PO33 Gene therapy for X-linked Inhibitor of Apoptosis Protein (XIAP) deficiency

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X-linked inhibitor of apoptosis protein (XIAP) deficiency, caused by mutations in BIRC4, is an immunodeficiency with variable clinical features including haemophagocytic lymphohistiocytosis (HLH) and colitis. Current therapy includes HLH treatment protocols followed by haematopoietic stem cell transplant (HSCT). However, survival in XIAP-deficient patients is significantly lower compared to patients receiving HSCT for other forms of HLH with significant graft versus host disease and disease relapse. Autologous HSC gene therapy could offer an alternative treatment option for these patients. Using a XIAP-knockdown THP-1 cell line we show normalisation of IL-1β levels upon inflammasome activation following lentiviral XIAP gene transfer. Moreover, we are able to demonstrate restoration of TNF-α secretion in response to L18-MDP following XIAP gene transfer in patient monocytes. In a XIAP−/− mouse model, immunization with the Dectin-1 ligand curdlan induces features associated with XIAP-deficiency due to impaired innate immune responses. Serum levels of TNF-α, IL-6, IL-10 and MCP-1 were significantly reduced in XIAP−/− mice 2 hours post-curdlan administration compared to wild-type controls. This profile was reversed after 7 days with XIAP−/− mice secreting higher levels of proinflammatory cytokines alongside splenomegaly. Preliminary data in XIAP-knockdown THP-1 cells challenged with curdlan indicate that TNF-α and IL-1β can be completely restored to control levels following XIAP gene transfer. We now plan to correct immune defects in XIAP−/− mice using lentiviral mediated HSC gene correction to abrogate excessive inflammasome activation following curdlan challenge. In parallel we are developing a targeted gene editing approach for XIAP correction allowing utilisation of endogenous genomic regulatory elements and therefore allow physiological expression of this highly regulated protein.