Acronym of the project	**DISTALZ**
Titre du projet en français	Développement de stratégies innovantes pour une approche transdisciplinaire de la maladie d'Alzheimer
Project title in English	Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease
Project manager (chercheur, enseignant chercheur…)	**AMOUYEL Philippe** Université de Lille 2 – CHRU de Lille Laboratoire / Laboratory : Public Health and Molecular Epidemiology of Ageing Diseases Numéro d'unité/Unit number : UMR744 Inserm-Lille2-IPL
Requested funding	21 545 723,68 € TVA non récupérable incluse
Scientific field(s) of the project	☐ Sciences de la Matière et de l'Energie ☐ Sciences du Système Terre-Univers-Environnement ☑ Sciences de la Vie et de la Santé ☐ Sciences du Numérique et Mathématiques ☐ Sciences Sociales ☐ Humanités

Ce projet, ou un projet proche, a-t-il été soumis pour LABEX2010 ?	☑ Non	☐ Oui Acronyme du projet : Coordinateur du projet :
Ce projet est-il la suite, pour tout ou partie, d'un ou plusieurs projets soumis à LABEX2010 ?	☑ Non	☐ Oui Acronymes des projets Coordinateurs

Ce projet est-il partie prenante d'un projet d'Idex ?	☐ Non	☑ Oui Acronyme de l'Idex : LILLE EVOLUTIONS

Institution leading the project (project leader – see definition in the call for proposals)

Nom de l'établissement / Institution name	Statut / Status
PRES ULNF	EPCS

Institution managing the fundings (see definition in the call for proposals), to be completed if different from the project leader

Nom de l'établissement / Institution name	Statut / Status

projet/partner's affiliation (see definition in the call for proposals)

Laboratoire(s)/ Laboratory	Numéro(s) d'unité/ Unit number	Tutelle(s)/Research organization reference
Public Health and Molecular Epidemiology of Ageing Diseases	UMR744	Inserm, Université de Lille 2, Institut Pasteur Lille
Molecular and cellular biology of normal and pathological cerebral ageing	UMR6097 Eq 6	CNRS, Université de Nice Sophia Antipolis
Alzheimer & Tauopathies	UMR837 Eq 1	Inserm, Université de Lille 2, Centre Hospitalier et Universitaire de Lille
Nuclear Magnetic Resonance and structural biochemistry	UMR8576 Eq 2	CNRS, Université de Lille 1
Lille Memory Resources and Research Centre	Lille MRRC	Centre Hospitalier et Universitaire de Lille, Université Lille 2
Research Unit on Cognitive and Affective Sciences	EA1059	Université de Sciences Humaines et Sociales - Lille 3 Charles-de-Gaulle
Ethics, sciences, Healthcare and society	EA1610 ES3	Université de Paris Sud XI

GLOSSARY

Aβ: β-amyloid peptide
AD: Alzheimer's disease
ADC: European Alzheimer Disease Consortium
ADGC: AD Genetic Consortium
AERES: Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
AICD: APP IntraCellular Domain / APP: Amyloid Precursor Protein
AP-HP : Assistance Publique des Hôpitaux de Paris
AVIESAN: Alliance pour les sciences de la vie et de la santé
CATI: Automated Treatment Imaging Centre
CenGEPS: Centre National de Gestion des Essais des Produits de Santé
CNG: National Centre for Genotyping
CHARGE: Cohorts for Heart and Aging Research in Genomic
CNRS: Centre National de la Recherche Scientifique
CNS: National Centre for Sequencing
CNV: Copy Number Variations
CoEN: Centre of Excellence Network
CREST: Centre de Ressources et d'Expertise Scientifique et Technologique
CT: computed tomography
DIAN: Dominantly Inherited Alzheimer Network
DZNE: Deutsches Zentrum für Neurodegenerative Erkrankungen
EADI: European Alzheimer's Disease Initiative
ED: Ecole Doctorale
EGI: European Grid infrastructure
EREMA: Espace national de réflexion éthique sur la maladie d'Alzheimer
EOD : Early Onset Dementia
EU: European Union
FENS: Federation of European Neurosciences
FP: framework programme
GERAD: Genetic and Environmental Risk in AD
GMA: group methodology Alzheimer
GSAP: gamma secretase activating protein
GWAS: Genome Wide Association Studies
HDR: habilitation à Diriger des Recherches
IBiSA : Infrastructures Biologie Santé et Agronomie

ICM: Institut du Cerveau et de la Moëlle
IGAP: International Genomic AD Project
IHU: Institut Hospitalo-Universitaire
Inserm: Institut National de la Santé et de la Recherche Médicale
IPL: Institut Pasteur de Lille
IPMC: Institut de Pharmacologie Moléculaire et Cellulaire (Partner 2 : UMR6097)
ITMO : Institut Thématique Multi Organisme
JPND: Joint Programming on Neurodegenerative Diseases and Alzheimer's disease in particular
LECMA: European League against Alzheimer's Disease
LIGAN: Lille Integrated Genomics Advanced Network
MB: Management Board
MRI: Magnetic Resonance Imaging
MRRC: Memory Research and Resource Clinic (Partner 5)
NFT: Neurofibrillary Tangles
NHL: Nutrition Health Longevity (NSL: Nutrition Santé Longévité)
NMR: Nuclear Magnetic Resonance
NFD: Neurofibrillary degeneration
NRC: National Reference Centre
PET: positron emission tomography
PI: Principal Investigator
PRES ULNF: Pôle de recherche et d'enseignement supérieur Université Lille Nord de France
SAB: Scientific Advisory Board
SATT: Accelerated Technology Transfer Society
SC: Strategic committee
SMART: Simultaneous Multiple Acquisition in Resonance and Tomography
SME: small and medium entreprise
SNP: single nucleotide polymorphisms
SNRI: Stratégie nationale de recherche et d'innovation
T : Tesla
TMP21 : Transmembrane emp24 domain-containing protein 10
UMR : Unité Mixte de Recherche
UNSA : Université de Nice Sophia Antipolis
WES / WGS: Whole Exome Sequencing / Whole Genome Sequencing
WHO: World Health Organisation
WOK: Web of Knowledge
WP: workpackage
YOD: Young-Onset Dementia
3C: Three City Study

Summary

Context and objectives - Alzheimer's disease (AD) is the most common neurodegenerative disease, which progressively and ineluctably leads to massive brain neuronal death. After age 65, the likelihood of developing dementia roughly doubles every five years. The worrying medical, social and economic scale of AD is in marked contrast to the lack of solutions available to efficiently tackle this major threat to individuals and society. This challenge has been taken into account in France since 2008 through a five-year national plan aimed at fostering research in the AD field by promoting the emergence of additional research units and strengthening pre-existing ones with international visibility. To confirm this momentum and ensure its durability, several of these research units, which are among the very best and most productive in France, have decided to combine their multidisciplinary skills, from basic to social concepts, to create a unique laboratory of excellence (Labex). The Labex will integrate various basic approaches, from agnostic genomics to highly sophisticated biological models, and combine clinical approaches with social and ethical concerns. This will make it possible to join forces in a unique laboratory with a common research programme and a major critical mass ready to overcome some obstacles of AD research, and to accelerate discovery and translation of innovative solutions from new potential drug targets into socially and ethically appropriate answers. This Labex will be named DISTALZ, for Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease. It will rely upon the presence of international leaders in complementary AD basic research fields, bringing together genomics and epidemiology of aging diseases (UMR744, P. Amouyel, Lille), molecular and cellular biology of Tau pathology (UMR837 L. Buée, Lille) and amyloid related pathologies (UMR6097 F. Checler, Sophia Antipolis), and a biophysicist involved in atomic interactions of AD proteins (UMR8576 G. Lippens, Villeneuve d'Ascq). To go further in this multidisciplinary approach, internationally renowned clinicians and key opinion leaders involved in translational research (Lille MRRC, F. Pasquier, Lille), motivated social and healthcare researchers (EA1059 P. Antoine, Lille) and ethics specialists (EA1610 E Hirsch, Paris) will be also fully integrated in a common research project.

In this context, the objective of DISTALZ is to explore current and new hypotheses involved in the AD pathophysiological process, including amyloid and Tau-related pathways, especially in regard to new genetic findings emerging from genomic research, and to derive from this knowledge new biological clues that will be developed as potential biomarkers and putative drug targets. Moreover, the multidisciplinary approach of DISTALZ will allow to set up the biological, clinical, social and ethical bases of clinical trials aimed at recruiting individuals or patients with the highest AD risk, identified thanks to a sophisticated battery of biomarkers, years before any conversion to AD. DISTALZ will offer a common identity with a competitive critical mass in terms of researchers and research capacities, potentiating the existing international visibility of each individual team, significantly increasing their attractiveness, offering a unique setting for higher-education programmes, favouring translational medicine, technological transfers and public information, able to compete and collaborate with other centres of excellence in neurodegenerative disease around the world.

Research project – This objective will be developed along four research axes:

1. From gene to pathophysiological hypotheses. DISTALZ will pursue the characterisation of the genetic component of AD, decoding the missing heritability, performing a fine mapping of AD genes to identify functional variants and fuelling the following axes with putative new pathophysiological hypotheses.

2. From pathophysiological hypotheses to biological pathways. DISTALZ will study the impact of these genes and pathways on amyloid and tau metabolisms in experimental models and in particular the mechanisms controlling the enzyme activities that modulate production/clearance of Aβ, the implication of recently described APP fragments, the roles of Tau and finally the protein aggregation and propagation. This will lead to the development of more comprehensive experimental models for biological drug screening tests.

3. From biological pathways to effective targets. DISTALZ will aim to develop relevant genetic and biological tests stemming from the results of axes 1 and 2. The necessary validation of the new biomarkers will be carried out in the framework of the epidemiological and clinical activities of DISTALZ partners, taking into account the complex interactions with other neurodegenerative and cerebrovascular diseases and aiming ultimately at a personalised medicine approach to AD care.

4. From effective targets to clinical trials. DISTALZ will accelerate the translation of new findings to clinical activity by allowing access to precisely characterised patients at an early stage of the disease and by anticipating the psychological and social consequences of an early diagnosis, taking into account all ethical dimensions.

Teaching and training - Labex support for DISTALZ will enable to develop an international, cutting-edge education programme on AD and related disorders along four major educational axes:
1. Development of an AD-specific academic programme within the **advanced Erasmus Mundus European Masters programme** "Multifactorial diseases: from bench to society", that will be set up in Lille, Nice and Paris, in collaboration with eight other European universities.
2. **An international summer school** targeting physicians and scientists with a major interest in AD and other neurological disorders, as part of an educational programme covering both theoretical and practical aspects for AD and related disorders, taking place every two years.
3. In the field of **social and healthcare sciences, thematic workshops** and a summer university on ethics in AD will be expanded, and **an education programme for general practitioners** will be proposed.
4. A specific educational support will be provided to the DISTALZ students and fellows. This programme will combine: specific support to attend international conferences, a yearly internal meeting, mobility awards given to the PhD students and a large range of professional training courses.

Utilisation and exploitation of results - DISTALZ will have a major impact in the academic field, in the economic environment and in the societal context that will be key to its international visibility, its national return on investment and its social added value.
1. Scientific impact: DISTALZ discoveries will cover multidisciplinary approaches, from the discovery of new pathways to their potential impact assessment in human pathophysiology, and therefore should lead to comprehensive articles published in high quality peer review journals. DISTALZ will also firmly encourage presentations in scientific meetings to increase its international visibility, and will organise every two years an internal scientific meeting.
2. Economic impact: DISTALZ will benefit from the support of a consortium grouping several of its partners and two biotechs (Genoscreen, Alzprotect) to accelerate the development of biomarkers and of therapeutic targets, accelerating the translation to clinical practice. Collaboration strategy with large national and international companies, with existing start-ups and the establishment of new ones will be promoted in close interaction with the dedicated regional bodies (accelerated technology transfer society in progress and Eurasante bioincubator). This will aim at building up a long-term, sustainable source of funding.
3. Societal impact: DISTALZ will have intensive information and communication plans structured around its active participation in organising international, national and local scientific meetings, and conferences for the general public, publishing documents for non-specialised audiences. Furthermore it will contribute to any public or private initiatives aimed at informing and preparing the general public about presymptomatic diagnosis, prevention, social and ethical concerns and helping decision-makers with their health and social policies.

Governance – DISTALZ will group together five Universities (Lille 1, Lille 2, Lille 3, Nice Sophia Antipolis, Paris XI), three research organisations (Inserm, CNRS, Institut Pasteur de Lille) and the Lille University Hospital. The organisational structure will enable fair, simple and efficient management within a Strategic Committee (SC) and a Management Board (MB) advised by an external Scientific Advisory Board (SAB). The SC, composed of the DISTALZ Principal Investigator, the research directors from each partner and a representative of each supervising institution will be the reference body where strategic discussions will be debated. The MB, composed of the PI and the seven research directors, will be the management and operational body. DISTALZ will be managed and represented by a Director, assisted by three Deputy Directors, each in charge of a specific domain: research, education and innovation. Every two years, the MB will perform a thorough independent, international scientific evaluation to maintain a high level of productivity and competitiveness.

Integration within regional, national and international scientific policies - DISTALZ has the intrinsic support of the supervising universities, the PRES Lille Nord de France a cluster of higher-education institutions, the Institut Pasteur de Lille and all the local authorities and economic stakeholders of the Lille Region. DISTALZ will be a major research priority and its themes are already identified in the research axis related to dementia in neurological and mental diseases founded by the Conseil Régional Nord Pas de Calais. The DISTALZ programme is in step with the French national SNRI and AVIESAN priorities. DISTALZ is also in line with the European strategy for neurodegenerative research structured around the Joint Programming Initiative (JPND) involving 23 countries, aiming at improving funding efficiency at the EU level and headed by the DISTALZ PI.

1. TECHNICAL AND SCIENTIFIC DESCRIPTION OF THE PROJECT

1.1. PROGRAM DESCRIPTION, VISION, AMBITION AND SCIENTIFIC STRATEGY

Alzheimer's disease (AD) is the most common neurodegenerative disease, which progressively and inexorably leads to massive brain neuronal death. It firstly affects memory and cognitive functions, induces changes of mood, disorientation in time and space and finally disintegrates personality leading to medical but also social major burden[1]. After age 65, the likelihood of developing dementia roughly doubles every five years. Alzheimer's Disease International estimated that there are 35.6 million people living with dementia worldwide in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050. Nearly two-thirds live in low- and middle-income countries. The total estimated worldwide costs of dementia are US$604 billion in 2010. If dementia care were a country, it would be the 18th largest economy, between Turkey and Indonesia[2]. The scale of this issue, which may be one of the most worrying medical, social and economic questions affecting our society in the coming years, is in marked contrast to the lack of solutions available to efficiently tackle this major threat to individuals and society.

A) Vision and ambition

Evidence has accumulated during the last 25 years indicating that AD is a disorder of protein aggregation in which two major components are concerned: β-amyloid peptide (Aß) produced by the sequential endoproteolysis of the amyloid precursor protein (APP)[3], and Tau, a microtubule-associated protein. Alterations in the biogenesis of these proteins account for the main histological lesions that accumulate in the brain of AD patients, i.e. the senile plaques and the neurofibrillary tangles (NFT). These lesions underlie the two current major pathophysiological hypotheses: (i) the amyloid cascade, centred on Aß and its toxicity[4] and (ii) the neurofibrillary degeneration, resulting from the aggregation of microtubule-associated Tau proteins[5]. The amyloid cascade hypothesis proposes an overall increase in Aß load. In rare familial early onset AD, this accumulation results from an overproduction of Aβ; such augmentation could occur from reduced proteolytic rates in frequent sporadic late-onset AD[6]. Recent evidences suggest that the amyloid cascade could be linked to soluble Aβ oligomers rather than Aβ monomers[7]. These oligomers could be the pathogenic trigger of degenerative process, as with Tau fragments: once Aß oligomers begin to invade the brain, this triggers a series of downstream events including neurites damage and thereafter neuronal death, in which the accumulation of Tau could play a critical role. However, how aggregated Aß damages the brain and stimulates tangle formation continues to be an area of intensive research and a major challenge for basic research[8].

Our understanding of AD's pathophysiological pathways has considerably evolved over the last 15 years, unmasking new tracks and offering opportunities for the development of new pharmacological targets and cellular/animal models. However, to date, most treatments directed toward these pathways have failed in slowing down the degenerative processes[9]. One possible explanation might be related to the long standing process of brain damage and the delayed initiation of treatment at a stage where dementia is irremediably present, with no hope of resilience of the brain functions. In that context, a major challenge for treatment is to identify the optimal time windows for intervention. This will require a better understanding of the pathophysiological pathways and the development of appropriate biological and imaging markers tools, a *sine qua none* condition to obtain earlier diagnoses. In parallel, other solutions aiming at preventing or slowing-down neurodegeneration through risk factor modifications such as physical exercise and vascular risk treatment have been also proposed but not yet clinically validated[10,11]. Finally, in the absence of efficient therapeutic solutions, the major social impact of AD has to be considered and act as a spur to the development of social and ethical research.

Considering the major importance of neurodegenerative diseases and AD in particular, several countries have proposed highly structured research and prevention programmes. In 2008, France launched a five-year national plan for AD, which includes promoting research[12]. This plan made it possible to improve coordination of AD research in France and acted as a stimulus to catch up on delays compared to other countries. This plan, which ends in 2012, has led to the reinforcement and emergence of several research groups with international visibility, and made it possible to set up efficient multidisciplinary collaboration at a national level.

To capitalise on this momentum and ensure its durability, some of the very best and most productive French research units in the field of AD research have decided to scale up their complementary skills and collaborations by creating a laboratory of excellence (Labex). This Labex will promote a comprehensive view of the current AD pathophysiological models, bringing together basic, clinical, social and healthcare researchers and joining academic and private sectors for the benefit of the patients and their families.

This approach will reduce the current fragmentation of AD research that hampers the necessary interactions required to tackle complex diseases. This Labex will integrate more efficiently the skills of the partners' research groups offering a unique opportunity to develop multidisciplinary approaches, thereby accelerating discoveries and the translation of innovative solutions with socially and ethically appropriate answers.

The Labex relies upon the presence of international leaders in complementary and multidisciplinary fields of AD research, from bench to society. It brings together specialists in genomics and epidemiology of aging diseases (UMR744, Lille, AERES A+), source of the discovery of new AD genes, driving research on new pathophysiological AD processes. Two outstanding research units will participate, both of which are involved in the two major AD pathways: UMR6097 (Sophia Antipolis, F. Checler, AERES A+), source of the deciphering of APP and amyloid metabolism regulation and UMR837 (Lille, L. Buée, AERES A+), internationally renowned for its work on the molecular and cellular biology of Tau pathology. The Labex has also attracted biophysicists involved in the study of atomic interactions of AD-related proteins such as Tau in UMR8576 (Villeneuve d'Ascq, G. Lippens, AERES A) that has performed in-depth nuclear magnetic resonance spectroscopy (NMR) analysis of proteins involved in AD such as Tau. An internationally renowned neurologist, F. Pasquier, head of the Lille Memory Resource and Research Centre, a hospital department (Lille MRRC), has joined the project to develop translational research. To address the major social and ethical consequences of this research and of this disease, two research units are also participating in this Labex: the EA1059 (Lille, P. Antoine, AERES A), which is developing a research programme on cognitive and affective sciences, psychology and health, especially in the family environment, and the EA1610 (Paris, E. Hirsch, AERES A) the French specialist in AD ethics. **All these researchers are deeply involved in national or international structures related to AD research**. P. Amouyel, who will be the principal investigator, is in charge of coordinating the research part of the National Alzheimer's Plan and chairs the European Joint Programming initiative on neurodegenerative disease and AD in particular; four of the researchers (P. Antoine, L. Buée, F. Checler, F. Pasquier) are on the operational committee of the Fondation Plan Alzheimer, the national entity that coordinates AD research; Emmanuel Hirsch heads the national centre for ethical reflections on AD (EREMA); Florence Pasquier is the coordinator of the National Reference Centre for Young Onset Dementia (NRC-YOD).

Such a concentration of high-level specialists from various complementary fields, unique in France, will aim at generating transdisciplinary approaches, to unlock some of the dead ends where AD research is blocked and to help make breakthrough hypotheses emerge in an evolving landscape.

B) Scientific strategy

The Labex named DISTALZ (Development of **I**nnovative **S**trategies for a **T**ransdisciplinary approach to **ALZ**heimer's disease) will stimulate permanent cross-sectional interactions in a structured organisation based on a common scientific research project to which each team will bring its complementary and specific skills. Gathering these skills will unify under a common identity a huge competitive critical mass of researchers and research capacities, potentiating the existing international visibility of each individual team, significantly increasing their attractiveness, offering a unique setting for higher-education programmes in the field of AD, favouring translation to medical practice, technological transfers and public information.

Each partner will put forward its most innovative hypotheses enriching or modifying the classical way of thinking in AD research. Some of these hypotheses will emerge from the new genes identified through agnostic whole genome approaches generating unexpected pathophysiological hypothesis or interconnecting existing ones. Other hypotheses will emerge from the characterisation of new players in the amyloid cascade, such as the role of Aβ oligomers and newly revealed APP fragments, and from the dissection of new functions of Tau, such as its nuclear function or its propagation. By integrating the results of these different hypotheses, it will be possible to characterise new biomarkers, new putative drug targets, novel cellular and *in vivo* experimental models intended to improve diagnosis and to accelerate treatment discovery. Finally, the analysis of the social and ethical consequences will allow the translation of these transformative approaches in clinical research in the best conditions for the patients.
The scientific strategy of the multidisciplinary scientific programmes of DISTALZ will be organised from bench to society along four major axes where the wide and complementary expertise of DISTALZ partners will give rise to multi-directional approaches allowing filling up the main gaps in our understanding of AD pathology:

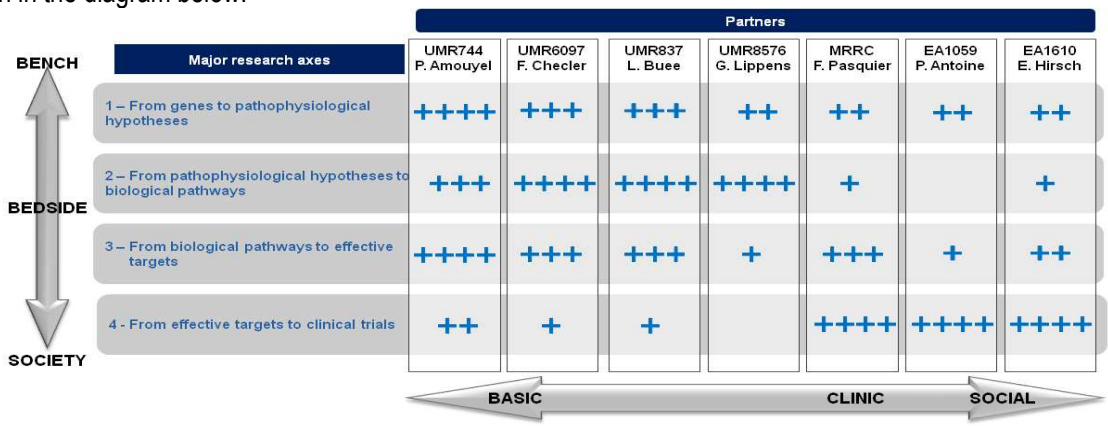
1. From genes to pathophysiological hypotheses: DISTALZ partners will complete the characterisation of genetic risk factors and decode the missing heritability of AD, using genomics high-throughput techniques, bioinformatics and new statistical approaches, exploring both early- and late-onset forms, hereditary and sporadic cases in international collaborations. Benefiting from the experience of DISTALZ molecular and cellular biologists, new metabolic pathways, genes, transcripts and peptides or proteins will be identified, potentially useful for diagnosis and therapeutic purposes.

2. From pathophysiological hypotheses to biological pathways: the new pathophysiological hypotheses will be investigated addressing simultaneously the most advanced amyloid and tau pathophysiological mechanisms. These pathways will be investigated in depth using classical and new cellular and animal models with a particular focus on the mechanisms controlling secretase/protease activities to modulate production/clearance of Aβ, on the implication of recently described APP fragments and on the additional roles of Tau in protein aggregation and propagation.

3. From biological pathways to effective targets: DISTALZ partners will aim at characterising and developing biomarkers and therapeutic targets, taking into account the complex interactions with neurodegenerative and cerebrovascular diseases. The necessary validation of these new biomarkers and putative drug targets will be carried out in the framework of DISTALZ partners' epidemiological and clinical activities, taking into account the complex interactions with other neurodegenerative and cerebrovascular diseases in particular, and aiming ultimately at a personalised medicine approach to AD.

4. From effective targets to clinical trials: the development and implementation of biological, clinical, social and ethical strategies useful for the early detection of patients. DISTALZ will build up proposals for a comprehensive approach to the questions raised by the implementation of early diagnosis necessary to optimise treatment efficacy in clinical trials and, later, in the population. DISTALZ will also address the ethical issues triggered by its scientific approaches, such as the use of genetic biomarkers.

At least six DISTALZ partners will simultaneously participate in each of these four multidisciplinary axes, as shown in the diagram below:

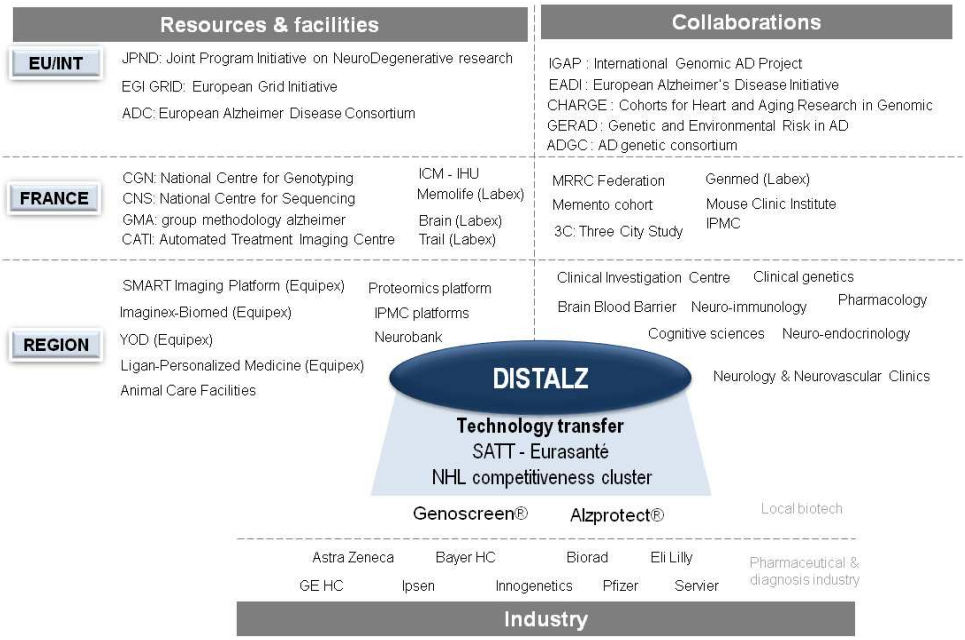


DISTALZ partners have access to several facilities and platforms enabling them to reach their common objectives. Most of the genomics production is outsourced to national facilities like the CNG (National Centre for Genotyping) or the CNS (National Centre for Sequencing). Moreover, UMR744 is a partner of the Lille Integrated Genomics Advanced Network, the core of the LIGAN-Personalised Medicine Equipex platform. For bioinformatics, DISTALZ uses a grid computing facility developed by UMR744 and the European Grid Infrastructure[13]. DISTALZ can access the ImaginEX Bio Med Equipex platform for cellular and molecular imaging and functional and proteomics platforms both in Lille and Nice. DISTALZ benefits from an imaging facility for small animals with two MRI devices (0.2T and 7T), a micro-PET/CT and Xenogen and Cell Vizio imaging systems. DISTALZ partners are registered users of a high-level human brain imaging platform composed of three 3T MRI, including one dedicated to research only, and one PET scanner. Moreover, a 7T MRI and a PET-MRI should soon be acquired in Lille. This imaging platform, named SMART, has been submitted to Equipex 2011. DISTALZ stores its biological samples in two Biological Resource Centres identified at the Research Ministry level, one under the control of the Institut Pasteur de Lille managed by UMR744 and storing the largest DNA bank of AD cases and controls (with more than 30,000 individuals) in Europe, and the other one under the control of the University Hospital of Lille within a Clinical Centre for Investigation, an official Inserm facility that allows phase

1 and 2 clinical trials. A longitudinal study of early-onset forms of AD with clinical, biological, and imaging data collection is in progress, the young-onset dementia data (YOD) platform, submitted to the Equipex 2011 and coordinated by the Lille MRRC. YOD will offer a unique opportunity to study the largest French data repository of early cases and to participate in the international DIAN and EU-EOD networks. DISTALZ researchers will be able to access animal care facilities, in both the Lille and Nice regions.

DISTALZ will benefit from all the facilities that have been created by the National Alzheimer's Plan 2008-2012: (i) the Memento Cohort, which will recruit individuals at very early stages of the disease with memory complaint before the end of 2012, (ii) the Automated Treatment Imaging Centre (CATI) that standardises, collects, stores and analyses the affected human brain images, and (iii) the Three City study (3C), a prospective cohort on neurodegenerative and vascular risk in ageing. Thus, DISTALZ will be in the continuation of the National Alzheimer's Plan, well known internationally, in particular since the last International Conference on AD, which it helped to organise in Paris. **DISTALZ will be considered as a Centre of Excellence dedicated to AD,** able to compare in its long-term objective with other centres around the world, among them are the DZNE in Germany, the AD dedicated research section of the Karolinska Institute in Sweden, the Gladstone Institute of Neurological Diseases in San Francisco or the Tanz Centre for Research in Neurodegenerative Diseases in Toronto.

C) Site structuration and pull effects



DISTALZ will make it possible to consolidate a significant critical mass of researchers that will be identified as a major player in AD research. This will have several impacts: i) enable transformative transdisciplinary research that would otherwise not be possible; ii) attract new talents; iii) provide an unprecedented training platform for the current and next generation of clinicians and scientists; and iv) drive translational research, bringing results from the bench to clinical application via interactions with clinical researchers and with industry.

The Labex support to DISTALZ will make it highly attractive by offering multidisciplinary skills, high level education capacities and possibilities for development to top-level senior and junior scientists, alone or with associated teams. This is already evidenced by the settlement of one Belgian senior scientist and one junior scientist coming from the UK, both of whom are ready to join UMR744 by the end of 2011. Moreover, four other scientists have declared their willingness to join DISTALZ partners in the next four years (see n°8.2).

DISTALZ partners have already established several partnerships with biotechs (Genoscreen, Alzprotect) and pharmaceutical and diagnosis industries (Biorad, Innogenetics, Janssen, Ipsen, Sanofi Aventis, Astrazeneca, Eli Lilly, etc). DISTALZ will make it possible to reinforce these collaborations, accelerating the dissemination of research findings to the benefit of patients.

DISTALZ partners work in close collaboration with clinical and scientific groups involved in neurosciences research in their own region, including: the neurology department, with the cerebrovascular

unit (Prof. Didier Leys) and the movement disorders unit (Prof. Alain Destée), the clinical genetics unit (Prof. S Manouvrier), the pharmacology department (Prof. R Bordet), the neuropathology department (Prof. CA Maurage), the neurophysiology department (Prof. P Derambure), the cognitive science research group (Dr. M. Boucart), the blood-brain barrier research unit (Prof. R Cecchelli), the neuro-immunology unit (Prof. L Prin), the neuro-endocrinology research group (Prof. V Prévot), the Nice MRRC (Prof. P Robert) and the Neurobiology of Cellular Interactions and Neurophysiopathology laboratory (Dr. S Rivera). According to their levels of scientific development and concordance with DISTALZ objectives, some of these teams may contribute to the scientific aims of our program and thus help to structure and further reinforce our task force.

Several projects from the "Investissements d'Avenir" 2010 are dedicated to neurosciences but none of them focuses specifically on AD research. The ICM-IHU (Paris) targets all forms of neurodegenerative diseases and AD is represented in two out of 20 teams. The Memolife Labex (Paris) studies the fundamental bases of memory in living organisms, but is not particularly focusing on pathologies. The IEC Labex (Paris) is conducting research in cognitive science, Celya (Lyon) is dedicated to acoustics and Lifesenses (Paris) to hearing and vision. The Brain Labex (Bordeaux) is a large, multidisciplinary organisation aimed at improving treatment of neurodegenerative diseases by focusing mainly on the normal brain. The Trail Labex (Bordeaux) concentrates on imaging techniques, mainly centred on the functional and cognitive domain, and Genmed develops a genomic platform already collaborating with a DISTALZ partner (UMR744). **DISTALZ will encourage the development of collaborations with these centres of excellence in neuroscience research.**

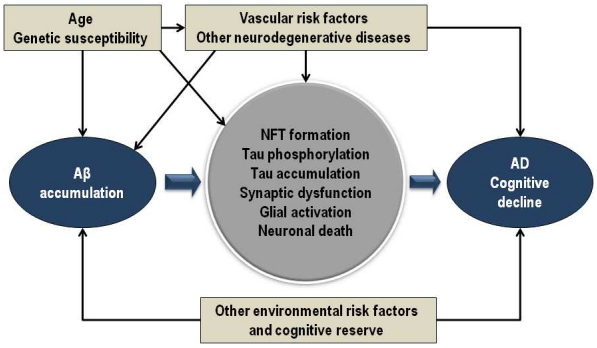
DISTALZ is also in line with the European strategy for neurodegenerative research initiated during the French Presidency of the European Union. In 2008, the European Council and the European Commission considered research on neurodegenerative disease and Alzheimer's disease as a major challenge for society. In line with the Lisbon Agenda, the European Council suggested creating the first Joint Programming Initiative on Neurodegenerative Disease Research and AD (JPND)[14], chaired by Philippe Amouyel, the head of UMR744. JPND involves 23 countries and aims at improving funding efficiency by reducing fragmentation and redundancy and increasing leverage effects at the EU level. This programme has launched the Centres of Excellence Network (CoEN), the objective of which is to create interaction between outstanding European research centres which are mainly oriented toward AD: the UK, Ireland, Germany, Italy, Belgium and Canada are committed, but not yet France. **Thus DISTALZ would offer a major opportunity to join this initiative and begin to offer a clear international visibility for France in this outstanding network on AD research.**

The creation of such a unique international centre of excellence dedicated to AD will allow France to maintain and improve the high visibility in research and development initiated during the National Alzheimer's Plan 2008-2012, and to provide meaningful discoveries that bring practical benefits to patients and their carers.

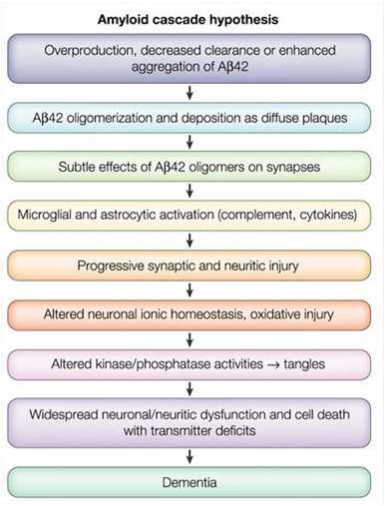
1.2. SCIENTIFIC DESCRIPTION OF THE RESEARCH PROJECT

A. State of the art and challenges, objectives, national and international context

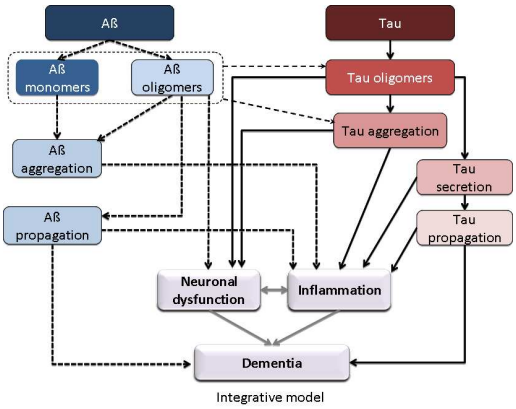
Major scientific advances in the areas of genetics, biochemistry, cell biology, and neuroscience over the past 25 years have made it possible to build up mainly accepted molecular pathways underlying AD pathophysiological pathways (see right figure). The most common cascade begins with an initial Aβ accumulation inducing a toxic effect triggering NFT formation and other brain molecular dysfunctions[4]. All these sequences are influenced or interact with various modifiable and non-modifiable risk factors. One of the biggest challenges consists in translating these basic molecular and cellular discoveries into clinical therapies.



From a pathological point of view, AD is characterised by the coexistence of two types of brain lesions, the parenchymal amyloid deposits centred around Aβ peptide and the intraneuronal neurofibrillary tangles (NFT) composed of abnormally modified Tau proteins that occur through a sequential model that is still discussed (see one admitted view in left-hand diagram[4]). However, thanks to their experience, DISTALZ partners will explore a more dynamic and parallel vision (see right-hand diagram) that will constitute the backbone of a global approach to the AD pathophysiology integrating the time-line development and functional interplays through the dissection of propagation mechanisms. DISTALZ gathers international specialists in these two proteins, making it possible to test both molecular mechanisms associated with Aβ and Tau, focusing on specific aspects of these two proteins related to their production, function, molecular cross-talks, regulation and degradation, including clearance and reversion mechanisms. Amyloid β-peptides, C-terminal counterpart APP IntraCellular Domain (AICD)[15] and the various forms of Tau[16] will be studied and analysed for their dysfunctions in AD and functional interplay in classical and new pathways identified thanks to genomics.



Sequential model



Integrative model

From an epidemiological viewpoint, AD is a long-term process that begins many years before any clinical symptom of dementia is detectable. Since it has been estimated that delaying the disease by five years would reduce its prevalence by 50%[17], evaluating the risk of developing AD may be essential. Unfortunately, we still lack accurate diagnostic/prognostic biomarkers. This can be partly explained both by the heterogeneity of dementia, encompassing a large range of pathologies (AD, mixed/vascular dementia, frontotemporal dementia, Lewy body dementia, etc.), and also by intrinsic disease heterogeneity (even if sometimes included under a single neurodegenerative disease terminology). Until recently, the differential diagnosis of dementia was almost exclusively based on a combination of neurological examinations and neuropsychological tests. More recently, complementary tools, mainly brain imaging and cerebrospinal fluid (CSF) biomarkers, have been proposed in addition to clinical examination[18]. However, despite their obvious contribution to diagnosis, these tools do not provide unambiguous differential diagnoses.

In this context, several conceptual barriers to overcome have been identified that will pave the way for DISTALZ scientific strategy:

1. Although some of the new genes discovered by agnostic genome wide association studies (GWAS) appear to be involved in Aβ metabolism, several others point out alternative mechanisms like inflammation or cholesterol metabolism[6]. The key elements (GWAS-defined gene products or other major actors, such as non-coding RNA) of these potential pathways will tell us about new directions for understanding AD. Moreover, the new genes identified through GWAS do not explain all of the genetic heritability[19-23]. **Decoding this "missing heritability" will also allow DISTALZ to identify other potential pathways.**

2. Elucidating the initial events in the pathogenesis cascade and progressing all the way up to clinical disease onset is critical for understanding disease and for developing new treatments. To this end a major challenge lies in developing animal and cellular models for AD that have to address brain changes associated with Aβ deposition but also additional changes seen in AD brains (Tau propagation, neuroinflammation, vascular damage and other potential pathways). Such models are drastically lacking yet. **The characterisation of new pathways will allow DISTALZ to generate new experimental models and to suggest more comprehensive biological hypotheses.**

3. To identify patient populations at high risk of converting from cognitively normal to cognitively impaired over a three- to four-year window, and to target this population for clinical trials, it will be necessary to change the way in which clinical trials are designed. We will have to incorporate as much genetic, biomarker and pathophysiological data as possible to identify such high-risk populations and target them with mechanistically based therapies. However today we need to improve the composition and the accuracy of biomarkers. **The new biological**

hypotheses suggested by DISTALZ partners will make it possible to derive new and more detailed batteries of biomarkers to be validated in human samples.

4. Deciding whether such biomarkers should be used more widely in patients or whether to restrict their use to clinical research until there is an effective disease-modifying therapy is a major challenge. What will be the psychological, social and ethical consequences of agreeing to participate in such trials without any clear perspective of treatment? Indeed, if asymptomatic individuals can participate, this means that they are at very high risk while not yet having any symptoms. Over the next decade of their life, they will be aware on a daily basis that one day or the other, they will be affected. **With this trend in AD research intensifying the need for early diagnosis, DISTALZ partners will be urged to develop critical social and ethical viewpoints and reflections.**

In this competitive and challenging international context, the objective of DISTALZ is to explore new pathways involved in AD pathophysiological processes, some being suggested by agnostic genomic approaches. From this knowledge, DISTALZ will identify new biological clues that will be developed as potential biomarkers and drug targets. The multidisciplinary approach of DISTALZ, from bench to society, will set up the clinical, social and ethical bases of new clinical trials to test promising new components in high-risk patients or individuals, identified thanks to a sophisticated battery of biomarkers, years before any conversion to AD.

B. Scientific program

Axis 1. From genes to pathophysiological hypothesis. *The characterisation of genetic risk factors and of the missing heritability of AD for the identification of new causative pathways.* This axis will aim at stimulating new biological hypotheses by a systematic agnostic approach to the genetic susceptibility risk factors of AD, making it possible to identify new pathways to feed more comprehensive pathophysiological hypotheses. It will benefit from exchanges with the input from other axes, in particular in the identification of functional variants.

WP1: Exploratory genomics approaches and the deciphering of the "missing heritability". (UMR744, UMR837, UMR6097, MRRC). Thanks to whole genome high-throughput techniques and the largest high quality collections of AD patients and controls from various countries which they have access to, DISTALZ partners will systematically characterise the molecular bases of the genetic components that support the 60 to 80% heritability of AD. In the last three years, UMR744 has made a significant contribution to characterising AD genetic susceptibility using Genome Wide Association Studies (GWAS) to locate genes harbouring single nucleotide polymorphisms (SNP) associated with AD risk. The EADI consortium (European Alzheimer's Disease Initiative), gathering five countries, 6,322 cases and 10,373 controls, has made it possible to identify 10 new genes, alone or in collaboration with other consortia (GERAD, CHARGE and ADGC). However, this only explains less than 50% of AD heritability[19-23].

Objective: This WP will characterise the most comprehensive genetic background of AD thanks to meta-analyses and to specific approaches that will make it possible to identify the remaining 50% of missing heritability.

Description of the work: As a first step, the principal investigators of the GERAD, EADI, CHARGE and ADGC consortia have agreed to pool all their biological resources and data in a major international collaboration, the International Genomics Alzheimer's Project (IGAP), conducted by UMR744 to increase the discovery capacity of their GWAS. Studies should gather over 60,000 individuals in a mega-meta-analysis exploratory step based on the 1,000 genome imputations and a follow-up study using a dedicated I-select chip with 60,000 SNP.

In a second step, approaches will be developed to unravel the missing heritability, not accessible by classical SNP GWAS analyses using various technologies: complex haplotype[24] and epistasis[25] analyses on GWAS data, detection of copy number variations (CNV)[26], whole exome sequencing (WES)[27] in selected groups, non synonymous SNP GWAS (Illumina microarray currently under development) and targeted whole genome sequencing (WGS) (collaboration with GENMED Labex). These studies will be performed in close interaction with the Lille MRRC.

Outcomes: Identification of new genes as a road map to examine new metabolic pathways

WP2: Fine variant mapping and identification of the functional variants (UMR744, UMR8576, UMR6097, UMR837, MRRC)

Objective: In parallel to the gene discovery experiments described above, this WP will perform a fine mapping of the gene identified in WP1 to characterise gene variants and identify their functionality.

Description of the work: We will intensify the use of high throughput genome techniques by focusing on the specific loci identified in WP1 through a development of massive parallel sequencing approaches searching for all

rare or common variants. These targeted re-sequencing efforts combined with large-scale genotyping will provide a pool of genetic variants liable to be functional and will increase estimates of complex trait heritability explained by known loci[28]. A first screen based on *in silico* approaches will be performed for potential functionality evaluation (impact on protein expression or function, pathogenicity score[29,30], gene expression prevision[31], modulation of mRNA stability and/or translation or miRNA binding[32-35], alternative splicing event identification[36-37]. Moreover a functional relevance of these potential AD genes will be assessed thanks to models available in the different research units: (i) immunohistochemistry staining of brain sections of cases and controls from the Lille Neurobank to determine which types of cells express the AD genes and to detect colocalisation with disease brain lesions[38]; (ii) expression of genes in brain cases and controls[39]; (iii) analysis in D. melanogaster model of quantifiable AD phenotypes[40]; (iv) effect of over- or under-expression of genes on APP and Tau metabolisms with expression vector[39, 41]; and (v) comparative NMR spectroscopy of gene products[42].
Outcomes: Identification of potentially relevant functional variants and first links with AD pathways

Overall this axis will identify new genes pointing to new possible metabolic hypotheses completing, altering or interfering with classical pathophysiological processes of AD, and thereby leading toward new biological pathways through axis 2.

Axis 2. From pathophysiological hypothesis to biological pathways: *the study of the impact of these new genes/pathways in biological models addressing, in a complementary way, both amyloid and Tau metabolism, and of cutting-edge pathophysiological hypotheses explored by DISTALZ partners.* This axis will aim at generating new biological thinking, shaking up the usual amyloid cascade/Tau induced neurofibrillary tangles, integrating the discoveries and the knowledge generated by genomics and the most advanced hypotheses of DISTALZ partners related to APP and Tau metabolisms.

WP1. APP and Aβ metabolism, impacts of the newly discovered genes. (UMR6097, UMR837, UMR8576, UMR744).
Objective: This WP will analyze the fundamental aspects of the impact of the AD genes identified with genomics approaches to APP and Aβ metabolism integrating all the advancements of DISTALZ partners in this field and their most advanced hypotheses related to APP metabolism and its interaction with Tau pathways.
Description of the work: UMR6097 has many years' experience in the study of several key steps involved in the so-called amyloid cascade. This group has all the expertise and tools to examine the influence of novel genes identified in axis 1 not only in the classical amyloid cascade context but also in less explored tracks involving potential new cellular components at the crossroad of various cellular pathways. UMR6097 has set up a series of original enzymatic, biochemical, cell models and in vivo assays making it possible to monitor Aβ production and function[43-45], activities of forming enzymes (secretases)[46], and to follow inactivating proteases or Aβ-truncating activities[47,48]. More recently, UMR6097 focused on the regulation of Aβ production by cellular regulators such as GSAP or TMP21[49,50] and more recently transcription factors and micro RNA, or by cellular processes such as inflammation[51], proposed as an "accomplice" of Aβ-related toxicity. As a read-out of Aβ-related function/dysfunction, several cellular functions such as control of cell death or proteasomal machinery will be studied. This set of state-of-the-art techniques and models will be central tools for the study of novel genes identified in axis 1 and will be developed in coordination with UMR837 mainly specialised in Tau metabolism, with UMR8576, for NMR spectroscopy approaches, and with UMR744. They will be also extremely important for further investigation of the contribution of two newcomers in the amyloid cascade. Thus, a modification of the "classical" amyloid cascade was recently proposed suggesting that soluble oligomers could actively participate in the pathogenic cascade[52]. UMR6097 has in its hands cell models producing soluble dimers and trimers as well as human pathological brain tissues from which endogenous oligomers could be extracted[53] that can be used as an external source of Aβ-species and as a pathogenic trigger. How do these oligomers affect pathways modulated by the newly identified genes? Are these genes enhancers/modifiers of Aβ toxicity, oligomerisation or aggregation? In addition, another βAPP catabolic product called AICD was proposed as a transcription factor and UMR6097 contributed as a pioneer to this view. They showed that AICD controls the Aβ inactivating enzyme neprilysin[48,54]. AICD also enhances the expression of βAPP and some of the enzyme generating Aβ[55]. One of a series of outstanding questions could be: is AICD directly modulating the promoter transactivation or mRNA levels of novel AD risk genes ? Is AICD interfering with gene-products-associated pathways?
Outcomes: This project should permit a better understanding of AD pathology, lead to animal models being available for pharmacological and preclinical approaches aimed at slowing down or blocking the AD degenerative process, and to the proposition of new biomarkers and putative drug targets.

WP2. Tau phosphorylation, microtubule polymerisation and other functions: potential alterations by the newly discovered genes. (UMR837, UMR6097, UMR8576, UMR744)

Objective: This WP will analyze the fundamental aspects of the impact of the AD genes identified with genomics approaches on Tau metabolism and regulation, integrating all the achievements of DISTALZ partners in this field and their most advanced hypotheses related to Tau metabolism and its interaction with APP pathways.

Description of the work: Neurofibrillary degeneration (NFD) results from the hyperphosphorylation and the intracellular aggregation of microtubule-associated Tau proteins[5]. UMR837 is a pioneer on Tau research in the human brain and differential diagnosis of Tauopathies[56]. It is commonly thought that these phospho-proteins lead to microtubule depolymerisation and axonal transport defects. UMR837 has all the expertise and tools to examine the influence of novel genes in this classical context[57-59]. The role of phosphorylation is a key step in Tau binding to microtubules or aggregation, although a precise interpretation of the phosphorylation code is still missing. Notably, the link between (hyper- and abnormal) phosphorylation and aggregation remains obscure, and hampers the rational development of kinase inhibitors to counter-act this post-translational modification mechanism. UMR8576 is an expert in NMR spectroscopy[60,61] that makes it possible to get both qualitative (which sites?) and quantitative (to what extent?) views of the phosphorylation status of the resulting samples, and aims at elucidating the structural features linking Tau phosphorylation and its physiological and pathological functions. However, new hypotheses have now been put forward which give specific insights into Tau aggregation and its consequences. Among them, UMR837 has developed renowned expertise in the exploration of new biological roles of Tau in the plasma membrane, in dendrites and in nuclei. For instance, UMR837 has recently identified a new role of Tau in DNA protection[16]. It has also developed experimental models (cell lines, primary neuronal cultures, animal models and engineering of viral vectors) to explore which environmental (Aß oligomers, physical exercise, caffeine, anaesthetic agents, etc) and genetic factors (miRNA, splicing regulators, genes coming out from genomics, etc) modulate Tau aggregation and its propagation[62,63]. It will work closely with UMR6097 and UMR744 on these aspects. Moreover, the discovery of extracellular Tau and its involvement in NFD propagation has impacts on diagnostic and therapeutic strategies, and the new pathway identified by GWAS, including cholesterol metabolism, inflammation and immunity, will encourage testing Tau-related therapeutic approaches such as immunotherapy, modulators of inflammation and cholesterol esterification.

Outcomes: Like WP1, WP2 should permit a better understanding of AD pathology, lead to animal models being available for pharmacological and preclinical approaches aimed at slowing down or blocking the AD degenerative process, and to the proposition of new biomarkers and putative drug targets.

WP3. From biological pathways to the development of biological models for drug screening (UMR6097, UMR837, UMR744).

Outcomes from WP1 and 2 will make possible DISTALZ partners to build new experimental models that will integrate both the amyloid and Tau classical pathways, but also the new pathways identified thanks to axis 1 in particular.

Objective: To build-up new experimental models based on both classical and newly discovered pathways that integrate amyloid, Tau and new gene products that will reconcile their putative functional interplay and disease-related alterations.

Description of the work: DISTALZ partners have an outstanding experience of cellular and mouse models. They have already developed, alone or in collaboration with industrial partners, models that mimic AD[59,64]. Major collaborations have been established with the Mouse Clinic Institute in Strasbourg (Dr. Yann Herault) to benefit of their existing mouse models and to develop new ones, including models based on functional variants of the new AD genes. These mice will be interbred with relevant AD-like transgenic mice models. Viral vectors will be also designed to overexpress or silence the targeted genes. These models will be explored according to the new approaches developed in WP1 and WP2. Furthermore, the ability to generate primary cell cultures from the different transgenic mice and the access to a brain-blood barrier model (Dr. Laurence Fénart, Lens University)[65] will allow for thorough exploration of these new pathways. Moreover, the availability of experimental models and molecular interactors from axis 2, will allow deriving biological screening tests at the different levels of these new pathways, that can be used by academic or private chemists to develop biological models for drug discovery approaches.

Outcomes: development of more comprehensive experimental models that will make it possible to propose biological screening tests for drug discovery.

Overall this axis will propose new comprehensive views of the classical pathways involved in AD, integrating the role of the new AD genes previously identified and of the advanced hypotheses raised by

DISTALZ partners. In addition, this will make it possible to develop comprehensive new experimental animal and cellular models offering a more complete picture of the AD process which is closer to the human disease. Finally, this axis will delineate new biomarkers leading to original biological tests that can be used for early diagnosis and drug discovery.

Axis 3. From biological pathways to effective targets: DISTALZ partners will aim at characterising and developing relevant genetic and biological tests stemming from their results, taking into account the complex interactions with other neurodegenerative diseases. DISTALZ will offer a unique opportunity to develop new and efficient biomarkers based on the outcomes of the original approaches described in axes 1 and 2. The validity of these biomarkers will be assessed on a large collection of samples, ensuring that the heterogeneity of the different types of dementia is handled in the best possible way[66]. The necessary validation step will be carried out in the framework of the epidemiological and clinical activities of DISTALZ partners[67], taking into account the complex interactions with other neurodegenerative and cerebrovascular diseases, and aiming ultimately at a personalised medicine approach to AD[68].

WP1. A thorough approach to biomarkers validation. (UMR744, UMR6097, UMR837, MRRC).

Objective: Characterisation of new biomarkers and potential targets for drug discovery emerging from the new hypotheses generated in axes 1 and 2.

Description of the work: DISTALZ partners will enable the development of new biomarkers based on a thorough analysis of the AD genetic component of individuals in independent prospective population-based cohorts (the 3C study[69], the CHARGE consortium[21] and the European Network for Early-Onset Dementia) and of the predictive value of these genetic biomarkers in the high AD prevalence populations of the MRRC, MEMENTO and YOD. Importantly, DISTALZ is a major player in an international initiative aiming at creating a NEUROCHIP, a genomic integrated diagnosis tool targeting the genetic variability of most neurodegenerative diseases loci (AD, Parkinson's disease, multiple sclerosis, frontotemporal dementia, etc). This project is in line with hypotheses explored by DISTALZ partners stating that most neurodegenerative diseases can be seen as disturbed protein folding and degradation, leading to aggregation and accumulation linked to proteasome-deficient catabolisms. Genetic tools will also be assessed to predict disease progression in patients with early cognitive impairment and for dedicated pharmacogenetics for therapeutic trials[68]. Beside genomics markers, biological samples will be analyzed for their content in various proteins or fragment-related proteins issued from axes 1 and 2. In this respect, the DISTALZ partners have developed a complementary expertise in proteomics approaches[70]. However, such a hunt to characterise new protein biomarkers in dementia encounters several limitations that may be partly overcome by the precise selection of candidate-proteins from above analysis of targeted pathways and skill sets of DISTALZ partners in APP and Tau metabolism. In this context, it should be emphasised that identification of new Aβ- or Tau-related fragments uncovered by the study of the alterations triggered by new genes could delineate abnormal catabolites. These catabolites identified as early markers could have not been considered previously, thereby explaining the previous failure of Aβ-related therapies directed towards inadequate targets linked to the "classical amyloid cascade".

Outcomes: Detailed characterization of new relevant biomarkers and screening biological tests that will be proposed to biotech or pharmaceutical industries for development.

WP2. Towards personalised care and management of Alzheimer's disease (UMR744, MRRC, EA1059, EA1610, UMR6097, UMR837).

Objective: To facilitate the translation of these new biomarkers together with existing clinical or radiological approaches to improve positive and differential diagnosis, prognostic and when available, drug efficiency.

Description of the work: For a physician, making a definite diagnosis of AD may be long and complex process due to atypical features or multiple interactions with other neurodegenerative or cerebrovascular diseases. Moreover, this diagnosis needs to be confirmed by post-mortem histological analysis[71]. Over the last five years, new imaging approaches, better identification of genetic susceptibility and improvements in proteomic CSF biomarker assays have enable more accurate AD early diagnoses but still remain largely insufficient[18]. However, access to this work-up is not always possible or straightforward. DISTALZ partners will aim to establish whether the systematic collection of these different kinds of biomarkers for all individuals visiting a memory clinic can help the physicians, in their daily activity, to diagnose out-patients earlier and with greater reliability. AD evolves in the context of an aging brain exposed to environmental factors among which vascular risk is a major actor[11]. The neuropathology substrate of cognitive impairment in later life is often a mixture of Alzheimer's disease and microvascular brain damage. Thus, advanced MRI techniques like functional MRI, resting-state functional connectivity MRI, diffusion tensor imaging, arterial spin-labelling, and magnetic resonance spectroscopy will be

used together with molecular and biological markers to monitor disease progression and to differentiate the contribution of vascular disease to cognitive impairment[72]. Given the caseload of the Lille MRRC, it should be possible to recruit 300 patients a year. Within a specific study, designed from an ethical perspective, each eligible patient, in addition to clinical assessment, after giving informed consent, will undergo a DNA screening and a proteomic screening, and a 3T MRI scan and a PET scan thanks to the SMART Equipex project. All this information will be stored in electronic medical records and will be systematically accessible during any consultation for immediate use. This will make it possible to estimate the relevance and the benefits of such approaches. In addition, we will validate these strategies in the National Cohort MEMENTO and in the 3C Study a prospective study intended to explore the links between vascular and neurodegenerative disorders with a 10-year follow-up.

Outcomes: We expect that this systematic approach could help to reduce the time to diagnosis, improve case flows and encourage early care. The extent to which these new tools will be accepted by physicians and other medical staff will be estimated.

From the understanding of the AD pathways, we will rapidly derive new biomarkers. We will go over the results and interpretation of epidemiological and clinical studies. We will assess the risk factors of cognitive decline and AD using the improved diagnostic tools offered by the biomarkers and neuroimaging. Finally, we will provide a better differentiation of other neurodegenerative processes and vascular risk in particular. Overall this axis will develop new tools for early and accurate differential diagnosis, for progression of the disease, and for personalising care and management.

Axis 4. From effective targets to clinical trials: *the development and implementation of all biological, clinical, social and ethical conditions useful for the early detection of patients to be involved in clinical trials and in the general population.* DISTALZ aims at developing tools and procedures for the early identification of patient populations at high risk of converting from cognitively normal to cognitively impaired. Moreover, DISTALZ will transfer these results by establishing a translational research facility open to any collaboration with industry or academic partners to optimise recruitment of patients. The Lille MRRC will be the core of this translational facility. DISTALZ will facilitate access to precisely characterised patients at early stages of the disease anticipating the psychological and social consequences of an early diagnosis taking into account all ethical dimensions. These last issues will be addressed in detail thanks to the participation of specialists in social sciences and ethics in this transdisciplinary Labex.

WP1. Anticipating the psychological and social consequences of such approaches (MRRC, EA1059, EA1610, UMR744, UMR6097, UMR837)

Objective: This WP will identify the changes in behaviours and lifestyles, the changes in interpersonal relations, especially at family scale, and the subjective changes (attitudes with respect to the disease, meaning of life) generated by the DISTALZ approaches, from genetic tests to participation of asymptomatic patients in clinical trials, whether unfavourable or favourable.

Description of the work: The consequences and the participation in a genetic test will be studied according to what already exists for hereditary disease[73,74] taking into account the specificity of AD, and in particular its very late age of occurrence. DISTALZ partners will analyse both personal and family approaches, potentially revealing latent conflicts between the individuals of the family group. We will study the interactions between the medical screening scheme, the dissemination of information before and after screening[75], the decision-making and consent-giving processes[76] and the family dynamics. Moreover, increasing knowledge of the genetic forms of the disease, the development of screening capacities and its media coverage may trigger spontaneous and non-guided actions from certain individuals with independent structures, which offer screening tests, especially in web-based laboratories. It is important to measure the extent of this phenomenon and the way it meets these users' needs, as well as the related psychological risks. We will also explore another significant issue in AD genetic counselling[77]: the role of the counsellor him/herself. There is a need to illustrate the manner in which information about risk should be passed on, which is not as clear-cut as it is often perceived.

Early identification of AD patients before any symptoms occur will have major psychological and social consequences[78,79] both on the individual to be recruited and on his/her family environment[80,81]. We will develop specific research programmes on social approaches to address the major issues resulting from this early identification. Among others, two main specific areas of concerns will be treated: awareness and unawareness in AD[82,83], and the need to analyse and provide psychological guidance to carers[84]. This work will enable DISTALZ partners to develop pedagogical and clinical tools for nursing staff[85] relating to patients' perception of the disease[86] and of their situation. This perspective will integrate a medico-psychological guidance project in the

long term[87]. Finally, we will identify the psychosocial problems encountered by informal carers who take care of early-diagnosed patients[88]. In addition to assessing the adequacy of the professional help already available[89], DISTALZ partners will specifically develop help and support programmes for that population[90,91].
Outcomes: We should enable a better understanding of the social and psychological consequences of AD, especially in the event of an early diagnosis in the absence of treatment. We will produce guidance for professionals and support programmes for carers in particular.

WP2. Analysis and understanding of the ethical concerns linked to DISTALZ research and scientific approaches (UMR744, UMR6097, UMR837, UMR8576, MRRC, EA1059, EA1610).
Objective: DISTALZ partners will address the ethical consequences of their scientific and translational programmes that need to be fully integrated for a transdisciplinary approach to AD.
Description of the work: At the societal level, early diagnosis of a disease whose symptoms may appear years afterwards and for which no treatment is available raises important ethical issues that need to be anticipated. The EA1610 is a renowned benchmark in the field of biomedical ethics and leads the Alzheimer's disease's national centre for ethical reflections[92] created as part of the National Alzheimer's Plan 2008-2012. Within DISTALZ, EA1610 will supervise the ethical background of the various aspects of the research programmes from gene selection to clinical trial implementation, by ensuring documentary watch and staying in contacts with the competent ethical institutions, keeping track of the ethical framework applied to research, counselling research teams when drawing up protocols, supporting DISTALZ's communication strategy and monitoring translational research. Specific issues related to AD will be addressed such as: i) Setting up a multidisciplinary steering committee ii) Organizing thematic think-tanks for researchers and other professionals concerned, iii) Regularly publishing a newsletter nourished by a systematic review of literature, iv) disseminating information to the general public about this specific research field by the means of a seminar and an annual day centred on these themes. In addition, up-to-date information will be available on the national centre for ethical reflexion website.
On the other hand, concerning the scientific support of DISTALZ : i) An organ will be created (monitoring committee) dedicated to the evaluation of the harm-benefit ratio accounted for eventual prejudice when drawing up a clinical protocol (for instance, according to what ratio and criteria can we include someone in a research program when we don't know how the illness, early diagnosed, will evolve? Is there a risk that the treatment could speed up this evolution?) ii) We will discuss and define the modalities of access to early diagnosis, to disclosure of the results and the specific methods of information during the consent procedures. In that context, we will participate in the creation of an independent monitoring group who would have access to intermediate results and the capacity to raise the alert should any problems arise. Furthermore, during the time of the research programme and when the results are given to participants we may consider to set a systematic follow-up for people involved, especially from a psychological point of view. This would lead to the establishment of crystal-clear guidelines. More generally, we must ask ourselves what information must be spread before, during and after the end of the research.
Outcomes: The purpose followed is to allow a better understanding of the ethical impacts of DISTALZ research programmes, especially in the event of an early diagnosis in the absence of treatment. We will produce guidelines for professionals and open discussion with patients, carers and family associations.

Overall this axis will make it possible to build up proposals for a comprehensive approach including social and ethics questions due to the implementation of early diagnosis in clinical trials and, later, in the population. DISTALZ will address the social and ethical issues resulting from its scientific approaches, such as the use of genetic biomarkers, by assessing the harm-benefit ratio for patients, family members, caregivers and researchers involved in such clinical trials.

C. Attraction and multidisciplinary structure
Attractiveness will be a major achievement of DISTALZ. The Labex support will allow us to develop a highly competitive policy for attracting scientific researchers and students by providing: (1) a stimulating scientific and intellectual environment; (2) high-tech infrastructure and cutting-edge technical facilities; (3) individual career development prospects; (4) financial incentives; and (5) quality of life and support to facilitate relocating researchers and their families to France.
The distribution of DISTALZ partners throughout the country in multiple sites will facilitate the ability to recruit national and international students. In this process, we will also target students coming from the "grandes ecoles", including the Ecoles Normales Supérieures, and high-tech engineering schools, for instance students of computer and imaging sciences. DISTALZ will offer postdoctoral positions and attractive grants to attract foreign students.

The Institut Pasteur de Lille has developed a collaboration with the Howard Hughes research centres to attract young US PhD scientists for an eight-month period, paving the way for a more prolonged stay after completion of their PhD. DISTALZ partners will host several of these students each year. Competitive financial incentives will be offered: prizes for high quality publications, a welcome package for young researchers, and funds for short-term and long-term international laboratory exchanges.
Attracting high-level foreign scientists to DISTALZ will be one of the major strategic impacts of the Labex support. In order to be attractive, DISTALZ will supply both competitive packages and tailor-made relocation services to the scientists selected through a permanent international call for candidates. DISTALZ will offer (with the assistance of the supporting partners and supervising institutions) substantial resources to build up a research group and to start ambitious projects. The calls will provide access to individual funding through Chairs of Excellence for talented scientists. Two types of researchers will be targeted: “senior” scientists at an advanced stage of their career (at the highest possible international level) and “junior” scientists at a very high level in a new, highly competitive and complementary scientific field linked with DISTALZ’s topics. These scientific fellows will also benefit from personalised relocation assistance, including: assistance with finding accommodation within the Lille, Paris or Nice areas; help with finding for a job for the scientist’s partner, and legal and administrative assistance (residency visas, social security, driving licence, etc.). The promotion of women scientists and physicians will be important and encouraged through mentorship, affirmative recruitment and childcare facilities; the results will be easy to assess by regularly calculating the number of female principal investigators. DISTALZ will assist them with their applications to Chairs of Excellence programmes provided by Universities in collaboration with Inserm and Cnrs, and with regional entities and calls for proposals regularly launched by the Conseil Régional Nord Pas de Calais and the Conseil Général Provence Alpes Côte d’Azur. DISTALZ has already shown how attractive it is through its success in securing the arrival of two researchers and prompting strong interest from four others (see appendix n°7.2).

In conclusion, one of the primary concerns of DISTALZ is to offer a more comprehensive view of the disease from bench to society, bringing together basic, clinical, social and ethics researchers to address the main challenges and concerns of AD research. Despite the different disciplines and the distances between workplaces, DISTALZ partners have clearly identified the relevance of a multidisciplinary collaboration leading to transformative approaches supported by a common scientific programme based on four major axes with different WPs on which at least four partners collaborate systematically.

1.3. IMPACT ON TRAINING

Each partner has longstanding experience in training Masters and Doctorate students. In 2011 the number of HDR (an accreditation to supervise research allowing researchers to supervise graduate student) of DISTALZ partner is 36, the number of PhD students is 54 and the number of “Masters 2” is 50. All DISTALZ researchers have teaching commitments in topics related to AD, neuroscience and basic sciences from genomics to ethics. For instance, at the Faculty of Medicine and Pharmacy of Université Lille 2 this includes genetics, biochemistry, cell and molecular biology, and physiology, providing the necessary training for laboratory work. DISTALZ members are also involved in the Masters and Doctoral programs ED446 “Biologie et Santé” and ED85 (UNSA) “Sciences de la vie et de la Santé" which were recently evaluated by the AERES and received an "A" rating. As part of their responsibilities DISTALZ researchers (i) give lectures and seminars, (ii) take part to Masters and Doctorate juries, and (iii) are heavily involved in the management boards of the Doctoral School of their respective universities. DISTALZ partners are also involved in different educational programmes for post-graduates and professionals (clinicians and basic scientists), in the European FP6 Marie Curie programmes (NEURAD) and in AD dedicated summer schools (Alzheimer's symposium, European Society for Neurochemistry, Leipzig, Germany, 2009; FENS sponsored Summer School, Smolenice, Slovakia, 2010).

Over the coming years, Labex support for DISTALZ will make it possible to develop a cutting-edge, international education and training programme on AD and related disorders within the participating universities and create an environment likely to attract the best students for their Masters and Doctorate. The wide range of abilities and training skills associated with the multidisciplinary approaches to DISTALZ partners will be a unique advantage to propose a wide range of training, such as epidemiology of chronic disease, genetic epidemiology, genomics, transcriptomics, proteomics, bioinformatics, molecular and cellular biology, animal models, clinical and neuropsychological research, high resolution imaging, social and healthcare research and ethics. The teaching programme will be structured around four major education projects.

1. DISTALZ partners will participate in an advanced Erasmus Mundus European Masters programme in "Multifactorial diseases: from bench to society" that will be set up with the supervising universities in collaboration with eight other European universities. This programme aims to attract foreign students to Lille, Nice or Paris, promoting and facilitating networking and mobility between the universities taking part in the Masters thanks to specific travel grants for young scientists. All European students will follow a first-year postgraduate course with lectures on "omics", epidemiology, biomathematics, biostatistics, cell biology and therapeutics. The second year will be dedicated to specialised courses dealing with the main pathologies targeted: Alzheimer's disease, Inflammatory Bowel diseases and Diabetes. A preliminary programme has been drafted for AD and involves, besides universities in Lille, Nice and Paris, other universities in Antwerp, Ghent, Lausanne, Rome, Gottingen, Groningen, Copenhagen and Stockholm (see appendix n°6).This international Masters will be an opportunity to identify outstanding students who may become future MD/PhD managers in their fields of interest in France and Europe. They will have special access to DISTALZ labs and clinical departments.

2. An international dedicated summer school will be launched for both clinicians (continuing medical education) and scientists. As part of its translational activities, every two years DISTALZ will organise a summer school open to physicians and scientists with a major interest in AD and other neurological disorders (see appendix n°6). The one-week intensive course (teaching courses and plenary lectures, plus workshops) will cover both theoretical and practical aspects for AD and related disorders. It will also be an opportunity to stimulate interaction between top-level scientists and clinicians. It is expected that the summer school will be an opportunity to develop a network of physicians for translational research.

3. In the field of social and healthcare sciences, thematic workshops will be organised under the auspices of EA1059 with participation of the dedicated structure ("Maison Européenne des Sciences de l'Homme et de la Société") and with the EA1610 and EREMA for ethics. All these training sessions will be accessible to students, health professionals who may have to deal with AD patients at any time, carers, family associations and decision-makers. The programmes will incorporate theoretical knowledge and practical skills, which are indispensable in steering projects in the healthcare field and giving guidance to individuals or families. The programmes will also deal with prevention and screening strategies, announcement schemes, assistance to carers and supporting care. Training in health psychology will prepare the future practitioners for global management of the patient in his/her context and in the supporting care networks. Medical team support is integrated in this training course. A Summer University on ethics in Alzheimer's disease will be organised every two years.

4. A specific educational and training support will be provided to the DISTALZ students. DISTALZ will enable funding of PhD theses in *co-tutelle* with national and regional bodies to attract and keep in-house the very best students. As part of the DISTALZ Masters-PhD programme, the student will be required to spend at least six months in one of the DISTALZ laboratories in order to broaden his/her skills and reinforce joint programmes among laboratories. Lastly, besides the weekly laboratory meetings, each student will be encouraged to present, the results of his/her research at international meetings at least once a year. This will be done by providing the appropriate funding and scientific support. To this end, in addition to formal scientific training, each student will be given a choice of courses designed to develop their ability to present at scientific meetings and write scientific manuscripts, as well as a mandatory course in statistics. The postdoctoral fellows will benefit from the large range of professional training courses available through the PRES Département Carrières et Emplois which will contribute to reinforcing their career development. Finally, DISTALZ partners will benefit from support of the PRES foreign office to help students from abroad to settle in comfortable conditions.

In conclusion, Labex support will help DISTALZ to develop a systematic and packed training programme aiming at disseminating its experience and know-how to students and clinicians. This will allow DISTALZ to attract outstanding students and to share in the visibility of the five universities supporting DISTALZ partners.

1.4. SOCIO ECONOMIC IMPACT

One of DISTALZ's major concerns will be the dissemination and exploitation of its results in the academic field, the economic environment and the societal context. DISTALZ partners are clearly aware that the sustainability of their projects relies on the impact of their scientific results on these three domains, which will be cornerstones of the return on investment of the Labex, for economic utilisation, international visibility and social added value.

a. Scientific impact

The research and clinical units involved in DISTALZ already have an international scientific and academic reputation as evidenced by the quality of their publications (469 publications since 2007, 4% of which in journal with IF>20, 6% with 10<IF<20 and 34% with 5<IF<10), the numerous invitations to national and international conferences (see appendix 2.3) and the frequent involvement in scientific advisory boards. One major objective of DISTALZ will be to further develop and strengthen this scientific commitment. It is expected that bringing together, under a unique laboratory of excellence, specialists from different disciplines (such as epidemiology, genetic, molecular and cellular biology, biophysics, clinicians, social and healthcare researchers and ethicists) will enable the emergence of a multidisciplinary programme embracing a large scope of hypotheses and themes and providing transversal solutions from bench to bedside for the benefit of patients. The need to bring global answers to scientific questions is already required in the field of genomics where, in addition to the traditional genetic association study, the biological mechanisms underlying the observation must be unravelled to be published in high-ranking journals. Thus, DISTALZ should expect, at least, an increase of the number of publications, but also further progression of quality (that could be reflected at least in part by higher impact factors and citation level).
DISTALZ will encourage its members' participation in scientific meetings to present their most recent findings, but also to gather relevant information and new trends, to join relevant consortia and networks to expand collaborations. Particular attention will be given to encouraging the participation of PhD students, postdoctoral fellows and young scientists in order to complete their education and develop their scientific skills. The goal is to increase interaction with national and international laboratories, to favour the emergence of original hypotheses and to promote exchanges and collaboration with other top-level laboratories. Finally, as part of its coordination management strategy, DISTALZ will organise every two years an internal scientific workshop (alternating between Lille, Nice and Paris), open to scientists and physicians from collaborating laboratories as well as to researchers and clinicians hoping to develop interactions with DISTALZ.

b. Economic impact

Context and strategy: After the recent disappointing results of AD prevention clinical trials, the scientific and industrial communities recognised that AD requires a more comprehensive view of current pathophysiological models. This still highlights the need to bring together researchers from the academic world and the pharmaceutical industry. The overall strategy of DISTALZ research dissemination is to ensure partnership with SMEs as well as major national and international enterprises to facilitate exchanges between scientists from the industrial and academic worlds, and to promote the utilisation of its research findings at an industrial scale.
DISTALZ partners already have longstanding utilisation experience, as evidenced by:

1. A portfolio of 7 patents as a direct utilisation of laboratory discoveries (see list of patents in appendix n°3)
2. Two successful biotechnical SMEs created in 2001 (Genoscreen SAS, http://www.genoscreen.fr) and in 2008 (Alzprotect, http://www.alzprotect.com) to outsource the development of specific research programmes and accelerate the technological transfer
3. Industry research contracts with major pharmaceutical companies (Sanofi Aventis, Ipsen, Pfizer, AstraZeneca, Servier, Eli Lilly, etc)
4. Participation in clinical trials with industry for phases 2 and 3
5. Integration in the Nutrition Health Longevity competitiveness cluster programmes to contribute to the effectiveness of regional socioeconomic development

DISTALZ aims to further develop this experience to increase private resources for its long-term financial support and to foster local and national economic added value. This strategy will be developed by the DISTALZ management group with strong support from local and national bodies in charge of economic development. Among these, the dedicated structure Eurasanté GIE and the Nutrition Health Longevity (NHL) competitiveness cluster are already partners of several ongoing projects of the Lille laboratories. DISTALZ is entirely in step with the priorities of the NHL competitiveness cluster. The latter brings together, in the Lille area, 80 companies and research institutes in the fields of nutrition and therapeutic innovation among which several are linked to Alzheimer's disease and vascular diseases. The NHL cluster is managed by Eurasanté, a non-profit agency dedicated to economic development for biotechnology & healthcare in Lille/Nord-Pas de Calais. Its mission is to facilitate and accelerate business opportunities between academic research laboratories and industrial partners. Eurasanté also manages an incubator specialised in the biotechnology and healthcare sector as well as a science park located at the outskirts of Lille's University Hospital Site. DISTALZ will also benefit from the development of the SATT (Accelerated Technology Transfer Society), a regional development platform. Thanks to the "Investissements d'Avenir" programme, the PRES ULNF has decided to merge the pre-existing exploitation structures in an SATT called "Nord de France Valo". The SATT will focus on the maturation steps of the

technologies sought to be licensed out and will also act as a tool devoted to both commercialising those technologies and negotiating their transfer to the industrial partners. Further utilisation of DISTALZ findings will be promoted by the mobilisation of seed funding for pre-commercial research, money for early filing of patents and workshops with industry through regional and national maturation funds.

Foreseeing partnerships. DISTALZ will generate proofs of concepts for the development of new biomarkers and putative pharmacological targets. The multidisciplinary skills of DISTALZ partners will make it possible to validate these biomarkers at the clinical and epidemiological level and to create biological tools and models to screen putative pharmacological targets. However, to ease the translation of DISTALZ's finding to a broader public, DISTALZ will work closely with SMEs and pharmaceutical industries by:

1. Further developing collaboration with a regional biotech and a start-up. This relates to two SME, Genoscreen and Alzprotect. Genoscreen, founded in 2001 on the impetus of DISTALZ's partners, develops and performs innovative service activities in genomics (human, animal, plantlet micro-organisms). The company increasingly contributes to the engineering of many research projects led by academic and industrial teams and is mainly involved in the development of diagnosis tests. Alzprotect is a start-up company founded in 2008, developing proprietary anti-Alzheimer drugs acting through an original mechanism discovered by DISTALZ partners. A consortium named Medialz (for MEdication and DIagnosis of ALZheimer's disease) has been initiated between UMR744, UMR837, Lille MRRC and these two SMEs to structure their collaboration. This consortium will be a major lever for the DISTALZ utilisation strategy. It will help to accelerate the validation of biomarkers and therapeutic targets proposed by DISTALZ, facilitate procedures and the transfer of these biomarkers to clinical trials, and support drug discovery based on the biological screening tests. By partly outsourcing development to these SMEs, DISTALZ partners aim to decrease the lag time between bench and application. A work programme is under discussion between DISTALZ partners and these two SMEs with clear and achievable deliverables.

2. Developing collaboration with national and international pharmaceutical companies. This will be implemented through formal alliances with industrial partners on specific programmes. In light of this, scientists and research groups from the pharmaceutical industry may be hosted within DISTALZ laboratories for medium-term stays under specific collaboration agreements. Specific funding from both DISTALZ and industrial partners will be allocated to support PhD and Postdoctoral fellowships as well as laboratory expenses. Besides selective programmes, DISTALZ aims at participating in the creation of innovative business models promoting interaction with the pharmaceutical industry for more efficient, win-win partnerships. This economic strategy will be developed along four main axes: (i) stimulate the translation of scientific concepts into intellectual property (IP); (ii) accelerate the development of this IP into products by outsourcing business development; (iii) reinforce industrial partnerships and proactively initiate others and; (iv) develop communication of DISTALZ achievements in order to attract investors. Finally, DISTALZ will encourage its scientists to participate in scientific advisory boards of international companies. Altogether, this may allow DISTALZ to become an essential partner for AD diagnosis and treatment development for industry, and help to build up a long-term, sustainable source of funding.

c. Societal impact

In 2009, the National Institute for Prevention and Health Education published a study on the perception of AD in the general public in France (http://alzheimer.inpes.fr/). The results showed that AD is seen as the number three disease, ranked according to severity, just after cancer and AIDS. Approximately 40% of the population considers lack of information on AD to be an issue. Information on research is one of the general public's biggest expectations and the search for new AD treatments should be one of the nation's top three priorities. Finally, 42% mention that being updated on AD research is among their highest priorities. For this reason, informing the lay public will be the highest priority for the DISTALZ communication project. Over the next 10 years, DISTALZ will develop intensive information and communication plan organised along three major axes of active participation in:

1. The organisation of international, national and local scientific meetings for scientists. DISTALZ partners are involved in the organisation of scientific meetings participating to international visibility: P. Amouyel was at the forefront of Paris's application to organise, for the very first time in France, the International Conference on Alzheimer's Disease, which gathers each year the very best scientists and physicians in the world. He was deeply involved, together with the Fondation Plan Alzheimer, in organising both the scientific and the logistical aspects, of this world class meeting, held from 16th to 21st July 2011 (5,630 registered participants from 85 countries and 2,348 scientific communications); F. Pasquier organised the VASCOG meeting in Lille from 11th to 14th September 2011; F. Checler organised The 9th reunion Francophone sur la maladie d'Alzheimer. In order to reinforce this participation in national and international scientific meetings, a communication tool kit will be

prepared together with Eurasanté, which has longstanding experience in the preparation and organisation of large international meetings.

2. The organisation of conferences and the publication of pamphlets for the general public. In collaboration with Fondation Plan Alzheimer and working closely with France-Alzheimer, the patient association for AD, DISTALZ partners will be able to prepare pamphlets explaining the advances in DISTALZ research in language which is easy to understand. Thanks to the experience of EA1610 in public debate, the societal and ethical concerns associated with AD, early diagnosis, lack of treatment, or carer burden will be discussed publicly with specific contributions from DISTALZ researchers. In line with this proposal, the Lille MRRC set up a regional medico-social network "Meotis" (www.meotis.fr) in 2002. This network is dedicated to care, medico-social coordination and promotion/communication of all related initiatives, including providing information, training and continuous education to healthcare assistants, social workers and the general public. DISTALZ will take advantage of this network to disseminate information locally.

3. The participation of DISTALZ researchers in any public or private initiative aimed at informing the general public. The 21st of September each year is "Alzheimer's day". During the week surrounding this annual event, numerous initiatives are launched throughout the world. DISTALZ will take advantage of this AD day to disseminate information and to support local and national initiatives related to ageing and neurodegenerative disorders. For instance, DISTALZ researchers will participate in local initiatives targeting adolescents, such as KID CAMPUS (to promote the scientific professions at the Institut Pasteur de Lille), "les 5 à 7 de l'IPL" (free conference for the general public on research carried out by the Institut Pasteur de Lille), " la Fête de la Science" organised each year in October by the French government, the "Brain awareness week" organised in collaboration with the French Neuroscience Society in early spring, and the Alzheimer's train, organised by the SNCF for the past two years.

DISTALZ places a great deal of importance on having a socioeconomic impact and this will only be possible with the support of the Labex. Indeed, this constitutes an investment in the future development of DISTALZ, essential for its long-term sustainability, beginning during Labex support and continuing after the end of its eight year term. DISTALZ will hire sufficient staff to immediately implement this socioeconomic development plan. Together with its transdisciplinary scientific programme, these socioeconomic and communication agendas will be essential to propel DISTALZ to achieving the highest level of recognition and to becoming a French centre of excellence on AD with an international reputation, able to compete and network with comparable centres in Europe and all over the world.

2. ORGANISATION AND GOVERNANCE

2.1. PRINCIPAL INVESTIGATOR

Philippe Amouyel, MD, PhD (aged 52) is a Professor of Epidemiology and Public Health at Lille University Hospital. He is head of a large academic research unit working on public health and molecular epidemiology of ageing diseases, UMR744 a major partner of DISTALZ. He develops large epidemiological, population-based studies in an attempt to decipher individual susceptibilities to age-related diseases using molecular techniques (high-throughput genomics, transcriptomics, proteomics, bioinformatics, etc.). He mainly developed his research activity at the end of the 1980's in the field of cardiovascular diseases in general and understanding the multiple determinants of coronary artery disease and strokes in particular. He was involved in the WHO's worldwide MONICA study and was last author of the Lancet article (1999; 353: 1547-1558) - one of the world's most cited papers on cardiovascular epidemiology which described trends and determinants of cardiovascular disease in 37 populations over a 10-year period. The other part of his work is focused on the study of (mainly genetic) determinants of the neurodegenerative diseases associated with cognitive decline and of AD in particular. He recently published (as last author) a large collaborative, GWAS presenting two new susceptibility genes for AD in Nature Genetics (Nature Genetics. 2009. 41: 1094-1099). Beside these two major highly cited papers, during his career he has also published one article in Nature, four in Nature Genetics, 21 in The Lancet, and several others in high-ranking journals. All together, he has a total of 576 publications referenced in the Web of Knowledge (427 in PubMed) and an H-Index of 61.

Between 1999 and 2008, he headed the Lille Genopole, a regional network of more than 300 researchers aimed at developing high-tech platforms, launching large collaborative projects and favouring start-up creation and

development. This experience of management of large projects encouraged him to apply for and obtain the post of Chief Executive of the Institut Pasteur de Lille (a non-profit private foundation dedicated to molecular research) in 2002. This foundation has several missions in biomedical research, public health and environmental control and hosts more than 1,300 staff. He now has longstanding experience of the management of research, technology transfer and business development. In 2007, he participated in the AD and related disorders national report prepared by Professor Joel Menard and was appointed as the Chief Executive of the Scientific Cooperation Foundation, the Fondation Plan Alzheimer, dedicated to AD research. This foundation underpins the research initiative of the National Alzheimer's Plan launched by the French government after the publication of Professor Menard's report. He helped create this foundation and developed its nationwide role, with a strong willingness to support public-private partnerships. He thus has high-level expertise of setting up a large research programme and managing national and international projects. His scientific experience in the field of worldwide multicentre epidemiological studies has given him an international profile, which was reinforced recently by his election as chair of the Joint Programming Initiative on Neurodegenerative Disease Research and AD in particular (JPND), a project bringing together 23 European countries and supported by an FP7 contract (JUMPAHEAD) which he coordinates. This last European initiative is in a leverage phase aimed at raising within the next two years a European fund of between 300 and 400 million euros to develop a European programme of research in the field of neurodegenerative diseases and AD in particular; the DISTALZ strategy may benefit from this, especially if it is recognised as a European centre of excellence participating in the CoEN initiative of the JPND.
A detailed CV is presented at appendix n°4.

2.2. PARTNERSHIP

2.2.1 PARTNERS' DESCRIPTIONS, RELEVANCE AND COMPLEMENTARITY

Partner 1: UMR744 "Public Health and Molecular Epidemiology of Ageing Diseases"

1. Research and innovation

1.1. AERES, Evaluation: A+

The UMR744 is a world-class research unit established for 15 years at the Institut Pasteur de Lille, staffed with 50 persons dedicated to the identification and the dissection of determinants of ageing vascular and neurodegenerative diseases, using high-tech molecular epidemiology and cutting-edge approaches.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A	A

The UMR744 has been rated "excellent" by the AERES agency and is headed by Prof. Philippe Amouyel who has a longstanding interest and experience in cognitive decline Alzheimer's disease (AD) research.

1.2. Research led by leading scientists

The UMR744 develops large epidemiological programmes to decode individual susceptibility to AD and its interactions with environmental factors, using classical **epidemiology** coupled to high-throughput **genomics**, **transcriptomics**, **proteomics** and **bioinformatics** The UMR744 is organised into three transversal teams with complementary scientific and technical skills. **The first, headed by Jean-Charles Lambert, works on the molecular determinants of neurodegenerative diseases. The second team, headed by Jean Dallongeville, is devoted to the study of vascular risk factors and the interaction between vascular and neurodegenerative risk. The third team, headed by Florence Pinet**, is highly specialised in proteomic exploration of human and animal tissues. All are internationally recognised in their area. To go forward in the post-GWAS era, UMR744 has developed biological and cellular approaches to decipher the biological plausibility of the genes identified. These basic projects are translated in clinics for pre-clinical diagnosis implementation of AD, thanks to the Memory Clinic of the Lille University hospital, and in partnership for exploitation with various industry contracts.

1.3. Equipment and infrastructure

As much as is possible, UMR744 uses existing regional (genomics, imaging and proteomics facilities) and national (CNG) facilities. UMR744 has created a Centre for Biological Resources to store more than 30,000 samples of AD cases and controls and has participated in the awarding of the Equipex label to the LIGAN-PM platform and the Labex label to Genmed. The UMR744 manages its own cluster composed of 224 CPUs for its bioinformatics needs. UMR744 has access to and participates in the development of the whole national

infrastructure reinforced by the National Alzheimer's Plan, including the Memento cohort, the CATI imaging centre and the three-city cohort study.

2. International visibility

This unit was among the pioneers of the study of genetic susceptibility in unrelated subjects, beginning in the mid-1990s, and among the first to dissect the implication of APOE in AD. We discovered two new genes for late-onset AD with GWAS in 2009, plus eight others in international collaborations. UMR744 is managing the International Genomics Alzheimer Project (IGAP) a collaboration involving the four largest consortia on AD genomics (125 research units in 11 countries) for a decisive mega-meta-analysis. This unit participated in the organisation of the 2011 International Conference on AD, held in Paris for the first time.

3. Exploitation of results

About 283 PubMed indexed papers have been published during the last 10 years. The total number of citations (from Web of Science related to Amouyel's name) is 16,000, H-index=61. A selection of the best publications (three Nature Genetics, one JAMA, one Cell, six Lancet) is given in appendix n°2. This unit has 4 patents (appendix 3), participated in the creation of a start-up (Genoscreen) and interacts with various industry partners (Ipsen, Pfizer, Sanofi, AstraZeneca, etc).

4. Higher education

Each year UMR744 has several PhD students in each group and the 11 researchers are involved in three Masters programmes, in the development of summer schools dedicated to AD and included in a European Masters degree (Erasmus Mundus) in conjunction with other international research units.

Partner 2: UMR6097 "Molecular and cellular biology of normal and pathological cerebral ageing"

1. Research and innovation

1.1 AERES, Evaluation: A+

Team 6 of UMR6097 is one of the largest research laboratories of the "Institut National des Sciences Biologiques" (CNRS) and of the University of Nice Sophia Antipolis, and was rated A+ at the last AERES evaluation (2011)

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A	A+

1.2 Research led by leading scientists

The team headed by F. Checler has led research on three neurodegenerative diseases, namely Alzheimer's, Parkinson's and prion diseases, with the aim of delineating common denominators underlying these various pathologies. As regards Alzheimer's disease, the group has been mainly involved in the understanding of the biogenesis and fate of βAPP-derived catabolites Aβ and AICD, i.e. in improving knowledge of Aβ-forming and catabolising enzymes. Furthermore, the group is working on the functional influence of proteolytic perturbations or alterations on Aβ- and AICD-associated functions, particularly in the control of cell death. Importantly, the group has strong links with clinics and, more particularly, with the MRRC of the Nice CHU.

1.3 Equipment and infrastructure

IPMC has always been at the forefront of the development of new technologies, as illustrated by the recognition by IBiSA (a French consortium coordinating policy regarding Infrastructure in Biological Sciences) of its platforms in functional genomics (2009) and cellular imaging (2010). The functional genomics platform has been ISO 9001 certified since June 2006. The cellular imaging facility (histology, confocal microscopy, video microscopy, flow cytometry and cell sorting) offers a large selection of tools and methods. Flow cytometers allow more than 10 simultaneous colour analyses on large cell populations. The platform is one of the seven components of the MICA project (Microscopy Imagery Côte d'Azur) identified in 2010 by the IBiSA consortium. The animal care facility includes a mouse SPF facility (called ANIPRO, 600 m²) and a platform devoted to functional studies (called ANIMEX, 200 m²). Two engineers specialised in mass spectrometry operate a mass spectrometer MALDI-TOF-TOF 4800 (Applied Biosystems), a nano-LC U3000 chromatography system (Dionex), a spotting robot (Probot), a two-dimensional electrophoresis system (BioRad), a Procise amino acid sequencer (Applied Biosystems), a Sprayer Leap Tech, and an HPLC alliance Waters, combined with several software analysis programmes (MASCOT server, from Matrix Science/Applied Biosystems; Protein Pilot, Applied Biosystems). Information technology now represents a key issue in many aspects of modern biology, and currently mobilises two engineers.

2. International visibility

UMR6097 was among the very first to link proteasome dysfunction to AD pathology and, in particular, p53 to the function of members of the γ-secretase complex. They were also first to show that it was possible to inhibit Aβ production without affecting Notch cleavage and that there could exist PS-independent γ-secretase-like activity. Furthermore, they evidenced a novel mechanism by which the APP metabolite AICD could control neprilysin and p53 at a transcriptional level. Finally, they recently unravelled a novel function for parkin as a transcriptional repressor of p53. Until recently, Dr. Checler was President of the scientific committee of the European League against Alzheimer's Disease (LECMA), a member of the scientific committees of the Mediterranean Neuropôle, the Neuropôle Francilien and France Alzheimer, deputy Chief Editor of Journal of Neurochemistry, European Editor of Current Alzheimer Research, and a member of the editorial board of the Journal of Biological Chemistry. Dr. Checler has been invited to 50 national and international conferences during the last five years and is on the scientific committees of a number of congresses, including AD/PD meetings.

3. Exploitation of results

About 181 PubMed indexed papers for Dr. Checler have been published. The total number of citations (from Web of Science related to Dr. Checler's name) is 7,622, H-index=47. Dr. Checler is ranked among the top 1% of scientists in the world in the field of Biology/Biochemistry (essential science indicators ISI Web of Knowledge).

4. Higher education

Dr. Checler's team includes five permanent researchers and two permanent engineers, four postdoctoral researchers, five PhD students and three Masters students. Several of the permanent researchers, including Dr. Checler, have participated in teaching. Dr. Checler has created, together with P. Robert, the German-French summer school for Alzheimer's disease.

Partner 3: UMR837 "Alzheimer & Tauopathies"

1. Research and innovation

1.1 AERES, Evaluation: A+

The UMR837-team 1 "Alzheimer & Tauopathies" is a world-class research unit which has been established for more than 20 years on the Lille hospital campus. It is staffed by about 30 people (18 of whom have permanent positions), and is dedicated to the molecular, cellular and physiological aspects of neurodegenerative disorders characterised by aggregation of the microtubule-associated Tau protein and referred to as Tauopathies. Of the latter, Alzheimer's disease is the best known.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A	A+	A+	A+

The UMR837-1 has been rated "excellent" by the AERES agency and is headed by Dr. Luc Buée who has a longstanding interest and experience in Alzheimer's disease (AD) research.

1.2 Research led by leading scientists

The UMR837 develops experimental models for understanding mechanisms underlying Tau toxicity, propagation and neuronal death. It also has an interest in the development and validation of diagnostic biomarkers (mostly at the peptide/protein level). Luc Buée leads the team and is internationally recognised in the field of AD as attested by numerous invitations to worldwide meetings, symposia and conferences. Claude-Alain Maurage, neuropathologist, is a key player in the characterisation of brain lesions and participates in international publications to define neuropathological criteria for diagnosis among neurodegenerative disorders. The team has also worked on splicing regulators and how they may affect neuronal pathophysiology. It is part of a national consortium on myotonic dystrophy, a specific Tauopathy that is a disease model for studying Tau alternative splicing. The team is also particularly interested in how environmental factors affect brain disorders. Thus, UMR837 focuses on the biology and pathology of Tau proteins and the development of diagnostic and therapeutic strategies. These basic projects are translated in clinics for pre-clinical diagnosis implementation of AD, thanks to the Memory Clinic of the Lille University hospital, and in partnership for exploitation with various industry contracts.

1.3 Equipment and infrastructure

As much as possible, UMR837-1 uses existing regional facilities (animal housing, L2, L3 biosafety level facilities, viral vectors, micro-PET and micro-MRI for rodents, behaviour and electrophysiological platforms, stereology, microscopy and proteomics facilities). UMR837 has initiated with the Lille-MRRC a brain bank which now includes more than 200 brains from AD cases (Head: Prof. CA Maurage).

2. International visibility

This laboratory was a pioneer in the discovery of Tau protein as components of neurofibrillary tangles, developing experimental models including a unique transgenic Tau model that displays a hippocampal related phenotype (THY-Tau22). The laboratory is involved in European programmes (former partner in MEMOSAD FP7 project, submitted FP7 project ValidAD, etc.). The laboratory is regularly invited to all of the international conferences on AD (AD/PD (2009, 2011), AAICAD (2009, 2010 and 2011 as plenary speaker), Alzheimer Springfield Symposium (2008, 2012)) and has co-organised a number of workshops (Neurotau at ICAD, Madrid 2006; NEURAD workshop, Lille, 2010, etc.).

3. Exploitation of results

About 90 PubMed indexed papers have been published during the last 10 years. A selection of the best publications (one Nature Medicine, two Mol Psychiatr, two Hum Mol Genet) is given in appendix n°2. The total number of citations (from Web of Science only related to Dr. Buée's name) is 5000, H-index=31. This unit participated in the creation of a start-up (AlzProtecT) and interacts with Johnson&Johnson (Janssen Pharm.), Sanofi-Aventis, and Servier.

4. Higher education

UMR837 welcomes each year several PhD students and the permanent researchers are involved in teaching in three different Masters (Biology-Health and Drug Design in Lille 2; Biology of Aging in Paris; Proteomics in Nancy). Bernard Sablonnière is the head of the Biology-Health Masters at the University of Lille in which David Blum, Luc Buée, Morvane Colin and Malika Hamdane are also involved in organisation and design. Luc Buée organises and participates in different summer schools dedicated to AD. UMR837 is also part of a project for developing a European Masters degree (Erasmus Mundus) in conjunction with other international research units

Partner 4: UMR8576 "Nuclear Magnetic Resonance and structural biochemistry"

1. Research and innovation

1.1 AERES, Evaluation: A

This team 2 is part of the UMR8576, an internationally known CNRS laboratory in structural and functional (glyco)biology at the University of Lille 1, with 10 staff dedicated to the molecular identification of molecules, using high-tech NMR and mass spectrometry methods. They have been among the first to explore proteins interacting with Tau as PIN-1.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A	A

The UMR8576-2 has been rated "very good" by the AERES agency and is headed by Dr. Guy Lippens, who has a longstanding interest and experience in the molecular factors that lead to cognitive decline Alzheimer's disease (AD), with a special focus on Tau biology.

2.2 Research led by leading scientists

The UMR8576-2 develops a novel methodology to determine the molecular structure of complex glycans and/or proteins with their post-translational modifications, in order to understand the molecular basis of human disease. Research is based on classical **chemical methods** coupled to high-resolution **mass spectrometry and NMR. The NMR group, headed by Guy Lippens and Isabelle Landrieu, works on Tau phosphorylation and its influence on molecular function and interactions with other protein partners.** These basic projects aim to understand the role of Tau in AD pathology, but equally to provide for potential novel drug targets.

1.3 Equipment and infrastructure

UMR8576-2 is in charge of the 900MHz NMR spectrometer, integrated in the TGIR-RMN national facility (www.tgir-rmn.org). Together with the 800MHz, also installed at the University of Lille 1, this is the sole Large Scale Facility installed in the Region. UMR8576 also has direct access to the proteomics facility at the University of Lille 1, which houses a large panel of mass spectrometers including an FT-MS. The NMR group has set up all the biochemistry required for protein expression, purification and isotopic labelling, and has all the equipment and expertise for complex enzymology with notably phosphorylation reactions.

2. International visibility

This unit was one of the first to apply NMR spectroscopy to an intrinsically unstructured protein of the complexity of Tau. We were also the first to use NMR to evaluate phoshorylation at a qualitative and quantitative level, and recently performed an extensive study comparing immunochemistry, mass spectrometry and NMR to evaluate a complex phosphorylation pattern.

3. Exploitation of results

About 80 PubMed indexed papers have been published by the Lippens-Landrieu group during the last 10 years.

4. Higher education

UMR8576 is at the heart of Biochemistry teaching at the University of Lille 1, with over 10 Professors. Each year the Lippens group has several PhD students and the researchers are involved in both chemistry and biochemistry Masters degrees. Dr. Lippens is also actively participating in the Erasmus Mundus programme "Advanced Chemistry and Spectroscopy" in conjunction with other international research units.

Partner 5: Lille MRRC "Lille Memory Resources and Research Centre"

1. Research and innovation

1.1 Clinical ward

Created in 1991 as part of the Neurology department, the MRRC is headed by Prof. Florence Pasquier and consists of a multidisciplinary consultation and day hospital (seven beds) open five days a week. In addition, two secure beds in the neurology ward are dedicated to patients with dementia and delirium. It has an advanced memory clinic in Bailleul, in a nursing home partly dedicated to young patients and patients with severe behavioural troubles. The clinic has an active line of 2,758 patients (15% with young onset dementia), including 924 new patients per year, and is one of the three most active clinics in France. It develops translational research and is currently involved in 20 academic clinical trials and 12 clinical trials (phases 2 or 3) of innovative treatments or new radiotracers sponsored by pharmaceutical companies. More than 500 patients are included in a study: 52 in an industrial trial and 450 in an academic study. It is part of the CenGEPS network.

1.2. Research led by leading scientists and physicians

The MRRC is developing specific research projects on the relationships between AD and vascular pathology which studies the clinical consequences of the combination of vascular and neurodegenerative disease, including the neuropathological level. It notably showed that in patients with MCI, vascular subcortical hyperintensities predict conversion to vascular dementia with prominent executive dysfunction, and that AD patients with untreated vascular risk factors had a higher cognitive decline than those without or with treated vascular risk factors. MRRC is currently conducting a national, multicentre prospective study of the impact of controlling vascular risk factors on the progression of Alzheimer's disease (COVARAD: ClinicalTrials.gov registration 2009-A00269-48). This research group also studies the cognitive consequences of cerebrovascular lesions, especially the determinants of poststroke dementia, as well as the impact of pre-existing dementia or cognitive decline on strokes. The MRRC participates in the Strokedem and Strokavenir project, a database of clinical biological imaging and therapeutic characteristics of patients with ischaemic or haemorrhagic strokes followed-up over an eight-year period evaluating the pre-stroke period, the acute stage and the post-stroke period, including cognitive decline. As the Reference centre for YOD patients, the MRRC is particularly interested in the characterisation of young patients, in a broad, multidisciplinary approach and is PI of the YOD Equipex project.

1.3 Equipment and infrastructure

Accurate clinical diagnosis of dementia is increasingly important for therapeutic and scientific investigations. The Lille MCCR was concerned from the start by early and accurate etiological (differential) diagnoses of cognitive decline. It uses multidisciplinary tools and skills: in neurology, neuropsychology, psychiatry, CSF biomarkers, structural and molecular imaging. The comprehensive technical support at the same site includes: a biological platform, a neurophysiology platform (EEG, ERPs , EMG, TMS , Sleep recording, etc.) a 1.5 T and a research 3T MRI machines, a CT scanner, a PET scanner, a SPECT camera and hopefully a 7T MRI and a PET-MRI enabling simultaneous acquisition of multimodal sequences, and functional and activation studies (SMART Equipex 2011 project).

2. International visibility

The Lille MCCR is internationally-renowned for its expertise in clinical diagnosis of AD and non-AD dementias, and in clinical-neuropathological comparison. It has participated in diagnostic criteria setting, in validation of new scales and tools and is invited to write a number of editorial comments, reviews and books. MRRC was a member of the international network of the CERAD (Consortium to Establish a Registry for Alzheimer's disease), and is a founding member of the European Alzheimer's Disease Consortium (EADC). It has a particular interest in non-AD dementias that are encountered especially in young patients, raising difficult differential diagnostic problems: frontotemporal dementia, Lewy body disease and dementia with a vascular component. F. Pasquier is an active member of several international advisory boards, is a member of the Vas-Cog executive committee, and hosted the 5th congress of Vas-Cog in Lille in September 2011

3. Exploitation of results

Since 2005, the Lille MRRC has authored or co-authored 98 articles, of which 61 were collaborative studies: 33 clinical collaborative studies and 28 basic research collaboration. In addition, the MCCR has signed up as a member of a collaborative group in 40 clinical research articles and three basic research articles. Florence Pasquier has an H-index of 42 and has published more than 240 articles in peer-reviewed journals and is frequently invited to give conferences and teaching courses in France and abroad.

4. Higher education

The Lille MRRC participates in the Ethics group of the University Hospital, holds meetings for the staff and students, and runs courses and conferences. It organised the first meeting on "Alzheimer's and young patients- Approaches and ethical challenges" in Lille with the Espace national de réflexion éthique sur la maladie d'Alzheimer (EREMA) in 2011.

The MRRC is involved in primary education and continuous training, and in 2000 it set up a course for general practitioners and specialists on "Diagnosis and care of patients with dementia".

Partner 6: EA1059 "Research Unit on Cognitive and Affective Sciences"

1. Research and innovation

1.1 AERES, Evaluation: A

The EA1059 is a university research laboratory which deals with cognitive and affective sciences, psychology and health. The EA1059 has received an "A" rating. The Family Health Emotions team works on psychopathology and the family interactions in chronic diseases and Pascal Antoine leads the projects on AD with research activities funded by Mederic Alzheimer, France Alzheimer and ANR-FRSQ.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

The scientific programme relates to modelling the cognitive and emotional processes governing the normal and pathological behaviours of individuals, and to studying the conditions of emergence of such behaviours.

1.2 Research led by leading scientists

The Family Health Emotions team includes specialists in family, social, and clinical psychology who are focused on emotional regulation, social interaction and family organisation in health contexts (e.g. addiction, cancer, dementia, etc.). The group performs several types of inter-connected activities: scientific knowledge development; research and professional training for graduate students in psychology; collaborative work and knowledge transfer to both medical professionals and social workers involved in health or therapeutic education; recommendations to decision-makers with a view to improving policies and practices regarding patients and their families' health and quality of life. The team's research interests include development of measures for psychological assessment of various subgroups of carers and patients, development of dyadic analysis in couples or families faced with illness, mixed methodology (including qualitative, quantitative and physiological assessments), and development and evaluation of innovative interventions in patient and family counselling.

1.3. Equipment and infrastructure

EA1059 consists of 40 researchers who, within the framework of their scientific activities, use high-technologies which they provide thanks to a technical centre grouping together the laboratory's material and human skills. This technical centre is CREST-certified (Centre de Ressources et d'Expertise Scientifique et Technologique). This certification, launched in 2007, is a guarantee of confidentiality, ability to react and precise technical and financial propositions for scientific expertise. CREST certification is awarded by the Regional Platform for the Innovation and Valuation of Research. Our techniques apply as much to children as to groups of adults who are healthy or suffering from illnesses. They also enable evaluation and specification of individual behaviour, interactions between individuals and human-machine interactions.

2. International visibility

The group's work has earned it a solid reputation at both the national and the international level. Scientific articles in psychological and medical journals, presentations at scientific conferences and dissemination of theoretical and practical knowledge all ensure that research findings are shared with the medical and psychological scientific community and the public at large.

3. Exploitation of results

About 30 research projects have been financed by between one and four foundations (at the European, national or regional level) during the last five years. More than 200 indexed papers have been published between 2007/2011 and about 150 Web of Science indexed papers have been published during the last 10 years.

4. Higher education

Each year EA1059 has several PhD students and its researchers are involved in four Masters: (1) Neurocognitive Psychology and Affective Sciences; (2) Experimental and Applied Behaviour Analysis; (3) Psychopathology: Psychotherapy and Clinical Approach; and (4) Clinical and Social Health Psychology.

Partner 7: EA1610 "Ethics, sciences, Healthcare and society"

1. Research and innovation

1.1 AERES, Evaluation: A

The EA1610 is a university research laboratory, the framework of which concerns the fields of the cognitive and affective sciences, psychology and health. The EA1610 has received an "A" rating and is headed by Hélène Gispert, full professor director of the hosting team 1610 "Studies on sciences and techniques".

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans 'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

The ES3 Module – Ethics, sciences, healthcare and society is headed by Emmanuel Hirsch, full professor of medicine working in the field of AD ethical research.

1.2 Research led by leading scientists

As early as 1997, Espace éthique/AP-HP was engaged in reflections on predictive medicine. The hosting team 1610 has pursued this line of questioning and produced various papers collected in the book, "Traité de bioéthique". Future causal treatments and therapeutic trials on Alzheimer's disease involve members of groups subject to high risks (especially genetic ones). These individuals are potential volunteers for research conducted many years before they have reached the age at which Alzheimer's disease often presents. An appropriate ethical framework is necessary for epidemiologic and clinical research, as well as clinical trials. An international conceptual framework is required, but it must be considered in this context, which has a number of specific features. A practical ethical approach must study research protocols before they are submitted to the ethics committee (CPP). It must also monitor its concrete application in order to analyze actual practices, to anticipate possible harm and to improve, if necessary, the framework.

1.3 Equipment and infrastructure

EA1610 ES3 is considered to be a benchmark in biomedical ethics. It is based on a partnership between: Espace éthique Assistance Publique – Hôpitaux de Paris (a WHO collaborating centre for bioethics); Espace national de réflexion éthique sur la maladie d'Alzheimer (national centre for ethical reflections on Alzheimer's disease) (National Alzheimer's Plan 2008-2012); and Université Paris-Sud 11 research department in ethics.

2. International visibility

Emmanuel Hirsch is head of the module ES3 – Ethics, science, healthcare and society – of the hosting team 1610, director of the research department in ethics, université Paris-Sud 11, director of the Espace éthique/AP-HP and director of the Espace national de réflexion éthique sur la maladie d'Alzheimer.

3. Exploitation of results

Members of the team contributed to the following publications among others

- Traité de bioéthique, (dir. E. Hirsch), 3 tomes, 2056 p., Toulouse, Erès, 2010;
- Pandémie grippale. L'ordre de mobilisation, (dir. E. Hirsch), 390 p., Paris, Cerf 2010.

4. Higher education

Academic programmes ranging from the diplôme universitaire (a one-year course including two specialties) to the Masters degree "Ethics, sciences, healthcare and society" are taught to health professionals. The Masters degree is composed of three specialties ranked A+ by the AERES (evaluating agency for research and academic teaching): Ethics for healthcare practices and hospital institutions; Ethics for scientific research practices ; Ethics, chronic diseases, end of life and palliative care.

During the 2011/12 academic year, there will be 22 doctoral students. The Hosting team 1610 is associated with the ED400 "Epistemology, history of sciences, discipline didactics", university Paris Diderot Paris 7.

2.2.2 QUALIFICATION, ROLE AND INVOLVEMENT OF THE PARTNER UNITS

Surname	First name	Position	Domain	Partner	Organization	Contribution in the project
AMOUYEL	Philippe	Professor	Genetic epidemiology and Public Health	UMR 744	Inserm - Université de Lille 2 - Institut Pasteur de Lille	PI, Head of UMR744
LAMBERT	Jean-Charles	Research Director	Neuroscience, genomics and cell biology	UMR744	Inserm - Université de Lille 2 - Institut Pasteur de Lille	Head of team 3 in UMR744
DALLONGEVILLE	Jean	Research Director	epidemiology and Public Health	UMR744	Inserm - Université de Lille 2 - Institut Pasteur de Lille	Head of team 1 in UMR744
PINET	Florence	Research Director	Proteomics	UMR744	Inserm - Université de Lille 2 - Institut Pasteur de Lille	Head of team 2 in UMR744
RICHARD	Florence	Research associate	Neuroscience, epidemiology and Public Health	UMR744	Inserm - Université de Lille 2 - Institut Pasteur de Lille	Epidemiology
CHECLER	Frédéric	Research director	Cellular and Molecular biology	UMR6097	Université de Nice - CNRS	Head of UMR6097
CHAMI	Mounia	Researcher	Biology of the modulation of calcium signalling	UMR6097	Université de Nice - CNRS	Calcium thematic
CISSÉ	Moustapha	Researcher	Biology of EPHB2/NMDA cascade	UMR6097	Université de Nice - CNRS	Signalling cascade
PARDOSSI-PIQUARD	Raphaëlle	Researcher	Biology and design of animal models	UMR6097	Université de Nice - CNRS	Design of Transgenic animal models
BUÉE	Luc	Research Director	Neurobiology – Expert in Tauopathies	UMR837	Inserm – Université de Lille 2 – CHR&U de Lille	Head of UMR837
BLUM	David	Research associate	Neurobiologist – Expert in environmental factors	UMR837	Inserm – Université de Lille 2 – CHR&U de Lille	animal experiments
SERGEANT	Nicolas	Research associate	Biochemist and molecular biologist –alternative splicing	UMR837	Inserm – Université de Lille 2 – CHR&U de Lille	Tau alternative splicing APP processing
MAURAGE	Claude-Alain	Professor	Neuropathologist	UMR837	Inserm – Université de Lille 2 – CHR&U de Lille	Head of the Brain bank
LIPPENS	Guy	Research Director	Structural Biology	UMR8576	Université de Lille1 - CNRS	Head structural biology team
LANDRIEU	Isabelle	Researcher	Structural biochemistry	UMR8576	Université de Lille1 - CNRS	Head Biochemistry
PASQUIER	Florence	PUPH	Neurology	MRRC	Université de Lille 2 – CHR&U de Lille	Head of MRRC
DERAMECOURT	Vincent	PHU	Neurology-Histology	MRRC	Université de Lille 2 – CHR&U de Lille	Investigator
BOMBOIS	Stéphanie	PH	Neurology	MRRC	CHR&U de Lille	Investigator
DELBEUCK	Xavier	Psychologist	Neuropsychology	MRRC	CHR&U de Lille	Patient recruitment and follow-up
ANTOINE	Pascal	Professor	Psychopathology and Clinical Health Psychology	EA1059	Université de Lille 3	Unawareness in AD ; Caregivers YOD
NANDRINO	Jean-Louis	Professor	Psychopathology and family Psychology	EA1059	Université de Lille 3	Family interventions in chronic disease
CHRISTOPHE	Véronique	Professor	Social Health psychology	EA1059	Université de Lille 3	Genetic councelling, emotional regulation
HIRSCH	Emmanuel	Professor	Ethics	EA1610	Université de Paris 11	Head of team
PITCHO	Benjamin	CM	Law	EA1610	Université de Paris 11	Investigator
HIRSCH	François	Research Director	Ethics	EA1610	Université de Paris 11	Investigator

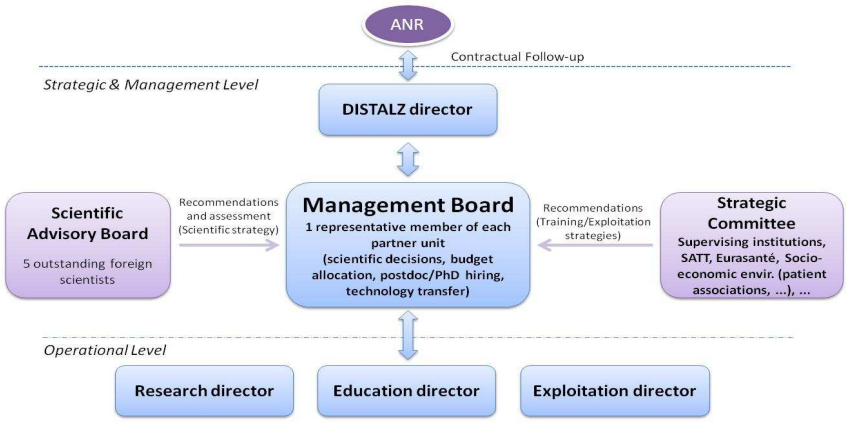
See appendix n°5 for an exhaustive list of the persons involved in the project.

Nom du partenaire	*Affiliation*	*Effectifs / Catégorie de personnel*
1-U744 P Amouyel	IPL, U Lille 2, Inserm	33 permanent staff including 16 professors & researchers, 7 engineers, 10 technicians, 4 Postdocs
2-IPMC F Checler	U Nice CNRS	7 permanent staff including 5 professors & researchers, 1 engineer, 1 technician, 4 postdocs
3-UMR837 L Buée	Inserm, Lille2, CHRU	19 permanent staff including 13 professors & researchers, 2 engineers, 3 technicians, 2 Postdocs
4-UMR8576 G Lippens	Lille1, CNRS	4 permanents staff, including 4 professors & researchers, 3 engineers
5-CMRR F Pasquier	CHRU	14 permanent staff including 5 professors & researchers, 2 engineers, 4 technicians and 3 psychologists and Speech therapists
6-EA1059 P. Antoine	Lille 3	6 permanent staff including 5 professors & researchers, 1 engineer, 2 Postdocs
7-EA1610 E Hirsch	U Paris XI APHP	6 permanent staff including 3 professors & researchers, 1 engineer, 2 technicians

2.3. GOVERNANCE

Labex support will provide DISTALZ with the means to closely link the seven partners to improve their research efficiency and productivity through (i) a common multidisciplinary scientific programme, (ii) pooling of the Labex resources and (iii) creation of efficient, responsive governance. It will integrate the specific governance of each research unit with its own constraints into a simple, responsive governance scheme bringing together the supervising organisations (Universities, Inserm, Cnrs, IPL) and the partners.

1. **Governing bodies and missions**



The organisational structure must enable fair, simple and efficient management. Three main bodies will be created: a Strategic Committee, a Management Board and a Scientific Advisory Board.

Strategic Committee (SC)

It will be composed of:

- a representative of each partner supervising institution (Université de Lille 1, Université de Lille 2, Université de Lille 3, Université de Nice, Université Paris XI sud, Inserm, Cnrs, IPL, CHRU de Lille, PRES);
- the DISTALZ Director, Philippe Amouyel, PI of the project;
- seven research directors, one from each partner (Jean-Charles Lambert for UMR744, Frederic Checler for UMR6097, Luc Buée for UMR837, Guy Lippens for UMR8576, Florence Pasquier for Lille MRRC, Pascal Antoine for EA1059, Emmanuel Hirsch for EA1610);
- a representative of the patient association France-Alzheimer and of the Eurasanté GIE as permanent observers.

The SC will meet once a year and will be informed of the options and scientific orientations suggested by the Scientific Advisory Board. The Management Board will present the strategy and the results obtained, and will discuss the opportunities for development in accordance with the strategy of each supervising institution and the comments of the observers. Thus, the SC may provide recommendations, in particular on the education and exploitation strategy, but also on the yearly budget, vision, objectives, key strategic options and long-term plans.

Management Board (MB)

The MB will be composed of the seven research directors and the DISTALZ Director. The MB will be the key operational body and will be in charge of implementing the DISTALZ project. The MB will take all major decisions affecting the overall activities of the DISTALZ programme by consensus. The MB will prepare and monitor the financial aspects, and the completion of the scientific programme. The MB will meet at least once a month in face-to-face meetings or by videoconference.

Scientific Advisory Board (SAB)

The SAB will be composed of five outstanding foreign researchers who are as independent as possible. The composition of the Scientific Advisory Board shall reflect recognised leadership in specific relevant fields, with the ability to deal with scientific, medical, social and policy issues, including public health, and the capacity to cover the four axes integrated in the DISTALZ scientific programme. These scientists will be chosen in the list of scientists prepared for the constitution of the SAB of the European JPND programme and of the Fondation Plan Alzheimer. The SAB will review and challenge the scientific objectives of DISTALZ. It will participate in the monitoring and follow-up of the Labex. It will work closely with the MB to prepare a report on DISTALZ. The SAB will meet at least twice a year in face-to-face meetings and may hold discussions on specific questions.

DISTALZ Director and Deputy Directors

The DISTALZ programme will be headed by a Director. The Director will be the spokesman for the DISTALZ project and communicate directly with the ANR, the participating Institutions (Université de Lille 1, Université de Lille 2, Université de Lille 3, Université de Nice, Université Paris XI sud, Inserm, Cnrs, IPL, CHRU de Lille, PRES), and other national or regional institutions. The Director will also be the direct contact person with other local, national and international bodies involved in the DISTALZ programme and the external Scientific Advisory Board. The Director will be responsible for organising regular management meetings with the MB. The Director will be assisted by three Deputy Directors from among the seven research directors on the MB, each being in

charge of a specific domain: research, education and exploitation. They will be appointed for a period of four years after approval by the SC, and can be reappointed. The first Director will be Philippe Amouyel.

2. Organisation chart

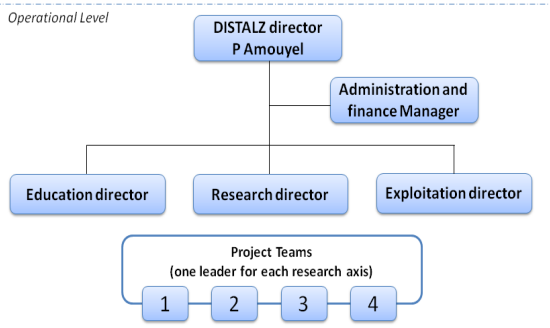
The operational level will be administered by the Director and the three Deputy Directors chosen from among the directors of the partner research units according to their willingness and commitment to actively participate in the daily management of DISTALZ. For each axis, a project team will be constituted that will closely monitor the progress of the scientific programme and of the implementation of each WP. Several persons will be recruited to act as: administrative and finance manager, education manager, communication manager, innovation manager, IT manager and secretary, for the cross-sectional missions. All partners will be equipped with dedicated videoconference systems and will meet at least weekly to manage the Labex in its daily development.

3. Monitoring and assessment of DISTALZ objectives

Despite its long-term vision, every two years the DISTALZ MB will be required to perform a thorough independent international scientific evaluation to maintain its high level of competitiveness. DISTALZ will appoint a consulting company specialised in the evaluation of large scientific international programs. This evaluation will be performed regularly and independently. Its major tasks will be to identify indicators, to collect these indicators independently all along the DISTALZ duration and to produce every two years a report that will be transmitted to the SAB for critical assessment of DISTALZ strategy and results.

2.4. INSTITUTIONAL STRATEGY

DISTALZ is fully in line with the local organisations and will be presented under the auspices of the PRES Lille Nord de France. The University Lille Nord de France is involved in a project of "Initiative d'Excellence" gathering the three universities of Lille and entitled "Lille Evolutions" that groups all the supervising institutions from the Lille area. DISTALZ will be actively involved in reaching the objectives of the IDEX. Firstly, it will help structuring local research around academic research clusters of excellence by enabling the setting-up of a research centre of excellence in Alzheimer's disease and related disorders with a national influence and an international reputation.



This centre will develop a unique and interdisciplinary basic, clinical and social sciences approach. Secondly, it will increase the international attractiveness of research and training programs as it will for sure attract both highly talented researchers and students. For these reasons, DISTALZ will be a major player of one of the 5 clusters constituting the IDEX project "Lille Evolutions", the "Personalized Medicine-New Generation" cluster, which gathers the anchor projects in the fields of Biology and Health. The Institut Pasteur de Lille strategy centred on "live longer, better" focused on chronic disease research is fully in line with DISTALZ aims. The Paris XI and Nice Universities are also strongly supporting the Labex project DISTALZ as they foresee a significant fallout on their respective research communities and territories. The Lille 2 and Nice Universities are also strongly supporting the labex project DISTALZ for their respective partners: Lille 2 will allocate 6 positions (4 assistant professor positions, 1 research engineers and 1 study engineers) and Nice 3 positions (2 assistant professor positions and a junior excellence chair). The strong support of these supervising institutions is associated with a commitment to, at least, maintain their participation in a difficult economic context. They will preferentially target new teaching and research positions to the DISTALZ partner strongly reinforcing their willingness to make AD a major axis of their excellence strategy. Finally the local authorities, as the Conseil Régional Nord Pas de Calais, the Conseil Général du Nord and Lille Metropole Communauté Urbaine, the Conseil Général des Alpes Maritimes involved in research are also actively supporting DISTALZ and will offer help for attractive logistic packages to host new researchers and integrate DISTALZ topics in their research funding strategies.

This labex is fully in phase with the French National Strategy for Research and Innovation (SNRI) and the AVIESAN life science and healthcare objectives. Neurodegenerative diseases are priorities in the SNRI and are defined as major health challenges by AVIESAN's ITMOs "Neurosciences, Cognitives Sciences, Neurology, Psychiatry" and "Public Health". Moreover the potential valorization and economical development associated with this objective are in perfect adequacy with the SNRI scheme and AVIESAN's incentives to increase industrial collaborations. **DISTALZ could emerge thanks to the National Alzheimer Plan** with which it is in step.

DISTALZ will constitute a major achievement of this National Alzheimer Plan ending in 2012 by allowing creating a research excellence centre dedicated to AD with a high international visibility able to compete with other international neurodegenerative centres.

DISTALZ is in line with the European strategy for neurodegenerative research whose best example is illustrated by the Joint Programming Initiative on NeuroDegenerative research and AD in particular (JPND) that represents the pilot of an innovative way of collaboration within Europe. Indeed neurodegeneration has been considered as a "Grand Challenge" for Europe beside energy, food and health and climate change. DISTALZ topic covers the most frequent neurodegenerative disease in Europe, AD, and will aim at increasing the visibility of its partners in this European research ambition. JPND has begun to identify in Europe excellence research centre and to connect them through an attractive funding scheme, the CoEN (Centres of Excellence Network) and DISTALZ aims to be one of them. Moreover, the three pillars of DISTALZ, research, education and innovation, are the key drivers of the knowledge-based society as identified in the European Union and the Lisbon strategy referred to as the "knowledge triangle" at the heart of the European Research Area.
(see support letters in appendix n°7)

3. FUNDING JUSTIFICATION

3.1.1 RESEARCH PROJECT

Equipment: The most significant new equipments are intended to improve the productivity and the efficiency of DISTALZ's basic science laboratories. Beyond their access to national or regional genomic platforms, UMR744 will need an in-house next generation sequencer platform (Illumina Miseq system) to be able to perform rapid, customised deep sequences of the candidate genes identified through classical genomic approaches. Moreover the development of the functional screening tests in drosophila will make it necessary to have in hands a confocal microscope. UMR8576 will complete the laboratory equipment necessary to handle and purify biological sample for NMR and thus increase its ability to analyse a larger number of samples. UMR837 will invest in a new ultracentrifuge for the preparation of the different cellular fractions and viral vectors purification. See doc A2 and appendix n°8 for more details.

Staff costs: The cornerstone of DISTALZ research strategy is the manpower that will be allocated to common research programs. So far the estimated additional number of people needed to develop DISTALZ multidisciplinary programme is 3 PhD students, 5 Post-Doctorate fellowships and 10 engineer/technician/nurse per year. Furthermore, two stipend packages will be created for senior and junior scientists, respectively.

The Senior package: DISTALZ will offer a five-year salary (maxi 70,000-80,000€/year – net salary: about 3,500€/month – for Professor/Research Director salary, duration 3 years plus extension for 2 years) per senior scientist joining DISTALZ. This package will also include funding for 2 additional co-applicants (post-doctoral fellow and/or technician) and will be completed with a budget of 100,000€/year for consumables and small materials for three years.

The Junior package will offer a three-year salary (50,000-60,000€/year – net salary: about 2,800€/month Assistant/Associate Professor salary, duration 3 years) completed with a budget of 15,000€/year for consumables and small materials for the same period.

The two packages will be powerful tools intended to attract new researchers all along the next 8 years of DISTALZ initial creation. As indicated above, at least six applicants have been already identified. Two of them will join DISTALZ laboratories before the end of 2011 with an academic positions strongly supported by the supervising institutions. The four others are still pending (see appendix n°7.2) allowing to anticipate two senior and two junior packages. The goal of this policy is to provide the best conditions for their rapid integration within DISTALZ laboratories and allowing them to benefit, in the medium term, of tenure positions offered by the supervising institutions based upon dedicated Excellence Chairs for assistant or full professor.

Subcontracting: Two major activities will be outsourced (i) high throughput genomics (mainly to CNG) and (ii) transgenic mouse models development and screening (mainly to the Mouse Clinic Institute). Moreover, some part of the implementation of the personalized medicine trial developed by the MRRC will be also outsourced to Clinical Research Organisations.

Travel: Most travel expenses will be taken from the regular partner budget and from the common teaching and exploitation budgets described below.

Expenses for internal billing: These expenses will be mainly related to animal facilities, use of technological platforms developed by supervising institution and Equipex platforms for genomics and imaging.
Other running costs: These costs will be partly supported by the Labex to ensure a timely development of the scientific project. They will be related to molecular and cell biology consumables, high throughput proteomics reagents and structural biology experiments.

Research project = 14 713 122 € (71%)					
Equipment	**Staff**	**Subcontracting**	**Travel**	**Internal billing**	**Other costs**
1 484 592	6 818 073	1 974 357	0	1 166 100	3 270 000
10%	46%	14%	0%	8%	22%

3.1.2 TEACHING PROJECT

This educational project will be largely dedicated to student training, to offer them a direct access to the very best researchers in the field. They will benefit from this access as soon as their Masters classes, and during the Summer University and thematic workshops. they will be offered travel grants for stays in the European Universities involved in the Masters, offering them as early as possible an international vision of research. All the training sessions will be opened to the DISTALZ researchers to favour a better knowledge of these multidisciplinary approaches and tighten the levels of collaboration.
Equipment: A percentage of the research project equipments will be dedicated to the teaching project (genome sequencer, NMR spectroscopy).
Staff costs: Three position related to DISTALZ educational program will be opened to ensure the implementation and the coordination of the project: (i) an assistant professor will manage the educational program, (ii) a project manager, assisted by a secretary (both hired on the 4% management costs of the Labex) will ensure the coordination - including logistic aspects - of DISTALZ post-graduate and post-doctoral interchange and career within and out of DISTALZ's laboratories. The researchers recruited on the senior package will devote 25% of their time for educational purpose paving the way for their application to sustainable Excellence Chair position in the framework of the proposals of the supervising organisations.
Subcontracting: Translation and publication costs will be supported
Travel: Travel expenses will be affected for students participating in the European Master (4000€/ year/student for 2 years 4 sessions in total) allowing them to attend the courses in the partnering universities and to high level international invited professor (10K€/year). Travel costs for summer universities (40K€/2 years), for workshops (50 K€ /year) and for invited professors (10K€/year) will be included.
Other running costs: Specific fundings will be allocated to support the running costs for the dedicated Summer Schools (40K€/2 years), for the Ethical Symposium (20K€/2 years) and for Social Workshops (10K€/2 years). Finally specific grants will be attributed to post-graduate and post-doctorate fellowships to attend the PRES Département Carrières et Emplois through inscription fees (10K€/year), a dedicated course to ease their insertion in the professional world.

Teaching project = 2 431 047 € (12%)					
Equipment	**Staff**	**Subcontracting**	**Travel**	**Internal billing**	**Other costs**
12 772	1 228 729	16 266	813 280	0	360 000
0.5%	51%	0,5%	34%	0%	14%

3.1.3 EXPLOITATION OF RESULTS AND TECHNOLOGY TRANSFER

Equipment: A percentage of the research project equipments will be dedicated to the exploitation of results and technology transfer (NMR spectroscopy for instance).

Staff costs: A project manager (100K€/year) with skills in patent engineering will be recruited. This engineer will have a share scientific and management role in helping to protect DISTALZ intellectual properties, and to help DISTALZ researcher in their translation and exploitation initiatives for development with industrial partners.
Subcontracting: Eurasanté, the regional structure dedicated to interaction with the SME and industrial partners, will produce the necessary communication material (50K€) for interaction with partners from the industrial sphere - a material that will be regularly updated (30K€). In order to comply with DISTALZ's goals to keep the public informed of AD's research progression, additional funds will be allocated to the publication of lay articles, reviews and books by journalists (10K€/year).

Travel: One important goal of DISTALZ partners is to increase the visibility of their findings. This will be ensured by travel grants for students and young scientists (i) to attend international meetings, (ii) to spend time in other laboratories within DISTALZ partners and (iii) visit external laboratories (320K€). In order to stimulate the exchanges in DISTALZ a scientific internal workshop is schedule every two year in Lille, Paris, Nice. The cost of this meeting (80K€) will be covered by DISTALZ as part of its willingness to create a strong internal dynamic. Travel grants will be also secured for the meetings organized with the industry for business development.
Other running costs: Additional funds will cover the publication costs (5 K€/years), the internal scientific meetings (10K€/year) and the organisation of public meetings (10K€/year), the participation of DISTALZ researchers to general public action as part of their mission towards society (10K€/year).

Exploitation of results and technology transfer = 2 357 072 € (11%)					
Equipment	**Staff**	**Subcontracting**	**Travel**	**Internal billing**	**Other costs**
9 830	1 365 536	207 626	574 080	0	200 000
0.5%	58%	9%	24%	0%	8.5%

3.1.4 GOVERNANCE

Equipment: A professional videoconference system (176 100€) will be implemented in each laboratory: (i) to run the weekly management meetings across the different laboratories, (ii) to ease the communication and exchanges while suppressing the travel time losses, (iii) to decrease the travel expenses. See doc A2 and appendix n°8 for more details.
Staff costs: A DISTALZ administrative manager and a secretary will be recruited on the 4% management cost budget.
Subcontracting: Daily fees will be paid to the SAB members (1000€/day, for 5 members, 2 days twice a year for a total of 160K€). The website extranet data management will be outsourced to a dedicated company (20K€/year). The evaluation will be implemented and followed-up by an independent company all along the DISTALZ duration (25K€/year).
Travel: Travel tickets for SAB members will be provided (25K€/year)

Exploitation of results and technology transfer = 1 215 802 € (6%)					
Equipment	**Staff**	**Subcontracting**	**Travel**	**Internal billing**	**Other costs**
220 445	134 237	621 920	239 200	0	0
18%	11%	51%	20%	%	%