Lysosomal Storage Disorders (LSDs) are inherited metabolic disorders due to the deficit of lysosomal enzymes causing accumulation of mucopolysaccharides which is responsible for cell apoptosis with time.

Since lysosomal enzymes are ubiquitous molecules, their deficiency has important effects in all organs, in particular the central nervous system (CNS), liver, spleen, heart and bones.

With the advent of recombinant DNA technology, the identification and cloning of all the known lysosomal enzymes has been recently achieved, and therefore, expression and purification of recombinant proteins is now possible and enzyme replacement therapy (ERT) is now available for a growing number of storage disorders.

However, although ERT has proven to be valuable to possibly change the clinical history of the disease it has been evident that the recombinant proteins do not have any effect on the CNS, as they are unable to cross the blood brain barrier.

Furthermore, the mechanisms and etiology of CNS pathology in LSDs are still poorly understood.

We still do not know whether storage and accumulation of mucopolysaccharide is really the “primum movens” of the metabolic disaster or whether other processes might be more important (inflammation, alteration of ion channel activity, lack of chaperone molecules etc.). The understanding of these basic aspects might be extremely valuable to unravel why most of the LSDs have an attenuated and a severe form without and with CNS involvement, respectively, depending on whether there is a total enzymatic deficiency or not.

THE BRAINS FOR BRAIN TASK FORCE

The task force takes advantage from the expertise of the most distinguished European scientists, leaders in basic and applied neurotechnology and neurology grouped together to create a coordinate effort toward the comprehension of the pathophysiological processes of the neurological disorders, the implementation of knowledge on the blood brain barrier and the development of new molecular and or biochemical strategies to overcome the blood brain barrier and treat neurological disorders.

The B4B nickname of the group has been created to acknowledge the effort of the 4 initial industrial sponsors (ACTELION, BIOMARIN, GENZYME and SHIRE Human Genetic Therapies) without the support of which this brainstorming panel could not have been created.

Brains For Brain (B4B) was formally founded in March 2007 as a research group formed by international specialists and leaders on clinical and basic research in the field of neuro-pediatrics and neuroscience.

The group has attracted interest from major biotech companies working on the development of new therapeutical strategies for lysosomal diseases, and furthermore has a strong interaction with international family associations, involved in taking care of the needs of lysosomal patients, and has stimulated collaborations toward coordinate actions to disseminate knowledge about the diseases.

B4B has also collaborated with International Scientific Associations, such as the European Study Group for Lysosomal Diseases (ESGLD) and the International Blood Brain Barriers Society (IBBS) and it is a member of the European Brain Council.
THE BRAINS FOR BRAIN FOUNDATION

The BRAINS FOR BRAIN FOUNDATION is a no-profit international organization addressed to disabled children who are affected (or healthy carriers) by rare neurological diseases.

The purposes of the FOUNDATION are:

- scientific research;
- dissemination of knowledge;
- social and socio-medical assistance;
- health assistance.

In the field of Neurodegenerative Lysosomal Disorders the aims of the FOUNDATION are:

- to support medical and scientific research with regard to paediatric rare neurodegenerative diseases (with particular regard to Lysosomal Storage Disorders and genetic pathologies);
- to increase public awareness and interest on such diseases;
- to organize and promote national and international research activities;
- to coordinate and promote preclinical and clinical trials;
- to organize conferences and workshops on the abovementioned topics;
- to share cultural and scientific backgrounds with different stakeholders to implement knowledge on Neurodegenerative Disorders;
- to raise funds to support research;
- to fund fellowships or prizes;
- to campaign to increase public and stakeholders awareness to Neurodegenerative Disorders and for public fund raising.

THE EUROPEAN PARLIAMENT MEETINGS

Rare neurological diseases of childhood pose a serious medical health issue in Europe. Although individually uncommon, collectively there are thousands of rare diseases that affect a large number of people. The need to collaborate to focus on these disorders was highlighted during the meeting: RARE NEUROLOGICAL DISEASES OF CHILDHOOD: WE TREAT THE CHILD TO TREAT THE ADULT organized by the Brains for Brain Foundation at the European Parliament in Brussels on December 2nd 2010. The main aim of the meeting was to acknowledge the growing interest of the European Union Commission in both rare and neurological disorders.

To reinforce the necessity to work together and center attention on rare neurological disorders of infants and children the B4B Foundation has more recently organized the roundtable: "PAVING THE WAY FOR A COMPETITIVE AND DYNAMIC EU KNOWLEDGE ECONOMY: THE WAY FORWARD IN RARE DISEASES" which was held again at the EU Parliament in Brussels, on November 26, 2013. The meeting rallied numerous relevant stakeholders to discuss initiatives aiming to create a model of intersectoral cooperation that could facilitate the set-up of a European PhD Programme in the area of rare neurological diseases of children. In line with the core principles established by “Towards a Maastricht for Research”, the Brains for Brain Foundation has in fact created a network of Universities and Scientific Societies to start a doctorate programme aimed at furthering the knowledge on neurometabolic diseases amongst young physicians and scientists in order to establish an European Network of specialized experts and maintain excellence in Europe. Such initiative intends to enhance an advance awareness and knowledge about rare diseases via cross-border collaboration and to enable better diagnosis and management of patients affected by these diseases.
Holding these meetings, B4B wished to demonstrate the unity of intent of family associations, biotechnology and pharmaceutical industries and the scientific community in stimulating interest in rare neurological diseases and advance care for affected children.

The B4B EP Roundtable in particular represents a major step toward the establishment of a successful EU cross border collaboration and cooperation to raise awareness about rare diseases of childhood and keep them on the health-care agenda. Although individually rare by definition, rare diseases collectively affect millions of people worldwide. Joint forces to tackling them are essential to ensure that affected children are given the priority they deserve and that their needs are met.

**Inherited NeuroMetabolic Diseases INFORMATION NETWORK**

The Inherited NeuroMetabolic Diseases INFORMATION NETWORK (InNerMeD-I-Network) has been funded by the Executive Agency for Health & Consumers (DG-SANCO) under the Second Programme of Community action in the field of Health, 2008-2013 (contract id 20121212) to be the first European Network on paediatric neurometabolic diseases.

InNerMeD-I-network wants to create a network of information targeted on diagnosis and treatment of iNMDs based on the collection and exchange of proper information among scientific community, health professionals, patients, patient associations and all interested stakeholders. The project aims to increase current knowledge on iNMDs and speed up the timely and precise identification of patients, who may benefit of the available (experimental and marketed) treatments. The network will also favour biomedical research, straightening research capacities and fostering innovative therapeutic tools derived from the recent scientific advancements based on biomarkers use and personalised approaches.

The InNerMeD-I-Network, coordinated by the Brains for Brain Foundation, includes four associated partners (Gianni Benzi Pharmacological Research Foundation, Center for Metabolic Disorders at the University of Copenhagen, University of Zagreb School of Medicine, Hospital Sant Joan de Déu) plus fifteen collaborating partners, including clinical and research centres, patients and parents associations and scientific societies.

**AIMS OF THE WORKSHOP**

The aims of the nineth Meeting of the Brains For Brain Foundation are:

- to discuss research achievements in the field of neurodegenerative disorders at clinical and basic science level in the field of neurodegenerative lysosomal storage disorders and Blood Brain Barrier;
- to discuss new recent advances on natural history and pathophysiology of LSDs particular attention to the important role of an early intervention in preventing the morbidity and mortality associated with each of the disorders;
- to discuss factors which control the entry into the brain of medicines and other therapeutic agents which may be helpful in treating central nervous disease;
- to discuss how B4B might collaborate with the European Union to stimulate interest in the research on LSDs and BBB. For this reasons representatives from EU Commission will be invited;
- to discuss collaborations with international family associations and corporations to increase knowledge about storage diseases and research projects;
- to discuss the role of the industries in driving innovation for new therapeutical approaches for true unmet needs.

This Workshop arises from the project **Inherited NeuroMetabolic Diseases Information Network** (InNerMeD-I-Network, agreement no. 2012 12 12) which has received funding from
the European Union, Executive Agency for Health and Consumers, in the framework of the Second Health Programme.

**Organization**
Maurizio Scarpa (IT), David Begley (UK), Coordinators

**Scientific Officer:**
Cinzia Maria Bellettato, (IT)

**Logistics:**
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SCIENTIFIC PROGRAMME

February 5th

10.30-10.45 Welcome and Opening

10.45-11.05 Opening Lecture: Maria da Graca Carvalho, Member of the European Parliament
The effort of the EU Commission for research: the Horizon 2020 programme and the vision for the future.

11.15-12.00 Plenary Lecture: Stefan Liebner, Goethe University, Frankfurt, DE
Molecular Regulation of Endothelial Barrier Properties in the Central Nervous System
Discussion

12.00-16.15 BASIC ASPECTS
Chair Discussants: Gert Fricker, D and Romeo Cecchelli, F

12.00-12.25 Paul Saftig, Christian-Albrechts-Universität zu Kiel, DE
Emerging roles of lysosomal membrane proteins in health and disease
Discussion

12.30 LUNCH

14.30-14.45 Jeffrey Iliff, Oregon Health & Science University, Portland, USA
Paravascular Cerebrospinal Fluid (CSF) Recirculation: From Housekeeping to Neurodegeneration
Discussion

15.05-15.30 Michael W Salter, University of Toronto, Canada
Microglia: Guardians of the Brain
Discussion

15.40-16.05 Jean Gruenberg, University of Geneva, CH.
Endosomal lipids in trafficking and signaling
Discussion

16.15 COFFEE

16.30-18.15 BASIC ASPECTS 2
Chair Discussants: Fran Platt, UK and Ingolf Blasig, D

16.30-16.55 Romeo Cecchelli, University of Artois, FR
A Human in vitro model presenting a Blood Brain Barrier phenotype is a prerequisite for a proper study of cancer cells metastasis to the brain
Discussion
17.05-17.30 Svitlana Garbuzova-Davis, University of South Florida, Morsani College of Medicine, Tampa, USA. Human Umbilical Cord Blood Cells in Treatment of MPS IIIB  
Discussion

17.40-18.05 Maria Francisca Coutinho, Research and Development Unit, Department of Human Genetics, INSA, Porto, PT The role of the mannose-6-phosphate receptor in lysosomal function and dysfunction  
Discussion

18.15-18.40: Mika Ruonala, NeuroToponomics Group, CMP, University of Frankfurt, D The quest towards CNL3 function

19.30 DINNER

FEBRUARY 6th

9.00-13.0 Basic Aspects 3  
Chair Discussants: Timothy Cox UK and Greg Pastores, EIRE

9.00-925 Danica B Stanimirovic, National Research Council of Canada, Human Health Therapeutics Portfolio, Ottawa, Canada  
Mechanisms of antibody trafficking and transcytosis across the blood-brain barrier: A role for extracellular microvesicles?  
Discussion

9.35-10.00 Rodney Pearlman, President of The Bluefield Project to Cure Frontotemporal Dementia.  
Progranulin Accumulation and Fronto-Temporal Lobe Degeneration, a link with NCL  
Discussion

10.10-10.35 Gert Fricke, Ruprecht-Karls-Universität Heidelberg, DE  
Drug targeting to the brain by colloidal carrier systems  
Discussion

10.45 COFFEE

11.15-11.40 Jörg Kreuter, Goethe-Universität Frankfurt, DE  
Drug Delivery to the CNS by Polymeric Nanoparticles: What Do We Know  
Discussion

11.50-12.15 Ulrich Matzner, Rheinische Friedrich-Wilhelms Universität, Bonn, DE  
Anti-inflammatory therapy with simvastatin improves CNS pathology and function in a mouse model of metachromatic leukodystrophy  
Discussion

12.25-12.50 Tim Spector, Kings College, UK  
How May Two Individuals, With The Same Genetic Mutation, Display Quite Different Phenotypes
9th BRAINS FOR BRAIN PLENARY WORKSHOP
and
InNerMeD Information Network 2nd OPEN CONFERENCE

Discussion

13.00 LUNCH

14.30-16.15 CROSSING THE BLOOD BRAIN BARRIER AND THERAPEUTIC OPTIONS
Chair Discussants: Tony Futermann, IL and Generoso Andria, I

14.30-14.55 Beverly Davidson, University of Pennsylvania, Philadelphia, USA
"Bypassing the BBB: Gene Based Therapies for the Lysosomal Storage Diseases"
Discussion

15.05-15.30 Alfred Kohlschütter, University Medical Center Hamburg-Eppendorf, Hamburg, DE
Experience with intracerebroventricular delivery of a lysosomal enzyme in the clinical trial for CLN2 disease
Discussion

15.40-16.05 Joseph Muenzer, University of North Carolina at Chapel Hill, USA
Crossing the Blood Brain Barrier by direct injection of lysosomal enzymes: the clinical trial for the Hunter syndrome
Discussion

16.15 COFFEE

16.45-19.30 CROSSING THE BLOOD BRAIN BARRIER AND THERAPEUTIC OPTIONS 2
Chair Discussants: Alfried Kolschutter, D and Danica Stamirovic, USA

16.45-17.10 Emyr-Lloyds Evans, University of Oxford, Uk
A Zebra fish model for NPC for phenotyping and drug screening
Discussion

17.20-17.45 James Callaway, ArmaGen Technologies, Inc.
Delivery to the CNS with antibody-targeted receptor-mediated transcytosis
Discussion

18.00-18.45 Plenary Lecture Alessandra D’Azzo, St. Jude Children’s Research Hospital, Memphis Tennessee, USA
Lysosomal multienzyme complex: pros and cons of working together
Discussion

20.30 DINNER

February 7th

08.30-10.00 BRAINS FOR BRAIN AND INNERMED EUROPEAN ACTIONS
Chair Discussants: David Begley, UK and Maurizio Scarpa, DE
8.30-8.45 Update on the activity of B4B at EU  
Maurizio Scarpa and David Begley, Brains for Brain Foundation, (IT)

Discussion

9.00-9.25. Presentation of the Inherited NeuroMetabolic Diseases Information Network (InNerMeD-I-Network) and website platform to increase awareness on Neurometabolic Diseases  
Maurizio Scarpa (B4B) and Fedele (Duccio) Bonifazi (FGB) on behalf of All InNerMed Partners

Discussion

9.35-10.00 How InNerMeD-I-Network is addressing patients unanswered needs  
Maurizio Scarpa (B4B) and Fedele (Duccio) Bonifazi (FGB) on behalf of All InNerMed Partners

Discussion

COFFEE

10.30-14.00 B4B AND BIOTECH COLLABORATIONS  
Chair Discussants: Joseph. Muenzer, USA and David Begley UK

10.30-10.55 Anne Christiansen, Drug Discovery and Translational Research, Shire

Innovation at Shire – Drug discovery approach for central nervous system targeting

Discussion

11.05-11.30 Richard W. D. Welford, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Plasma lysosphingolipids as biomarkers for Niemann-Pick disease type C: use in diagnose and potential further applications

Discussion

11.40-12.05 Reinhard Gabathuler, biOasis Technologies Inc, Canada

Using a Peptide derived from Transcend (MTf, p97) to Deliver Biologics to the CNS using a Physiologic Pathway

Discussion

12.15-12.40 Mirko Essing, Biomarin

Discussion

LUNCH AND FAREWELL to the next 2016 meeting (10th)