The novel designer cytokine IC7Fc protects against obesity-induced metabolic disease

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The gp130 receptor cytokines interleukin-6 (IL-6) and ciliary neurotrophic factor (CNTF) can improve obesity and insulin resistance in mice and humans. However, due to the known pro-inflammatory effects of IL-6 and the antigenic response in some patients to the clinically used form of CNTF (AxokineTM), both proteins have limited, if any, therapeutic utility for treatment of type 2 diabetes (T2D). In an attempt to overcome these issues, we engineered a chimeric gp130 ligand, termed IC7Fc, where one gp130 binding site has been removed from IL-6 and replaced with the leukemia inhibitory factor receptor (LIFR) binding site from CNTF and then fused with the fragment crystallizable (Fc) domain of immunoglobulin G (IgG), creating a new cytokine with CNTF-like, but IL-6R- dependent signaling. We have demonstrated that IC7Fc significantly improves glucose tolerance and hyperglycemia and prevents weight gain and liver steatosis in diet-induced and genetically modified obese mice. In addition, IC7Fc improves glucose tolerance and is safe in non-human primates. In comprehensive human cell based assays, we have also shown that IC7Fc treatment results in no signs of inflammation or immunogenicity. Thus, IC7Fc is a realistic next generation biological for the treatment of obesity and T2D, disorders that are currently pandemic.