THE CYPRUS INSTITUTE OF
NEUROLOGY & GENETICS

PHD TOPICS

APPLICATION DEADLINE: 10/05/23 12:00 NOON

ACADEMIC YEAR 2023-2024

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Message from the Dean

Dear Prospective PhD Candidates,

I am pleased to announce the PhD Research Projects offered by the Cyprus Institute of Neurology and Genetics (CING) for 2023-24.

At the CING, we are committed to producing a high calibre research output that contributes to improving the quality of human life in Cyprus and worldwide. We aim to challenge our students with a wide variety of research projects and concepts, and we enforce international standards of excellence throughout our curricula.

Our programmes aim to train and expose you to competitive research and a stimulating scientific environment. We will provide you with the knowledge and experience needed to enable you to cope with future demands and set you on a promising career path, considering how competitive the employment market has become. Our graduate PhD students have successfully entered the labour market, acquiring positions in Cyprus and abroad.

As you explore science and learn with us, you will have many opportunities to make new friends and acquire life-long skills. You will meet dedicated and experienced scientists who will mentor and guide you. CING departments headed by highly accomplished scientists and doctors will host you. You will have the opportunity to work in a professional environment, learn state-of-the-art techniques and how these are applied to solve real everyday problems, which benefit patients and our community. The present pandemic shows us that we need to intensify our efforts to advance knowledge through scientific discovery and innovation. Join us in this quest and experience the exciting promise that molecular biology and genetics hold for advancing the frontiers of both science and medicine.

We designed this booklet to provide helpful information about the currently available PhD positions and topics, the hosting departments and the research supervisors. We are all here to assist you in developing critical thinking and accomplishing your tasks, to challenge and support you to prepare for a prosperous professional career.

We are looking forward to receiving your applications and joining hands in the fight to reduce the suffering caused by human diseases and to create a better tomorrow, especially for our patients!

Prof Kyproula Christodoulou

Deadline for PhD applications: 10/05/2023 (12noon, Cyprus Time).

The topic is eligible for the following Program(s):

- ✓ PhD in Neuroscience, Full-Time
- ✓ PhD in Molecular Medicine, Full-Time
- ✓ PhD in Medical Genetics, Full-Time

T1: Gene therapy for Charcot-Marie-Tooth Type 4D

Hosting Department/Clinic/Group:
Neuroscience Department
(https://www.cing.ac.cy/en/about-us/clinical-sciences/nce)

Contact Persons:
Prof Kleopas Kleopa (kleopa@cing.ac.cy)
Dr Irene Sargiannidou (irenes@cing.ac.cy)

Abstract:
Charcot-Marie-Tooth Type 4D (CMT4D) is a rare, recessively inherited severe childhood onset demyelinating neuropathy, characterized by distal muscle weakness and atrophy, foot deformities, and sensory loss affecting all modalities. It is caused by loss-of-function mutations in N-myc downstream-regulated gene-1 (NDRG-1) gene. Although *NDRG1* is ubiquitously expressed and has been proposed to play a role in growth arrest and cell differentiation, possibly as a signaling protein shuttling between the cytoplasm and the nucleus, a particular high expression level is detected in Schwann cells and peripheral neuropathy remains the main manifestation of the disease. There is currently no effective treatment for CMT4D. Therefore, we propose to develop a gene replacement therapy by replacing the human *NDRG1* gene specifically in Schwann cells throughout the peripheral nervous system. This approach will be tested at first in the *Ndrg1* knockout mouse model of the disease. A cell-specific myelin protein zero (MPZ) promoter will be used in order to target expression of the human *NDRG1* coding sequence in myelinating Schwann cells. The stretcher mouse model, with total Ndrg1 deficiency which displays normal initial myelination and a transition to overt pathology between weeks 3 and 5 will be used. Overall, it represents an authentic model of CMT4D that recapitulates the major pathological aspects of the disease and provides the opportunity to test therapeutic approaches. The AAV9 viral vector, which is currently used in clinical trials for other disorders, will be used to deliver the gene by the clinically translatable route of lumbar intrathecal injection. The level of pathology rescue will be evaluated both following pre- as well as with post-onset intervention by motor behavioral, electrophysiological, and morphological analysis 2 months after treatment, in order to provide a proof of principle for clinical translation.

The topic is eligible for the following Program(s):

- ✓ PhD in Medical Genetics, Full-Time
- ✓ PhD in Molecular Medicine, Full-Time

T2: Effects of ER stress on glycogen metabolism

Hosting Department/Clinic/Group/Unit:
Biochemical Genetics

Contact Persons:
Dr Petros P. Petrou (petrosp@cing.ac.cy)

Abstract:
Endoplasmic reticulum (ER) stress refers to a cellular state characterized by the accumulation of misfolded or unfolded proteins within the ER. This activates an evolutionary conserved cell signalling pathway known as the Unfolded Protein Response (UPR) aiming at restoring ER homeostasis and promoting cell survival [1]. ER stress occurs both under physiological conditions such as cell development and differentiation and is also a hallmark of pathological states including insulin resistance and diabetes, neurodegenerative diseases and cancer. Thus, understanding the cellular and molecular mechanisms of the cellular response to ER stress may reveal attractive sites for therapeutic intervention.

ER stress and the activation of the UPR pathway has profound effects on metabolic processes, particularly glucose metabolism. We have recently identified an ER stress-induced response of mouse myoblasts resulting in a net increase of glycogen levels and the build-up of intracytoplasmic glycogen clusters [2]. The formation of the above clusters induced by ER stress was found to depend on the expression of the glycogen-binding protein Stbd1 and support cell survival during ER stress. Building on this previous work, the project aims to: a) shed light on the biochemical and molecular basis of the impact of ER stress on glycogen metabolism, b) investigate cell type-dependent similarities and differences of ER stress-induced effects on glycogen metabolism and c) examine the specificity of the above cell response by addressing glycogen metabolism in response to additional cell stress stimuli such as oxidative stress and starvation. The above questions will be addressed in vitro in cell lines of muscle (skeletal and cardiac) and liver origin, representing the primary sites of glycogen storage and results will be accordingly validated in mice.

References

[1] Hetz C., Zhang K., Kaufman R. J. Mechanisms, regulation and functions of the unfolded protein response. Nat. Rev. Mol. Cell Biol. 2020;21(8):421–438.

[2] Lytridou A. A., Demetriadou, A., Christou, M., Potamiti, L., Mastroyiannopoulos, N. P., Kyriacou, K., Phylactou, L. A., Drousiotou, A., Petrou, P. P. J. Cell Sci. 2020; 133(20): jcs244855,

Project plan (years 2, 3 & 4):

Year 2: Assessment of intracellular glycogen levels, glycogen clustering and investigation of the effects of ER stress induction on the expression and activity of proteins implicated in glycogen metabolism and autophagic glycogen degradation in muscle- and liver-derived cell lines.

Year 3: The role of Stbd1 on glycogen metabolism in the different cell lines in relation to ER stress. The above involves the study of the effects of Stbd1 loss of function or overexpression on glycogen metabolism (including autophagic glycogen degradation) following ER stress activation in muscle and liver-derived cell lines. Validation of the results in Stbd1 knockout mice.

Year 4: Assessment of the biological significance of the effects of ER stress on glycogen metabolism (evaluation of cell viability, apoptosis during ER stress). In vivo validation in mice. Investigation of the specificity of the ER stress-induced effects on glycogen metabolism. This involves the induction of additional types of cellular stress (e.g oxidative stress, starvation) and the assessment of parameters related to glycogen metabolism.

The topic is eligible for the following Program(s):

- ✓ PhD in Medical Genetics, Full-Time
- ✓ PhD in Molecular Medicine, Full-Time
- ✓ PhD in Neuroscience, Full-Time

T3: Computational Investigation on the Progression of Monoclonal Gammopathies to Multiple Myeloma

Hosting Department/Clinic/Group/Unit:
Bioinformatics Department

Contact Persons:
Prof George Spyrou, (georges@cing.ac.cy)
Dr Anastasis Oulas (anastasioso@cing.ac.cy)
Dr George Minadakis (georgem@cing.ac.cy)
Dr Margarita Zachariou (margaritaz@cing.ac.cy)
Dr Marios Tomazou (mariost@cing.ac.cy)

Abstract:
Multiple Myeloma is a chronic malignancy characterized by slow progression and recurrences. Currently there is no effective cure since eventually the disease develops resistance to all the available therapeutic approaches. Although recent advances have expanded our understanding of the cellular functions associated with health to disease transition, recurrence and response to therapy, critical aspects of this complex pathology remain to be elucidated. Application of omics technologies, and bioinformatics approaches on highly annotated samples obtained from all informative states (monoclonal gammopathy of undetermined significance [MGUS], smoldering MM [sMM], active MM [MM]) could identify biological pathways and molecules responsible for the onset, progression and resistance to therapy of Multiple Myeloma [1]. In parallel, particular emphasis should be given to elucidating the health determinants and risk factors associated with progression to active MM from MGUS/sMM by using extensive demographic, lifestyle and exposure datasets.

The PhD Candidate will work in the framework of a big European Consortium in the Project "ELMUMY" funded by the European Union (Call: HORIZON-MISS-2021-CANCER-02, Research and Innovation actions supporting the implementation of the Mission on Cancer, Topic: HORIZON-MISS-2021-CANCER-02-03). This Project will bring together clinicians and researchers aiming to integrate epidemiological, clinical and experimental datasets in order to create a molecular model of cellular processes associated with the onset of active MM and response to therapy. Specifically, in the Bioinformatics-related Work Package where the PhD candidate will contribute, we are going to organize the data information flow, integrate omics and other available data generating a comprehensive holistic profile of each biological state, computationally highlight the underlying molecular mechanisms by using the generated holistic profiles, propose candidate repurposed drugs, discover complex patterns of biomarkers using omic profiling, contribute in the development of predictive AI models for MM onset [2-6].

Project plan

Years 2,3: Omics data integration for creating a molecular model for MM onset and progression

Year 4: Computational Biomarker Discovery and Drug repurposing

References

1. Bolli N, Maura F, Minvielle S, Gloznik D, Szalat R, Fullam A, Martincorena I, Dawson KJ, Samur MK, Zamora J, Tarpey P, Davies H, Fulciniti M, Shammas MA, Tai YT, Magrangeas F, Moreau P, Corradini P, Anderson K, Alexandrov L, Wedge DC, Avet-Loiseau H, Campbell P, Munshi N. Genomic patterns of progression in smoldering multiple myeloma. Nat Commun. 2018 Aug 22;9(1):3363.
2. Tomazou M, Bourdakou MM, Minadakis G, Zachariou M, Oulas A, Karatzas E, Loizidou EM, Kakouri AC, Christodoulou CC, Savva K, Zanti M, Onisiforou A, Afxenti S, Richter J, Christodoulou CG, Kyprianou T, Kolios G, Dietis N, Spyrou GM. Multi-omics data integration and network-based analysis drives a multiplex drug repurposing approach to a shortlist of candidate drugs against COVID-19. Brief Bioinform. 2021 Nov 5;22(6):bbab114.
3. Karatzas E, Zachariou M, Bourdakou MM, Minadakis G, Oulas A, Kolios G, Delis A, Spyrou GM. PathWalks: identifying pathway communities using a disease-related map of integrated information. Bioinformatics. 2020 Jul 1;36(13):4070-4079.
4. Minadakis G, Zachariou M, Oulas A, Spyrou GM. PathwayConnector: finding complementary pathways to enhance functional analysis. Bioinformatics. 2019 Mar 1;35(5):889-891.
5. Zachariou M, Minadakis G, Oulas A, Afxenti S, Spyrou GM. Integrating multi-source information on a single network to detect disease-related clusters of molecular mechanisms. J Proteomics. 2018 Sep 30;188:15-29.
6. Oulas A, Minadakis G, Zachariou M, Sokratous K, Bourdakou MM, Spyrou GM. Systems Bioinformatics: increasing precision of computational diagnostics and therapeutics through network-based approaches. Brief Bioinform. 2019 May 21;20(3):806-824.

The topic is eligible for the following Program(s):
- ✓ PhD in Medical Genetics, Full-Time
- ✓ PhD in Molecular Medicine, Full-Time

T4: Functional analyses of candidate repressors of γ-globin gene expression

Hosting Department/Clinic/Group/Unit:
Molecular Genetics Thalassaemia Department

Contact Persons:
Dr. Marios Phylactides (mphylact@cing.ac.cy)

Abstract:
Reactivation of γ-globin for the production of HbF can ameliorate β-thalassemia and sickle cell disease. Although therapeutic strategies involving addition of a functional β-globin gene or genome editing for γ-globin reactivation are promising, the high cost and limited availability together with safety and efficacy issues constrain such therapies to younger patients with access to sophisticated clinical care. The only FDA-approved HbF-inducing drug is hydroxyurea but its use in β-thalassemia patients is restricted because of efficacy and toxicity reasons. Luspatercept, a recently FDA/EMA-approved medication, despite its benefits for β-thalassemia patients, has limited effectiveness in severely affected patients. Additionally, the multiple functions of some of the most prominent regulators of γ-globin expression, such as BCL11A and LRF, make their targeting with small molecules a real challenge. Hence, reactivation of γ-globin with pharmacological means is still a useful and much needed avenue to explore. **To identify novel γ-globin repressors as potential druggable targets**, we performed a custom CRISPR/Cas9 knockout screen targeting 293 genes selected from previously published literature. Screening this library in the HUDEP-2 cell line resulted in the identification of six candidate genes.

Project details: Six candidate repressor genes have been identified through a CRISP Cas9 knock-out screen of 293 targets and this studentship aims to validate and perform functional analyses on at least two of these candidate genes and investigate their potential to ameliorate key pathophysiological features of β-haemoglobinopathies. As there is already an ongoing project investigating some of these candidate genes, the precise genes to be analysed will depend on the progress of this current investigation.

The candidate genes will be knocked out in the HUDEP2 erythroid progenitor cell line to validate the preliminary screening results. This will be followed by analyses of the effects of the genes on the differentiation profile of the HUDEP2 cells and on known key players that regulate γ-globin gene expression. Depending on the results generated and the genes involved, transcriptomics and discovery proteomics may be utilised at a later stage to complement the studies carried out for the investigation of the biological

pathways in which the genes are involved. Functional studies will be carried out to determine their mode of action and their interacting partners.

The techniques expected to be employed during the project include cell culture, gene knock-out through use of CRISPR/Cas9 via lentiviruses or RNPs, flow cytometry and standard molecular biology procedures such as DNA extraction/sequencing/cloning, PCR, real time PCR, western blotting, etc.

As part of the PhD work, the role of two shortlisted genes in the regulation of the expression of the γ-globin genes (*HBG1* and *HBG2*) will carried out.

Project Plan Years for 2-4

Year 2

VALIDATION OF TWO CANDIDATE GENES FOR THE UPREGULATION OF HBF IN HUDEP-2

1. **Literature investigation of the two candidate genes identified through the CRISPR screen analysis:** For two shortlisted genes, we will perform detailed investigation of the available literature to extract information relating to their possible involvement in erythropoiesis, globin gene expression and haemoglobinopathies.
2. **Validation of the results of our custom CRISPR screen in HUDEP-2 cells:** It is important to experimentally validate that depletion of the two genes indeed results in the upregulation of γ-globin gene expression before performing any follow-up experiments on their mechanism of action. The validation experiments will be performed in HUDEP-2 cells. Ribonucleoprotein (RNP) delivery by nucleofecting RNP SpCas9:sgRNA complexes will be initially employed to deplete each of the two genes in HUDEP2 cells but if this proves to be a problem, then viral-mediated delivery will be employed instead.

Year 2 and 3

BASIC INVESTIGATION INTO THE MECHANISM OF ACTION OF THE CANDIDATE GENES IN HUDEP-2 AND PRIMARY ERYTHROID PROGENITORS:

HUDEP-2 and primary erythroid progenitors will be used for a number of basic investigations into the mechanism of action of the two candidate genes. The expression of a number of key genes involved in erythroid differentiation and haemoglobin switching will be evaluated. Cell staining with differentiation markers together with cytocentrifugations will be performed for the assessment of the erythroid maturation and cell morphology.

Year 3 and 4

CRISPR-MEDIATED DEPLETION OF THE GENE OF INTEREST FOLLOWED BY RNA-SEQ AND PROTEOMICS

If the approaches above do not adequately explain the mechanism of action of the candidate genes, then a proteomics and transcriptomics approaches can then be utilised to further out understanding of their biological role in regulating γ-globin expression.

Year 4

STUDY THE EFFECT OF DEPLETION OF THE TWO CANDIDATE GENES IN PRIMARY ERYTHROID PROGENITORS FROM B-THALASSAEMIA PATIENTS

To evaluate if the depletion of the two genes results in clinically meaningful γ-globin upregulation, primary erythroid progenitors will be isolated from fresh peripheral blood of β-thalassaemia patients, the two genes will be knocked out in them, and the effect on the disease phenotype will be investigated.

The topic is eligible for the following Program(s):

- ✓ PhD in Medical Genetics, Full-Time
- ✓ PhD in Molecular Medicine, Full-Time

T5: Mapping breakpoints and identifying cryptic chromosomal rearrangements using next-generation cytogenomic tools

Hosting Department/Clinic/Group/Unit:

Cytogenetics and Genomics Department/Clinical Genetics Clinic

Contact Persons:

Prof Carolina Sismani (csismani@cing.ac.cy)

Dr Constantia Aristidou (constantiaa@cing.ac.cy)

Abstract

Chromosomal rearrangements, including structural variations (SVs), contribute significantly to the development of human genetic diseases. In routine genetic investigation, they can be identified using conventional cytogenetic and molecular approaches, including karyotype analysis, fluorescence in situ hybridisation (FISH), and array comparative genomic hybridisation (array-CGH). However, some of these methods can be considerably time-consuming, whilst others are limited by their resolution and therefore unable to detect cryptic rearrangements or accurately delineate the SV breakpoints. As a result, there is no single comprehensive test to allow detailed characterization of all types of chromosomal abnormalities. Whole-genome and long-read sequencing approaches are currently applied for the detection of such rearrangements; however, the high cost and complexity of analysis may prevent these methods from being widely used in a research setting. Optical Genome Mapping (OGM) is a next-generation cytogenomic tool based on reading uniformly-spaced labels throughout long DNA molecules, enabling the genome-wide identification of changes in copy number and position of sequence at a high resolution.

The aim of this PhD project is to apply OGM for the investigation of patients with intellectual disability (ID) and other congenital developmental disorders in order to detect any cryptic SVs and characterize them in detail with accurate delineation of their breakpoints. The test population will include unresolved cases with negative prior testing, structural variation (SV) carriers and families with unexplained abnormal phenotype, as well as new cases referred to the Department of Cytogenetics and Genomics for investigation. As a result, this next-generation cytogenomic tool will offer new insights into the genetic aetiology of ID and developmental disorders by revealing novel candidate genes and disease mechanisms.

This project will begin upon approval by the National Bioethics Committee.

Project Plan for years 2, 3 and 4

During **year 2,** patients will be recruited after signing the appropriate consent form. The test samples will be categorized into 3 groups: Group 1 will include unresolved cases with negative prior testing; Group 2 will include affected carriers of balanced SVs, that do not explain the patient's phenotypes; Group 3 will include new cases, referred to the Department of Cytogenetics and Genomics for investigation.

Initially, ultra-high molecular weight DNA will be isolated from fresh/frozen blood samples or cryopreserved lymphoblastoid cell lines, followed by labelling and processing on a Bionano Saphyr instrument. Next, OGM data will be analysed and filtered accordingly using specific pipelines allowing detection of rare SVs and copy number variants (CNVs).

In year 3, the novel SVs/CNVs detected by OGM will be validated by other methodologies such as Real-time PCR or FISH. Furthermore, each SV will be studied in depth to assess its functional impact, e.g. check for overlaps with coding genes or disruptions of topological domains. Where necessary, functional studies will be performed to confirm the association of the patient's phenotype with the genetic findings.

For patients with previously detected genetic aberrations, any additional observations and complexity revealed by OGM will be registered and assessed.

In year 4, all experiments relevant to functional studies will be finalized and clinical correlations will be derived. All data will be gathered and conclusions will be drawn regarding the performance of OGM, its practical applicability and possible target patient groups. Recommendations will also be made regarding its use in clinical research.

The research outcome of the project will be published in at least one peer-reviewed scientific journal and presented in at least one national/international scientific conference. Once all experimental procedures have been finalized, the PhD thesis report will be prepared towards the end of year 4.

The topic is eligible for the following Program(s):

- ✓ PhD in Medical Genetics
- ✓ PhD in Molecular Medicine
- ✓ PhD in Neuroscience

T6: Whole transcriptome profiling of PBMC subsets of Multiple Sclerosis patients to identify disease specific gene expression profiles

Hosting Department/Clinic/Group/Unit:
Molecular Virology Department

Contact Persons:
Dr Jan Richter (richter@cing.ac.cy)
Dr George Krashias (georgek@cing.ac.cy)
Prof Christina Christodoulou (cchristo@cing.ac.cy)

Abstract:
Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the CNS, characterized by substantial clinical and biological heterogeneity. Up to 85% of MS patients develop the relapsing-remitting (RR) course of MS, characterized by periodic neurologic deterioration followed by partial or complete remission, and several RR MS subjects eventually evolve to secondary progressive (SP) MS, where worsening of neurologic function occurs in the absence of recognizable relapses. Approximately 15 % of MS patients develop the primary progressive (PP) course from onset of the disease. However, information regarding key gene expression and genetic pathways related to each clinical form is still limited. In addition, the transition from relapsing-remitting to progressive forms is not totally understood.

For the purpose of this study, in collaboration with the clinic C of the Cyprus Institute of Neurology and Genetics, blood samples will be obtained from patients with clinically definite MS as well as from healthy controls (HC) matched for age and gender. Immune cell subsets (T-cells, B-cells, NK-cells) will be isolated and separated from the Peripheral blood mononuclear cells (PBMCs) using a high-throughput flow cytometer. Following RNA extraction, sequencing will be performed on a NExtseq 2000 for mRNA, lncRNA, miRNA and circRNA (RNA-seq).

With support by the Bioinformatics department, the RNA-seq data obtained will be analysed to evaluate differential gene expression, identify up or downregulated pathways and association of these with specific immune cell subsets. The results of this study will contribute to our understanding of disease onset and progression, help to identify or repurpose new potential drugs as well as shed further light on the potential role of viruses in MS.

Year 2:

- Protocol optimization for (a) isolation of highly purified T cells, B, cells and NK cells (b) isolation of RNA, (c) sequencing on a NExtseq 2000 for mRNA, lncRNA, miRNA and circRNA (RNA-seq)
- Training on bioinformatics tools
- Initiate the collection of blood samples from MS patients and healthy controls

Year 3:

- Finalize the collection of blood samples from MS patients and healthy controls
- Isolation of highly purified T cells, B cells, and NK cells, followed by the isolation of RNA and s sequencing on a NExtseq 2000 for mRNA, lncRNA, miRNA and circRNA (RNA-seq)
- Initiate the analysis of RNA-seq data

Year 4:

- analysis of differential gene expression
- pathway analysis of up- or downregulated genes and correlation with disease status and/or pharmaceutical intervention
- analysis of association of gene expression with immune cell subsets
- Publish at least one article on a peer-reviewed journal -Thesis write-up.

The topic is eligible for the following Program(s):

- ✓ PhD in Medical Genetics
- ✓ PhD in Molecular Medicine
- ✓ PhD in Neuroscience

T7: Treatment of 2 models of familial Alzheimer's disease with high fat feed to evaluate the disease's phenotype through proteomic and metabolic analysis.

Hosting Department/Clinic/Group/Unit:
Neuropathology Department

Contact Persons:
Dr Elena Panagiotou Worth (panagiot@cing.ac.cy)

Abstract:
Alzheimer's disease (AD) is a global epidemic now affecting over 47 million people worldwide. This number is projected to reach 76 million by 2030 (Alzheimer's Association- www.alz.org). Furthermore, AD poses a humongous financial cost in both indirect (lost wages, family planning costs, etc.) and direct costs (medications, doctor appointments, public health burden). The current cost of AD in Europe is about €200 billion annually and is projected to reach €250 billion by 2030 (www.alzheimer-europe.org) whereas the cost in the US was $290 billion for the year 2019 (Alzheimer's Association, alz.org). It should be noted that there is a 43% increase in expected costs from 2008 to 2030, again indicating the exponential increase in both AD patients and their needs. Currently, there's no cure or effective therapy for AD and once an individual begins displaying symptoms such as memory loss there is inevitable deterioration leading to death. Amyloid deposition starts up to twenty years before symptoms can be diagnosed in vivo by PET scanning.

According to the amyloid hypothesis of Alzheimer Disease (AD) the deposition of prefibrillar and fibrillar Aβ peptide sets off pathogenic cascades of neuroinflammation and neurodegeneration that lead to synaptic and neuronal loss and cognitive decline. Various approaches to reduce amyloid load by reducing prefibrillar production of the Aβ peptide or enhance amyloid clearance have proven unsuccessful in clinical trials.

Over 44% of the world's population is estimated to be overweight. The global obesity pandemic has far-reaching implications in terms of the quality of life, life expectancy, and immense associated healthcare costs. Obesity is a major risk factor for several metabolic syndromes associated with diseases such as Type 2 Diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), atherosclerosis, cardiovascular disease, and dementia. Also, metabolic syndromes (MeTs) such as T2D have been implicated in the development of autoimmune diseases, such as multiple sclerosis (MS), as well as

affecting the onset and progression of several neurodegenerative syndromes. The adipose tissue is heavily involved in the development and pathogenicity of insulin resistance, dyslipidemia, obesity, and MeTs. Adipose tissue experiences severe adipocyte hypertrophy and massive vascularisation, as well as distinct changes in secreted adipokines which affect both the organ itself and remote organs. Diabetes mellitus or T2D is a worldwide disease that negatively affects the quality of patients' lives as well as their lifespan.

We thus propose to examine the proteomic and metabolomics profile of animal models of familial Alzheimer's disease (3xTg and 5XFAD) following their treatment with high fat diet which induces the development of diabetes and metabolic conditions. The profile of the animals will be examined under regular feed as well as the high fat diet conditions. Animals will be kept on the diet for a period of 9 months. At the end of treatment, adipose tissue and brain tissue will be analysed in order to uncover merging pathways.

Timeline: