Targeted IL-22 as a therapeutic approach to islet and hepatic dysfunction in obesity

John Prins, Sumaira Hasnain and **Michael McGuckin**
University of Melbourne, Australia

IL-22 is and endogenous cytokine with recognized actions to reduce cellular oxidative and ER stress. IL-22 is under therapeutic investigation and clinical trial in a range of inflammatory disorders but off-target effects are reported, particularly in skin and gut. To address this challenge and improve the therapeutic window for IL-22, we have developed a range of IL-22-based peptide drugs that have a specific moiety targeting the IL-22 to pancreatic islets and liver. Preclinical studies confirm that IL-22 is preferentially targeted to these organs, with minimal exposure to skin and gut. *In vitro* and preclinical data show that the action and efficacy of the IL-22 in unimpaired by the targeting moiety. In a range of mouse models of obesity, T2D and NAFLD twice- weekly sc administration of targeted IL-22 provides significant improvement in insulin levels and glucose tolerance (GTT and ITT). Therapy also significantly improves hepatic steatosis and inflammation, liver weight, and serum transaminases in a dose- dependent manner. Total body weight is reduced with therapy. Hepatic and islet tissue analyses demonstrate reduction in oxidative and ER stress in response to the targeted IL-22 therapy, confirming the proposed mechanism of action. We are currently evaluating the effect of targeted IL-22 in a range of preclinical models of liver disease with prominent steatosis and/or fibrosis and comparing this effect to existing therapies. To date, we have not observed any off-target organ adverse effects of targeted IL-22 and there is no evidence of systemic toxicity. We believe that targeted IL-22 is a promising approach to harnessing the beneficial effects of this endogenous anti-inflammatory cytokine. Given the dual action to improve glucose metabolism and reduce steatosis and hepatic dysfunction, targeted IL-22 may be a useful and efficacious therapy in a range of patients with metabolic dysfunction associated with obesity.

Speaker Biography

John Prins is an endocrinologist and scientist with a longstanding interest in obesity and associated metabolic dysfunction, particularly T2D and NAFLD. He is currently head of the medical school at the University of Melbourne, and senior consultant endocrinologist at Royal Melbourne Hospital. He has over 150 publications and his H-index is 54.

e: john.prins@unimelb.edu.au

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