Received: 11 May 2020 | Accepted: 26 May 2020 | Published online: 25 June 2020

DOI: 10.1002/trc2.12044

Alzheimer's & Dementia
Translational Research & Clinical Interventions

PERSPECTIVE

Targeting dementias through cancer kinases inhibition

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Funding information
This work was supported by the University of Pavia (grant from FR&G 2019, Fondo Ricerca & Giovani) to CL.

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Abstract

The failures in Alzheimer's disease (AD) therapy strongly suggest the importance of reconsidering the research strategies analyzing other mechanisms that may take place in AD as well as, in general, in other neurodegenerative dementias. Taking into account that in AD a variety of defects result in neurotransmitter activity and signaling efficiency imbalance, neuronal cell degeneration and defects in damage/repair systems, aberrant and abortive cell cycle, glial dysfunction, and neuroinflammation, a target may be represented by the intracellular signaling machinery provided by the kinome. In particular, based on the observations of a relationship between cancer and AD, we focused on cancer kinases for targeting neurodegeneration, highlighting the importance of targeting the intracellular pathways at the intersection between cell metabolism control/duplication, the inhibition of which may stop a progression in neurodegeneration.

KEYWORDS
Alzheimer's disease, c-Abl, c-kit, cancer kinases, dementia, Fyn, GSK-3β, kinase inhibitors, neurodegeneration, p38 MAPK

1 | OBJECTIVE

The present review aims to dissect the burgeoning landscape of druggable kinases in Alzheimer's disease (AD), focusing on selected cancer kinases currently under investigation in clinical trials as therapeutic targets. The present review intends to: (1) examine the dysregulation of intracellular signaling pathways, regulated by protein kinases, involved in the activation/inhibition of either pro-survival or cell death pathways, playing a central role both in cancer and neurodegeneration; (2) pinpoint the most relevant druggable kinases to counteract neurodegeneration in AD, with strong implications also in other dementias; (3) discuss cancer kinases inhibition as a therapeutic approach for AD treatment, repurposing existing anti-cancer drugs for non-oncological indications; and (4) summarize current challenges and discuss future limitations of such a rapidly evolving field. Groundbreaking understating of kinase signaling networks at molecular level may lead to major advances in repurposing existing drugs for new targets or disease indications.

2 | BACKGROUND

The current knowledge on the pathogenesis of AD, as well as the existing models of etiology, have been unable to provide an effective therapeutic option for the treatment of AD. As an example, therapeutic approaches targeting amyloid beta (Aβ), on which a great effort has been spent by the scientific and clinical communities, have so far largely failed to reach a significant clinical outcome. Several thousands of patients have been treated with anti-Aβ drugs, ranging from strategies targeting the levels of Aβ peptides, either by interfering with Aβ production (eg, β- and γ-secretase inhibitors), by promoting Aβ clearance, or neutralizing it with humanized monoclonal antibodies. However,

although, using the latter, plaques may be cleared, so far no convincing and significant clinical advantages in affecting the ongoing degenerative processes have been reported. Notably, results from trials involving anti-Aβ antibodies, such as gantenerumab, solanezumab, and aducanumab, suggested that to appreciate cognitive improvements in AD patients the treatment should probably be started at the very early stages of the disease.[1] Accordingly, to avoid the challenges associated with prevention trials design in late-onset sporadic AD, the pioneering DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit) was launched. DIAN-TU is phase 2/3 trial based on a primary prevention of the autosomal dominant form of AD, which has been shown to be linked to Aβ dysfunction and to cause cognitive impairment at a younger and predictable age.[1] Unfortunately, a topline analysis of the trial reported that both of the investigational anti-amyloid drugs, Roche's gantenerumab and Lilly's solanezumab, missed the primary endpoint, consisting of a composite of four cognitive tests (ie, DIAN-Multivariate Cognitive Endopoint). Several considerations (small sample size, heterogeneity of the disease stage, secondary outcomes still under scrutiny) suggest caution in interpreting these preliminary disappointing data. Some encouragement derives from the application in October 2019 to the U.S. Food and Drug Administration (FDA) for the marketing approval of aducanumab[2] after that the reanalysis of the phase 3 studies, originally discontinued after a futility analysis showing no clinical advantage of the treatment, revealed some significant results.[2]

The discouraging results observed in AD therapy emphasize the need to redirect the research strategies by better rethinking the biological mechanisms and intracellular signaling machinery involved in AD, as well as, more in general, in other neurodegenerative dementias. Even if the pathological profile of neurodegenerative disorders is different, common biological traits are present including neuronal cell degeneration, defects in damage/repair systems, aberrant and abortive cell cycle events, and neuroinflammation. The further observations of a relationship between cancer and neurodegenerative disorders, such as AD and Parkinson's disease (PD),[3] may direct to cancer kinases for targeting neurodegeneration. The field of cancer kinase inhibition for non-oncological indications, such as AD, is emerging as a challenging area to develop disease-modifying therapies. Indeed, tyrosine kinase inhibition provides a double-edged swordby manipulating autophagy to inhibit cell division and tumor growth in cancer, and by inducing toxic protein degradation as well as neuronal survival in neurodegeneration on the other hand.

Highlights

- New therapeutic strategies have to be considered in dementias.
- Pathways controlling cell metabolism/duplication are relevant targets.
- Kinases may represent modulable druggable targets in neurodegenerative diseases.
- Tyrosine kinase inhibition appears promising in treating neurodegenerative diseases.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (eg, PubMed, ClinicalTrials.gov) sources.
2. Interpretation: Data from literature suggest that the dysregulation of intracellular signaling pathways at the crossroad between pro-survival and cell death pathways, regulated by protein kinases, play a key role both in cancer and neurodegeneration. In particular, the inhibition of kinases presently targeted in cancer is emerging as a challenging strategy to counteract neurodegenerative dementias.
3. Future directions: The present work emphasizes the urgent need to refocus the research strategies by rethinking the biological mechanism and intracellular signaling machinery, regulated by protein kinases, involved in neurodegenerative dementias. The authors aim to propose a frame of reference for the generation of new hypotheses in the field of neurodegenerative diseases.

3 | NEW OR UPDATED HYPOTHESIS

Over the past decades, kinases have emerged as one of the most intensively investigated drug targets in current pharmacological research, due to their pivotal roles in modulating a wide array of cellular processes. A great effort has been directed toward the development of molecules specifically targeting the human kinome.[4] To date, the majority of molecules show a spectrum of kinase inhibitors, with >250 currently in clinical trials and 48 approved by U.S. FDA, mostly to treat malignancies.[5] The therapeutic potential of kinase manipulation, as well as the functions of kinases as tumor biomarkers for diagnosis, prognosis, and treatment, have widely been characterized in oncology. Several kinase inhibitors have revolutionized the treatment of malignancies driven by a single oncogenic kinase, such as chronic myeloid leukemia and gastrointestinal stromal tumors. Initially focused on cancer therapy, kinase drug discovery has recently broadened its focus to include an expanded range of therapeutic areas, such as autoimmune and inflammatory diseases, as well as neurodegenerative disorders (reviewed by Ferguson and Gray[6]), including AD. However, the contribution of the dysregulation of human kinome to neurodegeneration has not been clarified so far and the field of kinase-directed therapies is still immature compared to their application in cancer therapy. The neuronal functions of many kinases are still largely uncharacterized, with a sparse indication of how these targets influence the major signaling pathways involved in AD. Further investigations on human brains are needed to profile the changes in protein kinase activity in the different brain areas during aging and the progression of neurodegeneration.

TABLE 1 Clinical trials of cancer kinase inhibitors in Alzheimer's Disease

Agent	Mechanism of action	Therapeutic purpose	Clinicaltrials.gov ID	Phase/status	Sponsor
Saracatinib (AZD0530)	Selective Src tyrosine kinase inhibitor	Effect on cerebral metabolic rate for glucose	NCT02167256	Phase 2 Completed	Yale University
Masitinib (AB1010)	Tyrosine kinase inhibitor targeting c-Kit, platelet-derived growth factor receptors, and, a lesser extent, Lyn, Fyn, and the FAK pathway	Activity on mast cells, modulation of inflammatory processes	NCT01872598	Phase 3 Active, not recruiting	AB Science
			NCT00976118	Phase 2 Completed	AB Science
Neflamapimod (VX-745)	Selective p38 MAPK inhibitor	Affects multiple cellular processes including inflammation and cellular plasticity; reduces amyloid plaque burden (DMT)	NCT03402659 NCT03435861	Phase 2 Completed Phase 2 Recruiting	EIP Pharma Inc, VU University EIP Pharma Inc, Toulouse University, Foundation Plan Alzheimer
Nilotinib (AMN107)	Abl Tyrosine kinase inhibitor	Reduce amyloid and tau phosphorylation (DMT)	NCT02947893	Phase 2 Active, not recruiting	Georgetown University
DNL747	RIPK1 inhibitor	Reduce cytokines and other inflammatory factors (DMT)	NCT03757325	Phase 1 Active, not recruiting	Denali Therapeutics Inc
Tideglusib (NP031112)	GSK inhibitor	Reduce tau phosphorylation	NCT00948259	Phase 1 and 2 Completed	Noscira SA
			NCT01350362	Phase 2 Completed	Noscira SA

Unlike cancer, for which the identification of the specific kinase target led to the development of successful treatments, such lack of knowledge complicates the identification of single or clusters of specific kinases as drug target to counteract AD. The recognition of AD complexity suggests that addressing more than one target might be needed to set up a successful AD treatment. Accordingly, the complex and multifactorial pathophysiology of AD would suggest a multi-pharmacological approach rather than single target therapy, also in the context of kinase-directed drug discovery. Therefore, targeting multiple kinases rather than inhibiting any single kinase, by using either single drugs binding multiple proteins or cocktails of highly selective inhibitors, might be a promising strategy. In particular, some of the investigated protein kinase inhibitors show a "target promiscuity" profile. Owing to the fact that all kinases share a high degree of sequence conservation as well as common substrate recognition motifs, profiling the kinome selectivity of these inhibitors represents a fundamental step to attain the selectivity necessary for pharmacological target validation, as well as to predict and avoid off-target adverse effects. Such aspects may also present positive implications by allowing the identification of novel drug targets for already approved drugs and their repurposing for new targets or clinical indications. However, such wide diversity of interaction patterns shows a number of limitations. For instance, Karaman et al. screened 38 kinase inhibitors against a panel of 317 distinct human kinases, by using an in vitro competition binding assay, and identified a total of 3175 potential binding interactions,[7] with several kinase inhibitors showing higher affinity for their secondary targets rather than for their primary recognized targets. Such wide diversity of interaction patterns strongly suggests the importance of fully characterizing the target spectrum of kinase inhibitors to better interpret their biological activity observed in preclinical and clinical studies. Furthermore, some kinase inhibitors exhibit a paradoxical effect, thus resulting in the activation of the same target kinase or different kinases. As an example, c-Raf (rapidly accelerated fibrosarcoma) inhibitors have been reported to trigger a reactivation of c-Raf, without affecting other targets involved in the same signaling pathway, such as MKK1 (mitogen-activated protein kinase kinase 1) or p42 MAPK (mitogen-activated protein kinase)/ERK2 (extracellular signal-regulated kinase 2).[8] In addition, some Bcr (break point cluster)-Abl (Abelson) inhibitors possess off-target activity against Raf and stimulate paradoxical activation of BRAF and CRAF in a Ras-dependent manner.[9]

Based on these observations, in the following sections, we will focus on some selected kinase inhibitors, repurposed in AD and other dementias, that are currently under investigation in clinical trials as therapeutic tools (Table 1), highlighting the strength and weakness of their use.

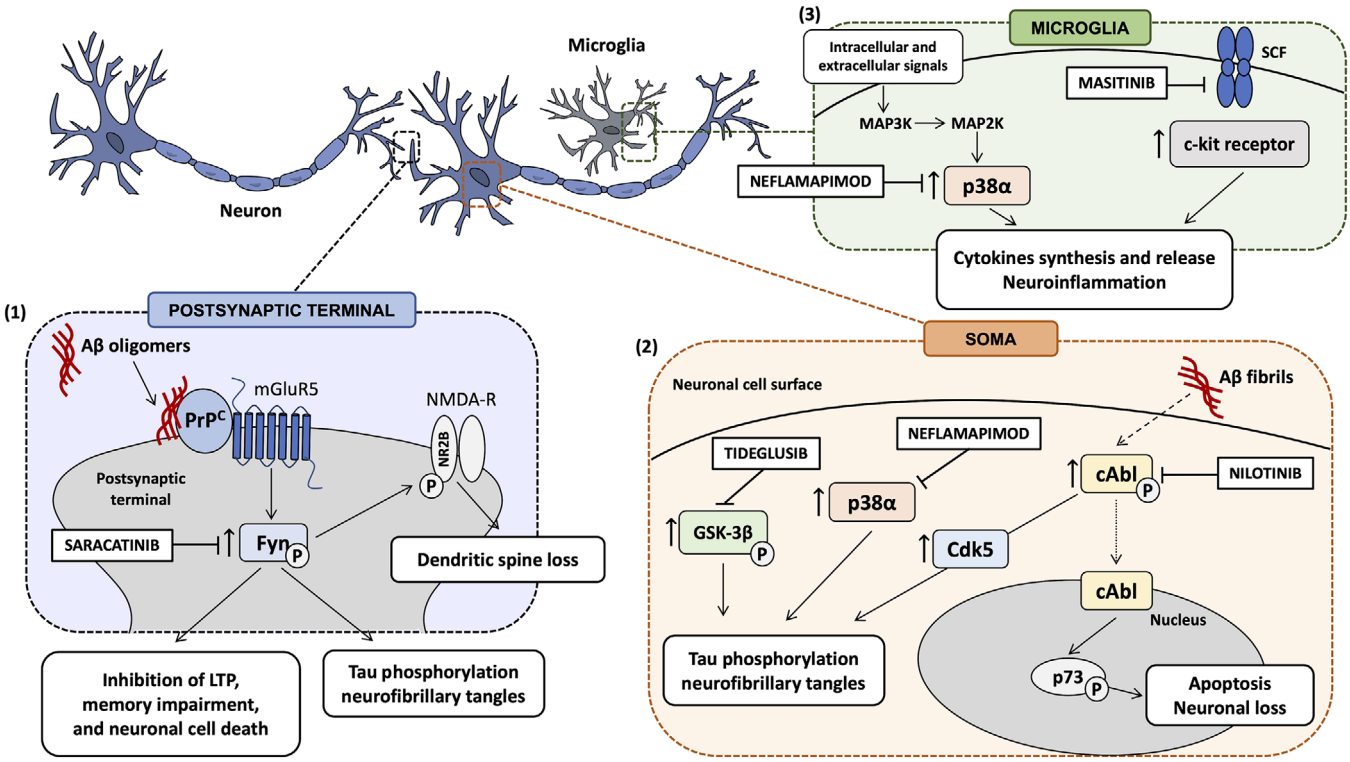

FIGURE 1 Targeting cancer kinases with inhibitors in dementias. (1) The intracellular pathway involving Fyn kinase has been demonstrated to be altered in Alzheimer's disease (AD), in which Fyn modulates both amyloid beta (Aβ)-driven synaptic dysfunction and neurotoxicity. At postsynaptic terminal, the extracellular soluble Aβ oligomers bind with nanomolar affinity to cellular prion protein (PrPC) on neuronal cell surface, thus triggering the activation of the downstream intracellular signaling pathway involving Fyn kinase. This activation of Fyn kinase by oligomeric Aβ-PrPC, which requires the participation of mGluR5, leads to the activation of N-methyl-D-aspartate receptors (NMDA-Rs) by phosphorylating their intracellular segment NR2B subunit, inducing dendritic spine loss. In addition, Fyn triggers the downstream phosphorylation of tau, by possibly contributing to neurofibrillary tangles formation. Saracatinib, a Fyn inhibitor, has been repurposed as disease-modifying therapy in AD. (2) At neuronal cell surface, Aβ fibrils increase c-Abl kinase activity, thus stimulating the nuclear translocation of c-Abl and inducing apoptosis and neuronal loss through c-Abl-mediated p73 phosphorylation. Furthermore, the activation of c-Abl kinase by Aβ fibrils promotes tau phosphorylation, both directly and indirectly, by activating the tau kinase Cdk5. c-Abl has been found to be hyperactivated in human AD and PD brains, as well as in Lewy body dementia (LBD), and its inhibitor nilotinib has been repurposed for PD, LBD, and AD. Moreover, in neurons, the overactivation of GSK-3β and p38α contributes to tau phosphorylation. Tideglusib, a GSK-3 inhibitor, and neflamapimod, a p38α inhibitor, have been repurposed in AD as potential disease-modifying therapies. Moreover, the U.S. Food and Drug Administration recently granted fast-track designation to neflamapimod for the treatment of LBD. (3) In microglia, several extracellular and intracellular signals trigger the consequential activation of MAPK3, MAPK2, and p38α, stimulating the synthesis and release of pro-inflammatory cytokines, thus promoting neuroinflammatory processes. Neflamapimod has been investigated as therapeutic approach to counteract neuroinflammation in AD. Finally, the activation of the stem cell factor (SCF)/c-kit pathway mediates neuroinflammatory responses and the c-kit inhibitor, masitinib, has been tested in clinical trials for the treatment of rheumatoid arthritis, asthma, and as add-on therapy to riluzole in amyotrophic lateral sclerosis

4 | KINASE INHIBITORS TO COUNTERACT TAU AND Aβ-DRIVEN NEUROTOXICITY

4.1 | Saracatinib

Saracatinib (also known as AZD0530), a Fyn kinase inhibitor, has been largely investigated for its inhibitory effect on cell growth. Originally developed by AstraZeneca as a therapy for solid tumors to counteract tumor cell adhesion, migration, invasion, and cell proliferation,[10] saracatinib was deprioritized due to its limited benefits as a single agent for oncological conditions and is currently being investigated in clinical and preclinical programs for a variety of non-oncological conditions, including AD, pain, and psychosis. In particular, it has been repurposed as a disease-modifying therapy in AD, as Fyn modulates both Aβ-induced synaptic dysfunctions and neurotoxicity, as well as tau phosphorylation. In particular, the capability of extracellular oligomeric Aβ to bind with nanomolar affinity to cellular prion protein (PrP^C) on neuronal cell surface and to activate the downstream signaling pathway involving Fyn kinase has been demonstrated (Figure 1).[11,12] Notably, Aβ binding to PrP^C has been shown to be highly specific for the soluble oligomeric form, with low or no affinity for fibrillary or monomeric Aβ peptides.[13] Such connection between oligomeric Aβ–PrP^C complexes at the cell surface and intracellular Fyn kinase has been found to require the participation of the metabotropic glutamate receptor 5 (mGluR5).[14] Fyn activation by oligomeric Aβ–PrP^C has been reported to activate *N*-methyl-D-aspartate receptors (NMDA-R) by phosphorylating the

intracellular segment of the NR2B subunit at Y-1472 [11,15] and to induce dendritic spine loss.[11] In addition, Fyn kinase has been demonstrated to induce the downstream phosphorylation of tau. Accordingly, Fyn has been found to directly associate with tau and to phosphorylate tyrosine residues near the amino terminus.[16–18]

Taken together, these data prompted intense investigations on targeting Fyn kinase for the treatment of AD. Accordingly, Kaufman et al. demonstrated that AZD0530 at a dose of 5mg/kg/d for 4 weeks fully rescued both spatial learning and memory deficits in 11/12-month-old APP/PS1 transgenic mice.[19] In addition, after 6 weeks of AZD0530 or vehicle treatment, the AZD0530-treated APP/PS1 mice exhibited performance equal to wild type mice in novel object recognition,[19] demonstrating that AZD0530 was capable of reversing the age-dependent memory impairment produced by the transgene. Moreover, AZD0530 at a dose of 5 mg/kg/day for 5 weeks decreased total tau and phosphorylated tau in 11-month-old APP/PS1/Tau transgenic mice.[19] However, a recent multicenter randomized clinical trial (NCT02167256) of 159 participants with mild AD, whose primary outcome was the reduction in relative CMRgl (cerebral metabolic rate for glucose) measured by 18F-fluorodeoxyglucose (18F-FDG) PET (positron emission tomography), reported non-statistically significant effects of AZD0530 treatment on the relative cerebral metabolic rate for glucose or on secondary clinical or biomarker measures.[20] AZD0530 treatment did not slow cerebral metabolic decline and did not improve cognitive function, compared to placebo. In particular, the treatment groups did not significantly differ in secondary clinical outcomes, such as rates of change in ADAS-Cog11 (Alzheimer's Disease Assessment Scale–Cognitive Subscale), ADCS-ADL (Alzheimer's Disease Cooperative Study–Activities of Daily Living), CDR-SB (Clinical Dementia Rating–Sum of Boxes), NPI (Neuropsychiatric Inventory), or MMSE (Mini-Mental State Examination) scores.[20] Moreover, in patients receiving saracatinib, consistent trends in worsening cognitive, functional, as well as clinical global outcome, have been observed compared to placebo as measured by ADAS-Cog, ADCS-ADL, CDR-SB, respectively.[20] It is likely that such negative trends did not reach statistical significance due to the limited sample size. In addition, almost two-fold number of dropouts in the group receiving saracatinib (n = 21) has been reported, compared to placebo group (n = 12), mostly due to adverse events.[20] In detail, 73 participants (92.4%) treated with saracatinib and 65 participants (81.2%) receiving placebo have been reported to experience at least one adverse event.[20] In particular, the most frequent adverse events were diarrhea and other gastrointestinal disorders that occurred in 38 participants (48.1%) receiving saracatinib and 23 participants (28.8%) receiving placebo.[20] On the other hand, trends for slowing the decrease in hippocampal volume and entorhinal thickness were observed.[20]

Therefore, although such results are discouraging, Fyn kinase cannot be excluded as a potential therapeutic target in AD. First of all, further optimization of selective Fyn inhibition is required to achieve a complete target engagement that can give us clues on Fyn kinase as a target of disease modification in AD. Moreover, given the well-established effect of saracatinib on glutamatergic transmission, it can be speculated that the drug does not modify the cognitive ability, but it may affect other behavioral disturbances. Notably, the inhibition of Fyn kinase may be addressed to specific subpopulations of AD patients. The identification of kinase-based molecular signatures in AD patients may allow us to identify patients more prone to respond to the therapy. In particular, AD patients carrying a specific Tyr_{682} APP phosphorylation might be more likely to respond to Fyn kinase inhibitor therapy. This hypothesis arises from literature data showing that Fyn binds to amyloid-β precursor protein (APP) on the $_{682}$YENPTY$_{687}$ domain in human AD neurons and mediates APP phosphorylation on the Tyr_{682} residue, in turn altering APP trafficking and sorting[21,22] and these effects are completely prevented by the Src tyrosine kinase inhibitor PP2.[21] Specific investigation of saracatinib on AD subpopulations carrying Tyr_{682} APP phosphorylation may solve this problem and help to better select the responsive patients. Notably, the identification of specific molecular signatures and biomarkers may be useful to better select and stratify subpopulations of AD patients for an appropriate drug treatment. However, this approach, yet theoretical, has to be investigated to practically translate it from the bench to the bedside and, to date, no clinical data are available to substantiate this hypothesis.

4.2 | Nilotinib

Nilotinib (Tasigna, AMN107, Novartis, Switzerland), a Bcr-Abl tyrosine kinase inhibitor, was approved by EMA in 2007 and by the U.S. FDA in 2010 and authorized for the treatment of adults with Philadelphia chromosome positive chronic myeloid leukemia.[23] Nilotinib has been recently repurposed in a number of neurodegenerative diseases, such as PD, Lewy body dementia (LBD), and AD. The rationale for c-Abl inhibition as treatment for neurodegenerative diseases relies on the hyperactivation of such kinase in human AD and PD brains, as well as in a variety of tauopathies.[24–27] Accordingly, Schlatterer et al. reported an increased activation of the tyrosine kinase c-Abl both in in vivo and in vitro transgenic AD models.[28] Notably, the activation of c-Abl signaling has been reported as a crucial event mediating the synaptic damage induced by Aβ.[29] The exposure of rat hippocampal neurons to 5 μM Aβ fibrils has been found to increase c-Abl activity, thus inducing apoptosis through c-Abl-mediated p73 phosphorylation (Figure 1).[30] The neuronal death of hippocampal neurons exposed to Aβ fibrils was prevented by the treatment with the c-Abl inhibitor STI571 (imatinib mesylate, Gleevec). Moreover, the intraperitoneal administration of STI571 has been shown to reduce rat cognitive impairment on spatial memory performance, induced by the bilateral hippocampal injection of 5 μM Aβ fibrils, and to ameliorate spatial learning and memory impairment in 11-month-old APP/PS1 transgenic mice.[31] Furthermore, the activation of c-Abl by Aβ has been found not only to stimulate proapoptotic signaling pathway through p73, but also to promote tau phosphorylation,[29] by activating the tau kinase Cdk5 (cyclin-dependent kinase 5) and by directly phosphorylating tau at tyrosine 394.[29,32] Notably, tau phosphorylated at tyrosine 394 has been shown to be present in pre-tangle neurons in AD brains, supporting the hypothesis that c-Abl may contribute to neurofibrillary

tangle formation and to their associated cognitive deficits.[26,32] It can be speculated that nilotinib, via c-Abl inhibition, may prevent Aβ-driven apoptosis and neurodegeneration by reducing both the activation of c-Abl/p73 proapoptotic signaling pathway and c-Abl/Cdk5-mediated tau phosphorylation, possibly preventing neurofibrillary tangle formation. However, Aβ-driven effects on c-Abl activity and its downstream intracellular pathways require further investigations.

Taken together, these findings suggest that c-Abl abnormal activation may contribute to neuronal dysfunction and support the use of c-Abl inhibitors as potential AD treatments.

On the basis of preclinical data, nilotinib has been considered for a clinical application. A randomized, double-blind, and placebo-controlled phase 2 study (NCT02947893) is currently evaluating the impact of low doses of nilotinib in 42 patients with mild to moderate AD and ended in February 2020. Safety has been assessed as primary endpoint based on the number of participants who experienced adverse effects or had abnormal laboratory values after 12 months of treatment, whereas cerebrospinal fluid (CSF) biomarkers (eg, levels of Aβ and tau), clinical outcomes, as well as target engagement and proof of mechanism (c-Abl inhibition) have been evaluated as secondary endpoints. Despite the strong limitations related to the study design, some preliminary results came from Pagan etal. open label pilot study, enrolling only 12 participants, that evaluated the safety and tolerability of nilotinib in patients with advanced PD with dementia or LBD, exposed to once daily oral dose of nilotinib for 6 months.[33] Nilotinib has been reported to be safe and well tolerated, to penetrate the blood brain barrier (BBB), as well as to significantly reduce CSF total tau and p-tau.[33] Moreover, positive trends for cognitive improvement, measured by MMSE and the Scales for Outcomes in Parkinson's Disease-Cognition, were observed.[33] In addition, c-Abl target engagement was demonstrated, with an observed 30% reduction in c-Abl activation.[33] Such decrease in c-Abl phosphorylation may account, at least in part, for the observed reduction in CSF p-tau. Beyond c-Abl inhibition, however, nilotinib showed the capability to interfere with other signaling pathways. In particular, in a variety of lines expressing oncogenic RAS, nilotinib has been found to possess the spectrum of weak RAF inhibitor, and to lead to the formation of BRAF: CRAF dimers, thus stimulating paradoxical activation of the pathway.[9] Moreover, in a recent phase 2 placebo-controlled randomized clinical trial testing the safety and tolerability of nilotinib in 75 patients with PD, doses of 150 or 300 mg nilotinib have been found reasonably safe, although serious adverse effects (eg, cardiovascular, gastrointestinal, renal, neurological, pulmonary) have been observed in 24% and 48% of the nilotinib-150 mg and nilotinib-300 mg groups, respectively, compared to 16% of the placebo group.[34] However, further larger and long-term studies are required to assess the safety and tolerability of nilotinib in PD patients. In addition, nilotinib-150 mg, but not nilotinib-300 mg, treatment has been shown to significantly reduce the levels of oligomeric α-synuclein, with no change of CSF total α-synuclein at 12 months.[34] This result is consistent with previous findings reporting a higher reduction of α-synuclein levels upon treatment with lower dose of nilotinib (1 mg/kg) compared to higher dose (10 mg/kg) in animal models of α-synucleinopathies.[35]

5 | TIDEGLUSIB

Tideglusib (NP-12, NP031112), a selective non-ATP competitive GSK-3 inhibitor, is repurposed for the treatment of AD. GSK-3 represents a therapeutic node at the intersection of multiple disorders, ranging from cancer to neurodegenerative disorders. According to "the GSK-3 hypothesis" of AD postulated by Hooper et al., the overactivation of GSK-3β accounts for cognitive impairment, tau hyperphosphorylation, increased Aβ production, and neuronal death in AD.[36] Tideglusib has been reported to reduce a range of disease markers (Figure 1), including tau hyperphosphorylation, amyloid deposition, neuron loss, and gliosis in mouse entorhinal cortex and hippocampus, and to reverse a spatial memory deficit in AD transgenic mice.[37–39] Furthermore, GSK-3β inhibition has been shown to reduce Aβ production and to ameliorate the AD-like neuropathology and behavioral deficits in the water maze in hAPP transgenic mice.[40]

A pilot, double-blind, randomized phase II trial (NCT00948259) evaluated the safety and efficacy of tideglusib in 30 patients with mild to moderate AD, reporting good tolerability and positive trends for cognitive benefits in MMSE, ADAS-cog, GDS (Geriatric Depression Scale), and GCA (Global Clinical Assessment).[41] A subsequent double-blind, randomized, placebo-controlled phase II trial (NCT01350362), testing the efficacy of tideglusib in a cohort of 306 mild to moderate AD patients, reported to have missed its primary cognitive endpoint.[42] Recently, Matsunaga et al. proposed a systematic review and meta-analysis of randomized controlled trials testing the efficacy and safety of GSK-3 inhibitors in mild cognitive impairment and AD patients.[43] Among the five trials included in study, no significant differences in cognitive function scores between GSK-3 inhibitors and placebo groups were observed, further corroborating data demonstrating the ineffectiveness of such a therapeutic approach.[43] A better focused analysis might be useful to understand whether a marker, a subgroup of patients, and/or other different parameters may refine the effectiveness of such a therapeutic approach.

6 | KINASE INHIBITORS TO COUNTERACT NEUROINFLAMMATION

6.1 | Neflamapimod

Neflamapimod (previously code-named VX-745) is an oral selective small molecule initially tested for rheumatoid arthritis and then repurposed as a disease-modifying drug for AD.[44] It is classified as an inhibitor of the intracellular signal transduction enzyme p38 MAPKα (p38α), a key modulator of microglia regulation and neuroinflammation (Figure 1).[45] Indeed, p38α is expressed in microglia where it mediates inflammatory responses stimulating the release of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and Interleukin-1β (IL-1β) [46], and in neurons where it modulates memory formation through effects on long-term potentiation (LTP)/depression.[47] Moreover, neuronal p38α has been implicated in tau phosphorylation[48] and

in Aβ oligomer-induced neurotoxicity,[49] and its role has been investigated as a therapeutic target for neuroinflammatory conditions, including AD.[50] In AD transgenic models, p38α inhibition has been found to reverse Aβ induced synaptic dysfunction and loss,[51,52] and p38α gene knockout improves synaptic function and memory as well as reduces Aβ production in AD transgenic mice.[53,54]

Preclinical studies demonstrated that neflamapimod improved performance in the Morris water maze test and significantly reduced hippocampal IL-1β protein levels in cognitively impaired aged (20 to 22 months) rats.[55] Such effects appear to be independent because the behavioral improvement in the Morris water maze was evident at a lower dose than that required to reduce IL-1β.[55] A blinded and placebo-controlled Phase 2b study (REVERSE-SD), enrolling 161 people with mild AD, compared a 6-month course of neflamapimod group with placebo on change in total and delayed recall on the Hopkins Verbal Learning Test, Revised (HVLT-R).[56] The REVERSE-SD trial failed to meet its primary endpoint of improving episodic memory at the end of the study period, as measured by HVLT-R and, secondarily, by the Wechsler Memory Scale (WMS) immediate and delayed recall (https://www.prnewswire.com/news-releases/eip-pharma-announces-clinical-trial-results-of-reverse-sd-a-phase-2b-study-of-neflamapimod-in-early-stage-alzheimers-disease-300953422.html). Notably, a pharmacokinetics-pharmacodynamic analysis showed positive trends toward improvement in the HVLT-R and WMS in patients with the highest plasma drug concentrations, suggesting that the clinical outcome may be dose-dependent. Thus, the observed effects of neflamapimod on CSF biomarkers, associated with those on episodic memory in patients with the highest blood concentrations, highlight the need to further investigate neflamapimod at higher doses and for long-term exposure. Such promising results are currently under investigation. In the REVERSE-SD trial, neflamapimod met its secondary objectives of target engagement and proof-of-mechanism, demonstrating statistically significant reductions in the CSF biomarkers phospho-tau and total tau. Moreover, the CSF levels of the postsynaptic protein neurogranin have been measured as biomarker of AD correlating with cognitive decline [57], and a trend toward reduced CSF neurogranin has been reported.[56] Notably, the observed reduction in CSF phospho-tau and total tau by neflamapimod provides the rationale for the extended application of neflamapimod to tauopathies, such as LBD. Consistently, the FDA recently granted fast track designation for the treatment of LBD to neflamapimod, which is currently being studied in separate Phase 2 trials in patients with LBD.

Another Phase 2 study (NCT03435861), enrolling 40 people with prodromal AD and with cerebral amyloidopathy (as measured by CSF analysis or amyloid PET), is currently monitoring brain inflammation in response to a 12-week course of treatment with neflamapimod or placebo, by using the microglial activation tracer DPA-714. Three DPA-714 SUV (standard uptake value) measures accounting for microglia activation and neuroinflammation represent the primary outcome. Secondary outcomes span 35 different parameters ranging from neuropsychological assessments to blood and CSF markers of inflammation. The trial is expected to run until January 2021.

6.2 | Masitinib

Originally approved for veterinary therapeutics for the treatment of mast cell tumors in dogs [58,59], masitinib (also known as AB1010) is a tyrosine kinase inhibitor with a wide spectrum of targets, among which are c-kit; platelet-derived growth factor receptors; and, to a lesser extent, lymphocyte-specific kinase (Lck), Lck/Yes-related protein (Lyn), Fyn, and FAK (focal adhesion kinase) pathways.[58] By combined targeting of c-Kit and Lyn, masitinib is particularly efficient in controlling the survival, differentiation, and degranulation of mast cells, thus indirectly controlling the release of proinflammatory and vasoactive mediators.[58] Promising results come from human clinical trials testing masitinib for the treatment of mastocytosis,[60] rheumatoid arthritis,[61] and asthma,[62] and as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis.[63] Recently, the potential clinical application of masitinib in neurodegenerative diseases, such as AD, has emerged due to the involvement of the stem cell factor (SCF, the c-kit natural agonist) receptor/c-kit in mast cells-mediated neuroinflammation (Figure 1). A randomized, placebo-controlled, phase 2 study (NCT00976118) was performed in patients with mild to moderate AD, receiving masitinib as an adjunct to cholinesterase inhibitor and/or memantine.[64] Compared to placebo, masitinib administration as an adjunct to standard treatments slowed the rate of cognitive decline at 24 weeks, as evident from the sustained and statistically significant response in ADAS-Cog.[64] Moreover, significant improvement in cognitive function and functional capacity was evident through the mean change in ADAS-Cog, MMSE, and ADCS-ADL values relative to baseline.[64] However, the weaknesses of this study concern the small sample size, with only 34 participants, and the high rate of discontinuation, with 17 dropouts (65.4%) in the group receiving masitinib versus 2 dropouts in the placebo group (25.0%). Moreover, the effective penetration of the BBB by masitinib was not assessed and, consequently, the mechanism underlying the positive cognitive outcome remains to be fully elucidated. One can speculate that, in the event that masitinib passes through BBB and accumulates to a sufficient high therapeutic concentration, it can reduce neuroinflammation by directly modulating microglial activity via disruption of SCF/c-Kit signaling pathway.[58] Moreover, masitinib may also reduce tau phosphorylation via targeting Fyn and FAK intracellular pathway, thus providing a dual benefit in AD.

Currently, masitinib is under phase 3 clinical trial (NCT01872598) to test its efficacy and safety as add-on therapy in patients with mild to moderate AD treated for a minimum of 6 months with a stable dose of cholinesterase inhibitor and/or memantine. As reported by the investor communication, the interim results showed positive trends of masitinib efficacy at one of the doses tested. However, the status of the trial is currently unknown.

7 | CONCLUDING REMARKS

Among the drug discovery programs currently testing disease-modifying strategies in AD, the field of protein kinase inhibition is

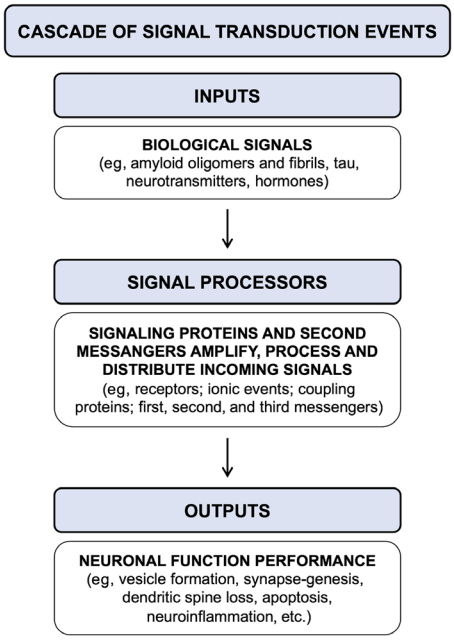

FIGURE 2 Cascade of signal transduction events: a schematic representation. Several biological signals, such as amyloid oligomers and fibrils, tau, neurotransmitters as well as hormones, trigger the activation of signaling proteins and cellular messengers that amplify, process, and distribute the incoming signals. The activation of intracellular signal processors induces neuronal responses, including vesicles trafficking, synapse-genesis, dendritic spine loss, apoptosis, and neuroinflammation, as outputs affecting neuronal performance.

BOX 1 Emerging key questions while studying cancer kinase role in neurodegenerative diseases

QUESTION BOX

How do different disease-associated biological signals (eg, amyloid oligomers, tau, neurotransmitters, and/or other signals) trigger the cascade of signal transduction events within the neurons?

Where do such biological signals activate the described intracellular pathways within the neurons? Is the activation of these cascades related to a specific portion (eg, soma, synaptic terminal) of the neuron?

Are there different receptors for each type of signal or is a given receptor involved in diverse signal derangements?

Are the cascades of intracellular events the same or different for each signal? If different, how do such intracellular pathways crosstalk?

How do protein kinase expression and activity change in different brain areas during aging and neurodegenerative processes?

Which are the most relevant signaling pathways to target?

What would be the best: targeting a hierarchically organized pathway or multiple parallel pathways?

emerging as a challenging area, with several molecules originally developed for oncological indications recently repurposed for the treatment of neurodegenerative diseases (Table 1). Notably, protein kinases represent key nodes at the intersection of multiple intracellular pathways, also acting as critical regulators of divergent signaling cascades. As well as in cancer, where mutated cells have to be counteracted, in neurodegenerative diseases the target is represented by dysfunctional cells. In both conditions, a common dysfunctional process is represented by an imbalance in the intracellular pathways regulating cell metabolism control and duplication, the inhibition of which may hence contribute to stop the disease progression (Figure 2). Therefore, kinases may represent modulable druggable targets in neurodegenerative diseases (Figure 1). However, despite promising preclinical results obtained in animal models, all the clinical trials testing kinase inhibitors in AD have ended in failure, with only few potential and still unconfirmed positive trends, further indicating that animal models cannot completely recapitulate the complexity of human biology and this is especially evident in the context of neurodegenerative diseases. The discouraging results may be justified by the fact that still few attempts have been made and few therapeutic strategies have been so far explored. In particular, addressing a single target and its related signaling pathway may not be an appropriate therapeutic strategy for AD, whose etiology is complex and multifactorial. The recognition of AD complexity suggests that using either single drugs binding multiple protein kinases or cocktails of highly selective inhibitors might be more effective, pending the assessment of their tolerability by frail elderly patients. The toxicity burden associated to kinase inhibitors and, in particular, substantial side effects due to off-target effects (eg, cardiovascular, gastrointestinal, and hematologic toxicity) cannot be neglected.[65]

Moreover, another major weakness related to the field of kinase inhibition in AD is that most of the preclinical studies testing kinase inhibitors in AD-like models investigated their impact on Aβ-centered pathways. However, this vision is too limited and, considering the failures of the anti-amyloid strategies, including the DIAN-TU trial on familial cases, may not be optimal in addition to be limited to AD among the neurodegenerative diseases (1; https://www.reuters.com/article/us-roche-alzheimers/roche-lilly-drugs-fail-to-halt-gene-driven-alzheimers-disease-idUSKBN2040JQ). However, as well as in cancer, in neurodegeneration it is important to target the drug to the dysfunctional cells and to differentiate them from the healthy ones. A differential mapping of the kinases is fundamental to selectively identify the right target in the affected tissue depending on the disease to be treated. To date, it cannot be discounted that we still have a partial knowledge regarding the functions of protein kinases in the major signaling pathways in neurodegenerative processes and several key questions have yet to be addressed (Box 1). In particular, an accurate profile of degenerative modifications of protein kinase expression and activity in different brain areas, associated with aging and neurodegenerative processes, is still lacking.

To this end, the recent advancements in proteomic technologies will facilitate a detailed profiling of the human brain kinome.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Fagiani F, Lanni C, Racchi M, Govoni S. Targeting dementias through cancer kinases inhibition. *Alzheimer's Dement*. 2020;6:e12044. https://doi.org/10.1002/trc2.12044