a critical role in angiogenesis, vascularisation and neuroprotection following cerebral ischemia.[77] Furthermore, PDGF-BB has demonstrated neuroprotection of primary hippocampal neurons from glutamate-induced excitotoxicity by selectively inhibiting NMDA receptor subtype 2B (NR2B)-containing NMDA receptors.[78] It is well-known that both glutamate toxicity and ischemia lead to cell death following TBI, therefore PDGFs, and PDGF-B in particular, are of interest in TBI treatment.

2.1.6. Fibroblast growth factors

Fibroblast growth factors (FGFs) are crucial signalling proteins involved in the development, maintenance and repair of the brain. Twenty-three FGFs have been identified, with ten discovered in the brain.[79] FGFs act as dimers, linked by heparan sulfate proteoglycan molecule, predominantly signalling through four tyrosine kinase receptors: FGFR1, FGFR2, FGFR3, and FGFR4. Upon receptor binding, FGFs activate several signal transduction pathways. Mechanisms of FGF signalling in the CNS have been reviewed elsewhere.[80–81] FDF1 (acidic) and FGF2 (basic) are expressed in neurons and glial cells in the CNS and are involved in synaptic plasticity.[82] Both are widely researched neurotrophic factors promoting neuron survival, proliferation and migration and therefore will be the main focus here.

FGF1 is the only FGF family member to have been tested in clinical trials. It is currently in a phase I/II randomised, rehabilitation-controlled clinical trial (NCT02490501) for patients with spinal cord injury. Subjects will undergo surgical implantation of a biodegradable device (SC0806) containing herapin-activated FGF1 and nerve implants, and the motor-evoked potential score of participants and adverse events will be recorded over a period of 18 months. The results of this trial have not yet been reported. Additionally, a phase I clinical trial is planned but not yet recruiting for the intranasal delivery of human FGF1 to patients with PD (NCT05493462). The study will involve the delivery of a low dose (6 μg/kg) of FGF1, followed by a high dose (12 μg/kg) to measure the safety, tolerability and efficacy of the two dose levels.

Various FGFs have demonstrated positive therapeutic outcomes in animal models of TBI, with significant literature focusing on FGF1 and FGF2. In one example, FGF1 preserved the blood–brain-barrier integrity in a mouse model of TBI, by activating the anti-apoptotic PI3K-Akt-Rac1 pathway while inhibiting the RhoA pathway.[83] FGF2 was also neuroprotective when delivered alone and in combination with VEGF in a rat model of TBI, though there was no significant difference between the combination and individual growth factors, suggesting FGF alone was just as effective.[22,84]

3. Peptide growth factor mimetics

Despite growth factor therapies showing promising results in preclinical studies, translation to the clinic is not simple. Translation is often limited by the delivery system in humans, the expense of purchasing recombinant growth factors, variability between batches, the short *in vivo* half-life of the protein (minutes-hours) and diffusion of the growth factor from the target delivery site. Using supraphysiological doses has not overcome issues with the short half-life and diffusion from the delivery site, and led to severe side effects in many cases, therefore an alternative solution must be proposed.[14] To address these issues, synthetic mimetics of growth factors could be used as alternative therapies.

Many different types of growth factor mimetics have been reported, including small molecules, oligonucleotides, peptides, peptoids and proteins. Each approach can be used to create mimetics with potential applications in neuroprotection and regeneration. Here, we have focussed on peptides. Peptide growth factor mimetics reported in the literature are commonly derived from the sequence of the growth factor itself or generated by peptide display methods. Peptides have some key advantages over other types of mimetic, including lower immunogenicity, improved pharmacokinetics and cheaper production than proteins, coupled with the potential for increased interaction with large receptor surfaces compared with small molecules.[98] Decreasing the size of the active agent also has the advantage that delivery formulations can often be loaded with higher doses, meaning that longer-term treatments become possible without repeated dosing.

For the purposes of this review, we have used a broad definition of peptide mimetic. We have considered a peptide growth factor mimetic to be a peptide which is able to mimic any of the biological activity of a growth factor, including any of the molecular or pharmacological mechanisms. For example, this could be by mimicking the shape of the growth factor and the binding interactions it forms with its receptor, or by activating any of the same cellular signalling pathways as the growth factor via an alternative or allosteric mechanism. The mimetics described below have all demonstrated the ability to activate growth factor receptor signalling pathways and/or promote cell survival and growth. These peptides therefore have potential as therapeutics for TBI, though to our knowledge in all but two cases this remains to be demonstrated experimentally. In addition to peptide mimetics, we have also briefly highlighted examples of other classes of receptor agonist, and examples of peptide antagonists which demonstrate tight binding to the target receptor without causing receptor activation.

3.1. NGF

Recent encouraging evidence from the clinical use of NGF to treat TBI in a child[33] suggests that mimetics of this growth factor may have applications in neuroprotection and regeneration following TBI. Several promising peptide mimetics of NGF have been reported to date, some of those discussed here have also been reviewed recently elsewhere (Fig. 3).[99–100]

Many of the reported NGF mimetics are based on the β-turn

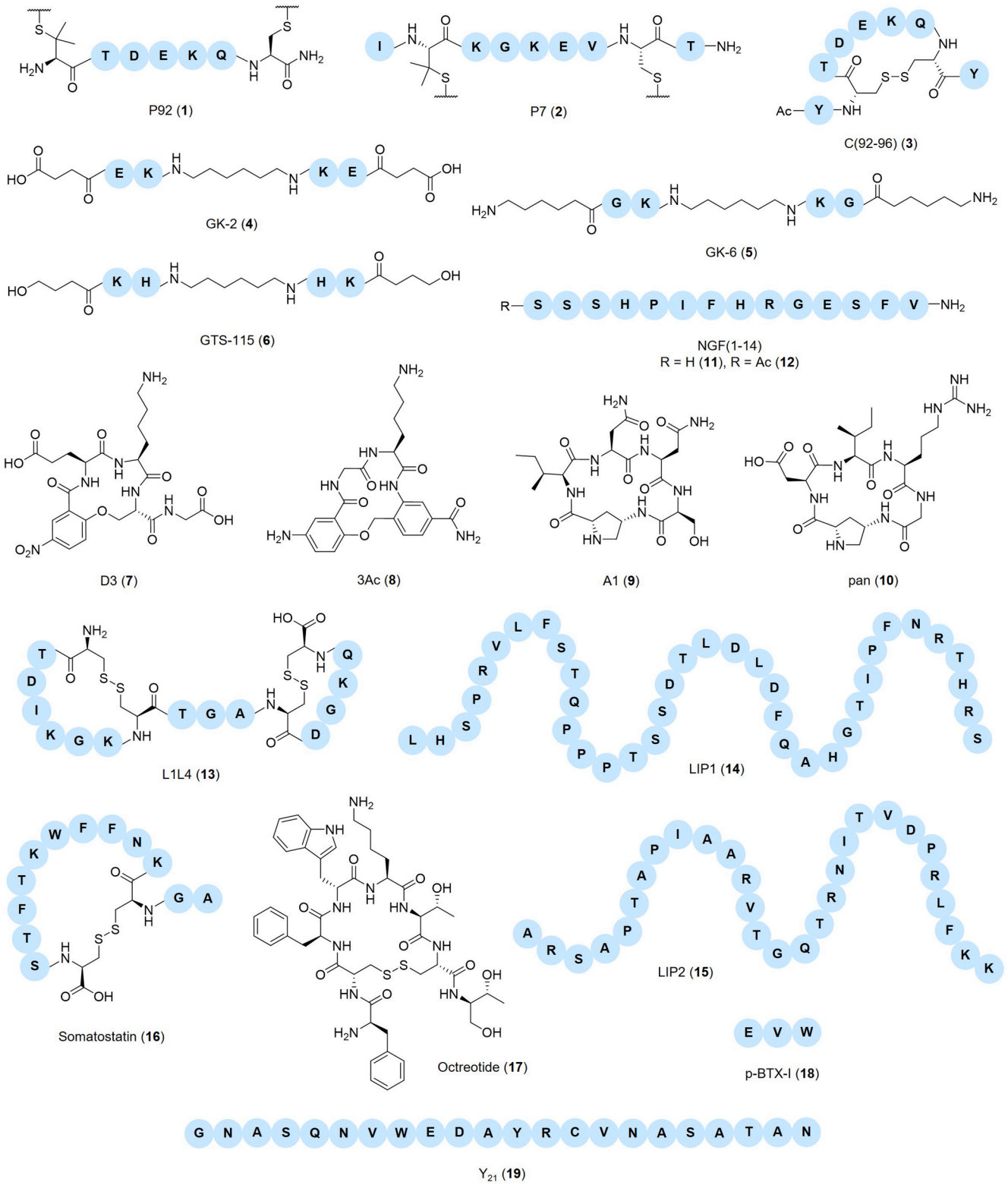

Fig. 3. Structures of NGF mimetics. (NB. For peptides P92 (**1**) and P7 (**2**) only the monomer sequences are shown, though active peptides are dimers formed by disulfide bridging. It is unclear from the initial reports[102,103] whether the peptides were produced as dimers with exclusively Pen-Pen/Cys-Cys disuldifes or mixed Pen-Cys disulfides. Based on the kinetic oxidation conditions employed, we expect that mixed Pen-Cys disulfides are likely.[138.]

sequences of loops 1 and 4 of NGF. Following initial work identifying antagonists derived from the NGF sequence,[101] Longo *et al.* reported dimeric peptides based on NGF loops 1 and 4 which are partial agonists of TrkA. P92 (**1**) is a loop 4 mimetic which promoted survival and neurite outgrowth of dorsal root ganglia *in vitro*. This survival was shown to be dependent on the interaction of P92 with TrkA but not with $p75^{NTR}$. P92 induced phosphorylation of ERK and Akt in a TrkA-dependent manner.[102] P7 (**2**) is a loop 1 mimetic which promoted survival of dorsal root ganglia *in vitro* but had no effect on neurite outgrowth. In contrast to P92, this activity was dependent on $p75^{NTR}$ but

not TrkA.[103] In both cases, monomeric peptides did not promote cell survival. Other authors have also investigated cyclic mimetics derived from NGF loop 4. The peptide C(92–96) (**3**) was originally reported as a competitive inhibitor of NGF binding to TrkA,[104] but in the presence of the $p75^{NTR}$ monoclonal antibody MC192, it improved survival and neurite outgrowth in neuronal cell lines by increasing TrkA phosphorylation.[105–106] A dimeric form of C(92–96) showed the best responses when used in conjunction with MC192, resulting in TrkA phosphorylation levels comparable to that produced by 10 pM NGF.[105]

Several lower molecular weight dipeptide mimetics have also been designed based on the β-turn sequences of loops 1 and 4 of NGF.[107] Of these, GK-2 (**4**) and GK-6 (**5**) have been most widely investigated, with GK-2 showing promising neuroprotective activity both *in vitro* and *in vivo* without any effect on body weight or pain sensitivity in rats (hyperalgesia and weight loss are common side effects of NGF treatment).[108–109] Both peptides increased TrkA, Akt and PLC-γ1 phosphorylation in a neuronal cell line, while only GK-6 increased ERK phosphorylation and induced neurite outgrowth.[110–111] GK-2 exhibited neuroprotective effects in H_2O_2-treated primary cerebellar granule neurons[112] and in a neuronal cell line which was dependent on PI3K/Akt signalling.[110] In embryonic mouse hippocampal neurons, GK-2 was neuroprotective in models of glutamate toxicity and MPTP-induced cell damage at nanomolar concentration.[113] In rat models of ischemia, GK-2 stimulated neurogenesis and synaptogenesis when systemically administered, leading to significantly decreased infarct volume, improved sensorimotor limb recovery and counteraction of amnesia.[114–115] GK-2 also prevented neuronal death and reduced neurological deficits in a rat model of hypoxic encephalopathy,[116] displayed activity in animal models of both AD and PD,[117–118] and significantly improved limb motor function compared with untreated animals in an *in vivo* TBI model.[112] The same researchers have also reported a mimetic of the β-turn sequence of loop 3 of NGF, GTS-115 (**6**), which stimulated phosphorylation of TrkA, Akt and ERK in a hippocampal cell line. *In vitro* GTS-115 stimulated axon growth in a neuronal cell line and displayed neuroprotective effects in H_2O_2-treated cells. In a rat model of ischemia, GTS-115 displayed similar effects to GK-2, decreasing infarct volume by 25% compared to untreated animals.[119] Together, this evidence suggests that both GK-2 and GTS-115 could be promising treatments for neuroregeneration and neuroprotection from secondary injury following TBI.

A small library of peptidomimetic compounds was designed to mimic the pharmacophore of C(92–96), from which the peptide D3 (**7**) was identified. D3 was shown to bind to the extracellular domain of cell surface TrkA, resulting in receptor dimerisation. D3/TrkA interaction led to increased neurite outgrowth and protection from apoptosis in dorsal root ganglia *in vitro*, and both of these effects were shown to be additive with NGF.[120] *In vivo*, D3 was shown to be neuroprotective for cholinergic neurons, improved learning and memory in an aged rat model of cognitive impairment,[121] and was neuroprotective for retinal ganglion cells in a rat model of ocular hypertension.[122] In a mouse model of AD, D3 reduced β-amyloid in the cortex and increased phosphorylation of Akt in the cortex and hippocampus. This was associated with improved learning and short-term memory.[123] In contrast to C(92–96) which demonstrated improved activity on dimerisation, dimers of D3 were antagonists of NGF-promoted cell survival.[124] The same authors also identified neurotrophic peptidomimetics from a library based on the β-turn structure of neurotrophin-3 (NT-3).[123] Some of the identified peptides, for example 3Ac (**8**), were agonists of both TrkA and TrkC, inducing phosphorylation of both receptors and leading to neurite outgrowth in neuronal cell lines selectively expressing either TrkA or TrkC.[125] A further two peptides, A1 (**9**) and pan (**10**), were designed using similar principles to D3 and 3Ac, but with the aromatic nitro functional group removed to reduce any potential toxicity. Both A1 and pan increased survival in HeLa cells modified to express TrkA. A1 was TrkA selective, whereas pan also increased survival in cell lines expressing TrkB and TrkC.[126]

Several studies have been conducted to understand the neurotrophic activities of peptides derived from the *N*-terminal of NGF. A peptide comprising the first 14 *N*-terminal residues of human NGF, NGF(1–14) (**11**), has been shown to induce proliferation in cultures of undifferentiated SH-SY5Y cells. This effect was increased in the presence of Cu^{2+} and Zn^{2+} ions.[127] NGF(1–14) protected cells from apoptosis and induced slight neurite outgrowth in a neuronal cell line. Signalling activated by NGF(1–14) was shown to be similar to that caused by NGF itself, resulting in increased phosphorylation of TrkA, PI3K/Akt and ERK.[128] NGF(1–14) also increased phosphorylation of cAMP response element-binding protein (CREB) and expression of BDNF mRNA in the presence of either Cu^{2+} or Zn^{2+}.[128–129] The effect of NGF(1–14) and an *N*-terminally acetylated derivative (**12**) were investigated in primary cholinergic neurons and dorsal root ganglia *in vitro*, finding that the acetylated peptide was the optimal NGF mimetic.[130]

A set of peptides with combination sequences derived from NGF loop 1, loop 4 and the *N*-terminal have also been investigated, bringing together some of the aforementioned mimetic designs. Of these, L1L4 (**13**, later named BB14), displayed the most promising *in vitro* activities. L1L4 is comprised of two cyclic sequences derived from loop 1 and loop 4, joined by a linker of three amino acids. L1L4 induced TrkA phosphorylation to approximately 75% of the level induced by NGF, and induced neurite outgrowth from both dorsal root ganglia and the PC12 neuronal cell line. In a rat peripheral nerve injury model of neuropathic pain, L1L4 effectively restored thermal and mechanical sensitivity and reduced reactive gliosis.[131] L1L4 also showed similar effects in a spared sciatic nerve injury model, where it restored thermal and mechanical sensitivity and reduced reactive astrogliosis.[132–133] These positive outcomes in peripheral nerve injury models suggest that L1L4 may be a promising therapeutic option for reducing the negative effects of glial scarring following TBI.

Two peptides resulting from proteolytic cleavage of pro-NGF were shown to have neurotrophic activities. The peptides, named LIP1 (**14**) and LIP2 (**15**), correspond to the pro-NGF sequences −71 to −43 (29 residues) and −40 to −3 (38 residues) respectively.[134] Studies of LIP1 and LIP2 in hypothyroid rats indicated that the peptides may play a role in the development of cholinergic neurons in the CNS *in vivo*.[135] Additionally, both peptides induced Trk phosphorylation in a neuronal cell line,[134] induced Akt phosphorylation in murine microglial cells, and were neuroprotective against glutamate excitotoxicity in cultures of murine primary neurons and in a mouse model of excitotoxic brain lesions.[136] This suggests that these peptides may have a neuroprotective effect on secondary injury following TBI.

In addition to peptides derived from human NGF, the neuroactive peptides somatostatin (**16**) and its more metabolically stable analogue octreotide (**17**) have been shown to significantly the increase neurite outgrowth induced by NGF in a neuronal cell line. However, neither peptide was able to induce neurite outgrowth in the absence of NGF. The authors suggested that this potentiation was dependent on protein kinase-dependent pathways, but the mechanism remains to be fully elucidated.[137]

Further to this, TrkA agonists have been derived from proteins produced by non-human species. A tripeptide identified in the venom of the common lancehead snake, named p-BTX-I (**18**), was found to increase neurite outgrowth and protect against MPTP-induced cell damage and death in a neuronal cell line. The effects of p-BTX-I were shown to be dependent on TrkA, ERK and Akt signalling.[139] A second example is a peptide derived from parasite-derived neurotrophic factor (PDNF), a protein expressed by *Trypanosoma cruzi*, the causative agent of Chagas' disease. PDNF is known to promote survival of neurons and glial cells.[140] Based on this, Chuenkova *et al.* investigated the neurotrophic activity of the PDNF-derived peptide Y_{21} (**19**). Y_{21} induced ERK and Akt phosphorylation which was dependent on TrkA signalling, and promoted neurite outgrowth and survival of primary dorsal root ganglia to comparable levels to NGF (though at a higher concentration). Y_{21} also competitively inhibited PDNF binding to TrkA but had no effect on NGF binding, indicating that Y_{21} occupies a TrkA binding site which is

distinct from that occupied by NGF.[141] Together, these examples provide evidence that the search for novel peptide growth factor receptor agonists need not be limited to mammalian-derived sequences.

In addition to peptides, protein and small molecule TrkA agonists and $p75^{NTR}$ receptor modulators have been reported. Protein agonists of TrkA include mutant NGFs,[142] NGFs isolated from viper and cobra venom,[143] and antibodies.[144–145] Small molecules affecting TrkA/$p75^{NTR}$ have been recently reviewed elsewhere.[100] The small molecule TrkA agonist gambogic amide has also been widely researched,[146–147] though literature evidence suggests that this compound would not be effective in TBI treatment.[148]

3.2. HGF

Due to the association of the HGF/Met pathway with biological responses which aid in wound healing, such as angiogenesis and cell survival, there has been much research interest in generating HGF mimetics. The most potent of these is a set of dimeric macrocyclic peptides which are selective and potent Met receptor agonists, identified using the random non-standard peptide integrated discovery (RaPID) mRNA display method. The cyclic peptides bind to the Met ectodomain (K_d = 2–19 nM) via a different binding site to HGF, and therefore do not inhibit HGF-Met activation. It is therefore predicted that they will act synergistically with endogenous HGF. Phosphorylation and receptor activation studies concluded that one of the peptides, aMD5-PEG11 (**20**, Figure 4), strongly activated the Met receptor with a similar intensity and time dependency as HGF. aMD5-PEG11 induced HGF-like responses, such as cell proliferation and wound healing, in a variety of human cell lines.[149–150] More recently, the same authors have also created mimetics by grafting the sequence of the Met-binding macrocycles into the loops of the fragment crystallizable (Fc) region of a human immunoglobulin. The resulting agonists induced Met dimerisation and phosphorylation in a comparable manner to HGF *in vitro*, and had increased pharmacokinetic stability compared with HGF (serum concentration remained above the minimum Met activation concentration (1 nM) for 200 h, compared with <1 h for HGF).[151] An adapted sequence based on another of the reported macrocycles (**21**) has also been used in a single-chain tandem macrocyclic peptide (STaMPtide) system. The resulting bicyclic peptide was found to promote Met phosphorylation and activate ERK signalling to comparable levels to HGF in a human cancer cell line, though at higher concentrations. Similarly to **20**, the STaMPtide was also shown to promote wound healing in a human cell line to the same extent as HGF.[152]

Allosteric activation of HGF by peptides has also been reported. An angiotensin IV analogue named dihexa (*N*-hexanoic-Tyr-Ile-(6) aminohexanoic amide, **22**) has been shown to bind to HGF with high affinity. This allosteric activation by dihexa was shown to result in Met activation in a human cell line even at subthreshold concentrations of HGF and is thought to be the result of induction of an active HGF conformation. Addition of dihexa was also shown to result in stimulation of spinogenesis and synaptogenesis in rat hippocampal neurons, again at subthreshold HGF concentrations.[153] *In vivo*, dihexa was shown to have a procognitive effect in rat models of dementia (aged and scopolamine-treated rats). The fact that dihexa is also orally active and blood–brain barrier permeable further increases its therapeutic potential as an HGF mimetic.[154] Another allosteric activation mechanism is displayed by an 8-residue sequence derived from the *N*-terminus of the HGF β-chain (**23**). Though pro-HGF alone is unable to activate downstream signalling pathways via Met, presence of the peptide was shown to enhance the Met phosphorylation activity displayed by an analogue of pro-HGF in a lung carcinoma cell line to 25% of that of native HGF. The authors showed that Met phosphorylation resulted in cellular responses characteristic of HGF/Met signalling, including Akt phosphorylation, promotion of cell survival and wound healing in human cancer cell lines. Similarly to dihexa, the authors suggest that peptide binding to pro-HGF stabilises an active conformation which in turn increases its binding affinity for Met.[155]

Although not a mimetic of HGF, a hexapeptide agonist of the formyl-peptide receptor 2 (WKYMVm, **24**) has been shown to induce Met phosphorylation *in vitro* in a prostate epithelial cell line. Receptor phosphorylation was also shown to activate some of the same Met signalling which is triggered by HGF binding, including STAT3, PI3K and Akt phosphorylation, indicating that formyl-peptide receptor 2 activation can trigger Met activation.[156] The therapeutic potential of

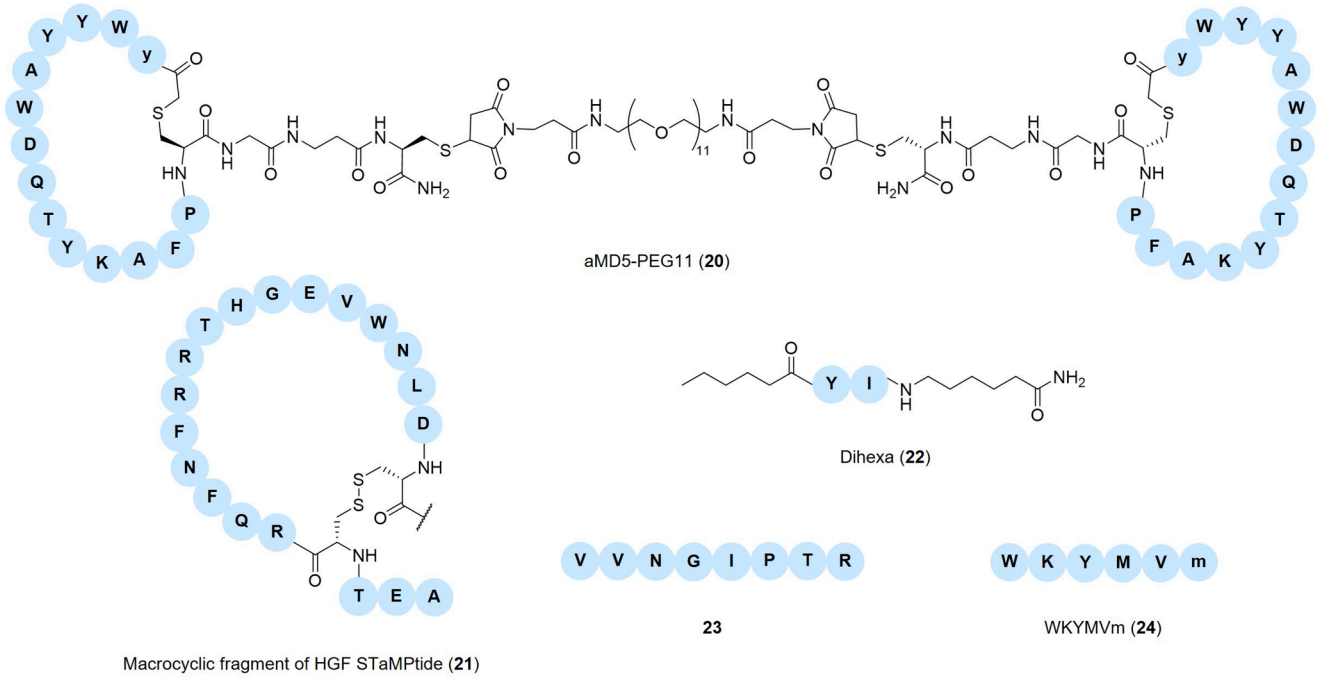

Fig. 4. Structures of HGF mimetics. In HGF STaMPtide (**21**) the *C*-terminus of first macrocycle is linked to the second macrocycle via a Pro-Ala linker. Lower case letters are D-amino acids.

WKYMVm, including in wound healing, ischemia and neurodegenerative disease, has been reviewed elsewhere.[157]

In addition to the aforementioned peptide mimetics, many other types of HGF mimetic have also been reported in the literature and some examples are given here. These include small molecules,[158–159] oligonucleotides,[160] antibodies,[161–162] and proteins.[163] Regarding protein mimetics, several proteins derived from the sequence of HGF itself have been reported, with sequence engineering and/or dimerization found to improve their Met signalling activity.[164–167] A 285-residue sequence derived from the internalin protein InlB from *Listeria monocytogenes* has also been shown to bind to Met and activate downstream signalling similar to HGF.[168] Although these sequences are too large to be considered peptide mimetics, there is potential that smaller fragments derived from these proteins could display similar activity if modified to maximise binding efficiency, for example by macrocyclization or dimerization as seen above with reported HGF mimetics.

Although to our knowledge none of these HGF peptide mimetics have been tested in models of TBI, evidence of the efficacy of HGF in animal models of spinal cord injury[21–22] indicates the potential for HGF mimetic peptides to display the same promotion of cell survival and prevention of cell death in TBI applications. In particular, it is worth noting that most of the HGF mimetics described in the above studies have not looked at the effect of the mimetic on neurons or other CNS cells. However, it is known that neural precursors and neurons express the Met receptor, and that expression of Met is upregulated in response to both SCI[21] and cerebral ischemic injury.[169] The same response could therefore be expected in neurons as has been observed in other cell lines, though this remains to be determined experimentally.

The HGF/Met pathway is also associated with invasive growth responses which contribute to tumorigenesis, such as migration, invasion and metastasis.[170–171] For this reason, HGF/Met is also a target of interest in cancer therapy, and thus many peptide antagonists of Met have been reported.[172–177] This highlights that though it is possible to generate peptides which are tight binders of Met, tight binding does not necessarily equate to receptor agonism. It is therefore essential that potential mimetics are screened for their ability to activate receptor signalling to ensure that the desired physiological effect is achieved *in vivo*.

3.3. GDNF

Significant evidence that GDNF can protect dopaminergic neurons *in vivo* and in pre-clinical PD models[25,27-31] suggests that mimetics of this growth factor may have application in neuroprotection following TBI. However, few GNDF peptide mimetics have been reported to date (Fig. 5). In 2011, Bradley *et al.* reported the neurobiological activity of dopamine neuron stimulating peptide (DNSP-11, **25**). The peptide consists of 11 consecutive amino acids derived from the pro-region of human GDNF. DNSP-11 displayed similar neurotrophic actions to GDNF *in vitro*: the peptide led to ERK phosphorylation at comparable levels to GDNF in a human dopaminergic neuronal cell line,[178] and promoted survival and neurite outgrowth in dopaminergic neurons.[178] Unlike GNDF, DNSP-11 was found to protect dopaminergic cells from staurosporine- and gramicidin-induced cytotoxicity, suggesting that its neuroprotective effects *in vitro* include mitochondrial protection.[179] DNSP-11 was also shown to protect and restore dopaminergic activity *in vivo*

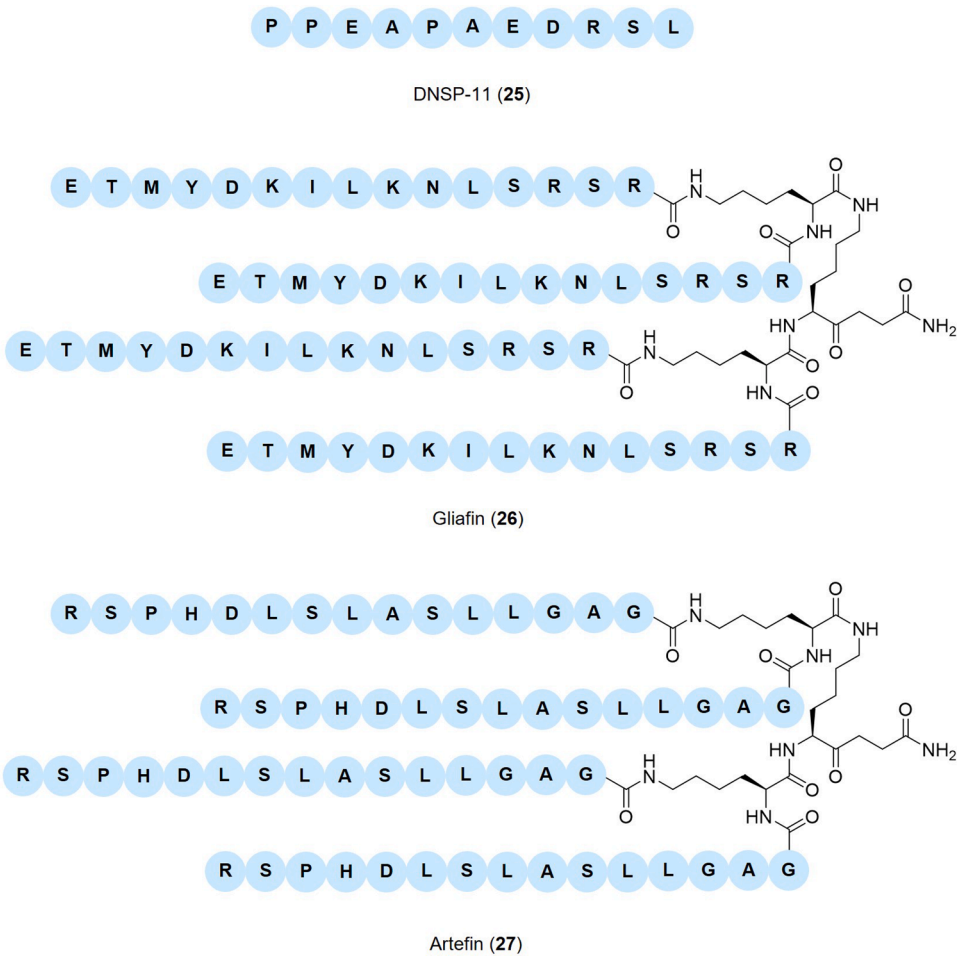

Fig. 5. Structures of GDNF mimetics.

in a 6-hydroxydopamine (6-OHDA) model of PD,[180–181] suggesting that the peptide may offer protection from secondary injury in TBI. Further, a proof-of-concept study demonstrated the potential for DNSP-11 to be delivered intranasally biweekly in an awake non-human primate, though repeated dosing was required due to the peptide's short half-life.[182]

Gliafin (**26**), also derived from GDNF, is a tetrameric dendrimer comprising 4 copies of a 15-mer from the heel region of rat GDNF, coupled to a lysine backbone. The peptide was found to induce neurite outgrowth in hippocampal neurons *in vitro* via neural cell adhesion molecule (NCAM) signalling.[183] NCAM is involved in a number of developmental processes such as cell migration and neurite outgrowth, and is known to act as an alternative receptor for GDNF family ligands (GFLs).[184] Additionally, GDNF/NCAM interactions have been shown to lead to signalling via FGFR1 to stimulate neurite outgrowth in hippocampal neurons.[185] Gliafin was found to cause FGFR phosphorylation in a human cell line in a similar manner to that observed for GDNF. Gliafin is not expected to be able to bind to GFRα1, though whether gliafin/NCAM-mediated neurite outgrowth is independent of GFRα1 has not been determined.[183] In an *in vivo* model of spinal cord injury, a combination of gliafin and the ciliary neurotrophic factor mimetic cintrofin were shown to promote survival and differentiation of mouse embryonic stem cell-derived motor neuron precursors and improved neurite outgrowth.[186]

A dendrimer derived from the heel region of artemin, another member of the GFLs, has also been reported by the same authors. The resulting peptide, named artefin (**27**), was shown to bind to GFRα1, GFRα2 and GFRα3, and induced phosphorylation of RET *in vitro* in a rat cell line. Artefin was able to stimulate neurite outgrowth and promote neuronal survival in cerebellar granule neurons *in vitro* in a similar way to artemin but was less potent (active in the micromolar range).[187]

Several small molecule ligands targeting RET/GFRα receptors or

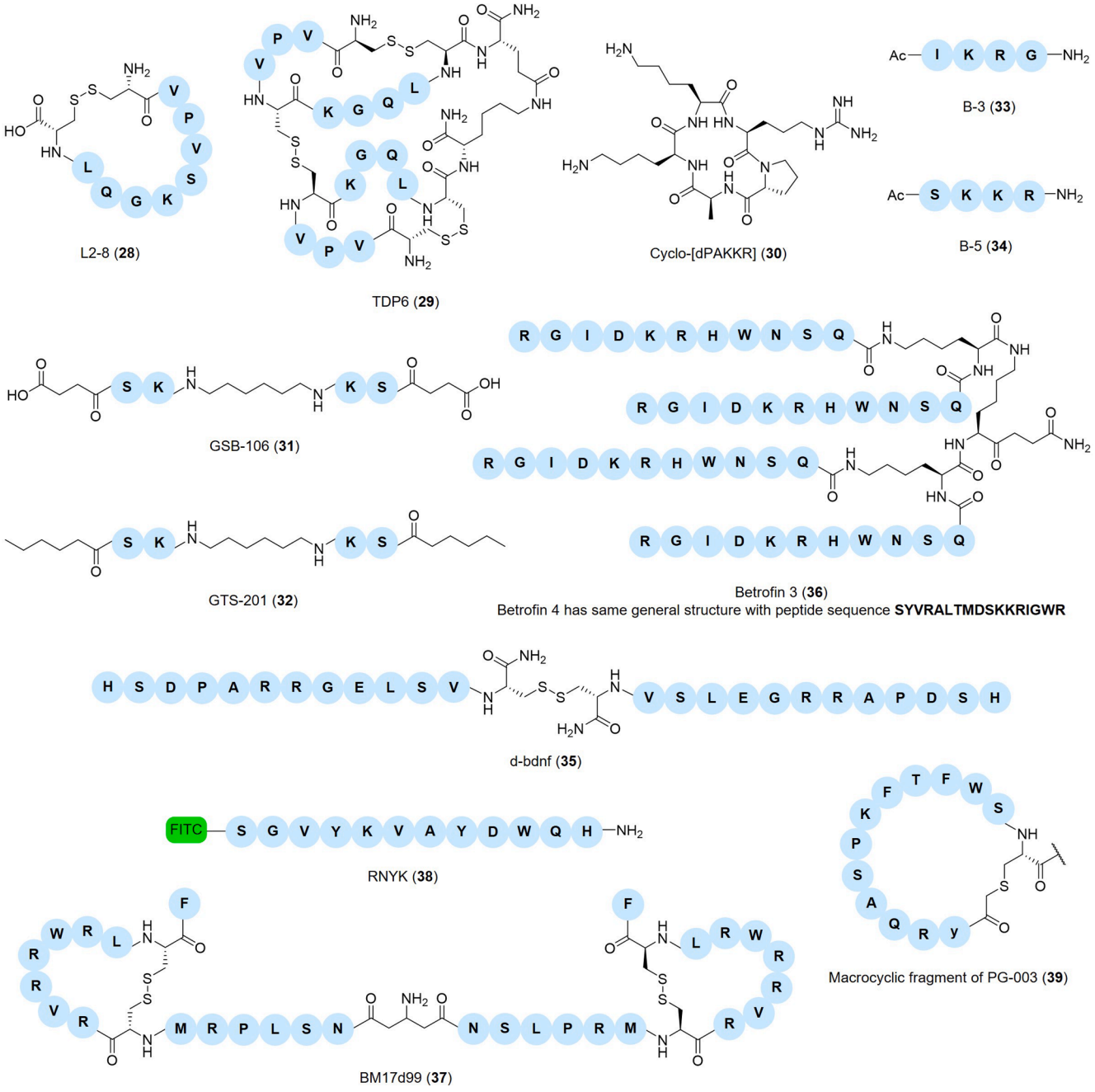

Fig. 6. Structure of BDNF mimetics.

activating GFL signalling have also been reported. These have been recently reviewed elsewhere.[188]

3.4. CDNF

Due to the increasing pool of pre-clinical and clinical evidence of its efficacy in neurodegenerative diseases, there is growing interest in the use of CDNF as a therapeutic. CDNF itself was only reported relatively recently,[189] and to our knowledge the only reported CDNF mimetic is an 81-residue protein derived from the *C*-terminal of CDNF.[190] This protein is a cell membrane and BBB penetrant, and demonstrated better efficacy than CDNF in restoring neuronal function in a 6-OHDA rodent model of PD. More research is needed to determine if lower molecular weight peptides or small molecule mimetics would also be efficacious.

3.5. BDNF

There is growing pre-clinical and clinical evidence that modulating BDNF/TrkB signalling is beneficial in treatment of neurological disease and injury.[66–67] Accordingly, significant research efforts towards the development of peptide mimetics of BDNF have also been reported (Figure 6). A series of mimetics have been developed based on the structure of the loop 2 region of the BDNF homodimer. Initially, a set of monocyclic loop 2 mimetics were reported as competitive antagonists of TrkB, of which L2-8 (**28**) showed 50% inhibition of BDNF-mediated survival in neuronal cultures.[191] Following this, a series of dimeric and tricyclic peptides were reported.[192–193] Of these, the tricyclic-dimeric peptide 6 (TDP6, **29**) was found to be a partial TrkB agonist and promoted a concentration-dependent increase in neuronal survival *in vitro*.[192] In primary rat oligodendrocytes, TDP6 increased levels of phosphorylated TrkB and ERK, which led to enhanced oligodendrocyte myelination both *in vitro* and in a cuprizone model of toxic demyelination *in vivo*.[194–195] A cyclic mimetic of loop 4 of BDNF, cyclo-[dPAKKR] (**30**), was also reported by the same authors. Cyclo-[dPAKKR] promoted neuronal survival *in vitro*,[196] and enhanced myelination of neurons *in vitro* and *in vivo*, but this was *via* $p75^{NTR}$ rather than TrkB signalling.[197] Interestingly when cyclo-[dPAKKR] was incorporated into a self-assembling peptide amphiphile, it was shown to activate TrkB signalling, leading to ERK and Akt phosphorylation and enhanced maturation of primary cortical neurons *in vitro*.[198] Lipidated analogues of cyclo-[dPAKKR] displayed improved plasma stability and improved potency over the parent peptide.[199] In an animal model of peripheral demyelinating neuropathy, cyclo-[dPAKKR] protected against demyelination and axonal damage. This suggests that $p75^{NTR}$ agonists may be a promising approach for targeting myelin repair following TBI.

A dimeric dipeptide mimetic of BDNF, GSB-106 (**31**), was designed based on the β-turn sequence of loop 4 in BDNF.[200] *In vitro*, GSB-106 has been shown to increase TrkB, Akt and ERK phosphorylation, protect neuronal cell lines from glutamate and 6-OHDA induced toxicity,[201] and inhibit apoptosis *via* activation of the TrkB pathway.[202] In an *in vivo* rat model of stroke, GSB-106 was shown to improve sensorimotor function and decrease cerebral infarct volume by ~ 66% (comparable to values previously reported for BDNF).[203] GSB-106 also exhibited an anti-depressive effect in rodent models of depressive-like states which was shown to be regulated by TrkB signalling.[204–205] The same authors reported a similar peptide named GTS-201 (**32**) based on the β-turn sequence of loop 2 in BDNF. GTS-201 also increased TrkB, ERK and PLC-γ1 phosphorylation (though it had no significant effect on Akt) and protected a neuronal cell line from H_2O_2-induced oxidative stress *in vitro*.[111,206] Further examples of low molecular weight mimetics were reported by Cardenas-Aguayo *et al.*. A set of five tetrapeptides derived from the sequence of BDNF were synthesised, two of which, B-3 (**33**) and B-5 (**34**), are partial agonists of TrkB. In neuronal cultures, both peptides were found to increase the expression of BDNF and activate phosphorylation of TrkB, though the latter effect was weak in comparison to BDNF. In non-neuronal fibroblast cells, both peptides also increased expression of TrkB. In combination with BDNF, B-3 showed an additive neuroprotective effect against H_2O_2-induced toxicity *in vitro*.[207] This evidence that low molecular weight peptides can protect neurons against oxidative stress and toxicity suggests that these compounds may have potential as neuroprotective agents for ameliorating secondary injury in TBI.

A dimeric linear peptide named d-bdnf (**35**) containing the first 12 *N*-terminal residues of BDNF was reported to promote TrkB, ERK and Akt phosphorylation in cell-based assays, which correlated with observed TrkB dimerisation in a neuronal cell line. *In vitro*, d-bdnf promoted neurite outgrowth in differentiated SH-SY5Y cells and the differentiation of neuronal precursors.[208] Linear tetrameric dendrimers have also been reported. Betrofin 3 (**36**) and betrofin 4 are based on the sequences of loops 3 and 4 of BDNF respectively. Both peptides were found to bind to TrkB and $p75^{NTR}$, though with 1000-fold lower affinity than BDNF. In rat cerebellar granule neurons, this binding resulted in a dose-dependent increase in Akt and ERK phosphorylation, stimulation of neurite outgrowth and promotion of cell survival.[209] Additionally, the peptide sequence of betrofin 3 has been appended to a self-assembling peptide to create a functionalised nanofiber hydrogel.[210] The same authors later showed that they could create dual-functionalised hydrogels by incorporating self-assembling peptides displaying the peptide sequence of betrofin 3 and a) a VEGF mimetic;[211–212] b) a laminin mimetic;[213] or c) an NGF mimetic.[214] In all cases, the resulting hydrogels were found to facilitate axon regrowth and functional muscle regeneration in an animal model of peripheral nerve injury.

Peptide agonists of TrkB have also been developed by library display methods. Ohnishi *et al.* reported a dimeric peptide, the monomeric form of which was identified from phage display by panning against the extracellular domain of human TrkB. The resulting peptide (dimeric BM17d99(K1N/K11R), **37**), which has no sequence similarity to BDNF, activated TrkB and ERK phosphorylation *in vitro* to approximately 50–60% of the level caused by BDNF, and induced TrkB phosphorylation in the hypothalamus *in vivo* following intracerebroventricular injection in mice.[215] In another phage display study, a peptide which conformationally mimicked loop 2 of BDNF was identified and subsequently modified to produce a mimetic named RNYK (**38**). RNYK was shown to bind to TrkB and promote cell survival to a comparable level to BDNF in a culture of SH-SY5Y cells, though whether this is via the same signalling pathways remains to be determined experimentally.[216] A dimeric macrocyclic peptide named PG-003 has been developed which is reported to promote phosphorylation of TrkB to the same level as BDNF, although to our knowledge no *in vivo* data has been reported for this peptide. The macrocyclic portion of the peptide (**39**) was developed using the RaPID mRNA display method.[217–218]

Several small molecule and antibody TrkB agonists have also been reported in the literature.[219–225] Regarding small molecule mimetics, a recent publication by Boltaev *et al.* suggests that these compounds may not in fact lead to phosphorylation of TrkB.[226] Though the authors acknowledged that *in vivo* activity is of primary importance for the development of therapeutics, they highlighted that these compounds likely act via a mechanism other than TrkB agonism, emphasising the importance of examining the activity of potential agonists *in vivo* as well as *in vitro*. Similarly to HGF/Met, GDNF/TrkB are targets of interest in cancer therapy as they have been shown to be upregulated in a variety of tumours.[227] Examples of peptide antagonists have therefore also been reported in the literature, again highlighting the importance of investigating receptor activation to ensure that tight binders are also agonists.[228–229]

3.6. PDGF

There is much pre-clinical and some clinical evidence in PD that PDGF/PDGFR signalling can regulate neurogenesis, cell survival and differentiation.[75] However, few PDGF peptide mimetics have been identified, and the effect of these on CNS cells has not been investigated

in all cases. Of the mimetics that have been reported, many are derived from the sequence of PDGF-B which is the best characterised of the PDGFs (Fig. 7).

The pentapeptide sequence VRKKP from loop III of PDGF-B has been incorporated into a self-assembling peptide (**40**) hydrogel. The resulting gel was found to bind PDGFR with nanomolar affinity, leading to phosphorylation of PDGFR, ERK, Akt, mitogen-activated protein kinase (MEK) and mTor to comparable levels as PDGF. In a fibroblast cell line, the gel promoted cell proliferation and migration and protected cells against X-ray induced apoptosis.[230] The gel also demonstrated good functional recovery *in vivo* in a rat model of SCI when co-administered with neural stem cells.[231] A dimerised sequence derived from PDGF-B loop III, which included the VRKK motif, has been incorporated into a conjugate with a heparin-binding peptide. The resulting conjugate PBA2-1c (**41**) bound to both PDGFR-α and PDGFR-β, and induced PDGFR, Akt and ERK phosphorylation in a murine myoblast cell line (though to a lesser extent than PDGF). In the same cell line, PBA2-1c induced cell proliferation and migration to a similar extent as PDGF.[232] Brennand *et al.* reported two decapeptide sequences P4 (**42**) and P6 (**43**), also derived from PDGF-B loop III, but with added Cys residues to enable dimerisation. These peptides induced proliferation and stimulated DNA synthesis in human fibroblasts *in vitro*.[233] Intriguingly, head-to-tail cyclisation of P6 to produce cyclo(RKIEIVRKKC) (**44**) abolished this activity, with this peptide instead inhibiting the binding of PDGF-BB to PDGFR and inducing apoptosis in human fibroblasts.[234] Other peptide antagonists of PDGFR-β derived from the sequence of PDGF-B have also been reported, again highlighting the importance of ensuring peptides are able to both bind and activate target receptor signalling in agonist drug discovery efforts.[235–236]

Recently a peptide derived from loop I of PDGF-B, named PDGF2 (**45**), was reported to stimulate proliferation in a keratinocyte cell line and stimulated wound healing *in vivo*. Transcriptomic analysis of fibroblasts treated with PDGF2 indicated that the peptide-induced effects related to cell migration and movement, but whether this was due to PDGFR activation was not demonstrated.[237]

3.7. FGF

Both FGF1 and FGF2 have been investigated in animal models of TBI,[21,83,84] and many of the reported FGF-derived mimetics are based on the sequences of these FGFs. However, only FGF1 has entered clinical trials to date, suggesting that peptides mimicking this sequence in particular may be promising for treatment of TBI. Nonetheless, this section reviews mimetics which induce FGFR activation that are derived from any of the FGFs.

Since the early discovery that FGF-derived peptides are able to act as partial FGFR agonists,[238–239] many FGFR-activating peptides have been reported. FK18 (**46**, Fig. 8) is an 18 residue sequence derived from the receptor-binding domain of FGF2. FK18 was found to increase FGFR1 and Akt phosphorylation in SH-SY5Y cells under normoxic conditions. After oxygen–glucose deprivation and glutamate-induced excitotoxicity, FK18 increased SH-SY5Y cell viability, protected cells against apoptosis and increased Akt phosphorylation.[240–241] This suggests that FK18 could potentially protect neurons from secondary injury following TBI. *In vivo*, intravitreal administration of FK18 showed neuroprotective effects (attenuation of apoptosis) and no toxicity in a rat model of ischemic neuronal injury.[240] A second sequence derived from FGF2, which overlaps with the sequence of FK18, has been incorporated into a dimeric conjugate with a heparin-binding peptide. The resulting conjugate F2A4-K-NS (**47**, also known as fibratide) bound to FGFR1 with K_d in the nanomolar range. Receptor binding was shown to induce ERK phosphorylation in an endothelial cell line, which led to cell proliferation and migration.[242] *In vivo*, F2A-K-NS has been shown to stimulate angiogenesis to comparable levels to FGF2 in a subcutaneous implant assay,[242] and augmented ectopic bone formation in rats with a demineralized bone matrix implant.[243] This evidence suggests that F2A-K-NS would have positive effects on repair processes following TBI. The FGFR1-binding sequence from F2A-K-NS has also been widely used in other peptides and conjugates. For example, the cysteine modified peptide FGF-P (**48**) increased ERK phosphorylation in a human fibroblast cell line *in vitro*. In an *in vivo* animal model of acute radiotoxicity, FGF-P increased animal survival, recovered normal platelet aggregation function, and increased proliferation of bone marrow cells in a dose-dependent manner.[244] A self-assembling peptide amphiphile

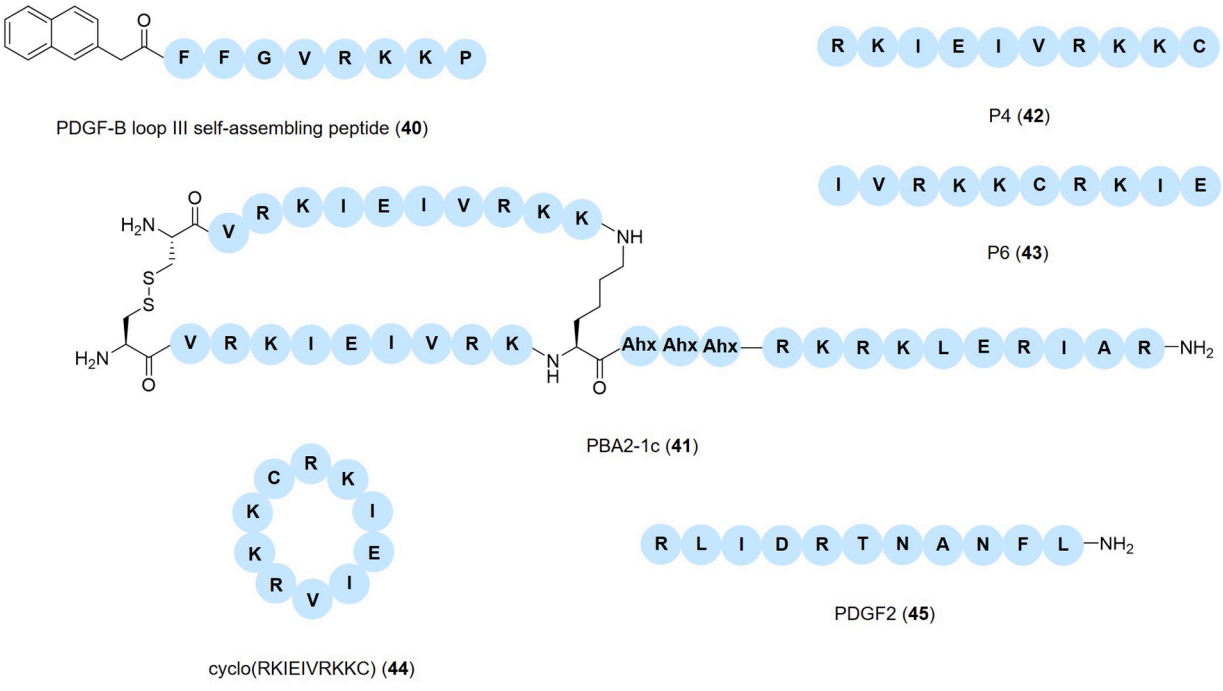

Fig. 7. Structure of PDGF mimetics. Ahx = 6-aminohexanoic acid.

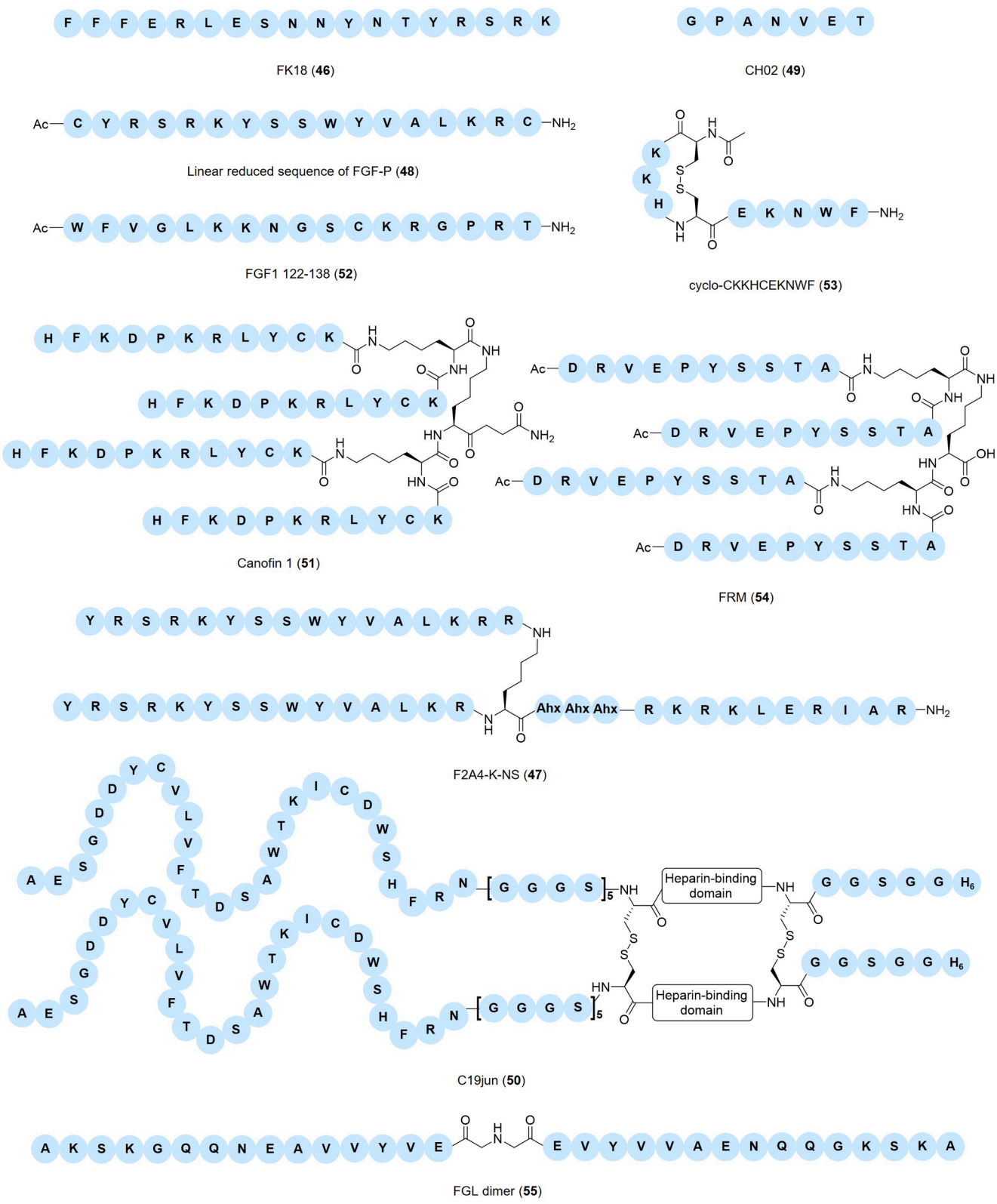

Fig. 8. Structures of mimetics which activate FGFRs. H_6 = hexa histidine tag; Ahx = 6-aminohexanoic acid. Many of the peptides mimicking FGF or CAMs were synthesised as tetrameric dendrimers with a central lysine backbone. The general structure of these dendrimers is exemplified with the peptide sequence of canofin 1 (**51**). Peptide sequences of dendrimers with the same general structure as **51** are given in Table 2.

containing the F2A-K-NS sequence increased phosphorylation of FGFR1 and ERK to comparable levels to FGF2 (though at higher concentrations), and promoted cell proliferation and migration in a human endothelial cell line.[245] A bifunctional peptide-DNA conjugate containing the F2A-K-NS sequence and a laminin mimetic peptide also increased phosphorylation of FGFR1 and ERK, and led to the proliferation and migration of neural stem cells *in vitro*.[246]

FGFR-binding sequences have also been identified using phage

display methods. CH02 (**49**) is a 7-residue sequence which was identified from phage display against the extracellular domain of FGFR2. CH02 bound to both FGFR1 and FGFR2 *in vitro*, leading to increased phosphorylation of FGFR, Akt and ERK, and increased cell survival. In *in vitro* and *ex vivo* rat dorsal root ganglia, CH02 promoted axonal growth and protected cells from H_2O_2-induced apoptosis. Furthermore, in a rat dorsal root injury model of SCI, subcutaneous injection of CH02 promoted axon regeneration and recovery of sensory function.[247] This is promising for potential applications in TBI. Phage display has also been conducted against the FGFR1 extracellular domain. This identified a 26-residue peptide named C19 with no homology to FGFs. This peptide was incorporated into a dimeric fusion peptide with a heparin-binding sequence to produce C19jun (**50**). In the presence of heparin, C19jun was shown to induce FGFR and MAPK phosphorylation, stimulate proliferation in a fibroblast cell line, and induced neurite outgrowth in a neuronal precursor cell line with comparable potency to FGF2.[248]

Researchers from the University of Copenhagen have developed several FGFR agonists with peptide sequences derived from FGFs. The peptides are the canofins (**51**, sequences derived from the FGFR1-binding regions of FGF2),[249] hexafins (sequences derived from the β6–β7 loops of various FGFs),[250] and dekafins (sequences derived from the β10–β11 loops of various FGFs).[251] These agonists are tetrameric dendrimers bound to a lysine backbone to promote receptor oligomerisation, and thus all have the same general structure as **51** (for individual peptide sequences see Table 2). The neuritogenic and neuroprotective properties of these agonists have been reviewed elsewhere, but will be briefly summarised here.[252] Canofins are only partial FGFR1 agonists, but were found to induce FGFR1 phosphorylation, and in rat primary cerebellar granule neurons they protected cells from apoptosis and caused a significant increase in neurite outgrowth.[249] All hexafin peptides have been shown to cause FGFR1 phosphorylation, though not to the same extent as FGF2. The peptides did not all have the same effects on rat primary cerebellar granule neurons *in vitro*, though each promoted either neurite outgrowth or neuronal survival.[250] *In vivo*, hexafin 2 promoted short-term memory and exerted anxiolytic effects in rats, and alleviated social cognitive deficits in a mouse model of Huntington's disease.[253] Like the canofins, the dekafins are also partial FGFR1 agonists. All dekafin peptides induced FGFR1 phosphorylation in a human cell line and increased neurite outgrowth in cerebellar granule neurons, though not all of the peptides protected neurons from apoptosis.[251] Two other non-dendrimeric peptides derived from the same FGF1 sequence as dekafin 1, one linear (FGF1 122–138, **52**) and one cyclic (cyclo-CKKHCEKNWF, **53**), have additionally been shown to induce a mitogenic response in a murine fibroblast cell line. The cyclic peptide also inhibited binding of FGF1 to the cell surface, though whether the observed mitogenic effect was FGFR-mediated was not determined.[254–255]

Table 2
Peptide sequences of FGFR agonist dendrimers with the same general structure as **51** (see Fig. 8).

Peptide source	Peptide Name	Peptide Sequence
FGFs	Canofin 1	HFKDPKRLYCK
	Canofin 2	FLPMSAKS
	Canofin 3	KTGPGQKAIL
	Hexafin 1	TGQYLAMDTDGLLYGS
	Hexafin 2	ANRYLAMKEDGRLLAS
	Hexafin 3	SGRYLAMNKRGRLYAS
	Hexafin 8	TGLYICMNKKGKLIAK
	Hexafin 9	SGLYLGMNEKGELYGS
	Hexafin 10	SNYYLAMNKKGKLYGS
	Hexafin 17	SEKYICMNKRGKLIGK
	Dekafin 1	WFVGLKKNGSCKRG
	Dekafin 2	WYVALKRTGQYKLG
	Dekafin 3	WYVSVNGKGRPRRG
	Dekafin 5	WYVALNKRGKAKRG
	Dekafin 6	TYIALSKYGRVKRG
	Dekafin 8	WYMAFTRKGRPRKG
	Dekafin 9	YYVALNKDGTPREG
	Dekafin 10	MYVALNGKGAPRRG
	Dekafin 17	WFMAFTRQGRPRQA
NCAM	Encamin A	SIDRVEPYSSTAQVQFD
	Encamin C	KAEWKSLGEEAWHSK
	Encamin E	TIMGLKPETRYAVR
	DekaCAM	AALNGKGL
	FGL	EVYVVAENQQGKSKA
	BCL	NLIKQDDGGSPIRHY
	Plannexin	DVRRGIKKTD
L1 cell adhesion molecule	Elcamin 1	DLAQVKGHLRGYN
	Elcamin 2	RHVHKSHMVVPAN
	Elcamin 3	RFHILFKALPEGKVSPD
	Elcamin 4	LHHLAVKTNGTG
Neuroplastin	Enplastin	DPKRNDLRQNPSITWIR
	Narpin	RIVTSEEVIIRDS
FGFR1	Enreptin	AKTVKFK
Combinatorial library	C3	ASKKPKRNIKA
	NBP10	AKKMWKKTW

The same researchers, among others, have also developed FGFR agonists with sequences derived from cell adhesion molecules (CAMs) including NCAM, L1 and neuroplastin. Similarly to FGF-derived peptides, many of these CAM-derived agonists are also tetrameric dendrimers with a central lysine backbone (same general structure as **51**, for individual peptide sequences see Table 2). Several peptides have been produced based on the extracellular modules of NCAM. In addition to GDNF/NCAM activation of FGFR as discussed above (see Section 3.3.), NCAM has been shown to regulate neurite outgrowth via FGFR activation.[185,256] NCAM-derived peptides which have been reported are the ecamins,[257] FGFR activation motif (FRM, **54**),[258] dekaCAM,[251] FG loop peptide (FGL, **55**),[185] and BCL.[259] The encamins, FRM and dekaCAM have sequences derived from the first NCAM fibronectin type III (FN3) module, while FGL and BCL sequences are derived from the second NCAM FN3 module. The neuritogenic and neuroprotective properties of these agonists have also been reviewed, and will be briefly summarised here for completeness.[252,260] The encamins bind to FGFR1 with nanomolar potency and induce receptor phosphorylation. Encamins A and E also increased Akt phosphorylation, while encamin E increased ERK phosphorylation. Furthermore, encamins C and E increased neurite outgrowth and cell survival in cerebellar granule neurons in a dose-dependent manner.[257] The sequence of FRM overlaps with that of encamin A. Unsurprisingly therefore, FRM exhibited similar effects to the encamins, increasing cell survival and neurite outgrowth *in vitro* in an FGFR-dependent manner.[258] Although bearing a different sequence, dekaCAM also induced FGFR1 phosphorylation and increased neurite outgrowth in cerebellar granule neurons.[251] Similarly, BCL increased FGFR1 phosphorylation in a human cell line and induced neurite outgrowth *in vitro*, but had no effect on cell survival.[259] Extensive research has been conducted on FGL. FGL contains a 15-residue sequence derived from the FGFR1 binding site of NCAM,[185] and its activity has been investigated as both a tetrameric dendrimer on a lysine backbone similar to aforementioned peptides, and as a dimer with the FGL sequence *N*-linked to a central iminodiacetate (**55**).[261] Both forms of the peptide have similar potencies, but the dimeric form has progressed in clinical development.[262] *In vitro* FGL was found to induce FGFR1, Akt and ERK phosphorylation,[185,261] leading to neurite outgrowth and promotion of cell survival in dopaminergic, hippocampal and cerebellar granule neurons.[261] In a rodent model of transient global ischemia, FGL was shown to protect neurons from death.[263] Importantly, in a cryo-induced rat model of TBI, FGL altered the expression of genes involved in regulation of apoptosis, neurogenesis and differentiation, among others.[264] This highlights the potential neuroprotective role of FGL in treatment of TBI. Furthermore, following subcutaneous or intranasal administration in rats, FGL was found in blood plasma and cerebrospinal fluid after only 10 min,[265] and pre-clinical studies indicated no adverse effects in rats, dogs and monkeys. A safety study in healthy human males also indicated FGL is well tolerated with no adverse effects.[262] A further set of peptides, named the elcamins, are derived from the cell adhesion molecule L1 which has important roles in

nervous system development. The sequences of the peptides are derived from the third and fifth extracellular FN3 modules of L1, and were found to bind to, and induce phosphorylation of, FGFR1. Three of the peptides, elcamins 1, 3 and 4, induced neurite outgrowth in primary cerebellar neurons *in vitro* in a dose-dependent manner. At high concentrations however, the elcamins inhibited FGF1-induced FGFR1 phosphorylation, suggesting that the peptides are partial agonists of FGFR.[266] Two peptides derived from the neuroplastin sequence have also been reported. Neuroplastin is a cell adhesion molecule which exists in two isoforms, neuroplastin-65 (Np65) and neuroplastin-55 (Np55), and the biological effects of both isoforms have been shown to be FGFR-mediated. Dendrimeric peptides derived from the sequences of Np65 and Np55 are named enplastin and narpin respectively. Narpin induced FGFR phosphorylation in a human cell line, increased neurite outgrowth in hippocampal neurons in an FGFR1-dependent manner, and exhibited antidepressant-like behaviour in an *in vivo* animal model.[267] Enplastin is a partial agonist which was found to stimulate neurite outgrowth in hippocampal neurons *in vitro* (dependent on FGFR1 and MAPK signalling), but also significantly reduced neurite outgrowth caused by Np65.[268]

In addition to the aforementioned FGF- and CAM-derived peptides which bind FGFR, research has shown that peptides designed to bind to NCAM directly are also able to induce neurite outgrowth in an FGFR-dependent manner. The following peptides were each synthesised as tetrameric dendrimers with a central lysine backbone (same general structure as **51**, for individual peptide sequences see Table 2). Plannexin contains a discontinuous sequence derived from the Ig2 module of NCAM, and was found to bind to NCAM Ig3 and induce neurite outgrowth in both cerebellar granule neurons and dopaminergic midbrain neurons. This outgrowth was NCAM- and FGFR-dependent and additive to the neurite outgrowth produced by NCAM-NCAM homophilic binding. Plannexin also protected cerebellar granule neurons from apoptosis *in vitro*.[269] In an animal model of status epilepticus, plannexin did not protect mature neurons from cell death, but did protect neuronal progenitor cells.[270] It has been suggested that plannexin may achieve this by interfering with neuronal hyperexcitability,[271] and may therefore help to protect cells from hyperexcitability following TBI, though this remains to be demonstrated. A peptide named enreptin, with sequence derived from the Ig2 module of FGFR1, was found to bind to both NCAM and FGFR leading to FGFR phosphorylation. In primary cerebellar neurons *in vitro*, enreptin induced neurite outgrowth (FGFR- and NCAM-dependent) and protected cells from apoptosis. Neurite outgrowth caused by enreptin was synergistic with NCAM-mediated neurite outgrowth. Additionally, enreptin was detected in cerebrospinal fluid of rats after subcutaneous injection, suggesting it crosses the BBB, and attenuated neuroinflammation in an *in vivo* model by rescuing decreased FGFR phosphorylation caused by lipopolysaccharide (LPS).[272] Screening of combinatorial peptide libraries has identified two further NCAM-binding peptides which were investigated for their neuritogenic properties. C3 was identified by screening against a recombinant protein corresponding to the extracellular Ig1 module of NCAM.[273] C3 stimulated neurite outgrowth in primary cerebellar neurons which was dependent on FGFR expression,[274] and was later shown to directly bind to and activate FGFR phosphorylation in the absence of NCAM. In the presence of NCAM however, C3 inhibits NCAM-mediated FGFR phosphorylation.[275] A similar effect was observed with NBP10, identified from library screening against NCAM isolated from rats. This peptide promoted neurite outgrowth in primary hippocampal neurons grown in conditions which prevent NCAM-NCAM homophilic binding, but inhibited neurite outgrowth caused by NCAM-NCAM binding.[276]

In contrast to the large tetrameric FGFR agonists previously discussed, there is limited evidence from literature that a Pro-Ile dipeptide may increase cell proliferation in a human keratinocyte cell line in an FGFR-dependent manner, though not significantly compared with FGF1.[277] This indicates that very minimal sequences may be sufficient for receptor activation. However, it is clear from the aforementioned *in vitro* and *in vivo* studies that larger or multimerised sequences which are capable of inducing receptor oligomerisation are more likely to elicit the desired neuroprotective and neuroregenerative effects which would be beneficial in treatment of TBI.

Other classes of FGFR agonists have been reported in the literature including small molecules,[278] peptoids,[279] oligonucleotides,[280] and antibodies.[281] Inhibition of FGFR signalling is of therapeutic interest in cancer,[282] and examples of peptide antagonists of FGFR have therefore also been described.[283–286]

4. Conclusion and perspectives

4.1. Growth factors

Despite promising preclinical evidence, few growth factors have crossed the hurdle from animal preclinical studies to human clinical trials for the treatment of TBI. In addition, other neurotrophic factors have demonstrated safety and in some cases efficacy in human clinical trials for other indications. Growth factors such as HGF, GDNF, BDNF, PDGF and FGF should also be considered for the treatment of TBI, with the potential to modulate secondary injury. The translation of growth factors however can be limited by their short half-lives and suboptimal pharmacokinetic properties. Exogenous neurotrophic factor therapies are still promising therapeutic options but to be successful, more studies are needed to investigate dosing, administration methods and timing of the delivery.

4.2. Growth factor peptide mimetics

Some of the synthetic peptide mimetics discussed here have the potential to be used in place of recombinant growth factors for treatment of TBI. Many of the presented peptides activate the same downstream signalling pathways as the growth factor, often also with a decrease in size and more favourable pharmacokinetic properties. However, not all mimetics may be suitable alternatives to growth factor therapies. In particular, partial agonists of growth factor receptors may reduce rather than enhance neuroprotective and neuroregenerative effects by competing with endogenous growth factors for receptor binding sites *in vivo*. For example, enplastin is a partial FGFR1 agonist, but significantly reduces neurite outgrowth caused by Np65, and the elcamins inhibit FGF1-induced FGFR1 phosphorylation. On the other hand, mimetics with complementary binding sites to native growth factors, or those which have been shown to be additive with growth factors such as B3, D3 and plannexin, have the potential to enhance endogenous neuroprotective and neuroregenerative processes.

Many of the above-mentioned mimetics still face challenges in translation for TBI. Despite often having a longer *in vivo* half-life than the native growth factor, peptide mimetics still only survive minutes-hours and may not have sufficient potency. Delivery strategies must also be carefully considered. Some of the mimetics discussed here are BBB penetrant and would therefore be compatible with systemic administration (e.g. enreptin, FGL), and there may also be a possibility for oral delivery of low molecular weight peptides. However, the large molecular weight and high polarity of many of the described mimetics means that direct administration to the brain may still be necessary. Progress in intranasal delivery of peptides and proteins suggests that this may be a promising route for high molecular weight mimetics, particularly considering the advantages that it is less invasive and can help to limit peripheral side effects.[287]

Furthermore, growth factor receptors can become desensitised when exposed to continually high concentrations of growth factor. Controlled release formulation strategies can be used to overcome such limitations associated with the use of growth factors and their mimetics and may additionally help to protect peptides from proteolysis and thus increase half-life. Hydrogel formulations are of particular interest for CNS therapies due to their biocompatibility, and also enable delivery of a wide

range of cargoes. Current *in vitro* and *in vivo* research suggests that growth factor-based treatments can be combined with cell therapies in a hydrogel formulation to a) control the release and improve the longevity of the growth factor-based therapy and b) improve the survival and integration of cell-based therapy. This enables the benefits of both individual therapies to be combined while reducing some of their limitations.[288]

4.3. Mimetic design and preclinical testing considerations

Although many of the peptide growth factor mimetics described here are derived from the sequence of the parent growth factor, this is not a prerequisite for efficacious compounds. For example, we have highlighted peptides derived from display methods against growth factor receptors, which often approach similar potencies to the native growth factor. Receptor-binding sequences can also be derived from proteins of non-mammalian species, the examples presented here have been shown to activate TrkA downstream signalling pathways involved in neuroprotection and neuroregeneration. Once a receptor-binding peptide is identified, multimerisation can be a simple strategy for mimetic optimisation. Many of the aforementioned mimetics have been dimerised or multimerised to improve their agonist activity. For example, the dimeric BDNF mimetic TDP6 produced positive effects on neuronal survival, whereas the monomeric sequence was a competitive TrkB antagonist. However, this effect is not universal, as the NGF mimetic D3 antagonised NGF-promoted cell survival on dimerisation.

Investigating the molecular mechanism of peptides is an essential step during mimetic development to ensure that compounds of interest are agonists rather than antagonists. Producing peptides which bind tightly to the target receptor does not guarantee that they will activate receptor signalling, so confirmation of phosphorylation of the receptor and downstream proteins is required. However, it is worth noting that this confirmation is often conducted by Western blotting, which in the case of TrkB has recently been shown to not always provide accurate indication of receptor activation.[226] This emphasises the need to use a range of complementary techniques to investigate mechanism, including examining the activity of potential agonists *in vivo* as well as *in vitro*.

The cells used for screening and developing mimetics *in vitro* are also an important consideration, as subtle differences between receptor structure in human and animal cells can lead to the generation of peptides which are species-specific. For example, the dimeric HGF mimetics reported by Ito *et al.* were selected against the human Met ectodomain and did not display any binding to murine or canine Met ectodomains.[149] This highlights the importance of using human growth factor receptors for screening in peptide display methods.

4.4. Patient enrolment in TBI trials

Individuals with TBI will have injuries to different areas of the brain with varying severities, so the selection criteria for participant selection and comparison should be carefully considered. In addition, enrolling patients in clinical trials for TBI can be challenging as they commonly are unable to provide informed consent due to the nature of their injury. Trials often rely on proxy-informed consent and very occasionally deferred consent for the study to be ethical. This can be challenging if a close family member or a legally authorised representative is not available for consent to emergency research, where time is critical.[289]

4.5. Summary

Here we have highlighted potential growth factors and their mimetics which could provide therapeutic benefits in TBI. However, to our knowledge only two of the presented peptides, the NGF mimetic GK-2 and the NCAM mimetic FGL, have previously been tested in *in vivo* models of TBI. To accelerate the development of viable treatment options for TBI patients, more preclinical testing of growth factor mimetics in TBI models is needed. In particular, we believe that the mimetics presented here which have demonstrated beneficial effects on cell survival, neurite outgrowth and functional recovery, particularly in neurons and in *in vivo* models of relevant pathologies (ischemic stroke, SCI, ALS, PD, AD) would be worth investigating in models of TBI.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Emily Atkinson is a PhD researcher from North East England. She achieved her MChem in Medicinal Chemistry with Year in Industry from Newcastle University in 2020. Emily has two years of experience working in industry on medicine formulation and scale-up of metabolite syntheses at CPI, NewChem Technologies and AstraZeneca. She is currently completing her PhD as part of the Transformative Pharmaceutical Technologies Centre for Doctoral Training Programme (2020-2024). Her project focuses on growth factor mimetics for treatment of central nervous system damage, under the supervision of Dr Rachael Dickman, Professor Alethea Tabor and Professor James Phillips. Further research interests include cell therapies and hydrogel delivery systems.

Rachael Dickman was born in 1991 in London. She obtained her MChem in Medicinal Chemistry from the University of Manchester in 2013, and her PhD from UCL in 2018 under the supervision of Professor Alethea Tabor, focussing on synthesis and structural analysis of lantibiotics. After a postdoctoral fellowship with Professor Stefan Howorka at UCL (2018-2020), she was appointed as Lecturer in Drug Discovery at the UCL School of Pharmacy in 2020. Her current research interests include the synthesis of complex (multi)cyclic peptides produced in nature, particularly those with thioether bridges, and development of peptide therapeutics for neurodegeneration as a result of injury or disease.