Retinal dystrophies encompass a diverse range of inherited diseases that result in a progressive, severe, and irreversible loss of vision by causing structural and/or functional changes in the retina. Although a definitive cure is currently unavailable, research is underway to explore gene and cell therapies as potential treatments. The retina, responsible for converting light into visual signals transmitted to the brain, consists of specialized cells called photoreceptors. These cells, comprising rods and cones, are crucial components of the visual pathway, characterized by intricate and sophisticated structures, including a cilium. Due to the close association between retinal dystrophies and abnormalities in photoreceptor cilia, these conditions are often referred to as retinal ciliopathies. Depending on the specific disease, damage can primarily affect cones (which facilitate detailed vision and color perception), rods (essential for low-light and peripheral vision), or both simultaneously. Retinal ciliopathies can manifest as either exclusive visual impairment (non-syndromic retinal ciliopathies) or can be accompanied by other systemic symptoms (multi-syndromic retinal ciliopathies), especially involving kidneys (renal ciliopathies).

Retinitis Pigmentosa, the most prevalent retinal ciliopathy, occurs in approximately 1 in 3500 individuals and stands as the leading cause of hereditary blindness worldwide. It affects up to 2.5 million people, frequently manifesting during childhood and leading to irreversible disability. While most retinal ciliopathies are confined to the eye, some may exhibit additional symptoms beyond ocular manifestations, such as Usher syndrome or Bardet-Biedl syndrome. In such cases, they are classified as multi-syndromic retinal ciliopathies. Except the retina, the second most affected organ is kidney with clinical manifestations of renal ciliopathies that vary widely, but common features include kidney cysts, renal impairment, hypertension, and sometimes extrarenal involvement. Management typically involves supportive care, treating symptoms, and monitoring kidney function. In severe cases, kidney transplantation may be necessary. There is no causative treatment available. The most common renal ciliopathy, autosomal recessive polycystic kidney disease (ARPKD) alone affects 1:2,500 in the EU.

Ciliopathies often remain unnoticed until the advanced stages when symptoms become apparent. The presence of specific genes within an individual's DNA determines the likelihood of developing a retinal ciliopathy. Consequently, these hereditary conditions cannot be prevented. However, advancements in genetic editing allow scientists to manipulate the genetic information in our DNA, aiming to repair or eliminate faulty genes. In the case of retinal ciliopathies, the challenge lies in the fact that multiple genes can contribute to the disease, making gene therapy approaches complex. These various genes involved in retinal ciliopathy pathogenesis encode specific proteins that interact with each other. By identifying these protein interactions, researchers can gain insights into the intricate mechanisms underlying retinal ciliopathies and propose innovative causative treatments.

The primary objective of the project is to elucidate the mechanisms underlying both non-syndromic retinal ciliopathies and multi-syndromic retinal ciliopathies with renal involvement using system and molecular biology approaches, with the aim of identifying new targets for diagnosis and treatment. Based on previously constructed PPI networks for retinal ciliopathy genes, we have selected several candidate proteins, being common interactors for multiple causative genes of retinal ciliopathies and in current project, we plan to associate them with the retinal ciliopathies phenotype to evaluate the impact of the candidate genes silencing on the healthy photoreceptors phenotype and to investigate the effects of augmentation therapy for these genes in retinal ciliopathies animal models. Our methodology will involve cloning and cell culture techniques, followed by Mass Spectrometry (MS) analysis to generate protein interaction data. In parallel, we will conduct in vivo studies using transgenic non-syndromic and multi-syndromic retinal ciliopathies mice to test selected drug candidates and assess retinal function through electroretinography. These two workflows will complement each other, and the results obtained from each approach will be examined and integrated to provide a comprehensive understanding of different aspects of ciliopathies.