Each year, neurodevelopmental disorders affect a significant number of newborn babies, the prevalence of which is reported to be steadily increasing in recent years. According to the latest WHO report, globally 2 million children die annually in the first month of life. This report also indicated that premature birth and perinatal asphyxia are the leading causes of neonatal morbidity and mortality. Furthermore, pregnant women with moderate to severe COVID-19 were shown to be at much higher risk of preterm delivery, neonatal infection, and birth asphyxia. It has been proven that **the SARS-CoV-2 global pandemic has significantly increased the numbers of premature and complicated births, which often result in perinatal brain injuries in newborns.** The resulting disabilities of premature or asphyxiated babies typically involve moderate or severe neurological deficits, such as cerebral palsy, mental retardation, epilepsy, and spastic paresis, and seriously reduce the quality of life.

Unfortunately, there is currently no effective therapy protecting premature or injured neonatal brain from the spread of the insult, which features a sequence of events involving necrosis of neurons and glial cells, development of inflammatory processes, and malformation of brain structures (e.g., formation of aberrant myelin sheaths surrounding neurons). There is thus an urgent need for new treatment options that exert neuroprotective effects on the fragile developing brain and promote natural endogenous mechanisms leading to restoration of the nervous tissue cytoarchitecture and functions. One of the major objectives of potential therapy is to modulate brain neuroinflammation to make the local tissue microenvironment conducive to the initiation of natural, compensative processes, leading to restoration of the diseased nervous tissue.

Our project addresses the aforementioned issues and proposes the derivation of glial cells from MSCs located in Wharton's jelly (WJ) of human umbilical cord. Owing to MSCs' paracrine activity, resulting in the secretion of a spectrum of immunomodulatory and trophic factors, these cells hold great promise for therapeutic strategies in regenerative medicine. Taking into account the existence of a great number of biobanks for cryopreserving human umbilical cord components worldwide, this project focuses on WJ as a highly available source of MSCs. However, it should be taken into consideration that the cells of the nervous tissue have special metabolic requirements due to their unique functions in nerve signal transduction. This is why, in the next step of the project, by applying biomimetic molecules, the MSCs derived from WJ will be differentiated into oligodendrocytes, which are glial cells providing neurotrophic and energy support to neurons. Our previous studies also showed that oligodendrocytes can secrete anti-inflammatory cytokines (such as IL-10). Thus, we hypothesize **that the oligodendrocyte-derived secretome is specially tailored to the requirements of nervous tissue and therefore its content is adjusted to achieve communication between cells forming the developing central nervous system. We assume that generating oligodendrocyte progenitorss from MSCs of Wharton's jelly will allow us to combine the immunomodulatory and neuroregenerative capacity of the cell secretome**. The anti-inflammatory and regenerative potential of WJ-derived MSCs and oligodendrocytes generated from MSCs will be confirmed in ex vivo and in vitro culture systems with neonatal rat neurons and glial cells, as well as organotypic nervous tissue explants.

By applying this approach, the major results of our project should include elaborating the detailed protocol of deriving oligodendrocytes from WJ-derived MSCs by applying biomimetic, xeno-free molecules in physiologically normoxic conditions mimicking those typical of nervous tissue. Next, the anti-inflammatory and regenerative potential of WJ-derived MSCs and generated human oligodendrocytes will be assessed to evaluate their efficiency in nervous tissue protection and restoration. Finally, the new treatment options of MSCs and oligodendrocytes will be tested with the aim of increasing the secretion of neurotrophins and immunomodulatory molecules by the cells in question. Extracellular vesicles will also be isolated to determine whether the anti-inflammatory and regenerative cell potential is conferred by soluble factors or by exosomes. Taking these approaches together, the main goal of the study is to gain basic knowledge about the cell secretome and its properties and to present a new protocol of translational potential, as a new treatment option to cure selected neurodevelopmental disorders.