TRV045, a novel, selective S1PR\textsubscript{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\textsubscript{1}) modulators in treating neuropathic pain.
- However, S1PR modulators available on the market, including fingolimod (GILENYA®) are not selective for S1PR\textsubscript{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\textsubscript{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**

**RESULTS**

**Figure 3. TRV045 is a selective S1PR\textsubscript{1} modulator**

![CAMP assay](image1.png)

Efficacy relative to fingolimod; EC\textsubscript{50} = 32 nM in CAMP assay

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

![Peripheral Blood Lymphocytes](image2.png)

3.7 mg/kg dose is >10-fold higher than the ED\textsubscript{50} dose in the mouse CIPN study

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

![Mechanical Allodynia](image3.png)

Statistical analysis: * P<0.05, ** P<0.001, treatments vs. vehicle group, one-way ANOVA followed by Dunnett’s test

**CONCLUSIONS**

- TRV045 is a selective S1PR\textsubscript{1} modulator that is an effective analgesic in rodent models of neuropathic pain.
- Our findings confirm that the modulation of the S1P/S1PR\textsubscript{1} axis is a promising therapeutic target in reversing chemotherapy-induced peripheral neuropathy and show for the first time that modulation of S1PR\textsubscript{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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4. Sim-Selley et al., 2018, J Pharmacol Exp Ther, 366: 509-518
5. Chow et al., 2016, Pharm Res, 113: 521-32

**Disclosure**

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