



Network of Centres of Excellence in Neurodegeneration (COEN)

Industry Workshop

Friday 29th November 2013
BIS Conference Centre, London, SW1H 0ET

Meeting note

1. Background

COEN is an international initiative launched in 2010 involving national research funders in the UK, Canada, Germany, Flanders, Ireland, Italy, Slovak Republic and Spain¹, which links established Centres of Excellence to undertake collaborative neurodegeneration research. The aim of the initiative is to stimulate innovative research into new mechanistic approaches and therapeutics between some of the best laboratories working in this area in Europe and Canada. A long term goal of COEN is to provide a mechanism for industry to link to these Centres of Excellence to develop novel and effective industry-academic partnerships in pre-competitive research.

As a first step to engagement with industry a one day workshop was held on 29th November 2013 involving over 40 participants drawn from the COEN executive, researchers from the Centres of Excellence in the 8 partner countries, and representatives from the biopharma and diagnostics sector. The meeting agenda and list of delegates can be found at [Annexes 1 & 2](#) respectively.

The central aims of the workshop were:

- to showcase research funded under COEN² and raise awareness of the potential of COEN;
- explore what COEN can do for industry in support of academia and industry's joint aims of developing and testing new therapeutic approaches in neurodegeneration;
- scope the opportunities for connecting the well-resourced and cutting edge science available through the network of COEN labs with industry R&D; and
- inform the future development of the COEN strategy in a way that is complementary to the needs of industry.

2. Note of meeting

Welcome and Introduction to COEN

The meeting was opened by Professor Hugh Perry, chair of the COEN Oversight Group³, who welcomed participants and explained the key aims of the day. Dr Rob Buckle, MRC, then presented a background to the initiative and overview of the activities of COEN to date.

¹ Canada: Canadian Institutes of Health Research (CIHR); Flanders: Flanders Institute of Biotechnology (VIB); Germany: Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE); Ireland: Health Research Board (HRB), Ireland / Science Foundation Ireland (SFI); Italy: Ministero della Salute (MDS, Italy); Slovak Republic: Ministry of Ministry of Education, Science, Research and Sport of the Slovak Republic (MESRS); Spain: The Instituto de Salud Carlos III; UK: Medical Research Council (MRC)

² Phase I projects <http://www.coen.org/news/details/news/funding-international-cooperations-between-centres-of-excellence-in-neurodegenerative-disease-resea.html>

Phase II projects <http://www.coen.org/news/details/news/funding-international-cooperations-between-centres-of-excellence-in-neurodegenerative-disease-resea-3.html>

³ <http://www.coen.org/governance/oversight-group-members.html>

Project presentations

Representatives of COEN funded projects provided brief presentations followed by questions. Phase I projects focused on the aims, progress, key deliverables and future directions of the research, while the recently funded Phase II projects provided a synopsis of the aims of the project and progress to date. Professor Perry chaired the session.

Phase I Speakers and projects

- Joanna Wardlaw (Edinburgh UK) *Standards for determining the vascular contribution to neurodegeneration,*
- Christine Van Broeckhoven (VIB, Flanders) *Integrated approach to identify novel genes for frontotemporal lobar degeneration,*
- Donato Di Monte (Bonn, Germany) *Mitochondrial dysfunction and susceptibility to Parkinson's disease: New models of pathogenetic interactions*
- Michael Rowan (Trinity College Dublin) *Early synaptic plasticity and network dysfunction in transgenic (tg) rat models of Alzheimer's disease (AD)*
- Walter Maetzler (Tubingen, Germany) *Immune subtype in Parkinson disease*
- Daniele Bano (Bonn, Germany) *C. elegans models of mitochondrial deficiency in the nervous system*
- David Rubinsztein (Cambridge, UK) *Identification of generic suppressors of proteinopathies*
- Martin Rossor (University College London, UK) *The GENetic Frontotemporal Dementia Initiative (GENFI): a new multi-centre platform for the study of frontotemporal lobar degeneration*

Phase II Speakers and projects

- Fabio Blandini (Pavia, Italy) *Targeting glucocerebrosidase for disease-modifying treatments in Parkinson's disease*
- Antonio Cuadrado (Madrid, Spain) *WNT signaling: biomarker and target evaluation in Alzheimer's disease*
- Danica Stanimirovic (Ottawa, Canada) *Mechanisms of amyloid- β clearance in models of vascular cognitive impairment and mixed dementia*
- Jochen Prehn (Royal College of Surgeons, Ireland) *microRNA as novel therapeutic targets and disease biomarkers in Alzheimer's Disease, Frontotemporal dementia and Amyotrophic lateral sclerosis (NEURO-MIR)*
- Josè Luis Lanciego (Navarra, Spain) *In vivo neuronal cell reprogramming for a new regenerative approach in Parkinson's disease*

Brief details of the COEN Phase I & II funding calls, the research abstracts and key outputs of the projects presented can be found at [Annexes 3 & 4](#)

Q&A: COEN Process and Delivery

Dr Buckle gave a brief presentation on COEN governance and operation. This included a summary of how the cross-border funding process is implemented, and a description of the COEN Oversight Group and Secretariat who have responsibility for COEN strategy and the running of funding calls.

Breakout groups

Participants formed three groups to discuss the current needs of industry and how academic partnerships might be used to address challenges and opportunities in neurodegeneration research. The groups were chaired by COEN Oversight Group members Professor Adriana Maggi, Professor Pierluigi Nicotera, and Professor Yves Joannette. Each group included industry representatives who began the session by providing a perspective on pharmaceutical research needs. This introduction was provided by Dr Mike O'Neill (Lilly), Dr Derek Hill (IXICO), and Dr Paul Wren (GSK). Key points of discussion were then considered in the plenary session.

Each group considered the following questions:

- What are the current needs of industry and how can they be addressed through academic partnerships?
- Are there any perceived barriers to collaboration?
- How can COEN and existing COEN consortia address the needs identified?
- What are the key opportunities and potential routes for delivery?

Plenary Session

Neurodegeneration is a high risk area for industry investment given the incomplete understanding of disease mechanisms, the lack of robust diagnostic procedures, and the expense of undertaking lengthy clinical studies. Barriers to progress include the varied aetiology, the difficulties of studying preclinical phases and monitoring disease progression, which when coupled to previous failures in the translation of promising studies from animal models means that a high threshold of evidence from basic and preclinical studies is needed prior to industry commitment to a "target". Industry currently has limited resource for discovery research compared to translation and therefore partnerships with academia in this space could make a real impact in identifying new targets and moving promising areas forward.

The mechanism of industry-academia interaction will be important for productive partnerships. Different areas of industry have different needs and therefore a 'one size fits all' model of industry engagement will not be appropriate. Flexibility, understanding and confidence are likely to prove more effective than formal mechanisms, and underpinning this is a need to improve the flow of information between the two sectors such that research opportunities can be identified.

Dialogue and interactions must be bilateral. While academia can provide a pipeline of discovery research for translation and new approaches to help define and stratify human subjects for experimental medicine, the opening-up of industry data from clinical studies will be equally important to enable reverse translation to stimulate further discovery. Furthermore, learning what pathways or compounds have or haven't proved successful in terms of early drug development can equally provide information on potential mechanisms of neurodegeneration and guide academic research strategies.

Differences in research culture between academia and industry and the establishment of trust were also considered significant barriers to progress. Shared fellows and students may offer a productive route to help to build relationships and facilitate the exchange of ideas and expertise, in addition to developing a cadre of next generation researchers able to operate comfortably within both industry and academic research environments.

Fundamental to establishing such relationships will be a more complete understanding of the constraints and drivers of both academic and industry research. Issues highlighted were the levels of flexibility and focus within projects regarding timelines and the approach to go/no go decision points, the importance and effect of IP on development and exploitation of findings, the

optimal time for research to be communicated for pick up by industry, and regulatory perspectives.

In terms of enabling mechanisms that might foster productive academic-industry interaction, it was agreed that access to research tools and assets was of mutual benefit. For example, a quicker release and more flexible use of tool compounds to stimulate blue skies research would be an important facilitator for academic research. Industry representatives acknowledged that there are issues in providing access to such collections which have yet to be resolved, but that they were working with funders and other stakeholders to facilitate this. In parallel, it was recognised that academic groups could provide access to well phenotyped and stratified cohorts to provide subgroups to explore novel therapies, as well as to human tissue samples. Furthermore academic centres of excellence were well placed to develop novel assays and methodologies and promote the harmonisation of approaches in support of larger, cross-site studies with increased statistical power.

It was agreed that a shift in the funder and academic mind-set towards the support of innovation and high risk / high pay off studies would be key to generating game changing ideas, and in this respect the focus of the last (phase 2) COEN call was welcomed. The Pathfinder concept of supporting the generation of innovative yet robust pilot data on mechanism and target validation should help de-risk new pathways for industry engagement, and offers the potential to promote industry-academic interaction through providing a fast and agile mechanism to support collaborations able to address targeted research questions. The provision of future networking opportunities will be vital to establish and maintain the information flow to facilitate this. For example, while the current COEN projects are still at very early stages, continued dialogue should help ensure projects can be picked up at the right time as opportunities emerge.

Next Steps

A number of potential “next steps” to promote partnerships were identified. Relationship building and information flow were considered the most important aspects at this stage, and attendees unanimously supported the idea that future events should be hosted to provide updates on COEN project outputs or address areas of mutual benefit through more focused and targeted workshops. It was further recognised that COEN has the potential to act as a central resource and point of coordination through providing a portal to tools and other resources on its website, while it could also help promote understanding of differing research cultures through sponsored laboratory exchanges between students and fellows in academia and industry.

Annexes

1. Meeting Agenda
2. List of Attendees
3. COEN Phase 1 – call and project details
4. COEN phase 2 – call and project details

Network of Centres of Excellence in Neurodegeneration (COEN) Industry Workshop

Friday 29th November 10.00 – 17.00
BIS Conference Centre, 1 Victoria Street, London, SW1H 0ET

AGENDA

10.30 – 10.40 Welcome and Introduction to COEN – Chair Hugh Perry + Rob Buckle

10.40 – 11.45 **Phase I project presentations** – Chair Hugh Perry

Joanna Wardlaw (Edinburgh UK)
Standards for determining the vascular contribution to neurodegeneration - Joanna Wardlaw (MRC), Martin Dichgans (DZNE), Dr Eric Smith (CIHR)

Christine Van Broeckhoven (VIB, Flanders)
Integrated approach to identify novel genes for frontotemporal lobar degeneration - Marc Cruts (VIB), Christine Van Broeckhoven (VIB), Christian Haass (DZNE), Dieter Edbauer (DZNE)

Donato Di Monte (Bonn, Germany)
Mitochondrial dysfunction and susceptibility to Parkinson's disease: New models of pathogenetic interactions - Donato A. Di Monte (DZNE), David S. Park (CIHR), Fabio Blandini (MDS), Anthony H.V. Schapira (MRC)

Michael Rowan (Trinity College Dublin)
Early synaptic plasticity and network dysfunction in transgenic (tg) rat models of Alzheimer's disease (AD) - Michael Rowan (HRB/SFI), Claudio Cuello (CIHR), Martin Fuhrmann (DZNE), Michel Goedert (MRC) and Stefan Remy (DZNE)

11:45 – 12.10 **Tea and Coffee**

12.10 – 13.15 **Phase I project presentations**

Walter Maetzler (Tubingen, Germany)
Immune subtype in Parkinson disease - Thomas Gasser (DZNE), Antonio P. Strafella (CIHR)

Daniele Bano (Bonn, Germany)
C. elegans models of mitochondrial deficiency in the nervous system - Daniele Bano (DZNE), Siegfried Hekimi (CIHR), Mario de Bono (MRC)

David Rubinsztein (Cambridge, UK)
Identification of generic suppressors of proteinopathies - David Rubinsztein (MRC), Joerg Gsponer (CIHR)

Martin Rossor (University College London, UK)
The GENetic Frontotemporal Dementia Initiative (GENFI): a new multi-centre platform for the study of frontotemporal lobar degeneration - Martin Rossor (MRC), Giovanni B. Frisoni (MDS), Mario Masellis (CIHR)

13:15 – 14.05 *Networking Lunch*

14:05 – 15.05 *Phase II project presentations* - Chair Hugh Perry

Fabio Blandini (Pavia, Italy)
Targeting glucocerebrosidase for disease-modifying treatments in Parkinson's disease - Anthony H.V. Schapira (UK), David Park (Canada), Donato Di Monte (Germany) and Fabio Blandini (Italy)

Antonio Cuadrado (Madrid, Spain)
WNT signaling: biomarker and target evaluation in Alzheimer's disease - Antonio Cuadrado (Spain), James Woodgett (Canada) and Simon Lovestone (UK)

Danica Stanimirovic (Ottawa, Canada)
Mechanisms of amyloid- β clearance in models of vascular cognitive impairment and mixed dementia - Gabor Petzold (Germany) and Danica Stanimirovic (Canada)

Jochen Prehn (Royal College of Surgeons, Ireland)
microRNA as novel therapeutic targets and disease biomarkers in Alzheimer's Disease, Frontotemporal dementia and Amyotrophic lateral sclerosis (NEURO-MIR) - Jochen Prehn (Ireland), Andre Fischer (Germany), Pierre Lau (Flanders), Jose Lucas (Spain)

Josè Luis Lanciego (Navarra, Spain)
In vivo neuronal cell reprogramming for a new regenerative approach in Parkinson's disease - Vania Broccoli (Italy), Alexander Dityatev (Germany) and Josè Luis Lanciego (Spain)

15:05 – 15.15 *Q&A: COEN Process and Delivery* - Rob Buckle

15:15 – 15.40 *Tea and Coffee*

15:40 – 16.25 *Break out group discussions* - Chairs Adriana Maggi, Pierluigi Nicotera and Yves Joannette + All

Creating effective industry-academic partnerships through international consortia

Break out group discussions
Creating effective industry-academic partnerships through international consortia:
- Needs of industry - how can they be addressed through partnership?
- Opportunities and routes for delivery?

16:25 – 17.00 *Plenary Session* - Chair Hugh Perry

Drawing together outputs of breakout sessions

17.00 *Departure*

List of Attendees

COEN Researchers

1. Professor Joerg Gsponer, University of British Columbia, Canada
2. Professor Mario Masellis, University of Toronto, Canada
3. Professor Dana Stanimirovic, University of Ottawa, Canada
4. Professor Christine van Broeckhoven, VIB, Flanders
5. Dr Daniele Bano, DZNE, Bonn, Germany
6. Professor Donato Di Monte, DZNE, Bonn, Germany
7. Professor Walter Maetzler, DZNE, Tübingen, Germany
8. Professor Jochen Prehn, Royal College of Surgeons, Ireland
9. Professor Michael Rowan, Trinity College, Dublin, Ireland
10. Professor Fabio Blandini, IRCCS, Pavia, Italy
11. Dr Roberta Ghidoni, IRCCS, Brescia, Italy
12. Professor Michal Novak, Institute of Neuroimmunology, Bratislava, Slovak Republic
13. Professor Antonio Cuadrado, CIBERNED Madrid, Spain
14. Professor José Luis Lanciego, CIBERNED University of Navarra, Spain
15. Professor Martin Rossor (part of meeting only), University College London, UK
16. Dr Jonathon Rohrer, University College London, UK
17. Professor Simon Lovestone, NIHR Biomedical Research Unit, Kings College London, UK
18. Professor David Rubenztein, University of Cambridge, UK
19. Professor Joanna Wardlaw, University of Edinburgh, UK

Industry participants⁴

20. Dr Roman Sivak, Axon Neuroscience
21. Dr Mike O'Neill, Eli Lilly & Co Ltd
22. Dr Saga Johansson, GE Healthcare
23. Dr Paul Wren, GSK
24. Dr Derek Hill, IXICO
25. Dr Declan Jones, J&J
26. Dr Rob Pinnock, MSD Ltd
27. Dr Max Mirza, Neusentis (Pfizer)
28. Dr Sophie Claudel, Sanofi
29. Dr Takashi Takenoshita, Shionogi Ltd
30. Dr Craig Buckley, Siemens Healthcare

COEN Oversight Group

31. Professor Hugh Perry (Chair) – MRC, UK
32. Dr Rob Buckle – MRC, UK
33. Professor Paul Matthews – MRC, UK
34. Professor Pierluigi Nicotera – DZNE, Germany
35. Dr Sarah Jewell – DZNE, Germany
36. Professor Yves Joanette – CIHR, Canada
37. Dr Eimear Holohan – SFI, Ireland
38. Professor Adriana Maggi – MDS, Italy
39. Dr Miguel Medina – ISCIII, Spain
40. Dr Lubica Pitlova – MESRS, Slovakia

41. Dr Katherine Giles (Secretariat) – MRC, UK

Other attendees

42. Helen Page, MRC
43. Adam Manhi, UKTI

⁴ Confirmed but unable to attend on the day: Declan Jones, Takashi Takenoshita, Craig Buckley

COEN Phase I

Projects run ~ January 2012 - December 2013

- Pilot projects (up to 24 months) to address key barriers to progress in the field, and serve to underpin future studies in the neurodegenerative diseases field.
- Eight collaborative projects totalling £3.7m (€4.6m) funded.
- Projects spanned the development of new disease models, the identification of biomarkers and the harmonization of methodologies for clinical studies.

Projects and key outputs

Standards for determining the vascular contribution to neurodegeneration

Joanna Wardlaw (MRC), Martin Dichgans (DZNE), Dr Eric Smith (CIHR)

Neurodegeneration during ageing is commonly associated with certain features of small vessel disease (SVD) that can be observed with neuroimaging methods. The terminology and definitions used to describe these imaging features vary widely, impairing clinical characterisation and the comparison of different research studies. Research in this project aims to create expert consensus on these specifications for SVD neuroimaging, as well as create standards for image acquisition, analysis and reporting.

Key outputs:

- Coordination of a group of 35 international enthusiastic experts in small vessel disease from Europe, North America, and the Far East. The consortia researched and drafted a proposed standard for imaging small vessel disease, received comment from six independent advisors and published the final standard in *Lancet Neurology* in July 2013 (Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration: a united approach. *Lancet Neurol* 2013;12(8):822-38).
- The work attracted considerable interest, including an editorial in *Lancet Neurology* 2012;11:293, and invited presentations at the International and European Stroke Conferences, several annual international conferences on dementia, and national stroke conferences.
- The proposals are adopted on the Equator Network Guideline website, in the International Stroke Genetics Consortium, are being incorporated in other Societies' guidance; the international expert collaboration is developing multicentre trials of prevention of small vessel disease, genetic and mechanistic studies.

Integrated approach to identify novel genes for frontotemporal lobar degeneration

Marc Cruts (VIB), Christine Van Broeckhoven (VIB), Christian Haass (DZNE), Dieter Edbauer (DZNE)

Frontotemporal lobar degeneration (FTLD) is a type of dementia clinically characterized by behavioural and language disturbances and affects generally people between 40 and 60 years of age, thus strongly impacting their career and social activities. In this age group, it is the second common cause of dementia after Alzheimer's disease. The molecular and cellular mechanisms underlying FTLD are still inadequately understood. To gain a better understanding of the disease processes, researchers in this project aim to identify novel genetic contributors and to generate novel animal and laboratory models to study the biological pathways involved in disease initiation and propagation.

Key outputs:

- Identification and genetic and clinical characterization of C9orf72 repeat expansions in chromosome 9p-linked FTLD ALS diseases (Gijssels et al. *Lancet Neurology* 2012; van der Zee, Gijssels et al. *Human Mutation* 2013; Van Langenhove et al. *JAMA Neurology* 2013)

- Characterization of the functional mechanisms associated with pathological C9orf72 repeat expansions, including gene expression, dipeptide repeat protein expression and RNA-binding protein sequestration (van der Zee, Gijssels et al. Human Mutation 2013; Mori et al. Science 2013; Mori et al. Acta Neuropathologica 2013a; Mori et al. Acta Neuropathologica 2013b)
- Characterization of a TARDBP knockout zebrafish and mouse p.M337V models of FTL and ALS TDP-43 proteinopathies (Schmid et al. PNAS 2013; Janssens et al. Molecular Neurobiology 2013)

Mitochondrial dysfunction and susceptibility to Parkinson's disease: New models of pathogenetic interactions

Donato A. Di Monte (DZNE), David S. Park (CIHR), Fabio Blandini (MDS), Anthony H.V. Schapira (MRC)

The scope of this project is to develop and use animal models that better mimic the complex interactions that underlie Parkinson's disease (PD) development. Abnormalities in mitochondria, organelles responsible for the energy balance of the cell, are likely to play an important role in neuronal dysfunction and neurodegeneration in PD. Using animal models that feature neuronal mitochondrial impairment, we will determine how this deficiency acts together with other toxic mechanisms in promoting neurodegenerative processes. We will also study novel strategies that counteract mitochondria-mediated pathology and could ultimately lead to neuroprotective intervention in PD.

Early synaptic plasticity and network dysfunction in transgenic (tg) rat models of Alzheimer's disease (AD)

Michael Rowan (HRB/SFI), Claudio Cuello (CIHR), Martin Fuhrmann (DZNE), Michel Goedert (MRC) and Stefan Remy (DZNE)

The objective of the project is to generate as complete a model of Alzheimer's disease (AD) as possible in the rat. "McGill-R-Thy1-APP" is a new rat model of AD that recapitulates one central aspect of Alzheimer's disease, the formation of amyloid beta (A β) protein deposits in the brain. This model will be further developed by incorporating additional aspects of the pathology, the formation of tau protein aggregates. The rat model will then be used to investigate the role of tau and A β in synaptic plasticity, network dysfunction and memory impairment in AD.

Key Outputs:

- Building on the sophisticated behavioural repertoire of rats we have characterized impairments of performance on a wide range of learning tasks in the McGill-R-Thy1-APP model.
- Prior to plaque formation these rats also have age-dependent deficits in long-term potentiation (LTP) that have been tracked longitudinally in freely behaving animals.
- The generation of a bigenic McGill APP-tau transgenic rat is underway and promises to provide a very comprehensive and attractive model, closer to the human pathology.

Immune subtype in Parkinson disease

Thomas Gasser (DZNE), Antonio P. Strafella (CIHR)

Several lines of evidence point to an influence of inflammation on the onset and progression of Parkinson's disease (PD). Nonetheless, clinical studies have not clearly shown that the use of anti-inflammatory compounds is protective against PD. This may be explained by the existence of different subgroups of PD. Possibly, only a proportion of PD subjects suffer from concomitant inflammation, and/or inflammatory cascades may differ in subgroups. The aim of this project is to test this hypothesis and define such "inflammatory subgroups". These patients may be excellent candidates for clinical trials of anti-inflammatory agents as disease-modifying treatment in PD.

Key outputs:

- "Inflammatory PD endophenotype" defined by use of a genetic immune pathway genotype analysis, and classification of 100 with, and 100 PD patients without this genotype out of a cohort of 800 PD patients out of the outpatient clinic of Tuebingen

- Clinical / quantitative assessment and collection of biomaterial in 150 of these PD patients, recruitment will be finalized in 2013 (Tuebingen), clinical assessment and collection of biomaterial in 100 PD patients (validation cohort, Toronto)
- Testing of blood-based test systems for inflammatory markers and validation of new PET radiotracer for neuroinflammation.

C. elegans models of mitochondrial deficiency in the nervous system

Daniele Bano (DZNE), Siegfried Hekimi (CIHR), Mario de Bono (MRC)

Mitochondria are the intracellular organelles responsible for energy production. Broad decline in energy metabolism is strongly associated with the age-dependent loss of neuronal structures. Thus, the accumulation of mitochondrial defects during aging likely promotes neurodegeneration. The proposal aims to study the molecular pathways and events that link mitochondrial defects and neurodegenerative diseases using the nematode *Caenorhabditis elegans* as a model system. The use of genetic approaches will help to better understand the neurodegenerative process and might provide new therapeutic targets.

Key outputs:

- Identification of new signalling pathways that alter dendritic branching in animals with impaired mitochondrial respiration;
- Investigation of the impact of altered mitochondrial function on polyglutamine tracks-induced protein aggregation and ubiquitin-dependent proteostasis;
- Generation of new *C. elegans* strains for in-vivo imaging of dendritic remodelling. As a proof-of-principle, we demonstrated the possibility to use these animal models for screening of a small number of chemical compounds.

The GENetic Frontotemporal Dementia Initiative (GENFI): a new multi-centre platform for the study of frontotemporal lobar degeneration

Martin Rossor (MRC), Giovanni B. Frisoni (MDS), Mario Masellis (CIHR)

Recent advances in molecular biology and neuropathology of frontotemporal lobar degeneration (FTLD) have yet to be translated into effective, disease-modifying therapies. Further progress toward this goal will depend on largescale collaborative efforts that harness resources and expertise across specialist centres. The proposed programme will develop and evaluate the feasibility of a platform for mounting future large-scale natural history studies of FTLD and for conducting clinical trials of disease-modifying interventions.

Key outputs:

- 11 sites have recruited members of families with mutations in the tau, progranulin and C9ORF72 genes with a uniform methodological platform and central quality assurance of MRI and clinical data
- 220 patients have been recruited at the time of the first data freeze on 30/9/13
- The initial analysis demonstrates premanifest cognitive and structural change 5-10 years prior to symptom onset

Identification of generic suppressors of proteinopathies

David Rubinsztein (MRC), Joerg Gsponer (CIHR)

The formation of protein aggregates in the brain is a feature of many late-onset neurodegenerative diseases, called proteinopathies. These include Alzheimer's disease, Parkinson's disease, tauopathies, forms of motor neuron disease and the nine polyglutamine expansion diseases exemplified by Huntington's disease (HD). On the basis of previous studies it is assumed that certain modifiers of one proteinopathy may influence another. The aim of the project is to identify such "generic" suppressors of neurodegeneration.

Key outputs:

- Creation of NeuroGeM, the first comprehensive knowledgebase providing integrated information on genetic modifiers of nine different neurodegenerative diseases in the model organisms *D. melanogaster*, *C. elegans*, and *S. cerevisiae*.
- Experimental analyses to identify genetic modifiers of more than one neurodegenerative disease in *Drosophila* models.
- Characterisation of a druggable target that modifies aggregation and toxicity of different neurodegenerative disease proteins.

COEN Phase II

Projects run ~ January 2014-December 2015

- “Pathfinder” projects (up to two 24 months) for innovative and high risk/high pay off approaches to better understand disease mechanisms and provide new avenues for therapeutic development.
- Potential for “programme” level support, later in the initiative to take forward successful pathfinders.
- Engagement with Industry at each stage is encouraged
- £2.6 m (€3.1m) awarded for 5 ‘pathfinder’ projects
- Projects spanned PD, AD, vascular dementia and included approaches to develop novel therapies, biomarkers and pathways

Project abstracts

Targeting glucocerebrosidase for disease-modifying treatments in Parkinson’s disease Anthony H.V. Schapira (UK), David Park (Canada), Donato Di Monte (Germany) and Fabio Blandini (Italy)

Parkinson disease is a progressive neurodegenerative disorder treatment for which is limited to improving symptoms and there is an urgent need to develop drugs that slow progression. It has recently been shown that mutations of the glucocerebrosidase gene result in a very significant increased risk for PD, and that approximately 10% of patients carry such mutations. Our project is designed to explore the mechanisms by which the mutations increase the risk for PD and to test candidate drugs that reverse the biochemical changes induced by the mutations. We hypothesise that this will result in a reduction in alpha-synuclein levels, the protein that builds up in Parkinson neurons and that is thought to be at the centre of the degenerative process. The candidate drugs will first be tested in cell and animal models of the mutations as part of this international collaboration in confirming this proof of principle. Positive results will lead to drug development for patients.

WNT signaling: biomarker and target evaluation in Alzheimer’s disease Antonio Cuadrado (Spain), James Woodgett (Canada) and Simon Lovestone (UK)

The consistent failure of biopharmaceutical pipelines to modify Alzheimer's disease progression indicates a need for new and creative solutions. In this project we will explore elements of the canonical (WNT/GSK3) and non-canonical (WNT/JNK) signaling pathways as novel targets that could be used to monitor and modify Alzheimer's progression. Our teams are applying a multidisciplinary approach that combines brain-oriented drug screening, new genetic and pharmacological tools, new animal models and human blood and cerebrospinal fluid samples, which, together, explore the impact on AD of novel WNT elements, including but not limited to the apolipoprotein clusterin, the WNT inhibitor DKK1 and the transcription factor Nrf2.

Mechanisms of amyloid-β clearance in models of vascular cognitive impairment and mixed dementia

Gabor Petzold (Germany) and Danica Stanimirovic (Canada)

Perturbation of cerebral blood flow and the blood brain barrier are prominent features of Alzheimer's disease. The central hypothesis of this project is that these changes directly affect the transport of amyloid-β, a peptide centrally involved in AD initiation and progression, across the blood brain barrier, leading to increased accumulation of amyloid-β in the brain. We aim to identify the molecular mechanisms responsible for this imbalance of amyloid-β trafficking in mouse models of AD, vascular dementia and mixed dementia (i.e. vascular dementia and AD). Finally, we will also investigate whether pharmacological intervention specifically targeting Aβ trafficking can be therapeutically beneficial in these models.

In vivo neuronal cell reprogramming for a new regenerative approach in Parkinson's disease

Vania Broccoli (Italy), Alexander Dityatev (Germany) and José Luis Lanciego (Spain)

Degeneration of mesencephalic DA neurons triggers the initial phases of PD, which raises the concept that cell replacement might represent a long-term restorative option for this neuropathology. Indeed, previous studies in PD patients have indicated that cell therapy has the potential to significantly sustain an enduring symptomatic relief in at least some of them. However, an ideal renewable source of transplantable human DA neurons is lacking in many aspects. We have recently developed a methodology that promotes transdifferentiation of mouse and human fibroblasts into functional induced dopaminergic neurons (iDANs), which display sophisticated neuronal properties including pacemaking firing activity, synaptic integration, and activity-dependent dopamine release. Therefore, iDANs offer an unprecedented cellular source with ideal features for cell therapy in PD, since they can be generated from the patients in high amounts. Herein, we plan to push forward this technology by elaborating methods of direct in vivo reprogramming to induce in situ local neuronal transdifferentiation in relevant animal models of PD (mouse and monkey). Local delivery of the reprogramming factors will be optimized and the best cellular substrate identified in order to achieve the most efficient recovery of the neurological symptoms in the PD animal models.

microRNA as novel therapeutic targets and disease biomarkers in Alzheimer's Disease, Frontotemporal dementia and Amyotrophic lateral sclerosis (NEURO-MIR) **Jochen Prehn (Ireland), Andre Fischer (Germany), Pierre Lau (Flanders), Jose Lucas (Spain)**

NEURO-MIR focuses on the role of microRNA (miRNA) in neurodegeneration. miRNA are small (~22 nucleotide), non-coding RNA that control the expression of multiple genes. Data from members of the NEURO-MIR consortium has shown that deregulation of miRNA contributes to the pathogenesis of Alzheimer's disease and motoneuron disorders. NEURO-MIR aims to explore the full potential of miRNAs as key contributors to disease progression and as therapeutic targets and biomarkers. NEURO-MIR also realises that the complexity of miRNA biology can only be tackled through bioinformatics and computational modelling approaches, and will develop a computational platform that will allow to approach the role of miRNA in neurodegeneration on a 'holistic', systems level.