

Plasticise – FP7 Collaborative Project 223524

Promotion of plasticity as a treatment for neurodegenerative conditions

FINAL PUBLISHABLE SUMMARY

1.1. Project Objectives

The overall concept behind the Plasticise project is that restoration of the function in neurodegenerative conditions can be achieved through plasticity (the formation of new circuits in the nervous system to bypass lesions). Promoting increased plasticity in selected parts of the adult nervous system back to the level seen in children is a powerful method of enhancing recovery of function in animal models. Plasticity-promoting treatments could therefore be beneficial in a wide range of conditions that damage the CNS.

Along these lines, the project has developed **new treatment concepts to promote plasticity** and methods to measure and visualise their effects, focussing on **Alzheimer's disease/tauopathy, stroke** and the **visual system**. Although the project uses several animal models, the focus has been on the ability of plastic changes to alleviate CNS dysfunction after stroke, spinal cord injury and Alzheimer's pathology. This melds the project into a single concept, which uses the appropriate animal and human models to test the basic hypothesis that activation of plasticity can restore function. In parallel the project has developed **new clinical tools** that will be needed for clinical trials of plasticity treatments. The clinical work has concentrated on stroke patients (the chronic neurodegeneration phase, not acute neuroprotection) and Alzheimer's disease patients. Plasticity can be driven by motor rehabilitation in stroke, by language and memory training in Alzheimer's disease, and combined rehabilitation and plasticity-promoting treatments have been tested. The clinical and basic science strands of the project developed in parallel with interactions focused around imaging methodology. The strands come together in the development of plans for clinical testing of the treatments that have proven effective in animal models.

The **specific objectives** of the project were to develop:

- New treatments to modulate CNS plasticity
- Studying plasticity at the micro level
- A novel *in vivo* model of neurodegeneration
- Promoting plasticity in animal models
- Novel methods for studying plastic changes in human patients and primates
- Testing plasticity modulating treatments in human patients

1.2. Work performed since beginning of the project

Scientific

The work performed in the Plasticise project followed closely the aims of the original proposal, summarized above. Several discoveries that will have significant impact on the treatment of neurodegeneration have been made. New plasticity-activating treatments have been developed based on proteoglycans, semaphorins and NogoA. New methods to assay and image plasticity at the micro scale have been produced. The consortium has worked out the cellular machinery that allows new connections to be formed and old ones removed. We have shown the mechanism by which plasticity of connections leads to the formation of memory and have demonstrated that a plasticity treatment can restore memory in a model of Alzheimer's disease. In addition, major advances have been made on the clinical side, with the development of new imaging methods for evaluating plasticity in human patients and a trial of stroke patients with combined rehabilitation and plasticity-inducing TMS. These major scientific achievements have been published in high-ranking journals.

Consortium management, Integration and training activities, Dissemination activities

At the beginning of Plasticise, a particular emphasis of the coordinator and the management team was rapid establishment of strong management structure for Plasticise in order to assure a smooth implementation of the research and training goals of the consortium (see WP7), assess any risky situation and take rapid action. The management team has provided energetic and effective support for the executive team of the partnership, ensuring a successful implementation of the grant and its contractual requirements. Following their rapid integration into the project, the students and post docs recruited on the grant received capacity building and career support via the workshops and plenary meetings organized within Plasticise as well as via the different communication tools developed during Periods 1 and 2. Web conferences and tutorials stimulated and maintained regular exchanges of ideas and materials between the PIs and the young researchers (see WP8). In the 2nd and 3rd part of the project the management team placed an emphasis on the dissemination of the major achievements of the consortium. The Plasticise website was renewed for a more accessible and more attractive design, press releases were sent out, a flyer developed and communication with

European patient groups initiated. Finally, the network successfully disseminated the major scientific advances to the scientific community, the European Commission, and the broad public via several outreach events.

1.3. Main results achieved so far

Workpackage 1: Development of new treatments to modulate CNS plasticity

- Combined treatment with NogoA antibody and ChABC produces better recovery of function after spinal cord injury than the individual treatments.
- Link protein *crtl1* is essential for the formation of the perineuronal nets (PNNs) that restrict plasticity in the adult CNS, and its genetic deletion results in animals that retain plasticity into adulthood.
- An *in-vitro* model for PNNs has been created, which is currently in use to develop new treatments to promote plasticity through inhibition of PNN function.
- Receptor bodies were created as a treatment to interfere with chemorepulsive Axon Guidance Protein Semaphorin 3A, which is an effector of PNNs in the adult nervous system.
- Semaphorin 3A interacts with Chondroitin Sulphate type E (CS-E) in binding to glycosamino-glycans (GAGs) of PNNs in rodent brain; the antibody is therefore a potential plasticity promoter.
- Neutralization of Semaphorin 3A with receptor bodies expressed in the visual cortex via AAV vectors enhanced ocular dominance plasticity (see also WP4)
- Nogo-A / EphA4 double KO mice showed enhanced axonal sprouting and regeneration after spinal cord injury compared to single Nogo-A KO and EphA4 KO mice.
- Demonstration that Wnt signalling is involved in enhanced synapse formation due to exposure to an enriched environment in rodents.

Workpackage 2: Studying plasticity at the micro level in response to neurodegeneration

- We have established several new methods (inc. imaging of genetically-encoded calcium indicators and a transgenic rat) and paradigms to study plasticity using state of the art microscopic methods, both in brain slices and *in vivo*.
- We have obtained important results on subcellular, microscopic changes within the local microcircuits. Such linking of how structural changes will affect computational properties of the neuronal network and thus are a prerequisite for a better understanding of the functional losses induced by neurodegeneration.
- We have used various functional assessments such as two-photon calcium imaging and intrinsic signal imaging to visualize plasticity changes following impairments.
- Studies of synaptic changes have been made in various models of neurodegeneration, including AD mice, deprived animals, animals with corticospinal lesions and mice with focal strokes induced by photothrombosis.
- We have demonstrated that memory circuits in the hippocampus are regulated by the formation of new synapses on inhibitory interneurons.
- Metalloproteinases affecting the extracellular matrix are essential for stimulation of dynamics in dendritic spines
- Spine dynamics are controlled intracellularly by beta adducin.
- We show that degradation of chondroitin sulphate proteoglycans (CSPGs) by Chondroitinase ABC in mouse visual cortex enhances motility and reactivates functional plasticity of dendritic spines

Workpackage 3: A novel *in vivo* model of neurodegeneration

- Alzheimer-like focal lesions have been produced using viral vectors expressing mutant forms of APP and tau
- Profound deficits in memory have been found in animals with neurodegeneration due to expression of mutant tau.
- The loss in object recognition memory following neuropathology in the perirhinal cortex can be reversed by the plasticity treatment chondroitinase, which digests perineuronal nets.

Workpackage 4: Promoting plasticity in animal models of neurodegeneration

- Removal of PNNs is a treatment with general efficacy. It reactivates plasticity in various brain structures and in various forms of plasticity.
- Learning mechanisms can be enhanced by targeting perineuronal nets. This evidence constitutes the conceptual starting point for the use of PNN-related treatments to hinder cognitive deterioration in neurodegenerative disease.
- Blocking the receptors of semaphorin3 reactivates plasticity in the adult brain.
- Chondroitinase treatment improves recovery from stroke in rats.
- Plasticity-enhancing treatments profoundly interact with rehabilitation strategies. Anti-Nogo treatments work best with sequential treatment with anti-Nogo and rehabilitation whereas chondroitinase treatment is more effective if administered concurrently with rehabilitation. The beneficial effect of combined treatment was observed at the level of improving functional recovery in behavioural tests and could be traced down to plasticity at synaptic level.
- Combination treatment with anti-Nogo and chABC for spinal cord injury is more effective than either treatment alone.
- Chondroitinase treatment may be begun at least a month after spinal cord injury, making it much more practicable than treatments that need to be given immediately.

- A peptide mimicking PSA ameliorates locomotor recovery after brain contusion.

Workpackage 5: Novel methods for studying plastic changes in human patients and primates

- Methodology for assessing changes in connectivity between brain regions after stroke has been validated. These approaches are now being applied to patient data.
- The functional relevance of contralesional hemisphere activity has been established by assessing the cortical peak of cortico-muscular coherence with magnetoencephalography and electromyography in stroke patients.
- Advances have been made in quantifying the degree of damage to critical descending corticospinal tract pathways after stroke. In particular, we are now able to look at those fibres that contribute to upper limb function in human subjects.
- We have visualised changes in both anatomy (cortical thickness) and functional organisation of motor and cognitive brain networks in neurodegenerative diseases as a marker of neuroplastic change.
- Several studies have now examined changes in brain reorganisation with novel treatment approaches after stroke (repetitive TMS, Mirror training therapy, Constraint induced movement therapy).
- Technical advancements that allow high-resolution imaging at high field scanners have been established
- A macaque with juvenile macular degeneration has been characterized with fMRI, optical coherence tomography and multifocal ERG. It can potentially serve as a model for studying human macular degeneration.
- Human rehabilitation training is currently performed in human patients suffering from hemianopia after cortical infarcts affecting primary visual cortex. Preliminary fMRI data on changes in their population receptive field maps have been obtained in these patients.
- New MRI imaging probes have been developed that will allow *in vivo* characterization of brain connectivity and plasticity

Workpackage 6: Testing plasticity modulating treatments in human patients

- A major new controlled clinical trial of the effectiveness of add-on brain stimulation therapy to conventional rehabilitation in chronic stroke. When behavioural training is well-controlled, 2 weeks of daily therapy can increase scores of arm and hand function and that this is maintained for at least 3 months. Additional brain stimulation did not enhance the effect in this group of patients. A new trial is underway to examine training effects on proximal shoulder and trunk control in a more severely affected group of stroke survivors.
- A second major trial was mirror therapy for restoration of hand function after stroke. It showed that mirror training remodels the motor system by functionally connecting hand movement to the ipsilateral sensorimotor cortex. A follow-up Proof of concept study in patients is on its way, preliminary data suggest that success of the treatment depends on the location of the lesion.
- A third trial has indicated an improved method of rehabilitation for stroke patients. It was found that a better transfer of training to other tasks could be obtained when people practised the task moving as fast as possible compared with a group that trained to be as accurate as possible. We are therefore testing the efficiency of training at fast speeds in chronic stroke patients.
- A fourth advance was continuing progress in the multicentre Phase 1 trial of anti-NOGO-A in spinal cord injury. This is approaching completion with the last patients having reached 1 year follow up in October 2011. So far the treatment has proved safe and without complications attributed to the treatment with anti-Nogo antibodies. A follow on trial testing safety on incomplete spinal injury is currently underway.
- Progress has been made in indentifying parameters that might predict recovery in individual patients after stroke as well as showing which patients may benefit from particular forms of therapy.
- Completed Phase 3 studies for DP-b99 in stroke patients.

1.4. Expected final results & their potential impact and use

The proposed project capitalized on combined expertise in different areas of regenerative medicine. Furthermore, Plasticise involves collaborative interactions that allow us to merge our unique and complementary expertise in the field, from the bench to the bedside.

Impact on science

Plasticise has been designed to address the societal-economic impacts of neurodegenerative diseases, integrated with advanced research, aligned with what is required to identify and validate optimal treatment regimens. This requires a detailed molecular/cellular understanding of synaptic change to provide new knowledge for developing new plasticity enhancement treatments for promoting recovery of function in human patients with neurodegenerative disease. As described above, major achievements done throughout the grant both in the pre-clinical and clinical settings have seen that Plasticise is going beyond the state of the art. These scientific highlights have been largely disseminated to the scientific community through peer-reviewed publications, talks and poster presentations.

Economic benefits

In Europe overall, neurological damage accounts for 40% of people severely disabled and who require daily help (Wade & Hewer, 1997; Office of Population Censuses and Surveys, 1998). Neurodegenerative diseases, including stroke and Alzheimer's disease, are the major causes of chronic disability in European communities. With the increasing number of elderly people, coupled with successful treatment of non-neurological causes of chronic illness, the incidence of neurodegenerative disease will increase. In total, by 2013 it has been estimated that there will be some 8.5 million European citizens afflicted with a neurodegenerative disorder.

Alzheimer's disease: It has now been reported that the world is on the brink of an Alzheimer's epidemic in which the number of sufferers could quadruple over the next 40 years. The Alzheimer's disease market across the seven major markets is set to double in value over the next 10 years, from **\$5.3bn in 2011 to \$12.6bn in 2021**. The catalysts for this growth include an increasingly elderly population, earlier and improved diagnosis, and the introduction of new therapeutic classes.

Stroke: Europeans suffer nearly one million strokes each year, highlighting the need for efficacious therapy and the tremendous market potential for effective stroke therapy. Between 15-30% of ischemic stroke victims are permanently disabled and 20% require prolonged institutional care. As a result, stroke is one of the most common causes of long-term serious disability and represents an economic burden similar in scale to myocardial infarction. The potential **combined market size in US and EU for stroke is estimated at \$12.56 billion**.

Spinal cord injury: estimated to be at least 330 000 people living with spinal cord injury (paraplegia and tetraplegia) with over 15 000 new cases reported each year. In two-thirds of cases, road accidents are the cause of injury, with sporting accidents making up another 10%. Most occur at a young age: average age of 19; about 80% of males with spinal cord injuries are aged 18-25 years. The cost of treatment and aftercare for sufferers is phenomenal: the average lifetime costs directly attributable to spinal cord injury for an individual injured at age 25 range from € 0.45 M to € 2.1 M and have to prepare to spend an average of forty years or more in a wheelchair. GlobalData estimated the acute spinal cord injury (ASCI) therapeutics market to be worth \$44.78m in 2010 and forecasts it to grow at a CAGR of 6.3% to reach \$68.76m in 2017.

Plasticise is thus contributing to the alleviation of these chronic diseases by understanding the underlying pathological mechanisms and by developing new promising treatments.

Impact on society

Degenerative diseases create a life-altering experience for the person with injury, for their partner, parents, siblings, and children. The impact on and subsequent dimishment of body functions associated with the diseases can cause depression and loss of self-esteem. Given the diversity of degenerative diseases indicated above, pathological manifestation can occur at any age: either as a child, during an individual's most productive years, or as an aged person. In most cases, patients require continuous physical and medical care depending on the disease, severity of manifestation, degree of disability, and location of injury. The burden of care giving most frequently falls on the partner. Care giving partners are often severely stressed, particularly due to health issues that arise after tissue degeneration initiates and suffer emotional stress that is comparable to or greater than those of the injured partner. Caregivers have a higher incidence of physical stress, emotional stress, burnout, fatigue, anger, and resentment.

Hope is considered an important coping strategy for both the person and family with degenerative diseases. Goal-directed hope based on realistic perceptions of life, focusing on progress, positive interpretation of events, are important in helping people and families cope with the disease. Hope is also focused towards the society at large, that new therapeutics are developed.

In addition to imposing direct medical costs on society, degenerative diseases also result in indirect costs, primarily related to reduced productivity due to disability with a further loss of self-esteem of the sufferer and diminished integration into society. Plasticise aims to provide more than hope: we aim to provide validated treatments to promote brain plasticity.

1.5. Project contact details and Logo

Project coordinator:
 Prof. James Fawcett
 Cambridge Brain Repair Centre
 University of Cambridge, UK
 Tel: +44.1223.33.11.60
 Email: jf108@cam.ac.uk



Website of the project: www.plasticise.eu