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## DYRK1A Inhibitors

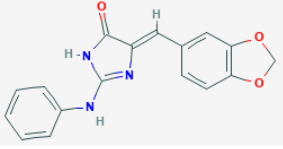
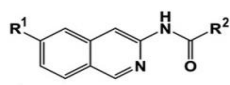
### Evidence Summary

May reduce Alzheimer's pathology and promote islet proliferation, but benefits could be counteracted by elevated homocysteine levels. May be most relevant for Down syndrome related Alzheimer's disease.

**Neuroprotective Benefit:** Inhibitors that can normalize DYRK1A levels in Down syndrome may improve synaptic plasticity and delay the onset of Alzheimer's disease pathology, including tau hyperphosphorylation.

**Aging and related health concerns:** DYRK1A inhibitors may promote pancreatic islet cell proliferation, but may raise circulating homocysteine levels.

**Safety:** Safety will likely vary with kinase selectivity of individual inhibitors. Possible concern for neurological side effects with chronic over-inhibition.

<b>Availability:</b> Research use or in clinical trials	<b>Dose:</b> Not established	<u>Leucettine L41</u>
<b>Half-life:</b> Varies SM07883 3.3 hours (in mice)	<b>BBB:</b> Varies SM07883 penetrant	<b>Chemical formula:</b> C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> <b>MW:</b> 307.3 g/mol
<b>Clinical trials:</b> SM07883 is being tested in Phase 1 study	<b>Observational studies:</b> DYRK1A protein levels are altered in AD	 <p>Source: <a href="#">PubChem</a></p> <p><u>SM07883</u></p>  <p>Source [1]</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 [2]. Because it is constitutively active, **its activity is dosage dependent**, and both higher and lower levels can lead to neurological deficits [3]. 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 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 [2].

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 also inhibit other CMGC family members, and thus lack selectivity. Many DYRK1A kinases identified were originally identified as inhibitors of a related CMGC family member [4]. 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 [3]. 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 [4]. 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 [5]. L41 is a synthetic analog of leucettamine B that has been optimized for DYRK1A inhibition. The leucettine analogs are being developed as therapeutics by ManRos Therapeutics.

SM07883 is an orally bioavailable (%F 92% in mice, 109% in monkey), BBB penetrant, DYRK1A inhibitor (IC<sub>50</sub> 1.6 nM) [1]. 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 is being developed by Samumed for Alzheimer's disease. It is currently being tested in a Phase 1 safety study in healthy volunteers.

**Neuroprotective Benefit:** Inhibitors that can normalize DYRK1A levels in Down syndrome may improve synaptic plasticity and delay the onset of Alzheimer's disease pathology, including tau hyperphosphorylation.

*Types of evidence:*

- 2 clinical trials for EGCG in Down syndrome (n=31, n=84)
- 5 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 [2]. 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) [3]. Many novel mutations in DYRK1A have also been associated with autism phenotypes [6; 7]. 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 [8]. 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 [9]. 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 [9; 10]. 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 [9].

The catechin epigallocatechin gallate (EGCG) has been identified as a DYRK1A inhibitor, although its *in vivo* potency within tissues has not been clearly established [9; 10]. 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 3 months with 9 mg/kg EGCG showed improvements in visual recognition memory and working memory, which were not sustained during the post-treatment period [11]. 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 [12].



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 [13]. In mice, DYRK1A overexpression decreases excitability and gamma oscillations in the prefrontal cortex [14], while haploinsufficiency leads to hyperexcitability and seizures [15].

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 [9]. 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 [16]. 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: MIXED (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 [8]. **DYRK1A has been shown to phosphorylate APP in a manner which promotes the production of pathogenic A $\beta$ , increase tau levels, and promote the phosphorylation of tau** both directly and indirectly [2]. DYRK1A phosphorylates tau on S396 and primes it for further phosphorylation by GSK3 $\beta$  [17].

In the T65Dn mouse model of Down syndrome, aged (13-14 month old) mice with a normalized DYK1A 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 [18]. 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.

The DYRK1A inhibitor, DYR219, reduced levels of insoluble p-tau (S396), 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) [19]. 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 [20]. Other DYRK1A inhibitors have similarly shown protective effects in lowering tau and amyloid related pathology, and mitigating neurological deficits. SM07883 reduced tau hyperphosphorylation and aggregation in JNPL3 mice with the FTD P301L tau mutation [1]. Leucettine L41 prevented A $\beta$  induced oxidative stress and synaptic deficits when co-injected in the intracerebroventricular A $\beta$  model [21], and improved synaptic plasticity and memory in the APP/PS1 model [22]. Although these preclinical studies suggest that DYRK1A inhibition is protective against AD, biomarker studies looking at DYRK1A levels in AD patients indicate that the dysregulation of DYRK1A is complex and varied across tissues.

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 [23]. 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 S-adenosylhomocysteine hydrolase (SAHH) [23]. The circulating homocysteine can then enter the brain, where it has been shown to exert neurotoxic effects through activation of the mitochondrial apoptotic pathway [24]. 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 [25]. Homocysteine can lead to the activation of the cysteine protease calpain-1 by increasing the level of intracellular calcium [24], and calpain-1 cleaves the PEST sequence from DYRK1A to generate a truncated form with altered kinase activity, localization, and selectivity [26]. 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 [27].

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** [28; 29]. One study found that a composite biomarker of plasma DYRK1A, homocysteine, and BDNF had receiver operating characteristic (ROC) 0.952 sensitivity, 0.889 specificity, and 0.933 accuracy for AD, with DYRK1A being the most predictive marker [29]. Consistent with the mouse studies, **plasma DYRK1A**



**levels were reduced** ( $77.70 \pm 13.80$  vs  $102.4 \pm 15.88$ ;  $p < 10^{-14}$ ) **while homocysteine levels were increased** ( $16.85 \pm 5.77$  vs  $12.14 \pm 3.00$ ;  $p < 10^{-6}$ ). 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 blood-derived peripheral blood mononuclear cell (PBMC) samples could be used to distinguish AD patients from controls [30]. 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 [31]. 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 [32]. 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** [26]. 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. Calpain activity is activated in response to inflammation and has been reported to be dysregulated in AD [33]. Studies in mice found that the **truncated form of DYRK1A may have increased tau phosphorylation activity** [26], and increased affinity for STAT3a in astrocytes, which drives pro-inflammatory signaling [22].

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; 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. **Since peripheral levels of DYRK1A appear to be reduced in AD (not associated with Down syndrome), systemically administered DYRK1A inhibitors may not have a net benefit if they promote homocysteine production.** Additionally, since DYRK1A has dosage dependent activity, over-inhibition could also potentially impair synaptic plasticity and cognitive function. A biomarker would be needed to determine which AD patients have elevated levels/activity of DYRK1A in the brain, and it is not clear whether that could be ascertained through the decrease in peripheral levels. 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 phenotypes [22], but it is not yet known if this is specific to L41 or a common feature of DYRK1A inhibitors.

*APOE4 interactions:* UNCLEAR

One study found plasma DYRK1A levels were lower in ApoE4 carriers [28], but another study found there was no significant difference between carriers and non-carriers [29].

**Aging and related health concerns:** DYRK1A inhibitors may promote pancreatic islet cell proliferation, but may raise circulating homocysteine levels.

*Types of evidence:*

- 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 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.

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 [34; 35; 36]. 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 [37]. 5-IT and GNF4877 were found to be 10-fold more potent at inducing human beta cell proliferation [38]. 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 [38], 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 glucagon-like peptide 1 receptor (GLP-1R) agonists [37]. The





combination had a synergistic effect mediated by cyclic AMP 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, adenovirus (AAV) mediated overexpression of DYRK1A can inhibit phenylephrine-induced cardiomyocyte hypertrophy through inhibition of NFAT [39], however, the protective effect was not seen in a mouse model (aortic banding) of cardiac hypertrophy with transgenic overexpression of DYRK1A [40]. Meanwhile, two studies in rats showed protective effects for DYRK1A inhibition. DYRK1A levels were increased 3-fold in rats with myocardial infarction, which was accompanied by a dysregulation in the alternative splicing of CaMKII $\delta$  [41]. 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 [42]. 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:** MIXED

Adults with Down syndrome have decreased incidence of solid tumor cancers; however, children are at increased risk for leukemias [43]. 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 [2].** 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.

#### **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 [44] and low rates of atherosclerosis [45]. The increased dosage of DYRK1A may underlie the protection against cardiovascular phenotypes in this population [23].

**Hepatic DYRK1A and plasma homocysteine levels have been found to be inversely correlated** in mice [23]. Meanwhile there is a positive correlation between DYRK1A protein levels and liver activity of cystathionine beta synthase (CBS), the primary enzyme involved in the metabolism of homocysteine [46]. Hepatic DYRK1A expression has also been positively correlated with hepatic SAHH activity, another enzyme involved in homocysteine metabolism [23]. AAV targeted hepatic expression of DYRK1A in hyperhomocysteinemic mice (CBS+/-) decreased plasma homocysteine levels, increased cystathionine beta synthase activity, and increased apoA1 levels [47]. These studies suggest that DYRK1A inhibitors could exacerbate homocysteine related cardiovascular disease.

**Safety:** Safety will likely vary with kinase selectivity of individual inhibitors. Possible concern for neurological side effects with chronic over-inhibition.

*Types of evidence:*

- 2 Phase 1 clinical trials for CX-4945 in cancer
- 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 [4]. However, studies suggest that *in vivo* these inhibitors may exert biologically meaningful effects on a narrower range of kinases and associated signaling pathways [5]. 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, 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 [31]. 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 [3; 48]. 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 [49]. 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 [3].

CX-4945 (silmiteasertib) is a casein kinase 2 inhibitor that is currently in clinical testing for various cancers [50]. It was subsequently found to also inhibit several CLK and DYRK family members with high potency, including DYRK1A, and was able to inhibit DYRK1A related tau phosphorylation in a Down syndrome mouse model [51]. 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 [52].

#### **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. CX-4945 is currently in Phase 1 and 2 clinical trials for cancer, and SM07883 is being tested in a Phase 1 clinical trial in healthy subjects. The therapeutic doses of DYRK1A inhibitors have not been established.

#### **Research underway:**

There are a multitude of primarily academic groups working to develop DYRK1A inhibitors, though most are still in the medicinal chemistry phase [4].

SM07883 is being tested in a Phase 1 open label, multicenter, dose-escalation SAD trial (5 to 180 mg) in healthy subjects (n=28) in Australia ([ACTRN12619000327189](https://www.anzctr.org.au/Trial/Registration/TrialRegistration.aspx?ACTRN12619000327189)). The primary endpoints are safety,

tolerability, and pharmacokinetics. Enrollment and data collection were completed in late 2019, but results have not yet been made available.

#### 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](https://clinicaltrials.gov) (CX-4945)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov) (Leucettine L41)

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