MyRIAD

(Micro)RNA and informatics approaches for diagnosis, prognosis and treatment of Alzheimer's disease and Dementia

Neurodegenerative disorders are often associated with genetic causes that manifest with changes in core cellular mechanisms and changes in the expression of specific genes, resulting in milder to a very severe phenotype. Emerging evidence suggests that genes, with pathogenic variants associated with early onset neurodegeneration, are dysregulated in conditions, such as Alzheimer's disease (AD). The advent of omics approaches highlighted multiple novel pathways likely involved in AD, how-ever functional approaches are lacking. Moreover, among novel players in neurodegeneration are microRNAs (miRs), as well as extracellular vesicles (EVs) mediating cell to cell communication, but their biomarker or therapeutic potential is not understood. There is an urgent need for a better under-standing of mechanisms underlying AD and the spectrum of undiagnosed diseases in the wider population.

Early detection is a key factor in modifying disease course. To date, definitive diagnosis often re-quires post-mortem examination of brain tissue. While a number of biomarkers are available (e.g. PET, MRI, CSF markers), their utility is limited by costs or poor scalability. Circulating and EV-enriched miRs hold a promising potential as diagnostic and prognostic non-invasive biomarkers of AD and neurodegenerative conditions. One of the earliest reported events in AD is redox imbalance, and by-products of RNA oxidation have been detected in patients with AD. Our data supports oxidised miRs, only recently discovered, as a potential as specific biomarkers of early pathology.

Specific proteins which accumulate during AD, have been characterised, however their targeting presents significant challenges due to the need for their tight regulation. Lysosomal dysregulation is strongly associated with AD and our preliminary data suggests that changes in V-ATPase function, which affect lysosomal function and metabolism, may be an early and targetable pathogenic mechanisms in AD to restore lysosomal function and metabolic homeostasis. Other mechanisms which may underlie neuronal vulnerability and initiate adverse cellular processes several years before symptoms, is oxidative damage to DNA, proteins and lipids. Our data also suggests pathogenic miR oxidation and supports therapeutic regulation of multiple genes underlying AD using miR/oxi-miR and RNA-based approaches.

This timely proposal combines disruptive findings on mechanistic basis of AD with drug developmental opportunities of novel RNA-based interventions by uncovering novel mechanisms of neurodegeneration applicable beyond AD. MyRIAD will address the unmet need for non-invasive biomarkers, using omics and data science approaches to comprehensively investigate circulating and miRs and oxi-miRs within extracellular vesicle profiles in the context of biomarkers and pathogenic processes underlying AD. An in silico model of neurodegeneration built in this project using omics and data science, clinical datasets and complementary in vitro screening in models relevant to human physiology, will be validated using RNAs and ASOs, which will simultaneously validate novel targets and provide proof-of-principle for their therapeutic regulation using RNA-based approaches. By identifying the potential of RNA-based non-invasive biomarkers and providing proof-of-principle for the use of RNA approaches as therapeutics for neurodegeneration, this research has the potential to advance healthcare and societal wellbeing.

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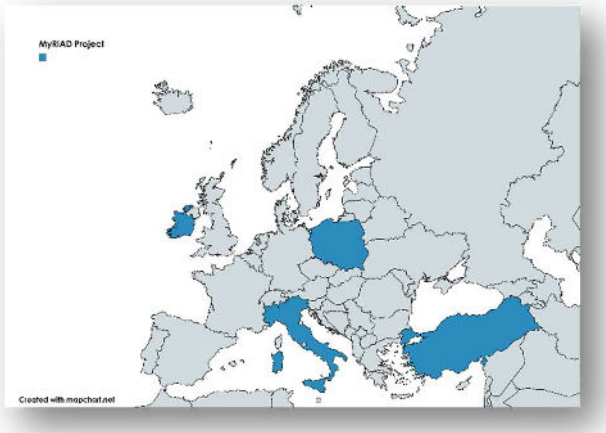

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