

# KTIN Therapeutics

## First-in-Class Osteocalcin Peptide Analogs for Cognitive Decline

\$2M Seed Round | Columbia University Spinout

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### THE PROBLEM

- **6+ million Americans** suffer from Mild Cognitive Impairment (MCI) with limited treatment options
- **\$300+ billion** annual healthcare costs from cognitive decline
- Current treatments (donepezil, Leqembi, Kisunla) offer **marginal efficacy** at **\$26-32K annually** with **serious side effects**
- **Critical intervention window:** MCI represents the transition phase before dementia when treatment may be most effective

### OUR SOLUTION: KTIN-200

- **Novel Mechanism:** First-in-class osteocalcin peptide analogs targeting the bone-brain endocrine axis
- **Endogenous peptide restoration** strategy vs. synthetic neurotransmitter manipulation
- **Oral bioavailability** with engineered analogs overcoming native hormone limitations
- **Natural safety profile** as endogenous peptide restoration

### Four-Pillar Neuroprotective Action (Single Peptide, Multiple Pathways):

- **Synaptic Plasticity:** Direct neuronal binding via Gprc6a, GPR158 (hippocampus, memory centers), and GPR37 receptors enhances LTP and memory formation
- **Adult Neurogenesis:** Stimulates hippocampal stem cell proliferation, differentiation, and survival through cAMP/PKA signaling
- **BDNF Signaling:** Upregulates BDNF expression via CREB activation, enhancing TrkB-mediated neuronal survival and synaptic maintenance
- **Metabolic Homeostasis:** Activates insulin signaling pathways, enhances glucose uptake in neurons, improves mitochondrial function - critical for MCI as "Type 3 Diabetes"

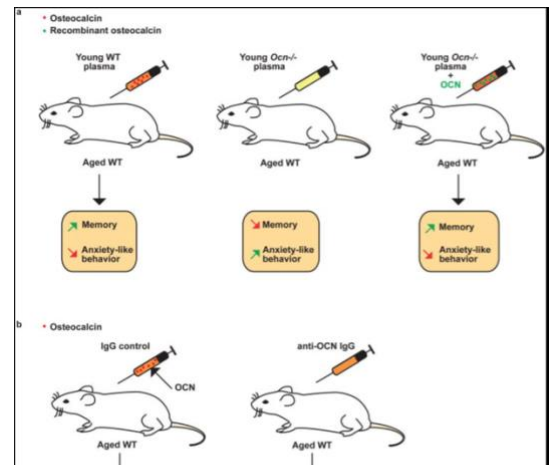


Figure 1. Osteocalcin is sufficient to improve cognition in aged mice (a) Injections of plasma from young wild-type (WT) mice to aged WT mice improve memory performance and prevent anxiety-like behavior. This does not occur when plasma from young Osteocalcin<sup>-/-</sup> (PMID: [29376523](https://pubmed.ncbi.nlm.nih.gov/29376523/))

*Unlike single-target competitors, OCN addresses root metabolic dysfunction driving cognitive decline*

### VALIDATED SCIENCE

20+ Years of Research | \$10M+ NIH Funding | 150+ Publications

Foundational Research (Dr. Gerard Karsenty, Columbia):

- OCN-deficient mice show significant memory deficits and reduced hippocampal neurogenesis
- OCN crosses blood-brain barrier and enhances cognitive function in aging mice

### Clinical Validation:

- Multiple human studies demonstrate **strong correlations** between OCN levels and cognitive performance
- Higher OCN levels associated with better memory, executive function, and processing speed

## MARKET OPPORTUNITY

- **MCI Market:** \$8B+ addressable with limited competition
- **Total Cognitive Decline Market:** \$40B+ including age-related impairment and Alzheimer's support
- **Growing market drivers:** Aging population, limited current efficacy, hormone replacement acceptance

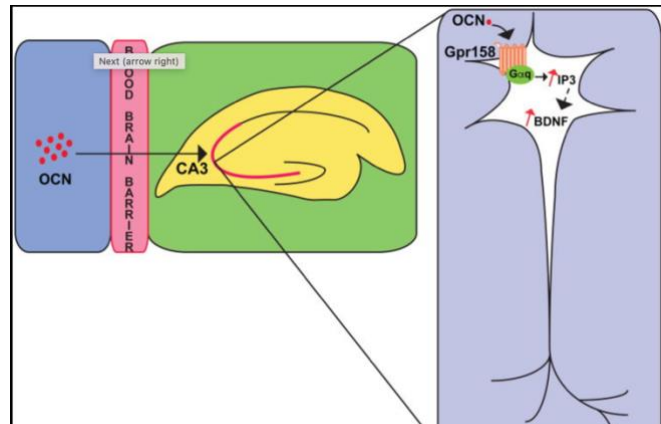


Figure 2. *Gpr158* mediates osteocalcin's functions in the brain. Osteocalcin binds *Gpr158* in pyramidal neurons of the CA3 region of the hippocampus. This interaction promotes an increase in the accumulation of IP3 and BDNF in neurons. (PMID: [28851741](#))

## DEVELOPMENT PLAN & FUNDING

**Phase 1: Preclinical Proof-of-Concept** (9 months, \$2M)

- Analog synthesis and characterization (6 candidates)
- Stability, CNS uptake, and functional activity validation
- Human organoid studies and in vivo efficacy testing
- **Key Milestone:**  $\geq 20\%$  cognitive improvement in aged mice

### Future Funding:

- **Series A** (\$8M): IND-enabling studies and regulatory preparation
- **Series B** (\$12M): Phase 1 clinical trials with proof-of-concept

**Clear Go/No-Go Gates** at months 4, 8, 9, and 21 with objective success criteria

## COMPETITIVE ADVANTAGES

- **First-in-class** mechanism targeting validated bone-brain axis
- **Patient stratification** via circulating OCN biomarkers
- **Oral formulation** vs. injectable competitors
- **20+ years** of target validation vs. novel mechanisms
- **Strong IP position** around engineered OCN analogs

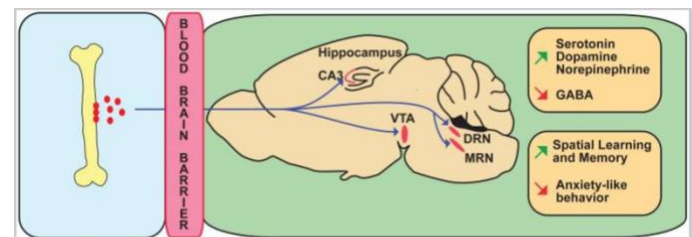


Figure 3. Osteocalcin promotes spatial learning and memory and prevent anxiety-like behavior. (PMID: [29376523](#))

## LEADERSHIP & STRATEGY

- **Martin Duenas, CEO:** Experienced biotech entrepreneur
- **Scientific Advisory:** Led by Dr. Gerard Karsenty (Columbia University)
- **Regulatory Strategy:** FDA engagement, Fast Track potential, biomarker-driven development
- **Commercial Strategy:** Specialty neurologists, premium pricing (\$25-50K), companion diagnostic

## EXIT OPPORTUNITIES

- **Target Acquirers:** Roche, Biogen, Eisai, J&J
- **Partnership Timeline:** Phase 2 development with cognitive-focused biotechs
- **ROI Potential:** 10x+ through partnerships and licensing deals

## EXPANSION PIPELINE

OCN's multi-system biology enables future applications in Alzheimer's disease, Parkinson's cognitive decline, and other neurodegenerative conditions - providing multiple value creation opportunities beyond core MCI program.

**Investment Ask:** \$2M seed funding to complete 9-month preclinical proof-of-concept program and achieve key value inflection points for Series A fundraising.

## Human Studies supporting Dr. Karsenty work in osteocalcin

Shan, C., Ghosh, A., Guo, Xz. *et al.* **Roles for osteocalcin in brain signaling: implications in cognition- and motor-related disorders.** *Mol Brain* **12**, 23 (2019). <https://doi.org/10.1186/s13041-019-0444-5>

**Summary:** This review explores the role of osteocalcin, a bone-derived hormone, in regulating brain function. It highlights its potential to influence cognitive abilities and suggests it may be a therapeutic target for neurodegenerative diseases.

Bradburn S, McPhee JS, Bagley L, Sipila S, Stenroth L, Narici MV, Pääsuke M, Gapeyeva H, Osborne G, Sassano L, Meskers CG, Maier AB, Hogrel JY, Barnouin Y, Butler-Browne G, Murgatroyd C. **Association between osteocalcin and cognitive performance in healthy older adults.** *Age Ageing.* 2016 Nov;45(6):844-849. [doi: 10.1093/ageing/afw137](https://doi.org/10.1093/ageing/afw137). Epub 2016 Aug 11. PMID: 27515675; PMCID: PMC5105824.

**Summary:** This study found a positive correlation between higher levels of osteocalcin in the blood and better cognitive performance in healthy older women. The results suggest that osteocalcin may have a protective effect on cognitive function during aging.

## TARGET APPLICATIONS FOR FUTURE DEVELOPMENT

Condition	Key Symptoms OCN May Address	Rationale for OCN Therapy	Development Priority
<b>Alzheimer's Disease</b>	Cognitive decline, behavioral symptoms, metabolic dysfunction	Neuroprotective + metabolic support; OCN levels decline in AD patients	<b>High</b> - Natural extension of MCI program
<b>Parkinson's Cognitive Decline</b>	Cognitive impairment, motor symptoms, depression	Neurotransmitter regulation + muscle function improvement	<b>High</b> - Dual cognitive-motor benefits
<b>Huntington's Disease</b>	Cognitive decline, motor dysfunction, metabolic abnormalities	Triple mechanism addresses cognitive, motor, and metabolic pathology	<b>Medium</b> - Orphan drug opportunity
<b>Multiple Sclerosis Cognitive Impairment</b>	Cognitive processing speed, memory issues, fatigue	Neuroprotection + metabolic support may slow cognitive decline	<b>Medium</b> - Growing recognition of cognitive MS
<b>ALS (Cognitive Symptoms)</b>	Frontotemporal cognitive decline, metabolic dysfunction	Metabolic support + neuroprotection in subset with cognitive involvement	<b>Low</b> - Limited cognitive component
<b>Frontotemporal Dementia</b>	Executive function decline, behavioral symptoms	OCN's GABA/glutamate regulation may address behavioral/cognitive symptoms	<b>Medium</b> - Distinct from amyloid-focused approaches