JPco-fuND Intermediate Symposium

Date and time: **30 November 2017** (14:00 – 18:35hrs) – **01 December 2017** (09:00 – 13:15hrs)
Place: The Netherlands Organisation for Scientific Research (NWO),
Room 300, Laan van Nieuw Oost-Indië 334, 2593 CE The Hague, The Netherlands

Abstracts project pitches

November 30th, 2017	
14:15 - 15:50	**Scientific session I** **Topic 1: Advanced animal or cell experimental models of neurodegenerative diseases** *Chair: Thomas GASSER, short introduction*
14:20 -14:35	**3DPD: Advanced modelling of Parkinson's disease with three-dimensional human midbrain organoids (1)** *Jens Schwamborn, University of Luxembourg* *Abstract* One of the main limitations in neuroscience and in the modeling of neurodegenerative diseases is the lack of advanced experimental *in vitro* models that truly recapitulate the complexity of the human brain. Therefore, it is the aim of the 3DPD project to generate brain-like organoids that resemble the human midbrain and their integration into a multifunctional lab-on-a-chip device. We focus on Parkinson's disease, which is the second most common neurodegenerative disease. The midbrains-on-a-chip are generated from induced pluripotent stem cells derived from Parkinson's disease patients that carry defined disease causing mutations as well as from idiopathic patients. This allow us to elucidate how Parkinson's disease imparts architectural remodelling, dopamine release and network formation of the midbrain tissue. The successful cultivation of in vitro midbrain organoids in a micro-analytical analysis platform will yield substantial insights and open new avenues for exploring the mechanisms of onset and progression under physiologically relevant measurement conditions. Moreover by the usage of microfluidics devices the whole approach is cost-effective and suitable for screening purposes. Here we will present the progress in the generation and characterization of cellular models as well as of extracellular matrix components for 3D cultures. Furthermore we will present first results concerning disease specific phenotypes in midbrain organoids and the progress of culturing midbrain organoids in sensor containing microfluidics devices.
14:35 -14:50	**DACAPO-AD: Deciphering Interactions of Acquired Risk Factors and ApoE-mediated Pathways in Alzheimer's Disease (1)** *Gabor Petzold, German Center for Neurodegenerative Diseases, Bonn, Germany* *Abstract* Alzheimer's disease (AD) is the most common form of dementia. Although our understanding of the pathomechanisms underlying familial AD has greatly been advanced because of research in established animal models, there is a translational roadblock in the development of treatments targeted at sporadic (late-onset) AD. We propose that this discrepancy can be mainly attributed to the fact that most traditional animal models do not adequately reflect the complex and multifactorial pathophysiology of sporadic AD, which is composed of a combination of inherited and acquired risk factors. Therefore, our goal is to investigate the interplay between the strongest and most common inherited risk factor for late-onset AD – the apolipoprotein E (ApoE) □4 genotype – and the most common environmental and acquired factors, i.e. traumatic brain injury, sleep disorders, dietary

	factors vascular pathology and systemic inflammation. To this end, we generated mouse lines that express the human ApoE-□4 or ApoE-□2 isoforms in the APP/PS1 mouse model of AD. We expect that amyloid pathology will change in the presence of the disease-aggravating □4 isoform or the disease-attenuating □2 isoform. To investigate this hypothesis within work package (WP) 1, we characterize the animal model by assessing changes in disease initiation and progression with respect to the different ApoE isoforms. Specifically, we will monitor A□ metabolism, clearance and pathology, assess systemic inflammation and blood-brain barrier integrity and vessel density using state-of-the-art techniques. In addition, we plan to investigate cellular and network functions in the brain and perform a battery of behavioural tests to assess the influences of the ApoE isoforms on the onset and progression of cellular changes resulting in cognitive deficits. In WP 2, we will expose these mouse models to environmental and acquired risk factors to reflect the 'real-world' scenarios leading to AD. We will subject the animals to high-fat and western diets, traumatic brain injury, systemic inflammation, vascular pathology and perturbed sleep homeostasis. The physiological and cognitive outcome of the animals exposed to the risk factors of WP 2 will be assessed by the same methods as in WP 1. With this combination of genetic and environmental risk factors, we aim to generate next-generation disease models that better monitor the multifactorial pathophysiology of late-onset AD with the ultimate goal to discover novel pathways that may be more predictive for a possible translation into clinical studies.
14:50 -15:05	**MADGIC: Generation of Improved Cellular and Animal Models for Identification of Disease Phenotype and New Therapeutic Targets of Alzheimer's Disease (1)** *Jari Koistinaho, University of Eastern Finland, Finland* *Abstract* *J. Koistinaho (COORD), University of Eastern Finland, Finland; L. Roybon, University of Lund, Sweden; G. Gouras, University of Lund, Sweden; C. Rampon, University of Toulouse, France; D. Brites, University of Lisbon, Portugal; M.T. Heneka, University of Bonn, Germany; F. Edenhofer, University of Innsbruck, Austria; T. Malm, University of Eastern Finland, Finland.* **Background:** Despite decades of research, the molecular pathophysiology of AD is poorly understood and treatment strategies of patients with AD remain inadequate. This is mainly because conventional rodent models of AD do not sufficiently recapitulate AD phenotype and do not translate laboratory findings into clinics. While 1% of the cases (fAD) are caused by single mutations, AD is a multifactorial and heterogeneous disease where both genotype and environmental factors influence one's susceptibility. We take advantage of novel reprogramming technologies - iPSC and direct conversion of somatic cells into specific brain cell types - to explore the functional implications of particular genotypes of AD authentically expressed in a cell type specific context, which may have superior clinical relevance and aid development of therapies and biomarkers for AD. **Key questions:** 1) Are reprogramming-based human cellular models relevant and reliable models of AD? If so, can we confirm previously assumed mechanisms of AD and identify new ones, which so far have not been evident due to the lack of robust *in vitro* and *in vivo* models. 2) Do fAD and ultimately sporadic (sAD) patients' iPSCs grown as 3D models or organoids recapitulate AD phenotypes over time with or without adding stressors that mimic environmental risk factors? 3) Do hippocampal and cortical neurons show AD pathology or sensitivity to synaptic damage/dysfunction when carrying AD-linked mutations or genetic risk factors with or without the contribution of microglia and astrocytes, or with additional environmental stress? 4) To which extent and by which mechanisms do AD-linked mutations and genetic risk or protective factors influence neuroinflammation? 5) Can we reproduce cognitive dysfunctions characteristic of AD in human chimeric mice generated by transplantation of IPSC derived brain cells? **MADGIC strategy for tackling the questions**: First, we characterize and validate the properties of neurons (cortical and hippocampal), astrocytes (forebrain), microglia and endothelial cells differentiated from the iPSC lines derived from fibroblasts of fAD (PS1 and APP mutant) patients, sAD patients carrying genetic risk factors (ApoE4, TREM2) and healthy ApoE3 controls, some of which carry protective A673T APP mutation. Also, isogenic control cell lines are generated when appropriate. The microglia model is supplemented with microglia-like cells differentiated from monocytes. Next, we analyze the impact and mechanisms of interaction

	between different cell types, including cell-to-cell trafficking of exosomal inflammatory microRNAs, by setting up 2D and 3D cultures containing neurons together with astrocytes and/or microglia, and even endothelial cells. Cerebral organoids, eventually supplemented with microglia and endothelial cells and genetic acceleration of aging, are generated to model AD – linked pathology and synaptic deficiency when the brain is self-organized in a dish. To analyze the impact of the human brain cells linked genetically to AD *in vivo*, we generate humanized chimeric mice by transplanting iPSC-derived cells into immunodeficient mouse brains prior to analysis of brain pathology and cognitive functions. Throughout the selection of these models, we test the effect of selected small molecules and potentially therapeutic genes on AD-linked cell and brain pathology, including cognitive function in humanized chimeric mice. **Expected outcomes:** Our reprogramming-based human AD models, including 3D, organoid and animal models are clinically relevant for both fAD and sAD as they recapitulate the AD pathologies previously observed in human autopsy material and animal models. We also observe novel cell-type and genotype specific pathologies and functional alterations relevant for AD that form foundation for new therapeutic strategies and biomarkers. Synaptic dysfunction is a central feature observed both in *in vitro* and *in vivo* models of AD and is contributed not only by neurons themselves but also by the glia carrying AD-linked mutations or genetic risk variants. The role of microglia and astrocytes varies depending on the mutation and risk factor, but these cells show strong phenotype with altered functions related to mitochondrial functions and energy metabolism, clearance and release of toxic molecules, and neuroinflammation. Exosomes are involved in glial regulation of neuronal functions. The humanized mouse models show altered cognitive functions associated with AD-related cell pathology. Potentially therapeutic small molecules and gene therapies of AD can be demonstrated in the novel *in vitro* and *in vivo* models. **Discussion:** Possibilities for collaboration between different consortia, including possibilities to share expertise and technology platforms. Discussion whether the models of various neurodegenerative diseases complement each other. Impact of hPSCs in research of neurodegenerative disorders and its challenge when modelling aging in the dish. The role of extracellular vesicles in neuron-glia communication.
15:05 -15:20	**ModelPolyQ: Advanced models of polyglutamine disorders (HD, SCA3 and SCA7) (1)** *Luis Pereira de Almeida, Center for Neuroscience and Cell Biology of Coimbra, Portugal* *Abstract* Pereira de Almeida, L1, Álvaro, AR1, Matos, C1, Santana, M1, Lopes, S1, Nguyen, HH2, Trottier, Y3, Niewiadomska-Cimicka, A3, Déglon, N4, Perrier, A5, Cattaneo, E6 1 Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal; 2 Institute of Medical Genetics and Applied Genomics Germany; and Centre for Rare Diseases, University of Tuebingen, Tuebingen, 3 IGBMC/CNRS/INSERM/UNISTRA, Department of Translational Medicine & Neurogenetics 1, Illkirch Cedex, France; 4 Lausanne University Hospital (CHUV), Dep. of Clinical Neurosciences (DNC), Lab of Cellular and Molecular Neurotherapies (LNCM), Lausanne, Switzerland; 5 Inserm/UEVE U861, I-Stem, Evry, France; 6 University of Milan, Dep. of Biosciences, Laboratory of Stem Cell Biology and Pharmacology of Neurodegenerative Diseases, Milano, Italy. Polyglutamine (PolyQ) diseases are a group of 9 neurodegenerative diseases caused by over-repetition of the CAG codon, which translates into polyglutamine tracts within specific proteins for each disorder. Despite important progresses in the knowledge of the pathological mechanisms involved we still miss effective therapies. Advances in this field depend on innovative, predictive, models of disease for which there is an urgent need for both mechanistic and preclinical studies. In this proposal we focus on 3 polyglutamine (polyQ) disorders: Huntington's disease, and spinocerebellar ataxias type 3 and 7. We propose to a) generate novel, improved disease models, b) to thoroughly characterize and compare both these and previously generated models and, c) to standardize, reproducible methodologies to investigate pathomechanisms that present commonalities between polyQ diseases. We will concentrate on the leading models, namely the genetically-modified rodent models and the induced pluripotent stem cells (iPSC).

	We expect that this project can make a truly important contribution to the field of polyglutamine diseases by providing the models and methodologies to enable significant advances in a) the knowledge of the mechanisms of these diseases and b) provide the tools for pre-clinical identification and validation of new effective therapies for polyglutamine disorders. ModelPolyQ project is organized in six work packages and was successfully initiated in July 2016 and all project activities have been started as planned. So far all scheduled deliverables have been in progress as planned. In this JPND Intermediate Symposium it would be interesting to involve the entire network of JPND partners and know the main strategies and aligments in which the consortium intends to focus on the future. This interaction could increase collaboration with consortium partners in order to share doubts/difficulties about project execution and to get suggestions on project progress and management. PolyQ diseases are widely seen as model neurodegenerative diseases as they have features in common with other neurodegenerative diseases such as Alzheimer's and Parkinson's so, as a take home message, therapeutics developed for polyQ disease are likely to have potential to be rapidly retooled for other neurodegenerative diseases. The novel and thoroughly characterized iPS-based models and rodent models of HD, SCA3 and SCA7 which will be developed in this project will be a unique tool set and are expected to have enormous impact in research in the field. They will form the basis for biomarker identification, pathogenesis studies and the discovery of disease modifying drugs. This is an EU Joint Programme – Neurodegenerative Disease Research (JPND) Project. The project is supported through the following organisations under the aegis of JPND – www.jpnd.eu (France, French National Research Agency (ANR); Germany, Federal Ministry of Education and Research (BMBF); Italy: Ministry of Health or Ministry of Education, Universities and Research (MIUR); Portugal, Foundation for Science and Technology (FCT); Switzerland, State Secretariat for Education, Research and Innovation (SERI)). This Project has received funding from the European Union´s Horizon 2020 research and innovation programme under Grant agreement No 643417.
15:20 -15:35	**NAB3: Development of a Novel Multicellular In Vitro Model of Alzheimer's disease-like Blood-Brain Barrier (1)** *Francesca Re, School of Medicine and Surgery, University of Milano-Bicocca, Italy* *Abstract* Recent statistics indicate that over three million people in the EU have Alzheimer's disease (AD). This number is expected to rise as the population ages, doubling by 2040 in Western Europe and trebling in Eastern Europe. Therefore, the search for effective therapies and early diagnosis is imperative. The process of discovering and developing drugs for neurological disorders, like AD, is extremely challenging and expensive, with an average cost of about $6 billion. Furthermore, the alteration of the blood-brain barrier (BBB), which prevents the passage of 98% of potential neuropharmaceuticals, worsen this situation. Since only BBB in vitro models mimicking healthy conditions are currently available, the lack of suitable models of diseased human BBB clearly contributes to the major difficulties encountered in designing efficient drug-based treatments. The primary focus of NAB_3 project is therefore to develop an in vitro model of human BBB that reflects the barrier alterations in response to AD state; this will represent a novel and highly valuable tool for drug design and testing. Moreover, the project also aims to accelerate the development of novel drugs for efficient treatment of AD and potentially of other CNS diseases. This will be made possible by the identification of the global alterations occurring at the BBB level in AD patients: we will then capitalize on sophisticated in vitro co-culture systems to model the AD-like human BBB. This model will be of tremendous interest to pharmaceutical companies to devise new diagnostic or therapeutic strategies and to conduct more advanced early drug development and pre-clinical studies. Especially in early drug development such model could be used as a step in the evaluation of selected compounds assuring their ability to penetrate the BBB. Once validated, novel concepts arising from this work will be patented and this model will be available to academic laboratories and to pharmaceutical companies under licenses for basic to clinical researches devoted to neurological disorders.

15:35 -15:50	**GBA-PARK: GBA1 mutations in Parkinson disease: clinical and biochemical prodrome, risk profile and pathogenetic modelling for therapeutic intervention (1,2,3)** *Anthony Schapira, University College London, Institute of Neurology, UK* *Abstract* Partners: F. Blandini, Ministry of Health- Mondino Foundation IRCCS National Neurological Institute, Pavia, Italy; D. Di Monte, DZNE, Bonn, Germany; P. Ciana, Ministry of Education, Universities and Research - University of Milan, Italy; D. Park, CIHR-University of Ottawa, Canada **Which urgent and important questions does the project address?** Mutations of the glucocerebrosidase gene (GBA1) are the most important risk factor for Parkinson disease (PD). In Europe, approximately 5-10% of all PD patients have GBA1 mutations. Both heterozygous and homozygous mutations increase risk by 10-30% developing Parkinson's disease by the age of 80. The main purpose of this project is to define the clinical and biochemical prodrome of GBA1 mutation carriers at risk of PD. Moreover, this project aims to understand better the molecular interactions of glucocerebrosidase and alpha-synuclein and how this relationship may be manipulated to reduce disease progression. To this aim, we developed a co-ordinated and integrated international cohort of GBA1 mutation carriers and we combined different approaches using *in vitro* and *in vivo* human and animal based models. **What are the expected outcomes of the project?** This international GBA1 mutation cohort will provide the opportunity to: - define clinical and biochemical features to stratify patients groups for clinical trial to slow PD progression, - develop human cell-based models in which to study the pathogenetic mechanisms of GBA mutations and identify target pathways for drug intervention. Moreover, by using *in vivo* animal models, we expect to: - elucidate the reciprocal interaction between GCase deficiency, alpha-synuclein accumulation and PD development - assess the neuroprotective efficacy of new drug compounds targeting the glucocerebrosidase-alpha-synuclein pathway. **Collaboration with consortium partners and preliminary results:** The strong collaboration with JPND consortium partners produced first impressive results, both on animal and human model. Our first results are set out in more detail below. In an recently published article (Migdalaska-Richards et al. Brain 2017), the UK and German groups, analyzed on two aged Gba1 mouse models, one carrying a knock-out mutation (KO/+) and the other a L444P knock-in mutation (L444P/+), the link between Gba1-deficiency, alpha-synuclein overexpression and dopaminergic neurodegeneration.. In particular their findings revealed that the reduction of glucocerebrosidase (GCase) activity was associated to a prominent increase in alpha-synuclein accumulation in L444P/+ and KO/+ mice, but was not able alone to induce the degeneration of nigral dopaminergic neurons nor to affect striatal dopamine levels. In this study, they also assessed the effects of overexpression of human alpha-synuclein in the substantia nigra of L444P/+ mice by using intraparenchymal injections of adeno-associated virus carrying the SNCA gene. Stereological counts of nigral dopaminergic neurons revealed a significantly greater cell loss in Gba1-mutant than wild–type mice suggesting that GCase deficiency increases neuronal vulnerability to neurodegenerative processe induced by alpha-syunuclein overexpression From the clinical point of view, we started to expand and harmonize the assessment of GBA1 mutation carriers within the UK, Italian and Canadian cohorts in order to developed a unique protocol for their clinical and biochemical phenotyping to identify the prodromal features of PD and the potential clinical signs of early neurodegeneration. The UK group has already established a large cohort of GBA1 mutation carriers with subjects followed longitudinally (McNeill et al. Mov Dis. 2012; Beavan et al. JAMA Neurology 2015). Only recently, 6 year follow-up assessment was completed.

	In all, this cohort included one hundred and thirty-five participants which have been followed longitudinally with target follow-up assessments at two year intervals beginning in 2012. Among them, sevent-six participants (thirty-five previously diagnosed Type 1 Gaucher disease (GD) patients, nineteen heterozygous GBA1 mutation carriers, and twenty-two controls) completed the 6 years follow-up that comprised: a complete neurological assessment including the Unified Parkinson's Disease Rating Scale motor subscale (UPDRS parts III), olfactory function using the University of Pennsylvania Smell Identification Test (UPSIT), cognitive function using the Montreal Cognitive assessment (MoCA), rem behavior disorder (RBD) with the RBD Questionnaire (RBDQ) and Parkinson's Disease Sleep Scale (PDSS), depression using the Beck's Depression Inventory (BDI), and autonomic dysfunction using a subscale of the Unified Multiple System Atrophy Rating Scale (UMSARS) and Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT). For both GD and carrier subjects, exclusion criteria included a diagnosis of PD or dementia and for controls, any existing neurological disease. The GBA1 mutation status in all participants was confirmed by Sanger sequencing of the GBA1 gene. Results from individuals with homozygous or heterozygous mutations in GBA1 were combined together in a pooled analysis comparing all GBA1 mutation positive individuals versus controls. At 6 years follow-up, GBA1 mutation positive individuals demonstrated significantly worse mean BDI, UPSIT, UPDRS III, UMSARS scores compared to controls. Similarly, at 6 years, GBA1 mutation positive subjects showed a significant difference in mean PDSS and SCOPA-AUT when compared to controls. There was no significant difference between mean MoCA or RBD scores in GBA1 mutation positive individuals and controls at follow-up. **Take-home message for other scientists:** GBA1 mutations represent the most important risk factor for PD indentified to date. GBA1 deficiency in mice model enhances neuronal vulnerability to neurodegenerative processes triggered by increased alpha-synuclein expression. GBA1 mutation positive individuals show deterioration in clinical markers consistent with the prodrome of PD.

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16:20 - 17:40	**Scientific session II** **Topic 2: Genetic, epigenetic and environmental risk and protective factors of neuro-degenerative diseases** *Chair: Myrra VERNOOIJ-DASSEN*
16:25 -16:40	**ADAGE: Alzheimer's Disease pathology within the ageing physiology (2)** *Prof. Claudio Franceschi, Azienda USL di Bologna, Italy* *Abstract* Project coordinator: Claudio Franceschi, Azienda USL di Bologna - IRCCS Istituto delle Scienze Neurologiche (ISNB), Italy E-mail: claudio.franceschi@isnb.it Paolo Garagnani a,b, Chiara Pirazzini b,c, Maria Giulia Bacalini b,c, Claudio Franceschi b,c.a. Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum-University of Bologna, Bologna 40138, Italy. b.Interdepartmental Center "L. Galvani", University of Bologna, Bologna 40126, Italy. c.Azienda USL di Bologna - IRCCS Istituto delle Scienze Neurologiche (ISNB), Italy Late onset Alzheimer's disease (AD) may have a long natural history and the search for peripheral biomarkers that could be used for screening in the preclinical phase of the disease is a major challenge. Ageing is the major risk factor for AD and the most recent conceptualizations of ageing and age-related diseases, including neurodegeneration and AD, indicate that they share basic mechanisms, e.g. (neuro)-INFLAMMAGING. Thus, to better understand AD pathogenesis and to identify such early biomarkers capable of distinguishing AD from physiological ageing without dementia, it is mandatory to fully posit AD within the framework of ageing process and to study LONGITUDINAL COHORTS OF PRESYMPTOMATIC INDIVIDUALS. The main goal of ADAGE is to identify preclinical circulating biomarkers deviating from healthy ageing trajectories towards AD. To this aim the project will adopt the innovative strategy of comparing extreme phenotypes, i.e. blood samples from AD patients collected years before the clinical onset of the disease versus blood samples from DEMENTIA-FREE CENTENARIANS (100+) and their offspring (CO), and HEALTHY NONAGENARIAN SIBLINGS (90+ sibs) characterized by familial longevity, who maintain a good cognitive status despite their very advanced age. Accordingly, ADAGE will exploit unique, large and very informative EXISTING COHORTS where biomaterials (blood, plasma, serum and brains) are available and whole genome genetic and epigenetic studies (as well other omics investigations) have been recently performed: i) old TWINS OF THE SWEDISH TWIN REGISTRY (STR) FOLLOWED LONGITUDINALLY FOR >45 YEARS, assessed for lifestyle, cognitive status and exposure to toxicants. Here, incident and prevalent cases of AD DISCORDANT TWINS have been identified, blood/serum/plasma have been collected at different time points before AD clinical manifestation and post-mortem brains are available; ii) 100+ and their CO as well as 90+ sibs as gold standard of healthy ageing, who have never shown any signs of cognitive disability/decline and are fully characterized phenotypically and with a variety of omics, including genetics and epigenetics. In these cohorts, ADAGE will perform a metanalysis of existing omics data, an analysis of circulating proteome (several hundred proteins) and metabolome integrated by studies on circulating miRNA, advanced flow cytometry and an in depth neuropathological analysis of AD versus normal old brains, focused on markers of inflammation/cell senescence, to be correlated with cognitive status and omic data.
16:40 -16:55	**aSynProtec: Alpha-synuclein pathology propagation in Parkinson's disease and quest for novel protective strategies (2)** *Prof. Jia-Yi Li,* Lund University, Sweden *Abstract* Misfolding and aggregation of α-synuclein (α-syn) in the form of Lewy bodies and Lewy neurites are the major hallmarks of Parkinson's disease (PD). Available evidence shows that

	exogenous human α-syn fibrils can be taken up into neurons and inoculate aggregation of endogenous α-syn in the recipient cells. Up to date, it is still obscure on the origin and the molecular mechanisms leading to the development of α-syn amyloid aggregate formation, for example: 1) when, why and how are the endogenous α-syn aggregates formed; do they initiate in the brain or in the peripheral tissues and how do environmental factors, including the microbiome, contribute to this process? 2) what are the structural requirements for α-syn cell-to-cell propagation and spreading? 3) how do the aggregation state and structural properties of the aggregates influence conversion of endogenous α-syn and pathology spreading? 4) how, and through which route(s), is/are misfolded/aggregated α-syn transported and spread from one cell to another? 5) how does genetic susceptibility contribute to the propagation and aggregation of α-syn? 6) how do posttranslational modifications of α-syn impact on α-syn spreading, aggregation and cytotoxicity 7) can small molecule compounds and biological reagents, such as specific antibodies, block α-syn spreading, seeding and aggregation? In the last two years, the *aSynProtec* teams have made great progresses on all the above mentioned issues. We expect that the fulfilment of this project will significantly advance our understanding of the interplay between genetic and environmental risk factors and their role in the initiation of α-syn aggregation and pathology spreading in PD and related synucleinopathies, which will lead to the identification of novel targets and open new paths for the development of novel therapeutic preventive and therapeutic interventions.
16:55 -17:10	**BRIDGET: BRain Imaging, cognition, Dementia and next generation GEnomics: a Transdisciplinary approach to search for risk and protective factors of neurodegenerative disease (2)** *Stephanie Debette, Inserm U897, University of Bordeaux, France* *Abstract* Establishing efficient prevention strategies for dementia and Alzheimer disease (AD) is a major health priority for the coming years. An important hurdle is that pathological processes leading to AD begin many years before clinical diagnosis, hence efficient prevention should be initiated very early. This requires identifying individuals in the general population who are at high risk of developing dementia and exploring the molecular pathways underlying the structural brain alterations that precede the occurrence of dementia, an essential step for identifying novel relevant drug targets. With a unique combination of expertise in Epigenomics, Genomics, Epidemiology and Brain Imaging, the BRIDGET Consortium explores the genetic and epigenetic determinants of quantitative MRI-markers of brain aging that are powerful predictors of dementia/AD risk, and examines the clinical significance of the markers in a population-based setting. The outcomes of this project are expected to enrich our understanding of the biological mechanisms underlying early structural brain alterations that portend an increased dementia risk, and thus contribute to the discovery of novel therapeutic targets. McGill genome center is currently conducting whole genome sequencing of 1,886 participants from the general population with brain MRI and longitudinal follow-up and Methyl-C-Sequencing of 902 participants with an extreme distribution of MRI-defined endophenotypes of dementia (through JPND and complementary funding). Analyses exploring the association of rare variants with MRI-markers of brain aging have been performed on already available samples with whole exome sequencing and exome-chip data and will be expanded with the aforementioned data. In addition several association analyses of common and low frequency variants in relation with previously unexplored MRI-markers of brain aging are in progress or completed, using highly innovative approaches. We have also generated cutting-edge novel MRI-markers of brain aging across participating cohorts for which genomic analyses have been initiated. Finally, facilitated by the contribution of external collaborators, we are exploring the genomics of MRI-markers of brain aging in a transethnic setting and focusing on MRI-

	endophenotypes of dementia across the lifetime with the complementary contribution of large cohorts across the lifespan.
17:10-17:25	**EADB: A European DNA bank for deciphering the missing heritability of Alzheimer's disease (2)** *Jean-Charles Lambert, Université de Lille, Inserm UMR1167, Institut Pasteur de Lille, Lille, France* *Abstract* Luca Kleineidam[a,b,c], Michael Wagner[a,c], Agustin Ruiz[e], Wiesje van der Flier[f,g], Frank Jessen[b,c], Jean-Charles Lambert[h,I,j] , Alfredo Ramirez[a,b,k] a) Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany b) Department of Psychiatry, University of Cologne, Cologne, Germany c) German Center for Neurodegenerative Diseases, Bonn, Germany d) Memory Clinic and Research Center of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain e) Alzheimer Centre & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands f) Department of Epidemiology & Biostatistics, Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands g) Inserm UMR1167, Laboratoire d'Excellence Distalz, Lille, France h) Institut Pasteur de Lille, Longevity Research Center, Lille, France i) Université de Lille, Lille, France j) Institute of Human Genetics, University of Bonn, Bonn, Germany Alzheimer's disease (AD) is a highly heritable complex disease in which less than 50% of its genetic attributable risk has been characterized so far. The EADB project aims to uncover this missing heritability. To this end, the EADB will perform the world's largest GWAS case-control study to date using innovative analysis techniques. In addition, genetic determinates of disease progression will be studied in up to 9109 individuals at-risk of developing AD dementia, i.e. mild cognitive impairment (MCI). Identifying genetic modulators of disease progression will offer a powerful tool to enhance our predictive ability in pre-dementia stages of AD with the potential of translating findings directly into clinical practice. However, in a multicohort setting, such as that of EADB, several methodological challenges need to be addressed including, harmonization of inclusion MCI criteria and harmonization of disease progression measurements. In our first step, we compared three MCI definitions differing in the stringency with which MCI is defined. Our results suggest that the cohort-specific MCI definition (lowest level of stringency) provides the largest sample sizes and the highest statistical power. We then compared different methods to harmonize the assessment of disease progression across cohorts using Cox-regression for conversion to AD dementia and linear mixed models for cognitive decline. For the latter, neuropsychological assessments were harmonized across cohorts using three approaches: a) the Mini Mental State Examination (MMSE) as a common measure across cohorts; b) standardized composite based of specific neuropsychological tests from each cohort analyzed (z-score); and c) Moderated non-linear factor analysis (MNLFA) which harmonizes these tests into demography-adjusted latent factors. These three harmonization methods were then compared on their sensitivity to detect genetics effects on cognitive decline. For genetics, a polygenic risk score was constructed using genome-wide significant genetic variants reported by the IGAP consortium. This analysis revealed that the MMSE was the most sensitive method to detect genetic effects in a multicohort set-up as EADB. Using the MMSE, we then explored individual genetic effects on disease progression. To this end, we analyzed 2644 from four cohorts with available genotypes for SNPs reported by IGAP, excluding APOE. Only the effects of clusterin (CLU, $p=3.4*10^{-5}$) survived adjustment for multiple testing. Power analyses suggest that the effect of CLU would be detected with 99.1% power at the genome-wide significance level if the planned MCI sample size is reached. In conclusion, MMSE will provide a powerful tool to uncover novel genetic markers of AD progression. The poor results of our initial analysis on susceptibility gene for AD suggest that genetics underpinning of disease progression in AD might differ from those related to disease susceptibility. EADB findings in MCI will contribute to our understanding of disease processes underlying AD.

17:25 - 17:40	**INSTALZ: Genomic Instability in Alzheimer's Disease and Related Disorders: a Single-Cell Approach (2)** *Bart Dermaut, Université de Lille, Inserm U1167, CHU Lille, Institut Pasteur de Lille, Lille, France* *Abstract* **Partners:** 1. Bart Dermaut, Institut Pasteur de Lille, Inserm U1167, Université de Lille 2, Lille, France 2. Marie-Christine Galas, Centre de Recherche Jean-Pierre Aubert, Inserm UMR-S1172, Lille, France 3. Thierry Voet, Sanger Institute-EBI Single-Cell Genomics Centre, Hinxton, Cambridge, UK 4. Bart De Strooper, VIB Department for the Biology of Disease, KU Leuven, Leuven, Belgium 5. Vilhelm Bohr, Copenhagen University, Copenhagen, Denmark 6. Joakim Lundeberg, Science for Life Laboratory, KTH Royal Institute of Technology, Stockholm, Sweden **What are the most urgent and important questions in your field of research?** Increasing evidence suggests that the genetic information in our brains varies from cell to cell. The INSTALZ consortium aims at understanding how altered stability of the neuronal genome in the developing and adult brain determines the risk of developing these chronic disorders in late adulthood. Specific questions include: • What is the role of genomic and transcriptomic instability in human AD and primary Tauopathies? • Do mosaic genetic mutations in brain cause prion-like spreading in AD and/or primary Tauopathies? • Does Tau pathology involve DNA/RNA protection and damage? • Does the Tau protein play a role in mitotic chromosomal instability? **How does your project address these questions?** We use single-cell genome and transcriptome sequencing (G & T) technology, spatial transcriptomics and cell biological assays to address these questions in mouse models, *Drosophila* models and human AD and tauopathy brains. These collaborative studies are all ongoing and the first results have already been published: • Malmanche N, Dourlen P, Gistelinck M, Demiautte F, Link N, Dupont C, Vanden Broeck L, Werkmeister E, Amouyel P, Bongiovanni A, Bauderlique H, Moechars D, Royou A, Bellen HJ, Lafont F, Callaerts P, Lambert JC, Dermaut B. Developmental Expression of 4-Repeat-Tau Induces Neuronal Aneuploidy in *Drosophila* Tauopathy Models. **Sci Rep. 2017** Jan 23;7:40764. • Mansuroglu Z, Benhelli-Mokrani H, Marcato V, Sultan A, Violet M, Chauderlier A, Delattre L, Loyens A, Talahari S, Bégard S, Nesslany F, Colin M, Souès S, Lefebvre B, Buée L, Galas MC, Bonnefoy E. Loss of Tau protein affects the structure, transcription and repair of neuronal pericentromeric heterochromatin. **Sci Rep. 2016** Sep 8;6:33047. **What are the expected outcomes of your project?** • Novel mechanistic insights: *Cellular state* that causes a particular but not the adjacent neuron to die in AD and related diseases. This could explain why particular neurons/brain regions are more vulnerable than others. *Somatic mutations* may explain the pathogenesis of a consistent part of sporadic AD cases. • Diagnostic or biomarker tests: We anticipate that disease-relevant mosaicism can also be detected in peripheral proliferating tissues such as blood or skin e.g. buccal swabs. The market for such peripheral biomarkers is huge. **What would you like to discuss with the attendees (e.g. a challenge or success of your project, collaboration with consortium partners, data collection etc.)?** The major challenge we are currently facing is the prioritization of single-cell and spatial transcriptomics experiments because of budget constraints. We would like to discuss the possibilities to obtain additional funding for our consortium.

November 30th, 2017	
17:40 - 18:35	Data sharing / Open Access – Open Science Rob HOOFT and Jan-Willem BOITEN The Presentation aims to demonstrate the merits of open data to projects, and the relationships to the open science and open access movements. The concept of sharing FAIR data (Findable, Accessible, Interoperable, Reusable) will be introduced; the objective is to outline how to avoid open but useless data and to provide a proper solution for privacy-sensitive data. The presentation will include information about available data infrastructures and practical suggestions for data management (how to make the most of your own data) and data publishing (how and where to put resulting data before a project ends). Rob Hooft, is programme manager Dutch Techcentre for Life Sciences (DTL)* data and Jan-Willem Boiten is Program manager at Lygature** ***The Dutch Techcentre for Life Sciences (DTL)** is a **public-private partnership** of more than 50 life science organisations in the Netherlands. The majority of Dutch universities and university medical centres are DTL partners, and a growing number of companies are joining the organisation. DTL connects scientists, data experts, technical experts and trainers that are specialised in a variety of high-end wet lab and data technologies, and working in life science domains ranging from health to nutrition, agro, biotech and biodiversity. For more information see https://www.dtls.nl ****Lygature**: As a not-for-profit organization, Lygature aims to accelerate the development of new medical solutions for patients by driving public-private collaboration between academia, industry and society. For more information see: http://www.lygature.org/

December 1st, 2017	
9:10 – 10:30	**Scientific session III** **Topic 1: Advanced animal or cell experimental models of neurodegenerative diseases** **Topic 2: Genetic, epigenetic and environmental risk and protective factors of neuro-degenerative diseases,** **Topic 3: Longitudinal cohort approaches in neurodegenerative diseases,** *Chair: Philippe AMOUYEL*
9:15 – 9:30	**ESMI: European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (3)** *Thomas Klockgether, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany* *Abstract* **Background**: Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3) is worldwide the most common autosomal dominantly inherited ataxia disorder. It is caused by expansion of polyglutamine encoding CAG repeats in the ATXN3 gene. This disorder is characterized by degeneration of spinocerebellar tracts, dentate nucleus, brainstem nuclei, and basal ganglia. Ataxia usually starts around 35 years with large variability that partly depends on the repeat length. The clinical syndrome is characterized by prominent cerebellar ataxia in combination with supranuclear gaze palsy and peripheral neuropathy. Patients with an earlier disease onset may also present with spasticity, dystonia or parkinsonism, while peripheral involvement is more prevalent in patients with a later disease onset. SCA3 takes a progressive course and leads to severe disability and premature death with a median survival after ataxia onset of 25 years. Currently, there is no treatment for SCA3. However, there are several novel treatment approaches that are being or will be evaluated in clinical trials. **Goals of the project**: To enable interventional trials, availability of large cohorts that consist of preclinical mutation carriers and mildly affected patients is mandatory. For this purpose, the European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (ESMI) will set up a trial ready cohort by bringing together 7 European cohorts and 1 US cohort, which together comprise more than 800 subjects. We will integrate the existing data in a common database and apply standardized and quality-controlled clinical assessment, MRI and biobanking protocols. A major part of our initiative is the development and validation of innovative assessment instruments and disease markers, including a new highly sensitive motor test battery, ambulatory sensor-based activity measurement, automated MRI volumetric evaluation, diffusion tensor imaging (DTI), and blood as well as CSF markers based on transcript profiling and disease protein (ataxin-3) measurement. In addition, we will assess the impact of lifestyle on disease evolution by appropriate questionnaires. By exploiting the data obtained in this cohort, we will develop a revised model of SCA3 disease evolution that conceives the preclinical (pre-ataxia) stage and the ataxia stage as the graded manifestation of one disease process, and that will take lifestyle factors into account. Our research directly impacts not only on feasibility and design of interventional trials, but also on routine health care because the new instruments, such as automated activity measurement and MRI analysis, can be used in diagnosis and routine management of ataxia patients. The European and national ataxia patient organizations are directly involved in the planning and management of this project.
9:30 – 9:45	**CureALS: Stress granules and proteostasis in motor neurons: towards a mechanistic understanding of ALS (1,2)** *Simon Alberti, Max Planck Institute of Molecular Cell Biology and Genetics, Germany* *Abstract* Amyotrophic lateral sclerosis (ALS) and related diseases such as frontotemporal dementia (FTD) are among the most severe age-related disorders, and therapeutic interventions are still unavailable. Due to the complex etiology of these diseases, the mechanistic basis has been difficult to pinpoint. In recent years, evidence has been accumulating that ALS/FTD are caused or exacerbated by protein/RNA aggregates and a failure of the cellular stress response and the protein quality control (PQC) machinery. However, how these different processes are functionally connected and eventually lead to disease remains poorly understood. In this project, we investigate

	the molecular underpinnings of cellular degeneration, focusing on the role of RNA/protein aggregates as key mediators of cellular decline. We show that an impairment of the PQC machinery triggers a conversion of physiological RNP granules into an aberrant aggregated state. We further identify drug-like compounds that prevent the formation of aberrant RNA/protein aggregates, restore a normal stress response and prevent cellular degeneration. Our approach gives insight into the molecular mechanisms underlying ALS and related disorders, thus providing a solid mechanistic basis for diagnostics and therapy development.
9:45 – 10:00	**SNOWBALL: The interplay of amyloid and ischemia and their influence on the blood-brain barrier, amyloid transportation systems and neurodegeneration in cerebral amyloid angiopathy (CAA) (1,2)** *Marc Fatar, Universitätsmedizin Mannheim, University of Heidelberg, Germany* *Abstract* Project director: Prof. Dr. med. Marc Fatar[1] Young scientist: Veronika Chevyreva[2], PhD student Project partners: Dr. Anne Mahringer[2], Dr. Claudia Borrmann[1], Prof. Dr. Laurence Fenart[3], Prof. Dr. Fabien Gosselet[3], Prof. Dr. Rick M. Dijkhuizen[4], Dr. Romain Goulay[4], Prof. Dr. med. Klaus Fassbender[5], Dr. med. Alex Yang Liu, Dr. Yann Decker[5], Dr. Mar Hernández-Guillamon[6] 1. Department of Neurology, Medical Faculty Mannheim at Heidelberg University, Mannheim, Germany. 2. Department of Pharmaceutical Technology und Biopharmacy, Institute for Pharmacy and Molecular Biotechnology (IPMB), Heidelberg University, Heidelberg, Germany. 3. Blood Brain Barrier Laboratory, Jean Perrin Science Faculty Artois University, Lens, France. 4. Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht, Utrecht, Netherlands. 5. Department of Neurology, Saarland University, Homburg, Germany. 6. The Neurovascular Research Laboratory, Vall d'Hebron Research Institute, Autonomous University of Barcelona, Barcelona, Spain. Alzheimer's disease, cerebral amyloid angiopathy (CAA) and ischemic stroke are age-associated diseases that affect the central nervous system. CAA develops as a result of amyloid-β (Aβ) deposits in the cerebrovasculature which increases the risk of microbleeds, lobar haemorrhages and ischemic stroke, and inversely, stroke patients show a higher degree of Aβ deposits[1, 2]. While there is mounting evidence that impairment of the neurovascular unit (NVU) and amyloid-associated neurodegeneration interact in an intricate and mutually detrimental way (resulting in a snowball effect), relatively little is known about the exact nature of the relationship. The SNOWBALL[3] project makes use of the collaborative efforts between 5 international partners in order to investigate the interplay of CAA and ischemic stroke on the vascular level. We will use a combination of molecular and imaging techniques in *in vitro* (primary cell cultures) and *in vivo* (APP23[4], TgCRND8[5] mice) models of CAA and ischemic stroke to study Aβ deposition and transport, as well as structural, morphological and immunological changes at the BBB. For cell culture models, single, double and triple cell cultures of primary brain endothelial cells, pericytes and glial cells as well as intact brain microcapillaries will be employed from wild-type and APP23 mice to observe transcriptional, translational, functional and localisation changes at the BBB during the combined effects of Aβ and oxygen-glucose deprivation (OGD). ABC transporters (P-gp, BCRP, MRPs), endocytic mechanisms (RAGE, LRP1, Caveolin-1, Clathrin), tight junction integrity (Occludin, Claudins, JAMs, ZOs, MMPs), modifications in microenvironment and signalling cascades (inflammation, oxidative stress) will be studied using established molecular techniques (qPCR, Western botting, Transwell® transport studies, ELISA, immunostaining and confocal and SPDM microscopy). For *in vivo* experiments, APP23 and TgCRND8 mice exposed to middle cerebral artery occlusion (MCAO) will be used to investigate combined effects of CAA and ischemic stroke. Imaging techniques such as MRI and PET will be employed to analyse BBB permeability, blood flow/volume, vascular reactivity, functional connectivity and Aβ deposition. Immunohistochemistry and laser microdissection of microvessels combined with transcriptomic (microarrays, qPCR) and proteomic (DIGE, MALDI-TOF MS) approaches will be used to analyse molecular and morphological changes at the NVU. The final goal of the project is the identification of potential novel biomarkers and therapy strategies which will be confirmed using cerebrospinal fluid (CSF) and plasma samples gathered from CAA and stroke patients. The collaborative efforts between the partners heavily encourages exchange of data, protocols, manuscripts, training opportunities and personnel to make the most out of the

	combined individual expertise of the members, creating a strong strategy to tackle the underlying mechanisms behind neurovascular diseases at the BBB. 1. Garcia-Alloza, M. *et al.* (2011). Cerebrovascular lesions induce transient β-amyloid deposition. Brain: A Journal of Neurology, 134(Pt 12), 3697–707. 2. Attems, J., *et al.* (2011). Review: Sporadic cerebral amyloid angiopathy. Neuropathology and Applied Neurobiology, 37(1), 75–93 3. Fernández-de Retana, S., *et al.* (2017). Intravenous treatment with human recombinant ApoA-I Milano reduces beta amyloid cerebral deposition in the APP23-transgenic mouse model of Alzheimer's disease. Neurobiology of Aging, 60, 116–128 4. Sturchler-Pierrat, C., *et al.* (1997). Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Neurobiology, 94, 13287–13292 5. Watzlawik, J., *et al* (2006). Prion protein helix1 promotes aggregation but is not converted into β-sheet. *Journal of Biological Chemistry*, *281*(40), 30242–30250
10:00 - 10:15	**SYNACTION: Unravelling the pathophysiological role of alpha-synuclein aggregation, transmission and neuroinflammation in neurodegeneration (1,2)** *Veerle Baekelandt, KU Leuven, Belgium* *Abstract* **Project aim, work plan, exploitation of the results** We observed that alpha-synuclein (αSYN) assemblies with different structural characteristics or 'strains' display distinct spreading, tropism, clearance and neurotoxicity in the rodent brain. Strain-specific pathology is induced resembling pathological hallmarks found in Parkinson's disease (PD) and Multiple System Atrophy (MSA) patients. We postulate that neuroinflammatory processes are linked to αSYN transmission and neurotoxicity. We will study the relationship between αSYN transmission, neurotoxicity and neuroinflammation in rodent and non-human primate brain. The αSYN assemblies will be made de novo in vitro or purified and amplified from human brain samples of PD, MSA and Dementia with Lewy Bodies (DLB) patients. Samples of both sexes are represented. Readouts include behavioural, imaging, biochemical and histochemical analysis of αSYN assemblies, aggregation and propagation of the induced lesions in the rodent brain and affected areas. Furthermore, we will study the involvement of the innate and adaptive immune system by investigating the activation of microglia and the infiltration of peripheral leukocytes following the injection of different αSYN assemblies in rodent brain. A better understanding of the role of intercellular transmission and neuroinflammation in αSYN-linked neurodegeneration will contribute to early diagnosis, prevention and the development of novel therapeutic strategies for synucleinopathies and other ageing-related disorders.
10:15 - 10:30	**STAD: Synapse-to-nucleus communication in Alzheimer's disease (1)** *Monica DiLuca, University of Milano* *Abstract* Early synaptic dysfunction as well as defect of plasticity are key aspect of early pathogenesis of Alzheimer Disease. Recent evidence demonstrates that protein transport from synapse-to-nucleus plays key roles in synaptic function and plasticity. Moreover, several studies suggest that disturbance of intracellular transport processes is a common principle in many neurodegenerative diseases. STAD primary hypothesis is that alterations in synapse-to-nucleus transport represent a main pathway leading to synaptic dysfunction in Alzheimer's disease (AD), which can be exacerbated by dysmetabolism. Different synaptic versus extra-synaptic signals induce the nuclear import of specific protein messengers. The consortium evaluated the properties of these messengers by testing whether interfering with their nuclear import can be beneficial or detrimental with respect to progression of neurodegenerative diseases. In particular, we will focus on recently described synapto-nuclear messengers (Jacob, RNF10) addressing their role in the regulation of gene expression in AD and on glutamatergic synapses in a brain region, the hippocampus, where synaptic dysfunction has been described to occur in the early stages of the disease. This research question will be attained through the development and use of innovative experimental models, in which synaptic failure, amyloid load and dysmetabolism may reveal the complexity of pathways involved in the human pathology. STAD consortium characterized and compared different synapto-nuclear messengers through the development and use of novel AD models. In particular, in the first period we achieved interesting

	results on the effect of Aß to activate synaptic nuclear pathways mediated by Jacob and RNF10. The possibility that such trafficking effects are related to maladaptive plasticity is under investigation.

11:00 - 12:20	**Scientific session IV** **Topic 1: Advanced animal or cell experimental models of neurodegenerative diseases** **Topic 2: Genetic, epigenetic and environmental risk and protective factors of neuro-degenerative diseases,** *Chair: Jesus DE PEDRO*
11:05 - 11:20	**3DMiniBrain: High-Throughput, High-Content Screening of human neuroectodermal organoids for innovative drug discovery in neurodegenerative diseases (1,2)** *Jean-Philippe Deslys, CEA, France* ***No abstract available***
11:20 - 11:35	**CircProt: Synaptic circuit protection in Alzheimers's disease (AD) and Huntingtion's disease (HD): BDNF/TrkB and Arc signaling as rescue factors (1,2)** *Volkmar Lessmann, Institute of Physiology, Otto-von-Guericke-University Magdeburg, Germany* *Abstract* **Background:** Regulation of synaptic plasticity by brain-derived neurotrophic factor (BDNF) is crucial for brain function, as it pilots adaptive changes in neuronal networks. Pathological changes in BDNF availability and tropomyosine related kinase B (TrkB) signaling are therefore among the most relevant pathomechanisms in neurodegenerative disorders (NDs). Huntington´s disease (HD) and Alzheimer´s disease (AD) are both strongly associated with BDNF related impairments. While BDNF is recognized as an endogenous protective factor in both diseases, the development of therapeutic strategies has been hampered by the lack of knowledge on BDNF transport and release, and on BDNF/TrkB downstream signaling networks in these NDs. We propose that BDNF/TrkB signaling via Arc function is key for the management and treatment of synaptic dysfunction and neuronal degeneration in AD and HD. This project aims at identifying novel combinatorial and synergistic strategies to alleviate AD and HD related impairments based on regulation of TrkB and its downstream signaling cascades. In addition, since BDNF is an important TrkB upstream regulator, mobilization of endogenous BDNF synthesis, transport and release are investigated for their therapeutic potential. **Hypothesis and Strategy:** The key protective mechanism addressed is enhancement of endogenous BDNF protein expression induced by: enriched environment (EE), physical exercise (EXE), or application of drugs that enhance BDNF expression (fingolimod, fluoxetine) and BDNF vesicle transport (tubastatin and cysteamine), respectively. Advanced molecular imaging, synapse electrophysiology, spine density/morphology, biochemistry, and behavioral testing combined with computer assisted realistic neural network modeling, are used to determine optimal therapeutic strategies. The parallel analysis of AD and HD associated synaptic circuit dysfunctions and its drug-induced rescue will help us to identify common and divergent cellular pathways. Disease models used: 6-7 months old APP/PS1 mice as AD model. Long-term cultures (>80 days) of human HD patient iPSC-derived neuronal networks as HD model. **Results:** AD: Untreated AD mice held in standard housing conditions show reduced LTP and reduced spine densities in CA1 pyramidal cells of the hippocampus, compared to their wild type littermates. Preliminary behavioral data suggest that also context fear conditioning (CFC) and Morris water maze (MWM) performance are decreased in these cohorts of AD mice. Biochemical analysis of hippocampi obtained from untreated AD mice suggest alterations in translational control and Arc expression in APP/PS1 mice. These changes appear to be specific to CYFIP1/FMRP and eIF4E – pathways that are downstream of TrkB-ERK-MNK signaling. Providing AD mice with EE and EXE opportunities leads to increased hippocampal BDNF levels and rescues the LTP and the spine deficits. First biochemical analyses suggest that in AD mice provided with EXE the Arc/PS1 interaction is dysregulated in the hippocampus. This effect appears to be EXE treatment-dependent and induces Arc expression in the hippocampus. Treatment of AD mice with fingolimod also rescued LTP and spine deficits compared to untreated standard housed AD mice. Preliminary results indicate that deficits in hippocampal memory function (MWM) are also rescued in fingolimod treated AD mice. Detailed proteome

	analysis and completion of behavioral analyses of all cohorts is currently under way. Computational modeling of BDNF/TrkB dependent spike timing-dependent synaptic plasticity (STDP) in CA1 pyramidal neurons reveals a comprehensive understanding of BDNF-dependent vs. BDNF-independent mechanisms that are affected in the CA1 region of AD mice. HD: Neuronal differentiation of 3 different lines of HD patient derived iPS cells (iPSCs) was achieved. Differentiation of these long-term cultures (80 days) into either striatal or cortical neurons was obtained using distinct protocols. All 3 lines of HD patient iPSC-derived neuronal cultures show the expected decline in BDNF protein expression and TrkB signaling that was previously observed for HD affected brains *in vivo*. Microfluidic chambers allowing co-culture of striatal and cortical neurons in separate compartments that are connected by channels in which cortico-striatal synapses can form has been achieved. BDNF vesicle transport and TrkB signaling were quantified using live cell fluorescence imaging. When culturing HD mouse derived striatal and cortical neurons in this system, we observed reduced BDNF transport in cortical axons and reduced pERK activation, respectively, as previously described in HD mouse models. The microfluidic system will now be used to analyze BDNF/TrkB transport and signaling defects in HD patient-derived neurons, differentiated from iPS cells, to test the efficiency of potential anti-HD drugs (e.g. tubastatin) *in vitro*.
11:35 - 11:50	**PROP-AD: Propagation behaviour of peripheral amyloid-β towards brain structures: effects of the blood-brain barrier (1)** *Jens Pahnke, University of Oslo, Norway* **No participation from this project. No abstract available. Information about the project can be found on:** http://pahnkelab.eu/funding/prop-ad-jpnd/
11:50 - 12:05	**REfrAME: Pathway complexities of protein misfolding in neurodegenerative diseases: a novel approach to risk evaluation and model development (1,2)** *Giuseppe Legname,* SISSA, Trieste, Italy *Abstract* REfrAME consortium: Giuseppe Legname (partner 1), Giuseppe Di Fede (partner 2), Mathia Jucker (partner 3), Michel Goedert (partner 4), Jia-Yi Li (partner 5), Adriano Aguzzi (partner 6), Michal Novak (partner 7), Bernardino Ghetti (external collaborator) To address the hypothesis that the clinicopathological heterogeneity of AD, human primary tauopathies and synucleinopathies may be related to different Aβ, tau and a-syn conformers possessing distinct strain-like properties, we are collecting brain tissues from cases of AD, primary tauopathies and synucleinopathies, in addition to those already available in our labs. After the basic neuropathological characterization, the aggregates from human brains are being isolated and analyzed from a biochemical/biophysical point of view. Distinct conformers from human material are further characterized for their seeding activity and toxicity to answer the question whether these preparations are really strains with different biological activities. Recent progress in RNA interference and genome editing technologies (siRNA, CRISPR-Cas9) has enabled us the interrogation of the entire genome. Using these technologies, we have developed a "digital prion infectivity assay" for screening large numbers of genes for their potential to perturb prion propagation. We are now extending it to the study of α-syn aggregation. Here, we show to use the newly developed technology performing a systematic, comprehensive genomic screen aimed at identifying pathways mediating the propagation of pathogenic α-syn species. This endeavor will enable the discovery of novel genes and pathways involved in PD and potentially also in other neurodegenerative conditions.
12:05 - 12:20	**EPI-AD: Targeting epigenetic dysregulation in the brainstem in Alzheimer's disease (1, 2)** *Daniel van den Hove, Maastricht University, The Netherlands*

	Alzheimer's disease (AD) is a severe neurodegenerative disorder resulting in progressive cognitive impairment. Previous work indicates that epigenetic mechanisms (i.e. reversible changes to the DNA induced by the environment) represent critical factors in the development and course of AD. Moreover, neuropathological findings as well as the early occurrence of various neuropsychological symptoms suggests a key role for the brainstem, a brain region known to be critically important for the regulation of the stress response, in AD. Therefore, we aim to elucidate the exact role of epigenetic dysregulation in the brainstem in the pathogenesis of AD. For this purpose, we will examine post-mortem brainstem tissue derived from AD patients, and matched controls, for epigenetic differences. By investigating AD-specific epigenetic profiles in the blood of individuals suffering from Mild Cognitive Impairment (MCI), we aim to determine the predictive (biomarker) value of selected epigenetic signatures. Furthermore, we will test a novel model for AD using neuronal cells generated from blood cells of AD patients. By doing so, we aim to fill the vital gap in our understanding of the link between stress, epigenetic dysregulation and the development of AD, which may lead to novel targets to better diagnose, prevent, attenuate or possibly reverse the pathophysiology of this disorder. Central questions addressed within the EPI-AD project: - What is the exact role of the DNA (hydroxy)methylome within the brainstem (i.e. the dorsal raphe nucleus [DRN] and locus coeruleus [LC]) in the development and course of AD? - What about cell-type specific epigenetic signatures (e.g. DRN/5-HT cells)? - What is the relationship between AD-specific epigenetic signatures in the brainstem and in peripheral blood samples of the same individuals? - Are the observed AD-specific epigenetic changes causally involved in the development of AD-hallmarks or do they rather represent a consequence of their formation? Expected project outcomes include the identification of novel AD-specific epigenetic loci and molecular pathways that can be used for the establishment of non-invasive and clinically-relevant biomarker assays for the early diagnosis of AD, i.e. predicting vulnerability and/or resilience towards cognitive decline and the development of AD. Furthermore, this project will aid the development of novel therapeutic approaches that could prevent, attenuate or possibly cure AD. Project progress: - Methylome & hydroxymethylome analyses in DRN and LC nearly finalized (using BS- & oxBS-treated DNA and Illumina EPIC Beadarrays). - Laser-capture microdissection (LCM) on DRN tissue (5-HT cells) completed. - Single cell limiting diluting bisulfite sequencing (LDBS) established using candidate genes derived from middle temporal gyrus (MTG) study. - Serotonergic differentiation of iPSCs ongoing. - Epigenetic editing (CRISPR/cas9) being validated *in vitro*. - Biomarker assessment in German AgeCoDe cohort highlighting various differentially methylated regions (DMRs) predicting conversion to AD. - Pronounced overlap between blood and brain (MTG) methylome and hydroxymethylome profiling.
12:20 - 12:55	**Demonstration of new JPND tools** *Experimental models site, cohort portal, mapping database* Marie Therese FUZZATI-ARMENTERO and Catherine MOODY See www.neurodegenerationresearch.eu