**From Diagnosis toward Therapy: Building an International Translational Research Pipeline for Ultra-Rare CFC4 Syndrome**

Cardio-facio-cutaneous syndrome type 4 (CFC4) is an ultra-rare genetic disorder belonging to the RASopathy spectrum, caused by pathogenic variants in MAP2K2, encoding the MEK2 kinase, a key component of the RAS/MAPK signaling pathway. The molecular mechanisms underlying CFC4 remain insufficiently characterized, and no disease-modifying therapy is currently available.

This lecture will introduce MEK2 Research, a research-focused foundation established in 2024 following the CFC4 diagnosis of the founder's daughter. The foundation aims to build an international, multidisciplinary translational research programme that moves from understanding an individual genetic variant towards identifying potential therapeutic strategies for a broader patient population, following an N-of-1 to N-of-many approach.

The presentation will provide an overview of the foundation's research pipeline, encompassing clinical phenotyping, the development of patient-derived cellular models, functional characterization of RAS/MAPK signaling, metabolic profiling, molecular modelling, structural biology and the development of animal models.

Particular attention will be given to pharmacological strategies, including drug repurposing, planned compound screening using high-content cellular phenotyping (Cell Painting) and ERK phosphorylation assays, and the exploration of more selective MEK inhibitors. The lecture will also introduce ongoing research into oligonucleotide-based therapies (ASOs and siRNAs).

The scientific section will highlight recent publications arising from collaborations supported or initiated by MEK2 Research, including a clinical case report describing the MEK2 E207K variant, a comprehensive clinical review of CFC4, a review of its molecular pathogenesis, and recent molecular docking and dynamics studies of mutant MEK2 conducted in collaboration with the Maj Institute of Pharmacology, Polish Academy of Sciences.

Beyond laboratory research, the presentation will briefly address the foundation's patient advocacy activities and its efforts to strengthen the rare disease research ecosystem.

The presentation will discuss how coordinated collaboration between scientists, clinicians and patient organisations can accelerate the development of therapies for ultra-rare genetic diseases.