Background: Direct correlation between the density of hyperphosphorylated tau (tangles) and the extent of cognitive decline in Alzheimer’s disease patients qualifies this microtubule-associated protein as an attractive therapeutic target. We propose that reducing total tau production would diminish free tau available for aggregation and potentially inhibit tangle formation. To this end, we investigated whether interference with splicing of tau-encoding gene (MAPT) can decrease tau levels. Methods: Morpholino antisense oligos (10 μM) designed to mask splice sites of constitutively spliced MAPT exons and/or the translation start codon, were nucleofected in in vitro models (human neuroblastoma cell lines, SH-SY5Y and IMR-32). In vitro studies were followed by injecting morpholinos in Mapt−/− transgenic mice expressing human tau protein. Exon 1-targeting oligos described above were injected either individually or in combination. Results: One of the most striking findings of our investigations was a significant decline in tau protein levels, by 80–90%, after 1-week treatment with antisense oligos masking the start codon and the 5′-splice site to exon 1. Total transcript expression was also reduced, by half of that evident in controls. PCR amplification confirmed that masking splice sites did indeed exclude morpholino-targeted exon from the final MAPT transcript. In vivo experiments: Effective drug delivery past the blood-brain barrier constitutes a major challenge. Therefore, for in vivo studies, we targeted intramuscular tau as a proxy for brain-localized tau. Gastrocnemius muscles were harvested at 1-day, 1-week or 2-weeks post-injection and changes in tau protein quantified by ELISA. Analysis of injected muscles revealed noteworthy decreases in tau levels at all time points, compared to controls. Conclusions: Similar outcomes in vitro and in vivo models reflect the efficacy of splicing interference as a mechanism for decreasing tau production. Tau abnormality constitutes a common link across the broad spectrum of neurodegenerative diseases. Therefore, it is our assertion that tau knockdowm can be a potential curative mechanism not only for Alzheimer’s disease but also for related tauopathies.