Received: 20 December 2024 | Revised: 29 January 2025 | Accepted: 30 January 2025

DOI: 10.1002/alz.70034

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Calcineurin inhibition may prevent Alzheimer disease in people with Down syndrome

Jacob Dohl[1] | **Zoe Treadwell**[1] | **Christopher Norris**[2] | **Elizabeth Head**[1]

[1]Department of Pathology & Laboratory Medicine, University of California, Irvine, California, USA

[2]Department of Pharmacology & Nutrition Sanders-Brown Center on Aging, University of Kentucky, Lexington, Kentucky, USA

Correspondence
Elizabeth Head, Department of Pathology & Laboratory Medicine, University of California, Irvine, CA, 92697, USA.
Email: heade@uci.edu

Funding information
NIH National Institute on Aging, Grant/Award Numbers: RF1AG056998, U19AG068054; NSF Graduate Research Fellowship, Grant/Award Number: DGE-1839285

Abstract

Virtually all people with Down syndrome will develop Alzheimer disease pathology during their lifetime. As Alzheimer disease is the third leading cause of death and a significant factor in end-of-life complications for adults with Down syndrome, identifying interventions is a medical necessity. Calcineurin, a Ca2+/calmodulin-dependent protein phosphatase, has recently been investigated as a possible Alzheimer treatment. This review explores the histories behind Down syndrome and Alzheimer disease, and their intersecting pathologies. This is followed by the role that calcineurin and its U.S. Food and Drug Administration–approved pharmacological inhibitor, tacrolimus, may play in the prevention or treatment of Alzheimer disease. Finally, this review discusses the gap in the literature surrounding the role of calcineurin, its regulators, and calcineurin inhibitors in the context of Down syndrome and comorbid Alzheimer disease. Future studies investigating the role that calcineurin plays in this pathology will be essential in determining the viability of calcineurin inhibitors to treat Alzheimer disease in people with Down syndrome.

KEYWORDS
Alzheimer's disease, calcineurin, Down syndrome, tacrolimus, therapeutics

Highlights

- Calcineurin, a Ca2+/calmodulin-dependent protein phosphatase, has become prominent as a possible therapeutic target to treat Alzheimer disease.
- People with Down syndrome develop Alzheimer pathology as they age, requiring novel therapeutics for treatment.
- People with Down syndrome may exhibit contraindications to calcineurin inhibition–based therapy, as they overexpress RCAN1 and DYRK1A, regulators of calcineurin.

- There is a significant gap in the literature involving the expression of calcineurin, RCAN1 and DYRK1A, in people with Down syndrome and Alzheimer disease, which must be addressed to determine the efficacy and safety of newly developed therapeutics.

1 | BACKGROUND

1.1 | Down syndrome

First characterized in 1866 by John Langdon Down, Down syndrome (DS) stems from a trisomy of the 21st chromosome (Hsa21) and affects 1 of ≈750 children born in the United States.[1] DS is characterized by intellectual disability, altered brain development, and immunological disorders.[2–4] Nondisjunction during meiosis is the leading cause of DS, accounting for around 95% of cases. Of interest, however, advances in genetic testing reveal cases of partial trisomy in which only a segment of the triplicated Hsa21 is present in the cell.[5–8] Exploration into the areas essential for the development of DS has led to the characterization of a Down syndrome critical region (DSCR), a length of 1–8 Mb within Hsa21, of which triplication is essential in generating the DS phenotype.[9,10]

Complete trisomy of Hsa21 results in elevated expression of several critical developmental and homeostatic genes, including *Amyloid precursor protein* (*APP*), *Beta-secretase 2* (*BACE2*), *Dual specificity tyrosine phosphorylation regulated kinase 1A* (*DYRK1A*), *Regulator of Calcineurin 1* (*RCAN1*), and *Superoxide Dismutase 1* (*SOD1*).[11,12] Although the gene dosage effect would imply a 50% elevation of gene expression in DS, many of these genes, including *DYRK1A*, *RCAN1*, and *SOD1*, exhibit RNA expression above typical levels but below the high level that would be predicted.[13,14] Nonetheless, people with DS are susceptible to a number of adverse health outcomes, including autoimmune disorders, cognitive impairment, hypothyroidism, and obesity.[15,16] Autoimmunity is a significant factor in DS, as people with DS have consistently increased cytokine expression, altered $CD4^+$ T-cell number and activation, and atypical B-cell activation.[17–19] Stemming from these autoimmune disorders, Type 1 diabetes and chronic systemic inflammatory diseases are common among people with DS.[20,21]

Resulting from the preceding comorbidities, the life expectancy for someone with DS before 1980 was below 25 years of age.[22,23] With advancements in modern medicine and, perhaps more importantly, a shift in mental health perspectives that prioritize care, socialization, and activity, people with DS now have an average life expectancy into their 60s.[23,24] However, increasing age is a risk factor for Alzheimer disease (AD). Furthermore, the overexpression of the precursor protein to amyloid beta (Aβ) on Hsa21, results in people with DS developing AD neuropathology by age 40 years.[25,26] Currently, AD is third among the leading causes of death for adults with DS.[27,28] However, studies imply that this is a gross underestimation and may account for a much higher percentage than currently reported.[27]

1.2 | Alzheimer disease

Named after Alois Alzheimer, AD was first characterized in 1906 as a "severe disease process of the cerebral cortex."[29] Clinically, AD presents as a progressive cognitive impairment involving memory loss, poor judgment, a loss of orientation, and personality changes, with a diagnosis requiring two or more of these symptoms.[30,31] On a cellular level, AD is characterized by Aβ plaques, neurofibrillary tangles (NFTs) containing phosphorylated tau (p-tau), neuronal loss, and elevated neuroinflammation.[32–34] AD and clinical dementia are also associated with several comorbid pathologies, with pure AD remaining an uncommon occurrence; vascular pathology, amyloid and tau load, Lewy bodies, and hippocampal sclerosis cumulatively account for much of the risk of AD and dementia.[35,36] Clinical confirmation of neuronal loss (brain atrophy) or the presence of Aβ and tau can be through neuroimaging (magnetic resonance imaging [MRI] imaging or positron emission tomography [PET] scans, respectively).

Aβ has long been studied in AD due to its ubiquity in the disease. In healthy adults, APP protein is cleaved by α-secretase and then cleaved by γ-secretase to form P3 and APP intracellular domain (AICD), which are readily cleared from the cell.[37] In amyloidogenic conditions, APP is cleaved by β-secretase, followed by γ-secretase, yielding AICD and Aβ.[37] Aβ begins as a soluble protein, cleared in the early stages of AD; however, it accumulates with aging, transitioning from soluble proteins to insoluble aggregates, which attract additional Aβ accumulation in a seeding process.[38,39] This accumulation progresses through the brain in a well-characterized pathway known as Thal phases, beginning in the prefrontal cortex before progressing into the hippocampus, post-cingulate gyrus, medulla oblongata, and, finally, the cerebellum.[40,41] The presence of Aβ plaques drives microglial activation, inducing neuroinflammation that worsens as plaque formation continues.[42,43]

Alongside Aβ accumulation, AD also involves the accumulation of NFTs formed from phosphorylated p-tau. Expressed mainly in neuronal axons, tau promotes microtubule assembly.[44,45] Phosphorylation of tau causes decreased interaction with microtubules, perhaps acting as an inhibitory mechanism, but hyperphosphorylation results in misfolding and tangle aggregation.[45–48] NFTs operate in a mechanism similar to that of Aβ, spreading progressively through the brain, termed Braak staging, and initiating neuroinflammation and neuronal cell death as aggregates prevent axonal trafficking.[49–51] Together, Aβ plaques and NFTs exert significant pressure on the aging brain, resulting in rampant neuroinflammation, synaptic dysregulation and loss, and neuronal cell death, resulting in the clinical presentation of AD.

1.3 | Alzheimer disease in people with Down syndrome

As mentioned previously, due to the increase in APP production, people with DS develop Aβ pathology at an early age.[52,53] Children with DS as young as 3 years can exhibit small diffuse accumulations of Aβ.[54] Diffuse Aβ plaques systematically begin to form in the 20s and 30s of people with DS; the extent of plaques increases exponentially after the 40s, with Aβ pathology typically progressing into clinically relevant AD diagnoses.[52,55,56] By age 40 years, most people with DS are classified as Thal Stage 5, with plaques found in the cerebellum and cognitive decline tending to begin in earnest at ≈53–54 years of age.[57,58] Compared with the general population, which experiences lower rates of AD pathology and an average age at onset around 70 years, people with DS deal with increased risk and early progression of the disease.

Neuroimaging studies also reveal early progression of Aβ and tau tangle accumulation in people with DS. As mentioned in Section 1.2, PET scans are commonly used to determine the brain's Aβ load, tau load, and metabolic activity. Aβ pathology, determined through Pittsburgh Compound B (PiB) labeling on PET scans, is seen by the age of 40 in people with DS, although sparse accumulation is occasionally seen earlier.[59] Of interest, Aβ pathology begins in the striatum before progressing to the prefrontal cortex, suggesting an alternate initiation of amyloidopathy in people with DS compared to sporadic AD cases.[60,61] Tauopathy, determined through ^{18}F-AV-1451 tracer PET scans, is similar in cerebral distribution to sporadic AD.[62] However, in people with DS, the onset of tau tangles is only 2.5–5 years after the onset of Aβ pathology, much faster than the estimated 5–10 years in sporadic AD.[63,64] Together, these findings indicate an earlier and faster progression of AD pathology in people with AD, which must be addressed in conjunction with other DS-related comorbidities.

Elevated levels of Aβ results in neurovascular deposits is known as cerebral amyloid angiopathy (CAA).[65] CAA is a leading cause of microhemorrhages in AD, elevating neuroinflammation and positively correlating with increased cognitive decline.[66,67] Although reporting criteria for CAA are varied, recent estimates place the incidence rate at ≈50%–75% in people with AD.[68,69] Not surprisingly, given the overproduction of APP, people with DS have a roughly 85% incidence rate of CAA, significantly higher than that of the general population.[68] General vascular pathologies, including microbleeds and infarcts, are also prevalent in people with DS, with the onset occurring in the early to mid-30s.[70] Of interest, these early microbleeds and infarcts occur before significant amyloid deposition and CAA development, suggesting a role in the early development of AD rather than late-stage development. Thus, vascular pathologies, including CAA, microbleeds, and infarcts, are increasingly noted as an essential factor in AD progression and the development of clinical dementia; therefore, it is crucial to consider the contributions of vascular disease when discussing AD in people with DS.

Disrupted sleep and poor sleep quality may enhance the risk of and can also be a consequence of progressive AD.[71,72] Poor sleep quality, caused by sleep disturbances, dysregulated sleep/wake cycles, and obstructive sleep apnea (OSA), increases the risk of cognitive impairment and hinders memory formation.[73–75] Severe sleep disruptions and OSA are highly prevalent in DS.[76] Over 50% of children under age 10 with DS show evidence of OSA, and nearly 80% showed abnormal sleep scores, reflecting a lifelong struggle with restful sleep that likely contributes to the prevalence of AD later in life.[77]

There is a need for new treatments and therapies for AD to prevent and combat its progression. For people with DS, this is even more pressing, as recent studies suggest that the current life-limiting factor for people with DS is AD.[58] Indeed, DS has been considered to be the most common form of genetic AD, and people with DS have mortality rates that coincide with autosomal dominant AD.[25,58] Currently, several U.S. Food and Drug Administration (FDA)–approved pharmaceuticals, including donepezil and galantamine, and two newer treatments, lecanemab and donanemab, show promise in treating the symptoms and slowing AD progression, respectively.[78–80] However, some treatments may address the symptoms of the disease and not the etiology (e.g., donepezil). Others may slow progression but have significant side effects, thereby limiting their effectiveness for all patients with AD (lecanemab, donanemab). Therefore, new targets are being explored in search of a therapeutic that can successfully stop or prevent AD progression. Of these targets, calcineurin has shown great promise in its ability to influence AD progression and is worth investigating in depth.

RESEARCH IN CONTEXT

1. **Systematic review**: This article utilized Pubmed to review the literature surrounding the utilization of calcineurin inhibitors as a therapy for Alzheimer disease in people with Down syndrome. Calcineurin inhibitors have gained prominence as a possible therapeutics for Alzheimer disease in the general public. However, people with Down syndrome demonstrate possible contraindications.
2. **Interpretation**: Our findings reveal a lack of conclusive information on the role calcineurin plays in the development of Alzheimer disease in people with Down syndrome. The expression of calcineurin, calcineurin regulators, and the activity of calcineurin-induced inflammatory pathways is poorly characterized in people with Down syndrome and Alzheimer disease.
3. **Future directions**: Investigations into the expression of calcineurin, its regulators, and the activation of calcineurin-induced inflammatory pathways in people with Down syndrome are needed to elucidate the role calcineurin inhibitors may play in the treatment of Alzheimer disease in people with Down syndrome.

2 | CALCINEURIN

Calcineurin (CN) is a heterodimeric Ca^{2+}/calmodulin-dependent protein phosphatase expressed ubiquitously throughout the body and

in neurons and reactive astrocytes.[81,82] Calcineurin A (CaNA) is the catalytic subunit of the CN heterodimer, containing an N-terminal catalytic domain, which is essential for CN's phosphatase activity.[83] In addition, CaNA contains a calcineurin B (CaNB) binding domain, a calmodulin (CaM) binding domain, and an autoinhibitory domain, which restricts the CN active site in the absence of CaM.[84,85]

CaNB is generally described as a regulatory subunit with four helix-loop-helix EF-hand Ca^{2+} binding domains that sense variable Ca^{2+} concentrations within the cell. The pair of C-terminal EF-hands are exquisitely sensitive to Ca^{2+}, with dissociation constants (Kds) between 50 and 150 nM.[83,86,87] The N-terminal hands are less sensitive to Ca^{2+} concentrations; their Kds range from 1 to 1.7 μM.[87] Point mutation studies on each EF-hand have demonstrated that the highly sensitive C-terminal hands are likely structural; in contrast, the less sensitive N-terminal hands contribute to sensing Ca^{2+} levels and stabilize the protein during its interaction with CaNA.[88] Notably, Ca^{2+} binding is cooperative, with a loss of any Ca^{2+} molecule from one EF-hand increasing the dissociation rate for all other hands, and vice versa.[88] CN is sensitive to Ca^{2+} due to the ability of CaNB to sense and act upon minuscule variations in Ca^{2+} concentration within the cell. This distinguishes CN from other Ca^{2+} sensing enzymes, which generally have lower sensitivity or slower kinetics. This may also explain why CN is so acutely sensitive to the Ca^{2+} dysregulation so often seen in aging. Of interest, elevated calcium levels alone cannot fully activate CN; only about 10% of the activity is observed at calcium saturation, with CaM and another divalent cation required to activate the phosphatase fully.[89] Upon binding with CaM, the CN-CaM complex regulates cellular events throughout the body. CN can also be permanently and irreversibly activated through its interaction with calpain, which cleaves the auto-inhibitory domain and CaM-binding domain of CN; this cleaved version is typically denoted as ΔCN.[90,91]

Important for this review, one of the main targets of the CN-CaM complex is the nuclear factor of activated T cells (NFAT) pathway. The NFAT family consists of five transcription factors, NFAT 1–5, of which calcium concentrations and CN dephosphorylation regulate NFAT 1–4.[92] The NFAT family of proteins contains several highly conserved domains, including an N-terminal regulatory domain and a C-terminal DNA-binding domain.[93] The N-terminal regulatory domain is essential for CN to interact with and dephosphorylate the NFAT family. The NFAT PxIxIT and LxVP motifs are well conserved across the family and have a high affinity for CN binding, with CaNA and CaNB able to bind these motifs at similar rates.[94,95] The binding of CN to the PxIxIT and LxVP sites forms a loop containing the serine-rich region and serine-proline-rich boxes where NFAT phosphorylation occurs, allowing for enhanced dephosphorylation by CN.[93,94] Dephosphorylation of NFAT by CN initiates nuclear translocation of the NFAT protein, where it functions as a transcription factor.[96] NFAT activation can result in the expression of a plethora of genes, including cytokines, surface receptors, apoptotic genes, transcription factors, and genes involved in calcium signaling and regulation.[97,98]

CN is perhaps the most studied in its interaction with the peripheral immune system as a T-cell activator.[92,99] In brief, the binding of T-cell receptors triggers a cascade of interactions that flood the cell with calcium by releasing intracellular calcium and opening calcium channels to influx extracellular calcium.[100] This elevated calcium concentration activates CN and generates the CN-CaM complex, which activates NFAT translocation to the nucleus. As the NFAT signaling cascade takes effect, T cells activate, initiating cytokine release, lytic enzyme release, and replication (illustrated in Figure 1).[101] This integral role of CN in T-cell activation and immune response has made it an appealing target for immune therapies, including preventing transplant rejection and alleviating autoimmune disorders. CN's activity within the brain and neuronal landscape is less known, which is the focus of this review.

2.1 | Calcineurin's neuronal interactions

2.1.1 | The neuronal cytoskeleton

CN is expressed in neurons and plays varied and significant roles within the neuronal landscape, as demonstrated in Figure 2. There is evidence that CN can directly dephosphorylate microtubules, with Goto et al. finding a 22% decrease in tubulin phosphorylation when placed in solution with CN; of interest, CN-catalyzed tubulin dephosphorylation is dependent upon CaNB, which binds directly to tubulin.[102,103] Perhaps more importantly, CN interacts with several microtubule-binding proteins (MTBPs), including Microtubule-Associated Protein 2 (MAP2), neuromodulin (NM), and tau.[102,104–106]

MTBPs are a broad classification of proteins, performing tasks such as regulating microtubule assembly, enabling tubule crosslinking, integrating new cytoskeletal elements, and assisting with intracellular transport along microtubules.[107] MAP2 is expressed mainly in mammalian neurons and binds to the sides of microtubules to promote stability and rigidity.[108–111] The binding of MAP2 to microtubules is regulated by several microtubule-binding KXGS motifs, which become active when phosphorylated.[108] Thus, CN's phosphatase activity improves MAP2's ability to bind microtubules and is essential for dendrite and synapse formation.[112–116]

NM acts similarly to MAP2, interacting with actin microtubules in axon terminals, especially during synaptogenesis.[117–119] Four closely related factors regulate NM: phosphorylation status by protein kinase C (PKC), Ca^{2+} concentration, CaM binding, and CN dephosphorylation. At low Ca^{2+} concentrations, NM is dephosphorylated and bound to CaM, acting as a barbed end-capping protein for actin, preventing cytoskeletal polymerization.[120,121] However, at high Ca^{2+} concentrations, PKC becomes activated, phosphorylating NM and causing the loss of CaM.[117] Phosphorylated NM binds and facilitates stable actin polymerization, promoting neuronal axonal growth. Elevated Ca^{2+} concentration and free CaM are the perfect recipe for CN activation; CN dephosphorylates NM directly, which may regulate NM/CaM interactions.[122,123] Therefore, it seems that, at high Ca^{2+} concentration, CN acts as a limiter to NM activation, ensuring that growth remains controlled. CN aggregates into axonal and dendritic growth cones during the first 7 days of culture in developing rat cerebellar cultures.[113] Aggregation shifts to the neurite shaft in the next 7 days,

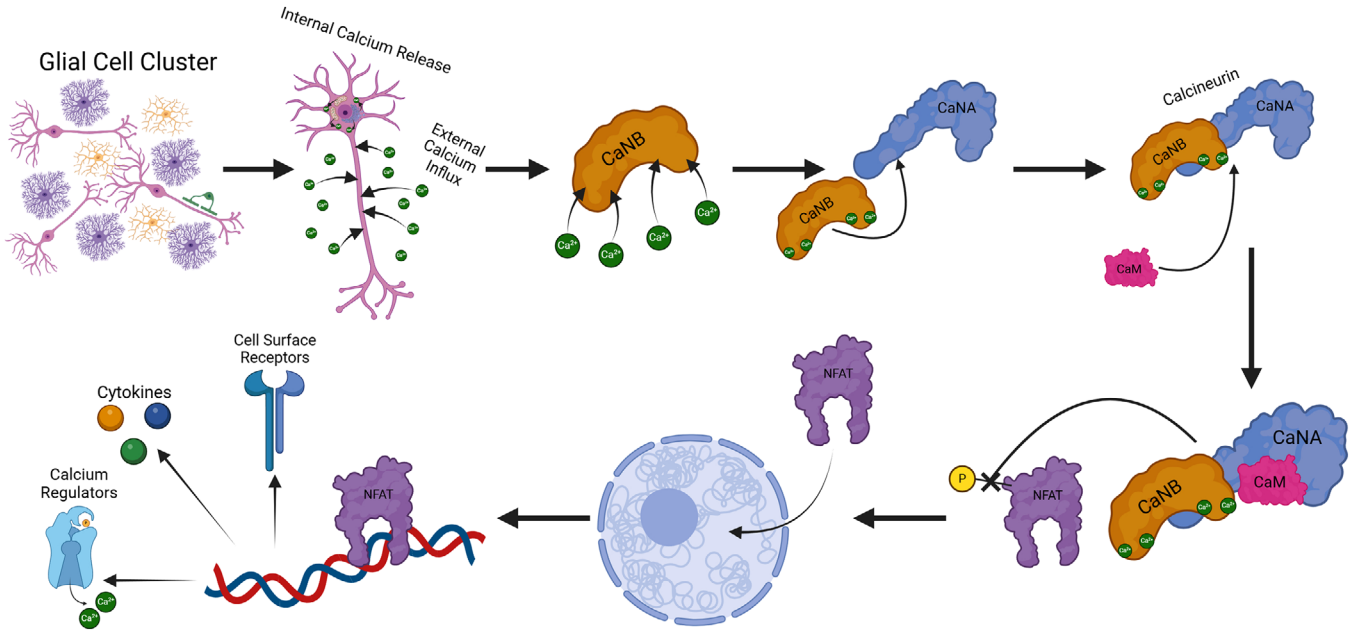

FIGURE 1 The Calcineurin pathway and regulation of NFAT. Following elevated cellular calcium levels, either from external influx or internal storage release, CaNB binds calcium in its four EF-hand domains. This prompts complexing with CaNA and CaM, activating the CN complex. CN then dephosphorylates NFAT, allowing nuclear translocation and transcriptional activation. CaM, calmodulin; CaNA, calcineurin A; CaNB, calcineurin B; CN, calcineurin; NFAT, nuclear factor of activated T cells.

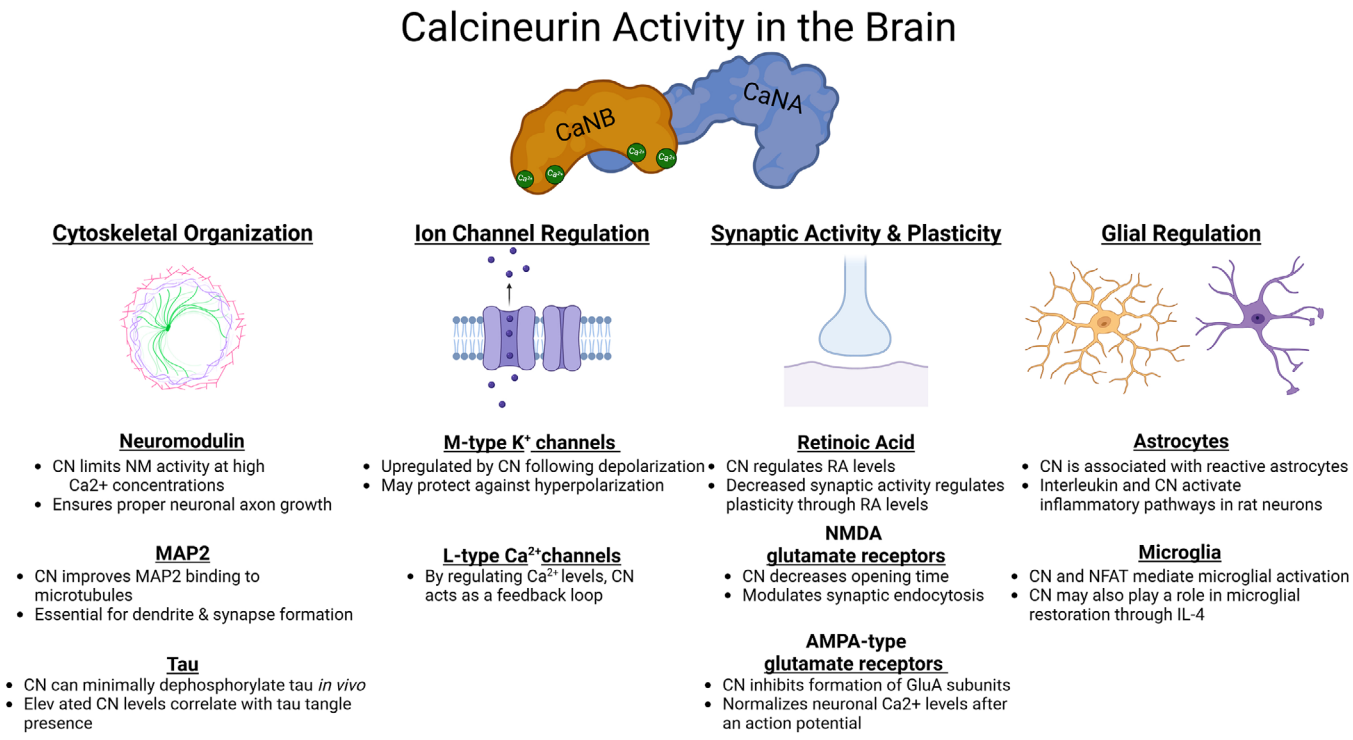

FIGURE 2 Calcineurin's activity in the brain. CN is a regulatory component in several key neurological processes, as described in Section 2.1. CN, calcineurin.

suggesting a role in axonal elongation. Indeed, inhibition of CN through cyclosporin A prevents axonal formation.[113,124]

Perhaps the most interesting MTBP in AD is tau, given its role in microtubule regulation and as a neuroinflammatory factor through the formation of NFTs. Although CN can dephosphorylate tau directly, it accounts for less than 10% of tau dephosphorylation within the cell.[125] CN directly activates glycogen synthase kinase-3 β (GSK-3β) through dephosphorylation of GSK-3β Ser-9.[126,127] GSK-3β is a proline-directed serine/threonine kinase that phosphorylates tau at several sites, inducing NFT aggregation and accelerating fibrilization.[128–130] In addition, the upregulation and overactivation of GSK-3β have been linked to Aβ accumulation and microglial activation, driving AD progression.[131,132] Thus, CN accelerates NFT pathology by activating GSK-3β. Indeed, there is evidence that elevated CN activity increases tau tangle pathology.[91,133] This supports the hypothesis that overexpression and elevated activity of CN is detrimental to the aging brain rather than acting as a guard against tau hyper-phosphorylation and NFT formation.

2.1.2 | Neuronal regulation of ion channels and synapses

Neuronal function is essential to a healthy brain, and CN is implicated in the effectiveness of neuronal signaling. As Ca^{2+} signaling is essential for neuronal depolarization, tight control of Ca^{2+} concentrations is necessary for proper neuronal activity.[134] CN is typically assumed to act as negative feedback to elevated neuronal activity and Ca^{2+} influx.[90] For instance, the M channels are vital for neuronal excitability, and their activation suppresses the likelihood of action potentials.[135] Through the NFAT pathway, CN can upregulate M-type K^+ channels following Ca^{2+} influx related to depolarization, indicating a possible negative feedback loop to protect against neuronal hyper-excitability.[136] Patch-clamped bullfrog neurons incubated with and without CN demonstrate a decrease in M current activity, implying that CN can inhibit the M current directly.[137] CN also regulates L-type Ca^{2+} channel activity following Ca^{2+} influx, controlling Ca^{2+} levels within neurons.[138] Although CN is noted primarily for its association with and regulation of Ca^{2+} channels, there are instances of CN associating with the channels of other ions. CN dephosphorylates voltage-sensitive sodium channels in rat neurons, with cyclosporin A inhibition of CN increasing phosphorylation levels by 40%.[139]

CN also plays a pivotal role in regulating synaptic activity and plasticity. CN decreases the opening time of the *N*-methyl-D-aspartate (NMDA) glutamate receptor, inhibiting excitation, and influences the slow and rapid endocytosis of synapses, regulating receptor turnover.[90,140] GluA1 and 2, which can assemble into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (AMPARs) that regulate glutaminergic synaptic transmission, are dephosphorylated by CN; inhibition of CN in Sprague–Dawley rats increases the prevalence of postsynaptic AMPARs, which allows for elevated Ca^{2+} levels within the cell, disrupting regular neuronal firing.[141–144] CN can modify synaptic plasticity by regulating retinoic acid (RA) levels.[145] RA is synthesized following diminished synaptic activity, resulting in a signal cascade that increases excitatory synaptic strength.[146,147] Arendt et al. determined that the reduced synaptic activity in neurons resulted in diminished Ca^{2+} concentrations, inactivating CN and allowing RA-induced synaptic plasticity; inhibition of CN in active neurons led to the same synaptic plasticity as inactive neurons.[145]

Long-term potentiation (LTP) is a potent form of synaptic plasticity that underlies memory and learning.[148,149] The cyclic AMP response element-binding protein (CREB) transcription factor is essential in LTP and memory formation, with CREB knockout mice consistently showing deficiencies in long-term memory.[150–154] CREB activity depends upon prolonged Ser113 phosphorylation and the recruitment of cofactors, including CREB Binding Protein.[155–157] CN regulates LTP and memory formation by regulating CREB activity, with CN overactivity being associated with CREB dephosphorylation and preventing CREB-induced gene expression.[158–163] The dephosphorylation of CREB by CN has been studied as a possible regulatory mechanism, but studies suggest that CN is not dephosphorylating CREB directly, as seen by Naqvi et al. in 2013.[157,159] Protein phosphatase 1 (PP1), a target of CN, may be the driving force behind CREB dephosphorylation, although further investigation is warranted.[164] Of interest, there is evidence that CREB promotes the degradation of RCAN1 through ubiquitination and subsequent proteasomal degradation.[165] This suggests a negative feedback loop, with CREB activation degrading RCAN1, activating CN to inhibit CREB signaling.

CN inhibition can result in chronic calcineurin inhibitor–induced pain syndrome, seen in patients treated with CN-targeting immunosuppressant drugs.[166–168] This syndrome is thought to stem from the dysregulation of synaptic firing and neuroprotective M channel expression.[90,169] Therefore, any chronic treatment with CN inhibitors must be weighed against the possibility of inducing a chronic pain syndrome.

2.1.3 | Glial regulation

It is also essential to understand the role of CN in glial cells, as the support of the many glial cells within the brain dictates neuronal and cognitive well-being. Microglia are the brain's resident immune cells and regulate inflammatory and regenerative processes. CN inhibition significantly decreases microglial activation.[170] Studies in murine cell lines show that CN and NFAT signaling mediate microglial activation.[171–173] Perhaps unsurprisingly, CN is a driver in neuroinflammatory processes much like in the rest of the body; however, some studies show a role for CN in promoting neuroprotective microglial activation. Ting et al. found that primary rat cortical neurons subjected to excitatory stress released interleukin (IL)-4, which polarized microglia toward a restorative phenotype.[174] Neurons subjected to CN inhibition showed no IL-4 expression, implying a role for CN-mediated cytokine expression in this pathway. Therefore, the association between CN and microglia must be considered contextually despite the generally understood role of CN as "pro-inflammatory."[175]

Astrocytes perform many homeostatic tasks, including stabilizing neuronal activity, maintaining the blood–brain barrier (BBB), and mediating immune responses.[176,177] Many of these mechanisms are partially regulated by carefully controlled Ca^{2+} signaling pathways, which can become dysregulated with aging.[178–180] The connection between reactive astrocytes, aberrant Ca^{2+} regulation, and CN activity suggests a critical role in the regulation of astrocytic neuroinflammation. CN is associated with reactive astrocytes, overexpressed and hyperactive in Aβ-adjacent human astrocytes, which increases with age; these Aβ-adjacent astrocytes often contain the hyperactive calpain-cleaved ΔCN.[181–183] In addition, IL-1β, an integral signaling molecule in neuroinflammation, recruits CN and activates the NFAT pathway in rat primary cortical neurons.[184] Applying CN directly onto astrocyte culture prompts the activation of the NFAT pathway and stimulates secondary astrocytes, suggesting a communal reactivity to the activation of the CN/NFAT pathway.[184] Perhaps most important for AD, the inhibition of the CN/NFAT pathway in the astrocytes of AD mouse models benefits several key markers of AD pathology, including improved cognitive function, decreased Aβ levels, improved astrocytic dendrite morphology and synaptic strength, and reduced glial activation.[185,186] Similar benefits are noted in mouse models of traumatic brain injury (TBI), with CN/NFAT inhibition decreasing injury-related loss of synaptic activity and susceptibility to depression.[187] These data elucidate a key role for CN signaling in maintaining the neuronal cytoskeleton, neuronal activity, and the induction of glial reactivity.

3 | CALCINEURIN AS A THERAPEUTIC TARGET FOR ALZHEIMER DISEASE

Ca^{2+} and CN regulation play an integral role in maintaining neuronal homeostasis. However, aberrant Ca2+ regulation within the brain is prevalent as aging progresses, with Ca^{2+} influx outpacing removal in aging neurons.[188–191] In AD, Aβ can form pores in the cell membrane, allowing Ca^{2+} influx into the cell.[192,193] CN is exquisitely sensitive to Ca^{2+} fluctuations within the cell; thus, it is adversely affected by these aging processes early and dramatically. CN is implicated during the early stages of cognitive decline in AD, suggesting a preclinical role in the disease, which worsens in conjunction with increasing AD pathology.[194,195] CN activity is elevated, often hyperactive, in cells near Aβ plaques.[181–183] CN can also exacerbate Ca^{2+} dysregulation through its interactions with L-type Ca^{2+} channels, causing a positive feedback loop to elevate Ca^{2+} levels to pathological levels.[196–198] CN also drives neuronal cell death through the Bcl-2-associated death promoter (BAD).[199,200] Overactive CN facilitates the dephosphorylation of BAD and its translocation to the mitochondria, which initiates caspase-3-mediated apoptosis.[201–203]

Perhaps the most striking evidence for CN being a significant player in neuroinflammatory progression is that numerous studies show that modulation of CN results in altered aging and AD phenotypes. CN overexpression leads to an exacerbation of cognitive decline, glial reactivity, and neuronal atrophy.[183,204–207] Conversely, CN suppression decreases neuronal degradation, prevents synaptic loss, reduces neuroinflammation, and even extends the lifespan in a murine model of tauopathy.[185,186,208–211] Thus, investigating CN inhibition as a possible therapeutic for AD in the general population is essential. One of the significant early breakthroughs in this area has been Giulio Taglialatela's research into tacrolimus (TAC) and its effect on AD prevalence.

3.1 | Tacrolimus

TAC, or FK506, is an FDA-approved CN inhibitor permeable to the BBB.[212] In 1987, TAC was initially isolated from *Streptomyces tsukubaensis* derived from Fujisawa soil; it was approved for human use in 1994.[213] As an immunosuppressant, TAC operates by complexing with FKBP12.[214,215] This FKBP12-TAC complex binds to the CN complex, occluding the active dephosphorylation site and preventing NFAT interactions.[216] Despite a wide-ranging bioavailability, from 5% to 90% but averaging around 25%, and a narrow therapeutic window, TAC benefits many transplant recipients.[217,218] Since its introduction as a liver transplant immunosuppressant, TAC has become widely used to treat heart, lung, liver, and kidney transplant recipients.[219–222] TAC has also been investigated as a treatment for autoimmune disease and has been approved in South Korea for treating rheumatoid arthritis, lupus nephritis, and myasthenia gravis.[223]

Notably, for this review, a series of groundbreaking studies by Giulio Taglialatela on the incidence of dementia in people prescribed TAC found that TAC provided robust protection from clinical dementia. The incidence of dementia in the general population $\geq$75 years old is typically $\approx$10%; people taking TAC had only a 1% incidence.[224] A 2023 follow-up of this work using a larger sample size and more robust statistical analysis reports that patients taking TAC were protected from dementia and death compared to the general population and those taking cyclosporine, another immunosuppressant targeting CN but unable to cross the BBB.[225]

3.2 | Tacrolimus in preclinical animal models of Alzheimer disease

Preclinical studies on the effects of TAC on AD pathology utilize rodent models due to their genetic and physiological similarity to humans and well-characterized genomes.[226] Scaduto et al. exposed ex vivo mouse brains to human brain–derived tau oligomers followed by TAC; this improved synaptic plasticity in the mouse hippocampus.[227] In addition, wild-type mice exposed to exogenous tau followed by acute TAC treatment demonstrated enhanced memory and restored synaptic function, whereas in 3xTgAD mice, chronic TAC treatment reduced hippocampal tau levels.[127] Together, these studies suggest a role for CN in AD pathology; however, as rodents do not naturally develop AD, further preclinical trials on species that spontaneously develop AD-like pathologies are helpful.[228,229]

Beagles are a natural canine model of AD as they develop amyloid plaques, neuronal morphology changes, and cognitive deficits as a function of age.[228,230,231] Beagles share many anatomic and metabolic

similarities with humans and provide a model for human aging, as their lifespan and aging process more closely mimic those seen in humans.[228] In addition, canines show pharmacokinetics similar to those of humans, making them useful for drug therapy research.[231] Therefore, groundbreaking work is being performed in beagle models of AD to determine if abnormal CN hyperactivity, a known correlate to Aβ plaque aggregation in humans and rodents, is conserved in canines.[195]

Building on prior research, a longitudinal prevention study has been conducted using a preclinical canine model of human aging and AD.[207,232–234] Over 5 years, 43 beagles were treated with either a CN inhibitor TAC or an NFAT inhibitor Q134R. MRI studies revealed that twice-daily oral TAC improved brain morphology, including improved neurite density index, decreased orientation dispersion index, and increased prefrontal cortex area before the onset of cognitive decline.[234] Furthermore, both TAC and Q134R slowed cognitive decline, as measured by spatial learning and memory tasks.[232] In addition, low-dose oral TAC reduced white matter microstructural pathology and promoted neuronal health in the aging beagle brain.[233] This work highlights the potential of CN/NFAT inhibitors for maintaining cognitive and structural brain health during aging, offering valuable insights for translation to human AD.

3.3 | Tacrolimus therapy for people with Alzheimer disease and Down syndrome

3.3.1 | Clinical and translational challenges in the use of tacrolimus for the prevention of Alzheimer disease in people with Down syndrome

Although TAC shows promise as a therapeutic option for AD and comorbid Down syndrome and Alzheimer disease (DSAD), several challenges are associated with its use in a clinical population, including in people with DS. First, the pharmacokinetics of TAC are variable and influenced by several factors, including the first-pass effect, interpersonal genetics (with the cytochrome P450 [CYP] enzymes being a primary concern), and diet.[218,235,236] Of interest, polymorphisms in the CYP enzyme family are known to contribute to AD susceptibility, which may prove challenging in addressing AD with TAC.[237–240] In addition, high-fat diets and gastrointestinal difficulties, including constipation and diarrhea, contribute to altered TAC processing by the body.[235] People with DS have gastrointestinal difficulties at higher rates than the general population, including chronic constipation, Hirschsprung disease, and celiac disease, which may influence acute TAC levels and make therapeutic dosages difficult to manage.[241–243]

Second, as mentioned in Section 3.1, TAC has a narrow therapeutic window, between 5 and 15 ng/mL.[244] The time in therapeutic range (TTR) is also a notable metric for measurement with TAC, as this contributes significantly to organ rejection rates.[244–247] In TAC's traditional role in immune suppression following transplantations, being below this therapeutic window or having a low TTR results in high rates of organ rejection, whereas being above the window increases the chances of experiencing adverse effects.[248–250] To address this issue, population-based pharmacokinetic models of TAC treatment are in development; however, these models are limited in scope and relevance to clinical settings.[251–254] The significant limitations of these models are restricted patient demographics and comorbidities, making broader applications challenging. To date, no models have been generated that focus on patients with DS, and there is no significant consideration of the comorbidities of people with DS, including diabetes and autoimmune disorders.

Finally, the adverse effects of TAC are notable when considering long-term therapeutics, especially in people with DS. The most common side effects of TAC include nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, and opportunistic infections.[255–257] Neurotoxicity is typically limited to tremors, headache, insomnia, and mood imbalances but may result in more significant disorders, including seizures.[258,259] Alterations in neurological status when attempting to evaluate AD and DSAD progression is a limitation that future work should seek to address. Significant for people with DS is the elevated rate of opportunistic infections, as they are at a higher risk for pneumonia at baseline.[260,261]

TAC as a treatment for AD does not come without its hurdles, including pharmacokinetics, dosages, and adverse reactions; this is compounded in people with DS, who typically present with comorbidities that may interfere with TAC dosages or efficacy. Despite this, TAC remains the most prescribed post-transplantation immune suppressant, demonstrating robust and safe usage within the clinic, which could be adapted to new diseases.[235,262] TAC has also been used to treat people with DS for several reasons, including acute lymphoblastic leukemia, Graves' disease, and alopecia areata, with minimal adverse reactions.[263–265] In addition, mounting evidence shows that TAC may act therapeutically for AD at lower dosages than transplantation necessitates; APP mice demonstrate improved cognition and decreased neuroinflammation following low-dose TAC treatment.[266] These mice showed higher levels of brain-localized TAC, 15 ng/g, than plasma, 4.5–6.5 ng/mL, suggesting an accumulation in the brain that may decrease the necessary peripheral dose. Aging canines treated with TAC show similar cognitive improvement while having plasma TAC levels averaging 2.54 ng/mL, half the trough dose for immunosuppression.[232]

Should TAC prove to be an effective therapeutic for people with DS and DSAD, it will be essential to determine biomarkers (neuroimaging and fluids) for inclusion criteria and as outcome measures for clinical trials. Several recent studies and reviews highlight that plasma or cerebrospinal fluid (CSF) tau (p-tau181, p-tau217), neurofilament light (NfL) protein levels, and amyloid or tau PET imaging can distinguish people who are cognitively stable, have mild cognitive impairment, or have dementia in DS.[267–271] We can speculate that, given the mechanisms by which TAC may benefit brain health through astrocyte function, plasma glial fibrillary acidic protein (GFAP) may be a potential outcome measure given that it rises prior to the development of dementia in people with DS.[269,272,273] Of interest, plasma GFAP may mediate the progression of tau and amyloid pathology in people with DS.[274] Furthermore, plasma or tau PET may reflect the benefits of TAC

for tau pathway outcomes.[267,268] The optimal therapeutic window for people with DS to consider TAC interventions could be preventative or as a treatment. For example, as mentioned in Section 1.1, people with DS show AD neuropathology by 40 years of age. Thus a prevention study could include younger adults with DS (e.g., 20–30 years). A treatment study may benefit people with DS younger than 50 years of age prior to evidence of cognitive decline (typically observed at ≈53 years of age). In regards to treatment studies, it will be important to consider that AD progression can occur rapidly in people with DS, as recent work by Zammit et al. suggests that tau PET positivity occurs within 5 years of amyloid PET accumulation.[63]

3.3.2 | Unknowns of calcineurin inhibition in people with Down syndrome and Alzheimer disease

Inhibition of neural CN signaling may be a novel approach for preventing or treating AD.[207] This may be coupled with calpain inhibition to prevent the formation of CN and improve outcomes. As mentioned in Section 2, calpain irreversibly activates CN through proteolytic cleavage of its regulatory domain.[90,91] Inhibitors of calpain, including calpeptin and calpain inhibitors I–III, bind to the active site of calpain, preventing its proteolytic activity.[275] These inhibitors have proven beneficial in animal models of AD, suggesting that they may play a role in future AD therapies.[276–279] The potential for preventing or lowering the impact of AD pathology, prevention of cognitive decline, and minimal off-target effects is a goal of the field. However, the role of CN, how CN inhibition interacts with AD pathology, and the benefits of CN therapies are notably understudied in people with DS. Several gene expression alterations in DS may influence CN's role in DSAD. They must be studied to determine whether CN therapies may be helpful, harmful, or ineffective in people with DS.

4 | HSA21 GENES AND THEIR IMPACT ON CALCINEURIN REGULATION

The *CN* gene, being on Hsa8, is not differentially expressed in people with DS. However, the genes for several regulators of the CN protein, including *RCAN1* and *DYRK1A*, are encoded on Hsa21 and have elevated RNA expression in people with DS.[14] These proteins are encoded within the DSCR, suggesting a role in the development and pathology of DS. Therefore, it is essential to understand how their overexpression factors into DS pathology and how that may interact with CN expression, activity, and AD progression.

4.1 | RCAN1

RCAN1 protein expression is divided into three isoforms, RCAN1-1 L, RCAN1-1 S, and RCAN1-4, stemming from alternate splicing patterns.[280,281] RCAN1-4 is expressed primarily in muscle tissue and is inducible by exercise, prompting speculation that it is part of the slow-fast muscle switching pathway along with CN.[282] RCAN1-1 is found in neurons and is expressed in a long and short form (L and S) dependent upon two start codon placements within the gene.[283] RCAN1-1 L is the main form of RCAN expressed in neurons and associated with neuroinflammatory and neurodegenerative disorders and is, therefore, the focus of this review.[284]

RCAN1 was initially noted for its ability to inhibit the activity of CN within the cell; current research indicates that the RCAN1 exon 7 can interact with and competitively inhibit CN phosphatase activity directly.[285,286] This prevents the activation of the NFAT pathway and mitigates acute calcium and oxidative stresses.[287] However, further exploration has revealed that RCAN1 can facilitate CN activity in vivo, with RCAN1 and 2 knockouts demonstrating cardiac and neurological dysfunction similar to that of CN knockouts.[288] In addition, the interaction between TAB2, which recruits TAB1 and TAK1, and RCAN1 results in the phosphorylation of RCAN1 at Ser 94 and 136, enabling RCAN1 activation of CN signaling.[289] Other phosphorylation effects are unclear, with phosphorylation at Ser 108 and 112 being reported to promote RCAN1 inhibition of CN by Genesca et al.[290] At the same time, Abbasi et al. found that phosphorylation of Ser 108 and 112 decreases RCAN1 binding to CN, alleviating RCAN1 inhibition.[291] The dual function of RCAN1 is suggested to occur based on the concentration of RCAN1 within the cell, with RCAN1 acting as a facilitator when concentrations are low or as an inhibitor when concentrations are high.[292]

An interesting point to note is that NFAT activation induces the expression of RCAN1.[293,294] This points to a regulatory mechanism that can operate as a positive or negative feedback loop as the cell requires. When RCAN1 levels are low, RCAN1 will facilitate CN activation, driving NFAT translocation and the production of additional RCAN1, which will continue a positive feedback cycle. However, when RCAN1 levels are high, RCAN1 will inhibit CN, preventing the transcription of new RCAN1, providing negative feedback, and returning the system to a more manageable level. RCAN1 plays a complex role in CN's positive and negative regulation, which has yet to be fully elucidated.

Despite the mixed studies on RCAN1's role in CN regulation, RCAN1 has long been understood as a critical player in the pathology of DS. Developmentally, RCAN1 is significantly expressed in cardiac tissue and neurons, and overexpression of RCAN1 in a transgenic mouse line induced a DS-like phenotype, including decreased hippocampal neuron number and volume and decreased long- and short-term memory.[295,296] Patel et al. developed a transgenic mouse model of DS with decreased RCAN1 levels.[297] They found an elevation in the number of sympathetic neurons and their innervation in the nasal epithelium. Although the decrease in RCAN1 did not fully alleviate the DS phenotype, it provides significant evidence that RCAN1 overexpression contributes to the development of DS phenotypes.

RCAN1 is also linked to AD and its progression. Several studies link elevated neuronal RCAN1 to AD.[298,299] An overexpression of RCAN1 induces altered circadian rhythms and rest cycles, similar to those seen in AD and DS.[300] Primary cortical neurons incubated with Aβ demonstrate increased tau phosphorylation, which is abolished with RCAN1

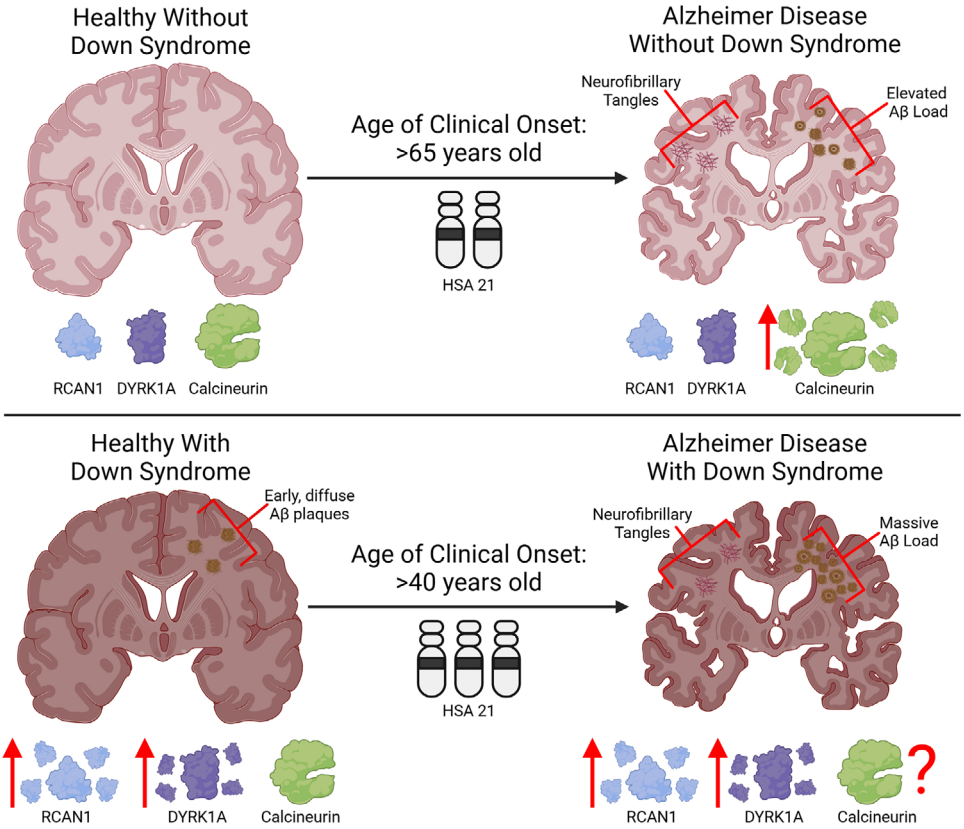

FIGURE 3 Comparison of Alzheimer disease progression in the general population and people with Down syndrome. The general population develops AD pathology around age 65, including Aβ plaques, NFTs, and elevated CN expression. People with DS develop pathologies much earlier, with diffuse plaques beginning as young as childhood. Full clinical pathology begins around age 45, presenting similarly to the general population. However, it is currently unknown if CN levels are increased with age in people with DS. Aβ, amyloid beta; AD, Alzheimer disease; CN, calcineurin; DS, Down syndrome; NFTs, neurofibrillary tangles.

knockdown.[301] RCAN1, thus, may play a role in the progression of AD pathology.

4.2 | DYRK1A

Belonging to the dual-specificity tyrosine kinase family of enzymes, the DYRK1A protein phosphorylates a wide range of cellular targets upon its activation through autophosphorylation of tyrosine 321.[302,303] Although there is little evidence that dephosphorylation regulates DYRK1A after autophosphorylation, translational regulation and protein–protein interactions significantly impact DYRK1A activity.[302,304] Cytosolic DYRK1A influences cell cycle regulation and cytoskeletal organization; nuclear DYRK1A is less understood.[305–309] However, several studies have shown that DYRK1A phosphorylates NFAT proteins within the nucleus, inhibiting its ability to drive transcriptional changes and promoting cytosolic translocation.[310,311] In addition, DYRK1A directly phosphorylates RCAN1, enhancing its ability to inhibit CN.[312] DYRK1A is upregulated by NFAT activation, generating a negative feedback loop, as DYRK1A inhibits NFAT nuclear translocation.[310] Of interest, however, NFAT-induced transcription also generates MicroRNA-199b, which targets and inhibits DYRK1A kinase activity, implying several interlocking regulatory NFAT mechanisms.[313] It is important to note that DYRK1A and CN do not directly interact; however, their functions within the cell run are opposing. Thus, therapies targeting CN and DYRK1A may achieve the same goals regarding NFAT regulation, but off-target effects may differ.

The elevated expression of DYRK1A seen in DS has been studied extensively in mouse models to determine how it may influence development and DS pathology. The transgenic TgDyrk1a mouse line exhibits an overexpression of DYRK1A, similar to people with DS.[314] Developmentally, TgDyrk1a mice exhibit slower neuronal cell cycle phases, decreased hippocampal and neocortex volume, and reduced forebrain size.[315] When exposed to a Morris Water maze, adult TgDyrk1a mice show decreased search times compared to wild-type (WT) mice, suggesting decreased cognitive ability.[316,317] In addition, motor development is delayed in children with DS, which is mimicked with the TgDyrk1a mouse line; the line exhibits difficulty in treadmill tests, crossing less distance and experiencing more shocks than WT mice, and demonstrating decreased swimming proficiency, stopping frequently and swimming in circles compared to WT mice.[317–319]

In AD, DYRK1A plays a role in tauopathies and may contribute to Aβ pathology, although its contribution to Aβ accumulation is less

understood. DYRK1A influences tauopathies through two main routes: influencing tau splicing and directly phosphorylating tau.[320] In brief, DYRK1A influences the production of the 3R isoform of tau over the 4R isoform through phosphorylation of alternative splicing factor 1 (ASF1); the 3R isoform of tau, named for its three microtubule-binding domains, is elevated in late AD progression.[321–323] A multiple sites, tau is also directly phosphorylated by DYRK1A, although Thr-212 is notable as this primes tau for additional phosphorylation by GSK-3.[320,324] The link between DYRK1A and Aβ is less established; however, it is known that DYRK1A can directly phosphorylate APP, which may induce preferential Aβ cleavage and accumulation.[325]

The interplay between CN, RCAN1, and DYRK1A in regulating the NFAT pathway and the pathology of DS and AD need to be better understood. This provides a unique opportunity to illuminate a potentially significant pathway in AD progression. Ultimately, understanding the roles of these proteins in DS and AD is essential, as it may provide an avenue for developing novel therapeutics that can improve the quality of life for millions affected by these pathologies.

5 | CONCLUSION

This review has presented evidence showing that BBB permeable CN inhibitors may effectively prevent AD, with the studies of Taglialatela being a notable point of interest. Although the mechanism of action is yet to be fully elucidated, CN therapy seems promising for several reasons. First, CN inhibition has been utilized in a medical capacity for decades. Although side effects and contraindications accompany these therapies, they have remained standard medical practice for transplantation and autoimmune disease patients, meaning the tolerances and long-term effects are well understood. Second, preliminary research in mice and dogs finds improvements in cognition and decreases in AD pathology following CN inhibition (at low doses), hopefully paving the way for future human clinical trials. Finally, CN therapy provides an opportunity to prevent AD progression before it begins.

Despite this, the role of CN inhibition in DSAD pathogenesis is still understudied and poorly understood, as shown in Figure 3. Does the overexpression of NFAT and CN regulatory proteins RCAN1 and DYRK1A reduce CN's contribution to the disease? Does elevated Aβ pathology contribute to altered calcium signaling and CN overactivity? Because people with DS are more susceptible to autoimmune disease, will CN inhibition, a common immunosuppressant, benefit people with comorbid autoimmune disease? Future investigations into the importance of CN in DS, AD, and DSAD will be critical in generating the information necessary to determine if CN inhibition is a possible target for AD prevention in people with DS.

ACKNOWLEDGMENTS

The authors are grateful to people with Down syndrome and their families and the research community for their contributions. Funding provided by the National Institutes of Health/National Institute on Aging (NIH/NIA) RF1AG056998 (E.H., C.N., and Z.T.), NIH/NIA U19AG068054 (E.H.), and the National Science Foundation (NSF) Graduate Research Fellowship DGE-1839285 (J.D.).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

As no human subjects were utilized in this review, informed consent was not necessary.

REFERENCES

1. De Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*. 2015;167A:756-767. doi:10.1002/ajmg.a.37001
2. Down syndrome. Eunice Kennedy Shriver National Institute of Child Health and Human Development - NICHD. Accessed July 30, 2024. https://www.nichd.nih.gov/health/topics/factsheets/downsyndrome
3. Rafii MS, Kleschevnikov AM, Sawa M, Mobley WC. Down syndrome. *Handb Clin Neurol*. 2019;167:321-336. doi:10.1016/B978-0-12-804766-8.00017-0
4. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurol*. 2010;9(6):623-633. doi:10.1016/S1474-4422(10)70112-5
5. Lyle R, Béna F, Gagos S, et al. Genotype–phenotype correlations in Down syndrome identified by array CGH in 30 cases of partial trisomy and partial monosomy chromosome 21. *Eur J Hum Genet* 2009;17(4):454-466. doi:10.1038/ejhg.2008.214
6. Pelleri MC, Locatelli C, Mattina T, et al. Partial trisomy 21 with or without highly restricted Down syndrome critical region (HR-DSCR): report of two new cases and reanalysis of the genotype–phenotype association. *BMC Med Genomics*. 2022;15(1):1-12. doi:10.1186/S12920-022-01422-6/FIGURES/4
7. Sinet PM, Théophile D, Rahmani Z, et al. Mapping of the Down syndrome phenotype on chromosome 21 at the molecular level. *Biomed Pharmacother*. 1994;48(5-6):247-252. doi:10.1016/0753-3322(94)90140-6
8. Barlow GM, Chen XN, Shi ZY, et al. Down syndrome congenital heart disease: a narrowed region and a candidate gene. *Genet Med*. 2001;3(2):91-101. doi:10.1097/00125817-200103000-00002
9. Pelleri MC, Cicchini E, Locatelli C, et al. Systematic reanalysis of partial trisomy 21 cases with or without Down syndrome suggests a small region on 21q22.13 as critical to the phenotype. *Hum Mol Genet*. 2016;25(12):2525. doi:10.1093/HMG/DDW116
10. Pelleri MC, Cicchini E, Petersen MB, et al. Partial trisomy 21 map: ten cases further supporting the highly restricted Down syndrome critical region (HR-DSCR) on human chromosome 21. *Mol Genet Genomic Med*. 2019;7(8):e797. doi:10.1002/MGG3.797
11. Gardiner K. Gene-dosage effects in Down syndrome and trisomic mouse models. Genome Biol. 2004;5(10):244. doi: 10.1186/gb-2004-5-10-244.
12. Plaiasu V. Down syndrome—genetics and cardiogenetics. *Maedica*. 2017;12(3):208-213.
13. Kahlem P. Gene-dosage effect on chromosome 21 transcriptome in trisomy 21: implication in Down syndrome cognitive disorders. *Behav Genet*. 2006;36(3):416-428. doi:10.1007/S10519-006-9053-Z/TABLES/2
14. Aït Yahya-Graison E, Aubert J, Dauphinot L, et al. Classification of human chromosome 21 gene-expression variations in Down syndrome: impact on disease phenotypes. *Am J Hum Genet*. 2007;81(3):475. doi:10.1086/520000

15. Whooten R, Schmitt J, Schwartz A. Endocrine manifestations of Down syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2018;25:61-66. doi:10.1097/MED
16. Hom B, Boyd NK, Vogel BN, et al. Down syndrome and autoimmune diseases. *Clin Rev Allergy Immunol*. 2024;66:261-273. Published online 2016. doi:10.1007/s12016-024-08996-2
17. Bordon Y. Immune dysregulation in Down syndrome. *Nat Rev Immunol*. 2023;23:201. doi:10.1038/s41586-023-05736-y
18. Harris E. Autoimmunity in Down syndrome linked to immune system dysregulation. *JAMA*. 2023;329(12):968-968. doi:10.1001/JAMA.2023.3194
19. Duse M, Condino-Neto A, Carneiro-Sampaio M, Huggard D, Doherty DG, Molloy EJ. Immune dysregulation in children with Down syndrome. *Front Pediatr*. 2020;8:73. doi:10.3389/fped.2020.00073
20. Aslam AA, Asaad Baksh R, Pape SE, et al. Diabetes and obesity in Down syndrome across the lifespan: a retrospective cohort study using U.K. electronic health records. *Diabetes Care*. 2022;45:2892-2899. doi:10.2337/dc22-0482
21. Huggard D, Kelly L, Ryan E, et al. Increased systemic inflammation in children with Down syndrome. *Cytokine*. 2020;127:154938. doi:10.1016/J.CYTO.2019.154938
22. Weijerman ME, de Winter JP. Clinical practice. The care of children with Down syndrome. *Eur J Pediatr*. 2010;169:1445-1452. doi:10.1007/s00431-010-1253-0
23. Tsou AY, Bulova P, Capone G, et al. Medical care of adults with Down syndrome: a clinical guideline. *JAMA*. 2020;324(15):1543-1556. doi:10.1001/JAMA.2020.17024
24. Bull MJ. Down syndrome. *N Engl J Med*. 2020;382(24):2344-2352. doi:10.1056/NEJMRA1706537
25. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Down syndrome-associated Alzheimer's disease: a genetic form of dementia. *Lancet Neurol*. 2021;20(11):930. doi:10.1016/S1474-4422(21)00245-3
26. Andrews EJ, Martini AC, Head E. Exploring the role of sex differences in Alzheimer's disease pathogenesis in Down syndrome. *Front Neurosci*. 2022;16:954999. doi:10.3389/FNINS.2022.954999
27. Landes SD, Finan JM, Turk MA. Reporting Down syndrome on the death certificate for Alzheimer disease/unspecified dementia deaths. *PLoS One*. 2023;18(2):e0281763. doi:10.1371/JOURNAL.PONE.0281763
28. Down Syndrome And Alzheimer's Disease. Alzheimer's Association. Accessed July 29, 2024. https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/down-syndrome
29. Hippius H, Neundörfer G. The discovery of Alzheimer's disease. *Dialogues Clin Neurosci*. 2003;5(1):101. doi:10.31887/DCNS.2003.5.1/HHIPPIUS
30. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. *F1000Res*. 2018;7. doi:10.12688/F1000RESEARCH.14506.1
31. What Are the Signs of Alzheimer's Disease?. National Institute on Aging. Accessed July 30, 2024. https://www.nia.nih.gov/health/alzheimers-symptoms-and-diagnosis/what-are-signs-alzheimers-disease
32. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016;164(4):603-615. doi:10.1016/J.CELL.2015.12.056
33. Sarlus H, Heneka MT. Microglia in Alzheimer's disease. *J Clin Invest*. 2017;127(9):3240-3249. doi:10.1172/JCI90606
34. Tönnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. *J Alzheimer's Dis*. 2017;57(4):1105. doi:10.3233/JAD-161088
35. Power MC, Mormino E, Soldan A, et al. Combined neuropathological pathways account for age-related risk of dementia. *Ann Neurol*. 2018;84(1):10. doi:10.1002/ANA.25246
36. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197-2204. doi:10.1212/01.WNL.0000271090.28148.24/ASSET/C30F5ECB-87AF-404A-8CC9-D3735F3948CD/ASSETS/GRAPHIC/5FSM1.JPEG
37. O'brien RJ, Wong PC. Amyloid precursor protein processing and Alzheimer's disease. *Annu Rev Neurosci*. 2011;34:185-204. Published online. doi:10.1146/annurev-neuro-061010-113613
38. Sehar U, Rawat P, Reddy AP, Kopel J, Reddy PH. Amyloid beta in aging and Alzheimer's disease. *Int J Mol Sci*. 2022;23(21):12924. doi:10.3390/IJMS232112924
39. Ashrafian H, Zadeh EH, Khan RH. Review on Alzheimer's disease: inhibition of amyloid beta and tau tangle formation. *Int J Biol Macromol*. 2021;167:382-394. doi:10.1016/J.IJBIOMAC.2020.11.192
40. Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58(12):1791-1800. doi:10.1212/WNL.58.12.1791
41. Calderon-Garcidueñas AL, Duyckaerts C. Alzheimer disease. *Handb Clin Neurol*. 2017;145:325-337. doi:10.1016/B978-0-12-802395-2.00023-7
42. Minter MR, Taylor JM, Crack PJ. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *J Neurochem*. 2016;136(3):457-474. doi:10.1111/JNC.13411
43. Hemonnot AL, Hua J, Ulmann L, Hirbec H. Microglia in Alzheimer disease: well-known targets and new opportunities. *Front Aging Neurosci*. 2019;11:233. doi:10.3389/FNAGI.2019.00233
44. Kempf M, Clement A, Faissner A, Lee G, Brandt R. Tau binds to the distal axon early in development of polarity in a microtubule- and microfilament-dependent manner. *J Neurosci*. 1996;16(18):5583-5592. doi:10.1523/JNEUROSCI.16-18-05583.1996
45. Naseri NN, Wang H, Guo J, Sharma M, Luo W. The complexity of tau in Alzheimer's disease. *Neurosci Lett*. 2019;705:183. doi:10.1016/J.NEULET.2019.04.022
46. Lindwall G, Cole RD. Phosphorylation affects the ability of tau protein to promote microtubule assembly. *J Biol Chem*. 1984;259(8):5301-5305. doi:10.1016/S0021-9258(17)42989-9
47. Bramblett GT, Goedert M, Jakes R, Merrick SE, Trojanowski JQ, Lee VMY. Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. *Neuron*. 1993;10(6):1089-1099. doi:10.1016/0896-6273(93)90057-X
48. Alonso ADC, Zaidi T, Novak M, Grundke-Iqbal I, Iqbal K. Hyperphosphorylation induces self-assembly of tau into tangles of paired helical filaments/straight filaments. *Proc Natl Acad Sci*. 2001;98(12):6923-6928. doi:10.1073/PNAS.121119298
49. Busche MA, Wegmann S, Dujardin S, et al. Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo. *Nat Neurosci*. 2019;22(1):57. doi:10.1038/S41593-018-0289-8
50. Zhou L, McInnes J, Wierda K, et al. Tau association with synaptic vesicles causes presynaptic dysfunction. *Nat Commun*. 2017;8:15295. doi:10.1038/NCOMMS15295
51. Braak H, Del Tredici K. The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain*. 2015;138(Pt 10):2814-2833. doi:10.1093/BRAIN/AWV236
52. Head E, Lott IT, Wilcock DM, Lemere CA, Alzheimer C, Author R. Aging in Down syndrome and the development of Alzheimer's disease neuropathology. *Curr Alzheimer Res*. 2016;13(1):18-29. Accessed July 30, 2024. www.ndss.org
53. Farzan M, Schnitzler CE, Vasilieva N, Leung D, Choe H. BACE2, a β-secretase homolog, cleaves at the β site and within the amyloid-β region of the amyloid-β precursor protein. *Proc Natl Acad Sci*. 2000;97(17):9712-9717. doi:10.1073/PNAS.160115697/ASSET/6FDC25A6-1C47-4F66-88D3-11F74F2A929A/ASSETS/GRAPHIC/PQ1601156006.JPEG
54. Mori C, Spooner ET, Wisniewski KE, et al. Intraneuronal Aβ42 accumulation in Down syndrome brain. *Amyloid*. 2002;9(2):88-102. doi:10.3109/13506120208995241

55. Mann DMA, Esiri MM. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. *J Neurol Sci*. 1989;89(2-3):169-179. doi:10.1016/0022-510X(89)90019-1
56. Nistor M, Don M, Parekh M, et al. Alpha- and beta-secretase activity as a function of age and beta-amyloid in Down syndrome and normal brain. *Neurobiol Aging*. 2007;28(10):1493. doi:10.1016/J.NEUROBIOLAGING.2006.06.023
57. Davidson YS, Robinson A, Prasher VP, Mann DMA. The age of onset and evolution of Braak tangle stage and Thal amyloid pathology of Alzheimer's disease in individuals with Down syndrome. *Acta Neuropathol Commun*. 2018;6(1):56. doi:10.1186/S40478-018-0559-4
58. Iulita MF, Garzón Chavez D, Klitgaard Christensen M, et al. Association of Alzheimer disease with life expectancy in people with Down syndrome. *JAMA Netw Open*. 2022;5(5):e2212910. doi:10.1001/JAMANETWORKOPEN.2022.12910
59. Neale N, Padilla C, Fonseca LM, Holland T, Zaman S. Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome. *Neuroimage*. 2018;17:263. doi:10.1016/J.NICL.2017.10.022
60. Annus T, Wilson LR, Hong YT, et al. The pattern of amyloid accumulation in the brains of adults with Down syndrome. *Alzheimer's Dement*. 2016;12(5):538. doi:10.1016/J.JALZ.2015.07.490
61. Lao PJ, Handen BL, Betthauser TJ, et al. Longitudinal changes in amyloid positron emission tomography and volumetric magnetic resonance imaging in the nondemented Down syndrome population. *Alzheimers Dement*. 2017;9:1-9. doi:10.1016/J.DADM.2017.05.001
62. Rafii MS. Tau PET imaging for staging of Alzheimer's disease in Down syndrome. *Dev Neurobiol*. 2019;79(7):711-715. doi:10.1002/DNEU.22658
63. Zammit MD, Betthauser TJ, McVea AK, et al. Characterizing the emergence of amyloid and tau burden in Down syndrome. *Alzheimer's Dement*. 2024;20(1):388. doi:10.1002/ALZ.13444
64. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. *Alzheimers Dement*. 2020;12(1):e12007. doi:10.1002/DAD2.12007
65. Carmona-Iragui M, Videla L, Lleó A, Fortea J. Down syndrome, Alzheimer disease, and cerebral amyloid angiopathy: the complex triangle of brain amyloidosis. *Dev Neurobiol*. 2019;79:716-737. Published online 2019. doi:10.1002/dneu.22709
66. Rosidi NL, Zhou J, Pattanaik S, et al. Cortical microhemorrhages cause local inflammation but do not trigger widespread dendrite degeneration. *PLoS One*. 2011;6(10):e26612. doi:10.1371/JOURNAL.PONE.0026612
67. Ungvari Z, Tarantini S, Kirkpatrick AC, Csiszar A, Prodan CI. Advances in cardiovascular geroscience: cerebral microhemorrhages: mechanisms, consequences, and prevention. *Am J Physiol Heart Circ Physiol*. 2017;312(6):H1128-H1143. doi:10.1152/AJPHEART.00780.2016
68. Head E, Phelan MJ, Doran E, et al. Cerebrovascular pathology in Down syndrome and Alzheimer disease. *Acta Neuropathol Commun*. 2017;5(1):93. doi:10.1186/S40478-017-0499-4/FIGURES/6
69. Jäkel L, De Kort AM, Klijn CJM, Schreuder FHBM, Verbeek MM. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimer's Dement*. 2022;18(1):10. doi:10.1002/ALZ.12366
70. Lao P, Edwards N, Flores-Aguilar L, et al. Cerebrovascular disease emerges with age and Alzheimer's disease in adults with Down syndrome. *Sci Rep*. 2024;14(1):12334. doi:10.1038/S41598-024-61962-Y
71. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol*. 2019;18(3):296-306. doi:10.1016/S1474-4422(18)30450-2
72. Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. *Sleep Med Rev*. 2015;19:29-38. doi:10.1016/J.SMRV.2014.03.007
73. Schlosser Covell GE, Dhawan PS, Lee Iannotti JK, et al. Disrupted daytime activity and altered sleep-wake patterns may predict transition to mild cognitive impairment or dementia: a critically appraised topic. *Neurologist*. 2012;18(6):426-429. doi:10.1097/NRL.0b013e318272f7ef
74. Westerberg CE, Lundgren EM, Florczak SM, et al. Sleep influences the severity of memory disruption in amnestic mild cognitive impairment: results from sleep self-assessment and continuous activity monitoring. *Alzheimer Dis Assoc Disord*. 2010;24(4):325-333. doi:10.1097/WAD.0b013e3181e30846
75. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*. 2013;36(7):1027-1032. doi:10.5665/sleep.2802
76. Giménez S, Videla L, Romero S, et al. Prevalence of sleep disorders in adults with Down syndrome: a comparative study of self-reported, actigraphic, and polysomnographic findings. *J Clin Sleep Med*. 2018;14(10):1725. doi:10.5664/JCSM.7382
77. Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea should all children with Down syndrome be tested?. *Arch Otolaryngol Head Neck Surg*. 2006;132:432-436.
78. Lista S, Imbimbo BP, Grasso M, et al. Tracking neuroinflammatory biomarkers in Alzheimer's disease: a strategy for individualized therapeutic approaches?. *J Neuroinflammation*. 2024;21(1):187. doi:10.1186/S12974-024-03163-Y
79. Passeri E, Elkhoury K, Morsink M, et al. Alzheimer's disease: treatment strategies and their limitations. *Int J Mol Sci*. 2022;23(22):13954. doi:10.3390/IJMS232213954
80. Beshir SA, Hussain N, Menon VB, Al Haddad AHI, Al Zeer RAK, Elnour AA. Advancements and challenges in antiamyloid therapy for Alzheimer's disease: a comprehensive review. *Int J Alzheimers Dis*. 2024;2024(1):2052142. doi:10.1155/2024/2052142
81. Chen L, Song M, Yao C. Calcineurin in development and disease. *Genes Dis*. 2022;9(4):915. doi:10.1016/J.GENDIS.2021.03.002
82. Alothaid H, Aldughaim MSK, Alamri SS, Alrahimi JSM, Al-Jadani SH. Role of calcineurin biosignaling in cell secretion and the possible regulatory mechanisms. *Saudi J Biol Sci*. 2021;28(1):116. doi:10.1016/J.SJBS.2020.08.042
83. Lim D, Tapella L, Dematteis G, Talmon M, Genazzani AA. Calcineurin signalling in astrocytes: from pathology to physiology and control of neuronal functions. *Neurochem Res*. 2023;48(4):1077. doi:10.1007/S11064-022-03744-4
84. Husi H, Luyten MA, Zurini MGM. Mapping of the immunophilin-immunosuppressant site of interaction on calcineurin. *J Biol Chem*. 1994;269(19):14199-14204. doi:10.1016/S0021-9258(17)36774-1
85. Rusnak F, Mertz P. Calcineurin: Form and function. *Physiol Rev*. 2000;80(4):1483-1521. doi:10.1152/PHYSREV.2000.80.4.1483/ASSET/IMAGES/LARGE/9J0400099012.JPEG
86. Kakalis LT, Kennedy M, Sikkink R, Rusnak F, Armitage IM. Characterization of the calcium-binding sites of calcineurin B. *FEBS Lett*. 1995;362(1):55-58. doi:10.1016/0014-5793(95)00207-P
87. Burroughs SE, Horrocks WD, Ren H, Klee CB. Characterization of the lanthanide ion-binding properties of calcineurin-B using laser-induced luminescence spectroscopy. *Biochemistry*. 1994;33(34):10428-10436. doi:10.1021/BI00200A026
88. Feng B, Stemmer PM. Interactions of calcineurin A, calcineurin B, and Ca2+. *Biochemistry*. 1999;38(38):12481-12489. doi:10.1021/BI990492W/ASSET/IMAGES/LARGE/BI990492WF00008.JPEG
89. Stewart AA, Ingebritsen TS, Manalan A, Klee CB, Cohen P. Discovery of a Ca2+- and calmodulin-dependent protein phosphatase: probable

identity with calcineurin (CaM-BP80). *FEBS Lett*. 1982;137(1):80-84. doi:10.1016/0014-5793(82)80319-0
90. Huang Y, Chen SR, Pan HL. Calcineurin regulates synaptic plasticity and nociceptive transmission at the spinal cord level. *Neuroscientist*. 2022;28(6):628-638. doi:10.1177/10738584211046888/ASSET/IMAGES/LARGE/10.1177_10738584211046888-FIG3.JPEG
91. Liu F, Iqbal-Grundke I, Iqbal K, Oda Y, Tomizawa K, Gong CX. Truncation and activation of calcineurin a by calpain I in Alzheimer disease brain. *J Biol Chem*. 2005;280(45):37755-37762. doi:10.1074/JBC.M507475200
92. Macian F. NFAT proteins: key regulators of T-cell development and function. *Nat Rev Immunol*. 2005;5(6):472-484. doi:10.1038/nri1632
93. Yang TTC, Xiong Q, Enslen H, Davis RJ, Chow C-W. Phosphorylation of NFATc4 by p38 mitogen-activated protein kinases. *Mol Cell Biol*. 2002;22(11):3892. doi:10.1128/MCB.22.11.3892-3904.2002
94. Gal M, Li S, Luna RE, Takeuchi K, Wagner G. The LxVP and PxIxIT NFAT motifs bind simultaneously to overlapping epitopes in calcineurin's catalytic domain CnA distant to the regulatory domain CnB. *Structure*. 2014;22(7):1016. doi:10.1016/J.STR.2014.05.006
95. Aramburu J, García-Cózar F, Raghavan A, Okamura H, Rao A, Hogan PG. Selective Inhibition of NFAT activation by a peptide spanning the calcineurin targeting site of NFAT. *Mol Cell*. 1998;1(5):627-637. doi:10.1016/S1097-2765(00)80063-5
96. Müller MR, Rao A. NFAT, immunity and cancer: a transcription factor comes of age. *Nat Rev Immunol*. 2010;10(9):645-656. doi:10.1038/NRI2818
97. Mognol GP, Carneiro FRG, Robbs BK, Faget DV, Viola JPB. Cell cycle and apoptosis regulation by NFAT transcription factors: new roles for an old player. *Cell Death Dis*. 2016;7(4):e2199-e2199. doi:10.1038/cddis.2016.97
98. Rao A, Luo C, Hogan PG. Transcription factors of the NFAT family: regulation and function. *Annu Rev Immunol*. 1997;15:707-754.
99. Park YJ, Yoo SA, Kim M, Kim WU. The role of calcium–calcineurin–NFAT signaling pathway in health and autoimmune diseases. *Front Immunol*. 2020;11:195. doi:10.3389/FIMMU.2020.00195
100. Shah K, Al-Haidari A, Sun J, Kazi JU. T cell receptor (TCR) signaling in health and disease. *Signal Transduct Target Ther*. 2021;6(1):1-26. doi:10.1038/s41392-021-00823-w
101. Chen B-S, Li C-W. Big regeneration mechanisms via systems biology and big database mining methods. In: *Big Mechanisms in Systems Biology*. Published online Academic Press; 2017:373-430. doi:10.1016/B978-0-12-809479-2.00008-1
102. Goto S, Yamamoto H, Fukunaga K, Iwasa T, Matsukado Y, Miyamoto E. Dephosphorylation of microtubule-associated protein 2, τ factor, and tubulin by calcineurin. *J Neurochem*. 1985;45(1):276-283. doi:10.1111/J.1471-4159.1985.TB05504.X
103. Li W, Handschumacher RE. Identification of two calcineurin B-binding proteins: tubulin and heat shock protein 60. *Biochim Biophys Acta*. 2002;1599(1-2):72-81. doi:10.1016/S1570-9639(02)00402-8
104. Lautermilch NJ, Spitzer NC. Regulation of calcineurin by growth cone calcium waves controls neurite extension. *J Neurosci*. 2000;20(1):315. doi:10.1523/JNEUROSCI.20-01-00315.2000
105. Gong CX, Wegiel J, Lidsky T, et al. Regulation of phosphorylation of neuronal microtubule-associated proteins MAP1b and MAP2 by protein phosphatase-2A and -2B in rat brain. *Brain Res*. 2000;853(2):299-309. doi:10.1016/S0006-8993(99)02294-5
106. Hoffman A, Taleski G, Sontag E. The protein serine/threonine phosphatases PP2A, PP1 and calcineurin: A triple threat in the regulation of the neuronal cytoskeleton. *Mol Cell Neurosci*. 2017;84:119-131. doi:10.1016/J.MCN.2017.01.005
107. Goodson HV, Jonasson EM. Microtubules and microtubule-associated proteins. *Cold Spring Harb Perspect Biol*. 2018;10(6):a022608. doi:10.1101/CSHPERSPECT.A022608
108. Dehmelt L, Halpain S. The MAP2/tau family of microtubule-associated proteins. *Genome Biol*. 2005;6(1):1-10. doi:10.1186/GB-2004-6-1-204/TABLES/2
109. Hirokawa N, Shiomura Y, Okabe S. Tau proteins: the molecular structure and mode of binding on microtubules. *J Cell Biol*. 1988;107(4):1449. doi:10.1083/JCB.107.4.1449
110. Lewis SA, Ivanov IE, Lee GH, Cowan NJ. Organization of microtubules in dendrites and axons is determined by a short hydrophobic zipper in microtubule-associated proteins MAP2 and tau. *Nature*. 1989;342(6249):498-505. doi:10.1038/342498a0
111. Felgner H, Frank R, Biernat J, et al. Domains of neuronal microtubule-associated proteins and flexural rigidity of microtubules. *J Cell Biol*. 1997;138(5):1067. doi:10.1083/JCB.138.5.1067
112. Morioka M, Nagahiro S, Fukunaga K, Miyamoto E, Ushio Y. Calcineurin in the adult rat hippocampus: different distribution in CA1 and CA3 subfields. *Neuroscience*. 1997;78(3):673-684. doi:10.1016/S0306-4522(96)00626-4
113. Ferreira A, Kincaid R, Kosik KS. Calcineurin is associated with the cytoskeleton of cultured neurons and has a role in the acquisition of polarity. *Mol Biol Cell*. 1993;4(12):1225. doi:10.1091/MBC.4.12.1225
114. Sánchez C, Díaz-Nido J, Avila J. Phosphorylation of microtubule-associated protein 2 (MAP2) and its relevance for the regulation of the neuronal cytoskeleton function. *Prog Neurobiol*. 2000;61(2):133-168. doi:10.1016/S0301-0082(99)00046-5
115. DeGiosio RA, Grubisha MJ, MacDonald ML, McKinney BC, Camacho CJ, Sweet RA. More than a marker: potential pathogenic functions of MAP2. *Front Mol Neurosci*. 2022;15:974890. doi:10.3389/FNMOL.2022.974890
116. Plucarová J, Jansen S, Narasimhan S, et al. Specific phosphorylation of microtubule-associated protein 2c by extracellular signal-regulated kinase reduces interactions at its Pro-rich regions. *J Biol Chem*. 2022;298(10):102384. doi:10.1016/J.JBC.2022.102384
117. Lisek M, Tomczak J, Boczek T, Zylinska L. Calcium-associated proteins in neuroregeneration. *Biomolecules*. 2024;14(2):183. doi:10.3390/BIOM14020183
118. Meiri KF, Pfenninger KH, Willard MB. Growth-associated protein, GAP-43, a polypeptide that is induced when neurons extend axons, is a component of growth cones and corresponds to pp46, a major polypeptide of a subcellular fraction enriched in growth cones. *Proc Natl Acad Sci*. 1986;83(10):3537-3541. doi:10.1073/PNAS.83.10.3537
119. Chung D, Shum A, Caraveo G. GAP-43 and BASP1 in axon regeneration: implications for the treatment of neurodegenerative diseases. *Front Cell Dev Biol*. 2020;8:567537. doi:10.3389/FCELL.2020.567537
120. Haruta T, Takami N, Ohmura M, Misumi Y, Ikehara Y. Ca2+-dependent interaction of the growth-associated protein GAP-43 with the synaptic core complex. *Biochem J*. 1997;325(Pt 2):455-463. doi:10.1042/BJ3250455
121. He Q, Dent EW, Meiri KF. Modulation of actin filament behavior by GAP-43 (neuromodulin) is dependent on the phosphorylation status of serine 41, the protein kinase C site. *J Neurosci*. 1997;17(10):3515. doi:10.1523/JNEUROSCI.17-10-03515.1997
122. Liu Y, Storm DR. Dephosphorylation of neuromodulin by calcineurin. *J Biol Chem*. 1989;264(22):12800-12804. doi:10.1016/S0021-9258(18)51557-X
123. Boczek T, Ferenc B, Lisek M, Zylinska L. Regulation of GAP43/calmodulin complex formation via calcineurin-dependent mechanism in differentiated PC12 cells with altered PMCA isoforms composition. *Mol Cell Biochem*. 2015;407(1-2):251. doi:10.1007/S11010-015-2473-4
124. Graef IA, Wang F, Charron F, et al. Neurotrophins and netrins require calcineurin/NFAT signaling to stimulate outgrowth of embryonic axons. *Cell*. 2003;113(5):657-670. doi:10.1016/S0092-8674(03)00390-8
125. Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. *Eur J Neurosci*. 2005;22(8):1942-1950. doi:10.1111/J.1460-9568.2005.04391.X

126. Kim Y, Lee Y Il, Seo M, et al. Calcineurin dephosphorylates glycogen synthase kinase-3 beta at serine-9 in neuroblast-derived cells. *J Neurochem*. 2009;111(2):344-354. doi:10.1111/J.1471-4159.2009.06318.X
127. Marcatti M, Tumurbaatar B, Borghi M, et al. Inhibition of calcineurin with FK506 reduces tau levels and attenuates synaptic impairment driven by tau oligomers in the hippocampus of male mouse models. *Int J Mol Sci*. 2024;25(16):9092. doi:10.3390/IJMS25169092/S1
128. Toral-Rios D, Pichardo-Rojas PS, Alonso-Vanegas M, Campos-Peña V. GSK3β and tau protein in Alzheimer's disease and epilepsy. *Front Cell Neurosci*. 2020;14:19. doi:10.3389/FNCEL.2020.00019
129. Chakraborty P, Ibáñez de Opakua A, Purslow JA, et al. GSK3β phosphorylation catalyzes the aggregation of tau into Alzheimer's disease-like filaments. *Proc Natl Acad Sci*. 2024;121(52):e2414176121. doi:10.1073/PNAS.2414176121
130. Song L, Oseid DE, Wells EA, Robinson AS. The Interplay between GSK3β and Tau Ser262 phosphorylation during the progression of tau pathology. *Int J Mol Sci*. 2022;23(19):11610. doi:10.3390/IJMS231911610/S1
131. Hernandez F, Lucas JJ, Avila J. GSK3 and tau: two convergence points in Alzheimer's disease. *J Alzheimers Dis*. 2013;33(Suppl 1):S141-S144. doi:10.3233/JAD-2012-129025
132. Lauretti E, Dincer O, Praticò D. Glycogen synthase kinase-3 signaling in Alzheimer's disease. *Biochim Biophys acta Mol cell Res*. 2020;1867(5):118664. doi:10.1016/J.BBAMCR.2020.118664
133. Qian W, Yin X, Hu W, et al. Activation of protein phosphatase 2B and hyperphosphorylation of tau in Alzheimer's disease. *J Alzheimer's Dis*. 2011;23(4):617. doi:10.3233/JAD-2010-100987
134. Brini M, Calì T, Ottolini D, Carafoli E. Neuronal calcium signaling: function and dysfunction. *Cell Mol Life Sci C*. 2014;71(15):2787. doi:10.1007/S00018-013-1550-7
135. Bordas C, Kovacs A, Pal B. The M-current contributes to high threshold membrane potential oscillations in a cell type-specific way in the pedunculopontine nucleus of mice. *Front Cell Neurosci*. 2015;9:121. doi:10.3389/FNCEL.2015.00121
136. Zhang J, Shapiro MS. Activity-dependent transcriptional regulation of M-Type (Kv7) K(+) channels by AKAP79/150-mediated NFAT actions. *Neuron*. 2012;76(6):1133-1146. doi:10.1016/J.NEURON.2012.10.019
137. Marrion N V. Calcineurin regulates M channel modal gating in sympathetic neurons. *Neuron*. 1996;16(1):163-173. doi:10.1016/S0896-6273(00)80033-1
138. Oliveria SF, Dittmer PJ, Youn DH, dell'Acqua ML, Sather WA. Localized calcineurin confers Ca2+-dependent inactivation on neuronal L-type Ca2+ channels. *J Neurosci*. 2012;32(44):15328-15337. doi:10.1523/JNEUROSCI.2302-12.2012
139. Chen TC, Law B, Kondratyuk T, Rossie S. Identification of soluble protein phosphatases that dephosphorylate voltage-sensitive sodium channels in rat brain. *J Biol Chem*. 1995;270(13):7750-7756. doi:10.1074/JBC.270.13.7750
140. Sun T, Wu XS, Xu J, et al. The role of calcium/calmodulin-activated calcineurin in rapid and slow endocytosis at central synapses. *J Neurosci*. 2010;30(35):11838. doi:10.1523/JNEUROSCI.1481-10.2010
141. Zhou JJ, Shao JY, Chen SR, Chen H, Pan HL. Calcineurin regulates synaptic Ca2+-permeable AMPA receptors in hypothalamic presympathetic neurons via $\alpha 2\delta$-1-mediated GluA1/GluA2 assembly. *J Physiol*. 2024;602(10):2179-2197. doi:10.1113/JP286081
142. Kilonzo K, Strahnen D, Prex V, et al. Distinct contributions of GluA1-containing AMPA receptors of different hippocampal subfields to salience processing, memory and impulse control. *Transl Psychiatry*. 2022;12(1):102. doi:10.1038/S41398-022-01863-8
143. Royo M, Escolano BA, Madrigal MP, Jurado S. AMPA receptor function in hypothalamic synapses. *Front Synaptic Neurosci*. 2022;14:833449. doi:10.3389/FNSYN.2022.833449
144. Zhang J, Abdullah JM. The role of GluA1 in central nervous system disorders. *Rev Neurosci*. 2013;24(5):499-505. doi:10.1515/REVNEURO-2013-0021
145. Arendt KL, Zhang Z, Ganesan S, et al. Calcineurin mediates homeostatic synaptic plasticity by regulating retinoic acid synthesis. *Proc Natl Acad Sci*. 2015;112(42):E5744-E5752. doi:10.1073/PNAS.1510239112/SUPPL_FILE/PNAS.201510239SI.PDF
146. Chen L, Lau AG, Sarti F. Synaptic retinoic acid signaling and homeostatic synaptic plasticity. *Neuropharmacology*. 2014;78(C):3-12. doi:10.1016/J.NEUROPHARM.2012.12.004
147. Aoto J, Nam CI, Poon MM, Ting P, Chen L. Synaptic signaling by all-trans retinoic acid in homeostatic synaptic plasticity. *Neuron*. 2008;60(2):308-320. doi:10.1016/J.NEURON.2008.08.012
148. Lynch MA. Long-term potentiation and memory. *Physiol Rev*. 2004;84(1):87-136. doi:10.1152/PHYSREV.00014.2003/ASSET/IMAGES/LARGE/9J0140284006.JPEG
149. Cooke SF, Bliss TVP. Plasticity in the human central nervous system. *Brain*. 2006;129(7):1659-1673. doi:10.1093/BRAIN/AWL082
150. Sakamoto K, Karelina K, Obrietan K. CREB: a multifaceted regulator of neuronal plasticity and protection. *J Neurochem*. 2010;116(1):1-9. doi:10.1111/J.1471-4159.2010.07080.X
151. Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell*. 1994;79(1):59-68. doi:10.1016/0092-8674(94)90400-6
152. Graves L, Dalvi A, Lucki I, Blendy JA, Abel T. Behavioral analysis of CREB $\alpha\Delta$ mutation on a B6/129 F1 hybrid background. *Hippocampus*. 2002;12(1):18-26. doi:10.1002/HIPO.10003
153. Pittenger C, Huang YY, Paletzki RF, et al. Reversible inhibition of CREB/ATF transcription factors in region CA1 of the dorsal hippocampus disrupts hippocampus-dependent spatial memory. *Neuron*. 2002;34(3):447-462. doi:10.1016/S0896-6273(02)00684-0
154. Kogan JH, Frankland PW, Blendy JA, et al. Spaced training induces normal long-term memory in CREB mutant mice. *Curr Biol*. 1997;7(1):1-11. doi:10.1016/S0960-9822(06)00022-4
155. Groth RD, Dunbar RL, Mermelstein PG. Calcineurin regulation of neuronal plasticity. *Biochem Biophys Res Commun*. 2003;311(4):1159-1171. doi:10.1016/J.BBRC.2003.09.002
156. Mansuy IM. Calcineurin in memory and bidirectional plasticity. *Biochem Biophys Res Commun*. 2003;311(4):1195-1208. doi:10.1016/J.BBRC.2003.10.046
157. Naqvi S, Martin KJ, Arthur JSC. CREB phosphorylation at Ser133 regulates transcription via distinct mechanisms downstream of cAMP and MAPK signalling. *Biochem J*. 2014;458(3):469-479. doi:10.1042/BJ20131115
158. Yin Y, Gao D, Wang Y, et al. Tau accumulation induces synaptic impairment and memory deficit by calcineurin-mediated inactivation of nuclear CaMKIV/CREB signaling. *Proc Natl Acad Sci*. 2016;113(26):E3773-E3781. doi:10.1073/PNAS.1604519113/-/DCSUPPLEMENTAL
159. Kingsbury TJ, Bambrick LL, Roby CD, Krueger BK. Calcineurin activity is required for depolarization-induced, CREB-dependent gene transcription in cortical neurons. *J Neurochem*. 2007;103(2):761-770. doi:10.1111/J.1471-4159.2007.04801.X
160. Lam BYH, Zhang W, Enticknap N, Haggis E, Cader MZ, Chawla S. Inverse regulation of plasticity-related immediate early genes by calcineurin in hippocampal neurons. *J Biol Chem*. 2009;284(18):12562. doi:10.1074/JBC.M901121200
161. Bito H, Deisseroth K, Tsien RW. CREB phosphorylation and dephosphorylation: a Ca2+- and stimulus duration-dependent switch for hippocampal gene expression. *Cell*. 1996;87(7):1203-1214. doi:10.1016/S0092-8674(00)81816-4
162. Reese LC, Taglialatela G. A role for calcineurin in Alzheimer's disease. *Curr Neuropharmacol*. 2011;9(4):685. doi:10.2174/157015911798376316

163. Foster TC, Sharrow KM, Masse JR, Norris CM, Kumar A. Calcineurin links Ca2+ dysregulation with brain aging. *J Neurosci*. 2001;21(11):4066. doi:10.1523/JNEUROSCI.21-11-04066.2001
164. Genoux D, Haditsch U, Knobloch M, Michalon A, Storm D, Mansuy IM. Protein phosphatase 1 is a molecular constraint on learning and memory. *Nat*. 2002;418(6901):970-975. doi:10.1038/nature00928
165. Seo SR, Chung KC. CREB activates proteasomal degradation of DSCR1/RCAN1. *FEBS Lett*. 2008;582(13):1889-1893. doi:10.1016/J.FEBSLET.2008.04.059
166. Varma A, Loya J, Junaid Hussain M, et al. Calcineurin-inhibitor induced pain syndrome after stem cell transplant. *Leuk Lymphoma*. 2020;61(9):2230-2233. doi:10.1080/10428194.2020.1765235
167. Ilonze OJ, Giovannini M, Jones MA, Rao R, Ballut K, Guglin M. Calcineurin-inhibitor induced pain syndrome in a heart transplant patient. *Transplant Proc*. 2021;53(8):2630-2635. doi:10.1016/J.TRANSPROCEED.2021.08.014
168. Ullah A, Aly A, Ali T, Alahmadi I. Calcineurin inhibitor-induced pain syndrome: an uncommon but a debilitating complication of calcineurin inhibitors use. *Saudi J Kidney Dis Transpl*. 2021;32(6):1795-1799. doi:10.4103/1319-2442.352443
169. Chen SR, Hu YM, Chen H, Pan HL. Calcineurin inhibitor induces pain hypersensitivity by potentiating pre- and postsynaptic NMDA receptor activity in spinal cords. *J Physiol*. 2013;592(Pt 1):215. doi:10.1113/JPHYSIOL.2013.263814
170. Dirks M, Buchert R, Wirries AK, et al. Reduced microglia activity in patients with long-term immunosuppressive therapy after liver transplantation. *Eur J Nucl Med Mol Imaging*. 2021;49(1):234. doi:10.1007/S00259-021-05398-W
171. Nagamoto-Combs K, Combs CK. Microglial phenotype is regulated by activity of the transcription factor, NFAT (nuclear factor of activated T cells). *J Neurosci*. 2010;30(28):9641. doi:10.1523/JNEUROSCI.0828-10.2010
172. Kataoka A, Tozaki-Saitoh H, Koga Y, Tsuda M, Inoue K. Activation of P2×7 receptors induces CCL3 production in microglial cells through transcription factor NFAT. *J Neurochem*. 2009;108(1):115-125. doi:10.1111/J.1471-4159.2008.05744.X
173. Shiratori M, Tozaki-Saitoh H, Yoshitake M, Tsuda M, Inoue K. P2×7 receptor activation induces CXCL2 production in microglia through NFAT and PKC/MAPK pathways. *J Neurochem*. 2010;114(3):810-819. doi:10.1111/J.1471-4159.2010.06809.X
174. Ting SM, Zhao X, Zheng X, Aronowski J. Excitatory pathway engaging glutamate, calcineurin, and NFAT upregulates IL-4 in ischemic neurons to polarize microglia. *J Cereb Blood Flow Metab*. 2020;40(3):513-527. doi:10.1177/0271678X19838189
175. Furman JL, Norris CM. Calcineurin and glial signaling: Neuroinflammation and beyond. *J Neuroinflammation*. 2014;11(1):1-12. doi:10.1186/S12974-014-0158-7/FIGURES/5
176. Wei DC, Morrison EH. Histology, Astrocytes. *StatPearls*. Published online May 1, 2023. Accessed November 8, 2024. https://www.ncbi.nlm.nih.gov/books/NBK545142/
177. Jiang J, Yang M, Tian M, Chen Z, Xiao L, Gong Y. Intertwined associations between oxytocin, immune system and major depressive disorder. *Biomed Pharmacother*. 2023;163:114852. doi:10.1016/j.biopha.2023.114852
178. Sompol P, Norris CM. Ca2+, astrocyte activation and calcineurin/NFAT signaling in age-related neurodegenerative diseases. *Front Aging Neurosci*. 2018;10:199. doi:10.3389/FNAGI.2018.00199
179. Bazargani N, Attwell D. Astrocyte calcium signaling: the third wave. *Nat Neurosci*. 2016;19(2):182-189. doi:10.1038/NN.4201
180. Rusakov DA. Disentangling calcium-driven astrocyte physiology. *Nat Rev Neurosci*. 2015;16(4):226-233. doi:10.1038/NRN3878
181. Norris CM, Kadish I, Blalock EM, et al. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. *J Neurosci*. 2005;25(18):4649. doi:10.1523/JNEUROSCI.0365-05.2005
182. Kraner SD, Sompol P, Prateeptrang S, et al. Development of a monoclonal antibody specific for a calpain-generated Δ48 kDa calcineurin fragment, a marker of distressed astrocytes. *J Neurosci Methods*. 2024;402:110012. doi:10.1016/J.JNEUMETH.2023.110012
183. Pleiss MM, Sompol P, Kraner SD, et al. Calcineurin proteolysis in astrocytes: implications for impaired synaptic function. *Biochim Biophys Acta*. 2016;1862(9):1521-1532. doi:10.1016/J.BBADIS.2016.05.007
184. Sama MA, Mathis DM, Furman JL, et al. Interleukin-1β-dependent signaling between astrocytes and neurons depends critically on astrocytic calcineurin/NFAT activity. *J Biol Chem*. 2008;283(32):21953. doi:10.1074/JBC.M800148200
185. Furman JL, Sama DM, Gant JC, et al. Targeting astrocytes ameliorates neurologic changes in a mouse model of Alzheimer's disease. *J Neurosci*. 2012;32(46):16129. doi:10.1523/JNEUROSCI.2323-12.2012
186. Sompol P, Furman JL, Pleiss MM, et al. Calcineurin/NFAT signaling in activated astrocytes drives network hyperexcitability in Aβ-bearing mice. *J Neurosci*. 2017;37(25):6132. doi:10.1523/JNEUROSCI.0877-17.2017
187. Furman JL, Sompol P, Kraner SD, et al. Blockade of astrocytic calcineurin/NFAT signaling helps to normalize hippocampal synaptic function and plasticity in a rat model of traumatic brain injury. *J Neurosci*. 2016;36(5):1502-1515. doi:10.1523/JNEUROSCI.1930-15.2016
188. Thibault O, Landfield PW. Increase in single L-type calcium channels in hippocampal neurons during aging. *Science*. 1996;272(5264):1017-1020. doi:10.1126/SCIENCE.272.5264.1017
189. Landfield PW, Pitler TA. Prolonged Ca2+-dependent afterhyperpolarizations in hippocampal neurons of aged rats. *Science*. 1984;226(4678):1089-1092. doi:10.1126/SCIENCE.6494926
190. Michaelis ML, Bigelow DJ, Schöneich C, et al. Decreased plasma membrane calcium transport activity in aging brain. *Life Sci*. 1996;59(5-6):405-412. doi:10.1016/0024-3205(96)00319-0
191. Nikoletopoulou V, Tavernarakis N. Calcium homeostasis in aging neurons. *Front Genet*. 2012;3:200. doi:10.3389/FGENE.2012.00200
192. Pannuzzo M. Beta-amyloid pore linked to controlled calcium influx into the cell: a new paradigm for Alzheimer's disease. *Alzheimer's Dement*. 2022;18(1):191-196. doi:10.1002/ALZ.12373
193. Popugaeva E, Pchitskaya E, Bezprozvanny I. Dysregulation of neuronal calcium homeostasis in Alzheimer's disease—a therapeutic opportunity?. *Biochem Biophys Res Commun*. 2017;483(4):998-1004. doi:10.1016/J.BBRC.2016.09.053
194. Mohmmad Abdul H, Baig I, LeVine H, Guttmann RP, Norris CM. Proteolysis of calcineurin is increased in human hippocampus during mild cognitive impairment and is stimulated by oligomeric Abeta in primary cell culture. *Aging Cell*. 2011;10(1):103-113. doi:10.1111/J.1474-9726.2010.00645.X
195. Abdul HM, Sama MA, Furman JL, et al. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. *J Neurosci*. 2009;29(41):12957-12969. doi:10.1523/JNEUROSCI.1064-09.2009
196. Norris CM, Blalock EM, Chen KC, et al. Hippocampal "zipper" slice studies reveal a necessary role for calcineurin in the increased activity of L-type Ca(2+) channels with aging. *Neurobiol Aging*. 2010;31(2):328-338. doi:10.1016/J.NEUROBIOLAGING.2008.03.026
197. Norris CM, Blalock EM, Chen KC, Porter NM, Landfield PW. Calcineurin enhances L-type Ca2+ channel activity in hippocampal neurons: increased effect with age in culture. *Neuroscience*. 2002;110(2):213-225. doi:10.1016/S0306-4522(01)00574-7

198. Lim D, Iyer A, Ronco V, et al. Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-kB. *Glia*. 2013;61(7):1134-1145. doi:10.1002/GLIA.22502
199. Wang HG, Pathan N, Ethell IM, et al. Ca2+-induced apoptosis through calcineurin dephosphorylation of BAD. *Science*. 1999;284(5412):339-343. doi:10.1126/SCIENCE.284.5412.339/ASSET/979D94C1-A50D-4CA9-A2A0-B33D997B1897/ASSETS/GRAPHIC/SE1497410004.JPEG
200. Wang J, Bai X, Chen Y, Zhao Y, Liu X. Homocysteine induces apoptosis of rat hippocampal neurons by inhibiting 14-3-3ε expression and activating calcineurin. *PLoS One*. 2012;7(11):e48247. doi:10.1371/JOURNAL.PONE.0048247
201. Vicente-Torres MA, Schacht J. A BAD link to mitochondrial cell death in the cochlea of mice with noise-induced hearing loss. *J Neurosci Res*. 2006;83(8):1564. doi:10.1002/JNR.20832
202. Springer JE, Azbill RD, Nottingham SA, Kennedy SE. Calcineurin-mediated BAD dephosphorylation activates the caspase-3 apoptotic cascade in traumatic spinal cord injury. *J Neurosci*. 2000;20(19):7246. doi:10.1523/JNEUROSCI.20-19-07246.2000
203. Shou Y, Li L, Prabhakaran K, Borowitz JL, Isom GE. Calcineurin-mediated Bad translocation regulates cyanide-induced neuronal apoptosis. *Biochem J*. 2004;379(Pt 3):805. doi:10.1042/BJ20031107
204. Winder DG, Mansuy IM, Osman M, Moallem TM, Kandel ER. Genetic and pharmacological evidence for a novel, intermediate phase of long-term potentiation suppressed by calcineurin. *Cell*. 1998;92(1):25-37. doi:10.1016/S0092-8674(00)80896-X
205. Mansuy IM, Mayford M, Jacob B, Kandel ER, Bach ME. Restricted and regulated overexpression reveals calcineurin as a key component in the transition from short-term to long-term memory. *Cell*. 1998;92(1):39-49. doi:10.1016/S0092-8674(00)80897-1
206. Fernandez AM, Fernandez S, Carrero P, Garcia-Garcia M, Torres-Aleman I. Calcineurin in reactive astrocytes plays a key role in the interplay between proinflammatory and anti-inflammatory signals. *J Neurosci*. 2007;27(33):8745. doi:10.1523/JNEUROSCI.1002-07.2007
207. Norris CM. Is it time to repurpose calcineurin inhibitors for the treatment of cognitive impairment and dementia?. *J Alzheimers Dis*. 2023;95(2):599. doi:10.3233/JAD-230780
208. Rozkalne A, Hyman BT, Spires-Jones TL. Calcineurin inhibition with FK506 ameliorates dendritic spine density deficits in plaque-bearing Alzheimer model mice. *Neurobiol Dis*. 2011;41(3):650-654. doi:10.1016/J.NBD.2010.11.014
209. Wu HY, Hudry E, Hashimoto T, et al. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *J Neurosci*. 2010;30(7):2636-2649. doi:10.1523/JNEUROSCI.4456-09.2010
210. Yoshiyama Y, Higuchi M, Zhang B, et al. Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron*. 2007;53(3):337-351. doi:10.1016/J.NEURON.2007.01.010
211. Sompol P, Gollihue JL, Weiss BE, et al. Targeting astrocyte signaling alleviates cerebrovascular and synaptic function deficits in a diet-based mouse model of small cerebral vessel disease. *J Neurosci*. 2023;43(10):1797-1813. doi:10.1523/JNEUROSCI.1333-22.2023
212. Grimbert P, Azema C, Pastural M, et al. Tacrolimus (FK506)-induced severe and late encephalopathy in a renal transplant recipient. *Nephrol Dial Transplant*. 1999;14(10):2489-2491. doi:10.1093/NDT/14.10.2489
213. Pritchard DI. Sourcing a chemical succession for cyclosporin from parasites and human pathogens. *Drug Discov Today*. 2005;10(10):688-691. doi:10.1016/S1359-6446(05)03395-7
214. Thomson AW, Bonham CA, Zeevi A. Mode of action of tacrolimus (FK506): molecular and cellular mechanisms. *Ther Drug Monit*. 1995;17(6):584-591. doi:10.1097/00007691-199512000-00007
215. Liu J, Farmer JD, Lane WS, Friedman J, Weissman I, Schreiber SL. Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell*. 1991;66(4):807-815. doi:10.1016/0092-8674(91)90124-H
216. Griffith JP, Kim JL, Kim EE, et al. X-ray structure of calcineurin inhibited by the immunophilin-immunosuppressant FKBP12-FK506 complex. *Cell*. 1995;82(3):507-522. doi:10.1016/0092-8674(95)90439-5
217. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2004;43(10):623-653. doi:10.2165/00003088-200443100-00001
218. Yu M, Liu M, Zhang W, Ming Y. Pharmacokinetics, pharmacodynamics and pharmacogenetics of tacrolimus in kidney transplantation. *Curr Drug Metab*. 2018;19(6):513. doi:10.2174/1389200219666180129151948
219. Berloco P, Rossi M, Pretagostini R, Sociu-Foca Cortesini N, Cortesini R. Tacrolimus as cornerstone immunosuppressant in kidney transplantation. *Transplant Proc*. 2001;33(1-2):994-996. doi:10.1016/S0041-1345(00)02301-0
220. Busuttil RW, Holt CD. Tacrolimus is superior to cyclosporine in liver transplantation. *Transplant Proc*. 1998;30(5):2174-2178. doi:10.1016/S0041-1345(98)00579-X
221. Swenson JM, Fricker FJ, Armitage JM. Immunosuppression switch in pediatric heart transplant recipients: cyclosporine to FK 506. *J Am Coll Cardiol*. 1995;25(5):1183-1188. doi:10.1016/0735-1097(94)00551-Z
222. Treede H, Klepetko W, Reichenspurner H, et al. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. *J Heart Lung Transplant*. 2001;20(5):511-517. doi:10.1016/S1053-2498(01)00244-3
223. Yoo WH, Lee S Il, Kim TH, et al. Safety of tacrolimus in autoimmune disease: results from post-marketing surveillance in South Korea. *J Rheum Dis*. 2021;28(4):202. doi:10.4078/JRD.2021.28.4.202
224. Taglialatela G, Rastellini C, Cicalese L. Reduced incidence of dementia in solid organ transplant patients treated with calcineurin inhibitors. *J Alzheimer's Dis*. 2015;47(2):329. doi:10.3233/JAD-150065
225. Silva JD, Taglialatela G, Jupiter DC. Reduced prevalence of dementia in patients prescribed tacrolimus, sirolimus, or cyclosporine. *J Alzheimer's Dis*. 2023;95(2):585. doi:10.3233/JAD-230526
226. Medicine M, Bryda EC. The mighty mouse: the impact of rodents on advances in biomedical research. *Mo Med*. 2013;110(3):207. Accessed December 19, 2024. https://pmc.ncbi.nlm.nih.gov/articles/PMC3987984/
227. Scaduto P, Marcatti M, Bhatt N, Kayed R, Taglialatela G. Calcineurin inhibition prevents synaptic plasticity deficit induced by brain-derived tau oligomers. *Brain Commun*. 2024;6(5):fcae277. doi:10.1093/BRAINCOMMS/FCAE277
228. Head E. A canine model of human aging and Alzheimer's disease. *Biochim Biophys Acta*. 2013;1832(9):1384. doi:10.1016/J.BBADIS.2013.03.016
229. Yokoyama M, Kobayashi H, Tatsumi L, Tomita T. Mouse models of Alzheimer's disease. *Front Mol Neurosci*. 2022;15:912995. doi:10.3389/FNMOL.2022.912995/BIBTEX
230. Cotman CW, Head E. The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches. *J Alzheimers Dis*. 2008;15(4):685-707. doi:10.3233/JAD-2008-15413
231. Davis PR, Head E. Prevention approaches in a preclinical canine model of Alzheimer's disease: benefits and challenges. *Front Pharmacol*. 2014;5:47. doi:10.3389/FPHAR.2014.00047
232. Sordo L, Ubele MF, Boaz KA, et al. Calcineurin/NFAT inhibitors maintain cognition in a preclinical prevention study in an aging canine model of Alzheimer disease. *Neurobiol Aging*. 2025;146:1-14. doi:10.1016/J.NEUROBIOLAGING.2024.11.003

233. Noche JA, Radhakrishnan H, Ubele MF, et al. Age-related brain atrophy and the positive effects of behavioral enrichment in middle-aged beagles. *J Neurosci*. 2024;44(20):e2366232024. doi:10.1523/JNEUROSCI.2366-23.2024
234. Radhakrishnan H, Ubele MF, Krumholz SM, et al. Tacrolimus protects against age-associated microstructural changes in the beagle brain. *J Neurosci*. 2021;41(23):5124-5133. doi:10.1523/JNEUROSCI.0361-21.2021
235. Henkel L, Jehn U, Thölking G, Reuter S. Tacrolimus—why pharmacokinetics matter in the clinic. *Front Transplant*. 2023;2:1160752. doi:10.3389/FRTRA.2023.1160752
236. Möller A, Iwasaki K, Kawamura A, et al. The disposition of 14C-labeled tacrolimus after intravenous and oral administration in healthy human subjects. *Drug Metab Dispos*. 1999;27(6):633-636. doi:10.1016/S0090-9556(24)15298-1
237. Chace C, Pang D, Weng C, et al. Variants in CYP17 and CYP19 cytochrome P450 genes are associated with onset of Alzheimer's disease in women with Down syndrome. *J Alzheimer's Dis*. 2012;28(3):601. doi:10.3233/JAD-2011-110860
238. Iivonen S, Corder E, Lehtovirta M, et al. Polymorphisms in the CYP19 gene confer increased risk for Alzheimer disease. *Neurology*. 2004;62(7):1170-1176. doi:10.1212/01.WNL.0000118208.16939.60
239. Corbo RM, Gambina G, Ulizzi L, Moretto G, Scacchi R. Genetic variation of CYP19 (aromatase) gene influences age at onset of Alzheimer's disease in women. *Dement Geriatr Cogn Disord*. 2009;27(6):513-518. doi:10.1159/000221832
240. Butler HT, Warden DR, Hogervorst E, Ragoussis J, Smith AD, Lehmann DJ. Association of the aromatase gene with Alzheimer's disease in women. *Neurosci Lett*. 2010;468(3):202-206. doi:10.1016/J.NEULET.2009.10.089
241. Bermudez BEBV, de Oliveira CM, de Lima Cat MN, Magdalena NIR, Celli A. Gastrointestinal disorders in Down syndrome. *Am J Med Genet Part A*. 2019;179(8):1426-1431. doi:10.1002/AJMG.A.61258
242. Holmes G. Gastrointestinal disorders in Down syndrome. *Gastroenterol Hepatol From Bed to Bench*. 2014;7(1):6-8. Accessed January 13, 2025. https://pmc.ncbi.nlm.nih.gov/articles/PMC4017552/
243. Skotko, B. Gastrointestinal System and Down Syndrome. National Down Syndrome Society (NDSS). Accessed January 13, 2025. https://ndss.org/resources/gastrointestinal-tract-syndrome#p_870
244. Davis S, Gralla J, Klem P, et al. Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation. *Am J Transplant*. 2017;18(4):907. doi:10.1111/AJT.14504
245. Rodríguez-Espinosa D, Broseta JJ, Montagud-Marrahí E, et al. Tacrolimus's time below therapeutic range is associated with acute pancreatic graft rejection and the development of de novo donor-specific antibodies. *Transpl Int*. 2024;37:12591. doi:10.3389/TI.2024.12591/BIBTEX
246. Adie SK, Bitar A, Konerman MC, et al. Tacrolimus time in therapeutic range and long-term outcomes in heart transplant recipients. *Pharmacother J Hum Pharmacol Drug Ther*. 2022;42(2):106-111. doi:10.1002/PHAR.2653
247. Ensor CR, Iasella CJ, Harrigan KM, et al. Increasing tacrolimus time-in-therapeutic range is associated with superior one-year outcomes in lung transplant recipients. *Am J Transplant*. 2018;18(6):1527-1533. doi:10.1111/AJT.14723
248. Banas B, Krämer BK, Krüger B, Kamar N, Undre N. Long-term kidney transplant outcomes: role of prolonged-release tacrolimus. *Transplant Proc*. 2020;52(1):102-110. doi:10.1016/J.TRANSPROCEED.2019.11.003
249. Kuypers DRJ, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. *Clin Pharmacol Ther*. 2004;75(5):434-447. doi:10.1016/J.CLPT.2003.12.009
250. Undre NA, Stevenson P, Schäfer A. Pharmacokinetics of tacrolimus: clinically relevant aspects. *Transplant Proc*. 1999;31(7):21-24. doi:10.1016/S0041-1345(99)00788-5
251. Størset E, Åsberg A, Skauby M, et al. Improved tacrolimus target concentration achievement using computerized dosing in renal transplant recipients—a prospective, randomized study. *Transplantation*. 2015;99(10):2158. doi:10.1097/TP.0000000000000708
252. Passey C, Birnbaum AK, Brundage RC, Oetting WS, Israni AK, Jacobson PA. Dosing equation for tacrolimus using genetic variants and clinical factors. *Br J Clin Pharmacol*. 2011;72(6):948. doi:10.1111/J.1365-2125.2011.04039.X
253. Boughton O, Borgulya G, Cecconi M, Fredericks S, Moreton-Clack M, Macphee IAM. A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. *Br J Clin Pharmacol*. 2013;76(3):425. doi:10.1111/BCP.12076
254. Elens L, Hesselink DA, van Schaik RHN, van Gelder T. The CYP3A4*22 allele affects the predictive value of a pharmacogenetic algorithm predicting tacrolimus predose concentrations. *Br J Clin Pharmacol*. 2012;75(6):1545. doi:10.1111/BCP.12038
255. Fung JJ, Alessiani M, Abu-Elmagd K, et al. Adverse effects associated with the use of FK 506. *Transplant Proc*. 1991;23(6):3105. Accessed January 13, 2025. https://pmc.ncbi.nlm.nih.gov/articles/PMC2952509/
256. Schagen MR, Volarevic H, Francke MI, et al. Individualized dosing algorithms for tacrolimus in kidney transplant recipients: current status and unmet needs. *Expert Opin Drug Metab Toxicol*. 2023;19(7):429-445. doi:10.1080/17425255.2023.2250251
257. Emal D, Rampanelli E, Claessen N, et al. Calcineurin inhibitor tacrolimus impairs host immune response against urinary tract infection. *Sci Reports*. 2019;9(1):1-11. doi:10.1038/s41598-018-37482-x
258. Wu G, Weng FL, Balaraman V. Tacrolimus-induced encephalopathy and polyneuropathy in a renal transplant recipient. *BMJ Case Rep*. 2013;2013:bcr2013201099. doi:10.1136/BCR-2013-201099
259. Verona P, Edwards J, Hubert K, et al. Tacrolimus-induced neurotoxicity after transplant: a literature review. *Drug Saf*. 2024;47(5):419-438. doi:10.1007/S40264-024-01398-5/TABLES/9
260. Fitzpatrick V, Rivelli A, Chaudhari S, et al. Prevalence of infectious diseases among 6078 individuals with Down syndrome in the United States. *J Patient-Centered Res Rev*. 2022;9(1):64. doi:10.17294/2330-0698.1876
261. Chicoine B, Rivelli A, Fitzpatrick V, Chicoine L, Jia G, Rzhetsky A. Prevalence of common disease conditions in a large cohort of individuals with Down syndrome in the United States. *J Patient-Centered Res Rev*. 2021;8(2):86. doi:10.17294/2330-0698.1824
262. Gaber AO, Alloway RR, Bodziak K, Kaplan B, Bunnapradist S. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): a phase 2 trial of stable renal transplant recipients. *Transplantation*. 2013;96(2):191. doi:10.1097/TP.0B013E3182962CC1
263. Hitzler JK, He W, Doyle J, et al. Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. *Pediatr Blood Cancer*. 2014;61(6):1126. doi:10.1002/PBC.24918
264. Bimbi C, Kyriakou G, Wollina U. Occlusive treatment enhances efficacy of tacrolimus 0.1% in a pediatric patient with severe alopecia areata: case report and literature review. *Pediatr Dermatol*. 2021;38(1):339-340. doi:10.1111/PDE.14474
265. Lee Y, Butani L, Glaser N, Nguyen S. Resolution of Graves' disease after renal transplantation. *Pediatr Transplant*. 2016;20(4):590-593. doi:10.1111/PETR.12709

266. Stallings NR, O'Neal MA, Hu J, Shen ZJ, Malter JS. Long-term normalization of calcineurin activity in model mice rescues Pin1 and attenuates Alzheimer's phenotypes without blocking peripheral T cell IL-2 response. *Alzheimers Res Ther*. 2023;15(1):179. doi:10.1186/S13195-023-01323-5
267. Kac PR, Alcolea D, Montoliu-Gaya L, et al. Plasma p-tau212 as a biomarker of sporadic and Down syndrome Alzheimer's disease. *medRxiv*. Published online November 2, 2024:10.1101/2024.10.31.24316469
268. Lleó A, Zetterberg H, Pegueroles J, et al. Phosphorylated tau181 in plasma as a potential biomarker for Alzheimer's disease in adults with Down syndrome. *Nat Commun*. 2021;12(1):4304. doi:10.1038/S41467-021-24319-X
269. Montoliu-Gaya L, Strydom A, Blennow K, Zetterberg H, Ashton NJ. Blood biomarkers for Alzheimer's disease in Down syndrome. *J Clin Med*. 2021;10(16):3639. doi:10.3390/JCM10163639
270. Fagan AM, Henson R L, Li Y, et al. Comparison of CSF biomarkers in Down syndrome and autosomal dominant Alzheimer disease: a cross-sectional study. *Lancet Neurol*. 2021;20(8):615-626. doi:10.1016/S1474-4422(21)00139-3
271. Carmona-Iragui M, O'Connor A, Llibre-Guerra J, et al. Clinical and research application of fluid biomarkers in autosomal dominant Alzheimer's disease and Down syndrome. *eBioMedicine*. 2024;108:105327. doi:10.1016/J.EBIOM.2024.105327
272. Montoliu-Gaya L, Alcolea D, Ashton NJ, et al. Plasma and cerebrospinal fluid glial fibrillary acidic protein levels in adults with Down syndrome: a longitudinal cohort study. *eBioMedicine*. 2023;90:104547. doi:10.1016/J.EBIOM.2023.104547
273. Henson RL, Doran E, Christian BT, et al. Cerebrospinal fluid biomarkers of Alzheimer's disease in a cohort of adults with Down syndrome. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2020;12(1):e12057. doi:10.1002/DAD2.12057
274. Boerwinkle AH, Wisch JK, Handen BL, et al. The mediating role of plasma glial fibrillary acidic protein in amyloid and tau pathology in Down's syndrome. *Alzheimers Dement*. 2025;21(1):e14359. doi:10.1002/ALZ.14359
275. Reinke PYA, de Souza EE, Günther S, et al. Calpeptin is a potent cathepsin inhibitor and drug candidate for SARS-CoV-2 infections. *Commun Biol*. 2023;6(1):1-13. doi:10.1038/s42003-023-05317-9
276. Sinjoanu RC, Kleinschmidt S, Bitner RS, Brioni JD, Moeller A, Ferreira A. The novel calpain inhibitor A-705253 potently inhibits oligomeric beta-amyloid-induced dynamin 1 and tau cleavage in hippocampal neurons. *Neurochem Int*. 2008;53(3-4):79. doi:10.1016/J.NEUINT.2008.06.003
277. Binyamin O, Nitzan K, Frid K, Ungar Y, Rosenmann H, Gabizon R. Brain targeting of 9c,11t-conjugated linoleic acid, a natural calpain inhibitor, preserves memory and reduces Aβ and P25 accumulation in 5XFAD mice. *Sci Rep*. 2019;9(1):18437. doi:10.1038/S41598-019-54971-9
278. Qiao L, Yi S, Li T, et al. Calpeptin improves the cognitive function in Alzheimer's disease-like complications of diabetes mellitus rats by regulating TXNIP/NLRP3 inflammasome. *J Diabetes Investig*. 2024;15(10):1365. doi:10.1111/JDI.14292
279. Fa M, Zhang H, Staniszewski A, et al. Novel selective calpain 1 inhibitors as potential therapeutics in Alzheimer's disease. *J Alzheimers Dis*. 2016;49(3):707. doi:10.3233/JAD-150618
280. Fuentes JJ, Pritchard MA, Estivill X. Genomic organization, alternative splicing, and expression patterns of the DSCR1 (Down syndrome candidate region 1) gene. *Genomics*. 1997;44(3):358-361. doi:10.1006/GENO.1997.4866
281. Lao M, Zhang X, Yang H, Bai X, Liang T. RCAN1-mediated calcineurin inhibition as a target for cancer therapy. *Mol Med*. 2022;28(1):69. doi:10.1186/S10020-022-00492-7
282. Lee SK, Ahnn J. Regulator of calcineurin (RCAN): beyond down syndrome critical region. *Mol Cells*. 2020;43(8):671. doi:10.14348/MOLCELLS.2020.0060
283. Wu Y, Song W. Regulation of RCAN1 translation and its role in oxidative stress-induced apoptosis. *FASEB J*. 2013;27(1):208-221. doi:10.1096/FJ.12-213124
284. Ermak G, Daviesn KJA. Chronic high levels of the RCAN1-1 protein may promote neurodegeneration and Alzheimer disease. *Free Radic Biol Med*. 2013;62:47. doi:10.1016/J.FREERADBIOMED.2013.01.016
285. Chan B, Greenan G, McKeon F, Ellenberger T. Identification of a peptide fragment of DSCR1 that competitively inhibits calcineurin activity in vitro and in vivo. *Proc Natl Acad Sci*. 2005;102(37):13075. doi:10.1073/PNAS.0503846102
286. Rothermel B, Vega RB, Yang J, Wu H, Bassel-Duby R, Williams RS. A protein encoded within the down syndrome critical region is enriched in striated muscles and inhibits calcineurin signaling. *J Biol Chem*. 2000;275(12):8719-8725. doi:10.1074/JBC.275.12.8719
287. Ermak G, Harris CD, Davies KJA. The DSCR1 (Adapt78) isoform 1 protein calcipressin 1 inhibits calcineurin and protects against acute calcium-mediated stress damage, including transient oxidative stress. *FASEB J*. 2002;16(8):814-824. doi:10.1096/FJ.01-0846COM
288. Sanna B, Brandt EB, Kaiser RA, et al. Modulatory calcineurin-interacting proteins 1 and 2 function as calcineurin facilitators in vivo. *Proc Natl Acad Sci*. 2006;103(19):7327-7332. doi:10.1073/PNAS.0509340103/ASSET/B58E500A-95EE-4CDD-816D-E8DD8F1D2AE1/ASSETS/GRAPHIC/ZPQ0190621260005.JPEG
289. Liu Q, Busby JC, Molkentin JD. Interaction between TAK1–TAB1–TAB2 and RCAN1–calcineurin defines a signalling nodal control point. *Nat Cell Biol*. 2009;11(2):154-161. doi:10.1038/ncb1823
290. Genescà L, Aubareda A, Fuentes JJ, Estivill X, De La Luna S, Pérez-Riba M. Phosphorylation of calcipressin 1 increases its ability to inhibit calcineurin and decreases calcipressin half-life. *Biochem J*. 2003;374(2):567-575. doi:10.1042/BJ20030267
291. Abbasi S, Lee JD, Su B, et al. Protein kinase-mediated regulation of calcineurin through the phosphorylation of modulatory calcineurin-interacting protein 1. *J Biol Chem*. 2006;281(12):7717-7726. doi:10.1074/JBC.M510775200
292. Hilioti Z, Gallagher DA, Low-Nam ST, et al. GSK-3 kinases enhance calcineurin signaling by phosphorylation of RCNs. *Genes Dev*. 2004;18(1):35. doi:10.1101/GAD.1159204
293. Lange AW, Molkentin JD, Yutzey KE. DSCR1 gene expression is dependent on NFATc1 during cardiac valve formation and colocalizes with anomalous organ development in trisomy 16 mice. *Dev Biol*. 2004;266(2):346-360. doi:10.1016/J.YDBIO.2003.10.036
294. Canellada A, Ramirez BG, Minami T, Redondo JM, Cano E. Calcium/calcineurin signaling in primary cortical astrocyte cultures: Rcan1-4 and cyclooxygenase-2 as NFAT target genes. *Glia*. 2008;56(7):709-722. doi:10.1002/GLIA.20647
295. Casas C, Martínez S, Pritchard MA, et al. Dscr1, a novel endogenous inhibitor of calcineurin signaling, is expressed in the primitive ventricle of the heart and during neurogenesis. *Mech Dev*. 2001;101(1-2):289-292. doi:10.1016/S0925-4773(00)00583-9
296. Martin KR, Corlett A, Dubach D, et al. Over-expression of RCAN1 causes Down syndrome-like hippocampal deficits that alter learning and memory. *Hum Mol Genet*. 2012;21(13):3025-3041. doi:10.1093/HMG/DDS134
297. Patel A, Yamashita N, Ascaño M, et al. RCAN1 links impaired neurotrophin trafficking to aberrant development of the sympathetic nervous system in Down syndrome. *Nat Commun*. 2015;6:10119. doi:10.1038/NCOMMS10119
298. N M, AIBL Research Group, C F, et al. The Down syndrome-associated protein, regulator of calcineurin-1, is altered in Alzheimer's disease and dementia with Lewy bodies. *J Alzheimer's Dis Park*. 2019;9(2):462. doi:10.4172/2161-0460.1000462
299. Harris CD, Ermak G, Davies KJA. RCAN1-1L is overexpressed in neurons of Alzheimer's disease patients. *FEBS J*. 2007;274(7):1715-1724. doi:10.1111/J.1742-4658.2007.05717.X

300. Wong H, Buck JM, Borski C, et al. RCAN1 knockout and overexpression recapitulate an ensemble of rest-activity and circadian disruptions characteristic of Down syndrome, Alzheimer's disease, and normative aging. *J Neurodev Disord*. 2022;14(1):33. doi:10.1186/S11689-022-09444-Y
301. Lloret A, Badia MC, Giraldo E, et al. Alzheimer's amyloid-β toxicity and tau hyperphosphorylation are linked via RCAN1. *J Alzheimers Dis*. 2011;27(4):701. doi:10.3233/JAD-2011-110890
302. Becker W, Sippl W. Activation, regulation, and inhibition of DYRK1A. *FEBS J*. 2011;278(2):246-256. doi:10.1111/J.1742-4658.2010.07956.X
303. Himpel S, Panzer P, Eirmbter K, et al. Identification of the autophosphorylation sites and characterization of their effects in the protein kinase DYRK1A. *Biochem J*. 2001;359(Pt 3):497. doi:10.1042/0264-6021:3590497
304. Adayev T, Chen-Hwang MC, Murakami N, Lee E, Bolton DC, Hwang YW. Dual-specificity tyrosine phosphorylation-regulated kinase 1A does not require tyrosine phosphorylation for activity in vitro. *Biochemistry*. 2007;46(25):7614-7624. doi:10.1021/BI700251N/SUPPL_FILE/BI700251N_SI.PDF
305. Guard SE, Poss ZC, Ebmeier CC, et al. The nuclear interactome of DYRK1A reveals a functional role in DNA damage repair. *Sci Reports*. 2019;9(1):1-12. doi:10.1038/s41598-019-42990-5
306. Najas S, Arranz J, Lochhead PA, et al. DYRK1A-mediated cyclin D1 degradation in neural stem cells contributes to the neurogenic cortical defects in Down syndrome. *eBioMedicine*. 2015;2(2):120-134. doi:10.1016/J.EBIOM.2015.01.010
307. Tejedor FJ, Hämmerle B. MNB/DYRK1A as a multiple regulator of neuronal development. *FEBS J*. 2011;278(2):223-235. doi:10.1111/J.1742-4658.2010.07954.X
308. Ryoo SR, Hey KJ, Radnaabazar C, et al. DYRK1A-mediated hyperphosphorylation of tau: a functional link between Down syndrome and Alzheimer disease. *J Biol Chem*. 2007;282(48):34850-34857. doi:10.1074/JBC.M707358200/ASSET/51269F2F-129D-4490-978A-562430E26D08/MAIN.ASSETS/GR6.JPG
309. Álvarez M, Estivill X, de la Luna S. DYRK1A accumulates in splicing speckles through a novel targeting signal and induces speckle disassembly. *J Cell Sci*. 2003;116(15):3099-3107. doi:10.1242/JCS.00618
310. Arron JR, Winslow MM, Polleri A, et al. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. *Nature*. 2006;441(7093):595-600. doi:10.1038/nature04678
311. Gwack Y, Sharma S, Nardone J, et al. A genome-wide drosophila RNAi screen identifies DYRK-family kinases as regulators of NFAT. *Nature*. 2006;441(7093):646-650. doi:10.1038/nature04631
312. Jung MS, Park JH, Ryu YS, et al. Regulation of RCAN1 protein activity by Dyrk1A protein-mediated phosphorylation. *J Biol Chem*. 2011;286(46):40401. doi:10.1074/JBC.M111.253971
313. Da Costa Martins PA, Salic K, Gladka MM, et al. MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signalling. *Nat Cell Biol*. 2010;12(12):1220-1227. doi:10.1038/ncb2126
314. Arque G, Casanovas A, Dierssen M. Dyrk1A is dynamically expressed on subsets of motor neurons and in the neuromuscular junction: possible role in Down syndrome. *PLoS One*. 2013;8(1):54285. doi:10.1371/JOURNAL.PONE.0054285
315. Chakrabarti L, Galdzicki Z, Haydar TF. Defects in embryonic neurogenesis and initial synapse formation in the forebrain of the Ts65Dn mouse model of Down syndrome. *J Neurosci*. 2007;27(43):11483. doi:10.1523/JNEUROSCI.3406-07.2007
316. Reeves RH, Irving NG, Moran TH, et al. A mouse model for Down syndrome exhibits learning and behaviour deficits. *Nat Genet*. 1995;11(2):177-184. doi:10.1038/ng1095-177
317. Altafaj X, Dierssen M, Baamonde C, et al. Neurodevelopmental delay, motor abnormalities and cognitive deficits in transgenic mice overexpressing Dyrk1A (minibrain), a murine model of Down's syndrome. *Hum Mol Genet*. 2001;10(18):1915-1923. doi:10.1093/HMG/10.18.1915
318. Martínez De Lagrán M, Altafaj X, Gallego X, et al. Motor phenotypic alterations in TgDyrk1a transgenic mice implicate DYRK1A in Down syndrome motor dysfunction. *Neurobiol Dis*. 2004;15(1):132-142. doi:10.1016/J.NBD.2003.10.002
319. Malak R, Kostiukow A, Krawczyk-Wasielewska A, Mojs E, Samborski W. Delays in motor development in children with Down syndrome. *Med Sci Monit*. 2015;21:1904. doi:10.12659/MSM.893377
320. Arbones ML, Thomazeau A, Nakano-Kobayashi A, Hagiwara M, Delabar JM. DYRK1A and cognition: a lifelong relationship. *Pharmacol Ther*. 2019;194:199-221. doi:10.1016/J.PHARMTHERA.2018.09.010
321. Cherry JD, Esnault CD, Baucom ZH, et al. Tau isoforms are differentially expressed across the hippocampus in chronic traumatic encephalopathy and Alzheimer's disease. *Acta Neuropathol Commun*. 2021;9(1):86. doi:10.1186/S40478-021-01189-4
322. Pathak A, Rohilla A, Gupta T, et al. DYRK1A kinase inhibition with emphasis on neurodegeneration: a comprehensive evolution story-cum-perspective. *Eur J Med Chem*. 2018;158:559-592. doi:10.1016/J.EJMECH.2018.08.093
323. Lindberg MF, Meijer L. Dual-specificity, tyrosine phosphorylation-regulated kinases (DYRKs) and cdc2-like kinases (CLKs) in human disease, an overview. *Int J Mol Sci*. 2021;22(11):6047. doi:10.3390/IJMS22116047
324. Woods YL, Cohen P, Becker W, et al. The kinase DYRK phosphorylates protein-synthesis initiation factor eIF2Bε at Ser539 and the microtubule-associated protein tau at Thr212: potential role for DYRK as a glycogen synthase kinase 3-priming kinase. *Biochem J*. 2001;355(3):609-615. doi:10.1042/BJ3550609
325. Ryoo SR, Cho HJ, Lee HW, et al. Dual-specificity tyrosine(Y)-phosphorylation regulated kinase 1A-mediated phosphorylation of amyloid precursor protein: evidence for a functional link between Down syndrome and Alzheimer's disease. *J Neurochem*. 2008;104(5):1333-1344. doi:10.1111/J.1471-4159.2007.05075.X

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dohl J, Treadwell Z, Norris C, Head E. Calcineurin inhibition may prevent Alzheimer disease in people with Down syndrome. *Alzheimer's Dement*. 2025;21:e70034. https://doi.org/10.1002/alz.70034