UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

Tutor's Name	Andrea Cignarella
Cotutor's Name	Carlotta Boscaro

1) Project title

Direct vascular effects of SGLT2 inhibitors

2) Abstract (max 500 words)

Dapagliflozin, canagliflozin and empagliflozin are competitive reversible inhibitors of the sodium-glucose co-transporter type 2 (SGLT-2) in the proximal convoluted tubule of the kidney. Gliflozins reduce glucose absorption from the tubular filtrate and increase urinary glucose excretion. The resulting glycosuria is associated with an osmotic diuresis and salt excretion. The osmotic diuretic effect and the caloric loss from glucose in the urine also leads to reduction in systolic blood pressure and body weight (Abdul-Ghani et al., 2015). A clinical trial of empagliflozin (EMPA-REG OUTCOME) reported substantial reductions in cardiovascular endpoints (Paneni and Luscher, 2017). Empagliflozin, canagliflozin, and dapagliflozin reduce CV events in patients with type 2 diabetes and CVD, or in those who are at very high/high CV risk (Cosentino et al., 2020). The sodium-glucose cotransporter-2 is present in isolated vascular tissue and its inhibitor, empagliflozin, preserves endothelial function under hyperglycaemic conditions (El-Daly et al., 2018). In vitro, canagliflozin suppressed the increased HUVEC proliferation and tubular formation that were observed in co-cultures with human liver cancer cells (Kaji et al., 2018), suggesting the potential of SGLT2i to impair pathological angiogenesis. Whether SGLT2i affect resting HUVEC function has not been explored.

Hence, the **central hypothesis** of this project is that the endothelium is a direct target of gliflozin regulation within the vasculature and, thereby, may provide a mechanistic basis for the role of the glucose transporters and possibly glycolytic proteins in mediating some of the unexplained protective effects of gliflozins within the CV system. Therefore, the **overall aim** is to establish whether gliflozin actually regulates the endothelium-monocyte crosstalk. Specifically, it is aimed to investigate whether gliflozin treatment may influence the functional expression of PFKFB3 and GLUT-1 along with the key steps of angiogenic responses in resting HUVECs. Further, it will be tested whether conditioned media of gliflozin-treated HUVECs affect the levels of inflammatory markers CD162, CD11c and CD62L in LPS-challenged primary human monocytes. Finally, blood samples will be taken before and following treatment of type-2 diabetic patients in collaboration with the Diabetology Unit at the University of Padova Medical Centre. Changes in patients' monocyte function as well as in metabolic responses of HUVECs challenged with patients' serum will be assessed.

The anticipated **outcome** of this project should have implications for the understanding of the role of SGLT2i in CV disease progression in type-2 diabetic patients.

References

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