1. Publishable Summary

1.1. MEMORIES project objectives

Alzheimer's disease (AD) is a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason, make judgments, communicate and carry out daily activities. The disease is the major kind of dementia affecting elderly people. It accounts up to 26.6 million people worldwide. The global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, at which time 1 in 85 persons worldwide will be living with the disease It is estimated

AD is characterized from the neuropathological standpoint, by characteristic hallmarks in the brains of affected people. The pathological hallmarks of AD include the presence of intracellular and extracellular inclusions, deriving from the abnormal processing of the APP protein, neurofibrillary tangles (NFT), from the microtubule associated protein tau, and neuronal cell loss. The basal forebrain nuclei (which provide cholinergic innervation to the neocortex and hippocampus, to perform learning, memory and attention task) are severely and selectively affected in AD brains

Notwithstanding major efforts, no early diagnosis, no clear aetiology and no cure have been found for AD. Indeed, although there have been significant advances in understanding the biology and subsequent diagnosis of AD, such

research has not been translated into a disease modifying treatment, yet.

One major hurdle, in target discovery and drug screening for AD, is the lack of suitable animal models fully reproducing the AD neurodegeneration. It is clear that an animal model that fully reproduces the characteristics of the disease, will allow to characterize the targets and the pathways involved, and to test the efficacy of mechanism related therapies, in the long-standing quest towards a disease-modifying therapy for AD. In the past decade, AD research has been fundamentally influenced by the development of genetically modified animal models of amyloid-driven or tau-driven neurodegeneration. These *in vivo* models were developed on the basis of early-onset forms of the disease determined by rare, inherited mutations were advantageously used to screen the efficacy of compounds or treatments directly targeting the AD targets (e.g. amyloid active and passive vaccination, gamma and beta secretase inhibitors), but are of more limited use to investigate mechanisms leading to sporadic forms of AD. Therefore, there is a need for new models that would allow studying the mechanisms leading to sporadic AD.

A model for sporadic AD should involve molecular and cellular mechanisms upstream of the common core of AD hallmarks and should take into consideration the multifactorial nature of sporadic AD.

The MEMORIES project aimed at developing new mouse models for sporadic AD, based on the hypothesis that a deficit (or an unbalance) of neurotrophic processing, transport or signalling, contributes to the onset and progression of AD neurodegeneration. The neurotrophic hypothesis for AD neurodegeneration links deficits in the neurotrophic activity in the brain to the pathological activation of amyloid and tau post-translational processing.

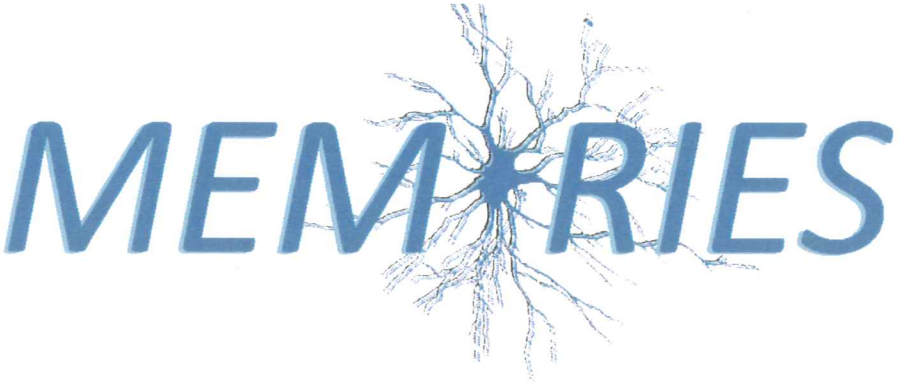
Previous work on the anti-NGF model was crucial to provide experimental grounds to the formulation of the "neurotrophic imbalance" hypothesis as an upstream driver to sporadic AD neurodegeneration.

The MEMORIES project gathered together 8 partners from 6 different countries towards the aim of developing, characterising and validating new animal models that have a real potential for becoming a gold standard in the AD field.

Using a multidisciplinary approach, a panel of mouse models have been produced and analyzed for the presence of neurodegeneration. These models include mice with modified NGF and BDNF signalling, mice expressing uncleavable forms of pro-NGF, and mice in which the genes for NGF and NGF receptor TrkA are conditionally deleted. Anti-NGF mice,

which already represent a good model for sporadic AD, were crossed to mice in which proconvertases or SorLA receptors and Sortilin are knocked-out. Mice were analyzed using standardized methods for neuroanatomy and behavioural analysis. We found that the modulation of different signalling or processing pathways in these mice improved our knowledge on mechanism leading to neurodegeneration and allowed to identify new candidate biomarkers with diagnostic potential.
The potential medical benefits that will derive from this study, although indirect, are invaluable.

Project logo:



The Public website www.fp6-alzheimer-memories allowed the dissemination of MEMORIES results to scientific, clinical and citizen communities.

1.2. Contractors involved in MEMORIES project and Coordinator contact details

MEMORIES Consortium:

Role	*No*	*Partner*	*Short name*	*Country*
CO	1	European Brain Research Institute Foundation	EBRI Foundation	Italy
CR	2	Neuréva Inc.	Neuréva	France
CR	3	Max Delbrück Centrum Für Molekulare Medizin	MDC	Germany
CR	4	European Molecular Biology Laboratory	EMBL	Italy
CR	5	-	-	-
CR	6	University of Helsinki	UHEL	Finland
CR	7	-	-	-
CR	8	-	-	-
CR	9	NeuronIcon	NeuronIcon	Denmark
CR	10	-	-	-
CR	11	Ecole Polytechnique Fédérale de Lausanne	EPFL	Switzerland
CR	12	Projets et Réseaux de Recherche	P2R	France

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1.3. Work performed during the MEMORIES project

The main research work involved a preliminary period during which partners exchanged, standardized and validated experimental protocols to evaluate the neurodegeneration phenotype of the mice produced. During this first phase lines of existing transgenic mice were exchanged between the partners, to start crossbreeding programs to establish new lines. Then, the construction and experimental validation of trasngenes, the derivation of corresponding lines of mice and the phenotypic characterization of these mice were obtained. In addition, mechanistic studies on AD11 mice and cell biology studies on neurotrophic signalling, pro-protein convertase activity, and APP processing were performed.

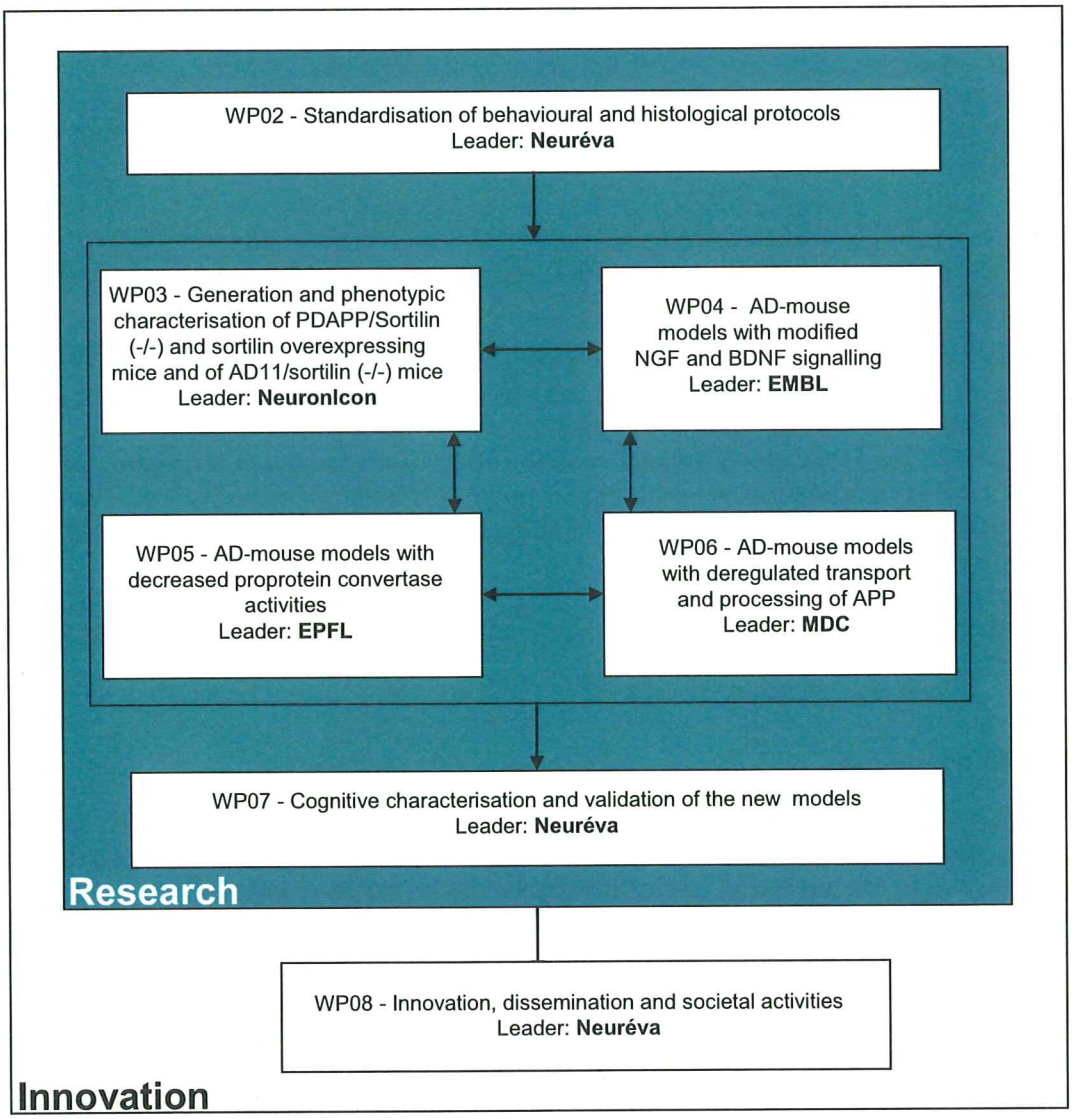

Figure 1: Overview of the MEMORIES project

1.4. Results obtained during the MEMORIES project and achievements related to the state-of-the-art

The results achieved during the Memories project have allowed to:

1) confirm an important role for sortilin in acute and chronic neurodegenerative processes, identifying a role not only in proNGF signaling but also in control of amyloid peptide production and plaque burden,
2) characterize *Trka* conditional knockout mice a s a model for sporadic AD. The results obtained from this model and Ngf conditional knockout mice confirmed that a

proNGF/p75 mediated neurodegenerative signalling could be responsible for the AD-like phenotype

3) Neither increase nor decrease in trkB signaling in brain influences memory deficits in APP mice, showing a lack of interaction between this two genes.
4) The phenotypic characterization of AD11; F+SS and proNGF mice confirmed the possible contribution of an altered proconvertase expression and of proNGF to the mechanisms leading to AD-like neurodegeneration.
5) The role of SORLA as negative regulator of APP processing and modulator of AD risk in transgenic mouse models *in vivo* was confirmed by the studies performed on the amyloidogenic process in SorLA Knockout mice and by crossing them to anti-NGF mice
6) Confirm that SAM R1 and SAMP8 mice are global senescence models and not AD models.
7) Propose innate and adaptative immune systems mRNAs and SorLA fragments as candidate biomarkers for other AD mouse models and for human Alzheimer's disease.

1.5. Expected outcome, intention for use and Impact of the MEMORIES project

The creation of mouse models that, based on a well defined and understood molecular mechanism, provided not only insights into the neurobiology of the disease but to identify new biomarkers with a diagnostic potential.
The anti-NGF and the new mouse models were comparatively analyzed and validated through the use of standardized protocols. The identification of proteins linked to the specific cellular pathways will provide the possibility to develop new diagnostic assays and new drug targets for the treatment of AD.
In future, mouse models will also make it possible to visualize neural circuits in their normal and abnormal states, which is likely to have an impact on the diagnosis of disease and the evaluation of the effectiveness of therapy.

1.6. Conclusion

In the field of human Alzheimer's disease, it is assumed that the familial early onset and the sporadic late onset forms of the disease (EOAD and LOAD respectively) are clinically equivalent, save for the much earlier onset. However, there is presently a gap in translating the mechanistic information available for FAD into useful concepts for LOAD. Part of this gap is due to the issue of mouse models. Most mouse models available are based on the expression of mutant forms of human AD genes as found in FAD (APP or PS1 and PS2), but fail to recapitulate the comprehensive picture of neurodegeneration. On the other hand, mouse models for LOAD need to be derived based on a hypothesis about mechanisms. The AD11 anti NGF mouse model has been derived, based on the hypothesis that neurotrophic deficits in the adult CNS can represent an upstream driver for neurodegeneration and aberrant APP processing as found in LOAD. Similarly, targets such as sortilin and sorLA, are important in providing mechanistic links between neurotrophin signalling and APP processing and trafficking. The MEMORIES study confirmed the validity of approach used by the different partners to dissect mechanisms underlying the onset of neurodegeneration linked to LOAD, and provided new information on different models and different mechanisms highly relevant for human sporadic AD.

5. Dissemination of knowledge (M1-M42)

The document includes the section 3 "Publishable results" of the final Plan for using and disseminating the knowledge. Deliverable D8.9: Final exploitation plan report (M42) provides extensive information on dissemination and exploitation activities carried out during the MEMORIES project and beyond.

Publishable results

#	Self-descriptive title of the result	Current stage of development	Partner(s) owning the result(s) (
Period 1			
1	2008: P1895DK00. "Modulation of the Vps10p-domain receptors for treatment of cardiovascular disease". Inventors: M. Kjølby, P. Jansen, A. Nykjaer	Patent filing, achieved	Neuronicon
2	2008: P1896DK00. "Treatment of neuropathic pain by modulation of the Vps10p-domain receptor family". Inventors: O.J. Bjerrum, P. Jansen, C.B. Vægter, A. Nykjaer	Patent filing, achieved	Neuronicon
#	**Self-descriptive title of the result**	**Current stage of development**	**Partner(s) owning the result(s) (**
Period 2			
3	Trade sale of patent portfolio in NeuronIcon to Lundbeck A/S related to the activities in MEMORIES	Trade sale to pharmaceutical partner	NeuronIcon
4	PC reporter substrate (screening for regulators of PCs)	Technology licencing filed	EPFL
5	2009: USA patent n°61/248,888	Provisional patent granted	EPFL