Two main interfaces between the blood and the central nervous system

- Protection and cerebral homeostasis/Neuroprotective therapeutic strategies
- Cerebral drug delivery
- Neuroimmune Interactions/neuroinflammatory diseases
Expertise

Ex vivo models

Cellular models

BIP

In vivo investigations (developing rodents)

R&D

Blood-brain interfaces exploratory platform

to develop and propose original tools to study blood-brain interfaces functions
Blood-brain interfaces exploratory platform

Neurocampus Louis Jouvet, CRNL
Hôpital du Vinatier, Bron

Contacts: Jean-François Ghersi-Egea, PharmD, PhD
jean-francois.ghersi-egea@inserm.fr

Nathalie Strazielle, PharmD, PhD
ns.brain.i@gmail.com
Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Primary cultures to obtain an optimal differentiation

choroid plexus epithelial cells

- Blood/CSF barrier (rat, mouse)

brain capillary endothelial cells

- Blood-brain barrier (rat)

Analytical expertise

- Immunocytology
- Spectrophotometry
- Immunofluorescence
- Protein extraction

- UV-Fluorescence HPLC
- Radiodetection
- RNA isolation
- Elisa
**Blood-brain interfaces exploratory platform**

**Cellular models of blood-brain interfaces**

- **Pharmacotoxicological applications**
  - ✓ Drug delivery
  - ✓ Transport

- **In vitro / in vivo correlation of epithelial permeability towards passive diffusion markers**

- **Epithelial permeability coefficient (cPe) of antiretroviral nucleoside analogs**

<table>
<thead>
<tr>
<th>Nucleoside analog</th>
<th>Concentration</th>
<th>Basolateral to apical</th>
<th>Apical to basolateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>5 μM</td>
<td>0.335 ± 0.030</td>
<td>0.914 ± 0.154</td>
</tr>
<tr>
<td></td>
<td>1 mM</td>
<td>0.604 ± 0.020 **</td>
<td>0.644 ± 0.039 *</td>
</tr>
<tr>
<td>d4T</td>
<td>5 μM</td>
<td>0.109 ± 0.008</td>
<td>0.174 ± 0.018 55</td>
</tr>
<tr>
<td></td>
<td>1 mM</td>
<td>0.136 ± 0.002 **</td>
<td>0.165 ± 0.012 5</td>
</tr>
<tr>
<td>ddl</td>
<td>5 μM</td>
<td>0.018 ± 0.015</td>
<td>0.106 ± 0.035 55</td>
</tr>
<tr>
<td></td>
<td>1 mM</td>
<td>0.027 ± 0.013</td>
<td>0.058 ± 0.010 ** 55</td>
</tr>
<tr>
<td>3TC</td>
<td>5 μM</td>
<td>0.024 ± 0.014</td>
<td>0.127 ± 0.026 55</td>
</tr>
<tr>
<td></td>
<td>1 mM</td>
<td>0.035 ± 0.006</td>
<td>0.055 ± 0.004 * 55</td>
</tr>
<tr>
<td>ddC</td>
<td>5 μM</td>
<td>-0.009 ± 0.050</td>
<td>0.009 ± 0.028</td>
</tr>
<tr>
<td></td>
<td>1 mM</td>
<td>0.007 ± 0.012</td>
<td>0.035 ± 0.009</td>
</tr>
</tbody>
</table>

- AIDS, 2003, 17:1473-1485
Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Pharmacotoxicological applications
✓ Drug delivery
✓ Transport

- IgG transport

- Manganese transport

- Mol Pharmaceutics, 2013, 10:1473-1491
Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Pharmacotoxicological applications
✓ Metabolic barrier towards drugs and toxicants

Metabolism en passage of the toxic compound MCB and polarized elimination of its glutathione-conjugated metabolite

- J Neurosci, 2018, 38:3466-79
- J Cereb Blood Flow Metab, 2006, 26:1165-75
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Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Physiopathological applications
- Secretion and transport of inflammatory mediators

• Polarity of Cinc-1 secretion induced by the cytokine IL-1
• PGE2 transcellular flux

- In preparation
- J Infectious Dis 2006, 194:341-9
- J Neurochem 2005, 94:1580-1593
Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Physiopathological applications

✓ Cellular infiltration
✓ Neuroinfection

Transepithelial traffic of immune cells

- PLoS ONE 11(3): e0150945
Blood-brain interfaces exploratory platform

Cellular models of blood-brain interfaces

Exemps of molecular transport

- receptor-mediated

- mediated by SLC/ABC transporters

Blood-brain barrier

Occludin

Claudin-5

ABCB1

Pe (µl.min⁻¹.cm⁻²)
Cellular models of blood-brain interfaces

Applications

- Drug delivery
- Transport
- Neuroprotection
- Neuroinflammation
- Neuroinfection

- Saturability of the blood-to-brain transport of a pharmacological polypeptide

- Polarized transport of an inflammatory modulator

- J Neurotrauma. 2020 doi: 10.1089/neu.2020.7229,
- One article in preparation
- One patent deposited by a partner
Instrumentation available on the facility

- **Analytic**
  - **HPLC** (equipped with 2 detectors Dual UV and fluorescence, automatic refrigerated sample holder, Shimadzu)
  - **Liquid Scintillation** ($^{14}$C, $^3$H) (Tricarb 4910 TR, Packard)
  - **Thermostated fluorescence plate reader** (Spark, Tecan)

- **Histology and cellular imaging**
  - **Cryostat** (NX50, Microm)
  - **Fluorescence Macroscopy** (Axiozoom V16, Zeiss)
  - **Access to epifluorescence** (Axioimager M.2, Zeiss (FLUID) and confocal (LSM800, Zeiss, CRNL) microscopes)
  - **Access to light sheet microscope** (Zeiss Spim, IFR Lyon-Est)

- **Molecular analyses through qRT-PCR**
  - **Lightcyclers LC 2.0 et LC 480 Roche instrument**
Blood-brain interfaces exploratory platform

**Partnerships**

Public laboratories: Brown University, Göttingen Medicin University, Institut Cochin, Observatoire Français des nocardioses, Université de Lyon, Tokyo University

Private companies: Axoltis, Gaoma, Merck-Serono, Neurogen, Novartis, Servier, SAAT Université Grenoble-Alpes, Vect-Horus

- **Fee-for-services**: - ADR Rhône-Alpes Auvergne INSERM
  - Brain-

- **Research contracts**: (quotes, Brain-)

- **Collaborations**: Development of innovative blood-brain interfaces-oriented tools and approaches

**Institutional fundings**

EC-FP7, ANR-IHU
Permeability constants Blood/CSF and Blood/Brain

\[ K_{in\ csf} = \frac{C_t}{AUC_{0\rightarrow t}} \]

\[ K_{w\ csf} = K_{in\ csf} \times V_{csf} \]

\[ K_{in\ cx,\ pons,\ cb} \]

Cell tracking at the blood-CSF barrier

- Acta Neuropathol Commun 2020, 8:4
- Fluids Barriers CNS 2015, 12:8.
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Blood-brain interfaces exploratory platform

➢ Ex vivo models of blood-brain interfaces

Isolated cerebral microvessels and choroid plexuses (live tissue), from healthy and diseased animals

• Molecular studies
  (transcriptomic, proteomic)

• Functional studies
  (uptake, metabolism, secretion)


➢ Primate tissue bank (Partnership : Cynbiose)

Macaca fascicularis (mRNA, proteins, paraffin sections, cryopreserved tissue, validated through quality control)

Analytical tools

- Immuno-cytology
- Immuno-fluorescence
- Protein extraction
- UV/fluorescence-HPLC
- Radiodetection
- RNA isolation
- Elisa
Selected publications BIP : Developed Méthodologies, exemple of applications, expert reviews.


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