EPD/25/45 - Mapping the therapeutic potential of targeting endothelial cell dysfunction in Multiple Sclerosis

Background
Multiple sclerosis (MS) is a debilitating condition of the brain and spinal cord, that affects approximately 17,000 people in Scotland. It is the most common cause of non-traumatic disability in young adults and progressively reduces mobility and quality of life. Despite research efforts, the exact cause of MS remains unclear, and current treatments are limited in their ability to stop disease progression.

The brain relies on a continuous supply of oxygen and nutrients, delivered through a complex network of blood vessels. These vessels are lined by endothelial cells, which form the crucial blood-brain barrier (BBB)—a protective layer that controls what enters the brain from the blood. In MS, the BBB breaks down at the earliest stages of disease, allowing harmful substances and immune cells to enter and attack the brain, resulting in brain injury and disease progression. However, there is a critical gap in knowledge: what causes BBB breakdown? Emerging research suggests that abnormal endothelial cells may be responsible, but the reason for this has not been fully explored.

Purpose of Study
This project aims to understand why endothelial cells are abnormal in MS, as early changes in these cells may drive BBB breakdown. By identifying these early changes, we may find ways to prevent disease progression before significant damage occurs. This research will also identify potential new strategies for treatment that could protect endothelial cells, prevent BBB breakdown, and ultimately slow MS progression.

Methodology
This laboratory project will recruit twenty newly diagnosed MS patients from the Queen Elizabeth University Hospital, Glasgow, alongside healthy volunteers from the University of Glasgow. This study design was developed with patient involvement. A patient advisory group will be setup at the start of the project to ensure the research remains patient focused.

Aim 1: Developing Patient-Derived Endothelial Cell Models
Blood samples will be collected from MS patients and healthy volunteers. Endothelial cells will be extracted from these and grown in the lab using well-established techniques to create a new, state-of-the-art MS-patient endothelial cell model for further study.

Aim 2: Understanding Endothelial Cell Abnormalities
Using this model, MS and healthy endothelial cells will be compared to identify differences in their shape, function, and behaviour. Advanced molecular techniques will be applied to explore the mechanisms causing these abnormalities.

Aim 3: Investigating the Influence of Blood on Endothelial Cells
Applying new technology, MS and healthy endothelial cells will be mixed with blood from MS-patients to reveal whether immune cells in the blood or other substances contribute to endothelial cell abnormalities. Advanced molecular techniques will then

explore internal endothelial cell mechanisms that may have changed following blood exposure.

Aim 4: Identifying Endothelial Cell Changes as Potential Treatment Targets
Abnormal endothelial cell mechanisms, identified in aims 2 and 3, will be visualised in post-mortem MS brain tissue, to ensure that our model correctly represents what we see in patients. This will help pinpoint potential molecules that could be targeted to correct endothelial abnormalities.

Project Milestones
In 3 years, this project will:
1) Establish a new model of MS-patient endothelial cells.
2) Identify key differences between MS-patient and healthy endothelial cells.
3) Determine how blood contributes to endothelial cell abnormalities,
4) Confirm findings in patient tissues and identify potential therapeutic targets.

Potential Results and Impact
This project provides a new and exciting research direction that could significantly improve our understanding of MS. By defining the role of endothelial cells in MS, we can explore new treatment strategies to protect endothelial cells, which should in turn prevent BBB breakdown and slow disease onset and progression, offering hope for more effective treatments that improve patient outcomes and quality of life.