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Title

Pharmacological modulation of CXCL12/CXCR4/ACKR3 for brain disorders – an overview

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Abstract (350 words)

The CXCL12/CXCR4/ACKR3 axis is essential for brain development and homeostasis. Dysregulation of CXCL12 or its receptors has been associated with various CNS disorders related to neurodevelopmental defects, neuroinflammation, neurodegeneration and brain tumors. This signaling axis represents an attractive therapeutic target, and large efforts have led to the development and use of specific pharmacological modulators for brain diseases. While pharmacological modulation of CXCR4 has extensively been studied in the last decades, targeting ACKR3 has only recently emerged as a critical component of the CXCL12 signaling network, driving growing interest in the development of ACKR3-specific modulators. This review synthesizes CXCL12-induced distinct signaling mechanisms downstream of the receptors: G protein-dependent for CXCR4, and β-arrestin-biased for ACKR3, which acts as a scavenger. We also describe the expression and function of CXCL12, CXCR4 and ACKR3 under physiopathological conditions in the CNS. We exhaustively depict the current status of specific modulators of CXCL12 and its receptors, from *in vitro* testing to preclinical studies and clinical trials, through exploring various neuropathological contexts , e.g. multiple

sclerosis, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis or cancer. We highlight how pharmacological modulation of one or another triad component drives context-dependent outcomes, and we point out the limitations that should carefully be addressed in the future, to advance CXCL12/CXCR4/ACKR3 targeting approaches for CNS pathologies.

Plain English summary (250 words)

Chemokines are small molecules that regulate many essential biological processes by guiding oriented cell movement. The chemokine CXCL12 and its two receptors, CXCR4 and ACKR3, are crucial in tissue development and balance. In the central nervous system (CNS), dysregulation of this signaling axis leads to the development of various pathologies including Alzheimer's and Parkinson's diseases, multiple sclerosis, amyotrophic lateral sclerosis or brain cancer. As a consequence, several drugs targeting CXCL12, CXCR4 or ACKR3 have been developed aiming at treating such diseases. Here, we sum up current knowledge regarding the molecular mechanisms of CXCL12/CXCR4/ACKR3 signaling and the role of this pathway in the brain, under normal and diseased conditions. We also summarize and discuss the effect of pharmacological modulators in various contexts, from their early development to their validation in experimental models and human patients.

Keywords (3-10)

Chemokines, neuroinflammation, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, neuro-oncology

1. Background

G protein-coupled receptors (GPCRs) represent the largest class of cell membrane receptors in human, counting over 800 gene members. Their location at the plasma membrane allows the transduction of extracellular signals and their transformation into physiological outputs. Main endogenous ligands include hormones, odors, neurotransmitters, or chemokines. Coupling between ligands and GPCRs is crucial for physiological processes related to sensory, neurological and immune functions. Consequently, defective or abnormal GPCR

signaling is observed in various pathological conditions, such as cardiac deficits, type 2 diabetes, obesity, depression, Alzheimer's disease (AD) chronic inflammation and cancer [1]. These receptors therefore constitute attractive targets for drug development and GPCR-targeting compounds represent over a third of all current FDA-approved drugs [2]. Moreover, central nervous system (CNS) diseases are the most prominent disorders implicating GPCR pharmacological targeting [3].

Among the large GPCR family, chemokines and their receptor(s) form a complex network that orchestrates immune responses by guiding the migration of immune cells to inflammation sites. Chemokine receptors are part of the *Rhodopsin-like* (or class A) family of GPCRs [1], and are mostly activated by chemokines. Chemokines are small secreted peptides (8-10 kDa) that belong the functional superfamily of cytokines. Upon binding to their receptor(s), they induce an oriented cell migration process called chemotaxis, which is essential to embryogenesis, adult tissue homeostasis and wound healing [4].

Most chemokine receptors are promiscuous, i.e., can bind and respond to more than one ligand. However, their different interactors belong to one chemokine structural group, defined by the position of two cysteine residues (C, CC, CXC or CX3C). Chemokine receptors are consequently coded by their ligand group specificity [5].

Chemokine receptors can be divided into two major functional groups, based on their downstream cellular effectors: (i) "classical" chemokine receptors, which are G protein-coupled receptors that primarily signal through Gi-type G proteins to induce intracellular cascades and cell migration, and (ii) "atypical" chemokine receptors (ACKRs) that generally do not activate canonical G protein signalling but rather regulate chemokine availability and distribution through high-affinity ligand binding, ligand internalization and trafficking. These mechanisms, often involving β-arrestin-dependant pathways, shape chemokine gradients and thereby modulate leukocyte migration and inflammatory responses [5].

Besides their well-described role in the immune system, chemokines play an important role in the central nervous system (CNS). In the adult CNS, three chemokine signaling pathway have mostly been studied: CCL2/CCR2, CXCL12/CXCR4/ACKR3 and CX3CL1/CX3CR1.

Changes in their expression and function have been associated with various CNS disorders such as Alzheimer's and Parkinson's (PD) diseases, HIV-associated encephalopathy, stroke, multiple sclerosis (MS), and also with brain tumor development [6]. Among these, the CXCL12/CXCR4/ACKR3 triad stands out with its essential role in CNS development.

In this review, we summarize the broad implication of CXCL12/CXCR4/ACKR3 chemokine-receptor axis in the CNS, and we especially focus on recent approaches for modulating CXCL12/CXCR4/ACKR3 in CNS disorders.

2. CXCL12/CXCR4/ACKR3 signalisation

The CXCL12/CXCR4/ACKR3 signalling axis plays a critical role in various tissues, in both developmental and adult physiopathology (Figure 1). The CXCL12/CXCR4 duo has first been described in tissue organization during embryogenesis, hematopoietic cell trafficking and immune surveillance. Shortly later, this axis was rapidly associated with disease, such as cancer (e.g., various solid tumors and non-Hodgkin lymphoma) or acquired (e.g., AIDS) or innate defects in the immune system (e.g., WHIM syndrome and multiple myeloma) [7].

ACKR3 and CXCR4 are the two most conserved chemokine receptors among vertebrates, indicating their essential function. Indeed, CXCR4 deletion in mice has lethal consequences related to disrupted development of the immune, circulatory and central nervous system [8][9][10][11]. This phenotype is very similar to what was observed in mice lacking CXCL12 (i.e., reduced haematopoiesis and cardiac defects) [12]. In the same line, mice deficient in ACKR3 exhibit severe abnormalities in cardiovascular and lymphatic systems, also leading to perinatal lethality [13][14]. The three components of this signalling pathway show strong homology between human and mouse, at the level of both gene and protein. Mice models therefore allow an appropriate preclinical investigation for various pathologies [15].

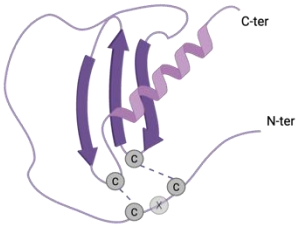
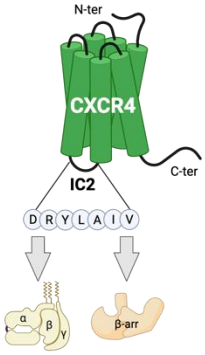
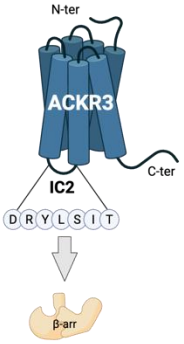
	CXCL12 *SDF-1, PBSF*	CXCR4 *CD184, fusin, LESTR*	ACKR3 *RDC1, CXCR7*
Structure			
Isoforms	Human: 7 (α, β, γ, δ, ε, θ, iso7) Mouse: 3 (α, β, γ)	Human: 2 (A, B) Mouse: 2 (A, B)	Human: 1 Mouse: 1
Endogenous interactors	CXCR4 ACKR3 ACKR1* ACKR5	CXCL12 vCCL2 MIF β-defensins 2 and 3 eUb gp120 (HIV)	CXCL12 CXCL11 vCCL2 MIF PAMP-12 opioid peptides

Figure 1 - General properties of CXCL12, CXCR4 and ACKR3. CXCL12 structure is represented, with its characteristic CXC motif, three parallel β-strands, overlapping α-helix and its unstructured amino and carboxy-terminal ends. CXCR4 is represented as a GPCR with a DRYLAIV amino acid sequence in its second intracellular loop (IC2), allowing the recruitment of G protein and β-arrestin upon ligand binding. ACKR3 has a structure similar to CXCR4, with a modified sequence in IC2 (DRYLSIT), and only recruits β-arrestin. The number of isoforms in human and mouse proteins are indicated, as well as all known endogenous interactors. * indicates that ACKR1 only binds CXCL12 homodimers. Created with Biorender.

2.1. **CXCL12**

The chemokine CXCL12, previously known as stromal cell-derived factor-1 (SDF-1) or pre-B cell growth-stimulating factor (PBSF), is probably the most studied member of the chemokine family. Although classified as a homeostatic chemokine, CXCL12 also plays an important role during inflammation, cell proliferation and chemotaxis [16]. It is the major chemokine produced in the bone marrow, where it regulates the homing, quiescence and differentiation of hematopoietic progenitor cells [17].

In human, the *Cxcl12* gene is located on chromosome 10q11 and initiates the production of seven isoforms resulting from alternative splicing (α, β, γ, δ, ε, θ and the predicted isoform iso7), CXCL12α being the most prevalent and ubiquitously expressed protein [18]. The splice variants differ by their fourth exon and display tissue-dependent expression and functions [7]. It is to be noted that the splice variant CXCL12 γ is located in very active, less vascularized organs such as the brain and the heart [18]. The homologous sequence in *Mus musculus* genome is located on chromosome 6 and gives rise to only three protein isoforms (α, β, γ).

The mature protein has a typical chemokine fold, characterized by three parallel β-strands, an overlapping C-terminal α-helix and disordered N- and C-terminal ends that play crucial role in receptor activation [19]. As part of the CXC chemokine subfamily, characterized by the presence of two cysteines separated by one other amino acid at the amino-terminal part, CXCL12 three-dimensional structure is defined by two disulphide bonds, Cys9-Cys34 and Cys11-Cys50, essential for its conformation and binding to CXCR4.

Besides its well established interactions with CXCR4 and ACKR3, CXCL12 has recently been described for binding the atypical chemokine receptors ACKR1 (binding the dimeric form of CXCL12) and the newly described member ACKR5 (formerly known as GPR182) [20]. CXCL12 binding to those receptors leads to different molecular and biological consequences.

2.2. **CXCR4**

CXCR4, also known as cluster of differentiation 184 (CD184), fusin or leukocyte-derived seven-transmembrane domain receptor (LESTR), was originally discovered for its role as co-factor for human immunodeficiency virus (HIV) cell entry, via gp120 binding, and then identified as receptor for the CXCL12 chemokine [21][22].

CXCR4 is highly expressed in the thymus, particularly in immature double positive CD4+/CD8+ thymocytes [9]. It is found at the surface of all leukocytes, especially hematopoietic stem cells and progenitors.

In the human genome, *Cxcr4* is located on chromosome 2q22. Transcription forms two splice variants, namely CXCR4-A and -B. It is thought that CXCR4-B is the most active isoform, while CXCR4-A is more of a back-up receptor with reduced efficiency. Like its chemokine ligand CXCL12, CXCR4 is an evolutionary conserved protein showing 89% similarity between human and mouse, suggesting the biological importance of the CXCL12/CXCR4 pathway, at least in mammals [23].

While CXCL12 is the most widely described ligand for CXCR4, the receptor also binds the macrophage migration inhibitory factor MIF, the viral protein vCCL2, β-defensins 2/3 and the extracellular ubiquitin (eUb) [9][24][25][26]. CXCR4 also oligomerizes with other chemokine and non-chemokine receptors, such as CCR5 and ACKR3, the cannabinoid receptor 2 (CB2), or the delta opioid receptor, inducing distinct functional consequences [27][28].

2.3. **ACKR3**

ACKR3 was initially described as the orphan G-protein coupled receptor RDC1 (Receptor-Deficient Chemokine 1) [29]. Several years later, the RDC1 was renamed as CXCR7 after uncovering the binding of two CXC-chemokine ligands, i.e., CXCL12 and CXCL11 [30][31][32]. Genomic proximity between *Ackr3* and *Cxcr4* genes (position 2q22 and 2q37, respectively) as well as their sequence similarity facilitated the deorphanization of the receptor. In 2014, CXCR7 was assigned to the family of atypical chemokine receptors, and finally renamed as ACKR3 [5].

ACKR3 shares its chemokine ligands CXCL12 and CXCL11 with the chemokine receptors CXCR4 and CXCR3, respectively. Interestingly, CXCL12 binding affinity is approximately 10-fold higher for ACKR3 than CXCR4 [31]. Besides, ACKR3 also has non-chemokine binding partners: vCCL2, MIF, the 12 C-terminal residues of the proadrenomedullin peptide (PAMP-12) and a broad range of opioid peptides [33][34][35].

Expression of ACKR3 has been described in vascular endothelial cells, B cells, mesenchymal cells, in diverse regions of the CNS and in the adrenal glands [36].

ACKR3 and CXCR4 share very similar structural features (i.e., seven transmembrane domains, three intracellular and three extracellular loops), yet are radically different in their ligand-induced response (see section 2.5.). Atypical chemokine receptors are unified by their inability to signal via G proteins and consequent failure to induce Ca^{2+} transients and mediate cell migration [37]. Accordingly, ACKR3 is widely recognized as a β-arrestin-biased receptor [38], although it has been reported to exceptionally signal through G proteins in primary human astrocytes and human glioma cells [39]. Interestingly, ACKR3 transmembrane helices adopt a basal conformation that is similar to active canonical receptors. This active-like structure is likely to contribute to the constitutive binding to β-arrestin and might potentially participate in receptor trafficking between cell membrane and intracellular vesicles [40]. This G protein-independent response characteristic to atypical receptors is explained by a variation in sequence in the second intracellular loop of the receptor (IC2), where the DRYLAIV amino acid motif present in CXCR4 is modified into a DRYLSIT sequence in ACKR3, unable to interact with G protein [41].

2.4. **Other CXCL12 receptors (ACKR1 and ACKR5)**

The atypical receptors ACKR1 and ACKR5 are two promiscuous receptors, both binding over ten chemokine ligands, including CXCL12.

ACKR1, or DARC (Duffy Antigen/Receptor for Chemokines) has also been reported for CXCL12 binding, but only in its dimeric form [42]. Unlike with its other receptors, interaction between CXCL12 homodimers and ACKR1 does not lead to G protein coupling, nor β-arrestin recruitment, and consequently does not lead to intracellular signaling [20].

ACKR5, also known as GPR182, is the newest member of the ACKR family [43]. As part of the atypical chemokine receptors, ACKR5 does not induce G protein-mediated signaling but shows strong constitutive interaction with β-arrestins 1 and 2. In the amino acid sequence, the DRYLAIV motif located in the IC2 of CXCR4 is modified into DRYVTLT, supporting the lack of G protein coupling [43]. ACKR3 is the closest paralogue of ACKR5, and both receptors have overlapping ligand binding for CXCL11 and CXCL12. However, unlike

CXCL12 binding to CXCR4 or ACKR3, CXCL12-ACKR5 interaction hardly influences β-arrestin recruitment [44].

As ACKR5 was very recently added in the ACKR family and ACKR1 does not directly impact CXCL12/CXCR4/ACKR3 signaling, their contribution in this axis remains to be determined and will not be further discussed in the following sections.

2.5. **CXCL12-mediated signalling pathways**

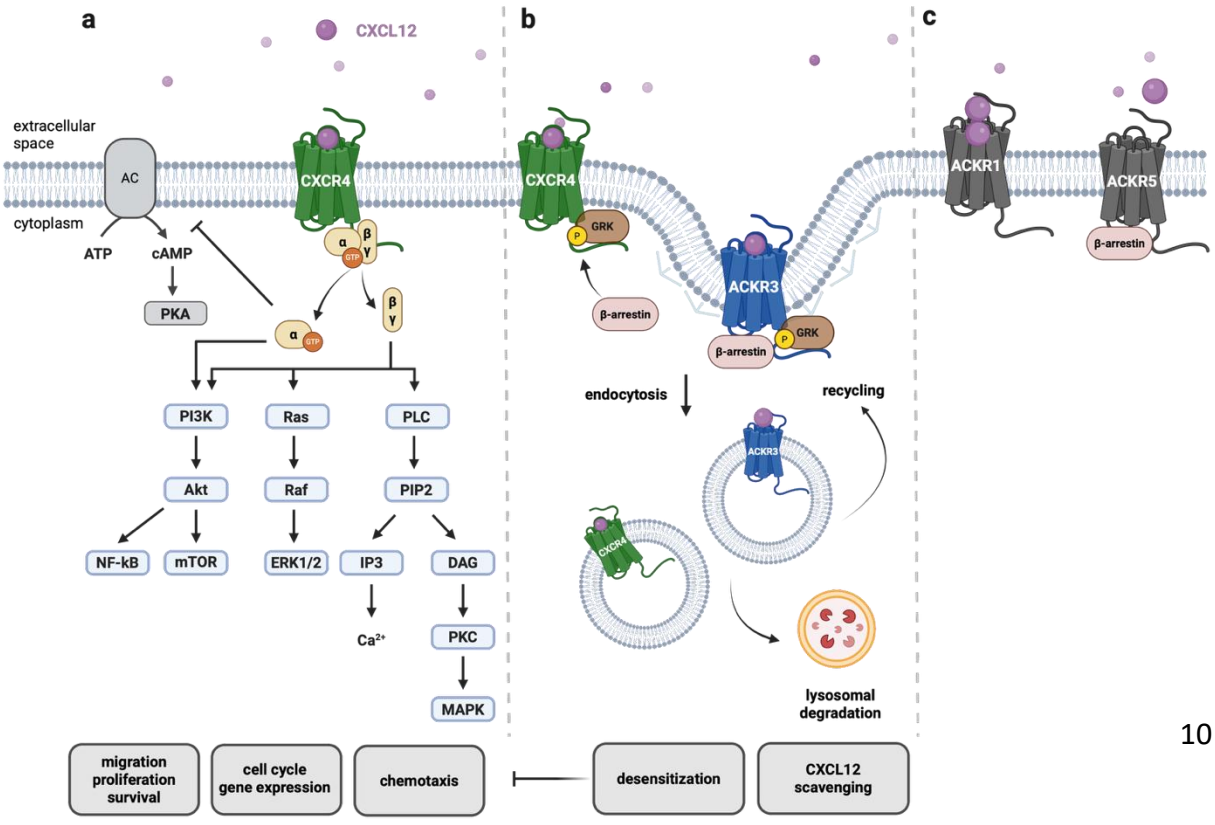
CXCL12 is a ligand for CXCR4 and ACKR3 and induces different molecular and biological consequences when binding to one or the other receptor (Figure 2).

CXCL12 binding to CXCR4 triggers the conformational change of the receptor, promoting both the GDP/GTP exchange at the $G_{\alpha i}$ and the consecutive $G_{\alpha i}/G_{\beta\gamma}$ dissociation. The GTP-loaded $G_{\alpha i}$ inhibits the adenylyl cyclase-mediated cyclic adenosine monophosphate (cAMP) production and thereby reduces the activation of the downstream effector protein kinase A (PKA). Upon receptor activation, both $G_{\alpha i}$ subunit and $G_{\beta\gamma}$ heterodimer can activate phosphoinositide-3 kinase (PI3K), followed by protein kinase B (also known as Akt) and mTOR, leading to cell migration, proliferation and survival. The dissociated $G_{\beta\gamma}$ dimer is involved in the activation of Ras/Raf/ERK cascade, inducing cellular consequences related to gene expression and cell cycle progression. $G_{\beta\gamma}$ dimer also triggers phospholipase C (PLC) activation, which in turn catalyzes the hydrolysis of PIP2 (phosphatidylinositol 4,5-bisphosphate) into DAG (diacylglycerol) and IP3 (inositol 1,4,5-triphosphate). DAG promotes the activation of protein kinase C (PKC) and mitogen associated protein kinase (MAPK), eventually leading to chemotaxis. IP3 triggers the release of Ca^{2+} from the endoplasmic reticulum into the cytoplasm [45][46][47].

Following CXCL12 binding, CXCR4 is rapidly phosphorylated by G protein-coupled receptor kinases (GRKs) on serine residues located on the intracellular carboxy-terminal extremity. The phosphorylated residues recruit β-arrestin, promoting the uncoupling of G proteins and inducing clathrin-mediated receptor endocytosis, thereby inducing receptor desensitization [48].

Unlike CXCR4, ACKR3 functions as G protein-independent receptor by directly recruiting β-arrestin2 upon binding of CXCL11 or CXCL12 [38]. While β-arrestin-dependant receptor internalization is by far the most described signalling function for ACKR3, recent work identified BMP2K (bone morphology protein 2-inducible kinase) as a novel ACKR3-interactor capable of inducing receptor endocytosis in a β-arrestin-independent manner [49]. Internalization of the receptor-ligand complex in turn leads to their lysosomal degradation and recycling. ACKR3 continuously cycles between the plasma membrane and endosomal compartment. However, receptor internalization increases upon ligand binding [50]. As a result, ACKR3 acts as a scavenger for CXCL12, thereby regulating extracellular concentration of the chemokine and indirectly influencing CXCL12-induced CXCR4 signalisation.

The two chemokine receptors for CXCL12, CXCR4 and ACKR3 can form homo- and heterodimers, leading to different signaling pathways. CXCR4-CXCR4 homodimers lead to G protein-independent JAK/STAT activation [51], while CXCR4-ACKR3 heterodimers influence CXCL12-induced signals, thereby inhibiting $G_{\alpha i}$-mediated signalization [52]. It is to be noted that CXCR4 also can heterodimerize with other GPCRs (e.g., CCR2, CCR5, CXCR3, beta-2 adrenergic receptor and opioid receptors), leading to various complex cellular responses



[27][53][54][55].

Figure 2 - Schematic representation of the CXCL12/CXCR4/ACKR3 signalling pathways. **a)** CXCL12 binding to CXCR4 recruits a Gi-type G protein, leading to Gαi and Gβɣ dissociation. Gαi suppresses cAMP production by adenylyl cyclase (AC) and stimulates the PI3K/Akt/mTOR pathway, thereby promoting cell migration, proliferation, and survival. The Gβγ subunit also activates PI3K, in addition to triggering the Ras/Raf/ERK cascade, promoting cell-cycle progression and gene expression, as well as phospholipase C activation, contributing to chemotaxis. **b)** CXCR4 desensitization occurs after intracellular phosphorylations by GRKs, β-arrestin recruitment, and clathrin-mediated endocytosis, eventually dampening CXCR4-mediated signaling mechanisms. In a similar way, CXCL12-ACKR3 interaction triggers specific phosphorylations by GRKs, followed by β-arrestin recruitment and ligand-receptor complex internalization. This eventually leads to chemokine scavenging, their degradation and/or receptor recycling. **c)** ACKR1 binds CXCL12 homodimers, without inducing G protein nor β-arrestin recruitment. ACKR5 constitutively recruits β-arrestin, with or without CXCL12 interaction. Receptor homo/hetero-dimerization upon CXCL12 binding is not represented. Figure adapted from [44]. Created with Biorender.

3. Physiopathology: focus on the CNS

The CXCL12/CXCR4/ACKR3 chemokine axis plays a critical role in the CNS, both during development and in adult brain homeostasis.

Similarly to its function in other organs, CXCL12 guides neuronal precursor migration during embryogenesis, contributing to hippocampal and cortical organization [56]. CXCR4 null mice have defects in neural precursor survival and oligodendrocyte progenitor cell (OPCs) migration during embryonic and postnatal CNS development [57].

In postnatal and adult stages, CXCL12 also participate in axonal guidance, synaptic functions and stemness maintenance. High levels of CXCR4 and CXCL12 are observed in the subventricular zone (SVZ) adjacent to the lateral ventricles and the subgranular zone (SGZ) located in the dentate gyrus, which are both neural stem cell niches in the adult brain [58][59]. Numerous studies have underscored the regulatory role of CXCL12 through both CXCR4 and ACKR3 for the proper functioning of neural progenitor cells (NPC), favouring their survival, promoting quiescence and guiding NPC migration towards CNS damaged sites [60][61][62].

Among ACKRs, ACKR3 is considered as endowed with the most prominent functions [63] and is broadly expressed across various brain regions, such as the cortex, hippocampus

(including the dentate gyrus), hypothalamus, cerebellum, olfactory bulbs, subventricular zone and spinal cord [64]. In ACKR3-Venus knock-in mice, strong expression of the receptor has been shown in brain endothelial vascular cells, hippocampal GABAergic interneurons and neuroblast neighbouring cells [65]. In addition to its role in chemokine scavenging and gradient regulation, ACKR3 has been shown to exert non-canonical functions in the CNS through its interaction with Connexin 43 (Cx43), the most abundant gap junction protein. In astrocytes, ACKR3 can interact with Cx43, promoting its internalization, thereby reducing astrocytic gap junctions and intracellular communication [66]. Such relationship between ACKR3 and gap junctions might be relevant in CNS physiopathology, such as demonstrated in the context of subarachnoid hemorrhage [67].

In adults, the CXCL12/CXCR4 pathway has been shown to exert neuroprotective effects, favouring neural repair after cerebral ischemia [68]. Although CXCL12 is constitutively expressed in the CNS, its expression increases under pathological conditions such as brain ischemia, brain tumor or multiple sclerosis [69].

Given its multifaced roles in neurodevelopment, neural stem cell regulation and neuroprotection, dysregulation of the CXCL12/CXCR4/ACKR3 axis contributes to CNS pathogenesis, making CXCL12 and its receptors attractive targets for pharmacological intervention [6].

4. An overview of the modulators of the CXCL12/CXCR4/ACKR3 axis

Like other GPCRs, CXCR4 and ACKR3, as well as their shared ligand CXCL12, have been in the center of recent drug development endeavors. After a brief description of these compounds in this section, we will thoroughly review ongoing research in the context of various CNS-diseases (Table 1).

GPCR targeting compounds can be from different classes, ranging from synthetic small molecules, metabolites, peptides or antibodies [1]. The principal modulators of the CXCL12/CXCR4/ACKR3 axis that have been tested in CNS-related pathological conditions are listed in Table 1. Clinical trials are indicated when applicable.

Target	Modulator	Type of modulator	Structure	IC_{50} (nM)	MW (g/mol)	BBB permeant	Condition/disease addressed (preclinical or clinical)	Clinical trial			FDA approved indication	First publication
								Reference(s)	Phase(s)	Status		
CXCL12	**NOX-A12** *Olaptesed Pegol*	Antagonist	RNA aptamer	< 1 nM	472.5	LOW	Glioblastoma (MGMT unmethylated)	NCT04121455	1/2	Active	NA	[82]
CXCR4	**AMD3100** *Plerixafor©, Mozobil M3100*	Antagonist	Small molecule (bicyclam)	44 nM	502.78	LOW	Recurrent high-grade glioma	NCT01339039 (+ bevacizumab)	1	Terminated	Multiple myeloma Non-Hodgkin lymphoma	[67]
							Newly diagnosed glioblastoma	NCT01977677; NCT03746080 (+ IR and TMZ)	1/2 ; 2	Completed		
							WHIM syndrome	NCT02231879	3	Completed		
							Multiple myeloma	NCT00103662	3	Completed		
							Non-Hodgkin lymphoma	NCT00103610	3	Completed		
							Amyotrophic lateral sclerosis	NA	NA	NA		
							Multiple sclerosis	NA	NA	NA		
							B-ALL and T-ALL brain invasion	NA	NA	NA		
							West Nile Virus encephalitis	NA	NA	NA		
	AMD11070 *AMD070 Mavorixafor©*	Antagonist	Small molecule (noncyclam)	13 nM	349.47	YES	WHIM syndrome	NCT03995108	3	Active	WHIM syndrome	[71]
							Meningeal leukemia	NA	NA	NA		
	ZINC49067615	Antagonist	Small molecule (noncyclam, AMD11070 derivatives)	?	359.47	YES	Neurodegeneration (AD, PD)	NA	NA	NA	NA	[107]
	ZINC103242147			?	364.53	YES						
	CPZ1344	Antagonist	Small molecule	?	?	?	Glioblastoma	NA	NA	NA	NA	[129]
	PRX177561			~ 1 uM	?	YES						[133] [134]
	Peptide R			~ 5 uM	900,08	?						[130]
	P2G	Antagonist	Peptide (chimeric CXCL12)	562 nM	~ 8 000	unlikely	Glioblastoma	NA	NA	NA	NA	[135]
ACKR3	**ACT-1004-1239**	Antagonist	Small molecule (piperidine scaffold)	3.2 nM	522.55	YES	Healthy	NCT03869320; NCT04286750	1 ; 1	Completed	NA	[78]
							Multiple sclerosis	NA	NA	NA		
	CCX771	Agonist or Antagonist	Small molecule (undisclosed)	4.1 nM	?	?	Glioblastoma Multiple sclerosis Alzheimer's disease	NA	NA	NA	NA	[76]
	AMD3100	Agonist	Small molecule (bicyclam)	uM range	502.78	LOW	Alzheimer's disease	NA	NA	NA	NA	[75]
	VUF11207	Agonist	Small molecule (styrene-amide scaffold)	8.8 nM	470.58	?	Glioblastoma	NA	NA	NA	NA	[77]
	X7Ab	Antagonist	Chimeric monoclonal antibody	30 nM	~ 150k	unlikely	Glioblastoma	NA	NA	NA	NA	[80]

Table 1 - Overview of the modulators of the CXCL12/CXCR4/ACKR3 axis that have been addressed in CNS pathologies. Listed condition/diseases are restricted to CNS pathologies, or others only when tested in clinical trials. *Legend*: ? =unknown/unpublished, NA = Not Addressed. First publication refers to the first authors discovering/mentioning the modulator.

From all pharmacological modulators of the axis, the bicyclam AMD3100, also known as Plerixafor, is by far the most widely described. From 1990's until early 2000's, AMD3100 was initially named JM3100 and tested to block HIV-1 virus entry into CD4+ T cells for the treatment of AIDS [70]. While its application was discontinued due to cardiac toxicity and insufficient efficiency, researchers unexpectedly highlighted the upregulated level of hematopoietic cells in blood circulation following Plerixafor administration. This effect was then further investigated for different diseases and the use of Plerixafor was approved in 2008 by the FDA for non-Hodgkin lymphoma and multiple myeloma patients [71]. The increase in CD34+ hematopoietic cells also showed promising therapeutic effects for the treatment of WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and

Myelokathexis), a rare hereditary immunodeficiency caused by a gain-of-function mutations in the *Cxcr4* gene where young mature leucocytes are retained in the bone marrow. In a phase 3 clinical trial, Plerixafor administration significantly improved WHIM patients' quality of life (NCT02231879) [72]. Besides its positive contribution in immunological pathologies, the use of Plerixafor for cancer treatment also is highly investigated. While overall well tolerated, mild adverse events associated with Plerixafor include diarrhea, nausea, fatigue, injection site reactions, headache, dizziness and arthralgia [73]. To cope with Plerixafor-induced toxicity and its lack of oral bioavailability due to its lipophilic nature, numerous other small CXCR4 antagonists have been developed and tested in various pathological conditions.

The second FDA-approved CXCR4 antagonist is Mavorixafor, also known as AMD070, AMD11070 or XOLREMDI©□. Initially, AMD070 was described as an anti-HIV drug, just as AMD3100 [74]. This compound was then tested for its immunomodulatory properties, particularly for the treatment of WHIM syndrome. In a phase 3 trial (NCT03995108), Mavorixafor administration was well tolerated and demonstrated a clinically relevant increase of circulating lymphocytes and neutrophils in WHIM patients [75]. This led to Mavorixafor approval by the US FDA in April 2024 [76].

While Plerixafor has a lower antagonism efficacy *in vitro* compared to Movarixafor (IC_{50} values are 44 nM and 13 nM, respectively), it has a superior effect in hematopoietic stem cells mobilization *in vivo*. This biological difference was attributed to pharmacological properties of the two modulators, with Movarixafor acting as a full antagonist (inhibiting both G protein and β-arrestin recruitment) and Plerixafor acting as a biased antagonist, stimulating β-arrestin recruitment while fully antagonizing G protein activation [77].

In contrast to CXCR4, fewer studies describe molecules that target ACKR3. In 2009, the CXCR4 inhibitor AMD3100 was also demonstrated as ACKR3 agonist at high concentration (> 10 uM) [78]. Besides, ACKR3-specific modulators have also been described. Among the most common small molecules, one can cite CCX771, VUF11207, and ACT-1004-1239 [79][80] [81]. VUF11207 and ACT-1004-1239 are respectively specific agonist and antagonist of the receptor, while CCX771 has controversial pharmacological properties. This molecule

was initially described by Zabel et al. as a selective ACKR3 agonist, inducing β-arrestin recruitment and reducing CXCL12-induced tumor cell migration [79]. However, Cruz-Ortengo et al. rather described CCX771 as an ACKR3 antagonist in the context of multiple sclerosis [82]. In 2018, Salazar et al. generated X7Ab, an anti-ACKR3 single chain antibody for the treatment of glioblastoma [83]. Regarding their clinical application, ACT-1004-1239 is the first-in-class ACKR3 modulator that has undergone phase 1 clinical trials for assessing its safety, tolerability and pharmacokinetics (NCT03869320 and NCT04286750). Its oral administration was well tolerated in healthy humans and induced a dose-dependent increase of CXCL12 concentration [84].

Regarding the targeting of the ligand, NOX-A12 stands out in literature as RNA aptamer anti-CXCL12 [85]. In preclinical and clinical studies, NOX-A12 is safe and mobilizes leucocytes and hematopoietic stem cells into peripheral blood in a dose-dependent manner [86]. This CXCL12-inhibitor has already undergone clinical trials for stem cell transplantation (NCT00976378 and NCT01194934), multiple myeloma (NCT01521533), chronic lymphocytic leukemia (NCT01486797), metastatic colorectal and pancreatic cancer (NCT03168139) and glioblastoma (NCT04121455).

5. Targeting the CXCL12/CXCR4/ACKR3 axis in CNS pathologies

As previously said, while CXCL12 and its receptors have been described in neurological development, they also participate the pathogenesis of different CNS disorders. This section summarizes both the possible role of the CXCL12/CXCR4/ACKR3 axis in various CNS diseases and the applications for CXCL12/CXCR4/ACKR3 modulators in those disorders, divided between the fields of neuroinflammation and neuro-oncology.

5.1. Neuroinflammation

The understanding of brain immunity has drastically evolved in the last decades. Originally, it was widely thought that the brain was isolated from peripheral immune system because of the existence of a specialized barrier, later designated the blood–brain barrier (BBB). In this

first model, the brain was considered as an “immune privileged” organ, where microglial cells are the only CNS resident immune component, and peripheral immune cell infiltration is restricted to disease states and inflammation. Between 1990 and 2010, studies showed immune cell infiltration in healthy contexts, including CNS plasticity and repair. This belief was called the “protective immunity” paradigm, in which the CNS is subjected to immune surveillance in homeostasis. More recent work identified specialized immunological compartments in the brain, containing immune cells and preventing excessive neuroinflammation. These so-called “brain immunological niches” include the meninges, the choroid plexuses and the perivascular spaces [87].

While neuroinflammation can be protective in some contexts, it can also be deleterious and lead to various pathologies. The contribution of the CXCL12/CXCR4/ACKR3 axis has been extensively investigated in multiple conditions involving inflammation ranging from multiple sclerosis (MS), neurodegenerative disorders (e.g., AD, PD or amyotrophic lateral sclerosis (ALS)), or stroke-induced acute CNS inflammation (Figure 3).

Recent literature review supports and describes the potential of targeting CXCL12/CXCR4/ACKR3 chemokine/receptor axis in those various pathological conditions, aiming for neuroprotection and cognitive improvement [88].

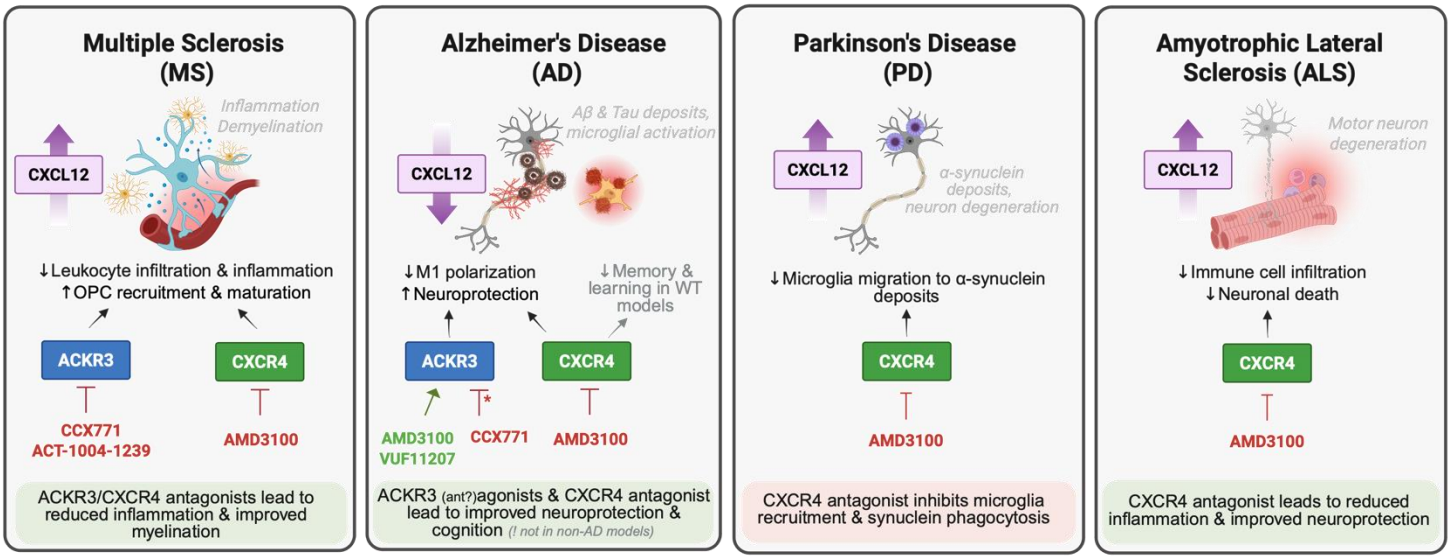


Figure 3 - Impact of the pharmacological modulation of the CXCL12/CXCR4/ACKR4 axis in neuroinflammation. In Multiple Sclerosis (MS), pharmacological inhibition of ACKR3 using CCX771 or ACT-1004-1239 increases the maturation of OPCs into myelinating oligodendrocytes. AMD3100 abolishes the protective function of CXCR4 in OPC maturation. In Alzheimer's Disease (AD), ACKR3 has a neuroprotective effect, increasing microglial phagocytic capacities and amyloid beta clearance. CXCR4 blockage also leads to neuroprotection in AD models, while it induces learning and memory deficits in non-AD animals. In Parkinson's physiopathology (PD), CXCR4 antagonism contributes to a reduced inflammation related to synuclein aggregates, and a decreased neurotoxicity, which here suggests that CXCR4 targeting may be deleterious for the disease. In Amyotrophic Lateral Sclerosis (ALS) affecting motor neurons, CXCR4 inhibition with AMD3100 decreases inflammation and prevents neurons degeneration.
Legend: Green compounds/arrows represent agonists, and red compounds/arrows represent antagonists (*) Note that CCX771 was initially described as an antagonist, although data suggest it may act as an agonist (Das et al). Created with Biorender.

5.1.1. **Multiple sclerosis (MS)**

The relation between the CXCL12/CXCR4/ACKR3 axis and multiple sclerosis (MS), the most common autoimmune disease affecting the CNS, has been extensively reviewed in 2017 by Chu et al. [69].

Several studies investigated the function of CXCL12 and its receptors in MS, using preclinical experimental murine autoimmune encephalomyelitis models (EAE). This experimental model for human MS recapitulates the key pathological features of the disease, including chronic inflammation, demyelination and neurodegeneration [89].

In EAE models, CXCL12 has been reported to exert anti-inflammatory effects by restricting CXCR4+ leukocytes to perivascular spaces [90]. In contrast, elevated CXCL12 levels within the *corpus callosum* (a major myelinated fiber tract between the two cerebral hemispheres) promote the migration of CXCR4-expressing OPCs, facilitating their recruitment to demyelinated lesions and supporting remyelination. These effects were demonstrated by CXCR4 antagonism using AMD3100 [91].

These apparently opposing effects on cell migration in the context of MS might be explained by the spatial distribution of CXCL12 within the CNS. High CXCL12 expression at the abluminal side of the BBB retains CXCR4+ leukocytes, confining them to perivascular niches and thereby limiting excessive immune cell infiltration into the CNS. Conversely, under

pathological conditions such as demyelinating lesions where CXCL12 levels increase within the brain parenchyma, including the *corpus callosum*, CXCR4+ OPCs exhibit enhanced migratory capacities, promoting their recruitment and maturation at sites of damage and ultimately contributing to remyelination.

Besides the CXCR4-mediated function described hereabove, Cruz-Orengo et al. identified ACKR3 as key factor facilitating leukocyte entry into the CNS parenchyma, suggesting that this receptor blockade could be beneficial for the treatment of multiple sclerosis [92]. In a follow-up study, they showed that ACKR3 blocking using CCX771 as potent antagonist improves EAE mice clinical outcome, both by preventing excessive inflammation and preserving axonal integrity [82]. The benefits of ACKR3 antagonism in MS could most likely be attributed to a subsequent increase of abluminal CXCL12 levels, preventing excessive leukocyte abundance in the CNS parenchyma.

The use of CCX771 in EAE preclinical models was further supported by Williams et al., showing that CCX771 promotes maturation of OPCs towards pro-myelinating oligodendrocytes [93]. More recently, Pouzol et al. also validated ACKR3 as a valuable target for multiple sclerosis using another promising potent antagonist, ACT-1004-1239, capable penetrating into the CNS and improving mice clinical score [94][95]. Taken together, these data suggest that the CXCL12/CXCR4/ACKR3 is a promising therapeutic candidate to improve remyelination in MS. While no evidence in human has yet been described, ACT-1004-1239 was shown safe in early phase trials and might be further tested in conditions where ACKR3 blocking is a promising approach in preclinical studies, such as MS [84].

Besides the function of CXCL12 and its receptors in the context of MS, Andrés-Benito et al. showed in increased CXCL12 level in the cerebrospinal fluid (CSF) of MS patients, which can be useful for diagnosis [96].

5.1.2. **Neurodegeneration**

Studies indicated that CXCL12, CXCR4 and ACKR3 play important roles in brain plasticity, resulting in different outcomes in neurodegenerative disorders.

AD is the most common form of dementia, characterized by extracellular amyloid beta (Aβ) accumulation and hyperphosphorylated tau protein neurofibrillary tangles. In AD patients, the expression of CXCL12 and its receptors is inversely correlated, CXCL12 being downregulated while CXCR4 and ACKR3 levels are elevated in comparison with healthy tissue. While *CXCL12* gene expression decreases and *CXCR4* gene expression significantly increases in all brain regions [97], ACKR3 increased protein level stands out in astrocytes from AD patients' hippocampus [98].

In this context, CXCL12 has been indicated as pro-inflammatory and neuroprotective, increasing microglial phagocytosis of Aβ deposits [7][99]. The function of CXCR4 is however controversial in this context. Administration of the CXCR4 antagonist AMD3100 in acute Aβ-injected mice and chronic 3xTg AD mice led to neuroprotective effects, reduced neuroinflammation and improved cognitive abilities [100]. However, it induced memory deficits according to other studies performed in young adult wild-type mice [101][62]. Of note, cell targets of AMD3100 were not systematically addressed, and treatment schemes (i.e. administration routes, dose, timing, etc) were variable across studies. However, we may hypothesize that AMD3100 treatment impacts neuronal physiology and cognition in a context-dependent manner. On the other hand, ACKR3 has also been investigated in AD pathology using different experimental models. ACKR3 knockdown in mice is accompanied by a reduction of *CXCL12* and *CXCR4* expression in hippocampal homogenates, a decreased number of doublecortin-positive cells in the hippocampus, and learning and memory deficits [62]. The neuroprotective function of ACKR3 was also described in a study led by Das et al. using siRNA and different pharmacological modulators of the receptor: AMD3100, VUF11207 (agonists) and CCX771 (antagonist). ACKR3 agonists reduced neurodegeneration by increasing microglial inflammatory functions, while ACKR3 siRNA worsens memory impairments [102].

In PD, the main neuropathological hallmarks are the formation of abnormal α-synuclein aggregates called Lewy bodies and the degeneration of dopaminergic neurons, mainly of the *pars compacta* of the *locus niger*, leading to motor disabilities and other non-motor

symptoms [103]. Studies reported that PD patients exhibit higher levels of inflammatory markers in blood and cerebrospinal fluid that differ from healthy subjects. Among these, CXCL12 is upregulated and stands out as a putative diagnostic marker [104]. Besides, Li et al. shown that CXCL12 is upregulated in postmortem brain tissue of PD patients, and that CXCL12/CXCR4 axis is associated with α-synuclein-mediated neuroinflammation through microglial accumulation, a response significantly reduced upon AMD3100 treatment *in vitro* [105]. While microglia is described as a key player in PD neurodegeneration, CXCR4-guided migration of CD4+ T cells also participate in this process, further supporting the therapeutic inhibition of the CXCL12/CXCR4 axis for slowing down PD physiopathology [106]. In addition to the pharmacological effects of the compounds listed here above, AMD3100 also might improve the efficacy of neural stem cell transplantation in a rat model of Parkinson's disease [107]. This therapeutic approach represents a promising strategy for neurodegenerative diseases for replacing damaged neurons, as well as promoting neural network regeneration via the modulation of neurotrophic and inflammatory factors [108].

CXCR4 downregulation therefore appears as a promising therapeutic approach for neuroprotection and/or slowing down disease progression in AD and PD [109]. Recently, Tripathi and Kumar discovered about fifty molecules structurally similar to the FDA-approved CXCR4 antagonist Mavorixafor by molecular docking and simulation. Among them, ZINC49067615 and ZINC103242147 appeared as the most interesting candidates by their ability to cross the BBB, their higher affinity towards CXCR4 as well as a stable interaction with the receptor [110]. Thus, authors suggest that these molecules could show higher inhibitory activity toward CXCR4 as compared to Mavorixafor and should be biologically validated in the context of neurodegenerative disorders.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative pathology defined by the loss of motor neurons in the motor cortex and spinal cord, leading to progressive muscle weakness and paralysis [111].

Studies led by Andrés-Benito et al. highlighted increased CXCL12 levels in ALS patient CSF, suggesting its potential as complementary diagnostic biomarker, together with NF-L and

YKL40 proteins [96]. In their study, they demonstrated that both CXCL12, CXCR4 and ACKR3 are localized in motor neurons in both control and ALS tissue. Under pathological conditions, CXCL12 is also present in a few glial cells, CXCR4 in degenerating motor neurons and in a subset of oligodendroglia-like cells, and ACKR3 in reactive astrocytes from pyramidal tracts in ALS.

Finally, ACKR3 is found in motor neurons of both control and ALS samples, as well as in reactive astrocytes in the pyramidal tracts in ALS [96]. The clinical implication of CXCR4 was addressed in a transgenic mouse model of ALS, using chronic AMD3100 administration. CXCR4 antagonism alleviates symptoms of the disease by attenuating the breakdown of the blood-spinal cord barrier (BSCB), decreasing microglial inflammatory response and preventing motor neuron destruction [112]. Therefore, approaches targeting CXCR4 might be clinically relevant in ALS patients and should further be addressed.

5.2. **Neurooncology**

Over the last years, literature has recognized the role of the tissue ecosytem in tumor progression, for both primary tumor development and metastasis establishment. The tumor microenvironment (TME) is a complex system that comprises all the non-cancerous host cells in the tumor, as well as non-cellular components, including the extracellular matrix and soluble molecules such as growth factors, extracellular vesicles, cytokines and chemokines [113]. While chemokines are critical in directing the spatial organization of immune cells within tumors to deliver an effective anti-tumor response, they also participate in the recruitment of pro-tumorigenic immune cells that favor tumor development [114][115]. Chemokine circuits were shown to shape TME in solid tumors, including brain tumors [116] [117]. Targeting of key chemokine players in such context is a strategy that has raised interest for improving responses to cancer therapies.

Compared to normal tissue, the expression of CXCR4 receptor is upregulated in many cancers, including kidney, breast, lung, ovarian, pancreas, prostate, melanoma and brain [118]. Overall, the CXCL12/CXCR4/ACKR3 axis is considered as an active participant in the

formation of primary CNS tumors and brain metastases. The expression of these three genes correlates with tumor grade, recurrence, treatment resistance and poor prognosis [71][83][119][120]. Considering the relevance of this chemokine axis in cancer, different chemical modulators have been tested in the field of neuro-oncology, and some compounds have entered clinical trials (Table 1).

5.2.1. **Primary brain tumors (with a focus on glioblastoma)**

Primary tumors affecting the CNS cause significant mortality worldwide, in spite of their low incidence. The wide histo-molecular diversity of such tumors renders the development of treatments extremely challenging [121]. From all brain tumors, glioblastomas are the most prevalent (accounting for about 50%), as well as the deadliest [122].

5.2.1.1. **CXCR4 antagonists in glioblastoma**

The contribution of the CXCL12/CXCR4/ACKR3 chemokine axis in glioblastoma has been extensively studied in the last years, notably using pharmacological modulators, showing promising outcomes in (pre)clinical studies (Figure 4). In the field, the CXCR4 antagonist AMD3100, or Plerixafor, is the most used compound. Overall, literature has shown that AMD3100 exerts its antitumoral effect through different mechanisms, leading to reduced tumor growth *in vitro* and in preclinical models. At the molecular scale, studies led on different cell types (e.g., breast and prostate cancer) showed that AMD3100 is associated with reduced activation of downstream CXCR4 effectors, ERK1/2 and Akt, involved in tumor cell migration, proliferation and survival [71]. Kioi et al. demonstrated that AMD3100 administration blocks vasculogenesis, thereby preventing glioblastoma recurrence in orthotopic xenografts [123]. CXCR4 antagonism also contributes to the modulation of glioblastoma TME by reducing the infiltration of pro-tumoral myeloid-derived suppressor cells [124]. The use of Plerixafor has also been tested in combination with the immunotherapeutic agent anti-PD-1 (pembrolizumab) in preclinical models, leading to an improved survival [125]. Additionally, preclinical studies showed that the CXCL12/CXCR4 axis promotes radio- and chemoresistance, and AMD3100 treatment significantly reverses this phenotype [126][127].

Considering its promising effects as new therapeutics in preclinical models, Plerixafor has entered phase 1/2 clinical trials testing for brain tumors (Table 1). Overall, a low toxicity was reported, alone or in combination with radio/chemotherapy or with the anti-angiogenic agent bevacizumab [128][129]. To date, no phase 3 trial has proven the efficiency of Plerixafor treatment in glioblastoma patients.

In an *in vitro* study, Luo et al. shown that CPZ1344, a compound structurally similar to AMD3100, was efficient on the U87 glioblastoma cells [130]. In this study, CPZ1344 inhibited U87 proliferation and migration, as well as angiogenesis in HUVEC cells, suggesting that CPZ1344 might serve as new anti-tumor therapeutics [131].

In the same line, another CXCR4-specific antagonist named peptide R has shown promising effects in inhibiting CXCL12-mediated glioblastoma growth and migration *in vitro* [132]. In U87 cells orthotopic xenograft models, peptide R also impaired tumor vasculature and favored the polarization of tumor associated macrophages towards a “M1-like” anti-tumoral phenotype [133]. In 2019, a peptide R derivative (Pep R54) showing a higher affinity towards CXCR4 was efficient in combination with anti-PD-1 for melanoma treatment [134]. This approach might also be relevant and could be considered for glioblastoma.

PRX177561 was also described as novel CXCR4 antagonist, showing promising effects both *in vitro* and in preclinical models. This compound was tested alone or in combination with bevacizumab and sunitinib [133][134].

A mutated form of CXCL12 called P2G, where a proline is switched by a glycine at position 2 in the amino acid sequence of the chemokine [137], demonstrated encouraging antagonistic effects towards CXCR4 in glioblastoma [138]. In this article, the modified chemokine delivered by an oncolytic herpes simplex virus impairs glioblastoma cells properties (e.g., stemness, proliferation, migration) and significantly reduces tumor growth *in vivo*.

5.2.1.2. **ACKR3 modulators in glioblastoma**

ACKR3, the other receptor for CXCL12, has also gained interest in the field of neuro-oncology.

In 2014, ACKR3 antagonist CCX771 was administered after irradiation in glioblastoma-bearing mice, preventing tumor recurrence and leading to a prolonged survival [139]. Salazar et al. later demonstrated that combining the chemotherapeutic agent temozolomide and the chimeric antibody X7Ab anti-ACKR3 was efficient for improving overall survival in glioblastoma preclinical models [83]. Their study also suggested that this combinational treatment was efficient in engaging an anti-tumoral immune response, as shown with the enhanced M1-like macrophage polarization.

More recently, the impact of ACKR3 modulation on glioblastoma immune microenvironment was described using VUF11207, a potent ACKR3 agonist [140]. In this study, they showed that ACKR3 activation elicits anti-tumor immunity by promoting T cell activation. Moreover, VUF11207 potentiated an anti-PD-L1 response, indicating a promising effect for favoring immune checkpoint blocker (ICB) response in glioblastoma.

5.2.1.3. **CXCL12 antagonists in glioblastoma**

Besides investigating the receptors, other studies also focused on CXCL12. Liu et al. showed that CXCL12 inhibition using the CXCL12-specific RNA aptamer NOXA-12 inhibits tumor recurrence in rats [141]. In 2024, the phase 1/2 GLORIA trial (NCT04121455) combining radiotherapy and NOX-A12 administration validated treatment safety in newly diagnosed glioblastoma patients and suggested its positive impact on progression-free survival [142].

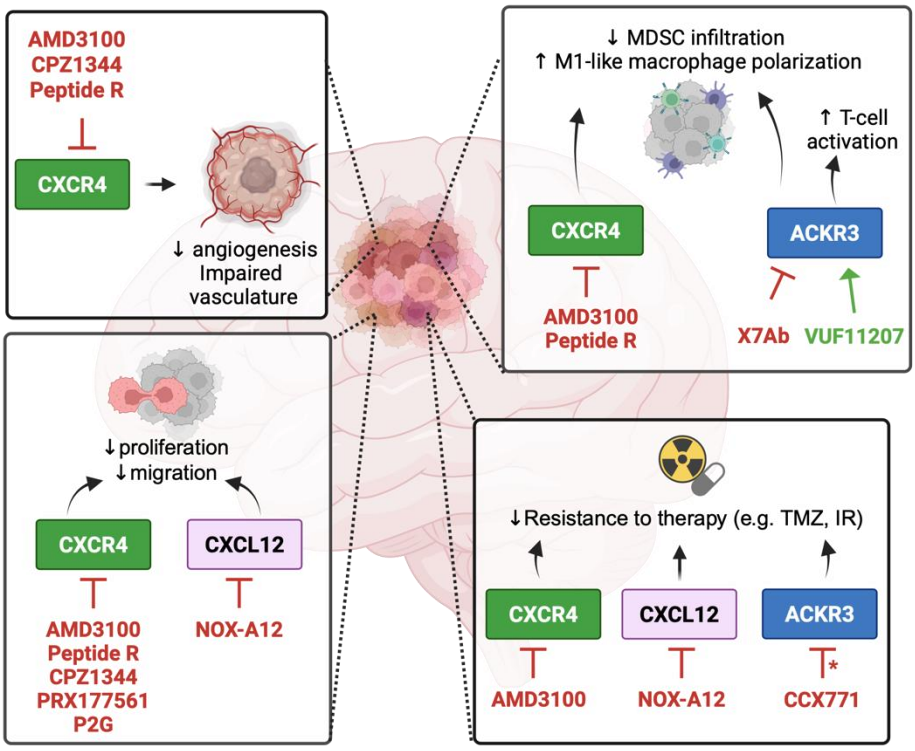


Figure 4 - CXCL12/CXCR4/ACKR4 modulation in glioblastoma. Targeting of this chemokine axis acts on different tumor properties, including angiogenesis, tumor cell proliferation & migration, anti-tumoral immunity and therapeutic resistance. Modulators of CXCL12, CXCR4 and ACKR3 are indicated regarding their anti-tumoral functions described in the literature. *Legend*: Green compounds/arrows represent agonists, and red compounds/arrows represent antagonists. (*) Note that CCX771 was initially described as an antagonist, although data suggest it may act as an agonist (Das et al). Created with Biorender.

5.2.2. **Brain metastases**

The CXCL12/CXCR4/ACKR3 chemokine axis has also been demonstrated to guide the migration of CXCR4-positive metastatic tumor cells in CXCL12-rich organs such as the brain, the liver, the lungs and the bone marrow [18][118]. The establishment of brain metastases has been widely studied in breast and lung cancers, or in acute lymphoblastic leukemia. Unlike CXCR4, while ACKR3 promotes primary tumor growth in both breast and non-small-cell lung cancer (NSCLC), no evidence suggests a function in brain metastasis [143].

In breast cancer metastasis, CXCL12 expression in the brain attracts CXCR4 positive tumor cells from primary site. In this context, AMD3100 administration was shown efficient in diminishing breast tumor cells brain invasion. [144].

In NSCLC, CXCL12/CXCR4 signalling has been associated with the spread of lung cancer cells to the brain [145]. Multiple studies have shown that blocking the CXCL12/CXCR4 axis efficiently reduced lung cancer cell migration. Depletion of CXCL12 using a monoclonal anti-CXCL12 antibody *in vivo* impaired tumor establishment at secondary sites, including in the brain [146]. In another study, Li et al. described AMD3100 as a candidate to decrease brain-specific metastasis in lung cancer, by strengthening tight junctions of the BBB and limiting the penetration of tumor cells [147].

Inhibiting CXCR4 with AMD3100 has also shown promising effects in B and T precursor acute lymphoblastic leukemia (B-ALL and T-ALL, respectively) by preventing CNS colonisation of tumor cells [148] [149]. Similarly, a blockade of the CXCL12/CXCR4 axis with

AMD11070 (Mavorixafor), inhibits the leukemia-meningeal cell adhesion, thereby attenuating chemoresistance [150].

6. Conclusions

Chemokines and their receptors, in particular the CXCL12/CXCR4/ACKR3 axis, play a crucial role in tissue development and homeostasis, including in the CNS. Dysregulation of this axis lays the foundation for several neurological disorders, both during development and in adulthood. This observation led to intense research efforts harnessing pharmacological modulators in neuropathological contexts. Although several compounds targeting CXCL12, CXCR4 or ACKR3 have been developed in the latest years, only few of them have been addressed in CNS conditions. The CXCL12-targeting aptamer NOX-A12 stands out as the lead modulator, showing promising antitumor effects in patients with newly diagnosed glioblastoma. Concerning CXCR4, Plerixafor and Mavorixafor remain the reference compounds for a large number of CNS diseases, including glioblastoma and brain metastasis, neurodegenerative diseases (AD, PD, ALS) and multiple sclerosis. More recently, ACKR3 pharmacological modulation also shown promising effects in reducing neuroinflammation and favoring anti-tumoral immunity. Agonists and antagonists of the receptor have been tested in these contexts, notably ACT-1004-1239, CCX771 and VUF11207. Although numerous other modulators targeting CXCL12, CXCR4 or ACKR3 have been developed, their application remains limited to *in vitro* testing or preclinical models, and several of them have not yet been explored for CNS disorders.

One of the greatest challenges for translating drug candidates into clinical applications for such pathologies is the presence of the blood brain barrier, which significantly limits the number of compounds that can penetrate the brain.

When considering the development of new modulators (or the improvement of existing molecules), it is essential to question their biophysical properties. Alternatively, delivery methods such as nanoparticles also might facilitate drug delivery into the CNS (such as demonstrated by Alghamri et al. for glioblastoma treatment) [124]. However, BBB crossing

might not be strictly necessary for treatment efficacy in CNS pathologies. Some compounds can indeed act through systemic mechanisms that indirectly influence the CNS microenvironment, for instance by modulating peripheral immune responses, circulating cytokines or chemokine gradients, despite limited direct brain exposure. This concept is illustrated by the GLORIA trial in glioblastoma patients using the NOX-A12 aptamer, which exhibits low BBB penetration but appears to act primarily through systemic disruption of CXCL12 signaling and subsequent modulation of immune cell recruitment in the CNS [142].

Overall, the CXCL12/CXCR4/ACKR3 axis represents a valuable, yet context-dependent therapeutic target in CNS disorders. As an example, the use of AMD3100 (Plerixafor) might be beneficial in Parkinson's disease by promoting Lewy bodies clearance, while it is suggested deleterious in multiple sclerosis. Targeting one or another component of this axis also leads to drastically different outcomes, such as CXCR4 inhibition being detrimental in multiple sclerosis, while ACKR3 antagonism shows beneficial effects.

In summary, the CXCL12/CXCR4/ACKR3 axis emerges as a central regulator of CNS physiology and pathology, with significant therapeutic promise. Addressing the current limitations in drug delivery and target selectivity, and most especially contextual signalling will be pivotal for future success. Continued exploration of CXCL12/CXCR4/ACKR3 pathway will help to yield novel insights and therapeutic opportunities across a broad spectrum of CNS disorders.

7. List of abbreviations

AC: Adenylyl cyclase

ACKR1: Atypical chemokine receptor 1

ACKR3: Atypical chemokine receptor 3

ACKR5: Atypical chemokine receptor 5

AD: Alzheimers' disease

AIDS: Acquired immunodeficiency syndrome

Akt: Protein kinase B

ALS: Amyotrophic lateral sclerosis

Aβ: Amyloid beta

B-ALL: B precursor acute lymphoblastic leukemia

BBB: Blood-brain barrier

BSCB: Blood-spinal cord barrier

cAMP: Cyclic adenosine monophosphate

CB2: Cannabinoid receptor 2

CD184: Cluster of differentiation 184

CNS: Central nervous system

CSF: Cerebrospinal fluid

CXCL11: CXC-Ligand 11

CXCL12: CXC-Ligand 12

CXCR3: CXC-Receptor 3

CXCR4: CXC-Receptor 4

CXCR7: CXC-Receptor 7

DAG: Diacylglycerol

DARC: Duffy Antigen/Receptor for Chemokines

EAE: Experimental autoimmune encephalomyelitis

eUb: Extracellular ubiquitin

FDA: Food and drug administration

GDP: Guanosine diphosphate

gp120: Glycoprotein 120

GPCR: G protein-coupled receptor

GPR182: G protein-coupled receptor 182

GRK: G protein-coupled receptor kinase

GTP: Guanosine triphosphate

HIV: Human immunodeficiency virus

IC2: Intracellular loop 2

ICB: Immune checkpoint blocker

IP3: Inositol 1,4,5-triphosphate

LESTR: Leukocyte-derived seven-transmembrane domain receptor

MAPK: Mitogen associated protein kinase

MIF: Macrophage migration inhibitory factor

MS: Multiple sclerosis

NPC: Neural progenitor cell

NSCLC: Non-small-cell lung cancer

OPC: Oligodendrocyte progenitor cell

PAMP: Proadrenomedullin peptide

PBSF: Pre-B cell growth-stimulating factor

PD: Parkinsons'disease

PI3K: Phosphoinositide-3 kinase

PIP2: Phosphatidylinositol 4,5-bisphosphate

PKA: Protein kinase A

PLC: Phospholipase C

RDC1: Receptor-Deficient Chemokine 1

SDF-1: Stromal cell-derived factor-1

SGZ: Subgranular zone

SVZ: Subventricular zone

T-ALL: T precursor acute lymphoblastic leukemia

TME: Tumor microenvironment

US: United States

WHIM: Warts, Hypogammaglobulinemia, Infections, and Myelokathexis syndrome

8. Declarations

- *Conflicts of interest* : Authors do not declare any conflict of interest.
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- *Author contributions*: AK: conception and design, data analysis and interpretation, manuscript drafting and revision. BR: Data interpretation, manuscript revision, project

funding. VN: Conception and design, data interpretation, manuscript revision, project funding. All authors approve the submitted version of the manuscript.

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