Anne Eichmann.
Ensign Professor (Cardiology).
Professor of Cellular and Molecular Physiology
Yale University Medical School
Yale innovator awardee 2022

Drug Delivery across the Blood Brain Barrier
Vascular and CNS - Global Authority

Anne Eichmann, PhD.
Ensign Professor of Medicine (Cardiology)
Professor of Cellular and Molecular Physiology

Entrepreneur - Science

Kevin Boye, PhD
Research Scientist
Entrepreneur

Entrepreneur - Science

Luiz Geraldo, MD, PhD
Resident
Entrepreneur

Business - Science

Morag Grassie, PhD
Associate director of business development
Yale OCR
Most drugs do not cross the BBB. Therefore, most brain diseases remain incurable. **This is a major unmet medical need.**

- **Does the drug cross the BBB?**
  - **Yes**
    - 2% small molecules
    - **Drugs developed**
  - **No**
    - 98% small molecules
    - 100% large molecules
    - **Drugs not developed**
Most drugs do not cross the BBB. Therefore, most brain diseases remain incurable. **This is a major unmet medical need.**

- Does the drug cross the BBB?
  - Yes
    - 2% small molecules
    - Drugs developed

**Overcomes this obstacle**
Most drugs do not cross the BBB. Therefore, most brain diseases remain incurable. **This is a major unmet medical need.**

Does the drug cross the BBB?

- Yes
  - 2% small molecules
    - Drugs developed
  - + MAB: open BBB
  - - MAB: Intact BBB
Brain selective transient BBB opening

**Adult WT**

- Antibodies (i.v., 10mg/kg, 1h)
- Cadaverine (1Kda) (i.v., 30min)

**CTRL IgG**

**Anti-Unc5B-3**

- Cadaverine (i.v., 30min)

**CTRL IgG: Intact BBB**

**+ MAB: open BBB**

The effect lasts <8 hours

**Adult WT**

- Antibodies (i.v., 10mg/kg, 8h)
- Cadaverine (i.v., 30min)

**CTRL IgG**

**Anti-Unc5B-3**

**Lung**

**Heart**

**Kidney**

- Cadaverine (1Kda) (i.v., 30min)

**ng (cadaverine) / mg (organ)**

- Lung: NS
- Heart: NS
- Kidney: NS

**p = 0.0079**

**ng (cadaverine) / mg (brain)**

- Adult WT
- CTRL IgG
- Anti-Unc5B-3

**20um**

**The effect lasts <8 hours**

**Adult WT**

- Antibodies (i.v., 10mg/kg, 8h)
- Cadaverine (i.v., 30min)
Nanobodies
BDNF (brain)
BDNF (Plasma)
pTyr-IP (TrkB-IP)

Nanobodies
CTRL IgG
Anti-Unc5B-3

BDNF (brain)
CTRL IgG
Anti-Unc5B-3

BDNF (Plasma)
CTRL IgG
Anti-Unc5B-3

pTyr-IP (TrkB-IP)
CTRL IgG
Anti-Unc5B-3

CTRL Ab
Anti-Unc5B-3

DMSO
Vincristine

CTRL Ab
p = 0.0219
brain cancer, brain metastasis, neurological diseases, infections

Global CNS drug market size **USD $130 billion** in 2022 (200 billion in 2030)
Ref: Precedence research press release Jan 2023

**We outperform the Competition**

<table>
<thead>
<tr>
<th></th>
<th>MRI-guided focused ultrasound with micro-bubbles</th>
<th>Receptor-Mediated-Transcytosis</th>
<th>Mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known BBB maintenance mechanism</td>
<td>✔️</td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Reversible</td>
<td>✔️</td>
<td>✗</td>
<td>✔️</td>
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<tr>
<td>Non damaging</td>
<td>✔️</td>
<td>✗</td>
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<td>Brain-wide</td>
<td>✔️</td>
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<td>Delivery of various drugs</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>IV Injection</td>
<td>✔️</td>
<td>✔️</td>
<td>✗</td>
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</tbody>
</table>

Endothelial Unc5B controls blood-brain barrier integrity

Kevin Boyé1, Luiz Henrique Geraldo1, Jessica Furtado1, Laurence Pibouin-Fragner2, Mathilde Poulet1, 2, Doyeon Kim2, Bryce Nelson3, Yunling Xu2, Laurent Jacob2, Nawal Maissa4, Dritan Agalli4, Lena Claesson-Welsh5, Susan L. Ackerman7 & Anne Eichmann1, 2, 8, 9

![nature COMMUNICATIONS](nature-communications.png)
MAB target: Endothelial transmembrane receptor Unc5B
Guardian of BBB integrity

Discovered pathway function

World-authority in Neurovascular Research (> 150 publications, > 20,000 citations)

Selected publications:
- Nature 2004; 432: 179-86
- Dev Biol. 2008; 318: 172-83
- Circ Res. 2009; 104: 428-41
- Dev Cell. 2011; 20: 33-46
- Nat Commun. 2016; 7:13517
- Science 2018; 361:599-603
- Nat Commun. 2022; 13: 1169
Human monoclonal AB
Isolated from synthetic human Fab library F

9 backup hits
CROs produce and test recombinant antibodies

The Science

Anti-Unc5B
Netrin1
Unc5B

BBB opening

Lead anti-Unc5B-3:

<table>
<thead>
<tr>
<th>Human Unc5B</th>
<th>Rat Unc5B</th>
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<tr>
<td>KD=1.29nM</td>
<td>KD=1.34nM</td>
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</tbody>
</table>

Can be applied to humans
Tested in preclinical rodent models
No significant toxicity expected
(anti-ligand Mabs are Clinically tested)
## Milestones and capital plan

<table>
<thead>
<tr>
<th>Timeline</th>
<th>6/23</th>
<th>1/24</th>
<th>12/24</th>
<th>6/25</th>
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<tbody>
<tr>
<td>Milestones</td>
<td></td>
<td>lead candidate</td>
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<td>IND filed</td>
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<tr>
<td>Progress to date (Blavatnik funds $400K)</td>
<td>CRO reproduced transient BBB opening</td>
<td>Dose-escalation studies underway</td>
<td>Backup Abs tested in vivo POC studies</td>
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<tr>
<td>Activities</td>
<td>Chemotherapeutics delivery ☑️</td>
<td>Neoplastic meningitis</td>
<td>Infection Neurological diseases</td>
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<td>Pre-clinical efficacy in brain cancer ☑️</td>
<td>Brain metastases</td>
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<td>Toxicology (in vivo, single and repeat ascending dose)</td>
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<td>CMC (Formulation)</td>
<td>Stability, standards, scale-up</td>
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<td>Regulatory advisory</td>
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<tr>
<td>Capital plan</td>
<td>Lead optimization and IND enabling studies</td>
<td></td>
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<td>$ 5-8 Million</td>
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</table>
Thank you. D²B³

Interested in investing in our technology?
Please contact
Anne.Eichmann@yale.edu or
Morag.Grassie@yale.edu