

## **ADDENDUM I**

### **FWO ONDERZOEKSPROJECT G.0551.04 EINDVERSLAG SEPTEMBER 2010**

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**Toelage van de Vlaamse Gemeenschap door FWO uitgevoerd.**

# 1. SCIENTIFIC RESULTS

## I. INTRODUCTION

This report summarizes the scientific results of research in the fields of neurology and cardiology performed in the period 2008 till present within the framework of an agreement between the Research Fund – Flanders, the University of Antwerp and the Institute Born Bunge (IBB). The previously submitted report described the scientific results of the period 1/Jan 2004 – 31/Dec 2007.

The IBB encompasses the following laboratories: 1) Laboratory of Neuropathology and Electronmicroscopy (Prof. em. J-J. Martin and Prof. C. Ceuterick); 2) Laboratory of Neurobiology (Prof. P. Cras) focussing on the study of prion diseases; 3) Laboratory of Neurogenetics (Prof. C. Van Broeckhoven) focussing on the study of central and periferal nervous system disorders; 4) Laboratory of Theoretical Neurobiology (Prof. E. De Schutter and Prof. dr. M. Guigliano) focussing on neuronal computer simulations; 5) Laboratory of Neurochemistry and Behaviour (Prof. P.P. De Deyn); and 6) Laboratory of Cardiovascular Research (Prof. P.-P. van Bogaert).

Since 2005, Prof. P.P. De Deyn is Scientific director of the IBB, and in 2006, a new organigram was implemented to further support the expansion of the Biobank Central Core Facility; the Laboratory for Ultrastructural Neuropathology was established and three task forces were defined: 1) Neuromuscular Diseases; 2) Prion Diseases, and 3) Central Nervous system Neurodegenerative Disorders.

## II. STUDY OF DEMENTIA AND THE ESTABLISHMENT OF A BRAIN BANK

### II.1 *From the Laboratory of Neurochemistry and Behaviour (P.P. De Deyn, S. Engelborghs and co-workers)*

#### A. Improved characterisation of the MCI and Dementia study population:

This research project led to a better clinical, behavioural and neuropsychological characterisation of the dementia population included (across diagnostic categories).

A cross-sectional analysis of frontal lobe features, behavioural characteristics and neuropsychological data demonstrated that, in Alzheimer's disease (AD) patients, frontal lobe symptoms were associated with more pronounced cognitive deficits (of frontal origin). Moreover, frontal lobe symptoms were associated with increased severity and frequency of agitated and aggressive behaviour, and with increased severity of psychosis and depressive symptoms. We demonstrated that the evolution of frontal lobe symptoms in relation to dementia severity is significantly different comparing AD and frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) patient groups putting emphasis on behavioural observation as a tool to discriminate between several forms of dementia (Aries et al., 2010).

To determine the reliability of the 30-item Geriatric Depression Scale (GDS-30) for the screening of depressive symptoms in dementia and mild cognitive impairment (MCI), we set up a study using the Cornell Scale for Depression in Dementia (CSDD) as the 'gold standard'. Diagnosed according to strictly applied clinical diagnostic criteria, patients with MCI (n=156) and probable Alzheimer's AD (n=247) were included. In MCI patients, moderate but highly significant correlations were found between GDS-30 and CSDD scores. In mildly, moderately and severely affected AD patients, only weak correlations between GDS-30 and CSDD scores were calculated. ROC curve analysis showed that sensitivity and specificity values of respectively 95% and 67% were achieved when a GDS-30 cut-off score of 8 was applied in MCI patients. In AD patients, too low sensitivity and specificity values did not allow selecting an optimal cut-off score by means of ROC curve analysis. Using the CSDD as 'gold standard', we demonstrated that the GDS-30 is a reliable screening tool for depressive symptoms in MCI but not in AD patients (Debruyne et al., 2009).

## B. Biomarkers in cerebrospinal fluid

To establish diagnostic performance of the cerebrospinal fluid (CSF) biomarkers  $\beta$ -amyloid peptide ( $A\beta$ 1-42), total tau-protein (T-tau) and tau phosphorylated at threonine 181 (P-tau181P) compared to clinical diagnosis, biomarker levels were determined in CSF samples from 100 autopsy-confirmed dementia and 100 control subjects (Engelborghs et al., 2008a). New biomarker-based models were constructed by means of logistic regression. Using all biomarkers, dementia could be discriminated from controls (sensitivity (S) = 86 %, specificity (Sp) = 89 %). T-tau and  $A\beta$ 1-42 optimally discriminated AD from other dementias (non-AD) and controls (S = 90 %, Sp = 89 %). AD was optimally discriminated from non-AD using P-tau181P and  $A\beta$ 1-42 (S = 80 %, Sp = 93 %). Diagnostic accuracy of the latter model (82.7 %) was comparable to clinical diagnostic accuracy (81.6 %) that was based on a whole clinical work-up (including imaging). This study has demonstrated the value of a combined assessment of CSF biomarkers in differential dementia diagnosis, using pathological diagnosis as a reference. New biomarker-based models have been developed, achieving sensitivity, specificity, and diagnostic accuracy levels, consistently exceeding 80 %. These findings meanwhile support the original hypothesis that the combined assessment of the CSF biomarkers  $A\beta$ 1-42, T-tau and P-tau181P reveal S, Sp and diagnostic accuracy levels that are high enough to discriminate AD from other forms of dementia.

To establish diagnostic accuracy and optimal cut-off levels of CSF P-tau181P for discriminating AD from non-AD dementias in autopsy-confirmed dementia patients, CSF levels of  $A\beta$ 1-42, T-tau and P-tau181P from patients with definite AD (n=95) and non-AD dementias (n=50) were determined with single-parameter ELISA kits (Koopman et al., 2009). Optimal P-tau181P cut-off levels for differentiating AD from pooled non-AD dementias, DLB and FTD were 50.4 pg/mL (diagnostic accuracy: 73%), 52.8 pg/mL (diagnostic accuracy: 73%) and 35.3 pg/mL (diagnostic accuracy: 90%) respectively. It was concluded that the optimal CSF P-tau181P cut-off level for discriminating AD from non-AD dementias was 50.4 pg/mL. Optimal CSF P-tau181P cut-off levels differed between non-AD diagnostic dementia categories.

To investigate whether CSF biomarkers could have helped the clinician in differential dementia diagnosis in case of clinically ambiguous diagnoses, we set up a study using autopsy-confirmed dementia diagnosis as gold standard (Le Bastard et al., 2010b). Twenty-two patients of our autopsy-confirmed dementia population totalling 157 patients had an ambiguous clinical diagnosis at CSF sampling and were included in statistical analysis. CSF levels of  $A\beta$ 1-42, T-tau and P-tau181P were determined. A biomarker-based model was applied to discriminate between AD and non-AD dementias. AD and non-AD patients showed no significant differences in  $A\beta$ 1-42 and T-tau concentrations, whereas P-tau181P concentrations were significantly higher in AD compared to non-AD patients. The biomarker-based diagnostic model correctly classified 18 of 22 (82%) patients with clinically ambiguous diagnoses. It was concluded that using a biomarker-based model in patients with clinically ambiguous diagnoses, a correct diagnosis would have been established in the majority of autopsy-confirmed AD and non-AD cases, indicating that biomarkers have an added diagnostic value in cases with ambiguous clinical diagnoses.

The clinical diagnosis of AD is highly uncertain and error prone in the early stages of the disease. We therefore sought to identify biomarker patterns typical for AD in an independent, unsupervised way, without using information on the clinical diagnosis (De Meyer et al., 2010). Application of a mixture modeling approach using CSF-derived  $A\beta$ 1-42, total tau protein, and P-Tau181 protein as biomarkers on a clinically well-characterized data set that included cognitively normal persons, AD patients, and individuals with MCI. The outcome of the qualification analysis was validated on two additional data sets, one of which was autopsy-confirmed. Using the US-ADNI data set, a CSF- $A\beta$ 1-42/ P-Tau181P biomarker mixture model identified one feature linked to AD, while the other matched the 'healthy' status. The AD signature was found in 90%, 72%, and 36% of patients in the AD, MCI, and cognitively normal groups, respectively. The cognitively normal group with the AD

signature was enriched in apolipoprotein E e4 allele carriers. Results were validated on other data sets. In one study consisting of 68 autopsy-confirmed AD cases, 64 of 68 patients (94% sensitivity) were correctly classified with the AD feature. In another data set with MCI patients followed up for 5 years, the model showed a sensitivity of 100% (57/57) in patients progressing to AD. The mixture modeling approach, totally independent of clinical AD diagnosis, accurately correctly classified AD patients. The unexpected presence of the AD signature in more than one third of cognitively normal subjects suggests that AD pathology is active and detectable earlier than has heretofore been envisioned.

To identify neurochemical correlates of behavioural and psychological signs and symptoms of dementia (BPSD), we set up a prospective study (Engelborghs et al., 2008b). CSF levels of metabolites of (nor)epinephrine (MHPG), serotonin (5HIAA) and dopamine (DOPAC, HVA) were determined by HPLC and electrochemical detection. Spearman Rank-Order followed by Bonferroni correction was used for calculating correlations. In FTD patients, CSF norepinephrine levels were positively correlated with dementia severity ( $r=0.539$ ;  $p=0.021$ ). CSF DOPAC levels were correlated with BPSD in general ( $r=0.539$ ;  $p=0.021$ ), associated caregiver burden ( $r=0.567$ ;  $p=0.004$ ) and agitated and aggressive behaviour ( $r=0.568$ ;  $p=0.004$ ). In a subgroup of FTD patients who did not receive psychotropic pharmacological treatment, a strong correlation between CSF HVA/5HIAA ratios (reflecting serotonergic modulation of dopaminergic neurotransmission) and aggressive behaviour ( $r=0.758$ ;  $p=0.009$ ) was found. In MXD patients, (verbally) agitated behaviour was positively associated with the turnover of norepinephrine ( $r=0.633$ ;  $p=0.002$ ). No significant correlations were found in AD and DLB groups. In FTD, increased activity of dopaminergic neurotransmission and altered serotonergic modulation of dopaminergic neurotransmission was associated with agitated and aggressive behaviour respectively (Engelborghs et al., 2008b). This study demonstrated that neurochemical mechanisms underlying the pathophysiology of BPSD are both BPSD-specific and disease-specific which might have implications for future development of new and more selective pharmacological treatments of BPSD.

### C. Biomarkers in plasma

Plasma  $\beta$ -amyloid protein ( $A\beta$ ) isoforms are considered potential biomarkers for AD and dementia. We recently set up two pilot studies.

To evaluate the diagnostic performance of full-length and N-truncated plasma  $A\beta$  forms in patients with AD and non-AD as compared to healthy control subjects, a pilot study was set up (Le Bastard et al., 2010a). Plasma samples from 50 AD, 50 non-AD and 49 control subjects were included and analysed using a multiparameter fluorimetric bead-based immunoassay for the simultaneous quantification of different  $A\beta$  forms. No significant differences in  $A\beta$  isoforms were detected between dementia and controls; or AD, non-AD and controls. Compared to control subjects, pooled dementia patients (AD and non-AD) and AD patients alone had significantly lower plasma  $A\beta_{1-42}/A\beta_{N-42}$  ratios. In each diagnostic group, all plasma  $A\beta$  concentrations were significantly correlated. Except for the  $A\beta_{1-42}/A\beta_{1-40}$  ratio in controls, no significant correlations between plasma  $A\beta$  forms and age were found. In conclusion, low diagnostic performance of cross-sectional plasma  $A\beta$  measurements hampers future application as diagnostic markers. The possible application of longitudinal plasma  $A\beta$  measurements as screening tools for dementia remains to be elucidated.

The relation between plasma and CSF levels of  $A\beta$  isoforms remains unclear. In order to identify possible correlations between  $A\beta$  levels in plasma and CSF we determined  $A\beta$  levels in time-linked plasma and CSF samples (Le Bastard et al., 2009).  $A\beta$  concentrations in plasma ( $A\beta_{1-42}$  and  $A\beta_{N-42}$ ) and CSF ( $A\beta_{1-42}$ ) samples from 49 AD patients, 47 non-Alzheimer's disease dementia (non-AD) patients, 39 MCI patients and 29 controls were determined using a multi-parameter fluorimetric bead-based immunoassay using xMAP® technology (for plasma) and a conventional single-parameter ELISA (for CSF). Plasma  $A\beta_{1-42}$  concentrations did not correlate with CSF  $A\beta_{1-42}$  concentrations in the total study population, or in the different diagnostic groups. No correlations

between plasma A $\beta$ N-42 and CSF A $\beta$ 1-42 levels were found either. The CSF/serum albumin index did not show any significant differences between AD, non-AD, MCI and controls. These results suggest that the A $\beta$  levels in plasma are independent of the A $\beta$  levels in CSF both in dementia and controls. The fact that CSF and plasma A $\beta$  do not correlate in patients as well as controls and no significant differences in plasma A $\beta$ 1-42 or A $\beta$ N-42 between patients and controls can be detected, might hamper the diagnostic utility of the plasma A $\beta$  levels as diagnostic markers for dementia.

We investigated whether blood N-glycan changes can be used as a diagnostic biomarker for AD (Chen et al., 2010). We used DNA sequencer-assisted, fluorophore-assisted carbohydrate electrophoresis (DSA-FACE) technology to assay N-glycans in sera from 79 autopsy-confirmed dementia patients and 149 healthy controls. One N-glycan (NA2F) was substantially decreased in AD patients but not in controls. Use of NA2F for discriminating AD between dementia patients and healthy controls showed a diagnostic accuracy of 85.7% +/- 2.8% with 92% specificity and 70% sensitivity. The decrease in the level of NA2F in AD patients compared to non-AD patients was more pronounced in females ( $p < 0.0001$ ) than in males ( $p < 0.014$ ). Use of NA2F to differentiate female AD from female non-AD patients reached a diagnostic accuracy of 90.7% +/- 4.8 %. Pearson correlation analysis showed that in female dementia patients, serum NA2F levels were significantly correlated with the CSF A $\beta$ 1-42 and P-tau181P levels, whereas in male dementia patients serum NA2F levels were significantly correlated only with CSF total tau protein (T-tau) level. Thus, we suggest that the serum N-glycan marker might be suitable for longitudinal and follow-up studies.

#### D. Behavioural Neurology / Behavioural Psychology

By means of case histories, neuropsychological and neurolinguistic aspects of language and behaviour in various syndromes were studied (Baillieux et al., 2008a, 2008b, 2009, 2010; De Smet et al., 2009; De Witte et al., 2008a, 2008b; Mariën et al., 2008, 2009a, 2009b, 2010; Vandervliet et al., 2008). In addition, a DLB patient with olanzapine-induced head drop was described (Aries et al., 2008).

With regard to AD, several new hypotheses were formulated that will be subjected to prospectively controlled clinical studies in the near future (Wostyn et al., 2008a, 2008b, 2009a, 2009b, 2009c, 2010a, and 2010b). In addition, we set up a study to investigate whether neuropsychological tests are able to predict conversion to AD among MCI patients. At baseline the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG), the Mini Mental Status Examination (MMSE), the Geriatric Depression Scale (GDS), a Dutch variation of Rey's Auditory Verbal Learning Test, the Memory Impairment Screen plus (MISplus) and the Visual Association Test (VAT) were administered to 40 patients diagnosed with MCI. After 18 months, MCI-patients were reassessed and a follow-up diagnosis was established. This prospective, longitudinal study shows that a score of 0 or 1 out of 6 on the MISplus may be a good indicator of future (within 18 months) progression to AD among MCI-patients (Dierckx et al., 2009).

#### E. Study of Cerebrovascular Disease

Actigrafic recording was validated as an objective instrument to assess stroke-related motor deficits (Gebruers et al., 2008). In addition, clinimetric properties and clinical applicability of different accelerometry-based measurement techniques in persons with stroke were reviewed (Gebruers et al., 2010).

Within the framework of the Middelheim Interdisciplinary Stroke Study (MISS) relevant results regarding clinical, biochemical and imaging parameters were generated. In a review concerning the ischemic cascade a detailed description of important processes in the acute phase of stroke was given (Brouns et al., 2009a).

Improved insight in the role of neurotransmitters in acute cerebral ischemic injury may be fundamental for the successful development of novel therapeutic approaches. We investigated excitatory amino acids and monoaminergic neurotransmitters in CSF of acute ischemic stroke patients and their relation to stroke characteristics, i.e., stroke severity (NIHSS score at admission, lesion volume), stroke evolution in the subacute phase, long-term stroke outcome, lesion location, and stroke etiology. Neurotransmitter systems display relevant interrelations, however, no significant associations between neurotransmitter concentrations in CSF and stroke characteristics were found, with the exception of higher 5-hydroxyindoleacetic acid levels in CSF of patients with progressing stroke and poor long-term outcome (Brouns et al., 2010c).

Both from clinical and research standpoints, it may be highly relevant to differentiate between small-artery and large-artery infarction in the acute phase of ischemic stroke. Diagnosis of acute lacunar infarction can reliably be made, based on the conjunctive use of clinical evaluation and measurement of D-dimer levels either by a standard assay or by a bedside testing kit (Brouns et al., 2009e).

We studied the role of oxidative stress in acute ischemic stroke and hypothesised that asymmetric and symmetric dimethylarginine (ADMA, SDMA) are released in CSF due to ischemia-induced proteolysis and that CSF dimethylarginines are related to stroke severity. Logistic regression analysis confirmed that dimethylarginines were independently associated with stroke severity. CSF dimethylarginine levels are increased in hyperacute ischemic stroke and are associated with stroke severity (Brouns et al., 2009c). We investigated the kinetics of serum uric acid concentrations in the acute, subacute and chronic phase of ischemic stroke and its relation with initial stroke severity, stroke evolution in the subacute phase and long-term stroke outcome, and observed that decreases in uric acid during the first week after onset of stroke correlates with more severe stroke, unfavorable stroke evolution, and poor long-term stroke outcome (Brouns et al., 2010f). These observations indicate that prolonged oxidative stress is an important source of secondary damage following cerebral ischemia.

Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia were assessed (Sheorajpanday et al., 2009).

We investigated the predictive value of standard neurological evaluation, a commercially available biomarker assay and neuroimaging in the subacute phase for outcome after thrombolytic therapy in ischemic stroke. Routine clinical evaluation, bedside testing of biochemical markers by the Triage Stroke Panel and infarct volumetry on neuroimaging at 72 h after thrombolytic therapy are predictors for long-term outcome of ischemic stroke patients. Clinical assessment is the most reliable parameter for outcome prediction, but its predictive value is substantially improved when combined with the biomarker panel (Brouns et al., 2009d).

Within the MISS project, we also focussed on the crucial role of hemostatic activation in acute ischemic stroke. We indicated the clinical relevance of the procarboxypeptidase U / carboxypeptidase U system in the treatment of acute ischemic stroke (Brouns et al., 2009b), as well as in the spontaneous evolution of stroke (Brouns et al., 2010b).

Post-stroke inflammation may induce upregulation of the kynurenine pathway for tryptophan oxidation, resulting in neuroprotective and neurotoxic metabolites. The activity of the kynurenine pathway for tryptophan degradation in acute ischemic stroke correlates with stroke severity and long-term stroke outcome. Tryptophan oxidation is related to the stroke-induced inflammatory response (Brouns et al., 2010d.)

Accumulation of lactate in ischemic regions has been documented in acute stroke. We evaluated the relation between lactate levels in blood and CSF and ischemic stroke evolution and outcome. Lactate was measured in blood of 187 acute ischemic stroke and TIA patients at admission, 24 h, 72 h and 7 days after stroke onset. In a subpopulation of 85 stroke patients and in 51 controls, lactate was measured in CSF. Lactate levels in CSF, but not in blood, are a reliable marker for metabolic

crisis in acute ischemic stroke and correlate with the stroke evolution in the subacute phase and with long-term outcome (Brouns et al., 2008).

Ischemic injury to the central nervous system causes cellular activation and disintegration, leading to release of cell-type-specific proteins into the CSF. We investigated CSF concentrations of myelin basic protein (MBP), glial fibrillary astrocytic protein (GFAP), the calcium-binding protein S100B, and neuron-specific enolase (NSE) in acute ischemic stroke patients and their relation to initial stroke severity, stroke location, and long-term stroke outcome. We observed that MBP, GFAP, S100B, and NSE display relevant differences in cellular and subcellular origins, which are reflected in their relation to stroke characteristics. MBP is a marker for infarct location. GFAP and S100B correlate with stroke severity and outcome (Brouns et al., 2010a).

Data on the prevalence of Fabry disease in patients with central nervous system pathology are limited and controversial. In this study, we assessed the prevalence of Fabry disease in young patients presenting with cerebrovascular disease in Belgium. In a national, prospective, multicenter study, we screened for Fabry disease in 1000 patients presenting with ischemic stroke, transient ischemic attack, or intracranial hemorrhage; unexplained white matter lesions; or vertebrobasilar dolichoectasia. In male patients, we measured alpha-galactosidase A (alpha-GAL A) activity in dried blood spots. Female patients were screened for mutations by exonic DNA sequencing of the alpha-GAL A gene. Alpha-GAL A deficiency may play a role in up to 1% of young patients presenting with cerebrovascular disease. These findings suggest that atypical variants of Fabry disease with late-onset cerebrovascular disease exist, although the clinical relevance is unclear in all cases (Brouns et al., 2010e).

The Belgian Stroke Council prepared a consensus document providing a set of minimum criteria to meet international standards for stroke care. It is intended to provide help in the creation of stroke units in centers who do not currently have one and to provide a benchmark for centres already having organised stroke care (Thijs et al., 2009). The risk factors for depression after stroke were reviewed (De Ryck et al., 2009).

Employing biochemical parameters, we proofed that the extent of blood brain barrier failure after acute ischemic stroke correlates with stroke severity, evolution and clinical outcome (Brouns et al. revision submitted in Eur. Neurol.).

## *II.2 From the IBB Biobank and the Laboratory of Ultrastructural Neuropathology (C. Ceuterick, J-J. Martin and co-workers)*

### A. Neurodegenerative disorders

The diagnosis of a series of conditions characterized by dementia depends from the neuropathological and immunohistochemical study of representative areas of the central nervous system. The accurate description of the structure and of the topography of the histological lesions is a prerequisite for further research. As a result of this morphological approach and taking into account the recommendations of international collaborative groups it is possible to give a correct neuropathological diagnosis of a series of neurodegenerative disorders affecting the nervous system. These results are then used as a golden standard for research in the field of neurochemistry and molecular genetics. Conversely the results of this research can be used to improve the histopathological classification of the disorders, eg in the field of the fronto-temporal lobe dementias (FTLD).

The brains of patients who have been adequately examined during their life are removed within 2-3 hours after death. The right half of the brain, brainstem and cerebellum is fixed in formalin, while the left part of the brain is immediately deep-frozen. After a period of 2-4 weeks, the formalin-fixed

part of the brain is photographed and examined macroscopically. Representative parts of the brain (Brodmann's areas 6, 7, 8, 9, 10, 11, 12, 17, 18, 22, 24, 46, neostriatum, putamen and pallidum, thalamus at the level of the centrum medianum, corpus subthalamicum, mesencephalon, pons at the level of the locus coeruleus, medulla oblongata and cerebellum) are embedded in paraffin. Classical staining techniques like cresyl violet and HE are used for the cytology, the method of Gallyas for the neurofibrillary tangles, the method of Klüver-Barrera for the myelin. Immunohistochemistry is made with antibodies against hyperphosphorylated tau (AT8), amyloid A $\beta$ + (4G8), ubiquitine, alpha-synucleine and against glial fibrillary acidic protein according to standard methods.

The subsequent table summarizes the results obtained from Jan, 2008 to December 2010.

Neuropathological diagnosis	Number of cases		
	2008	2009	2010
Senile dementia Alzheimer type (SDAT)	19	29	23
Mixed dementia (vascular +SDAT)	3	5	4
Lewy body disease (various forms)	2	2	6
FTLD	5	2	1
Progressive supranuclear palsy	1	2	4
Huntington' chorea	2	4	1
Multiple system atrophy	0	1	5
Parkinson's disease	5	1	4
Amyotrophic lateral sclerosis	2	0	1
Creutzfeldt-Jakob disease	6	10	16
Nasu-Hakola disease	0	0	1
Control cases and other neurological disorders	17	78	33

The Laboratory of Ultrastructural Neuropathology, affiliated with the IBB Biobank provided over the years 2008 - 2010 well documented tissue samples, qualified technical support and expertise.

The research activities of LUN and Taskforce f1 concerned:

Scientific work and participation in interdisciplinary (Tf1 and Tf3 Biobank) scientific research projects and publications.

With regards to neurodegenerative, the following studies were established:

- Requiring ultrastructural expertise for the structural identification and description of inclusion bodies in dementias (Wils et al, 2010) and neurometabolic storage disorders (Boustany et al. – bookchapter, Feb 2011).
- We have contributed to a BEFAS project (principal investigator: Prof. Dr. P. P. De Deyn) examining skin biopsies by EM of patients suspected of Fabry disease. Our skin biopsy findings have been added in a paper concerning a patient with Fabry disease and Turner syndrome (Brouns et al, in press).

#### B. Genetic, inflammatory and metabolic myopathies

Study of the mutations of the ryanodine receptor may cause dominant and recessive forms of congenital myopathies with cores. The investigation of 9 families presenting with a recessive form of the disease has allowed the identification of a mutation of both alleles of the RYR1 gene for all patients. We demonstrated that the recessive core myopathies were caused by the presence of one recessive null allele and that the variability of the phenotype depended on the nature of the mutation present on the second allele (Monnier et al. 2008).

We reported the clinical and genetical characteristics of a young female patient with exertional muscle pain as the only presenting symptom of dystrophinopathy and of her family (Ceulemans et al. 2008).

The characteristics of different chaperone proteins was analyzed in inflammatory myopathies (de Paepe et al. 2009a). Our results point to a general protective role for both HSP90 and HSP70 families in damaged muscle fibres and a specific cytotoxic role for HSP90 in muscle fibre invasion associated with inclusion body myositis and polymyositis.

We have shown that the immunohistochemical detection of OXPHOS complexes could be a valuable additional diagnostic tool for the evaluation of mitochondrial cytopathy (de Paepe et al. 2009b).

Liver biopsies with COX staining could yield crucial data concerning mitochondrial myopathies. Mitochondrial mosaics are probably more frequent than initially thought (Roels et al. 2009).

Findings suggestive of a defect in biosynthesis of the mitochondrially encoded subunits of the OXPHOS complexes were discovered in a case of lactic acidosis in a newborn with adrenal calcifications (Zecic et al. 2009).

DNAJB2 a co-chaperone regulator of Hsp 70 that is expressed principally in the nervous system, is also expressed in mouse and human skeletal muscle at the neuromuscular junction of normal fibres, in the cytoplasm and membrane of regenerating fibres and in protein aggregates and vacuoles in protein aggregate myopathies. We propose a role for DNAJB2 protein turnover processes in skeletal muscle (Claeys et al., 2010).

### C. Inherited peripheral neuropathies

Our histopathological results regarding more remarkably the absence of minifascicle formation in a sural nerve biopsy of a patient with a XY gonadal dysgenesis and peripheral neuropathy, contributed to the expansion of the clinical and genetic heterogeneity in this entity (Baets et al. 2009).

We have contributed to the ultrastructural analysis of axonal ribosomes in inherited peripheral neuropathies. Increases of axonal ribosomes were noted in CMT1 and CMT2. This observation can be used as a diagnostic marker for diverse human nerve diseases (Verheijen et al, in press).

We have reported a patient with a GAN suggested by EM of a skin biopsy, due to a compound heterozygosity for a maternally inherited microdeletion and a paternally inherited point mutation (Buysse et al, 2010).

### D. Routine histopathology including electron microscopy (EM) of tissues for diagnostic purposes in a wide variety of neurological disorders

Over the years 2008 – 2010, Tfl and LUN have had the opportunity to perform the following histopathological studies:

- 210 LM analyses of skeletal muscles and peripheral nerves, using histology, histochemistry and histo-enzymology (see table 1).
- 415 EM analyses of resin embedded samples using a CM10 FEI transmission electron microscope (see tables 1 - 4).
- 79 Immunohistochemical studies of skeletal muscle and peripheral nerve: using a large panel of antibodies against resp. membranous-, cytoskeletal-, myelin- and axonal proteins and inflammatory parameters (see table 1).

Biopsies from patients for which no diagnosis had yet been available were reconsidered in attempt to make a precise diagnosis or to get more insight in the disease process. Biopsies from affected patients were reviewed for family members in the context of genetic counselling. Biopsies were retrieved for genotype-phenotype correlation of identified molecular genetic analyses in hereditary peripheral neuropathies. EM analyses/ research have been performed for centers without EM facilities/ expertise. Assistance, support and advice have been given to neuropathologists and researchers regarding a “second opinion” in complex diagnostical and technical work-ups.

*Neuromuscular biopsies* EM has been used within the histopathological work-up incl. light microscopy (LM) of skeletal muscle disorders and peripheral neuropathies (table 1). EM has been particularly useful for the diagnosis of some congenital myopathies (such as nemaline myopathy), glycogenoses (type II, V/ VI) mitochondrial myopathies and “inclusion body myositis”. Most biopsies were investigated for Centers of Reference for Neuromuscular Disorders and neurological departments. In collaboration with Prof. Dr. L. Heytens, we have examined muscle biopsies from numerous patients with a susceptibility to malignant hyperthermia (table 5). All investigated samples have been stored and continuously included within the database of the IBB Biobank, providing further research and exchanging facilities.

**Table 1:** Histopathological analyses: skeletal muscle and peripheral nerve

Year	Muscles	Peripheral nerves	TOTAL
2008			
- LM	77	3	80
- EM	73	5	78
- Immuno	23		23
2009			
- LM	74	3	77
- EM	76	3	79
- Immuno	26		26
2010			
- LM	59	1	60
- EM	73	1	74
- Immuno	30	1	30

*Skin and conjunctival biopsies* from children with a progressive encephalopathy and adult patients are still forwarded to LUN for its longstanding diagnostic expertise (table 2). This EM activity is a scientific service to third parties. Patients with problematical diagnostical work-ups and helpful clinical data are than selected. A neurometabolic storage disorder could be achieved (table 5) or ruled out. Our findings were of great help to orientate molecular genetic studies. We have also offered such diagnostic possibilities in CADASIL and in giant axonal neuropathy (GAN).

**Table 2:** EM of skin, conjunctiva and other tissues (chorion cells, liver, cellcultures)

Year	Skin	Conjunctiva	Other	TOTAL
2008	65		7	72
2009	62	3	1	66
2010	69			69

*Brain biopsies/ autopsies* were examined in rare neurological diseases (table 3). EM has been used to complete morphological data from LM and immunohistochemistry.

**Table 3:** EM of human brain samples

Year	Biopsies	Autopsies	Total
2008	0	1	1
2009	2	2	4
2010	1	1	2

*Mouse material* (table 4) has also been investigated for research purposes (in collaboration with Prof. Dr. V. Timmerman).

**Table 4:** EM of mouse material

	brain	spinal cord	peripheral nerve
2009	1	1	0
2010	0	0	6

**Table 5: Histopathological diagnosis**

<i>Muscular diseases</i>	Number of patients
Muscular dystrophies	11
Congenital myopathies	8
Metabolic myopathies	17
Inflammatory myopathies	18

In vitro test malignant hyperthermia (Prof. Dr. L. Heytens)	Positive tests
Number of patients: 39	21

<i>Peripheral neuropathies</i>	Number of patients
Hereditary PNP	1 (?)
Acquired PNP	4

<i>Neurometabolic disorders</i>	Number of patients
Lysosomal disorders	10
Peroxisomal diseases	1
Other (GAN, CADASIL)	2

### II.3 From Neurogenetics, Neurodegenerative Brain Diseases (C. Van Broeckhoven, M. Cruts and co-workers)

Over the years, the Laboratory of Neurogenetics has contributed to the identification of causal genes (positional cloning) and genetic predisposition (genetic association) for Alzheimer disease (AD). In the Laboratory of Neurogenetics researchers are active in the field of Neurodegenerative Brain diseases, Peripheral Neuropathies and Neurogenetics.

#### A. Alzheimer's Disease

Replication of genetic association findings in independent studies represents an important validation tool in the search for susceptibility genes for complex diseases such as AD. In a well-characterized memory-clinic based study comprising 1078 unrelated AD patients and 652 control individuals, we set out to replicate previously reported genome-wide association of four novel risk SNPs with AD and onset age, with first stage p-values ranging from 0.001 to 0.000004. We obtained evidence for association between rs179943, an intronic SNP in ATXN1 at 6p22.3, and affection status (OR = 0.63 (95% CI = 0.44-0.90; nominal p = 0.01)). Overall, our data provided independent support for association of at least one chromosomal locus with AD and warranted a more in-depth investigation of these regions for possible underlying functional variants (Bettens et al., 2010a).

Recently, it has been reported that the P86L polymorphism of the calcium homeostasis modulator 1 gene (CALHM1) is associated with the risk of developing AD. However, we could not replicate this finding in our Belgian study population. In order to independently assess the association, we took part in a meta-analysis of 7,873 AD cases and 13,274 controls of Caucasian origin (from a total of 24 centers in Belgium, Finland, France, Italy, Spain, Sweden, the UK, and the USA). Our results underscore our earlier findings that the CALHM1 P86L polymorphism is likely not a genetic determinant of AD but may modulate age of onset by interacting with the effect of the  $\epsilon$ 4 allele of the APOE gene (Lambert et al, 2010).

In two invited reviews the recent findings in the field of genetic of AD (identification of the new risk genes CLU, CR1 and PICALM) are placed in a broader context. Suggestions as how to these and future findings can be further explored and translated to the patient, are provided (Slegers et al, 2010c; Bettens et al, 2010b).

Both leukocyte telomere length and the apolipoprotein epsilon4 allele have been associated with mortality, cardiovascular disease, cognition, and dementia. We investigated whether leukocyte telomere length was associated with APOE genotype or cognitive abilities in the context of APOE genotype. The setting for this cross-sectional study was 427 non-demented individuals aged 41-81 years. We found that epsilon4 carriers overall exhibited significantly longer telomeres compared with non-carriers (difference of 268 bp,  $p = 0.001$ ). This difference was greatest at the lower limit of the age span and non-significant at the upper limit, which translated into a significantly higher telomere attrition rate ( $p = 0.049$ ) among epsilon4 carriers (37 bp/years) compared with non-carriers (21 bp/year). Further, longer telomeres among epsilon4 carriers significantly predicted worse performance on episodic memory tasks. No significant associations were found on tasks tapping semantic and visuospatial ability, or among epsilon3/epsilon3 carriers. In conclusion, APOE epsilon4 carriers had longer telomeres compared with non-carriers, but higher rate of attrition. Among them, longer telomeres predicted worse performance on episodic memory tasks. These observations suggest that the epsilon4 allele is associated with abnormal cell turnover of functional and possibly clinical significance (Wikgren et al, 2010).

The nuclear transactive response (TAR) DNA binding protein-43, TDP-43, is a major constituent of the ubiquitinated neuronal inclusions in patients with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Missense mutations in TDP-43 have been associated with familial and sporadic ALS. Since TDP-43 immunoreactivity was also frequently observed in Alzheimer's disease (AD) brains and elevated TDP-43 plasma levels were detected in a subset of AD patients, we sequenced the TDP-43 gene, TARDBP, in a well-documented group of AD patients ( $n=485$ ). We observed one mutation in exon 3 (c.269C>T) predicting a p.Ala90Val substitution in two patients. One extra p.Ala90Val carrier was observed by sequencing exon 3 of an additional set of 254 AD patients. The mutation was absent from 604 control individuals. Allele and haplotype analysis using microsatellite markers suggested that the three patients might share a common founder. However, co-segregation of p.Ala90Val with AD could not be realized leaving its pathogenic unclear at this moment. Also, sequencing in 190 additional AD patients of TARDBP exon 6 in which pathogenic mutations have been reported in FTLD and ALS was negative. Further, genetic association analyses using five single nucleotide polymorphisms did not detect significant differences between AD patients and control individuals. In conclusion, the genetic contribution of TARDBP to AD was restricted to the rare mutation p.Ala90Val (3/739, 0.4%) of unclear pathogenic nature that affects the nuclear localization signal in TDP-43 (Brouwers et al., 2010).

Serum or plasma progranulin (GRN) is a highly accurate of GRN-related frontotemporal lobar degeneration, which is caused by loss-of-function mutations in the GRN gene. Both null mutations and missense mutations in GRN have also been observed in patients with AD. Here, the evidence for a role of circulating GRN as a biochemical biomarker in neurodegeneration is reviewed, with a specific focus on its relevance in AD. We conclude that circulating GRN is a promising, noninvasive biomarker that warrants screening in both patients with dementia of the Alzheimer

type and people with mild cognitive impairment; specifically for, but not limited to, those that have a positive family history of neurodegenerative disease. Once a cure for GRN-related neurodegeneration becomes available, this biomarker will be an important tool in the effort to personalize treatment of dementia (Slegers et al., 2010a).

## B. Frontotemporal Lobe Dementia and Tauopathies

Neuronal cytoplasmic and intranuclear aggregates of RNA-binding protein TDP-43 are a hallmark feature of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). ALS and FTLD show a considerable clinical and pathological overlap and occur as both familial and sporadic forms. Though missense mutations in TDP-43 cause rare forms of familial ALS, it is not yet known whether this is due to loss of TDP-43 function or gain of aberrant function. Moreover, the role of wild-type (WT) TDP-43, associated with the majority of familial and sporadic ALS/FTLD patients, is also currently unknown. Generating homozygous and hemizygous WT human TDP-43 transgenic mouse lines, we show here a dose-dependent degeneration of cortical and spinal motor neurons and development of spastic quadriplegia reminiscent of ALS. A dose-dependent degeneration of nonmotor cortical and subcortical neurons characteristic of FTLD was also observed. Neurons in the affected spinal cord and brain regions showed accumulation of TDP-43 nuclear and cytoplasmic aggregates that were both ubiquitinated and phosphorylated as observed in ALS/FTLD patients. Moreover, the characteristic approximately 25-kDa C-terminal fragments (CTFs) were also recovered from nuclear fractions and correlated with disease development and progression in WT TDP-43 mice. These findings suggest that approximately 25-kDa TDP-43 CTFs are noxious to neurons by a gain of aberrant nuclear function (Wils et al., 2010).

Null mutations in progranulin (GRN) are associated with frontotemporal lobar degeneration characterized by intraneuronal accumulation of TAR DNA-binding protein-43 (TDP-43). However, the mechanism by which GRN-deficiency leads to neurodegeneration remains largely unknown. In primary cortical neurons derived from Grn knockout (Grn<sup>-/-</sup>) mice, we found that Grn-deficiency causes significantly reduced neuronal survival and increased caspase-mediated apoptosis, which was not observed in primary mouse embryonic fibroblasts (MEFs) derived from Grn<sup>-/-</sup> mice. Also, neurons derived from Grn<sup>-/-</sup> mice showed an increased amount of phosphorylated TDP-43 accumulations. Furthermore, proteasomal inhibition with MG132 caused increased caspase-mediated TDP-43 fragmentation and accumulation of detergent-insoluble 35- and 25-kDa C-terminal fragments (CTFs) in Grn<sup>-/-</sup> neurons and MEFs. Interestingly, full-length TDP-43 also accumulated in the detergent-insoluble fraction, and caspase-inhibition prevented MG132-induced generation of TDP-43 CTFs but did not block the pathological conversion of full-length TDP-43 from soluble to insoluble species. These data suggest that GRN functions as a survival factor for cortical neurons and GRN-deficiency causes increased susceptibility to cellular stress. This leads to increased aggregation and accumulation of full-length TDP-43 along with its C-terminal derivatives by both caspase-dependent and independent mechanisms (Kleinberger et al., in press).

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative condition that predominantly affects behavior, social awareness, and language. It is characterized by extensive heterogeneity at the clinical, pathological, and genetic levels. Recognition of these levels of heterogeneity is important for proper disease management. The identification of progranulin and TDP-43 as key proteins in a significant proportion of FTLD patients has provided the impetus for a wealth of studies probing their role in neurodegeneration. This review highlights the most recent developments and future directions in this field and puts them in perspective of the novel insights into the neurodegenerative process, which have been gained from related disorders, e.g., the role of FUS in amyotrophic lateral sclerosis (Slegers et al., 2010b).

The FUS gene was identified as a new causal gene for ALS in approximately 4% of patients with familial ALS. Since ALS and FTLN are part of a clinical, pathologic, and genetic disease spectrum, we investigated a potential role of FUS in FTLN. We performed mutational analysis of FUS in 122 patients with FTLN and 15 patients with FTLN-ALS, as well as in 47 patients with ALS. Mutation screening was performed by sequencing of PCR amplicons of the 15 FUS exons. We identified 1 patient with FTLN with a novel missense mutation, M254V, that was absent in 638 control individuals. In silico analysis predicted this amino acid substitution to be pathogenic. The patient did not have a proven family history of neurodegenerative brain disease. Further, we observed the known R521H mutation in 1 patient with ALS. No FUS mutations were detected in the patients with FTLN-ALS. While insertions/deletions of 2 glycines (G) were suggested to be pathogenic in the initial FUS reports, we observed an identical GG-deletion in 2 healthy individuals and similar G-insertions/deletions in 4 other control individuals, suggesting that G-insertions/deletions within this G-rich region may be tolerated. In a first analysis of FUS in patients with FTLN, we identified a novel FUS missense mutation, M254V, in 1 patient with pure FTLN. At this point, the biologic relevance of this mutation remains elusive. Screening of additional FTLN patient cohorts will be needed to further elucidate the contribution of FUS mutations to FTLN pathogenesis (Van Langenhove et al., 2010).

Frontotemporal lobar degeneration (FTLN) and amyotrophic lateral sclerosis (ALS) are overlapping neurodegenerative disorders. Mutations in the growth factor progranulin (PGRN) gene cause FTLN, sometimes in conjunction with ALS; such mutations are also observed in some ALS patients. Most PGRN mutations underlying FTLN are null mutations that result in reduced PGRN levels. We investigated PGRN expression in human ALS and in mouse models of motor neuron degeneration. Progranulin plasma or CSF levels in newly diagnosed ALS patients did not differ from those in healthy or disease controls (PGRN mutation-negative FTLN and Alzheimer disease patients). In the mutant SOD1 mouse model of ALS, spinal cord PGRN levels were normal in presymptomatic animals but increased during the degenerative process. This increase in PGRN correlated with enhanced expression of PGRN in microglia. In CSF, PGRN levels were normal in presymptomatic and early symptomatic animals, but with disease progression, a raise in PGRN was detectable. These data indicate that upregulation of PGRN is a marker of the microglial response that occurs with progression in motor neuron diseases (Philips et al, 2010).

Excitotoxicity is thought to play a pathogenic role in amyotrophic lateral sclerosis (ALS). Excitotoxic motor neuron death is mediated through the Ca<sup>2+</sup>-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type of glutamate receptors and Ca<sup>2+</sup> permeability is determined by the GluR2 subunit. We investigated whether polymorphisms or mutations in the GluR2 gene (GRIA2) predispose patients to ALS. Upon sequencing 24 patients and 24 controls no non-synonymous coding variants were observed but 24 polymorphisms were identified, 9 of which were novel. In a screening set of 310 Belgian ALS cases and 794 healthy controls and a replication set of 3157 cases and 5397 controls from 6 additional populations no association with susceptibility, age at onset, or disease duration was observed. We conclude that polymorphisms in the GluR2 gene (GRIA2) are not a major contributory factor in the pathogenesis of ALS (Bogaert et al, 2010).

### C. Parkinson's disease

Lewy body diseases (LBD) are a group of clinically and pathologically overlapping brain disorders characterized by specific brain lesions named Lewy bodies (LB). Parkinson disease marks one end (extrapyramidal) of the spectrum while the LB variant of AD marks the other (cognitive). We hypothesize that studying the genetic etiology of different members of the spectrum may eventually elucidate the links between them and the underlying mechanism involved.

Parkinson disease is the second most common neurodegenerative disorder. Five familial PD genes and many more loci have been identified during the last decade. The relative contribution of simple mutations and copy number variations (CNVs) in the 5 familial genes (SNCA, PARK2, PINK1,

PARK7, and LRRK2) to the genetic etiology of Parkinson disease (PD) is still unclear because most studies did not completely analyze each gene. To date, molecular genetic analyses have identified over 500 distinct DNA variants in five disease genes associated with familial Parkinson disease;  $\alpha$ -synuclein (*SNCA*), parkin (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), DJ-1 (*PARK7*), Leucine-rich repeat kinase 2 (*LRRK2*). These genetic variants include ~82% simple mutations and ~18% copy number variations. Some mutation subtypes are likely underestimated since only few studies reported extensive mutation analyses of all five genes, by both exonic sequencing and dosage analyses. We generated an update of all mutations published to date in the literature, systematically organized in a novel mutation database (<http://www.molgen.ua.ac.be/PDmutDB>). In addition, we addressed the biological relevance of putative pathogenic mutations. This study emphasizes the need for comprehensive genetic screening of Parkinson patients followed by an insightful study of the functional relevance of observed genetic variants. Moreover, while capturing existing data from the literature it became apparent that several of the five Parkinson genes were also contributing to the genetic etiology of other Lewy Body Diseases and Parkinson-plus syndromes, indicating that mutation screening is recommendable in these patient groups (Nuytemans et al., 2010).

In addition to the 5 familial PD genes we screen for mutations in newly reported functionally relevant NBD genes in order to estimate their contribution to the genetic etiology of PD in the Belgian patient group. In 2008 missense mutations were identified in the Grb10-Interacting GYF Protein-2 gene (*GIGYF2*), located in the chromosomal region 2q36-q37, in familial Parkinson disease (PD) patients of European descent. To determine the contribution of *GIGYF2* mutations in an extended (N=305) Belgian series of both familial and sporadic PD patients, we sequenced all 32 coding and non-coding exons of *GIGYF2*. In three sporadic PD patients we identified two novel heterozygous missense mutations (c.1907A>G, p.Tyr636Cys and c.2501G>A, p.Arg834Gln), that were absent from control individuals (N=360). However, since we lack genetic as well as functional data supporting their pathogenic nature, we cannot exclude that these variants are benign polymorphisms. Together, our results do not support a role for *GIGYF2* in the genetic etiology of Belgian PD (Meeus et al., 2011).

High-profile studies have provided conflicting results regarding the involvement of the *Omi/HtrA2* gene in Parkinson's disease (PD) susceptibility. Therefore, we performed a large-scale analysis of the association of common *Omi/HtrA2* variants in the Genetic Epidemiology of Parkinson's disease (GEO-PD) consortium. GEO-PD sites provided clinical and genetic data including affection status, gender, ethnicity, age at study, age at examination (all subjects); age at onset and family history of PD (patients). Genotyping was performed for the five most informative SNPs spanning the *Omi/HtrA2* gene in approximately 2–3 kb intervals (rs10779958, rs2231250, rs72470544, rs1183739, rs2241028). Fixed as well as random effect models were used to provide summary risk estimates of *Omi/HtrA2* variants. The 20 GEO-PD sites provided data for 6378 cases and 8880 controls. No overall significant associations for the five *Omi/HtrA2* SNPs and PD were observed using either fixed effect or random effect models. The summary odds ratios ranged between 0.98 and 1.08 and the estimates of between-study heterogeneity were not large (non-significant *Q* statistics for all 5 SNPs; *I*<sup>2</sup> estimates 0–8%). This largest association study performed to define the role of any gene in the pathogenesis of Parkinson's disease revealed no overall strong association of *Omi/HtrA2* variants with PD in populations worldwide (Krüger et al., 2010).

We attempted to identify the genetic defect underlying juvenile parkinsonism and dementia in a patient of Afghan origin, who was born to consanguineous parents using direct sequencing of known PD genes. The index patient developed tremor, right-sided dystonia and bradykinesia at age 10. Rapid cognitive decline resulted in dementia at age 13. A homozygous 2 bp deletion was detected in exon 23 of the *ATP13A2* gene in the index patient. We can conclude that the resulting frameshift mutation is most likely responsible for truncation and loss of function of the *ATP13A2*

protein. The clinical features of the index patient are consistent with Kufor-Rakeb syndrome (KRS), a rare juvenile parkinsonian disorder with pyramidal signs, supranuclear gaze palsy and dementia. The role of heterozygous mutations in *ATP13A2* remains elusive, as shown by the variable penetrance of the mutation in this family. This novel mutation in *ATP13A2* further extends the clinical and genetic spectrum of KRS. Further functional studies need to address the effect of this mutation on transcript and protein level (Crosiers et al., 2010).

Dementia with Lewy bodies (DLB) is a central player in the LBD spectrum and the second most frequent form of neurodegenerative dementia after AD. Since informative DLB families are scarce, little is presently known about the molecular genetic etiology of DLB. We recently mapped the first locus for DLB on chromosome 2q35-q36 in a multiplex Belgian family, DR246, with autopsy-proven DLB pathology in a region of 9.2 Mb. Here, we describe the ascertainment of additional DR246 family members and significant finemapping of the DLB locus to 3.3 Mb based on informative meiotic recombinants. Extensive sequencing of the 42 positional candidate genes within the DLB region did not identify a simple pathogenic mutation that co-segregated with disease in family DR246. Also high resolution analysis of copy number variations in the DLB locus did not provide evidence for a complex mutation. In conclusion, we confirmed the DLB locus at 2q35-q36 as a genetic entity but candidate gene-based sequencing and copy number variation analysis did not identify the pathogenic mutation in family DR246. Other detection strategies will be needed to reveal the underlying mutation explaining the linkage of DLB to 2q35-q26. Possibly the disease mutation in this family acts through a more complex mechanism than generally envisaged for monogenic disorders. Nevertheless, identifying the first familial DLB gene is likely to contribute an entry point into the pathogenic cascades underlying DLB pathology (Meeus et al., 2010a).

### III. PHENOTYPE-GENOTYPE CORRELATIONS IN NEUROMUSCULAR DISEASES

#### III. 1 From Neurogenetics

##### A. Peripheral Neuropathies (V. Timmerman and co-workers)

Damage to specific neuronal populations is a central feature of the disease process in monogenic hereditary peripheral neuropathies. The subgroup of distal hereditary motor neuropathies (distal HMN) is characterized by degeneration of motor neurons and their axons in the peripheral nervous system. Distal HMN patients display progressive muscle weakness and atrophy in lower legs and feet from their childhood or adolescence. The disease is clinically and genetically heterogenous and is divided into different subtypes based on the inheritance pattern. Despite the absence of sensory symptoms, distal HMN shows strong clinical resemblance with the axonal form of Charcot-Marie-Tooth disease (CMT2). Selective degeneration of motor neurons is also typical for sporadic amyotrophic lateral sclerosis (ALS). In contrast to distal HMN, sporadic ALS is a complex disease caused by different genetic risk factors and environmental factors. The underlying mechanisms of selective degeneration of motor neurons in both conditions is still not known. The identification of gene mutations linked to hereditary forms of these conditions, can provide insight in the underlying disease processes.

Up to 2008, mutations in six different genes had been identified for autosomal dominant distal HMN; glycyl-tRNA synthetase (GARS), dynactin 1 (DCTN1), small heat shock 27 kDa protein 1 (HSPB1), small heat shock 22 kDa protein 8 (HSPB8), Berardinelli-Seip congenital lipodystrophy (BSCL2) and senataxin (SETX). In addition a mutation in the (VAMP)-associated protein B and C (VAPB) was found in several Brazilian families with complex and atypical forms of autosomal dominantly inherited motor neuron disease. We have investigated the distribution of mutations in these seven genes in a cohort of 112 familial and isolated patients with a diagnosis of distal motor neuropathy and found nine different disease-causing mutations in HSPB8, HSPB1, BSCL2 and SETX in 17 patients of whom 10 have been previously reported. No mutations were found in

GARS, DCTN1 and VAPB. The phenotypic features of patients with mutations in HSPB8, HSPB1, BSCL2 and SETX fit within the distal HMN classification, with only one exception; a C-terminal HSPB1-mutation was associated with upper motor neuron signs. Furthermore, we provided evidence for a genetic mosaicism in transmitting an HSPB1 mutation. This study, performed in a large cohort of familial and isolated distal HMN patients, clearly confirmed the genetic and phenotypic heterogeneity of distal HMN and provided a basis for the development of algorithms for diagnostic mutation screening in this group of disorders (Dierick et al., 2008). One of the patients was separately published as a case report. This person displayed an autosomal dominant congenital spinal muscular atrophy, without a mutation in one of the known genes (Reddel et al., 2008).

Based on electrophysiological and histopathological criteria, two types of CMT can be identified: CMT type 1 (CMT1) is a demyelinating form characterized by reduced nerve conduction velocities (NCVs <38m/s), while CMT type 2 (CMT2) is the axonal form characterized by normal or only slightly reduced NCVs. In some CMT families, patients can display highly variable NCVs; from normal to severely reduced NCVs, leading to a phenotype that overlaps between CMT1 and CMT2. This form of CMT is described as intermediary CMT. Dominant-intermediate Charcot-Marie-Tooth neuropathy (DI-CMT) is characterized by axonal degeneration and demyelination of peripheral motor and sensory neurons. Three dominant mutations in the YARS gene, encoding tyrosyl-tRNA synthetase (TyrRS), have so far been associated with DI-CMT type C. The molecular mechanisms through which mutations in YARS lead to peripheral neuropathy are currently unknown, and animal models for DI-CMTC are not yet available. Here, we report the generation of a *Drosophila* model of DI-CMTC: expression of the 3 mutant--but not wild type--TyrRS in *Drosophila* recapitulates several hallmarks of the human disease, including a progressive deficit in motor performance, electrophysiological evidence of neuronal dysfunction and morphological signs of axonal degeneration. Not only ubiquitous, but also neuron-specific expression of mutant TyrRS, induces these phenotypes, indicating that the mutant enzyme has cell-autonomous effects in neurons. Furthermore, biochemical and genetic complementation experiments revealed that loss of enzymatic activity is not a common feature of DI-CMTC-associated mutations. Thus, the DI-CMTC phenotype is not due to haploinsufficiency of aminoacylation activity, but most likely to a gain-of-function alteration of the mutant TyrRS or interference with an unknown function of the WT protein. Our results also suggest that the molecular pathways leading to mutant TyrRS-associated neurodegeneration are conserved from flies to humans (Storkebaum et al., 2009).

Hereditary sensory and autonomic neuropathies (HSAN) are clinically and genetically heterogeneous disorders characterized by axonal atrophy and degeneration, exclusively or predominantly affecting the sensory and autonomic neurons. So far, disease-associated mutations have been identified in seven genes: two genes for autosomal dominant (SPTLC1 and RAB7) and five genes for autosomal recessive forms of HSAN (WNK1/HSN2, NTRK1, NGFB, CCT5 and IKBKAP). We performed a systematic mutation screening of the coding sequences of six of these genes on a cohort of 100 familial and isolated patients diagnosed with HSAN. In addition, we screened the functional candidate gene NGFR (p75/NTR) encoding the nerve growth factor receptor. We identified disease-causing mutations in SPTLC1, RAB7, WNK1/HSN2 and NTRK1 in 19 patients, of which three mutations have not previously been reported. The phenotypes associated with mutations in NTRK1 and WNK1/HSN2 typically consisted of congenital insensitivity to pain and anhidrosis, and early-onset ulcero-mutilating sensory neuropathy, respectively. RAB7 mutations were only found in patients with a Charcot-Marie-Tooth type 2B (CMT2B) phenotype, an axonal sensory-motor neuropathy with pronounced ulcero-mutilations. In SPTLC1, we detected a novel mutation (S331F) corresponding to a previously unknown severe and early-onset HSAN phenotype. No mutations were found in NGFB, CCT5 and NGFR. Overall disease-associated mutations were found in 19% of the studied patient group, suggesting that additional genes are associated with HSAN. Our genotype-phenotype correlation study broadens the spectrum of HSAN and provides additional insights for molecular and clinical diagnosis (Rotthier et al., 2009). In this study a new NTRK1 mutation causing Congenital insensitivity to pain with

anhidrosis (CIPA). We reported the clinical course of a 7-year-old girl with CIPA and proven NTRK1 mutation. In addition to recurrent dislocation of the left hip joint and avascular necrosis of the left talus, the patient also presented with recurrent infections secondary to hypogammaglobulinemia, a feature not previously known to be associated with CIPA. The patient was treated with regular administration of intravenous immunoglobulins. Conservative treatment of the recurrent left hip dislocation by cast immobilization and bracing was implemented to stabilize the joint. The implication of the immune system of the reported patient broadens the clinical phenotype associated with NTRK1 mutations (Kilic et al., 2009).

Hereditary sensory neuropathy type 1 (HSAN I) is an autosomal dominant inherited neurodegenerative disorder of the peripheral nervous system associated with mutations in the SPTLC1 subunit of the serine palmitoyltransferase (SPT). Four missense mutations (C133W, C133Y, V144D and G387A) in SPTLC1 were reported to cause HSAN I. SPT catalyses the condensation of Serine and Palmitoyl-CoA, which is the first and rate-limiting step in the de novo synthesis of ceramides. Earlier studies showed that C133W and C133Y mutants have a reduced activity, whereas the impact of the V144D and G387A mutations on the human enzyme was not tested yet. In this paper, we show that none of the HSAN I mutations interferes with SPT complex formation. We demonstrate that also V144D has a reduced SPT activity, however to a lower extent than C133W and C133Y. In contrast, the G387A mutation showed no influence on SPT activity. Furthermore, the growth phenotype of LY-B cells--a SPTLC1 deficient CHO cell line--could be reversed by expressing either the wild-type SPTLC1 or the G387A mutant, but not the C133W mutant. This indicates that the G387A mutation is most likely not directly associated with HSAN I. These findings were genetically confirmed by the identification of a nuclear HSAN family which showed segregation of the G387A variant as a non-synonymous SNP (Hornemann et al., 2009). Our recent research demonstrates that mutations in the second subunit of SPT, SPTLC2, likewise cause HSAN-I. Functional studies show that mutations in both subunits act in a similar way, namely by reducing the canonical SPT activity *in vitro* and increasing the levels of the atypical deoxysphingoid bases (DSBs) 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine. Of note, the accumulation of DSBs was found in all plasma samples of HSAN-I patients tested thus far, but this was not the case for all HEK293T cell lines stably expressing the mutant proteins. Our results confirm that the increased formation of DSBs is a key feature of HSAN-I, which provides opportunities for these compounds to serve as biomarkers. The absence of a consistent increase in DSBs in cell lines expressing the mutant proteins warrants for caution in the interpretation of *in vitro* data (Rotthier et al. 2010).

Besides the identification of mutations in known genes for HSAN, we also identified mutations in a new gene, FAM134B. Hereditary sensory and autonomic neuropathy type II (HSAN II) leads to severe mutilations because of impaired nociception and autonomic dysfunction. We showed that loss-of-function mutations in FAM134B, encoding a newly identified cis-Golgi protein, causes HSAN II. Fam134b knockdown results in structural alterations of the cis-Golgi compartment and induces apoptosis in some primary dorsal root ganglion neurons. This implicates FAM134B as critical in long-term survival of nociceptive and autonomic ganglion neurons (Kurth et al., 2009).

The HSPB1 and HSPB8 are widely expressed genes and code for chaperone proteins with essential cellular function. They protect cells from stress situations by refolding and protecting other proteins and cellular components. Motor neurons seem to be particularly vulnerable to mutations in HSPB1 and HSPB8 and thus cause the neurodegeneration. The mutant small HSP proteins may interfere with neuronal pathways by the formation of protein aggregates which could disrupt axonal cargo transport, affect neuronal cell survival or hamper their chaperone function. We have now investigated the influence of HSPB1 mutations on the basic biochemical properties of this protein using neuronal cell lines stably expressing either wild-type or mutant HSPB1 variants. Surprisingly, three mutations presented higher *in vivo* chaperone activity when compared to the wild-type protein. The enhanced activity of these mutations was accompanied by an increased fraction of the protein residing in a monomeric state. Consistently, analysis of the predicted protein structure of

HSPB1 suggested a mechanism for the monomeric tendency of hyperactive mutants. Furthermore, we were able to show that heat shock-induced activation of the wild-type HSPB1 is also accompanied by a similar increase in the fraction of the protein residing in the monomeric state, at the expense of the dimer fraction, indicating that the ratio between monomeric and dimeric HSPB1 is a key determinant for the activity of the protein (Almeida-Souza et al., 2010).

The mechanism through which mutant HSPB8 leads to a specific motor neuron disease phenotype is currently unknown. To address this question, we compared the effect of mutant HSPB8 in primary neuronal and glial cell cultures. In motor neurons, expression of both HSPB8 K141N and K141E mutations clearly resulted in neurite degeneration, as manifested by a reduction in number of neurites per cell, as well as in a reduction in average length of the neurites. Furthermore, expression of the K141E (and to a lesser extent, K141N) mutation also induced spheroids in the neurites. We did not detect any signs of apoptosis in motor neurons, showing that mutant HSPB8 resulted in neurite degeneration without inducing neuronal death. While overt in motor neurons, these phenotypes were only very mildly present in sensory neurons, and completely absent in cortical neurons or glial cells. These findings show that despite the ubiquitous presence of HSPB8, only motor neurons appear to be affected by the K141N and K141E mutations which explains the predominant motor neuron phenotype in distal HMN and CMT2L (Irobi et al., 2010).

Toll-like receptors (TLRs) comprise a family of evolutionary conserved pattern recognition receptors that act as a first defense line in the innate immune system. Upon stimulation with microbial ligands, they orchestrate the induction of a host defense response by activating different signaling cascades. Interestingly, they appear to detect the presence of endogenous signals of danger as well and as such, neurodegeneration is thought to trigger an immune response through ligation of TLRs. Though recent data report the expression of various TLRs in the central nervous system, TLR expression patterns in the peripheral nervous system (PNS) have not been determined yet. We observed that Schwann cells express relatively high levels of TLRs, with especially TLR3 and TLR4 being prominent. Sensory and motor neurons hardly express any TLR at all. Through the use of NF- $\kappa$ B signaling as readout, we could show that all TLRs are functional in Schwann cells and that bacterial lipoprotein (BLP), a ligand for TLR1/TLR2 receptors, yields the strongest response. In sciatic nerve, basal levels of TLRs closely reflect the expression patterns as determined in Schwann cells. TLR3, TLR4 and TLR7 are majorly expressed, pointing to their possible role in immune surveillance. Upon neurodegeneration, TLR1 becomes strongly induced, while most other TLR expression levels remain unaffected. Altogether, we found that similar to microglia in the brain, Schwann cells might act as sentinel cells in the PNS. Furthermore, neurodegeneration induces a shift in TLR expression pattern, most likely illustrating specialized functions of TLRs in basal versus activated conditions of the peripheral nerve (Goethals et al., 2010).

**B. Progressive external ophthalmologies and mitochondrial conditions (P. De Jonghe, A. Jordanova, G. Van Goethem and co-workers)**

In our research focusing on molecular genetic aspects of mitochondrial conditions, we described a Saudi Arabian family, which presented with adult onset autosomal dominant progressive external ophthalmoplegia (adPEO) complicated by late onset reversible failure of the CNS, respiratory, hepatic, and endocrine systems. Clinical findings were suggestive of mitochondrial dysfunction and multiple mitochondrial DNA deletions were demonstrated on long range and real time polymerase chain reaction assays but not on Southern blotting. The disorder is caused by a novel heterozygous PEO1 mutation predicting a Leu360Gly substitution in the twinkle protein. The peculiar clinical presentation expands the variable phenotype observed in adPEO and Twinkle gene mutations (Bohlega et al., 2009).

We have contributed to the European Federation of Neurological Sciences (EFNS) guidelines designed to provide practical help for the general neurologist to make appropriate use of molecular

genetics for diagnosing mitochondrial disorders (MIDs), which gain increasing attention and are more frequently diagnosed due to improved diagnostic tools. The guidelines summarise the possibilities and limitations of molecular genetic diagnosis of MIDs and provide practical recommendations and diagnostic criteria in accordance with the EFNS Scientific Committee to guide the molecular diagnostic work-up of MIDs (Finsterer et al., 2009).

### C. Congenital myopathies (P. De Jonghe, A. Jordanova, G. Van Goethem and co-workers)

We prospectively assessed magnetic resonance (MR) imaging findings of lower limb musculature in an axonal Charcot-Marie-Tooth disease (CMT2) pedigree due to mutation in the dynamin 2 gene (DNM2). The series comprises a proband patient aged 55 years and her two affected daughters aged 32 and 23. MR imaging study included T1- and fat suppressed T2-weighted spin-echo sequences. MR imaging study showed extensive fatty infiltration of all calf muscle compartments with relative preservation of the deep posterior one. Fatty muscle infiltration increased distally in 19 out of 66 (23%) visualized calf muscles in the three patients, but this percentage increased to 64% in the youngest and least severe patient. Muscle edema without contrast enhancement was present in 23% of calf muscles. There was massive fatty atrophy of foot musculature. We conclude that MR imaging study accurately depicts lower limb muscle involvement in CMT2 caused by DNM2 mutation (Gallardo et al., 2008).

Dominant intermediate Charcot-Marie-Tooth neuropathy type B is caused by mutations in dynamin 2. We studied the clinical, haematological, electrophysiological and sural nerve biopsy findings in 34 patients belonging to six unrelated dominant intermediate Charcot-Marie-Tooth neuropathy type B families in whom a dynamin 2 mutation had been identified: Gly358Arg (Spain); Asp551\_Glu553del; Lys550fs (North America); Lys558del (Belgium); Lys558Glu (Australia, the Netherlands) and Thr855\_Ile856del (Belgium). The Gly358Arg and Thr855\_Ile856del mutations were novel, and in contrast to the other Charcot-Marie-Tooth-related mutations in dynamin 2, which are all located in the pleckstrin homology domain, they were situated in the middle domain and proline-rich domain of dynamin 2, respectively. We report the first disease-causing mutation in the proline-rich domain of dynamin 2. Patients with a dynamin 2 mutation presented with a classical Charcot-Marie-Tooth phenotype, which was mild to moderately severe since only 3% of the patients were wheelchair-bound. The mean age at onset was 16 years with a large variability ranging from 2 to 50 years. Interestingly, in the Australian and Belgian families, which carry two different mutations affecting the same amino acid (Lys558), Charcot-Marie-Tooth cosegregated with neutropaenia. In addition, early onset cataracts were observed in one of the Charcot-Marie-Tooth families. Our electrophysiological data indicate intermediate or axonal motor median nerve conduction velocities (NCV) ranging from 26 m/s to normal values in four families, and less pronounced reduction of motor median NCV (41-46 m/s) with normal amplitudes in two families. Sural nerve biopsy in a Dutch patient with Lys558Glu mutation showed diffuse loss of large myelinated fibres, presence of many clusters of regenerating myelinated axons and fibres with focal myelin thickenings--findings very similar to those previously reported in the Australian family. We conclude that dynamin 2 mutations should be screened in the autosomal dominant Charcot-Marie-Tooth neuropathy families with intermediate or axonal NCV, and in patients with a classical mild to moderately severe Charcot-Marie-Tooth phenotype, especially when Charcot-Marie-Tooth is associated with neutropaenia or cataracts (Claeys et al., 2009).

Autosomal recessive demyelinating Charcot-Marie-Tooth neuropathy type 4H (CMT4H) manifests early onset, severe functional impairment, deforming scoliosis, and myelin outfoldings in the nerve biopsy. Mutations in the FGD4 gene encoding the Rho-GTPase guanine-nucleotide-exchange-factor frabin were reported in five families. We characterized a novel mutation in FGD4 and described the related phenotype. The proband disclosed a moderately severe, scarcely progressive CMT, markedly slowed nerve conduction velocities, and a demyelinating neuropathy characterized by prominent myelin outfoldings. Mutational analysis disclosed a c.1762-2a>g transition in the splice-

acceptor site of intron 14, which was predicted to cause a truncated frabin (p.Tyr587fsX14). The report confirms genetic heterogeneity of FGD4, demonstrates that CMT4H has variable functional impairment, and suggests that frabin plays a crucial role during myelin formation (Fabrizi et al., 2009).

Gonadal dysgenesis with normal male karyotype (46XY) is a sexual differentiation disorder. So far three patients have been reported presenting the association of 46XY gonadal dysgenesis with peripheral neuropathy. Examination of sural nerves revealed minifascicle formation in two of them. In one patient, a mutation was found in desert hedgehog homolog (*Drosophila*), a gene important in gonadal differentiation and peripheral nerve development. We studied neuropathological and molecular genetic aspects of a patient with 46XY gonadal dysgenesis and peripheral neuropathy. Examination of a sural nerve biopsy specimen revealed an axonal neuropathy with pronounced axonal loss, limited signs of axonal regeneration and no minifascicle formation. A normal male karyotype was found (46XY) without micro-deletions in the Y chromosome. No mutations were found in the sex determining region Y gene, peripheral myelin protein 22, Myelin Protein Zero, Gap-Junction protein Beta 1, Mitofusin 2 or desert hedgehog homolog. The absence of minifascicle formation and the absence of a mutation in desert hedgehog homolog in this patient with gonadal dysgenesis and peripheral neuropathy expand the clinical and genetic heterogeneity of this rare entity (Baets et al., 2009).

## EPILEPSIE-GERELATEERD ONDERZOEK

### Vanuit Neurogenetica

The phenotypes associated with SCN1A mutations are Dravet syndrome, Generalized Epilepsy with Febrile Seizures plus (GEFS+) and hemiplegic migraine.

The neuronal voltage-gated sodium channel Na(v)1.1 encoded by the SCN1A gene plays an important role in the generation and propagation of action potentials in the central nervous system. Altered function of this channel due to mutations in SCN1A leads to hypersynchronous neuronal discharges resulting in seizures or migrainous attacks. A large number of distinct sequence variants in SCN1A are associated with diverse epilepsy and migraine syndromes. We developed an online and freely available database containing all reported sequence variants in SCN1A (<http://www.molgen.ua.ac.be/SCN1AMutations/>). We verified 623 distinct sequence variants, listed them using standard nomenclature for description and classified them according to their putative pathogenic nature. We provided links to relevant publications and information on the associated phenotype. The database can be queried using cDNA or protein position, phenotype, variant type or publication. By listing all SCN1A variants in a comprehensive manner, this database will facilitate interpretation of newly identified sequence variants and provide better insight into the genotype-phenotype relations of the growing number of SCN1A mutations (Claes et al., 2009).

We reported the first patient with Dravet syndrome associated with a recessive mutation in SCN1B (p.R125C). Biochemical characterization of p.R125C in a heterologous system demonstrated little to no cell surface expression despite normal total cellular expression. This occurred regardless of coexpression of Na(v)1.1 alpha subunits. Because the patient was homozygous for the mutation, these data suggest a functional SCN1B null phenotype. To understand the consequences of the lack of beta1 cell surface expression *in vivo*, hippocampal slice recordings were performed in *Scn1b(-/-)* versus *Scn1b(+/+)* mice. *Scn1b(-/-)* CA3 neurons fired evoked action potentials with a significantly higher peak voltage and significantly greater amplitude compared with wild type. However, in contrast to the *Scn1a(+/-)* model of Dravet syndrome, we found no measurable differences in sodium current density in acutely dissociated CA3 hippocampal neurons. Whereas *Scn1b(-/-)* mice seize spontaneously, the seizure susceptibility of *Scn1b(+/-)* mice was similar to wild type, suggesting that, like the parents of this patient, one functional SCN1B allele is sufficient for normal

control of electrical excitability. We conclude that SCN1B p.R125C is an autosomal recessive cause of Dravet syndrome through functional gene inactivation (Patino et al., 2009).

Absence epilepsies of childhood are heterogeneous with most cases following complex inheritance. Those cases with onset before 4 years of age represent a poorly studied subset. We screened 34 patients with early-onset absence epilepsy for mutations in SLC2A1, the gene encoding the GLUT1 glucose transporter. Mutations leading to reduced protein function were found in 12% (4/34) of patients. Two mutations arose de novo, and two were familial. These findings suggest GLUT1 deficiency underlies a significant proportion of early-onset absence epilepsy, which has both genetic counseling and treatment implications because the ketogenic diet is effective in GLUT1 deficiency (Suls et al., 2009).

Incidence rates of epilepsy in children are highest during the first year of life. Most frequently, epilepsy results from a metabolic or structural defect in the brain. However, some infants have clearly delineated epilepsy syndromes for which no underlying etiology can be identified except for a genetic predisposition. We reviewed the current knowledge on the genetics of epilepsy syndromes starting in the first year of life. We focus on those epilepsy syndromes without a clear structural or metabolic etiology. This knowledge has consequences for clinical practice as it opens new perspectives for genetic testing, improving early diagnosis, and facilitating genetic counseling. (Deprez et al., 2009).

#### **IV. METABOLIC CONDITIONS WITH NEUROLOGICAL COMPLICATIONS**

The Laboratory of Neurochemistry and Behaviour continued its study of biochemical and pathophysiological parameters linked to hereditary disorders of the urea cycle and acquired renal failure.

In collaboration with Raymond Vanholder (Nephrological department of the University Hospital of Ghent) we reviewed the guanidino compounds as candidate uremic neurotoxins (De Deyn et al., 2009). Our collaborative scientific research with the same group was concentrated on the dialysability of specific guanidino compounds increased in the physiological fluids and tissue of patients with renal insufficiency. Before we found already that the dialysability of urea, creatinine and other guanidino compounds are different. A profound study on the dialysability of the specific guanidino compounds increased in the body fluids and tissue of the patients next to urea was done. This study was necessary to obtain a better understanding of the specific dialysability of each specific compound in order to optimize the future dialysis procedures to eliminate these accumulated compounds as much as possible from renal insufficient patients. The complex and compartmental behaviour of these water soluble uremic retention solutes has been shown after the determination of the concentration of these specific compounds in plasma and erythrocytes of patients (Eloot et al., 2007). Further we obtained more insight of the impact of increased haemodialysis frequency and haemodialysis duration on the removal of guanidino compounds: a much more adequate clearance of creatinine and methylguanidine was obtained by increasing the dialysis duration. Increasing the dialysis frequency resulted however in a better clearance of guanidinosuccinic acid, one of the highly accumulated compounds in patients (Eloot et al., 2009). Furthermore we highlighted the accumulation of methylguanidine in rats after furosemide administration and the change of other guanidino compound levels have been observed after supplementation of creatine to renal insufficient patients. Methylguanidine is accumulated in body fluids and tissue of patients with renal insufficiency as a consequence of reduced glomerular filtration, it is also one of the most proposed candidate neurotoxins in uraemia. A clear increase of methylguanidine in the body fluids and kidneys of furosemide-treated rats was seen (Levillain et al., 2008). To prevent loss of muscle mass in patients with renal insufficiency supplementation of creatine is given. As a consequence the plasma guanidinoacetic acid decreased with 15% due to inhibition of the creatine-creatinine biosynthesis pathway. The plasma levels of the epileptogenic

keto- and hydroxyl-analogue of arginine were also increased respectively 3 and 2 times compared to the levels before supplementation (Taes et al., 2008).

The Laboratory of Neurochemistry and Behaviour of the Institute of Born-Bunge had an of many years' standing experience in amino acid analyses. Their expertise concerning urea cycle disorders is acknowledged internationally. Detailed clinical and biochemical characteristics of patients with argininemia (last enzymatic deficiency in the urea cycle) were first described following our diagnosis in our laboratory at the end of the sixties of the former century. In this context our laboratory always investigated and investigates extensively studies concerning the arginine metabolism. Therefore a mouse model for argininemia was created by our collaborators from UCLA. Specific increased catabolites of arginine (guanidino compounds) were observed in plasma and tissues of the model (Deignan et al., 2008). This model helps us a lot to obtain a better understanding of the pathobiochemistry and pathophysiology seen in human argininemia. This way we observed that the increase of arginine levels together with specific catabolites of arginine in central nervous system of the mouse model as well in post mortem material of human patients is much less than those seen in periferic organs (Deignan et al., 2010). Therefore the question rises if other catabolites of arginine like nitric oxide or derivatives of it are not more associated with the symptomatology seen in patients with argininemia.

## **V. PHENOTYPICAL CHARACTERIZATION OF (TRANSGENIC) ANIMAL MODELS FOR NEURODEGENERATIVE CONDITIONS (Neurochemie & Gedrag)**

In-depth behavioural phenotyping of (transgenic) mouse models contributes to the unraveling of the influence of gene alterations and gene-environment interactions on the pgenotype of different forms of mental retardation and neurodegeneration, as well as our knowledge of underlying pathophysiological mechanisms and the identification of therapeutic targets for the development of novel treatment strategies.

As described in the previous report (2004-2007), the Behavioural Research Unit at the Laboratory of Neurochemistry and Behaviour has greatly added to the behavioural phenotyping of the APP23 transgenic mouse model for AD and is now mainly focusing on the assessment of BPSD-related behavioural alterations (BPSD = "behavioural and psychological signs and symptoms of dementia"). The APP23 model develops pathological features, learning and memory deficits analogous to dementing patients.

We investigated ingestive behavior in APP23 males of 3, 6 and 12 months using operant conditioning boxes equipped with an automated pellet feeder and optical lick-o-meter.. In addition, body weights of a naive male group were longitudinally monitored starting at weaning. Olfactory acuity was evaluated in mice of different age groups. Although olfactory functioning of APP23 mice appeared intact, they drank more and took more food pellets compared with wild-type littermates during a 1-week registration period. From the age of 4.5 weeks onward, APP23 males weighed significantly less than their control littermates, whereas this difference became more prominent with increasing age. Our results suggest the presence of a hypermetabolic state in this model (Vloeberghs et al., 2008b).

Learning and memory were previously assessed in the APP23 model using the Morris water maze (MWM) and passive avoidance learning. In search of a non-spatial alternative for assessment of hippocampus-dependent memory, we evaluated an odour paired-associate test, which is based on learning an association between two sets of odours. The protocol includes a shaping phase, in which the animals learn to dig up a reward, a preliminary training phase and a training phase, where the actual association is learned. Subsequently, mice are tested for transitive inference and subjected to a symmetry test. Impairment was seen in the APP23 mice, in comparison with wild type mice, in training; however, both groups failed the transitivity and symmetry test. Possible explanations for

this discrepancy with earlier published results are the advanced age of the mice or the C57Bl/6J background, in which the model was established (Van Dijck et al., 2008).

Valid animal models are indispensable in the drug discovery pipeline for dementia. Transgenic APP23 mice model Alzheimer's disease patients' memory deficits and additionally present with various behavioural disturbances, such as aggressive behaviour. The present study investigated and confirmed significant sensitivity of the model to the aggression-lowering ability of the antipsychotic agent risperidone (CAS 106266-06-2). The sensitivity for such anti-aggressive action contributes to the therapeutic predictive validity of the APP23 model of Alzheimer's disease, which can be used as a pre-clinical screening tool for the identification of novel anti-aggressive agents (Vloeberghs et al., 2008a).

The role of animal models in dementia research and the drug discovery pipeline for Alzheimer's disease in particular, were reviewed in a book entitled "Animal models of dementia", edited by De Deyn PP and Van Dam D (2010), and in an invited review by Van Dam & De Deyn, accepted for publication in *Br. J. Pharmacol.*

The potential disease-modifying efficacy of drugs currently used for the symptomatic treatment of AD are under debate. The interest for acetylcholinesterase inhibitors in the treatment of AD has been greatly renewed owing to the discovery of a broad range of additional cholinergic and non-cholinergic effects, exploitable to maximize the efficacy of these drugs beyond merely improving intellectual functions at the symptomatic level. The age-dependent cognitive decline in the valid APP23 transgenic mouse model for Alzheimer's disease was employed to evaluate disease-modifying efficacy of chronic treatment with donepezil. At age 6 weeks, heterozygous APP23 mice and control littermates were subcutaneously implanted with osmotic pumps delivering saline or donepezil (0.27 or 0.58 mg/kg per day). After 2 months of treatment, a 3-week wash-out period was allowed to prevent bias from sustained symptomatic effects before cognitive evaluation in the MWM commenced. Chronic donepezil (0.27 mg/kg per day) treatment improved spatial accuracy in APP23 mice as to reach the same level of performance as wild-type control animals on this complex visual-spatial learning task (Van Dam et al., 2008). A similar study design was employed to assess disease-modifying efficacy of ibuprofen in the APP23 mouse model (Van Dam et al., 2010).

NAPVSIPQ (NAP) is a small, active fragment of activity-dependent neuroprotective protein that has neuroprotective and memory enhancing properties at very low concentrations. Twelve-month-old male heterozygous APP23 mice and their wild-type control littermates were intraperitoneally injected with 0.3 microg NAP/g body weight or with saline vehicle for 22 consecutive days. Cognitive performance training in the MWM started on day 8 of treatment. The internal validity of our study was demonstrated by the fact that the APP23 mice performed significantly worse in the MWM than wild-type animals. Treatment with NAP, however, did not exert any significant effects on MWM performance. Although we failed to show significant memory enhancing effects in this study, NAP might be a promising peptide for disease-modifying therapy in neurodegenerative disease, but short-term effects are probably not to be expected. Also, most likely, treatment should start in an early stage, i.e. before full-blown pathology is eminent, and the necessary treatment period should enclose several months (Van Dijck et al., 2009a).

The development of AD is closely connected with cholesterol metabolism. Cholesterol increases the production and deposition of Abeta peptides that result in the formation of amyloid plaques, a hallmark of the pathology. In the brain, cholesterol is synthesized in situ but cannot be degraded nor cross the blood-brain barrier. The major exportable form of brain cholesterol is 24S-hydroxycholesterol, an oxysterol generated by the neuronal cholesterol 24-hydroxylase encoded by the CYP46A1 gene. We report that the injection of adeno-associated vector (AAV) encoding CYP46A1 in the cortex and hippocampus of APP23 mice before the onset of amyloid deposits markedly reduces Abeta peptides, amyloid deposits and trimeric oligomers at 12 months of age. The Morris water maze (MWM) procedure also demonstrated improvement of spatial memory at 6 months, before the onset of amyloid deposits. AAV5-wtCYP46A1 vector injection in the cortex and

hippocampus of amyloid precursor protein/presenilin 1 (APP/PS) mice after the onset of amyloid deposits also reduced markedly the number of amyloid plaques in the hippocampus, and to a less extent in the cortex, 3 months after the injection. Our data demonstrate that neuronal overexpression of CYP46A1 before or after the onset of amyloid plaques significantly reduces Abeta pathology in mouse models of AD (Hudry et al., 2009).

In 2005, we described important neurotransmitter alterations in specific brain regions of the APP23 model, including changes in the noradrenergic system. The integrity of the locus coeruleus (LC) noradrenergic system was studied in the APP23 model at the age of 3, 6 and 12 months through quantification of tyrosine hydroxylase (TH) mRNA expression. Despite the previous study suggesting alterations in the noradrenergic transmission system of APP23 mice, the current study failed to show altered TH-positive neuronal numbers or expression in LC noradrenergic neurons of APP23 mice versus wild-type (WT) littermates. However, the present study did demonstrate an age-dependent effect on TH mRNA expression. Both the number of TH-containing neurons and the amount of TH-positive grains/neuron significantly increased between the age of 3 and 6 months with no difference between 6 and 12 months. These observations indicate that any study comparing the noradrenergic system between WT (C57Bl/6) and experimental mice must strictly choose the age to be tested and limit age differences between control and experimental groups to the absolute minimum. More importantly, when long-term therapeutic interventions targeting the noradrenergic system are applied to mouse models, and related parameters are studied longitudinally, care should be taken to distinguish between potential therapeutic and strain-specific developmental or age-related alterations (Szot et al., 2009). Using HPLC, the region-specific concentration biogenic amines and metabolites in APP23 and WT mice brain was linked to the animals' performance in an isolation-induced resident-intruder aggression protocol. Matrix correlation is applied to search for the potential link between altered neurotransmitter levels or turnover and increased male aggression in the APP23 mice (Manuscript in preparation).

Within the framework of an SBO programme, the effects of centrally administrated obestatin on eating and drinking behaviour were studied. Obestatin is a ghrelin-associated peptide hormone with presumed anorexigenic and inhibitory effect on gastric propulsive motility activity. Recent literature, however, discloses much contestation over satiety and gastrointestinal motility-related functionalities of obestatin. In addition, antidipsinogenic effects in rodents by obestatin were recently reported. The present study was set up to bring more clarity into the contested effects of obestatin on food and water intake. Additionally, the stability of obestatin in brain tissue homogenate was investigated. The *in vitro* incubation of obestatin in brain homogenates revealed disappearance half-life times of 19 min for crude brain homogenate to 27 min for brain membrane homogenate. For the behavioural studies, male C57Bl/6 mice were intracerebroventricularly treated with 0.2 nmol murine amidated obestatin or vehicle at the age of 3 months. An additional group of mice was treated with 0.3 nmol of corticotropin releasing factor (CRF) as a positive control of suppression of food intake. Food and water intake were studied over a period of 5 h in metabolic cages. Under our experimental conditions, no suppressive effects of obestatin on food or water intake were observed, whereas CRF evoked a significant suppression of food intake, which proves the internal validity of the study design (Van Dijck et al., 2009b).

In collaboration with the Belgian Nuclear Research Centre (SCK-CEN, Mol), we studied the effects of prenatal exposure to low doses of ionising radiation on cognitive and behavioural parameters in the adult offspring. Exposure on E12, i.e. the embryonic development day on which the hippocampus is formed in the mouse, caused severe cognitive deficits in 3-month-old C57BL/6 mice, as tested in the MWM (Manuscript in preparation).

The role of altered expression of GABAergic system components in the fragile X syndrome and fragile X associated tremor/ataxia syndrome (FXTAS) was reviewed (D'Hulst et al., 2009).

The striatum is the major input structure of basal ganglia and is involved in adaptive control of behaviour through the selection of relevant informations. Dopaminergic neurons that innervate

striatum die in Parkinson disease, leading to inefficient adaptive behaviour. Neuronal activity of striatal medium spiny neurons (MSN) is modulated by dopamine receptors. Although dopamine signalling had received substantial attention, consequences of dopamine depletion on MSN intrinsic excitability remain unclear. Here we show, by performing perforated patch clamp recordings on brain slices, that dopamine depletion leads to an increase in MSN intrinsic excitability through the decrease of an inactivating A-type potassium current,  $I(A)$ . Despite the large decrease in their excitatory synaptic inputs determined by the decreased dendritic spines density and the increase in minimal current to evoke the first EPSP, this increase in intrinsic excitability resulted in an enhanced responsiveness to their remaining synapses, allowing them to fire similarly or more efficiently following input stimulation than in control condition. Therefore, this increase in intrinsic excitability through the regulation of  $I(A)$  represents a form of homeostatic plasticity allowing neurons to compensate for perturbations in synaptic transmission and to promote stability in firing. The present observations show that this homeostatic ability to maintain firing rates within functional range also occurs in pathological conditions, allowing stabilizing neural computation within affected neuronal networks (Azdad et al., 2009).

## **VI. STUDY OF SPONGIFORM ENCEFALOPATHIES (P. CRAS AND CO-WORKERS)**

The research of task force 2 focusses on the role of neuroprotective mechanisms in transmissible spongiform encephalopathies, i.e., Creutzfeldt-Jakob Disease (CJD); bovine spongiform encephalopathy (BSE) and scrapie. Since 1998 a brain bank containing both fixated and frozen brain tissue of neuropathologically confirmed CJD patients, as well as CSF of neuropathologically confirmed, probable and possible CJD patients is established.

Several molecular subtypes of sporadic CJD have been identified and EEG and CSF biomarkers have been reported to support clinical diagnosis but with variable utility according to subtype. In recent years, a series of publications have demonstrated a potentially important role for MRI in the pre-mortem diagnosis of sporadic CJD. A multi-centre international study aimed to provide a rationale for the amendment of the clinical diagnostic criteria for sporadic CJD (Zerr et al., 2009).

## **VII. CARDIOVASCULAR RESEARCH (P.P. VAN BOGAERT AND CO-WORKERS)**

### **A. Characteristics of the $I_h$ current in oocytes**

HCN1 and HCN2 channels of the mouse were expressed in *Xenopus Laevis* oocytes. The mechanism of progressive decrease of peak amplitude, evoked by a train of voltage-clamp pulses from -30 to -120 mV (during 1s) was studied by changing the ion composition of the extracellular solution. The presence of  $Na^+$  ions caused blocking of the HCN channel, which could be reversed again by replacing  $Na^+$  ions by  $K^+$  ions. This competitive interaction between  $Na^+$  and  $K^+$  at the selectivity filter of the HCN channel can explain the reversible decrease of the HCN current in the *Xenopus laevis* oocytes. This reversible decrease does not occur in native and HEK293 cells, where heterologous expression of HCN channels was applied. In conclusion, HCN channels expressed in *Xenopus laevis* have other characteristics than the native  $I_h$  channels.

### **B. Outward currents in mouse dorsal root ganglia (DRG) neurons**

Silent voltage-gated  $K^+$  ( $K_v$ ) subunits interact with  $K_v2$  subunits and primarily modulate the voltage dependence of inactivation of these heterotetrameric channels. Both  $K_v2$  and silent  $K_v$  subunits are expressed in the mammalian nervous system, but little is known about their expression and function in sensory neurons. This study reports the presence of  $K_v2.1$ ,  $K_v2.2$ , and silent subunit  $K_v6.1$ ,  $K_v8.1$ ,  $K_v9.1$ ,  $K_v9.2$ , and  $K_v9.3$  mRNA in mouse DRG. Immunocytochemistry confirmed the protein expression of  $K_v2.x$  and  $K_v9.x$  subunits in cultured small DRG neurons. To investigate if  $K_v2$  and silent  $K_v$  subunits are underlying the delayed rectifier  $K^+$  current (IK) in these neurons,

Kv2-mediated currents were isolated by the extracellular application of rStromatoxin-1 (ScTx) or by the intracellular application of Kv2 antibodies. Both ScTx- and anti-Kv2.1-sensitive currents displayed two components in their voltage dependence of inactivation. Together, both components accounted for approximately two-thirds of IK. A comparison with results obtained in heterologous expression systems suggests that one component reflects homotetrameric Kv2.1 channels, whereas the other component represents heterotetrameric Kv2.1/silent Kv channels. These observations support a physiological role for silent Kv subunits in small DRG neurons (Bocksteins et al., 2009).

C. Sensitivity of fresh DRG neurons and enteric neurons for enteric neurotransmitters

The modulation of submucosal enteric neurons in piglets by cGRP and histamine was studied. Both compounds modulate the excitability of enteric neurons causing ionic conductance changes. The effect of enteric neurotransmitters on the electric activity of fresh rat DRG neurons was studied as well.

## 2. COLLABORATIONS

### a) National

Benotmane R., (Studiecentrum voor Kernenergie - Centre d'étude de l'Energie Nucléaire, Mol), study behavioural effects intra-uterin exposure to ionising radiation

Beyaert R. (VIB Departement – Molecular Biomedical Research), Negative regulation of the innate immune system in the peripheral nerve

Callaerts P. (VIB Department – Molecular and Developmental Genetics), Genetic modifier screen with the YARS-DI-CMTC Drosophila model & Dominant mutations in the tyrosyl-tRNA synthetase gene recapitulate in Drosophila features of human Charcot-Marie-Tooth neuropathy

Callaerts P. (VIB Department – Developmental Genetics), Biochemical analysis of TDP43 in TDP43 Drosophila flies – 2009

Ceulemans B. (Child Neurology, University Hospital Antwerp and University of Antwerp), Family with juvenile parkinsonism and ATP13A2 mutation

Ceulemans B. (Department of Neurology, University Hospital Antwerp, Antwerp), Genotype-phenotype correlations in Inherited Epilepsies.

Chen Ch. (UGent, VIB), analysis N-glycan profiles in AD (human/APP23 mouse model)

De Meyer G, Martinet W (Physiopharmacology, UAntwerpen), development of an APP23 x ApoE ko model

De Strooper B. (KULeuven), FTD PS1 G183V mutation & Ab42- Ab40 TGFb normalized ELISA

Deforce D. (UGent), Isolation of potential targets modifying Abeta aggregation

Dewilde S., Moens L. (Eiwitchemie, UAntwerpen), behavioural phenotyping of NGB overexpression mice

Domnisse R (Dept. Chemistry, Applied NMR, UAntwerpen), NMR spectroscopy

Gettemans J. (UGent, VIB): biochemical experiments (HSP22 & YARS)

Haigh J. (VIB Department – Molecular Biomedical Research), HSPB1 and HSPB8 KI/KO modeling

Hochpied T. (VIB Department – Plant Systems Biology), Knock-in knock-out models

Huylebroeck D. (KULeuven, VIB): in situ hybridisations (SSH experiments)

Jansen A. (Department of Child Neurology, University Hospital VUB), AR GEFS+ in Gypsy families. Genotype-phenotype correlations in inherited epilepsies

Kooy F. (Medical Geneticc, UAntwerpen), behavioural phenotyping Fmr1 knockout mice

Medical Genetics (UAntwerpen): contribution to histopathological research and/or exchange of tissue samples

Michotte Y., Smolders I., (VUB), Glutamate transporters in APP23 mouse model for AD

Neuropathology (UZLeuven): contribution to histopathological research and/or exchange of tissue samples

Paesschen W. (Division of Neurology, University Hospitals Leuven), Genotype-phenotype correlations in Inherited Epilepsies

Robberecht W. & Van Damme Ph. (Department of Neurology, University Hospital, Gasthuisberg, Leuven, Belgium), Genotype-phenotype correlations in CMT and HSP

Robberecht W. & Van Den Bosch L. (VIB Department – Vesalius Research Center), GluR2 in ALS

Robberecht W. (Experimental Neurology, KULeuven), serum and CSF samples of progranulin mutation carriers

Robberecht W. (VIB Department – Vesalius Research Center), Mutation analysis SACSIN in ARSACS

Robberecht W. (VIB Department – Vesalius Research Center), Neuronal inclusion protein TDP-43 has no primary genetic role in FTD and ALS & PGRN in microglia

Robberecht W. (VIB Department – Vesalius Research Center), Peripheral neuropathy and 46 XY gonadal dysgenesis: a heterogenous entity & Mutant heat shock protein HSPB8 induces aggregation and a pro-apoptotic phenotype in distal motor neuropathy

Rousseau F. (VIB Department – Switch Laboratory), Biophysical characterisation of small HSPB1 and HSPB8

Santens P. (Department of Neurology, University Hospital Ghent and University of Ghent), Biosampling of FTLD patients for genetic studies

SBO consortium ‘Neuro-TARGET’, Integrated platform for target identification, validation and drug discovery applied to neurodegenerative diseases

Schoofs L. (Animal Physiology and Neurobiology, KULeuven), massspectrometric peptidomics analyses of human and animal samples

Schymkowitz J. (VIB Department – Switch Laboratory), Modelling of HSPB1 mutations

Stinissen P. (University of Hasselt), Serum proteomics of the DR8 founder family

Timmermans J.P. (UAntwerpen): Confocal microscopy (HSP22, HSP27 & YARS)

UZGent (Child Neurology and Neuropathology): contribution to histopathological research and/or exchange of tissue samples

Van den Bergh P. (Service de Neurologie, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels), Genotype-phenotype correlations in CMT and HSP

Van Den Bosch L. (VIB Department – Vesalius Research Center), Molecular pathomechanisms of HSPB1 and HSPB8 mutations in motor neuropathies: study of protein-protein interactions and axonal transport in cellular and animal models

Van Dijck P. (KULeuven, VIB): experiments with yeast (YARS)

Van Loo G. (VIB, UGent), behavioural phenotyping A20 ko mice.

Van Roy F. (UGent), Alzheimer & 5-HT7

Van Roy F. (VIB Department – Molecular Biomedical Research), SH-SY5Y-Flp-In cell line & pFRT/lacZeo construct

Vandenberghe R. (Department of Neurology, University Hospitals Leuven and University of Leuven), Brain amyloidosis and the brain's response in cognitively intact elderly volunteers & Biosampling of PD and DLB patients for genetic studies

Vanderlinden A. (Department of Biomedical Sciences, UAntwerp), Transgenic mice - Austrian APP714

Winderickx J. (Laboratory of Functional Biology, University of Leuven), Prioritizing genes within the DLB locus based on yeast-deletion screening results

Wuytack F. and Vangheluwe P. (Laboratory of Cellular Transport Systems, University of Leuven)  
Study of the effect of ATP13A2 mutations identified in PD patients on the activity and subcellular distribution of the protein

#### **b) International**

Amouyel P., Lambert J.-C. (Inserm U744, Institut Pasteur de Lille, Université de Lille Nord de France, Lille, France). European Alzheimer's Disease Initiative.

Aubourg P. Cartier N. (INSERM, Frankrijk), behavioural phenotyping of MLD and ALD mouse models and AD-related research in the APP23 model

Auer-Grumbach M. (Institute of Medical Biology and Department of Internal Medicine, Diabetes and Metabolism, Medical University Graz, Graz, Austria), Genotype-phenotype correlations in CMT and HSP

Barisic N. (Department of Paediatrics, University of Zagreb, Medical School, University Hospital Centre Zagreb, Croatia), Genotype-Phenotype correlations in CMT, HSP and Inherited Epilepsies

Battaloglu E. & Parman Y. (Boğaziçi Üniversitesi, Moleküler Biyoloji ve Genetik Bölümü, Bebek, İstanbul), Identification of novel AR CMT

Berciano J. (Service of Neurology, University Hospital "Marqués de Valdecilla", Santander, Spain), Genotype-phenotype correlations in CMT. Cloning of the CMT2G gene

Berkovic S. & Scheffer I. (Epilepsy Research Centre, Department of Medicine, University of Melbourne, Level 1, Neurosciences Building, Heidelberg Repatriation Hospital Austin Health, West Heidelberg, Australia), Genotype-Phenotype correlations in monogenic forms of epilepsies

Bolino A. (Dulbecco Telethon Institute, San Raffaele Scientific Institute, 20132 Milan, Italy), KIF13A as candidate gene for CMT

Brice A. (Hôpital de la Salpêtrière, Paris, France), MAPT H1 subhaplotypes & haplotyping of French FTD patients in FTDU-17 candidate region 17q21 & Mutations in a causative gene for FTD

Britain N. (Taconic Farms, Inc., Germantown, NY, USA), Taconic Transgenic Models

Brunt E. (Universitair Ziekenhuis Groningen, Nederland), Ataxine 7 antibodies CM189

Burgers R. (Jackson Laboratories, Bar Harbor, Main, USA), Modelling YARS mutations in mouse

Burgess R. (The Jackson Laboratory, 600 Main St. Bar Harbor, ME 04609, USA), Modifier genes in GARS

Chance Ph. (University of Washington, Seattle, USA): Identification of SEPT9 mutations in HNA.

Cremers T. (Biomonitoring en Sensoring, Rijksuniversiteit Groningen, The Netherlands), Neurochemical analyses

de Mendonça A. (Institute of Molecular Medicine, Faculty of Medicine of Lisbon, Portuga), refinement of the FTDU chromosom locus 17q21 and identification of the disease gene in Portuguese FTD families

Fabrizi G.M. (Department of Neurological and Vision Sciences, Section of Clinical Neurology, Verona, Italy), Genotype-phenotype correlation in CMT (Frabin; GDAP1, early onset CMT)

Fabrizi G.M. (Section of Clinical Neurology, Department of Neurological and Visual Sciences, University of Verona, Italy), Genotyping of FTLN ch9 families

Farrer M. (Mayo Clinic, Jacksonville, USA), tau htSNP haplotyping

Fischbeck K. (NIH, Bethesda, USA), Modelling GARS mutations in Drosophila

Goate A. (Washington University, USA), MAPT H1 SNP haplotyping in PSP patients

- Goebel H.H. (Mainz): neuronal ceroid lipofuscinoses
- Haass C. (German Center for Neurodegenerative Diseases (DZNE) & Adolf-Butenandt-Institute, Biochemistry, Ludwig-Maximilians-University, Munich, Germany). Biomaterial GRN mutation carriers for drug discovery.
- Henry M.W. (Athena Diagnostics, Worcester, Massachusetts, USA), Progranulin mutations for dementia diagnosis
- Hoh J. (Yale University, New Haven, USA), Genomic DNA of 300 Belgian Parkinson patients and 300 Belgian control subjects for genotyping of 25 SNPs
- Houlden H. (University College London, Institute of Neurology, Department of Molecular Neuroscience, London, UK) Genome wide association study for Multiple System Atrophy
- Hornemann T. (Institute for Clinical Chemistry, University Hospital of Zürich, Zürich, Switzerland), EMBO Short Term Fellowship for the visit of Annelies Rotthier in 2009: SPT analysis of mutant constructs
- Hutton M. (Mayo Clinic, Jacksonville, USA), FTDU-17
- Isom L., University of Michigan Medical School, Department of Pharmacology, Ann Arbor, Michigan, USA), Functional studies of SCN1Ba recessive mutation in Dravet syndrome
- Jordanova, A. (Medical University Sofia, Sofia, Bulgaria) Molecular genetic analysis and genotype-phenotype correlations in inherited neurological disorders – part neurodegenerative brain diseases
- Kaladjeva L. (Laboratory for Molecular Genetics, Western Australian Institute for Medical Research, UWA Centre for Medical Research, QEII Medical Centre, Hospital Avenue, Nedlands WA, Australia), Positional cloning of AR epilepsies in Gypsies
- Kennerson M. (Northcott Neuroscience Laboratory, ANZAC Research Institute, Concord, NSW, Australia), Missense Mutations in the Copper Transporter Gene ATP7A cause X-linked Distal Hereditary Motor Neuropathy
- Klein W. (Northwestern University, USA), ADDL-specific antibodies
- Kochanski A. (Neuromuscular Unit, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland), Genotype-phenotype correlations in CMT
- Kösler P. (Einzelhandelsfirma Kösler, Rottenburg, Germany), C57BL/6J-TgN (Thy1-APP; Thy1-PS1)
- Kuhlenbäumer G. (Institut für Experimentelle Medizin, c/o Klinik für Neurologie, Kiel, Germany), Cloning of the gene for autosomal dominant striatal degeneration. Positional cloning in dHMN and essential tremor
- Kurth I. & Hübner C.A. (Department of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, and Department of Clinical Chemistry, Friedrich-Schiller-Universität Jena, Germany), Mutations in FAM134B, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy
- Laing N. (Perth), Ferreira A. (Parijs), Wallgren-Pettersson C. (Helsinki), Guicheney P. (Parijs), Lunardi J. (France): histopathological results of muscles biopsies and DNA samples
- Lee V. (University of Pennsylvania, USA), GWA - TDP43/PGRN samples
- Lerche H. (Abt. Neurologie mit Schwerpunkt Epileptologie Zentrum für Neurologie Hertie Institut für Klinische Hirnforschung Universitätsklinikum Tübingen, Tübingen, Germany), Functional studies of ionchannels (SCN2A, GLUT1). Locus sequencing (Chr16) in Benign Familial Infantile Seizures and choreoathetosis
- Li Y. (Detroit): histopathological results of peripheral nerve biopsies and autopsy-derived tissues

Ludolph A. (University of Ulm, Germany), Localisation of genes and identification of mutated genes in a German multigenerational dominant ALS family

Maragnaore D. ((NorthShore University HealthSystem, Chicago, IL/ Mayo Clinic, Rochester, MN, USA), SNCA and survival in PD

Marti H.H. (Institute of Physiology and Pathophysiology, Faculty of Medicine, University of Heidelberg, Germany), Transgenic mouse line V1 (C57B1/6-TgN(NSEvegf)1651 hhm

McGowan E. (Mayo Foundation for Medical Education and Research, Rochester, USA), 3 BRI-Abeta40, 3 BRI-Abeta42 and 3 nontransgenic mice

Mitev V. (Department of Biochemistry, Faculty of Medicine, Medical University of Sofia, Bulgaria): Hereditary spastic paraplegia (HSP).

Murphy P. (Department of Molecular and Cellular Biochemistry, University of Kentucky, Lexington, USA) PS1 promotor-luciferase construct to test the hypothesis that leptin signaling is involved in regulating PS1 expression at the transcriptional level

Nicholson G. & Kennerson M. (The Northcott Neuroscience Laboratory, ANZAC Research Institute, Concord, Australia; the Molecular Medicine Laboratory, Concord Hospital, Concord, Australia), Genotype-phenotype correlations in CMT. Cloning of a novel X-linked dHMN gene

Oostra B. (Klinische Genetica, Erasmus MC, Nederland), Fmr1 knockout mice

Ramirez A. (Department of Neurology, University of Lübeck, Germany). Study of the pathophysiology of ATP13A2 mutations identified in PD patients

Rasic V. (Clinic of Child Neurology and Psychiatry, University of Belgrade, Belgrade, Serbia), Neuromyotonia. Genotype-phenotype correlations in CMT and HSP

Reitz C. (Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, USA) Meta analyse SORL1.

Revesz T. (Institute of Neurology, London, UK), antibodies against ataxin-7 (CM 189)

Robberecht W. (KULeuven): GluR2 sequence analysis, primary motor neuron cultures, HSP27

Rouleau G. & Rivière J-B. (The Centre of Excellence in Neuromics, CHUM Research Center Department of Medicine, University of Montreal, Montreal, Quebec, Canada), Cloning of a novel AR HSN gene

Rüb U. (Klinikum der Johann Wolfgang Göthe Universität, Frankfurt am Main, Germany), antibodies against ataxin-7 (CM 189)

Saido T. (Laboratory for Proteolytic Neuroscience RIKEN Brain Science Institute Japan) PSEN1 mutant constructs\

Sander Th. (Cologne Center for Genomics, University of Cologne, Cologne, Germany, Department of Neurology, Charité University Medicine, Humboldt University of Berlin, Berlin, Germany), GWAS in IGE

Schellenberg G. (University of Seattle, USA), MAPT H1 SNP haplotyping in PSP patients

Schenone A. (University of Genova, Italy): Experimental overexpression of PMP22 in CMT1A rat nerves via cDNA micro-arrays.

Seeman P. & Haberlova J. (DNA laboratory, Department of Child Neurology, Second School of Medicine, Charles University Prague, Prague, Czech Republic), Genotype-phenotype correlations in CMT

Senderek J. (nstitute of Cell Biology, ETH Zürich, Zürich, Switzerland), Identification of novel AR CMT loci and genes

Senderek J. (RWTH, Aachen): Identification of the FGD4 gene for CMT4H.

Shy M. & Garbren J. (Department of Neurology, Wayne State University School of Medicine, Detroit, Michigan, USA), Cloning of a novel gene for X-linked dHMN

Singh N. (Department of Human Genetics, University of Utah, Salt Lake City, USA), SCN9A in Dravet syndrome

Staufenbiel M. (Novartis Institutes of Biomedical Research Basel, Zwitterland), APP23 model

Stephani U. & Helbig I., Department of Neuropediatrics, Pediatric Epilepsy Genetics Research Group, University Medical Center Schleswig-Holstein (UKSH), Kiel, Germany), CNV analysis in IGE

Suomalainen A. (Research Program of Neurosciences, Biomedicum-Helsinki, Helsinki, Finland): PEO and Alpers Syndrome.

Szot P (Northwest Network for Mental Illness Research, Education, and Clinical Center, Veterans Administration Puget Sound Health Care System, and Department of Psychiatry and Behavioral Science, University of Washington, Seattle, USA), analyses noradrenergic system

Thomas F. (Spinal Cord Injury/Dysfunction Service, St. Louis Veterans Administration Hospital, Departments of Neurology & Psychiatry, and Molecular Microbiology & Immunology, Institute for Molecular Virology, Saint Louis University School of Medicine), Clinical and electrophysiological aspects of DI-CMTC

Topaloglu H. (Department of Pediatric Neurology, Faculty of Medicine, Hacettepe University, Ankara, Turkey), Identification of novel AR CMT loci and genes

Tournev I. (Department of Neurology, Medical University-Sofia, Bulgaria; National Genetic Laboratory, Molecular Medicine Center, Medical University-Sofia, Bulgaria), Cloning of a gene for distal myopathy. Genotype-phenotype correlations in CMT and Inherited Epilepsies

Van Deerlin V., Chen-Plotkin A.S. (Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine and Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA), Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration

van Minnen J. (Amsterdam): analysis axonal ribosomes employing IBB tissue bank.

Weis J. (Institut für Neuropathologie, Universitätsklinikum der RWTH, Pauwelsstrasse 30, 52074 Aachen, Germany), Genotype-phenotype correlations in CMT. Morphological study of CMT1B nerve biopsies

Weiss J. (RWTH, Aachen, Germany), Mutations in genes causing HSAN

Williams J. (MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff, UK). GERAD Consortium.

Windisch M. (JSW-Research Forschungslabor GmbH), plasmide DNA of neuron-specific mTUB promoter & transgenic animals

Yokes Baki M. (Haliç Üniversitesi, Moleküler Biyoloji ve Genetik Bölümü, Istanbul, Turkey). PS1 and 2 wild type constructs and vector.

Zabetian C.P. (GRECC S-182, VA Puget Sound Health Care System, Seattle, USA), haplotype analyses of the LRRK2 gene

Züchner S. (Center for Human Molecular Genomics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine; USA), Genotype-phenotype correlations in CMT and HSP. Whole exome sequencing in HSP

Züchner S. (Duke University, Durham, USA): MFN2 mutations in axonal neuropathy with optic atrophy identification of the DNM2 gene for dominant intermediary CMT.

### **3. INITIATIVES REGARDING TRANSFER OF KNOWLEDGE, ANNOUNCEMENT AND VALORISATION RESULTS**

Transfer of Knowledge and Education

- a. Master in Neurosciences (Master in Biomedical Sciences)
- b. Master in Biochemistry and Biotechnology
- c. Master after Master Biomedical Imaging
- d. Postacademic Education Laboratory Animal Sciences

Transfer of Knowledge and Announcements Results

- a. <http://www.bornbunge.be>

### **4. PAID CO-WORKERS**

De Leenheir Eveline

Degree: graduate clinical chemistry A1

Classification: ATP 5.1 (100% till 30/06/2008; 80% from 1/07/2008)

Department: IBB Biobank

Peeters Edith

Degree: graduate clinical chemistry A1

Classification: ATP 5.1 (80%)

Department: IBB Biobank

Franck Frieda

Degree: graduate clinical chemistry A1

Classification: ATP 5.1 (80% till 31/08/2008; 50% from 1/09/2008)

Department: Neurochemistry & Behaviour

Bats Ingeborg

Degree: Photography A1

Classification: ATP 5.1 (80%)

Department: Electron microscopy and IBB Biobank

In 2009: 3rd and 4th quarter

Possemiers Ilse for 60%

Degree: graduate clinical chemistry A1

Classification: ATP 5.1 (100%)

Department: Neurochemistry & Behaviour

### **5. EQUIPMENT**

N/A

## 6. SCIENTIFIC PUBLICATIONS

*a1 – papers included in ISI Web of Science*

### **2010 (+ in press, accepted, submitted papers)**

1. Aerts I, Martin JJ, Deyn PP, Van Ginneken C, Van Ostade X, Kockx M, Dua G, Slegers H. The expression of ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (E-NPP1) is correlated with astrocytic tumor grade. *Clin Neurol Neurosurg.* 2010 Dec 30. [Epub ahead of print] (I.F. 2009: 1.303; cites n/a)
2. Afawi Z, Suls A, Ekstein D, Kivity S, Neufeld MY, Oliver K, De Jonghe P, Korczy AD, Berkovic S.F.: Mild adolescent/adult onset epilepsy and paroxysmal exercise-induced dyskinesia due to GLUT1 deficiency. *Epilepsia* 51 (12): 2466-2469 (I.F. 2009: 3.733; cites: 0)
3. Almeida-Souza L, Goethals S, de Winter V, Dierick I, Gallardo R, Van Durme J, Irobi J, Gettemans J, Rousseau F, Schymkowitz J, Timmerman V, Janssens S (2010) Increased monomerization of mutant HSPB1 leads to protein hyperactivity in Charcot-Marie-Tooth neuropathy. *J Biol Chem.* 285(17):12778-86. (I.F. 2009: 5.328; cites: 0)
4. Appenzeller S, Schirmacher A, Halfter H, Bäumer S., Pendziwiat M., Timmerman V., De Jonghe P., Fekete K., Stögbauer F., Lüdemann P., Hund-Georgiadis M., Quabius E.S., Ringelstein B., Kuhlenbäumer G. (2010) Autosomal-dominant striatal degeneration is caused by a mutation in the phosphodiesterase 8B gene. *American Journal of Human Genetics* 86(1): 83-87 (I.F. 2009: 10.153; cites: 0)
5. Aretz S, Rautenstrauss B, Timmerman V (2010) Clinical utility gene card for: HMSN/HNPP HMSN types 1, 2, 3, 6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA). *Eur J Hum Genet* 18(9): 1070 (I.F. 2009: 3.564; cites: 0)
6. Aries MJH, Le Bastard N, Debruyne H, Van Buggenhout M, Nagels G, De Deyn PP, Engelborghs S (2010) Relation between frontal lobe symptoms and dementia severity across diagnostic categories. *Int J Geriatr Psychiatry*, 25(11): 1186-1195 (I.F. 2009: 1.981; cites: n/a)
7. Babiloni C, Visser PJ, Frisoni G, De Deyn PP, Bresciani L, Jelic V, Nagels G, Rodriguez G, Rossini PM, Vecchio F, Colombo D, Verhey F, Wahlund LO, Nobili F (2010) Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. *Neurobiol. Aging*, 31(10):1787-98 (IF 2009: 5.937; cites: 1)
8. Baets J, De Jonghe P (2011) Editorial: TRPV4 neuropathies: calcium channel inhibition as a therapeutic target? *Neurology* (2011) Epub: 02-Feb-2011 (I.F. 2009: 8.172; cites: n/a)
9. Baets J, Deconinck T, Goossens D, Van Den Berg P, Dahan K, Schmedding E., Santens P., Milic-Rasic V., Van Damme P., Robberecht W., De Meirleir L., Jordanova A., De Jonghe P.: Mutations in SACS cause atypical and late onset forms of ARSACS. *Neurology* 5(13):1181-1188 (I.F. 2009: 7.043; cites: 0)
10. Baillieux H, De Smet HJ, Dobbeleir A, Paquier PF, De Deyn PP, Mariën P (2010) Cognitive and affective disturbances following focal cerebellar damage in adults: A neuropsychological and SPECT study. *Cortex.*, 46(7):869-79 (I.F. 2009: 4.058; cites: 5)
11. Berciano J, Baets J, Gallardo E, Zimon M, Garcia A, López-Laso E, Combarros O, Infante J, Timmerman V, Jordanova A, De Jonghe P. Reduced penetrance in Charcot-Marie-Tooth disease type 2C caused by TRPV4 Arg269Cys mutation. *Journal of Neurology* (Accepted for Publication) (I.F. 2009: 2.903; cites: n/a)

12. Bettens K, Brouwers N, Van Miegroet H, Gil A, Engelborghs S, De Deyn PP, Vandenberghe R, Van Broeckhoven C, Sleegers K (2010a) Follow-up study of susceptibility loci for Alzheimer's disease and onset age identified by genome-wide association. *J Alzheimers Dis.* 19(4):1169-75. (I.F. 2009: 3.832; cites: 3)
13. Bettens K, Sleegers K, Van Broeckhoven C (2010b) Current status on Alzheimer disease molecular genetics: from past, to present, to future. *Hum Mol Genet.*, 19(R1):R4-R11. (I.F. 2009: 7.386; cites: 5)
14. Bogaert E, Goris A, Van Damme P., Geelen V., Lemmens R., van Es M.A., van den Bergh L., Sleegers K., Verpoorten N., Timmerman V., De Jonghe P., Van Broeckhoven C., Traynor B.J., Landers J.E., Brown Jr. R.H., Glass J.D., Al-Chalabi A., Shaw C., Birve A., Andersen P.M., Slowik A., Tomik B., Melki J., Robberecht W., Van Den Bosch L.: Polymorphisms in the GluR2 gene are not associated with amyotrophic lateral sclerosis. *Neurobiology of Aging* (2010) Epub: 19-Apr-2010 (I.F. 2009: 5.959; cites: 0)
15. Brouns R, De Vil B, Cras P, De Surgeloose D, Mariën P, De Deyn PP (2010a) Neurobiochemical Markers of Brain Damage in Cerebrospinal Fluid of Acute Ischemic Stroke Patients. *Clin Chem.* 56(3):451-458. (I.F. 2009: 6.263; cites: 2)
16. Brouns R, Eyskens F, De Boeck K, Ceuterick-de Grootte C, Van den Broeck M, Van Broeckhoven C, De Deyn PP (in press). Fabry disease in a patient with Turner syndrome. *J Inherit Metab Dis.* 2009 Apr 5. [Epub ahead of print]. (I.F. 2009: 3.598; cites: 0)
17. Brouns R, Heylen E, Willemse JL, Sheorajpanday R, DE Surgeloose D, Verkerk R, DE Deyn PP, Hendriks DF (2010b) The decrease in procarboxypeptidase U (TAFI) concentration in acute ischemic stroke correlates with stroke severity, evolution and outcome. *J Thromb Haemost.* 8(1):75-80. (I.F. 2009: 6.069; cites: 4)
18. Brouns R, Thijs V, Eyskens F, Van den Broeck M, Belachew S, Van Broeckhoven C, Redondo P, Hemelsoet D, Fumal A, Jeangette S, Verslegers W, Baker R, Hughes D, De Deyn PP; BeFaS Investigators (2010e) Belgian Fabry study: prevalence of Fabry disease in a cohort of 1000 young patients with cerebrovascular disease. *Stroke.* 41(5):863-8. (I.F. 2009: 7.041; cites: 5)
19. Brouns R, Van Hemelrijck A, Drinkenburg WH, Van Dam D, De Surgeloose D, De Deyn PP (2010c) Excitatory amino acids and monoaminergic neurotransmitters in cerebrospinal fluid of acute ischemic stroke patients. *Neurochem Int.*, 56(8):865-70. (I.F. 2009: 3.541; cites: 1)
20. Brouns R, Verkerk R, Aerts T, De Surgeloose D, Wauters A, Scharpé S, De Deyn PP (2010d) The Role of Tryptophan Catabolism along the Kynurenine Pathway in Acute Ischemic Stroke. *Neurochem Res.* 35(9):1315-1322. (I.F. 2009: 2.722; cites: 0)
21. Brouns R, Wauters A, De Surgeloose D, Mariën P, De Deyn PP. Biochemical markers for blood-brain barrier dysfunction in acute ischemic stroke correlate with evolution and outcome. *Eur. Neurol.* 65(1):23-31 (I.F. 2009: 1.494; cites: 0)
22. Brouns R, Wauters A, Van De Vijver G, De Surgeloose D, Sheorajpanday R, De Deyn PP (2010f) Decrease in uric acid in acute ischemic stroke correlates with stroke severity, evolution and outcome. *Clin Chem Lab Med.* 48(3):383-90. (I.F. 2009: 1.886; cites: 1)
23. Brouwers N, Bettens K, Gijssels I, Engelborghs S, Pickut BA, Van Miegroet H, Montoya AG, Mattheijssens M, Peeters K, De Deyn PP, Cruts M, Sleegers K, Van Broeckhoven C (2010) Contribution of TARDBP to Alzheimer's disease genetic etiology. *J Alzheimers Dis.*, 21(2):423-30. (I.F. 2009: 3.832; cites: 0)
24. Brouwers N, Van Cauwenberghe C, Engelborghs S, Lambert J-C, Bettens K, Le Bastard N, Pasquier F, Gil Montoya A, Peeters K, Mattheijssens M, Vandenberghe R, De Deyn P, Cruts M, Amouyel P, Sleegers K, Van Broeckhoven C. Alzheimer risk associated with a copy

number variation in the complement receptor 1 increasing C3b/C4b binding sites. *Molecular Psychiatry* (Accepted for Publication) (I.F. 2009: 15.049; cites: n/a)

25. Bulent K, Jaeken J, Van Hove J, Lagae L, Löfgren A, Everman,D., Jayakar,P., Naini,A., Wierenga,K.J., Van Goethem,G., Copeland,W.C., Dimauro,S. (2010) A novel PolG gene mutation in four children with Alpers-like hepatocerebral syndromes. *Archives of Neurology* 67(2): 239-244 (I.F.2009: 5.874; cites: 0)
26. Burgunder J-M, Finsterer J, Szolnoki Z, Fontaine B, Baets,J., Van Broeckhoven,C., Di Donato,S., De Jonghe,P., Lynch,T., Mariotti,C., Schöls,L., Spinazzola,A., Tabrizi,S.J., Tallaksen,C., Zeviani,M., Harbo,H.F., Gasser,T. (2010) EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. *European Journal of Neurology* 17(5): 641-648 (I.F. 2009: 2.732; cites: 2)
27. Burgunder J-M, Schöls L, Baets J, Andersen PM, Gasser,T., Szolnoki,Z., Fontaine,B., Van Broeckhoven,C., Di Donato,S., De Jonghe,P., Lynch,A., Mariotti,C., Spinazzola,A., Tabrizi,S.J., Tallaksen,C., Zeviani,M., Harbo,H.F., Finsterer,J. (in press) EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *European Journal of Neurology* Epub: 25-Mar-2010 (I.F. 2009: 2.732; cites: 0)
28. Buysse K, Vergult S, Mussche S, Ceuterick-de Groote C, Speleman F, Menten B, Lissens W, Van Coster R (in press) Giant axonal neuropathy caused by compound heterozygosity for a maternally inherited microdeletion and a paternal mutation within the GAN gene. *European Journal of Human Genetics. Am J Med Genet A.* 152A(11):2802-4. (I.F. 2009: 2.404; cites: 0)
29. Capell A , Liebscher S, Fellerer,K., Brouwers,N., Willem,M., Lammich,S., Gijssels,I., Bittner,R.A., Carlson,A.M., Dormann,D., Slegers,K., Cruts,M., Herms,J, Van Broeckhoven,C., Haass,C.: Rescue of progranulin haploinsufficiency by alkalizing reagents. *Journal of Neuroscience* (Submitted) (I.F. 2009: 7.178; cites: n/a)
30. Chen C, Engelborghs S, Dewaele S, Le Bastard N, Martin J-J, Vanhooren V, Libert C, De Deyn PP (2010) Altered serum glycomics in Alzheimer's disease: a potential blood biomarker? *Rejuvenation Res.*, 13(4):439-44. (I.F. 2009: 4.138; cites: 1)
31. Chen-Plotkin AS, Martinez-Lage M, Sleiman,P.M.A., Hu,W., Greene,R., McCarty Wood,E., Bing,S., Weiner,M.F., White III,C.L., Brooks,W., Halliday,G.M., Gearing,M., Beach,T.G., Graff-Radford,N.R., Dickson,D.W., Rademakers,R., Boeve,B.F., Pickering-Brown,Stuart M., Snowden,J., Van Swieten,J.C., Seelaar,H., Murrell,J.R., Ghetti,B., Spina,S., Grafman,J., Kaye,J.A., Woltjer,R.L., Mesulam,M., Iladó,A., Miller,B.L., Alzualde,A., Moreno,F., Rohrer,J.D., Mackenzie,I.R.A., Hamilton,R.L., Cruts,M., Engelborghs,S., De Deyn,P.P., Van Broeckhoven,C., Bird,T.D., Cairns,N.J., Goate,A., Frosch,M.P., Riederer,P.F., Bogdanovic,N., Lee,V.M-Y., Trojanowski,J.Q., Van Deerlin,V.M.: Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Archives of Neurology* (Accepted for Publication) (I.F. 2009: 5.874; cites: n/a)
32. Claeys K, Sozanska M, Martin J-J, Lacene E, Vignaud L, Stockholm D, Laforêt P, Eymard B, Kichler A, Scherman D, Voit T, Israeli D (2010) DNAJB2 expression in normal and diseased human and mouse skeletal muscle. *Am. J. Pathol.*, 176(6):2901-2910. (I.F. 2009: 5.673; cites: 2)
33. Craenenbroeck AV, Gebruers M, Martin JJ, Cras P (in press) Hallervorden-Spatz disease: Historical case presentation in the spotlight of nosological evolution. *Mov Disord.* 25 (15) :2486-2492 (I.F. 2009: 4.014; cites: 0)
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*a4 – papers not included in a1, a2 or a3*

*b1 – author or co-author of books*

*b2 – chapters in books*

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*B3 – Edited Books*

De Deyn P.P., Van Dam D. (Eds) Animal models of Dementia. Neuromethods series; Humana Press / Springer. December 2010.

*c1 – papers in Proceedings of Scientific Meetings*

*c2 – Dissertations, theses, internal reports, abstracts of presentations/posters at congresses*

### **Dissertations Professional Bachelors:**

*Brys Jolien*

Mutatiescreening van het microtubuli geassocieerde proteïne tau (MAPT) en progranuline gen (PGRN) in Alzheimer en frontotemporale dementie patiënten.

Promotoren: C. Van Broeckhoven, Co-promotor: J. van der Zee

*Coolman Sofie*

Gedragmatige validatie van het transgene APP23-muismodel voor de ziekte van Alzheimer.

Promotoren: P.P. De Deyn, Co-promotor: D. Van Dam

*De Ren Jan*

Onderzoek naar genetische factoren voor frontotemporale kwabdegeneratie aan de hand van mutatie-analyse van functionele kandidaatgenen

Promotor: M. Cruts

*De Ryck Jolien*

DNA diagnostiek voor de ziekte van Charcot-Marie-Tooth type 1: van klinische diagnose tot mutatie.

Promotoren: C. Van Broeckhoven

*Eysackers Nathalie*

Identificatie en karakterisatie van mutaties in genen voor Alzheimer dementie

Promotor: K. Sleegers

*Goudman Tom*

Analyse van biogene amines uit hersenweefsel door middel van HPLC met elektrochemische detectie.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

*Peeters Kristien*

Fijnmappen van de locus voor de ziekte van Charcot-Marie-Tooth type 2G.

Promotoren: V. Timmerman

*Roberts Josephine*

Mutatieanalyse van PRX bij vroeg beginnende vormen van de ziekte van Charcot-Marie-Tooth

Promotor: A. Jordanova

*Quisenaerts Iris*

Evaluatie van QC-Plex. Optimalisatie van Progranuline-MAQ

Promotor: D. Goossens

*Verstraeten Aline*

Mutatieanalyse van kandidaatgenen voor 'Lewy Body' hersenziekte gekoppeld aan chromosoom 2.

Promotoren: J. Theuns

*Waumans Yannick*

Moleculaire karakterisatie van dominant intermediaire vorm van de ziekte van Charcot-Marie-Tooth type D: op zoek naar een gemeenschappelijke voorouder.

Promotoren: A. Jordanova

*Lotte Van Hoeck*

Mutatieanalyse van het optineurine gen in amyotrofische laterale sclerose patiënten en van het microtubule-associated proteïne gen in frontaalkwabdementie patiënten.

Promotoren: KdG – IWT, Campus Hoboken & T. Van Langenhove

*Gregori Vingerhoets*

Identificatie en karakterisatie van mutaties in genen voor Alzheimer dementie

Promotoren: KdG – IWT, Campus Hoboken & N. Brouwers

*Tinne Schellekens*

Opsporen van het genetisch defect in een nieuwe locus voor frontotemporale kwab degeneratie en amyotrofe laterale sclerose.

Promotor: Plantijn Hogeschool & I. Gijselink

## **Master's theses**

*Busseniers Jonas*

Investigation of apoptosis in progranulin knockdown cell models

Promotoren: C. Van Broeckhoven & G. Kleinberger

*De Clerck Ben*

Optimalisatie van de Proximity Ligation Assay (PLA) methode als uitleessysteem voor TLR activering

Promotor: S. Janssens

*Dondelinger Yves*

Zoektocht naar nieuwe pathomechanismen voor CMT-geassocieerde HSPB1 en HSPB8 mutanten

Promotor: S. Janssens

*Fredrickx Evelien*

Characterisation of the Mtmr2/Fig4 double knockout mouse model

Promotoren: Vincent Timmerman & Alessandra Bolino

*Hardies Katia*

Moleculair genetische analyse van X-gebonden en recessieve epilepsieën

Promotor: Peter De Jonghe

*Holmgren Philip*

Moleculair genetische analyse van vroegtijdige epilepsieën

Promotoren: A. Jordanova & P. De Jonghe

*Janssens Jonathan*

Biochemische en neuropathologische karakterisering van een nieuw human TDP-43 overexpressing muismodel

Promotor: S. Kumar-Singh

*Janssen Leen*

Evaluatie van ziektemodulerende effecten van overmatige ethanolconsumptie in het transgene APP23 muismodel voor de ziekte van Alzheimer.  
Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

*Peeters Kristien*

Genetische koppelingsanalyse en identificatie van nieuwe FLNC mutaties in families met distale myopathie

Promotoren: Albena Jordanova & Peter De Jonghe

*Philtjens Stéphanie*

Pathway-based genetic analyses to detect novel genes associated with frontotemporal lobar degeneration

Promotoren: P. Stinissen & M. Cruts

*Sales Carbonell Carola*

Behavioural phenotyping of a transgenic mouse model of Alzheimer's disease: sleep and circadian rhythms.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

*Slaets Sylvia*

Karakteristieken van de ziekte van Alzheimer in neuropathologisch geconfirmeerde dementie met Lewy bodies

Promotoren: P.P. De Deyn; S. Engelborghs

*Smits Veerle*

Expressie van Nod-like receptors in het perifere en het centrale zenuwstelsel

Promotor: S. Janssens

*Van Avondt Kristof*

De rol van de aangeboren immuunrespons in acute perifere neuropathieën.

Promotor: S. Janssens

*Van Cauwenberghe Caroline*

Inleiding tot immunocytochemie en western blotting technieken voor FTLD

Promotor: S. Kumar-Singh

*Vanbeginne Stéphanie*

Characterization and identification of granulin missense mutations in patients with Alzheimer dementia

Promotoren: K. Sleegers & N. Brouwers

*Van Hoorenbeeck Kim en Yperzeele Laetitia*

Het klinisch spectrum van erfelijke polyneuropathieën.

Promotor: P. De Jonghe

*Van Langenhove Tim*

Genetic analysis of the valosin containing protein gene in Belgian frontotemporal lobar degeneration patients and clinico-pathological characterization of mutation carriers.

Promotor: C. Van Broeckhoven, Co-promotor: J. van der Zee

*Van Rossom Sofie*

Neurochemische correlaten van mannelijk aggressief gedrag in het transgene APP23 muismodel voor de ziekte van Alzheimer.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

*Verelst Quinten*

Mutatie-analyse van genen voor CMT: GDAP1 en SETX.

Promotor: I. Dierick

*Verelst Quinten*

Opsporen van het genetisch defect in een locus voor frontotemporale kwabdegeneratie

Promotoren: Marc Cruts & Ilse Gijselincx

*Vermeiren Yannick*

Gedragsscorrelaten van melatonine in serum bij dementie

Promotoren: P.P. De Deyn; S. Engelborghs

*Vervoort Jasha*

Effect van DI-CMTC mutaties in YARS op celgroei en eiwitinteracties

Promotoren: A. Jordanova & V. Timmerman

## Abstracts

### 2010

1. Baets,J., Zimon,M., De Vriendt,E., Deconinck,T, Spiegel,R., Parman,Y., Ceulemans,B., Vilain,C., Pou-Serradell,A., Bernert,G., Dinopoulos,A., Auer-Grumbach,M., Sallinen,S.-L., Fabrizi,G.-M., Pauly,F., Van den Bergh,P., Battaloglu,E., Madrid,R., Timmerman,V., Jordanova,A., De Jonghe,P.: Genetic spectrum of hereditary peripheral neuropathies with onset in the first year of life Peripheral Nerve Society Satellite Meeting, Sydney, Australia, July 5-7 : (2010)
2. Bettens,K., Brouwers,N., Gil,A., Van Miegroet,H., Engelborghs,S., De Deyn,P.P., Vandenberghe,R., Sleegers,K., Van Broeckhoven,C.: In-depth molecular genetic analysis of CLU in Alzheimer's disease. Alzheimer's Association International Conference on Alzheimer's Disease 2010 (ICAD 2010), July 10-15 : (2010)
3. Brouwers,N., Van Cauwenberghe,C., Bettens,K., Engelborghs,S., Van Miegroet,H., Gil Montoya,A., Peeters,K., Mattheijssens,M., Vandenberghe,R., De Deyn,P.P., Cruts,M., Sleegers,K., Van Broeckhoven,C.: Complement receptor 1 variability is associated with increased risk for Alzheimer's disease in an extended Flemish-Belgian population. Human Genome Meeting - HGM 2010, Montpellier, France, May 18-21 : (2010)
4. Crosiers, D., Meeus, B., Nuytemans, K., Van Broeckhoven, C., Theuns, J., and Cras, P., Self-reported non-motor symptoms in a cohort of 139 Parkinson's disease patients. Movement Disorders 25 (S3): S655 (2010)
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6. Crosiers,D., Ceulemans,B., Meeus,B., Nuytemans,K., Corsmit,E., Van den Broeck,M., Pals,P., Van Broeckhoven,C., Cras,P., Theuns,J.: Juvenile parkinsonism and dementia: a novel ATP13A2 frameshift mutation. VIB Seminar 2010, Blankenberge, Belgium, March 4 : P80 (2010)

7. de Almeida Souza,L., Goethals,S., De Winter,V., Dierick,I., Gallardo,E., Van Durme,J., Irobi,J., Gettemans,J., Rousseau,F., Schymkowitz,J., Timmerman,V., Janssens,S.: Increased monomerization of mutant HSPB1 leads to protein hyperactivity in CMT neuropathy. VIB Seminar 2010, Blankenberge, Belgium, March 4 : Oral Talk 13 (2010)
8. De Deyn P.P. Treatment of behavioural and psychological symptoms of dementia: which strategies? The 8th Summer School of Neuroscience: "Schizophrenia and other psychosis: what can clinics learn from basic sciences?" Abstract book p. 100 (2010)
9. Garbern,J.Y., Nicholson,G.A., Kowalski,B., Chu,S., Takata,R., Speck-Martins,C., Baets,J., Almeida-Souza,L., Fischer,D., Timmerman,V., Kaler,S.G., Bird,T.D., De Jonghe,P., Lewis,R.A., Feely,S.M.E., Shy,M.E., Ferguson,T., Scherer,S.S., Kennerson,M.L.: Upper as well as lower motor neuronal phenotypes associated with mutation affecting the copper-transporter ATP7A Peripheral Nerve Society Satellite Meeting, Sydney, Australia, July 5-7 : (2010)
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13. Kleinberger,G., Wils,H., Ponsaerts,P., Joris,G., Timmermans,J-P., Van Broeckhoven,C., Kumar-Singh,S.: Increased caspase activation and decreased TDP-43 solubility in progranulin knockout cortical cultures. VIB Seminar 2010, Blankenberge, Belgium, March 4 : P69 (2010)
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88. Nuytemans,K., Brouwers,N., Meeus,B., Pals,P., Engelborghs,S., Pickut,B., Bogaerts,V., Corsmit,E., Van den Broeck,M., De Deyn,P., Theuns,J., Van Broeckhoven,C.: Genetic characterization of a Belgian Parkinson's disease population: contribution of copy number variations and simple mutations. Genetic Epidemiology of Parkinson's Disease 4th Annual Meeting (GEO-PD), Trondheim, Norway, June 9-11 : No6 (2008)
89. Pereson,S., Vandewoestyne,M., Van Broeck,B., Cuijt,I., Peeters,E., Ceuterick,C., McGowan,E., Jucker,M., Van Broeckhoven,C., Deforce,D., Kumar-Singh,S.: Differential expression analysis to identify vascular abnormalities in Alzheimer disease mouse models. Intracellular traffic and neurodegenerative disorders, Paris, France, April 28 : (2008)
90. Slegers,K., Meeus,B., Brouwers,N., Bettens,K., Nyberg,L., Adolfsson,A., Nilsson,L-G., Van Broeckhoven,C.: Genetic variability in progranulin and episodic memory. Biology of Cognition Annual Meeting, Chantilly, France, October 16-18 : 40 (2008)
91. Suls,A., Dedeken,P., Goffin,K., Van Esch,H., Dupont,P., Cassiman,D., Kempfle,J., Wuttke,T.V., Weber,Y., Lerche,H., Afawi,Z., Korczyn,A.D., Berkovic,S.F., Vandenberghe,W., Ekstein,D., Kivity,S., Ryvlin,P., Claes,L., Deprez,L., Maljevic,S., Vargas,A., Van Dyck,T., Goossens,D., Del-Favero,J., Van Laere,K., De Jonghe,P., Van Paesschen,W.: Paroxysmal exercise-induced dyskinesia and epilepsy: delineation of the genetic defect and functional imaging. VIB Seminar 2008, Blankenberge, Belgium, March 6 : T16 (2008)
92. Van Broeckhoven,C.: Progranulin and neurodegeneration: A new pathway to treatment? 7th Research Day, University of Maastricht, April 11 : 13 (2008)

*c3 – octrooiën*

## 7. DOCTORATEN

### Finished PhD projects

*Van Broeck Bianca (21/04/2008)*

Loss-of-function mechanisms and intraneuronal A $\beta$  in cellular and mouse models of Alzheimer disease.

Promotors: S. Kumar-Singh, C. Van Broeckhoven

*Gijselinck Ilse (8/09/2008)*

Molecular genomics of tau-negative, ubiquitin-positive frontotemporal lobar degeneration.  
Promotors: C. Van Broeckhoven, M. Cruts

*Brouwers Nathalie (15/12/2008)*

Molecular genetic analysis of Alzheimer disease  
Promotor: C. Van Broeckhoven

*Pirici Daniel (20/03/2009)*

Molecular mechanisms of extracellular and intracellular proteinopathy in Alzheimer's disease and frontotemporal dementia  
Promotors: S. Kumar-Singh, C. Van Broeckhoven

*Suls Arvid (18/05/2009)*

Novel insights and broadening of the phenotypic spectrum for epilepsy caused by mutations in the SCN1A and SLC2A1 genes  
Promotor: P. De Jonge

*Nuytemans Karen (14/12/2009)*

Identification of novel genetic factors for Parkinson's disease  
Promotor: C. Van Broeckhoven, co-promotor: Jessie Theuns

*Brouns Raf (2/02/2010)*

The predictive value of biochemical parameters among wich amino acids and amino acid analogues in acute ischemic stroke  
Promotors: P. P. De Deyn, B. Marescau

*Bettens Karolien (21/10/2010)*

Molecular genetic analysis of Alzheimer dementia  
Promotors: C. Van Broeckhoven & K. Sleegers

*Wils Hans (7/12/ 2010)*

Elucidation of the role of progranulin (PGRN) in frontotemporal dementia (FTD) with mouse models  
Promotors: C. Van Broeckhoven & S. Kumar-Singh

*Rotthier Annelies (8/12/ 2010)*

Molecular genetic analysis of genes for inherited axonal peripheral neuropathies  
Promotors: V. Timmerman

*Gonçalves Ricardo (21/12/ 2010)*

Molecular Genetics and Biology of Intermediate Charcot-Marie-Tooth neuropathy  
Promotors: V. Timmerman & A. Jordanova

*Sheorajpanday Rishi (23/11/2010)*

Additional value of quantitative EEG in ischemic CVA.  
Promotor: P.P. De Deyn

*Gebruers Nick (27/01/2011)*

Secondary edema in patients with stroke: actigraphic and volumetric evaluation  
Promotor: P.P. De Deyn; Co-promotors: S. Engelborghs and S. Truijen

## Ongoing PhD projects

### *Baets Jonathan*

Clinical, electrophysiological and molecular genetic characterization of HMSN type II and intermediate type of CMT

Promotor: P. De Jonghe

### *Crosiers David*

Clinical and genetic epidemiology of Parkinson's disease: focus on disease progression and non-motor symptoms

Promotor: P. Cras, Co-promotor: C. Van Broeckhoven

### *Geerts Elly*

Sleep and circadian rhythm disturbances in Alzheimer's disease: the effect of pharmacological and non-pharmacological manipulations in preclinical and clinical settings.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

### *Janssens Jonathan*

Characterization of new mice models for frontal lobe degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)

Promotor: C. Van Broeckhoven

### *Janssens Katrien*

Functional implications of RAB7 mutations in the pathogenesis of an ulcero-mutilating neuropathy

Promotor: V. Timmerman

### *Janssen Leen*

Oplosbare amyloïd-beta oligomeren en cell-cycle events in het APP23-muismodel: waar, wanneer, hun verband met elkaar en hun rol in de pathologie van de ziekte van Alzheimer.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

### *Kleinberger Gernot*

Elucidation of the role of progranulin in frontotemporal dementia

Promotors: C. Van Broeckhoven, S. Kumar-Singh

### *Holmgren Anne*

Molecular biological research of HSPB8 mutations in relation to inherited motorneuron diseases'

Promotor: V. Timmerman, Co-promotor: J. Irobi

### *Holmgren Philip*

Molecular genetic analysis of idiopathic epilepsies: gene identification through array Comparative Genomic Hybridization (aCGH)

Promotors: P. De Jonghe & A. Jordanova

### *Le Bastard Nathalie*

Characterization and validation of biological markers in dementia and mild cognitive impairment.

Promotor: P.P. De Deyn; Co-promotor: S. Engelborghs

### *Meeus Bram*

Identification and characterization of new causal genes and risk factors for 'Lewy body' brain diseases

Promotors: C. Van Broeckhoven, J. Theuns

*Pereson Sandra*

Mechanisms of dense plaque formation in Alzheimer's disease

Promotors: C. Van Broeckhoven, S. Kumar-Singh

*Philtjens Stéphanie*

New causal genes and risk factors for FTL D

Promotor: C. Van Broeckhoven, M. Cruts

*Van Cauwenberghe Caroline*

Neuropathological image analysis in Alzheimer's disease (AD) patients and in AD mouse models treated with anti-amyloidotic and vasogenic compounds

Promotors: C. Van Broeckhoven, K. Sleegers

*Van der Mussele Stefan*

Karakterisatie van gedrag bij Mild Cognitive Impairment (MCI)

Promotors: P.P. De Deyn, S. Engelborghs

*Van Dijck Annemie*

Massaspectrometrische en functionele analyse van het neuropeptidoom in transgene muismodellen voor de ziekte van Alzheimer.

Promotor: P.P. De Deyn; Co-promotor: D. Van Dam

*Van Langenhove Tim*

Molecular genetic research towards the complex genetics of frontotemporal lobe dementia

Promotor: C. Van Broeckhoven

*Vermeiren Yannick*

Neurochemische karakterisatie van gedragsstoornissen bij dementie – Neurochemical characterization of behavioral disturbances in dementia.

Promotors: P.P. De Deyn; S. Engelborghs

*Verstraeten Aline*

Identification and characterization of novel causal genes for Lewy Body disorders using next-generation sequencing

Promotors: C. Van Broeckhoven, J. Theuns

*Wostyn Peter*

The role of reduced cerebrospinal fluid pressure in the pathogenesis of glaucoma in patients with Alzheimer's disease

Promotors: P.P. De Deyn, K. Oudenaert

*Ydens Elke*

Negatieve regulatie van de aangeboren immuunrespons in de perifere zenuw', 'Negative regulation of congenital immune respons in peripheral nerves

Promotor: V. Timmerman

*Zimon Magdalena*

Large scale genetic approach for the molecular characterization of autosomal-recessive Charcot-Marie-Tooth disease

Promotors: A. Jordanova, P. De Jonghe