Glymphatic Function in Alzheimer's Disease
The Surgeons Perspective

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Disclosures

- Consultant:
  - Medtronic
  - Stryker
  - Cerenovous
  - Microvention
  - Balt
  - Phenox
  - Q'Apel
  - MMI
  - NV Medtech
  - Spryte
- SAB: UpHill, Shape Medical
- Unrestricted Research Grants : NIH, StrokeNet, Interline Endowment, Microvention, Medtronic, Stryker, Phenox
- Investor: InNeuroCo, Cerebrotech, Endostream, 3Rivers Medical, RIST, Scientia, BlinkTBI, Prometheus, Deinde, NeuroFine, Radical Catheters, Hyperion

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- Jeff Illif, PhD U of Washington

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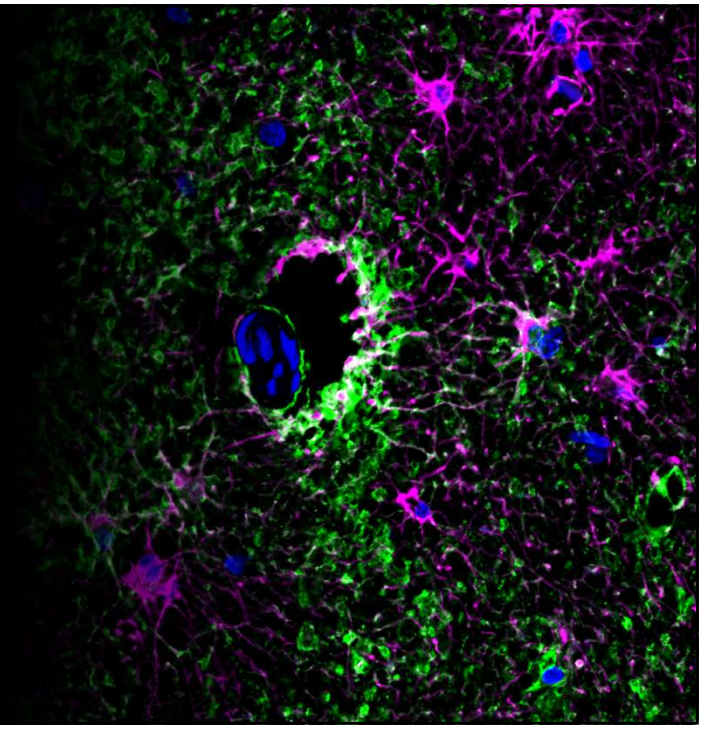
A primer on glymphatic and meningeal lymphatic brain clearance



Present understanding of glymphatic and meningeal lymphatic function

Data from rodent and human studies over the past twelve years demonstrate that perivascular glymphatic exchange is…

…anatomically organized and rapid.

…driven by arterial pulsation, vasomotor oscillations and synchronous neural activity.

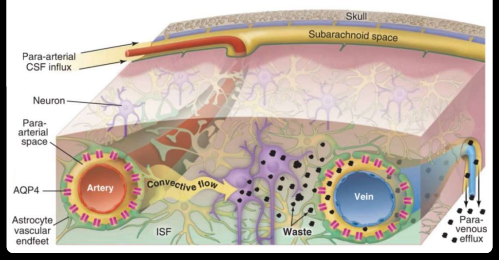
…supported by astroglial water transport.

…more rapid in the sleeping brain.

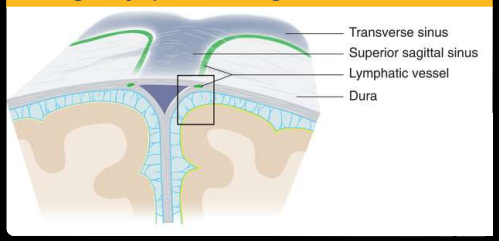
…coupled to meningeal lymphatic drainage.

…supports the clearance of amyloid β, tau and α synuclein.

Perivascular "Glymphatic" Exchange

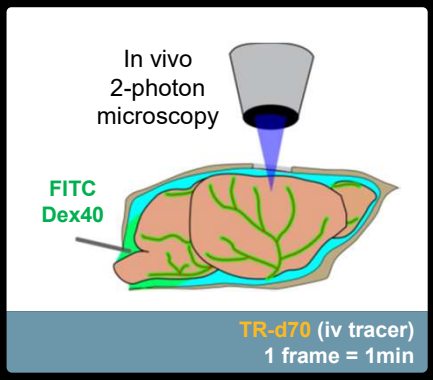


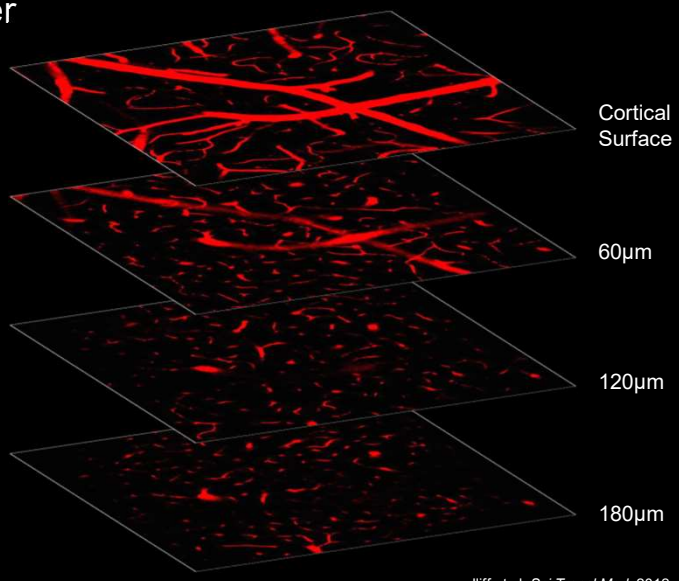
Meningeal Lymphatic Drainage



Nedergaard *Science* 2014, Louveau et al. *Nature* 2015

The Glymphatic System and Meningeal Lymphatics: A Primer





Iliff et al. *Sci Transl Med* 2012

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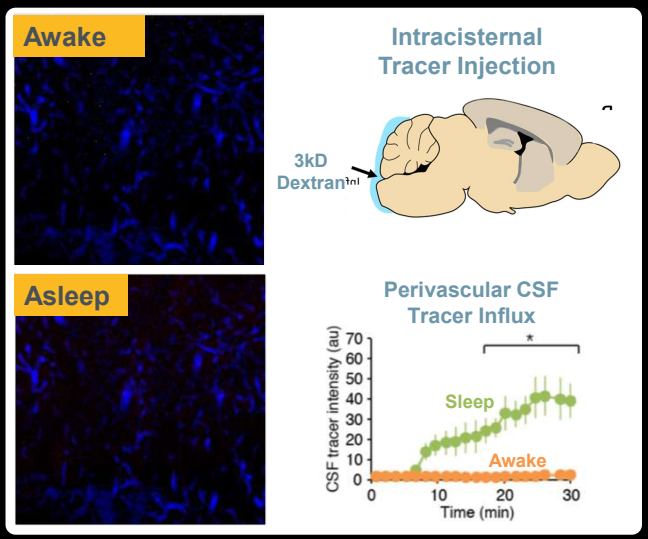

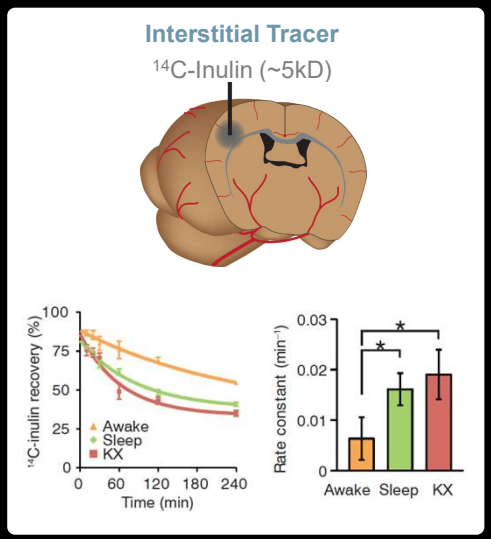

Xie et al. *Science* 2013

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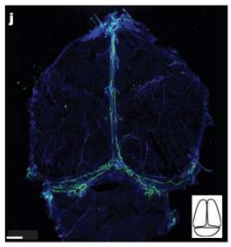
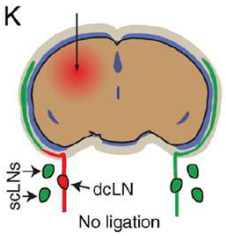
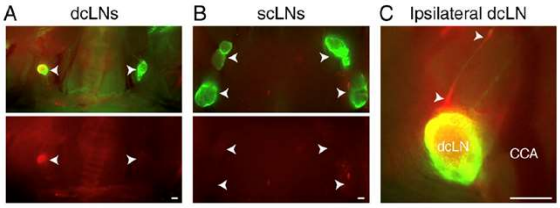
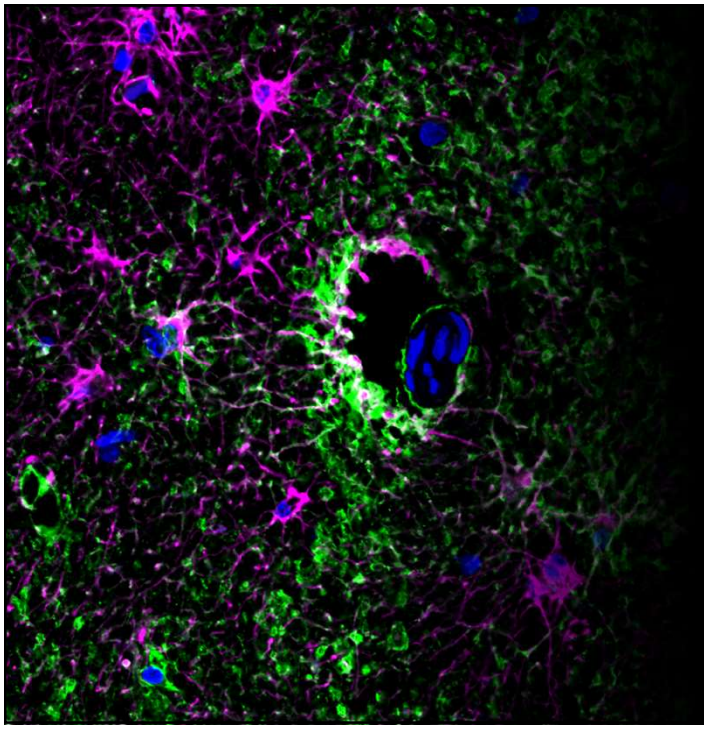






Louveau et al. *Nature* 2015



Preclinical evidence supporting a role in Alzheimer's disease pathogenesis

Evaluating the role of glymphatic dysfunction in Alzheimer's disease using preclinical animal models

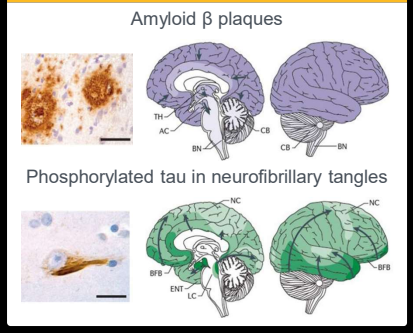
Alzheimer's disease is…

…associated with aggregation of Aβ and tau.

…influenced by non-genetic risk factors:

- Aging
- Chronic co-morbidities (hypertension, diabetes…)
- Cerebrovascular disease
- Traumatic brain injury
- Chronic sleep disruption

Alzheimer's disease pathology



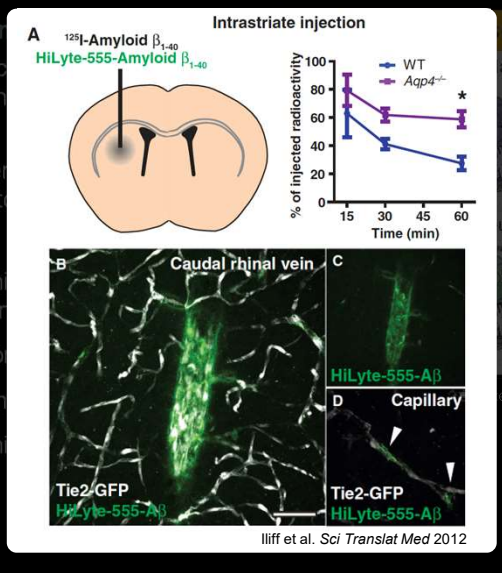
Adapted from Jucker and Walker *Nature* 2013

Does the glymphatic system contribute to the clearance of Aβ or tau?

Is glymphatic function impaired in animal models of non-genetic AD risk factors?

Does experimental impairment of glymphatic function promote Aβ or tau pathology?

Evaluating the role of glymphatic dysfunction in Alzheimer's disease using preclinical animal models



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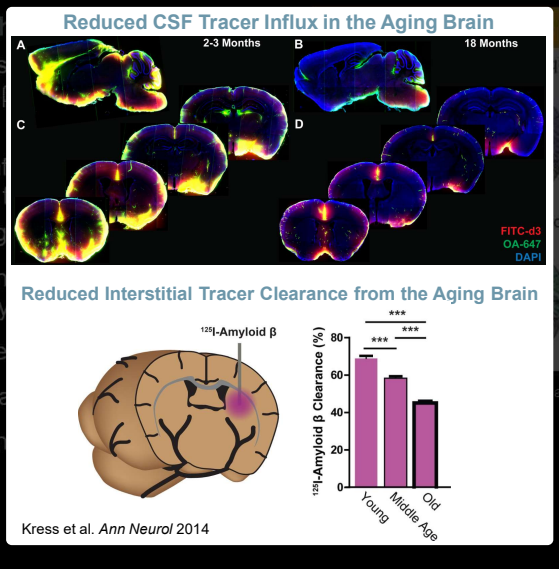

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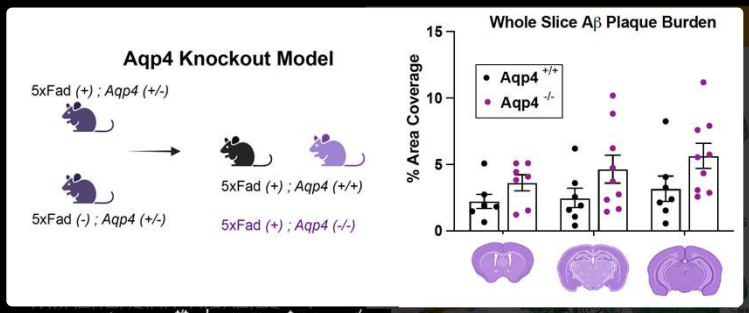

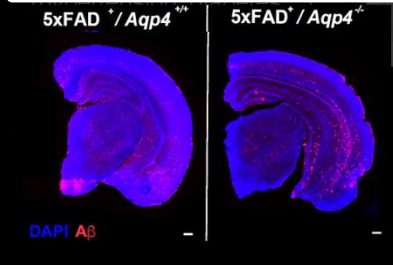

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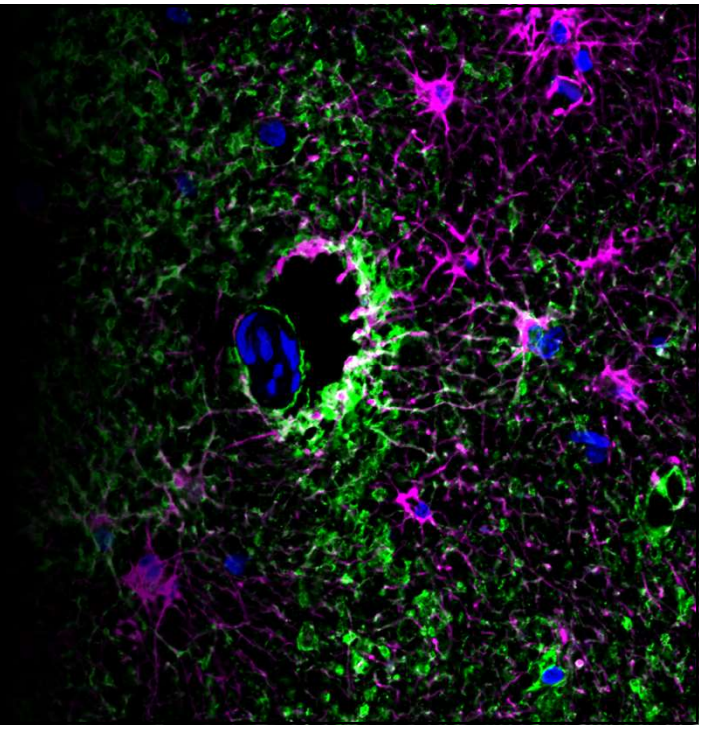
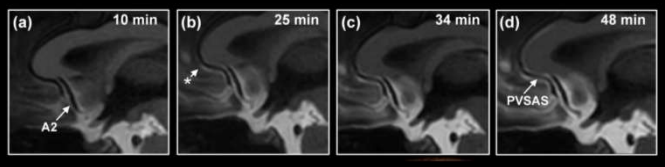
Glymphatic and meningeal lymphatic clearance is a feature of the human brain

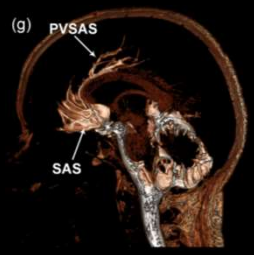


Lessons from Oslo: Defining glymphatic exchange and CSF clearance in humans by intrathecal contrast-enhanced MRI

Perivascular transport

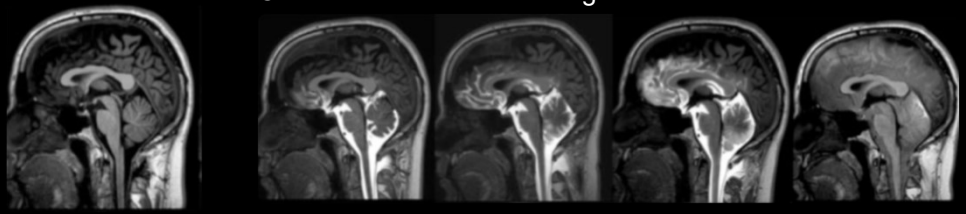


Ringstad et al. *Brain* 2017



Eide and Ringstad *Nat Comm* 2024

CSF-interstitial fluid exchange

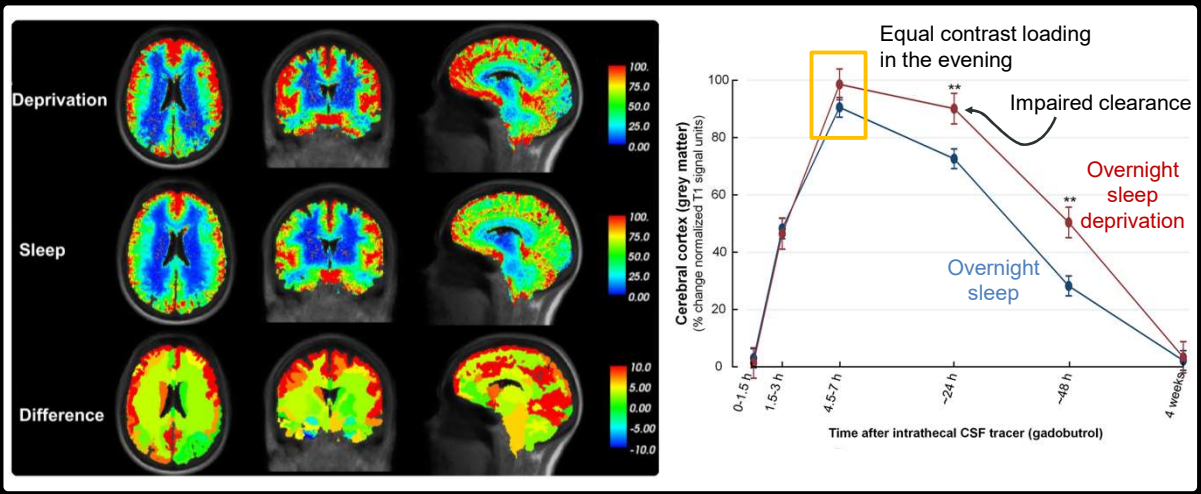


Baseline 1h ~3h 4.5h 24h

Lessons from Oslo: Defining glymphatic exchange and CSF clearance in humans by intrathecal contrast-enhanced MRI

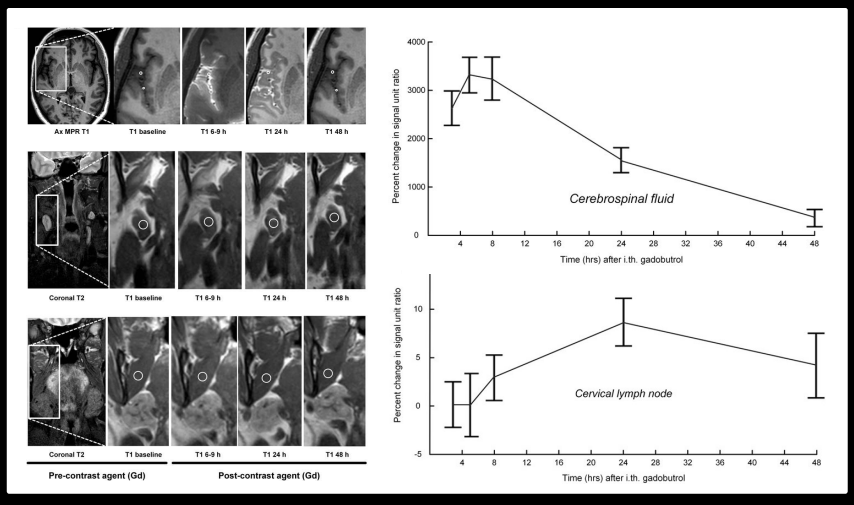
Sleep-active interstitial solute clearance

Eide et al. *Brain* 2021

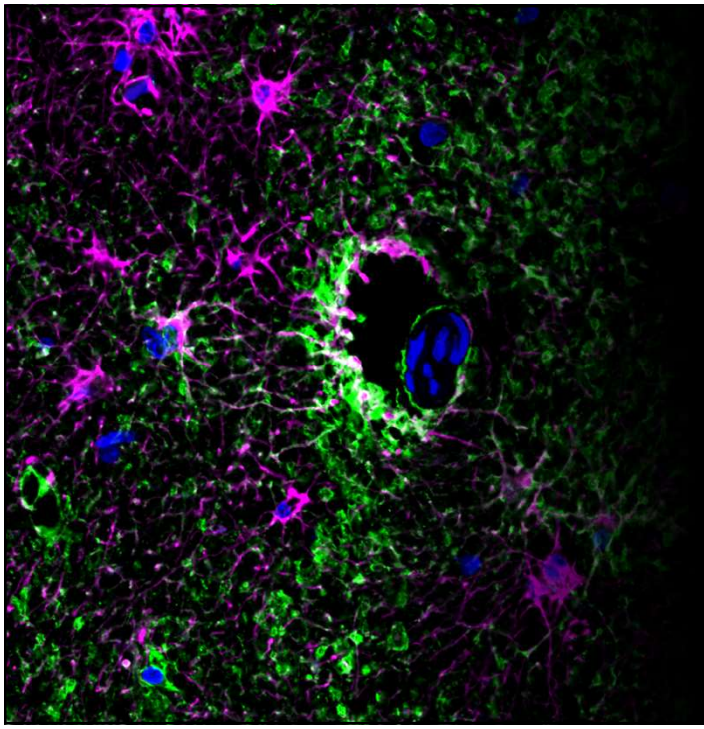


Lessons from Oslo: Defining glymphatic exchange and CSF clearance in humans by intrathecal contrast-enhanced MRI

CSF solute clearance via cervical lymphatics

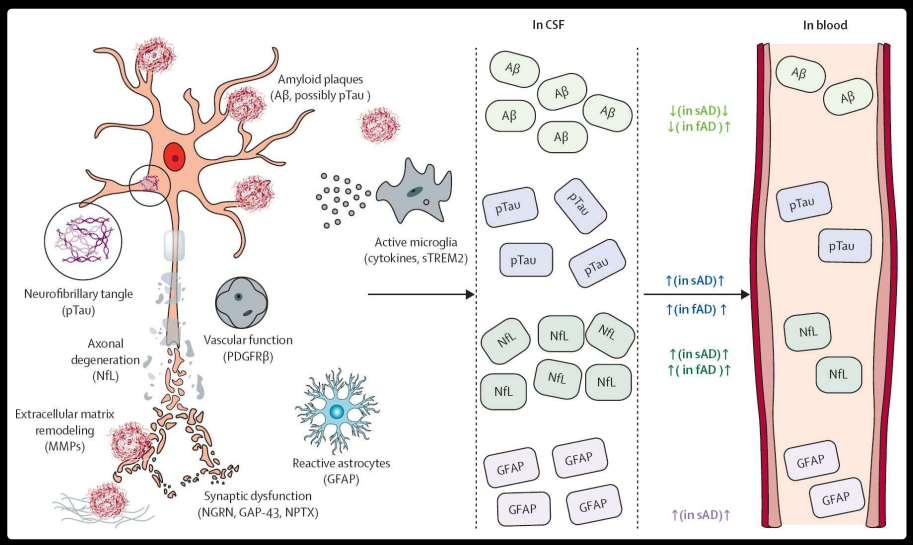


Eide et al. *Sci Rep* 2018



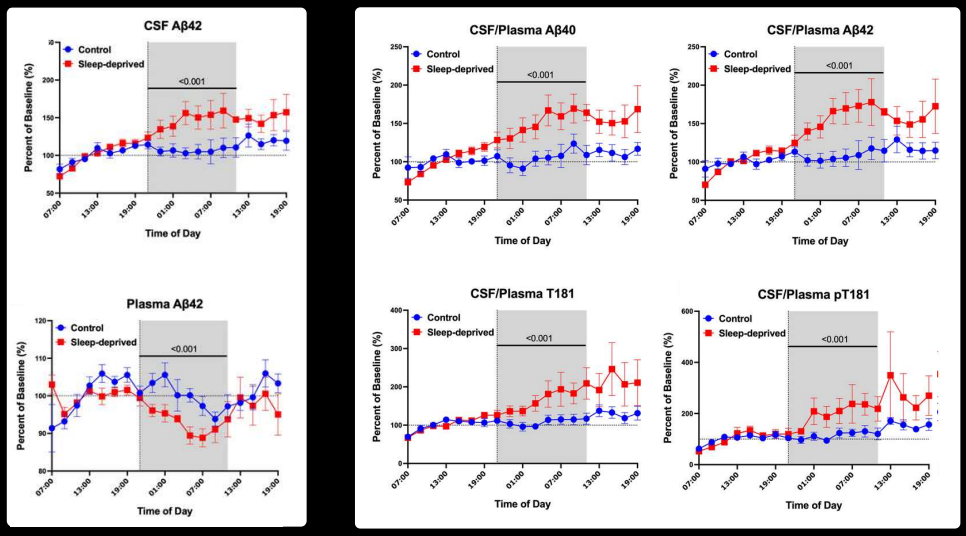
Brain-to-Blood Clearance is Reflected in Dynamic Fluid Biomarker Changes

Plasma-based Alzheimer's disease biomarkers as indicators of pathological status



Teunissen et al. *Lancet Neurol 2022*

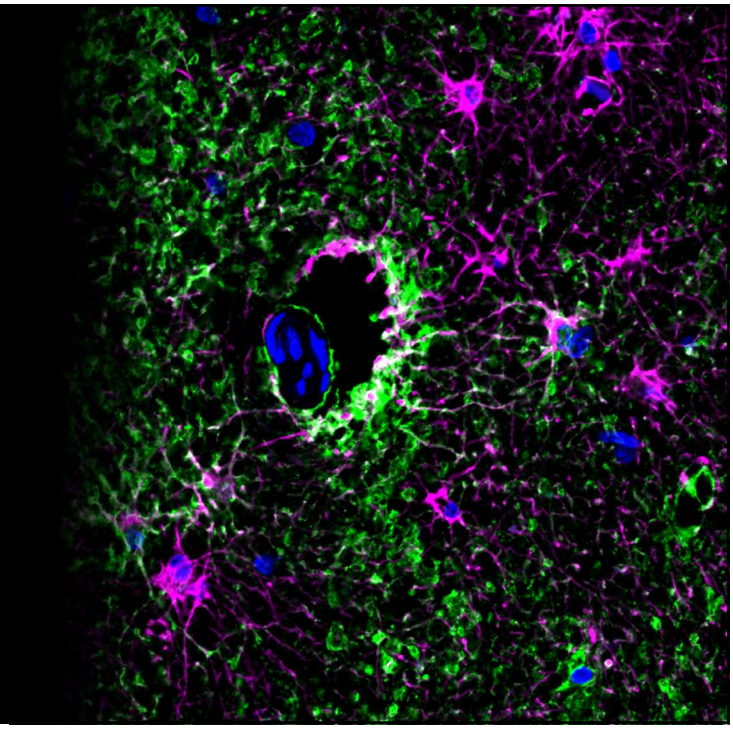
Evening-morning changes in plasma AD biomarker levels are influenced by sleep status



Liu et al. *Alzheimer's & Dementia* 2023

Key Take-Homes

1. Glymphatic exchange and meningeal lymphatic drainage contribute to the clearance of brain wastes, including A and tau.
2. Preclinical studies support a causal role for glymphatic impairment in the development of Alzheimer's pathology.
3. Contrast-enhanced MRI studies have confirmed that sleep-active brain clearance is a feature of the human brain.
4. Dynamic changes in CSF and plasma AD biomarker levels reflect brain-to-blood clearance of Aβ and tau.



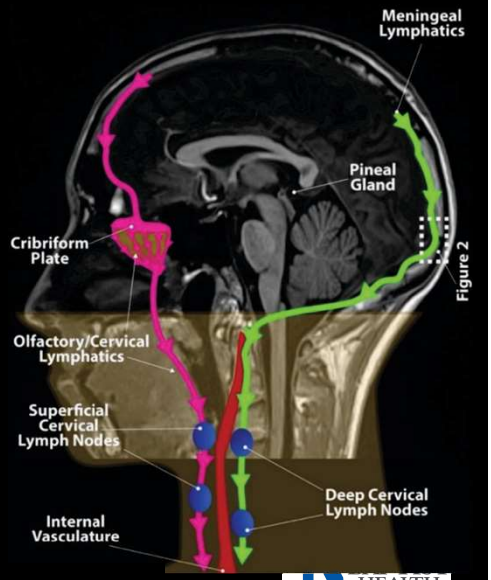
Neck Lymphatic Reconstruction For Brain Disease

Quoted Surgical Objective:

Remove hyperplastic lymph nodes in the deep cervical region and reduce interstitial edema in brain tissue through a lymphatic venous anastomosis or lymphatic node venous anastomosis procedure.

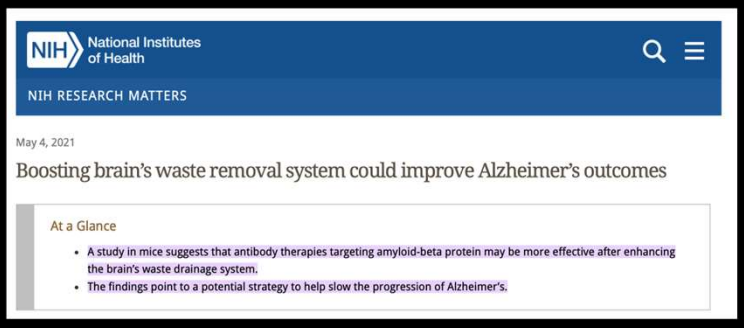
By improving the pressure and flow rate of lymphatic return, the procedure aims to facilitate the excretion of metabolic substances from the brain, thereby alleviating pathological symptoms, potentially enhancing the patient's quality of life and long-term improvement.

Dr. QingPing Xie, Hangzhou China



HEALTH

Improving Lymphatic Drainage Could Improve Outcomes



NIH National Institutes of Health

NIH RESEARCH MATTERS

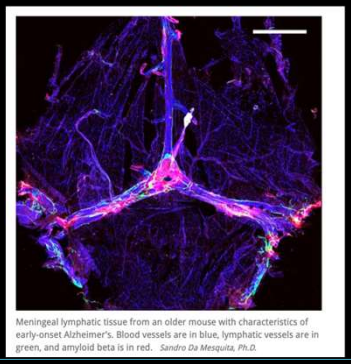
May 4, 2021

Boosting brain's waste removal system could improve Alzheimer's outcomes

At a Glance

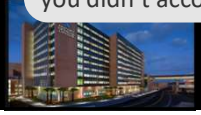
- A study in mice suggests that antibody therapies targeting amyloid-beta protein may be more effective after enhancing the brain's waste drainage system.
- The findings point to a potential strategy to help slow the progression of Alzheimer's.

Drs. Jonathan Kipnis, Oscar Harari, and Carlos Cruchaga of Washington University in St. Louis



Meningeal lymphatic tissue from an older mouse with characteristics of early-onset Alzheimer's. Blood vessels are in blue, lymphatic vessels are in green, and amyloid beta is in red. *Sandro Da Mesquita, Ph.D.*

Dr. John Kipnis:
"The lymphatics are a sink and neurodegenerative diseases are characterized by protein aggregation in the brain. If you break up these aggregates but have no way to get rid of the debris because the sink is clogged, you didn't accomplish much. **You have to unclog the sink to really solve the problem."**



https://www.nih.gov/news-events/nih-research-matters/boosting-brains-waste-removal-system-could-in

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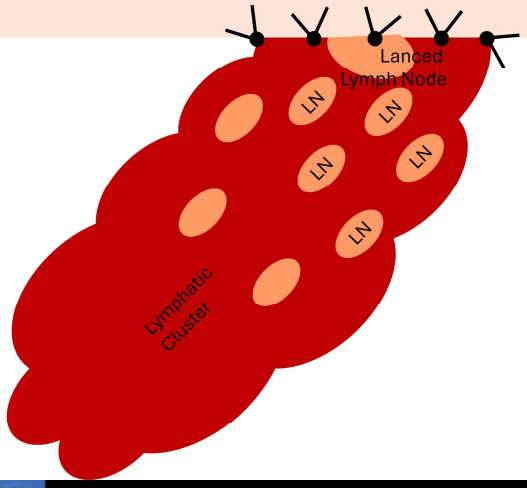
External Jugular Vein



Lymphatic Cluster Sewn into Internal Jugular Vein via a sliced node for improved drainage.

For Illustrative Purposes Only

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Early Published Results Of Brain Disease Procedure

Open access Letter

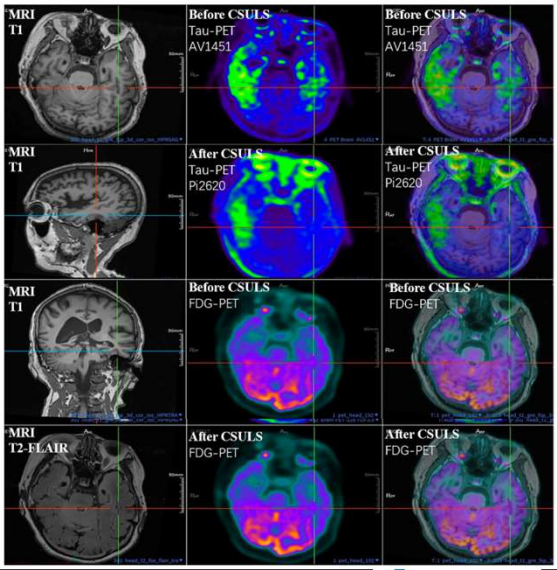
General Psychiatry

Promising outcomes 5 weeks after a surgical cervical shunting procedure to unclog cerebral lymphatic systems in a patient with Alzheimer's disease

Xia Li ,[1,2] Chenpeng Zhang,[3] Yuan Fang,[1,2] Mei Xin,[3] Jianbo Shi,[4] Zhiyuan Zhang,[4] Zhen Wang ,[1,5] Zhenhu Ren[4]

Four months after the surgery, during a phone interview, the patient's daughter stated:
"My mother's memory is improving and she is able to complete household chores every day."

Five weeks after the surgery, clinical assessments found improved cognitive function: the Mini-Mental Status Examination score increased from 5 to 7, and the score on the Clinical Dementia Rating-sum of boxes test improved from 10 to 8. Her depressive mood had resolved: the Geriatric Depression Scale score dropped from 9 to 0. Her PET scan provided objective evidence of this improvement (figure 1). The ^{18}F-fluorodeoxyglucose PET showed an overall improvement in brain glucose metabolism, which was most evident in the right frontal lobe. The T-sum within AD regions dropped from 92 176.3 to 81 949.8 (normal 95% prediction limit: 11 089.7). The maximum standardised uptake value increased from 8.52 to 8.98. The tau-PET showed an overall reduction of tau in the brain. Furthermore, the index of the diffusion tensor image analysis along the perivascular space increased from 1.19 to 2.26, indicating improved brain health.



https://pubmed.ncbi.nlm.nih.gov/39816183/

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dCLVA: Patients with mild to moderate dementia

A surgical therapy for Alzheimer's disease with lymphaticovenular anastomosis

Xiwen Ma[1,2,#], Feiyun Wang[2,#], Guiqing Wang[1,2,#], Meiying Zhao[1,2], Youmao Zheng[4], Yintao Guo[5], Jingheng Wu[2], Yuntao Liu[2], Yulin Liu[1], Guinv He[1,2], Lixuan Ren[1], Zhenping Gong[1], Jingxin Wang[4], Li Chen[1,2], Shoukui Hu[4], Qinjun Chu[2], Zhengkui Li[4], Jing Wu[2], Runtao Li[6], Xiaojie Zhang[1,2], Qian Shi[3], Hongkai Lian[7,8] and Jianping Ye[7,8,9]

Abstract

Background: Deep cervical lymphaticovenular anastomosis (dcLVA) surgery is able to control aging-associated Alzheimer's disease in patients. However, the efficacy rate remains unknown.

Objective: This study is designed to test the surgery efficacy in the treatment of mild-to-moderate AD patients.

Methods: This is a single-center retrospective study of dcLVA treatment of mild-to-moderate AD for 3 months. A total of 41 patients received the surgery, in which lymph vessels and lymph nodes in the district III of cervical area were identified using indocyanine fluorescence dye. The efferent lymphatics of the obstructed lymph nodes were connected to the jugular vein to fix the lymphatic blockage under a fluorescent microscope. The efficacy rate was examined at 3-month post-surgery by clinical scores and biomarkers.

Results: Lymph flow obstruction was observed on both sides of cervical area in the AD patients. The obstruction was successfully resolved through the surgery, and AD progression was attenuated or even reversed in the patients according to improvement in the scales of MMSE, ADL, NPI, CDR-SB, and CGI-SI. The average effectiveness rate was 50% by the CDR-SB score improvement. The efficacy was higher with shorter disease duration but not influenced by age and *APOE4* genotype. $A\beta_{42/40}$ ratio and p-tau181 were improved in more than 67% patients. There were 2 cases of mild adverse reactions that were controlled immediately by regular treatments.

Conclusions: The data demonstrate that dcLVA surgery is an effective and safe therapy for AD in mild-to-moderate patients with 50% efficacy rate as measured by improvement of the CDR-SB score.

Keywords

Alzheimer's disease, deep cervical lymphaticovenular anastomosis, lymph node, lymphatic system, surgical therapy

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JAD REPORTS
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Journal of Alzheimer's Disease

Highlights

Single-center, retrospective study of **41 mild-moderate patients** who receive the dcLVA procedure.

> The data demonstrate that dcLVA surgery is an effective and safe therapy for AD in mild-to-moderate patients with 50% efficacy rate as measured by improvement of the CDR-SB score and AB42/40 ratio and P-tau181 were improved in 67% of patients.

139 Severe AD Patients – Biomarker Shifts

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RESEARCH ARTICLE

Deep cervical lymphatic–venous anastomosis attenuates cognitive dysfunction and biomarker abnormalities in severe Alzheimer's disease: A prospective single-arm study

Xiaohong Fu[1] | Jing Zhang[2] | Qiuxia Xiao[2] | Tingting Li[3] | Qijun Li[2] | Shaofu Zhang[1] | Wen Zeng[2] | Min Gong[1] | Pan Cai[4] | Zhaojian Deng[1] | Xuan Zhang[1] | Yuanjun Xin[1] | Liping Su[5] | Xiaohe Tian[2] | Kaifeng Wu[6] | Liulin Xiong[2]

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Funding information
Key Projects of Guizhou Provincial Health and High-quality Development Medical Research Joint Fund, Grant/Award Number: 2024GZYXKYJJXM0058; Guizhou Provincial Higher Education Science and Technological Innovation Team, Grant/Award Number:

Abstract

INTRODUCTION: This study evaluated the efficacy of deep cervical lymphatic–venous anastomosis (dcLVA) for severe Alzheimer's disease (AD).

METHODS: A total of 139 severe AD patients undergoing dcLVA were enrolled, and changes in cognitive function and biomarkers were evaluated by comparing preoperative measures with postoperative outcomes over a 6-month follow-up period.

RESULTS: Patients undergoing dcLVA showed modestly elevated Mini-Mental State Examination (MMSE) scores from 48 hour postoperatively to 6-month follow-up. At 6-month, observable changes across functional status and neuropsychiatric symptoms were documented, as demonstrated by reductions in scores on the Activities of Daily Living (ADL) scale, Neuropsychiatric Inventory (NPI), Neuropsychiatric Inventory-Caregiver Distress (NPI-D), and Sleep Disorders Inventory (SDI). Biomarker analyses revealed decreased cerebrospinal fluid (CSF) β-amyloid (Aβ) 42, Aβ40, and p-Tau levels postoperatively, along with increased plasma concentrations of these markers. No deaths or serious procedure-related adverse events occurred during 6-month follow-up.

- **Study Overview**: Single-arm trial with **139 severe AD patients;** surgery connects neck lymphatics to veins to enhance brain waste clearance.
- **Cognitive Outcomes**: **Modest MMSE score improvement** (+1.28 points at 6 months)
- **Functional & Behavioral Gains**: **Improved daily living** (lower ADL scores); reduced neuropsychiatric symptoms (lower NPI, distress, and sleep issues).
- **Biomarker Shifts**: **Decreased CSF Aβ and p-Tau post-surgery; plasma Aβ increased, p-Tau217 decreased, indicating better protein clearance.**
- **Safety**: **No deaths or major complications;** 32% had temporary delirium (resolved quickly); mild side effects like swelling.

Defining the surgical protocol

A Proposed Role for Lymphatic Supermicrosurgery in the Management of Alzheimer's Disease: A Primer for Reconstructive Microsurgeons

Joon Pio Hong, MD, PhD, MMM[1] Wei F. Chen, MD[2] Dung H. Nguyen, MD[3] Qingping Xie, MD[4]

[1] Department of Plastic Surgery, Asan Medical Center, University of Ulsan, Seoul, Korea
[2] Cleveland Clinic, Center for Lymphedema Research and Reconstruction, Cleveland, Ohio
[3] Stanford Women's Cancer Center, Palo Alto, California
[4] Qiushi Hospital Hangzhou, Hangzhou, People's Republic of China

Address for correspondence Joon Pio Hong, MD, PhD, MMM, Department of Plastic Surgery, Asan Medical Center, University of Ulsan, 88 Olympicro 43 gil, Songpagu, Seoul 05505, Korea (e-mail: joonphong@amc.seoul.kr).

Arch Plast Surg

> …by relieving the obstruction of flow, lymphatic reconstruction along the drainage pathway could serve as a potential novel treatment

> the aim of advanced supermicrosurgical approaches is to preserve remnant lymphatic function and normal, physiologic flow to minimize the possibility of unintended long-term consequences and potential obstruction over time

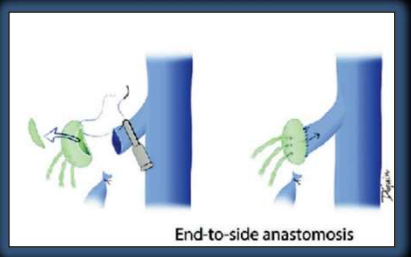
for Lymphatic Supermicrosurgery in ... Surgery. 52(1), 9...

BAPTIST HEALTH

Is A Supermicro Approach The Right Option?

The original manual technique includes severing the lymphatic bundle for anastomosis to the jugular vein. A **supermicro** connection of a node/lymphatic to a vein branch, could be a safer and more effective approach, but research is needed to prove this.

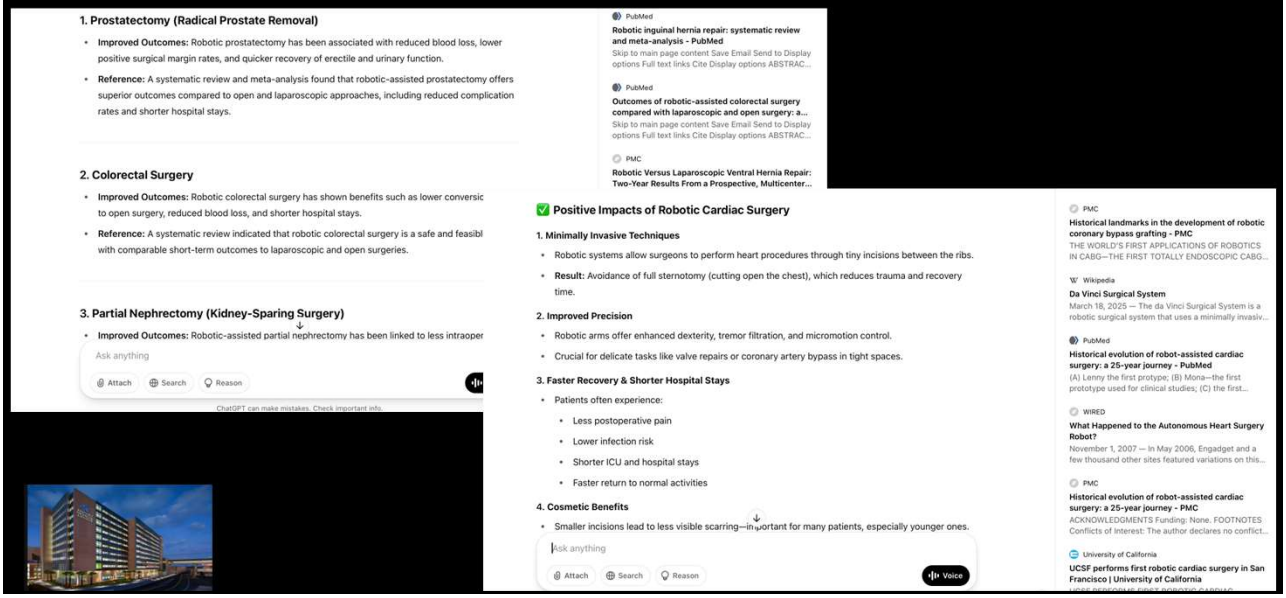
Dr. JP Hong, Thought Leader On Lymphatic Reconstruction
Asan Medical Center, Seoul Korea



"If you cut the bundle, you are potentially obstructing the distal flow. Ideally you want a supermicro approach with a side to end anastomosis to preserve the lymphatic flow distal along the neck. Research coming soon will show if this is the superior path."

BAPTIST HEALTH

Robotics has revolutionized many areas of surgery



Symani Surgical System

- Designed to support the complexity and scale of super-microsurgery
- Enabling Technology
  - Very few super-microsurgeons can perform lymphatic reconstructions on vessels this size
- Super-micro:
  - Lymphatic vessel diameter: 0.1 to 0.2mm
  - Healthy lymph node: 0.7 to 0.9mm
  - Vein branch diameter: <0.7mm
- Motion scaling and tremor reduction:
  - Stable platform allows more surgeons to treat smaller vessels

Challenges in microsurgical procedures

- Human limitations:
  - Impact of dexterity and tremor on precision
  - Procedural ergonomics and fatigue
- Capabilities of current instruments:
  - Difficult to access anatomy
  - Innovation limited to imaging
- Access to highly skilled specialists:
  - Lengthy training
  - <600 supermicrosurgeons worldwide

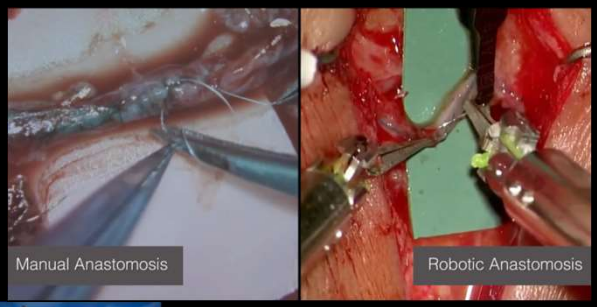
New technologies to address current challenges can enable microsurgery and supermicrosurgery techniques on a global scale

BAPTIST HEALTH

Tremor-reducing and motion scaling technologies in action

Tremor Reduction

Precise movements to reduce errors and cellular damage during suturing



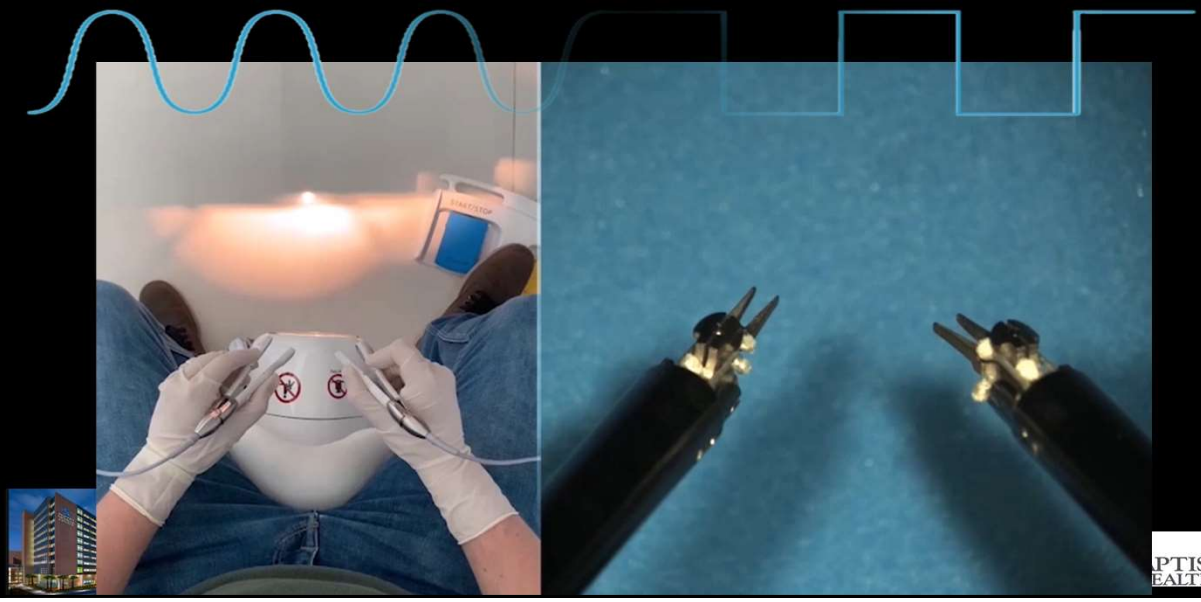
Motion scaling

Surgeon macro movements translated to NanoWrist microinstruments

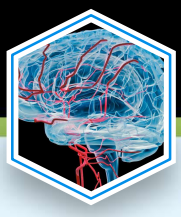
Video Courtesy of:
PRS Global Open. 2022 Jan; 10(1): e4013
Early Experience Using a New Robotic Microsurgical System for Lymphatic Surgery
Dr. Nicole Lindenblatt et al

BAPTIST HEALTH

Teleoperation Surgeon input translated to Symani output

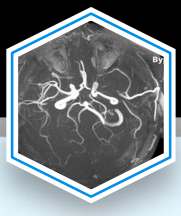


Neuro & Spine Applications



Lymphatic reconstruction for brain disease

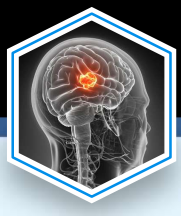
Concept: Anastomose the deep cervical lymphatics to veins to improve brain waste drainage.



Revascularization
STA/MCA bypass (EC-IC, IC-IC, EDAS)

MMI completed feasibility in animal/ cadaver model

First human procedures completed September 2025



Intracranial and skull base surgery

Define platform roadmap with potential to deliver micro and super-microsurgical robotic assistance to intracranial and skull base procedures.

Spine

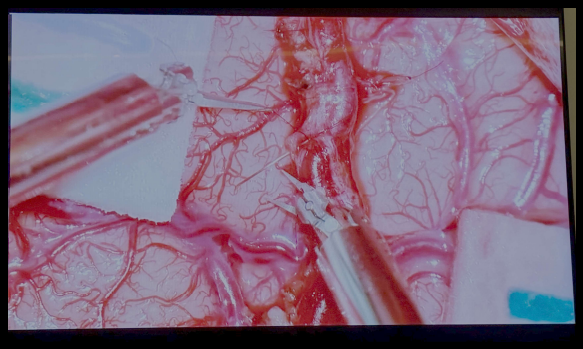
Potential benefits include distally articulating micro-instruments and tremor reduction to resection and support removal of tumors around sensitive structures.

In clinical study

Expanded indications

Early Feasibility Study - FDA EDAS

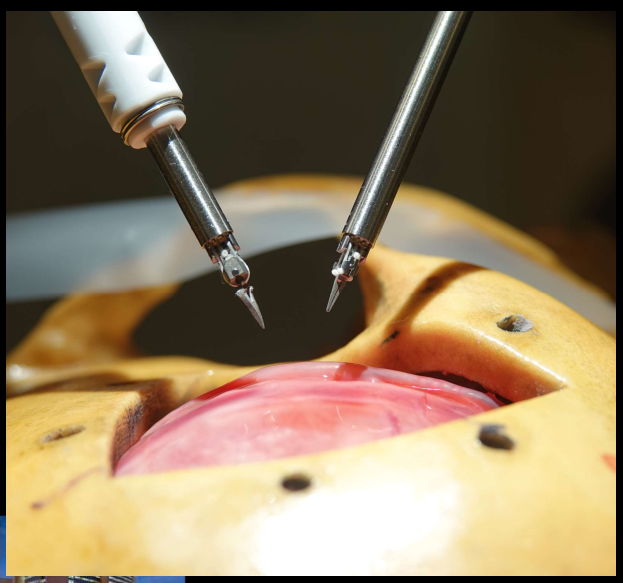
- EFS EDAS Study
  - Buffalo
  - Baptist Jacksonville
  - Mount Sinai
  - First cases- Adnan Siddiqui, MD

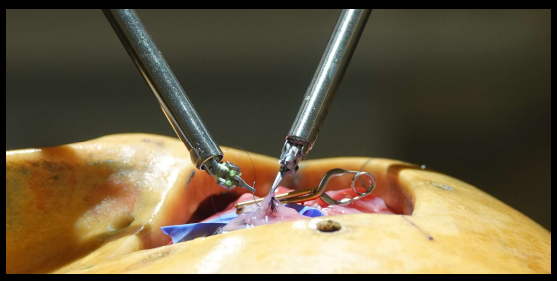


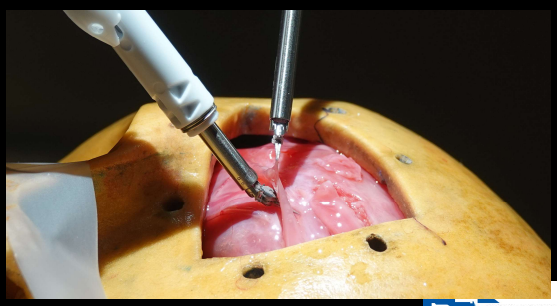
BAPTIST HEALTH

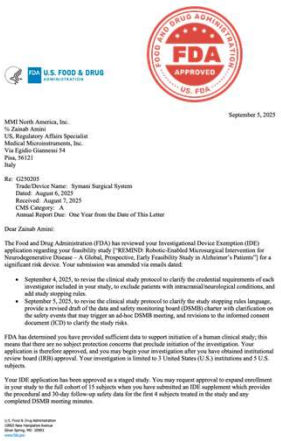
EDAS – First Case UBNS, 9/20/2025

BAPTIST HEALTH









September 5, 2025

MMI North America, Inc.
℅ Zainab Amin
US, Regulatory Affairs Specialist
Medical Microinstruments, Inc.
Via Egidio Gianneoni 54
Pisa, 56121
Italy

Re: G250305
Trade/Device Name: Synani Surgical System
Dated: August 6, 2025
Received: August 7, 2025
CMS Category: A
Annual Report Due: One Year from the Date of This Letter

Dear Zainab Amin:

The Food and Drug Administration (FDA) has reviewed your Investigational Device Exemption (IDE) application regarding your feasibility study ("REMIND: Robotic-Enabled Microsurgical Intervention for Neurodegenerative Disease – A Global, Prospective, Early Feasibility Study in Alzheimer's Patients") for a significant risk device. Your submission was amended via emails dated:

- September 4, 2025, to revise the clinical study protocol to clarify the credential requirements of each investigator included in your study, to exclude patients with intracranial/neurological conditions, and add study stopping rules.
- September 5, 2025, to revise the clinical study protocol to clarify the study stopping rules language, provide a revised draft of the data and safety monitoring board (DSMB) charter with clarification on the safety events that may trigger an ad-hoc DSMB meeting, and revisions to the informed consent document (ICD) to clarify the study risks.

FDA has determined you have provided sufficient data to support initiation of a human clinical study; this means that there are no subject protection concerns that preclude initiation of the investigation. Your application is therefore approved, and you may begin your investigation after you have obtained institutional review board (IRB) approval. Your investigation is limited to 3 United States (U.S.) institutions and 5 U.S. subjects.

Your IDE application has been approved as a staged study. You may request approval to expand enrollment in your study to the full cohort of 15 subjects when you have submitted an IDE supplement which provides the procedural and 30-day follow-up safety data for the first 4 subjects treated in the study and any completed DSMB meeting minutes.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

REMIND
Robot Enabled
MICROSURGICAL INTERVENTION
FOR NEURODEGENERATIVE DISEASE

Clinical Application	Study Design	2026 Q1	2026 Q2	2026 Q3	2026 Q4	2027 Q1	2027 Q2	2027 Q3	2027 Q4	2028 Q1
Alzheimer's Lymphatic Repair	**Multi center, early feasibility safety study** (15 patients, 3 sites)	Enrollment								
Alzheimer's Lymphatic Repair	**Multi center, pivotal safety and efficacy study** (300 patients, 30 sites)			Site Activation	Enrollment					

NCT07178210

24-36 Month Sprint: Generating clinical data and securing regulatory approval, alongside strong interest from providers, payers, investors and government agencies

Robotic-Enabled Microsurgical Intervention for Neurodegenerative Disease – A Global, Prospective, Early Feasibility Study in Alzheimer's Patients

- The **objective** of this study is to evaluate the safety and feasibility of using the Symani System and microsurgical techniques in the deep cervical lymph nodes (dCLNs) in the setting of mild to moderate Alzheimer's disease and lymphatic abnormalities.
- The **patients** selected for the REMIND Study will be adults diagnosed with mild to moderate Alzheimer's disease who are found to have abnormal lymphatic drainage in the neck, making them candidates for robotic-assisted microsurgical intervention.
- REMIND is an **Investigational Device Exemption (IDE)** study that will be run in up to **3 sites** globally.

BAPTIST HEALTH

Status: Active, enrolling

Robotic-Enabled Microsurgical Intervention for Neurodegenerative Disease – A Global, Prospective, Early Feasibility Study in Alzheimer's Patients

Objective: The objective of this investigational device exemption (IDE) study is to evaluate the safety and feasibility of using the Symani System and microsurgical techniques in the deep cervical lymph node region in the setting of mild to moderate Alzheimer's disease and lymphatic abnormalities.

1

Primary Endpoints:
- Device-related serious adverse events at 30 days

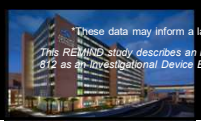
2

Secondary Safety Endpoints:
- All serious adverse events (SAEs)
- All adverse events (AEs)
- Anastomosis-specific reoperation rate

Secondary Effectiveness endpoints:
- Change in amyloid PETcentiloidvalue
- Change in plasma biomarkers: amyloidβ-42 and 40, ptau-217,NfL,GFAP
- Anastomosis patency prior to closure
- Intraoperative conversion to manual approach

Exploratory Endpoints
- Change in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) Score at 6 months from baseline
- Change in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) domains at 6 months from baseline
- Change in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13) score at 6 months from baseline
- Change in Montreal Cognitive Assessment (MoCA) score at 6 months from baseline
- Change in Mini Mental State Examination (MMSE) score at 6 months from baseline
- Change in Functional Activities Questionnaire (FAQ) at 6 months from baseline
- Change in Gait Speed and Quality, as assessed by Timed Up and Go (TUG) test at 6 months from baseline
- Hospital length of stay

- **Phase:**
- **Sites:**
- **Initial enrollment:**
  - **File IDE supplement:**
- **Estimated Enrollment period:**
- **Follow-up Period:**
- **Status:**



These data may inform a larger pivotal trial in the future

This REMIND study describes an investigational use of the Symani Surgical System. The investigational use of the Symani Surgical System described herein has been approved by FDA under the Code of Federal Regulations, Title 21 Part 812 as an Investigational Device Exemption.

BAPTIST HEALTH

Inclusion/Exclusion Criteria

Inclusion

To be eligible to participate in this study, individuals must meet all the following criteria:

1. Patient aged 50 or older
2. Patient has confirmed mild to moderate Alzheimer's Disease according to the National Institute of Aging-Alzheimer's Association (NIA-AA) criteria (alt text: International Working Group (IWG) Patient and has a positive core 1 Alzheimer biomarker according to the Alzheimer's Association (AA) criteria)
3. Patient has a positive amyloid PET test and/or a positive CSF t-tau/amyloid-beta-42 test
4. Patient has an MMSE score within the mild to moderate range (10-26)
5. Females only: Postmenopausal or taking medically acceptable form of birth control.
6. Investigator deems the candidate acceptable for lymphatic surgery with a robotic-assisted microsurgical anastomosis in accordance with the Symani System's Instructions for Use (IFU)
7. Patient or their legally authorized representative agrees to participate in the study, return for all required follow-up visits, complete all study procedures, and has willingly provided written informed consent after receiving all information related to the study, its requirements, and the robotic assisted procedure

Exclusion

Individuals will be excluded from participating in this study if any of the following criteria are met:

1. Patient (or their legally authorized representative) is unwilling to provide informed consent
2. Patient has suspected dementia of other type, e.g., Lewy body, frontotemporal disorder, vascular, etc.
3. Patient has documented or suspected neurological or intracranial conditions such as cerebrovascular accident, tumors, intracranial space occupying lesions, seizures or other intracranial/neurological conditions that may affect their safety in the study.
4. History of head and neck radiation exposure
5. Patient with severe kidney disease (GFR <30 mL/min/1.73m2)
6. Patient with acute kidney injury
7. Active systemic infection under treatment with intravenous antibiotics
8. Patient has a modified Rankin Score (mRS) of >4
9. Clinically significant cardiovascular, digestive, respiratory, endocrine, or central nervous system disorders, untreated sleep apnea, previous mental disorders, or other disorders that may significantly affect the data collection or the ability to comply with the protocol per the investigator's discretion
10. Known history of significant bleeding, coagulopathy, or Von Willebrand's disease
11. Patient with an active cancer diagnosis and/or currently receiving treatment for cancer or has received treatment within the past 6 months
12. Patient is currently receiving treatment or has been treated with anti-amyloid-beta monoclonal antibody therapy within the past 3 months
13. Patient has contraindication for MRI
14. Currently enrolled in any other investigational clinical studies that the investigator believes may impact patient safety or study outcomes
15. Patient is ineligible to participate for other reasons in the judgment of the investigator

BAPTIST HEALTH

Visit	Pre-Procedure	Index Procedure	Discharge	Follow-Up Visits			
Window	Within 30 days prior to index procedure	Day 0	Within 12-24 hours prior to discharge	30 days ±10 days post index procedure	3 mos ±2 weeks post index procedure	6 mos ±4 weeks post index procedure	12 mos ±6 weeks post index procedure
Patient Eligibility Criteria	X	X					
Medical History*	X						
MR Imaging**	X					X	X
Adverse Event Assessment	X	X	X	X	X	X	X
Amyloid PET	X					X	X
Plasma Markers	X			X	X	X	X
Cerebrospinal Fluid Biomarkers	X						X
Cognitive and Functional Questionnaires	X					X	X
Gait Assessment	X			X	X	X	X
Anastomosis Procedure Details		X					
Intraoperative Assessment		X					
Study Exit							X

** If the patient's APOE4 test is not already documented in their medical history, genetic testing for APOE4 shall be conducted.*

***MR Imaging at pre-procedure and 6-months includes intrathecal contrast; 12 months does not include intrathecal contrast.*

BAPTIST HEALTH

REMIND
First Three Patients in the US Complete

First Case April 30th 2026
Baptist Jacksonville

Michael DeFazio - Plastic Surgery
Ricardo Hanel - Neurosurgery
Steve Toenjes - Neurology

Strong Cross Specialty Execution Between Neurology, Neurosurgery & Plastics

Patient Profiles

Patient 1
- April 30, 2026
- 77 Years Old Male
- Moderate Alzheimer's Disease

Patient 2
- May 4, 2026
- 67 Years Old Male
- Moderate Alzheimer's Disease

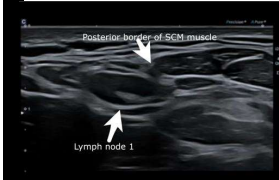
Patient 3
- May 4, 2026
- 71 Years Old Female
- Mild Alzheimer's Disease

Procedure details & learnings from first 3 cases

- **Bi-Lateral** LNVA procedures
- Confirmed **lymph node anomalies** via high frequency ultrasound
- **IV anesthesia,** no gas
- Total procedure times ranged from **4-5 hours** (2-3 hour procedure time anticipated after initial learning curve)
- No perioperative AEs reported
- All patients **discharged next day**
- Safety Data through 30 days
  - Three patients – mild AEs (unrelated to device)
  - No Serious Adverse Events

REMIND | Technology Enablers

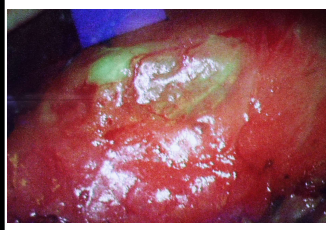
Diagnostic Imaging



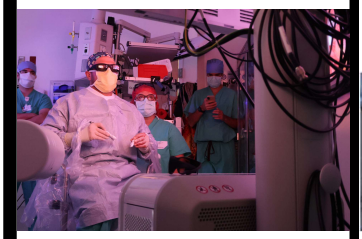
Cannon Ultra-High Frequency Ultrasound

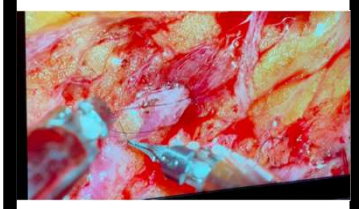
Intra Operative Advanced Imaging Techniques

Lymph Node Selection Supported By ICG & Fluorescein

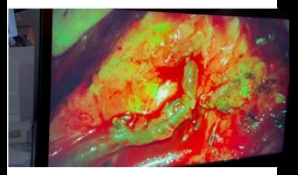


LNVA with Symani Precision





Confirmation of Anastomosis



Patient Demographics	
Mean Age	72 yrs (67-77)
Sex	2 male, 1 female
Mean BMI	23.9 kg/m² (20.2–29.8)
mRS Score	2 (all)
APOE4 Status	2 copies (n=1) 1 copy (n=2)
Baseline MMSE	12, 14, 21
AD Duration	64 mo (36-96)

Procedural Characteristics	
Mean OR Time	4.9 hrs (4.6-5.3)
Mean Anesthesia Time	4.6 hrs (4.2-5.1), IV only
Procedure Type	Bilateral Lymph Node to Vein Anastomosis (all)
Discharge	Day after surgery (all)

BAPTIST HEALTH

REMIND EFS | Future Research Plans

MMI.

UPDATE - MMI Receives IDE Approval from FDA for First Robotic Microsurgical Study in Alzheimer's Patients

First-of-its-kind study represents the potential for robotic-enabled microsurgical intervention for neurodegenerative diseases, including Alzheimer's

November 05, 2025 12:16 ET | Source: Medical Microinstruments, Inc.

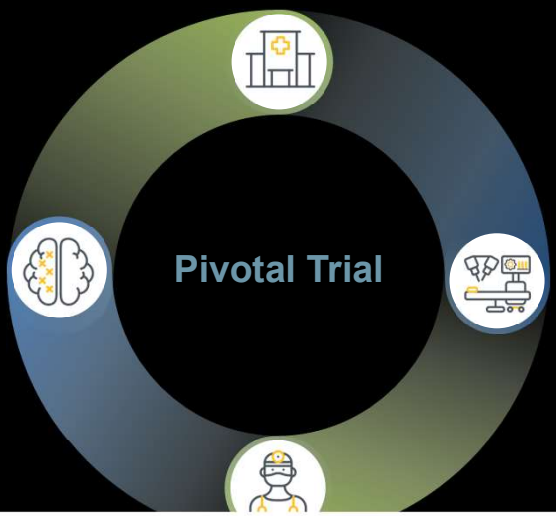
Follow

REMIND
Robot Enabled
MICROSURGICAL INTERVENTION
FOR NEURODEGENERATIVE DISEASE

JACKSONVILLE, Fla., Nov. 05, 2025 (GLOBE NEWSWIRE) – MMI (Medical Microinstruments, Inc.), a robotics company dedicated to increasing treatment options and improving clinical outcomes for patients with complex conditions, today announced the U.S. Food and Drug Administration's (FDA) approval of an Investigational Device Exemption (IDE) for a clinical study using a novel microsurgical intervention for Alzheimer's disease.

The feasibility study, entitled REMIND, Robotic-Enabled Microsurgical Intervention for Neurodegenerative Disease, will collect safety and effectiveness data of the Symani® Surgical System and microsurgical techniques to reestablish lymphatic drainage pathways in the deep cervical lymph

These data may inform a larger pivotal trial



MMI Receives FDA Approval to Advance to Phase II of Patient Enrollment in Groundbreaking REMIND Early Feasibility Study in patients with mild to moderate Alzheimer's Disease

Conclusions

- A lot to be learned
- Patient selection will be key
- The surgical procedure is simple and safe
- Are we changing the course of this dreadful condition?
  - We will learn a lot soon

Thank you!!!

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Instagram @drricardohanel