BtRAIN
Brain Barriers Training

Research

The endothelial **blood-brain barrier (BBB)** and the **epithelial blood-cerebrospinal fluid barrier (BCSFB)** at the level of the choroid plexus (CP) comprise the brain barriers. They protect the central nervous system (CNS) from changes in the blood thus ensuring CNS homeostasis, which is prerequisite for proper function of neurons. The anatomical basis of these barriers is represented by unique intercellular protein complexes formed in between BBB endothelial cells and the BCSFB epithelial cells, respectively, inhibiting paracellular diffusion of water soluble molecules. In addition BBB endothelial cells keep out unwanted compounds from the brain by their lack of fenestrae and low pinocytotic activity. To meet the high demand of the neuronal cells for energy and drive efflux of toxic metabolites at the same time, BBB endothelial and BCSFB epithelial cells express unique combinations of enzymes and transport molecules[1]. Brain barrier cells are thus unique and distinguishable from all other barrier forming cells in the body. However, their barrier characteristics are non-intrinsic but rather induced during CNS development and maintained in the adult by continuous cross-talk with cellular and acellular elements within the developing and adult CNS, respectively. This high complexity of the brain barriers has severely hampered progress in the CNS therapeutic market, as the brain barriers in their function to protect the CNS from neurotoxic compounds block delivery of drugs to the CNS, thus hindering proper diagnosis and effective treatment of neurological disorders including Alzheimer's disease (AD), multiple sclerosis (MS) and stroke. It remains therefore an **unmet need for the development of diagnostic or therapeutic tools at the level of the brain barriers**.

Understanding the cellular and molecular mechanisms regulating brain barrier development, maintenance and pathology are prerequisite to meet this challenge. The **BtRAIN research groups were instrumental** in establishing technically advanced procedures for purifying brain endothelial cells combined with novel technologies of transcriptome profiling, which have recently allowed to define the first CNS-specific pathways (e.g. Wnt/β-catenin) and molecules (e.g. GPR124) that are crucial in BBB differentiation and maturation (summarized in [2]). The equivalent knowledge on the developing BCSFB is, however, limited. Furthermore, how the brain barriers are maintained in the adult, change during ageing or during disease is barely understood.

To fill this gap and to advance the Euopean capacity to bring innovative approaches to the untapped potential of the CNS therapeutic market, BtRAIN has **two major objectives:**

- **Creating and disseminating unique knowledge** on the vertebrate brain barrier signature genes and their specific role in regulating brain barriers function in development, health, ageing and disease.
- **Instructing a novel generation of young researchers** to think out of the box and to bridge disciplinary interfaces by providing a trans-disciplinary training **along the complete value creation chain in research and technological development.**

To achieve such a holistic overview on the biology of the vertebrate brain barriers, BtRAIN provides a unique trans-disciplinary and trans-sectorial environment combining the expertise of clinical and non-clinical researchers in **bio-medical disciplines** (developmental biology, vascular and cell biology, physiology, pharmacology, neuroimmunology) and **technologies** (chemistry, bioenigneering and imaging of the brain barriers) with that of **bioinformatics** from the academic and non-academic sector, forstering intense contact of its 12 academic and 6 non-academic partners from 7 EU countries, CH, USA and the European Network Brains4Brain.

The research approach of BtRAIN is organized whithin **3 workpackages (WP)**. WP1 dedicated to **"Predicting brain barrier function with *in vitro* brain barrier models"** aims to certify available brain barrier models and by implementing modern bioenineering and live cell imaging tools to design novel *in vitro* brain barrier models with substantial impact regarding their value in predictability of *in vivo* brain barriers function. A specific focus will be on the analysis of drug effects (ESR1), flow (ESR2) and inflammation (ESR1, ESR2). Transcriptome profiling within WP1 will feed into WP2 entitled **"Brain barrier signatures in vertebrates"**. The innovative approach of WP2 is characterized by combining side-by-side cross-species (mouse, zebrafish, human) transcriptome analysis approaches (ESR3, ESR5, ESR6) with bioinformatics to identify novel, conserved mechanisms of vertebrate brain barriers function during development, health, ageing and disease. WP2 includes establishment of an online platform **BBBHub** by bioinformatics students (ESR4,ESR7) that will allow facilitated datamining of the brain barriers genomes, transcriptomes and epigenomes for the lifescience researcher. Inclusion of investigations of neurological disorder-induced changes in gene and microRNA expression in the brain barriers including the attempt to diagnose BBB dysfunction based on blood microRNA analysis (ESR7) bridges WP2 with WP3 entitled "**Brain barriers as diagnostic and therapeutic targets**". This WP aims to explore pathological alterations of the brain barriers during neurological disorders including animal models for MS and stroke (ESR8), AD (ESR9) or CNS infections (ESR11) as well as from tissue samples obtained from MS patients (ESR12) to allow for the development of diagnostic or therapeutic tools at the level of the brain barriers. Knowledge ceated in WP3 will be used to explore novel cellular pathways for drug delivery across the brain barriers (ESR10).

References

[1] Engelhardt & Sorokin. *Semin Immunopathol* **31**, 497-511, 2009.
[2] Engelhardt & Liebner. *Cell Tiss Res* **355**, 687-699, 2014. [3]Huntley et al. *Front Neurosci* **8**, 355, 2014.

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