Effects of TPI 287, a novel taxoid, on a transgenic mouse model of Alzheimer's disease

Erwin B Defensor[a], George Farmer[b], Li Gan[c,d], Adam Boxer[d,e], Mehrdad Shamloo[a]

[a]Behavioral and Functional Neuroscience Laboratory, and Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA
[b]Cortice Biosciences, New York, NY, USA.
[c]Gladstone Institute of Neurological Disease, San Francisco, CA, USA.
[d]Department of Neurology, University of California, San Francisco, CA, USA.
[e]Memory and Aging Center, University of California, San Francisco, CA, USA

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by a progressive decline in memory along with other cognitive abilities. The pathological hallmarks of AD include elevated levels of amyloid beta peptide and abnormal tau pathology, such as hyperphosphorylation of tau, a major microtubule-associated protein in neurons. The current pilot proof of concept study tested the hypothesis that systemic administration of TPI 287, a microtubule-stabilizing agent, reduces pathological aggregation and phosphorylation of tau and leads to cognitive improvements in a mouse model of AD and related tauopathies.

Methods & Materials

In vivo evaluation of TPI287 brain penetration

C57BL/6J mice were administered TPI 287, either IV or IP, on D0, D4, and D8. Plasma and brain tissue were collected 1 hour after D8 administration. Concentrations of TPI 287 were determined using liquid chromatography-mass spectrometry.

Behavioral and Biochemical effects of TPI287 on PS19 mice:

PS19 mice, expressing the P301S mutant human tau, were administered TPI 287, weekly, via IV at 0, 1, or 3 mg/kg or via IP at 0 or 4 mg/kg.

Mice were tested in the Morris Water Maze test for spatial learning and memory after 5 dose administrations. Training trials were conducted over 4 days to assess learning acquisition. After training, probe trials were conducted over 240h to assess memory retention.

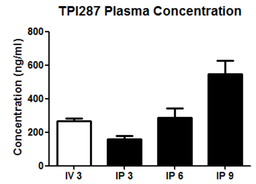
Blood and brain tissue were collected after 8 dose administrations.

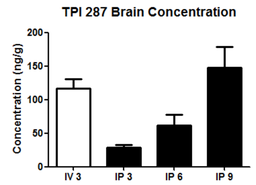
Results

In vivo evaluation of TPI 287 brain penetration

Microtubule-stabilizing taxanes have been identified as possible therapeutic agents for neurodegenerative disorders; however, taxanes generally have poor blood-brain barrier permeability and are thus unsuitable for treatment of CNS disease.

TPI 287 (mg/kg)	Route	n	Brain/Plasma Concentration (%)
3	IV	6	40
3	IP	5	17
6	IP	5	18
9	IP	5	25



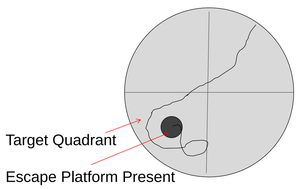


TPI 287, a novel taxane derivative, was detected in mouse the brain one hour after administration through either intravenous (IV) or intraperitoneal (IP) routes.

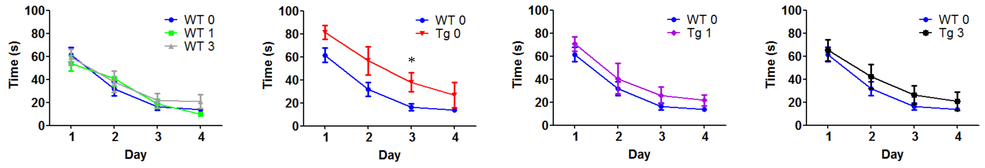
Behavioral effects of TPI 287 on PS19 mice

Morris Water Maze

Training Trials

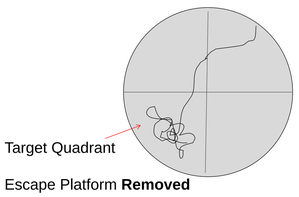


Escape Latency

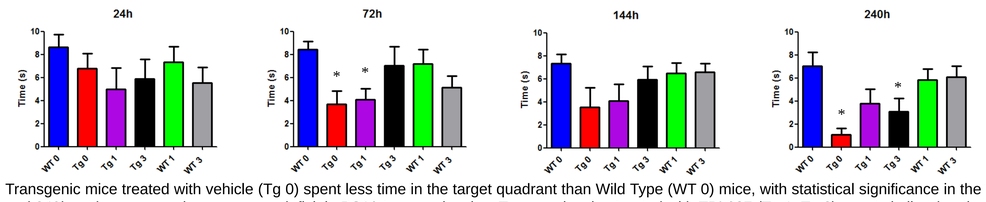


No differences were detected between WT vehicle (WT 0) and WT treated groups (WT 1, WT 3). Transgenic mice treated with vehicle (Tg 0) displayed a different pattern of learning than Wild Type mice, with statistical significance on day 3 (*, $p < 0.05$), suggesting a cognitive impairment in PS19 Transgenic mice. Transgenic mice treated with 1 or 3 mg/kg, TPI 287 (Tg 1, Tg 3) showed patterns of learning similar to WT mice, suggesting that TPI 287 improves the present learning deficits displayed by PS19 transgenic mice.

Probe Trials



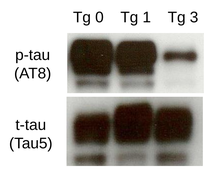
Target Quadrant Duration, First 15 seconds

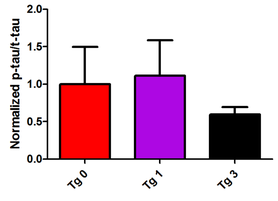


Transgenic mice treated with vehicle (Tg 0) spent less time in the target quadrant than Wild Type (WT 0) mice, with statistical significance in the 72h and 240h probes, suggesting a memory deficit in PS19 transgenic mice. Transgenic mice treated with TPI 287 (Tg 1, Tg 3) spent similar durations of time in the target quadrant when compared to WT 0, notably for Tg 1 in the 240 h probe, and for Tg 3 in the 72h and 144h probes. Taken together, these patterns of behavior suggest that TPI 287 improves the memory deficits displayed by PS19 transgenic mice in the present conditions.
*, Indicates difference from WT 0, $p < 0.05$.

In the Morris Water Maze, n=11, WT 0; n=9, WT 1; n=11, WT 3; n=5, Tg 0; n=6, Tg 1; n=7, Tg 3.

Biochemical effects of TPI 287 on PS19 mice

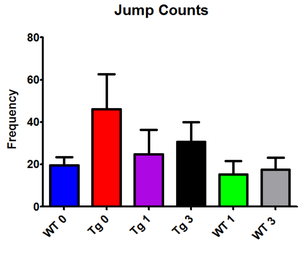




Transgenic mice treated with TPI 287 at 3 mg/kg, IV displayed a trend for reduced p-tau/t-tau when compared to the untreated transgenic group (Tg 0). n=5, Tg 0; n=5, Tg 1; n=4, Tg 3.

Activity Chamber

Jump Counts



Transgenic mice (Tg 0) displayed a trend for increased Jumping behavior in the activity chamber when compared to Wild Type mice.

n=11, WT 0; n=11, WT 1; n=11, WT 3; n=6, Tg 0; n=6, Tg 1; n=7, Tg 3.

Conclusions

TPI 287, a novel and clinically safe taxoid, is a microtubule-stabilizing agent that readily crosses the blood-brain barrier.

Although the current study contained a small sample size, trends within the data suggest that select AD-relevant behavioral impairments and biochemical hallmarks displayed by PS19 mice are improved by administration of TPI 287..

These results further suggest that modulation of tau phosphorylation and microtubule-stabilization may hold unexplored therapeutic potential with a novel mechanism of action in CNS disease

We are currently confirming and expanding upon these preliminary findings in a follow-on study

References

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Acknowledgements

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