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CNB-001: A novel synthetic curcumin derivative with neuroprotective and anti-inflammatory properties

INVENTION: Investigators at the Salk Institute have designed, synthesized, and optimized a novel pyrazole derivative of curcumin. CNB-001 displays much improved potency and metabolic stability over curcumin. This compound is also neuroprotective in multiple neurotoxicity assays in which curcumin is inactive while retaining anti-oxidant and anti-inflammatory activity.

APPLICATIONS: Therapeutic indications include stroke, Alzheimer's disease, Parkinson's disease, traumatic brain injury, and lung inflammation (asthma).

ADVANTAGES:

- Potent inhibitor of 5-lipoxygenase (IC^{50} ~70 nM)
- More potent than Zileuton, which is FDA approved for the prophylaxis and chronic treatment of asthma
- Compound profile: MW:440; cLogP:4.67; tPSA: 74.52
- Well tolerated in animal models with no reported adverse effects
- Orally bioavailable
- No predicted toxicity in CeeTOX assay for membrane integrity, mitochondrial function, cell proliferation, apoptosis, oxidative stress, and solubility
- EC^{50}: Between 500-1000 nM in cell culture assay, and as low as 10 mg/kg in a rodent object recognition memory assay
- Crosses blood-brain barrier (by gavage) at high levels with a plasma half-life of over 2 hours

STAGE OF DEVELOPMENT: Optimized compound with extensive in vitro and in vivo data available in multiple disease models. Target analysis, binding data, and additional safety profile available upon request. Ready for partnering to take into non-human primate models and IND.

BACKGROUND: Numerous studies have reported the anti-oxidant, anti-inflammatory and anti-amyloid effects of curcumin. However, its poor stability has led researchers at Salk to design and develop curcuminoid derivatives with improved potency and pharmacokinetic properties, resulting in the lead compound CNB-001. CNB-001 has been extensively investigated in animal models of traumatic brain injury (TBI), Alzheimer's disease (AD), lung inflammation and stroke. CNB-001 was found to be effective in protecting neurons in the *in vitro* stroke models through maintenance of the PI3K-Akt kinase pathway and ATP levels, and the modulation of calcium-calmodulin-dependent protein kinase IIa. Additional work in models of AD have shown that CNB-001 normalizes several markers for synapse loss and oxidative stress in the hippocampus caused by AD. CNB-001 also clears intracellular amyloid and other aggregated proteins in the brain that accumulate with old age. Total AB and plaque loads are not significantly reduced in treated AD mice, but CNB-001 reduces the more toxic soluble AB1-42. Two studies showed that CNB-001 is very effective in treating rodent models of TBI. CNB-001 was also tested and shown to have therapeutic efficacy in a rodent model of airway inflammation and remodeling.

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