

## **Control of Chemotherapy-Induced Peripheral Neuropathy and HMGB1 Cytosolic Translocation in Dorsal Root Ganglion Sensory Neurons Using Olaparib**

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**Background and Hypothesis:** Oxaliplatin (OXL)-associated Chemotherapy-induced Peripheral Neuropathy (CIPN) is a frequent, potentially severe, and dose-limiting toxicity of colorectal cancer treatment. CIPN can persist for years beyond chemotherapy completion, causing significant challenges for cancer survivors due to its negative influence on quality of life. This work builds upon preliminary observations that platinum drugs lead to the release of a damage-associated protein, high mobility group box-1 (HMGB1). Drug-induced release of this protein from the nucleus into the cytosol and eventually into the extracellular compartment can sensitize primary afferent sensory neurons for prolonged periods of time, eliciting CIPN pain behavior in rodents. Inhibition of HMGB1 nuclear translocation through administration of olaparib may serve to diminish CIPN pain in a rodent model.

**Experimental Design or Project Methods:** Sprague-Dawley rats were given intraperitoneal injections of oxaliplatin and olaparib and measured using Von Frey Filaments for mechanical sensitivity and Plantar's Test for thermal behavior. Lumbar dorsal root ganglions were collected for immunofluorescence to label tissues with anti-HMGB1 antibodies and analyzed.

**Results:** Olaparib transiently reverses the OXL-induced tactile allodynia one hour after drug administration. Olaparib-treated rats also exhibit diminished cytosolic HMGB1, indicating a lack of nuclear translocation in medium and large diameter sensory neurons.

**Conclusion and Potential Impact:** The reduced CIPN behavior after olaparib administration correlates with diminished cytosolic HMGB1. This identifies HMGB1 as an important co-regulator of neurotoxicity due to oxaliplatin, which may have important relevance for future techniques to reduce CIPN and increase efficacy of colorectal cancer treatment.