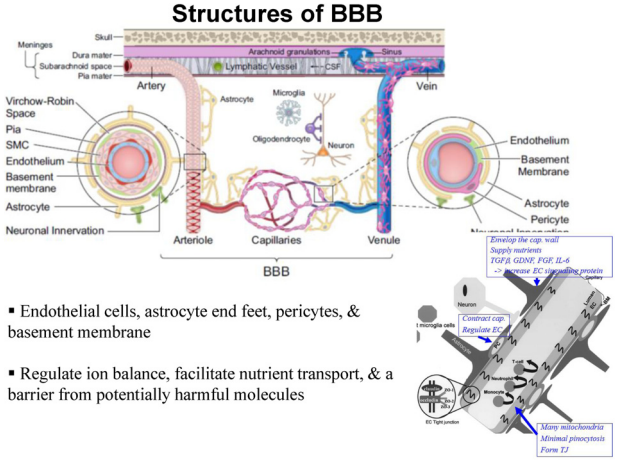
BBB dysfunction in neurodegenerative diseases

이 필 휴
연세의대

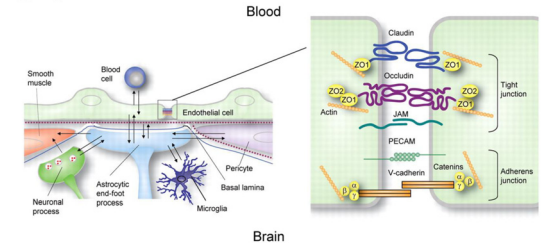
Phil Hyu Lee, MD, PhD
Department of Neurology, Severance Biomedical Science Institute, Yonsei University

Structures of BBB



- Endothelial cells, astrocyte end feet, pericytes, & basement membrane
- Regulate ion balance, facilitate nutrient transport, & a barrier from potentially harmful molecules

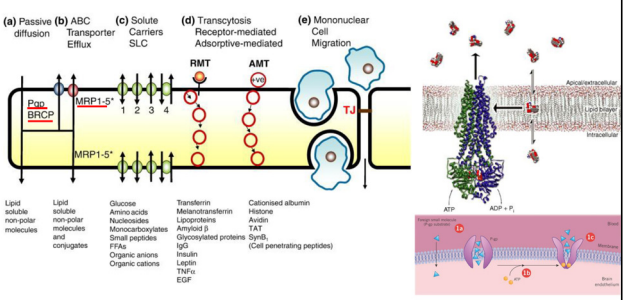
Tight junction



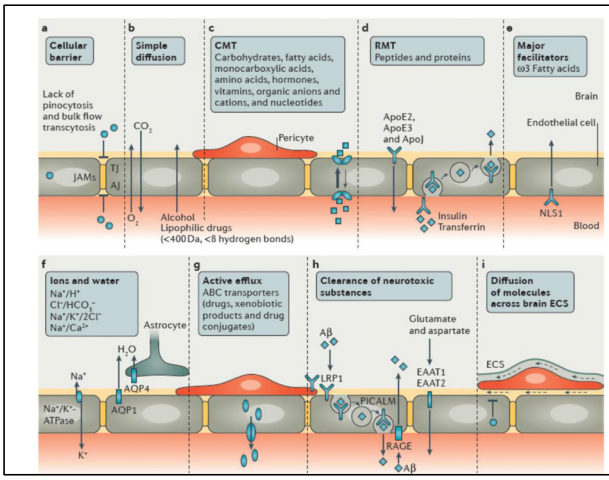
- Link adjacent endothelial cells and restrict paracellular diffusion of water-soluble substances into the brain
- A physical and chemical barrier
- Occludins, claudins, and junctional adhesion proteins
- Resistance of the BBB is greater than 1000 Ω/cm2, which is approximately

- *BBB is not static but dynamic*
- *The integrity of the BBB is not homogenous within the brain*

The BBB transport system



- The blood-to-brain influx transport systems supply nutrients such as glucose, amino acids and nucleotides from the blood to the brain
- The brain-to-blood efflux transport systems remove metabolites and neurotoxic compounds from the brain parenchyma to the blood

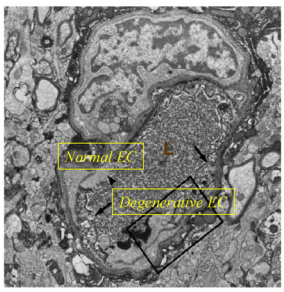


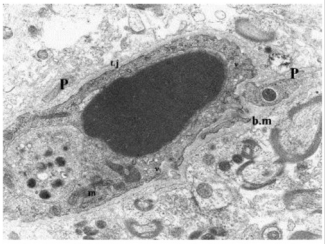
BBB breakdown in neurological diseases

- Stroke
- Brain Tumor
- Inflammatory conditions

BBB status in Alzheimer's disease

Endothelium





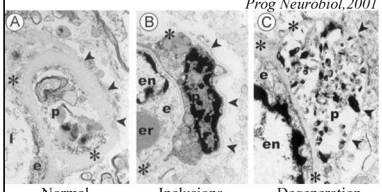
mitochondrial alterations (m), dilatation of the tight junctions (t,j), increased number of pinocytotic vesicles (v)

- Diminished TJ protein expression
- Capillary basement membrane alterations
- Brain endothelial degeneration

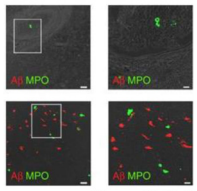
Acta Neuropathologica, 1996

Pericyte degeneration

Prog Neurobiol,2001



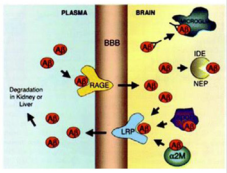
Cell extravasation



Nature Med,2015

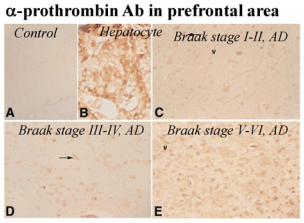
Dysregulated molecular transport

- Decreased endothelial-specific GLUT1 transporter at the BBB
- Reduced levels of LRP1, a major Aβ clearance receptor at the BBB
- Expression of RAGE, a major Aβ influx receptor, is increased in endothelium

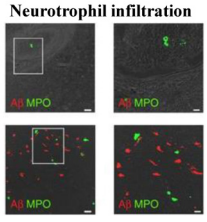


Cell extravasation

α-prothrombin Ab in prefrontal area



Neurotrophil infiltration

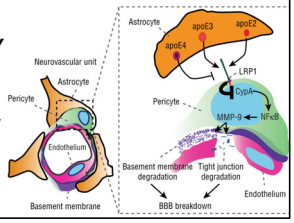


Nature Med,2015

Cyclophilin A and MMP9 pathway

- Astrocyte-secreted apoE2 and E3 maintain the BBB integrity by suppressing the proinflammatory cyclophilin A–MMP-9 pathway in pericytes via LRP1
- Increased activity CypA-MMP-9 pathway in AD apoE4 carrier than non-carriers

Cereb Blood Flow Metab, 2016



A population study on blood–brain barrier function in 85-year-olds

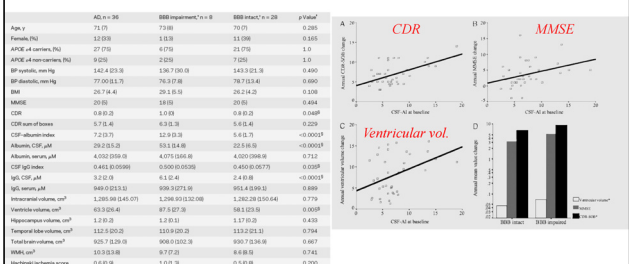
Article abstract—We investigated blood–brain barrier (BBB) function in relation to Alzheimer's disease (AD) and vascular dementia (VAD) in the very elderly. Sixty-five 85-year-old persons from a population-based sample were followed for 3 years; 29 were demented at age 85 (13 with AD, 14 with VAD, and 2 with other dementias), 7 developed dementia during follow-up, and 29 remained nondemented. CSF/serum albumin ratio was used as as a measure of BBB function. Dementia was defined according to the DSM-III-R, AD according to the NINCDS-ADRDA criteria, and VAD according to the NINDS-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria. Mean CSF/serum albumin ratio was higher in all dementias (8.5 ± 4.3; $p = 0.007$) and in the subtypes AD (8.9 ± 5.3; $p = 0.046$) and VAD (8.7 ± 3.5; $p = 0.002$) than in nondemented individuals (versus 6.5 ± 2.0), but it was not related to dementia severity. Nondemented women at age 85 (n = 3) who developed dementia during the follow-up had a higher CSF/serum albumin ratio than those not developing dementia (10.4 ± 2.0 versus 6.0 ± 1.9; $p = 0.007$). Nondemented individuals lacking the apolipoprotein E ε3 allele (n = 4) had a higher CSF/serum albumin ratio (9.3 ± 0.8 versus 6.6 ± 2.1; $p = 0.029$) than other individuals. A relative BBB dysfunction is associated with both AD and VAD among very elderly individuals. This finding is possibly found early in the disease before the onset of clinical dementia.

	All			Men			Women		
	n	Mean ± SD	p Value	n	Mean ± SD	p Value	n	Mean ± SD	p Value
No dementia at age 85 and 88	29	6.5 ± 2.0		11	7.3 ± 1.9		18	6.0 ± 1.9	
Dementia at age 85	29	8.5 ± 4.3	0.007	7	10.3 ± 4.2	0.063	22	8.0 ± 4.3	0.079
Dementia between age 85 and 88	7	8.3 ± 2.5	0.065	4	6.7 ± 1.3	0.555	3	10.4 ± 2.0	0.007
Dementia at age 85 or between age 85 and 88	36	8.5 ± 4.0	0.008	11	9.0 ± 3.8	0.216	25	8.3 ± 4.2	0.027
Cause of dementia at age 85									
Alzheimer's disease	13	8.9 ± 5.3	0.046	4	9.6 ± 3.0	0.115	9	8.6 ± 6.2	0.149
Vascular dementia	14	8.7 ± 3.5	0.002	2	14.5 ± 3.4	0.018	12	7.8 ± 2.6	0.046

Skoog et al, Neurology 1998

Blood–brain barrier impairment in Alzheimer disease

Stability and functional significance



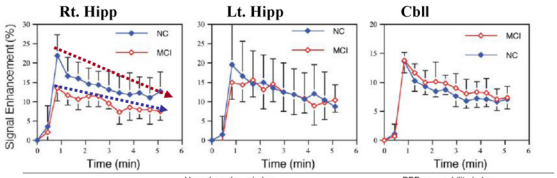
Bowman et al, Neruology 2008

JOURNAL OF MAGNETIC RESONANCE IMAGING 24:695–700 (2006)

Technical Note

Vascular Volume and Blood-Brain Barrier Permeability Measured by Dynamic Contrast Enhanced MRI in Hippocampus and Cerebellum of Patients with MCI and Normal Controls

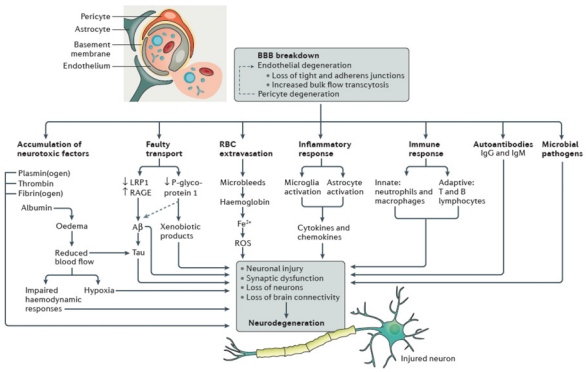
Huali Wang, MD, PhD,[1,2] Edward J. Golob, PhD,[3] and Min-Ying Su, PhD[1]*



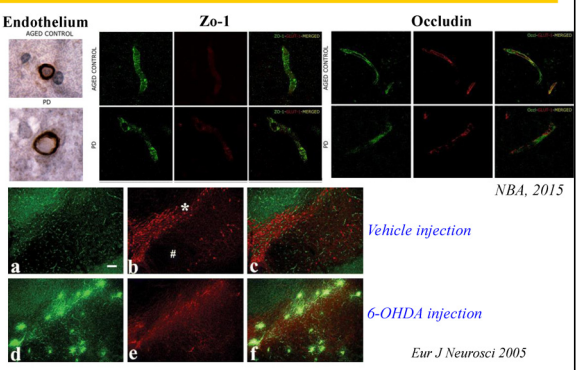
	Vascular volume index			BBB permeability index		
	HP_R	HP_L	Cerebellum	HP_R	HP_L	Cerebellum
Controls (N = 10)	0.22 ± 0.02	0.20 ± 0.004	0.14 ± 0.007	0.56 ± 0.06	0.58 ± 0.04	0.51 ± 0.02
MCI (N = 11)	0.14 ± 0.01*	0.15 ± 0.01	0.14 ± 0.004	0.60 ± 0.06	0.72 ± 0.08	0.57 ± 0.04

- *Degree of decay: slope between peak and late time*
- *BBB PI index: peak enhancement/late enhancement*

BBB breakdown promotes AD-related neurodegeneration



BBB status in Parkinson's disease



NBA, 2015

Vehicle injection

6-OHDA injection

Eur J Neurosci 2005

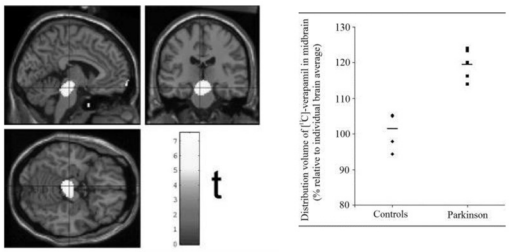
- Loss of endothelial cells, reduced levels of TJ proteins, and alteration of capillary basement membrane in PD

Blood–Brain Barrier Dysfunction in Parkinsonian Midbrain In Vivo

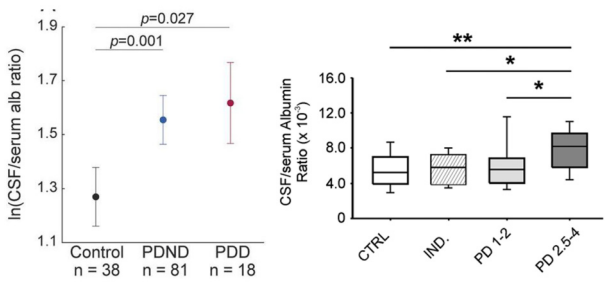
Rudie Kortekaas, PhD,[1,2] Klaus L. Leenders, PhD,[1,3] Joost C. H. van Oostrom, MD,[1,3] Willem Vaalburg, PhD,[3] Joost Bart, PhD,[4] Antoon T. M. Willemsen, PhD,[3] and N. Harry Hendrikse, PhD[5]

Ann Neurol 2005;57:176–179

- [11C]-verapamil PET
  - a substrate for P-gp
  - normally extruded from the brain by P-gp
- Increased distribution volume of [11C]-verapamil in midbrain but no changes of Ki
  → *reflection of reduced P-gp mediated efflux rather than EC dysfunction or perfusion changes*



In vivo evidence of BBB breakdown in Parkinson's disease

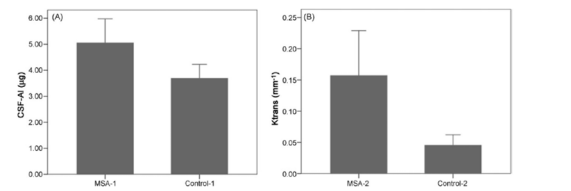


Neurology, 2015

J Neuroinflammation, 2012

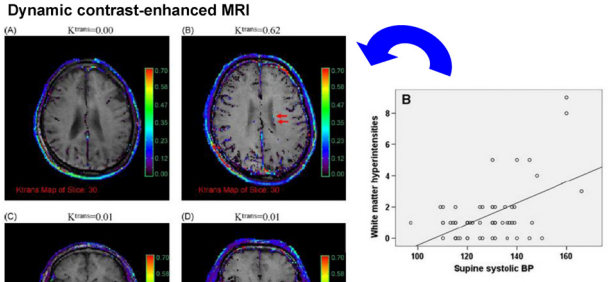
Blood–brain barrier impairment is functionally correlated with clinical severity in patients of multiple system atrophy

	Subjects					
	MSA-1 (n = 18)	Control-1 (n = 13)	p	MSA-2 (n = 16)	Control-2 (n = 13)	p
Age (years)	59.3 ± 8.3	60.6 ± 11.5	NS	59.0 ± 8.2	60.5 ± 10.3	NS
Female (%)	5 (27.8)	7 (53.8)	NS	7 (43.8)	8 (61.5)	NS
Vascular risk factors						
Hypertension	3 (16.7)	6 (46.2)	NS	1 (6.3)	1 (7.7)	NS
Diabetes mellitus	3 (16.7)	3 (23.1)	NS	1 (6.3)	3 (23.1)	NS
Smoking	4 (22.2)	2 (15.4)	NS	2 (12.5)	1 (7.7)	NS
Hyperlipidemia	7 (38.9)	4 (30.8)	NS	5 (31.3)	3 (23.1)	NS
Cerebrovascular lesions						
Lacune	1 (5.6)	2 (15.4)	NS	1 (6.3)	2 (15.4)	NS
Territorial infarct	0	0	NS	0	0	NS
WMH volume (cm^3)	3.7 ± 1.3	3.0 ± 1.2	NS	3.6 ± 1.2	3.0 ± 1.3	NS
UMSARS score	40.9 ± 7.9	–		42.3 ± 9.3	–	

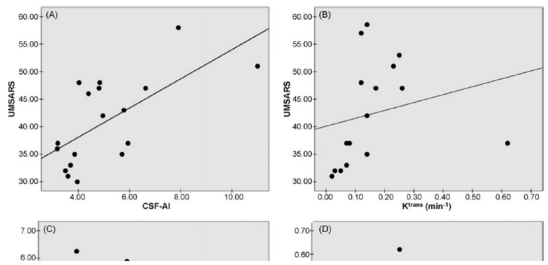


Song et al, NBA, 2010

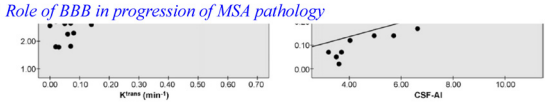
Dynamic contrast-enhanced MRI



Lim, et al. J Neurol 2009

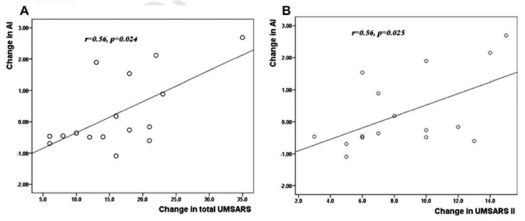


- ***BBB dysfunction is*** *related to the underlying nature of MSA and its dysfunction is closely coupled to disease severity*
- *Role of BBB in progression of MSA pathology*



Changes in the blood–brain barrier status closely correlate with the rate of disease progression in patients with multiple system atrophy: A longitudinal study

- We evaluated the 12-month longitudinal change of the BBB status in 16 MSA patients and analyzed its correlation with changes in clinical severity
- The baseline BBB index did not correlate with change in MSA severity for 12 months



- Changes in the BBB status ∝ change in clinical severity (UMSARS)
- ***Longitudinal changes in the BBB status rather than baseline BBB are more important contributor to MSA disease progression***

PRD, 2013

Associated with genetic susceptibility?

ELECTRONIC LETTER

MDR1, the blood–brain barrier transporter, is associated with Parkinson's disease in ethnic Chinese

C G L Lee, K Tang, Y B Cheung, L P Wong, C Tan, H Shen, Y Zhao, R Pavanni, E J D Lee, M-C Wong, S S Chong, E K Tan

J Med Genet 2004;41:e60 (http://www.jmedgenet.com/cgi/content/full/41/5/e60). doi: 10.1136/jmg.2003.013003

ORIGINAL CONTRIBUTION

Effect of *MDR1* Haplotype on Risk of Parkinson Disease

Eng-King Tan, MD; Daniel Kam-Yin Chan, MD; Ping-Wing Ng, MD; Jean Woo, MD; Y. Y. Teo, MSc; Kun Tang, BSc; Li-Peng Wong, Dip; Samuel S. Chong, PhD; Chris Tan, BSc; Hui Shen, PhD; Yi Zhao, MD, PhD; Caroline G. L. Lee, PhD

J Neurol (2009) 256:115–120
DOI 10.1007/s00415-009-0089-x

ORIGINAL COMMUNICATION

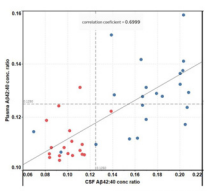
Katja Zschiedrich
Inke R. König
Norbert Brüggemann
Norman Kock
Meike Kasten

MDR1 variants and risk of Parkinson disease
Association with pesticide exposure?

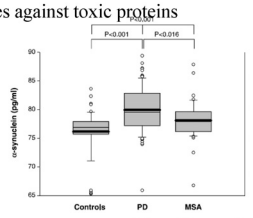
What's clinical significance or application?

Good or bad ????

- Increased toxic proteins in peripheral circulation of AD and PD patients
  - defense mechanism for clearance of toxic proteins via altered BBB??
  - epiphenomenon or resulted from disease pathogenesis ??
- Increased influx of endogenous antibodies against toxic proteins



Alzheimers Dement, 2017

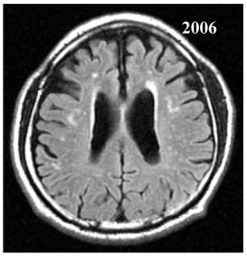


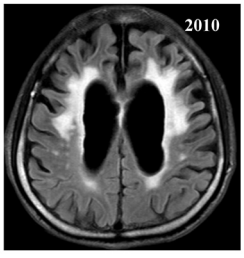
J Neural Transm. 2006

An illustration-1

White matter hyperintensities

- Initially, presented with frontal behavior and then, followed by parkinsonism with prominent gait problems.
- No amyotrophy



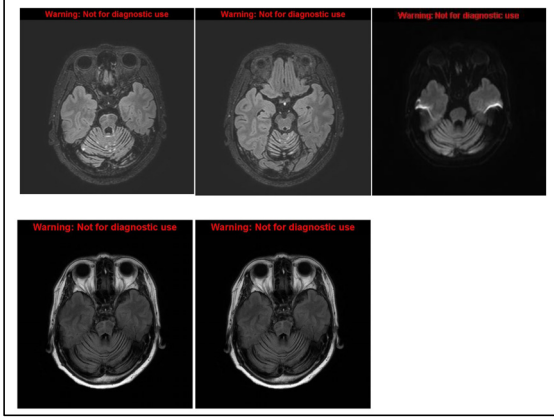


Neuropathologic correlates of white matter hyperintensities **= Vascular integrity**

Young et al, Neurology, 2008

An illustration-2

Stem cell injection



Protecting damaged BBB

Approach	Therapeutics	Mechanism	Disease	Animal Model	Clinical Trials	Reference Nos.
BBB sealing	APC and its analogs	β-Arrestin-mediated PAR1-biased signaling	Stroke	Rodent stroke models (arterial occlusion, embolic stroke)	Phase II	208
			ALS	SOD1 mutant models	NA	208
	Glucocorticoids	Upregulation of intercellular junctional proteins, suppression of MMPs and inflammation	Niemann-Pick disease, type C	NPC1	NA	500
Eliminating consequences of BBB breakdown	Ancrod	Depleting fibrin(ogen)	AD	TgCRND8	NA	452
			MS	EAE		126
	Deferoxamine	Iron chelation	ALS	SOD1 (G93A)	NA	624
	Glutathione monoethyl ester	Antioxidant				
	APC and its analogs	PI3K/Akt-mediated neuroprotection, endothelial protection	Stroke	MCAO, dMCAO, embolic stroke	Phase II	208
			ALS	SOD1 mutants	NA	208
Enhancing clearance function	LRP1 minigene	Improve efflux	AD	Tg2576	NA	624
	RAGE inhibitor (Azeliragon)	Reduce influx			Phase III	128
	Allopregnanolone	Promoting Aβ and cholesterol clearance		3xTgAD	Phase I	79
Cell therapy	Mesenchymal stem cells transplantation	Improve BBB functions	CNS injuries	Rodent experimental models	NA	250, 448, 559
	Pericytes transplantation		ALS	SOD1		110

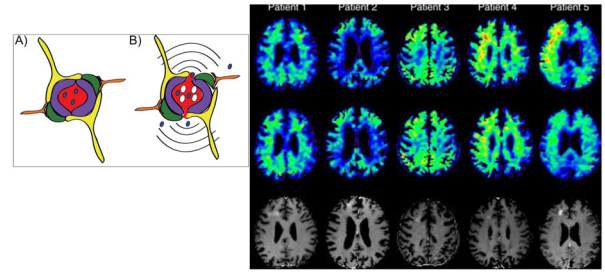
Traversing BBB for drug delivery

Direct opening of the BBB	Focused ultrasound	Doxorubicin delivery	Brain tumor	Multiple species and models	Phase I
		To promote therapeutic delivery	AD		Phase I
			PD		Phase I
Colloidal carriers	Nanoparticles Exosome	Entrap within or covalently bind to drugs	A broad spectrum of CNS diseases	Multiple species and models	Phase 1 NA
CMT	L-DOPA	LAT-1 large amino acid transporter	PD	MPTP	FDA approved
RMT	Bispecific antibodies	Anti-TfR-BACE1	AD	Tg2576	
		Anti-TfR-Aβ		PS2APP	
	Molecular Trojan horses	L-Iduronidase fused with anti-TfR	Mycopolysaccharoidosis I	Rhesus monkey	Phase II
		Iduronate 2 sulfatase fused with anti-HR	Mycopolysaccharoidosis II		Phase I
Viral vectors and variants	Gene delivery	Brain tropic AAV9 variants	PD	TgSNCA-A53T mouse	NA

MR-guided focused ultrasound

Indication	Stage	Subtype	US treated region	Drug	End points	US Device/US parameters	Status
Neurodegenerative disease	Phase I	Mild to moderate PDD	Right parieto-occipito-temporal lobes	No	Safety, feasibility of BBBD	ExAblate® (InSightec) 220 kHz	Recruiting (NCT03608553)
	Phase I	Mild AD	Frontal lobes	No	Safety, feasibility of BBBD, Δ Aβ plaques	ExAblate® (InSightec) 220 kHz 4.6 W for stage 1 4.5 W for stage 2	Completed and published[7] (NCT02986932)
	Phase I/II	Mild AD	Left supramarginal gyrus	No	Δ glucose metabolism, safety of BBBD	SonoCloud® (CarThera) unspecified	Recruiting (NCT03119961)
	Phase I	ALS	Primary motor cortex	No	Safety, feasibility of BBBD	ExAblate® (InSightec) unspecified	Recruiting (NCT03321487)

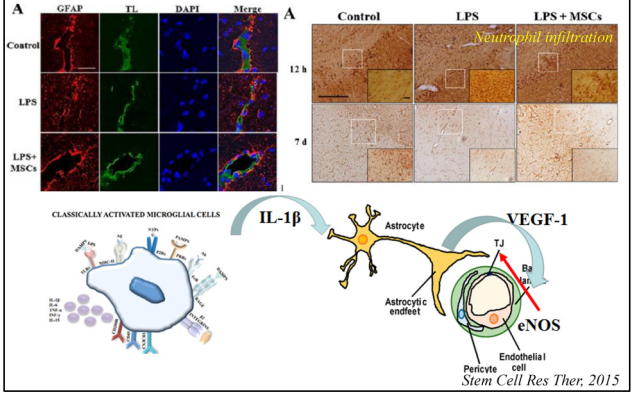
MRgFUS combined with microbubbles in AD



- Transient BBB opening lasts for 4 to 6 hours with spatial and temporal specificity
- Opening the blood–brain barrier did not result in serious clinical or radiographic adverse events, as well as no clinically significant worsening on cognitive scores at three months compared to baseline
- Exploratory analysis of the [18F]-flobetaben PET results did not identify a clear effect, in either direction, of MRgFUS BBB opening on beta-amyloid deposition.

Nat Commun, 2018

Mesenchymal stem cells stabilize the blood–brain barrier through regulation of astrocytes



Stem Cell Res Ther, 2015

What can we do? - Semiconclusions

- ***BBB alteration may be region-specific, depending on disease status??***
- ***Reflect disease progression ??***
- ***One of valuable targets for neuroprotective strategies??***