**Structure:activity relationships for the cytoprotective effects of epoxyeicosatrienoic acids (EETs) and their corresponding diols against palmitate-induced lipotoxicity in BRIN-BD11 cells**

**Introduction:** Palmitate is a well-established contributor to pancreatic beta cell death in type 2 DM, with effects ameliorated by polyunsaturated fatty acids, including arachidonic acid (AA, C20:4). Whilst AA-derived metabolites from COX and LOX enzymes have been extensively studied, little attention has focused on EETs derived from cytochrome-P450 (CYP450) enzymes. This study therefore aimed to investigate the cytoprotective effects of CYP450-derived EET regioisomers and their less-active vicinal diols against palmitate-induced lipotoxicity.

**Methods:** BRIN-BD11 cells were treated with 250µM palmitate in co-incubation with 8,9; 11,12; 14,15 EETs, or their dihydroxyeicosatrienoic acidderivatives (DHETs) for 24 hours. Cell viability was assessed by vital dye exclusion using Trypan Blue (results expressed as total and viable cells/ml +/-SEM), or multicaspase-activity assay.

**Results:** Data showed that all EETs protected cells against palmitate-induced cell death, such that palmitate decreased viable cell number from 1.02x106 (+/-0.8) to 0.21x106(+/-XX) and in co-incubation with 8,9EET, 11,12EET and 14,15EET, viable cell number was significantly increased to 1x106, 0.82x106 and 0.72x106,respectively (P<0.05). Structural differences for protective activity in relation to position of the epoxide group were also reflected in caspase activity, whereby palmitate alone increased activity to 71%(+/-2.9), decreasing to 13%(+/-), 23%(+/-) and 34%(+/-) in the presence of these EETs, respectively (P<0.05). In comparison, corresponding DHETs failed to significantly attenuate palmitate cytotoxicity.

**Conclusion:** CYP450-derived EETs protect against palmitate-toxicity, with position of epoxide group reflecting structural differences in cytoprotection. Ongoing work is exploring mechanistic actions of EETs in beta cells and the role of CYP450 isoforms in production of endogenous EETs.