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(54) **Title:** KIBRA PEPTIDES AND USES THEREOF

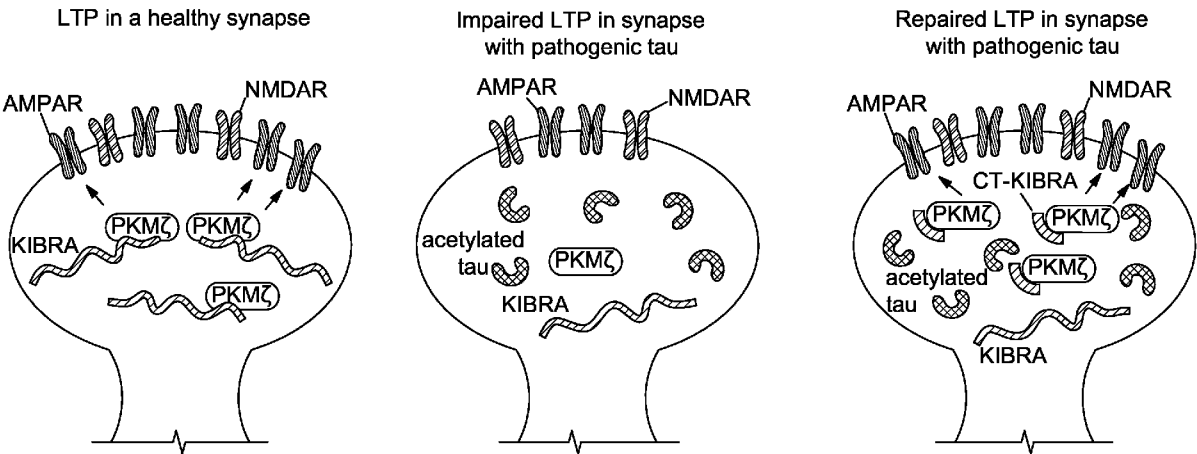


FIG. 5E

(57) **Abstract:** Provided herein are, *inter alia*, are C-terminal KIBRA peptides that are useful for treating tau-associated memory deficit disorders. Also provided are C-terminal KIBRA peptides that are useful for treating aging-associated cognitive decline.

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KIBRA PEPTIDES AND USES THEREOF

RELATED APPLICATION DATA

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Patent Application No. 63/486,441, filed on February 22, 2023, which is hereby incorporated by
5 reference in its entirety and for all purposes.

SEQUENCE LISTING

[0002] The material in the accompanying Sequence Listing is hereby incorporated by reference in its entirety. The accompanying file, named "048674-510001WO_SL_ST26.xml" was created on February 19, 2024 and is 29,172 bytes.

BACKGROUND

10 [0003] The dynamic function of synapses is critical for encoding memories in the brain. Pathogenic tau obstructs glutamatergic synapse function by blocking long-term potentiation (LTP), representing a key mechanism underlying memory impairment in tau-associated memory deficit disorders, for example Alzheimer's disease. However, there remains a lack of effective
15 clinical therapeutics to treat or prevent memory impairment in these disorders. The methods and compositions provided herein, *inter alia*, address these and other problems in the art.

BRIEF SUMMARY

[0004] In an aspect is provided a method of treating a tau-associated memory deficit disorder in a subject in need thereof, the method including administering to the subject a therapeutically
20 effective amount of a C-terminal KIBRA compound.

[0005] In another aspect is provided a method of treating aging-associated cognitive decline in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a C-terminal KIBRA compound.

25 [0006] In another aspect is provided a C-terminal KIBRA compound including the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5, wherein (a) at least one of the amino acids of the C-terminal KIBRA peptide is a non-natural amino acid analog; and/or (b) the C-terminal KIBRA compound further includes a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a

cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a glycine flexible linker, or a biotin amino acid sequence.

- [0007] In another aspect is provided a pharmaceutical composition comprising a
 5 therapeutically effective amount of a C-terminal KIBRA compound provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0008] FIGS. 1A-1F shows that CT-KIBRA reverses the impairment of activity-dependent postsynaptic AMPAR trafficking and LTP caused by pathogenic tau. FIG. 1A shows the design
 10 of full-length KIBRA and truncated KIBRA constructs fused to a flag tag. NT-KIBRA contained the first 86 residues and CT-KIBRA included the last 187 residues of KIBRA. FIG. 1B shows the quantification of the intensity of flag immunoreactivity in dendritic spines in neurons expressing full-length KIBRA, NT-KIBRA, or CT-KIBRA ($n = 12-14$ neurons/group; $*p < 0.05$, one-way ANOVA, Bonferroni post-hoc analyses). FIG. 1C shows the mean intensity of surface
 15 GluA1 immunofluorescence in spines was quantified for unstimulated and cLTP-induced neurons ($n = 13-17$ neurons/group; ns, not significant; $*p < 0.05$, unpaired Student's *t*-test). FIG. 1D shows TauKQ and ntg mice were injected with control empty vector lentivirus or CT-KIBRA lentivirus at 15-16 months old. Field recordings were performed in the dentate gyrus molecular layer of brain slices from mice at 17-18 months of age. The field excitatory postsynaptic
 20 potentials (fEPSP) slopes and the fiber volley (FV) amplitudes were measured in response to increasing stimulus intensities applied to the perforant pathway inputs. Representative traces and graphs of mean fEPSP slope and FV amplitude were generated from field recordings of slices from each group ($n = 12-14$ slices from four mice/group). TauKQ^{high} mouse brain slices exhibited significantly increased mean FV amplitude in dentate gyrus at the highest stimulus
 25 intensities (20 μ A stimulus: ntg lenti-control vs. taukQ^{high} lenti-control $*p < 0.05$, ntg lenti-control vs. taukQ^{high} lenti-CT-KIBRA $**p < 0.01$; 25 μ A stimulus: ntg lenti-control vs. taukQ^{high} lenti-control $**p < 0.01$, ntg lenti-control vs. taukQ^{high} lenti-CT-KIBRA $***p < 0.001$, repeated measures two-way ANOVA, Bonferroni *post-hoc* analyses). Scale bars, 0.5 mV and 5 ms. FIG. 1E shows representative traces of fEPSPs recorded in the dentate gyrus before and after TBS of
 30 the perforant pathway to induce LTP in dentate granule cells. Quantification of the fEPSP slopes 20 min before and 60 min after TBS was normalized to the average fEPSP slope during the first

20 min of the baseline recording for each slice ($n = 13-21$ slices from five to seven mice/group). Scale bars, 0.4 mV and 10 ms. FIG. 1F is a graph of the mean fEPSP slopes at 55-60 min after TBS induction representing the magnitude of LTP ($n = 13-21$ slices from five to seven mice/group; $*p < 0.05$, $**p < 0.01$, one-way ANOVA, Bonferroni *post-hoc* analyses). Values are given as means $\pm$ SEM.

[0009] FIGS. 2A-2L shows that CT-KIBRA expression in hippocampus reverses memory impairment in tauKQ^{high} mice despite pathological tau accumulation and CA1 synapse loss. FIGS. 2A-2B show data from the object-context discrimination test used to assess hippocampus-dependent pattern separation memory in mice ($n = 10-12$ mice/group). FIG. 2A shows that during the sample phase, the mean proportion of time that the mice spent exploring two identical objects in each context was calculated. Each mouse explored the identical X1 and X2 objects in Context 1, and the identical Y1 and Y2 objects in Context 2 which were distinct from the objects in Context 1. FIG. 2B shows the mean percent time spent exploring the incongruent and congruent objects in both contexts for each group was analyzed during the test phase of the object-context discrimination test ($*p < 0.05$, paired Student's *t*-test). FIG. 2C shows hippocampus-dependent spatial working memory was monitored from ntg and tauKQ^{high} mice in the Y-maze test ($n = 11-13$ mice/group). Graph of the mean percentage of spontaneous alternations completed by the mice in the Y-maze within 5 min (left, $*p < 0.05$, one-way ANOVA, Bonferroni *post-hoc* analyses). The average number of total Y-maze arm entries made by the mice (right) was equivalent across each group. FIGS. 2D-2G show data from mice tested for spatial learning and memory in the Morris water maze ($n = 11-13$ mice/group). FIG. 2D shows the mean distance travelled to the hidden platform and the average swim velocity were measured during hidden platform training ($p > 0.05$, repeated measures two-way ANOVA). FIG. 2E shows representative swim paths of mice during the probe trials for spatial memory testing performed at 24 h and 7 days after hidden platform training. Graph of the mean percent time spent in the target quadrant compared to the average time spent in the other quadrants in the 24 hr (FIG. 2F) and 7 day (FIG. 2G) probe trials ($**p < 0.01$ and $***p < 0.001$, paired Student's *t*-test). Values are given as means $\pm$ SEM. FIG. 2H shows an illustration of a mouse hippocampus depicting where the imaging of mossy fibers in CA3 (h) and the imaging of synapses in CA1 (l) was performed. FIG. 2I shows a graph of the mean integrated intensity of AT8 immunofluorescence in the CA3 mossy fibers ($n = 10-13$ mice/group, $***p < 0.001$, one-way ANOVA, Bonferroni *post-hoc* analyses). FIG. 2J shows representative immunoblots of

phosphorylated tau (AT180 and AT270 antibodies), human tau (HT7 antibody), and total tau (Tau5 antibody) from hippocampal homogenates of ntg lenti-control, tauKQhigh lenti-control and tauKQhigh lenti-CT-KIBRA mice. FIG. 2K shows the quantification of phosphorylated tau and total tau in hippocampal homogenates normalized to GAPDH (n = 10-13 mice/group, p > 0.05, unpaired Student's t-test). FIG. 2L shows the quantification of the mean integrated intensity of SV2 immunofluorescence in the stratum radiatum of CA1 (n = 10-13 mice/group; * p < 0.01, one-way ANOVA, Bonferonni post-hoc analyses). Values are given as means ± SEM.

[0010] FIG. 3A-3E shows that CT-KIBRA interacts with and stabilizes PKMζ at synapses in neurons with pathogenic tau. FIG. 3A shows a graph of mean PLA intensity quantification from HEK293 cells co-expressing HA-PKMζ with flag-tagged KIBRA variants normalized to PLA intensity of cells with full-length KIBRA expression (n = 15-20 cells/group; *** p < 0.001, one-way ANOVA, Bonferonni post-hoc analyses). FIGS. 3B-3D shows that HA-PKMζ and CT-KIBRA-flag expression constructs were transfected into HEK293 cells. One day later, the cells were treated with cycloheximide (CHX) to inhibit translation for 24 or 48 h. FIG. 3B shows immunoblots of HA-PKMζ, CT-KIBRA-flag and GAPDH from HEK cells treated with CHX to monitor PKMζ degradation. FIG. 3C shows the quantification of PKMζ immunoblotting results normalized to GAPDH at time 0 before CHX treatment (n = 4 replicates/group; ***p < 0.001, unpaired Student's t-test). FIG. 3D shows a graph showing HA-PKMζ stability in HEK293 cells with or without CT-KIBRA-flag co-expression. HA-PKMζ immunoreactivity at 0, 24h and 48h time points during the CHX treatment was normalized to the basal levels at time 0 before CHX application (n = 4 replicates/group; ***p < 0.001, two-way ANOVA, Bonferonni post-hoc analyses). FIG. 3E shows a graph of mean PKMζ integrated intensity quantified in postsynaptic spines normalized to control neurons without tauKQ expression (n = 17 cells/group; * p < 0.05, *** p < 0.001, one-way ANOVA, Bonferonni post-hoc analyses). Values are given as means ± SEM.

[0011] FIGS. 4A-4F shows that CT-KIBRA-induced resilience to tau-mediated synaptic and memory deficits is associated with higher PKMζ levels. FIG. 4A shows the quantification of PKMζ immunoreactivity in postsynaptic spines with or without cLTP induction normalized to postsynaptic PKMζ levels in control unstimulated neurons (n = 12-15 cells/group; ns, not significant; * p < 0.05, unpaired Student's t-test). FIG. 4B shows representative immunoblots of PKMζ, PSD-95, and GAPDH from hippocampal homogenates of three individual ntg lenti-

control, tauK^Qhigh lenti-control and tauK^Qhigh lenti-CT-KIBRA mice. FIG. 4C shows the quantification of total PKM ζ levels in hippocampal homogenates normalized to GAPDH and to PSD-95 levels (n = 10-13 mice/group; * p < 0.05, ** p < 0.01, one-way ANOVA, Bonferonni post-hoc analyses). Values are given as means $\pm$ SEM. FIG. 4D shows Pearson correlation analyses between PKM ζ levels analyzed from hippocampal homogenates and the percent time each mouse spent exploring the incongruent object in the object-context congruency test of pattern separation memory (n = 10-12 mice/group). FIG. 4E shows Pearson correlation analyses of the proportion of time each mouse spent in the target quadrant of the MWM during the 7 day probe test and the corresponding PKM ζ levels in hippocampus relative to PSD-95 (n = 10-13 mice/group). FIG. 4F shows Pearson correlation analyses showed no significant relationship between the percent of spontaneous alternations made in the Y-maze test and total PKM ζ levels in hippocampus (n = 11-13 mice/group).

[0012] FIGS. 5A-5E shows that CT-KIBRA restores AMPAR trafficking during LTP by interacting with PKM ζ in neurons with pathogenic tau. FIG. 5A shows a graph of the mean surface GluA1 immunofluorescence quantification in spines normalized to unstimulated neurons treated with the scrambled oligodeoxynucleotide (n = 13-18 neurons/group; * p < 0.05, unpaired Student's t-test). FIG. 5B shows a graph of the mean surface GluA1 immunofluorescence quantification in spines normalized to unstimulated control neurons (n = 14-19 neurons/group; * p < 0.05, unpaired Student's t-test). FIG. 5C shows the quantification of the mean PLA fluorescence intensity detected in HEK293 cells transfected with HA-PKM ζ alone, as a control, or co-transfected with flag-CT-KIBRA constructs (n = 27-30 cells/group; *** p < 0.001, one-way ANOVA, Bonferonni post-hoc analyses). FIG. 5D shows a graph of the quantification of surface GluA1 immunofluorescence in spines of tauK^Q-expressing neurons showing that cLTP-induced postsynaptic receptor insertion is re-established by CT-KIBRA, but not CT-KIBRA-AAA. GluA1 levels were normalized to the intensity of staining in spines of unstimulated tauK^Q neurons (n = 14 neurons/group; * p < 0.05, unpaired Student's t-test). Values are given as means $\pm$ SEM. FIG. 5E shows a model depicting the impact of KIBRA and PKM ζ on postsynaptic AMPAR trafficking LTP in healthy conditions (left) and in tauopathy (middle). Expression of CT-KIBRA in tauopathy neurons (right) with high pathogenic acetylated tau levels can restore postsynaptic AMPAR recruitment during plasticity, which mechanistically involves the interaction between CT-KIBRA and PKM ζ .

[0013] FIGS. 6A-6K shows that reduced KIBRA levels in human brain and increased KIBRA levels in human CSF correlate with pathological tau levels and cognitive impairment in tauopathy. FIG. 6A shows Immunoblot analyses of soluble homogenates from the middle temporal gyrus region of human brain from control, Alzheimer's disease and Pick's disease cases. Of the 20 cases analyzed, 12 were assigned a Clinical Dementia Rating (CDR) sum of boxes score based on cognitive function that are labeled above each lane. FIG. 6B shows the relationship between KIBRA and PKM ζ levels quantified in human brain homogenates from control, Alzheimer's disease (AD), and Pick's disease cases using Spearman correlation analyses (n = 6-7 cases/group). FIG. 6C shows Higher levels of soluble tau protein acetylated on lysine-274, recognized by the Mab359 antibody, in human brain is significantly correlated with lower KIBRA and PKM ζ levels (n = 6-7 cases/group; Spearman correlation). FIGS. 6D-6E show graphs of quantified (FIG. 6D) KIBRA and (FIG. 6E) PKM ζ levels in brain homogenate from the 12 cases that were assigned CDR scores (8 of the 20 brain samples used for this study were not assigned CDR scores). Cases with a CDR global score of 0-1, with no to mild dementia, were compared to CDR 2-3 cases, with moderate dementia (n = 4-8 cases/group; ns, not significant; * p < 0.05, unpaired Student's t-test). Values are given as means $\pm$ SEM. FIGS. 6F-6G show analyses of the relationship between CDR sum of boxes score of control, AD, and Pick's disease cases and the levels of (FIG. 6F) KIBRA or (FIG. 6G) PKM ζ in brain homogenate from 12 of the cases that were assigned CDR scores (n = 3-5 cases/group; Spearman correlation). FIGS. 6H-6J show Spearman correlation analyses show the relationship between KIBRA levels and (FIG. 6H) p-tau181, (FIG. 6I) total tau, and (FIG. 6J) the A β 42/A β 40 ratio detected in individual CSF samples (n = 25 subjects for total tau analyses; n = 24 subjects for p-tau181 and A β 42/A β 40 ratio analyses). FIG. 6K shows higher KIBRA levels in CSF are associated with worse cognition evaluated by Mini-mental State Exam (MMSE) score (n = 21 subjects, Spearman correlation).

[0014] FIG. 7 shows that CT-KIBRA rescues AMPAR trafficking during LTP in neurons expressing human tau with the P301L mutation that causes FTD related to FIG. 1. FIG. 7 shows the quantification of surface GluA1-containing AMPARs in spines revealed that tauP301L expression in neurons inhibited chemical LTP (cLTP)-induced postsynaptic AMPAR insertion, which was restored by the co-expression of CT-KIBRA (n = 12 neurons/group; * p < 0.05, ** p < 0.01, unpaired student's t-test). Values are given as means $\pm$ SEM.

[0015] FIGS. 8A-8D show a proteomics analysis of hippocampal lysates from tauKQ^{high} mice with or without CT-KIBRA expression related to FIG. 2. FIG. 8A shows a Venn diagram depicting the number of proteins identified that were either upregulated or downregulated in tauKQ^{high} lenti-control or tauKQ^{high} lenti-CT-KIBRA compared to non-transgenic (ntg) control mice (n = 4 mice/group). See also Table 1. FIGS. 8B-8C show Gene Set Enrichment Analysis (GSEA) on the proteins identified that were downregulated in tauKQ^{high} lenti-control mice (FIG. 8B) and tauKQ^{high} lenti-CT-KIBRA mice (FIG. 8C) compared to controls. FIG. 8D show ClueGO cellular component enrichment of proteins that were upregulated in hippocampus of tauKQ^{high} mice with or without CT-KIBRA expression compared to ntg lenti-control mice. Node colors denote grouped networks (p < 0.0005).

[0016] FIG. 9 shows that PICK1 interacts more with full-length KIBRA than the truncated KIBRA variants related to FIG. 3. FIG. 9 shows a graph of mean PLA intensity quantification in HEK293 cells normalized to PLAsignal in cells with full-length KIBRA (n = 22-28 cells/group; *** p < 0.001, one-way ANOVA, Bonferonni post-hoc analyses). Values are given as means ± SEM.

[0017] FIGS. 10A-10D show that PKM ζ and PICK1 levels in hippocampus of tauKQ^{high} mice related to FIG. 4. FIG. 10A shows immunoblots of PKM ζ , PSD-95 and GAPDH from hippocampal lysates of three non-transgenic (ntg) and three tauKQ^{high} mice that did not receive training in behavioral tests of hippocampal-dependent learning and memory. FIG. 10B shows graphs of PKM ζ levels relative to GAPDH and PSD-95 in mice that did not have training in behavioral tests (n = 13 mice/group; * p < 0.05, *** p < 0.001, unpaired student's t-test). FIG. 10C shows immunoblots of PICK1 and GAPDH from hippocampal lysates of three mice from ntg lenti-control, tauKQ^{high} lenti-control, and tauKQ^{high} lenti-CT-KIBRA groups that underwent training in learning and memory tests. FIG. 10D shows graphs of PICK1 levels in hippocampal lysates relative to GAPDH and PSD-95 (n = 10-13 mice/group; ns, not significant, one-way ANOVA, Bonferonni post-hoc analyses). Values are given as means ± SEM.

[0018] FIGS. 11A-11B show that expression of HA-PKM ζ and CT-KIBRA constructs in cultured hippocampal neurons related to FIG. 5. FIG. 11A shows the quantification of the mean intensity of HA-tagged PKM ζ immunolabeling in spines normalized to neurons without tauKQ co-expression (n = 13-14 neurons/group). FIG. 11B shows the quantification of the mean

intensity of flag immunofluorescence detected in spines of neurons with CT-KIBRA-AAA compared to CT-KIBRA (n = 14-16 cells/group). Values are given as means $\pm$ SEM.

[0019] FIGS. 12A-12D show that human KIBRA detection by ELISA and CSF KIBRA relative to phosphorylated tau and A β related to FIG. 6. FIG. 12A shows ELISA-based detection of KIBRA levels from lysates of HEK293 cells transfected with a human KIBRA construct (red) and untransfected control HEK293 cells (black). HEK293 cells with KIBRA overexpression had significantly higher KIBRA levels detected by ELISA at the different concentrations of total protein tested (n = 2 cultures/group; ** p < 0.01, *** p < 0.001, two-way ANOVA, Bonferonni post-hoc analyses). Values are given as means $\pm$ SEM. FIG. 12B shows the quantification of the concentration of KIBRA protein detected in cerebrospinal fluid (CSF) of human subjects that had either normal (< 61 pg/mL) or high (> 61 pg/mL) levels of phosphorylated tau (p-tau181) in CSF associated with Alzheimer's disease. Values are given as means $\pm$ SEM. FIGS. 12C-12D show Pearson correlation analyses show the relationship between levels of KIBRA with concentrations of A β 42 (FIG. 12C) and A β 42 (FIG. 12D) in CSF (n = 24 subjects).

[0020] FIGS. 13A-13F show that development of a cell-permeable TAT-tagged KIBRA peptide derived from CT-KIBRA to restore synaptic plasticity and memory in AD and tauopathy-related dementia. FIG. 13A shows the amino acid sequence of the peptide being tested. This peptide is biotinylated and includes a TAT sequence to enable cell membrane permeability together with the sequence from within CT-KIBRA that is important for PKM ζ binding. FIG. 13B shows the mean intensity of the biotinylated peptide labeling in HEK293 cells was analyzed at the different concentrations of the peptide that were added to the cells. FIG. 13C shows the quantification of the TAT-KIBRA peptide labeling in dendritic spines of cultured rat neurons. FIG. 13D shows immunoblots of lysates from rat neuron culture treated with the TAT-KIBRA peptide to assess whether interacting proteins are pulled down with the TAT-KIBRA peptide. These results confirm that the TAT-KIBRA peptide binds to the KIBRA-interacting proteins, PKM ζ and PKC γ , in rat neurons. FIG. 13E shows the quantification of immunoblot for PKM ζ from (FIG. 13D) showing the dose-dependent binding of the TAT-KIBRA peptide to PKM ζ . FIG. 13F shows the quantification of GluA1-containing AMPA-type glutamate receptors (AMPA-Rs) in postsynaptic spines of rat hippocampal cultured neurons with or without chemical LTP treatment. Consistent with LTP expression, control neurons have increased postsynaptic AMPAR delivery into spines with chemical LTP induction compared to unstimulated control

neurons. The LTP expression is blocked in neurons with expression of a human tauKQ mutant that mimics pathogenic acetylated tau found in Alzheimer's disease. The TAT-KIBRA peptide treatment rescues the postsynaptic AMPAR delivery during LTP in neurons expressing pathogenic tau, but the TAT-KIBRA peptide has no effect on activity-induced AMPAR trafficking in control neurons.

[0021] FIGS. 14A-14F show that TAT-KIBRA peptide improves memory and restores hippocampal synaptic plasticity in transgenic mice with pathogenic tau that causes Alzheimer's disease-related memory impairment. FIG. 14A shows data from an experiment in which non-transgenic (ntg) and tauKQ^{high} mice were treated with either a vehicle control or the TAT-KIBRA peptide from an implanted osmotic pump with intracerebroventricular administration. The treated mice were tested in the object-context discrimination test of pattern separation. The ntg control mice and the tauKQ^{high} TAT-KIBRA peptide-treated mice spent more time exploring the incongruent object compared to the congruent object while the tauKQ^{high} control mice did not, suggesting that the TAT-KIBRA peptide restored pattern separation memory in the tauKQ^{high} mice. FIGS. 14B-14D show results from an experiment in which the ntg and tauKQ^{high} mice treated with vehicle control and tauKQ^{high} mice treated with TAT-KIBRA peptide were tested in the Morris water maze of spatial learning and memory. FIG 14B: During hidden platform training, the distance the mice travelled to the hidden platform decreased within five days of training, indicating spatial learning in all the mice. The mice were subjected to 24-hour and 120-hour probe trials to test spatial memory. FIG. 14C: Representative swim paths of individual mice from each group within the maze during probe trials is plotted. FIG. 14D: Quantification of the percent time spent in the target quadrant compared to the average of time in the other quadrants revealed that in the 120-hour probe test the impairment in long-term spatial memory in tauKQ^{high} mice was rescued in those with TAT-KIBRA peptide treatment. FIGS. 14E-14F show data from field recordings performed in the dentate gyrus of mouse brain slices that were acutely treated with either a TAT-scrambled control peptide or the TAT-KIBRA peptide. FIG. 14E: The field excitatory postsynaptic potentials (fEPSP) were recorded in the dentate gyrus molecular layer in response to stimulation of the perforant pathway at increasing stimulus intensities. FIG. 14F: Long-term potentiation (LTP) expression in tauKQ^{high} mouse brain slices treated with the scrambled peptide was impaired, but the magnitude of LTP expression in tauKQ^{high} mouse brain slices treated with TAT-KIBRA peptide was comparable to ntg mouse brain slices.

DETAILED DESCRIPTION

DEFINITIONS

[0022] While various embodiments and aspects of the present invention are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0023] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0024] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0025] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, e.g., Singleton et al., *DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY* 2nd ed., J. Wiley & Sons (New York, NY 1994); Sambrook et al., *MOLECULAR CLONING, A LABORATORY MANUAL*, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989). Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0026] "Nucleic acid" refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides) and polymers thereof in either single-, double- or multiple-stranded form, or complements thereof; or nucleosides (e.g., deoxyribonucleosides or ribonucleosides). In embodiments, "nucleic acid" does not include nucleosides. The terms "polynucleotide," "oligonucleotide," "oligo" or the like refer, in the usual and customary sense, to a linear sequence of nucleotides. The term "nucleoside" refers, in the usual and customary sense, to a glycosylamine including a nucleobase and a five-carbon sugar (ribose or deoxyribose). Non limiting examples, of nucleosides include,

cytidine, uridine, adenosine, guanosine, thymidine and inosine. The term “nucleotide” refers, in the usual and customary sense, to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA, and hybrid molecules having mixtures of single and double stranded DNA and RNA. Examples of nucleic acid, e.g. polynucleotides contemplated herein include any types of RNA, e.g. mRNA, siRNA, miRNA, and guide RNA and any types of DNA, genomic DNA, plasmid DNA, and minicircle DNA, and any fragments thereof. The term “duplex” in the context of polynucleotides refers, in the usual and customary sense, to double strandedness. Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, e.g., such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0027] Nucleic acids, including e.g., nucleic acids with a phosphothioate backbone, can include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, e.g., a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an amino acid reactive moiety that reacts with an amino acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

[0028] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphodiester derivatives including, e.g., phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate having double bonded sulfur replacing oxygen in the phosphate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see Eckstein, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, Oxford University Press) as well as modifications to the nucleotide bases such as in 5-methyl cytidine or pseudouridine.; and peptide nucleic acid backbones and linkages. Other analog nucleic acids

include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (e.g. phosphorodiamidate morpholino oligos or locked nucleic acids (LNA) as known in the art), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, CARBOHYDRATE MODIFICATIONS IN ANTISENSE RESEARCH, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0029] Nucleic acids can include nonspecific sequences. As used herein, the term "nonspecific sequence" refers to a nucleic acid sequence that contains a series of residues that are not designed to be complementary to or are only partially complementary to any other nucleic acid sequence. By way of example, a nonspecific nucleic acid sequence is a sequence of nucleic acid residues that does not function as an inhibitory nucleic acid when contacted with a cell or organism.

[0030] A polynucleotide is typically composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); and thymine (T) (uracil (U) for thymine (T) when the polynucleotide is RNA). Thus, the term "polynucleotide sequence" is the alphabetical representation of a polynucleotide molecule; alternatively, the term may be applied to the polynucleotide molecule itself. This alphabetical representation can be input into databases in a computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. Polynucleotides may optionally include one or more non-standard nucleotide(s), nucleotide analog(s) and/or modified nucleotides.

[0031] The term "complement," as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanosine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with

corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0032] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other, may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[0033] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. The terms "non-naturally occurring amino acid," "non-natural amino acid," "non-natural amino acid analog," and "unnatural amino

acid” refer to amino acid analogs, synthetic amino acids, and amino acid mimetics which are not found in nature. In embodiments, a non-natural amino acid or a non-natural amino acid analog can replace a natural amino acid found in a KIBRA protein or a KIBRA peptide sequence described herein including embodiments thereof. In embodiments, a non-natural amino acid or a non-natural amino acid analog can substitute a natural amino acid found in a KIBRA protein or a KIBRA peptide sequence described herein including embodiments thereof. In embodiments, the non-natural amino acid or the non-natural amino acid analog is a D-amino acid.

[0034] The term “D-amino acid” refers to an amino acid where the stereogenic carbon alpha to the amino group has the D-configuration.

[0035] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0036] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may In embodiments be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. A "fusion protein" refers to a chimeric protein encoding two or more separate protein sequences that are recombinantly expressed as a single moiety.

[0037] An amino acid or nucleotide base "position" is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that must be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered amino acid position in the reference

sequence. In the case of truncations or fusions there can be stretches of amino acids in either the reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0038] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence. An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. One skilled in the art will immediately recognize the identity and location of residues corresponding to a specific position in a protein (e.g., KIBRA) in other proteins with different numbering systems. For example, by performing a simple sequence alignment with a protein (e.g., KIBRA) the identity and location of residues corresponding to specific positions of the protein are identified in other protein sequences aligning to the protein. For example, a selected residue in a selected protein corresponds to glutamic acid at position 138 when the selected residue occupies the same essential spatial or other structural relationship as a glutamic acid at position 138. In some embodiments, where a selected protein is aligned for maximum homology with a protein, the position in the aligned selected protein aligning with glutamic acid 138 is the to correspond to glutamic acid 138. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the glutamic acid at position 138, and the overall structures compared. In this case, an amino acid that occupies the same essential position as glutamic acid 138 in the structural model is the to correspond to the glutamic acid 138 residue.

[0039] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, "conservatively modified variants" refers to those nucleic acids that encode identical or essentially identical amino acid sequences. Because of the degeneracy of the genetic code, a number of nucleic acid sequences will encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively

modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence. In embodiments, the sequence of the “C-terminal KIBRA compound”, “C-terminal KIBRA peptide” and “CT-KIBRA” may be conservatively modified variant relative to a known C-terminal KIBRA peptide sequences, wherein the conservatively modified variant includes one or more conservative substitutions as described below.

[0040] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the disclosure.

[0041] The following eight groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Glycine (G);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);
- 7) Serine (S), Threonine (T); and
- 8) Cysteine (C), Methionine (M)

(see, e.g., Creighton, Proteins (1984)).

[0042] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 5 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (see, e.g., NCBI web site 10 <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids 15 or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0043] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as 20 compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the 25 percentage of sequence identity.

[0044] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of, e.g., a full length sequence or from 20 to 600, about 50 to about 200, or about 100 to about 150 amino acids or nucleotides in which a sequence may be compared to a reference sequence of the same number 30 of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for

comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat'l. Acad. Sci. USA* 85:2444, by computerized implementations of these
5 algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, e.g., Ausubel et al., *Current Protocols in Molecular Biology* (1995 supplement)).

[0045] An example of an algorithm that is suitable for determining percent sequence identity
10 and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short
15 words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative
20 alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum
25 achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences,
30 the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA*

89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0046] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5787). One
5 measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most
10 preferably less than about 0.001.

[0047] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for
15 example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0048] Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. A natural antibody molecule contains two identical pairs of polypeptide chains, each pair having one light chain and one heavy chain. Each light chain and heavy chain in turn consists of two regions: a variable ("V") region, involved in binding the target antigen, and a constant ("C") region that interacts with other components of
20 the immune system. The light and heavy chain variable regions (also referred to herein as light chain variable (VL) domain and heavy chain variable (VH) domain, respectively) come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). In human, two types of light chain are known: kappa chain (VK or V κ), encoded by the immunoglobulin kappa locus on chromosome 2, and the lambda chain (V λ),
25 encoded by the immunoglobulin lambda locus on chromosome 22. Within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called
30

the complementarity determining regions ("CDRs"). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The position and length of the CDRs have been precisely defined by Kabat, E. et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1983, 1987. The part of a variable region not contained in the CDRs is called the framework ("FR"), which forms the environment for the CDRs.

[0049] An "antibody variant" as provided herein refers to a polypeptide capable of binding to an antigen and including one or more structural domains (e.g., light chain variable domain, heavy chain variable domain) of an antibody or fragment thereof. Non-limiting examples of antibody variants include single-domain antibodies or nanobodies, monospecific Fab2, bispecific Fab2, trispecific Fab3, monovalent IgGs, scFv, bispecific antibodies, bispecific diabodies, trispecific triabodies, scFv-Fc, minibodies, IgNAR, V-NAR, hIgG, VhH, or peptibodies. A "peptibody" as provided herein refers to a peptide moiety attached (through a covalent or non-covalent linker) to the Fc domain of an antibody. Further non-limiting examples of antibody variants known in the art include antibodies produced by cartilaginous fish or camelids. A general description of antibodies from camelids and the variable regions thereof and methods for their production, isolation, and use may be found in references WO97/49805 and WO 97/49805 which are incorporated by reference herein in their entirety and for all purposes. Likewise, antibodies from cartilaginous fish and the variable regions thereof and methods for their production, isolation, and use may be found in WO2005/118629, which is incorporated by reference herein in its entirety and for all purposes.

[0050] The terms "CDR L1", "CDR L2" and "CDR L3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in to C-terminal direction a CDR L1, a CDR L2 and a CDR L3. Likewise, the terms "CDR H1", "CDR H2" and "CDR H3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a CDR H1, a CDR H2 and a CDR H3.

[0051] The terms "FR L1", "FR L2", "FR L3" and "FR L4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a FR L1, a FR L2, a FR L3 and a FR L4. Likewise, the terms "FR H1", "FR H2", "FR H3" and "FR H4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a FR H1, a FR H2, a FR H3 and a FR H4.

[0052] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL), variable light chain (VL) domain or light chain variable region and variable heavy chain (VH), variable heavy chain (VH) domain or heavy chain variable region refer to these light and heavy chain regions, respectively. The terms variable light chain (VL), variable light chain (VL) domain and light chain variable region as referred to herein may be used interchangeably. The terms variable heavy chain (VH), variable heavy chain (VH) domain and heavy chain variable region as referred to herein may be used interchangeably. The Fc (i.e. fragment crystallizable region) is the "base" or "tail" of an immunoglobulin and is typically composed of two heavy chains that contribute two or three constant domains depending on the class of the antibody. By binding to specific proteins, the Fc region ensures that each antibody generates an appropriate immune response for a given antigen. The Fc region also binds to various cell receptors, such as Fc receptors, and other immune molecules, such as complement proteins.

[0053] The term "antibody" is used according to its commonly known meaning in the art. Antibodies exist, e.g., as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)₂, a dimer of Fab which itself is a light chain joined to V_H-C_{H1} by a disulfide bond. The F(ab)₂ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)₂ dimer

into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology.

5 Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty *et al.*, *Nature* 348:552-554 (1990)). The term "antibody" as referred to herein further includes antibody variants such as single domain antibodies. Thus, in embodiments an antibody
10 includes a single monomeric variable antibody domain. Thus, in embodiments, the antibody, includes a variable light chain (VL) domain or a variable heavy chain (VH) domain. In embodiments, the antibody is a variable light chain (VL) domain or a variable heavy chain (VH) domain.

[0054] The phrase "specifically (or selectively) binds" to a protein or peptide, refers to a
15 binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For
20 example, polyclonal antibodies can be selected to obtain only a subset of antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select
25 antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, *Using Antibodies, A Laboratory Manual* (1998) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0055] A "ligand" refers to an agent, e.g., a polypeptide or other molecule, capable of binding to a receptor or antibody, antibody variant, antibody region or fragment thereof.

30 [0056] For specific proteins described herein, the named protein includes any of the protein's naturally occurring forms, variants or homologs that maintain the protein transcription factor

activity (e.g., within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the native protein). In some embodiments, variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring form. In other embodiments, the protein is the protein as identified by its NCBI sequence reference. In other embodiments, the protein is the protein as identified by its NCBI sequence reference, homolog or functional fragment thereof.

[0057] The term “KIBRA compound” as used herein refers to a compound comprising a KIBRA protein or KIBRA peptide provided herein including embodiments thereof. In embodiments, the KIBRA compound comprises a KIBRA peptide attached to an amino acid sequence that is not a KIBRA peptide or a sequence found within a KIBRA peptide sequence. In embodiments, the KIBRA compound does not include, and is not attached to, any additional amino acid sequence found within a KIBRA protein or any additional amino acid sequence found within a KIBRA peptide sequence. In embodiments, the KIBRA compound does not comprise an N-terminal KIBRA protein or an N-terminal KIBRA peptide as provided herein including embodiments thereof.

[0058] The terms “KIBRA protein”, “KIBRA peptide” and “KIBRA” as used herein include any of the recombinant or naturally-occurring forms of the kidney and brain expressed protein, also known as WW domain-containing protein 1 (WWC1), or variants or homologs thereof that maintain KIBRA activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to KIBRA (e.g. the UniProt reference number Q8IX03)). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100 continuous amino acid portion) compared to a naturally occurring KIBRA protein (e.g. UniProt reference number Q8IX03). In embodiments, the KIBRA protein is substantially identical to the protein identified by the UniProt reference number Q8IX03 or a variant or homolog having substantial identity thereto.

[0059] The term “C-terminal KIBRA compound” as used herein refers to a compound comprising a C-terminal KIBRA protein or C-terminal KIBRA peptide as provided herein including embodiments thereof. In embodiments, the C-terminal KIBRA compound does not comprise an N-terminal KIBRA protein or an N-terminal KIBRA peptide as provided herein

including embodiments thereof. In embodiments, the C-terminal KIBRA compound comprises a KIBRA peptide attached to an amino acid sequence that is not a KIBRA peptide or a sequence found within a KIBRA peptide sequence. In embodiments, the C-terminal KIBRA compound does not include, and is not attached to, any additional amino acid sequence found within a KIBRA protein or any additional amino acid sequence found within a KIBRA peptide sequence. In embodiments, the C-terminal KIBRA compound comprises a cell-penetrating peptide or a blood-brain barrier-penetrating peptide. In embodiments, the C-terminal KIBRA compound comprises a cell-penetrating peptide. In embodiments, the C-terminal KIBRA compound comprises a blood-brain barrier-penetrating peptide.

10 **[0060]** The terms “C-terminal KIBRA protein”, “C-terminal KIBRA peptide” and “CT-KIBRA” as used herein refers a peptide that includes a C-terminal amino acid sequence of the KIBRA protein (e.g. the UniProt reference number Q8IX03) and is less than 800 (e.g. 700, 600, 500, 400, 300, 200, 100, 50, 40, 20, or 10) amino acids in length. In embodiments, the C-terminal KIBRA peptide comprises a C-terminal amino acid sequence of the KIBRA protein
15 attached to an amino acid sequence that is not a KIBRA peptide or a sequence found within a KIBRA peptide sequence. In embodiments, the C-terminal KIBRA peptide does not include, and is not attached to, any additional amino acid found within a KIBRA protein or any additional amino acid sequence found within a KIBRA peptide sequence. In embodiments, the C-terminal KIBRA protein does not comprise an N-terminal KIBRA protein or an N-terminal KIBRA
20 peptide as provided herein including embodiments thereof. In embodiments, the “C-terminal amino acid sequence” is an amino acid sequence that includes at least 10 contiguous amino acids of the KIBRA protein within 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein
25 within 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that
30 includes at least 10 continuous amino acids of the KIBRA protein within 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10

continuous amino acids of the KIBRA protein within 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 10 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the CT-KIBRA protein sequence includes SEQ ID NO:1. In embodiments, the CT-KIBRA protein sequence includes SEQ ID NO:2. In embodiments, the CT-KIBRA protein sequence includes SEQ ID NO:3.

[0061] The terms “N-terminal KIBRA protein”, “N-terminal KIBRA peptide” and “NT-KIBRA” as used herein refers a peptide that includes an N-terminal amino acid sequence of the KIBRA protein (e.g., the UniProt reference number Q8IX03) and is less than 86 (e.g., 80, 70, 60, 50, 40, 30, 20, or 10) amino acids in length. In embodiments, the N-terminal KIBRA peptide comprises an N-terminal amino acid sequence of the KIBRA protein attached to an amino acid sequence that is not a KIBRA peptide or a sequence found within a KIBRA peptide sequence. In embodiments, the N-terminal KIBRA peptide does not include, and is not attached to, any additional amino acid found within a KIBRA protein or any additional amino acid sequence found within a KIBRA peptide sequence. In embodiments, the N-terminal KIBRA protein does not comprise a C-terminal KIBRA protein or a C-terminal KIBRA peptide as provided herein including embodiments thereof. In embodiments, the “N-terminal amino acid sequence” is an amino acid sequence that includes at least 10 contiguous amino acids of the KIBRA protein within 86 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 80 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 70 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-

terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 60 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 50 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 40 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 30 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 20 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the N-terminal amino acid sequence is an amino acid sequence that includes at least 10 continuous amino acids of the KIBRA protein within 10 amino acids of the N-terminus of the KIBRA protein (e.g., the UniProt reference number Q8IX03). In embodiments, the NT-KIBRA protein sequence does not include SEQ ID NO:1. In embodiments, the NT-KIBRA protein sequence does not include SEQ ID NO:2. In embodiments, the NT-KIBRA protein sequence does not include SEQ ID NO:3.

[0062] The terms “tau” and “tau protein” as used herein include any of the recombinant or naturally-occurring forms of the tubulin associated unit, or variants or homologs thereof that maintain tau activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to tau (e.g. UniProt reference number P10636)). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150, 200 continuous amino acid portion) compared to a naturally occurring tau protein (e.g. UniProt reference number P10636). In embodiments, the tau protein is substantially identical to the protein identified by the UniProt reference number P10636 or a variant or homolog having substantial identity thereto.

[0063] The term “cell-penetrating peptides” as used herein refers to short peptides that are able to pass through tissue and cell membranes. In embodiments, cell-penetrating peptides are used to transport biologically active conjugates into tissues or cells. In embodiments, the biologically active conjugates are peptides. In embodiments, the biologically active conjugate is a KIBRA peptide. In further embodiments, the KIBRA peptide is a CT-KIBRA peptide. Cell-penetrating peptides are well known in the art (Guidotti et al., *Trends Pharmacol Sci*, 2017, 38(4), pp. 406-24; Patel et al., *Sci Rep*, 2019, 9(1), pp.6298). In embodiments, the cell-penetrating peptide includes, but is not limited to, a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, or a cyclic transportan amino acid sequence. In embodiments, the cell-penetrating peptide includes the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25.

[0064] The term “blood-brain barrier-penetrating peptides” or “BBB-penetrating peptides” as used herein refer to polypeptides that are able to pass through the blood-brain barrier. In embodiments, the BBB-penetrating peptides are used to transport biologically active conjugates into the brain. In embodiments, the biologically active conjugate is a KIBRA peptide. In further embodiments, the KIBRA peptide is a CT-KIBRA peptide. Blood-brain barrier-penetrating peptides are well known in the art (Kariolis et al., *Sci Transl Med*, 2020, 12(545): eaay1359). In embodiments, the blood-brain barrier-penetrating peptide includes, but is not limited to, an Fc fragment blood-brain barrier transport vehicle.

[0065] The term "gene" means the segment of DNA involved in producing a protein; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). The leader, the trailer as well as the introns include regulatory elements that are necessary during the transcription and the translation of a gene. Further, a "protein gene product" is a protein expressed from a particular gene.

[0066] The terms "plasmid", "vector" or "expression vector" refer to a nucleic acid molecule that encodes for genes and/or regulatory elements necessary for the expression of genes. Expression of a gene from a plasmid can occur in cis or in trans. If a gene is expressed in cis, the gene and the regulatory elements are encoded by the same plasmid. Expression in trans refers to the instance where the gene and the regulatory elements are encoded by separate plasmids.

[0067] The terms "transfection", "transduction", "transfecting" or "transducing" can be used interchangeably and are defined as a process of introducing a nucleic acid molecule or a protein to a cell. Nucleic acids are introduced to a cell using non-viral or viral-based methods. The nucleic acid molecules may be gene sequences encoding complete proteins or functional portions thereof. Non-viral methods of transfection include any appropriate transfection method that does not use viral DNA or viral particles as a delivery system to introduce the nucleic acid molecule into the cell. Exemplary non-viral transfection methods include calcium phosphate transfection, liposomal transfection, nucleofection, sonoporation, transfection through heat shock, magnetofection and electroporation. In some embodiments, the nucleic acid molecules are introduced into a cell using electroporation following standard procedures well known in the art. For viral-based methods of transfection any useful viral vector may be used in the methods described herein. Examples for viral vectors include, but are not limited to retroviral, adenoviral, lentiviral and adeno-associated viral vectors. In some embodiments, the nucleic acid molecules are introduced into a cell using a retroviral vector following standard procedures well known in the art. The terms "transfection" or "transduction" also refer to introducing proteins into a cell from the external environment. Typically, transduction or transfection of a protein relies on attachment of a peptide or protein capable of crossing the cell membrane to the protein of interest. See, e.g., Ford *et al.* (2001) *Gene Therapy* 8:1-4 and Prochiantz (2007) *Nat. Methods* 4:119-20.

[0068] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ³²P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any appropriate method known in the art for conjugating an

antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego.

[0069] When the label or detectable moiety is a radioactive metal or paramagnetic ion, the agent may be reacted with another long-tailed reagent having a long tail with one or more
5 chelating groups attached to the long tail for binding to these ions. The long tail may be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which the metals or ions may be added for binding. Examples of chelating groups that may be used according to the disclosure include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), DOTA,
10 NOTA, NETA, TETA, porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups. The chelate is normally linked to the PSMA antibody or functional antibody fragment by a group, which enables the formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and
15 gadolinium are useful for MRI, when used along with the antibodies and carriers described herein. Macrocyclic chelates such as NOTA, DOTA, and TETA are of use with a variety of metals and radiometals including, but not limited to, radionuclides of gallium, yttrium and copper, respectively. Other ring-type chelates such as macrocyclic polyethers, which are of interest for stably binding nuclides, such as ^{223}Ra for RAIT may be used. In certain
20 embodiments, chelating moieties may be used to attach a PET imaging agent, such as an $\text{Al-}^{18}\text{F}$ complex, to a targeting molecule for use in PET analysis.

[0070] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. antibodies and antigens) to become sufficiently proximal to react, interact, or physically touch. It should be appreciated, however,
25 that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0071] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be, for example, a pharmaceutical composition as provided
30 herein and a cell. In embodiments contacting includes, for example, allowing a pharmaceutical composition as described herein to interact with a cell.

[0072] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include, but are not limited to, yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells.

[0073] The term "recombinant" when used with reference, *e.g.*, to a cell, nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. Transgenic cells and plants are those that express a heterologous gene or coding sequence, typically as a result of recombinant methods.

[0074] The term "isolated", when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0075] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, *e.g.*, a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (*e.g.*, a fusion protein).

[0076] The term "exogenous" refers to a molecule or substance (*e.g.*, a compound, nucleic acid or protein) that originates from outside a given cell or organism. For example, an "exogenous promoter" as referred to herein is a promoter that does not originate from the cell or organism it is expressed by. Conversely, the term "endogenous" or "endogenous promoter" refers to a molecule or substance that is native to, or originates within, a given cell or organism.

[0077] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0078] "Biological sample" or "sample" refer to materials obtained from or derived from a subject or patient. A biological sample includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histological purposes. Such samples include bodily fluids such as blood and blood fractions or products (*e.g.*, serum, plasma, platelets, red blood cells, and the like), sputum, tissue, cultured cells (*e.g.*, primary cultures, explants, and transformed cells) stool, urine, synovial fluid, joint tissue, synovial tissue, synoviocytes, fibroblast-like synoviocytes, macrophage-like synoviocytes, immune cells, hematopoietic cells, fibroblasts, macrophages, T cells, *etc.* A biological sample is typically obtained from a eukaryotic organism, such as a mammal such as a primate *e.g.*, chimpanzee or human; cow; dog; cat; a rodent, *e.g.*, guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish.

[0079] A "control" or "standard control" refers to a sample, measurement, or value that serves as a reference, usually a known reference, for comparison to a test sample, measurement, or value. For example, a test sample can be taken from a patient suspected of having a given disease (*e.g.* Alzheimer's disease) and compared to a known normal (non-diseased) individual (*e.g.* a standard control subject). A standard control can also represent an average measurement or value gathered from a population of similar individuals (*e.g.* standard control subjects) that do not have a given disease (*i.e.* standard control population), *e.g.*, healthy individuals with a similar medical background, same age, weight, *etc.* A standard control value can also be obtained from the same individual, *e.g.* from an earlier-obtained sample from the patient prior to disease onset. For example, a control can be devised to compare therapeutic benefit based on pharmacological data (*e.g.*, half-life) or therapeutic measures (*e.g.*, comparison of side effects). Controls are also

valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant. One of skill will recognize that standard controls can be designed for assessment of any number of parameters (e.g. RNA levels, protein levels, specific cell types, specific bodily fluids, specific tissues, etc).

[0080] One of skill in the art will understand which standard controls are most appropriate in a given situation and be able to analyze data based on comparisons to standard control values. Standard controls are also valuable for determining the significance (e.g. statistical significance) of data. For example, if values for a given parameter are widely variant in standard controls, variation in test samples will not be considered as significant.

[0081] “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a composition or pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0082] The terms “disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a tau-associated memory deficit disorder. For example, the tau-associated memory deficit disorder may include Alzheimer’s disease, progressive supranuclear palsy, Pick’s disease, corticobasal degeneration, chronic traumatic encephalopathy, or Frontotemporal lobar dementia-tau (FTLD-tau). In embodiments the condition may be aging-associated cognitive decline. In further embodiments, the aging-associated cognitive decline occur in the absence of tau-associated neurodegeneration.

[0083] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease, a memory deficit disorder associated with tau activity, memory deficits associated with tau pathology, tau-associated disease, tau-associated degeneration) means that the disease (e.g. memory deficit disorder) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a memory deficit disorder associated with tau activity or function or a tau-associated disease (e.g.,

memory deficit disorder), may be treated with a tau modulator or tau inhibitor, in the instance where increased tau activity or function (e.g. signaling pathway activity) causes the disease (e.g., memory deficit disorder).

5 [0084] The term “memory deficit disorder”, “memory deficit” and “memory disorder” as used herein refers to condition characterized by an impairment of memory as manifested by a reduced ability to remember things such as dates and names, and increased forgetfulness. In embodiments, the memory deficit disorder is associated with aberrant tau expression and activity or a tauopathy. In embodiments, the memory deficit disorder is a tau-associated memory deficit disorder.

10 [0085] The term “tauopathy” as used herein refers to a class of neurodegenerative diseases involving the aggregation of tau protein into neurofibrillary or gliofibrillary tangles in the human brain. In embodiments, the tangles are formed by hyperphosphorylation of tau, causing the protein to dissociate from microtubules and form insoluble aggregates.

15 [0086] The term “neurodegeneration” as used herein refers to a disease or condition which is characterized by a slow and progressive loss of neuronal cells in specified regions of the brain. In embodiments, the neurodegeneration is tau-associated.

[0087] The term “cognitive decline” as used herein refers to the gradual loss of cognitive or thinking abilities (e.g. learning, remembering, attention, reasoning) in a subject. In embodiments, the cognitive decline is aging-associated. In embodiments, the cognitive decline is mild. In
20 embodiments, the cognitive decline occurs in the absence of tau-associated neurodegeneration. In embodiments, the cognitive decline is associated with a cognitive disorder. In embodiments, the cognitive decline is tau-associated.

[0088] The term “signaling pathway” as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules,
25 ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

[0089] The term “aberrant” as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control
30 or the average of normal non-diseased control samples. Aberrant activity may refer to an amount

of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0090] As used herein, “treating” or “treatment of” a condition, disease or disorder or
5 symptoms associated with a condition, disease or disorder refers to an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of condition, disorder or disease, stabilization of the state of condition, disorder or disease, prevention of development of condition, disorder or disease,
10 prevention of spread of condition, disorder or disease, delay or slowing of condition, disorder or disease progression, delay or slowing of condition, disorder or disease onset, amelioration or palliation of the condition, disorder or disease state, and remission, whether partial or total. “Treating” can also mean prolonging survival of a subject beyond that expected in the absence of treatment. “Treating” can also mean inhibiting the progression of the condition, disorder or
15 disease, slowing the progression of the condition, disorder or disease temporarily, although in some instances, it involves halting the progression of the condition, disorder or disease permanently. As used herein the terms treatment, treat, or treating refers to a method of reducing the effects of one or more symptoms of a disease or condition characterized by expression of the protease or symptom of the disease or condition characterized by expression of the protease.
20 Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease, condition, or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%,
25 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition. Further, as used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level and such terms can
30 include but do not necessarily include complete elimination.

[0091] The terms “dose” and “dosage” are used interchangeably herein. A dose refers to the amount of active ingredient given to an individual at each administration. The dose will vary depending on a number of factors, including the range of normal doses for a given therapy, frequency of administration; size and tolerance of the individual; severity of the condition; risk of side effects; and the route of administration. One of skill will recognize that the dose can be modified depending on the above factors or based on therapeutic progress. The term “dosage form” refers to the particular format of the pharmaceutical or pharmaceutical composition, and depends on the route of administration. For example, a dosage form can be in a liquid form for nebulization, e.g., for inhalants, in a tablet or liquid, e.g., for oral delivery, or a saline solution, e.g., for injection.

[0092] By “therapeutically effective dose or amount” as used herein is meant a dose that produces effects for which it is administered (e.g. treating or preventing a disease). The exact dose and formulation will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Remington: *The Science and Practice of Pharmacy*, 20th Edition, Gennaro, Editor (2003), and Pickar, *Dosage Calculations* (1999)). For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as “-fold” increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a standard control. A therapeutically effective dose or amount may ameliorate one or more symptoms of a disease. A therapeutically effective dose or amount may prevent or delay the onset of a disease or one or more symptoms of a disease when the effect for which it is being administered is to treat a person who is at risk of developing the disease.

[0093] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal,

subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0094] The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In embodiments, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0095] As used herein, the term “pharmaceutically acceptable” is used synonymously with “physiologically acceptable” and “pharmacologically acceptable”. A pharmaceutical composition will generally comprise agents for buffering and preservation in storage, and can include buffers and carriers for appropriate delivery, depending on the route of administration.

5 [0096] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal
10 sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic
15 pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0097] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only,
20 sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0098] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with
25 or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0099] The pharmaceutical preparation is optionally in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active
30 component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules.

Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The unit dosage form can be of a frozen dispersion.

[0100] The terms “1-ethyl-3-(3-dimethylaminopropyl) carbodiimide”, “EDC”, “EDAC” and “EDCI” as used herein refer to a water-soluble carbodiimide usually handled as the hydrochloride. It is generally used as a carboxyl activating agent for the coupling of primary amines to yield amide bonds. Additionally, EDC can also be used to activate phosphate groups in order to form phosphomonoesters and phosphodiester. Common uses for this carbodiimide include peptide synthesis, protein crosslinking to nucleic acids, but also in the preparation of immunoconjugates. EDC is often used in combination with N-hydroxysuccinimide (NHS) for the immobilisation of large biomolecules. Recent work has also used EDC to assess the structure state of uracil nucleobases in RNA.

[0101] The terms “N-hydroxysulfosuccinimide”, “sulfo-NHS” and “NHS” refer to a compound that enables control and modification of carbodiimide crosslinking reactions involving activation of carboxylates (—COOH) for conjugation with primary amines (—NH_2). Derivatives can be synthesized by mixing the NHS with a carboxyl-containing molecule and a dehydrating agent such as the carbodiimide EDC. The method is the basis for generating many types of protein labeling reagents, including amine-reactive fluorescent dyes, biotin affinity tags and pegylation compounds.

[0102] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

25 METHODS OF TREATMENT

[0103] Provided herein are, *inter alia*, are methods for treating a memory deficit disorder (e.g. tau-associated memory deficit disorder). Thus, in an aspect is provided a method of treating a tau-associated memory deficit disorder in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a C-terminal KIBRA compound. In embodiments, the tau-associated memory deficit disorder is Alzheimer’s disease,

progressive supranuclear palsy, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, or Frontotemporal lobar dementia-tau (FTLD-tau).

[0104] In another aspect is provided a method of treating aging-associated cognitive decline in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a C-terminal KIBRA compound. In embodiments, the aging-associated cognitive decline occurs in the absence of tau-associated neurodegeneration.

[0105] In embodiments, the C-terminal KIBRA compound is a peptide. In embodiments, the C-terminal KIBRA compound includes a C-terminal KIBRA peptide. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 800 amino acids in length. In
10 embodiments, the C-terminal KIBRA peptide is between about 710 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 720 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 730 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
15 about 740 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 750 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 760 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 770 and about 800 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 780 and about 800 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 790 and about 800
20 amino acids in length.

[0106] In embodiments, the C-terminal KIBRA peptide is between about 700 and about 790 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 780 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 770 amino acids in length. In embodiments, the C-terminal KIBRA peptide
25 is between about 700 and about 760 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 750 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 740 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 700 and about 730 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 720
30 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 700 and about 710 amino acids in length.

length. In embodiments, the C-terminal KIBRA peptide is between about 570 and about 600 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 580 and about 600 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 590 and about 600 amino acids in length.

5 [0110] In embodiments, the C-terminal KIBRA peptide is between about 500 and about 590 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 580 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 570 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 560 amino acids in length. In embodiments, the C-terminal
10 KIBRA peptide is between about 500 and about 550 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 540 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 530 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and about 520 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 500 and
15 about 510 amino acids in length.

[0111] In embodiments, the C-terminal KIBRA peptide is between about 400 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 410 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 420 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide
20 is between about 430 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 440 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 450 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 460 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 470 and about 500
25 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 480 and about 500 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 490 and about 500 amino acids in length.

[0112] In embodiments, the C-terminal KIBRA peptide is between about 400 and about 490 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 400 and
30 about 480 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 400 and about 470 amino acids in length. In embodiments, the C-terminal KIBRA peptide

is between about 400 and about 460 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 400 and about 450 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 400 and about 440 amino acids in length. In
5 length. In embodiments, the C-terminal KIBRA peptide is between about 400 and about 420 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 400 and about 410 amino acids in length.

[0113] In embodiments, the C-terminal KIBRA peptide is between about 300 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 310 and
10 about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 320 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 330 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 340 and about 400 amino acids in length. In
15 embodiments, the C-terminal KIBRA peptide is between about 350 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 360 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 370 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 380 and about 400 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 390 and about 400 amino acids in length.

[0114] In embodiments, the C-terminal KIBRA peptide is between about 300 and about 390 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 380 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 370 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 360 amino acids in length. In embodiments, the C-terminal
25 KIBRA peptide is between about 300 and about 350 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 340 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 330 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and about 320 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 300 and
30 about 310 amino acids in length.

length. In embodiments, the C-terminal KIBRA peptide is between about 170 and about 200 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 180 and about 200 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 190 and about 200 amino acids in length.

5 [0118] In embodiments, the C-terminal KIBRA peptide is between about 100 and about 190 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 180 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 170 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 160 amino acids in length. In embodiments, the C-terminal
10 KIBRA peptide is between about 100 and about 150 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 140 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 130 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and about 120 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 100 and
15 about 110 amino acids in length.

[0119] In embodiments, the C-terminal KIBRA peptide is between about 50 and about 100 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 60 and about 100 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 70 and about 100 amino acids in length. In embodiments, the C-terminal KIBRA peptide is
20 between about 80 and about 100 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 90 and about 100 amino acids in length.

[0120] In embodiments, the C-terminal KIBRA peptide is between about 50 and about 90 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 50 and about 80 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
25 about 50 and about 70 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 50 and about 60 amino acids in length.

[0121] In embodiments, the C-terminal KIBRA peptide is between about 40 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 41 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
30 about 42 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 43 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA

peptide is between about 44 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 45 and about 50 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 46 and about 50 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 47 and about 50 amino acids in
length. In embodiments, the C-terminal KIBRA peptide is between about 48 and about 50 amino
acids in length. In embodiments, the C-terminal KIBRA peptide is between about 49 and about
50 amino acids in length.

[0122] In embodiments, the C-terminal KIBRA peptide is between about 40 and about 49
amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 40 and
about 48 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
about 40 and about 47 amino acids in length. In embodiments, the C-terminal KIBRA peptide is
between about 40 and about 46 amino acids in length. In embodiments, the C-terminal KIBRA
peptide is between about 40 and about 45 amino acids in length. In embodiments, the C-terminal
KIBRA peptide is between about 40 and about 44 amino acids in length. In embodiments, the C-
terminal KIBRA peptide is between about 40 and about 43 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 40 and about 42 amino acids in
length. In embodiments, the C-terminal KIBRA peptide is between about 40 and about 41 amino
acids in length.

[0123] In embodiments, the C-terminal KIBRA peptide is between about 20 and about 40
amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 21 and
about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
about 22 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is
between about 23 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA
peptide is between about 24 and about 40 amino acids in length. In embodiments, the C-terminal
KIBRA peptide is between about 25 and about 40 amino acids in length. In embodiments, the C-
terminal KIBRA peptide is between about 26 and about 40 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 27 and about 40 amino acids in
length. In embodiments, the C-terminal KIBRA peptide is between about 28 and about 40 amino
acids in length. In embodiments, the C-terminal KIBRA peptide is between about 29 and about
40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 30
and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between

about 31 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 32 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 33 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 34 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 35 and about 40 amino acids in length. In
5 embodiments, the C-terminal KIBRA peptide is between about 36 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 37 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 38 and about 40 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 39
10 and about 40 amino acids in length.

[0124] In embodiments, the C-terminal KIBRA peptide is between about 20 and about 39 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 38 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 37 amino acids in length. In embodiments, the C-terminal KIBRA peptide is
15 between about 20 and about 36 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 35 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 34 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 33 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 20 and about 32 amino acids in
20 length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 31 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 30 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 29 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between
about 20 and about 28 amino acids in length. In embodiments, the C-terminal KIBRA peptide is
25 between about 20 and about 27 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 26 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 25 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 24 amino acids in length. In
embodiments, the C-terminal KIBRA peptide is between about 20 and about 23 amino acids in
30 length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 22 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 20 and about 21 amino acids in length.

[0125] In embodiments, the C-terminal KIBRA peptide is between about 10 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 11 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 12 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 13 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 14 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 15 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 16 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 17 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 18 and about 20 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 19 and about 20 amino acids in length.

[0126] In embodiments, the C-terminal KIBRA peptide is between about 10 and about 19 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 18 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 17 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 16 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 15 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 14 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 13 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 12 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 10 and about 11 amino acids in length.

[0127] In embodiments, the C-terminal KIBRA peptide is between about 5 and about 10 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 6 and about 10 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 7 and about 10 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 8 and about 10 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 9 and about 10 amino acids in length.

[0128] In embodiments, the C-terminal KIBRA peptide is between about 5 and about 9 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 5 and about 8

amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 5 and about 7 amino acids in length. In embodiments, the C-terminal KIBRA peptide is between about 5 and about 6 amino acids in length.

[0129] In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 50 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 100 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 200 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 300 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 400 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 500 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 600 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 700 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 800 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0130] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 100 continuous

amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 200 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

- 5 In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 300 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 400 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 500 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 600 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 700 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 800 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

- [0131]** In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 50 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 100 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 200 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 300 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 400 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 500 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

- 5 In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 600 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 700 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 800 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

- [0132] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 100 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 200 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 300 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 400 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 500 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 600 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 700 continuous amino

acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 800 continuous amino acid portion of the sequence compared to a naturally occurring KIBRA protein (e.g. the UniProt reference number Q8IX03).

- 5 **[0133]** In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 500 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 500 amino acids of the C-
- 10 terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 200 continuous amino acid
- 15 sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85%
- 20 amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
- 25 the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

- [0134]** In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 400 amino acids of
- 30 the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity

across a 300 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0135] In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least

300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

5 **[0136]** In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity
across a 100 continuous amino acid sequence portion within at least 200 amino acids of the C-
terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 50
10 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid
sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g.
the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at
15 least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion
within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt
reference number Q8IX03).

[0137] In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence
identity across a 100 continuous amino acid sequence portion within at least 100 amino acids of
20 the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity
across a 50 continuous amino acid sequence portion within at least 100 amino acids of the C-
terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25
25 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid
sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g.
the UniProt reference number Q8IX03).

30 **[0138]** In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence
identity across a 50 continuous amino acid sequence portion within at least 50 amino acids of the

C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0139] In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0140] In embodiments, the C-terminal KIBRA peptide has at least 85% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 10 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0141] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 500 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90%

amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0142] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0143] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In

embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 100
5 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at
10 least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number
15 Q8IX03).

[0144] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity
20 across a 100 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
25 KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt
30 reference number Q8IX03).

[0145] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0146] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0147] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0148] In embodiments, the C-terminal KIBRA peptide has at least 90% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 10 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0149] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 500 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0150] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal

KIBRA peptide has at least 95% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0151] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0152] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 200 amino acids of

the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity
across a 100 continuous amino acid sequence portion within at least 200 amino acids of the C-
terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
5 the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 50
continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
KIBRA peptide has at least 95% amino acid sequence identity across a 25 continuous amino acid
sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g.
10 the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at
least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion
within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt
reference number Q8IX03).

[0153] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence
15 identity across a 100 continuous amino acid sequence portion within at least 100 amino acids of
the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity
across a 50 continuous amino acid sequence portion within at least 100 amino acids of the C-
terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
20 the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25
continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid
sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g.
25 the UniProt reference number Q8IX03).

[0154] In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence
identity across a 50 continuous amino acid sequence portion within at least 50 amino acids of the
C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25
30 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal

KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

5 **[0155]** In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

10 **[0156]** In embodiments, the C-terminal KIBRA peptide has at least 95% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 10 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

15 **[0157]** In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 500 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 300 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 500 amino acids of the

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C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 500 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

- 5 **[0158]** In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 400 continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity
across a 300 continuous amino acid sequence portion within at least 400 amino acids of the C-
10 terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 200
continuous amino acid sequence portion within at least 400 amino acids of the C-terminus of the
KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal
KIBRA peptide has at least 99% amino acid sequence identity across a 100 continuous amino acid
15 sequence portion within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g.
the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at
least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion
within at least 400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt
reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99%
20 amino acid sequence identity across a 25 continuous amino acid sequence portion within at least
400 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number
Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence
identity across a 10 continuous amino acid sequence portion within at least 400 amino acids of the
C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).
- 25 **[0159]** In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence
identity across a 300 continuous amino acid sequence portion within at least 300 amino acids of
the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In
embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity
across a 200 continuous amino acid sequence portion within at least 300 amino acids of the C-
30 terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments,
the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 100

continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 300 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0160] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 200 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 200 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0161] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 100 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 100 amino acids of the C-

terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 100 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0162] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 50 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 50 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0163] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 25 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03). In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 25 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0164] In embodiments, the C-terminal KIBRA peptide has at least 99% amino acid sequence identity across a 10 continuous amino acid sequence portion within at least 10 amino acids of the C-terminus of the KIBRA protein (e.g. the UniProt reference number Q8IX03).

[0165] In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:1. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:2. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:3. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:1,

SEQ ID NO:2, or SEQ ID NO:3. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:1. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:2. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:3.

- 5 **[0166]** In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:4. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:5. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5. In embodiments, the
- 10 C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:4. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:5.

- [0167]** In embodiments, the C-terminal KIBRA compound includes a cell-penetrating peptide or a blood-brain barrier-penetrating peptide. In embodiments, the C-terminal KIBRA compound includes a cell-penetrating peptide. In embodiments, the C-terminal KIBRA compound includes
- 15 a blood-brain barrier-penetrating peptide. In embodiments, the C-terminal KIBRA compound includes a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a
- 20 hydrocarbon stapling sequence, a glycine flexible linker, or a biotin amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a TAT amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a penetratin amino acid sequence. In embodiments, the C-terminal KIBRA compound includes an oligoarginine amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a xentry amino acid sequence. In
- 25 embodiments, the C-terminal KIBRA compound includes a transportan amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a cyclic-TAT amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a cyclic penetratin amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a cyclic oligoarginine amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a cyclic
- 30 xentry amino acid sequence. In embodiments, the C-terminal KIBRA compound includes a cyclic transportan amino acid sequence. In embodiments, the C-terminal KIBRA compound

includes a hydrocarbon stapling sequence. In embodiments, the C-terminal KIBRA compound includes a glycine flexible linker. In embodiments, the C-terminal KIBRA compound includes a biotin amino acid sequence.

[0168] In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:6. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:7. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:8. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:9. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:10. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:11. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:12. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:13. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:14. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:15. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:16. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:17. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:18. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:19. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:20. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:21. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:22. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:23. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:24. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:25.

[0169] In embodiments, at least one of the amino acids of the C-terminal KIBRA compound is a non-natural amino acid analog. In embodiments, at least two of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least three of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In
5 embodiments, at least four of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least five of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least six of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least seven of the amino acids of the C-terminal KIBRA compound are non-natural amino acid
10 analogs. In embodiments, at least eight of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least nine of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 10 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 11 of the amino acids of the C-terminal KIBRA compound are non-natural
15 amino acid analogs. In embodiments, at least 12 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 13 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 14 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 15 of the amino acids of the C-terminal KIBRA compound are non-
20 natural amino acid analogs. In embodiments, at least 16 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 17 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 18 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 19 of the amino acids of the C-terminal KIBRA compound are
25 non-natural amino acid analogs. In embodiments, at least 20 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 21 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 22 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 23 of the amino acids of the C-terminal KIBRA compound are
30 non-natural amino acid analogs. In embodiments, at least 24 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 25 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments,

at least 26 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 27 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 28 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 29 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 30 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 31 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 32 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 33 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 34 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 35 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 36 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 37 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 38 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 39 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 40 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs.

[0170] In embodiments, the C-terminal KIBRA compound includes at least one non-natural amino acid analog. In embodiments, the C-terminal KIBRA compound includes at least two non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least three non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least four non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least five non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least six non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least seven non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least eight non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least nine non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 10 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 11 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes

[illegible]

[0171] In embodiments, the C-terminal KIBRA compound does not include a N-terminal KIBRA peptide. In embodiments, the C-terminal KIBRA compound does not include the sequence of SEQ ID NO:29. In embodiments, the C-terminal KIBRA compound is not the sequence of SEQ ID NO:29.

5 C-TERMINAL KIBRA COMPOUNDS

[0172] The methods provided herein include administration of a C-terminal KIBRA compound as provided herein including embodiments thereof. Thus, in another aspect is provided a C-terminal KIBRA compound including a C-terminal KIBRA peptide including the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5, 10 wherein (a) at least one of the amino acids of the C-terminal KIBRA peptide is a non-natural amino acid analog; and/or (b) the C-terminal KIBRA compound further includes a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic 15 xentry amino acid sequence, a cyclic transportan amino acid sequence, a glycine flexible linker, or a biotin amino acid sequence.

[0173] In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5. In 20 embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:1. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:2. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:3. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:4. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:5. In embodiments, the C-terminal KIBRA 25 compound is the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:1. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:2. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:3. In embodiments, the C-terminal KIBRA compound is the amino acid 30 sequence of SEQ ID NO:4. In embodiments, the C-terminal KIBRA compound is the amino acid sequence of SEQ ID NO:5.

[0174] In embodiments, at least one of the amino acids of the C-terminal KIBRA compound is a non-natural amino acid analog. In embodiments, at least two of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least three of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In
5 embodiments, at least four of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least five of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least six of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least seven of the amino acids of the C-terminal KIBRA compound are non-natural amino acid
10 analogs. In embodiments, at least eight of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least nine of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 10 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 11 of the amino acids of the C-terminal KIBRA compound are non-natural
15 amino acid analogs. In embodiments, at least 12 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 13 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 14 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 15 of the amino acids of the C-terminal KIBRA compound are non-
20 natural amino acid analogs. In embodiments, at least 16 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 17 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 18 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 19 of the amino acids of the C-terminal KIBRA compound are
25 non-natural amino acid analogs. In embodiments, at least 20 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 21 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 22 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 23 of the amino acids of the C-terminal KIBRA compound are
30 non-natural amino acid analogs. In embodiments, at least 24 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 25 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments,

at least 26 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 27 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 28 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 29 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 30 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 31 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 32 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 33 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 34 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 35 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 36 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 37 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 38 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 39 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs. In embodiments, at least 40 of the amino acids of the C-terminal KIBRA compound are non-natural amino acid analogs.

[0175] In embodiments, the C-terminal KIBRA compound includes at least one non-natural amino acid analog. In embodiments, the C-terminal KIBRA compound includes at least two non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least three non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least four non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least five non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least six non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least seven non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least eight non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least nine non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 10 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 11 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes

at least 12 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 13 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 14 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 15 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 16 non-natural amino acid analogs. In
5 embodiments, the C-terminal KIBRA compound includes at least 17 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 18 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 19 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least
10 20 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 21 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 22 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 23 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 24 non-natural amino acid analogs. In embodiments, the C-
15 terminal KIBRA compound includes at least 25 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 26 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 27 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 28 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least
20 29 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 30 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 31 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 32 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 33 non-natural amino acid analogs. In embodiments, the C-
25 terminal KIBRA compound includes at least 34 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 35 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 36 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 37 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least
30 38 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 39 non-natural amino acid analogs. In embodiments, the C-terminal KIBRA compound includes at least 40 non-natural amino acid analogs.

[0176] In embodiments, the C-terminal KIBRA compound includes a cell-penetrating peptide or a blood-brain barrier-penetrating peptide. In embodiments, the C-terminal KIBRA compound includes a cell-penetrating peptide. In embodiments, the C-terminal KIBRA compound includes a blood-brain barrier-penetrating peptide. In embodiments, the C-terminal KIBRA compound further includes a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a hydrocarbon stapling sequence, a glycine flexible linker, or a biotin amino acid sequence. In 5
embodiments, the C-terminal KIBRA compound further includes a TAT amino acid sequence. In 10
embodiments, the C-terminal KIBRA compound further includes a penetratin amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a oligoarginine amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a xentry amino acid sequence. In 15
embodiments, the C-terminal KIBRA compound further includes a transportan amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a cyclic-TAT amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a cyclic penetratin amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a cyclic oligoarginine amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a cyclic xentry amino acid sequence. In 20
embodiments, the C-terminal KIBRA compound further includes a cyclic transportan amino acid sequence. In embodiments, the C-terminal KIBRA compound further includes a hydrocarbon stapling sequence. In embodiments, the C-terminal KIBRA compound further includes a glycine flexible linker. In embodiments, the C-terminal KIBRA compound further includes a biotin amino acid sequence.

[0177] In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25. In embodiments, the C-terminal KIBRA 25
compound includes the amino acid sequence of SEQ ID NO:6. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:7. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:8. In 30

embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:9. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:10. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:11. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:12. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:13. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:14. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:15. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:16. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:17. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:18. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:19. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:20. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:21. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:22. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:23. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:24. In embodiments, the C-terminal KIBRA compound includes the amino acid sequence of SEQ ID NO:25.

PHARMACEUTICAL COMPOSITIONS

[0178] The compositions provided herein include pharmaceutical compositions including the C-terminal KIBRA peptides provided herein including embodiments thereof. Thus, in another aspect is provided a pharmaceutical composition comprising a therapeutically effective amount of a C-terminal KIBRA compound provided herein including embodiments thereof and a pharmaceutically acceptable excipient.

[0179] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1**[0180] ABSTRACT**

[0181] The dynamic function of synapses is critical for encoding memories in the brain.

- 5 Pathogenic tau obstructs glutamatergic synapse function by blocking long-term potentiation (LTP), representing a key mechanism underlying memory impairment in Alzheimer's disease (AD). Here we developed a strategy for KIdney/BRAin (KIBRA)-mediated LTP repair in neurons with pathogenic tau using the C-terminus of KIBRA (CT-KIBRA). We show that CT-KIBRA restores LTP and memory in transgenic mice expressing human tau that mimics
- 10 pathogenic hyperacetylated tau found in AD and other tauopathies. CT-KIBRA did not alter tau levels or prevent tau-induced synapse loss in the transgenic mouse brain, instead, we show that CT-KIBRA binds to and stabilizes protein kinase M ζ (PKM ζ) to maintain plasticity and memory despite tau pathogenesis. Further, in humans we established that KIBRA levels in brain and cerebrospinal fluid correlate with tau and cognitive impairment in tauopathies. Our study
- 15 provides evidence to support KIBRA as a tauopathy-related synaptic biomarker and a synapse repair therapeutic to ameliorate cognitive impairment.

[0182] INTRODUCTION

- [0183]** Pathological tau protein accumulates and forms aggregates in the brain in neurodegenerative diseases classified as tauopathies, including Alzheimer's disease (AD), Pick's
- 20 disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Aberrant tau posttranslational modifications (PTMs) found in tauopathy brains can alter tau protein function, promote tau aggregation, and trigger toxicity in cells^{1,2}. The extent of pathologically modified tau that accumulates in human brain correlates with dementia severity in disease^{3,4}. Tau is predominantly localized within axons of healthy neurons, whereas an abundance of pathological
- 25 tau with PTMs is found at synapses in AD brain⁵⁻⁷. Synapse dysfunction is one of the earliest pathophysiological changes in tauopathy mouse models that precedes neurodegeneration and coincides with the start of cognitive impairments⁸⁻¹⁰. Long-term potentiation (LTP) is a key plasticity mechanism at synapses in the hippocampus that underlies the formation of new memories, and LTP is inhibited by tau with mutations that cause familial frontotemporal
- 30 dementia^{8,10,11}, as well as several AD-associated pathogenic forms of tau including

hyperacetylated tau⁹, hyperphosphorylated tau^{12,13}, and tau oligomers^{14,15}. Synapses, and their ability to express LTP, are particularly vulnerable to tau-induced toxicity in the brain.

[0184] KIDney/BRAin (KIBRA) is a postsynaptic protein encoded by the *WWC1* gene that has a single nucleotide polymorphism linked to memory and risk of late-onset AD in humans¹⁶⁻¹⁹.

5 The KIBRA protein is required for hippocampal LTP and memory in mice²⁰, and it contains multiple functional domains acting as a postsynaptic scaffold with approximately twenty binding partners identified^{21,22}, supporting a critical role for KIBRA in modulating synaptic signaling and strength. In humans, KIBRA protein is significantly diminished in the brain of severely impaired individuals with AD and reduced KIBRA levels are associated with abnormal hyperacetylated
10 tau⁹. Moreover, a mimic of hyperacetylated human tau expressed in transgenic mice (tauKQ^{high} mice) obstructs LTP by reducing KIBRA levels at synapses⁹, supporting that the loss of KIBRA function at synapses at least in part underlies AD-related plasticity and memory impairments.

[0185] Here, we show evidence that restoring KIBRA-dependent signaling at synapses can reverse LTP and memory deficits caused by pathogenic hyperacetylated tau, which accumulates
15 in the brain in most tauopathies²³. We generated a truncated version of the KIBRA protein, comprised of the C-terminal domain (CT-KIBRA), and demonstrate that expression of CT-KIBRA in neurons of transgenic mice with pathogenic tau is sufficient to reverse synaptic plasticity and memory impairments associated with AD and related dementias. Together with the observation that tauopathy-related pathology persists in the mouse brain, this provides evidence
20 that CT-KIBRA promotes synaptic and cognitive resilience to tau toxicity. We investigated the mechanistic effect of CT-KIBRA on LTP in neurons with pathogenic tau, finding that CT-KIBRA repairs synapse function through its interaction with protein kinase Mζ (PKMζ), an atypical protein kinase C (PKC) isoform that regulates postsynaptic AMPA-type glutamate receptors (AMPA-Rs) and sustains the maintenance of LTP and memory²⁴⁻²⁶. Finally, we show
25 that KIBRA levels in human brain and cerebrospinal fluid (CSF) correlate with tau levels and dementia severity in individuals with tauopathies. These results highlight the potential for a therapeutic strategy to re-establish KIBRA function in neurons, repair synapses, and reverse memory loss in tauopathy patients with altered KIBRA levels.

[0186] RESULTS

30 **[0187]** A functional domain of the KIBRA protein reverses AD-related synapse dysfunction

[0188] To dissect the functional effect of the KIBRA protein on tau-mediated synapse dysfunction, we generated constructs to express flag-tagged full-length human KIBRA or truncated forms of the KIBRA protein in neurons (FIG. 1A). Two functional domains of the KIBRA protein were tested, one with 86 residues of the N-terminus containing the WW domains (NT-KIBRA) that interacts with synaptopodin and dendrin^{27,28}, and the other with 187 residues of the KIBRA C-terminal domain (CT-KIBRA) that interacts with members of the PKC family including PKM ζ ²⁹⁻³¹. The constructs were expressed in cultured rat hippocampal neurons and immunostaining revealed that full-length human KIBRA and CT-KIBRA localized in dendritic spines, whereas the levels of NT-KIBRA in spines were significantly lower (FIG. 1B). We next examined the effect of the distinct KIBRA functional domains on the synaptic plasticity impairment caused by pathogenic tau. Neurons were transfected with either of the truncated KIBRA constructs together with human tau carrying lysine to glutamine mutations at lysine-274 and lysine-281 (tauKQ) to mimic hyperacetylated pathogenic tau found in Alzheimer's disease⁹. A chemical induction method, involving glycine treatment in the absence of magnesium, was applied to the neurons to induce LTP, which potentiates synapse function through recruitment of AMPARs to the surface of postsynaptic spines^{32,33}. There was a significant increase in immunolabeling of GluA1-containing AMPARs at the surface of spines in control neurons after chemical LTP induction whereas AMPAR insertion was obstructed in neurons expressing tauKQ with or without NT-KIBRA (FIG. 1D). Co-expression of CT-KIBRA with tauKQ in neurons rescued the increase in AMPARs on the spine surface triggered by chemical LTP (FIG. 1D). Likewise, the activity-induced recruitment of AMPARs to spines was blocked in neurons expressing human tau carrying the P301L mutation that causes familial frontotemporal dementia (FTD), and co-expression of CT-KIBRA with the FTD mutant tau rescued AMPAR recruitment during chemical LTP (FIG. 7).

[0189] Based on our finding that CT-KIBRA, but not NT-KIBRA, was sufficient to modulate AMPARs at synapses during plasticity, we next examined the effect of CT-KIBRA on LTP in aged transgenic mice expressing high levels of tauKQ (tauKQ^{high}). TauKQ^{high} mice have impaired LTP in the dentate gyrus by 6 months of age⁹. We generated lentivirus for flag-tagged CT-KIBRA expression in mouse hippocampus following stereotaxic injection. To determine the efficacy of CT-KIBRA in reversing synapse dysfunction in aged mice, the CT-KIBRA lentivirus (lenti-CT-KIBRA) or a control lentivirus (lenti-control) were bilaterally injected into the hippocampus of 15- to 16-month-old tauKQ^{high} mice and non-transgenic (ntg) controls. At 17 to

18 months of age, field recordings were performed in the dentate gyrus molecular layer with stimulation of the perforant pathway. Compared to ntg lenti-control mice, dentate granule cells in tauKQ^{high} mice with either lenti-control or lenti-CT-KIBRA exhibited similar basal postsynaptic responses to stimuli, but the fiber volley amplitudes recorded from perforant pathway projections into the dentate gyrus were significantly elevated at the highest stimulus intensities in both control and CT-KIBRA lentivirus treated tauKQ^{high} mice (FIG. 1D). This suggests that tauKQ alters the maximum strength of perforant pathway inputs to dentate gyrus in aged mice, however this presynaptic effect of tauKQ was not modulated by CT-KIBRA. Induction of LTP by theta burst stimulation (TBS) of the perforant pathway triggered a persistent enhancement of the postsynaptic response in ntg lenti-control mice which was impaired in tauKQ^{high} lenti-control mice (FIGS. 1E-1F). The magnitude of LTP in dentate granule cells was significantly increased in tauKQ^{high} lenti-CT-KIBRA compared to tauKQ^{high} lenti-control mice, and CT-KIBRA enhanced the persistent strengthening of synapses in tauKQ^{high} mice to the same level as ntg lenti-control mice (FIG. 1F). These results support that the C-terminal domain of the KIBRA protein is sufficient to restore AMPAR trafficking and LTP at synapses in hippocampal neurons with pathogenic tau.

[0190] CT-KIBRA improves hippocampus-dependent memory in mice with pathogenic tau despite tauopathy-related pathology

[0191] We next assessed the functional impact of CT-KIBRA on hippocampus-dependent memory impairment caused by pathogenic tau in aged mice. TauKQ^{high} mice have hippocampus-dependent pattern separation memory loss by 6-7 months of age coinciding with the LTP deficit in dentate gyrus⁹. To test the impact of CT-KIBRA treatment after the onset of memory impairment in aged tauKQ^{high} mice, injections of lenti-CT-KIBRA or lenti-control into bilateral hippocampi were performed on tauKQ^{high} mice and ntg littermates at 10-12 months old and behavior tests were performed 4-6 weeks later. During the sample phase of the object context congruency test of pattern separation memory, the mice spent equivalent time exploring the distinct pairs of identical objects in two different but similar contexts (FIG. 2A). In the memory test phase, one of the objects in each pair is switched between the contexts, thus presenting the mice with a familiar object that is incongruent with the context. The ntg mice explored the incongruent object significantly longer than the congruent object (FIG. 2B), which is an indication of hippocampus-dependent pattern separation memory. The tauKQ^{high} lenti-control

mice demonstrated impaired pattern separation memory, however lenti-CT-KIBRA restored the performance of tauKQ^{high} mice in discrimination of the mismatched object (FIG. 2B).

[0192] The tauKQ^{high} mice were next tested in the Y-maze to determine whether CT-KIBRA has an impact on hippocampus-dependent working memory. TauKQ^{high} lenti-control mice
 5 demonstrated impaired working memory, whereas the proportion of spontaneous alternations completed by tauKQ^{high} lenti-CT-KIBRA mice was significantly increased without affecting the total number of arm entries during the test (FIG. 2C). Thus, CT-KIBRA improved spatial working memory in the tauKQ^{high} mice. In the Morris water maze test of spatial learning and memory, ntg lenti-control, tauKQ^{high} lenti-control, and tauKQ^{high} lenti-CT-KIBRA mice showed
 10 comparable swim speeds and spatial learning to find the hidden platform during training (FIG. 2D). The ntg lenti-control, tauKQ^{high} lenti-control, and tauKQ^{high} lenti-CT-KIBRA mice spent a greater fraction of time in the target quadrant in the probe trial 24 h after the hidden platform training was completed (FIGS. 2E-2F). However, only the ntg lenti-control and tauKQ^{high} lenti-CT-KIBRA mice maintained a significant preference for the target quadrant probe trial after 7
 15 days, whereas tauKQ^{high} lenti-control mice did not (FIGS. 2E and 2G), indicating that CT-KIBRA reversed the long-term spatial memory impairment in tauKQ^{high} mice. Overall, these results support that CT-KIBRA enhances multiple forms of hippocampus-dependent memory that are compromised by pathogenic tau in the brain.

[0193] We next examined whether CT-KIBRA mitigates pathology in the brain caused by
 20 expression of the acetylated tau mimic. CT-KIBRA did not prevent the accumulation of phosphorylated tau at serine 202/205 (AT8) that was significantly increased in mossy fibers in the hippocampus of tauKQ^{high} mice. Total levels of human tau and tau phosphorylation at threonine 231 (AT180) and threonine 181 (AT270) in the hippocampus of tauKQ^{high} mice were also not altered by CT-KIBRA expression (FIGS. 2H-2I). Synaptic vesicle associated protein 2
 25 (SV2) has been used as an *in vivo* marker of synapse loss in human Alzheimer's disease brain^{34,35}. To assess synapse deterioration in tauKQ^{high} mice, we analyzed immunolabeling of SV2 and found that it was significantly decreased in the CA1 region of the hippocampus in tauKQ^{high} with or without CT-KIBRA compared to ntg controls (FIG. 2J). Thus, while CT-KIBRA is sufficient to restore hippocampal synaptic plasticity, it is not sufficient to reverse tau-mediated synapse loss in the CA1 region. Mass spectrometry analysis of protein extracted from
 30 whole hippocampus of tauKQ^{high} lenti-control and tauKQ^{high} lenti-CT-KIBRA mice was

performed to monitor changes in the global proteome compared to ntg lenti-control mice (FIG. 8A and Table 1). Notably, of the 64 hits identified that were either significantly increased or decreased in tauKQ^{high} compared to ntg mice, 33% of them changed in the hippocampi of both tauKQ^{high} lenti-control and tauKQ^{high} lenti-CT-KIBRA mice. A comparison of tauKQ^{high} mice with or without CT-KIBRA also yielded no significant differences ($Q < 0.05$) in the abundance of the proteins that were identified (Table 1). Cellular component classification of proteins that were significantly downregulated in both tauKQ^{high} lenti-control or tauKQ^{high} lenti-CT-KIBRA mice compared to ntg lenti-control mice revealed similar gene ontology terms including synapses and postsynaptic sites (FIGS. 8B-8C, Table 1). Proteins that were upregulated in tauKQ^{high} lenti-control and tauKQ^{high} lenti-CT-KIBRA mice compared to ntg lenti-control mice included microtubule and cytoskeleton components as well as axonal proteins (FIG. 8D, Table 1). These findings suggest that CT-KIBRA restores synaptic plasticity and reverses tau-induced memory impairment without altering levels of pathological tau in the brain and without recovering CA1 synapses lost in the hippocampus.

[0194] CT-KIBRA stabilizes and enhances PKM ζ at synapses with pathogenic tau

[0195] Previous studies established that KIBRA binds to PKM ζ and prevents PKM ζ degradation^{29,36}. KIBRA also interacts with PICK1, which modulates AMPAR trafficking during plasticity²⁰. To examine the interaction of CT-KIBRA with PKM ζ and PICK1 we used a proximity ligation assay (PLA) which detects protein-protein interactors within close proximity (<40 nm)³⁷. When expressed in HEK293 cells, full-length KIBRA and CT-KIBRA both exhibited significantly stronger PLA signal with HA-tagged PKM ζ than NT-KIBRA (FIGS. 3A-3B). These results are consistent with the requirement of the KIBRA C-terminus for PKM ζ binding²⁹, and confirm that the binding affinities of PKM ζ to CT-KIBRA and full-length KIBRA are comparable. The PLA signal intensity in HEK293 cells expressing HA-tagged PICK1 together with full-length KIBRA was significantly higher than in cells co-expressing NT-KIBRA or CT-KIBRA (FIG. 9), demonstrating that CT-KIBRA has a weaker association with PICK1 than full-length KIBRA. Given the strong interaction between CT-KIBRA and PKM ζ , we next tested the effect of CT-KIBRA on PKM ζ degradation kinetics in HEK293 cells. When HEK293 cells expressing PKM ζ alone were treated with cycloheximide (CHX) to block protein synthesis, PKM ζ levels quickly declined over 48 h (FIGS. 3B and 3D). Consistent with the stabilizing effect of KIBRA on PKM ζ , CT-KIBRA co-expression increased the total amount of PKM ζ in

HEK293 cells, and degradation of PKM ζ was significantly slower following CHX treatment in cells with CT-KIBRA compared to those that only expressed PKM ζ (FIGS. 3B-3D).

[0196] We next asked whether KIBRA stabilizes PKM ζ in postsynaptic spines. Flag-tagged CT-KIBRA co-localized with endogenous PKM ζ within postsynaptic spines and throughout the dendrites of cultured hippocampal neurons expressing tauKQ. To monitor the effect of CT-KIBRA on postsynaptic PKM ζ levels, cultured hippocampal neurons were co-transfected with mApple and tauKQ with or without CT-KIBRA and immunostained for PKM ζ . There was a significant increase in PKM ζ in postsynaptic spines of tauKQ-expressing neurons with CT-KIBRA compared to neurons with tauKQ alone and control neurons (FIG. 3E). These data support that the CT-KIBRA and PKM ζ interaction stabilizes and enhances PKM ζ levels in postsynaptic spines of neurons with pathogenic tau.

[0197] CT-KIBRA protects against PKM ζ downregulation associated with plasticity and memory impairments

[0198] A persistent increase in PKM ζ levels occurs in rodent neurons after LTP induction and learning^{24,38-41}. In cultured neurons expressing mApple, we found that PKM ζ levels were increased within spines 24 h after chemical LTP induction compared to neurons that were not stimulated (FIG. 4), in agreement with previous findings in cultured neurons⁴¹. This enhancement of PKM ζ was blocked in neurons expressing tauKQ, whereas co-expression of CT-KIBRA increased PKM ζ immunostaining in spines under both unstimulated and chemical LTP conditions (FIG. 4). These findings support that pathogenic acetylated tau blocks the increase in PKM ζ following LTP induction, which can be rescued by CT-KIBRA-mediated stabilization of PKM ζ in spines.

[0199] Hippocampal PKM ζ levels detected by immunoblotting were significantly reduced in 12–14-month-old tauKQ^{high} mice compared to littermate controls (FIGS. 10A-10B), and PKM ζ normalized to PSD-95, another postsynaptic protein, was also reduced in tauKQ^{high} mice (FIG. 10B). We further assessed the impact of tauKQ on PKM ζ levels in the context of learning and memory. PKM ζ was quantified in hippocampal lysates from ntg lenti-control, tauKQ^{high} lenti-control, and tauKQ^{high} lenti-CT-KIBRA mice that completed hippocampus-dependent learning and memory tests (FIG. 2). Total PKM ζ levels in tauKQ^{high} lenti-control mice remained significantly lower than ntg mice after learning whether or not PKM ζ was normalized to PSD-95, whereas tauKQ^{high} mice with CT-KIBRA showed a recovery of PKM ζ levels (FIGS. 4B-4C).

PICK1 was evaluated in the same mice, but the the PICK1 levels were not significantly different in tauKQ^{high} lenti-control mice compared to ntg lenti-control mice (FIGS. 10C-10D).

Experiments using acute PKM ζ knockdown in hippocampus suggest that PKM ζ plays a role in the maintenance of hippocampal dependent long-term memory^{40,42}, and the magnitude of PKM ζ enhancement after learning correlates with the capacity for long-term memory in mice⁴⁰.

Consistent with these studies we found a significant correlation between hippocampal PKM ζ levels and long-term memory among the ntg lenti-control, tauKQ^{high} lenti-control, and tauKQ^{high} lenti-CT-KIBRA mice. Higher levels of PKM ζ were associated with better memory retention in both the object context congruency test and the MWM (FIGS. 4D-4E). PKM ζ levels did not correlate with the performance of the mice in the Y-maze test of short-term working memory (FIG. 4F). These findings are consistent with the role of PKM ζ in long-term as opposed to short-term memory. Given that we found a recovery of short-term memory in tauKQ^{high} lenti-CT-KIBRA mice that did correlate with PKM ζ levels, CT-KIBRA may also enhance synapse function and other cognitive skills through additional mechanisms not yet identified.

[0200] The CT-KIBRA and PKM ζ interaction drives LTP repair in neurons with pathogenic tau

[0201] To investigate the mechanistic relationship between CT-KIBRA and PKM ζ in plasticity, we examined whether elevated PKM ζ levels are required for CT-KIBRA to restore AMPAR trafficking at synapses during LTP. An antisense oligodeoxynucleotide (PKM ζ -antisense) was chosen to acutely block PKM ζ expression in neurons to avoid compensation by other PKC isoforms²⁴, and because the ζ inhibitory peptide (ZIP) is not a specific inhibitor of PKM ζ ^{43,44}. Cultured hippocampal neurons co-expressing tauKQ and CT-KIBRA were treated with PKM ζ -antisense or a scrambled control 1 h before induction and throughout the expression of chemical LTP. The CT-KIBRA-mediated rescue of activity-induced postsynaptic AMPAR recruitment in tauKQ neurons was blocked by PKM ζ -antisense (FIG. 5A). We then tested whether overexpression of PKM ζ in neurons with pathogenic tau was sufficient to rescue synaptic plasticity. HA-tagged PKM ζ was expressed in neurons and immunolabeling with an HA antibody revealed comparable levels of HA-PKM ζ localized in spines of neurons with or without tauKQ (FIG. 11A). Interestingly, the overexpression of HA-tagged PKM ζ was not sufficient to restore AMPAR trafficking in tauKQ neurons in the absence of CT-KIBRA (FIG. 5B), supporting the critical role for KIBRA in the reversal of the tau-mediated plasticity deficit.

[0202] Mutations introduced at specific residues within the C-terminal domain of KIBRA block the interaction of KIBRA with PKM ζ ²⁹. We took advantage of these mutations to test the role of the CT-KIBRA and PKM ζ binding in the mechanism underlying the functional repair of synapses with pathogenic tau. We generated a CT-KIBRA-AAA mutant in which three residues, R965, S967 and R969, on the CT-KIBRA construct were changed to alanine residues (R965A, S967A and R969A), which block the binding of KIBRA to PKM ζ ²⁹. Using the PLA method in HEK293 cells, we confirmed that compared to wildtype CT-KIBRA, CT-KIBRA-AAA demonstrated a significantly diminished interaction with HA-PKM ζ (FIG. 5C). In cultured neurons the CT-KIBRA-AAA mutant was detected in dendritic spines similarly to wildtype CT-KIBRA (FIG. 11B). When tested in neurons with chemical LTP, tauKQ consistently impeded postsynaptic AMPAR recruitment during plasticity, but unlike wildtype CT-KIBRA, the CT-KIBRA-AAA mutant was not sufficient to reverse the impairment (FIG. 5D). These findings suggest that CT-KIBRA overcomes the plasticity impairment caused by pathogenic tau by promoting synaptic resilience through its interaction with and modulation of PKM ζ (FIG. 5E).

[0203] KIBRA levels in human brain and CSF are associated with pathological tau and cognitive impairment in older adults

[0204] To evaluate the potential applicability of KIBRA modulation as a therapeutic intervention for tau-mediated cognitive decline in humans, we investigated the relationship between KIBRA, PKM ζ and pathogenic tau levels in human tauopathy brain tissue. Immunoblot analyses were performed on brain homogenates from the middle temporal gyrus of control, Alzheimer's disease and Pick's disease cases (FIG. 6A and Table 2). There was a significant correlation between higher KIBRA levels and more PKM ζ in the brain (FIG. 6B), indicating a strong association between KIBRA and PKM ζ across healthy and pathological conditions. To assess the abnormal accumulation of acetylated tau in the brains, we used the Mab359 antibody which recognizes tau acetylated on K274 and labels pathological tau in most tauopathies, including both Alzheimer's disease and Pick's disease^{9,23}. The elevated levels of K274 acetylation on soluble tau exhibited a strong relationship with both lower KIBRA and lower PKM ζ levels in the brain (FIG. 6C).

[0205] KIBRA levels are significantly diminished in the brain in adults with severe Alzheimer's disease compared to non-demented controls⁹. Here we explored the relationship between cognition and KIBRA, as well as PKM ζ , in the brain across stages of dementia. Global

Clinical Dementia Rating (CDR) scores were analyzed in twelve participants that ranged in dementia severity from none-to-mild (CDR 0-1) to moderate-to-severe dementia (CDR 2-3). KIBRA levels were significantly reduced in individuals with moderate-to-severe dementia (CDR 2-3) compared to those with none-to-mild (CDR 0-1) impairment (FIG. 6D). Interestingly, total PKM ζ levels were reduced in only some of the cases with more advanced dementia compared to CDR 0-1 cases, and overall there was no significant difference in PKM ζ levels between the mild and impaired groups (FIG. 6E). Comparisons were also made using the CDR sum of box (CDRsum) scores, which enables more continuous characterization of the extent of functional impairment^{45,46}. KIBRA levels in control, Alzheimer's disease and Pick's disease brains were strongly correlated with the CDRsum score, with the most impaired individuals having the least amount of KIBRA in the brain (FIG. 6F). The correlational analysis of PKM ζ levels with CDRsum did not reach statistical significance (FIG. 6G). Thus, while the levels of both KIBRA and PKM ζ are linked to pathogenic tau in the brain in tauopathy, the total levels of KIBRA in the brain are more strongly associated with the clinical stage of dementia compared to PKM ζ levels.

[0206] Synaptic proteins can be detected in human CSF⁴⁷, including SNAP-25⁴⁸ and neurogranin^{49,50}, and are showing promise as biomarkers of *in vivo* synapse function in humans. Previous studies suggest that higher levels of several CSF synaptic proteins correlate with greater clinical dysfunction⁵¹. To establish a method for detection of human KIBRA in CSF, we first tested a KIBRA ELISA on lysates from HEK293 cells with or without KIBRA overexpression and we confirmed that the ELISA detected significant differences between KIBRA levels expressed at varying protein levels (FIG. 12A). We next used the ELISA to quantify the amount of KIBRA in CSF of 10 subjects with AD-related cognitive impairments as well as 15 control subjects with normal cognition (Table 3). KIBRA levels were compared to CSF tau biomarkers including phosphorylated tau (p-tau₁₈₁) and total tau which are both increased in CSF of AD patients and strongly correlate with worsened cognition⁵². CSF KIBRA was significantly increased in subjects with clinically elevated CSF p-tau₁₈₁ (FIG. 12B)⁵³. Furthermore, there was a strong correlation between higher KIBRA levels detected in CSF and increased p-tau₁₈₁ and total tau levels (FIGS. 6H-6I). In contrast, KIBRA did not correlate with concentrations of A β 40, A β 42 or the ratio of A β 42/A β 40 in CSF (FIGS. 6J, 12C-12D), indicating that CSF KIBRA is predominantly associated with biomarkers of tau pathology rather than with A β pathology. To assess CSF KIBRA as a synaptic biomarker related to cognition in AD, we examined the relationship between CSF KIBRA levels and cognitive performances across participants on tasks

of global cognition (Mini-Mental State Exam, MMSE). Higher CSF KIBRA levels significantly correlated with lower MMSE scores (FIG. 6K), supporting a link between worsened cognitive deficits and more abnormal levels of KIBRA in CSF. Together, these results demonstrate that reduced KIBRA in brain and increased KIBRA in CSF track strongly with cognitive impairment and tau pathology in human cases of tauopathy.

[0207] DISCUSSION

[0208] Our findings highlight the potential of KIBRA-mediated synapse repair as a novel therapeutic approach to alleviate memory loss associated with tauopathy. This targeted strategy to restore a precise functional role of KIBRA in synaptic plasticity could be leveraged to counteract the loss of KIBRA in human brain associated with cognitive impairment in tauopathy. Interestingly, CT-KIBRA improved memory performance and restored LTP in mice despite the accumulation of pathological tau in the brain, supporting that CT-KIBRA rescues mechanisms that promote synaptic resilience to tau toxicity in the brain. The therapeutic effect of CT-KIBRA involved its binding to and stabilization of PKM ζ to promote postsynaptic AMPAR trafficking during plasticity, enabling synapses to maintain function and overcome the adverse effects of pathogenic tau.

[0209] Our study provides evidence that CT-KIBRA can have a therapeutic effect when expressed in hippocampus after the onset of memory loss caused by pathogenic tau. This supports that CT-KIBRA recovers memory processes by repairing the molecular signaling at synapses required for plasticity. Enhancement of KIBRA signaling could also have therapeutic potential broadly across different tauopathies. CT-KIBRA improved synaptic plasticity and memory performance in a model of abnormal hyperacetylated tau, which is a common pathology found in most tauopathies including AD, Pick's disease, CBD and PSP^{2,23,54}. CT-KIBRA also restored synaptic plasticity in neurons expressing human P301L tau, confirming the protective effect of CT-KIBRA against tau toxicity associated with FTD. Nonetheless, it will be important to evaluate the impact of CT-KIBRA on synapse dysfunction and cognition in other tauopathy and neurodegenerative disease models. Notably, the mechanisms by which tau drives pathophysiology in neurons in disease are complex, involving not only synapse dysfunction and synapse loss^{8-10,55,56}, but also dysregulation of axonal transport and axon initial segment function as well as axon degeneration⁵⁷⁻⁵⁹, altered mitochondrial bioenergetics⁶⁰, nuclear transport disruption^{61,62}, altered proteostasis⁶³, and cytoskeletal destabilization^{64,65}. Given that CT-KIBRA

did not affect tau levels or synapse loss in hippocampus, it likely plays a specific role in modulating synaptic plasticity without impacting other tau-mediated pathophysiological outcomes.

[0210] KIBRA deficient mice have reduced PKM ζ protein levels in the hippocampus, and impaired plasticity and memory loss^{29,66}, which is consistent with a key role for KIBRA in PKM ζ stabilization and the maintenance of synaptic plasticity. Our results show that tauKQ^{high} mice, which have reduced KIBRA at synapses⁹, also had decreased PKM ζ levels in hippocampus associated with impaired LTP and hippocampus-dependent memory. CT-KIBRA had a protective effect by restoring levels of PKM ζ . The strong relationship between KIBRA and PKM ζ protein levels was further evident in human brain with and without pathology. Hyperacetylated tau correlated with lower levels of soluble KIBRA and PKM ζ proteins in tauopathy brains, supporting the mechanistic link between pathological tau and downregulation of KIBRA and PKM ζ . Aggregates of PKM ζ have been observed in neurofibrillary tangles containing hyperphosphorylated tau in AD brain⁶⁷, but whether KIBRA is also bound to PKM ζ -containing insoluble aggregates is unknown. Strikingly, there was a prominent correlation between KIBRA downregulation in human brain and dementia severity, supporting KIBRA as a critical synaptic component linked to cognitive decline in tauopathy.

[0211] The persistent increase in postsynaptic PKM ζ levels following plasticity induction underlies the maintenance of LTP³⁸, and we found that this activity-dependent increase in PKM ζ was blocked in neurons with pathogenic tau. Interestingly, CT-KIBRA expression enhanced the PKM ζ levels in spines of tauKQ neurons with or without chemical LTP induction; yet, CT-KIBRA only increased postsynaptic AMPAR trafficking following chemical LTP without altering AMPARs in unstimulated neurons. These findings indicate that CT-KIBRA restores potentiation at synapses both by elevating PKM ζ levels and by enabling an additional activity-dependent signal, which remains to be determined, that drives the AMPAR recruitment after LTP induction. Surprisingly, PKM ζ overexpression alone was incapable of rescuing plasticity in tauKQ neurons, supporting that CT-KIBRA has a mechanistic effect during synaptic plasticity beyond enhancing PKM ζ levels. Intriguing mechanisms that may be involved in the plasticity repair orchestrated by CT-KIBRA could involve the activation of PKM ζ or other PKC isoforms, the phosphorylation of the C-terminus of KIBRA by PKM ζ ³¹, or the phosphorylation of AMPARs. CT-KIBRA may also modify synapse strength through binding to other PKC isoforms

implicated in synaptic plasticity regulation, such as PKC γ , α , β , and ι , which were reduced in postsynaptic fractions prepared from KIBRA knockout mice⁶⁶. While our study highlights the critical role for KIBRA in modulating synapse repair to recover memory, and showed that PKM ζ overexpression alone is not sufficient alone to restore plasticity in neurons with pathogenic tau, a recent study found that the memory impairments caused by oligomeric amyloid β toxicity in rats were alleviated by PKM ζ overexpression in hippocampus⁶⁸. Thus, enhanced PKM ζ levels may be sufficient to promote synapse function under certain pathogenic conditions but not others. How KIBRA, PKM ζ , and other PKC family members could be modulated to restore plasticity in neurodegenerative diseases deserves further investigation.

10 **[0212]** The KIBRA protein has multiple functional domains that engage in interactions with numerous postsynaptic proteins to modulate synapse function, and here we identified a specific KIBRA domain and interaction that can have a beneficial impact in the context of disease. The N-terminal WW domains of KIBRA bind to dendrin, and an inhibitory peptide that blocks this interaction reduced KIBRA levels and AMPARs at synapses on neurons, blocked LTP, and
15 impaired memory in mice²⁷, indicating that the interaction between KIBRA and dendrin regulates synaptic KIBRA localization and plasticity. We expressed NT-KIBRA, comprised of only the WW domains, in neurons and detected it in dendritic spines, although to a lesser degree compared to full-length KIBRA, and it did not rescue LTP in neurons with pathogenic tau. This suggests that while the dendrin/KIBRA WW domain interaction is necessary for plasticity in
20 healthy neurons, it is not sufficient to reverse the plasticity impairment caused by pathogenic tau. The binding of KIBRA to PICK1 can also modulate activity-dependent AMPAR trafficking in neurons²⁰. Our findings show a weakened interaction of CT-KIBRA with PICK1 compared to full-length KIBRA and a modest effect of pathogenic tau on PICK1 protein levels, but whether CT-KIBRA could influence PICK1-dependent AMPAR trafficking in neurons, or additional
25 plasticity mechanisms, remains to be determined. In future studies it will be important to consider that the impact KIBRA has on synapse function and plasticity through its interactions with postsynaptic proteins may depend on normal or pathological conditions in the brain.

[0213] Our study also reveals for the first time compelling evidence that KIBRA levels in CSF are associated with tau biomarkers and cognition in AD. These results point toward KIBRA as a
30 biomarker for synapse dysfunction that could be useful for diagnosis and staging disease progression in tauopathy. The higher KIBRA levels detected in CSF may be linked to the

downregulation of KIBRA in the synaptic compartment in tauopathies. For example, KIBRA may be expelled from neurons with dysfunctional synapses and accumulate in the CSF, but the mechanisms underlying the changes in KIBRA levels at synapses and in CSF are unclear. Our findings are consistent with prior studies showing higher SNAP-25, synaptotagmin-1, GAP-43, and neurogranin levels in CSF are associated with cognitive impairment in AD⁴⁸⁻⁵⁰, which may be linked to synapse degeneration in the brain⁶⁹. To advance clinical application and potentially identify individuals that could benefit from a KIBRA therapeutic, future studies should focus on evaluating KIBRA as a biomarker of synapse dysfunction and cognitive decline together with engineering a CT-KIBRA-based therapeutic that can be delivered across the blood-brain barrier into the brain. CT-KIBRA-mediated synapse repair could be a valuable approach in combination with pathology-modifying strategies designed to slow progression of cognitive decline by reducing tau levels or clearing toxic forms of tau from the brain which are being tested in ongoing clinical trials^{70,71}. Our work supports a KIBRA-based synapse repair therapy that could promote the recovery of cognition in tauopathy with treatment by boosting the resilience of synapse function.

[0214] METHODS

[0215] Mice

[0216] TauKQ^{high} mice were previously generated (Tracy et al., 2016) and maintained in the C57BL/6 genetic background. TauKQ^{high} mice were crossed with FVB/N mice (Jackson Laboratories) to generate TauKQ^{high} mice in a FVB/N and C57BL/6 mixed background for experiments. Behavior experiments were performed in daylight hours. Mice were housed in a pathogen-free barrier facility with a 12h light-dark cycle and provided with ad libitum access to water and food. Female and male mice were used in all experiments. All animal procedures were completed under the supervision of the Buck Institute Research on Aging Institutional Animal Care and Use Committee.

[0217] Antibodies

[0218] Monoclonal antibodies used included: AT270 (MN1050, Thermo Fisher Scientific, RRID: AB_223651), AT180 (MN1040, Thermo Fisher Scientific, RRID: AB_223649), HT7 (MN1000, Thermo Fisher Scientific, RRID: AB_2314654), Tau5 (AHB0042, Thermo Fisher Scientific, RRID: AB_2536235), Mab359 (from Dr. Li Gan), anti-GAPDH (MAB374, Sigma-

Aldrich, RRID: AB_2107445), anti-FLAG (F1804, Sigma-Aldrich, RRID: AB_262044), AT8 (MN1020, Thermo Fisher Scientific, RRID: AB223647), anti-SV2 (University of Iowa DSHB, RRID: AB_2315387), anti-PICK1 (75-040, Antibodies Inc, RRID: AB_2164544), anti-KIBRA (sc-133374, Santa Cruz Biotechnology, RRID: AB_2216359). Polyclonal antibodies used
 5 included: anti-PKMz (from Dr. Todd C. Sacktor), anti-PSD95 (2507, Cell Signaling Technology, RRID: AB_561221), anti-HA (H6908, Sigma-Aldrich, AB_260070), GFP (A-21311, Thermo Fisher Scientific, RRID: AB_221477), anti-GluA1 (ABN241, Millipore, RRID: AB_2721164)

[0219] Cultured Neurons

[0220] Primary hippocampal neurons were prepared from embryonic day 22 rat brains.

10 Neurons were plated at a density of 100,000 cells / mL on coverslips coated with poly-L-lysine (Sigma) in Neurobasal medium with B27 supplement (Gibco) and Glutamax (Invitrogen). Half the media was replaced at 1 day in vitro (DIV). At 7 DIV, half the media was replaced again and 4 μ M cytosine β -D-arabinofuranoside (Sigma) was added. Neurons were transfected with plasmids using Lipofectamine 2000 (Invitrogen) at 10-11 DIV.

15 [0221] Chemical LTP

[0222] Chemical LTP experiments were performed at 14-15 DIV in extracellular solution (ECS) containing (in mM): 125 NaCl, 5 KCl, 25 HEPES, 1 NaH₂PO₄, 11 Glucose, 2.5 CaCl₂, 0.0005 tetrodotoxin, 0.1 picrotoxin, and 0.001 strychnine (pH 7.4) warmed to 37°C. Neurons were briefly washed in ECS then transferred to ECS containing 300 μ M Glycine for 5 min at
 20 room temperature to induce chemical LTP while unstimulated neurons were washed with ECS. After chemical LTP induction, all neurons were washed with ECS and incubated for 10 min at 37°C. Coverslips were treated with anti-GluA1 antibody (ABN241, Sigma) in ECS for 15 min at 37°C. After antibody labeling, neurons were briefly washed with ECS then fixed in 4% paraformaldehyde (PFA). Coverslips were washed three times in PBS then incubated in blocking
 25 solution containing PBS, 2% normal goat serum, and 0.1% Triton X-100 for 1 h. An anti-rabbit conjugated Alexa 647 (Invitrogen) secondary antibody was applied for 1 h at room temperature then the coverslips were washed three times in PBS. For experiments using GFP-TauKQ or GFP-tauP301L, neurons were labeled with anti-GFP conjugated to Alexa 488 (A21311, Invitrogen) to enhance the GFP signal. Coverslips were mounted on glass slides in Prolong Gold
 30 (Invitrogen). Images of transfected neurons were acquired on a Zeiss LSM 700 confocal microscope. Laser power and gain settings were kept constant across neurons within an

experiment. Settings were established to keep the brightest pixel intensities just below saturation, except when the morphology of dendritic spines had to be clearly defined (e.g., saturated pixels of mApple fluorescence in dendrites to detect the signal in spines). The integrated intensity of GluA1 immunolabeling within dendritic spines marked by was measured from at least 50 spines per neuron using ImageJ software. Analysis was performed blind to the experimental condition.

[0223] Stereotaxic Injection and Virus

[0224] Flag-tagged CT-KIBRA (residues 926 to 1112) was subcloned into a lentiviral FUGW2 plasmid. The FUGW2 plasmid containing CT-KIBRA was co-transfected with $\Delta 8.9$ and VSV-G packaging plasmids in HEK293T cells using calcium phosphate transfection. The lentivirus was propagated in HEK293 cells at 37°C and was collected twice over a 48-hour period. The collected media containing the lentivirus was purified using sucrose gradient ultracentrifugation. The purified lentivirus was resuspended in sterile PBS and stored at -80°C. Lentivirus titer was estimated using a p24 Rapid Titer Kit (Takara Bio USA, Inc). Mice were anesthetized by isoflurane inhalation, and a stereotax was used to position the lentivirus injection directly into the mouse hippocampus using the following coordinates from bregma: anterior-posterior: -2.0, medial-lateral ± 1.5 , dorsal-ventral -1.8. The lentivirus was injected into the hippocampus at a rate of 0.5 μ L/min. Mice received analgesic treatment with buprenorphine with one dose at the start of the surgery and two additional doses within 24 h after surgery.

[0225] Acute Slice Preparation

[0226] Mouse brains were quickly dissected into cold sucrose dissection solution containing (in mM): 210 sucrose, 2.5 KCl, 1.25 NaH_2PO_4 , 25 NaHCO_3 , 7 glucose, 2 MgSO_4 , and 0.5 CaCl_2 (perfused with 95% O_2 , 5% CO_2 with pH ~ 7.4). Horizontal slices were cut at 400 μ m thickness (VT1000S Vibratome, Leica) and incubated for 30 min in artificial ACSF at 35°C containing (in mM): 119 NaCl, 2.5 KCl, 26.2 NaHCO_3 , 1 NaH_2PO_4 , 11 Glucose, 1.3 MgSO_4 (gassed with 95% O_2 , 5% CO_2 pH ~ 7.4). After recovery, slices were kept at room temperature with continuous oxygen bubbling.

[0227] Electrophysiology

[0228] Extracellular field recordings were performed from acute horizontal brain slices. Recording electrodes were placed in the molecular layer of the dentate gyrus. Slices were placed in recording chambers perfused with oxygenated ACSF solution heated to 30°C. Recording

electrodes (~3 megaohms resistance) were filled with ACSF and lowered 50 μm into the dorsal blade of the molecular layer of the dentate gyrus. A bipolar tungsten electrode (FHC) was positioned ~150 μm away from the recording electrode to stimulate the perforant pathway inputs to the dentate gyrus. Stimulus pulses were elicited at an intensity range from 0.25 μA – 25 μA every 30 seconds with a 0.5 ms stimulus duration using a Model 2100 Isolated Pulse Stimulate (A-M Systems) to acquire the maximal fEPSP slope. The stimulus intensity was adjusted to 30% of the maximal fEPSP slope to record the baseline for LTP recordings. LTP recordings were performed in the presence of 100 μM picrotoxin (Sigma). Baseline fEPSPs were recorded for 20 min. Following the baseline, the stimulus intensity was increased to 60% of the maximal fEPSP slope for the theta burst stimulation (TBS) only. TBS consisted of 10 theta bursts applied every 15 seconds and each theta burst contained 10 bursts (4 pulses, 100 Hz) every 200 ms. After TBS the stimulus intensity was returned to the same level as during the baseline LTP recordings and fEPSPs were recorded for an additional 60 min. The fEPSP slope was normalized to baseline LTP responses. Recordings were acquired with WinLTP software (version 1.11b, University of Bristol) using a Multiclamp 700B amplifier (Molecular Devices). Recordings and analyses were performed blind to genotype.

[0229] Behavioral Tests

[0230] For the object-context congruency test, mice were habituated in the testing room while in their home cage for 30 min before the start of testing. During the sample phase, mice explored two similar, but distinct contexts in two different 10 min sessions that were 30 min apart. Context 1 was a white box that was cleaned with 70% ethanol. Context 2 was a white box with black and white checkered wallpaper on the 4 walls that was cleaned with 1% acetic acid. Context 1 contained two identical blue cylindrical containers (X_1 and X_2), and Context 2 contained two identical T25 flasks filled with yellow sand (Y_1 and Y_2). The mice were returned to their home cages for 4 h after the sample phase. For the test phase, one of the X objects in Context 1 was replaced with an incongruent Y object, and one of the Y objects in Context 2 was replaced with an incongruent X object. Half of the mice, balanced by genotype and sex, were tested in Context 1 and the other half were tested in Context 2. The amount of time mice spent exploring the congruent and incongruent objects during a 10-min session was calculated. The time spent exploring was established by monitoring the time the mouse's nose was directed

toward the object and within approximately 2 cm from it. Videos of the sessions were manually scored by an experimenter who was blind to mouse genotype and treatment.

[0231] Y-maze arena was constructed with plexiglass having three arms of equal length (20 cm) at equal angles. Mice were placed in the center and allowed to freely explore the arena for 5 min and recorded by video (Noldus). Each mouse was manually scored for the sequence and number of arm entries in the 5-min period and the experimenter was blind to the genotype and treatment of each mouse. An arm entry was defined as having all four paws within one arm. The percentage of spontaneous alternations for each mouse was calculated as the number of alternations divided by the total possible number of alternations in the 5-min session. An alternation is defined as the mouse having entered all three arms in succession without revisiting a previously entered arm.

[0232] The Morris water maze used a pool with a diameter of 120 cm and filled with water at a temperature $22 \pm 1^\circ\text{C}$ made opaque by the addition of white tempera paint. Visual cues were placed around the pool. The experimenter was blind to the genotype and treatment of each mouse. Mice were pretrained for one day with 4 trials to find a submerged hidden square platform (14 cm x 14 cm) that was 1.5 cm below the water surface located in the center of a rectangular channel. The day after pretraining, each mouse performed 4 days of hidden platform training with 2 trials per day where they had 60 seconds to find and sit independently on the platform for 10 s. Upon completion of hidden platform training, the platform was removed from the pool and mice were tested in a single probe trial for 60 s on subsequent days. Following probe trials, all mice were tested in cued platform training. Each mouse was recorded and tracked during hidden platform training, probe trials, and cued platform training using EthoVision XT software (Noldus).

[0233] Western Blot

[0234] A dounce homogenizer was used to homogenize human brain tissue samples in RIPA buffer containing 50 mM Tris, pH 7.5, 150 mM NaCl, 0.5% Nonidet P-40, 1 mM EDTA, 0.5% sodium deoxycholate, 0.1% SDS, 1 mM phenylmethyl sulfonyl fluoride, protease inhibitor cocktail (Sigma), phosphatase inhibitor cocktail (Sigma), 5 mM nicotinamide (Sigma) and 1 μM trichostatin A (Sigma). Homogenized tissue was sonicated 20 times with 1 sec pulses and then centrifuged using a SW55 Ti rotor (Beckman Coulter) at 42,700 rpm for 15 min at 4°C . Mouse

tissue was homogenized in RIPA buffer containing 50 mM Tris-HCl pH 7.5, 0.5% Nonidet P-40, 150 mM NaCl, 1 mM EDTA, 1 mM phenylmethyl sulfonyl fluoride, protease inhibitor cocktail (Sigma), phosphatase inhibitor cocktail 2 (Sigma) and phosphatase inhibitor cocktail 3 (Sigma). Tissue was homogenized with a hand-held homogenizer for 2 min and sonicated 10 times with 1 sec pulses. Lysates were then incubated on ice for 30 min and centrifuged at 18,000 g at 4°C for 20 min. The supernatants were collected from human or mouse brain homogenates after centrifugation and the protein concentration was measured by Bradford Assay (Bio-Rad). Equal amounts of proteins were run on a 4-12% gradient SDS-PAGE gel (Invitrogen) and the protein was transferred to a nitrocellulose membrane (GE Healthcare). The membranes were blocked with 5% nonfat dry milk in TBST for at room temperature for 1 hr followed by incubation with primary antibodies in TBST with 2% nonfat dry milk overnight at 4°C. Membranes were washed with TBST and incubated with secondary antibodies in TBST with 2% nonfat dry milk at room temperature for 1 hr. After washing, chemiluminescence (Pierce) was used to detect immunolabeled proteins and ImageJ software (NIH) was used for quantification.

15 [0235] Mass Spectrometry Analyses

[0236] Mouse hippocampal tissue was homogenized in RIPA buffer (50 mM Tris-HCl pH 7.5, 0.5% Nonidet P-40, 150 mM NaCl, 1 mM EDTA, 1 mM phenylmethyl sulfonyl fluoride, protease inhibitor cocktail, and phosphatase inhibitors). Gene Ontology (GO) term enrichment analyses were performed with Gene Set Enrichment Analysis (GSEA)^{72,73} or ClueGO version 2.5.4 in Cytoscape version 3.7.1^{74,75}. Enrichment analyses were applied from GO Cellular Compartments.

[0237] Plasmids

[0238] Flag-tagged full-length human KIBRA, NT-KIBRA and CT-KIBRA were cloned into the pCDNA 3.1 vector. The human KIBRA sequence originated from the pBabepuro-KIBRA vector⁷⁶ (Addgene #40887). For lentiviral-based expression, the flag-tagged CT-KIBRA sequence was inserted into FUGW2 (Gladstone Institutes) and packaged into virus using Δ8.9 and VSV-G plasmids. HA-tagged PKMζ and HA-tagged PICK1 were cloned into pcDNA 3.1 from human cDNA plasmids verified by sequencing (SinoBiological). GFP-tagged human tauKQ and tauP301L were expressed from the pEGFP-C1 plasmid (Clontech). Expression of mApple or GFP in cultured neurons was done using pGW1-mApple and pEGFP-C1 plasmids,

respectively. CT-KIBRA-AAA mutant was generated by site-directed mutagenesis of CT-KIBRA in pcDNA3.1 (Genscript).

[0239] Antisense Oligonucleotide

[0240] Antisense oligonucleotides against PKMzeta (C*T*C*TTGGGAAGGCAT*G*A*C) and scrambled oligonucleotides (A*A*C*AATGGGTCGTCT *C*G*G) were generated (IDT) with phosphorothioate bonds (*). For chemical LTP experiments, rat neurons were preincubated with oligonucleotides (20 µM final) for 1 h before chemical LTP, and the oligonucleotides remained in the media for the duration of the chemical LTP experiment.

[0241] Immunohistochemistry

[0242] Mouse brain sections (30-40 µm) were used for immunohistochemistry. For AT8 immunostaining, sections were washed with PBS and heated to 95°C for 5 min in 10 mM Sodium Citrate for antigen retrieval, followed by incubation at room temperature for 20 min. Sections were washed with PBS and incubated in blocking solution (PBST with 10% normal goat serum) for 2 h at room temperature. Next, sections were incubated with primary AT8 antibody (1:1000) diluted in PBST with 3% normal goat serum overnight at 4°C. Sections were then washed with PBST, incubated with Alexa-Fluor 488 secondary antibody (1:1000) diluted in 3% normal goat serum for 2 h at room temperature and washed with PBST before mounting. Images were acquired on a digital microscope (KEYENCE) using a 20x objective lens. For SV2 immunostaining, sections were washed with PBS and non-specific binding was blocked by 10% normal goat serum in PBST for 1 h at room temperature. Next, sections were incubated with SV2 antibody (1:500) diluted in PBST with 3% normal goat serum overnight at 4°C. Sections were then washed with PBST, incubated with Alexa-Fluor 488 secondary antibody (1:1000) diluted in 3% normal goat serum for 2 h at room temperature and washed with PBST before mounting. Images were acquired on LSM 700 laser scanning confocal microscope (Zeiss) using a 20x objective lens. ImageJ software (NIH) was used to quantify immunofluorescence from both AT8 and SV2 immunostaining.

[0243] Proximity Ligation Assay (PLA)

[0244] HEK293T cells were plated on glass coverslips coated with poly-L-lysine at a density of 80,000 cells/mL. Cells were transfected 24 h later with plasmid DNA with Lipofectamine 2000 (Invitrogen). HEK cells were fixed in 4% PFA 24 h after transfection and washed three

times with PBS. Following the manufacturers protocol, coverslips were blocked in Duolink blocking solution (DUO82007, Sigma) then labeled with primary antibodies and the secondary antibodies, anti-Rabbit PLUS (DUO92002, Sigma) and anti-Mouse MINUS (DUO92004, Sigma). PLA signals were detected using the red Duolink in situ detection reagent kit (DUO92008, Sigma) and imaged on the Zeiss LSM700. Images were analyzed using ImageJ software.

[0245] Protein Stability Assay

[0246] Plated 0.5×10^6 HEK293 cells on each well of a 12-well culture plate. The cells were then transfected with HA-PKMz or HA-PKMz and CT-KIBRA-flag using lipofectamine 2000 (Life Technologies). A day after transfection, untreated cells (0 hr timepoint) were harvested, while the rest of the cells were treated with 5 mg/ml of cycloheximide. Treated cells were then harvested after 24 and 48 h of incubation with cycloheximide. Harvested cells were resuspended in RIPA buffer containing 50 mM Tris-HCl pH 7.5, 0.5% Nonidet P-40, 150 mM NaCl, 1 mM EDTA, 1 mM phenylmethyl sulfonyl fluoride, protease inhibitor cocktail (Sigma), phosphatase inhibitor cocktail 2 (Sigma) and phosphatase inhibitor cocktail 3 (Sigma). Resuspended cells were sonicated 10 times with 1 sec pulses. Lysates were then incubated on ice for 30 min and centrifuged at 18,000 g at 4°C for 20 min. The supernatant was collected and western blot was performed to detect PKMz and KIBRA levels.

[0247] Human subjects

[0248] Brain Tissue Samples. Human brain tissue samples were from the middle temporal gyrus of control (n=6), Alzheimer's disease (n=7) and Pick's disease (n=7) cases. The samples were acquired from the Neurodegenerative Disease Brain Bank at the Memory and Aging Center of the University of California San Francisco.

[0249] CSF Samples. For in-vivo CSF KIBRA quantification, 25 older adults who were either clinically normal (n= 15) or diagnosed with Alzheimer's dementia (n=10) were included. All participants were community-dwelling older adults who completed comprehensive neurologic and neuropsychological evaluations, as well as study partner interview at the University of California San Francisco Memory and Aging Center. Participants were reviewed and determined to be either within normative standards or meet research consensus criteria for Alzheimer's dementia⁷⁷ at a multidisciplinary consensus conference by board-certified neurologists and

neuropsychologists. All clinically normal adults evidenced no functional decline (Clinical Dementia Rating (CDR)= 0), while Alzheimer's disease participants ranged from mild to moderate stages of functional impairment (CDR range 0.5 to 2).

5 [0250] CSF was collected via lumbar puncture in the morning following a 12-hour fast in sterile polypropylene tubes. Within 30 min of collection, CSF samples were centrifuged at 2000g at room temperature (20-25°C) for 5 min before being aliquoted into 500uL cryovials and stored at -80°C until analysis, following standard procedure⁷⁸.

[0251] All study procedures were conducted in accordance with the latest Declaration of Helsinki and approved by the local UCSF Institutional Review Board. Participants provided
10 written informed consent to participate in study procedures.

[0252] ELISAs

[0253] Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure levels of KIBRA (Wuhan Fine Biotech Co., Ltd, China), p-tau181, t-tau (INNOTEST, USA), Ab40 and Ab42 (ThermoFisher, USA) in CSF samples. ELISAs on CSF
15 were performed in duplicates and averaged. Samples with % CV > 20% were excluded from analyses.

[0254] Statistical Analyses

[0255] Differences between two means were analyzed by Student's *t*-test, and differences between multiple means were analyzed by one-way or two-way ANOVA with Bonferroni
20 multiple comparison *post-hoc* analyses. Repeated measures two-way ANOVA with Bonferroni multiple comparison was used to analyze input output results from field recordings of dentate gyrus and to analyze spatial learning in the MWM test. ClueGO analyses of mass spectrometry results showed networks with p-values < 0.05 with right-sided hypergeometric testing and Bonferroni adjustment. Either Spearman's or Pearson's correlational analyses were used to
25 evaluate the relationship between two variables.

[0256] Table 1. Patient information for human brain tissues described herein.

Case number	Sex	Age at death	Clinical	Primary Neuropath Dx	PMI (hrs) ^a	ADNC ^b
P2323.10	M	70	bvFTD	Pick's	10.2	-
P2494	M	72	bvFTD	Pick's	24.3	Not ADNC
P2533	F	76	bvFTD	Pick's	25.5	Not ADNC
P2682	F	74	nfvPPA	Pick's	9.8	Not ADNC
P2639	M	86	AD, Vascular	Pick's	14.8	Low
P3043	F	76	nfvPPA	Pick's	5.9	Low
P3052	M	78	svPPA (right)	Pick's	7.5	Not ADNC
P2345.11	F	86	control	none	7.8	Low
P2394.12	M	76	control	none	8.2	Low
P2577	M	94	control	VBI	20	Low
P2594	F	86	control	none	6.4	Not ADNC
P2850	F	92	control	none	8	Not ADNC
P2921	F	82	control	none	9.6	Low
P3045	F	84	control	none	7.7	Low
P2412.12	M	88	AD	AD	10.8	High
P2484	M	88	AD	AD	9.8	High
P2508	M	82	AD	AD	6.7	High
P2554	M	85	AD	AD	11.2	High
P2592	M	86	AD	AD	8.6	High
P2612	M	82	AD	AD	9	High
P2823	F	89	AD	AD	15.8	High

^aPMI = Post-mortem interval^bADNC = Alzheimer's disease neuropathological change

[0257] Table 2. Patient information for the cerebrospinal fluid (CSF) described herein.

Case number	Age	Sex	Cognition	MMSE ^a
2720	80	F	normal	28
5064	58	M	normal	x
7261	70	M	normal	29
7841	69	F	normal	30
8843	70	M	normal	29
12955	66	M	impaired	18
13690	62	M	impaired	24
14744	65	M	impaired	26
15035	69	F	impaired	30
15313	74	F	normal	29
15468	57	M	impaired	23
15508	60	F	normal	x
15590	68	F	impaired	21
15791	56	F	impaired	25
16304	60	F	impaired	8
17412	63	M	impaired	12
17615	53	M	normal	x
17735	71	F	normal	30
18176	55	M	normal	x
21514	68	F	normal	30
25992	54	F	normal	29
26161	80	M	impaired	25
26234	72	M	normal	30
26323	55	M	normal	30
29442	69	M	normal	39

^aMMSE = Mini Mental State Examination**[0258]** REFERENCES

- [0259]** 1 Alquezar, C., Arya, S. & Kao, A. W. Tau Post-translational Modifications: Dynamic Transformers of Tau Function, Degradation, and Aggregation. *Frontiers in neurology* **11**, 595532, doi:10.3389/fneur.2020.595532 (2020).
- [0260]** 2 Arakhamia, T. *et al.* Posttranslational Modifications Mediate the Structural Diversity of Tauopathy Strains. *Cell* **180**, 633-644.e612, doi:10.1016/j.cell.2020.01.027 (2020).
- [0261]** 3 Nelson, P. T. *et al.* Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *Journal of neuropathology and experimental neurology* **71**, 362-381, doi:10.1097/NEN.0b013e31825018f7 (2012).
- [0262]** 4 Tanner, J. A. & Rabinovici, G. D. Relationship Between Tau and Cognition in the Evolution of Alzheimer's Disease: New Insights from Tau PET. *Journal of nuclear medicine* :

official publication. *Society of Nuclear Medicine* **62**, 612-613, doi:10.2967/jnumed.120.257824 (2021).

- [0263] 5 Tai, H. C. *et al.* Frequent and symmetric deposition of misfolded tau oligomers within presynaptic and postsynaptic terminals in Alzheimer's disease. *Acta neuropathologica communications* **2**, 146, doi:10.1186/s40478-014-0146-2 (2014).
- [0264] 6 Tai, H. C. *et al.* The synaptic accumulation of hyperphosphorylated tau oligomers in Alzheimer disease is associated with dysfunction of the ubiquitin-proteasome system. *The American journal of pathology* **181**, 1426-1435, doi:10.1016/j.ajpath.2012.06.033 (2012).
- [0265] 7 Henkins, K. M. *et al.* Extensive p-tau pathology and SDS-stable p-tau oligomers in Alzheimer's cortical synapses. *Brain pathology (Zurich, Switzerland)* **22**, 826-833, doi:10.1111/j.1750-3639.2012.00598.x (2012).
- [0266] 8 Yoshiyama, Y. *et al.* Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* **53**, 337-351, doi:10.1016/j.neuron.2007.01.010 (2007).
- [0267] 9 Tracy, T. E. *et al.* Acetylated Tau Obstructs KIBRA-Mediated Signaling in Synaptic Plasticity and Promotes Tauopathy-Related Memory Loss. *Neuron* **90**, 245-260, doi:10.1016/j.neuron.2016.03.005 (2016).
- [0268] 10 Hoover, B. R. *et al.* Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron* **68**, 1067-1081, doi:10.1016/j.neuron.2010.11.030 (2010).
- [0269] 11 Sydow, A. *et al.* Tau-induced defects in synaptic plasticity, learning, and memory are reversible in transgenic mice after switching off the toxic Tau mutant. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **31**, 2511-2525, doi:10.1523/jneurosci.5245-10.2011 (2011).
- [0270] 12 Shipton, O. A. *et al.* Tau protein is required for amyloid {beta}-induced impairment of hippocampal long-term potentiation. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **31**, 1688-1692, doi:10.1523/jneurosci.2610-10.2011 (2011).

- [0271] 13 Shentu, Y. P. *et al.* CIP2A Causes Tau/APP Phosphorylation, Synaptopathy, and Memory Deficits in Alzheimer's Disease. *Cell reports* **24**, 713-723, doi:10.1016/j.celrep.2018.06.009 (2018).
- [0272] 14 Lasagna-Reeves, C. A. *et al.* Alzheimer brain-derived tau oligomers propagate pathology from endogenous tau. *Scientific reports* **2**, 700, doi:10.1038/srep00700 (2012).
- [0273] 15 Fá, M. *et al.* Extracellular Tau Oligomers Produce An Immediate Impairment of LTP and Memory. *Scientific reports* **6**, 19393, doi:10.1038/srep19393 (2016).
- [0274] 16 Papassotiropoulos, A. *et al.* Common Kibra alleles are associated with human memory performance. *Science (New York, N.Y.)* **314**, 475-478, doi:10.1126/science.1129837 (2006).
- [0275] 17 Comeveaux, J. J. *et al.* Evidence for an association between KIBRA and late-onset Alzheimer's disease. *Neurobiology of aging* **31**, 901-909, doi:10.1016/j.neurobiolaging.2008.07.014 (2010).
- [0276] 18 Burgess, J. D. *et al.* Association of common KIBRA variants with episodic memory and AD risk. *Neurobiology of aging* **32**, 557.e551-559, doi:10.1016/j.neurobiolaging.2010.11.004 (2011).
- [0277] 19 Rodriguez-Rodriguez, E. *et al.* Age-dependent association of KIBRA genetic variation and Alzheimer's disease risk. *Neurobiology of aging* **30**, 322-324, doi:10.1016/j.neurobiolaging.2007.07.003 (2009).
- [0278] 20 Makuch, L. *et al.* Regulation of AMPA receptor function by the human memory-associated gene KIBRA. *Neuron* **71**, 1022-1029, doi:10.1016/j.neuron.2011.08.017 (2011).
- [0279] 21 Schneider, A. *et al.* KIBRA: A New Gateway to Learning and Memory? *Frontiers in aging neuroscience* **2**, 4, doi:10.3389/neuro.24.004.2010 (2010).
- [0280] 22 Zhang, L. *et al.* KIBRA: In the brain and beyond. *Cellular signalling* **26**, 1392-1399, doi:10.1016/j.cellsig.2014.02.023 (2014).
- [0281] 23 Grinberg, L. T. *et al.* Argyrophilic grain disease differs from other tauopathies by lacking tau acetylation. *Acta neuropathologica* **125**, 581-593, doi:10.1007/s00401-013-1080-2 (2013).

- [0282] 24 Tsokas, P. *et al.* Compensation for PKM ζ in long-term potentiation and spatial long-term memory in mutant mice. *eLife* **5**, doi:10.7554/eLife.14846 (2016).
- [0283] 25 Sacktor, T. C. & Hell, J. W. The genetics of PKM ζ and memory maintenance. *Science signaling* **10**, doi:10.1126/scisignal.aao2327 (2017).
- 5 [0284] 26 Ling, D. S., Benardo, L. S. & Sacktor, T. C. Protein kinase Mzeta enhances excitatory synaptic transmission by increasing the number of active postsynaptic AMPA receptors. *Hippocampus* **16**, 443-452, doi:10.1002/hipo.20171 (2006).
- [0285] 27 Ji, Z. *et al.* Kibra Modulates Learning and Memory via Binding to Dendrin. *Cell reports* **26**, 2064-2077.e2067, doi:10.1016/j.celrep.2019.01.097 (2019).
- 10 [0286] 28 Duning, K. *et al.* KIBRA modulates directional migration of podocytes. *Journal of the American Society of Nephrology : JASN* **19**, 1891-1903, doi:10.1681/asn.2007080916 (2008).
- [0287] 29 Vogt-Eisele, A. *et al.* KIBRA (KIdney/BRAin protein) regulates learning and memory and stabilizes Protein kinase M ζ . *Journal of neurochemistry* **128**, 686-700, doi:10.1111/jnc.12480 (2014).
- 15 [0288] 30 Yoshihama, Y. *et al.* KIBRA suppresses apical exocytosis through inhibition of aPKC kinase activity in epithelial cells. *Current biology : CB* **21**, 705-711, doi:10.1016/j.cub.2011.03.029 (2011).
- [0289] 31 Büther, K., Plaas, C., Barnekow, A. & Kremerskothen, J. KIBRA is a novel substrate for protein kinase Czeta. *Biochemical and biophysical research communications* **317**, 703-707, doi:10.1016/j.bbrc.2004.03.107 (2004).
- 20 [0290] 32 Lu, W. *et al.* Activation of synaptic NMDA receptors induces membrane insertion of new AMPA receptors and LTP in cultured hippocampal neurons. *Neuron* **29**, 243-254 (2001).
- [0291] 33 Oku, Y. & Huganir, R. L. AGAP3 and Arf6 regulate trafficking of AMPA receptors and synaptic plasticity. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **33**, 12586-12598, doi:10.1523/jneurosci.0341-13.2013 (2013).
- 25

- [0292] 34 Chen, M. K. *et al.* Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging. *JAMA neurology* **75**, 1215-1224, doi:10.1001/jamaneurol.2018.1836 (2018).
- [0293] 35 Mecca, A. P. *et al.* In vivo measurement of widespread synaptic loss in
5 Alzheimer's disease with SV2A PET. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **16**, 974-982, doi:10.1002/alz.12097 (2020).
- [0294] 36 Yoshihama, Y., Hirai, T., Ohtsuka, T. & Chida, K. KIBRA Co-localizes with protein kinase Mzeta (PKMzeta) in the mouse hippocampus. *Bioscience, biotechnology, and biochemistry* **73**, 147-151, doi:10.1271/bbb.80564 (2009).
- 10 [0295] 37 Söderberg, O. *et al.* Direct observation of individual endogenous protein complexes in situ by proximity ligation. *Nature methods* **3**, 995-1000, doi:10.1038/nmeth947 (2006).
- [0296] 38 Osten, P., Valsamis, L., Harris, A. & Sacktor, T. C. Protein synthesis-dependent formation of protein kinase Mzeta in long-term potentiation. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **16**, 2444-2451, doi:10.1523/jneurosci.16-08-02444.1996 (1996).
15
- [0297] 39 Hsieh, C. *et al.* Persistent increases of PKM ζ in memory-activated neurons trace LTP maintenance during spatial long-term memory storage. *The European journal of neuroscience* **54**, 6795-6814, doi:10.1111/ejn.15137 (2021).
- 20 [0298] 40 Hsieh, C. *et al.* Persistent increased PKM ζ in long-term and remote spatial memory. *Neurobiology of learning and memory* **138**, 135-144, doi:10.1016/j.nlm.2016.07.008 (2017).
- [0299] 41 Palida, S. F. *et al.* PKM ζ , but not PKC λ , is rapidly synthesized and degraded at the neuronal synapse. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **35**, 7736-7749, doi:10.1523/jneurosci.0004-15.2015 (2015).
25
- [0300] 42 Wang, S., Sheng, T., Ren, S., Tian, T. & Lu, W. Distinct Roles of PKC ι/λ and PKM ζ in the Initiation and Maintenance of Hippocampal Long-Term Potentiation and Memory. *Cell reports* **16**, 1954-1961, doi:10.1016/j.celrep.2016.07.030 (2016).

- [0301] 43 Lee, A. M. *et al.* Prkcz null mice show normal learning and memory. *Nature* **493**, 416-419, doi:10.1038/nature11803 (2013).
- [0302] 44 Volk, L. J., Bachman, J. L., Johnson, R., Yu, Y. & Huganir, R. L. PKM- ζ is not required for hippocampal synaptic plasticity, learning and memory. *Nature* **493**, 420-423, doi:10.1038/nature11802 (2013).
- [0303] 45 Lynch, C. A. *et al.* The clinical dementia rating sum of box score in mild dementia. *Dementia and geriatric cognitive disorders* **21**, 40-43, doi:10.1159/000089218 (2006).
- [0304] 46 O'Bryant, S. E. *et al.* Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Archives of neurology* **65**, 1091-1095, doi:10.1001/archneur.65.8.1091 (2008).
- [0305] 47 Lleó, A. *et al.* Changes in Synaptic Proteins Precede Neurodegeneration Markers in Preclinical Alzheimer's Disease Cerebrospinal Fluid. *Molecular & cellular proteomics : MCP* **18**, 546-560, doi:10.1074/mcp.RA118.001290 (2019).
- [0306] 48 Brinkmalm, A. *et al.* SNAP-25 is a promising novel cerebrospinal fluid biomarker for synapse degeneration in Alzheimer's disease. *Molecular neurodegeneration* **9**, 53, doi:10.1186/1750-1326-9-53 (2014).
- [0307] 49 Casaletto, K. B. *et al.* Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. *Neurology* **89**, 1782-1788, doi:10.1212/wnl.00000000000004569 (2017).
- [0308] 50 Thorsell, A. *et al.* Neurogranin in cerebrospinal fluid as a marker of synaptic degeneration in Alzheimer's disease. *Brain research* **1362**, 13-22, doi:10.1016/j.brainres.2010.09.073 (2010).
- [0309] 51 Colom-Cadena, M. *et al.* The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. *Alzheimer's research & therapy* **12**, 21, doi:10.1186/s13195-020-00588-4 (2020).
- [0310] 52 Rosén, C., Hansson, O., Blennow, K. & Zetterberg, H. Fluid biomarkers in Alzheimer's disease - current concepts. *Molecular neurodegeneration* **8**, 20, doi:10.1186/1750-1326-8-20 (2013).

- [0311] 53 Vanderstichele, H. *et al.* Analytical performance and clinical utility of the INNOTEST PHOSPHO-TAU181P assay for discrimination between Alzheimer's disease and dementia with Lewy bodies. *Clinical chemistry and laboratory medicine* **44**, 1472-1480, doi:10.1515/cclm.2006.258 (2006).
- 5 [0312] 54 Irwin, D. J. *et al.* Acetylated tau, a novel pathological signature in Alzheimer's disease and other tauopathies. *Brain : a journal of neurology* **135**, 807-818, doi:10.1093/brain/aws013 (2012).
- [0313] 55 Lasagna-Reeves, C. A. *et al.* Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice. *Molecular neurodegeneration* **6**, 39, doi:10.1186/1750-1326-6-39 (2011).
- 10 [0314] 56 McInnes, J. *et al.* Synaptogyrin-3 Mediates Presynaptic Dysfunction Induced by Tau. *Neuron*, doi:10.1016/j.neuron.2018.01.022 (2018).
- [0315] 57 Zhang, B. *et al.* Retarded axonal transport of R406W mutant tau in transgenic mice with a neurodegenerative tauopathy. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **24**, 4657-4667, doi:10.1523/jneurosci.0797-04.2004 (2004).
- 15 [0316] 58 Ishihara, T. *et al.* Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron* **24**, 751-762, doi:10.1016/s0896-6273(00)81127-7 (1999).
- [0317] 59 Sohn, P. D. *et al.* Pathogenic Tau Impairs Axon Initial Segment Plasticity and Excitability Homeostasis. *Neuron*, doi:10.1016/j.neuron.2019.08.008 (2019).
- 20 [0318] 60 Tracy, T. E. *et al.* Tau interactome maps synaptic and mitochondrial processes associated with neurodegeneration. *Cell* **185**, 712-728.e714, doi:10.1016/j.cell.2021.12.041 (2022).
- [0319] 61 Eftekharzadeh, B. *et al.* Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer's Disease. *Neuron* **99**, 925-940.e927, doi:10.1016/j.neuron.2018.07.039 (2018).
- 25 [0320] 62 Cornelison, G. L., Levy, S. A., Jenson, T. & Frost, B. Tau-induced nuclear envelope invagination causes a toxic accumulation of mRNA in *Drosophila*. *Aging cell* **18**, e12847, doi:10.1111/acer.12847 (2019).

- [0321] 63 Myeku, N. *et al.* Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. *Nature medicine* **22**, 46-53, doi:10.1038/nm.4011 (2016).
- [0322] 64 Zempel, H. *et al.* Amyloid- β oligomers induce synaptic damage via Tau-dependent microtubule severing by TTL6 and spastin. *The EMBO journal* **32**, 2920-2937, doi:10.1038/emboj.2013.207 (2013).
- [0323] 65 Zempel, H., Thies, E., Mandelkow, E. & Mandelkow, E. M. Abeta oligomers cause localized Ca(2+) elevation, missorting of endogenous Tau into dendrites, Tau phosphorylation, and destruction of microtubules and spines. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **30**, 11938-11950, doi:10.1523/jneurosci.2357-10.2010 (2010).
- [0324] 66 Tian, M. *et al.* KIBRA-PKC γ signaling pathway modulates memory performance in mice and humans. 2021.2010.2026.465926, doi:10.1101/2021.10.26.465926 %J bioRxiv (2021).
- [0325] 67 Crary, J. F., Shao, C. Y., Mirra, S. S., Hernandez, A. I. & Sacktor, T. C. Atypical protein kinase C in neurodegenerative disease I: PKMzeta aggregates with limbic neurofibrillary tangles and AMPA receptors in Alzheimer disease. *Journal of neuropathology and experimental neurology* **65**, 319-326, doi:10.1097/01.jnen.0000218442.07664.04 (2006).
- [0326] 68 Amini, N. *et al.* Overexpression of protein kinase M ζ in the hippocampus mitigates Alzheimer's disease-related cognitive deficit in rats. *Brain Res Bull* **166**, 64-72, doi:10.1016/j.brainresbull.2020.11.001 (2021).
- [0327] 69 Höglund, K. *et al.* Cerebrospinal fluid neurogranin in an inducible mouse model of neurodegeneration: A translatable marker of synaptic degeneration. *Neurobiology of disease* **134**, 104645, doi:10.1016/j.nbd.2019.104645 (2020).
- [0328] 70 VandeVrede, L., Boxer, A. L. & Polydoro, M. Targeting tau: Clinical trials and novel therapeutic approaches. *Neuroscience letters* **731**, 134919, doi:10.1016/j.neulet.2020.134919 (2020).

- [0329] 71 Chang, C. W., Shao, E. & Mucke, L. Tau: Enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. *Science (New York, N.Y.)* **371**, doi:10.1126/science.abb8255 (2021).
- [0330] 72 Mootha, V. K. *et al.* PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nature genetics* **34**, 267-273, doi:10.1038/ng1180 (2003).
- [0331] 73 Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 15545-15550, doi:10.1073/pnas.0506580102 (2005).
- [0332] 74 Shannon, P. *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome research* **13**, 2498-2504, doi:10.1101/gr.1239303 (2003).
- [0333] 75 Bindea, G. *et al.* ClueGO: a Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics (Oxford, England)* **25**, 1091-1093, doi:10.1093/bioinformatics/btp101 (2009).
- [0334] 76 Moleirinho, S. *et al.* KIBRA exhibits MST-independent functional regulation of the Hippo signaling pathway in mammals. *Oncogene* **32**, 1821-1830, doi:10.1038/onc.2012.196 (2013).
- [0335] 77 McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **7**, 263-269, doi:10.1016/j.jalz.2011.03.005 (2011).
- [0336] 78 Ljubenkov, P. A. *et al.* Cerebrospinal fluid biomarkers predict frontotemporal dementia trajectory. *Annals of clinical and translational neurology* **5**, 1250-1263, doi:10.1002/acn3.643 (2018).

P EMBODIMENTS

- [0337] P Embodiment 1. A method of treating a tau-associated memory deficit disorder in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a C-terminal KIBRA compound.
- 5 [0338] P Embodiment 2. The method of P embodiment 1, wherein the tau-associated memory deficit disorder is Alzheimer's disease, progressive supranuclear palsy, Pick's disease, corticobasal degeneration, chronic traumatic encephalopathy, or Frontotemporal lobar dementia-tau (FTLD-tau).
- [0339] P Embodiment 3. A method of treating aging-associated cognitive decline in a
10 subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a C-terminal KIBRA compound.
- [0340] P Embodiment 4. The method of P embodiment 3, wherein the aging-associated cognitive decline occurs in the absence of tau-associated neurodegeneration.
- [0341] P Embodiment 5. The method of P embodiment 1, wherein the C-terminal KIBRA
15 peptide is between about 700 and about 800 amino acids in length.
- [0342] P Embodiment 6. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 600 and about 700 amino acids in length.
- [0343] P Embodiment 7. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 500 and about 600 amino acids in length.
- 20 [0344] P Embodiment 8. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 400 and about 500 amino acids in length.
- [0345] P Embodiment 9. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 300 and about 400 amino acids in length.
- [0346] P Embodiment 10. The method of P embodiment 1, wherein the C-terminal KIBRA
25 peptide is between about 200 and about 300 amino acids in length.
- [0347] P Embodiment 11. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 100 and about 200 amino acids in length.

[0348] P Embodiment 12. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 50 and about 100 amino acids in length.

[0349] P Embodiment 13. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 40 and about 50 amino acids in length.

5 [0350] P Embodiment 14. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 20 and about 40 amino acids in length.

[0351] P Embodiment 15. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 10 and about 20 amino acids in length.

10 [0352] P Embodiment 16. The method of P embodiment 1, wherein the C-terminal KIBRA peptide is between about 5 and about 10 amino acids in length.

[0353] P Embodiment 17. The method of any one of P embodiments 1-11, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.

15 [0354] P Embodiment 18. The method of any one of P embodiments 1-17, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5.

20 [0355] P Embodiment 19. The method of any one of P embodiments 1-18, wherein the C-terminal KIBRA compound comprises a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a hydrocarbon stapling sequence, a glycine flexible linker, or a biotin amino acid sequence.

25 [0356] P Embodiment 20. The method of any one of P embodiments 1-19, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25.

[0357] P Embodiment 21. The method of any one of P embodiments 1-20, wherein at least one of the amino acids of the C-terminal KIBRA compound is a non-natural amino acid analog.

[0358] P Embodiment 22. The method of any one of P embodiments 1-21, wherein the C-terminal KIBRA compound does not comprise the sequence of SEQ ID NO:29.

5 [0359] P Embodiment 23. A C-terminal KIBRA compound comprising the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5, wherein (a) at least one of the amino acids of the C-terminal KIBRA peptide is a non-natural amino acid analog; and/or (b) the C-terminal KIBRA compound further comprises a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry
10 amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a glycine flexible linker, or a biotin amino acid sequence.

[0360] P Embodiment 24. The C-terminal KIBRA compound of P embodiment 23, wherein
15 the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25.

20 [0361] P Embodiment 25. A pharmaceutical composition comprising a therapeutically effective amount of a C-terminal KIBRA compound of P embodiment 23 or 24 and a pharmaceutically acceptable excipient.

EMBODIMENTS

[0362] Embodiment 1. A method of treating a tau-associated memory deficit disorder in a
25 subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a C-terminal KIBRA compound.

[0363] Embodiment 2. The method of embodiment 1, wherein the tau-associated memory deficit disorder is Alzheimer's disease, progressive supranuclear palsy, Pick's disease,

corticobasal degeneration, chronic traumatic encephalopathy, or Frontotemporal lobar dementia-tau (FTLD-tau).

5 **[0364]** Embodiment 3. A method of treating aging-associated cognitive decline in a subject in need thereof, the method comprising administering to said subject a therapeutically effective amount of a C-terminal KIBRA compound.

[0365] Embodiment 4. The method of embodiment 3, wherein the aging-associated cognitive decline occurs in the absence of tau-associated neurodegeneration.

[0366] Embodiment 5. The method of embodiment 1, wherein the C-terminal KIBRA compound comprises a C-terminal KIBRA peptide.

10 **[0367]** Embodiment 6. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 700 and about 800 amino acids in length.

[0368] Embodiment 7. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 600 and about 700 amino acids in length.

15 **[0369]** Embodiment 8. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 500 and about 600 amino acids in length.

[0370] Embodiment 9. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 400 and about 500 amino acids in length.

[0371] Embodiment 10. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 300 and about 400 amino acids in length.

20 **[0372]** Embodiment 11. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 200 and about 300 amino acids in length.

[0373] Embodiment 12. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 100 and about 200 amino acids in length.

25 **[0374]** Embodiment 13. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 50 and about 100 amino acids in length.

[0375] Embodiment 14. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 40 and about 50 amino acids in length.

- [0376] Embodiment 15. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 20 and about 40 amino acids in length.
- [0377] Embodiment 16. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 10 and about 20 amino acids in length.
- 5 [0378] Embodiment 17. The method of embodiment 5, wherein the C-terminal KIBRA peptide is between about 5 and about 10 amino acids in length.
- [0379] Embodiment 18. The method of any one of embodiments 1-12, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.
- 10 [0380] Embodiment 19. The method of any one of embodiments 1-18, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5.
- [0381] Embodiment 20. The method of any one of embodiments 1-19, wherein the C-terminal KIBRA compound comprises a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a hydrocarbon stapling sequence, a glycine flexible linker, or a biotin amino acid sequence.
- 15 [0382] Embodiment 21. The method of any one of embodiments 1-20, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25.
- 20 [0383] Embodiment 22. The method of any one of embodiments 1-21, wherein at least one of the amino acids of the C-terminal KIBRA compound is a non-natural amino acid analog.
- [0384] Embodiment 23. The method of any one of embodiments 1-22, wherein the C-terminal KIBRA compound does not comprise the sequence of SEQ ID NO:29.
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- [0385] Embodiment 24. A C-terminal KIBRA compound comprising a C-terminal KIBRA peptide comprising the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, or SEQ ID NO:5, wherein (a) at least one of the amino acids of the C-terminal KIBRA peptide is a non-natural amino acid analog; and/or (b) the C-terminal KIBRA compound
- 5 further comprises a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan amino acid sequence, a glycine flexible linker, or a biotin amino acid sequence.
- 10 [0386] Embodiment 25. The C-terminal KIBRA compound of embodiment 24, wherein the C-terminal KIBRA compound comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID
- 15 NO:24, or SEQ ID NO:25.
- [0387] Embodiment 26. A pharmaceutical composition comprising a therapeutically effective amount of a C-terminal KIBRA compound of embodiment 24 or 25 and a pharmaceutically acceptable excipient.

INFORMAL SEQUENCE LISTING

SEQ ID NO:	Name of sequence	Sequence
1.	CT-KIBRA full protein sequence (187 aa)	RSKTFSPGPQSQYVCRLNRSDSDSSTLSKKPPFVRNS LERRSVRMKRPSSVKSLRSERLIRTSLDLELDLQATR TWHSQLTQEISVLKELKEQLEQAKSHGEKELPQWLR EDERFRLLLRMLEKRMDRAEHKGELQTDKMMRAA AKDVHRLRGQSCKEPPEVQSFREKMAFFTRPRMNIP ALSADDV
2.	Second splice variant of CT-KIBRA protein sequence (188 aa)	RSKTFSPGPQSQYVCRLNRSDSDSSTLSKKPPFVRNS LERRSVRMKRPSSVKSLRSERLIRTSLDLELDLQATR TWHSQLTQEISVLKELKEQLEQAKSHGEKELPQWLR EDERFRLLLRMLEKRQMDRAEHKGELQTDKMMRA AAKDVHRLRGQSCKEPPEVQSFREKMAFFTRPRMNI PALSADDV
3.	Third splice variant of CT-KIBRA protein sequence (193 aa)	RSKTFSPGPQSQYVCRLNRSDSDSSTLSKKPPFVRNS LERRSVRMKRPSPPPQSSVKSLRSERLIRTSLDLELD LQATRTWHSQLTQEISVLKELKEQLEQAKSHGEKEL PQWLREDERFRLLLRMLEKRMDRAEHKGELQTDK MMRAAAKDVHRLRGQSCKEPPEVQSFREKMAFFTR PRMNIPALSADDV
4.	CT-KIBRA ₄₀ peptide (40 aa)	DSDSSTLSKKPPFVRNSLERRSVRMKRPSSVKSLRSE RLI
5.	CT-KIBRA ₂₀ peptide (20 aa)	PPFVRNSLERRSVRMKRPSS
6.	TAT amino acid sequence 1	YGRKKRRQRRR
7.	TAT amino acid sequence 2	RRRQRRKKRG
8.	Penetratin amino acid sequence	RQIKIWFQNRMMKWKK
9.	Oligoarginine amino acid sequence 1	RRRRRRRR
10.	Oligoarginine amino acid sequence 2	RRRRRRRRRR
11.	Oligoarginine amino acid sequence 3	RRRRRRRRRRR
12.	Oligoarginine amino acid sequence 4	RRRRRRRRRRRR
13.	Oligoarginine amino acid sequence 5	RRRRRRRRRRRRR
14.	Xentry amino acid sequence	LCLRPVG
15.	Transportan amino acid sequence	GWTLNSAGYLLGKINLKALAALAKKL
16.	Cyclic TAT amino acid sequence 1	CYGRKKRRQRRRC
17.	Cyclic TAT amino acid sequence 2	CRRRQRRKKRGC
18.	Cyclic penetratin	CRQIKIWFQNRMMKWKKC

	amino acid sequence	
19.	Cyclic oligoarginine amino acid sequence 1	CRRRRRRRRC
20.	Cyclic oligoarginine amino acid sequence 2	CRRRRRRRRRC
21.	Cyclic oligoarginine amino acid sequence 3	CRRRRRRRRRRC
22.	Cyclic oligoarginine amino acid sequence 4	CRRRRRRRRRRRC
23.	Cyclic oligoarginine amino acid sequence 5	CRRRRRRRRRRRRC
24.	Cyclic xentry amino acid sequence	CLCLRPVGC
25.	Cyclic transportan amino acid sequence	CGWTLNSAGYLLGKINLKALAALAKKLC
26.	CT-KIBRA full DNA sequence (564 nt)	CGCTCTAAGACCTTCTCCCCAGGACCCCAGAGCCA GTACGTGTGCCGGCTGAATCGGAGTGATAGTGAC AGCTCCACTCTGTCCAAAAAGCCACCTTTTGTTCG AAACTCCCTGGAGCGACGCAGCGTCCGGATGAAG CGGCCTTCCTCGGTCAAGTCGCTGCGCTCCGAGCG TCTGATCCGTACCTCGCTGGACCTGGAGTTAGACC TGCAGGCGACAAGAACCTGGCACAGCCAATTGAC CCAGGAGATCTCGGTGCTGAAGGAGCTCAAGGAG CAGCTGGAACAAGCCAAGAGCCACGGGGAGAAG GAGCTGCCACAGTGGTTGCGTGAGGACGAGCGTT TCCGCCTGCTGCTGAGGATGCTGGAGAAGCGGAT GGACCGAGCGGAGCACAAGGGTGAGCTTCAGACA GACAAGATGATGAGGGCAGCTGCCAAGGATGTGC ACAGGCTCCGAGGCCAGAGCTGTAAGGAACCCCC AGAAGTTCAGTCTTTTCAGGGAGAAGATGGCATT TCACCCGGCCTCGGATGAATATCCCAGCTCTCTCT GCAGATGACGTCTAA
27.	Second splice variant of CT-KIBRA DNA sequence (567 nt)	CGCTCTAAGACCTTCTCCCCAGGACCCCAGAGCCA GTACGTGTGCCGGCTGAATCGGAGTGATAGTGAC AGCTCCACTCTGTCCAAAAAGCCACCTTTTGTTCG AAACTCCCTGGAGCGACGCAGCGTCCGGATGAAG CGGCCTTCCTCGGTCAAGTCGCTGCGCTCCGAGCG TCTGATCCGTACCTCGCTGGACCTGGAGTTAGACC TGCAGGCGACAAGAACCTGGCACAGCCAATTGAC CCAGGAGATCTCGGTGCTGAAGGAGCTCAAGGAG CAGCTGGAACAAGCCAAGAGCCACGGGGAGAAG GAGCTGCCACAGTGGTTGCGTGAGGACGAGCGTT TCCGCCTGCTGCTGAGGATGCTGGAGAAGCGGCA GATGGACCGAGCGGAGCACAAGGGTGAGCTTCAG ACAGACAAGATGATGAGGGCAGCTGCCAAGGATG TGCACAGGCTCCGAGGCCAGAGCTGTAAGGAACC CCCAGAAGTTCAGTCTTTTCAGGGAGAAGATGGCA

		TTTTTCACCCGGCCTCGGATGAATATCCCAGCTCTCTCTGCAGATGACGTCTAA
28.	Third splice variant of CT-KIBRA DNA sequence (582 nt)	CGCTCTAAGACCTTCTCCCCAGGACCCCAGAGCCA GTACGTGTGCCGGCTGAATCGGAGTGATAGTGAC AGCTCCACTCTGTCCAAAAAGCCACCTTTTGTTCG AAACTCCCTGGAGCGACGCAGCGTCCGGATGAAG CGGCCGTCCCCACCCCCACAGCCTTCCTCGGTCAA GTCGCTGCGCTCCGAGCGTCTGATCCGTACCTCGC TGGACCTGGAGTTAGACCTGCAGGCGACAAGAAC CTGGCACAGCCAATTGACCCAGGAGATCTCGGTG CTGAAGGAGCTCAAGGAGCAGCTGGAACAAGCCA AGAGCCACGGGGAGAAGGAGCTGCCACAGTGGTT GCGTGAGGACGAGCGTTTCCGCCTGCTGCTGAGG ATGCTGGAGAAGCGGATGGACCGAGCGGAGCACA AGGGTGAGCTTCAGACAGACAAGATGATGAGGGC AGCTGCCAAGGATGTGCACAGGCTCCGAGGCCAG AGCTGTAAGGAACCCCCAGAAAGTTCAGTCTTTCAG GGAGAAGATGGCATTTCACCCGGCCTCGGATGA ATATCCCAGCTCTCTCTGCAGATGACGTCTAA
29.	Truncated KIBRA (888 aa)	KKAITCGEKEKQDLIKSLAMLKDGFRTRDRGSHSDLW SSSSSLESSFPLPKQYLDVSSQTDISGSGINSNNQLA EKVRLRLRYEEAKRRIANLKIQLAKLDSEAWPGVLD SERDRLILINEKEELLKEMRFISPRKWTQGEVEQLEM ARKRLEKDLQAARDTQSKALTERLKLNSKRNLVR ELEEA TRQVATLHSQLKSLSSSMQSLSSGSSPGSLTSS RGS LVASSLDSSTSASFTDLYYDPFEQLDSELQSKVE FLLLEGATGFRPSGCITTIHEDEVAKTQKAEGGGRLQ ALRSLSGTPKSMSTLSLSPRSSLSSPSPCSPLMADPLLA GDAFLNSLEFEDPELSATLCELSLGNSAQERYRLEEP GTEGKQLGQAVNTAQGCGLKVACVSAVSDSV GDSGVYEASVQRLGASEAAAFDSESEAVGATRIQI ALKYDEKNKQFALIIQLSNLSALLQQQDQKVNIRVA VLPCSESTTCLFRTRPLDASDTLVFNEVFWVMSYP LHQKTLRVDVCTTDRSHLEECLGGAQISLAEVC RSGERSTRWYNLLSYKYLKKQSRELKPVGVMAPASGPA STDAVSALLEQTAVELEKRQEGRSSTQTLED SWRYEETSENEAVAE EEEEEVEEEEEGEEDVFTEKASPDMDG YPALKVDKETNTETPAPSPTVVRPKDRRVGTPSQGP FLRGSTIIRSKTFSPGPQSQYVCRLNRS SDSDSSTLSKKPPFVRNSLERRSVRMKRPSSVKSLR SERLIRTSLDLEL DLQATRTWHSQLTQEISVLKELKEQLEQAKSHGEKE LPQWLREDERFRLLLRMLEKRM DRAEHKGELQTDKMMRAAAKDVHRLRGQSCKEPPEVQSFREKMAFFTR PRMNIPALSADDV

WHAT IS CLAIMED IS:

- 1 1. A method of treating a tau-associated memory deficit disorder in a
2 subject in need thereof, the method comprising administering to said subject a therapeutically
3 effective amount of a C-terminal KIBRA compound.
- 1 2. The method of claim 1, wherein the tau-associated memory deficit
2 disorder is Alzheimer's disease, progressive supranuclear palsy, Pick's disease, corticobasal
3 degeneration, chronic traumatic encephalopathy, or Frontotemporal lobar dementia-tau
4 (FTLD-tau).
- 1 3. A method of treating aging-associated cognitive decline in a subject in
2 need thereof, the method comprising administering to said subject a therapeutically effective
3 amount of a C-terminal KIBRA compound.
- 1 4. The method of claim 3, wherein the aging-associated cognitive decline
2 occurs in the absence of tau-associated neurodegeneration.
- 1 5. The method of claim 1, wherein the C-terminal KIBRA compound
2 comprises a C-terminal KIBRA peptide.
- 1 6. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 700 and about 800 amino acids in length.
- 1 7. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 600 and about 700 amino acids in length.
- 1 8. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 500 and about 600 amino acids in length.
- 1 9. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 400 and about 500 amino acids in length.
- 1 10. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 300 and about 400 amino acids in length.
- 1 11. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 200 and about 300 amino acids in length.

- 1 12. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 100 and about 200 amino acids in length.
- 1 13. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 50 and about 100 amino acids in length.
- 1 14. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 40 and about 50 amino acids in length.
- 1 15. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 20 and about 40 amino acids in length.
- 1 16. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 10 and about 20 amino acids in length.
- 1 17. The method of claim 5, wherein the C-terminal KIBRA peptide is
2 between about 5 and about 10 amino acids in length.
- 1 18. The method of claim 1, wherein the C-terminal KIBRA compound
2 comprises the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, or SEQ ID NO:3.
- 1 19. The method of claim 1, wherein the C-terminal KIBRA compound
2 comprises the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5.
- 1 20. The method of claim 1, wherein the C-terminal KIBRA compound
2 comprises a TAT amino acid sequence, a penetratin amino acid sequence, an oligoarginine
3 amino acid sequence, a xentry amino acid sequence, a transportan amino acid sequence, a
4 cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic
5 oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan
6 amino acid sequence, a hydrocarbon stapling sequence, a glycine flexible linker, or a biotin
7 amino acid sequence.
- 1 21. The method of any claim 1, wherein the C-terminal KIBRA compound
2 comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ ID NO:8, or SEQ
3 ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14,

4 SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID
5 NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:25.

1 22. The method of claim 1, wherein at least one of the amino acids of the
2 C-terminal KIBRA compound is a non-natural amino acid analog.

1 23. The method of claim 1, wherein the C-terminal KIBRA compound does
2 not comprise the sequence of SEQ ID NO:29.

3 24. A C-terminal KIBRA compound comprising a C-terminal KIBRA
4 peptide comprising the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3,
5 SEQ ID NO:4, or SEQ ID NO:5, wherein (a) at least one of the amino acids of the C-terminal
6 KIBRA peptide is a non-natural amino acid analog; and/or (b) the C-terminal KIBRA
7 compound further comprises a TAT amino acid sequence, a penetratin amino acid sequence, an
8 oligoarginine amino acid sequence, a xentry amino acid sequence, a transportan amino acid
9 sequence, a cyclic-TAT amino acid sequence, a cyclic penetratin amino acid sequence, a cyclic
10 oligoarginine amino acid sequence, a cyclic xentry amino acid sequence, a cyclic transportan
11 amino acid sequence, a glycine flexible linker, or a biotin amino acid sequence.

12 25. The C-terminal KIBRA compound of claim 24, wherein the C-terminal
13 KIBRA compound comprises the amino acid sequence of SEQ ID NO: 6, SEQ ID NO:7, SEQ
14 ID NO:8, or SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13,
15 SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID
16 NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or
17 SEQ ID NO:25.

18 26. A pharmaceutical composition comprising a therapeutically effective
19 amount of a C-terminal KIBRA compound of claim 24 and a pharmaceutically acceptable
20 excipient.

1

1

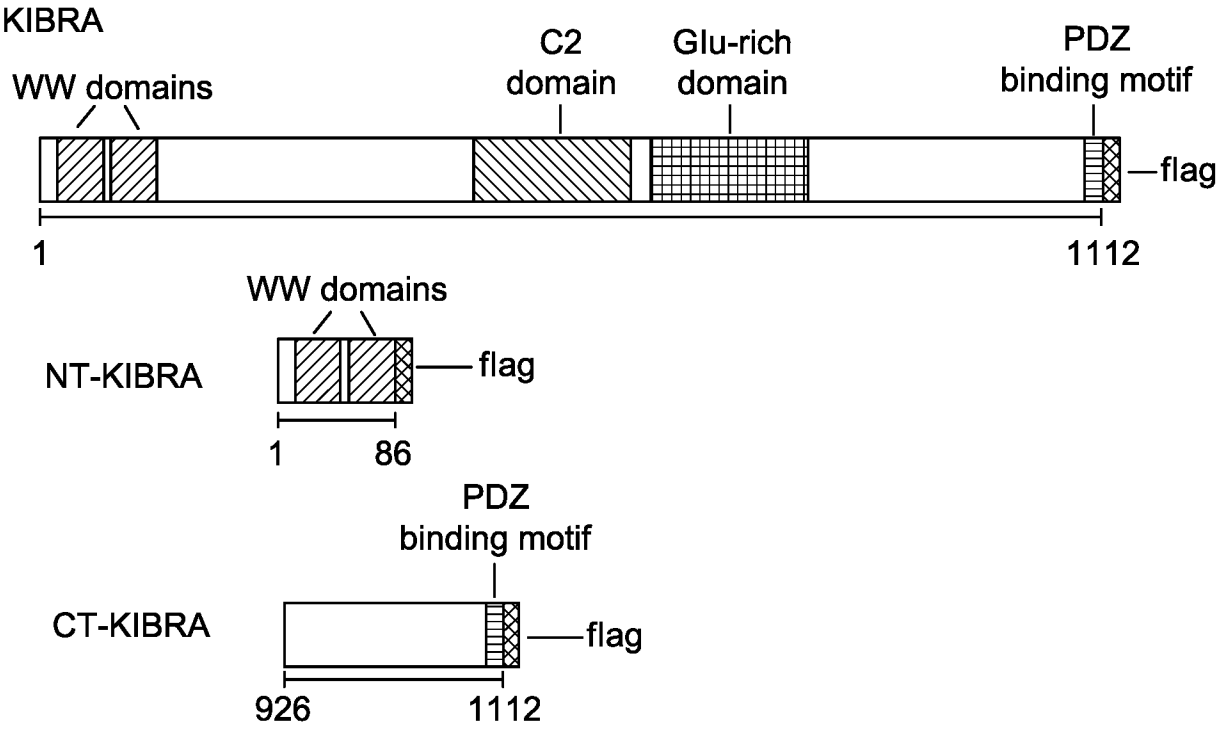


FIG. 1A

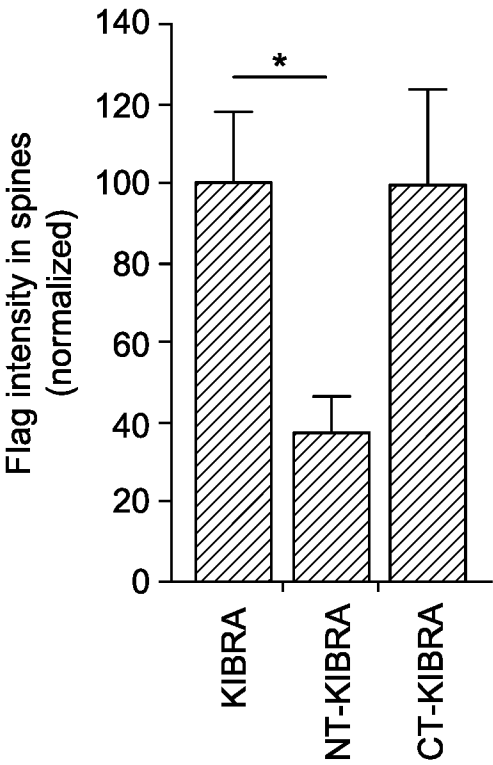


FIG. 1B

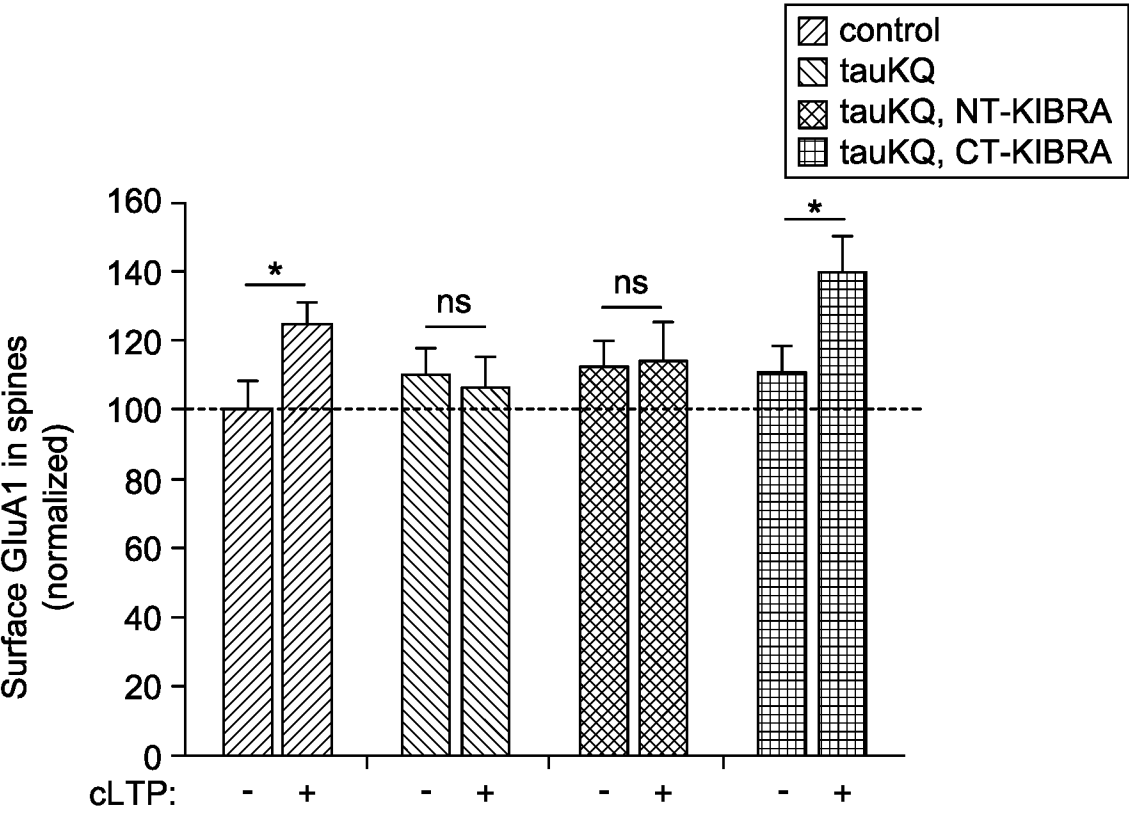


FIG. 1C

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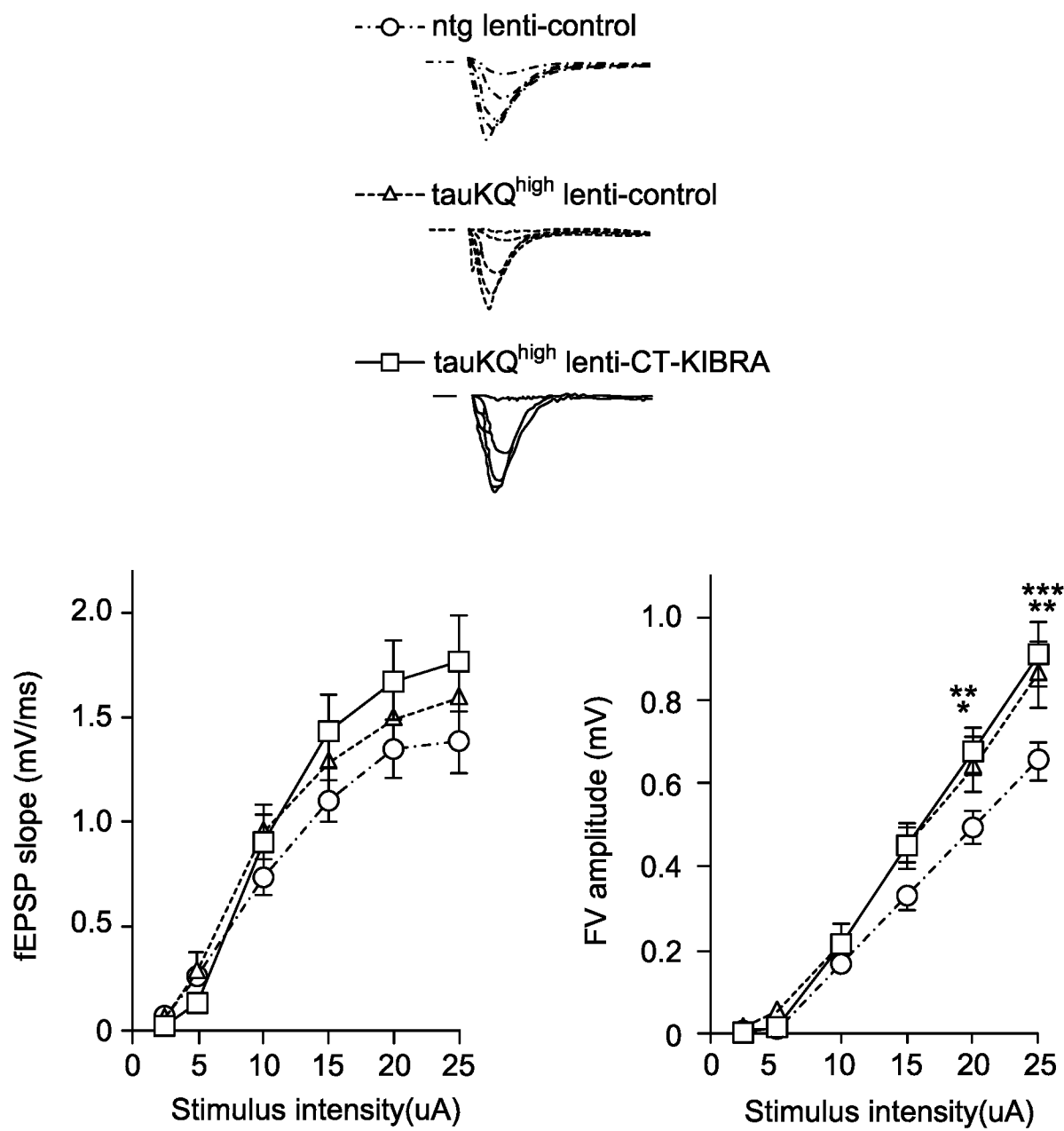


FIG. 1D

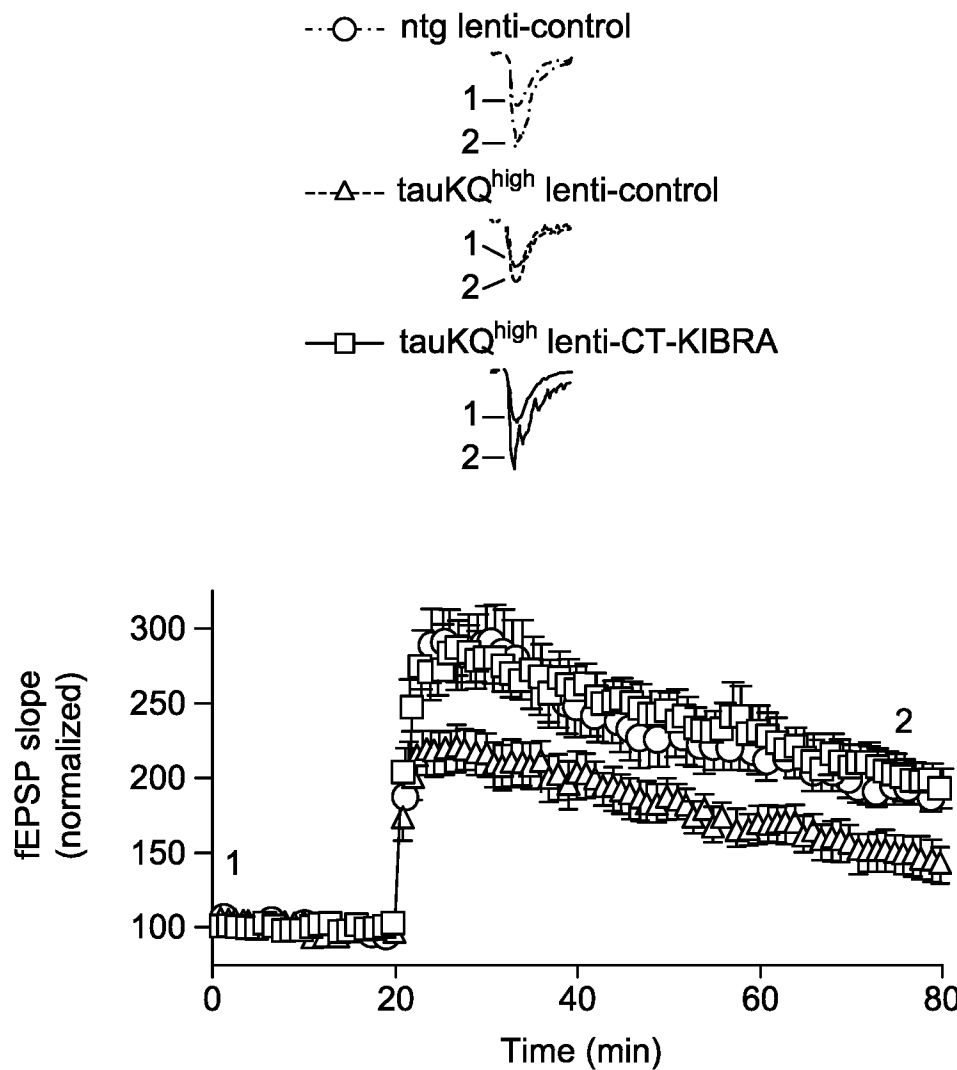


FIG. 1E

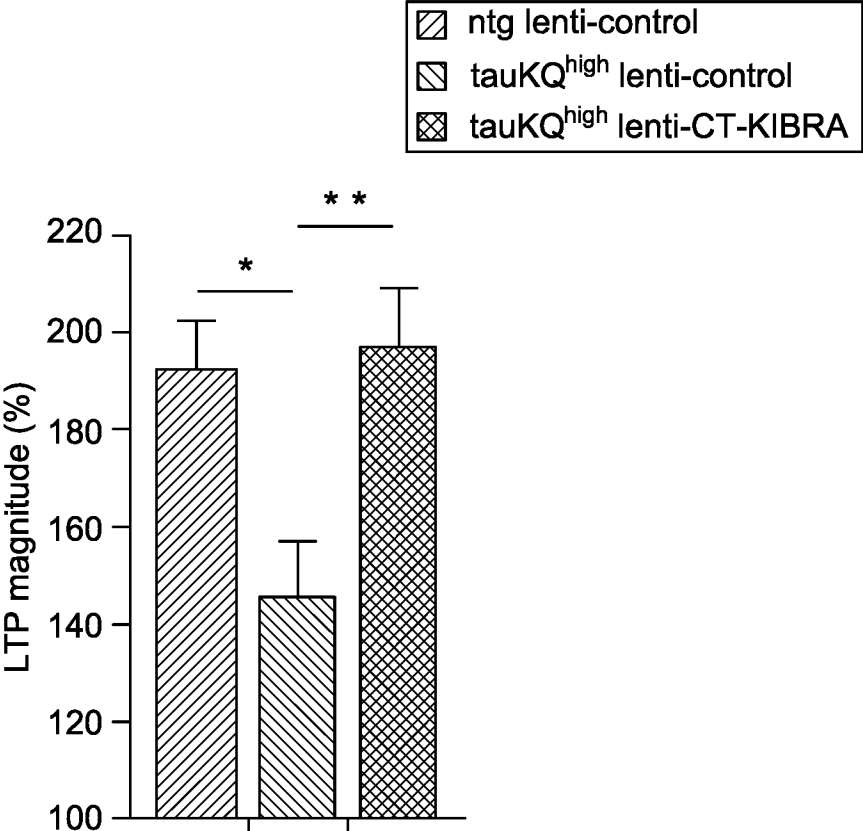


FIG. 1F

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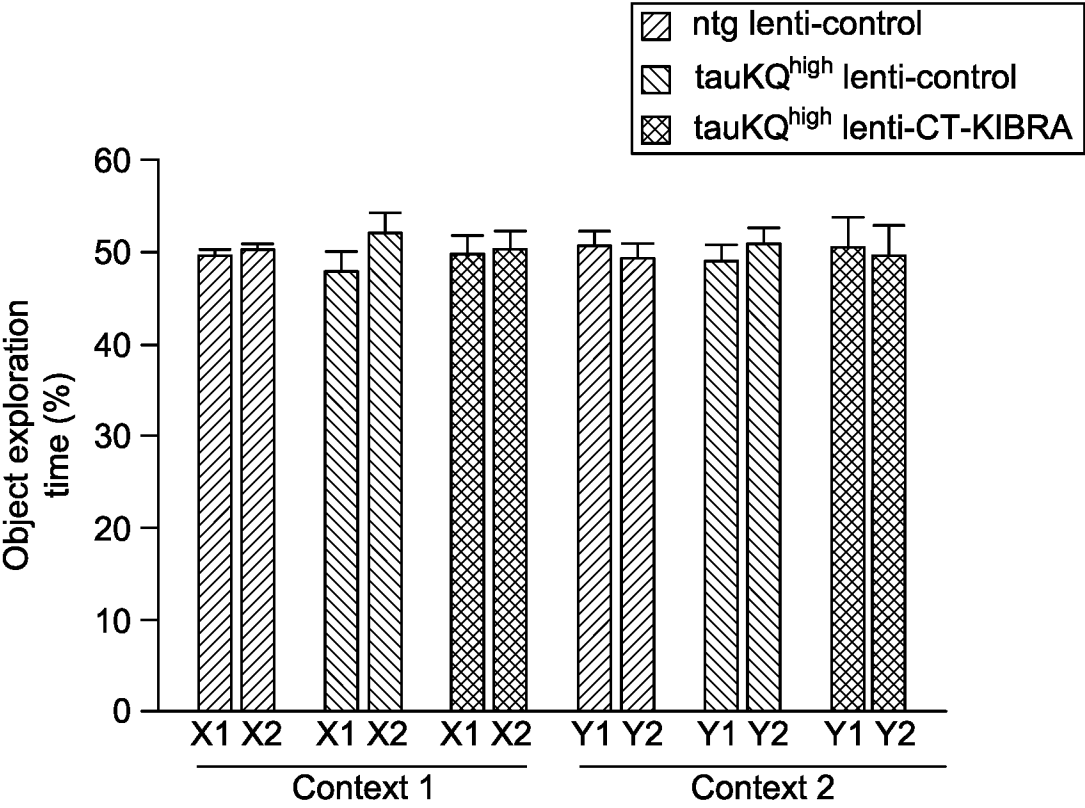


FIG. 2A

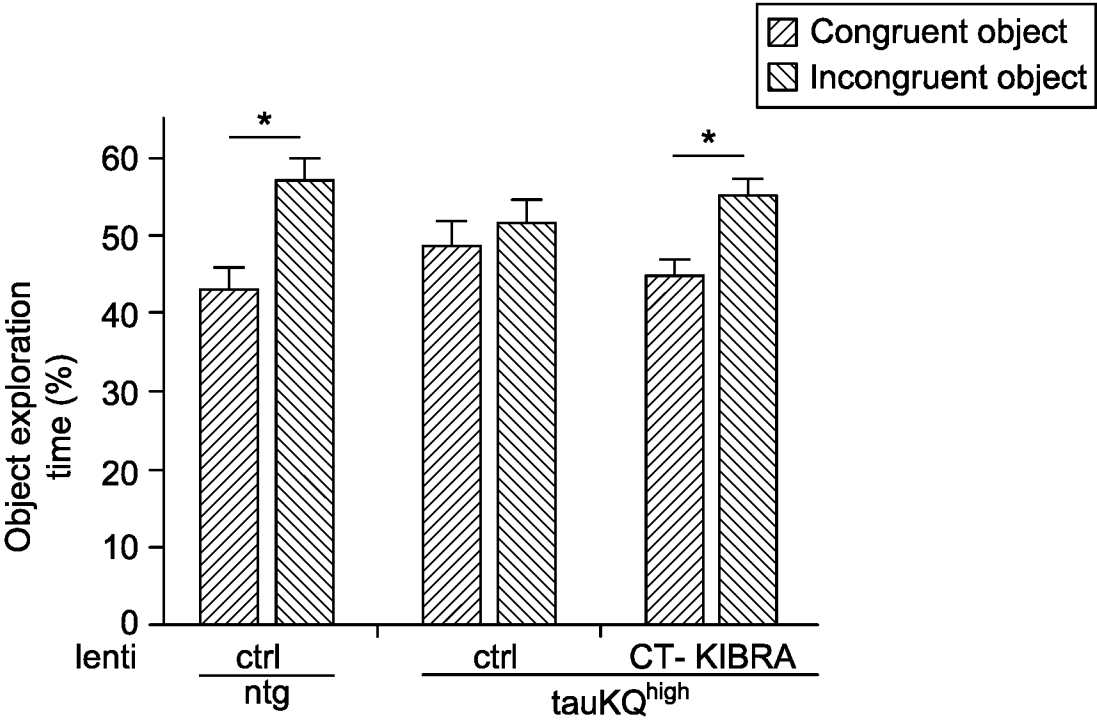


FIG. 2B

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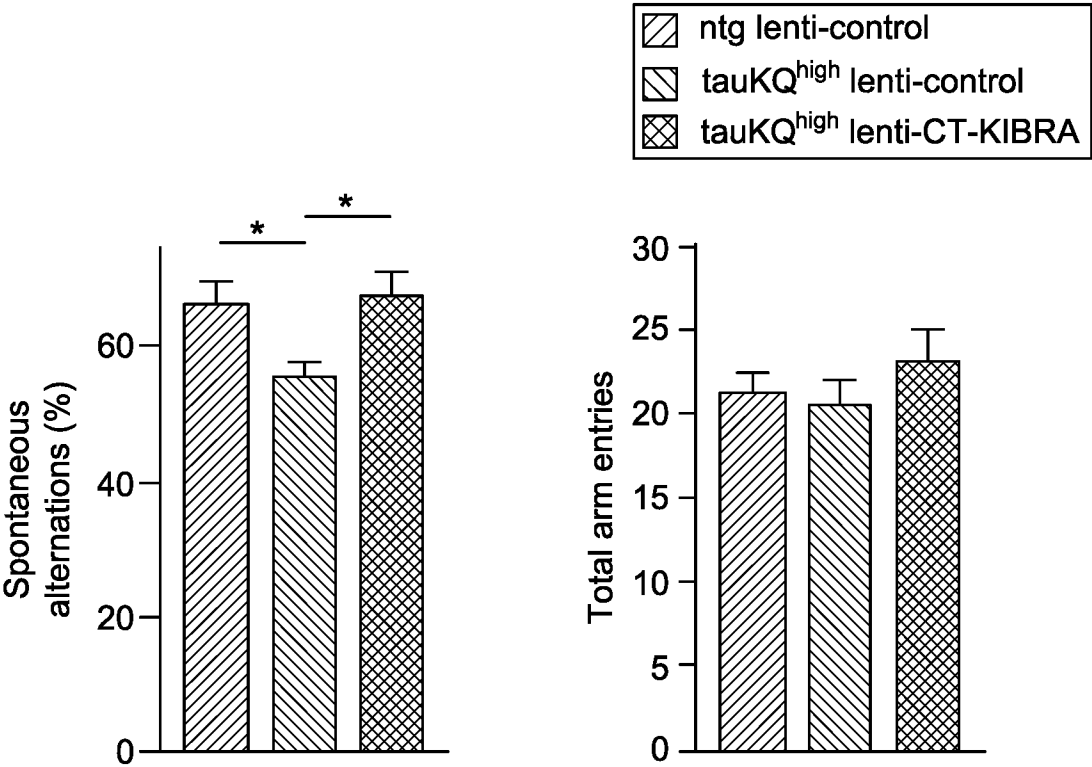


FIG. 2C

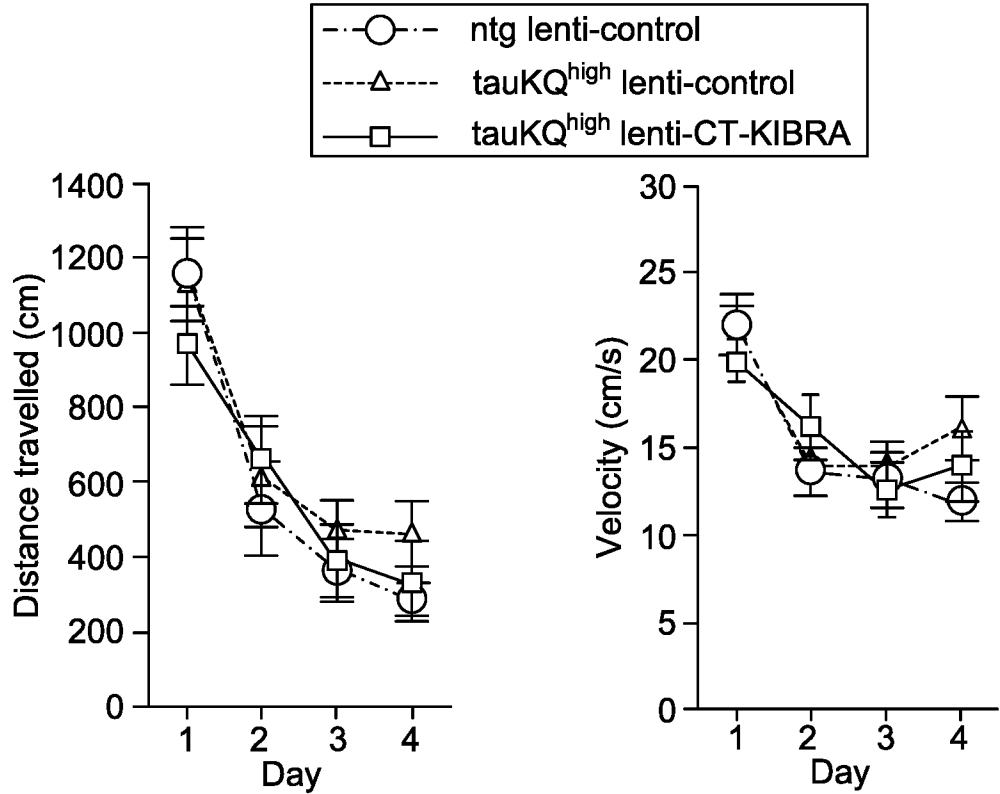


FIG. 2D

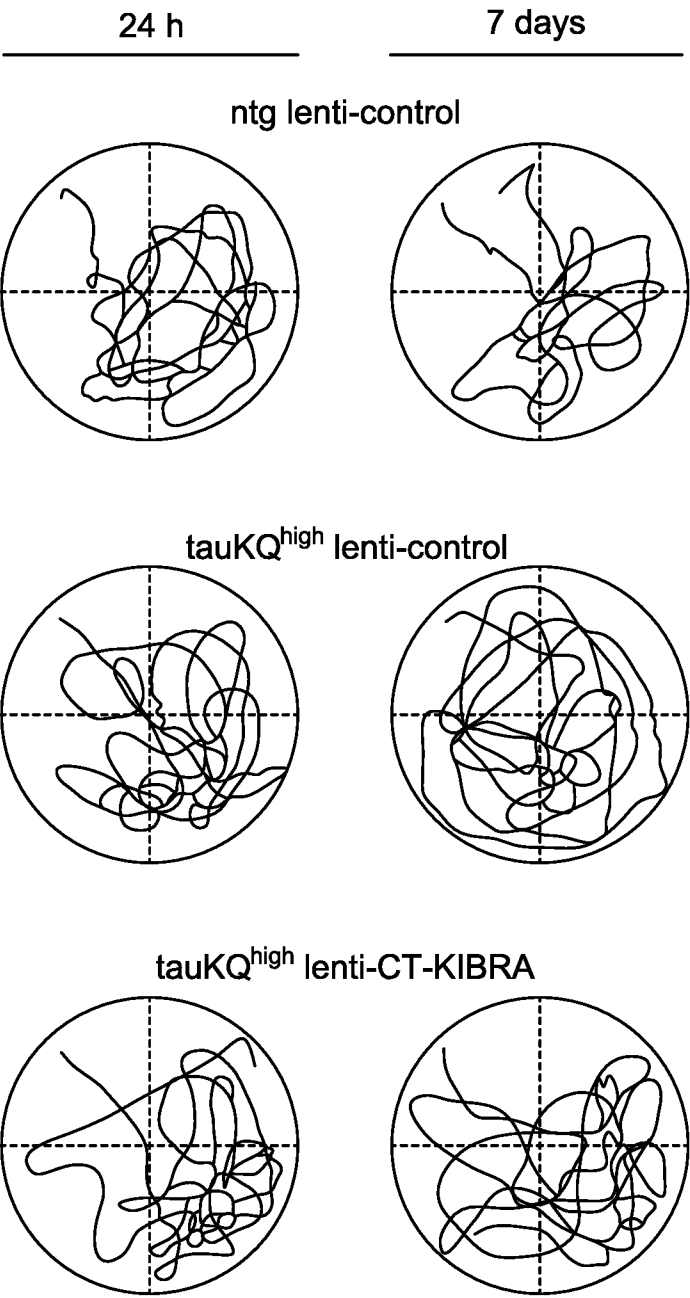


FIG. 2E

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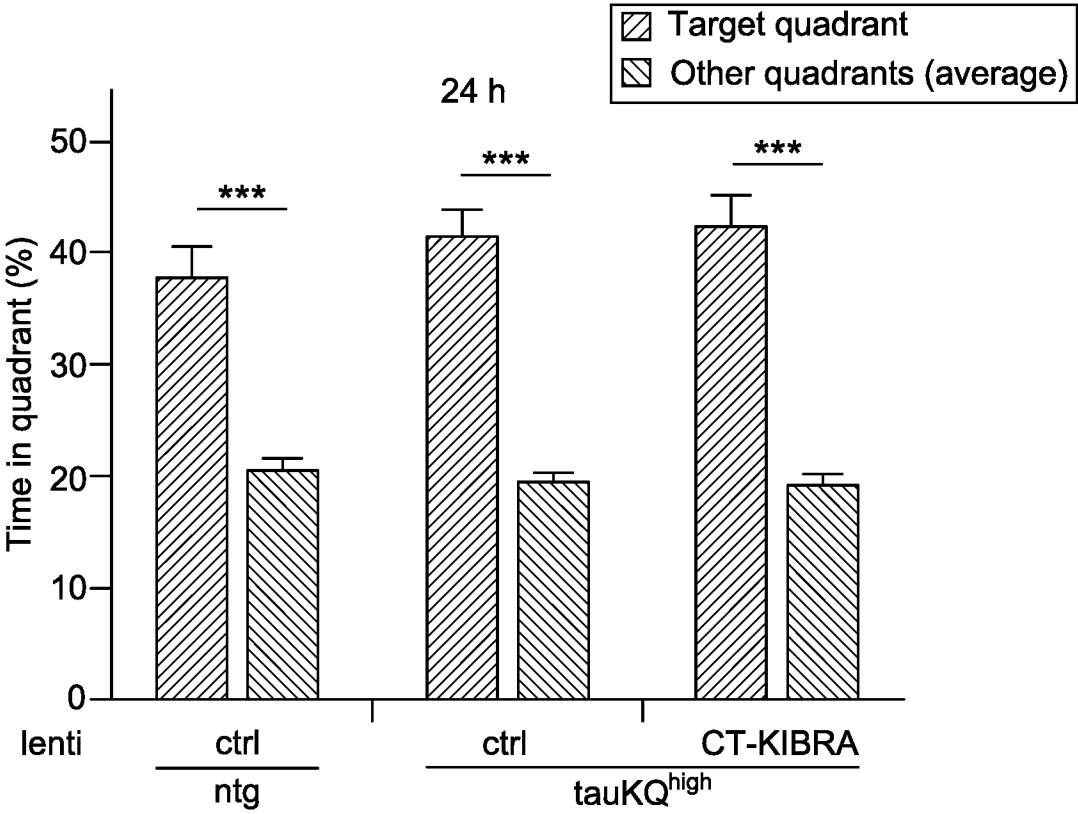


FIG. 2F

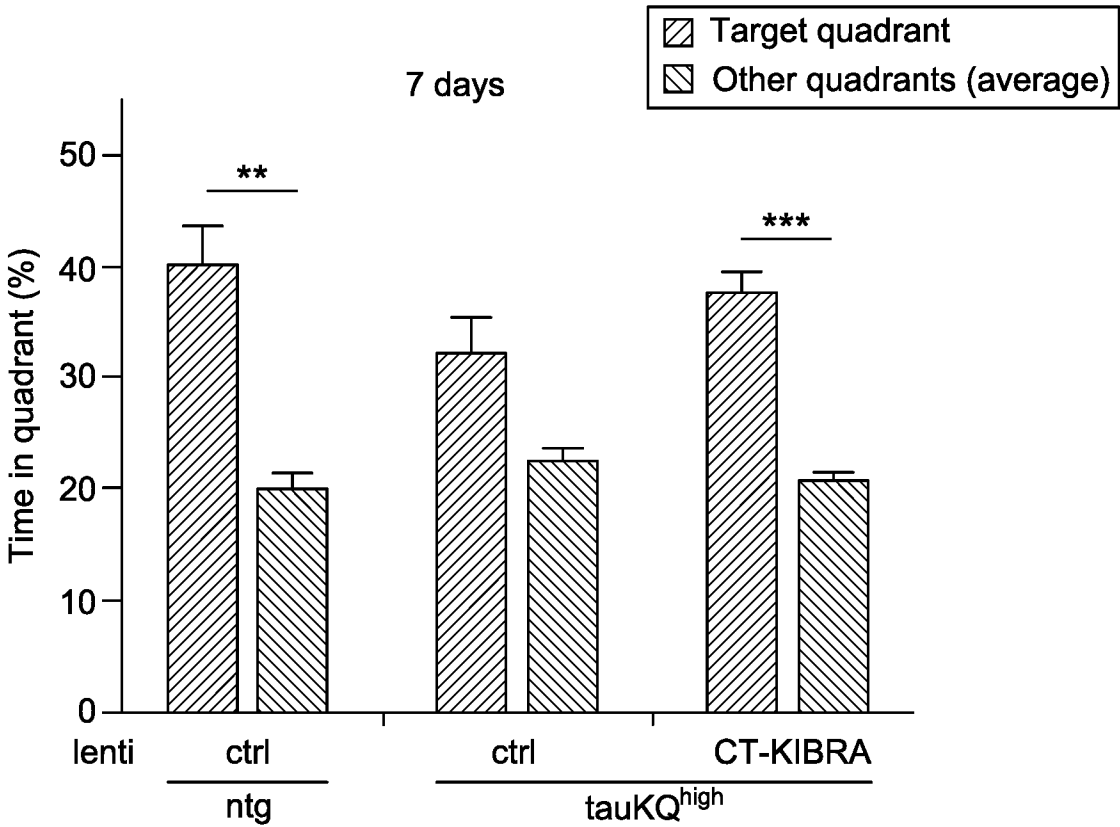
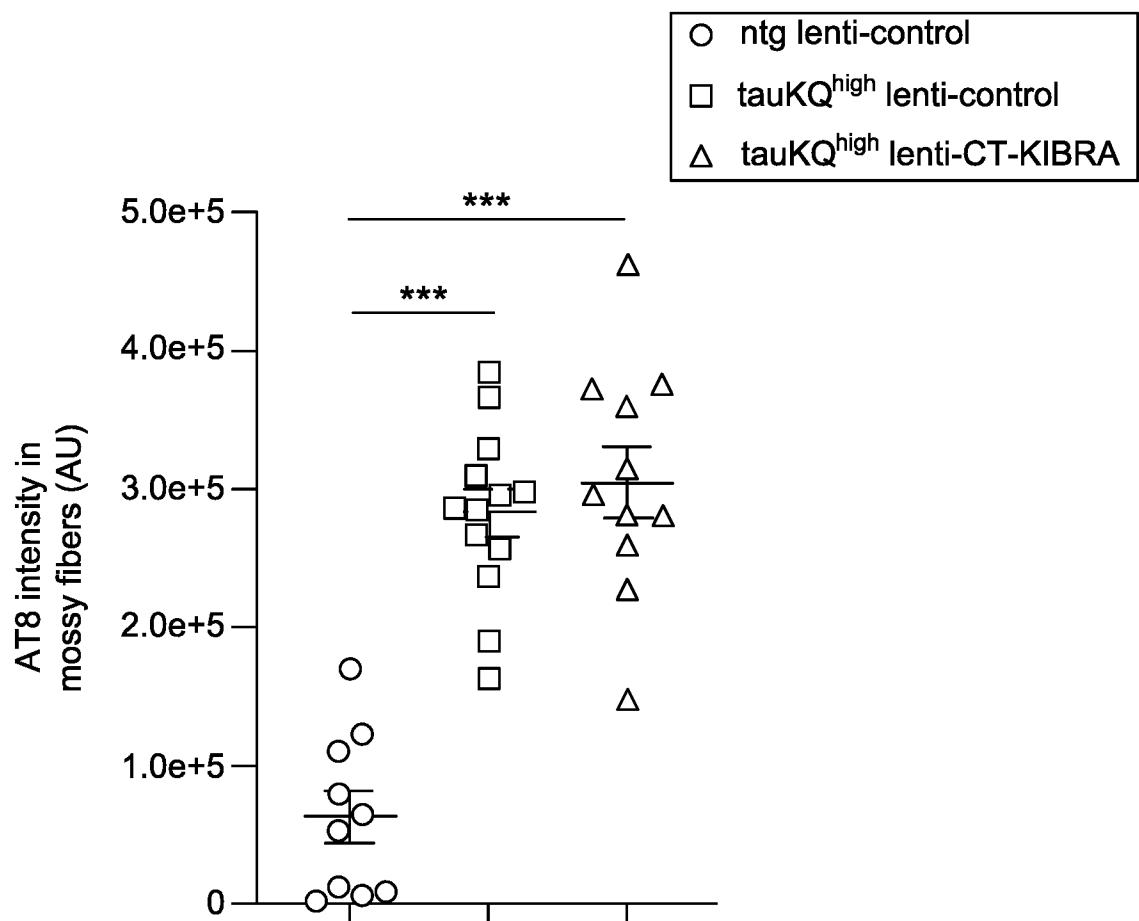
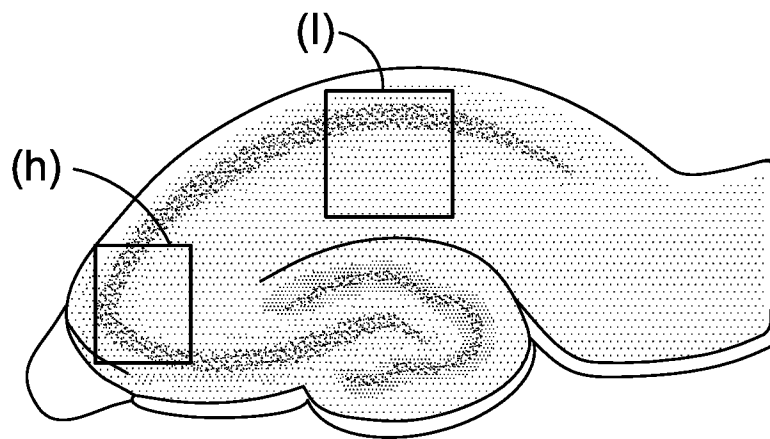


FIG. 2G

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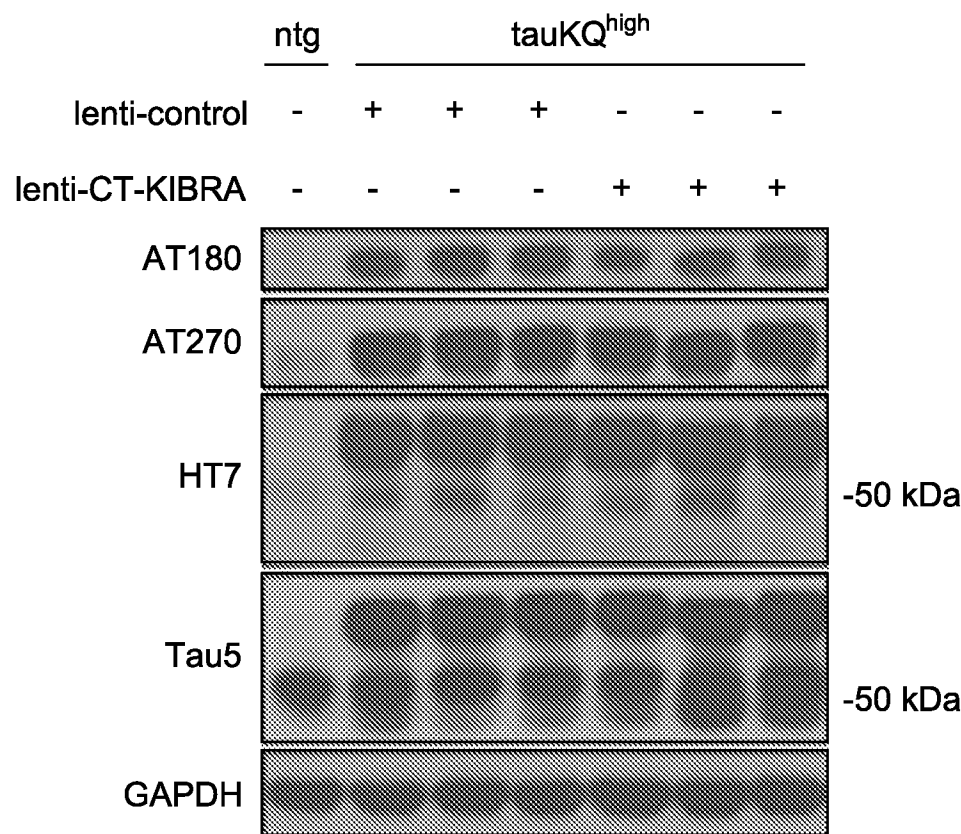


FIG. 2J

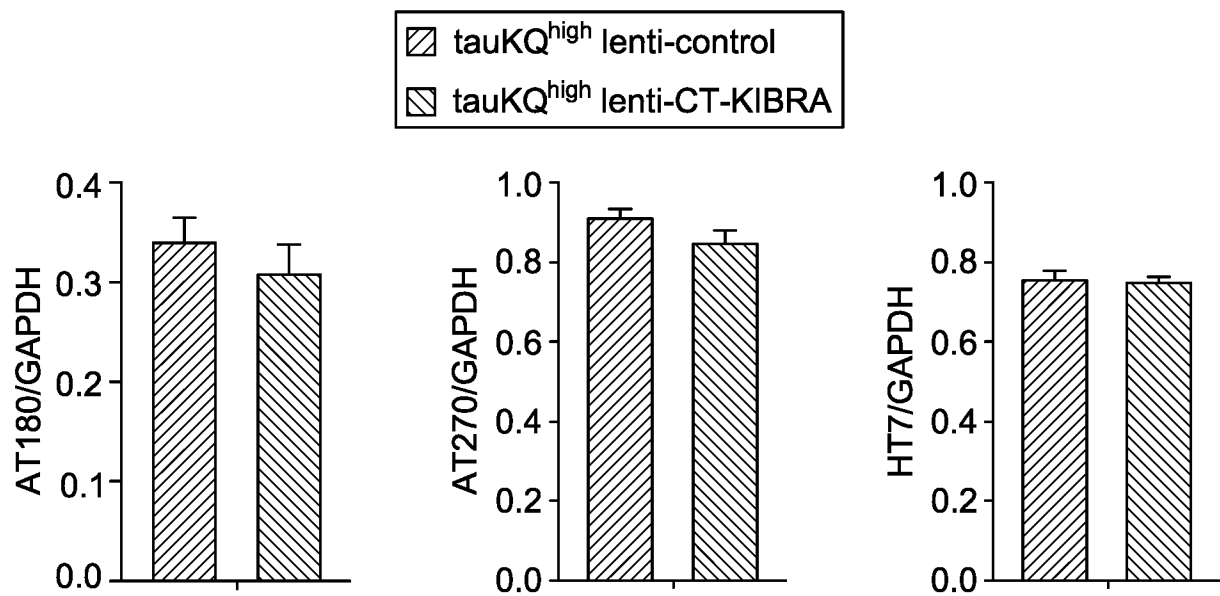


FIG. 2K

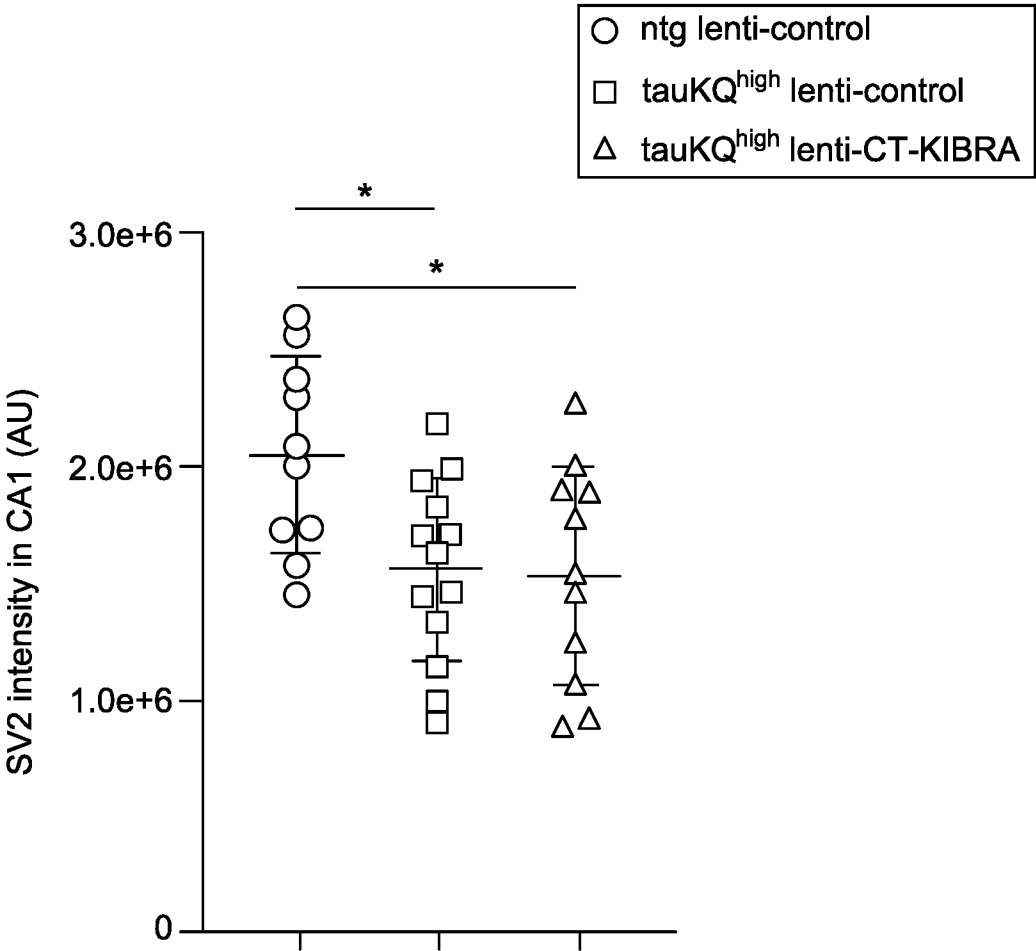


FIG. 2L

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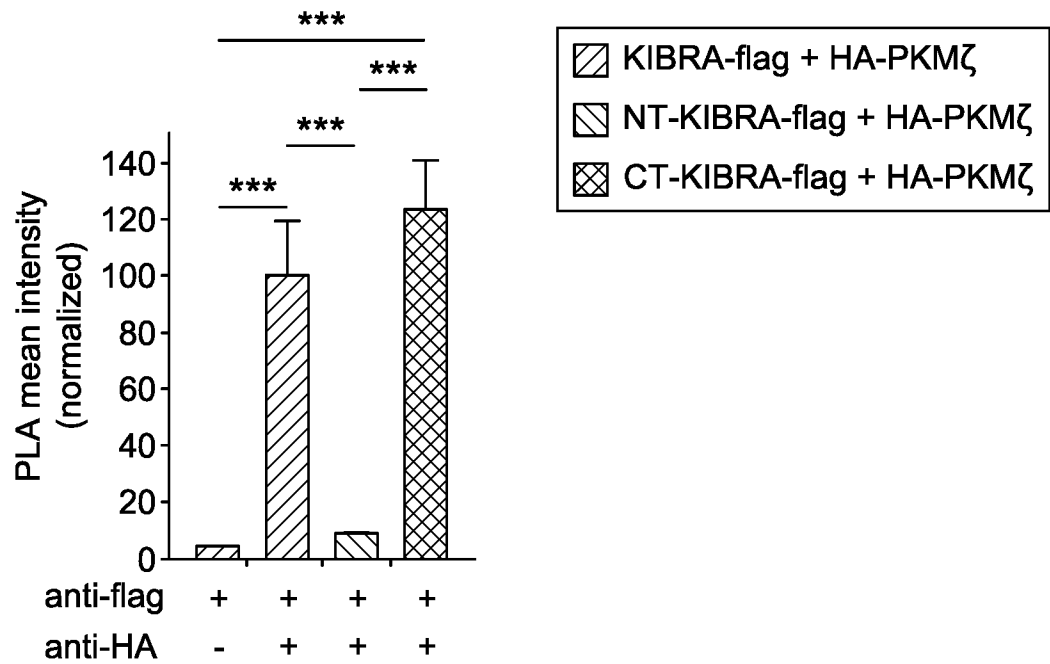


FIG. 3A

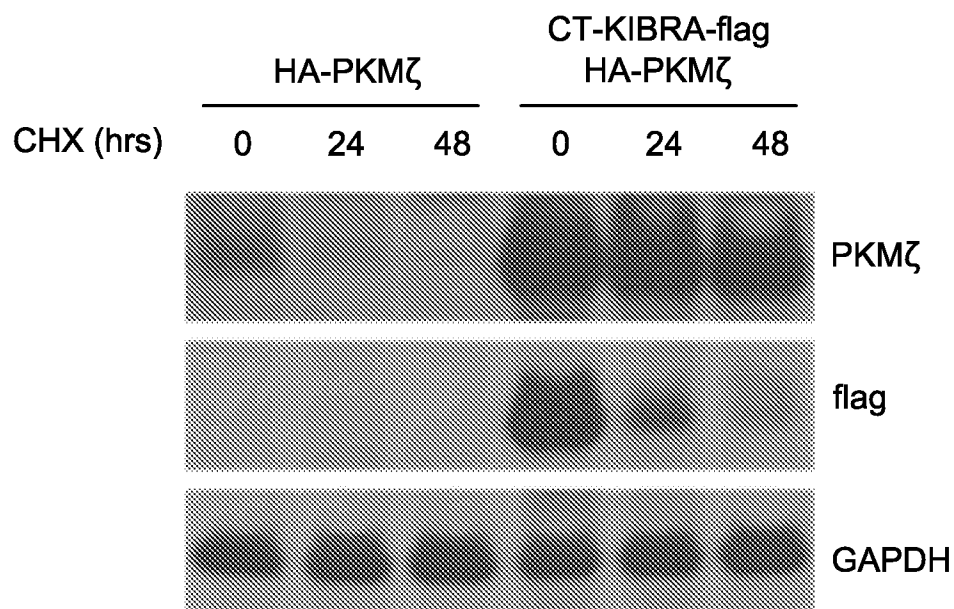


FIG. 3B

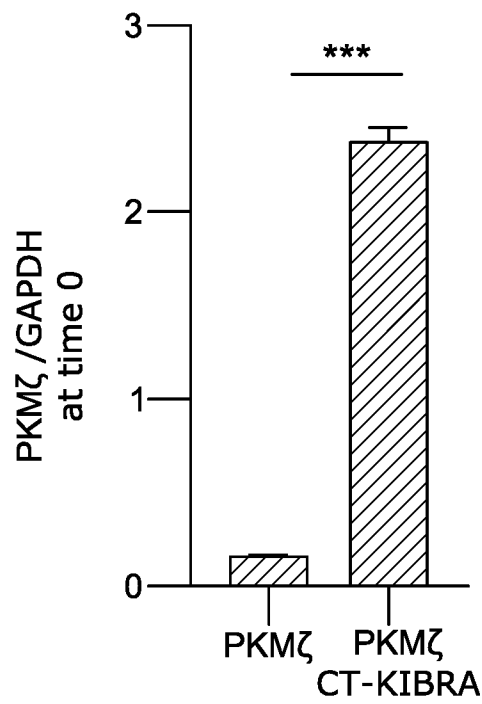


FIG. 3C

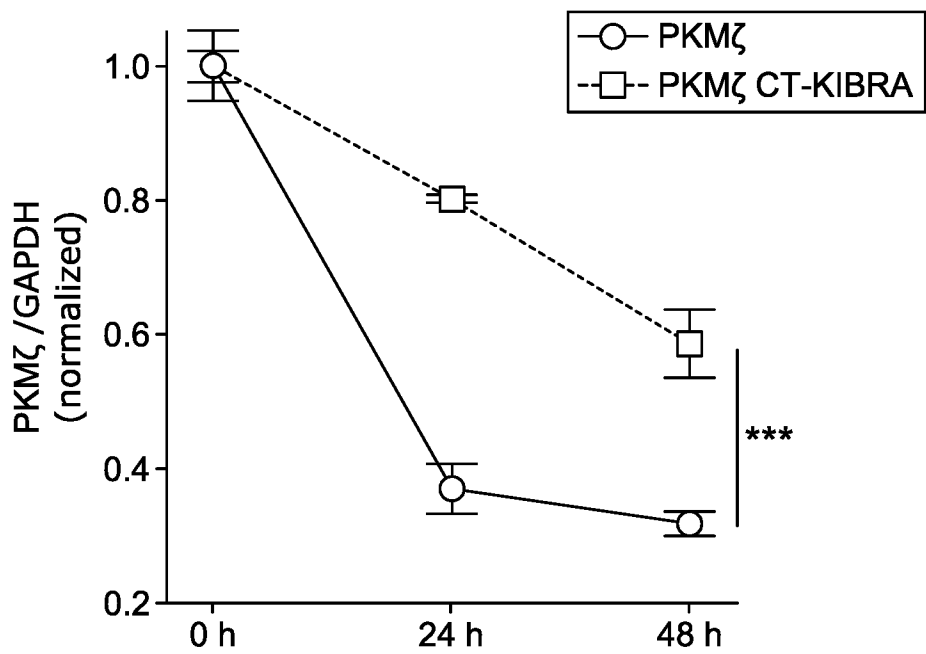


FIG. 3D

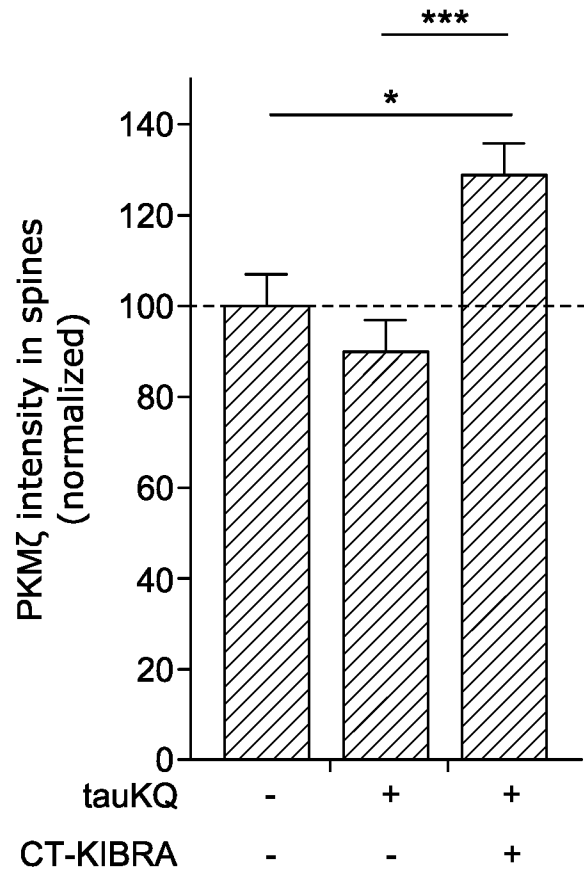


FIG. 3E

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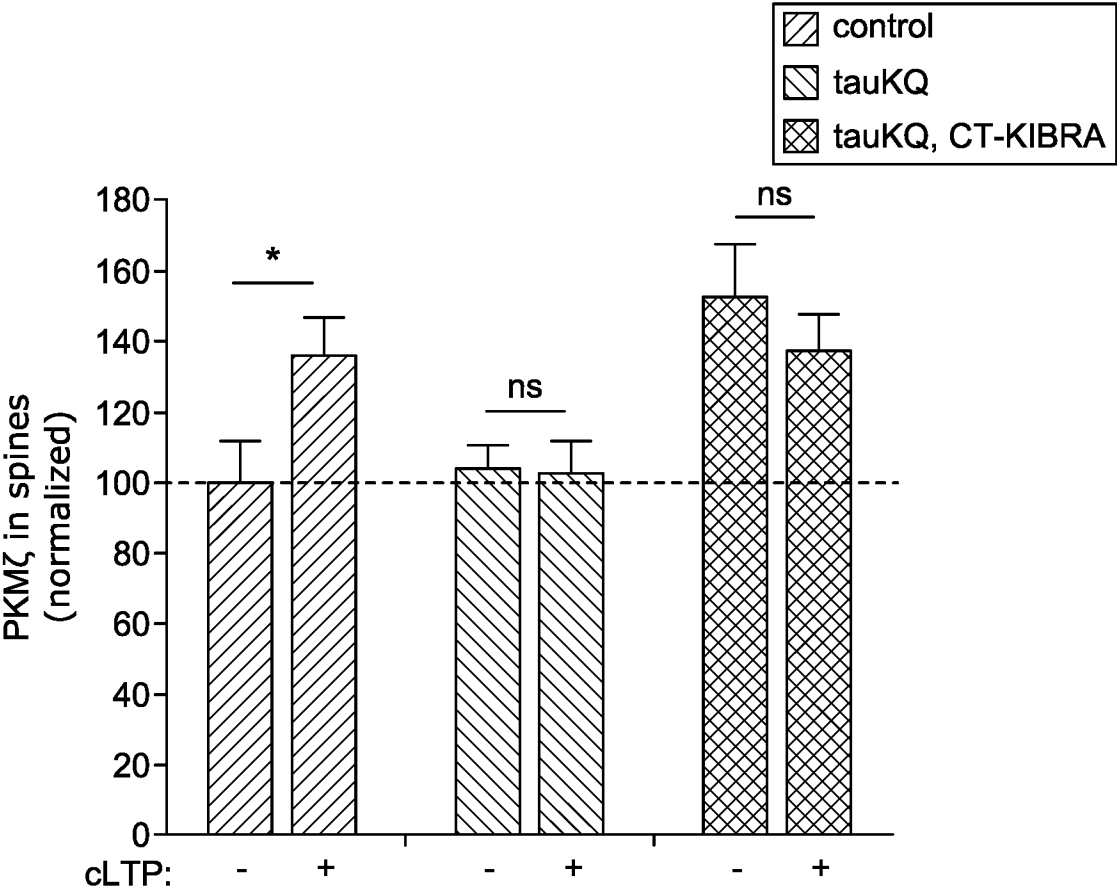


FIG. 4A

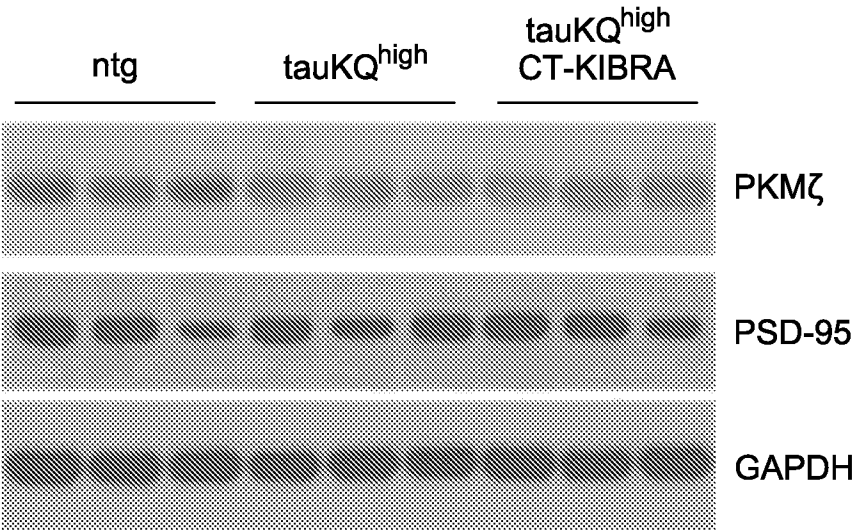


FIG. 4B

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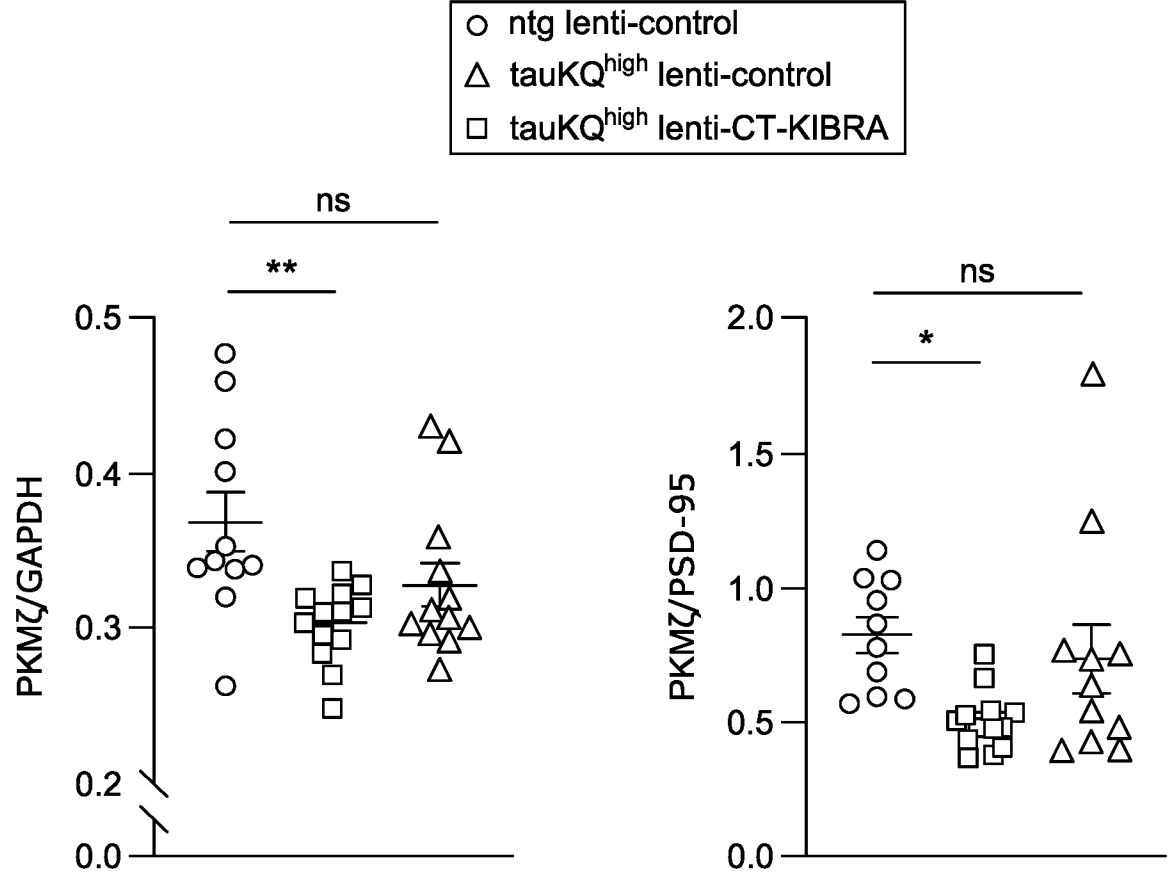


FIG. 4C

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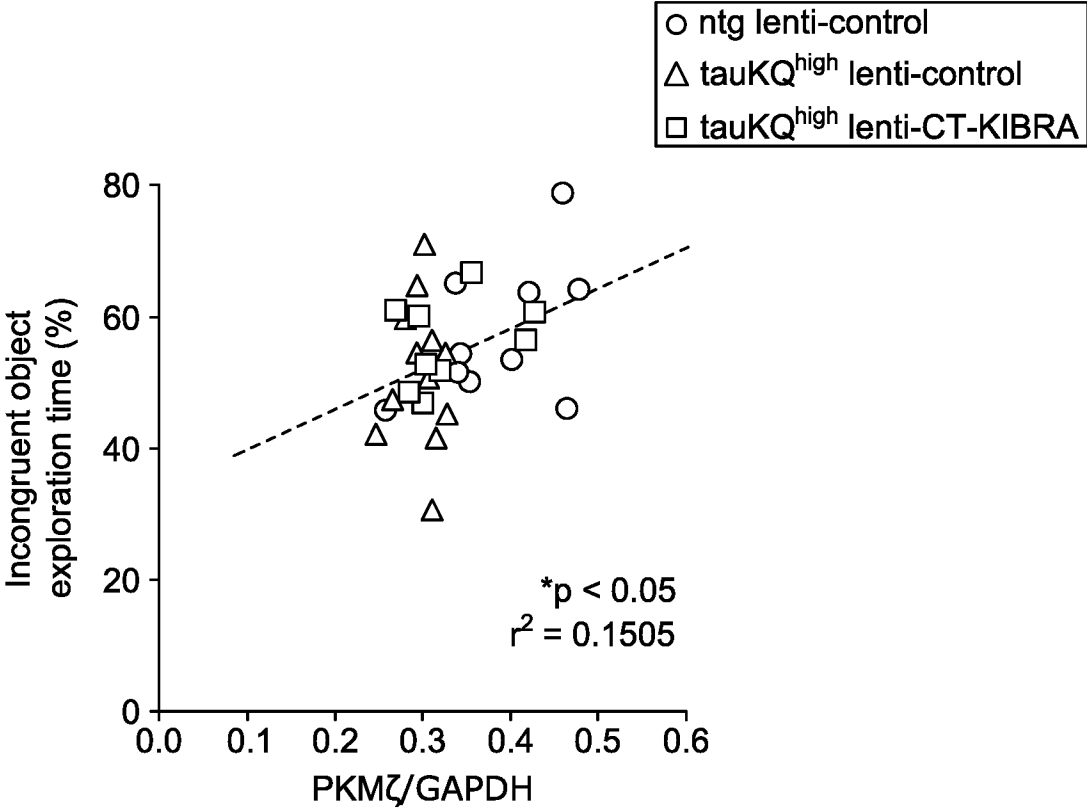


FIG. 4D

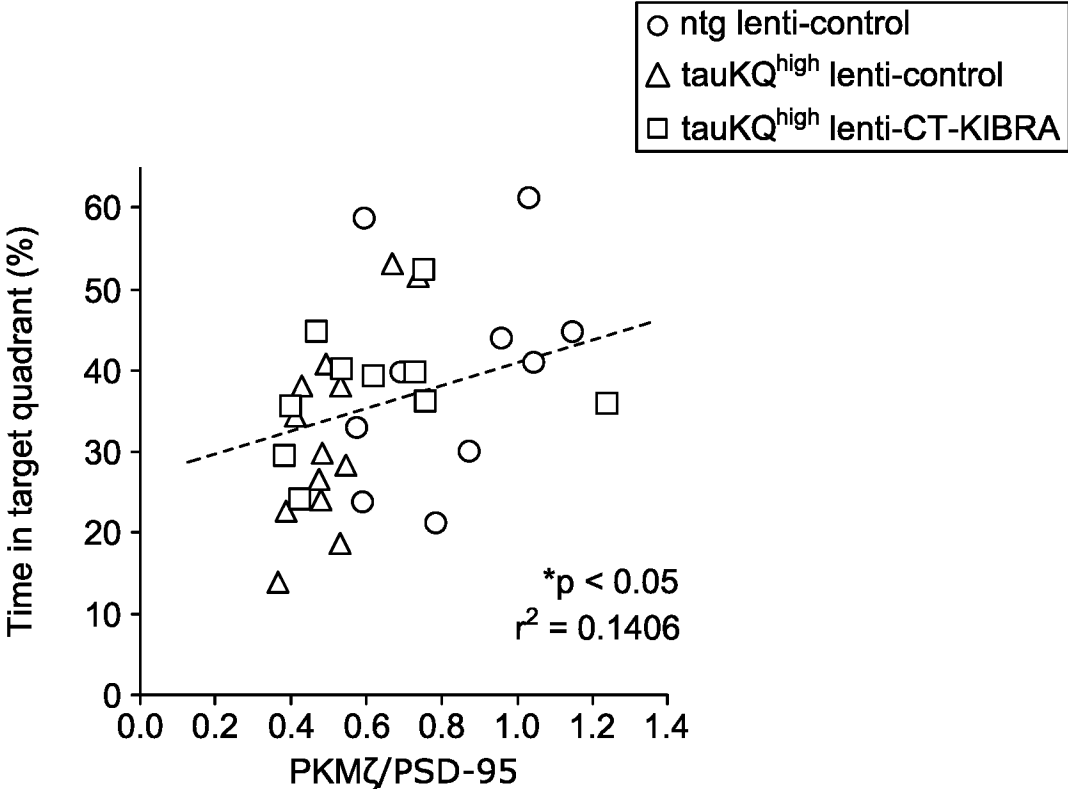


FIG. 4E

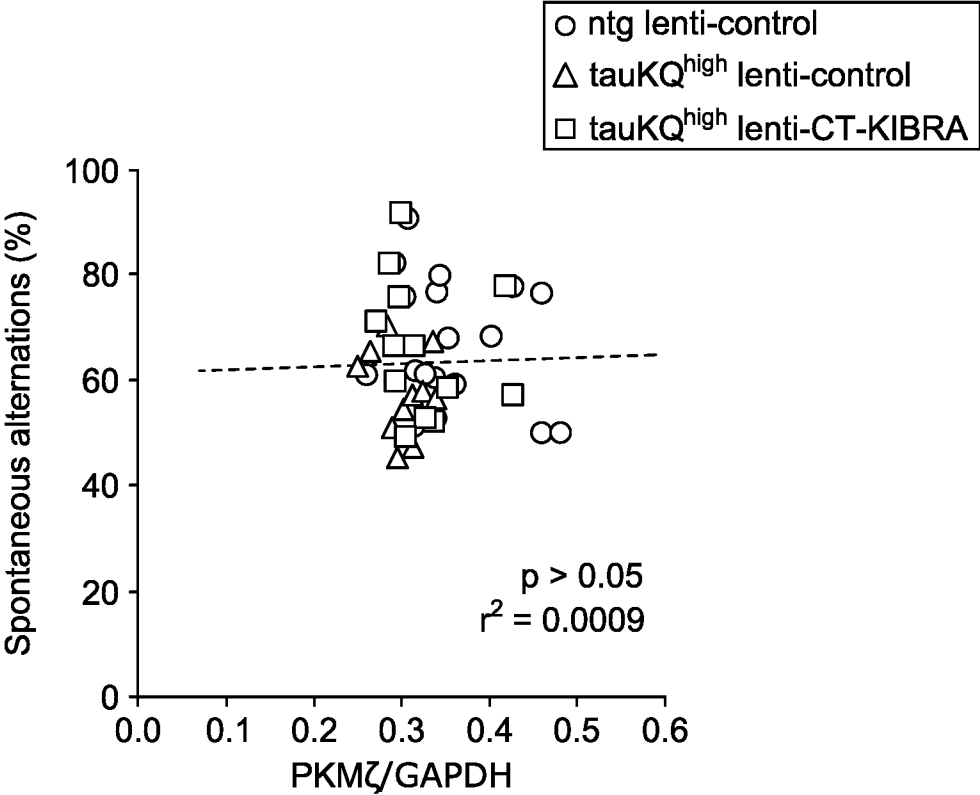


FIG. 4F

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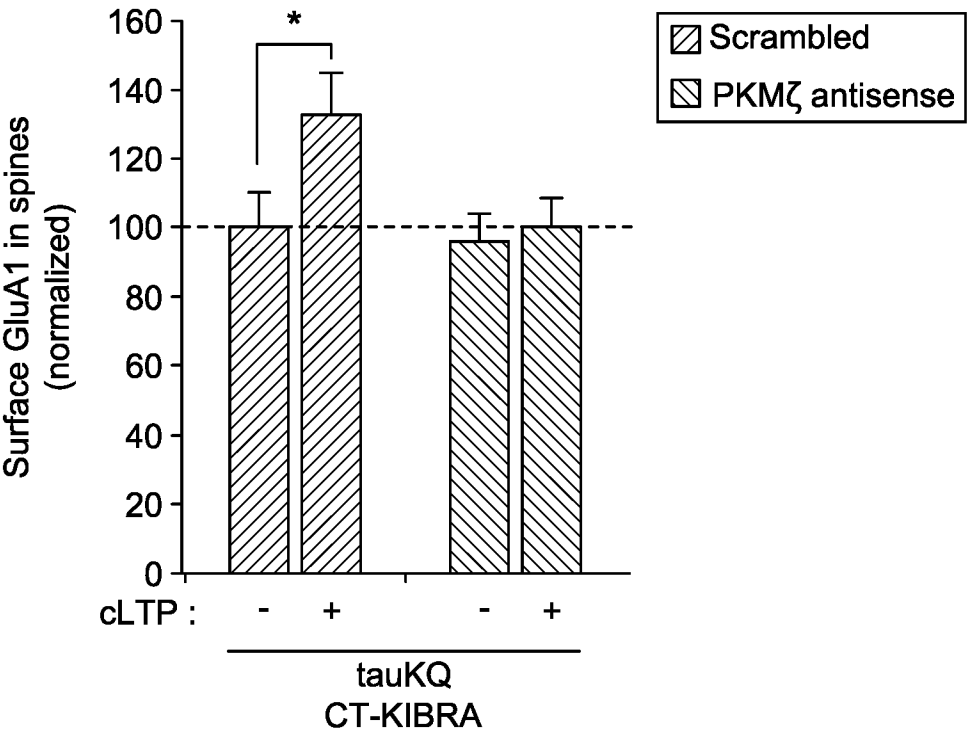


FIG. 5A

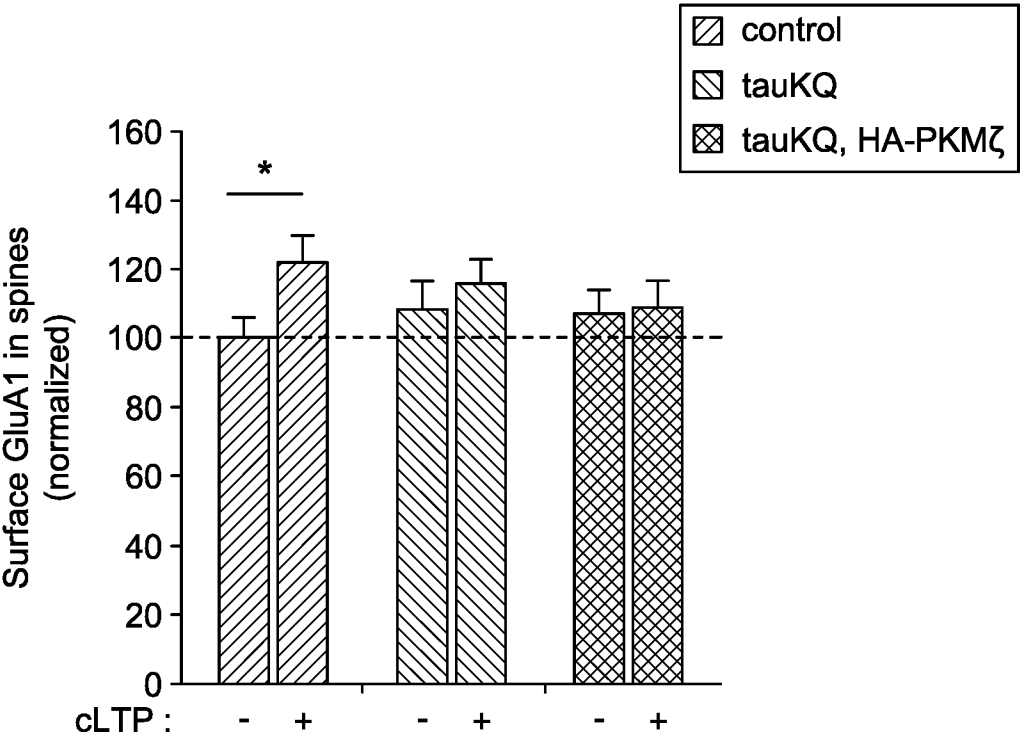


FIG. 5B

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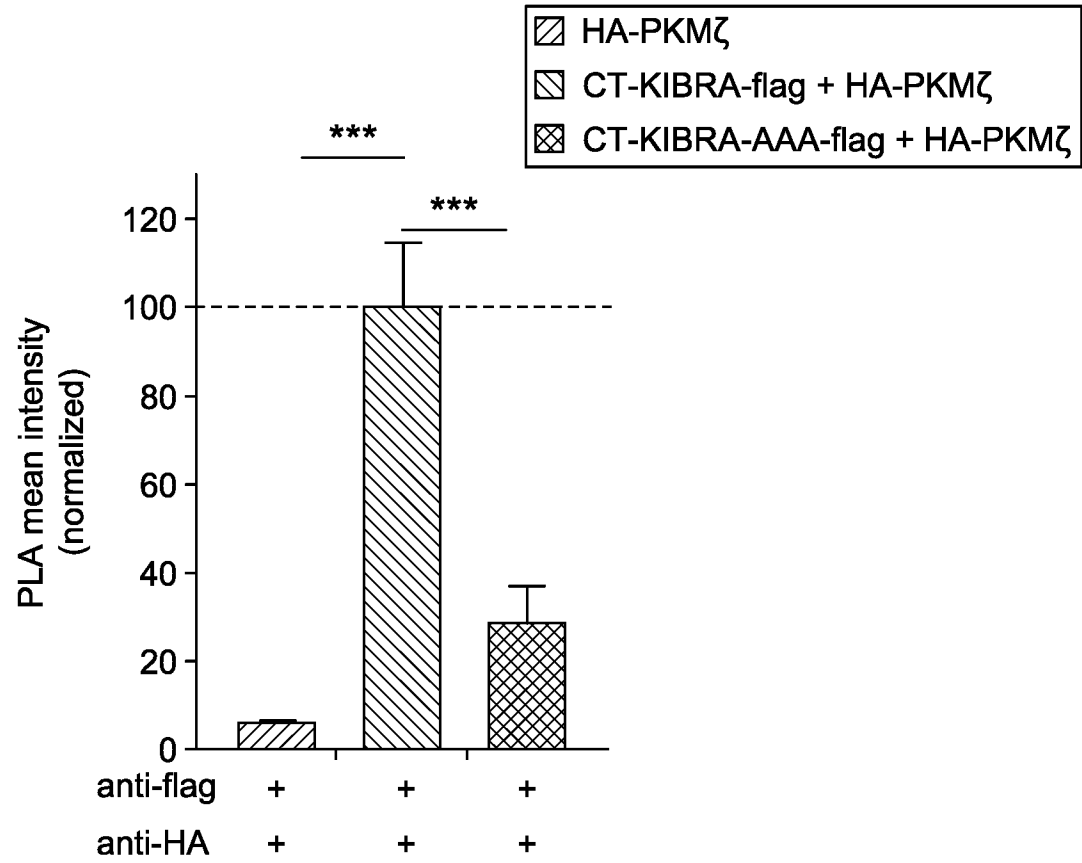


FIG. 5C

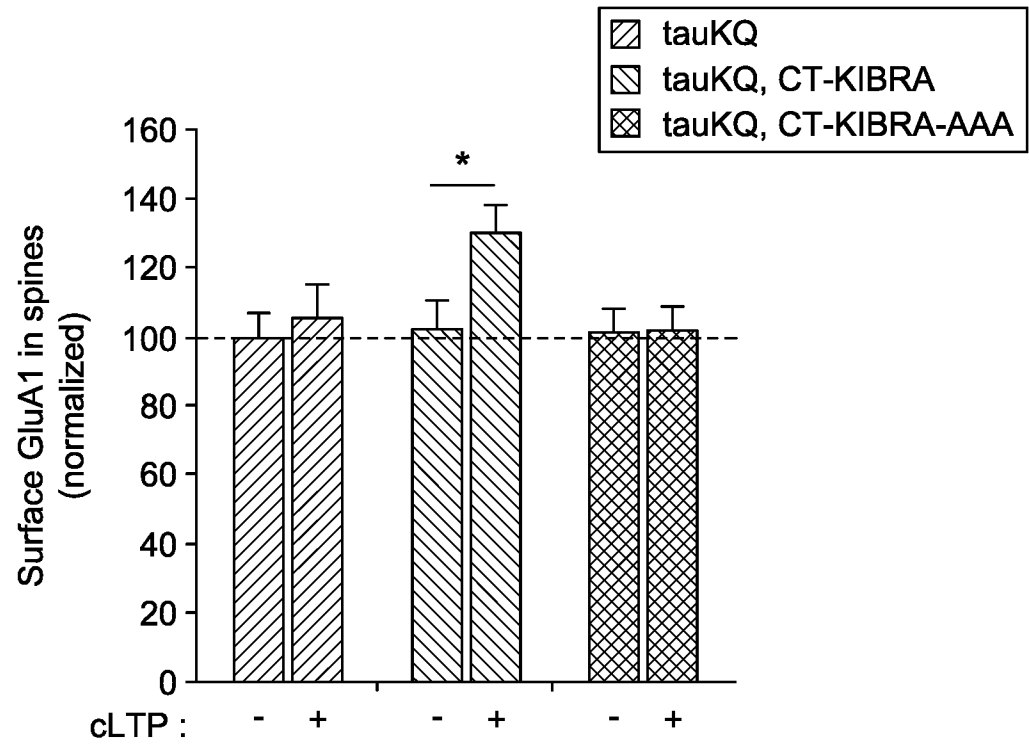


FIG. 5D

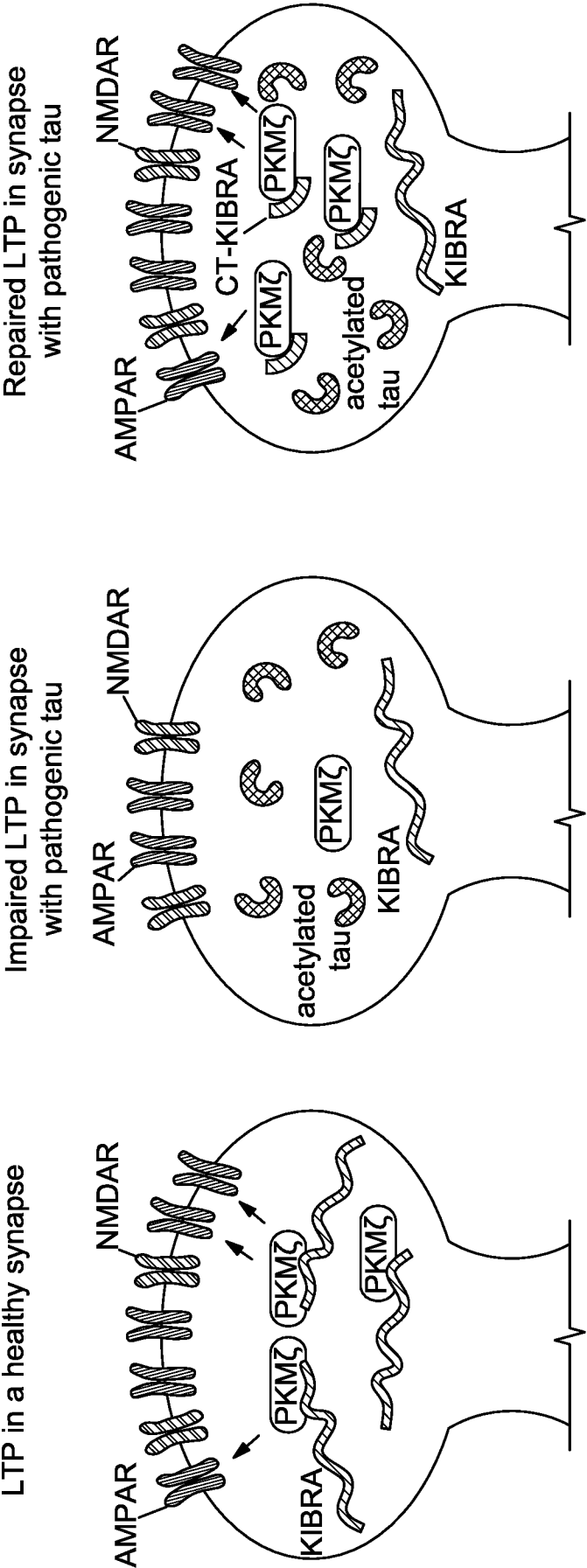


FIG. 5E

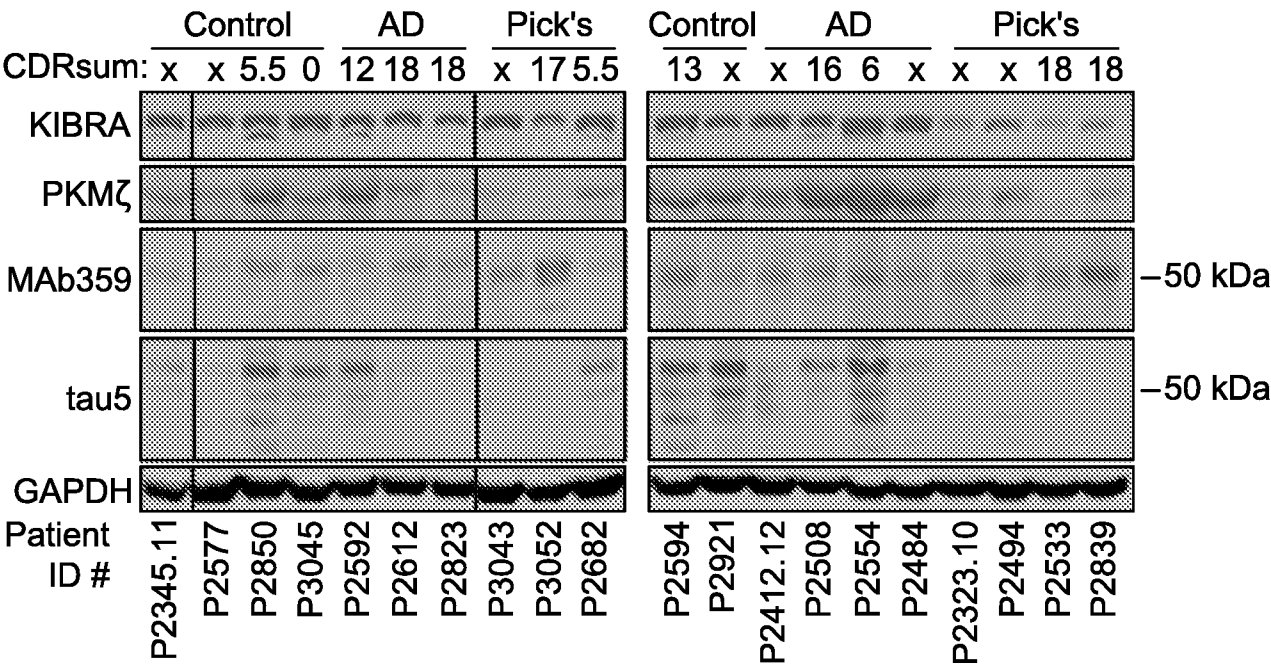


FIG. 6A

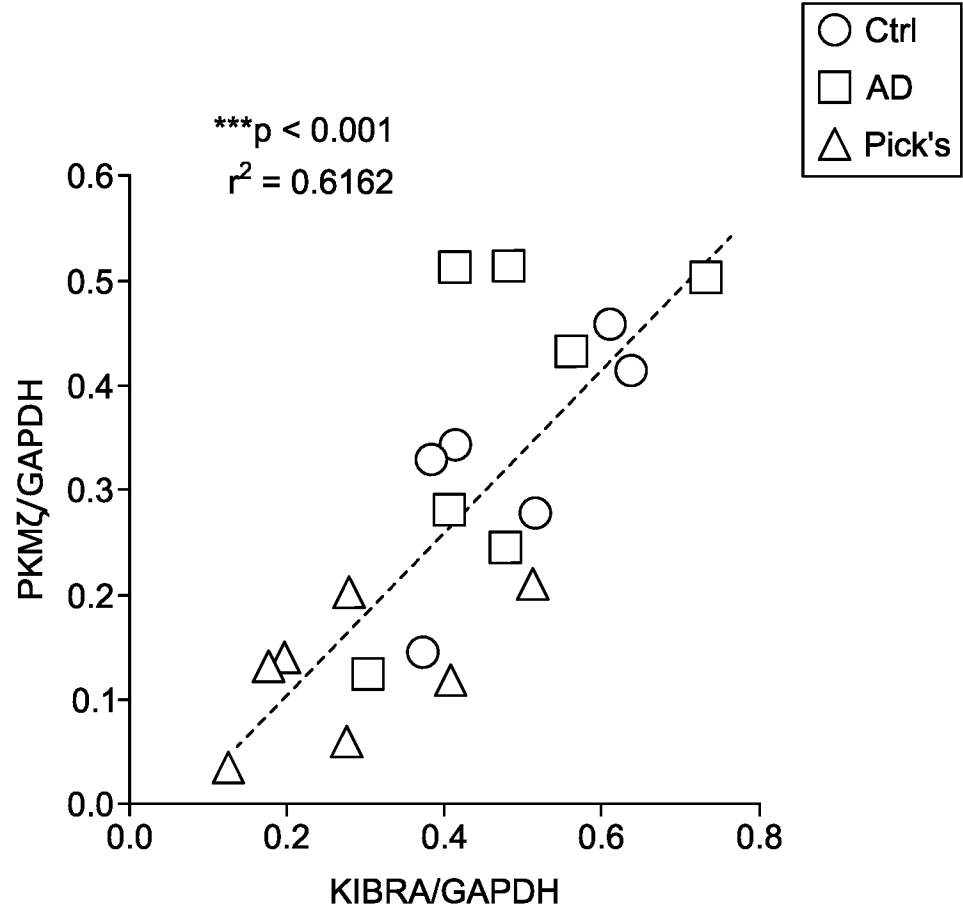


FIG. 6B

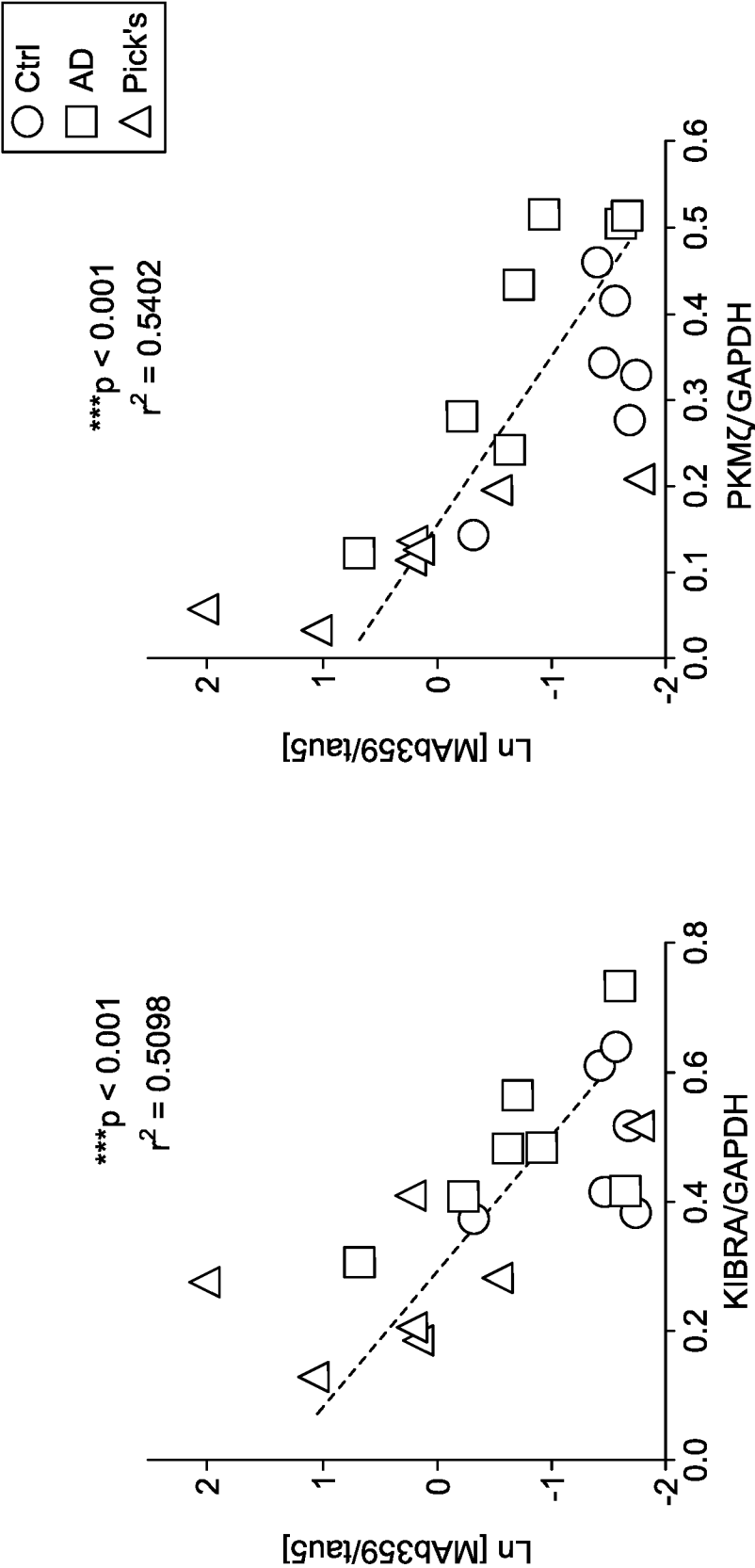


FIG. 6C

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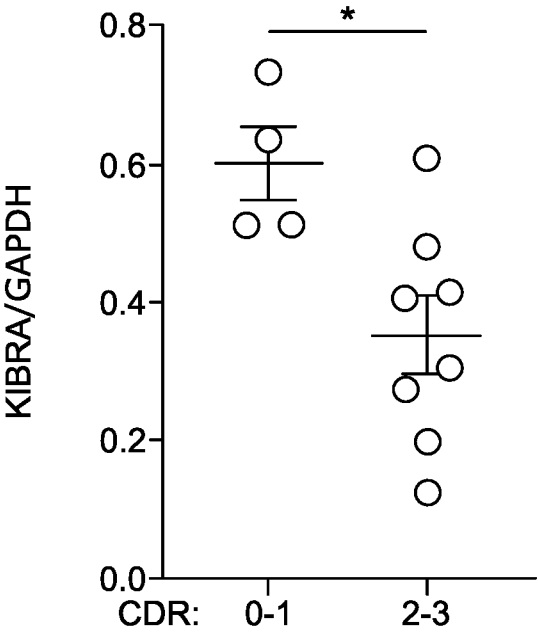


FIG. 6D

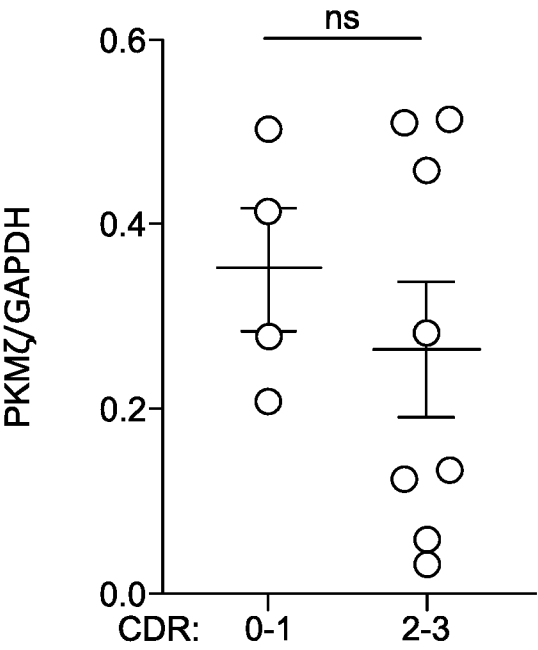


FIG. 6E

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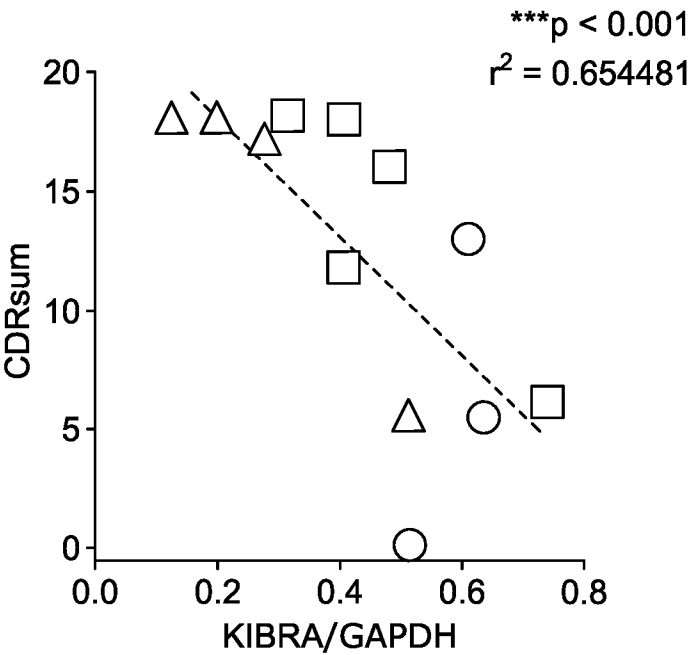


FIG. 6F

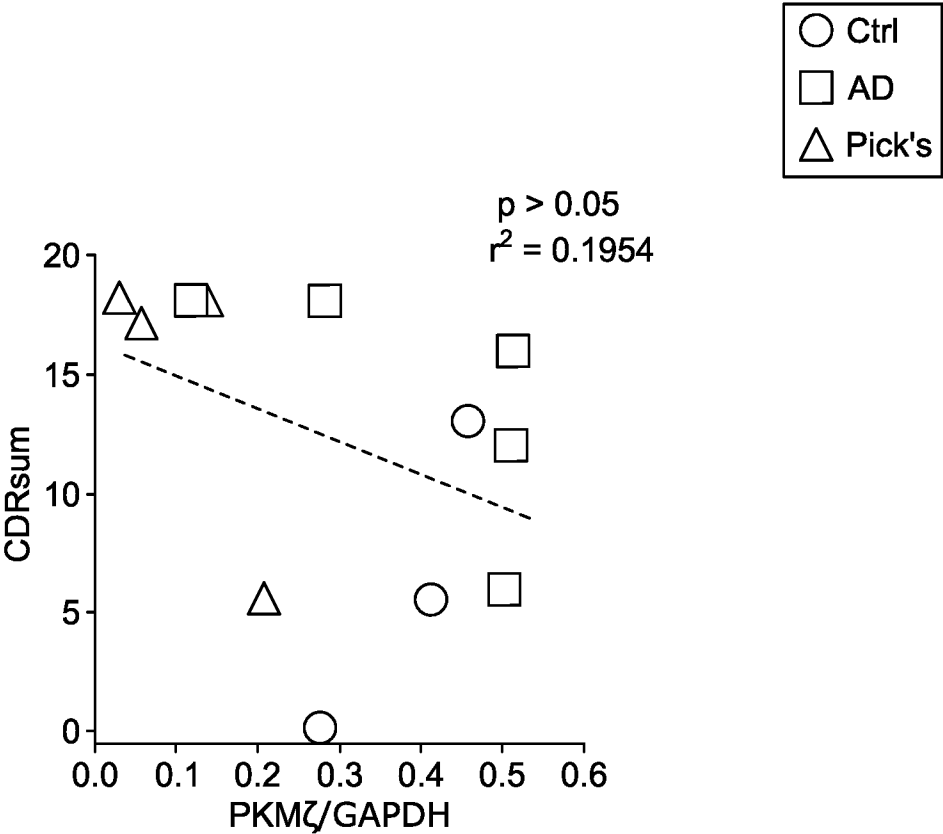


FIG. 6G

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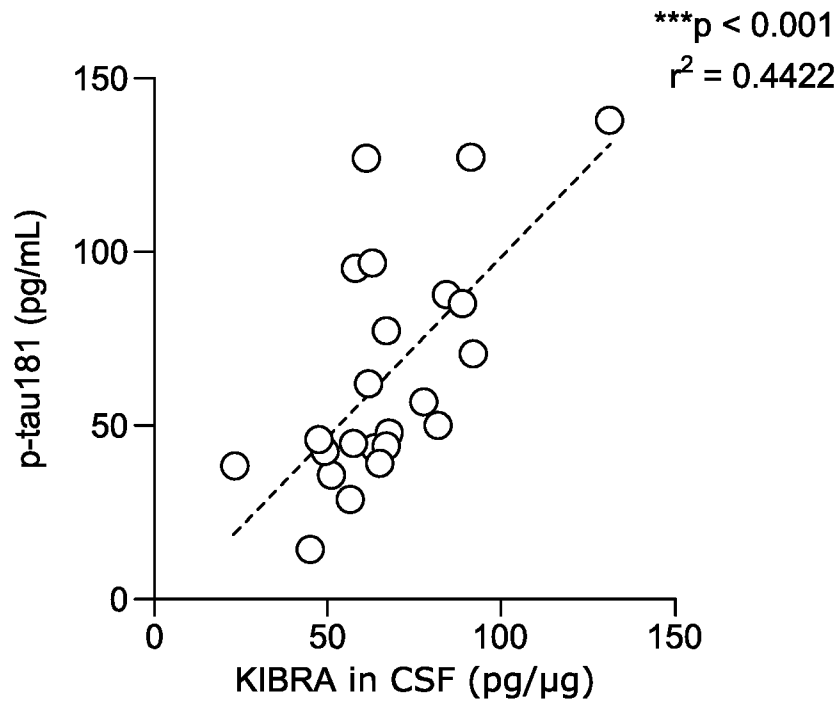


FIG. 6H

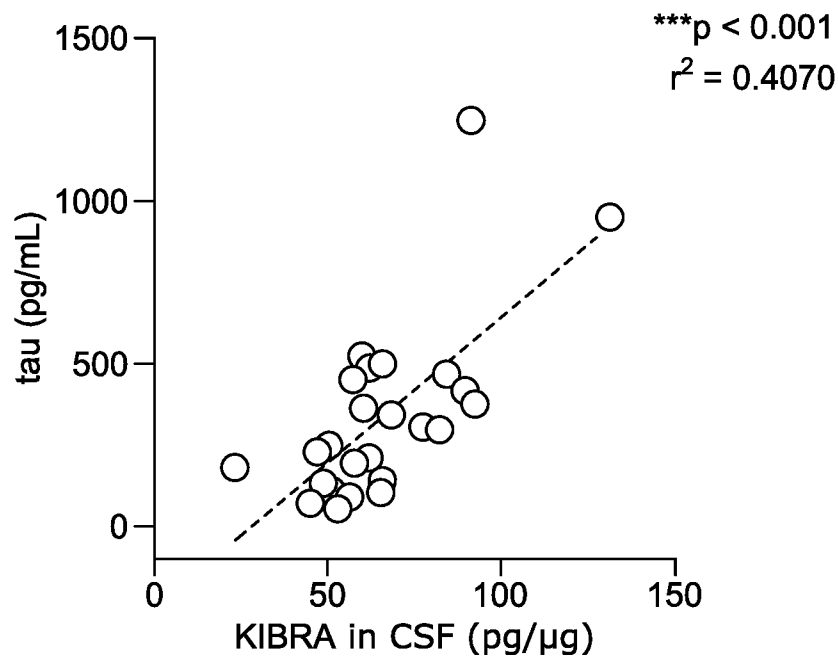


FIG. 6I

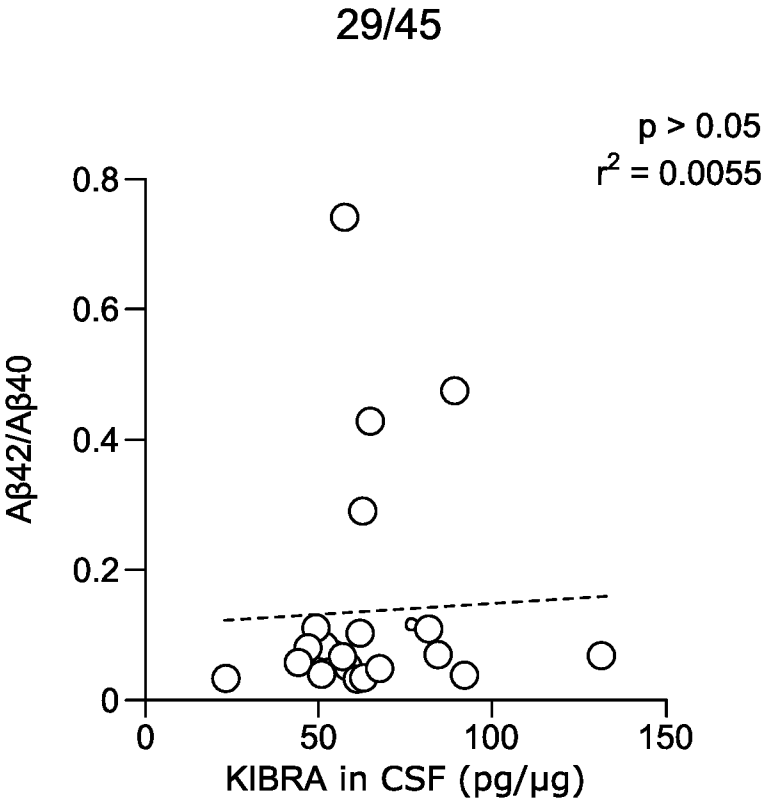


FIG. 6J

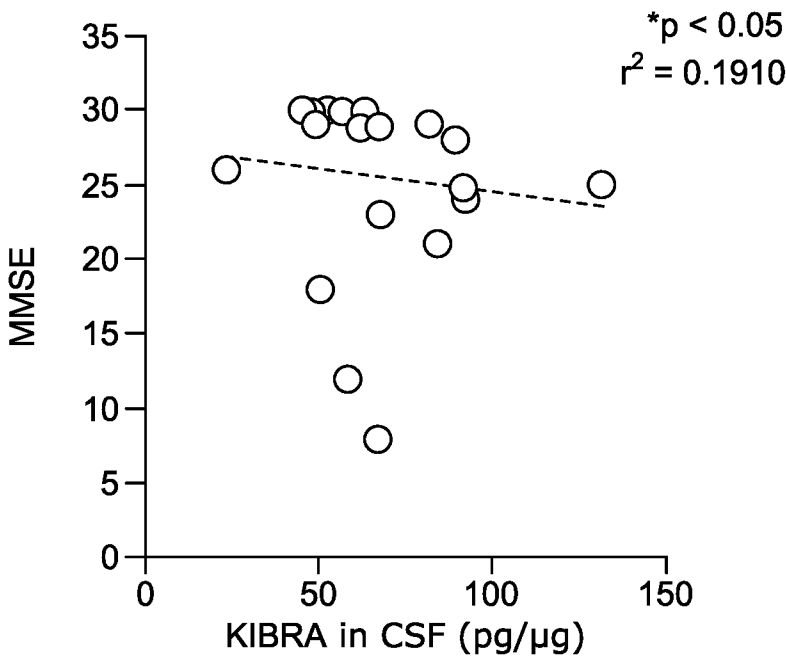


FIG. 6K

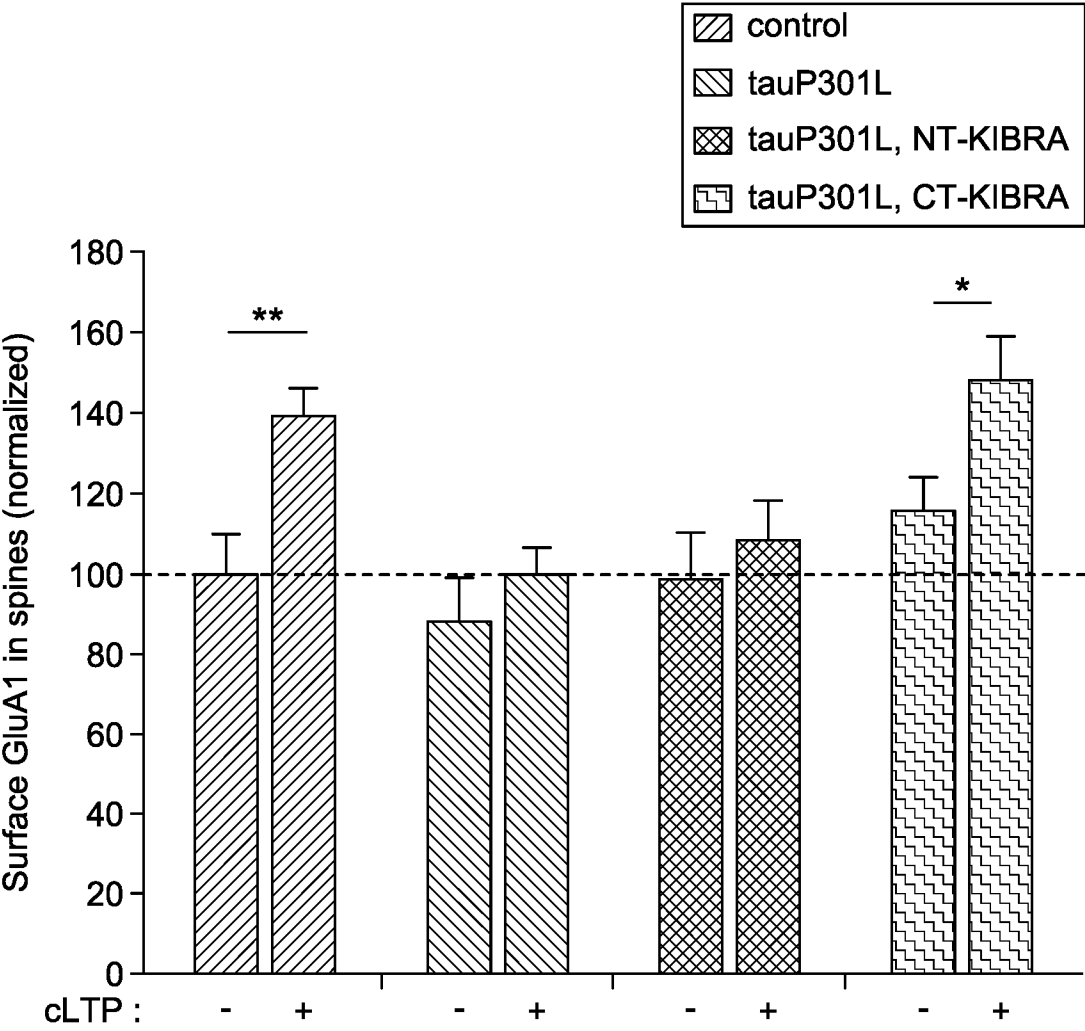


FIG. 7

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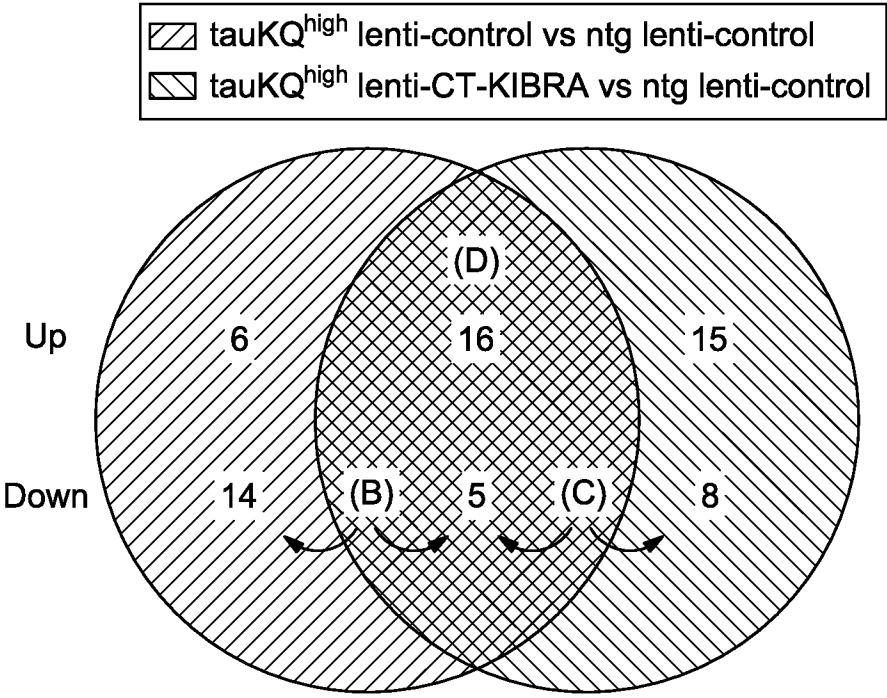


FIG. 8A

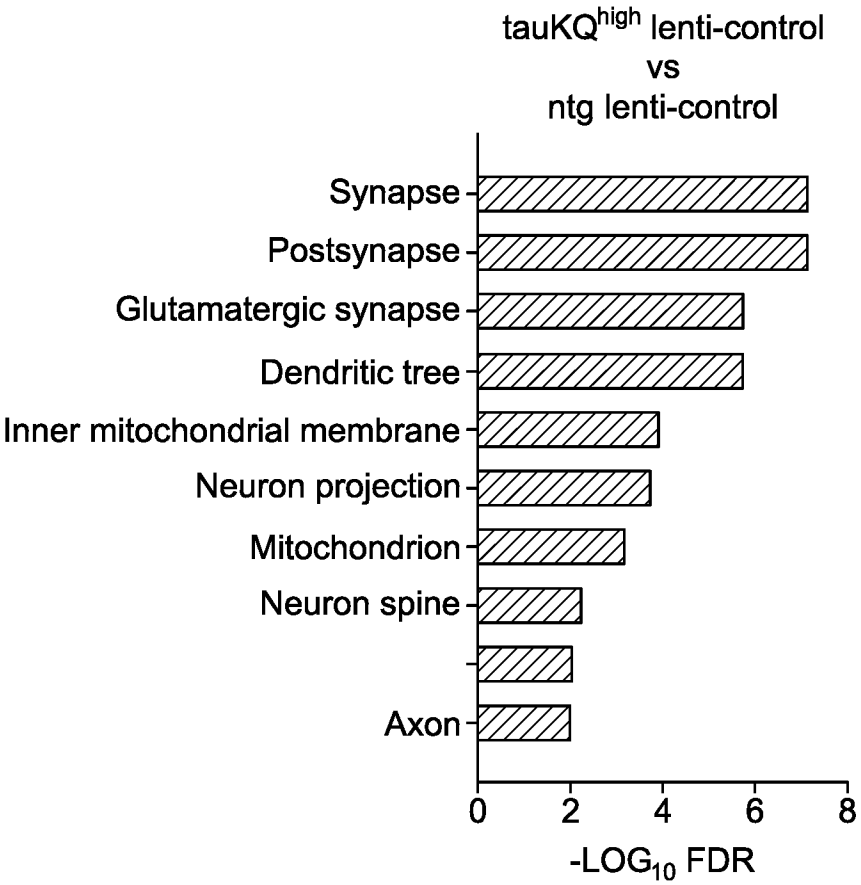


FIG. 8B

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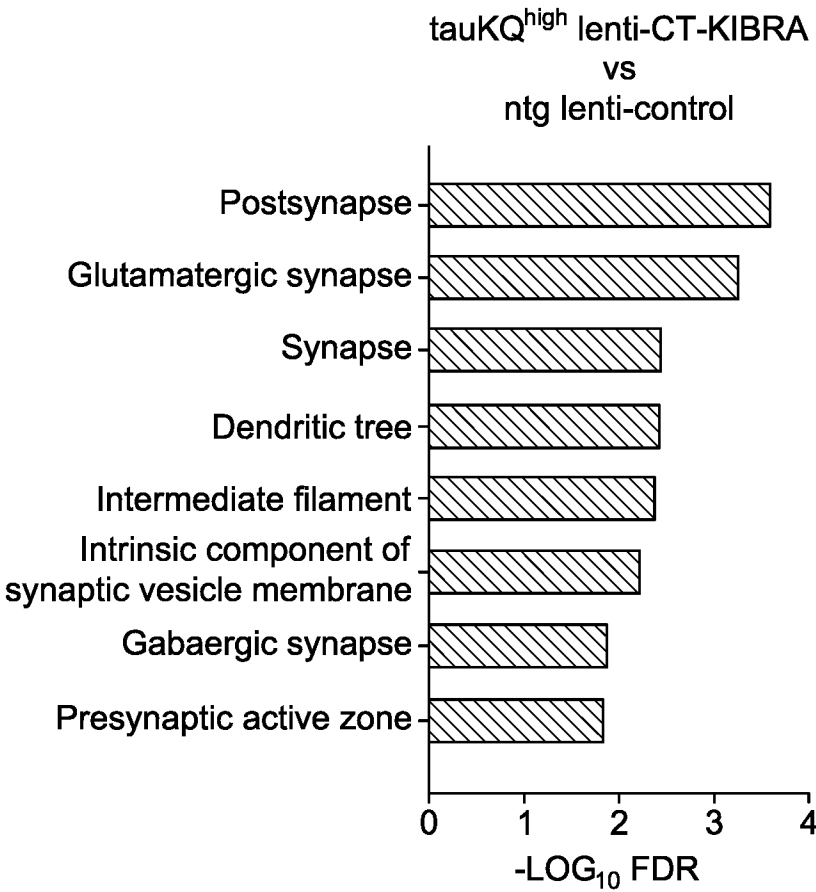


FIG. 8C

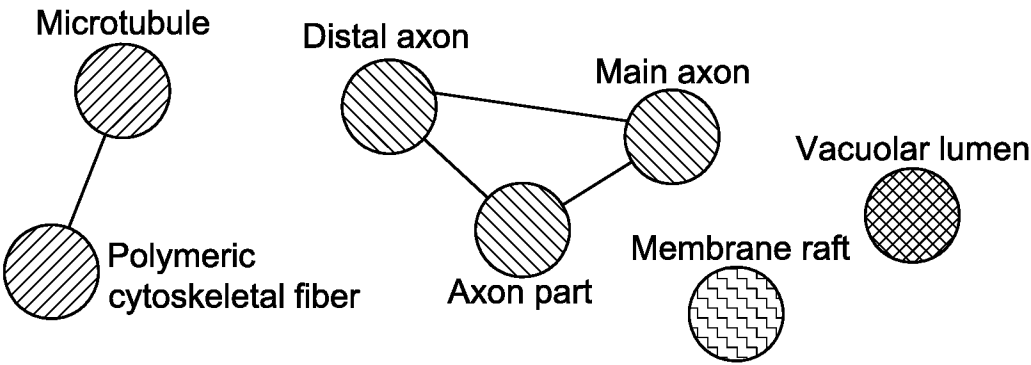


FIG. 8D

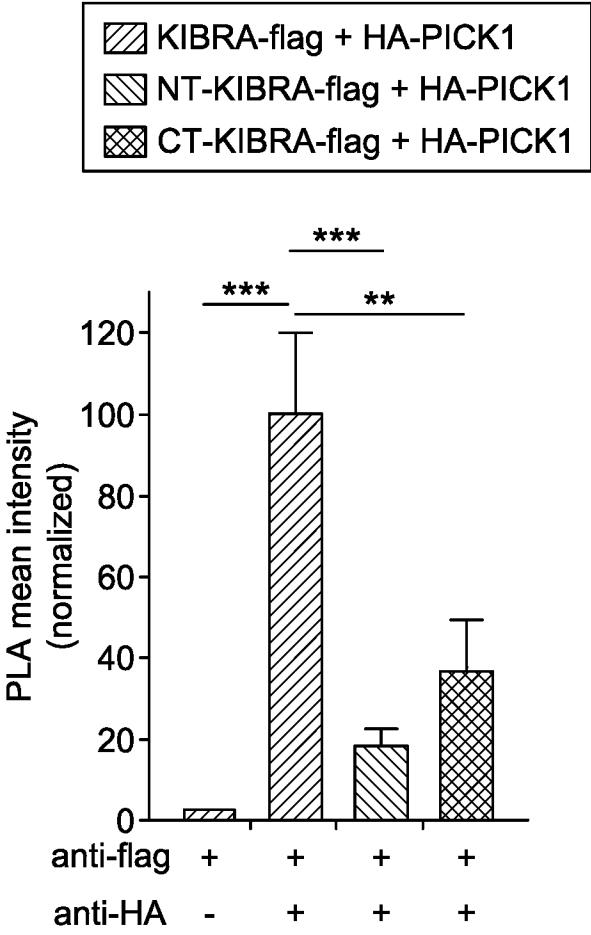


FIG. 9

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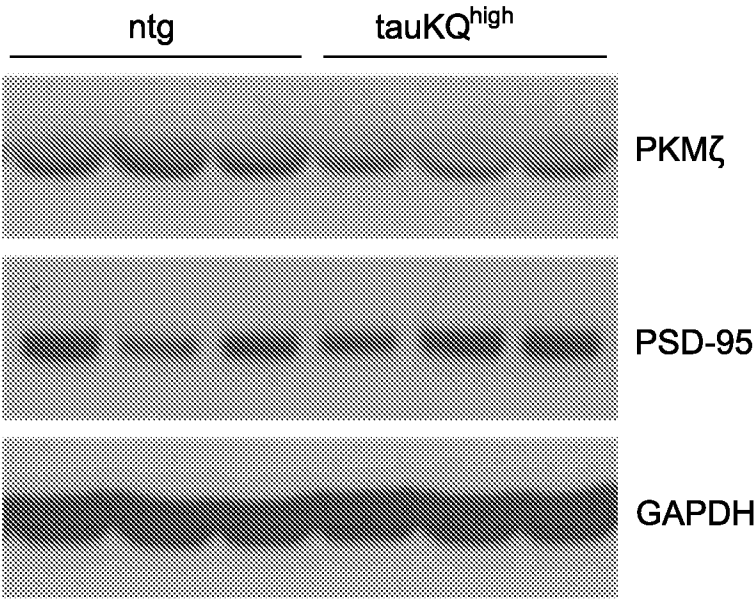


FIG. 10A

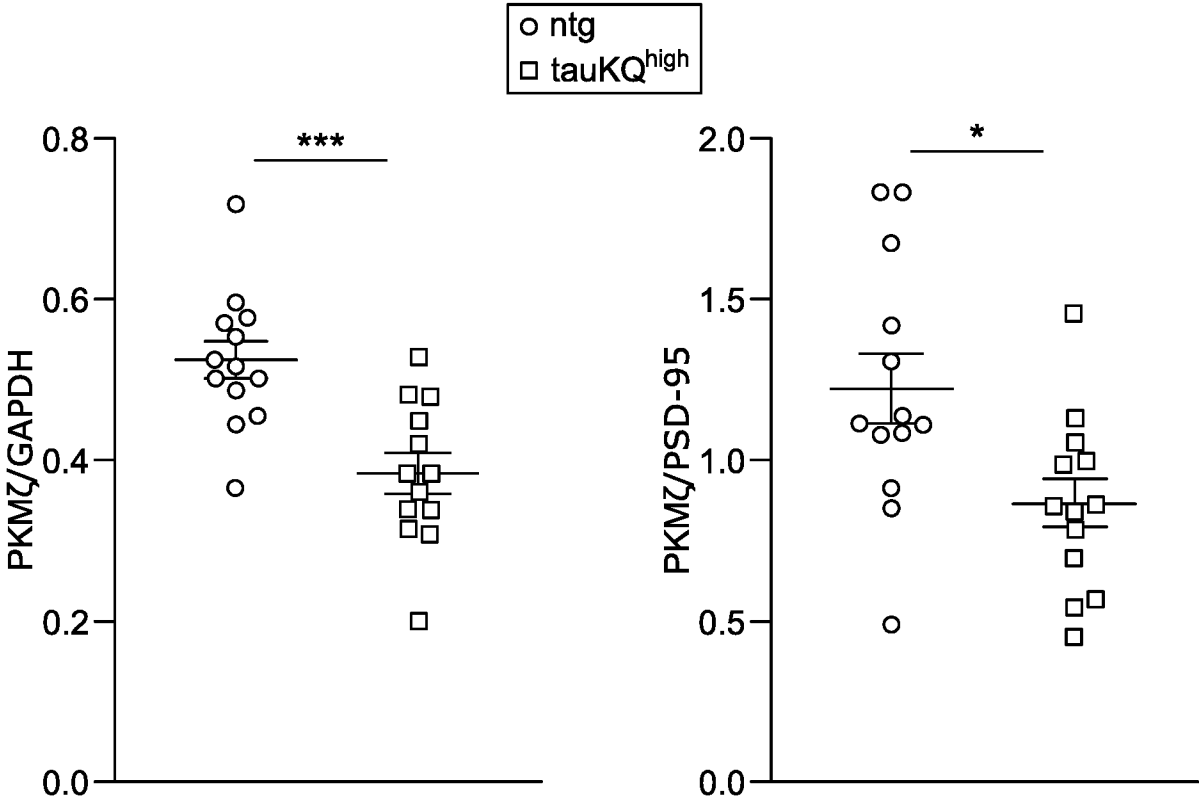


FIG. 10B

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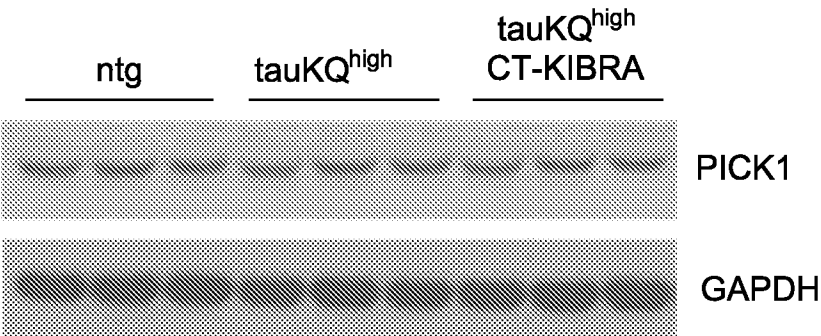


FIG. 10C

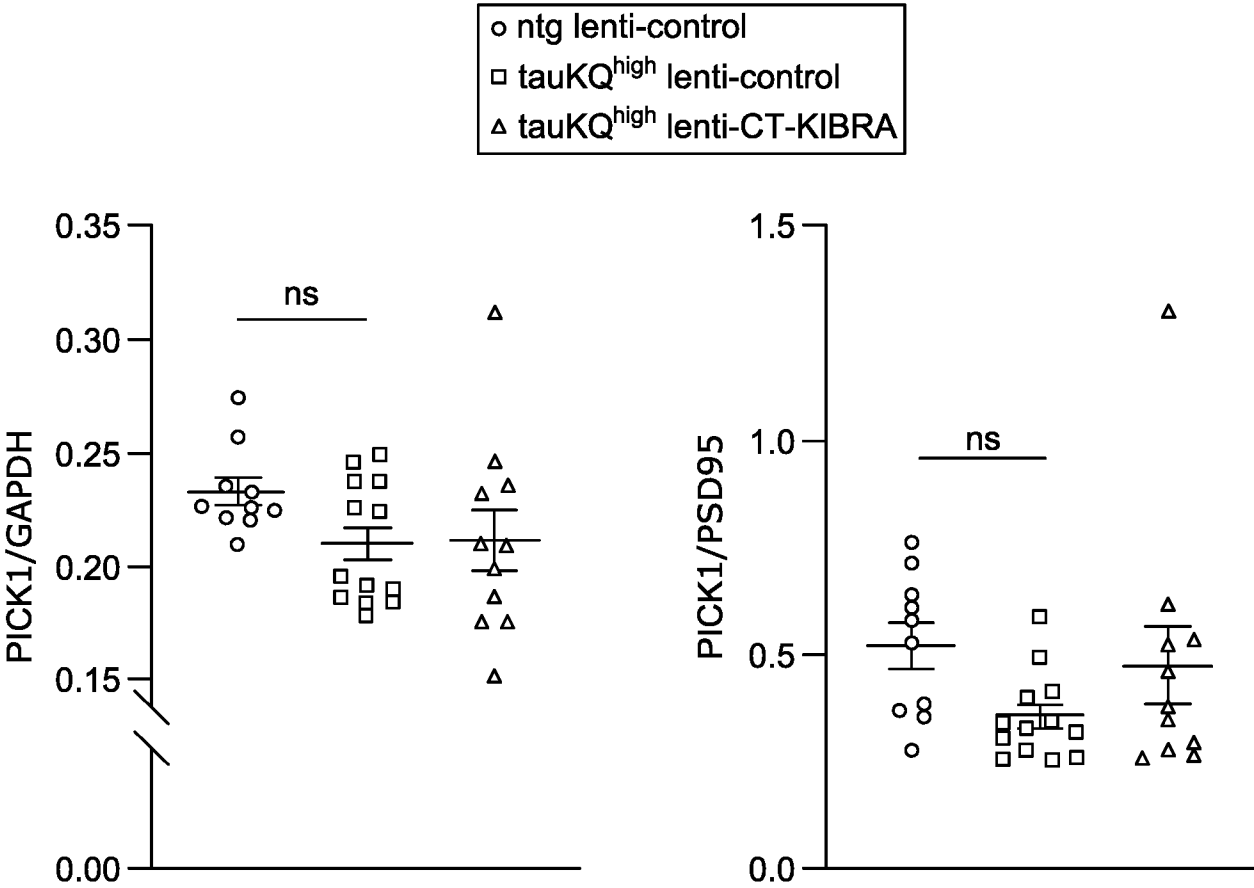


FIG. 10D

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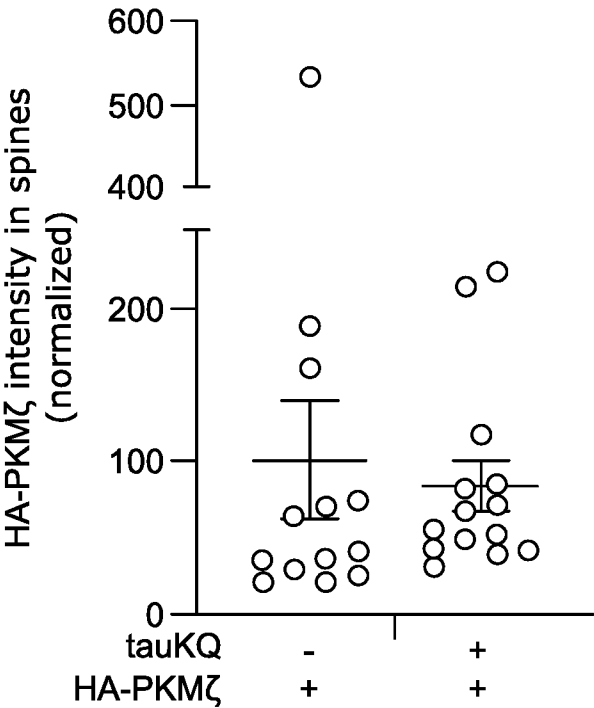


FIG. 11A

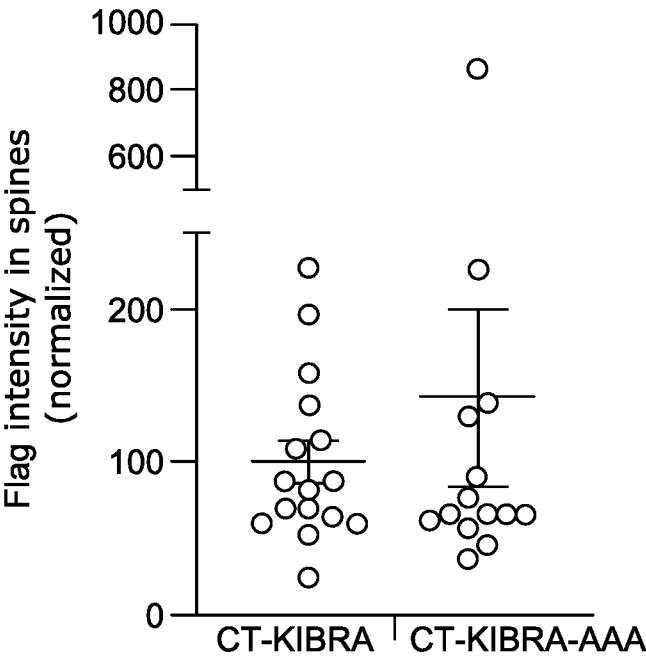


FIG. 11B

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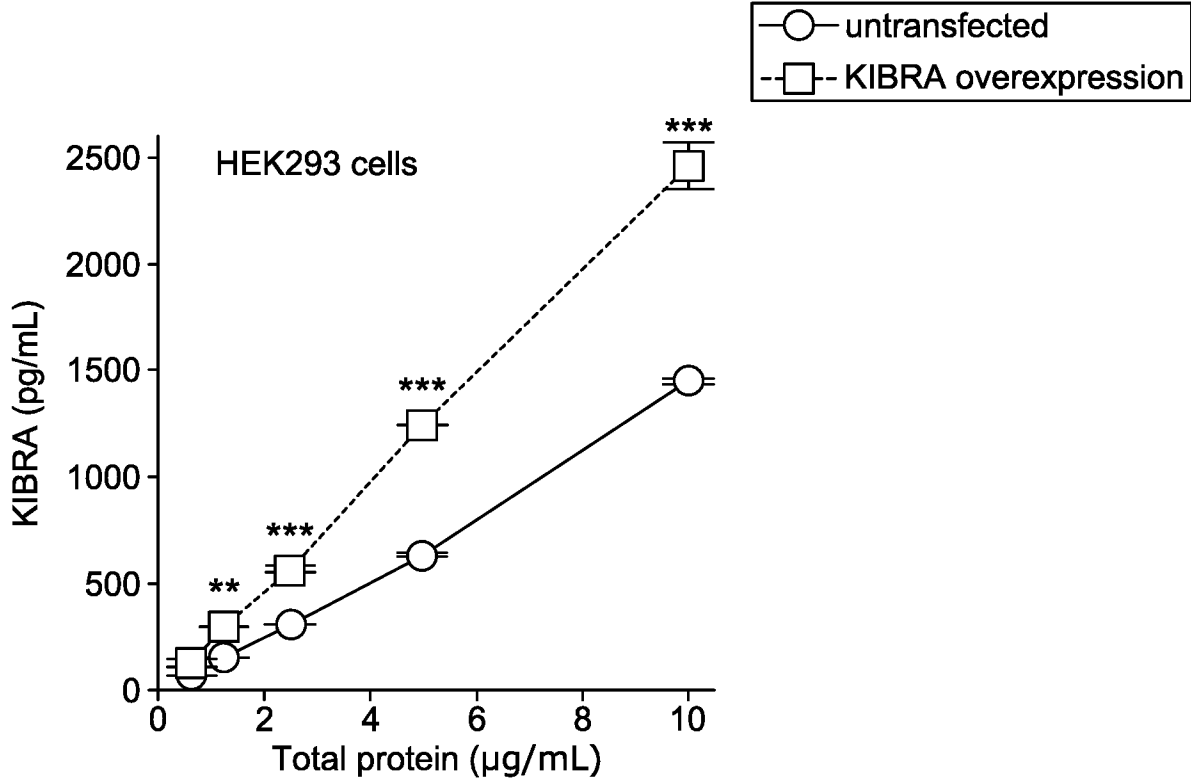


FIG. 12A

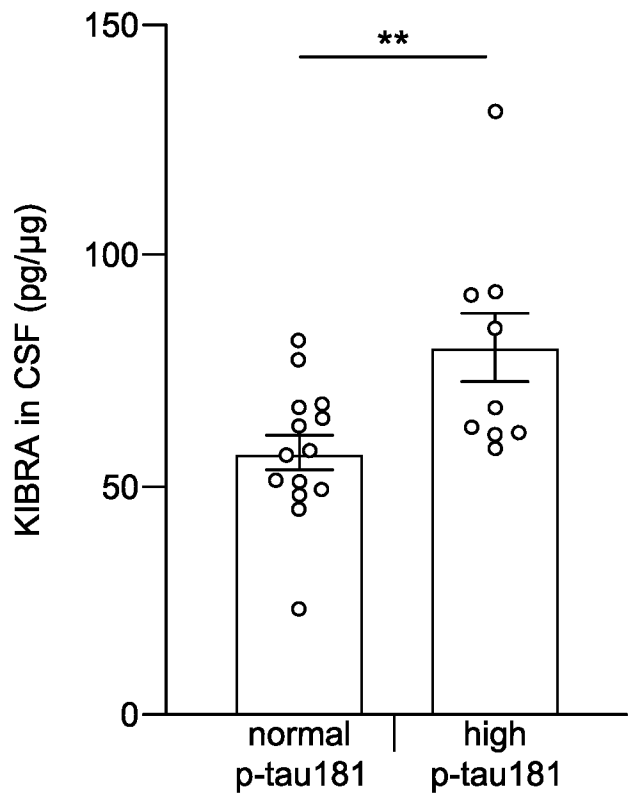


FIG. 12B

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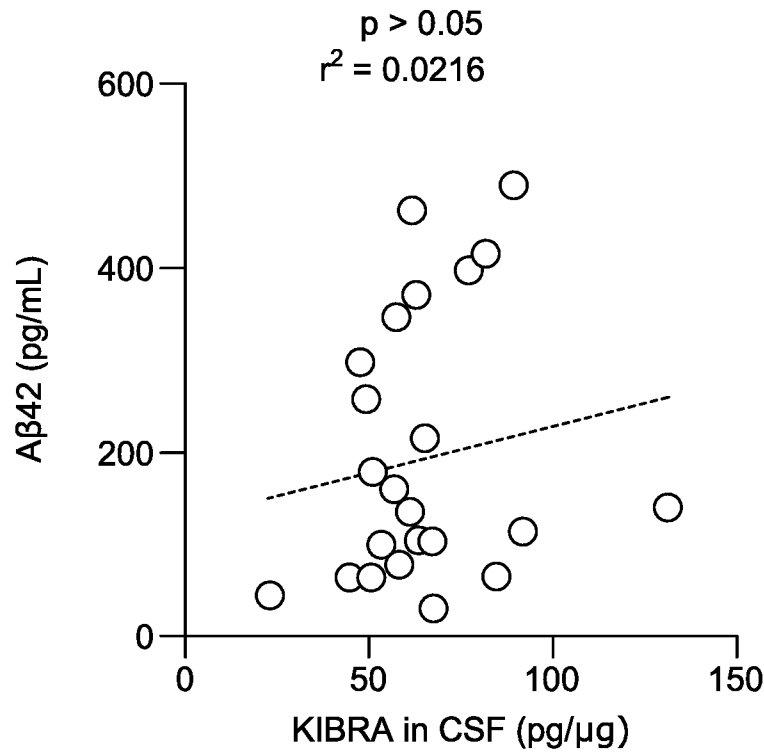


FIG. 12C

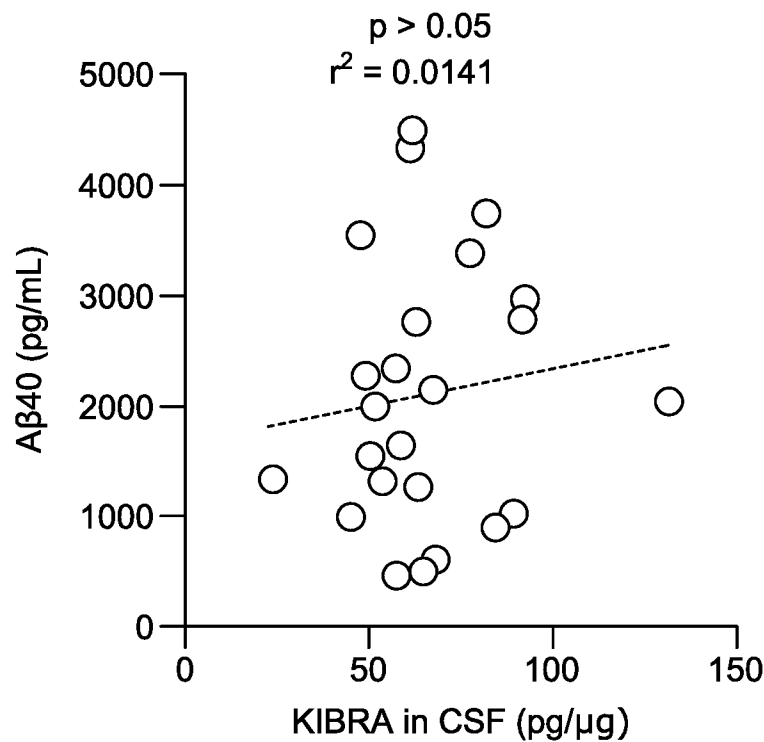


FIG. 12D

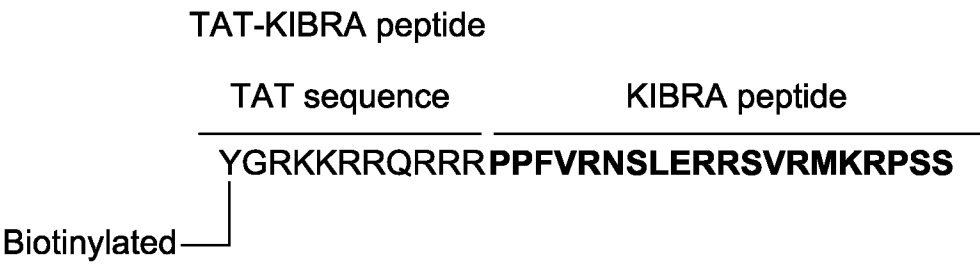


FIG. 13A

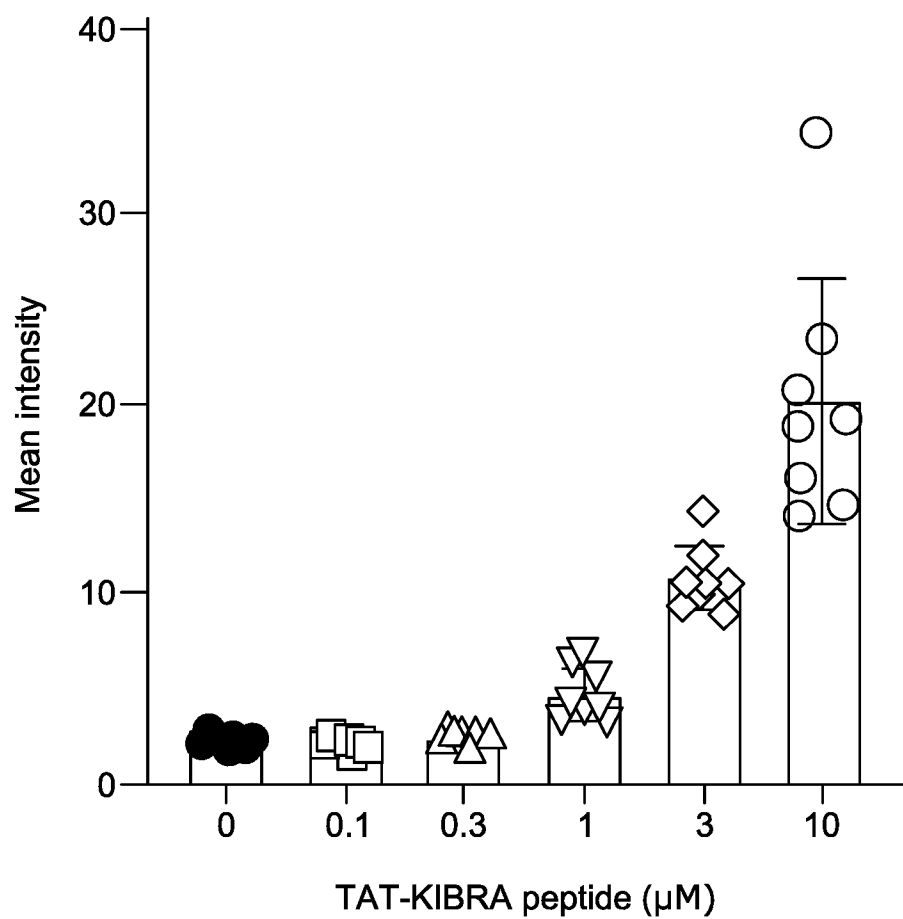


FIG. 13B

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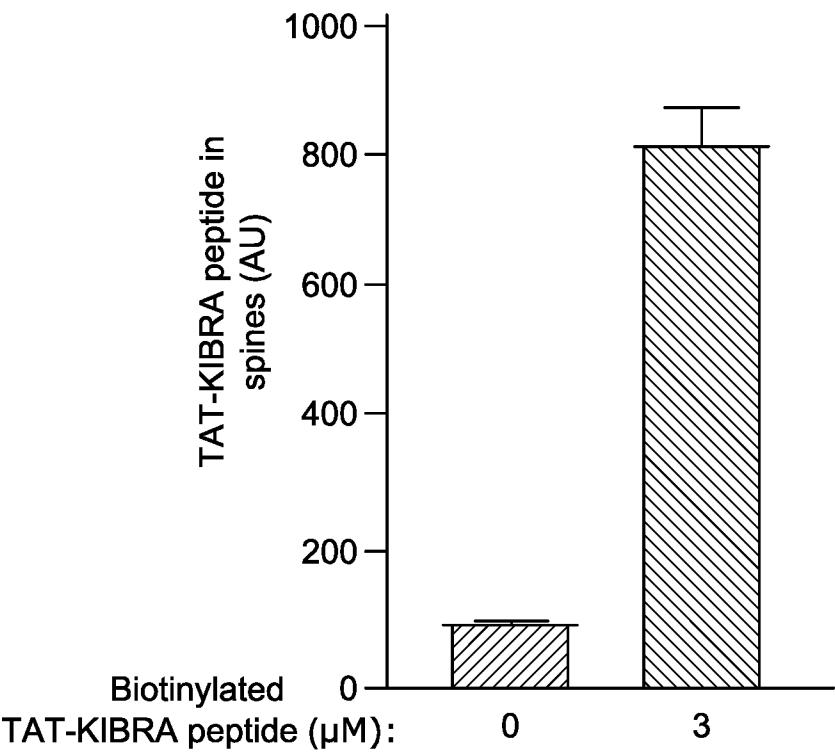


FIG. 13C

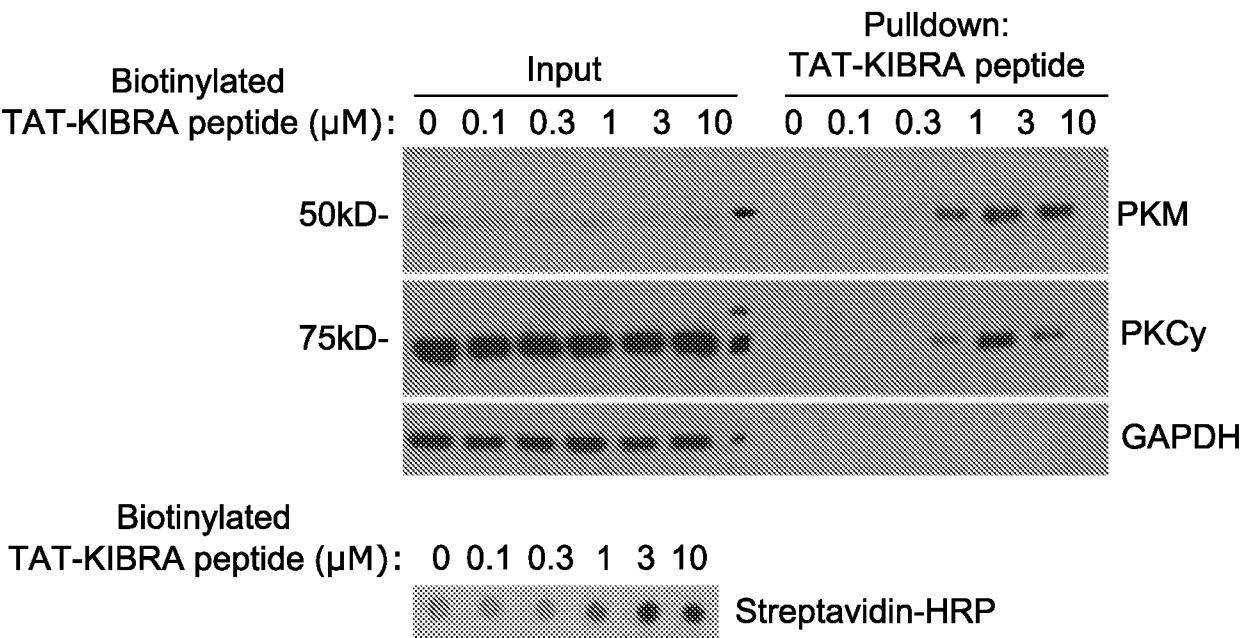


FIG. 13D

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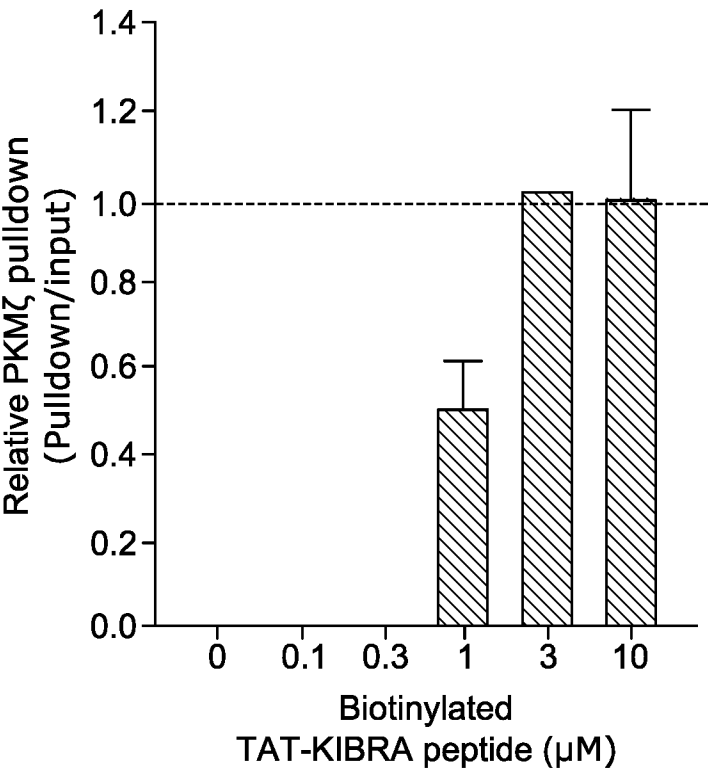


FIG. 13E

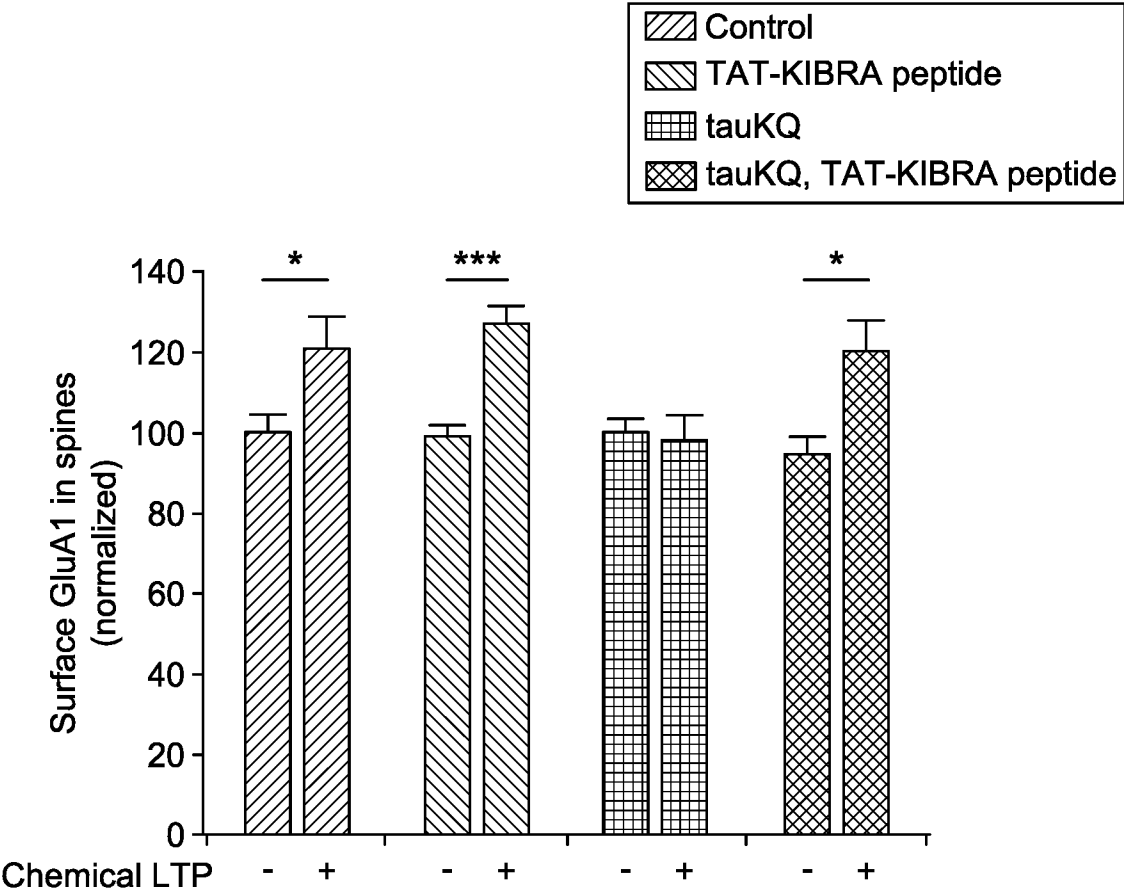


FIG. 13F

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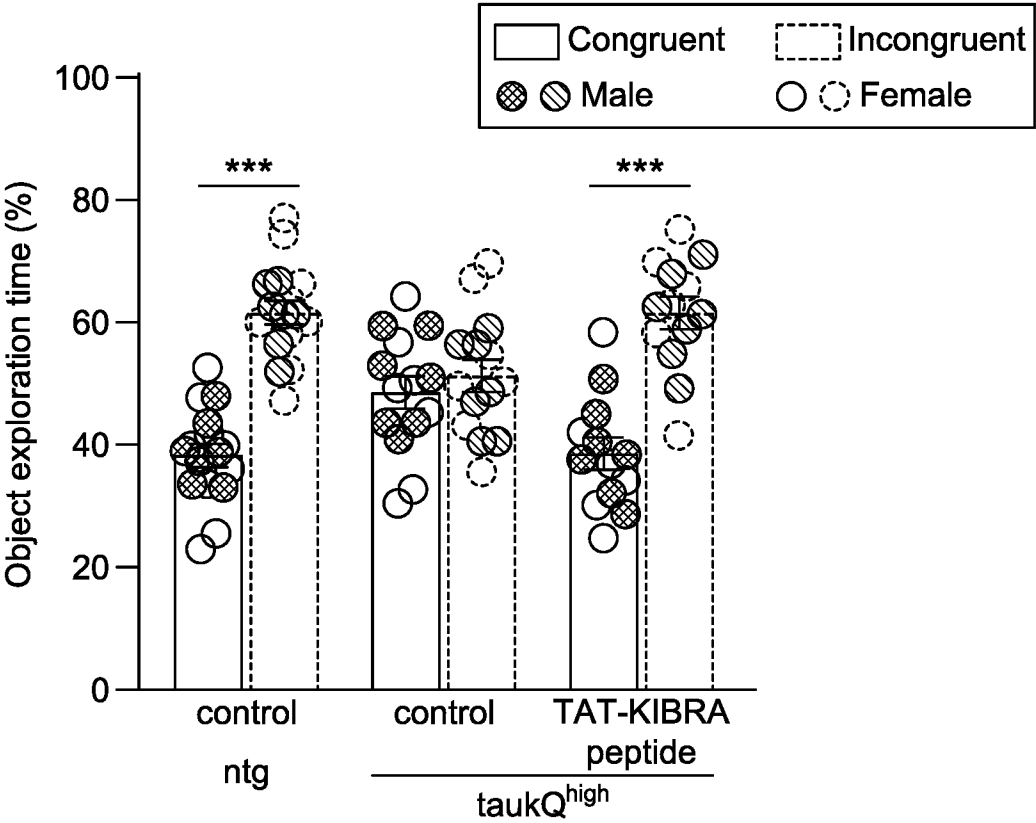


FIG. 14A

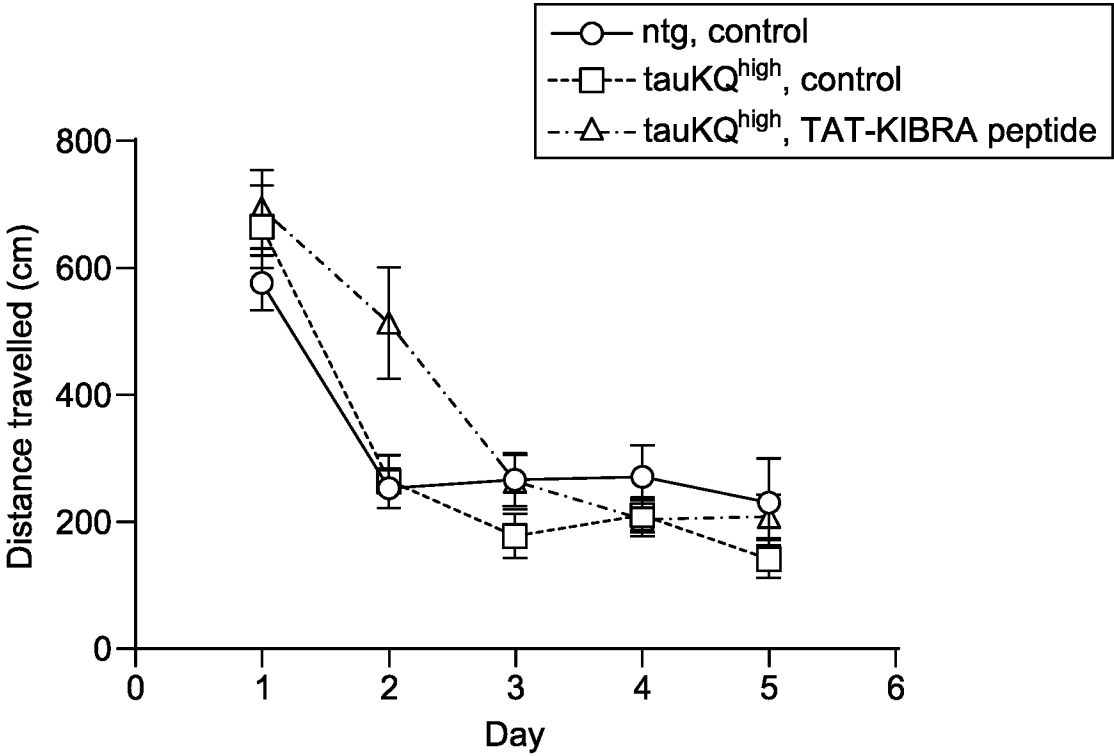


FIG. 14B

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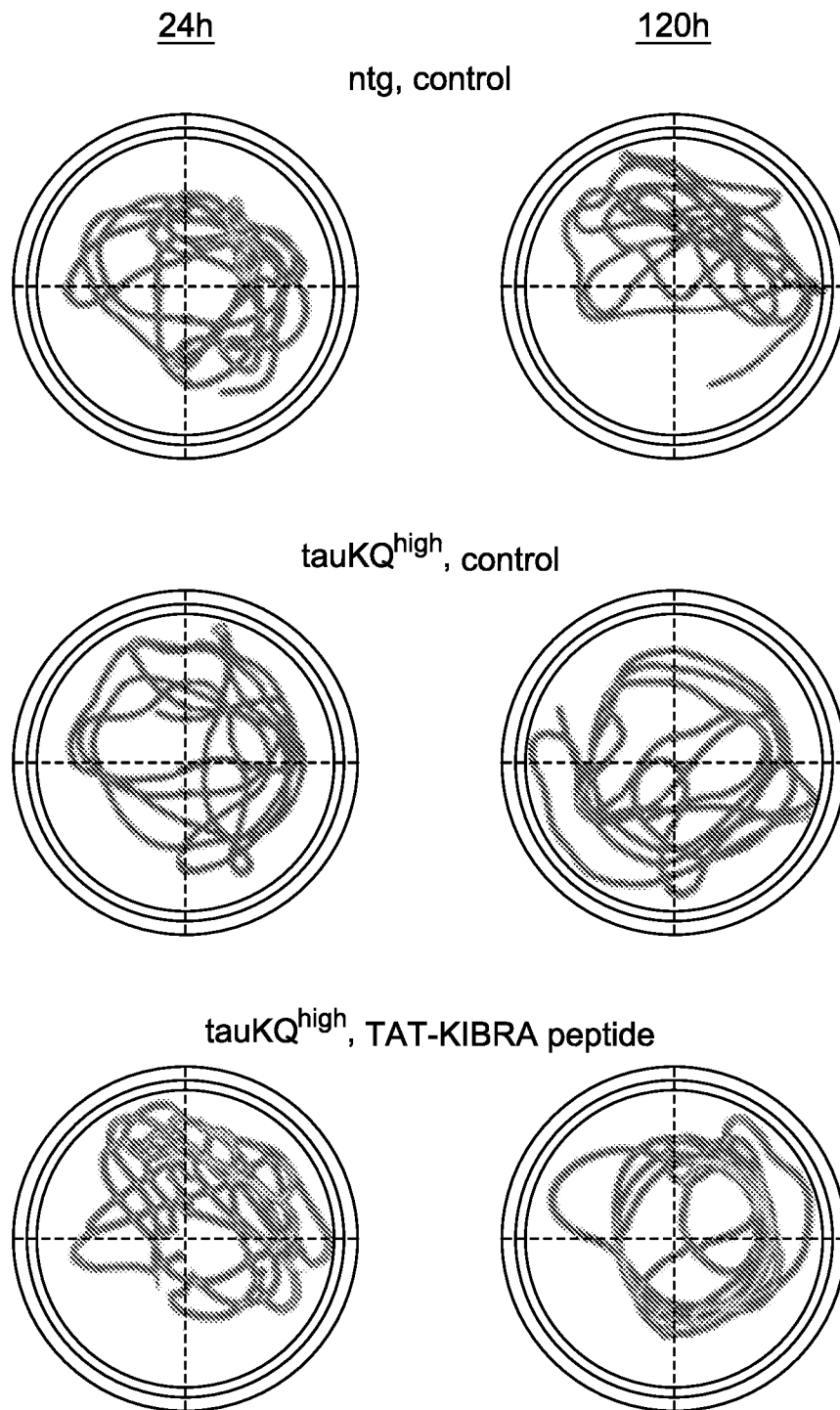


FIG. 14C

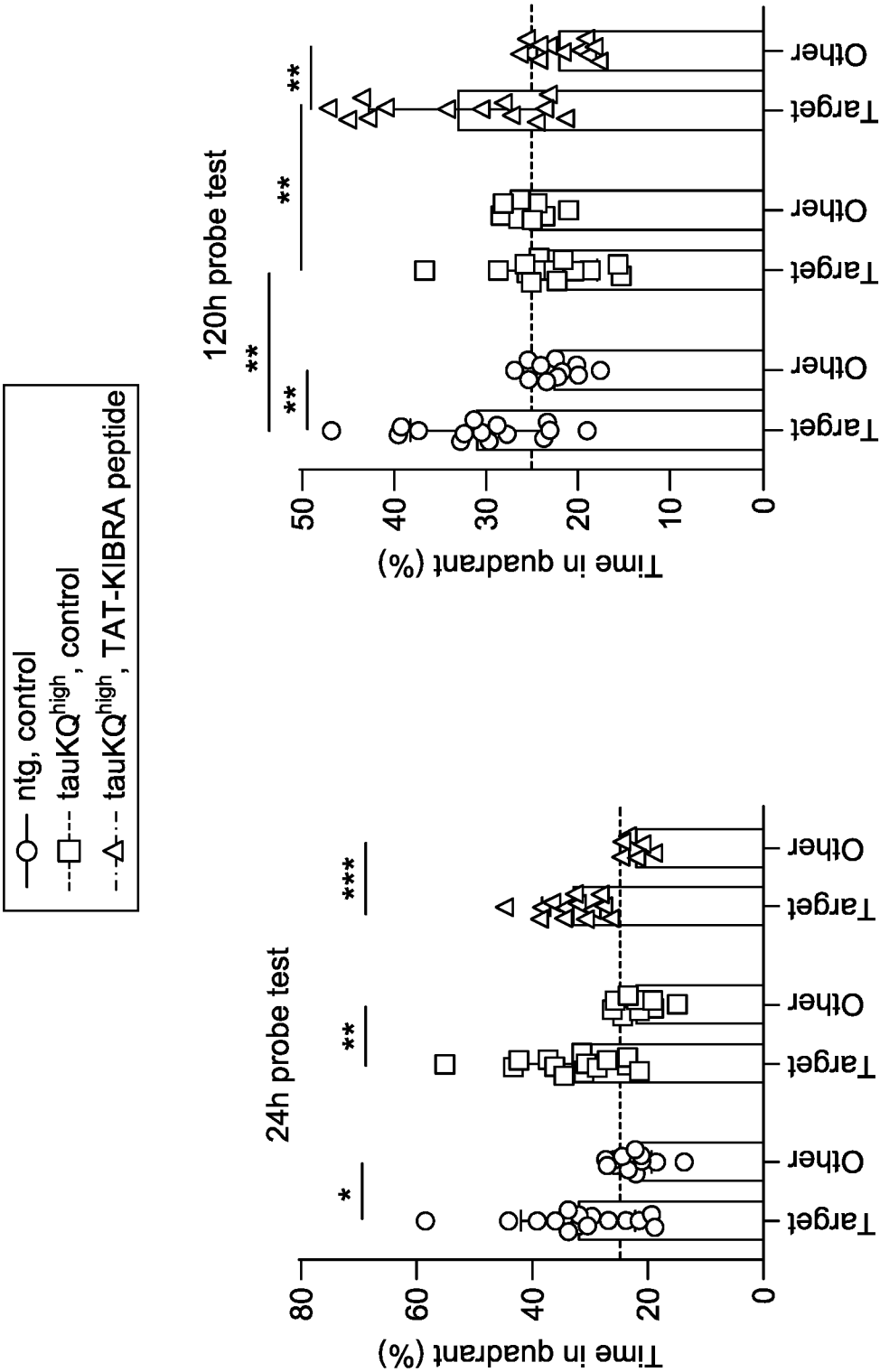


FIG. 14D

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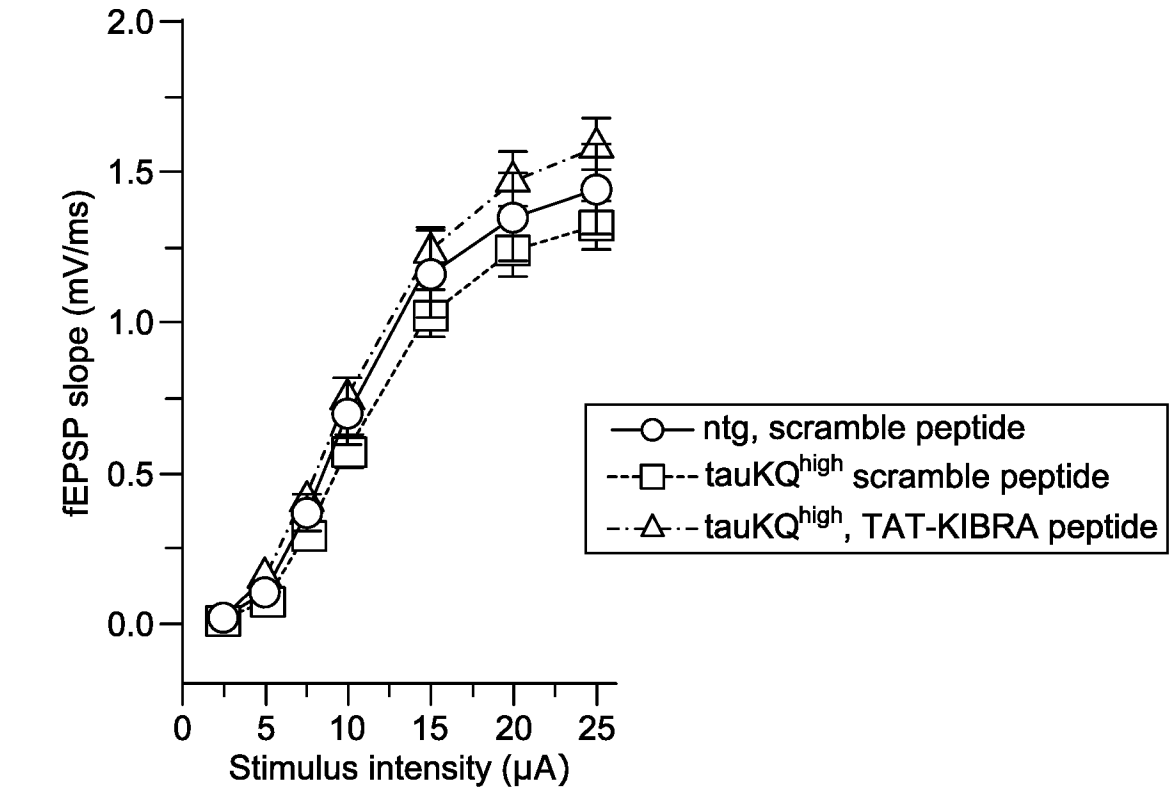


FIG. 14E

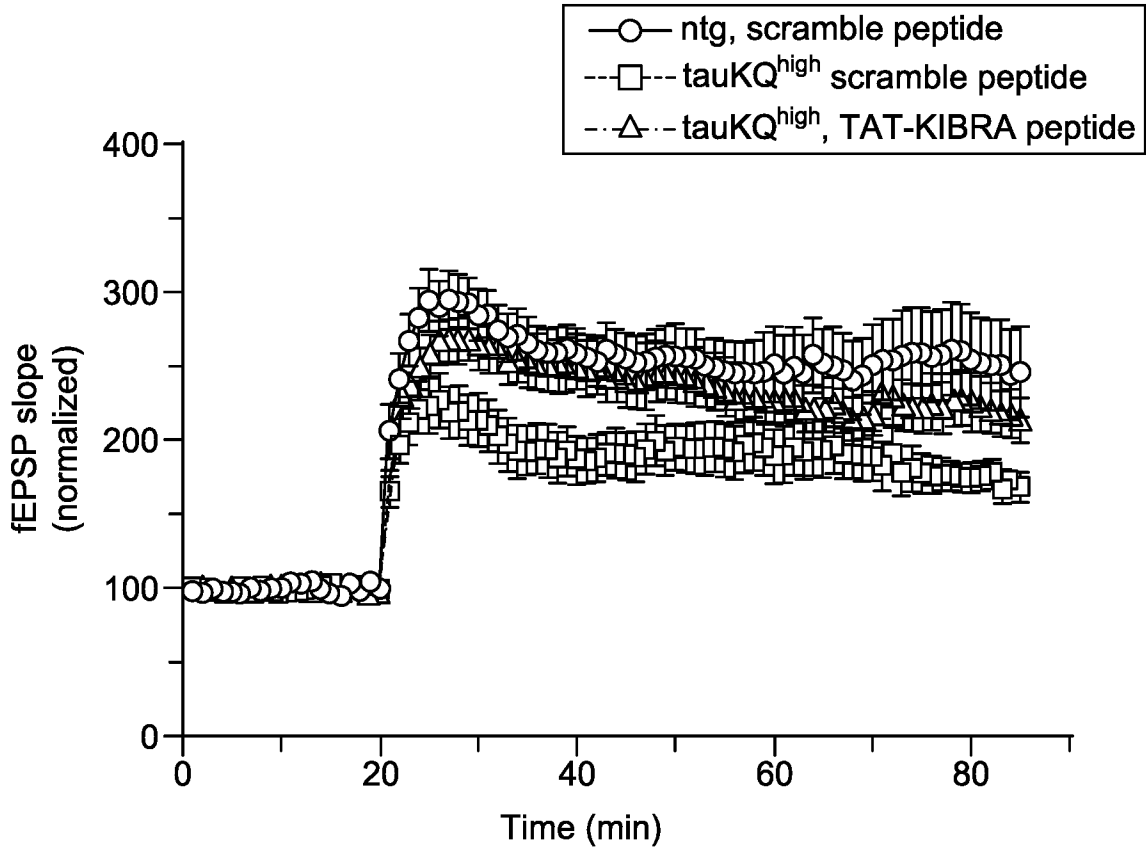


FIG. 14F