“Mitotherapy as a novel strategy for the modulation of immunometabolic phenotype of fibroblast-like synoviocytes (FLS) – a new avenue for the treatment of synovitis in horses”

Synovitis (SI) is one of the most common orthopedic diseases in horses of different age, breed and sex, which contributes to the development of osteoarthritis (OA). SI often eliminates horses from further sport activity and requires costly pharmacological intervention. Current treatments include complete rinsing of the affected joint and anti-inflammatory treatments, both systemic and local. Alternative methods include hyaluronic acid, platelet rich plasma and stem cells injections, yet none of them prevent OA development. On molecular level, synovitis is characterized by the loss of immunometabolic homeostasis between fibroblast-like synovicytes and macrophages, which in turn initiate the inflammatory reaction that underly disease development. One on its key factor is extensive proliferation of synoviocytes which results from mitochondria impairment and promote aggressive, pro-inflammatory phonotype o cells. Impaired mitochondria produce excessive amount of free radicals which triggers inflammatory state and enhanced angiogenesis that in turn leads to degenerative changes in the synovial membrane. As a consequence, this process results in damage to the articular surfaces, leading to irreversible changes in the locomotor system. Therefore, there is an urgent need to develop an effective method not only for the anti-inflammatory treatment of synovitis, but also for restoring the immunometabolic homeostasis of the affected joint.

The aim of the project is to develop an innovative, effective method of restoring the immunometabolic balance of joints in horses suffering from synovitis in order to prevent OA. For this purpose, our team has developed an innovative method of isolating mitochondria from peripheral blood, which are then administered to the affected joint. Although our preliminary data has shown that mitochondrial therapy is safe for horses, there are still many aspects that we intend to clarify within this project. These include: (i) understanding the mechanisms responsible for the internalization of transplanted mitochondria into synoviocytes, (ii) discovering the mechanisms regulating the transfer of mitochondria from synoviocytes to macrophages, (iii) evaluation of the immunomodulatory capacity of transplanted mitochondria, and (iv) evaluation of the clinical effectiveness of the therapy in horses suffering from synovitis.

The proposed project for the first time takes up a difficult subject at the intersection of molecular biology, translational medicine and clinical aspects of synovitis in horses. We aim to develop a new, previously unused treatment method in horses, based on the replacement of defective mitochondria in the affected tissue by restoring the immunometabolic balance. As a result of mitochondrial transfer, we expect that defective mitochondria in synoviocytic cells will be replaced by healthy ones, isolated from peripheral blood, which will lead to suppression of proliferative activity of synoviocytes, thus stopping osteoarthritis development. As part of the project, researchers will apply pioneering methods using the latest bioimaging equipment and molecular biology, allowing to verify the research hypotheses assumed in the project.

The proposed project, if it proves effective in horses suffering from synovitis, may in the future be used in human medicine to treat many other diseases at the root of which are mitochondrial defects.