An intact, molecularly active postmortem whole human brain model of Alzheimer's disease

Paul D. Wes, Congwei Wang, Josip Butkovic, Ivan Mumlek, Chunmin Ge, Jamie Maresca, Brian Hinger, Randall Buck, Mohammad Nabil, Francis Herman, David Crair, Leah Rosales, Lindsay Slupczewski, Karina Wong, Lucija Barisic, Zvonimir Vrselja

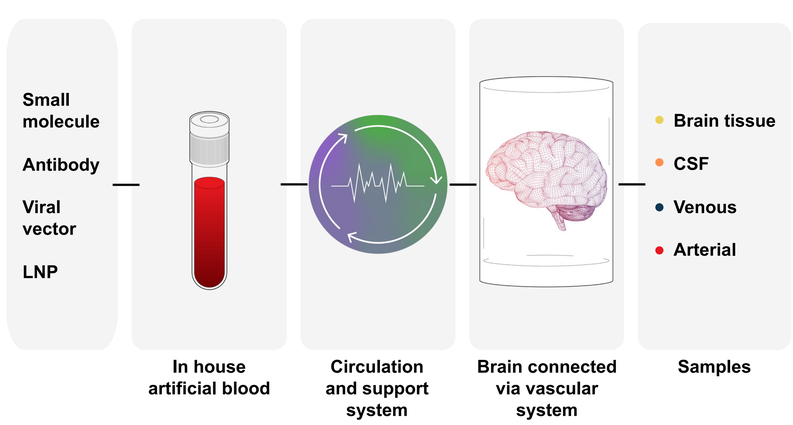
Bexorg, New Haven, CT.

Introduction

The inability of preclinical models to accurately predict efficacy in clinical trials remains a major obstacle in bringing effective treatments to Alzheimer's disease patients. Animal models diverge from the human disease due to differences in species biology and disease etiology, while human-derived in vitro models lack the complexity and mature cells phenotypes of the adult, aged brain. We have established a platform, called BrainEx, that enables the physiological maintenance of molecular and cellular function in the postmortem human brain, including brains from Alzheimer's disease patients. This provides a model for preclinical drug discovery directly in the human disease brain, allowing for target validation, optimization of pharmacokinetics (PK), dose-range finding, biomarker discovery, and more.

Ethical considerations

Acquisition of postmortem human brains adheres to the highest possible ethical standards, overseen by an independent board of world-renowned bioethicists. Brains are procured through Organ Procurement Organizations (OPOs) with enhanced levels of consent from patients and families that specifically cover the BrainEx platform. Measures are taken on the BrainEx device to ensure that there is no possibility of coordinated network activity associated with consciousness.



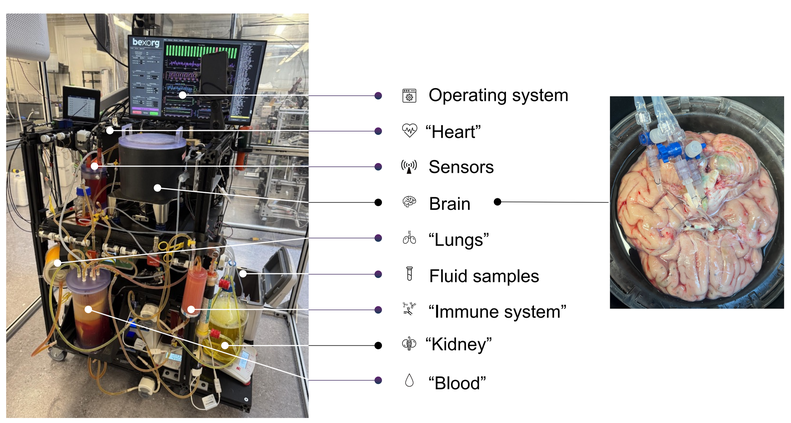


Figure 1. The BrainEx platform enables drug discovery in whole human disease brains. Bexorg has established a platform that maintains intact, molecularly and cellularly active postmortem human brains. The brain is connected to the BrainEx device via its endogenous vascular system. An acellular artificial perfusate supplies the brain with oxygen and nutrients, while a real-time operating system regulates physiological homeostasis. Drugs can be administered to the brain systemically, and pharmacokinetics, pharmacodynamics, and functional pharmacology can be assessed longitudinally in brain tissue and translational biofluids.

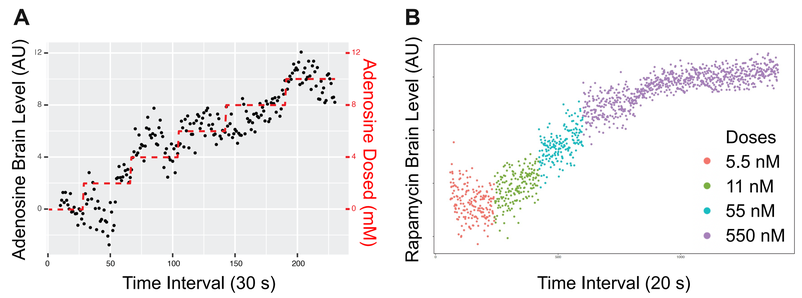


Figure 2. Pharmacokinetics of small molecules. (A) Adenosine and **(B)** rapamycin were systemically administered at successively higher concentrations on the BrainEx device, and measured in the brain parenchyma in real-time using Raman spectroscopy.

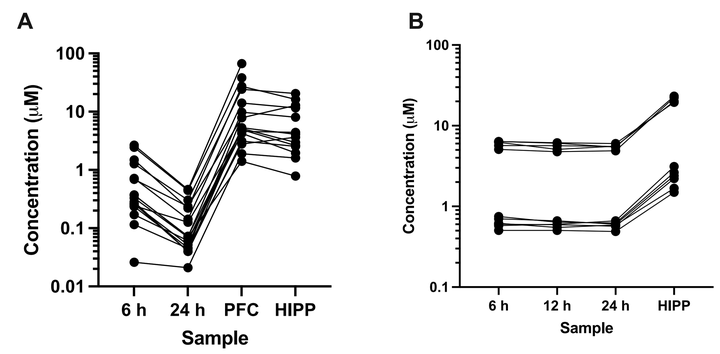


Figure 3. Systemic drug administration for target validation and lead optimization. (A) Tool molecules with high systemic clearance, poor brain penetrance, low potency, and/or systemic toxicity can be administered for target validation using a paradigm that achieves high exposures in brain tissue. **(B)** For lead compounds, drugs can be administered under more physiological conditions. 6 h, 12 h, 24 h indicate perfusate concentrations at these timepoints. PFC, prefrontal cortex. HIPP, hippocampus.

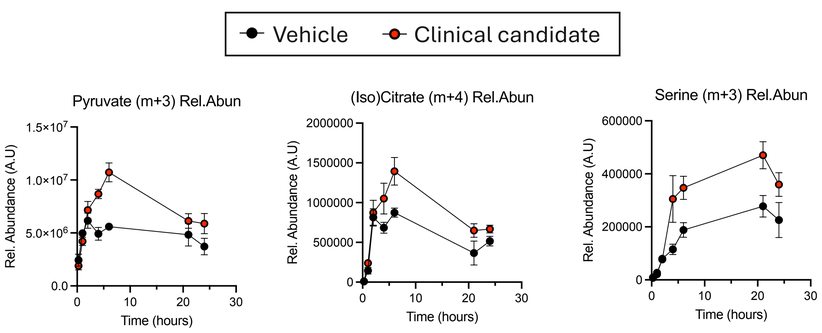


Figure 4. Pharmacodynamic and target engagement biomarkers. Brains were dosed in the presence of ^{13}C-glucose, and biopsies were taken from the prefrontal cortex at different timepoints. Measurements of metabolites by mass spectrometry indicated a robust drug effect.

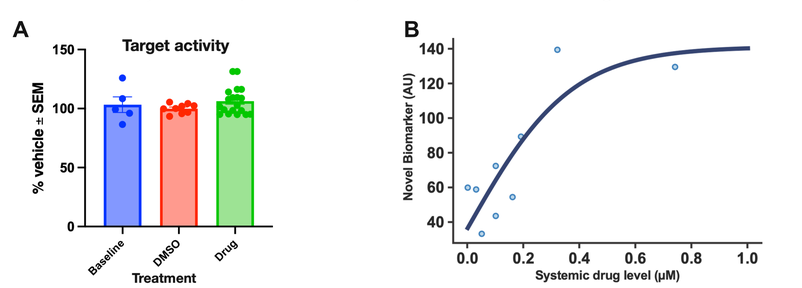


Figure 5. Novel biomarker discovery. (A) While a traditional biomarker did not show any response to drug in the intact brain, **(B)** a novel biomarker was identified by Raman spectroscopy of perfusate.

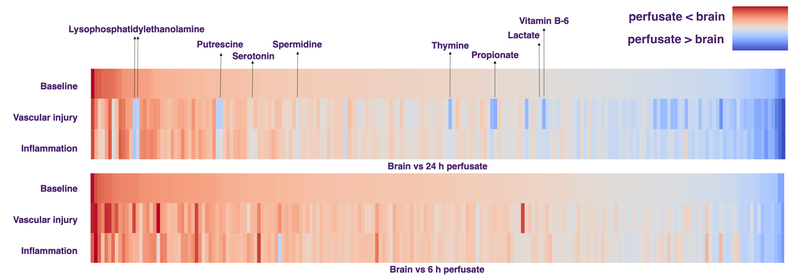


Figure 6. Biomarkers of neuronal damage. Metabolomics identified biomarkers of neuronal damage that preferentially leak out of the brain. CSF levels of the polyamines, putrescine and spermidine, correlate with cognitive impairment in humans.

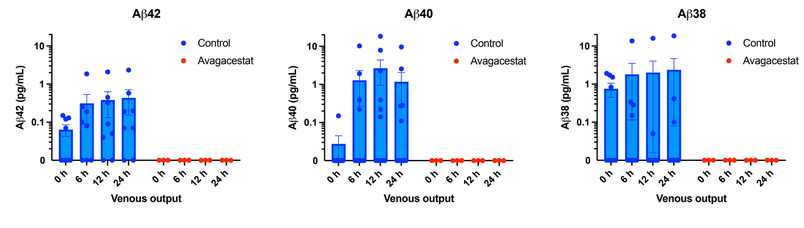


Figure 7. BrainEx recapitulates lowering of CSF Aβ with the γ-secretase inhibitor, avagacestat. Systemic administration of avagacestat at a clinically relevant dose lowers Aβ within 24 hours, as seen in clinical trials.

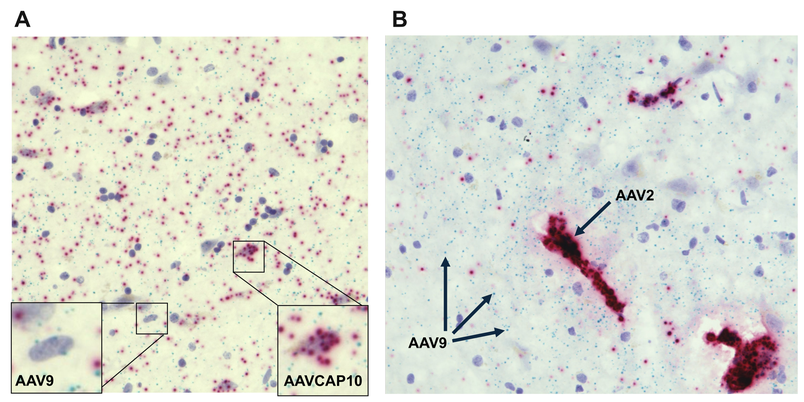


Figure 9. BrainEx faithfully predicts brain penetrance of gene therapy vectors. AAV viral vectors used for gene therapy were delivered systemically into human brains on BrainEx. After 24 h, expression of the AAV cargo was detected by RNAscope. **(A)** AAV9 (blue) and AAVCAP10 (blue), which cross the BBB, transduced cells in the brain parenchyma. **(B)** AAV2 (red), which does not effectively cross the BBB, was detected primarily in the vasculature, whereas AAV9 (blue) was detected throughout the parenchyma.

Conclusions

Bexorg has established the capabilities to deliver drugs systemically to physiologically maintained, postmortem human Alzheimer's disease brains. This enables preclinical experiments in human brains that previously could only be conducted in clinical trials. The BrainEx platform is predicted to provide higher fidelity preclinical data than previously possible, increasing the probability of success in clinical trials and of bringing effective treatments to Alzheimer's disease patients.

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