Non-electrophilic activation of the Nrf2 pathway ameliorated experimental Nonalcoholic Steatohepatitis

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**INTRODUCTION**

The transcription factor Nrf2 mediates adaptation to oxidative stress by inducing antioxidant and detoxifying enzymes. Although Nrf2 activation has multiple benefits, including decreased oxidative stress, enhanced redox capacity, and inflammation, modulation of lipopolysaccharides, glucagon receptors, regulation of atherogenesis, proteostasis, and mitochondrial biogenesis and energetics. Pharmacological activation of the Nrf2 pathway has been recognized as a potential strategy to reduce oxidative stress and resolve inflammation associated with acute and chronic illnesses.\(^1\)

vTv Therapeutics has developed non-electrophilic, orally bioavailable molecules that activate the Nrf2 pathway via the inhibition of Bach1 transcriptional repression and the stabilization of Nrf2. The non-electrophilic pathway could be a potential therapeutic target to treat chronic liver diseases such as NASH.

**AIM**

To assess the efficacy of the non-electrophilic Nrf2 pathway activator HPP3033 on a diet-induced NAFLD in a methionine-choline deficient diet (MCD) model.

**METHODS**

**In vitro**

- Methyl, NQO1, GCLC, and TNFα gene expression were measured in HepG2 cells in a normal human liver (NHLF).
- HepG2 cells were treated with HPP3033 (0.5, 1, 2, and 4 µM) for 24 h to measure glutathione (GSH).
- HepG2 cells were treated with 3,3'-dihexyloxacarbocyanine dye prior to treatment with DMSO, H2O2, or CoPPIX.
- HepG2 cells were treated with HPP3033 for 0.5, 1, 2, and 4 hrs.

**In vivo**

- Mice were fed a choline/methionine deficient diet for 4 weeks. After 1 week of diet, mice were randomized into 3 treatment groups balanced for: 1) ALT, 2) AST, and 3) body weight. After randomization, mice were treated QD for 3 weeks with vehicle (n=10), HPP3033 (10 mg/kg), or DMF and cobalt protoporphyrin (CoPPIX) for 0.5, 1, 2, and 4 hrs.

**RESULTS**

**In vitro**

- HPP3033 activates Nrf2 pathway in HepG2 cells.
- HPP3033 activates Nrf2 pathway without depletion of glutathione or increased ROS.

**HPP3033 activates Nrf2/Bach1/ARe regulated genes**

**In vivo**

- Mice were fed a choline/methionine deficient diet for 4 weeks. After 1 week of diet, mice were randomized into 3 treatment groups balanced for: 1) ALT, 2) AST, and 3) body weight. After randomization, mice were treated QD for 3 weeks with vehicle (n=10), HPP3033 (10 mg/kg) or DMF and CoPPIX for 0.5, 1, 2, and 4 hrs. After the treatment period, total NAS score, hepatic gene and protein expression of inflammatory markers, and hepatic GSH levels were measured by real-time PCR, western blot, and flow cytometry.

**Non-electrophilic activation of the Nrf2 pathway is hepatoprotective in MCD NASH model.**

**CONCLUSIONS**

- HPP3033 is hepatoprotective in MCD NASH model. Activation of the Nrf2 pathway by HPP3033 after 21 days of dosing with HPP3033.
- Trends toward lowering hepatic expression of TNF-α, IL-1β, and collagen alpha1 (Col1a1) after 21 days dosing with HPP3033.
- In vitro: HPP3033 is hepatoprotective in MCD NASH model. Activation of the Nrf2 pathway by HPP3033 after 21 days of dosing with HPP3033.

**ACKNOWLEDGEMENTS**

**REFERENCES**

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