

Abstract # C212

## **A critical role for the tissue distribution profile in heat shock protein (Hsp) 90 inhibitor-induced ocular toxicity in rats.**

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**Background:** In addition to regulating a number of oncogenic client proteins, the Hsp90 molecular chaperone also controls the folding of key signaling molecules required to maintain normal cell function in many organs, including the retina. In human clinical trials Hsp90 inhibition has been associated with visual disorders including blurred vision, flashes, delayed light/dark accommodation, and photophobia. These adverse effects involving injury to the retina may be attributable to photoreceptor degeneration and cell death, as previously reported in dogs following repeated doses of PF-04929113. In contrast, ganetespib, a potent Hsp90 inhibitor currently in phase II/III trials, has demonstrated promising clinical activity without manifesting ocular toxicity. This difference in vision deficits between ganetespib and other Hsp90 inhibitors likely depends on a number of contributing factors.

**Results:** In this study, we examined the relationship between retinal drug distribution profiles and photoreceptor degeneration in male SD rats treated with 17-DMAG, 17-AAG, and STA-9056 (an Hsp90 inhibitor with comparable *in vitro* activity to 17-DMAG). All compounds were tested in short-term studies at 1-3 dose levels administered i.v.. At necropsy, eyes were dissected and processed for histopathological examination. In subsets of animals, the retinal tissues, along with plasma and cerebrospinal fluid (CSF) samples, were collected for analysis. Our results indicate that all compounds evaluated showed greater exposure in the retinal tissue compared to plasma and CSF. 17-DMAG, for which visual changes have been reported in clinical subjects, produced marked photoreceptor cell death and was associated with a slow elimination rate (at 6 hrs post-dose, 50% of the drug present at 30 min remained in the retina) and a high retina/plasma (R/P) ratio. In contrast, and consistent with the absence of clinically-reported visual changes, 17-AAG at the maximum tolerated dose did not produce detectable photoreceptor injury. At 6 hr post dose, 94% of 17-AAG had been eliminated from the retina resulting in a low R/P ratio. Finally, STA-9056 showed 79% drug elimination at 6 hrs and an R/P ratio that was moderately low. Photoreceptor degeneration was not observed at doses of STA-9056 that are active in animal tumor models, and only minimal degeneration was seen at a higher dose.

**Conclusions:** Our findings suggest that the R/P exposure ratio and elimination rate profiles play crucial roles in ocular toxicity and can be used as indicators of potential Hsp90 inhibitor-induced damage in rats. In summary, Hsp90 plays an important role in the retina and prolonged Hsp90 inhibition can lead to vision disorders. However, ocular toxicity may be successfully minimized by administration of Hsp90 inhibitors with favorable drug properties that include, although not necessarily limited to, lower retina/plasma exposure ratios and faster retinal elimination.