Mucolipidosis type IV (MLIV) is an autosomal recessive developmental disorder with abnormal brain, eye and gastric functions. It is caused by mutations in the TRPML1 (also called mucolipin 1, MCOLN1) protein. MLIV is characterized by an abnormal buildup of fatty materials (lipids) in the cells, leading to organ and nerve damage. Children with MLIV appear normal at birth but develop signs of central nervous system deterioration during the first year of life. Symptoms include progressive mental and psychomotor retardation and eye disorders. Many patients never walk. Currently, there is no curative treatment option available. Treatment is symptomatic and supportive. Symptoms associated with clouding of the cornea may be treated by the use of contact lenses and/or artificial tears. Intense physical, occupational and speech therapy are also of benefit. Iron replacement is utilized for patients with anemia.

The protein which is mutated in MLIV patients (TRPML1) is an ion channel which is expressed in the membranes of lysosomes found in almost all cells of the human body. Ion channels are proteins that allow the flow of ions across membranes. If the channel resides in the plasma membrane it regulates the flow of ions from the lumen of the cell (cytosol) into the extracellular space or vice versa. In case of ion channels in the membrane of lysosomes which are tiny organelles within cells, they allow the flow of ions from the lumen of the lysosome into the cytosol or vice versa. Lysosomes are crucial for normal cell function and survival. Besides degradation of macromolecules, the lysosome is involved in various cell processes, including secretion, plasma membrane repair, cell signalling, and energy metabolism. The pH of the lysosome lumen is about 4.5 - 5.0 which is optimal for the lysosomal enzymes involved in hydrolysis, analogous to the activity of the stomach. Acidification and maturation of endolysosomal organelles including lysosomes is a highly critical process mediated by a large number of ion channels and transporters. Malfunction of these lysosomal membrane proteins results in various pathophysiological conditions and has been implicated in neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and lysosomal storage disorders such as MLIV. The endolysosomal transportome comprises at least 70 different proteins which, with few exceptions, still remain largely unexplored. Technical improvements including the ability to directly measure ion channel currents across lysosomal membranes (endolysosomal patch clamp technique) have now made it possible to directly assess the function of endolysosomal ion channels and transport proteins, opening up an unprecedented opportunity to investigate in-depth the physio- and pathophysiological roles of the multiple still barely characterized members of the endolysosomal transportome.

Aim of this proposal is to explore novel therapeutic strategies for MLIV with the focus being on the identification and characterization of potential surrogates for TRPML1 in
the endolysosomal transportome. Once identified, specific stimulation of such a surrogate with small molecule activators/modulators may compensate for the loss of TRPML1. To qualify as surrogate, the candidate must fulfill a range of criteria: 1. It must be expressed in the membranes of lysosomes. 2. It must be an ion channel transporting cations from the lumen of the lysosome into the cytosol. TRPML1 is a non-selective cation channel permeable for cations (not anions) as diverse as sodium, calcium or iron. Ideally, the surrogate would also be a largely non-selective cation channel. 3. The candidate must show a similar expression pattern as TRPML1. This means it must be expressed in particular in the same brain regions and within these brain regions in the same cells that would normally express TRPML1.

After identifying a suitable candidate, high-throughput screenings shall be performed to identify small molecule agonists for the surrogate protein. In a second step, specificity and potency of small molecule activators of the surrogate proteins shall be assessed in vitro. In a third step the compound effect in cellular models of MLIV will be analysed. In the final step the effect of the compound in the MLIV animal model (TRPML1 knockout mouse) will be examined.