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10 - 13 Aprilie 2023, Timișoara

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British-Romanian Academic Institute of Neuroscience (BRAIN), why it is such a mandatory need? Why now?

Roxana Carare MD, PhD
Professor of Clinical Neuroanatomy
University of Southampton, UK

UMFST “G.E. Palade” Targu Mures, Romania

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No efficient cure for any neurological/psychiatric disorder

The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017

Günther Deuschl, Ettore Beghi, Franz Fazekas, Timea Varga, Kalliopi A Christoforidi, Eveline Sipido, Claudio L Bassetti, Theo Vos, Valery L Feigin

Lancet Public Health 2020; 5: e551–67

Summary

Background Neurological disorders account for a large and increasing health burden worldwide, as shown in the Global Burden of Diseases (GBD) Study 2016. Unpacking how this burden varies regionally and nationally is

Results

In 2017, the total population in the EU28 was 512·4 million and the population of WHO Europe region was 925·6 million. In the same year, 307·9 million neurological diseases were counted in the EU28,

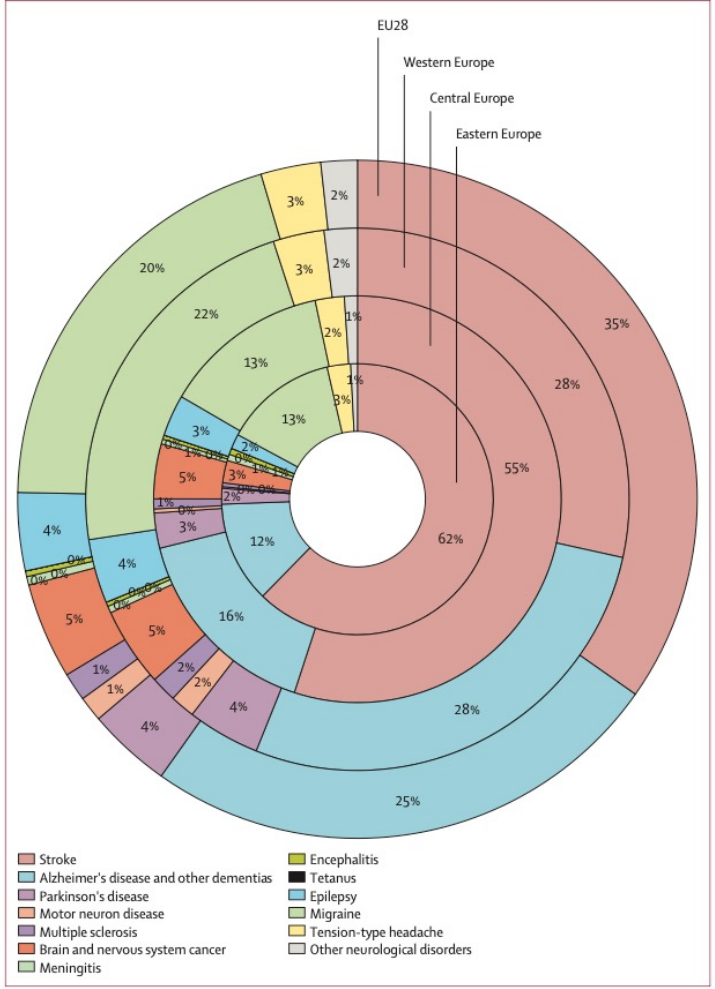

Figure 1: **Contribution of each disease to the overall burden of neurological disorders in the EU28, western, central, and eastern Europe in 2017**
Percentages represent proportion of DALYs. DALYs=disability-adjusted life-years. EU28=the 27 countries in the EU plus the UK.

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Complex, multifactorial diseases = interdisciplinary creative high risk, high gain actions

https://brain.umfst.ro

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2023

BRAIN British-Romanian Academic Institute of Neuroscience

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BRAIN: Neurology, Neurorehabilitation, Neurosurgery, Psychiatry meet Genetics, Mathematics, Physics, Computer science, Engineering

Romania also needs new recognized independent specialities: Neuropathology, Palliative Care

Published in final edited form as:
Annu Rev Neurosci. 2019 July 08; 42: 385–406. doi:10.1146/annurev-neuro-070918-050501.

Antisense Oligonucleotide Therapies for Neurodegenerative Diseases

C. Frank Bennett[1], **Adrian R. Krainer**[2], **Don W. Cleveland**[3]

[1]Ionis Pharmaceuticals, Carlsbad, California 92010, USA

[2]Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA

[3]Ludwig Institute for Cancer Research, University of California, San Diego, La Jolla, California 92093, USA

Abstract

Antisense oligonucleotides represent a novel therapeutic platform for the discovery of medicines that have the potential to treat most neurodegenerative diseases. Antisense drugs are currently in development for the treatment of amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease, and multiple research programs are underway for additional neurodegenerative diseases. One antisense drug, nusinersen, has been approved for the treatment of spinal muscular atrophy. Importantly, nusinersen improves disease symptoms when administered to symptomatic patients rather than just slowing the progression of the disease. In addition to the benefit to spinal muscular atrophy patients, there are discoveries from nusinersen that can be applied to other neurological diseases, including method of delivery, doses, tolerability of intrathecally delivered antisense drugs, and the biodistribution of intrathecal dosed antisense drugs. Based in part on the early success of nusinersen, antisense drugs hold great promise as a therapeutic platform for the treatment of neurological diseases.

Brain pharmacology of intrathecal antisense oligonucleotides revealed through multimodal imaging

Curt Mazur,[1] Berit Powers,[1] Kenneth Zasadny,[2] Jenna M. Sullivan,[2,3] Hemi Dimant,[2] Fredrik Kamme,[1] Jacob Hesterman,[2] John Matson,[1] Michael Oestergaard,[1] Marc Seaman,[2] Robert W. Holt,[2] Mohammed Qutaish,[2] Ildiko Polyak,[2] Richard Coelho,[2] Vijay Gottumukkala,[2] Carolynn M. Gaut,[2] Marc Berridge,[4] Nazira J. Albargothy,[5] Louise Kelly,[5] Roxana O. Carare,[5] Jack Hoppin,[2] Holly Kordasiewicz,[1] Eric E. Swayze,[1] and Ajay Verma[3]

[1]Ionis Pharmaceuticals, Inc., Carlsbad, California, USA. [2] Invicro, LLC, Boston, Massachusetts, USA. [3]Biogen, Cambridge, Masschusetts, USA. [4]3D Imaging, Little Rock, Arkansas, USA. [5]University of Southampton, Hampshire, United Kingdom.

JCI insight RESEARCH ARTICLE

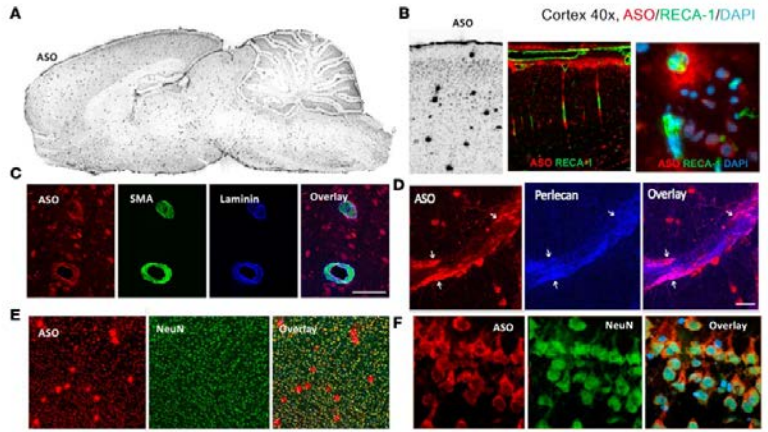


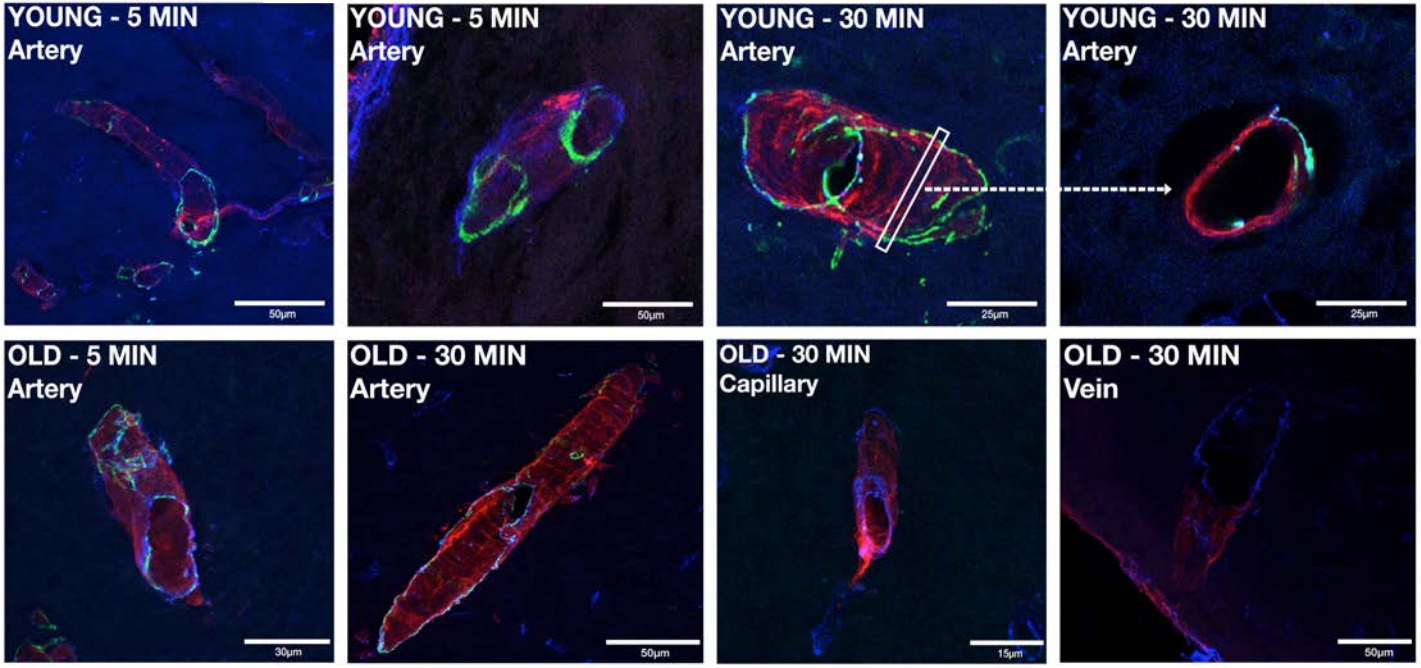
Figure 7. Perivascular and neuronal association of ASO 24 hours after dosing. (**A**) Punctate perivascular staining of ASOs by IHC throughout brain at 24 hours after IT dosing. (**B**) Colocalization of ASOs and the vascular endothelial marker Reca1 in cerebral cortex (×10 magnification left 2 images, ×40 magnification right image). (**C**) Colocalization of Cy7-ASO with vascular α-smooth muscle actin (αSMA) and basement membrane component laminin α2 (×20 magnification). (**D**) Colocalization of ASOs with basement membrane component perlecan (×20 magnification). (**E**) ASO colocalization with neurons and vessels in cerebral cortex (×10 magnification). (**F**) ASO colocalization with neuronal cells in hippocampus (×40 magnification).

Acta Neuropathologica
https://doi.org/10.1007/s00401-018-1862-7

ORIGINAL PAPER

Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways

Nazira J. Albargothy[1] · David A. Johnston[1] · Matthew MacGregor-Sharp[1] · Roy O. Weller[1] · Ajay Verma[2] · Cheryl A. Hawkes[3] · Roxana O. Carare[1]



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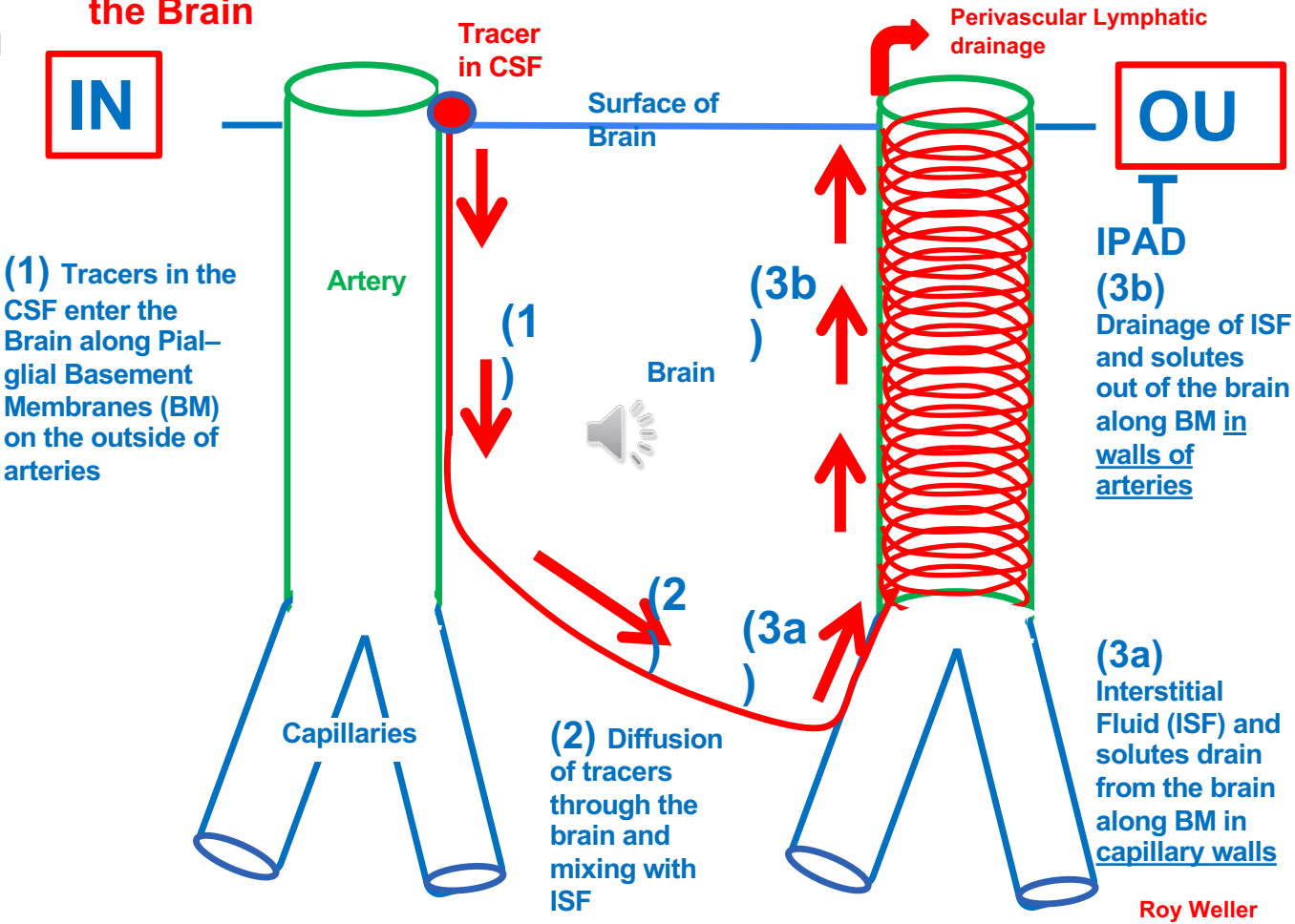
Tracers in the CSF: entry into the brain and drainage out of the Brain



Roy Weller 2018

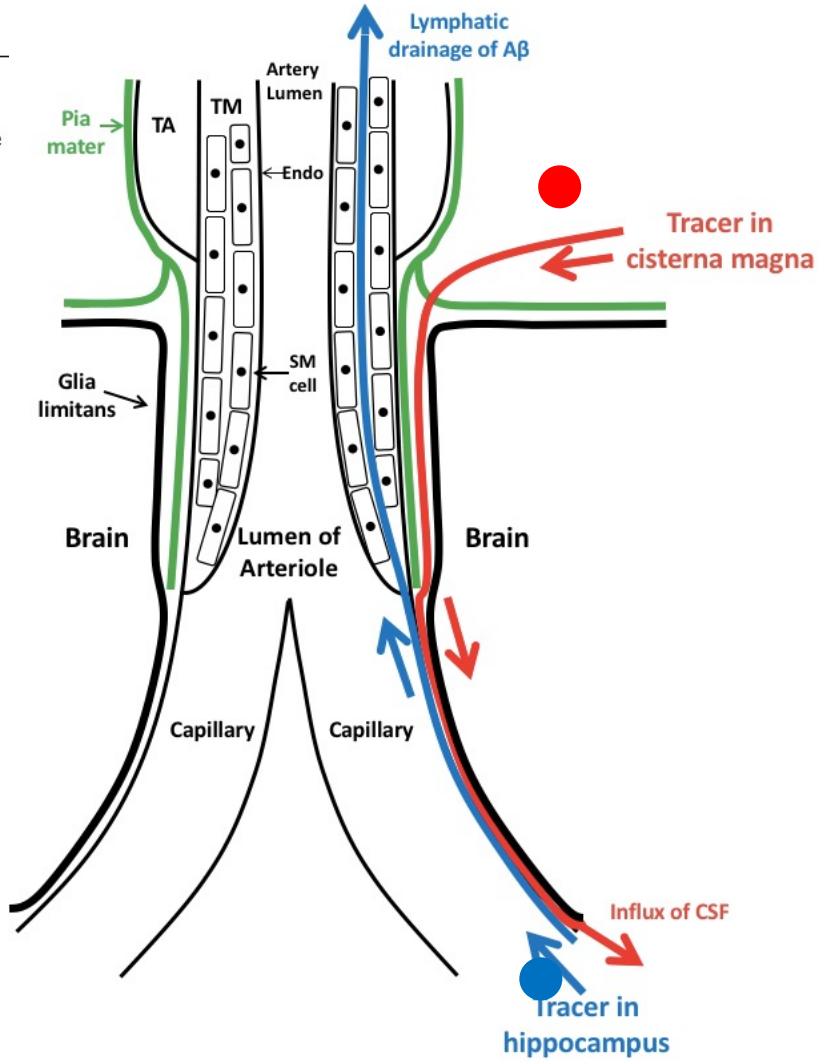
Acta Neuropathol (2016) 131:725–736
DOI 10.1007/s00401-016-1555-z

ORIGINAL PAPER

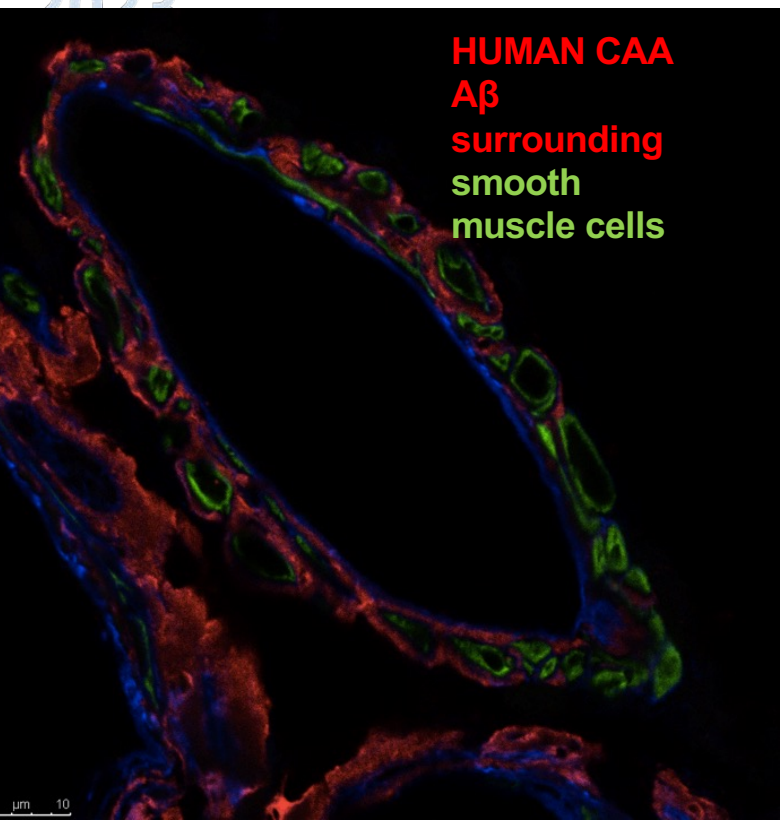
Vascular basement membranes as pathways for the passage of fluid into and out of the brain

Alan W. J. Morris[1] · Matthew MacGregor Sharp[1] · Nazira J. Albargothy[1] · Rute Fernandes[1] · Cheryl A. Hawkes[3] · Ajay Verma[2] · Roy O. Weller[1] · Roxana O. Carare[1]

- Cerebrospinal fluid (CSF) in subarachnoid space
  - Convective influx/glymphatic flow
- Interstitial fluid (ISF) in brain parenchyma
  - Intramural periarterial drainage (IPAD)
- Cerebral amyloid angiopathy (CAA)
  - Mirrors IPAD pathway

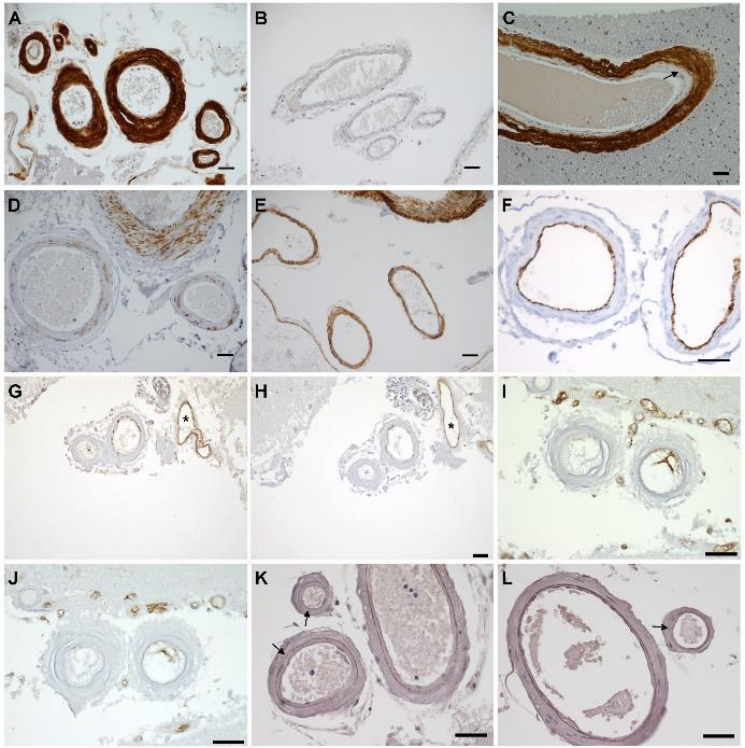


Hawkes et al, Brain Pathology 2015



Snorradottir AO et al, Brain Research 2013

Cystatin C



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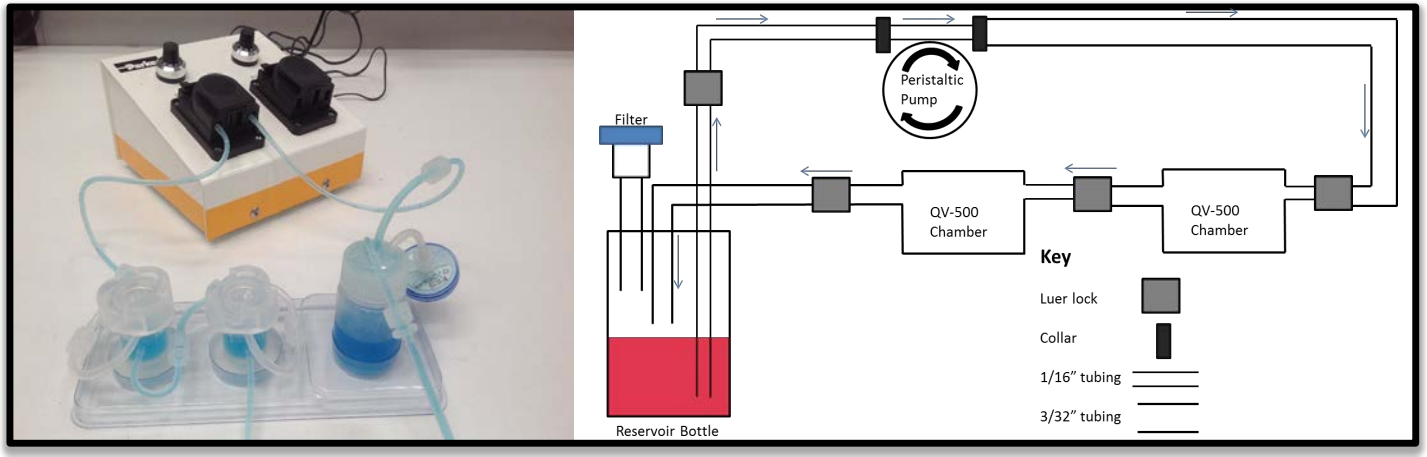
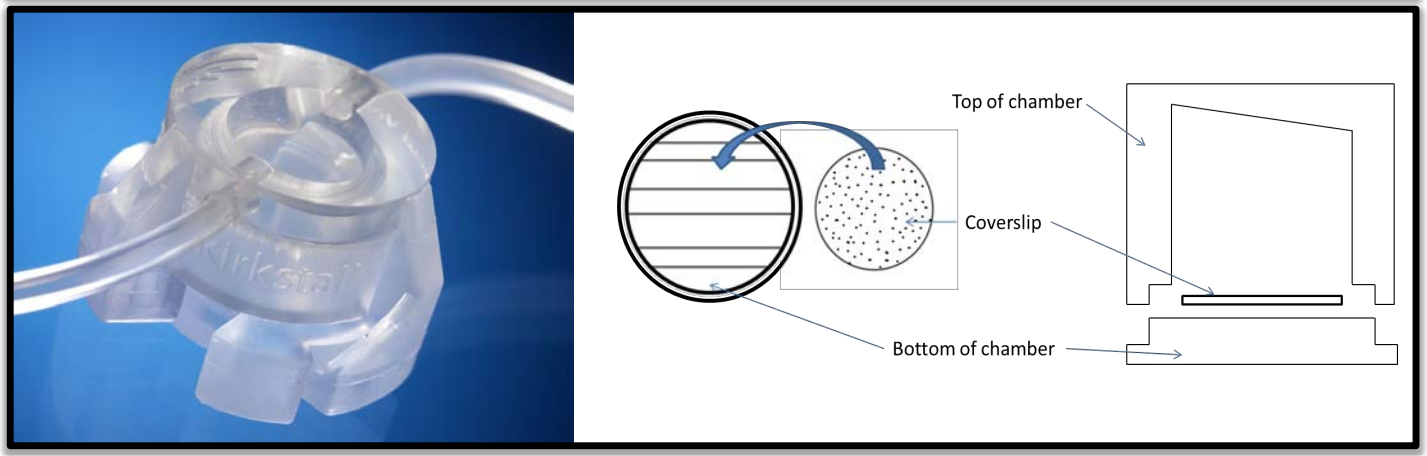
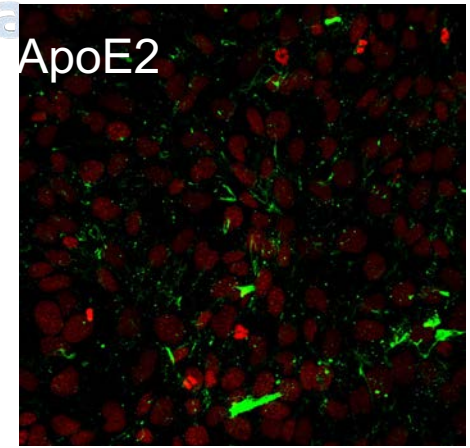
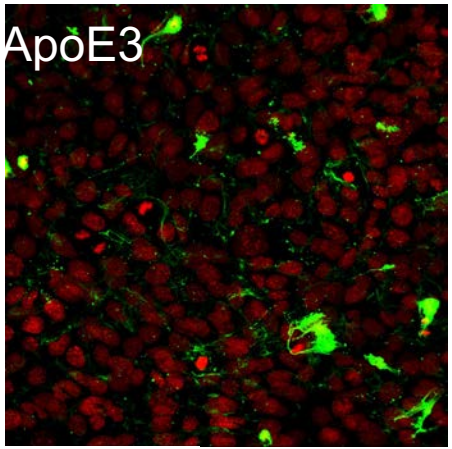
The Kirkstall Quasi Vivo System: an invitro model for IPAD

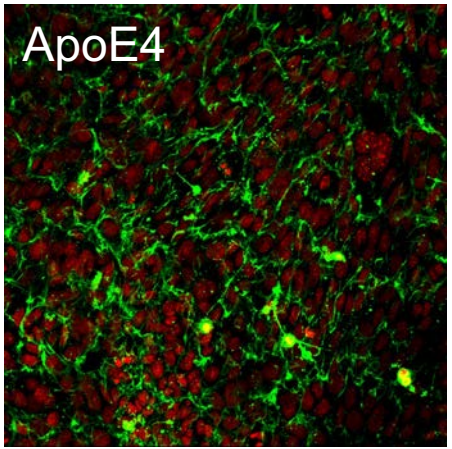


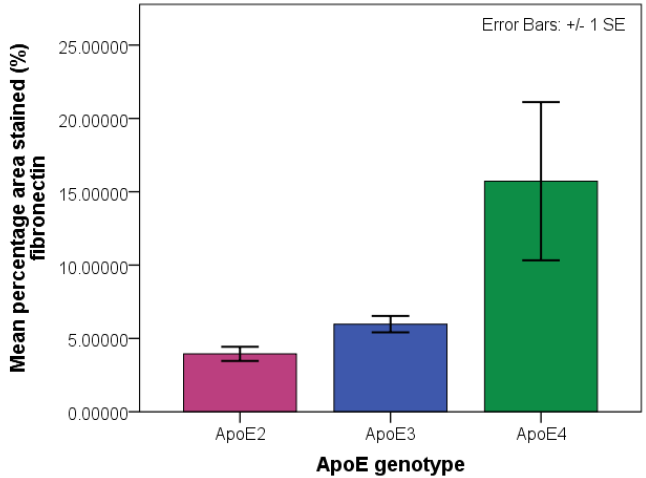


Fibronectin immunostaining

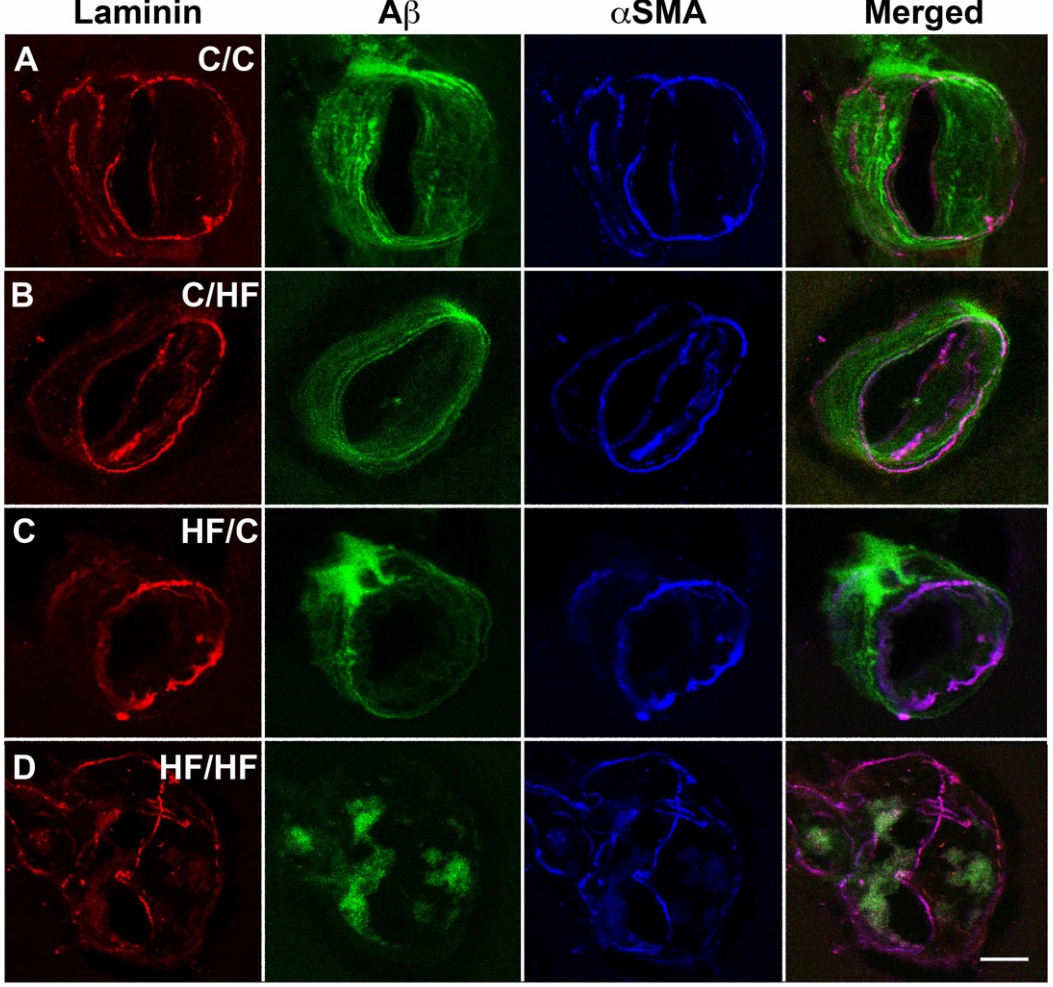








When cells are grown to confluence (all at the same cell density but different times) the amount of **fibronectin** expressed by the ApoE4 astrocytes is significantly higher than astrocytes expressing ApoE2 or E3



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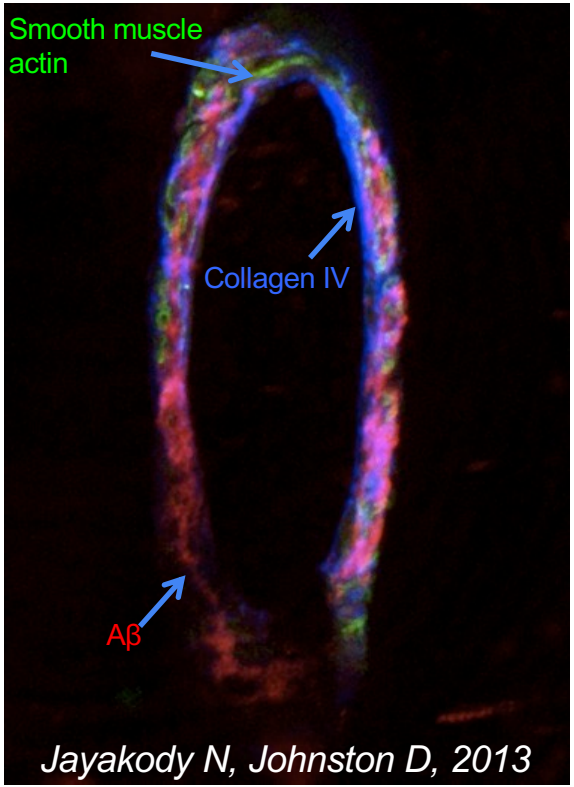
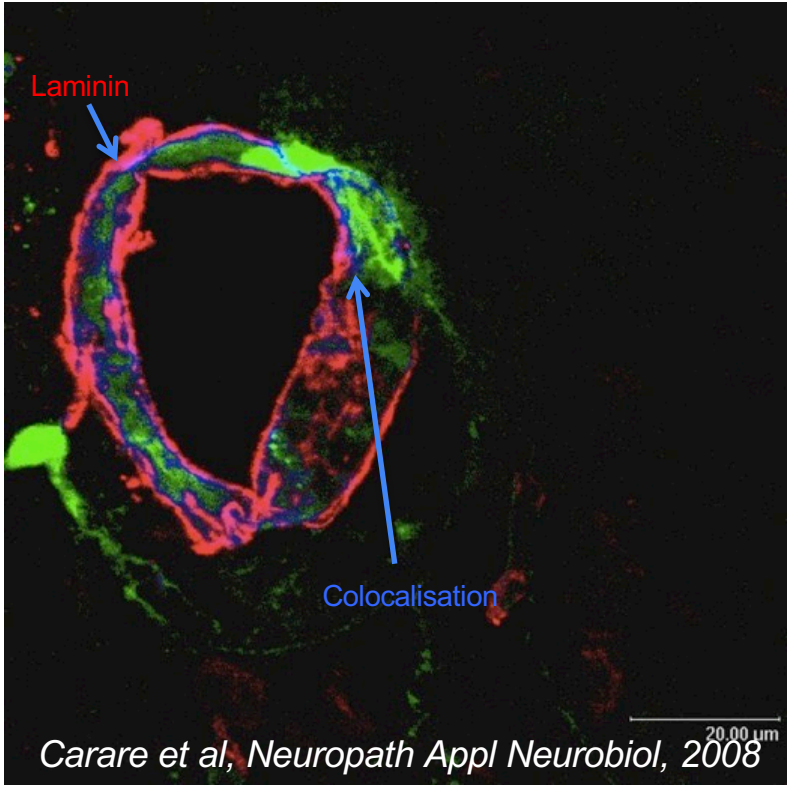
CAA=failure of perivascular drainage of Aβ

Carare R, 2008, 2013, Neuropathology and Applied Neurobiology

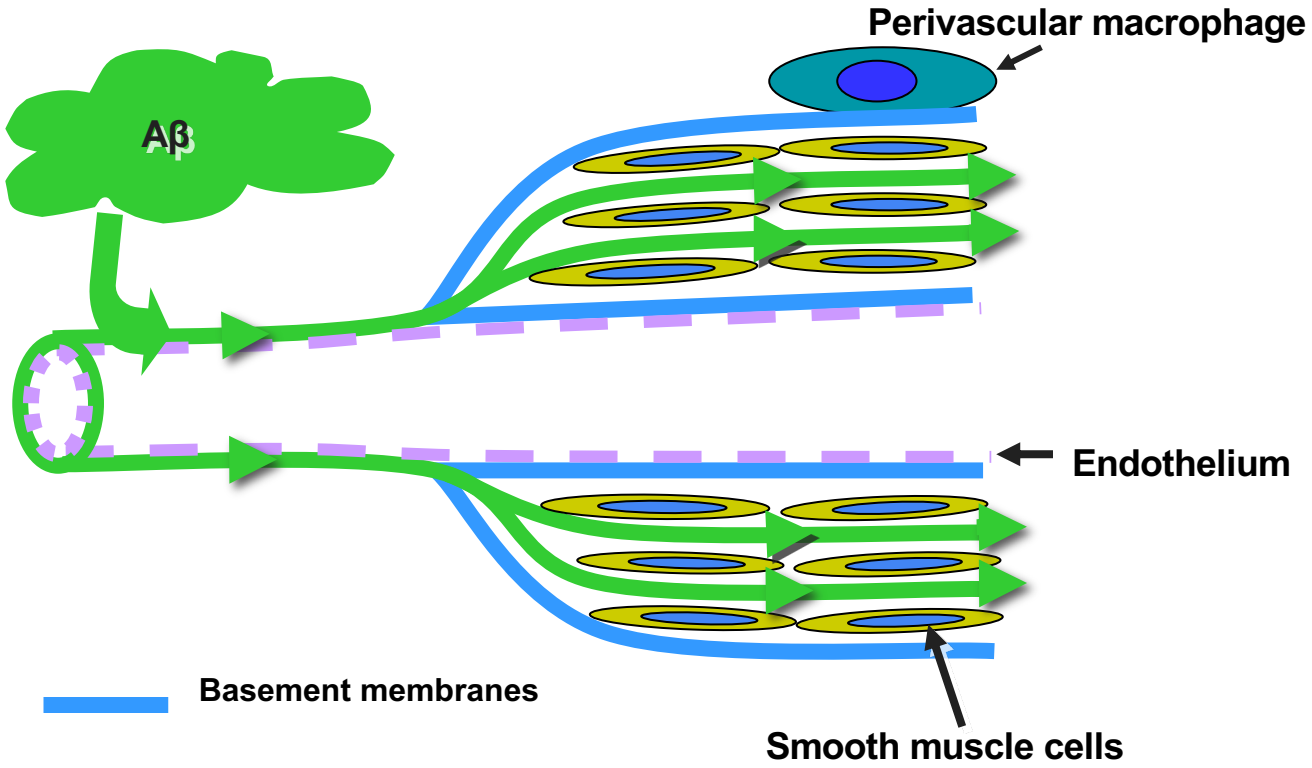


Jayakody N, Johnston D, 2013



Carare et al, Neuropath Appl Neurobiol, 2008

CAA: failure of elimination of Aβ along the walls of arteries & capillaries



Weller RO et al Brain Pathology 2008

Acta Neuropathol (2011) 121:431–443
DOI 10.1007/s00401-011-0801-7

ORIGINAL PAPER

Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy

Cheryl A. Hawkes · Wolfgang Härtig · Johannes Kacza · Reinhard Schliebs · Roy O. Weller · James A. Nicoll · Roxana O. Carare

OPEN ACCESS Freely available online

PLOS one

Disruption of Arterial Perivascular Drainage of Amyloid-β from the Brains of Mice Expressing the Human APOE ε4 Allele

Cheryl A. Hawkes[1], Patrick M. Sullivan[2], Sarah Hands[3], Roy O. Weller[1], James A.R. Nicoll[1], Roxana O. Carare[1]*

Journal of Pathology
J Pathol 2015; **235**: 619–631
Published online 7 January 2015 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4468

ORIGINAL PAPER

Prenatal high-fat diet alters the cerebrovasculature and clearance of β-amyloid in adult offspring

Cheryl A Hawkes[1]* Steve M Gentleman[2] James AR Nicoll[1] and Roxana O Carare[1,3]

Smart Diaspora 2023

Therapeutic targets for IPAD

1) Chaperone molecules for transport of proteins along basement membranes: ApoJ


PNAS

Loss of clusterin shifts amyloid deposition to the cerebrovasculature via disruption of perivascular drainage pathways

Aleksandra M. Wojtas[a,b], Silvia S. Kang[a], Benjamin M. Olley[c], Maureen Gatherer[c], Mitsuru Shinohara[a], Patricia A. Lozano[a], Chia-Chen Liu[a], Aishe Kurti[a], Kelsey E. Baker[a], Dennis W. Dickson[a,b], Mei Yue[a], Leonard Petrucelli[a], Guojun Bu[a,b], Roxana O. Carare[c], and John D. Fryer[a,b,1]

[a]Department of Neuroscience, Mayo Clinic, Jacksonville, FL 32224; [b]Neurobiology of Disease Graduate Program, Mayo Clinic Graduate School of

2) Improving the motive force for IPAD by acting upon the smooth muscle cells


ANNALS of Clinical and Translational Neurology — Open Access — ANA American Neurological Association

RESEARCH ARTICLE

Phosphodiesterase III inhibitor promotes drainage of cerebrovascular β-amyloid

Takakuni Maki[1,2], Yoko Okamoto[1,3], Roxana O. Carare[4], Yoshiki Hase[1], Yorito Hattori[1,5], Cheryl A. Hawkes[4], Satoshi Saito[1,5], Yumi Yamamoto[5], Yasukazu Terasaki[2], Hatsue Ishibashi-Ueda[3], Akihiko Taguchi[6], Ryosuke Takahashi[1], Taihei Miyakawa[7], Raj N. Kalaria[8], Eng H. Lo[2], Ken Arai[2] & Masafumi Ihara[1,9]

[1]Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2]Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts
[3]Department of Pathology, National Cerebral and Cardiovascular Center, Osaka, Japan


ELSEVIER — Alzheimer's & Dementia

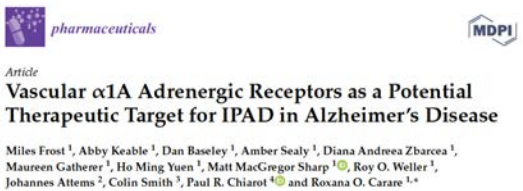
Featured Article

A multicenter, randomized, placebo-controlled trial for cilostazol in patients with mild cognitive impairment: The COMCID study protocol

Satoshi Saito[a,b,*], Shinsuke Kojima[c], Naoya Oishi[d,e], Ryosuke Kakuta[f], Takakuni Maki[b], Fumihiko Yasuno[g], Kazuyuki Nagatsuka[f], Haruko Yamamoto[h], Hidenao Fukuyama[d,e], Masanori Fukushima[c], Masafumi Ihara[a,f,*]

[a]Department of Regenerative Medicine and Tissue Engineering, National Cerebral and Cardiovascular Center, Suita, Japan
[b]Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[c]Department of MediScience, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan
[d]Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan
[e]Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan
[f]Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center, Suita, Japan
[g]Department of Psychiatry, Nara Medical University, Kashihara, Japan
[h]Center for Advancing Clinical and Translational Sciences, National Cerebral and Cardiovascular Center, Suita, Japan

Acting upon the 1) adrenergic and cholinergic receptors present on the vascular smooth muscle cells; 2) mitochondria (carbonic anhydrase inhibitors)


pharmaceuticals — MDPI

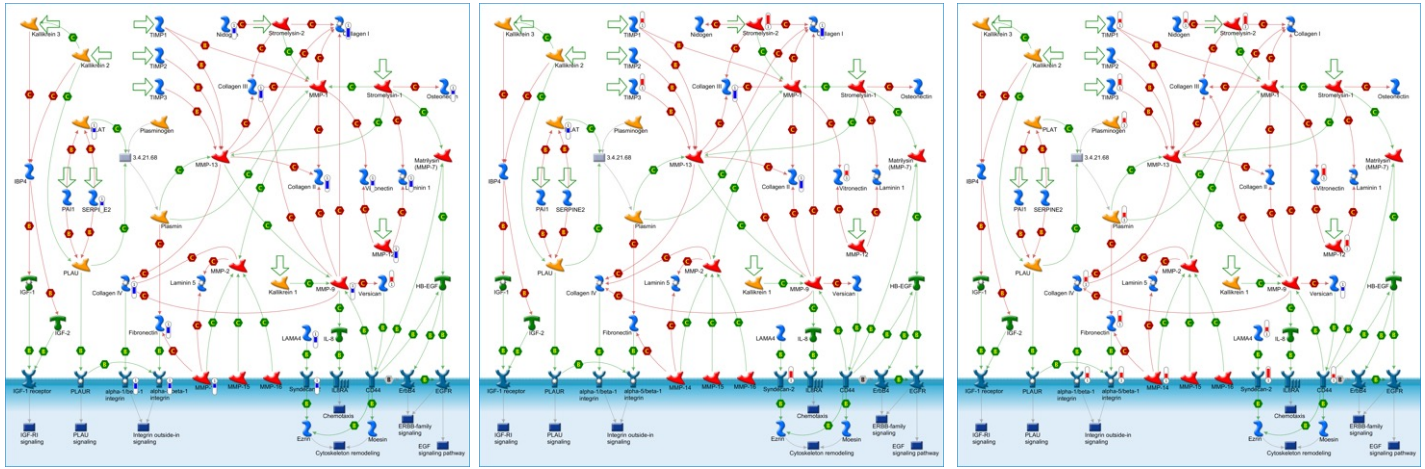
Article

Vascular α1A Adrenergic Receptors as a Potential Therapeutic Target for IPAD in Alzheimer's Disease

Miles Frost [1], Abby Keable [1], Dan Baseley [1], Amber Sealy [1], Diana Andreea Zbarcea [1], Maureen Gatherer [1], Ho Ming Yuen [1], Matt MacGregor Sharp [1], Roy O. Weller [1], Johannes Attems [2], Colin Smith [3], Paul R. Chiarot [4] and Roxana O. Carare [1,*]

Smart Diaspora 2023

Systems proteomics analysis reveals that clusterin and TIMP3 increase in leptomeningeal arteries affected by CAA Manousopoulou A et al, NAN 2016



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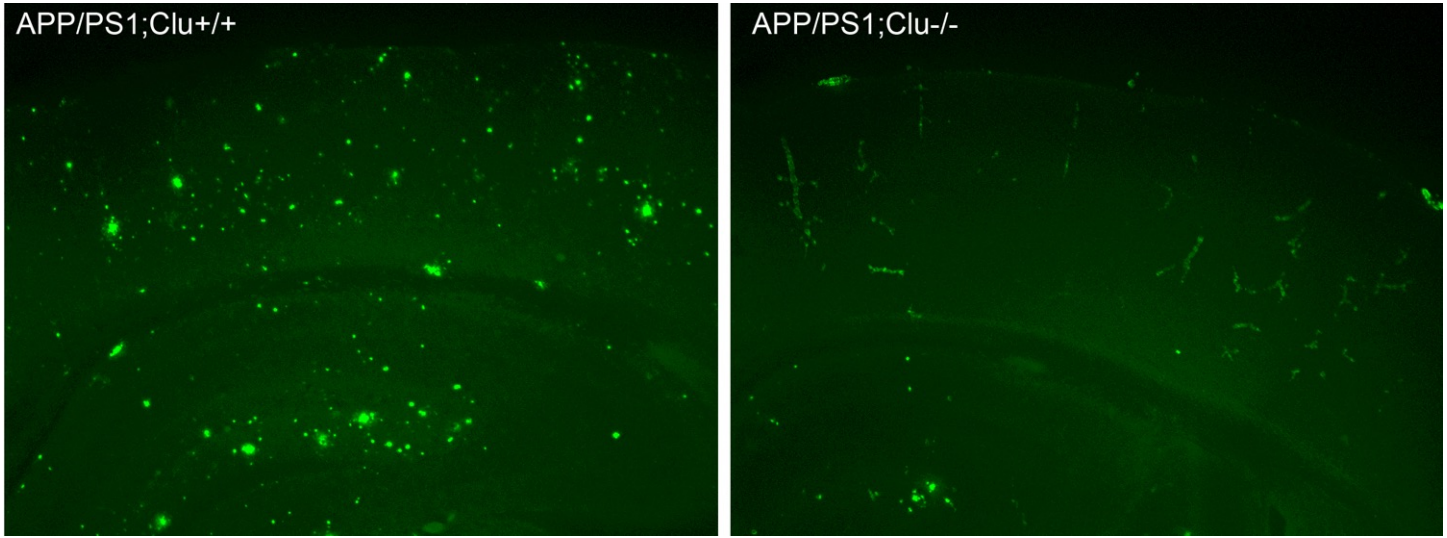
A look to the future: Chaperone molecules facilitating clearance of Aβ: clusterin



Retana *et al. Alzheimer's Research & Therapy* (2019) 11:42
https://doi.org/10.1186/s13195-019-0498-8

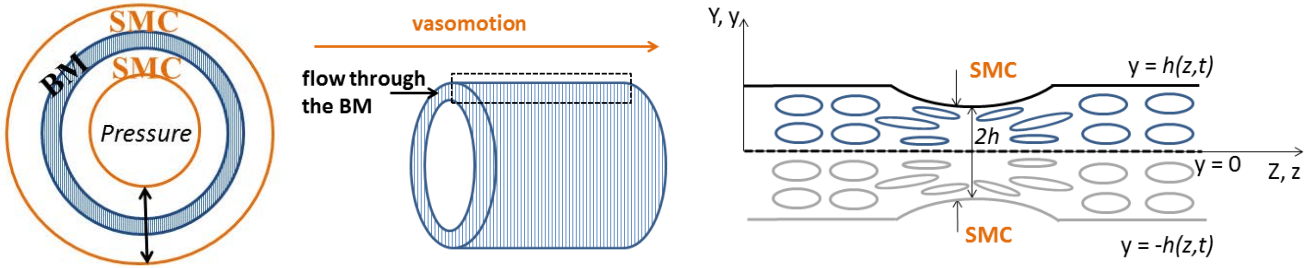
Re

RESEARCH

Peripheral administration of human recombinant ApoJ/clusterin modulates brain beta-amyloid levels in APP23 mice

Smart Diaspora 2023

Driving force for IPAD
Aldea R et al
Frontiers in Aging Neurosci 2019



Fluid drainage rate along one compartment of basement membrane by V-IPAD is **FIVE ORDERS OF MAGNITUDE (10^5) HIGHER** than that driven by arterial pulsations

The **vasomotion-driven IPAD** process may take between 45 minutes and 3.5 hours, depending on the BM elasticity and contractile abilities of the SMCs

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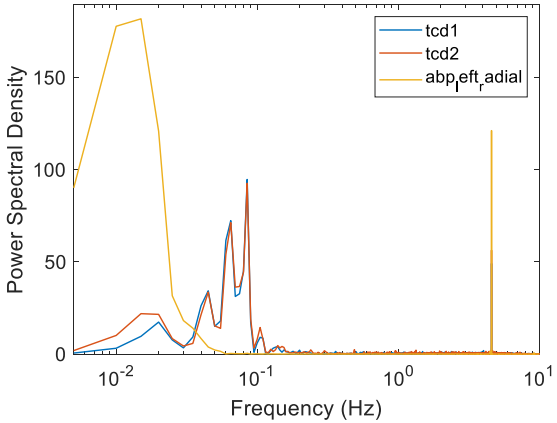
Vasomotion: 0.1-0.3Hz



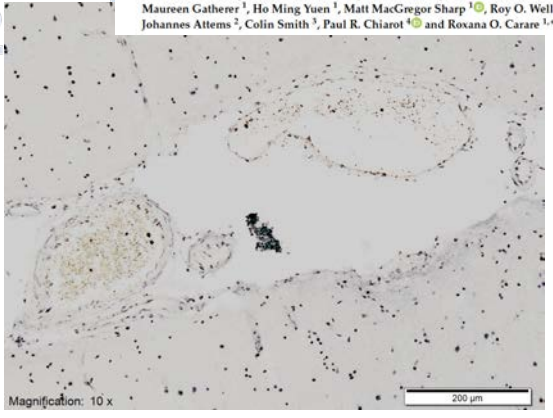
pharmaceuticals
MDPI

Article

Vascular α1A Adrenergic Receptors as a Potential Therapeutic Target for IPAD in Alzheimer's Disease

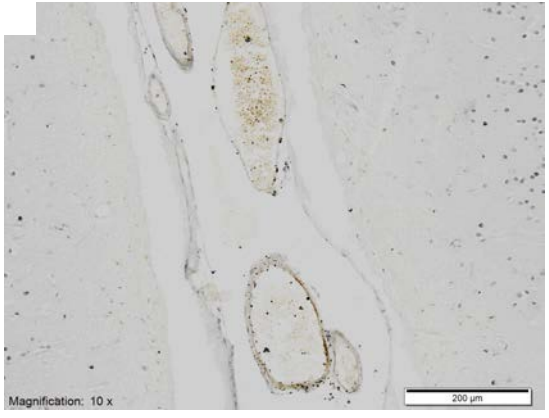
Miles Frost [1], Abby Keable [1], Dan Baseley [1], Amber Sealy [1], Diana Andreea Zbarcea [1], Maureen Gatherer [1], Ho Ming Yuen [1], Matt MacGregor Sharp [1], Roy O. Weller [1], Johannes Attems [2], Colin Smith [3], Paul R. Chiarot [4] and Roxana O. Carare [1,*]

Young



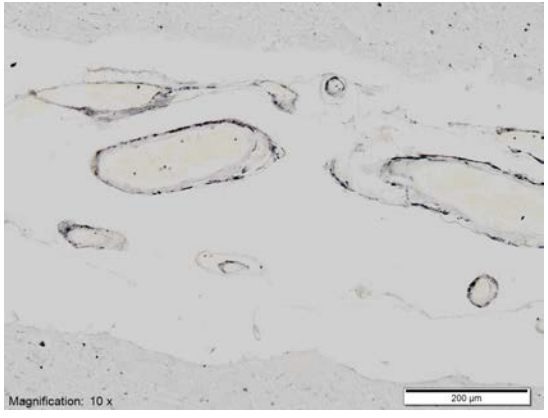
Distinct, punctate staining that is well defined throughout the vessel wall

Old

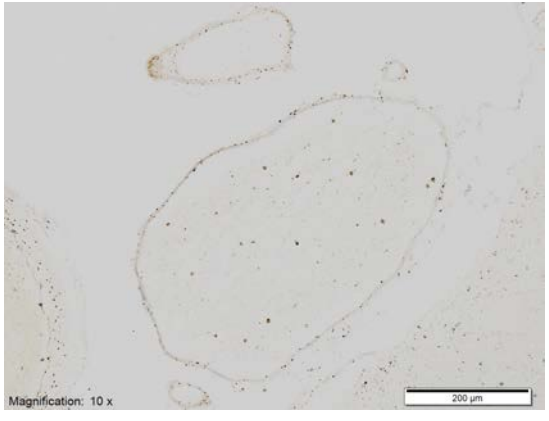


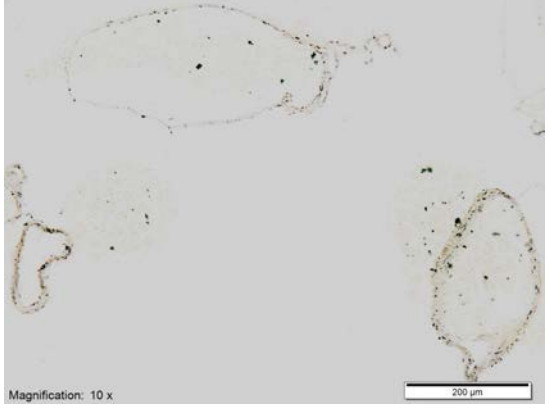
Punctate staining pattern but less evenly spread through the vessel, clustering in regions of the wall

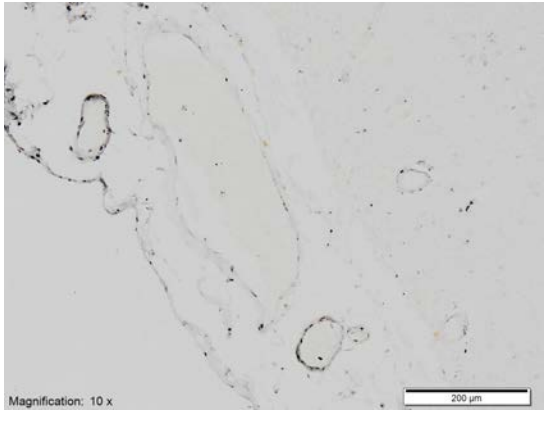
AD



Clustered staining gives uniform pattern of staining around vessel circumference








iDeAC
Interdisciplinary Dementia and Ageing Centre
Southampton
NHS
University Hospital
Southampton
NHS Foundation Trust
University of
Southampton
Institute
for Life Sciences
'The strength in iDeAC is the close collaboration between basic scientists (testing ideas), NHS staff (involved in day-to-day diagnosis and care), engineers (developing technology), mathematicians (modelling processes that cannot be seen with any current method) and industry (developing new treatments)'
www.ideac.org

Received: 22 May 2020 | Accepted: 26 May 2020 | Published online: 28 July 2020

DOI: 10.1002/dad2.12053

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

CEREBROSPINAL FLUID BIOMARKERS

Clearance of interstitial fluid (ISF) and CSF (CLIC) group—part of Vascular Professional Interest Area (PIA)

Cerebrovascular disease and the failure of elimination of Amyloid-β from the brain and retina with age and Alzheimer's disease-Opportunities for Therapy

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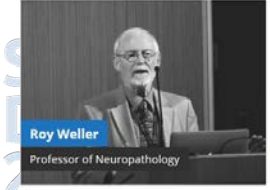
Thank you



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