

Investigating the Potential of Repurposing GLP1R and GIPR Agonists for the Treatment of Obesity-Driven Aggressive Prostate Cancer

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Obesity is the largest modifiable risk factor for cancer. In prostate cancer (PCa), obesity is associated with a more aggressive disease phenotype, characterised by accelerated tumour progression, extra-prostatic invasion and reduced therapeutic response. Weight gain and central obesity are also major side-effects of androgen-deprivation therapy and obese patients suffer greater complications from prostatectomy. These clinical outcomes are in-part mediated by obesity-induced changes to peri-prostatic adipose tissue (PPAT) cellular composition and secretory function. We have shown that PPAT undergoes pathological remodelling in obesity, resulting in altered secretion of extracellular-vesicles (EVs), which can promote tumour growth by enhancing proliferation, migration and invasion through EV-mediated modulation of Rho GTPase signalling and focal adhesions. Enhanced PPAT-specific infiltration of inhibitory immune cells is also observed in aggressive- *vs* indolent disease.

GLP-1R/GIPR agonists have revolutionised obesity management, and their use has been shown to reduce breast, endometrial, ovarian cancer risk in retrospective studies. Beyond their systemic mechanisms-of-action, evidence indicates that these drugs exert direct effects on adipose tissue such as adipose browning and decreased inflammation. In PCa, GLP-1R/GIPR agonists have been shown to alter PPAT adipocyte metabolism by reducing inflammation and altering adipokine signalling. Although preliminary data suggest that GLP-1R/GIPR agonists can induce apoptosis and inhibit proliferation of prostate and colon cancer cells *in vitro*, effects of such drugs on peri-prostatic adipocytes have not been characterised, and data on GLP1/GIPR expression/activity in PCa cells is conflicting. With this project, we aim to: 1) evaluate GLP1, GIPR expression in PCa cells, patient tumour explants and patient-derived PPAT models, 2) assess the impact of GLP-1R/GIPR agonists on PPAT adipocyte differentiation, proliferation and PCa-promoting secretome using our unique patient-derived immortalised PPAT pre-adipocytes with matched non-prostatic adipose, 3) test the ability of GLP-1R/GIPR agonists to inhibit obesity-associated PCa progression *in vivo*.

Our recent data shows GIPR/GLP1R expression varies significantly between different PCa cell lines and pre-adipocyte *vs* mature adipocytes. Moreover, GLP-1R/GIPR-agonists had no effect on PCa and adipocyte viability but caused significant changes to PPAT biology. Most notably, clinically relevant doses increased PPAT adipogenic potential, shown by upregulation of *PLIN1*, *FASN*, *LIPE* and *ADIPOQ* and decrease in pro-inflammatory markers such as *IL-8* and *CCL2*, important given altered PPAT immune infiltration in advanced PCa. Results of this study could highlight the potential of GLP-1R/GIPR-agonists to be used in combination with ADT to counter the metabolic impacts of treatment. Improved knowledge of the GLP-1R/GIPR-agonist-altered adipose transcriptome/secretome could also inform development of novel therapeutic strategies for obesity management.

The authors gratefully acknowledge funding from Prostate Cancer Research (UK), Prostate Cancer UK, Prostate Cancer Foundation.

No conflicts of interest are reported.