

## The Effect of Chronic Resveratrol Administration on Neurodegeneration and Blood Brain Barrier Stability Surrounding Intracortical Microelectrodes

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**Statement of Purpose:** Clinical implementation of many devices implanted in the central nervous system is limited due to a general lack of chronic stability months to years after implantation. While the exact mechanism for device stability is unclear, the ability of most neural interfaces to properly function is directly related to the proximity of viable neurons in the surrounding cortical tissue. To this end, our group recently identified oxidative stress events as a key mediator in neuronal health surrounding intracortical electrodes<sup>1</sup>. Here, we will present results suggesting that the use of anti-oxidative therapies can significantly improve neuronal health around implanted devices. We will also demonstrate that optimization of anti-oxidant administration can inhibit reactive oxygen species accumulation at the device-tissue interface and facilitate neuronal protection.

**Methods:** Here, the effect of systemically administered resveratrol, an anti-oxidant known to quench free radicals and attenuate microglial inflammatory cytokine expression, on neuroinflammation surrounding microelectrodes was examined in cortical tissue in parallel to control animals. To first determine the feasibility of resveratrol, a two-dose regime was employed and the neuroinflammatory response assessed at both two and four weeks after device implantation. Following this study, a new administration scheme, based on an initial bio-distribution characterization of resveratrol concentration around implanted devices, was investigated: daily administration (30 mg/kg) of resveratrol. Control animals included diluent-dosed and non-treated animals. In all conditions, histology for oxidative stress and neurodegeneration was assessed at both two and sixteen weeks after implantation. The extent of the inflammatory was quantified using a custom written MATLAB code. Significance was defined as  $p < 0.05$ .

**Results:** Here, we found that a two-dose administration of resveratrol was able to provide significant protection from neurodegeneration, as measured by fluorojade C, around implanted devices up to two weeks after implantation (**Figure 1**)<sup>1</sup>. However, by four weeks after device implantation, a heightened inflammatory response was noted in resveratrol-dosed animals, in comparison to controls, suggesting that the effects of resveratrol administration were beginning to wear off (**Figure 1**).

Given the time dependent effects of a two-dose administration scheme, we next investigated the utility of daily resveratrol administration on the neuroinflammatory response to implanted electrodes. However, prior to investigating the effects immunohistologically, a bio-distribution characterization was conducted to ensure that a therapeutic concentration of resveratrol was maintained

around the implanted device. Specifically, a dosing regime was optimized to ensure a concentration of 5 to 25  $\mu\text{M}$  of resveratrol around the implanted device; a concentration range that has shown to be effective *in vitro*<sup>2</sup>. Notably, we found that daily intraperitoneal injections of resveratrol, at 30 mg/kg, were capable of maintaining a therapeutic concentration of resveratrol around implanted electrodes for up to seven days after device implantation (**Figure 2**). The effects of daily administration of resveratrol on the neuroinflammatory response at both two weeks and sixteen weeks after device implantation are underway, and will be presented.

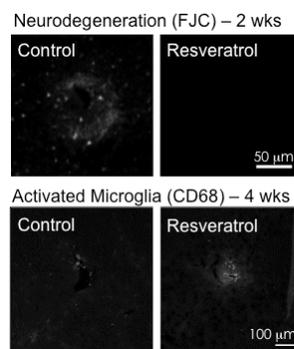


Figure 1. Two-dose administration of Resveratrol provides time-dependent neuroprotection.

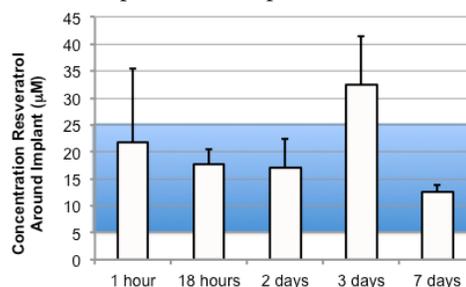


Figure 2. Bio-distribution of Resveratrol around implanted electrodes for up to seven days.

**Conclusions:** Here we have found that short-term dosing of resveratrol was capable of neuroprotection up to two weeks after administration. However, given the time dependence of efficacy of this scheme, we established a daily administration scheme capable of maintaining a therapeutic concentration of resveratrol around implanted devices. We anticipate that our results will demonstrate the utility of resveratrol in improving long-term reliability of devices implanted into the central nervous system.

**References:** [1] Potter KA. Biomaterials. 2013;34:7001-7015. [2] Ravikumar M. J Neurosci Meth. 2012;211:280-288.