Inhibition of SPRK1 *in vivo* in mice reduces nociceptive behaviour in a model of chemotherapeutic peripheral neuropathy.

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Background

- Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-limiting side effect of many antineoplastic drugs including Vincristine, which is used as a first line treatment in many childhood and adult cancers.
- The symptoms of CIPN can become so severe that patients are forced to reduce their dosage or cease chemotherapy altogether, resulting in suboptimal treatment of their cancer.
- SRPK1 inhibition has been shown to be associated with pain reduction via alterations in VEGF-A alternative splicing in *in vivo* models of diabetic neuropathy and traumatic nerve injury.
- Additional work by members of our lab has shown that inhibition of SRPK1 by SPHINX31, a novel small molecule therapeutic, attenuates both neurite dieback and neuronal sensitisation in *ex vivo* models of CIPN.
- In a previous pilot study, we demonstrated the induction of Vincristine induced mechanical hyperalgesia in an *in vivo* rodent model using male C57BL/6 mice (Figure 1).
- In the present study, we used this model to investigate the prophylactic potential of SPHINX31, a novel small molecule inhibitor of SRPK1 in the prevention of CIPN.

Results: Vincristine Pilot Study

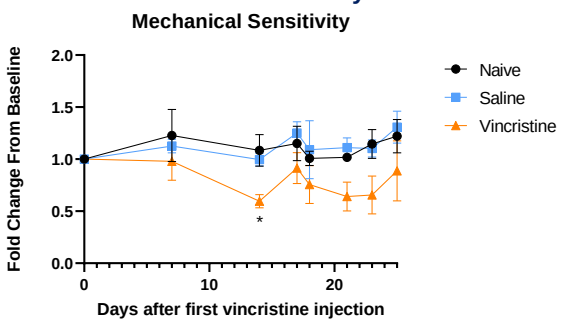


Figure 1: Vincristine induces mechanical hyperalgesia
Mechanical withdrawal thresholds normalised as fold change from baselines taken prior to vincristine dosing. 2-way ANOVA with Dunnett's multiple comparisons showed statistical significance (* p = 0.0230) at Day 14. Error bars show mean ± SD.

Methods: Dosing

SPHINX31 (0.8mg/kg) n=6

Vehicle (1% DMSO) n=6

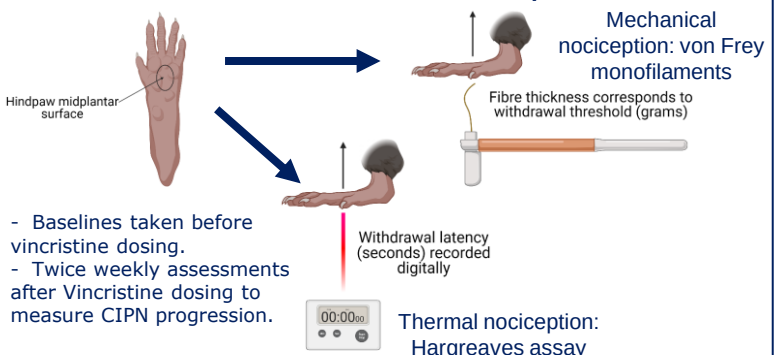
Vincristine (50µg/kg) + SPHINX31 (0.8mg/kg) n=6

Vincristine (50µg/kg) + Vehicle (1% DMSO) n=6

Animals dosed with SPHINX31 or DMSO vehicle via I.P injections twice weekly throughout the study. DMSO used to equalise injection volume with that of co-treated treatment groups.

Animals dosed daily I.P with vincristine for 2 weeks, twice weekly this was combined with SPHINX31/DMSO. After 2 weeks, DMSO replaced vincristine and injections of SPHINX31/DMSO continued twice weekly only.

Methods: Behavioural assessments of nociception



- Baselines taken before vincristine dosing.
- Twice weekly assessments after Vincristine dosing to measure CIPN progression.

Results: Prophylaxis Study

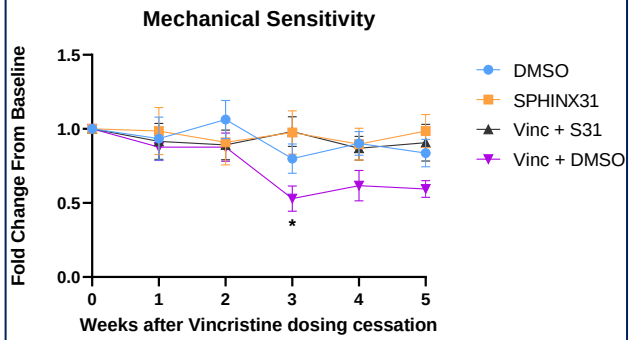


Figure 2: SPHINX31 prevents Vincristine-induced mechanical hyperalgesia
Mechanical withdrawal thresholds normalised as fold change from baselines taken prior to vincristine dosing. One Way ANOVA with Tukey's multiple comparisons showed statistical significance between Vinc + S31 and Vinc + DMSO (* p = 0.04) at Week 3. Error bars show mean ± SD.

Discussion

- This study has shown that SPHINX31, a novel inhibitor of SRPK1 prevents the development of vincristine-induced mechanical hyperalgesia, when given as an adjunct treatment.
- Systemic SPHINX31 dosing had no negative effect on nociception in control animals.
- The results of this study therefore show that SPHINX31 induced SRPK1 inhibition has efficacy as a prophylactic treatment, in the amelioration of CIPN.
- Tissue collected from animals in this study will be used for future investigations into the splicing events associated with both CIPN development and its prevention via SRPK1 inhibition.
- Further work is currently underway to investigate the therapeutic potential of SPHINX31 in the reversal of established CIPN.