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## DYRK1A Inhibitors

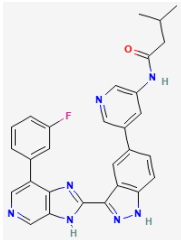
### Evidence Summary

DYRK1A inhibition may reduce Alzheimer's pathology prior to symptom onset, particularly in Down syndrome, and promote islet proliferation. It has been difficult to develop specific inhibitors.

**Neuroprotective Benefit:** Inhibitors that normalize DYRK1A levels in Down syndrome may delay the onset of AD disease pathology, including tau hyperphosphorylation, though treatment may need to start within a critical therapeutic window.

**Aging and related health concerns:** DYRK1A inhibitors may benefit diabetes and other autoimmune conditions by promoting pancreatic islet cell proliferation and reducing inflammation, but may raise circulating homocysteine levels.

**Safety:** Safety will likely vary with the kinase selectivity of individual inhibitors. There is possible concern for neurological side effects with chronic over-inhibition. Clinically tested inhibitors have shown good short-term safety thus far.

<p><b>Availability:</b> Research use or in clinical trials</p>	<p><b>Dose:</b> FRTX-02 and Silmitasertib have been administered orally in trials</p> <p>Lorecivint has been tested in Phase 3 trials at a dose of 0.07 mg via knee intraarticular injection annually</p>	<p><u>Lorecivint</u></p> <p><b>Chemical formula:</b> C<sub>29</sub>H<sub>24</sub>FN<sub>7</sub>O</p> <p><b>MW:</b> 505.5 g/mol</p> 
<p><b>Half-life:</b> Varies</p> <p>FRTX-02 16.0 to 28.0 hours in plasma Lorecivint ~ 55 days Silmitasertib ~14 hours in Phase 1 trial</p>	<p><b>BBB:</b> Varies</p>	<p>Source: <a href="https://pubchem.ncbi.nlm.nih.gov/compound/Lorecivint">PubChem</a></p>
<p><b>Clinical trials:</b> Silmitasertib has been tested in Phase 1 (n=43), 1b (n=50), 2 (n=74) trials for cancer. Lorecivint has been tested in trials for knee osteoarthritis including a Phase 2a (n=455), 2b (n=695), 3 (n=498; 501). FRTX-02 has been tested in a Phase 1 trial in healthy volunteers (n=89).</p>	<p><b>Observational studies:</b> DYRK1A protein levels are altered in AD</p>	

### What is it?

Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a serine/threonine kinase. Its catalytic activity is regulated by the autophosphorylation of a tyrosine residue (Y321), and then it has constitutively active serine/threonine kinase activity [1]. Because it is constitutively active, **its activity is dosage dependent**, and both higher and lower levels can lead to neurological deficits [2]. Individuals with Down syndrome (trisomy 21) have three copies of DYRK1A, while individuals with only one copy or loss of function mutations have mental retardation and other neurodevelopmental disabilities. DYRK1A plays important roles in cell cycle regulation in part by inhibiting nuclear factor of activated T cells (NFAT) transcription factors. Over 20 substrates have been identified thus far, and they encompass a wide range of cellular processes including cell signaling, chromatin modulation, gene expression, alternative splicing, cytoskeletal, and synaptic function [1].

A variety of groups have been working on developing DYRK1A inhibitors for the primary therapeutic indications of Down syndrome, Alzheimer's disease, diabetes, and cancer. DYRK1A is a challenging target because it is a member of the CMGC family of protein kinases, which also includes CLKs, CDKs, MAPKs, and GSK3. ATP-competitive inhibitors can be developed to target DYRK1A with high potency, but they

also inhibit other CMGC family members, and thus lack selectivity. Many DYRK1A kinase inhibitors identified were originally identified as inhibitors of a related CMGC family member [3]. Each inhibitor has a unique profile of CMGC and potentially non-CMGC kinase selectivity. Another complication is that molecules with good binding to DYRK1A tend to be hydrophobic and have low aqueous solubility [2]. While many prospective DYRK1A inhibitors have been tested in *in vitro* assays, only a few have been validated as DYRK1A inhibitors in *in vivo* models and have the potential for further clinical development.

Harmine is a natural beta-carboline alkaloid derived from the plant *Peganum harmala*. It is the most widely used DYRK1A inhibitor in preclinical research studies, however its kinase selectivity makes it unsuitable for clinical development [3]. It is a strong monoamine oxidase (MAO) inhibitor, and can induce parkinsonian-like and hallucinogenic effects at high doses. Many groups are using harmine as a scaffold to develop new DYRK1A inhibitors with a better kinase selectivity profile.

Leucettine L41 is a member of the class of DYRK1A inhibitors based on leucettines, which are dual CLK and DYRK inhibitors derived from marine sponges [4]. L41 is a synthetic analog of leucettamine B that has been optimized for DYRK1A inhibition. A second generation, the leucettinibs, are currently in preclinical development by [Perha Pharmaceuticals](#).

Epigallocatechin gallate (EGCG) is a catechin, a type of polyphenol, found in green tea. It has been shown to have inhibitory activity toward DYRK1A, and has been tested in clinical trials for Down syndrome [5; 6]. However, its clinical utility is limited by its poor pharmacokinetic properties, including its poor absorption and low metabolic stability [7]. Some groups are working to develop derivatives of EGCG with better drug-like properties [8].

PST-001 is an orally bioavailable (21%), BBB penetrant, selective DYRK1A inhibitor in use as a tool compound for *in vivo* animal studies [9]. It was developed by [Pharmasum Therapeutics](#), who has additional compounds in development for eventual clinical use, including PST-674.

Silmitasertib (CX-4945) is a casein kinase 2 inhibitor that is currently in clinical development for oncology by [Senhwa Biosciences](#) [10]. It was subsequently found to also inhibit several CLK and DYKR family members with high potency, including DYRK1A, and was able to inhibit DYRK1A related tau phosphorylation in a Down syndrome mouse model [11].

Lorecivivint (SM04690) is a pan-CLK/DYKR inhibitor that inhibits CLK2 with an IC<sub>50</sub> of 5.8 nM, and DYRK1A with an IC<sub>50</sub> of 26.9 nM [12]. It is currently in Phase 3 clinical development for knee osteoarthritis by [Biosplice Therapeutics](#), formerly known as Samumed.

FRTX-02 (VRN024219) is a DYRK1 inhibitor with an IC<sub>50</sub> of 2.9 nM for DYRK1A, which also has inhibitory activity toward other CMGC kinases, including DYRK1B (IC<sub>50</sub> 1.9 nM), CLK1 (IC<sub>50</sub> 4 nM), and CLK2 (IC<sub>50</sub> 3.7 nM) [13]. It was developed by Voronoi Inc. It was acquired by and is currently under clinical development for autoimmune conditions by [Fresh Tracks Therapeutics](#), formerly known as Brickell Biotech. It is currently in Phase 1 testing in healthy volunteers and patients with atopic dermatitis.

SM07883 is an orally bioavailable (%F 92% in mice, 109% in monkey), BBB penetrant, DYRK1A inhibitor (IC<sub>50</sub> 1.6 nM) [14]. It also shows potent inhibition toward DYRK1B, CLK4, and GSK3β in kinase assays. It was found to protect against tau hyperphosphorylation in mouse models, and was being developed by [Samumed](#), which is now called [Biosplice Therapeutics](#) for Alzheimer's disease. It was tested in a Phase 1 safety study in healthy volunteers ([ACTRN12619000327189](#)), however, there do not appear to be further development plans for this compound.

**Neuroprotective Benefit:** Inhibitors that normalize DYRK1A levels in Down syndrome may delay the onset of AD disease pathology, including tau hyperphosphorylation, though treatment may need to start within a critical therapeutic window.

*Types of evidence:*

- 2 clinical trials for EGCG in Down syndrome (n=31, n=84)
- 6 biomarker studies for DYRK1A expression in AD in plasma and/or brain tissue
- Numerous laboratory studies

**Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?** None

**Human research to suggest benefits to patients with dementia:** None

**Mechanisms of action for neuroprotection identified from laboratory and clinical research:**

DYRK1A plays an important role in brain development, such that elevated or reduced levels during neural development result in mental retardation phenotypes [1]. People with Down syndrome have increased dosage of DYRK1A (1.5X), whereas people with autosomal dominant mental retardation 7 (MRD7), a condition associated with microcephaly and severe cognitive deficits, have decreased dosage (0.5X) [2]. Many novel mutations in DYRK1A have also been associated with autism phenotypes [15; 16]. DYRK1A influences nervous system development and function in a variety of ways. It affects the proliferation and differentiation of neuronal progenitors, thereby influencing neurogenesis and brain growth [17]. It can also affect neurotransmission, dendritic spine formation, and synaptic plasticity through its interaction with synaptic proteins and the cytoskeleton.

#### **Down syndrome related cognitive impairment: POTENTIAL BENEFIT**

DYRK1A is located on chromosome 21 within the Down syndrome critical region, which is thought to be a major contributor to the Down syndrome phenotype [18]. DYRK1A is a dosage sensitive gene, thus the extra copy of DYRK1A in people with trisomy 21 profoundly affects the localization and function of the DYRK1A protein. Preclinical studies designed to elucidate the role of DYRK1A in Down syndrome suggest that DYRK1A is a key contributor to cognitive deficits stemming from altered neural development as well as synaptic dysfunction throughout life. The majority of studies using DYRK1A inhibitors have found that normalization of DYRK1A levels improve cognitive and behavioral deficits in transgenic models, however, there is considerable variation across studies in terms of outcomes. The discrepancies have been attributed to differences in model, composition of the inhibitor, route of administration, dose, and timing of administration [18; 19]. The expression of DYRK1A during development and over the course of the lifespan varies across tissues, which suggests that there may be an optimal therapeutic window to prevent or treat specific neurological phenotypes, but these critical windows have not yet been identified [18]. There may also be sex-specific variation in the life course pattern of DYRK1A, as male, but not female Down syndrome model mice (Ts65Dn) had elevated levels of DYRK1A expression in various brain regions, including the hippocampus, cerebral cortex, and cerebellum, at postnatal day 15 (P15), which is the equivalent to four months old in human infants [20]. Due to a lack of solubility, treatment with the casein kinase inhibitor silmitasertib (CX-4945), which also shows activity toward DYRK1A, did not meaningful impact outcomes in these animals, so it is unclear whether there may also be sex differences in the therapeutic windows.

The catechin epigallocatechin gallate (EGCG) has been identified as a DYRK1A inhibitor, although its *in vivo* potency within tissues has not been clearly established [18; 19]. EGCG has been tested in a variety of preclinical models and in two RCTs for Down syndrome. In the pilot study (n=31) young adults (age 14

to 29) treated for three months with 9 mg/kg EGCG showed improvements in visual recognition memory and working memory, which were not sustained during the post-treatment period [5]. Significant improvements were not seen on the TESAD and ABAS-II batteries in a 12-month study (n=84) with EGCG alone, but small improvements were seen in visual recognition memory, inhibitory control, functional connectivity, and cortical excitability when used in combination with cognitive training [6]. While the outcomes cannot conclusively be attributed to the effects of EGCG on DYRK1A in these studies, several of these changes are consistent with the modulation of DYRK1A in preclinical studies. For example, DYRK1A has been shown to regulate the excitatory/inhibitory balance of the brain with the overexpression of DYRK1A leading to an increase in inhibitory neurotransmission [21]. In mice, DYRK1A overexpression decreases excitability and gamma oscillations in the prefrontal cortex [22], while haploinsufficiency leads to hyperexcitability and seizures [23]. In male Down syndrome model mice (Ts65Dn), low doses (~9 mg/kg) of EGCG benefited some abnormalities to trabecular, but not cortical bone, whereas high doses (~200 mg/kg) negatively impacted bone strength and structure [24]. It is unclear whether this is related to differences in the degree of DYRK1A inhibition, but suggests that over-inhibition of DYRK1A could potentially have deleterious effects, likely during particular critical windows of development.

The clinical and preclinical studies suggest that normalization of DYRK1A during adolescence and young adulthood may help normalize neurological phenotypes associated with altered synaptic plasticity and cortical excitability [18]. Meanwhile, earlier intervention may be needed to correct neurodevelopmental phenotypes stemming from altered neurogenesis. However, the brain appears to be most sensitive to DYRK1A dosage during the prenatal period, since individuals with either an extra copy or missing a functional copy of DYRK1A are born with neurological deficits. Cortical neurogenesis was restored in mouse embryos with trisomy 21 (Ts1Cje) when the mother was treated with the DYRK1A inhibitor ALGERNON, whereas, the wildtype offspring showed a trend toward learning deficits [25]. Therefore, DYRK1A inhibitors would need to be carefully titrated when used during the prenatal period to ensure that DYRK1A is not overinhibited.

#### **Alzheimer's disease: POTENTIAL BENEFIT PRIOR TO SYMPTOM ONSET (Preclinical)**

Preclinical studies suggest that DYRK1A inhibitors **may be most effective for slowing the onset of Alzheimer's disease (AD) in people with Down syndrome**. Around fifty percent of individuals with Down syndrome develop AD, with symptoms typically starting between 40 and 60 years old. The increased levels of DYRK1A are hypothesized to facilitate the early onset of AD by driving AD pathology [17]. In trisomy 21 human induced pluripotent stem cells (iPSCs)-derived neurons, normalization of the copy



number for APP or DYRK1A, but not of other disease-associated triplicated proteins such as RCAN1 and SYNJ1, normalized tau phosphorylation, the cytoskeletal network, and endolysosomal function [26]. In the T65Dn mouse model of Down syndrome, aged (13-14 month old) mice with a normalized DYRK1A gene copy number (2 copies) had reduced numbers of senescent cells in the hippocampus and cortex, reduced cholinergic neurodegeneration, and reduced APP, A $\beta$ , and tau levels, relative to Down syndrome mice with 3 copies of DYRK1A [27]. This study suggests that DYRK1A normalization can reduce or delay AD neuropathology. However, since these mice had normal levels of DYRK1A throughout their lifespan, this study does not indicate the optimal point of intervention, and whether there is a critical window. Studies in AD models indicate that treatment with DYRK1A inhibitors is most effective prior to the onset of symptoms and pathology, suggesting that treatment starting in adolescence may be necessary to prevent or delay the onset of AD in people with Down syndrome.

A case-control study (n=374 cases, 375 controls) in Japan identified DYRK1A (rs2835740; cc genotype) as highly associated with late-onset AD (Odds Ratio [OR]: 2.99, 95% Confidence Interval [CI] 1.72 to 5.19; P = 0.001) [28]. mRNA expression of DYRK1A was also found to be elevated in the hippocampus of AD patients, in this study. Biomarker studies suggest that the systemic dysregulation of DYRK1A may play a role in AD. Several studies have found that plasma levels of DYRK1A in AD are lower than age -matched controls [29; 30; 31; 32]. Plasma levels of DYRK1A tend to increase with age, however, this increase does not occur in individuals with high levels of amyloid [31; 32]. The relationship between DYRK1A appears to be tied to amyloid and tau, rather than neurodegeneration more generally [32], suggesting it may have utility as a biomarker for AD. Notably, DYRK1A has been shown to phosphorylate tau on several residues that have shown utility as plasma biomarkers for AD, including, ptau-181 (Thr181), ptau-231 (Thr231), and ptau-212 (Thr212) [33]. Similar to DYRK1A, these plasma ptau species show an association with brain amyloid levels. In the SENIOR cohort (n=96) of cognitively healthy older adults (aged 50-70), plasma DYRK1A levels varied based on brain amyloid levels, such that average levels of DYRK1A were 4.1 ng/mL in those with low amyloid and 2.8 ng/mL in those with high amyloid [31]. The decrease in circulating full-length DYRK1A was seen in the context of both sporadic AD and Down syndrome-associated AD [31; 34]. The levels of full-length DYRK1A in plasma and CSF were decreased, while levels of a truncated (50 kDa) form were increased in those with symptomatic AD, relative to asymptomatic Down syndrome individuals [34]. A similar pattern was also seen in lymphoblastoid cell lines from these patient groups. The truncated form can be generated through C-terminal cleavage by calpain-1. Calpain activity is activated in response to inflammation and has been reported to be dysregulated in AD [35]. Studies in mice found that the **truncated form of DYRK1A may have increased tau phosphorylation**



**activity** [36], and increased affinity for STAT3a in astrocytes, which drives pro-inflammatory signaling [37].

The localization and substrate selectivity for DYRK1A also appears to be altered in AD, as it was found to have a 40% reduced association with actin, such that the electrophoretic mobility of G-actin in peripheral blood mononuclear cell (PBMC) samples could be used to distinguish AD patients from controls [38]. The reduced association of DYRK1A with cytoskeletal proteins was also seen in the postmortem brain tissue from AD patients. This could stem from a change in form and/or expression level, since overexpression has been shown to alter the localization of DYRK1A [39]. Studies examining whether the expression level of DYRK1A in the brain is altered in AD have been inconsistent, which likely stems from cellular and regional variation and the presence of multiple forms. One study found that the total levels of DYRK1A from brain homogenates were unchanged, but that in specific brain areas, such as the frontal cortex, there were significant increases in the proportion of cells very strongly immunoreactive for DYRK1A, suggesting that local levels may play a role in cell susceptibility to AD-related neurodegeneration [40]. Another study found that while overall levels of DYRK1A were relatively unchanged, there was a shift toward decreased levels of full length DYRK1A and an increase in a truncated form generated through C-terminal cleavage by calpain-1 [36]. The loss of the full-length form may explain the studies that show a decrease in brain levels, if the antibodies used did not readily recognize the truncated form.

**Amyloid:** DYRK1A has been shown to phosphorylate APP at Thr-668, which promotes the production and amyloidogenic cleavage of APP to generate pathogenic A $\beta$  [1]. Due to its role in regulating cytoskeletal network proteins, DYRK1A also appears to play a role in APP trafficking. Overexpression of DYRK1A increased the axonal density of APP vesicles, and the processivity of retrograde transport which may promote  $\beta$ -secretase processing in the endolysosomal compartment [41].

**Tau:** DYRK1A is involved in the regulation of various cytoskeletal proteins, including tau. DYRK1A phosphorylates tau on multiple residues, including Ser396 and Thr212, and this primes tau for further phosphorylation by GSK3 $\beta$  [42]. DYRK1A also phosphorylates alternative splicing factor which impacts the ratio of different tau isoforms, such that increased DYRK1A activity leads to an imbalance in the 3R/4R ratio [43].

**Neuroinflammation:** DYRK1A inhibitors have been shown to have anti-inflammatory properties, particularly in the context of LPS-induced neuroinflammation. The DYRK1A inhibitor, KVN93, reduced pro-inflammatory cytokine signaling in microglia following LPS stimulation through inhibition of





TLR4/AKT/STAT3 signaling [44]. Similarly, harmine suppressed microglial activation through the inhibition of TLR4/NF- $\kappa$ B signaling [45]. Anti-inflammatory effects in glia were also seen with the multi-kinase inhibitor, varlitinib, which was related to TLR4/AKT/NF- $\kappa$ B signaling [46], while pro-inflammatory cytokines were reduced in stimulated glia through a reduction in AKT/STAT3 with use of the CDK/DYRK1A inhibitor, abemaciclib mesylate [47].

**Neurogenesis:** DYRK1A acts as a regulator of cell cycle and cytoskeletal proteins, and is critical for neurogenesis during embryonic and postnatal brain development, such that haploinsufficiency results in microcephaly [48]. DYRK1A acts as a negative regulator of the G1-S transition, such that overexpression results in premature cell cycle exit and differentiation, as well as limit cell proliferation and promote quiescence [48]. A study in mice suggests that inhibition of DYRK1A could promote the neurogenic potential of neural stem cells [49]. The combined induction of Plagl2 and inhibition of DYRK1A rejuvenated aged (18-month-old) hippocampal neural stem cells in mice through epigenetic chromatin medication, leading to enhanced adult neurogenesis and improved performance on cognitive memory tests.

Various DYRK1A inhibitors have shown benefit in lowering amyloid and tau pathology and cognitive deficits in preclinical models of AD, primarily when administered starting prior to symptom onset. DYR219, a benzimidazole DYRK1A inhibitor, reduced levels of insoluble phosphorylated tau (Ser396), insoluble A $\beta$ , and APP, but had no effect on total tau levels in 3xTg AD mice after the onset of symptoms (10 months old) [50]. While 3xTg mice treated prior to the onset of pathology showed a significant delay in the onset of pathology (6 months old), along with significantly reduced levels of amyloid and tau pathology at 12 months of age [51]. In *Drosophila*, DYR219, which has a Kd of 16 nM for DYRK1A, reduced tau phosphorylation at Thr231 and Ser396, and was able to suppress the rough eye phenotype in flies overexpressing human tau (ON4R) or human A $\beta$  [52]. It also extended the lifespan of these mutant flies by 20% and 25%, respectively. DYR219 rescued the locomotor deficits of tau flies, without impacting wildtype flies. It also partially improved behavioral deficits in A $\beta$  or tau overexpressing flies. Similar effects were seen with the DYRK1A inhibitor, DYR533 (Kd 4 nM), which primarily reduced tau phosphorylation at the Ser396 and Ser262 sites. Relative to flies overexpressing the *Drosophila* homolog of DYRK1A (minibrain), these inhibitors were less effective at rescuing the phenotypes in tau or A $\beta$  overexpressing flies, which is indicative of the complex neuropathology in AD which is beyond the scope of a single kinase.

SM07883 reduced tau hyperphosphorylation and aggregation in JNPL3 mice with the FTD P301L tau mutation [14].

Leucettine L41 prevented A $\beta$  induced oxidative stress and synaptic deficits when co-injected in the intracerebroventricular A $\beta$  model [53], and improved synaptic plasticity and memory in the APP/PS1 model [37].

PST-001 is an orally bioavailable (21%) DYRK1A inhibitor (IC<sub>50</sub> 40 nM) with effective transport to the brain and shows excellent selectivity toward DYRK1A (GINI-index of 0.936), relative to other tested inhibitors and thus has utility as a tool compound for *in vivo* studies [9]. In *Drosophila*, it was able to reduce levels of phosphorylated tau at Ser262 by over 50% [54]. PST-001 partially restored eye phenotypes, extended lifespans (25-30%), restored locomotor behavior, improved sleep, and restored memory in flies overexpressing human mutant tau (ON4R) or A $\beta$ 42.

KVN93 is a BBB penetrant DYRK1A inhibitor (IC<sub>50</sub> 3.1–3.2 nM) [44]. Treatment with KVN93 (20 mg/kg i.p.) starting at three months of age reduced levels of A $\beta$  by increasing the levels of A $\beta$  degradation enzymes neprilysin and insulin-degrading enzyme and  $\alpha$ -secretase ADAM17, along with decreasing levels of the gamma-secretase, presenilin-1. This effect on A $\beta$  load and related enzymes was not seen when treatment began at eight months of age. While reductions in glial reactivity (Iba1+ and GFAP+) were seen at both ages, the anti-inflammatory effects were more pronounced in the younger mice.

ZDWX-25 is a BBB permeable harmine derivative with inhibitory activity toward DYRK1A (IC<sub>50</sub> 227.97  $\pm$  14.97 nM) and GSK-3 $\beta$  (IC<sub>50</sub> 248.73  $\pm$  22.76 nM) [55]. It was shown to inhibit tau phosphorylation at Ser396 and Thr212 in HEK293-Tau P301L cells and okadaic acid-induced SH-SY5Y neuroblastoma cells. Treatment with ZDWX-25 (15 mg/kg) starting at 10 months of age in the 3xTg AD mouse model reduced tau phosphorylation in the hippocampus at Thr181, Thr212, Ser396 and Ser416, but did not impact tau phosphorylation at Ser404, Thr231, or Ser202/Thr205. Plasma levels of ptau-181 and ptau-217 were also reduced with treatment. Treatment (15 mg/kg) for two months improved spatial memory performance on the Morris water maze, while treatment with a low dose of ZDWX-25 (1 mg/kg) starting at 30 weeks of age extended the median survival from 46 to 82 weeks of age in the 3xTg model.

Varlitinib is an EGFR/HER2 inhibitor that is FDA-approved for the treatment of cancer. It was shown to reduce DYRK1A levels in PS19 tauopathy mice, but did not impact levels of p-GSK-3 $\beta$  or p-CDK5. Three-month-old PS19 mice treated with varlitinib (20 mg/kg, i.p. for 14 days) showed a reduction in tau phosphorylation at Thr212/Ser214 in the cortex and hippocampus as well as at Thr231 in the dentate gyrus [46]. This was accompanied by a reduction in gliosis, based on Iba1 and GFAP immunostaining. Treatment with varlitinib starting at six months of age was less effective at reducing levels of tau phosphorylation and gliosis, suggesting that earlier intervention offers more potential benefit.

Abemaciclib mesylate is a CDK4/6 inhibitor that is FDA-approved for the treatment of breast cancer. It was also shown to exhibit inhibitory activity toward DYRK1A in the 5XFAD mouse model, which was accompanied by decreased tau phosphorylation at Ser202/Thr205 and Thr231 in the cortex and



hippocampus, as well as at Thr212 in the cortex of six-month-old 5XFAD mice [47]. A similar reduction in tau phosphorylation at Ser202/Thr205 and Thr231 was seen with abemaciclib mesylate (30 mg/kg i.p.) treatment in three- to four-month-old tau overexpressing PS19 mice. These effects were related to a reduction in the levels of DYRK1A and p-GSK3 $\beta$ . Abemaciclib mesylate also reduced A $\beta$  deposition by increasing the activity of the A $\beta$ -degrading enzyme neprilysin and the  $\alpha$ -secretase ADAM17 as well as reducing the activity of the gamma secretase, presenilin-1 in 5XFAD mice. Astrogliosis, stemming from STAT3 activation, was also reduced. Although the anti-amyloid and anti-inflammatory features have been seen with other DYRK1A inhibitors, it is not clear which CMGC kinases targeted by abemaciclib are mediating these non-tau-related effects.

DYRK1A is involved in the metabolism of homocysteine, which is itself a risk factor for AD. While elevated DYRK1A in the brain can promote AD pathology, the expression of DYRK1A in the liver may be neuroprotective through its connection with homocysteine. In mice, there is a negative correlation between plasma homocysteine and hepatic DYRK1A levels with a bi-directional relationship [56]. DYRK1A expression in the liver is reduced in hyperhomocysteinemic mice, while overexpression of DYRK1A reduces levels of homocysteine by increasing hepatic expression of NAD(P)H quinone oxidoreductase and SAHH [56]. The circulating homocysteine can then enter the brain, where it has been shown to exert neurotoxic effects through activation of the mitochondrial apoptotic pathway [57]. In contrast to the liver, the brains of mice with high homocysteine have elevated levels of DYRK1A and SAHH activity, which is likely a compensatory response to the elevated homocysteine [58]. Homocysteine can lead to the activation of the cysteine protease calpain-1 by increasing the level of intracellular calcium [57], and calpain-1 cleaves the PEST sequence from DYRK1A to generate a truncated form with altered kinase activity, localization, and selectivity [36]. In hyperhomocysteinemic mice, targeted hepatic expression of DYRK1A using AAV2/8-DYRK1A, decreased plasma homocysteine levels, increased brain BDNF, decreased brain calpain, and decreased brain DYRK1A [59]. One study in humans found that a composite biomarker of plasma DYRK1A, homocysteine, and BDNF had a sensitivity of 0.952, specificity of 0.889, and accuracy of 0.933 for AD, with DYRK1A being the most predictive marker [30]. Consistent with mouse studies indicating that homocysteine promotes the truncation of DYRK1A, AD patients had elevated levels of homocysteine (16.85 $\pm$ 5.77 vs 12.14 $\pm$ 3.00;  $p < 10^{-6}$ ), along with a reduction in plasma full-length DYRK1A levels (77.70 $\pm$ 13.80 vs 102.4 $\pm$ 15.88;  $p < 10^{-14}$ ), and BDNF levels (2.00 $\pm$ 0.80 vs 3.23 $\pm$ 1.25;  $p < 10^{-9}$ ).

Together this suggests a model where cellular insults such as homocysteine or inflammation leads to the induction and cleavage of DYRK1A within neurons in AD. This drives neurodegeneration by promoting



the generation of A $\beta$  and tau pathology. It additionally induces cognitive dysfunction by altering the normal functions of DYRK1A, such that less is associated with cytoskeletal synaptic proteins leading to changes in neurotransmission, and more associates with pro-inflammatory drivers. All of the substrates have not been fully characterized, so there are likely additional changes to transcriptional programs and chromatin regulators stemming from changes to the balance of its cytoplasmic and nuclear localization. A potential complication of systemic DYRK1A inhibitors is an increase in homocysteine production, which may counteract some of their neuroprotective benefit. Additionally, since DYRK1A has dosage dependent activity, over-inhibition could also potentially impair synaptic plasticity and cognitive function, thus proper dosing is likely to be a critical aspect of the therapeutic utility of this class of drugs. Biomarkers would be needed to determine which AD patients have elevated levels/activity of DYRK1A in the brain. Approaches that prevent the proteolytic cleavage of DYRK1A may have a better therapeutic profile. In APP/PS1 mice, leucettine L41 was shown to inhibit the proteolysis of DYRK1A as well as associated downstream inflammatory and synaptic phenotype [37], but it is not yet known if this is specific to L41 or a common feature of DYRK1A inhibitors.

#### **Parkinson's disease: POTENTIAL BENEFIT (Preclinical)**

A genome-wide functional mapping analysis identified a single nucleotide polymorphism (SNP) in DYRK1A (rs11088398; G $\rightarrow$ T) as a potentially causal SNP in Parkinson's disease (PD) [60]. This SNP falls within a neuron-specific enhancer and has direct interactions with the upstream promoter of DYRK1A. DYRK1A has been shown to phosphorylate several PD-associated proteins. Phosphorylation by DYRK1A inhibits the ubiquitin E3 ligase activity of Parkin, while phosphorylation of septin 4 enhances the aggregation of alpha-synuclein [43]. A novel 6-hydroxybenzothiazole urea derivative, b1, with inhibitory activity at DYRK1A was also found to protect against the aggregation of alpha-synuclein and protect against 6-OHDA induced cell death in SH-SY5Y cells [61]. A novel non-ATP competitive DYRK1 inhibitor derived from EGCG, 1c (IC<sub>50</sub> 73 nM), protected against the loss of dopaminergic neurons and motor deficits in mice when administered (30 mg/kg BID orally) prior to the neurotoxin MPTP [62].

#### **Huntington's disease: POTENTIAL BENEFIT PRIOR TO ONSET (Preclinical)**

In a 3-NP mycotoxin-induced neurotoxicity model in male rats, pretreatment with the multi-target DYRK1A inhibitor, harmine (10 mg/kg/day i.p.) reduced motor and cognitive deficits [63]. Notably, pretreatment restored redox homeostasis, which was attributed to the activation of the Nrf2 endogenous antioxidant system. DYRK1A primes GSK3 $\beta$  to inhibit Nrf2, thus the inhibition of DYRK1A relieves the inhibition on Nrf2.



***APOE4 interactions:*** UNCLEAR

One study found that plasma DYRK1A levels were lower in ApoE4 carriers [29], while other studies found there was no significant difference between carriers and non-carriers [30; 31].

**Aging and related health concerns:** DYRK1A inhibitors may benefit diabetes and other autoimmune conditions by promoting pancreatic islet cell proliferation and reducing inflammation, but may raise circulating homocysteine levels.

*Types of evidence:*

- 4 clinical trials for Silmitasertib (CX-4945) in cancer
- 4 clinical trials for Lorecivivint in knee osteoarthritis
- 1 clinical trial for FRTX-02 in healthy volunteers
- Several laboratory studies

**Diabetes:** POTENTIAL BENEFIT (Preclinical)

High throughput screens have identified **DYRK1A inhibitors as inducers of pancreatic beta-cell proliferation**, and thus potential therapeutic candidates to promote islet regeneration in patients with diabetes. The proliferative effect is driven by the induction and nuclear translocation of nuclear factor of activated T cells (NFAT) transcription factors, which act to transactivate the cell cycle. DYRK1A phosphorylates NFATs which keeps them in the cytosol, thereby acting to repress NFAT mediated transcription. DYRK1A also influences the proliferative state through regulation of the DREAM complex [64]. DYRK1A inhibitors can promote beta cell proliferation by disrupting the transcriptional repression of the DREAM complex.

Various DYRK1A inhibitors, including harmine, 5-IT, and GNF4877 have been shown to enhance islet cell proliferation in mice transplanted with human islet cells, and to improve insulin secretion and glucose tolerance in diabetic mice [65; 66; 67]. Harmine can modestly increase human beta cell proliferation in culture, by approximately 2%, and several other DYRK1A inhibitors, including leucettine-L41 and INDY, have comparable proliferative potential [68]. 5-IT and GNF4877 were found to be 10-fold more potent at inducing human beta cell proliferation [69]. DYRK1A inhibitors are generally non-selective and inhibit other DYRK family members to varying degrees. Inhibition of both DYRK1A and DYRK1B was found to be important for the effect on beta cell proliferation [69], so differences in activity toward these or other yet to be identified kinases may account for the differences in potency across inhibitors.



One study found it is possible to increase the efficacy and specificity of DYRK1A inhibitors for beta cell proliferation by combining them with GLP-1R agonists [68]. The combination had a synergistic effect mediated by cAMP signaling and was able to increase beta cell proliferation to around 5-6%. This synergism was found to be a class effect and was found in all tested combinations of DYRK1A inhibitors and GLP-1R agonists. This suggests that DYRK1A inhibitors may be most effective for diabetes as part of a combination therapy.

**Cardiac Hypertrophy:** UNCLEAR (Preclinical)

The effects of DYRK1A on cardiomyocytes appears to be context dependent, leading to different outcomes when it is modulated *in vitro* vs *in vivo* and across different animal models. In cultured rat cardiomyocytes, AAV mediated overexpression of DYRK1A can inhibit phenylephrine-induced cardiomyocyte hypertrophy through inhibition of NFAT [70], however, the protective effect was not seen in a mouse model (aortic banding) of cardiac hypertrophy with transgenic overexpression of DYRK1A [71]. Meanwhile, two studies in rats showed protective effects for DYRK1A inhibition. DYRK1A levels were increased three-fold in rats with myocardial infarction, which was accompanied by a dysregulation in the alternative splicing of CaMKII $\delta$  [72]. Treatment with DYRK1A non-selective inhibitors harmine or EGCG reversed the molecular changes and improved symptoms. The angiotensin receptor blocker valsartan inhibited cardiac hypertrophy in hypertensive rats, which was partially mediated by a decrease in cardiac DYRK1A and associated restoration of CamK11 $\delta$  splicing [73]. In a mouse model of myocardial infarction involving permanent ligation of left anterior descending coronary artery, treatment with the non-specific DYRK1A inhibitor harmine promoted cardiomyocyte cell cycle activation, which was accompanied by improved cardiac function based on left ventricular ejection fraction and left ventricular fractional shortening [74]. These studies suggest that the effects of DYRK1A inhibitors in the heart are dependent on the dominant signaling pathways in cardiac tissue at a given time.

**Cancer:** CONTEXT DEPENDENT

Adults with Down syndrome have decreased incidence of solid tumor cancers; however, children are at increased risk for leukemias [75]. DYRK1A may be oncogenic in megakaryocytes, contributing to the leukemia risk, and may be acting as a tumor suppressor in other tissues.

**DYRK1A has context dependent functions, and there is evidence to support its role as both an oncogene and a tumor suppressor [1].** DYRK1A acts as a negative regulator of the cell cycle, and the dosage can direct cells toward proliferating or exiting the cell cycle. It can also promote the survival of

malignant cells by inhibiting pro-apoptotic pathways, since the loss of DYRK1A can activate p53. DYRK1A likely plays a tumor type specific role, such that whether DYRK1A inhibition would promote or inhibit tumor cell growth depends on the tissue type and tumor microenvironment. In some tumor types, the reactivation of cell cycle activity with DYRK1A inhibition can sensitize the cancer cells to DNA damage-related cell death from chemotherapy or radiation [76].

Silmitasertib (CX-4945) was tested in a Phase 1b/2 trial at a dose of 1000 mg/day for ten days in combination with gemcitabine and cisplatin (on days 1 and 8 of a 21-day cycle) in patients with locally advanced/metastatic cholangiocarcinoma (n=144) (NCT02128282) [77]. The median progression free survival rate for the combination with silmitasertib was 11.2 months (95% CI 7.6 to 14.7) relative to 5.8 months (95% CI 3.1 to not evaluable) for gemcitabine and cisplatin alone. The median overall survival was 17.4 months (95% CI 13.4 to 25.7) for the combination versus 14.9 months (95% CI 9.9 to not evaluable). Based on these results, silmitasertib has been granted Orphan Drug Designation by the FDA for biliary tract cancer (Press release). In two Phase 1 trials testing silmitasertib as a monotherapy in patients with advanced solid tumors led to six-month disease stabilization in 15% of patients, but no partial or complete responses based on RECIST criteria [78]. Silmitasertib is currently being tested in patients with recurrent medulloblastoma (NCT03904862) and in patients with basal cell carcinoma (NCT03897036). Preliminary data indicates that two out of ten patients with locally advanced basal cell carcinoma showed partial responses in tumor size reduction (30%) (Press release).

#### **Hyperhomocysteinemia: POTENTIAL HARM (Preclinical)**

High homocysteine is a risk factor for atherosclerotic vascular disease. Individuals with Down syndrome, who have 1.5 times the level of DYRK1A due to an extra copy of chromosome 21, have low circulating homocysteine levels [79] and low rates of atherosclerosis [80]. The increased dosage of DYRK1A may underlie the protection against cardiovascular phenotypes in this population [56].

Hepatic DYRK1A and plasma homocysteine levels have been found to be inversely correlated in mice [56]. Meanwhile there is a positive correlation between DYRK1A protein levels and liver activity of cystathionine beta synthase, the primary enzyme involved in the metabolism of homocysteine [81]. Hepatic DYRK1A expression has also been positively correlated with hepatic SAHH activity, another enzyme involved in homocysteine metabolism [56]. AAV targeted hepatic expression of DYRK1A in hyperhomocysteinemic mice (CBS+/-) decreased plasma homocysteine levels, increased cystathionine beta synthase activity, and increased apoA1 levels [82]. These studies suggest that DYRK1A inhibitors could exacerbate homocysteine related cardiovascular disease.

**Knee osteoarthritis: POTENTIAL BENEFIT FOR MILD DISEASE**

Lorecivivint modulates the Wnt pathway by inhibiting CLK2 and DYRK1A [12]. DYRK1A phosphorylates and activates the chromatin regulator SIRT1, which is a positive regulator of canonical Wnt signaling. Wnt signaling has been found to be upregulated in osteoarthritic joints. Additionally, the phosphorylation of the transcription factor FOXO1 by DYRK1A results in its nuclear exclusion and degradation. FOXO1 enhances the function of chondrocytes, which produce the cartilage matrix, thus the activation of FOXO1 enhances joint repair.

In a Phase 2a placebo-controlled RCT (NCT02536833) (n=455), lorecivivint was administered as a single 2-ml intraarticular injection at a dose of 0.03 mg, 0.07 mg, or 0.23 mg in patients with knee osteoarthritis [83]. The study did not meet its primary endpoint of improvement ( $\geq 20$ -points) on the WOMAC pain scale at week 13, however, there were significant improvements in the WOMAC pain score (-11.21, 95% CI -20.99 to -1.43) and WOMAC function score (-10.26, 95% CI -19.82, -0.69) relative to placebo, at the 0.07 mg dose at 52 weeks in a prespecified subgroup with unilateral symptoms.

In a Phase 2b placebo-controlled RCT (NCT03122860) (n=695), lorecivivint was administered as a 2-ml intraarticular injection at a dose of 0.03, 0.07, 0.15, or 0.23 mg, in conjunction with standard of care NSAID treatment [84]. Significant improvements were seen in WOMAC pain (-7.36, 95% CI -14.03 to -0.69) and function (-7.99, 95% CI -14.54 to -1.45) subscores and Pain numeric rating scale (NRS) (-0.82, 95% CI -1.51 to -0.12) at the 0.23 mg dose at week 24, relative to placebo. Improvements in the Pain NRS and WOMAC scores were also seen at the 0.07 mg dose at week 12.

In the 28-week STRIDES-1 (NCT04385303) (n=498) and 56-week STRIDES-X-ray (NCT03928184) (n=501) Phase 3 placebo-controlled RCTs, intraarticular lorecivivint at a dose of 0.07 mg was tested in patients with knee osteoarthritis. The primary endpoint of change from baseline in Pain NRS at week 12 was not met in either study [85; 86]. A subset of participants (n=251) from the STRIDES-X-ray study continued into a year-long single-blind extension trial and received another dose of lorecivivint or placebo. Those in the lorecivivint group showed a statistically significant reduction in the WOMAC pain score relative to placebo (-5.18, 95% CI -10.28 to -0.08), as well as trends toward improvement in the Pain NRS and WOMAC function scores [86]. Participants in the placebo group that crossed over to lorecivivint during an open-label extension period also showed improvement on these measures within six months. Patients included in these studies had clinically and radiologically defined knee osteoarthritis with baseline Pain NRS levels between four and eight, on this ten-point scale and baseline medial joint space width between 1.5 to 4.0 mm. The sponsor concluded that the structural disease may have been too



advanced for benefit in the tested population, and has initiated a new Phase 3 RCT in patients with less advanced structural disease ([NCT05603754](#)).

**Skin autoimmune conditions:** POTENTIAL BENEFIT (Preclinical)

DYRK1A plays a role in the regulation of adaptive and innate immunity. NFAT transcription factors are regulators of T cell development, differentiation, and activation [87]. They also play a role in self-tolerance, such that dysregulation of NFAT signaling may contribute to autoimmune disorders. The phosphorylation of NFATs by DYRK1A inhibits their transcriptional activity via nuclear exclusion. Thus, overactive DYRK1A can disrupt the balance of NFAT signaling, and thus alter the balance of T cells. Consequently, the prevalence of autoimmune disorders, such as psoriasis, type 1 diabetes, and juvenile arthritis, is higher in individuals with Down Syndrome relative to the general population [88]. The DYRK1A inhibitor, FRTX-02, formerly known as VRN024219 is currently being developed for skin autoimmune conditions.

Oral and topical formulations of [FRTX-02](#) were tested in preclinical models of psoriasis and atopic dermatitis [88]. In a mouse (BALB/c) model of psoriasis induced by the application of imiquimod cream to the ear, oral administration of FRTX-02 (45 or 60 mg/kg twice per day) reduced ear inflammation to the same extent as current standard of care treatments, methotrexate or tofacitinib (JAK inhibitor). Once daily topical treatment (1% or 3%) also reduced ear inflammation in a dose-dependent manner. Similarly, in a mouse model of atopic dermatitis involving exposure to 4% SDS and house dust mite allergens, FRTX-02 administered orally (30 mg/kg twice daily) or topically (1.5% or 3% daily) reduced inflammation to at least the same degree as dexamethasone based on the dermatitis severity score and histological analysis. Improvements in skin thickness and reductions in serum IgE levels were seen with both formulations in both model systems. In cell culture, FRTX-02 biased the differentiation of *ex vivo* CD4+ T cells in favor of pro-tolerogenic T regulatory cells and away from pro-inflammatory Th-1 and Th-17 cells. FRTX-02 also reduced pro-inflammatory MyD88/IRAK4–NF-κB mediated signaling in a human mast cell line (HMC1.2).

FRTX-02 is currently being tested in a two-part Phase 1 trial ([NCT05382819](#)). The first part, a single and multiple ascending dose study in healthy volunteers was recently completed and will now move on to the second part testing FRTX-02 relative to placebo for 28 days in patients with moderate to severe atopic dermatitis ([Press release](#)). Exploratory cytokine analysis following *ex vivo* LPS stimulation of whole blood from healthy volunteers in the Phase 1 study found evidence of maximum reductions up to over 90% for IFN-γ, over 50% for IL-23, IL-10 and TNF-α, and around 40% for IL-6 following 14 days of 75 or 150 mg FRTX-02, relative to baseline ([Press release](#)).

**Antiviral: POTENTIAL BENEFIT**

DYRK1A has been shown to play a role in the replication of several viruses. It has been shown to promote viral infection by human papillomavirus type 16, human adenovirus type 5, and human cytomegalovirus [89]. It can also promote the reactivation of latent virus in the context of HIV, suggesting that it can have pro or anti-viral roles. Recently, DYRK1A inhibitors were found to block viral entry of pseudorabies virus in cell culture [90]. DYRK1A was also shown to promote infection by SARS-CoV2, which is consistent with the higher rates of severe Covid-19 in individuals with Down syndrome [91]. Silmitasertib (CX-4945), which inhibits casein kinase 2 as well as DYRK1A, was tested in a small Phase 2 open label clinical trial (n=31) in patients with severe Covid-19 (NCT04668209). Topline data from 20 patients with moderate Covid-19 found that silmitasertib treatment significantly shortened time to recovery relative to standard of care (median 6 days vs 14 days) (Press release).

**Safety:** Safety will likely vary with the kinase selectivity of individual inhibitors. There is possible concern for neurological side effects with chronic over-inhibition. Clinically tested inhibitors have shown good short-term safety thus far.

*Types of evidence:*

- 3 Phase 1 clinical trials for Silmitasertib (CX-4945) in cancer
- 4 clinical trials (2 Phase 2 and 2 Phase 3) for Lorecivivint in knee osteoarthritis
- 1 Phase 1 clinical trial for FRTX-02 in healthy volunteers
- Numerous laboratory studies

The safety profile for DYRK1A inhibitors will depend on their individual kinase selectivity profiles and their potency toward DYRK1A. It will also depend on the timing of administration for a given disease course, as well as the tissue distribution of the drug. All of the inhibitors developed at this point are relatively non-selective as they can inhibit multiple CMGC family members based on *in vitro* kinase assays [3]. However, studies suggest that *in vivo* these inhibitors may exert biologically meaningful effects on a narrower range of kinases and associated signaling pathways [4]. Furthermore, the effects may depend on the kinase profile of a given tissue, and the levels of activity of a given kinase relative to the IC<sub>50</sub> of the particular inhibitor. The good safety profiles of the non-selective DYRK1A inhibitors tested thus far may stem from incomplete inhibition of target kinases *in vivo*. Since each inhibitor has a different potency and selectivity profile, the safety profile cannot be generalized, and each will need to be tested independently.



The genetic dosage of DYRK1A plays a role as well, since individuals with Down syndrome have 1.5X higher levels throughout the body, whereas euploid individuals with other chronic conditions may have variable expression across tissues, with elevated levels in only a few tissues, and possibly a mix of elevated and reduced levels [39]. Because the localization and functions of DYRK1A are dosage dependent, the systemic inhibition of DYRK1A in individuals with a localized elevation could lead to a higher degree of side effects, through the over-inhibition of DYRK1A in unaffected tissues [2; 92]. At this point, most inhibitors have only been tested *in vitro* or in a few rodent preclinical models. The inhibitors were well-tolerated and had no overt effects on behavior in the rodent studies in disease models, but there is some evidence that DYRK1A inhibition in wildtype animals, at least at certain stages of development, could impact cognitive function [93]. The neurological phenotypes associated with reduced levels of DYRK1A including microcephaly, seizures, and autism-related behaviors stem from reduced DYRK1A throughout the lifespan. Altered DYRK1A dosage during the prenatal period of neural development appears to be the primary driver of these phenotypes, but it is not yet understood whether chronic over-inhibition of DYRK1A kinase activity during adulthood would produce clinically meaningful effects on neurological function [2].

There is a potential concern that due to their roles promoting insulin in the pancreas, DYRK1A and GSK3 inhibitors could impact liver glycogen content [55]. However, significant effects on liver glycogen were not seen in rodents following treatment with the dual DYRK1A/GSK3 inhibitor ZDWX-25.

Lorecivint (SM04690), a CLK/DYRK inhibitor with preferential activity toward CLK2 and DYRK1A, has been tested in clinical trials for knee osteoarthritis. Phase 2 studies used a paradigm of a single 2 ml intraarticular injection of lorecivint with doses up to 0.23 mg [83] [84]. In these studies, adverse events were generally balanced between the active and placebo arms, and there were no clinically significant changes to clinical laboratory results, or vital signs. The most common adverse event was arthralgia, defined as an exacerbation of an existing condition. There were no treatment-related serious adverse events. A similar safety profile was seen in Phase 3 studies using annual intraarticular injections of 0.07 mg lorecivint [85; 86].

FRTX-02 is a DYRK1 inhibitor which also shows activity towards CLKs. No adverse effects were identified in rodents treated with systemic (oral) or local (topical) treatment with FRTX-02 [88]. The doses used led to plasma levels that were ten times the IC<sub>50</sub>. A Phase 1 clinical trial is currently ongoing. The first phase tested single (10 to 600 mg) (n=56) and multiple (75, 150 and 300 mg) (n=33) ascending doses (MAD) for



14 days of once daily oral FRTX-02 in healthy volunteers ([Press release](#)). FRTX-02 was generally well-tolerated with no discontinuations due to adverse events. There was one case of moderate headache that was considered possibly drug related, otherwise treatment-emergent adverse events were mild. There were two cases of QT prolongation in the 300 mg MAD cohort that resolved upon drug cessation, but no other ECG or clinical laboratory abnormalities were seen in the other study cohorts.

[Silmitasertib \(CX-4945\)](#) is a casein kinase 2 inhibitor, which also shows activity towards DYRK1A, that is currently in clinical testing for various cancers [10]. Two Phase 1 studies involving a total of 43 cancer patients with solid tumors found that it was well tolerated, and had dose limiting toxicities of diarrhea and hypokalemia [78]. In a Phase 1/2 trial in patients with locally advanced/metastatic cholangiocarcinoma (n=144), the most common treatment-related adverse events attributed to silmitasertib were diarrhea (66%), nausea (51%), vomiting (33%), and fatigue (31%) [77]. Serious adverse events attributed to silmitasertib included anemia, thrombocytopenia, vomiting, neutropenia, febrile neutropenia, diarrhea, and nausea.

#### **Sources and dosing:**

Various non-selective ATP competitive DYRK1A inhibitors, such as harmine, INDY, 5-IT, leucettine L41, and GNF4877 are available from commercial suppliers for research purposes. The therapeutic doses for most DYRK1A inhibitors have not been established. CX-4945 is currently in Phase 1 and 2 clinical trials for cancer. Lorecivint has been tested in Phase 3 trials for knee osteoarthritis at a dose of 0.07 mg administered intraarticularly on an annual basis. FRTX-02 was found to be well-tolerated in a MAD study in healthy volunteers at an oral dose of 150 mg/day.

#### **Research underway:**

There are several companies working to develop DYRK1A inhibitors.

[Fresh Tracks Therapeutics](#) was formerly known as Brickell Biotech. They acquired the DYRK1A inhibitor VRN024219 from [Voronoi](#) ([Press release](#)) in 2021, which they renamed FRTX-02. This drug has shown efficacy in preclinical models of autoimmune disease, and is currently being tested in a Phase 1/2 study in healthy volunteers and patients with moderate to severe atopic dermatitis ([NCT05382819](#)).

[Biosplice Therapeutics](#), formerly known as Samumed LLC, is currently developing a series of DYRK1A inhibitors for different indications, including cancer, neurological diseases, such as AD, traumatic brain injury, and tauopathies, as well as osteoarthritis. They are developing DYRK1A inhibitors, CLK inhibitors, and dual DYRK/CLK inhibitors. Their most advanced program is for the pan-CLK/DYRK inhibitor Lorecivivint (SM04690), which has been tested in Phase 3 RCTs for osteoarthritis. Lorecivivint is currently being tested in a new Phase 3 trial for knee osteoarthritis ([NCT05603754](#)). Their [pipeline](#) for oral, BBB penetrant DYRK1A inhibitors for neurological conditions is currently listed as in preclinical development. The status of their former candidate, SM07883, which had undergone Phase 1 testing is unclear.

[Pharmasum Therapeutics](#) is a Norwegian company developing DYRK1A inhibitors. They have published data on PST-001, an orally bioavailable, BBB penetrant selective DYRK1A inhibitor tool compound. They are currently in preclinical development and according to their [pipeline](#) are developing the DYRK1A inhibitor PST-674 for dementia related to Down syndrome, AD, and PD.

[FeliciteX Therapeutics](#) is developing DYRK1 (1A and 1B) inhibitors for the treatment of cancer, as well as for autoimmune conditions, including type 1 diabetes. According to their [pipeline](#), they are currently in preclinical development, with some programs progressing into IND enabling studies.

[Perha Pharmaceuticals](#) is developing pharmaceuticals based on natural marine products, including the leucettines and more recently, the leucettinibs, which act as DYRK1A inhibitors. They aim to develop these for Down syndrome and AD. Their current preclinical lead is [leucettinib-21](#).

[Avanti Biosciences](#) is located in the Johnson & Johnson Innovation – JLABS incubator in San Diego. They are a preclinical stage company working on developing more potent and bioavailable DYRK1A inhibitors based off of EGCG for Down Syndrome and AD.

[Senhwa Biosciences](#) is developing small molecules for oncology. Their casein kinase 2 inhibitor, silmitasertib (CX-4945) was also shown to have inhibitory activity toward DYRK1A. It is in clinical development for cancer, but has also been tested in a clinical trial for Covid-19.

There are a multitude of primarily academic groups working to develop DYRK1A inhibitors, though most are still in the medicinal chemistry phase [[3](#); [7](#); [8](#); [94](#); [95](#); [96](#); [97](#); [98](#)]. Christopher Hulme, Travis Duncley, and Yeng-Jeng Shawat the University of Arizona hold a patent for a series of structurally

unique 6,5-heterocyclic DYRK1A inhibitors for use in AD, Down syndrome, glioblastoma, autoimmune diseases, inflammatory disorders, and other diseases [99].

#### Search terms:

Pubmed, Google: DYRK1A

- Alzheimer's disease, Down syndrome, cognition, aging, cancer, diabetes, cardiovascular, homocysteine, safety, inhibitors, clinical trials

Websites visited for DYRK1A Inhibitors:

- Clinicaltrials.gov ([Silmitasertib](#), [Lorecivivint](#), [FRTX-02](#))
- PubChem ([Leucettine L41](#), [Lorecivivint](#), [Silmatsertib](#))
- Drugbank.ca ([Lorecivivint](#), [Silmatsertib](#))

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