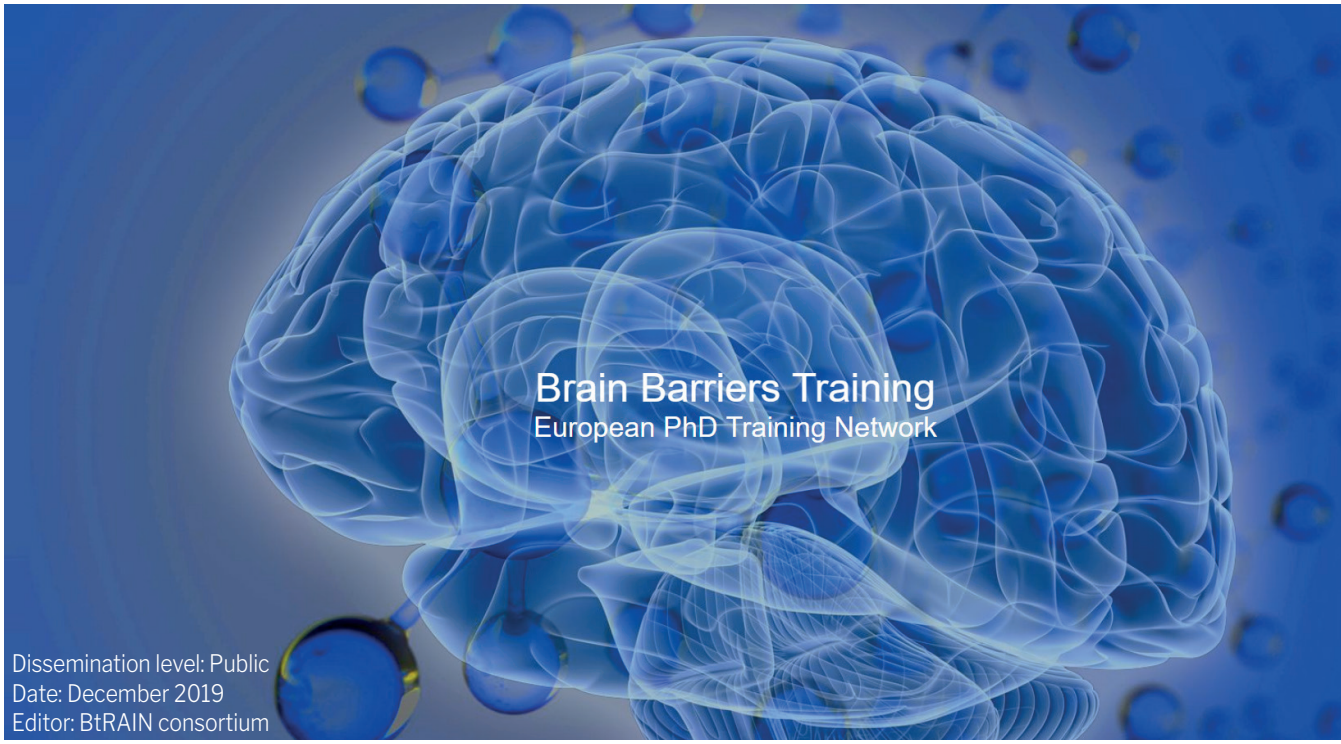
BtRAIN
Brain Barriers Training



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Project summary

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Public website

www.btrain-2020.eu

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Background

About Marie-Skłodowska-Curie actions

The Marie Skłodowska-Curie actions (MSCA) provide grants for all stages of researchers' careers - be they doctoral candidates or highly experienced researchers - and encourage transnational, intersectoral and interdisciplinary mobility. The MSCA enable research-focused organisations (universities, research centres, and companies) to host talented foreign researchers and to create strategic partnerships with leading institutions worldwide.

The MSCA aim to equip researchers with the necessary skills and international experience for a successful career, either in the public or the private sector. The programme responds to the challenges sometimes faced by researchers, offering them attractive working conditions and the opportunity to move between academic and other settings.

About BtRAIN: Brain Barriers Training, a MSCA project

In the European Research Fellowship Programme BtRAIN academic, non-academic partners and a European network jointly trained young researchers at unique interfaces of brain barrier research, bioinformatics, business development and science communication for an international research or entrepreneur career. To create this expert pool was the motivation for the involved institutions. These early stage researchers (ESRs) had the unique opportunity to be trained along the complete value creation chain in research and technology development to think out of the box and to bridge disciplinary interfaces in the field of brain barrier research. 12 PhD students were employed within the BtRAIN network. The topics for these 12 ESRs are described on the public BtRAIN website (fig. 1).
http://www.btrain-2020.eu

BtRAIN research

In their function to protect the central nervous system (CNS) from neurotoxic compounds the brain barriers block delivery of drugs to the CNS thus hindering proper diagnosis and effective treatment of neurological disorders. The high complexity of the brain barriers has severely hampered progress in the CNS therapeutic market.

BtRAIN trained a novel next generation of brain barriers researchers with trans-disciplinary know-how and understanding.

Their unique abilities to design out of the box research approaches make them highly desired researchers in the academic and non-academic sector devoted to brain barriers research.

BtRAIN provided unique knowledge on the vertebrate brain barrier signature genes and their specific role in regulating brain barriers function in development, health, ageing and disease. This is prere-

quisite to overcome the unmet need for the development of diagnostic or therapeutic tools at the level of the brain barriers.

BtRAIN training strategy

Non-academic partners were of utmost importances in the BtRAIN education. They had been specifically selected due to their intrinsic interest in the BtRAIN research and training.

The non-academic partners brought the ESRs‘ education to perfection by providing additional trainings in industrial strategies, product innovation, career development and science communication. Via BtRAIN, ESRs got in contact with start-up companies, SMEs and ‘big pharma’ offering specific secondments.

Figure 1: BtRAIN public website: Individual ESR projects, desktop layout

Objectives

In their function to protect the nerve cells in the brain and spinal cord of the central nervous system (CNS) from toxic compounds, the brain barriers also block delivery of drugs to the CNS. This hinders proper diagnosis and effective treatment of many neurological disorders as diverse as Alzheimer's disease, multiple sclerosis or brain tumors. The blood-brain barrier (BBB) is established by endothelial cells lining the wall of small CNS blood vessels. The blood-cerebrospinal fluid barrier (BCSFB) is established by epithelial cells of the choroid plexus, a structure protruding in the ventricles of the brain and producing the cerebrospinal fluid in which the entire brain is embedded and thus protected from physical impact. The high complexity of these brain barriers has severely hampered progress in the CNS therapeutic market.

BtRAIN has developed technologies allowing to i) predict in laboratory culture models the passing of drugs across the BBB, ii) in laboratory culture models to study the BBB under physiological flow conditions as they exist in the blood stream, iii) determine, which genes drive maturation of the brain barriers during embryonic development, iv) understand how the brain barriers change during ageing, and v) define novel therapeutic target structures on the brain barriers for therapeutic barrier stabilization in neurological disorders. For the scientific community BtRAIN has established a significant number of novel datasets allowing to search for genes expressed in the brain barriers during development health and disease. The BBBHub allows researchers to explore the genes expressed in the brain barriers during development, health and disease. For the lay community BtRAIN has developed BrainBarriers4You disseminating the knowledge created in BtRAIN to the public in the spoken languages in Europe.

BtRAIN has furthermore successfully educated a novel generation of young brain barriers researchers who have successfully pursued their research and created novel knowledge. BtRAIN ESRs have mastered to present and discuss their research data in international meetings and proven to be able to think out of the box and to bridge disciplinary interfaces. Their training across disciplines in addition to trainings in scientific communication, technology transfer and research management have shaped them to a highly skilled group of young researchers that created high visibility at the international brain barriers meetings. BtRAIN has thus succeeded to educate young researchers with a unique skillset who are able to work along the complete value creation chain in research and technological development.

Main results

BtRAIN employed a total of 12 ESRs with a different educational background. This interdisciplinary background was of fundamental importance the interdisciplinary background of the BtRAIN beneficiaries and the ESRs has provided the required skills and knowledge to successfully pursue the research projects at hand.

Under Objective 1 BtRAIN has aimed to create and disseminate unique knowledge on characteristic of the brain barriers and how these change during development, ageing and disease. To this end BtRAIN has established novel cell culture models of the brain barriers which allow for prediction if a specific drug can cross the BBB in the intact organism. Accordingly, BtRAIN has established culture models of the brain barrier better resembling the 3D situation in the live organism, e.g. exposing the cells to flow conditions mimicking the situation of the blood stream. These tissue culture models will now be suitable to mimic disease states of the BBB and investigate how this impact on drug delivery or immune cell migration into the CNS. Furthermore, BtRAIN has established state-of-the art protocols for purifying brain barrier cells and methodologies allowing to isolate the molecule RNA as a readout for gene expression from these cells. High quality RNA is needed to perform the next-generation high throughput sequence analysis of the RNA molecules named „RNAseq". Based on the number of copies found in the BBB one can determine, using modern bioinformatics tools, the precise profile of genes expressed at the brain barriers and their potential importance for regulating BBB specific mechanisms. BtRAIN has established a significant number of these novel RNAseq datasets, which are made available to the scientific community via the BBBHub, an online platform allowing to search these datasets. SOPs for the advanced protocols to purify brain barrier cells will be published accompanying the BBBHub. Making use of these datasets BtRAIN has found 77 conserved genes expressed in the BBB of vertebrates e.g. besides in man in zebrafish, mouse and rat that can thus be considered as "BBB signature". In addition, BtRAIN found genes specifically expressed in the BBB in Alzheimer's disease or during ageing in addition to genes expressed in the BCSFB of multiple sclerosis patients. Finally, BtRAIN was successful in defining and excluding novel therapeutic targets on the brain barriers suitable to influence immune cell trafficking across the brain barriers, stabilizing the brain barriers during neurological disorders and avoiding infection of the brain barriers.

Knowledge created in BtRAIN has been presented at many occasions at international meetings and has been published. A significant part of the knowledge created by BtRAIN will continue to be published in the near future. The RNAseq datasets are provided to the scientific community via the BBBHub in addition to the already available repositories.

Impact

The major progress beyond the state of the art achieved by the interdisciplinary work of BtRAIN is the development of the BBBHub and online platform designated to researchers allowing them to search for gene expression profiles of brain barriers provided by BtRAIN and in the future also by colleagues world-wide. BtRAIN realized that currently available datasets do not allow for comparative searches, e.g. metaanalyses as they lack the relevant information on the isolation of the brain barrier cells. BtRAIN has developed SOPs, which are foreseen to be published in Fluids and Barriers of the CNS, the journal of the International Brain Barriers Society allowing for future improvement of the purification of brain barrier cells and preparation of additional datasets. In this context BtRAIN provides a novel searching tool and contributes to reducing the number of animal experiments according to the 3R rules.
BtRAIN has identified a number of novel drug targets on the brain barriers which are presently explored for their suitability to develop therapies for brain barrier stabilization or inhibition of immune cell trafficking or infections in neuroinflammation. Last but not least BtRAIN has established methodology allowing to explore if immune cells can carry drugs across the BBB.

Additional training of the ESRs in skills such as scientific communication has advanced their abilities in presenting their research to colleagues but also to lay people. This is exemplified by the ESR outreach activity, the BrainBarriers4You.eu homepage, where they explained the brain barriers and their research within BtRAIN to the lay public in their respective mother languages. BtRAIN has educated a group of young researchers with a unique professional skillset and the advantage of a strong network allowing them to pursue a successful career.

BtRAIN consortium

Coordinator:
University of Bern, Switzerland

Partners:
The Open University, UK
GenXPro GmbH, Germany
Université d`Artois, France
University Heidelberg, Germany
Universite Libre de Bruxelles, Belgium
Goethe University Frankfurt, Germany
Biological Research Centre, HAS, Hungary
Fondazione Instituto FIRC di Oncologia Moleculare, Italy
École Polytechnique Fédérale de Lausanne, Switzerland
Stichting VU Medical Center Amsterdam, The Netherlands
Management and dissemination support: tp21 GmbH, Germany

For any question on BtRAIN project please contact the coordinator:
Prof. Dr. Britta Engelhardt
University of Bern
Theodor Kocher Institute
Freiestrasse 1
CH-3000 Bern 9
Tel. +41 31 631 41 41
Email: britta.engelhardt@tki.unibe.ch