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TRV045, a novel, selective S1PR$_1$ modulator, is efficacious in reversing neuropathic pain without affecting lymphocyte trafficking

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BACKGROUND

- Chemotherapy-induced peripheral neuropathy (CIPN) is a neuropathic pain condition that occurs in up to 70% of oncology patients undergoing chemotherapy and can result from a variety of chemotherapeutic agents (1)
- Diabetic peripheral neuropathy (DPN) is a complication of diabetes mellitus; nearly 50% of adults with diabetes will suffer from DPN during their lifetime (2)
- For these debilitating conditions there is still an unmet medical need for prophylactic and symptomatic treatment to effectively alleviate the symptoms
- Recent publications (3,4) have suggested a beneficial role for non-selective sphingosine 1-phosphate receptor subtype 1 (S1PR$_1$) modulators in treating neuropathic pain
- However, S1PR modulators available on the market, including fingolimod (GILENYA®) are not selective for S1PR$_1$ (5), and, importantly, affect lymphocyte trafficking (6), limiting their utility for the treatment of neuropathic pain
- We report here the analgesic properties of a new chemical entity, TRV045, in rodent models of neuropathic pain and demonstrate the lack of effect on lymphocyte trafficking in rodents and non-human primates

OBJECTIVES

- To evaluate the potency and selectivity of TRV045 for S1PR$_1$
- To evaluate the analgesic properties of TRV045 in a mouse CIPN model and a rat DPN model
- To evaluate the effects of TRV045 on lymphocyte trafficking in rats and monkeys

METHODS

Figure 1. Mouse chemotherapy-induced peripheral neuropathy (CIPN)

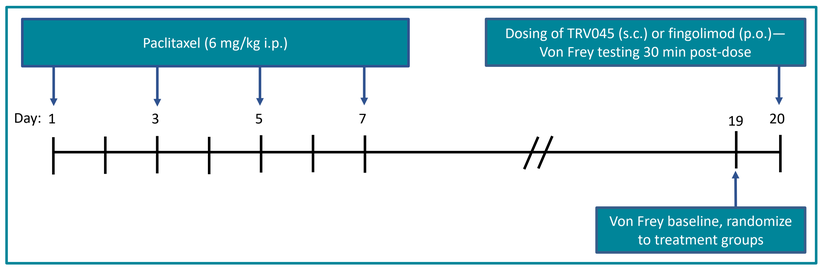
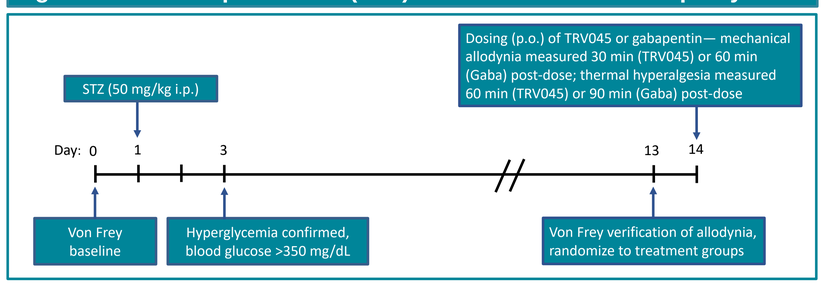


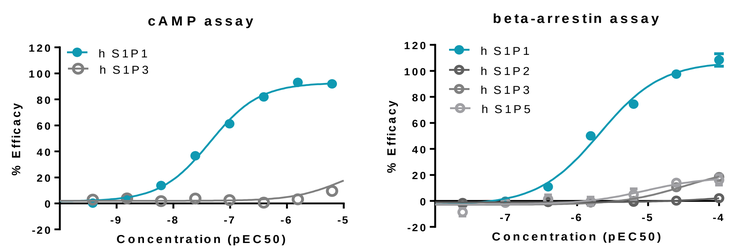
Figure 2. Rat streptozotocin (STZ)-induced diabetic neuropathy



Lymphocytes counts were determined in male C57BL/6 mice (n=6 to 12/group) following 3 consecutive days of dosing with vehicle, 3.7 mg/kg TRV045 s.c., or 0.03 mg/kg fingolimod p.o. Lymphocyte counts were also determined in male cynomolgus monkeys (n=3) following p.o. dosing with saline, vehicle or 60 mg/kg TRV045.

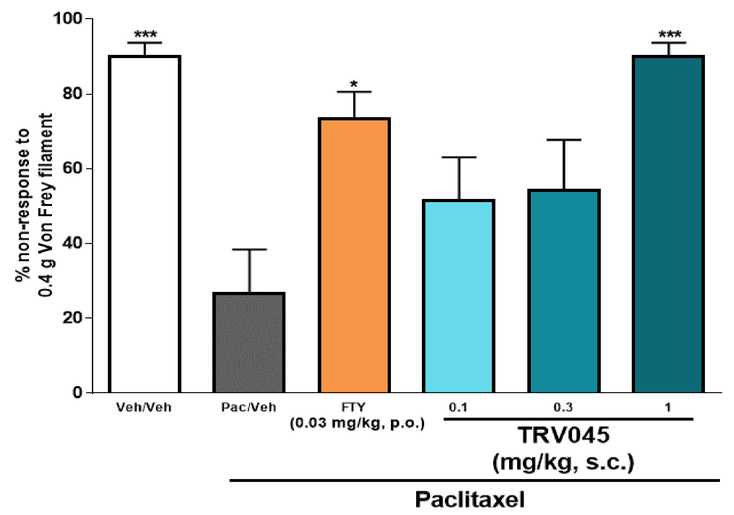
RESULTS

Figure 3. TRV045 is a selective S1PR$_1$ modulator



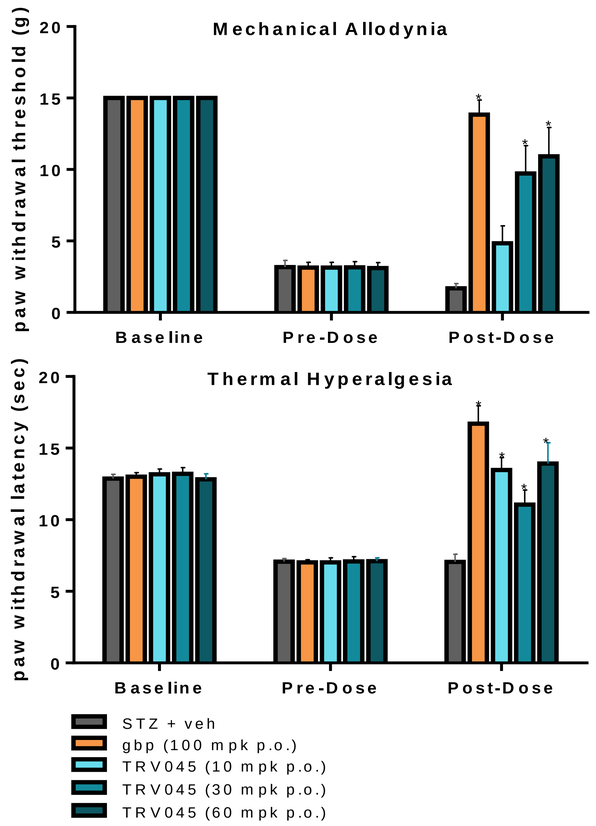
Efficacy relative to fingolimod; EC$_{50}$ = 32 nM in cAMP assay

Figure 4. TRV045 reverses paclitaxel-induced hypersensitivity in the mouse CIPN assay with efficacy comparable to fingolimod (FTY)



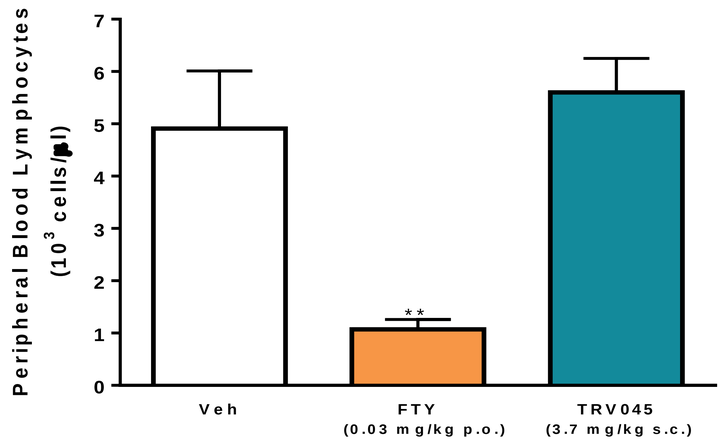
Statistical analysis: * P<0.05; *** P<0.001, treatments vs. Pac/Veh group, one-way ANOVA followed by Dunnett's test

Figure 5. TRV045 reverses STZ-induced diabetic neuropathy in rats with efficacy comparable to gabapentin (gbp)



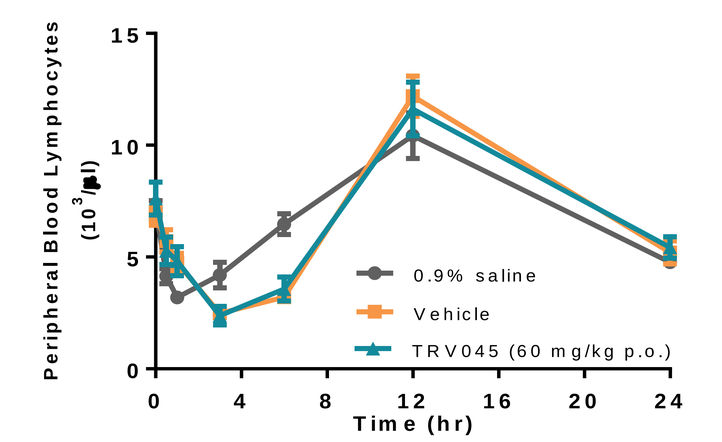
Statistical analysis* P<0.05, treated vs. vehicle control, one-way ANOVA followed by Dunnett's test

Figure 6. Unlike other S1PR$_1$ modulators such as fingolimod, TRV045 does not cause lymphopenia in mice



3.7 mg/kg dose is >10-fold higher than the ED$_{50}$ dose in the mouse CIPN study
Statistical analysis: ** P<0.01, treatments vs. vehicle group, one-way ANOVA followed by Dunnett's test

Figure 7. TRV045 does not cause lymphopenia in cynomolgus monkeys



CONCLUSIONS

- TRV045 is a selective S1P1R$_1$ modulator that is an effective analgesic in rodent models of neuropathic pain
- Our findings confirm that the modulation of the S1P/S1PR$_1$ axis is a promising therapeutic target in reversing chemotherapy-induced peripheral neuropathy and show for the first time that modulation of S1PR$_1$ might reverse diabetic neuropathic pain
- We also demonstrate that TRV045 does not cause lymphopenia and therefore may provide a new, safe, and specific therapeutic option for the treatment of neuropathic pain

References

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Disclosure

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