



European Task Force on Brain and  
Neurodegenerative Lysosomal Storage Diseases

## THE BLOOD BRAIN BARRIER AND LYSOSOMAL STORAGE DISEASES

### A NEW INITIATIVE

#### EXECUTIVE SUMMARY

The small blood-vessels which supply the brain are highly specialised and regulate very closely all substances that are able to cross between the bloodstream into the brain. This phenomenon of selectivity in these blood vessels is termed the blood-brain-barrier.

Effective treatment of many diseases of the brain and spinal cord (together called the central nervous system - CNS) requires that medicines are able to pass from the bloodstream into these tissues. This research effort aims to study what controls the passage of medicines across the blood-brain barrier, and how we can improve this, thereby improving treatments of often life-threatening diseases in man.

The brain is a very complex organ made up of millions of nerve cells. Because cells in the brain communicate with each other by chemical messages, the brain requires a very stable background against which these messages can be sent between cells. The composition of the fluids bathing the cells must be kept constant; if this does not happen, the background 'interference' against which the cells would have to communicate would be excessive and messages would become 'scrambled'. A simple analogy is seen in the situation of trying to have a sensible conversation at a very noisy party.

## **WHAT IS THE BLOOD BRAINS BARRIER AND WHY WE SHOULD STUDY IT**

In a similar manner to a large main-frame computer, the brain works best if kept in a sealed climate-controlled environment. A major factor controlling the environment is the blood-brain barrier formed by the small blood vessels of the brain, which serves as both a regulatory and protective barrier for the brain. The blood-brain barrier is formed by specialised cells (endothelial cells) which line the blood vessels of the brain. The endothelial cells form 'tight' junctions between each other, and these stop the free exchange of substances in solution occurring between the blood and the brain. The blood-brain barrier has special transporters in it to enable the brain to get the nutrients that its needs, for example glucose, from blood. However, in doing its job, the blood-brain barrier prevents many medicines from reaching the brain in curative quantities and this represents a formidable problem in treating many diseases of the central nervous system. Examples include brain tumours, Parkinson's disease, Alzheimer's disease, epilepsy, malaria, HIV (AIDS), sleeping sickness, lysosomal storage diseases and bacterial and viral meningitis.

### **AIM OF THE PROJECT**

In this research project we wish to increase our understanding of how the blood-brain barrier handles medicines and why some can enter the brain and others cannot. Armed with this knowledge medicinal chemists will then be better able to design new medicines and treatments which can reach their target inside the brain. In addition, we will investigate the way in which the blood-brain barrier becomes damaged in model diseases. To this aim, lysosomal storage diseases, (conditions seen primarily in children leading to early death), where waste products build up in brain cells, leading to neuronal death will be studied, so that strategies to maintain brain function in such conditions can be devised.

### **THE STUDY OF BLOOD BRAIN BARRIER IS A STRATEGIC PROJECT**

#### **a) Interaction with Biotech Companies**

Pharmaceutical companies in their search for new therapies to treat central nervous diseases often produce medicines, which although effective when assessed in isolated cells grown in tissue culture are never-the-less unable to cross the blood-brain barrier in a living animal or person. The potential usefulness of the medicine is then lost and its development is abandoned. In this project we intend to study the factors which control the entry into the brain of medicines and other therapeutic agents which may be helpful in treating central nervous disease. By understanding the factors which allow some substances to cross the blood-brain barrier and others not to, the design of new more effective medicines for the treatment of central nervous disease becomes possible.

## **b) Potential application of the study to socially relevant disorders**

It is also becoming clear that in some central nervous diseases, for example multiple sclerosis, Alzheimer's disease and many of the lysosomal storage diseases, the blood-brain barrier itself becomes defective and contributes to the disease process. We intend to study these changes in animal models, to identify ways in which we may halt the deterioration of function of the barrier.

The blood-brain barrier is a very complex structure and at present cannot be completely re-constituted in cell-based culture systems, as the cells forming the barrier lose many of their specialised properties under these conditions. Our group has pioneered the development of many alternative methods for studying the blood-brain barrier, using cell culture systems. However, we do still need to study the function of the blood-brain barrier in a living animal, in order to fully understand its function.

This work has the potential to improve the treatment of many human and animal diseases which involve the central nervous system. It is estimated by the World Health Organisation that nearly a quarter of human suffering due to ill health can be attributed to diseases affecting the central nervous system. By better understanding of the functions of the blood-brain barrier in health and disease much of this suffering may be preventable or ameliorated and the treatment of many diseases affecting the central nervous system can be improved.

## **THE NEED FOR AN EUROPEAN EFFORT AND FOR THE BRAINS FOR BRAIN CONSORTIUM**

Because of their relatively rare nature a project aimed at restorative therapy for lysosomal storage diseases is ideally suited for a European research effort. In each individual country the medical and scientific manpower available and devoted to the diseases, both in their treatment and in research, is of necessity limited. By forming a European Consortium a pooling of skills, expertise, manpower and patients will form a critical mass of researchers and laboratories to enable considerable progress to be made.

Multi-centre international collaboration is vital for developing research in the field of rare diseases with CNS involvement, at least in most industrialised countries, where a large number of clinical centres each care for a relatively small number of children.

The Brains for Brain consortium (B4B) ([www.brains4brain.eu](http://www.brains4brain.eu)) was recently established as a task force which takes advantage of the expertise of a large number distinguished European scientists, consisting of leaders in basic and applied neurotechnology and neurology, and are grouped together to create a coordinated and forceful effort toward the comprehension of pathophysiology processes of neurological disorders in LSDs, the implementation of this knowledge of the blood brain barrier and the development of new molecular and or biochemical strategies to overcome this barrier, and to exploit brain plasticity and regeneration in order to treat these CNS diseases.

The task force was formed after the “9<sup>th</sup> International Symposium on Mucopolysaccharide and Related Disorders”, held in Venice-Italy on June 29<sup>th</sup> -July 2<sup>nd</sup> 2006, where for the first time, a specific Blood Brain Barrier Workshop in the context of lysosomal storage diseases was held. This workshop emphasised strongly how important the contact between basic scientists and clinicians must become in order to help each other in the progress toward a better understanding of the pathogenesis and the optimisation of cures and treatments for LSDs.

Following this very positive event we have thought to further continue this discussion, by creating “B4B”, a task force of experts in the different fields of neurosciences. A second symposium was held in Madrid in March (2<sup>nd</sup> – 4<sup>th</sup> ) 2007 at which the current problems of treating lysosomal storage diseases were addressed. The workshop was attended by forty European scientists and clinicians, either experts in lysosomal storage disorders or the blood-brain barrier. Countries represented included France, Germany, Greece, Italy, Spain, the Netherlands, the United Kingdom and Israel. Also attending were a number experts in lysosomal storage diseases from the North and South America as advisors, and a number of representatives of global pharmaceutical

companies, currently manufacturing therapies, and dedicated to the treatment of these diseases. Over twenty scientific papers were presented during the meeting covering the vital issues of how to deliver relevant therapy to the central nervous system to treat these diseases. The programme concluded with a general discussion of developing the way forward in improving front-line treatment for and reversing the neurodegeneration seen in many of these diseases.

The unanimous resolution from the Madrid meeting was that a European Consortium named the “**European Task Force on Brain and Neurodegenerative Lysosomal Storage Diseases**” (B4B) should be formed and an application for funding made to the EU 7th Framework to enable a co-ordinated collaborative European research effort to proceed. It was felt that this powerful combination of European experts in lysosomal storage diseases and the blood-brain barrier offered a unique opportunity to combine the skills and expertise of these clinicians and scientists to progress research. It was universally felt that the only way to achieve success in this area was to form this consortium with the support of the relevant pharmaceutical companies operating within the 7th EU Framework. There are also a number of family and patient organisations dedicated to lysosomal storage disorders established in Member Countries throughout Europe and they are currently organising a European-wide support for this new consortium.

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