SUPPLEMENTARY MATERIALS

Figure S1. TPP1 expression constructs.

Figure S2. Subacute toxicology behavioral analysis.

Figure S3a. Subacute toxicology histological analysis of brain.
Figure S3b. Subacute toxicology histological analysis of kidney.
Figure S3c. Subacute toxicology histological analysis of liver.

Figure S4. Order of injection of K16ApoE and TPP1.

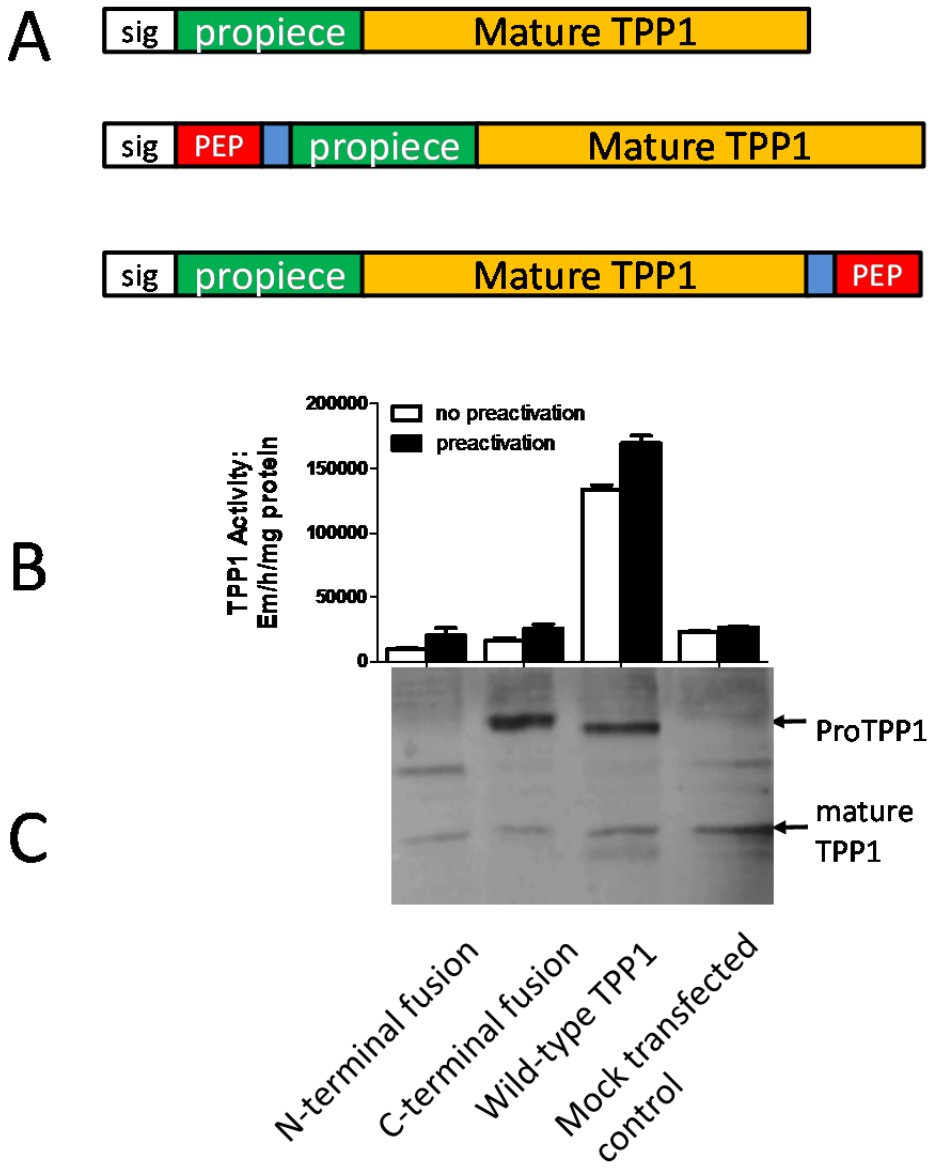
Figure S5a. Immunostaining for SCMAS in the cerebellum.
Figure S5b. Immunostaining for SCMAS in the cerebral cortex.

Figure S6. Immunostaining for TPP1 in the brain.

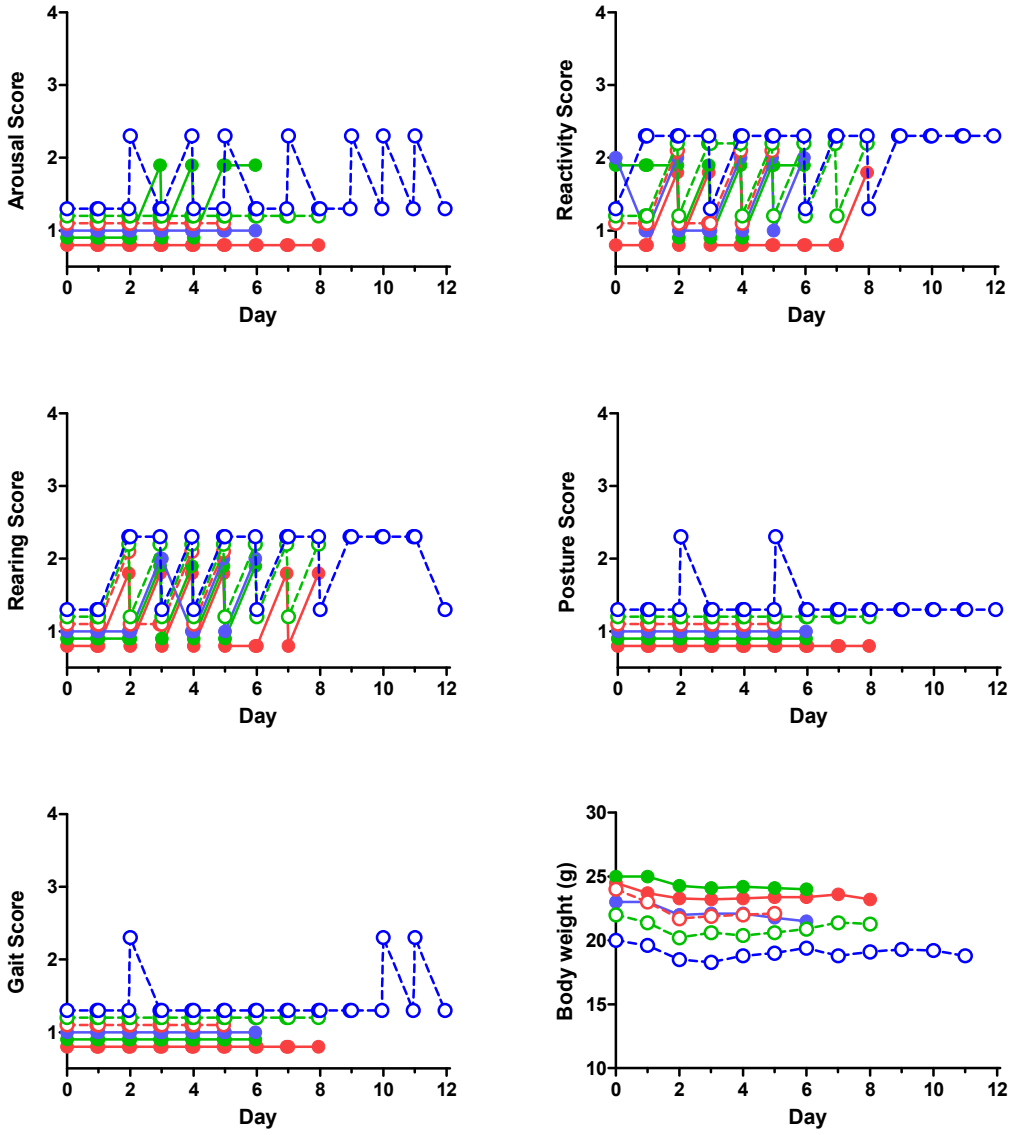
Video S1. Representative 164-day old LINCL mouse treated with TPP1 and K16ApoE as described in Figure 5. Note that no untreated or mice treated with TPP1 alone were alive at this age.

Video S2. Representative untreated 126-day old LINCL mouse.

Supplemental figure 1. TPP1 expression constructs. (**a**) Schematic of proteins. Sig, signal peptide; PEP, peptide of interest; green, propiece, mature TPP1, GSGSG linker (hatched). (**b**) TPP1 enzyme activity. Cell extracts were either assayed directly or preincubated at pH 3.5 to activate proTPP1. (**c**) Immunoblotting for TPP1 in transiently transfected CHO cells with wild type and ApoE-TPP1 fusion proteins.



Supplemental Figure 2. Subacute toxicicology behavioral analysis. Saline was injected on Day 0 as a baseline followed by daily co-administation of K16ApoE (28 nmol and TPP1 (17 nmol) in 200 µl. Tail vein injections were initiated at seven weeks of age. Behavior parameters as indicated were measured using the functional observational battery (FOB) four scale scoring system . (1=normal, 2=mild, 3=moderate, 4=impaired) conducted 10 min after and one day after (10 min before) each injection. The study was continued until tail-vein trauma precluded further administration. Individual mice are represented by different colored symbols symbol (LINCL, filled circles; wild type, open circles; 3 mice per group) with the last indicated point representing a measurement one day after the final injection.



Supplemental Figure 3a. Subacute toxicology histological analysis of brain. Light microscopic examination from uninjected control (top) and treated (bottom) mice showed no evidence of cellular injury. Hematoxylin and eosin stained image taken using 10x objective.

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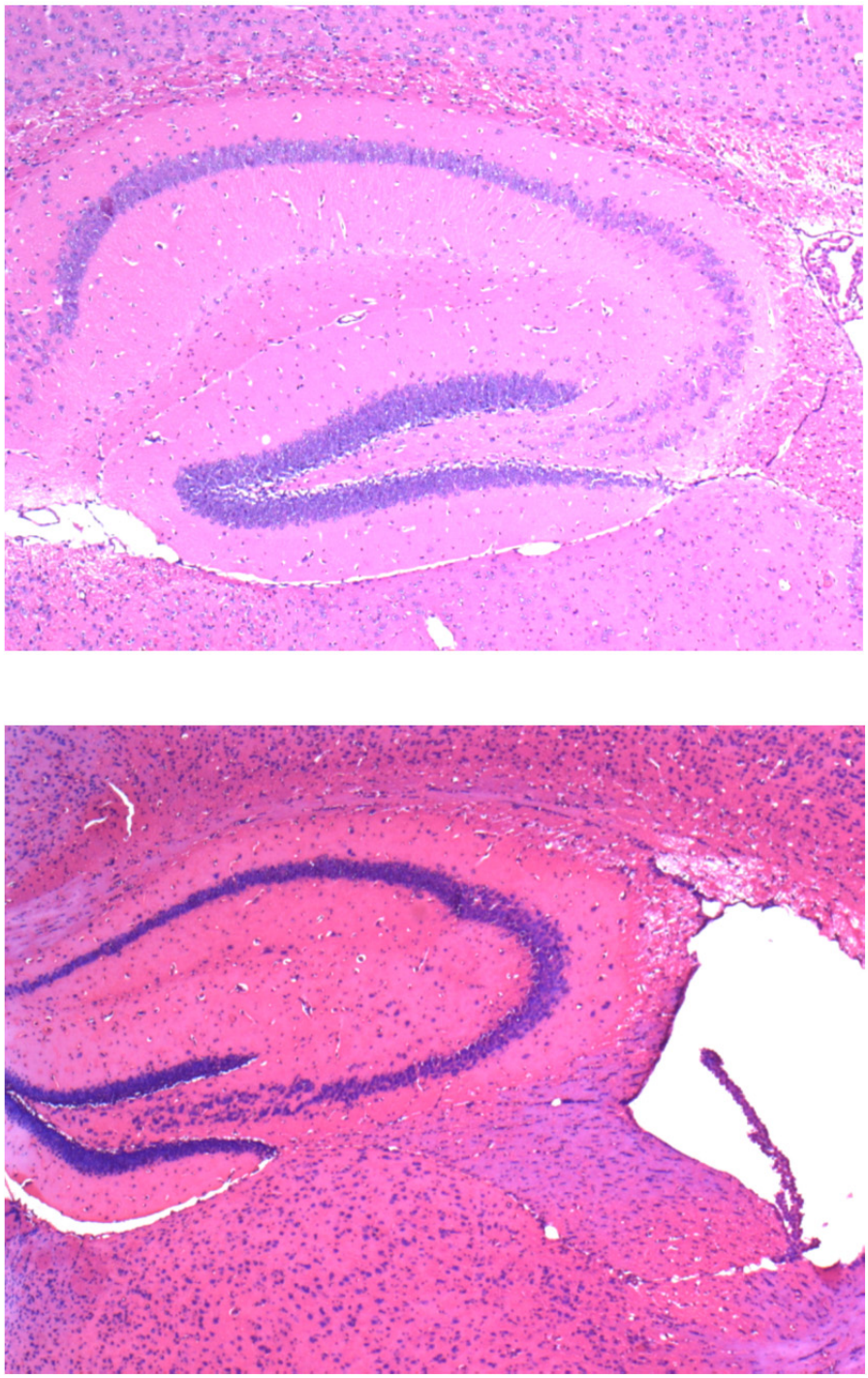
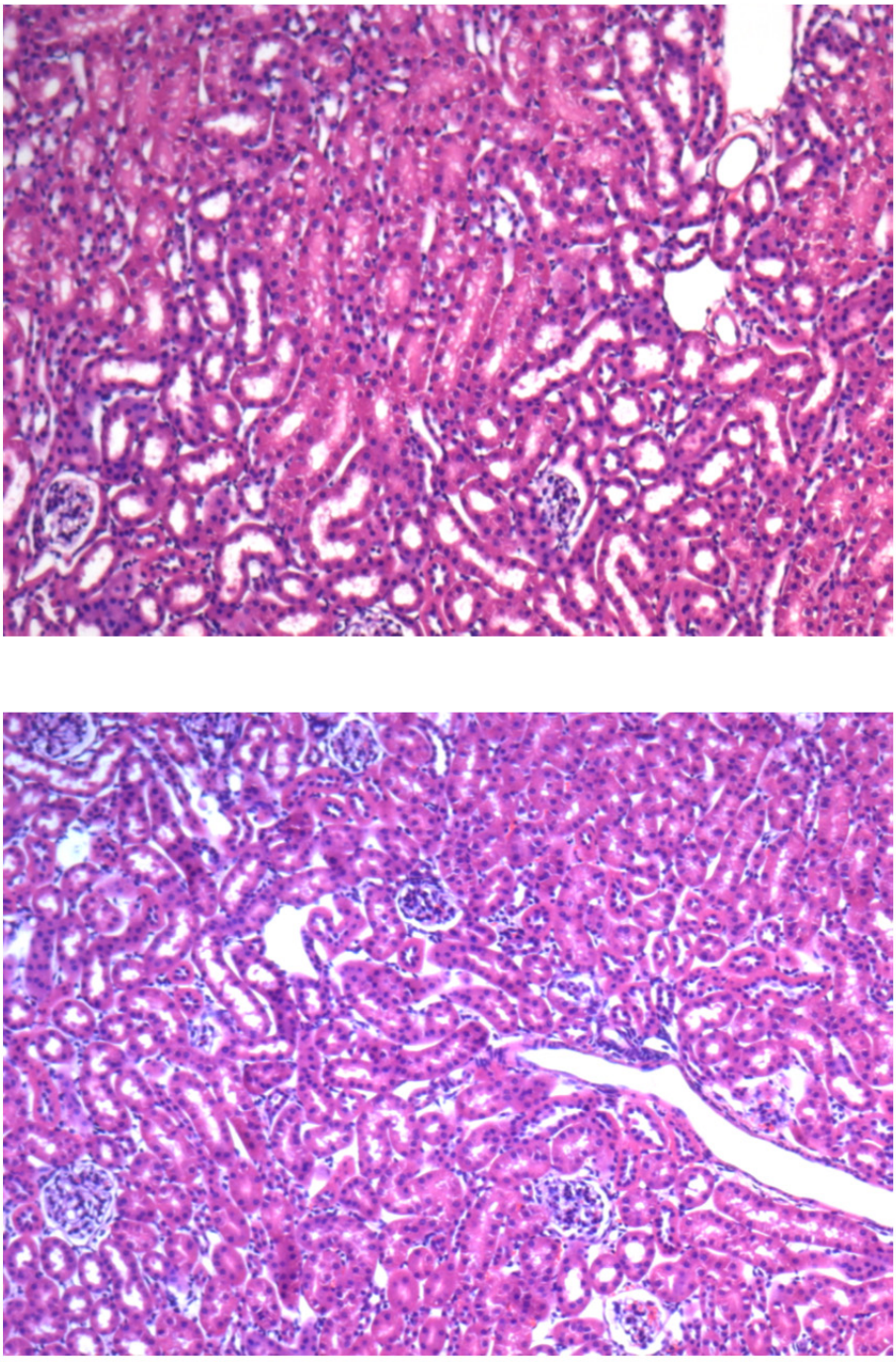
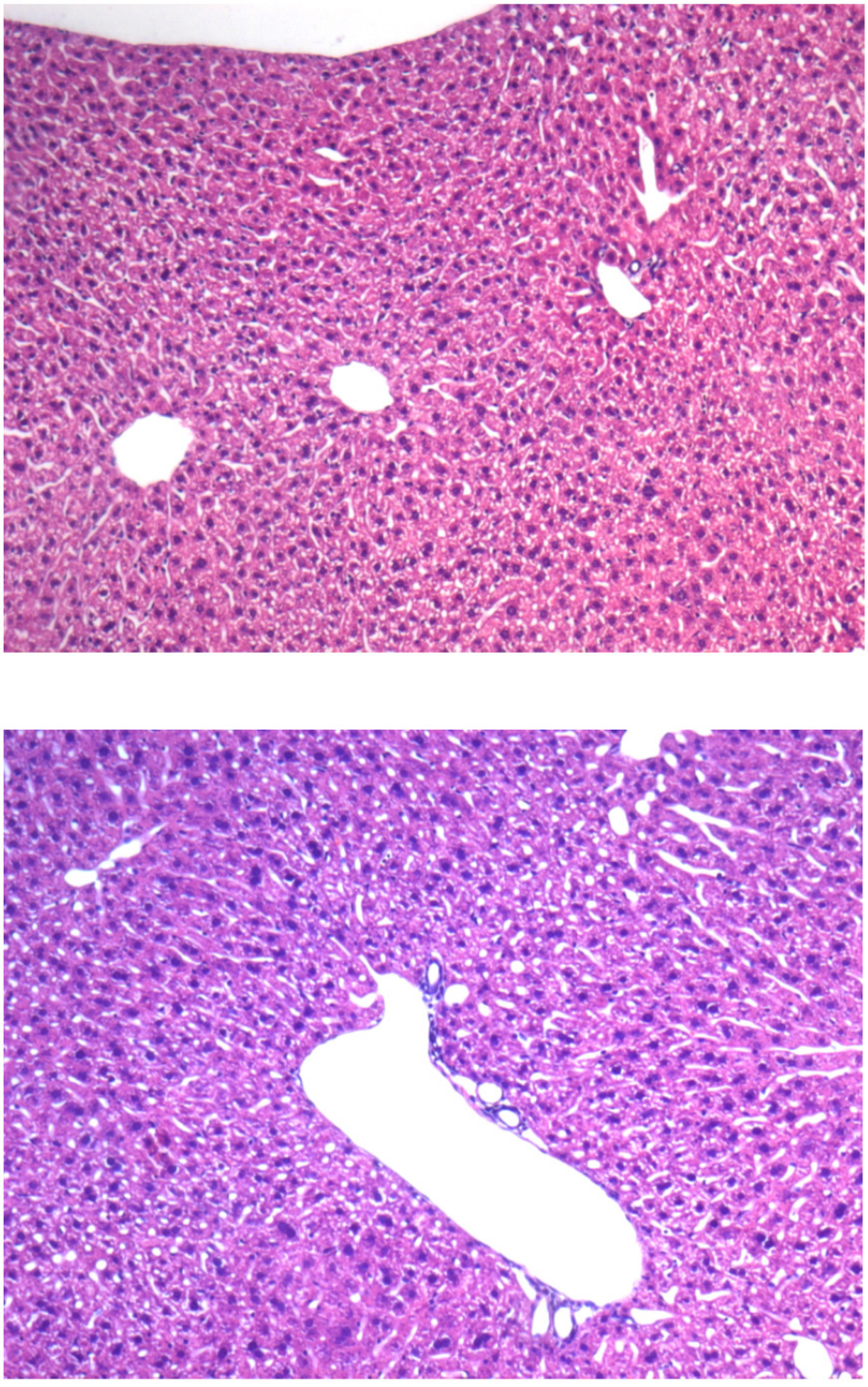


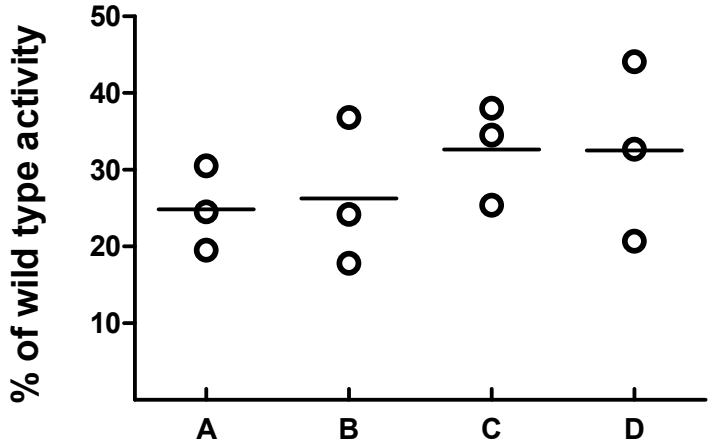
Supplemental Figure 3b. Subacute toxicology histological analysis of kidney. Light microscopic examination from uninjected control (top) and treated (bottom) mice showed no evidence of cellular injury. Hematoxylin and eosin stained image taken using 10x objective.



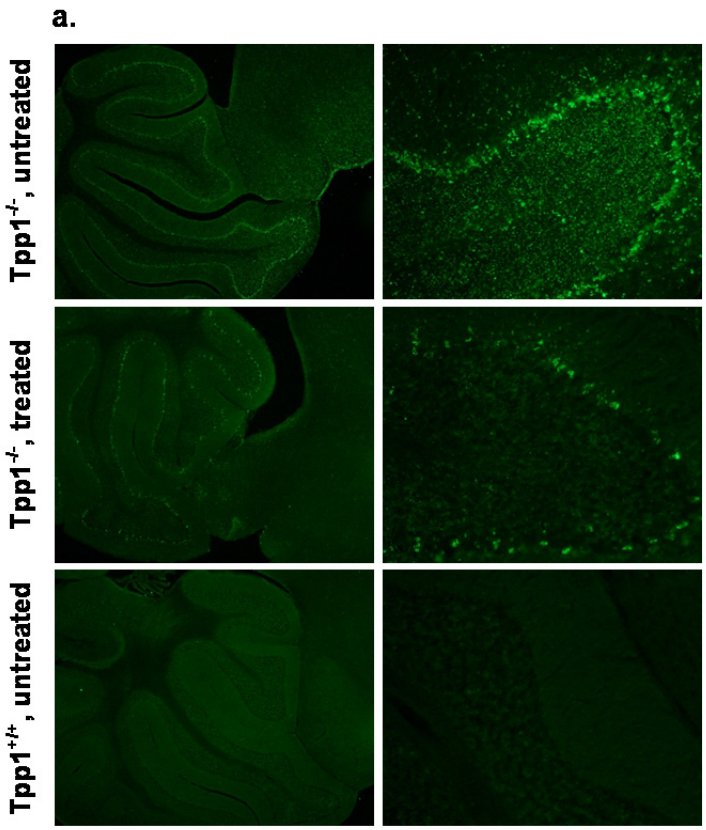
Supplemental Figure 3c. Subacute toxicology histological analysis of liver. Light microscopic examination from uninjected control (top) and treated (bottom) mice showed no evidence of cellular injury. Hematoxylin and eosin stained image taken using 10x objective..



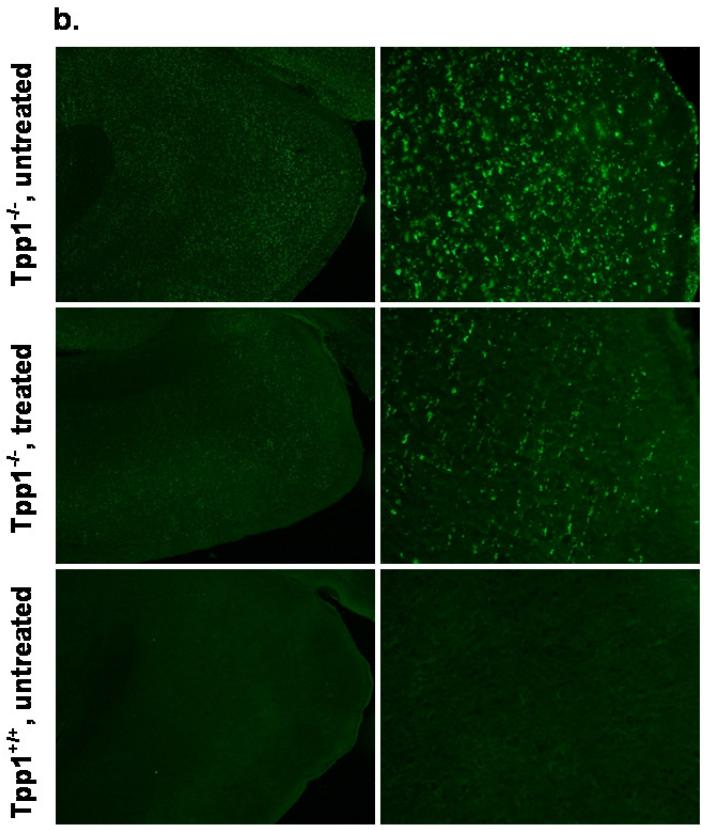
Supplemental Figure 4. **Order of injection of K16ApoE and TPP1.** TPP1 (8 nmol in 100 µl) and K16ApoE (12 nmol in 100 µl) were either administered separately or together in 6 week old LINCL mice. Animals were killed 24 h after injection and TPP1 activity was assayed in brain. Treatments were: (A) K16ApoE injected 1 min prior to TPP1; (B) TPP1 injected 1 min prior to K16ApoE; (C) mixed immediately before injection; (D) mixed 1h before injection.



Supplemental Figure 5a. **Immunostaining for SCMAS in cerebellum**. Mice were treated as described in Fig. 4. All animals were 16 weeks old. Images were acquired using 4x (left panel) and 20x (right panel) objectives.



Supplemental Figure 5b. **Immunostaining for SCMAS in cerebral cortex**. Mice were treated as described in Fig. 4. All animals were 16 weeks old. Images were acquired using 4x (left panel) and 20x (right panel) objectives.



Supplemental Figure 6. **Immunostaining for TPP1 in the brain**. Mice were treated as described (Fig. 5). Images were acquired by confocal microscopy using a 60x objective.