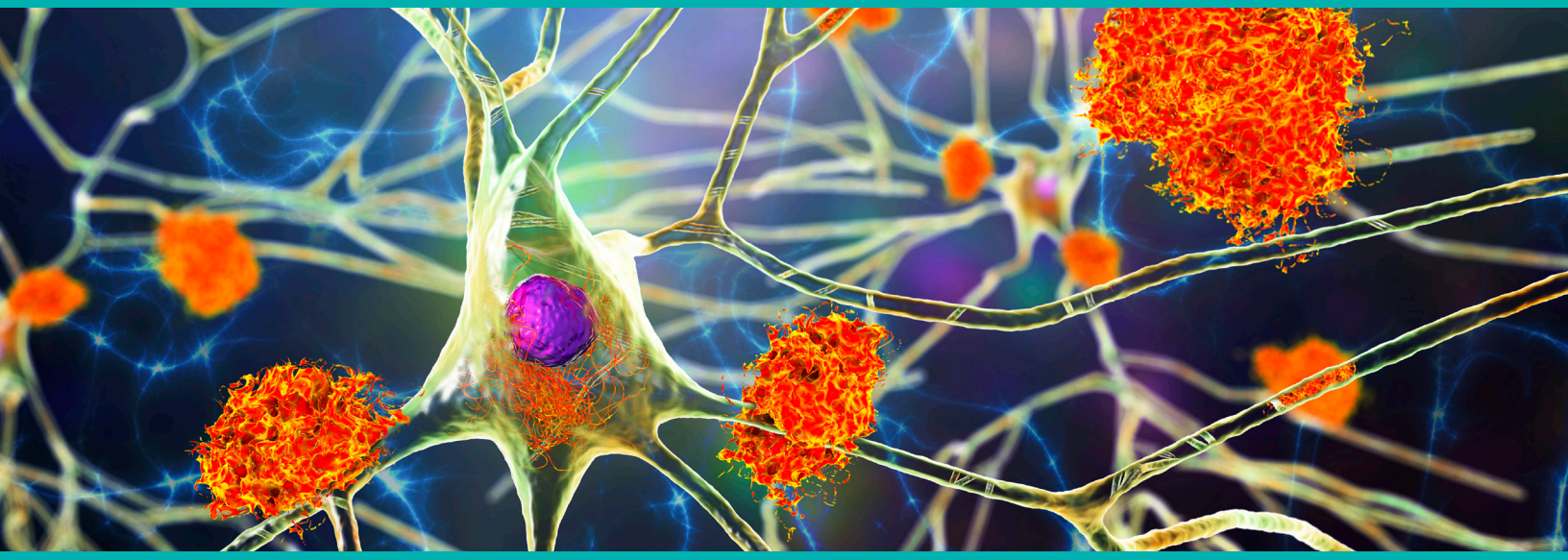
Longitudinal Push-Pull Microdialysis

A translational approach for the preclinical study of Alzheimer's Disease (AD)



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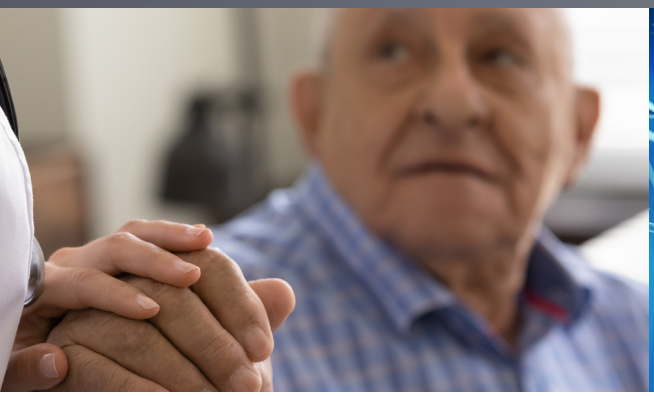
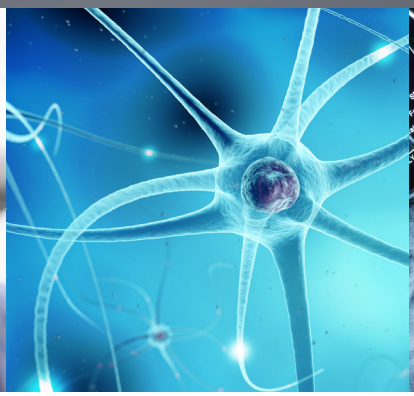
Preclinical models of Alzheimer's Disease (AD) can provide valuable insights into the pathology and treatment of the disease in humans. Of translational importance is the ability to measure amyloid-β (Aβ) and tau proteins, which are key biomarkers of AD progression.

In the preclinical setting, the measurement of Alzheimer's related proteins is challenged by a variety of technical limitations that confine studies to single subject, acute experiments, often requiring sacrifice to achieve the desired end point (i.e. imaging or chemical analysis). Such short-term observations can suffer in their ability to capture long-term disease dynamics while requiring higher number of subjects.

From a translational standpoint, an ideal approach would allow for longitudinal sampling of Aβ and tau in CSF—mimicking the technique used in patient monitoring.


Probing Alzheimer's pathology with microdialysis

As a probe-based localized sampling and delivery technique, microdialysis offers an elegant way to explore the molecular microenvironments of the diseased brain. Traditionally used for small molecules such as neurotransmitters, microdialysis is increasingly employed for larger targets such as peptides and proteins that may serve as specific biomarkers.

In the study of AD, microdialysis presents as a versatile tool for translational experimentation comparable to lumbar punction CSF collection in patients. Researchers (Bjorkli C et al.) have demonstrated how microdialysis can uniquely provide:

- **Simultaneous Sampling** of Aβ (Aβ40, Aβ42) and Tau (t-tau, p-tau) Isoforms in Human and Mouse CSF Using a Single Probe
- **Local Delivery of Alzheimer's Drugs,** Allowing for Pharmacological Assessment During Sampling and Bypassing the Blood Brain Barrier
- **In Vivo Longitudinal Measurement** of Alzheimer's Proteins over 12 Months, Allowing Each Subject to Serve as Its Own Control
- **Monitoring from Awake, Freely Moving Subjects** Minimizing Handling Stress and Influence of Anesthesia
- **Minimal Fluid Loss** through Use of Probes with Selectively Permeable Membranes and High-Precision Push-Pull System, Reducing Potential for Tissue Damage and Perturbation

The combination of these elements in a single study permits long-term, high-throughput measurements that save time, reduce animal use, and stand to provide better translational understanding of CSF biomarkers.

System requirements:

Targeting Aβ and tau longitudinally necessitate a specialized push-pull microdialysis set-up optimized for large molecules. Key components include:

- Ultra-high molecule weight cut-off probes (2MDA) to permit sufficient sampling of Aβ and tau
- Push-Pull System using both a syringe and a peristaltic pump to mitigate sample loss through ultrafiltration
- High-precision peristaltic pump capable of supporting flow rates as low as 0.1 uL/min for maximum recovery
- Beta-irradiated probes and guides minimizing immune response to implantation
- Swivel systems for measurement in awake, freely moving subject

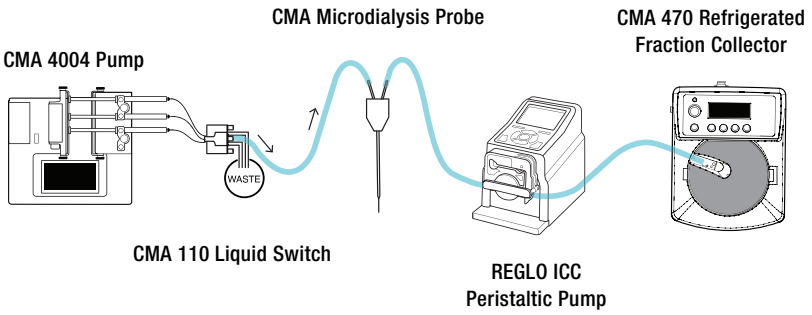
Our solution:

From perfusion to collection, CMA offers complete microdialysis solutions for study of Aβ and tau proteins in preclinical models. A typical setup will include a syringe pump, an ultra-high cutoff probe optimized for CNS applications, a specialized 12-roller peristaltic pump validated for microdialysis applications, and a refrigerated fraction collector to minimize sample degradation during collection.

Customize configurations to best meet the particular needs of your lab. Whether you are involved with multiple animal/multiple probe applications, or need customizable probe sizes, our CMA and Harvard Apparatus brands offer a variety of instruments, including pump options, to help you optimize your set-ups for each study.

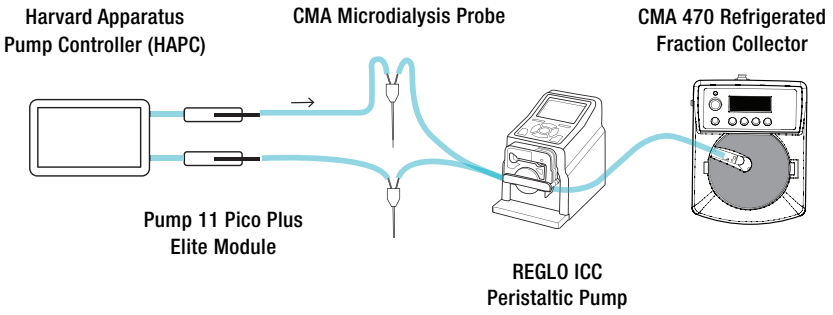
Push-Pull Example Setup 1:

Single-probe configuration with CMA 4004 Pump. Syringe source-to-probe can be changed using liquid switch to introduce pharmacological agents



Push-Pull Example Setup 2:

Multiple probe/animal configuration with Harvard Apparatus Pump Controller and Pump 11 Pico Plus Elite Module. Space-saving configuration that permits independent flow rate control for each subject



Please contact our global team of specialists for more information.

Related Literature:

1. Bjorkli C, Hemler M, Julian JB, Sandvig A, Sandvig I. Using intracerebral microdialysis to probe the efficacy of repurposed drugs in Alzheimer's disease pathology. bioRxiv; 2022. DOI: 10.1101/2022.01.14.476357.

2. Bjorkli C, Hemler M (2021) Push-Pull Microdialysis Sampling Protocol. Oct 2021, www.protocols.io

3. Bjorkli C, Louet C, Flo TH, Hemler M, Sandvig A, Sandvig I. In Vivo Microdialysis in Mice Captures Changes in Alzheimer's Disease Cerebrospinal Fluid Biomarkers Consistent with Developing Pathology. J Alzheimers Dis. 2021;84(4):1781-1794. doi: 10.3233/JAD-210715. PMID: 34719495.

4. Bjorkli C, Sandvig A, Sandvig I. Bridging the Gap Between Fluid Biomarkers for Alzheimer's Disease, Model Systems, and Patients. Front Aging Neurosci. 2020 Sep 2;12:272. doi: 10.3389/fnagi.2020.00272. PMID: 32982716; PMCID: PMC7492751.

5. CMA Microdialysis Push Pull Application Note: https://microdialysis.com/media/wysiwyg/application_notes/push-pull_system_appsheet.pdf

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