Supplemental Table 1 Reagent and resource list.

| Reagent or Resource | Source          | Identifier       | Dilution          |
|---------------------|-----------------|------------------|-------------------|
| Antibodies          |                 |                  |                   |
| PSD95 (Clone K28/43)| Millipore       | RRID:AB_11212169 | 1:1000 WB        |
| PSD95 (D27E11) XP   | Cell Signalling | RRID:AB_2292883  | 1:500 IHC        |
| PTEN (138G6)        | Cell Signalling | RRID:AB_390810   | 1:1000 WB        |
| Phospho-PTEN (Ser380/Thr382/383) | Cell Signalling | RRID:AB_331411 | 1:1000 WB        |
| Cleaved Caspase-3 (Asp175) (5A1E) | Cell Signalling | RRID:AB_2070042 | 1:1000 IHC        |
| C1q                 | Abcam           | RRID:AB_2732849  | 1:1000 IHC        |
| MAP2                | Abcam           | RRID:AB_2138147  | 1:1000 IHC        |
| Total Tau           | DAKO            | RRID:AB_10013724 | 1:1000 WB        |
| Total Human Tau (HT7)| ThermoFisher  | RRID:AB_2314654  | 1:5000 WB        |
| Phospho-Tyr18 Tau (Tyr18) | MediMabs     | 1944110227-P | 1:1000 WB/IHC     |
| Phospho-Ser396 Tau  | Thermofisher    | RRID:AB_2533745  | 1:1000 WB        |
| Phospho-Tyr97 FAK   | Cell Signalling | RRID:AB_10891442 | 1:500 WB         |
| FAK                 | Cell Signalling | RRID:AB_2269034  | 1:500 WB         |
| Phospho-Ser473 AKT  | Cell Signalling | RRID:AB_2315049  | 1:1000 WB        |
| AKT                 | Cell Signalling | RRID:AB_329827   | 1:1000 WB        |
| CD68                | BioRad          | RRID:AB_324217   | 1:1000 IHC        |
| AT8 Tau             | ThermoFisher    | RRID:AB_223647   | 1:1000 WB        |
| AT180 Tau           | ThermoFisher    | RRID:AB_223649   | 1:1000 WB        |
| Phospho-Ser404 Tau  | ThermoFisher    | RRID:AB_2532674  | 1:1000 WB        |
| Iba1                | Wako            | RRID:AB_839504   | 1:1000 IHC        |
| Cd11b               | Abcam           | RRID:AB_306831   | 1:1000 IHC        |
| Anti-rat IgG (H+L), (Alexa Fluor® 488 Conjugate) | Cell Signalling | RRID:AB_10693769 | 1:1000 IHC        |
| Goat anti-Mouse Alexa Fluor 488 | ThermoFisher | RRID:AB_2534069 | 1:1000 IHC        |
| Goat anti-Rabbit Alexa Fluor 555 | ThermoFisher | RRID:AB_2536100 | 1:1000 IHC        |
| Goat anti-Chicken Alexa Fluor 647 | ThermoFisher | RRID:AB_2535866 | 1:1000 IHC        |
| IR DYE 680RD Goat anti-Mouse | Licor            | RRID:AB_10956588 | 1:10000 WB       |
| IR DYE 800RD Goat anti-Rabbit | Licor            | RRID:AB_621843   | 1:10000 WB       |
| Chemicals           |                 |                  |                   |
| pSIVA               | Novous Bio      | NBP2-29382       |                   |
| Calcein AM Blue     | ThermoFisher    | C1429            |                   |
| F2N12S              | ThermoFisher    | A35137           |                   |
| pHrodo Red AM       | ThermoFisher    | P35372           |                   |
| Dipotassium Bisperoxovanadium(pic) | Sigma/Merck | SML0885         |                   |
| Revert Total Protein Stain | Licor | 926-11011 |                   |
| VECTASHIELD Hardset antifade mounting medium, | Vector Labs | H-1400          |                   |
| DMEM F12            | ThermoFisher    | 11320033         |                   |
| Live Cell Imaging Solution | ThermoFisher | A14291DJ |
|----------------------------|--------------|----------|
| Odyssey Blocking buffer in TBS | Licor | 927-50000 |
| Neurobasal Medium | ThermoFisher | 21103049 |
| B27 Supplement | ThermoFisher | 17504044 |
| Lipofectamine 2000 | ThermoFisher | 11668019 |
| Lamda Phoshatase | NEB | P0753S |

**Experimental Models: Organisms/Strains**

| 129S6.Cg-Tg(Camk2a-tTA)1Mmay/JlwsJ; Fgf14Tg(tetO-MAPT*P301L)4510Kha/J. | Jackson Laboratory | RRID:IMSR_JAX:024854 |
| B6.129P2(Cg)-Cx3cr1tm1Litt/J | Jackson Laboratory | RRID:IMSR_JAX:005582 |
| K3 | In house | Ittner et al. PNAS 2008 |
| APP23 | Jackson Laboratory | RRID:IMSR_JAX:030504 |

**Software**

| Prism 7 | GraphPad | RRID:SCR_002798 |
| FIJI | NIH | RRID:SCR_002285 |
| Imaris 9.4.2 | Bitplane | RRID:SCR_007370 |
| Image Studio Software | LI-COR | RRID:SCR_015795 |
| Huygens Deconvolution | Scientific Volume Imaging | RRID:SCR_014237 |
Supplemental Figure 1

**Cleaved caspase-3 mean gray value vs WT control (%)**

MAP2
Cleaved caspase-3
Dapi
rTg4510
WT

**a**
Supplemental Figure 2

A

|          | 2 months | 6 months |
|----------|----------|----------|
| WT       | rTg4510  |          |
| Cortex   |          |          |
| P-Tyr18 Tau/PTEN |          |          |
| P-Tyr18 Tau/PTEN |          |          |
| P-Tyr18 Tau/PTEN |          |          |

B

![Graph showing PTEN mean gray value](image)

C

![Scatter plot showing correlation](image)
Supplemental Figure 3

(a) Wild-type total brain extract

| Control | 0.0 | 200 | 400 | 600 |
|---------|-----|-----|-----|-----|
| P-PTEN  |     |     |     |     |
| Actin   |     |     |     |     |

(b) Cortex (total extract)

| 2 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

| 4 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

| 6 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

(c) Hippocampus 2 month PSD

| Total Tau | P-Tyr18 Tau |
|-----------|-------------|
| WT        |             |
| rTg4510   |             |

(d) Synaptosomes

| 2 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

| 4 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

| 6 m.o. | P-PTEN | PTEN |
|--------|--------|------|
| WT     |        |      |
| rTg4510|        |      |

(e) Cortex (total extract)

| P-PTEN | WT | K3 |
|--------|----|----|
|        |    |    |
|        |    |    |

(f) Whole brain total extract

| P-PTEN | WT | APP |
|--------|----|-----|
|        |    |     |
|        |    |     |

| PTEN | GAPDH |
|------|-------|
|      |       |
|      |       |

| P-PTEN | WT | APP |
|--------|----|-----|
|        |    |     |
|        |    |     |

| PTEN/GAPDH of WT control (%) |
|------------------------------|
| 2 m.o. | 4 m.o. | 6 m.o. |
|        |        |        |

| PTEN vs WT control (%) |
|------------------------|
| 2 m.o. | 4 m.o. | 6 m.o. |
|        |        |        |

| PTEN/P-PTEN vs WT control (%) |
|-------------------------------|
| 2 m.o. | 4 m.o. | 6 m.o. |
|        |        |        |
Supplemental figure 4

- Total protein
- PTEN
- Hippocampus
- Synaptosomes

- 2 months
- 4 months
- 6 months

- WT
- rTg4510
- WT
- rTg4510
- WT
- rTg4510
- WT
- rTg4510

- p-Y18 Tau
- pS404 Tau
- pTEN
- pS473 AKT
- AT8 Tau
- AKT
- pY397 FAK
- FAK
- pS9 GSK3β

- Revert total protein stain.
Supplemental figure 5

Human frontal cortex (total extract)

PTEN  p396 Tau

Gapdh

Related to figure 8

Supplemental figure 5