Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

CK2 Inhibitors

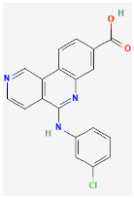
Evidence Summary

CK2 impacts a wide variety of cell signaling pathways. CK2 inhibitors are best suited for cancer, and show good safety for this indication. More selective inhibitors may be needed for other indications.

Neuroprotective Benefit: CK2 is implicated with the aggregation of pathological proteins in several neurodegenerative diseases, but due to the pleiotropic functions of CK2, the impact of inhibiting CK2 on cognition is not yet clear.

Aging and related health concerns: CK2 activity promotes cell growth and survival, and inhibitors may be beneficial for cancer as part of combination therapy. CK2 inhibitors may also show utility for some viral infections, including covid-19.

Safety: Clinically tested CK2 inhibitors have been well-tolerated. Allergic reactions were most common with a peptide inhibitor and gastrointestinal events were common with a non-selective small molecule inhibitor. The safety profile will be influenced by the selectivity profile.

Availability: In clinical trials and research use.	**Dose**: Therapeutic doses have not been established for CK2 inhibitors. CX-4945 is administered via oral capsules. CIGB-300 is administered intravenously.	**CX-4945** **Chemical formula:** $C_{19}H_{12}ClN_3O_2$ **MW**: 349.8 g/mol  Source: PubChem CIGB-300 (peptide) Sequence: H-Gly-DL-Arg-DL-Lys-DL-Lys-DL-Arg-DL-Arg-DL-Gln-DL-Arg-DL-Arg-DL-Arg-DL-Pro-DL-Pro-DL-Gln-bAla-DL-Cys(1)-DL-Trp-DL-Met-DL-Ser-DL-Pro-DL-Arg-DL-His-DL-Leu-Gly-DL-xiThr-DL-Cys(1)-OH Source: PubChem
Half-life: Varies. CX-4945: ~14 hours in Phase 1 trial CIGB-300: ~45 minutes in Phase 1 trial (i.v administration)	**BBB**: Varies. CX-4945 is penetrant.	
Clinical trials: CX-4945 has been tested in Phase 1 trials (n=43), 1b/2 (n=144) for cancer, as well as a pilot Phase 2 trial for covid-19 (n=31) CIGB-300 has been tested in Phase 1 trials for cancer (n=10; 12; 12; 14; 16; 18; 31), Phase 2 in cancer (n=30), and a pilot trial in covid-19 (n=20).	**Observational studies**: Elevated CK2 expression is a marker for worse prognosis in a variety of cancers. CK2 is elevated in the brains of Alzheimer's disease patients.	

What is it?

Protein kinase CK2, formerly known as casein kinase 2, is a constitutively active serine/threonine kinase. It has hundreds of substrates and highly pleiotropic functions [2]. CK2 plays a role in the regulation of most of the major pathways involved in cell growth and survival, and thus is considered a relevant target for cancer. CK2 forms a tetrameric holoenzyme consisting of two alpha and two beta subunits. The alpha units are the catalytic units, whereas the beta units have regulatory function. The alpha subunits can also have free standing catalytic activity outside of the holoenzyme. There are two types of alpha subunits, alpha (CK2α) and alpha prime (CK2α'), encoded by the genes CSNK2A1 and CSNK2A2, respectively. The CK2α and beta (CK2β) subunits are essential genes, such that loss of either one results in embryonic lethality. CK2α' has lower affinity for CK2β relative to CK2α, and is less dependent on heterodimerizing with CK2β to enter a catalytically active conformation [3]. The expression profile of CK2α' is far more limited than CK2α, and only shows high expression, at least in rodents, in the brain and

testes [4]. As a result, CK2α' plays a more limited role in CK2 regulated physiological processes. If found to be relevant in a particular pathological process, drugs specifically modulating CK2α' would be expected to have a superior safety profile relative to those targeting CK2α, CK2β, or the holoenzyme. The ATP binding site of CK2 is identical between the CK2α and CK2α' subunits, so allosteric modulators would likely be needed to achieve subunit specific inhibition [5].

Due to the high homology between the ATP binding pocket of CK2 with related kinases, small molecule inhibitors with high specificity and selectivity for CK2 have not yet been developed [6]. The majority of the CK2 inhibitors used in research studies show activity toward multiple kinases, and some of the more selective kinases have poor drug-like properties, which preclude their use in the clinical studies.
To date, the only small molecule CK2 inhibitor that has been clinically tested is CX-4945, also called silmitasertib. CX-4945 also shows inhibitor activity toward related CLK and DYRK family members and is discussed in the DYRK1A inhibitors report. It has been tested in clinical trials for oncology and covid-19, and is currently in clinical development by Senhwa Biosciences.
CIGB-300 is a synthetic peptide containing a CK2 substrate attached to the cell permeating TAT peptide derived from HIV. It was developed by the Cuban Center for Engineering and Biotechnology, who holds the patents on this molecule. It has been tested in clinical trials for oncology and covid-19.

Neuroprotective Benefit: Elevated CK2 is implicated with the aggregation of pathological proteins in several neurodegenerative diseases, but due to the pleiotropic functions of CK2, the impact of inhibiting CK2 on cognition is not yet clear.

Types of evidence:

- 4 studies showing an association between elevated CK2 in brain tissue with pathology in neurodegenerative diseases
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

CK2 inhibitors have not been clinically tested for cognitive indications. Due to the ubiquity of CK2 and its pleiotropic functions, inhibition of CK2 is not expected to be a viable prevention strategy in healthy individuals. It is currently unclear whether CK2 is elevated during prodromal stages of dementia, and whether inhibition of CK2 during this early period could halt symptomatic disease progression.

Protein levels of CK2 have shown to be elevated in brain regions containing pathology in several neurodegenerative diseases [7], and CK2 has been implicated in facilitating the aggregation of several of these pathologically misfolded proteins, including tau, alpha-synuclein, huntingtin, and TDP-43 [7; 8; 9; 10]. CK2 was found to be increased in the hippocampus of patients with Alzheimer's disease (AD) [7]. The elevation of CK2 was inversely associated with cognition, based on MMSE scores [7]. The increase in CK2 was also associated with altered synaptic localization of the NMDA receptor subunit NR2B and tau hyperphosphorylation. Notably, these associations were not seen in the context of other tauopathies, including corticobasal degeneration, progressive supranuclear palsy, and Pick's disease, suggesting that CK2 may play a more prominent role in mixed tauopathies (3R and 4R) relative to single isoform tauopathies. An increase in CK2, specifically the CK2α' subunit, has been associated with altered proteostasis machinery in the striatum of patients with Huntington's disease (HD) [9].

In contrast to HD, the relevance of the different CK2 subunits in AD and other dementias has not been well characterized. Most studies use CK2 antibodies directed toward the CK2α subunit or ones that recognize both the CK2α and α' subunits [7; 11]. Both CK2α and CK2α' are highly expressed in the brain. While the ratios differ across brain regions, CK2α is found to be at higher levels than CK2α' in all examined brain regions [12]. CK2α' expression is highest in the hippocampus and prefrontal cortex, such that the levels in these regions in relation to CK2α is around 1:4. This suggests that CK2α' may have particular relevance in regions such as the hippocampus, prefrontal cortex, and striatum, such that brain disorders involving these regions may preferentially benefit from a CK2α' modulator. However, even in these regions, CK2α is still the predominant driver of CK2-mediated activity in the brain. It is currently unclear whether there is a preferential upregulation of one of these subunits, or whether there is an imbalance in the levels or activity of the subunits in the context of AD. As such, the therapeutic utility of selectively targeting one of the subunits, relative to the currently available inhibitors which target multiple subunits, is unclear.

Human research to suggest benefits to patients with dementia:

CK2 inhibitors have not yet been clinically tested in dementia patients.

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

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)
The role of CK2 in AD is complex, as multiple AD-associated proteins have been identified as substrates, including MAPT, APP, PSEN2, and APOE [13].
Tau hyperphosphorylation: CK2 has been found to be elevated in the hippocampus in neurons and glial cells of AD patients and in rodent AD models, and associated with hyperphosphorylated tau [7; 11; 14]. The phosphorylation of Ser9 on SET, a PP2A inhibitor, by CK2 was found to promote tau hyperphosphorylation and disrupted synaptic plasticity, leading to cognitive impairments in AD models [14]. An increase in CK2-mediated Ser1480 phosphorylation on the glutamatergic NMDA receptor subunit NR2B, along with its altered localization, was seen in hippocampal tissue in AD patients, and may be a driver of altered synaptic plasticity and cognitive dysfunction [7]. Treatment with the CK2 inhibitor, TBB, normalized the synaptic to extrasynaptic balance of NR2B in hippocampal neurons.

Inflammation: CK2 is a regulator of signaling pathways involved in immune responses, and AD models suggest that elevated CK2 activity may serve as a driver of neuroinflammation. CK2 has been shown to be elevated in astrocytes in AD patients, which may promote a reactive pro-inflammatory phenotype [11]. The induction of inflammatory cytokines MCP-1 and IL-6 in human astrocytes in response to pro-inflammatory stimuli (TNFα and IL-1β) could be mitigated by treatment with the CK2 inhibitor CX-4945 [11]. Similarly, CX-4945, as well as the more selective CK2 inhibitor, SGC-CK2-1, blunted the LPS-induced production of the pro-inflammatory cytokines IL-1β and IL-6 in human induced pluripotent stem cell (iPSC)-derived microglial like cells with AD (PSEN1) mutations [15]. Additionally, PSEN1 was shown to promote pro-inflammatory NF-kB signaling by acting as a scaffold for the breakpoint cluster region (BCR)-CK2α-p65 complex, leading to the phosphorylation of p65 and triggering NF-kB activation [16].

Amyloid processing: Aβ42 has been shown to activate CK2 *in vitro*, suggesting that elevated levels of amyloid may promote the overactivation of CK2 and downstream effects on neuroinflammation and tau pathology [2]. Additionally, the induction of CK2 activity has been implicated in mediating synaptic transmission dysfunction downstream of oligomeric Aβ42 [17]. CK2 has been shown to induce the upregulation of BACE1, an enzyme involved in the amyloidogenic processing of APP, via activation of translation initiation factor eIF4B [18]. This pattern was observed in human AD brain tissue and multiple AD models. Treatment of organotypic brain slice cultures from APP/PS1 model mice with the CK2 inhibitor TBB led to a reduction in levels of phosphorylated eIF4B, as well as levels of Aβ42 and BACE1.

Proteostasis: CK2 plays a role in regulating the folding and cellular interactions of intrinsically disordered proteins [19]. The pattern of phosphorylation and dephosphorylation appears to have chaperone-like

function. Intrinsically disordered proteins are overrepresented in the aggregated misfolded proteins associated with neurogenerative disease, including tau, Aβ, alpha-synuclein, and TDP-43 [20], and CK2 is implicated in phosphorylation and/or aggregation of all of these disease-associated proteins. Elevated CK2 activity facilitates protein aggregate formation, which may be detrimental in the context of impaired autophagy, such as in AD [19]. Furthermore, CK2 impacts protein folding through the regulation of chaperone proteins, including Hsp90 [21]. As a result, chronically elevated CK2 activity, as has been seen in the brain tissue of AD patients, may promote the buildup of pathological misfolded proteins and negatively impact overall cellular protein homeostasis and signaling cascades.

Together, these studies suggest that inhibition of CK2 to physiological levels could impact a variety of disease-related processes. However, it is not yet clear whether the effects are preferentially driven by CK2α or the holoenzyme, as well as the relative contribution of CK2α'.

Huntington's disease: POTENTIAL BENEFIT (Preclinical)
Unlike other neurodegenerative conditions where the contribution of CK2α' relative to CK2α in driving pathology has not been clearly established, studies in HD suggest that elevated CK2α' is a prominent contributor to the aggregation and buildup of mutant huntingtin (mHtt) protein [9]. Heat shock transcription factor 1 (HSF1) is activated under stress conditions, is involved in proteostasis, and helps remove misfolded proteins. Loss of HSF1 promotes the accumulation of aggregated mHtt, leading to shortened lifespan in animal models of HD [9]. HSF1 levels have been shown to be decreased in HD patient striatal tissue, as well as in HD cell and animal models [9]. The reduction in HSF1 was associated with increased phosphorylation at Ser 303/307, which promotes its degradation. This phosphorylation event was shown to be catalyzed by CK2α', which is elevated in striatal tissue from HD patients and HD models. Heterozygosity at CK2α' prevented the decrease of HSF1 in the KIQ175 HD mouse model, and also led to a reduction in mHtt aggregations, partial preservation of medium spiny neurons, and preservation of body/muscle mass. The preservation of HSF1 levels increases the expression of chaperone proteins in the striatum of these mice. HSF1 is reciprocally regulated with p53 [22]. The stabilization of p53 by mHtt promotes the induction of CK2α', thereby facilitating the degradation of HSF1 [22]. Heterozygosity at CK2α' also reduced mHtt aggregation, Ser129 alpha-synuclein accumulation in the striatum, synaptic alterations, pro-inflammatory cytokine production, and fine motor deficits in the zQ175 HD mouse model [23; 24]. These studies suggest that a CK2α' selective inhibitor may be beneficial for HD, though the prospective benefits appear to be relatively minor and restricted to the early phases of disease.

Lewy body dementia: POTENTIAL BENEFIT (Preclinical)
Serine 129 phosphorylated alpha-synuclein is a key component of Lewy bodies. CK2 is one of several kinases that can phosphorylate alpha-synuclein at Ser129 [8], which is consistent with CK2's role in the phosphorylation and folding of intrinsically disordered proteins. However, the relationship between CK2 and alpha-synuclein aggregation appears to be complex. Alpha-synuclein deposits in the Lewy bodies in brain tissue from patients with Lewy body dementia (LBD) were found to be phosphorylated at Ser129 and tyrosine (Y) 136 [8]. Phosphorylation at Y136 prevents phosphorylation at S129 and alpha-synuclein aggregation *in vitro*. CK2 inhibition resulted in a reduction in S129 and an increase in Y136 phosphorylation, leading to the reduced aggregation of alpha-synuclein in cell culture. While further *in vivo* validation studies are needed, this suggests that CK2 inhibition may play a protective role in synucleinopathies.

Frontotemporal dementia: POTENTIAL BENEFIT (Preclinical/Theoretical)
In preclinical models, CK2 had been shown to be involved in several pathological features associated with Frontotemporal dementia (FTD). Elevated CK2 activity was found to be associated with altered synaptic localization of NR2B in AD patients and animal models [7]. Although CK2 inhibitors weren't tested directly, a similar disrupted localization of NR2B coupled with altered synaptic transmission was seen in the A152T (hTauAT) mouse model of FTD [25]. CK2 has also been implicated in promoting the conversion of TDP-43 from the soluble to the disease-associated filamentous form [10]. A mutation (p.Ser621Gly) in the gene CCNF, which encodes cyclin F, has been identified in a familial form of ALS/FTD, and is associated with defective protein degradation [26]. Cyclin F is part of an E3 ubiquitin-protein ligase complex. CK2 was identified as a regulator of Skp1-Cul-F-box (SCF) E3 ubiquitin-protein ligase via phosphorylation of cyclin F at Ser621. Phosphorylation at Ser621 results in a reduction in E3 ubiquitin ligase activity. The Ser621Gly mutation prevents phosphorylation by CK2, resulting in chronically elevated E3 ubiquitin ligase activity. These studies suggest that the proper balance of CK2 activity is necessary for proteostasis, and whether CK2 activity needs to be titrated up or down is context dependent.

Ischemic stroke: POTENTIAL BENEFIT (Preclinical)
The inhibition of CK2 has been shown to preserve white matter integrity in preclinical models of ischemic stroke [27]. The preservation of axon structure and function in the mouse optic nerve in response to pre or post treatment with the CK2 inhibitor, CX-4945, was associated with the preservation of axonal mitochondrial integrity [28]. The effect on mitochondria may stem from CK2α'. The natural small molecule echinacoside was found to target CK2α' as an allosteric modulator resulting in the

recruitment of basic transcription factor 3 (BTF3), induction Wnt/β-catenin signaling, and mitochondrial fusion via the via the transcription of mitofusin (Mfn2) [29]. Echinacoside treatment reduced neurological injury and preserved mitochondrial morphology in the rodent middle cerebral artery occlusion (MCAO) cerebral ischemic injury model.

Hemorrhagic stroke: POTENTIAL HARM (Preclinical)
In contrast to ischemic stroke, the downregulation of CK2 appears to promote neuron loss and neurological injury in the context of intracerebral hemorrhage. CK2 expression was found to be downregulated in brain tissue from patients with intracerebral hemorrhage (n=10), relative to controls (n=10) [30]. In a rat model, overexpression of CK2 protected against neuronal loss, reactive astrocyte-mediated neuroinflammation, edema, and neurobehavioral deficits.

APOE4 interactions: Human apoE has been shown to be phosphorylated by CK2 *in vitro* [31]. Additionally, apoE was found to stimulate the activation of CK2, which may, in turn, promote the hyperphosphorylation of tau [31]. Notably, the lipidated apoe3 was less effective at activating CK2. While the relationship between apoe4 and CK2 remains to be characterized, apoe4 is known to be hypolipidated [32], suggesting that it may be a more potent activator of CK2 relative to apoe3.

Aging and related health concerns: CK2 activity promotes cell growth and survival, and inhibitors may be beneficial for cancer as part of combination therapy. CK2 inhibitors may also show utility for some viral infections, including covid-19.

Types of evidence:

- 4 clinical trials for CX-4945 in cancer
- 8 clinical trials for CIGB-300 in cancer
- 1 clinical trial for CX-4945 in covid-19
- 1 clinical trial for CIGB-300 in covid-19
- Numerous laboratory studies

Lifespan: CK2 PLAYS A ROLE IN LIFESPAN REGULATION (Preclinical)
CK2 has been implicated in the regulation of lifespan and senescence in various preclinical model systems, however, the effects have not been consistent across studies, suggesting that CK2 has context-dependent effects on aging.

Yeast: One study found that deletion of cka2, which is the yeast equivalent of CK2α', nearly doubled the mean lifespan of yeast (strain BY4741) under starvation conditions [33]. However, while a separate study using this strain also found that deletion of CK2 increased chronological lifespan, the effect was mediated by cka1 (CK2α) rather than cka2 (CK2α') [34]. The phosphorylation of the histone H3pT11, a marker of nutritional stress and aging, by CK2 was found to regulate nutritional stress responses, and blocking this phosphorylation event increased chronological lifespan in the yeast [34].
C. elegans: Similar to the yeast studies, one study examining the differential phosphorylation in long-lived daf-2 (insulin-like growth factor 1 receptor) mutants found that CK2 limits lifespan in *C. elegans*, and that knockdown of kin-2 (CK2α) or kin-10 (CK2β), or treatment with a CK2 inhibitor, extended lifespan in the worms [35]. In contrast, a separate study found that CK2 was an upstream regulator of daf-16 (FoxO), which is an activator of pro-longevity genes, and that knockdown of kin-10 (CK2β) shortened lifespan in *C. elegans* [36]. However, the study also found that CK2 did not regulate the transcriptional activity of all daf-16 target genes in the same manner, and that the role of CK2 in this pathway may differ across species.
Mammalian cells: CK2 has been implicated as a regulator of cellular senescence in mammalian cell culture models. In human cancer cell lines (MCF-7 cells and HCT116 cells), the downregulation of CK2α in response to knockdown of the lncRNA KCNQ1O led to the induction of senescence markers (i.e. β-galactosidase, the p53-p21Cip1/WAF1, H3K9 trimethylation) and phenotypes (i.e. SASP) [37]. Ectopic expression of CK2α prevented the induction of these senescence markers. Additionally, calorie restriction also induced CK2α and suppressed replicative senescence [37; 38]. CK2α was found to activate SIRT1 and AMPK, leading to the induction of autophagy in these cancer cells [38]. Mice lacking CK2α' have normal lifespans, suggesting that CK2α' is not a major regulator of lifespan in mice/mammals [39].

Overall, these studies suggest that CK2 expression and activity is dynamically regulated under conditions of nutrient stress/calorie restriction. The relevance of the different catalytic subunits and the downstream impact on aging processes appears to be highly influenced by species and experimental conditions. As a result, it seems that the impact of CK2 inhibitor on aging phenotypes is likely to be complex. Further studies are needed to see if these effects can be replicated *in vivo* in higher order animals.

Cancer: POTENTIAL BENEFIT
CK2 acts upon numerous cell signaling pathways that control development, cell growth, and survival, and thus is essential for cell viability [2]. The loss of CK2α or CK2β subunits results in embryonic lethality,

however, CK2α' knockout mice are viable. Cancer cells appear to be more vulnerable to the loss of CK2 relative to healthy cells. A study in cell culture found as little as 10% of CK2α activity was sufficient to ensure the survival of normal myoblasts, whereas cancer cells appear to require at least 50% (i.e. one functional allele) CK2α activity [40]. As a result, tumor cells appear to be preferentially targeted by CK2 inhibitors. To date, only two CK2 inhibitors have been clinically tested in cancer patients.

CX-4945 (Silmitasertib) is a casein kinase 2 inhibitor in clinical development for cancer, however, it also shows inhibitory activity toward related kinases in the DYRK and CLK families. The clinical development for CX-4945 was detailed in the DYRK1A Inhibitors report (included below).
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) [41]. The median progression free survival rate for the combination with CX-4945 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, CX-4945 has been granted Orphan Drug Designation by the FDA for biliary tract cancer (Press release). In two Phase 1 trials testing CX-4945 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 [42]. CS-4945 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).

CIGB-300 is a synthetic cell-penetrating peptide containing a fusion of a CK2 substrate domain with residues 48 to 68 of the Trans-Activator of Transcription (Tat) protein of HIV [43]. It shows dose dependent inhibition of CK2 as well as anti-proliferation and pro-apoptotic effects in a variety of tumor cell lines. CIGB-300 has been clinically tested in Phase 1 and 2 trials in patients with cervical cancer [43]. The first in human trial tested CIGB-300 (intralesional injections of five consecutive doses ranging from 14 to 490 mg) in 31 women with high-grade squamous intraepithelial lesions [44]. A reduction in lesions based on colposcopy was seen in 90% of patients (28/31), with full histologic regression in 19% (6/31) of patients. CIGB-300 administered intratumorally was subsequently tested as a neoadjuvant to standard chemoradiotherapy at doses ranging from 35 to 490 mg in three clinical trials in patients with locally advanced cervical cancer (n=12; 14; 12, respectively) [43; 45; 46]. A saturation of tumor uptake appeared to occur at doses ranging from 35 to 70 mg. CIGB-300 was also tested in combination with

chemoradiotherapy in Phase 1 and Phase 2 trials (n= 18; 30, respectively) [43]. Tumor reductions were seen with PET/CT and MRI scans, and the best response rate of 75% for the combined therapy was achieved within six months, relative to a best response rate of 50% at 12 months for chemoradiotherapy alone [43]. CIGB-300 was tested in an i.v. formulation (1.6 mg/kg) in a Phase 1 trial patients with relapsed/refractory solid tumors (n=16) [47]. Lung cancer patients appeared to show preferential survival benefit in this study. Studies using different acute myeloid leukemia (AML) cell lines found a potent anti-proliferative and pro-apoptotic effect in response to CIGB-300 treatment [48]. Intravenous CIGB-300 was tested in a Phase 1 trial in patients with hematological malignancies (n=10) and found to be well-tolerated, but efficacy was not assessed in this pilot study [49]. The future clinical development plan of CIBG-300 for oncology is unclear.

Elevated CK2 has been implicated as a prognostic marker for a variety of cancers. Elevated CK2α is a common feature, but the relevance of CK2α' has been less studied, and appears to be more variable across tumor types. CSNK2A2, which encodes for CK2α' has been shown to be upregulated in an oncogenic manner in breast cancer and non-small cell lung cancer [50]. The expression of CSNK2A2 was also shown to be elevated hepatocellular carcinoma, with higher levels associated with tumor size, tumor stage, tumor differentiation, and lower survival [51]. The proliferative effect appears to be related to the induction of NF-kB signaling by CK2α'. The impact of inhibiting CK2α' on cancer cell growth and survival in preclinical studies has been shown to vary across cell lines. Elevated CK2α' was associated with increased proliferative potential in GL261 glioblastoma cells [52]. In both SK-N-BE neuroblastoma and U2OS osteosarcoma cell lines, CK2α was a larger contributor to the metabolic shift, and consequently played a larger role in the proliferation and survival of these cancer cells, relative to CK2α' [53].

Covid-19: POTENTIAL MINOR BENEFIT FOR TREATMENT

CK2 has been shown to phosphorylate a variety of viral proteins, and was found to play a role in SARS-Cov2 infection *in vitro*. CK2 phosphorylates ACE2, the receptor by which SARS-Cov2 gains cell entry. CK2 also regulates a variety of cell signaling pathways that can impact viral infection and replication [54]. Both CX-4945 and CIGB-300 were tested in pilot clinical trials in patients with covid-19. In both cases, the effects were modest. The trial testing CX-4945 was previously described in the DYRK1A Inhibitors report (see below).

CX-4945, which inhibits CK2 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 sCX-4945 treatment significantly shortened time to recovery relative to standard of care (median 6 days vs 14 days) (Press release). Senhwa Biosciences received a Taiwan FDA IND for a Phase 2 trial of CX-4945 in moderate to severe covid-19 (Press release).

CIGB-300, referred to in this study as CIGB-325, was tested in an exploratory clinical trial in patients hospitalized with covid-19 (n=20) [55]. Patients received CIGB-325 2.5 mg/kg/day i.v. with standard of care or standard of care alone for five consecutive days. There were no significant effects on time to viral clearance, but there was a reduction in pulmonary lesions based on chest-CT analysis from baseline (9.5 ± 10) to day seven (5.5 ± 10) (p = 0.042) with CIGB-325 treatment that was not seen in the control group. CIGB-325 treatment was also associated with significant reductions in the plasma levels of creatinine phosphokinase (CPK), and lactate dehydrogenase (LDH).

Safety: Clinically tested CK2 inhibitors have been well-tolerated. Allergic reactions were most common with a peptide inhibitor and gastrointestinal events were common with a non-selective small molecule inhibitor. The safety profile will be influenced by the selectivity profile.

Types of evidence:

- 9 clinical trials for CIGB-300
- 5 clinical trials for CX-4945
- Numerous laboratory studies

CK2 is an essential protein, such that the loss of the CK2α or CK2β subunits results in embryonic lethality in rodents [39]. In contrast, CK2α' knockout mice are viable, though males are infertile, due to a defect in sperm maturation (globozoospermia) [4]. As a result, the safety profile of a CK2 inhibitor will depend on its selectivity profile, in terms of CK2 subunits, as well as other related kinases. Due to the similarity of the ATP binding pocket of CK2 with those of related kinases, the competitive ATP binding pocket targeted CK2 inhibitors to date are not specific for CK2. There are efforts underway to develop allosteric CK2 modulators as well as develop subunit specific CK2 modulators via screens and computational modeling [6; 56] .

CK2α' is predominantly expressed in the testes and brain of rodents, and appears to play a more essential function in reproduction in terms of the regulation of sperm maturation relative to its impacts on the brain [4]. This may be related to the discrepancy in CK2α and CK2α' levels in the brain, whereby

CK2α levels were at least four times higher than CK2α' in all examined brain regions [12]. Mice lacking CK2α' have normal cardiac function and lifespans [4; 39].

Although CK2 impacts a substantial number of proteins and essential cellular signaling cascades, the safety profile of clinically tested CK2 inhibitors to date has been good. This may be related to the preferential susceptibility of cancer cells to CK2 inhibition, such that the degree of inhibition needed to have a clinically meaningful impact on tumor progression may be lower than the level that negatively impacts healthy cells [39; 40].

The safety profile of CX-4945 has been described in the DYRK1A inhibitors report (see below).
Two Phase 1 studies involving a total of 43 cancer patients with solid tumors found that CX-4945 was well tolerated, and had dose limiting toxicities of diarrhea and hypokalemia [42]. In a Phase 1/2 trial in patients with locally advanced/metastatic cholangiocarcinoma (n=144), the most common treatment-related adverse events attributed to CX-4945 were diarrhea (66%), nausea (51%), vomiting (33%), and fatigue (31%) [41]. Serious adverse events attributed to CX-4945 included anemia, thrombocytopenia, vomiting, neutropenia, febrile neutropenia, diarrhea, and nausea.

CIGB-300 has generally been well-tolerated in clinical trials, though it led to a transient allergic-like syndrome associated with elevated plasma histamine levels in a Phase 1 trial testing intratumoral doses of 35 and 70 mg in women with locally advanced cervical cancer [43]. This side effect could be prevented through the prophylactic use of antihistamine medication in subsequent trials in this population. The reduction of injection volume from 2 mL to 1 mL also helped reduce drug spillover into the vasculature. The most frequent local injection site reactions, including events were pain, bleeding, hematoma and erythema at the injection site [44]. Systemic adverse events included rash, facial edema, itching, hot flashes, and localized cramps. Mild allergic syndrome, itching, and flushing were the most common adverse events in patients with solid tumors receiving CIGB-300 via intravenous infusion, and long-term toxicity was not observed [47]. The allergic responses were likely related to the correlation between plasma CIGB-300 levels and plasma histamine levels. With intravenous administration in patients with hematological malignancies, the most common adverse events were localized itching and rash. In patients with covid-19 receiving 2.5 mg/kg CIGB-300 i.v. for five days, mild to moderate pruritus, flushing, and rash occurred in the majority of patients treated with CIGB-300 [55].

Drug interactions: Interactions have not been established, and will likely vary with each CK2 inhibitor depending on its selectivity profile and pharmacokinetics.

Sources and dosing:

CX-4945 (also called silmitasertib) is in clinical development for oncology and covid-19 by Senhwa Biosciences. It is a small molecule that is administered orally via gelatin capsules. A therapeutically beneficial dose has not yet been established. CIBG-300 (also called CIGB-325) is a peptide developed by the Cuban Center for Genetic Engineering and Biotech (CIGB). It has been administered intratumorally for solid tumors, and intravenously for hematological cancers and covid-19. A variety of other CK2 inhibitors, most of which have poor selectivity and/or poor pharmacological profiles, are available for research use from commercial suppliers.

Research underway:

According to Clinicaltrials.gov, there is currently a trial testing CX-4945 in patients with medulloblastoma (NCT03904862).

There are efforts underway to develop selective CK2 inhibitors [6; 56].

Search terms:

Pubmed, Google: CK2 Inhibitors, CK2α'

- Alzheimer's disease, neurodegeneration, proteostasis, lifespan, aging, cancer, clinical trial, safety

Websites visited for CK2 Inhibitors:

- Clinicaltrials.gov (CX-4945), (CIGB-300)
- PubChem (CX-4945), (CIGB-300)
- DrugBank.ca (CX-4945),

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