Convened by:

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The European Science Foundation (ESF) is an association of 79 Member Organisations devoted to scientific research in 30 European countries. The Mission of ESF is to provide a common platform for its Member Organisations in order to advance European research and to explore new directions for research at the European level. Through its activities, the ESF serves the needs of the European research community in a global context.

The main objectives of ESF for the years 2006-2010 as defined by its current Strategic Plan are to promote Science Strategy and Science Synergy, paving the way for initiatives across disciplinary and geographic boundaries in the European Research Area (ERA).

The Exploratory Workshops scheme is one of the key instruments of the Science Strategy “pillar”. Each year, ESF supports approximately 50 Exploratory Workshops across all scientific domains. The focus of the scheme is on workshops aiming to explore an emerging and/or innovative field of research or research infrastructure, also of interdisciplinary character. Workshops are expected to open up new directions in research or new domains. It is expected that a workshop will conclude with plans for specific follow-up research activities and/or collaborative actions or other specific outputs either within the frame of ESF (e.g. prepare the ground to develop a Forward Look, a Research Networking Programme or a EUROCORES proposal; publication of a Policy Briefing…) or for submission to the EU 7th Framework Programme or to other European or international funding organisations.

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Main Objectives of the Workshop:

BRAINS4BRAIN – Treating Pediatric Neurodegenerative Diseases: From Laboratory Bench to Bedside

Neurodegenerative diseases are most prevalent in the elderly, but can in rare cases also affect individuals early in life. In children, neurodegeneration leads to severe mental retardation and premature death with devastating consequences on their immediate environment and relatively high costs for society. Within the EU pediatric neurodegenerative disorders are considered “Rare”. Because of the low-prevalence of these disorders, there is often a striking lack of information, research, treatment and expert availability. There is also often a significant delay before a definitive diagnosis is achieved. BRAINS4BRAIN calls for a collaborative research effort to focus the available multidisciplinary European brain-power with relevance to tackling pediatric neurodegenerative diseases.

BRAINS4BRAIN acknowledges that only by expanding and implementing basic knowledge of both the pathological process of disease development and the highly selective activity of the Blood Brain Barrier (BBB; impeding efficient drug delivery to the brain) effective therapy for clinical application can be developed. Importantly, it is foreseen that such knowledge and insights will also be valuable for understanding and treating other important neurological diseases such as Alzheimer's, Parkinson's Disease, and epilepsy.
BRAINS4BRAIN (www.brains4brain.eu) is a European task force aimed at developing and implementing new therapies for pediatric neurodegenerative diseases for which, at the moment, no effective therapy is available. The task force wishes to create a coordinated European effort towards i) the comprehension of pathophysiology processes of these pediatric neurological disorders, ii) the implementation of knowledge on the BBB, iii) the development of new molecular and/or biochemical strategies to overcome the BBB for brain-targeted drug delivery, and iv) the development and implementation of diagnostics and clinical therapies to timely detect and treat these devastating CNS disorders.

BRAINS4BRAIN focuses its effort towards the treatment of neurodegeneration associated with Lysosomal Storage Diseases (LSDs). In LSDs a genetic and biochemical deficiency of particular enzyme activities is responsible for the lack of degradation of macromolecules which then accumulate and lead to cell death and apoptosis. In the brain this leads to neuronal death and neurodegeneration. Therapeutic replacement of the enzyme or (compensation of) its activity by other means can reverse the toxic accumulation. However, the therapies developed to date can not efficiently cross the BBB to reach effective therapeutic levels in the brain.

This exploratory workshop is aimed at uniting the separate disciplines present within Europe that are required for the development of therapeutic treatment strategies for LSDs with neurodegenerative involvement from bench to bedside. To this end participants will include basic scientists (e.g. geneticists, biochemists, BBB specialists), clinicians (e.g. pediatricians, neurologists), experts on (pediatric) ethics, and IT experts (e.g. for improving data collection and –analysis, implementation of telemedicine). Importantly, also representatives of companies (e.g. developing neuropharmaceuticals or BBB-crossing technologies) will be invited. Furthermore, patient groups will be involved, as well as policy makers to include input from all relevant parties and to generate support for these activities at all levels.

SCIENTIFIC BASIS AND EXPECTED BREAKTHROUGHS

LSDs are metabolic disorders, caused by the lack of certain (lysosomal) enzymes or lysosome components, thus preventing the complete degradation of macromolecules and the recycling of their components. The accumulation of intermediate degradation products affects the appropriate functioning of lysosomes and other cellular organelles. Accumulation starts immediately after birth and progressively worsens, often affecting several organs, including the Central Nervous System (CNS). CNS pathology causes mental retardation and progressive neurodegeneration that ultimately ends in early death of these young patients.

LSDs are the only group of pediatric neurodegenerative diseases for which therapy that can reverse the natural history of the disease in peripheral organs is available (Enzyme Replacement Therapy, ERT). Unfortunately, ERT is currently unable to effectively reach the CNS to stop the lethal progression of the neurodegeneration. Nonetheless, ERT in combination with i) the advanced knowledge of the (genetic- and biochemical) causes for the development of neurodegeneration in LSDs and ii) the availability within Europe of well established in vitro and animal models, now provides the unique opportunity to decipher the cascade of events leading to loss of brain plasticity and mental retardation, as well as its possible reversal. For instance, suppressing the primary cause of neurodegeneration (e.g. by ERT) in a young brain –that at this stage of development retains considerable plasticity– maximizes the potential for neurological repair. Important to note is that common secondary events in both pediatric and adult neurodegenerative diseases lead to neurodegeneration. Studies on LSDs therefore have the ability to provide unique insights into the pathophysiology and restorative capacities of neurodegenerative diseases in general.

Ample knowledge, expertise and technology is available within Europe to enable the optimal exploitation of the research opportunity offered by the unique features of these neurodegenerative diseases. By agreeing on a collaborative research agenda with appropriate focus Europe can
Therapies based on ERT can modify the natural history of some LSDs in the peripheral organs (liver, spleen, joint mobility etc.). However, the BBB prevents the therapeutic enzymes used from reaching the CNS and modifying the course of neuro-degeneration\(^2\). This limitation can be circumvented by non-pharmaceutical therapy in which sources of enzyme (e.g. a viral vector) are created by surgical injection directly into the CNS. It might eventually also be achieved to some extent by pharmaceutical therapies based on BBB traversing small molecules aimed at reducing the accumulation of molecules requiring degradation (e.g. Substrate Reduction Therapy (SRT):inhibiting early enzymes in the biosynthetic pathway, or Chemical Chaperones: assisting the affected enzyme to attain its correct, active conformation\(^3\),\(^4\),\(^5\)). However, ERT is likely to be the most efficient strategy with the least side effects. As neurodegeneration in LSDs affects the entire brain, the technological challenge is to safely deliver ERT efficiently to all affected areas. This might be achieved only by developing strategies enabling the therapeutic enzyme to cross the BBB \(^6\)--\(^8\).

Tools to enable the entry of curative molecules across the BBB into the CNS will represent a major breakthrough for the long-term therapy of many (if not all) CNS diseases. Several cutting edge initiatives using different approaches to specifically deliver molecules across the BBB (e.g. exploiting certain transporters or manipulating BBB permeability) exist within Europe.

- It will be essential to reach consensus on which BBB-crossing developments will potentially be most suitable for delivery of LSD treatment to the brain. Efforts of both academia and companies working on these developments need to be coordinated and directed at further development towards technologies that are especially applicable for LSD treatment.

Diagnosis for LSDs is often significantly delayed. It is possible to detect the genetic defect(s) that cause(s) LSDs, and therefore to detect this disorder in newborn infants. Still, newborn screening is not routinely done as beneficial impact on the disease course is still unclear in the absence of curative treatment. However, once a therapy is developed that can at least prevent or slow progression of neurodegeneration, it will become extremely important to facilitate early detection of the genetic defect by newborn screening to enable early intervention. This is underscored by data indicating that treatment at older ages is less effective.

- Diagnostics for newborn screening of LSDs are being developed in Europe, but require improvements to enhance large scale implementation and reduce (or eliminate) the generation of false positives.

- The ethical paradox “the importance to protect the health and well being of any child with a neurodegenerative disorder vs. providing the opportunity to benefit from novel therapies” needs to be explored for LSDs. Requirements to be fulfilled by a new curative therapy to warrant the implementation of LSD newborn screening programs have to be determined. Views of those with personal experience with LSDs may significantly differ from the ‘societal view’. To tackle this issue views from the different stakeholders need to be collected and analysed by experts in ethics involving children with debilitating disorders. The outcomes need to be well communicated with those involved with therapy development.

Clinical polymorphism of LSDs include asymptomatic cases. As treatment options will often be risky, a reliable clinical prognosis is crucial – especially when new treatments become available and large-scale newborn screening programs for LSDs will be implemented\(^6\). Predicting clinical disease development and clinical effectiveness of (new) treatment options on the individual patient level is not

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\(^2\) Vellodi A. 2004 Brit J Heamatol 128: 413-431
\(^3\) Platt F. et al. 1997 Science 276: 428-431
\(^6\) Millington, 2008, Clin. Chem. 54, p1725
yet possible for LSDs. For this, reliable databases with comparable data on clinical progression need to be developed. In particular standards for collecting elaborate sets of clinical data require European wide implementation.

- When effective therapeutic approaches and newborn screening for LSDs come available following and predicting progression will be essential. New tools based on a better understanding of pathophysiology with the aim to diagnose the disease, prognosticate its severity and follow its progression, as well as the use of these tools for the assessment of therapeutic effectiveness will need to be developed in collaboration with basic researchers, clinicians and (pharmaceutical) companies.

The Quality of Life (QoL) of LSD patients and relatives will be improved when accurate predictions of clinical progression and therapy effectiveness are available. Also, specifically designed strategies for disease management (e.g. including modern technology as telemedicine) could further improve the QoL of patients and families.

- Research amongst all stakeholders will be required to assess how the QoL of patients and their families can be improved, and strategies need to be designed and implemented to facilitate such improvements. This will in particular require the collaboration of patient- and family organizations, and the pediatricians involved with LSD patients.

**Workshop Agenda**

The workshop is aimed to the production of a consensus document discussing the need of supporting research for the early diagnosis of neurodegenerative disorders caused by storage of macromolecules, their pathophysiology, the study of the physiology of the blood brain barrier by creation of in vitro models and analysis of in vivo models and the development of new strategies to cross the blood brain barrier as major goal to achieve brain therapy and positive modification of the natural history of these lethal progressive disorders.

The consensus document will be instrumental to produce a proposal for theme on this subject.

So far distinct calls for proposals on neurodegeneration and blood brain barrier studies were occasionally proposed. The workshop will demonstrate that pediatric diseases might be valuable models to discover new therapies for CNS by a combined multidisciplinary approach involving clinician, basic scientists and biotech companies.

**Report publication and dissemination**

The Workshop Report will be published in hard copy. Furthermore the report will be published on the website of the group [www.brains4brain.eu](http://www.brains4brain.eu). According to the outcome of the meeting a consensus paper will be possibly be published in an international peer review journal.
PRELIMINARY PROGRAMME

Wednesday 3 March 2010

Afternoon    Arrival
8.30 pm      Dinner

Thursday 4 March 2010

Chairpersons: D. Begley (UK) M. Scarpa (I)
08.30-08.45   Opening by ESF official
08.45-09.15   Introduction of Participants, definition of workshop goals
09.15-10.00   EUROPE AND BRAIN: Ian Ragan (EBC)
10.00-10.30   Overview and discussion of European funding opportunities, Q. Valent, NL
10.30-11.00   Coffee
Chairperson: F. Platt (UK) JM. Heard (F)
11.00-11.30   Key-lecture on Pathophysiology of Pediatric Neurodegenerative Diseases, T. Futerman (IL)
11.30-12.00   Key-lecture on 'Orphan Diseases of the Brain: determining interventional outcomes', T. Cox (UK)
12.00-13.00   Plenary discussion
13.00-14.00   Working lunch
14.00-15.00   Discussion for development of strategies for early diagnosis and understanding pathogenic mechanisms
15.00-15.30   Key-lecture on CNS therapy and Blood brain barrier crossing, D. Begley
15.30-16.30   Plenary discussion for drug delivery
16.30-17.00   Coffee
Chairperson: T. Cox (UK), I. Ragan (UK)
17.00-17.30   Key- lecture on clinical management of chronic Neurological patients, M. Scarpa (I)
17.30-18.00   Key-Lecture on ethical problems 'Tackling the ethical issues inherent in developing new treatments for paediatric neurodegenerative diseases', H. Russell (UK)
18.15- 19.00 Discussion on clinical management and comments on the topics of the day
19.30        Working Dinner
Friday 5 March 2010

Chairperson: D. Begley (UK), M. Scarpa (I)

09.00-9.30  Keynotes about rare diseases and EU A. (TBC) waiting for instruction by the representatives of the Italian government

09.30-10.00  The role of industry in drive innovation in the (European) life sciences area W. van Weperen (NL)

10.00-10.30  Keynotes on family support and care, interaction with families and family associations C. Lavery (UK)

10.30-10.45  Coffee Break

10.45-13.00  Discussion and generation of a preliminary draft and outline for an ESF EUROCORES Theme Application (to be submitted in 2010) and strategy for other FP 7 collaborative projects

13.00-14.00  Working Lunch

14.00  End of Workshop and departure
Objectives of the ESF Standing Committee for European Medical Research Councils (EMRC)

The ESF Standing Committee for the European Medical Research Councils (EMRC) has overall responsibility for initiating and coordinating ESF’s scientific activities in medical sciences and for providing expert advice on issues of science policy. It covers a broad range of disciplines and the Committee's main objectives range from promoting interactions between the biomedical and clinical research communities, through providing policy advice, to stimulating collaboration in emerging research areas.

The EMRC covers fields such as:

- Diagnostic and therapeutic medicine
- Neurobiology
- Immunology
- Clinical studies
- Communicable diseases
- Human genetics & functional genomics
- Medicinal biotechnology
- Public Health, etc.

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