Supporting information

Supplementary Figure legends

Fig. S1: Highly efficient gene silencing in hippocampal slice cultures.
(A) Influence of doxycycline (DOX) on reporter gene activity**.** Luciferase substrate D-luciferin was applied to slices prepared from the same $Tau_{RD}\Delta K$ mouse cultured either without DOX (left), with DOX (middle), or from a non-transgenic litter mate (right). Slices were imaged 30 min later. Note that no luciferase activity (photons/sec) is visible in DOX treated cultures (lower panel).
(B) To determine the rate of inhibition, slices were cultured without DOX until DIV14. Luciferase activity was measured before and 6 h after application of 2 µg/ml DOX. Already at 6 h the luciferase activity was reduced nearly to control level (n= 5 experiments, 6 slices each, 3 animals, *One way ANOVA followed by Tukey's post-hoc test ***p value < 0.001).*
(C,D) Slice cultures were prepared from the same transgenic animal, cultured with media alone or with DOX. Treatment was done from DIV1-DIV25 by refreshing DOX every 3 days. At DIV25 western blotting with pan-Tau antibody K9JA did not detect $Tau_{RD}\Delta K$ in DOX treated samples.

Fig. S2: Early mislocalization of Tau into the somatodendritic compartment.
(**A**) Immunoreactivity with K9JA antibodies in area CA1. Microphotographs of control slice cultures indicate an axonal distribution of mouse Tau at DIV5 and DIV25.
(**B**) Tau becomes mislocalized into somata and dendrites in the presence of pro-aggregant $Tau_{RD}\Delta K$. Mislocalization of Tau was already observed at DIV5, and neurons at DIV25 show dystrophic features like irregularly shaped cell bodies, ballooned and truncated apical dendrites (arrows).
(**C**) Treatment of $Tau_{RD}\Delta K$ expressing slice cultures with bb14 does not prevent mislocalization of Tau into the soma and dendrites but prevents neuronal dystrophy.
Scale bar**:** 20µm.

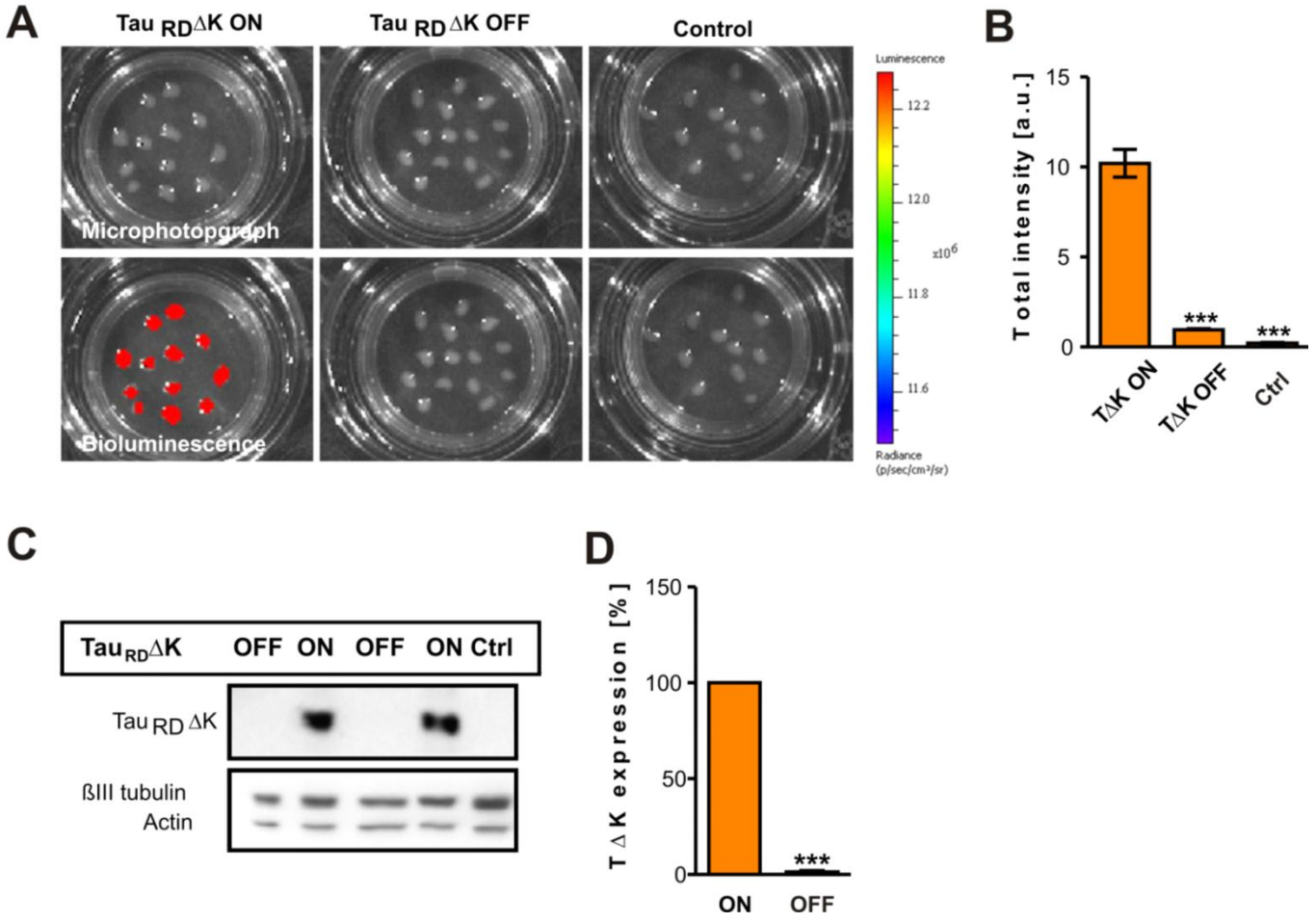
Fig. S3: Activation of microglia in $Tau_{RD}\Delta K$ expressing slice cultures.
(A) Immunolabelling of microglia by staining with an antibody against Iba1, a marker of activated microglia, indicating inflammatory processes, in control, $Tau_{RD}\Delta K$ slices

and $Tau_{RD}\Delta K$ slices treated with bb14 (starting from DIV1) at 25 DIV. $Tau_{RD}\Delta K$ slices show a higher number of microglia than slices prepared from control mice. $Tau_{RD}\Delta K$ slices treated with bb14 (from DIV1) showed lower numbers of microglia at DIV25, similar to controls.

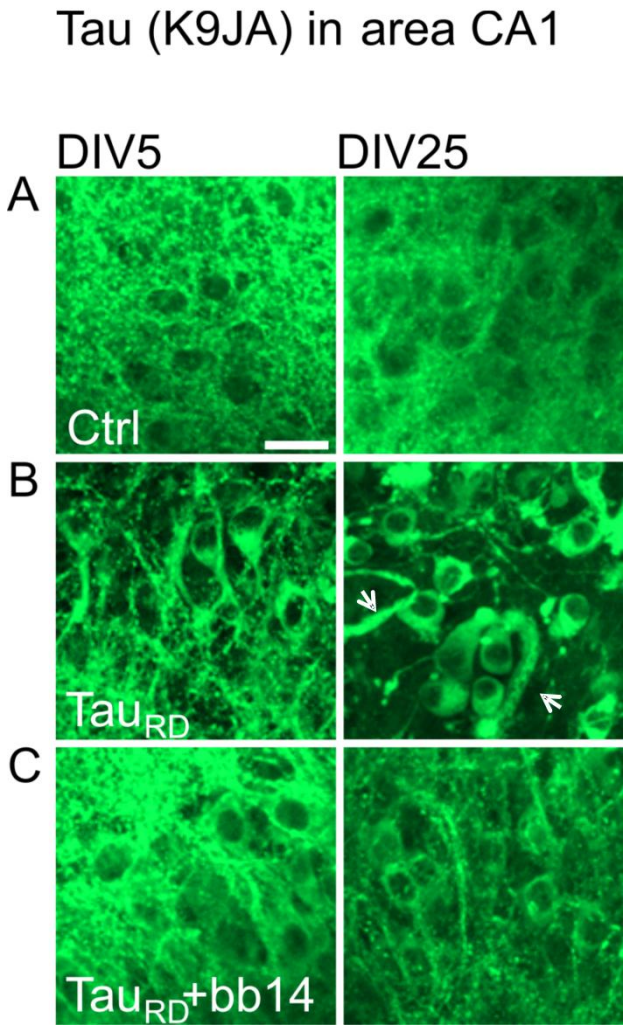
(**B**) Visualization of reactive oxygen species (ROS) in living $Tau_{RD}\Delta K$ slice cultures at DIV15 by the chemiluminescence of the ROS sensitive dye XenoLight RediJect Inflammation probe (Caliper) overlayed onto the photomicrograph.

(**C**) Quantification of ROS production (measured by chemiluminescence as photons/sec) in DIV25 slices from controls, $Tau_{RD}\Delta K$ and bb14-treated $Tau_{RD}\Delta K$ slices. $Tau_{RD}\Delta K$ slices show a significant increase in ROS production ($F_{(2/15)}$=3.789; p=0.0466) which was slightly (but not significantly) reduced due to the bb14 treatment (*one-way ANOVA followed by Tukey's post-hoc test * p- value < 0.05*). Scale bar in **A**: 50µm.

Supplementary Fig. 1



Supplementary Fig. 2



Supplementary Fig. 3