

ESF Exploratory Workshop on

**BRAINS FOR BRAIN
Treating Pediatric Neurodegenerative
Diseases: From Laboratory Bench to Bedside**

Frankfurt (Germany), 3-5 March 2010

Convened by:

Maurizio Scarpa^① and David Begley^②

① University of Padova (Department of Paediatrics, University of Padova, Italy)

② Blood Brain Barrier Group (Kings College London, UK)

SCIENTIFIC REPORT

CONTENT

EXECUTIVE SUMMARY.	3
SCIENTIFIC CONTENT OF THE EVENT.	5
ASSESSMENTS OF THE RESULTS, FUTURE DIRECTIONS AND OUTCOME	13
FINAL PROGRAMME	14
FINAL LIST OF PARTICIPANTS	16
STATISTICAL INFORMATION ON PARTICIPANTS	20

EXECUTIVE SUMMARY

Neurodegenerative diseases are most familiar in ageing adults, but they can affect individuals of all ages. In children, neurodegeneration leads to developmental regression and premature death with devastating consequences on life quality for the patient and their immediate family as well as the extended social environment. neurodegenerative diseases represent an enormous charge on the supporting and medical services in society. Within the EU, paediatric neurodegenerative disorders are of assigned to the “rare” or orphan category but they nonetheless represent a disproportionate burden on society and the well-being of those affected. Because of the individually low-prevalence of each disorder, there is a striking lack of information and dedicated research into their treatment and prevention; at the same time, provision of expert clinical care and diagnosis is often inadequate and unevenly distributed within European regions and Member States. As a result, there is a uniform complaint that definitive diagnosis is delayed unconscionably – often with tragic results in affected families.

BRAINS4BRAIN is a European task force aimed at developing and implementing innovative therapies for paediatric neurodegenerative diseases for which no effective therapy is currently available. In particular it focuses its effort towards the treatment of neurodegeneration associated with Lysosomal Storage Diseases (LSDs) which lend themselves to therapeutic correction as a consequence of the secretion-recapture process for lysosomal enzymes. In LSDs genetic deficiency of particular acid hydrolases impairs degradation of macromolecules which accumulate and, through molecular pathways that are little understood, cause apoptotic cell death frequently associated with neurological manifestations. Therapeutic protein-or gene replacement or restoration of enzymatic activity by other means can ameliorate the functional consequences of the various enzymatic defects, but a major challenge for the neurological component of these disorders remains the blood-brain barrier (BBB) which prevents efficient delivery of corrective therapies to brain parenchyma.

BRAINS4BRAIN recognizes that only by expanding and implementing basic knowledge of pathogenesis, and understanding of the physico-chemical mechanisms by which the BBB impedes individual drug delivery, can effective clinical development be undertaken.. Importantly, we recognize that such knowledge will immediately provide therapeutic insights to the understanding of other important neurological diseases - including Alzheimer’s disease, Parkinson’s Disease, and the epilepsies..

BRAINS4BRAIN has called for a focussed collaborative research effort involving all available multidisciplinary European expertise to combat neurodegenerative diseases that affect infants and children.

The exploratory workshop was aimed at reviewing the current state of knowledge and awareness of paediatric neurodegenerative diseases and at uniting the separate disciplines present within Europe that will be required to develop effective treatment strategies for LSDs with neurodegenerative involvement. An unashamed ‘bench to bedside’ approach was adopted from the outset and participants included basic scientists (e.g. geneticists, biochemists, cell biologists, 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, in addition, representatives of specialized companies (e.g. developing neuropharmaceuticals or BBB-crossing technologies) were invited. Furthermore, patient groups as well as policy makers were involved, to include input from all stakeholders and to generate support for the interdisciplinary activities.

The two-day workshop, held at the Intercontinental Hotel, Frankfurt, Germany, brought together twenty-one specialists from 10 Countries. The invited scientists, all opinion leaders in the biomedical and clinical research communities from different countries, worked together with the aim of stimulating an interdisciplinary collaborative effort, and identifying common

objectives in this emerging area of research. The main goal was to 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.

The general atmosphere was amiable, free-thinking and productive: all participants were highly motivated and overall there was a strong sense of collaboration. and of excitement. The outcome of the workshop was very encouraging and positive.

The workshop was organised in several presentations followed by a forum for discussion to discuss the principal issues.

The main following key points were highlighted in the discussions:

- ⇒ The necessity of a major collaborative effort, offering the best chance of utilizing European funding opportunities to scientific advantage
- ⇒ The importance of free information exchange to ensure proper evaluation of contemporary knowledge (pathophysiology) and clinical management of pediatric neurodegenerative disorders.
- ⇒ The essential need to foster close scientific interactions and collaboration with Industries and at all times to have in mind the needs of families and family associations
- ⇒ The key importance of generating a preliminary draft and outline for a ESF EUROCORES Theme Application (to be submitted in 2010) and strategy for other collaborative projects

Participants were clear that while LSDs are a group of pediatric disorders for which therapy that can reverse the natural course of the disease in **peripheral** organs (Enzyme Replacement Therapy, ERT), there is a striking lack of progress in the ability of **ERT to effectively reach the CNS – thereby arresting** ongoing neurodegeneration. In the plenary discussion the succeeding main points were also emphasized:

- ✓ The necessity to develop new tools based on a better understanding of pathophysiology aimed to:
 - improve and accelerate diagnosis
 - prognosticate their severity
 - predict their progression
 - assess therapeutic effectiveness accurately
- ✓ The necessity of developing new tools for the detection of biomarkers which will enable to
 - Follow the progression of the disease
 - Evaluate efficacy and safety of different therapeutic approaches
- ✓ The necessity to penetrate the BLOOD-BRAIN BARRIER (BBB) (with both pharmaceutical and non-pharmaceutical therapy aimed to promote entry of curative molecules across the BBB into the CNS) by
 - Gene therapy and virus-mediated gene therapy
 - Substrate Reduction Therapy (SRT)
 - Chemical Chaperones
 - Hematopoietic and neural stem cell transplantation
 - Nanoparticles
 - Protein engineering to target specific BBB receptors and carriers

SCIENTIFIC CONTENT OF THE EVENT

4th march 2010

Opening of the meeting

The workshop program was divided into four broad sessions and ample time was put aside for Discussions at the end of each day.

The **first session, chaired by D Begley and M Scarpa**, was dedicated to an overview of European funding opportunities.

Prof Hans Lassmann, ESF official rapporteur and member of ESF Medical Research Council, officially opened the Exploratory Workshop welcoming the participants and briefly introducing himself and his activities. He then went through a series of slides giving an overview of what ESF is and what is actually doing underlying its main goal: to advance European research and to explore new directions for research at the European level. He highlighted that through its activities, the ESF serves the needs of the European research community in a global context and in particular he stressed the need of science strategy and science synergy. Prof Lassmann went through a series of slides giving an overview of ESF funding schemes giving a detailed analysis and explanation of each opportunity.

There followed a brief self presentation of participants.

Next **Dr M. Scarpa**, gave a clear and concise description of LSDs underlying that 1 child every 5000 is affected by these rare diseases and 70% of these patients are affected by CNS involvement where neuropathy is progressive. He emphasized that, at present, therapies are effective only in the periphery but not at the CNS level, so in order to treat the neurological disease we must cross the Blood-Brain Barrier (BBB) and it's so extremely important to create a joint action of people, clinicians, basic scientists, family associations focused on optimizing research on the BBB and neurodegeneration in pediatric area. He underlined that the workshop is so aimed at encouraging EU to support the development of new therapeutic treatment for these diseases and in particular the main objectives are:

- the exchange of knowledge and the discussion of data quality, accuracy and validity through a very accurate review of the state of the art of the different topics related to neurodegenerative LSDs considering in particular the discussion of following key areas:
 - Where we are (in term of knowledge and EU funding)
 - What we need to know
 - What are the methods for diagnosis and related ethical problems
 - How do we interact with the family WORLD
 - How do we interact with industries.
- To identify the knowledge gaps we have and to develop strategy to fill these gaps.
- To write a consensus statement in order that this group leave a message to Europe, ESF, EBC, National Agencies, Political members,...in order to convince Europe about the relevance and importance of these topics.
- To Analyse the 5th call and also to promote calls through EUROCORES, COST project, FP7 Health,...

Dr I. Ragan, Executive director EUROPEAN BRAIN COUNCIL, gave a talk about Europe and Brain. He first focused the attention on the EBC mission and activities explaining that the EBC is determined to eliminate the discrepancy between the huge impact of brain diseases and the implications of understanding normal brain function on the one hand, and the modest financial and time resources allocated to brain research, teaching and the care of brain diseases on the other. In particular he highlighted that the mission of the EBC is to promote brain research in Europe and to improve the quality of life of those affected by brain diseases. He underlined that the *EBC* will achieve this *by*:

- Collaborating with member organisations, while avoiding duplication of their work

- Interacting with the European Commission, European Parliament and other relevant EU and international institutions
- Promoting education in brain-related subjects
- Disseminating information about brain research and brain diseases in Europe
- Promoting dialogue between scientists and society

He presented the results of the Cost of Disorders of the Brain in Europe (CBDE) study that took into account health care costs (including hospital care, ambulatory care, drugs), private and public costs outside the medical sector (including nursing home costs and services or goods for private homes) and indirect costs (including limits on work capability, absenteeism and early retirement). It was stressed that across 28 European countries (the EU plus Iceland, Norway and Switzerland) with a total population of 466 million, 127 million people or 27% are affected by at least one brain disease. The total cost of brain diseases amounts to €386 billion, or €829 per European inhabitant.

After that he reviewed the current level of resource allocation to brain research in the EU analysing both private and public funding and categorizing funding sources according to function or disease target. An examination of brain research (all diseases affecting the brain, spinal cord and peripheral nerves) funding vs cost and burden, An analysis of Europe vs USA and vs other diseases was made . A clear variation of costs was evident. Moreover despite the fact that brain diseases represent 35% of the burden of all diseases in Europe, these diseases have received relatively little attention, in fact the total funding for Brain Research per annum is only 1% of the annual cost of brain diseases. An analysis of the FP7 budget allocation by year was then presented and it was evident that even with a total budget some 60 % higher compared to FP6 there is relatively little funding for brain research. It was then underlined that In order to increase the chances of grant applications for brain research being funded it's important to consider: quality of science, management, importance and applicability even in other fields.

Dr I. Ragan stated that the EBC has prepared a green paper that outlines what EBC members believe are key brain research themes in Europe for the next decade. This consensus document, which was published in March 2006 in the *Journal of Neurology, Neurosurgery & Psychiatry*, provides an overview of 45 thematic areas covering brain research from bench to bedside—that is, from basic science to translational and clinical science. The Consensus document is currently being updated and expanded and the new version will be published in 2010.

He then concluded his talk announcing the establishment of a European Brain campaign for the year 2013 of which B4B is one of the organizers. It should contribute in stimulating EU efforts concerning brain research into brain neurodegenerative diseases.

Dr. Q. Valent on behalf of Hezelburcht BioTop a company that is specialised in subsidy applications for life sciences projects, gave then an overview and discussion of European funding opportunities. He underlined that the workshop is meant to raise appreciation and attention on neurodegenerative diseases and to create focus for the group and momentum for future efforts. He assessed that opportunities for the consortium lie within FP7 and EUROCORES made following very important points :

- Most grants require specific collaborations
- IP issues should receive ample attention
- No grant will cover all costs
- Most grants are earmarked for defined topics
- Receiving grants means accepting obligations

He then went through a detailed analysis of do & don'ts regarding funding opportunities evaluation and application.

A comprehensive description of EUROCORES purposes, funding, timelines was then made with a special attention to EUROCORES Programme calls for collaborative research projects (CRP) that promotes investigator-driven, multinational collaborative research in the social sciences.

He continued his analysis on funding opportunities outlining the new FP7 Joint Programming scheme that will see Member States combine resources and monitor and review progress together.

He concluded then his analysis exemplifying the JPND a Pilot Initiative on Combating Neurodegenerative Diseases and in particular Alzheimer's disease and introducing the FP7 Health call expected for next July that should take into account interesting topics as:

- Role of neuroinflammation in neurodegenerative diseases
- Clinical trials for childhood onset neurodegenerative diseases
- New therapies for chronic inflammatory and autoimmune diseases
- Clinical trials in regenerative medicine

He finished then his presentation with a discussion of these calls.

After the coffee break the meeting continued with a session chaired by Dr. F. Platt and J.M. Heard.

Dr. T Futerman gave a key lecture on Pathophysiology of pediatric neurodegenerative diseases in which he introduced the concept of neurological pediatric lysosomal storage disease underlying the significant differences of neurological symptoms but highlighting that there is also a significant variation in the symptoms which occur upon the accumulation of similar yet quite different glycolipids as in the case of the molecules responsible for Gaucher and Tay Sachs diseases. Maybe it is the result of a different distribution of the stored products in regions of the CNS which are responsible for disease specific pathology? Maybe it's due to different sub cellular distribution of this lipid? Unfortunately the real pathological and molecular mechanisms is still not well understood and the same can be said for the phenotype-genotype correlation. Things are even more complicated as LSDs are not just multi-organ diseases but also multi-organelle diseases and many biochemical events are affected by LSDs such as

- Lysosome membrane permeabilization
- Autophagy alteration
- Translocation of transcription factors
- ER (sphingolipids accumulation is not confined only to the lysosome but can also be found in other organelles as in ER)
- Mitochondria (oxidative stress)
- Altered cellular trafficking pathways

He stated that B4B LSD group is significant due to the importance of these diseases accumulation of lipids in the lysosome that can affect multiple subcellular organs. He added that it is so extremely important to study both normal and also pathological functioning of these organelles. Moreover the B4B group are beginning to appreciate the cellular complexity and the cellular changes that occurs in LSDs but we are long away from having a clear mechanistic pathway explaining the events. For all these reason he answered the questions "Why do we need B4B, why it is useful?" with the following main statements:

- Clinic and Close collaboration between basic science and physicians
- LSD research is generally underrepresented in neuroscience
- LSDs can act as great models for other pediatric neurodegenerative diseases
- Genuine pan European collaboration (plus Israel and USA)
- Contact and Collaboration with patient organizations
- Excellent contact with pediatric patient organization
- Great interest for many pharmaceutical companies

In his opening key lecture, **Dr. T Cox** discussed: 'Orphan diseases of the brain: determining interventional outcomes'. He introduced the concept of rare (orphan) diseases as those that occur infrequently or rarely in the general population (in less than 200,000 individuals in the USA, or less than 5 per 10,000 individuals in the European Union, however, a variety of definitions of rare diseases exist). He explained that there are almost 6-8000 rare diseases officially recognized as disease entities by the National Institutes of Health; he cited the paradox of rarity, so that that even though the "diseases are rare, patients with rare diseases are many" as reported in the last UK survey on volunteer people that revealed that 45% of

patients were affected by a rare genetic disease; the rarity of a disease was certainly no consolation for those who suffer from it.

Unfortunately rare diseases individually have little immediate general economic impact and hitherto the development of treatments has not been considered economically realistic for pharmaceutical companies.. The so-called Orphan Drug legislation, creatively generated to address this deficiency was promulgated in the United States almost 30 years ago and in Europe since 2001. It has brought with it some notable victories for patients, allowing companies to develop innovative treatments for diseases so rare that sponsors are reluctant to develop them under usual marketing conditions. Striking examples of spectacular commercial success have emerged as a result even with ultra-orphan' diseases such as Gaucher disease, where the provision of an effective enzyme replacement therapy was based on molecular targeting to the cellular focus of the disease. Treatment currently supplied to little more than 5000 individuals worldwide generated \$billions in revenues and had lifted the fortunes of the Genzyme corporation to its position as the world's third-largest biotechnology company – the corporation has set an example to other aspiring pharmaceutical/biotech organizations who seek to compete in the lysosomal disease field, the industrial scores for which have yet to be settled.

Dr Cox emphasised the continuing need to encourage pharmaceutical companies to invest in the lysosomal diseases – especially those cruel disorders affecting the brain. He made it clear that there remained many scientific, humanitarian and commercial opportunities for exploitation; moreover, the prestige associated with the development of the first successful therapy for a progressive neurodegenerative disease affecting young persons and infants would be beyond price. Cox stressed also that it was the special biology of the lysosome - recognized from the outset by Christian De Duve, the discoverer of this remarkable organelle and one of the Founding Fathers of the discipline of Cell Biology - that offers prodigious therapeutic opportunities for those investigators and companies brave enough to venture onto this battlefield. Irrespective of the devastating nature and ineluctable course of the lysosomal diseases that were the object of the B4B collaboration, the extraordinary molecular pathophysiology of these diseases and the capacity of the lysosome for functional complementation by receptor-mediated secretion-recapture acting at a distance that confers their unique susceptibility to definitive therapy.

In a brief survey of the challenging work taken on by the B4B collaboration, Dr Cox indicated how innovative therapies for the challenging diseases to be targeted requires understanding of:

- Pathogenesis
- Natural course of the disorder
- Timing, delivery mechanisms and immunology
- Safety and prediction of unwanted side effects of putative therapies

And the potential therapeutic approaches represented by

- ERT
- Bone marrow transplantation
- Substrate Reduction Therapy
- Chaperones
- Gene Transfer

Participants were introduced to the molecular basis of those classes of lysosomal disease commonly associated with neurodegenerative manifestations and emerging modalities for their treatment. Dr Cox concluded with a brief demonstration of how stereotaxic administration of gene therapy using recombinant adeno-associated viral vectors (rAAV) effectively, transducing the correct gene, can ameliorate storage pathology and greatly prolong survival and neurological function. Recently unexpected therapeutic achievements in terms of life prolongation and correction of motor function and activities in living animal

models of the devastating GM2 gangliosidosis were shown. Finally, amongst the clinical science, there was a reflection on the need to consider how gene therapy should be delivered optimally through the BBB and a practical request to improve early diagnosis and our clinical knowledge of the disorders chosen for clinical trials - so that clear rules for the demonstration of clinically meaningful outcomes could be developed and ethically explored.

A **Plenary discussion followed** during which participants underlined the solidity and commitment of the B4B Foundation in advancing understanding and treatment of neurodegenerative diseases which clearly affect an ever increasing portion of society, and in particular it was emphasized that the foundation focuses on a group of pediatric neurodegenerative diseases (LSDs), for which a therapy with proof-of-principle exists, but effective therapy is hampered by the presence of the BBB, that prevents the efficient delivery of therapeutics to the affected brain. It was therefore underlined how far and at the same time how close they are to specific applications and the market, and for this reason the involvement and support of companies in the development of therapies play a fundamental role. A active discussion took place about the involvement of companies and the necessity to find funding solution in order to allow research to progress.

After lunch a discussion for the development of strategies for early diagnosis and understanding pathogenic mechanisms took place. Starting from the point that the Brains for brain consortium represents a unique world-class collaboration of European scientists that work on scientific disciplines that have thus far progressed in parallel. However, these two scientific disciplines (LSD and BBB research) are extremely complementary and will greatly benefit from this structured collaboration. The concept of the importance of therapy and clinical trials was introduced in addition to diagnosis and it was analysed what B4B group should do regarding the pathogenetic field and what it can do within the clinical trial field. The opportunity of applying to the FP7 and suitable projects was emphasised. Discussion then moved toward how to make a set of proposals specifying the unique contribute of B4B and taking into account what was wrong in the previous applications. The consideration from within the group was that basic science has a important role and because of this it's much more difficult to find financial support, because it's too far removed to be translated into clinics applications and so it's not much appealing for the interest of pharmaceutical companies. The possibility was then discussed of how to create a collaboration between very basic science and the European Community looking for something that could have future application. In particular it the importance to create visibility, to create contact with European Commission and National representative sitting in Brussels was underlined, local financing agency, and to show all these agencies that the project is strong and very competitive.

Dr D. Begley gave then a key lecture on CNS therapy and Blood Brain Barrier crossing, He started with a clear elucidation of the BBB, the natural barrier between the brain and the peripheral organs, allowing only those molecules required by the CNS to enter the brain. He answered the question Why is BBB important in neuropathological LSDs explaining that unfortunately, by performing its essential task the BBB is effectively excluding therapeutics administered for the treatment of a variety of brain disorders, including neurodegenerative disorders. Since the proof-of-principle that restoring the primary defect can reverse the natural history of lysosomal storage diseases is already in place, crossing the BBB represents the main obstacle that research needs to overcome. He then examined different strategies for solute transport across the BBB examining the physico-chemical properties of different small molecules which determine their passive or active movement across the endothelial cells of the BBB and exploring vector systems for the delivery of difficult or large "biopharmaceuticals" such as growth factors, peptides/proteins and enzymes across the BBB. He therefore introduced the concept of vesicular trafficking at the BBB, receptor-mediated transcytosis, fusion proteins, nanoparticles (transcytotic uptake), and observed that function and integrity of BBB in LSDs could be altered because BBB may be damaged in these conditions due to storage or associated inflammation and thus it is extremely important

to understand how current treatments interact with the BBB. Dr Begley showed some experimental results highlighting how for these reasons basic research using *in vitro* and *in vivo* models of the BBB in health and disease, together with the use of electron microscopic studies, are extremely important for elucidating different routes available for transport of larger molecules across the BBB and for deciphering the role that BBB alterations may have on LSD neurodegenerative disease progression.

The session was then closed with a plenary discussion on drug delivery during which participants defined which kind of further studies are needed or are more appropriate to improve drug delivery across the BBB

After the coffee break the last session of the day was chaired by Dr. T Cox and I Ragan.

Dr. M. Scarpa opened the session with a key lecture on clinical management of chronic neurological patients. Before speaking about management of patients he showed a short movie (Allison's MPS awareness video 2009 from UTube) and emphasized some of Allison's words because they exemplify exactly what kids with LSDs are suffering every day in the clinic and what they really need :

- ⇒ Awareness (because nobody knows about these disorders)
- ⇒ Courage (because affected children are suffering)
- ⇒ Therapy (some is there, but after 6 six years of age the results are still relatively poor)
- ⇒ It is really hard sometimes (affected children are facing every day these kind of problems)

Regarding the management of the patient he underlined that one of the main things is to

- try to follow the patients
- give them a proper treatment which relies primarily on an early diagnosis,
- use a proper clinical protocol to evaluate the progression in order to be able to differentiate the different phenotypes and consequent progression,
- help these people improving their daily quality of life.
-

He stressed that even if inside the B4B group there are people working on tandem mass spectrometry newborn screening for Krabbe, Gaucher, NPC, Pompe, Fabry disease and soon for MPSII, VI, I, this is not completely successful . In fact as soon as we have a early diagnosis unfortunately we do not know the phenotype and thus the consequent progression of the disease. He stated that newborn screening is not helping in making a good prognosis, so he proposed to create a group of experts who under blinded conditions decides the phenotype in order to then come out with some milestones important for diagnosis and with some clinical markers to monitor and predict the disease course allowing an evaluation of the disease evolution. This is particular important considering that almost 70% of these patients develop neurological involvement and up to date there are no tools for evaluating CNS progression and so Dr Scarpa underlined the importance of creating a severity score system for the CNS and then create a software in order to speed up the exchange of data.

He talked then about therapies, defining it as a very difficult task because many therapies are not in the near future, He went through the different therapeutic approaches:

ERT, Substrate Inhibition, Chaperone, In vivo gene therapy, Gene modification (stop codon mutation) indicating advantage and disadvantage of each. Regarding the point When do we start therapy for a child he indicated to start as soon as possible for the best results. He concluded summarizing that B4B group could contribute to

- Methods to perform an early diagnosis,
- Generate protocol for trials and for evaluate ethic aspects
- Find methods to evaluate CNS involvement,
- Understanding how to find biomarkers

Followed then the key lecture of **Dr H. Russell** entitled "Tackling the ethical issue inherent in developing new treatments for pediatric neurodegenerative diseases". She underlined that the main objectives of the topic are Children with

- Untreatable/Progressive/Life-limiting diseases
- Variable/Limited communication capacity
-

After a brief description of REC Committee she elucidated the function of REC as follow:

- Education
- Awareness about ethical issues
- Provision of advices
- Protection (Protect the right and welfare of research participants but also of the research itself)

Then she underlined the Principals for Ethical conduct as follow explaining that it's important to achieve a balance of all of these, even if autonomy is normally considered the most important:

- Autonomy (right of the individual to choose for himself)
- Non maleficence (not harmful)
- Beneficence (do good)
- Justice (shouldn't make use of vulnerable population - fairness)

She discussed the 7 requirements (introduced by Emanuel et al JAMA 2000 Volume 283(20) pp 2701-2711) in order to make clinical research ethical.

1. VALUE—enhancements of health or knowledge must be derived from the research;
2. SCIENTIFIC VALIDITY—the research must be methodologically rigorous;
3. FAIR SUBJECT SELECTION—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects;
4. FAVORABLE RISK-BENEFIT RATIO—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks;
5. INDEPENDENT REVIEW—unaffiliated individuals must review the research and approve, amend, or terminate it;
6. INFORMED CONSENT—individuals should be informed about the research and provide their voluntary consent (respect for autonomy);
7. RESPECT FOR ENROLLED SUBJECTS—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored.

She then exemplified some particular case and situation and she gave some consideration to how it's not always very easy to find the right answer to some questions that could be argued on scientific design subject especially regarding young children affected by LSDs.

An active discussion about participants took then place and closed the session

There followed a working dinner.

5th march 2010

Dr. Begley, chairman of the morning session, opened the meeting pointing out that LSDs are an excellent opportunity for collaboration in Europe, the diseases themselves are rare, physicians who treat the patients are rare, scientists working on these diseases are rare, but within Europe we have 27 countries, multiplying the patients, multiplying the physicians, multiplying the scientists and hopefully increasing the finance that can be applied to study

and treat LSDs. A European collaborative effort for the LSDs is the perfect field for Europe to work together and have a combined and coordinated action.

He then introduced the speakers of the day summarizing the key points of their discussion.

This was followed **Dr W van Weperen** who gave a talk about “The role of industry in the drive for innovation in the (European) life sciences area”. After a brief introduction of himself he described to-BBB, his small Dutch biotechnology company operating in the field of brain-targeted drug delivery which uses its platform technologies to synergize with established and marketed drugs. He briefly reviewed the different approaches to brain delivery, focussing his attention on Targeting glutathione (GSH) transporters in enhancing transport of drugs across the BBB by encapsulating these compounds into proprietary glutathione coated liposomes. He showed results obtained with ribavirin (a water soluble compound) using the GSH brain uptake method. G-Technology needs to be further tested and optimized, it's still far from the market but it could significant represent an option for many unmet CNS needs. He then went through G-Technology development pro and contra underlying that even if there is a good academic knowledge, animal models are available, orphan drugs incentives exist, it requires large amounts of money, presents a high level of risk and so the willingness and support of the investors needs to be high. Moreover things are further complicated by the fact that is very difficult to measure CNS damage and because of the heterogeneity of disease progression it's crucial to make studies in order to improve knowledge on the natural history of these devastating diseases.

C Lavery gave then a talk entitled “Keynotes on family support and care, interaction with families and family associations”. She described the aims of patient organizations support groups for LSDs underlining that they have not changed over the passage of time and are common to groups worldwide:

- to offer support to patients affected and their families
- to provide an educational role providing information on the various LSDs
- to encourage and fund research and treatment
- to provide information or advice and individual advocacy on:
 -
 - ⇒ disability benefit applications
 - ⇒ special educational needs
 - ⇒ grants for equipment and holidays
 - ⇒ independent living
 - ⇒ respite care
 - ⇒ home adaptations
 - ⇒ sibling support
 - ⇒ bereavement

She elucidated how European and International collaborations by LSDs diseases groups in the UK are closely involved with their counterparts in Europe and globally and a number of international or global meeting are organised in order to promote clinical excellence and encourage basic research and improve the life of patients affected by LSDs. Moreover these meetings represent a great opportunity for facilitating the sharing of information and data. She then highlighted the common objectives of the different LSDs group are:

- Overcoming BBB and getting enzyme into the brain
- Addressing and Correction of bone diseases
- Improving biomarkers
- Understanding the new disease course manifestations in treated adults (understand the risk of these treatments)
- Achievement of effective scientific collaboration
- Building professional and effective relationship with industries

- Accurate tools for measuring treatment outcome (Quality of Life)
- Patient organizations working together (UK LSDs model)

Where the money will come from? From B4B prospective the answers are:

- Responding to EU calls
- Charitable Trusts and Foundations
- NHI, MRC,CSG
- Industries
- Partnerships
- Patient organizations

She then concluded her talk announcing the establishment of a B4B day in 2011 for raising funding and increasing awareness and visibility.

Followed a discussion and generation of a preliminary draft and outline for an ESF EUROCORES Theme Application (to be submitted in 2010) and strategy for other FP7 collaborative projects.

ASSESSMENT OF THE RESULTS, CONTRIBUTION TO THE FUTURE DIRECTION OF THE FIELD, OUTCOMES

The informal feedback given by the participants was very positive throughout. Many stressed that they had learnt a lot from colleagues working in different fields of science. The workshop was in fact very useful for establishing new interactions between the participants and strengthening existing ones. The Workshop objectives of sharing knowledge and experience and initiating joint work were achieved. Members were able to learn more about the pathophysiology of pediatric neurodegenerative diseases and state of the art of development of new therapeutical approaches for crossing the Blood Brain Barrier. It represented a great opportunity for facilitating the sharing of information and experimental unpublished data. The workshop clearly confirmed the fact that LSDs provide excellent models to develop the further understanding of neuro-pathophysiology and deciphering mechanisms responsible of brain alterations in neurodegeneration and consequently develop new approaches for:

- an early identification and diagnosis of neurodegenerative disorders caused by storage of macromolecules, and their pathophysiology,
- the study of the physiology of the blood brain barrier by creation of in vitro models and analysis of in vivo models
- the development of new strategies to cross the blood brain barrier as a major goal to achieve brain therapy and to modify in a positive manner the natural history of these lethal progressive diseases.

All the derived results will be important for the research and treatment of other neurodegenerative disorders in the adulthood (i.e. Alzheimer and Parkinson disease) where effective therapy, often of “difficult” molecules such as biopharmaceuticals may also be required.

The most effective way of achieving this aim is through the establishment of a combined multidisciplinary approach involving clinicians, basic scientists and biotech companies and Family Associations.

The participants came to the conclusion that because LSDs are rare diseases, and thus the resources in individual countries in terms of scientific manpower and finance for research are limited, it is extremely important to further consolidated the consortia concentrating the scientists and financial support into larger more effective international groups.

Participants agreed on the imperative of initiating similar discussions within National research Associations, National EU Representatives, National Research Financing Agencies and in as many venues as possible in order to increase awareness and visibility.

The first commitment of the group is to initiate a health and technology assessment paper estimating the overall cost of these LSD patients to The EU. It will be produced during next months in order to have a milestone to present to the EU Commission in order to illustrate the value of B4B activity.

Participants agreed to apply possibly to the Eurocores call for themed proposal, after a preliminary contact with the national financial agencies, and a Cost Project (exchanging oh PhD students, workshops, summer schools,) and further meetings and also to address applications to the two possible programs of the 5th FP7 Call of the European Commission: related to neurodegenerative diseases.

FINAL PROGRAMME

Thursday 4 March 2010

Chairpersons: D. Begley (UK) M. Scarpa (IT)

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 (UK)**

10.00-10.30 Overview and discussion of European funding opportunities, **Q. Valent, (NL)**

10.30-11.00 *Coffee Break*

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 (UK)**

15.30-16.30 Plenary discussion for drug delivery

16.30-17.00 *Coffee Break*

Chairperson: T. Cox (UK), I. Ragan (UK)

17.00-17.30 Key- lecture on clinical management of chronic Neurological patients, **M. Scarpa (IT)**

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)**

- 09.00-9.30** Summary of the meeting **M. Scarpa (IT)**
- 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*

FINAL LIST OF PARTICIPANTS

Convenor:

1. **Maurizio SCARPA**
Department of Pediatrics
University of Padova
Via Giustiniani 3
35128 Padova
Italy
maurizio.scarpa@unipd.it

Co-Convenor:

2. **David BEGLEY**
Blood Brain Barrier Group
Pharmaceutical Sciences
Hodgkin Building
Kings College London
Guy's Campus London SE1 1UL
UK
david.begley@kcl.ac.uk

ESF Representative:

3. **Hans LASSMANN**
Division of Neuroimmunology,
Immunopathology
Brain Research Institute
Vienna University Medical School
Spitalgasse 4
1090 Vienna
Austria
hans.lassmann@meduniwien.ac.at

Participants:

4. **Jean Micheal HEARD**
Department of Neuroscience
Pasteur Institute
25 Rue Docteur Roux
Paris 75015
France
jmheard@pasteur.fr
5. **Tim COX**
Department of Medicine
University of Cambridge
Box 157, Level 5
Addenbrooke's Hospital
Cambridge CB2 0QQ
UK
tmc12@medschl.cam.ac.uk
6. **Fran PLATT**
Department Of Pharmacology
University of Oxford
Mansfield Road
Oxford OX1 3QT
UK
frances.platt@pharm.ox.ac.uk
7. **Tony FUTERMAN**
Weizmann Institute
Ullman Building Room 13
Weizmann Institute of Science
Rehovot 76100
Israel
tony.futerman@weizmann.ac.il
8. **Ingolf BLASIG**
Mol Cell Physiology Leibniz Institute
Fur Molekular Pharmakologie
Forschungverbund Berlin E.v. House
81
Robert Rossle Sr 10
13125 Berlin Buch
Germany
iblasig@fmp-berlin.de
9. **Maria A. DELI**
Biological Research Center
Hungarian Academy of Sciences
Temesvari krt. 62.
H-6726 Szeged, Hungary
deli@brc.hu
10. **Jorg KREUTER**
Institut fuer Pharmazeutische
Technologie
Biozentrum-Niederursel
Johann Wolfgang Goethe-Universitaet
Max-von-Laue-Strasse 9
60438 Frankfurt
Germany
kreuter@em.uni-frankfurt.de

11. **Jonathan COOPER**
Pediatric Storage Disorders Lab
Department of Neuroscience, Centre
for the Cellular Basis of Behaviour
and MRC Centre for
Neurodegeneration Research
The James Black Centre
The Institute of Psychiatry
King's College London
125 Coldharbour Lane
London SE5 9NU
UK
Jonathan.Cooper@iop.kcl.ac.uk
12. **Bert de BOER**
LACDR/Pharmacology
University of Leiden
PO Box 9502
2300 RA Leiden
The Netherlands
B.Boer@LACDR.LeidenUniv.NL
13. **Willem van WEPEREN**
To-BBB
Bio Partner Center II
Niels Bohrweg 11
Bio-Science Park Leiden
2333 CA Leiden
The Netherlands
vanweperen@tobbb.com
14. **Quido VALENT**
Hezelburcht BioTop B.V.
Hillegomstraat 12-14
1058 LS Amsterdam
The Netherlands
q.valent@hezelburcht.nl
15. **Christine LAVERY**
UK MPS Society
MPS House
Repton Place
White Lion Road
Amersham
Buckinghamshire HP7 9LP
UK
c.lavery@mpsociety.co.uk
16. **Ian RAGAN**
EUROPEAN BRAIN COUNCIL
CIR Consulting Ltd
51 Slaidburn St
London SW10 0JW
UK
ian.ragan1@btinternet.com
17. **Michael Yeh**
Genzyme Therapeutics 500
Kendall Street 08-133
Cambridge MA 02142
UK
Michael.Yeh@genzyme.com
18. **Terence EAGLETON**
Shire HGT
Hamshire Int Business Park
Chineham, Basingstoke
RG24 8EP
UK
teagleton@shire.com
19. **Hilary RUSSELL**
Centre for Cancer Research & Cell
Biology
Queen's University Belfast
Belfast
BT9 7AB
United Kingdom
seh.russell@qub.ac.uk
20. **Steve WALKLEY**
Sidney Weisner Laboratory of Genetic
Neurological Disease
Department of Neuroscience
Rose F. Kennedy Center for Research
in Mental Retardation and Human
Development, Rm 618
Albert Einstein College of Medicine
1410 Pelham Parkway South
Bronx, NY 10461
USA
Steve.Walkley@einstein.yu.edu
21. **Ulrich Matzner**
Institut für Physiologische
Chemie - Rheinische Friedrich
Wilhelms Universität
Nussallee 11
53115 Bonn
Germany
matzner@institut.physiochem.uni-bonn.de

STATISTICAL INFORMATION ON PARTICIPANTS

Countries of Origin

(according to affiliation, including Convenors and ESF Representative)

- United Kingdom 7
- Germany 3
- The Netherlands 3
- Eire 1
- Austria 1
- France 1
- Hungary 1
- Israel 1
- Italy 1
- United States 2

Gender

- Female 4
- Male 17