The human brain is protected by a specialized and highly organized immune system that removes pathogens. Despite this immunological arsenal, certain viruses still manage to slip through and cause damage. One such virus is human herpesvirus type 1 (HHV-1), commonly known for causing cold sores. Individuals infected even once become lifelong carriers and hosts of the virus. This means that while treatments exist for herpes symptoms, eliminating its cause remains out of reach. The virus hides effectively in the host's nervous system ganglia, where it adopts a dormant (latent) form and can undergo reactivation. In some cases, HHV-1 can infect the central nervous system (CNS), leading to a life-threatening disease known as herpes simplex encephalitis. Most patients who survive this condition experience serious long-term neurological consequences. Scientific literature suggests that the virus may spread during reactivation to selected brain regions, where it can remain latent for the host's entire life without causing apparent clinical symptoms. Moreover, a growing body of research points to a possible link between HHV-1 presence in the brain and the development of neurodegenerative diseases, for e.g. Alzheimer's disease.

This research project proposes an innovative approach to regulating the cellular response to HHV-1 infection: activation of GLP-1 receptors (GLP-1R) in astrocytes. GLP-1Rs are located, among others, in hypothalamic neurons, enabling the regulation of metabolic pathways. An increasing number of studies show that GLP-1Rs are also present in other brain regions – not only in neurons – and their stimulation may beneficially influence the nervous system by reducing inflammation, mitigating damage, and supporting neuronal cell survival under stress and during neurodegenerative processes. Astrocytes are a type of glial cell (from the Greek *glia* – glue), forming the structural framework of the brain and playing a key role in maintaining its homeostasis – that is, the electrochemical, metabolic, and immunological balance necessary for proper neuronal function and overall brain health. In other words, neuronal well-being depends on functional astrocytes, which provide essential support. In recent years, the presence of GLP-1Rs has also been confirmed in astrocytes, opening new possibilities for modulating their processes – for instance, in the context of CNS infections. During HHV-1 infection, astrocytic function may be disrupted, leading to intensified inflammation and potential neuronal damage. The key question we aim to answer is **whether the activation of GLP-1Rs in astrocytes can limit the harmful effects of HHV-1 on these cells and indirectly protect neurons from infection-induced consequences.**

To investigate this, we will use primary murine astrocytes, which will be treated with GLP-1R activators (agonists) and then infected with a highly virulent strain of HHV-1. We will use modern laboratory techniques such as confocal microscopy, real-time gene expression analysis, and metabolic assays to characterize the cellular response. These methods will allow us to evaluate how GLP-1R activation affects the viral replication cycle, antiviral response, and cell viability. Specifically, we will examine whether GLP-1R stimulation can:

- interfere with viral entry and replication in astrocytes,
- enhance astrocyte survival during infection and reduce cellular stress,
- influence the astrocyte inflammatory response,
- affect the astrocytic secretion of metabolites that support neuronal function.

This will be the first study worldwide to investigate GLP-1R stimulation in the context of viral brain infections. The project proposes a novel therapeutic strategy during HHV-1 infection focused on strengthening the resilience of brain cells by regulating their function through GLP-1R stimulation. Additionally, we will determine which stage of the viral replication cycle is affected by GLP-1R agonists, providing key insights into HHV-1 replication in astrocytes. In the long term, this research may open new possibilities for supporting the functioning of brain cells, not only during HHV-1 infection but also in neurological diseases accompanied by inflammation and/or metabolic disorders. A better understanding of the mechanisms of the astrocytes' response to HHV-1 infection may contribute to developing new therapies to protect the brain from viral damage.