Intravitreal injection of COX-2 acetylating immunoresolvents for the treatment of ocular inflammation: In vitro assessment in THP-1-derived macrophages and in vivo assessment in a rat model of endotoxin-induced uveitis

Purpose: Current treatments for uveitis impede the body's endogenous inflammation-resolution pathways. COX-2 acetylating immuno-resolvents (CAIR) are agents capable of specifically acetylating COX-2 and redirecting its activity from pro-inflammatory to pro-resolving, amplifying the endogenous resolution of acute inflammation. Agents currently identified as CAIRs include locally delivered acetylsalicylic acid (ASA), and a more potent derivative, o-(acetoxyphenyl)hept-2-ynyl sulfide (APHS). We hypothesised that intravitreal (IVT) injection of CAIRs would reduce histological markers of inflammation in an animal model of uveitis and reduce pro- inflammatory gene expression in THP-1 macrophages.

Methods: Lewis rats received subcutaneous injection of lipopolysaccharide (LPS) to induce bilateral experimental uveitis. After five hours, IVT injection of ASA or APHS was carried out OD, and vehicle injected OS. Control animals received vehicle subcutaneously and IVT vehicle OU, and all underwent histopathology 25-hours follow- ing LPS-induction. In vitro, THP-1 macrophages were co- treated for 6 hours with LPS and either ASA or APHS. MTT and LDH assays evaluated cytotoxic effects; RT- qPCR assessed expression of pro-inflammatory tran- scripts IL-1?, TNF? and COX-2.

Results: In LPS-treated animals, IVT CAIRs induced a marked reduction in inflammatory cell infiltrate com- pared to the vehicle-injected contralateral eye. In vitro, LPS-treated macrophages demonstrated significant upregulation in inflammatory cytokines IL-1?, TNF? and COX-2, which was significantly reduced in the presence of CAIRs. CAIRs exhibited selective cytotoxicity towards LPS-stimulated macrophages.

Conclusion: CAIRs were well-tolerated and significantly reduced inflammatory markers in vitro and in vivo. CAIRs show promise as novel inflammation-resolving treatments, and evaluating their relative efficacy to cur- rent standard of care is warranted.