Empagliflozin's anti-oedematic effects in an ischemic stroke model using a lab-on-a-chip OGD/R system

Ischaemic stroke (IS) is one of the leading causes of death and disability worldwide. The rising global population age is the primary, unchangeable factor driving increased human IS incidence. Immediate pharmacological and/or endovascular treatment is the current standard for ischemic stroke, aiming to restore blood flow to the brain. Unfortunately, this early intervention is only effective in less than half of patients; the rest experience lifelong disabilities because of the absence of additional neuroprotective therapy to complement early reperfusion therapy. Empagliflozin (EMPA), a type of phlozin, is an antidiabetic medication. Its mechanism of action, sodium-glucose co-transporter 2 inhibition (SGLT2i), has proven effective for diabetes and, through repositioning, become the standard of cardiovascular care. Many studies show promise for repositioning this drug to treat central nervous system diseases, particularly ischemic stroke-related oedema. The potential of EMPA to reduce cerebral oedema in ischemic stroke lies in its ability to modulate glucose metabolism and electrolyte balance, protecting cells from the uncontrolled water influx triggered by ischemia. However, its mechanisms of action in IS remains unclear, and further research is needed given its high therapeutic potential.

We aim to understand the mechanisms through which EMPA influences post-ischemic stroke oedema. We hypothesize that by blocking SGLT2 transporters in NVU cells, EMPA will reduce sodium and glucose entry, thus decrease water influx and improving cell survival by reducing post-IS cellular oedema.

Methods: Human NVU cell lines (endothelial cells, pericytes and astrocytes) will be subjected to: (i) normoxia; (ii) normoxia with EMPA administration; (iii) oxygen glucose deprivation/reperfusion (OGD/R); and (iv) OGD/R with EMPA administration. We will assess (a) EMPA dosage; (b) glucose uptake; (c) sodium uptake; (d) blood brain-barrier (BBB) integrity; (e) cell oedema under static and microfluidic conditions using a range of different molecular and functional assays, and microscopic imaging techniques; including survival analysis, Western blotting, TEER, holographic microscopy and confocal microscopy.

Expected results: We predict EMPA will decrease glucose and sodium absorption and intracellular water transport, thus improving NVU cell survival during ischemia and reducing post-ischemic cell oedema.

Significance: This research could significantly advance our understanding of how EMPA protects the nervous system in stroke treatment. Successfully demonstrating EMPA's benefits could lead to faster approval for its use in stroke, ultimately reducing patient mortality and disability. Advanced microfluidic models will improve the translation between in-vitro and in-vivo studies in this project, reducing the failure rate of subsequent animal and human studies in drug repositioning. This will improve the accuracy of the results and better reflect the brain's actual physiological state after IS.