Molecular Pathogenesis and Precision Antisense Oligonucleotide Therapy for BAG3-Related Myofibrillar Myopathy Type 6 Using Mouse and Cellular Models

Myofibrillar Myopathy Type 6 (MFM6) is a very rare, inherited muscle disease that usually appears in early childhood. It is caused by a mutation in the BAG3 gene – one of the key genes responsible for maintaining order within muscle cells. In individuals with this mutation, the body begins to produce an abnormal version of the BAG3 protein, which, instead of helping, causes harm – it leads to the accumulation of toxic protein aggregates that disrupt the function of muscles, including the heart muscle. Patients rapidly lose muscle strength, stop walking and breathing on their own, and many die before reaching adulthood. Unfortunately, there is currently no effective therapy that could stop or reverse the progression of the disease.

In our project, we aim to develop a precise method to treat this disease using tools of molecular biology – so-called antisense oligonucleotides (ASOs). These are short, synthetic RNA fragments that can recognize and block a specific disease-causing version of a gene – in this case, the mutated BAG3. Importantly, ASOs can act very selectively, meaning they can silence only the damaged gene while leaving the healthy one untouched. This is crucial, because complete BAG3 silencing leads to severe side effects – hence the importance of therapeutic precision.

In the first part of the project, we will focus on testing selected ASOs in cell models. For this purpose, we will use skin cells from patients with MFM6 and reprogram them in the laboratory into cardiac and skeletal muscle cells. This will allow us to create models that faithfully mimic the disease in vitro. We will examine whether our ASOs effectively reduce the amount of toxic proteins, restore normal cell function, and do not cause unwanted effects.

In the second phase, we will test the most promising ASOs in mouse models of the disease. These mice carry the human mutated BAG3 gene and develop symptoms similar to those seen in patients. We will evaluate not only the effectiveness of treatment but also the strategies for delivering ASOs to muscles – testing different methods, such as combining ASOs with molecules that facilitate transport to specific tissues. We will also examine the safety of the therapy and its impact on the whole body – including the heart, muscles, immune, and nervous systems.

The goal of the project is to develop a new, precise, and safe RNA therapy for patients with MFM6 – but its significance is much broader. The disease mechanism, involving the toxic effect of a mutated protein, is common in other rare and currently incurable conditions. Therefore, the technology developed in this project could become the basis for treating many other genetic disorders in the future. The project aligns with the advancement of personalized medicine, which aims to create therapies tailored to the specific patient and their genetic mutation.