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The leukotriene signaling pathway: a druggable target in Alzheimer's disease

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The underlying pathology of Alzheimer's disease (AD) is complex and includes, besides amyloid beta (Aβ) plaque depositions and neurofibrillary tangles, brain atrophy and neurodegeneration, neuroinflammation, impaired neurogenesis, vascular and blood–brain barrier (BBB) disruptions, neurotransmitter disbalances, and others. Here, we hypothesize that such complex pathologies can only be targeted efficiently through pleiotropic approaches. One interesting drug target is the leukotriene pathway, which mediates various aspects of AD pathology. Approaching this pathway at different levels with genetic and pharmacological tools demonstrated beneficial outcomes in several *in vivo* studies using different mouse models of AD. Here, we review the current literature on the leukotriene signaling pathway as a target for drug development in AD.

Epidemiology, etiology, and current treatment of Alzheimer's disease

AD, the most prominent form of dementia, is a multifactorial and age-related neurodegenerative disease, distinguished by progressive loss of cognitive functions. Approximately 35.6 million people lived with dementia in the year 2010 worldwide. As a consequence of the demographic changes, the numbers are expected to almost double every 20 years to 65.7 million in 2030 and 115.4 million in 2050 [1]. With a rapidly accelerating worldwide prevalence, dementia has been identified as a major global health threat by the international medical community [2].

Human genetics has classified AD into two groups. The familial early-onset (FAD) form, which affects approximately 5% of patients with AD and emerges between 30 and 60 years of age, is hereditary and linked to mutations in several genes. These genes, encoding, for example, for Aβ precursor protein, presenilin 1 and/or 2, are mostly associated with the amyloid pathway and contribute to the early onset of symptoms [3]. The more common form of AD (95% of cases) is the sporadic late-onset (SAD) form, which is mostly seen in people >65-years old. The main risk factor for this form of AD is age [4]. In addition, several genes have been identified as risk factors for SAD. They are involved in various cellular processes, such as cholesterol metabolism (*ApoE* [5], *CLU* [6], and *ABCA7* [7]), immune response (*CR1* [8], *CD33* [9], *MS4A* [7], and *Trem2* [10,11]), and endocytosis (*PICALM* [6], and *EPHA1* and *CD2AP* [9]) [12]. Obviously, such genes are informative for the understanding of AD pathogenesis, but have so far not led to any therapy.

Treatment options for patients with AD remain poor and with only moderate efficacy. The US Food and Drug Administration (FDA) approved the acetylcholine esterase inhibitors tacrine [13], galantamine [14], rivastigmine [15], and donepezil, which compensate for the reduced levels of acetylcholine present in AD brains. These substances show moderate efficacy in patients with mild-to-moderate AD [3], but have adverse effects, such as nausea, vomiting, and loss of appetite [16]. Tacrine showed severe adverse effects, such as liver toxicity [13] and, therefore, its prescription was discontinued in the USA [17]. A further FDA-approved option for pharmacological treatment, used in more advanced stages of AD, is memantine [18], a NMDA-receptor antagonist, either in monotherapy or in combination with donepezil [19]. In monotherapy, memantine showed a slight cognitive benefit and reduced symptoms, such as aggression, agitation, and psychosis in patients

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with AD [20,21]. Adverse effects of memantine include headache, constipation, confusion, and dizziness [16]. Taken together, the above-mentioned drugs provide short-term symptomatic improvement, but with adverse effects affecting the quality of life of patients, and with no cure for AD [22].

Pathogenesis of AD

The amyloid cascade and the tau hypotheses [23–25] have been the basis of AD research for decades and, thus, many attempts targeting these structures have been developed. All of these approaches have completely failed, at least during the late clinical phases (Table 1) and, because of these failures, the amyloid cascade and the tau hypotheses as being causative in AD pathogenesis are increasingly questioned [26]. Other processes and structures, such as neuroinflammation, neurogenesis, gliosis and sclerosis, BBB and blood vessel integrity, are increasingly in focus in AD research and therapy development. In addition, neuronal loss as the final denominator of all neurodegenerative diseases and causative for the functional loss remains a therapeutic aim.

Neuronal cell death in AD

Neuronal cell death is a key component in AD [27]. As reviewed by Donev *et al.*, several pathological mechanisms in AD cause neuronal death. Besides inflammation and Aβ-induced neurotoxicity, the complement system as well as reactive oxygen and nitrogen species are discussed to promote neurodegeneration [28]. Additionally, the leukotriene system is involved in acute neuronal damage, either directly [29], or indirectly by influencing astrocytes and microglia, which have detrimental effects on neurons in, for example, postischemic phases [30]. Targeting the leukotriene system at the receptor level had protective effects regarding neuron loss in mice and rats after focal cerebral ischemia [31,32].

Neuroinflammation in AD

Neuroinflammation is characterized by the activity of brain-resident glial cells, in particular microglia [33]. The relevance of microglia in AD pathogenesis is highlighted by studies demonstrating that polymorphisms in *CD33* and *TREM2*, two genes expressed by microglia and important for phagocytosis, are associated with AD [34]. Microglia are highly dynamic, mobile cells responsible for tissue surveillance and phagocytosis of pathogens and debris in the brain. On a molecular level, microglia are triggered by danger-associated molecular patterns (DAMP), which are recognized via pattern recognition receptors [35,36]. As a consequence, microglia produce more proinflammatory cytokines in AD [37]. They are located closely to Aβ plaques, where they participate in plaque clearance, although not to a level to stop or revoke plaque formation [38]. In addition, during the course of AD pathology, microglia become increasingly dysfunctional in phagocytosis [39], and this functional decline of microglia correlates with Aβ deposition [40]. Therefore, microglia phagocytosis, in addition to the secretion of pro- and anti-inflammatory substances, is increasingly a focus of AD research.

Aside from microglia, astrocytes are involved in neuroinflammation. In healthy conditions, astrocytes regulate brain homeostasis via maintaining extracellular K^+ concentrations, they are also required for BBB integrity, and influence epithelial cells, neurons, and microglia by release of various neurotransmitters [41]. In AD, amyloid plaque-associated astrocytes are hypertrophic, whereas non-plaque-associated astrocytes become atrophic, resulting in dysfunctional transmission at glutamatergic synapses, which could be a contributor to cognitive decline [33]. Astrocytes associated with amyloid plaques are phagocytotic, and take up and degrade Aβ [42] and/or prevent plaque formation or plaque growth [43]. Interestingly, astrocytes and microglia need to be considered in the context of each other, because, for example, the release of ApoE by astrocytes stimulated microglia to clear fibrillary Aβ in an animal model of AD [33]. In addition to microglia and astrocytes, it becomes increasingly evident that peripheral immune cells of the myeloid lineage, such as macrophages, and of the lymphoid lineage, such as T cells, invade the AD brain, and likely shape AD pathology [44]. Therefore, neuroinflammation in AD is a complex issue involving a variety of central nervous system (CNS)-resident as well as peripheral immune cells.

Clearly, neuroinflammation is a major contributor to disease progression in AD and, therefore, is considered as a therapeutic target [45]. So far, several anti-inflammatory drugs have been tested, some of which have shown efficacy, such as rosiglitazone, which showed positive effects in terms of the delay of cognitive decline in early AD and mild cognitive impairment (MCI) [46]. The nonsteroidal anti-inflammatory drug (NSAID) indomethacin was tested for slowing the progression of AD and showed promising results in a double-blind, placebo-controlled clinical trial [47], but the results of a following Phase 3 trial were inconclusive [48]. Ibuprofen was shown to be ineffective for the prevention of AD in a Phase 2 trial [49]. Using a database search (Cochrane Dementia and Cognitive Improvement Group's Specialized Register) for randomized controlled trials of anti-inflammatory drugs, a review of 14 studies concluded that there was no evidence for the beneficial use of steroidal drugs and NSAIDs in AD [50]. Nevertheless, the extent of the beneficial effect of improved anti-inflammatory approaches remains open and requires further investigations.

Leukotrienes are lipid mediators of neuroinflammation (reviewed in Refs [51,52]). In the brain, leukotriene signaling acts proinflammatorily on microglia [53] and on astrocytes [54]. In particular, leukotriene D_4 (LTD_4) activates BV2 microglia cells [55] and rat astrocytes [54] in *in vitro* experiments. Microglial cells release cysteinyl leukotrienes (CysLTs), which can subsequently activate astrocytes [56]. In addition, autocrine release of CysLTs by astrocytes is thought to be involved in reactive astrogliosis [54]. Inhibition of the leukotriene system at the synthesizing enzyme [57,58] as well as the receptor level [59] led to less neurotoxicity of microglia and, therefore, had a beneficial effect on neuroinflammation.

Neurogenesis in AD

Adult neurogenesis describes the formation of new neurons from neural stem and progenitor cells and their integration into neuronal circuits in neurogenic niches, and is relevant for cognitive function [60]. There is good evidence that, although repeatedly questioned, adult hippocampal neurogenesis does exist in adult humans [61]. In animal models of AD and in human AD brains, neurogenesis is altered in a pathology stage-specific manner. During early and presymptomatic phases, neurogenesis, in particular the proliferation of neuroblasts, is elevated; by contrast, neural progenitor cell proliferation as well as the differentiation, maturation, and survival of neurons at later stages of the disease are impaired [62]. Therefore, neurogenesis is a target for AD therapy development.

TABLE 1

Failed anti-amyloid and anti-tau clinical trials[a]

Compound	Company/Sponsor	Target	Therapy	Status
AN-1792	Janssen, Pfizer	Amyloid related	Active immunotherapy	Discontinued
Clioquinol	Prana Biotechnology Limited	Amyloid related	Small molecule	Discontinued: toxic contaminant during manufacturing process
Alzhemed™	Neurochem, Inc.	Amyloid related	Dietary supplement	Inactive
Flurizan™	Myriad Genetics & Laboratories	Amyloid related	Small molecule	Failed: no difference to placebo
Ibuprofen	N/A	Amyloid related, inflammation	Small molecule	Failed: no difference to placebo
Semagacestat	Eli Lilly & Co.	Amyloid related, y-secretase inhibitor	Small molecule	Discontinued: no efficacy + Increased risk for skin cancer
Avagacestat	Bristol-Myers Squibb	Amyloid related, y-secretase inhibitor	Small molecule	Failed: no effect compared to placebo + adverse effects
Bapineuzumab	Janssen, Pfizer	Amyloid related	Passive immunotherapy	Failed: no clinical benefit
CHF 5074	CereSpir™ Incorporated, Chiesi Pharmaceuticals Inc.	Amyloid related, inflammation, other	Small molecule	Inactive
Tideglusib	Zeltia Group	Tau	Small molecule	Failed: missed primary endpoints
LY2886721	Eli Lilly & Co.	Amyloid related, BACE inhibitor	Small molecule	Discontinued: off-target toxicity
Epothilone D	Bristol-Myers Squibb	Tau	Small molecule	Discontinued
Gammagard®	Baxter Healthcare	Amyloid related, inflammation	Passive immunotherapy	Failed: no difference to placebo
RG7129	Roche	Amyloid related, BACE inhibitor	Small molecule	Discontinued: no official statement (suspected reason liver toxicity)
Vanutide cridificar	Janssen	Amyloid related	Active immunotherapy	Discontinued: one serious drug related adverse event
Rember TM	TauRx Therapeutics Ltd	Tau	Small molecule	Discontinued: replaced by TRx0237
Solanezumab	Eli Lilly & Co.	Amyloid related	Passive immunotherapy	Failed (Expedition 1 + 2): no improvement of cognition or functional ability
				Failed (Expedition 3): no statistical significant benefit
RG7345	Roche	Tau	Passive immunotherapy	Discontinued
BI 1181181	Boehringer Ingelheim, Vitae Pharmaceuticals	Amyloid related, BACE inhibitor	Small molecule	Discontinued
GSK933776	GlaxoSmithKline (GSK)	Amyloid related	Passive immunotherapy	Inactive
Octagam® 10%	Octapharma	Amyloid related, inflammation	Passive immunotherapy	Inactive
AAB-003	Janssen, Pfizer	Amyloid related	Passive immunotherapy	Discontinued
Ponezumab	Pfizer	Amyloid related	Passive immunotherapy	Discontinued: did not reach primary endpoint
TRx0237	TauRx Therapeutics Ltd	Tau	Small molecule	Failed
PF-06648671	Pfizer	Amyloid related, y-secretase modulator	Small molecule	Discontinued: Pfizer discontinued neurology research in 2018
PF-06751979	Pfizer	Amyloid related	Small molecule	Discontinued: Pfizer discontinued neurology research in 2018

[a] From www.alzforum.org

Molecular signals that are thought to contribute to alterations in neurogenesis during AD are PS1, soluble amyloid precursor protein (sAPP), Notch-1 and Aβ [63,64]. For example, Aβ inhibits proliferation and differentiation of progenitor cells and has adverse effects on the survival of young neurons [65]. Boosting neurogenesis through pharmacological interventions, for example through treatment with granulocyte colony-stimulating factor (G-CSF) [66], D5 receptor agonist 027075 [67], or NDP-α-MSH [68], showed improvement in cognitive performance assessed with several behavioral tests in several animal models of AD. However, monospecific drugs acting solely on neurogenesis are difficult to evaluate in clinical trials, because pharmacodynamic analysis is currently impossible because of the lack of validated neurogenesis-specific biomarkers and/or imaging modalities for the monitoring of neurogenesis.

In the context of neurogenesis, leukotrienes are thought to adversely affect neurogenesis, because inhibition of leukotriene receptors boosted the proliferation of neural progenitors in cell culture [69] and restored hippocampal neurogenesis in aged rats [53]. However, it was also suggested that 5-lipoxygenase (5-Lox), the rate-limiting enzyme in leukotriene biogenesis, could be necessary to support proliferation, because inhibition of 5-Lox dose-dependently reduced proliferation in neuronal precursors [70]. Moreover, leukotrienes in the context of acute inflammatory responses are required for the initiation of brain regeneration in zebrafish. [71] Therefore, the role of leukotrienes in the regulation of neurogenesis is still under discussion.

Vasculature and BBB in AD

The BBB separates the brain from the blood circulation. It is formed by endothelial cells tightly connected to each other and to the end feet of astroglia. In addition, pericytes and smooth muscle cells contribute to the BBB by forming a sheath around the vessels. Selective transport systems in the BBB have an important role in CNS homeostasis, because they selectively allow molecules and substances to enter the brain [72,73]. In AD, widespread leakage of the BBB occurs early during disease progression, leading to impaired transport and uncontrolled crossing of molecules into the brain [74]. AD is associated with further histopathological hallmarks related to the vasculature, such as in cerebral amyloid angiopathy (CAA), which occurs in 80% of patients with AD [75,76]. On a molecular level, several mechanisms are discussed to cause BBB leakage, although the actual cause remains elusive. Alterations and loss of tight junction proteins [77], as well as pericyte degeneration [76], might lead to BBB disruption at the capillary level. It is likely although currently speculative, that APP and its metabolites directly mediate toxic effects on vasculature in AD.

Leukotrienes have also been shown to increase BBB permeability following brain damage [78,79]. Given that receptors for leukotrienes are expressed on endothelial cells and treatment with the leukotriene receptor antagonist montelukast showed improved integrity of the BBB in an aging rat model [53], in a rat model of traumatic brain injury [80], in a rat model of focal cerebral ischemia [31], and in a mouse model of pharmacologically induced seizures [81], it is likely that leukotrienes have a role in BBB leakage.

Complex pathologies require complex and/or multimodal approaches

As illustrated above, the pathology of AD is complex and includes a variety of aspects, including neuronal cell death, neuroinflammation, affected neurogenesis, disrupted BBB and vasculature system, and others. Thus, a therapy should address as many aspects of these pathological hallmarks as possible. For example, a combined approach targeting neurodegeneration, neuroinflammation, neurogenesis, and vascular homeostasis, and resealing the BBB, could be considered. Ideally, this could be achieved with a drug that affects all of these issues simultaneously via a pleiotropic mechanism. A possible way to achieve this might be by targeting the leukotriene system, which mediates various aspects of AD pathology (Fig. 1).

The leukotriene system

Upstream of leukotriene synthesis, phospholipase 2 converts phospholipids into polyunsaturated fatty acids [PUFAs; i.e., docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA)]. DHA is further processed to anti-

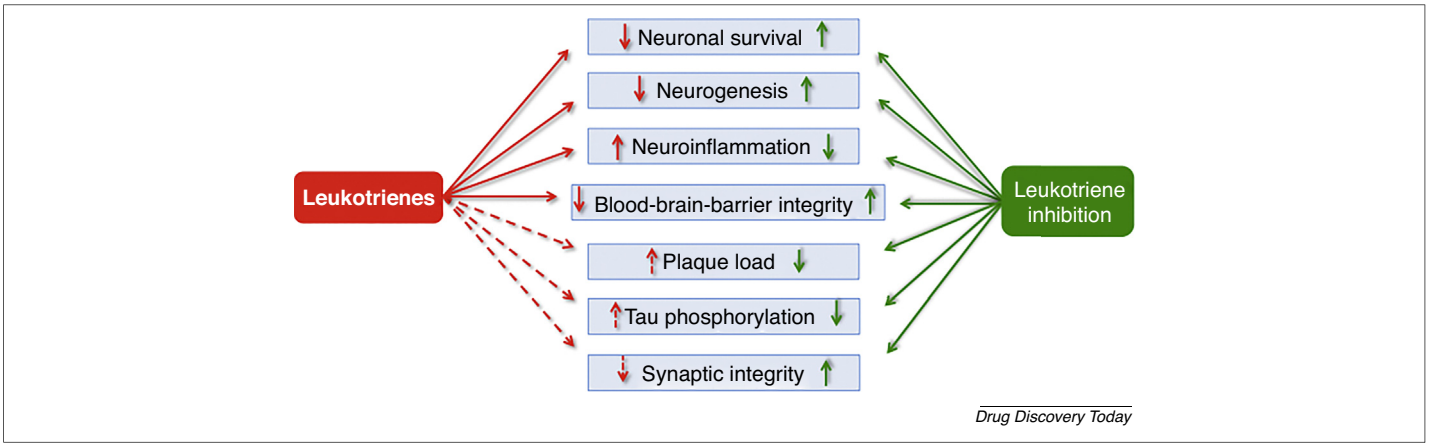

FIGURE 1

Pleiotropic effects of leukotrienes and leukotriene inhibition on the central nervous system (CNS). Pharmacological or genetic inhibition of leukotriene signaling leads to enhanced synaptic integrity and to a reduction in amyloid beta (Aβ) and tau pathology in several animal models of Alzheimer's disease (AD). Furthermore, several studies reported neuronal survival, increased neurogenesis, and increased blood–brain barrier (BBB) integrity after leukotriene inhibition. Leukotrienes promote neuroinflammation. Inhibition of leukotrienes leads to less neurotoxicity of microglia and also less activity of astrocytes. Broken lines symbolize putative actions of leukotriene signaling that require further investigations.

inflammatory small lipid molecules, such as resolvins, maresins, and protectins, summarized by the term 'specialized pro-resolving mediators' (SPM). EPA is converted into the proinflammatory molecules prostaglandins, thromboxanes, and prostacyclins, and into the anti-inflammatory resolvins and protectins. AA generates primarily proinflammatory prostanoids, such as prostaglandins, thromboxanes, and prostacyclins, anti-inflammatory lipoxins, as well as the proinflammatory leukotrienes. In more detail (Fig. 2), AA is converted into 5-hydroxy-peroxy-eicosatetraenoic acid (5-HPETE) and afterwards into leukotriene A_4 (LTA_4), both steps mediated by 5-Lox [82]. Therefore, 5-Lox needs to form a complex with 5-lipoxygenase activating protein (FLAP). LTA_4 is further processed either into leukotriene B_4 (LTB_4) by epoxide hydrolase or into leukotriene C_4 (LTC_4) by LTC_4 synthase. From LTC_4, the other two CysLTs LTD_4 and LTE_4 arise [83]. The CysLTs bind with different affinities to the receptors cysteinyl leukotriene receptor 1 and 2 (CysLT1R [84] and CysLT2R [85]) and G-protein-coupled receptor 17 (GPR17) [69,86]. For CysLT1R, LTD_4 is the strongest ligand, before LTC_4 and then LTE_4 [84]. LTD_4 and LTC_4 show similar affinity, whereas LTE_4 has a low affinity for CysLT2R [87]. The role of GPR17 in leukotriene signaling remains under debate [88,89]. In addition, a possible binding of leukotrienes (LTE_4) to the receptor P2Y12 is has been proposed [84,90].

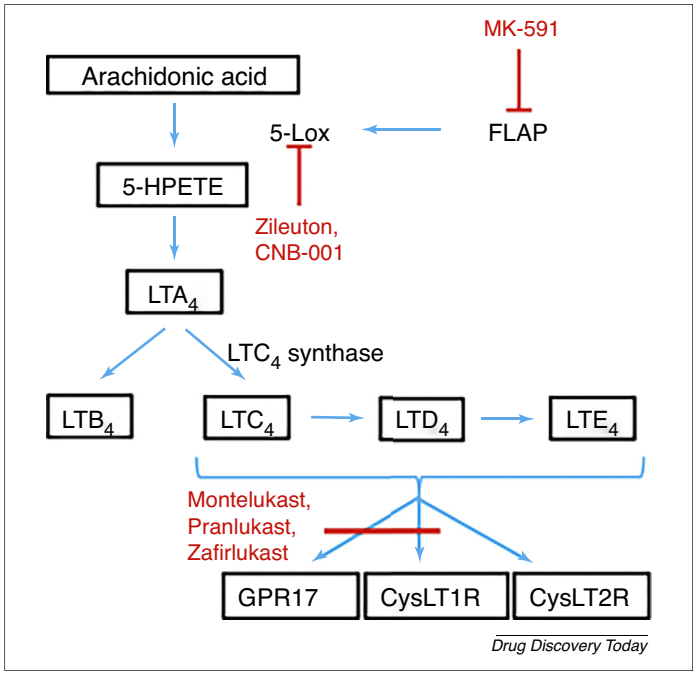

FIGURE 2

The leukotriene system and its inhibitors. Leukotrienes arise from arachidonic acid, which is converted into 5-hydroxy-peroxy-eicosatetraenoic acid (5-HPETE) and afterwards into leukotriene A4, both steps mediated by 5-Lox. 5-Lox needs to be activated by 5-lipoxygenase activating protein (FLAP). Leukotriene A4 is further processed either into leukotriene B4 by epoxide hydrolase or into leukotriene C4 by LTC4 synthase. From leukotriene C4, the other two cysteinyl leukotrienes, LTD_4 and LTE_4, arise. The cysteinyl leukotrienes bind with different affinities to the receptors CysLT1R, CysLT2R, and GPR17. Targeting the leukotriene system pharmacologically is possible at the enzyme level, for example with zileuton or CNB-001, which inhibit 5-Lox or with MK-591, which is a FLAP inhibitor. Further downstream leukotriene signaling can be blocked by receptor antagonists, such as pranlukast, zafirlukast or montelukast.

PUFAs and their metabolites have various functions in the context of inflammation, in particular during the different phases of inflammation. Whereas leukotrienes and prostanoids are proinflammatory and involved in the initiation of inflammation, SPMs are essential for dampening the immune system and are required for resolving the inflammatory processes. Thereby, SPMs might provide an opportunity for therapeutic interventions [91]. Indeed, in patients with AD, the levels of lipoxins are lower in the cerebrospinal fluid (CSF) and the hippocampus [92], and application of resolvin and lipoxin reduced inflammation and Aβ pathology in a mouse model of AD [93]. Nevertheless, and despite this potential, here we focus on leukotrienes as proinflammatory mediators in AD and as a therapeutic target.

Leukotrienes were originally found in leukocytes, but 5-Lox mRNA and protein are also widely expressed throughout the adult brain [94]. 5-Lox and FLAP are highly expressed in neurons of the hippocampus [95] and in microglia *in vitro* [96]. In addition, astrocytes can generate and release CysLTs, measured by enzyme immunoassay in cultures of rat cortical astrocytes [54]. 5-Lox also is expressed in the cerebellum, primary olfactory cortex, superficial neocortex, thalamus, hypothalamus, and brainstem [95]. After traumatic brain injury, glial fibrillary acidic protein (GFAP)-positive glia cells elevate 5-Lox expression and neutrophils infiltrating the lesioned brain, as well as endothelial cells, express 5-Lox [97].

Leukotrienes affect various cell types. For example, smooth muscle cells increase contractility and proliferation, and epithelial cells release more mucus following CysLT stimulation. In general, binding of leukotrienes to leukocytes enhances inflammatory cytokine release in the periphery [98]. LTB_4 and LTD_4 act chemotactically on neutrophils and eosinophils [99] and on endothelial cells [100]. CysLTs have vaso- and bronchoconstrictory effects on cells and, therefore, they are main targets in asthma therapy [83]. In the brain, leukotrienes induce the proliferation of astrocytes [54], and endothelial cells increase vascular permeability upon binding of CysLTs, contributing to BBB disruption. CysLTs have a role in several diseases of the CNS, because they influence the activity of microglia and of astrocytes [51]. With age, 5-Lox levels and the activity of the leukotriene pathway are elevated in the brain, likely contributing to age-related CNS diseases [101,102].

Expression of leukotriene receptors

CysLT1R is predominantly expressed in lymphoid cells of the spleen and in peripheral blood leukocytes [84]. It is also expressed at lower levels in lung, colon, small intestines, kidney, liver, heart, pancreas, and brain [103]. In primary cells derived from rodent brain, CysLT1R mRNA expression is found mainly in microglia and to a lower extent in endothelial cells and oligodendrocytes [96]. In humans, CysLT1R is expressed by microvascular endothelial cells of the healthy brain and in brain tumor (astrocytoma and ganglioglioma) tissue [104]. After traumatic brain injury or in brain tumors, CysLT1R is induced in neurons and astrocytes (identification based on location and morphology) [105]. Elevation of LTD_4 leads to significantly elevated levels of CysLT1R mRNA and protein [106]. Systemic injections of lipopolysaccharide (LPS), which induce cognitive dysfunctions and neuroinflammation, led to an upregulation of CysLT1R mRNA and protein in hippocampus homogenates of mice [107].

CysLT2R is expressed in spleen, heart, peripheral blood leukocytes, and lung [108]. Moderate expression of this receptor is also found in the CNS, with highest expression in spinal cord and pituitary [109]. In the healthy brain, CysLT2R is expressed by astrocytes, but not by neurons or microglia. After middle cerebral artery occlusion, mRNA expression of CysLT2R is found in neurons in the core during the acute phase (up to 1 day after reperfusion) and in the boundary zone in microglia and in hypertrophic astrocytes in the chronic phase (up to 2 weeks after reperfusion) [29,30]. After traumatic brain injury in humans, CysLT2R expression is induced in cerebral vascular endothelial cells [110]. In an *in vitro* oxygen-glucose-deprivation model of ischemia, CysLT2R induced and mediated astrocyte cell death [111]. Contrary to this, another *in vitro* study culturing rat astrocytes showed no expression of CysLT2R detectable by RT-PCR [54].

GPR17 is expressed in neurons and a subset of oligodendroglial progenitor cells in the cortex. After focal ischemia, GPR17 is upregulated in neurons within 48 h. Co-localization of GPR17 with the microglia marker Iba1 is not found in normal brain, but 72 h after middle cerebral artery occlusion, infiltrating microglia and/or macrophages (IB4 positive) show a positive staining for GPR17. This indicates an early and transient induction of GPR17 in neurons in the lesioned area and an induction in infiltrating cells during the chronic phase [112]. Expression of GPR17 can also be found in the dentate gyrus in some neuronal progenitors and granular neurons, olig2+ cells and in some Iba1+ cells, but not in neural stem cells or astrocytes [53].

Expression of all three leukotriene receptors is induced or upregulated in neurons upon insult and afterwards also in microglia, suggesting that the leukotriene pathway has a role during the acute and chronic phase of inflammation.

Targeting the leukotriene pathway in AD

5-Lox is elevated in the brain of AD animal models and human AD brains at the mRNA as well as the protein level [113,114], suggesting a role of the leukotriene pathway in AD. Recently, a single nucleotide polymorphism in *ALOX5AP*, the gene encoding FLAP, was identified to increase the risk for AD 1.41-fold, strengthening a putative role of the leukotriene system in AD [115]. Here, we summarize data on genetic as well as on pharmacological approaches targeting leukotriene signaling in the context of AD and amyloid pathology (summarized in Table 2).

Genetic approaches to modulate leukotriene signaling in the context of AD

In transgenic AD mice with an amyloid plaque pathology, a 5-Lox deficiency reduced the levels of Aβ and its depositions in the brain [113]. In addition, deletion of *ALOX5*, the gene encoding 5-Lox, led to memory improvement and enhanced synaptic integrity, and to a reduction in Aβ and tau pathology in AD mice [116]. Vice versa, overexpression of 5-Lox in 3xTg mice resulted in increased plaque formation, increased levels of γ-secretase, and increased levels of total tau and phosphorylated tau [117]. Also, dexamethasone injections, which elevate 5-Lox expression, resulted in significantly increased levels of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$. In animals lacking ALOX5, dexamethasone injections had no effect on $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ [118]. An influence of leukotrienes on tau pathology is substantiated by studies in two models of tauopathy: htau mice, a transgenic model bearing the human tau gene (*MAPT*), and PS19 mice, a model with a *MAPT* P301S mutation. In both models, overexpression of 5-Lox led to higher levels of activation (p25 and p35) in the cdk5 kinase pathway, resulting in higher tau phosphorylation. Furthermore, both models displayed a worsening of cognitive deficits in behavioral testing, probably as a result of disruption in synaptic integrity and increased neuroinflammation [119,120]. Vice versa, genetic knockout of *ALOX5* in PS19 mice had contrary effects, namely reduced levels of tau phosphorylation, insoluble tau and p25/p35, as well as amelioration of cognitive deficits, accompanied by preserved synaptic integrity and decreased neuroinflammation [121]. Effects of 5-Lox on tau phosphorylation, synaptic integrity, and neuroinflammation were also described in a mouse model of AD-related tau pathology (Tg2576) [122].

Pharmacological approaches to modulate leukotriene signaling in the context of AD

As illustrated in Fig. 2, the leukotriene system can be pharmacologically addressed with approved drugs at two different levels: at the level of 5-Lox and at the level of the leukotriene receptors.

Inhibition of leukotriene synthesis

In animal models of AD, zileuton, a specific 5-Lox inhibitor, reduced Aβ levels and plaque deposition in a mouse model of amyloidosis (Tg2576) [123], and reduced the levels of insoluble and of hyperphosphorylated tau in a mouse model with plaques and tangles (3xTG) [116,124]. In 12-month-old 3xTG mice, 3 months of zileuton treatment resulted in significant lower amyloid burdens compared with placebo treatment. In Y-maze and fear-conditioning tests, zileuton stabilized the behavior compared with baseline (12 month), whereas placebo-treated mice showed significant deterioration in the behavioral tests [125]. Another pharmacological 5-Lox blocker, CNB-001, led to significant lower amounts of soluble Aβ1-42 in treated APP/PS1 animals, improvements in contextual memory (fear conditioning) and better memory in the Y-maze test [126]. Flavocoxid, a pharmacological dual inhibitor of Cox1-2 and 5-Lox, improved learning and memory function in 3xTg mice after 3 months of treatment compared with vehicle-treated controls, and reduced amyloid deposition [127]. In another study, direct pharmacological blockade of 5-Lox with the inhibitor AA-861 as well as indirect pharmacological blockade of 5-Lox via the inhibition of FLAP with MK-591 in a N2A cell culture after dexamethasone challenge, counteracted the elevated levels of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ caused by dexamethasone, further supporting a beneficial effect of targeting the leukotriene pathway in AD [118]. Furthermore, targeting FLAP pharmacologically positively influenced tau pathology *in vivo* in Tg2576 mice [128] and ameliorated pathology in 3xTg mice [129]. The mode of action of 5-Lox inhibition on reduced plaque pathology is unclear, but could be via modulation of γ-secretase [130]. Indeed, a study by Chu *et al.* revealed a significant reduction of all four components of γ-secretase in WB = Western Blot after zileuton treatment in Tg2576 mice, which was confirmed at the mRNA level by RT-PCR [123]. In two mouse models of tauopathy, htau and PS19, 7 months of treatment with zileuton starting at an early stage of pathology (3 months) led to significant improvement in memory performance [Morris Water Maze (MWM) and Y-Maze] as well as decreased tau phosphorylation accompanied by lower levels of co-activators for

TABLE 2

Genetic and pharmacological inhibition of the leukotriene pathway and its effects in animal models of AD with amyloid pathology

Model	Modulation	Results	Refs
Tg2576/5LO$^{-/-}$ mice; 15-months old	Genetic: no expression of 5-Lox	↓ Aβ reactivity in hippocampus, somatosensory, and perihippocampal cortex ↓ $A\beta_{1-40}$ and $A\beta_{1-42}$ Unaltered level of total APP ↓ γ-secretase activity	[113]
Tg2576 mice; 7-months old	Pharmacological: inhibition of 5-Lox by orally administered Zileuton for 8 months	↓ $A\beta_{1-40}$ and $A\beta_{1-42}$ (soluble and insoluble forms) in hippocampus and cortex Unaltered level of total APP ↓ Components of γ-secretase (PS1, Pen2, APH-1, and nicastrin) on mRNA and protein level Unaltered levels of α- and β-secretase	[123]
5-LO$^{-/-}$ mice	Genetic: absence of 5-Lox; dexamethasone injection to boost 5-Lox	5-LO$^{+/+}$ mice injected with dexamethasone: ↑ levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ 5-LO$^{-/-}$ mice injected with dexamethasone: no significant effect on $A\beta_{1-40}$ and $A\beta_{1-42}$ levels	[118]
Tg2576 mice; 5-LO$^{-/-}$ mice; Tg2576/5-LO$^{-/-}$ mice	Genetic: no expression of 5-Lox; pharmacologic: inhibition of 5-Lox with AA-861 in Tg2576	Tg2576: significantly elevated levels of 5-Lox compared with WT; Upon treatment: ↓ Aβ, associated with ↓ of p-CREB Tg2576/5-LO$^{-/-}$: ↓ p-CREB and total CREB compared with untreated Tg2576 5-LO$^{-/-}$:↓ levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ ↓ mRNA levels of components of γ-secretase	[130]
3xTg mice; 13-months old	Genetic: 5-Lox overexpression	↑ Plaque formation ↑ Levels of four components of γ-secretase ↑ Total tau, phosphorylated tau	[117]
Tg2576 mice; 7-months old	Pharmacological: inhibition of FLAP by MK-591 for 8 month	No change in endogenous tau ↓ Phosphorylated tau (Ser396, Ser396/Ser404, Thr 231/Ser 235) ↓ Levels of insoluble tau ↓ Activity of GSK-3β	[128]
3xTg mice	Genetic: knockout of FLAP; pharmacological: inhibition of FLAP by MK-591	↑ Memory (MWM) ↓ Aβ-deposition, $A\beta_{1-40}$, $A\beta_{1-42}$ Unaltered levels of APP ↓ Levels of four components of γ-secretase Unaltered levels of total tau ↓ Phosphorylated tau (S396, S396/S404) ↓ insoluble tau ↓ Cdk5 kinase ↑ Synaptic integrity ↓ Astrocyte and microglia activity (GFAP, CD45)	[129]
3xTg mice; 2–3-months old	Pharmacological: inhibition of 5-Lox by orally administered Zileuton (approx. 0.6–0.8 mg per day) for 10 months	Cognitive improvement (MWM) ↓ Levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ ↓ Amyloid burden (IHC) ↓ PS1, Pen-2 and APH-1 (WB) ↓ Dendritic accumulation of phosphorylated tau (IHC) No change in overall tau (WB, IHC) ↓ Levels of insoluble tau and phosphorylated tau ↓ p25 and p35 fragments of cdk5 (WB) ↑ Proteins essential for synaptic integrity (synaptophysin, PDS-95, MAP-2) ↓ GFAP and CD45 immunoreactivity	[124]
APP/PS1 mice (line 85); 3-months old	Pharmacological: inhibition of 5-Lox by CNB-001 for 6 months	Behavioral improvement (Y-Maze) ↓ Soluble $A\beta_{1-42}$	[126]
3xTg; 12-months old	Pharmacological: inhibition of 5-Lox by zileuton for 3 months	Behavioral improvement (Y-Maze) ↓ Aβ-deposition, $A\beta_{1-42}$ ↓ PS1, Pen-2 ↓ p25 fragments of cdk5	[125]
3xTg/5LoKO; 6–8-months old; 12–14 months old; 3xTg mice; 5-months old	Genetic: knockout of 5-Lox; pharmacological: inhibition of 5-Lox by zileuton for 1 month	Cognitive improvement (Y-maze) ↓ Aβ-deposition, $A\beta_{1-40}$, $A\beta_{1-42}$ Unaltered levels of total APP ↓ Levels of four components of γ-secretase ↓ Levels of insoluble tau ↓ p25 and p35 fragments of cdk5 ↑ Synaptic integrity (PSD-95 and synaptophysin) ↓ GFAP and CD45 immunoreactivity	[116]

TABLE 2 (*Continued*)

Model	Modulation	Results	Refs
ICR mice: intracerebral infusion of $A\beta_{1-42}$	Pharmacological: inhibition of CysLT1R by Montelukast	↑ Learning deficits after $A\beta_{1-42}$ infusion (MWM, Y-Maze) ↓ Infusion induced expression of CysLT1R in hippocampus and cortex ↓ $A\beta_{1-42}$ activated NF-κB p65 signaling, proinflammatory cytokine levels of TNF-α and IL-1β ↓ Caspase 3 ↑ Bcl-2	[142]
ICR mice: LPS injections	Genetic: knockdown of CysLT1R; pharmacological: inhibition of CysLT1R	Prevented cognitive impairment by LPS ↓ Number of apoptotic cells (pretreatment with pranlukast) Inhibition of upregulation of proinflammatory cytokines (IL-1β, TNF-α) Lower expression of CysLT1R on mRNA and protein level	[107]
3xTg-AD mice	Pharmacological: inhibition of 5-Lox by flavocoxid (20 mg/kg/ip) for 3 months	↑ Learning and memory (MWM) ↓ Amyloid deposit compared with saline-treated animals ↓ LTB_4, IL1-β ↓ p-Tau compared with saline-treated animals (but not compared with WT levels)	[127]

cdk5, reduced GFAP and CD45 and increased synaptic integrity [131,132]. This effect was also present when pharmacological 5-Lox inhibition started after the onset of pathology (12 months of age) in htau mice [133].

Antagonizing leukotriene receptors

Oral treatment with the leukotriene receptor antagonist pranlukast improved cognitive deficits caused by intracerebroventricular injections of $A\beta_{1-42}$ in ICR mice and suppressed NF-κB signaling caused by Aβ [134]. Daily intraperitoneal injections of zafirlukast, another antagonist for CysLTRs, for 21 days improved learning behavior in Aβ intracerebroventricularly injected rats [135]. Another selective leukotriene receptor antagonist is montelukast, which is increasingly discussed as a treatment option in AD and other neurodegenerative diseases [51,52,136].

Montelukast is approved by the FDA for the treatment of asthma [137,138] and its effectivity and tolerance has been shown in many studies (reviewed in [136,139]). In the periphery, montelukast acts on cells expressing receptors for cysteinyl leukotrienes, mainly monocytes, eosinophils, basophils, and mast cells [98,140], but it was also shown that montelukast prevented reactive oxygen species (ROS) and LTB_4 production in isolated human neutrophils that were activated by chemoattractants [141]. In fetal murine neurons, montelukast blocked $A\beta_{1-42}$-induced cell death, suppressed the expression of CysLT1R, and reduced the production of proinflammatory cytokines and the activation of caspase-3 [142]. In another study, using rat

TABLE 3

Key pharmacological data of approved drugs targeting the leukotriene system

Drug	Effective dose		Efficacy in humans	Safety Profile/Tolerability	Refs
	In animal models of CNS disease	In humans			
Montelukast	0.1 mg/kg i.p.; 0.25 μmol i.c.v.; 0.3 μmol/μL i.c.v.; 1 mg/kg i.p.; 1 or 2 mg/kg i.g.; 10 mg/kg p.o.; 30 mg/kg i.p.; 40 mg/kg i.p.	10 mg/d p.o. for treatment of asthma	Excellent in 23.8% of patients Good in 39.6% of patients Fair in 19.8% of patients Poor in 16.8% of patients *N* = 101	Excellent in 89.6% of patients Good in 1.9% of patients Fair in 8.5% of patients *N* = 106	[31,53,81,143–148,152]
		80 mg/d (4 × 20 mg p.o.) for treatment of dementia (off-label use in case report)	Improved memory in patients with cognitive impairment Less agitation in patients with dementia	No adverse effects reported	[154]
Pranlukast	0.1 mg/kg i.p.; 0.4 mg/kg p.o.; 0.8 mg/kg p.o.; 1.5 ng/animal i.c.v.; 1 and 3 μmol i.c.v.	450 mg bd p.o. for treatment of asthma	27.4% improvement in symptoms compared with baseline	Well tolerated	[31,32,81,107,134,150]
Zafirlukast	30 mg/kg i.p.; 30 mg/kg i.p.	40 mg/d (2 × 20 mg p.o.) for treatment of asthma	3.7 ± 15.4% improvement in forced expiratory volume compared with baseline	Well tolerated	[135,144,151]
Zileuton	0.6–0,8 mg/day in drinking water (200 mg/l)	2400 mg/d (4 × 600 mg p.o.) for treatment of asthma	Excellent in 51.4% of patients Good in 35.8% of patients Fair in 10.1% of patients Poor in 2.8% of patients *N* = 109	Excellent in 92.8% of patients Good in 2.7% of patients Fair in 4.5% of patients *N* = 111 Hepatotoxic adverse effect	[123–125,131–133,149,152]

neuronal precursor cell (NPC) cultures, montelukast had a stimulating effect on proliferation without influencing differentiation [69].

Inhibition of CysLT1R by montelukast blocked the proinflammatory actions of LTD_4, for example on the BBB, *in vivo*. It prevented pentylenetetrazol injection-induced BBB disruption in mouse brains and acted as an anticonvulsive. The latter effect was revoked by administration of LTD_4 [81]. Other studies also revealed an anticonvulsive effect of montelukast alone or in combination with antiepileptics, which was reversible through administration of LTD_4 [81,143]. The sealing of the BBB after montelukast treatment was not reversible, suggesting independent modes of action. In addition, in the experimental autoimmune encephalomyelitis (EAE) mouse model for multiple sclerosis, where BBB leakage is linked to the severity of EAE, montelukast attenuated LTD_4-induced BBB disruption, reducing the severity of EAE, leading to a decreased number of infiltrating leukocytes in the spinal cord and counteracting the demyelination [144]. Pretreatment with montelukast in mouse models for brain ischemia [145] and Parkinson's disease [146] had neuroprotective effects: it improved neurological deficits and reduced infarct volume in brain ischemia and inhibited microglial reactivation and loss of dopaminergic neurons. In the context of AD, intracerebroventricular infusions of $A\beta_{1\text{-}42}$ in mice led to deficits in memory and learning, to an increase in proinflammatory cytokines (TNF-α, IL-1β, and NF-κB p65) and proapoptotic molecules (caspase 3). A 4-week treatment with montelukast (1.0 and 2.0 mg/kg/day) after $A\beta_{1\text{-}42}$ injection improved learning in the MWM and Y-Maze tests. In addition, montelukast treatment reduced the infusion-induced expression of CysLT1R in the hippocampus and cortex at both the mRNA and protein level as well as the levels of the proinflammatory cytokines TNF-α and IL-1β [147]. Furthermore, montelukast reduced $A\beta_{1\text{-}42}$-activated NF-κB p65 signaling [147]. In a rat model of kainic acid-induced cognitive impairment, the effect of montelukast was compared with effects of the Cox inhibitor rofecoxib and with effects of the Lox inhibitor caffeic acid. All treatments improved memory performance in MWM compared with animals not treated after injection. Montelukast significantly increased the time spent in the target quadrant, and additional treatment with rofecoxib boosted this positive effect. This was not seen in combinatory treatment with montelukast and caffeic acid. Montelukast also showed significant protective effects concerning oxidative stress parameters, glutathione, and TNFα levels. The combination of montelukast with rofecoxib was shown to potentiate these beneficial effects [148].

Druggability of the leukotriene signaling system: a comparative analysis of repurposing drugs

As presented above, intervention at the level of the LT synthesizing enzyme 5-Lox using zileuton, as well as at the level of the LTRs through the antagonists pranlukast, zafirlukast or montelukast, ameliorates AD pathology and improves function in a variety of *in vivo* models. All drugs mentioned above are generally well tolerated [149] and approved for treatment of asthma (Table 3) [150,151]. In asthma therapy, dosing is variable, ranging from 10 mg once daily (montelukast) to 600 mg (zileuton) four times daily [152]. It is speculative but tempting to conclude that, with higher and/or repeated dosing of montelukast, its efficacy could be intensified. Although studies using these drugs proved beneficial effects on AD pathology in animal models, at present there are no randomized controlled clinical studies on these drugs in patients with AD, except for montelukast, where a small Phase 2a trial in mild to moderate AD using a buccal film of montelukast was recently initiated (NCT03402503) [153].

A recent case study using montelukast in humans (17 patients with mini mental state examination scores ranging from 20 to 30) reported memory improvement in patients with mild cognitive impairment after treatment and beneficial effects on behavior of patients with dementia [154]. Further supporting beneficial effects of montelukast on dementia, a database analysis, using the Norwegian Prescription Database (NorPD), showed that patients above the age of 50 who had been prescribed montelukast, compared with patients prescribed alternative asthma medications, such as corticosteroids, had a significantly lower probability of requiring a dementia drug later in life and of requiring to be placed in a nursing home. This study suggested that montelukast has a preventive effect [155]. Dosing remains an issue, especially because the initial filing data for FDA approval suggested only a low BBB penetrance of montelukast [156]. In summary, montelukast is a promising candidate for the future treatment of neurodegenerative diseases, because it has already shown promising results and offers a multimodal approach to treat AD, which distinguishes it from single-target approaches.

Concluding remarks

In summary, there is a strong rational to target the leukotriene system with the aim to improve function in AD. We believe that approaching and repairing as many of the pathological hallmarks as possible might be a much better strategy to treat dementia compared with the monospecific approaches of the past decades, most of which, if not all, have completely failed. This might be achieved through pharmacological targeting of the leukotriene pathway by repurposing leukotriene-antagonizing drugs, which are already approved as anti-asthma medication. Currently, the leukotriene receptor antagonist montelukast is in a Phase 2a clinical trial in patients with mild to moderate AD and awaits demonstration of efficacy. Interestingly, as nicely summarized in a recent review, the spectrum of diseases in which montelukast might be effective, is broad and covers many of the typical age-related co-morbidities, such as myocardial and renal dysfunctions, neuropathic pain, and others, which are often also seen in patients with AD [136].

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Declaration of conflict of interest

L.A. declares that he is consultant at IntelGenx corp., Canada, which has a clinical program for the development of Montelukast in AD. Jo.Mi. declares that she has received a 1-year PhD fellowship from IntelGenx corp.

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