

Brains for Brain: Improving Therapy for Neurological Disorders

Meeting the needs of neurological disease and health...

One out of every 10 people will develop a severe neurological disease before the end of their life and many existing drugs cannot be used to treat neurological disorders since they are unable to reach the brain. It is therefore necessary to choose appropriate and accurate models of nervous diseases in order to develop new treatments that can be applied to paediatric and adult Central Nervous System (CNS) disorders.

For this reason, the Brain for Brain European Research Consortium was founded in 2007. It is an organisation formed by distinguished basic scientists and clinical neurologists, and is dedicated to improvement the scientific understanding of paediatric neurological rare diseases, in particular the lysosomal storage disorders (LSDs), and improving their therapy. These original approaches will also be applicable to more common disorders such as Alzheimer's and Parkinson's diseases, brain tumours, spinal lateral atrophy for example.

50 or more LSDs are recognised. These disorders are ideal models in which to study CNS disease since they arise from genetic mutations of single genes causing a single protein defect (enzyme) responsible for the storage of well characterised cellular toxic compounds, sugar-derived macromolecules. The toxic compound is stored in small organelles, called lysosomes, which are present in all the cells of the body. The accumulation of these storage products within cells then triggers pathology leading to cell damage and often cell death. The mechanisms by which storage products cause this damage are still poorly understood.



Although classified as rare diseases, affecting approximately one in 7,000 newborn babies, their overall incidence in Europe and globally represents a considerable burden of suffering for both the individual affected and their families. The economic burden in terms of health and care for affected individuals is very significant. As a whole, approximately 4% of the European population is affected by a rare disease, 60% of which have a severe and untreatable CNS involvement.

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In excess of 70% of the LSDs have neurological involvement where storage product accumulates in brain

cells and produces severe central nervous pathology loss of brain and higher mental function, and often an early death for the sufferer. Affected children are usually born after an uneventful pregnancy, and develop normally in the first year of life and then slowly degenerate both physically and neurologically to die before reaching adolescence.

Formerly, treatment for these diseases was purely palliative. In recent years, enzyme replacement therapy has become available where regular intravenous infusion of a normal copy of the damaged enzyme is given. This enzyme, which closely resembles the biological enzyme, is scavenged into body cells and can replace the damaged enzyme in the individual's body. Although ERT has proved very valuable in its application to therapy, the major drawback is that the enzyme does not readily enter the brain and is unable to halt or reverse the brain damage.

The brain is protected by a very special vascular system, which is termed the blood-brain barrier (BBB). The BBB exists to enable the brain to preserve a very stable internal environment, which is required for nervous and integrative function, and to protect the brain from harmful neurotoxins that are present in blood, either naturally produced or acquired from the environment. The cells forming the tiniest capillaries of the brain have specialised tight margins between the cells (tight junctions) that prevent even the smallest molecules from passing between the cells. Consequently, all substances, including oxygen, have to move into brain directly across the cells forming the capillaries. This phenomenon is what makes the BBB



very selective in what it will allow into the brain and this is the reason why the large molecules of the ERT and many other drugs do not readily penetrate the brain.

Clearly an improved scientific understanding of the BBB, its function and transport processes is going to be vital in directing therapy for neurodegenerative diseases to the brain where it is needed. Indeed, it is not only in the LSDs that the BBB proves to be a huge impediment to treatment. The treatment of many diseases affecting the central nervous system, from Alzheimer's disease to AIDS and depression have their treatment limited by the inability of many drugs to cross the BBB. Many promising compounds are dropped in their development by pharmaceutical companies because they do not cross the BBB in sufficient quantity to hit their target.

In response to this, an initial meeting was held in the spring 2007 in Madrid. Further meetings, which have been expanded to include Family Associations and Pharmaceutical Companies, are now held annually. At the moment, the Brain for Brain Research Consortium is formed by 85 independent researchers from 60 universities, collaborating with 11 biotech companies spanning 12 European countries, Australia, Brazil and the USA.

The B4B acronym of the group has been created to acknowledge the effort of the four initial industrial sponsors (ACTELION, BIOMARIN, GENZYME and SHIRE Human Genetic Therapies), without the

support of which this brain-storming group could not have been created.

B4B also collaborates actively 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 (EBC).

B4B members have submitted a number of scientific research proposals to the European Union in the FP7 Health 2008 programme and have presented projects related to the further understanding of the BBB and in the context of rare neurological diseases.

Brain for Brain was incorporated as a foundation and given charitable status under Italian law in 2008. The Brains for Brain Foundation is a non-profit international organisation addressed to disabled children who are affected (or healthy carriers) by rare neurological diseases. The Brains for Brain Foundation is the first organisation created by professionals sharing their expertise to meet patients' therapy needs.

The purposes of the foundation are:

- To promote scientific research into LSDs;
- To encourage the dissemination of knowledge;
- To facilitate social and socio-medical assistance;
- To increase public awareness and interest on such diseases;



- To organise and promote national and international research activities;
- To co-ordinate and promote preclinical and clinical trials;
- To organise conferences and workshops on the above mentioned 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 stakeholder awareness of neurodegenerative disorders and for public fund raising.

The Brains for Brain Foundation believes in and actively encourages focused and organised international collaboration in order to facilitate the achievement of the necessary scientific research needed to meet the needs of neurological disease and health, a fundamental right of modern society.



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