2015 Saul R. Korey Lecture

Working at the crossroads of neurodegeneration and cerebrovascular disease

Matthew P. Frosch, MD, PhD

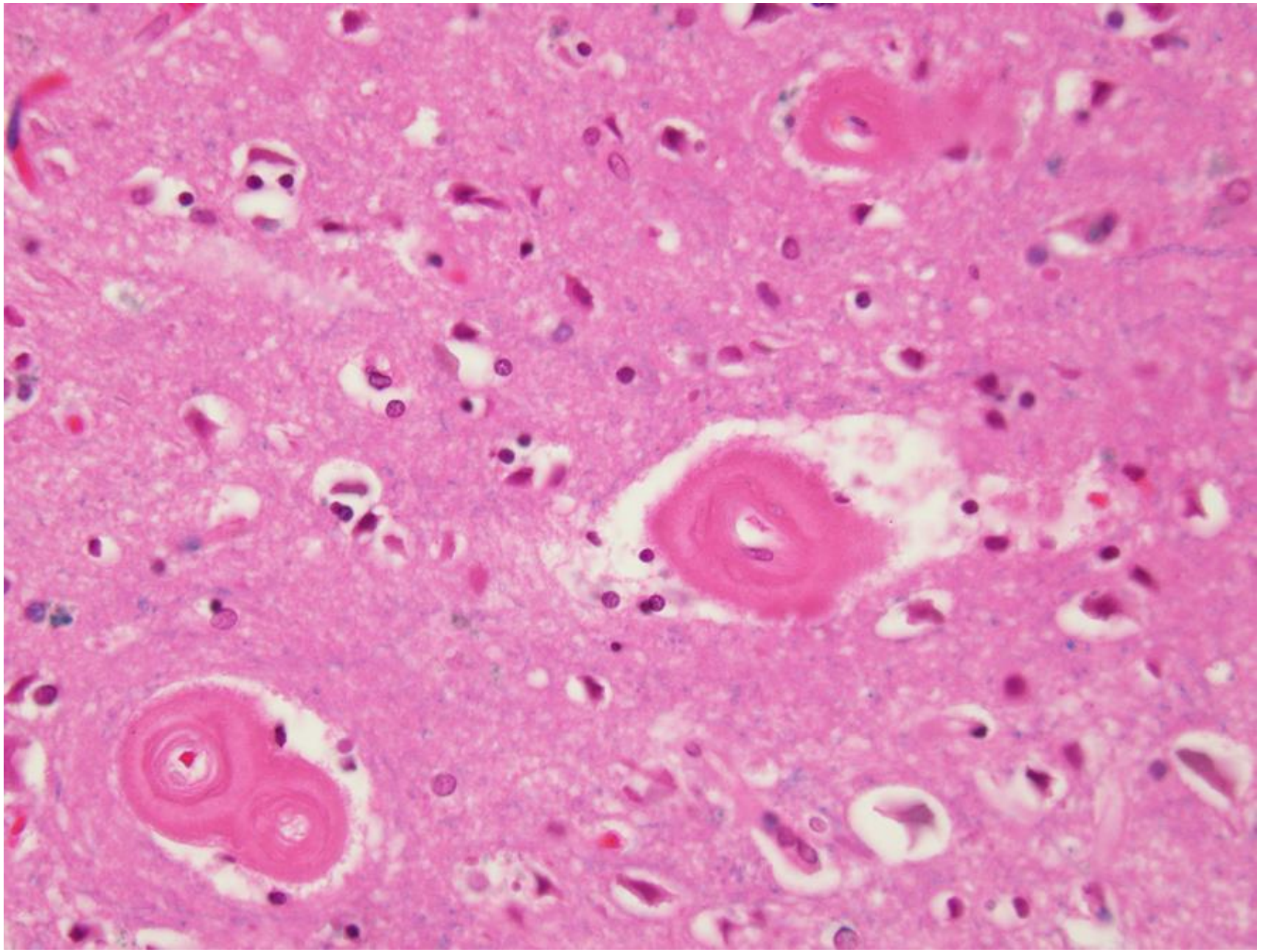
C.S. Kubik Laboratory for Neuropathology,
Massachusetts General Hospital
Harvard Medical School

DISCLOSURE

- Member of an advisory board for Biogen (related to clinical studies of therapeutics for Alzheimer disease)

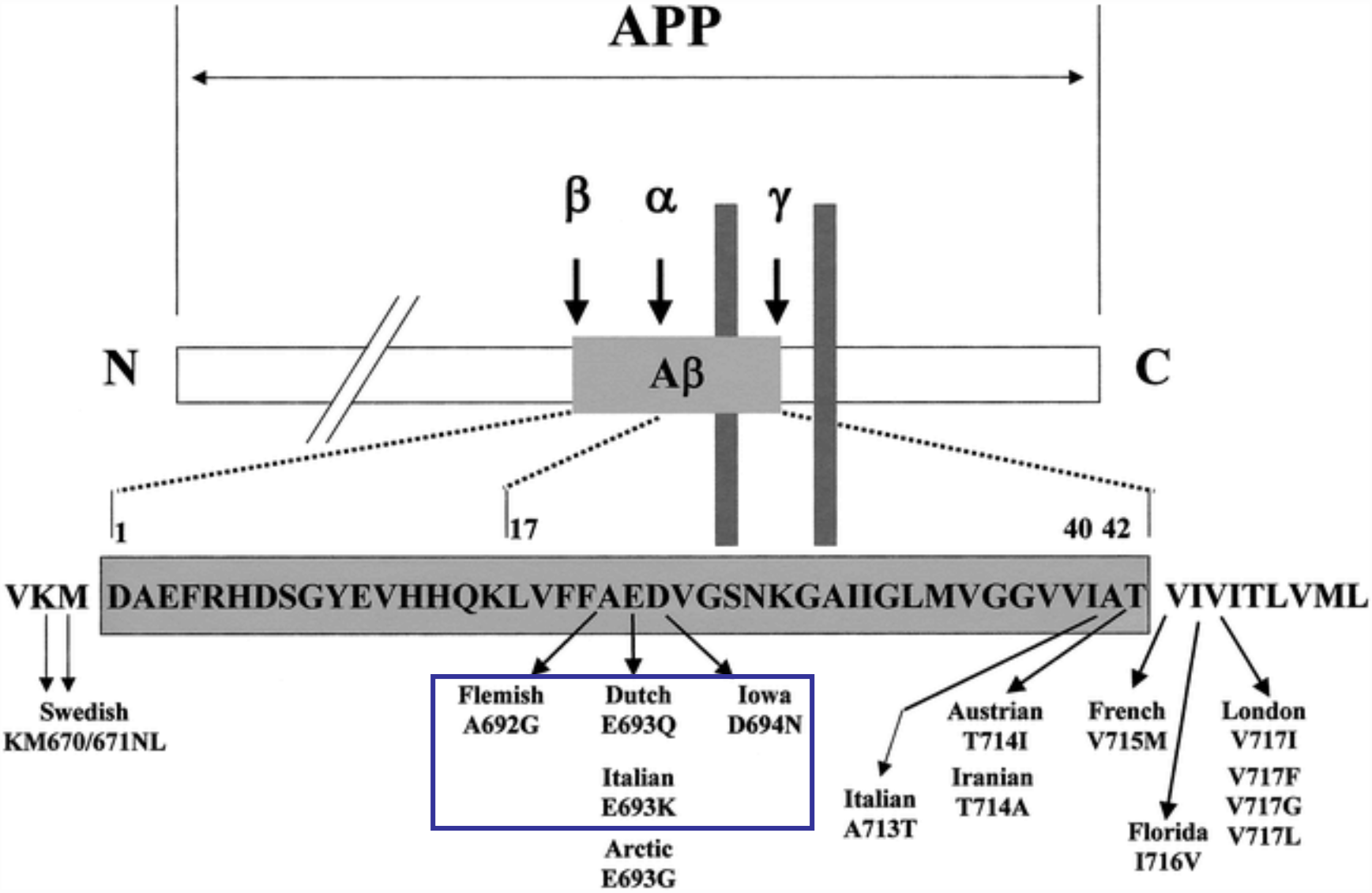
Abstract Topics

Category	Abstracts (n)	Abstracts (%)	Platform (n)	Platform (%)
Tumors	65	35%	24	38%
Neurodegenerative	61	32%	22	34%
Infectious	8	4%	2	3%
Opthalmic	2	1%	0	0%
Other	16	9%	3	5%
Pediatric	19	10%	6	9%
Muscle	12	6%	6	9%
Vascular	5	3%	1	2%
Total	188	100%	64	100%



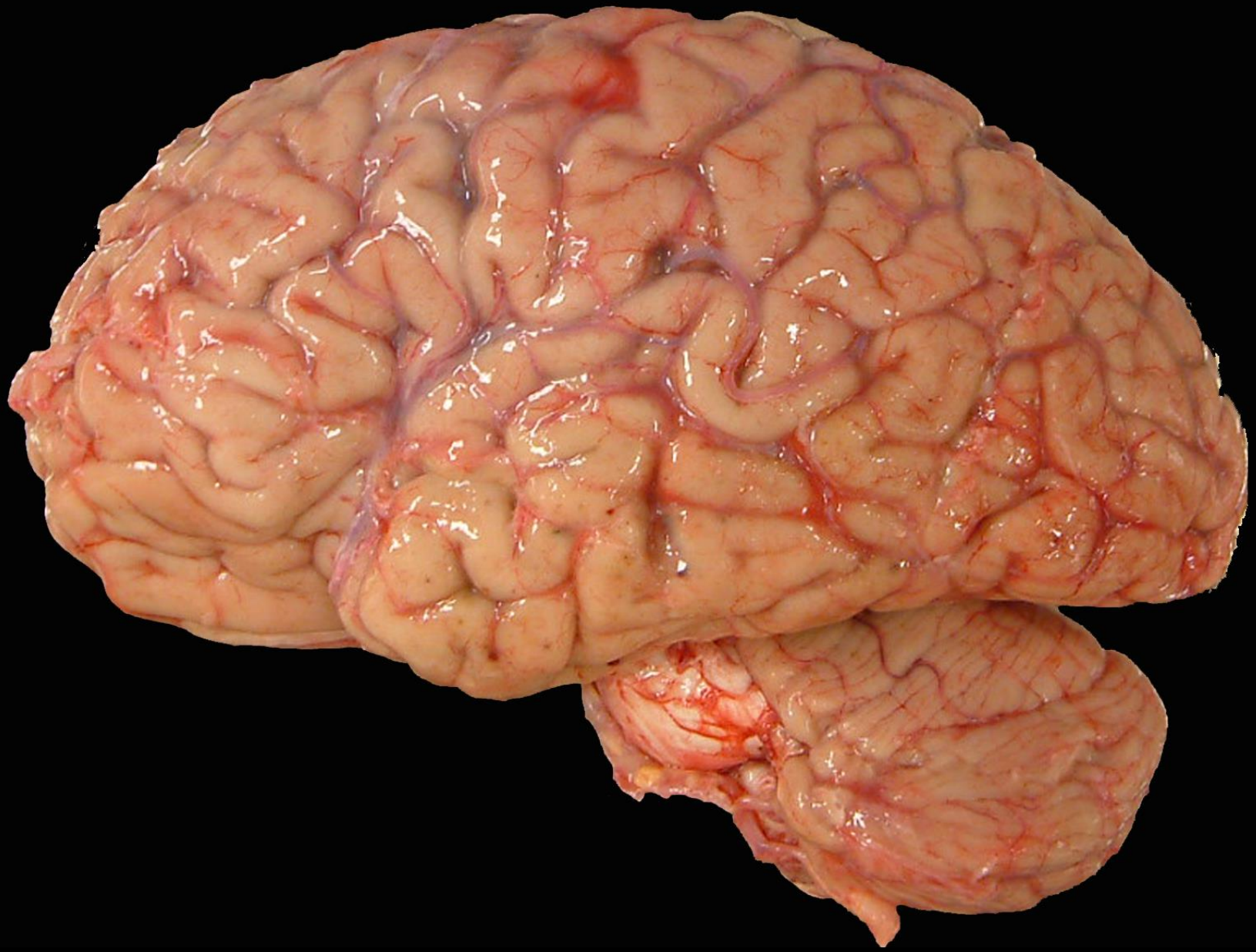
Cerebral amyloid angiopathy (CAA)

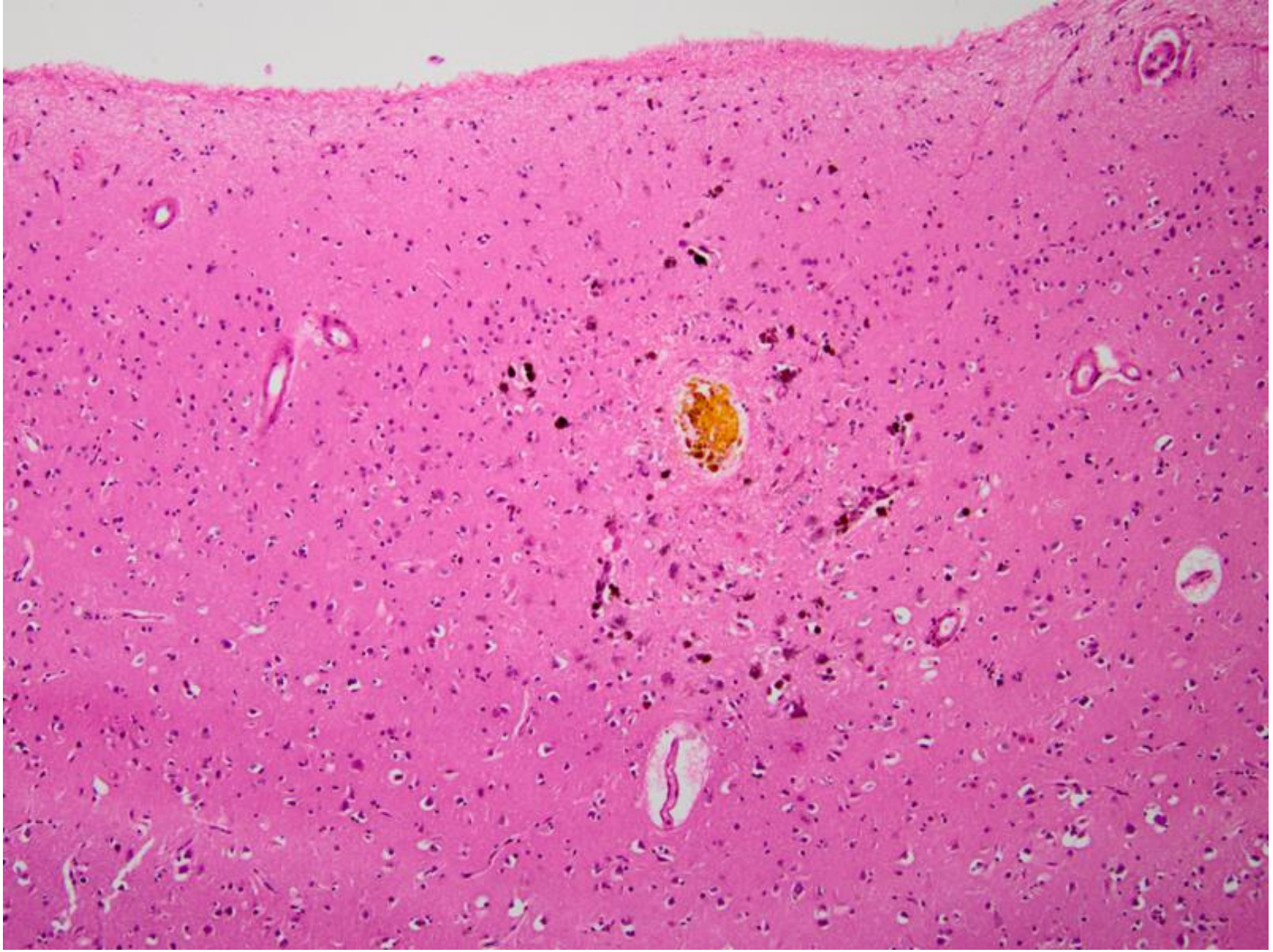
- Small vessel cerebrovascular disease
- Prevalence ~10% at age 60 (Rotterdam Scan Study)
- Consequences
  - Small (“micro”) hemorrhages (MR detection)
  - Large (lobar) hemorrhages
- Association with AD
  - Moderate to severe in about 25%


APP
β
α
γ
N
Aβ
C
1
17
40 42
VKM
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT
VIVITLVML
Swedish
KM670/671NL
Flemish
A692G
Dutch
E693Q
Iowa
D694N
Italian
E693K
Arctic
E693G
Italian
A713T
Austrian
T714I
Iranian
T714A
French
V715M
Florida
I716V
London
V717I
V717F
V717G
V717L

Cerebral amyloid angiopathy (CAA)

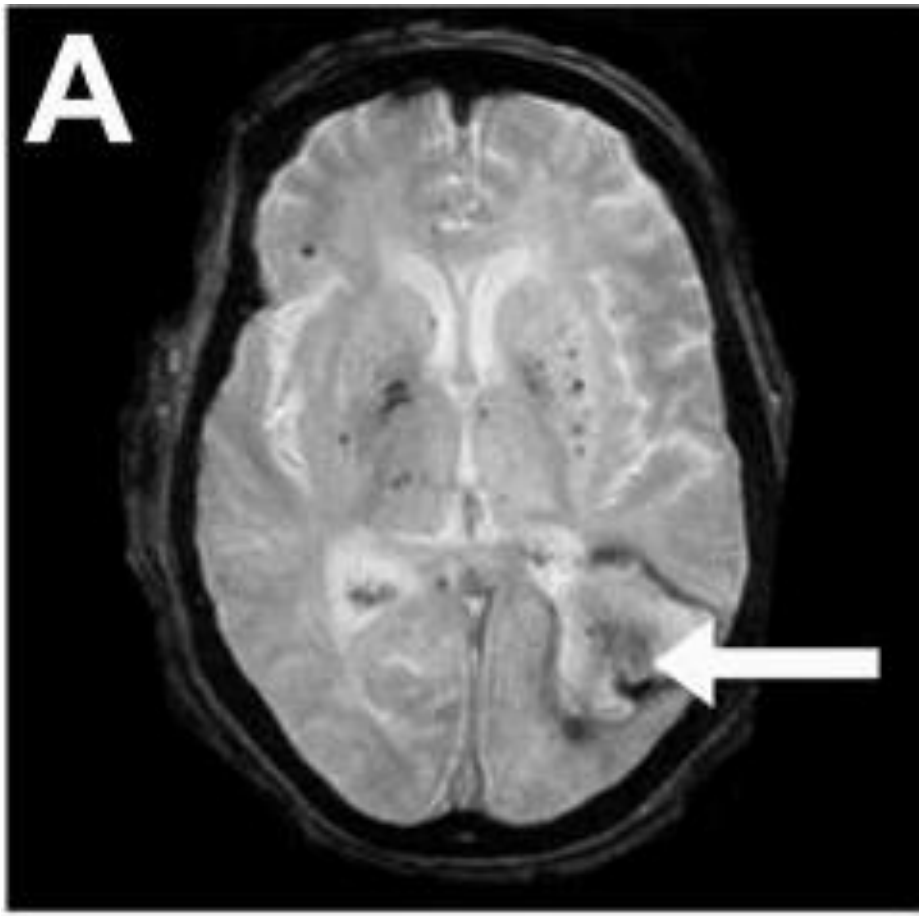
- Human studies
  - Types of bleeding
  - Inflammatory CAA
  - Impact of CAA on clinical trials for AD

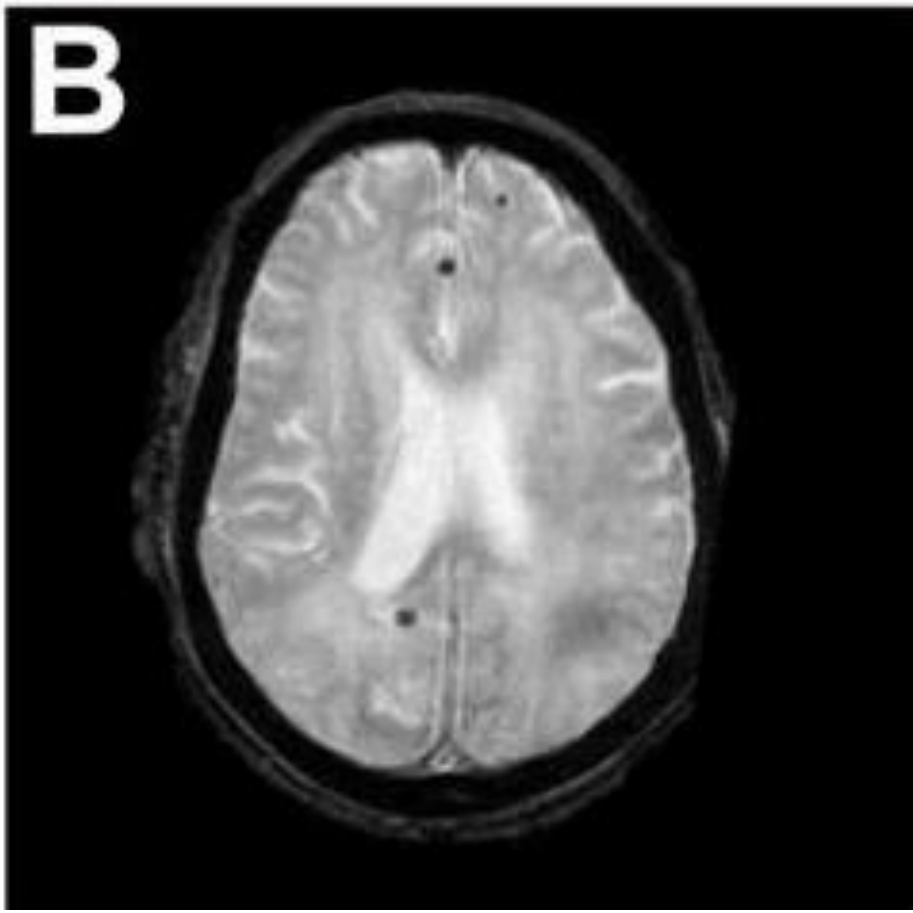


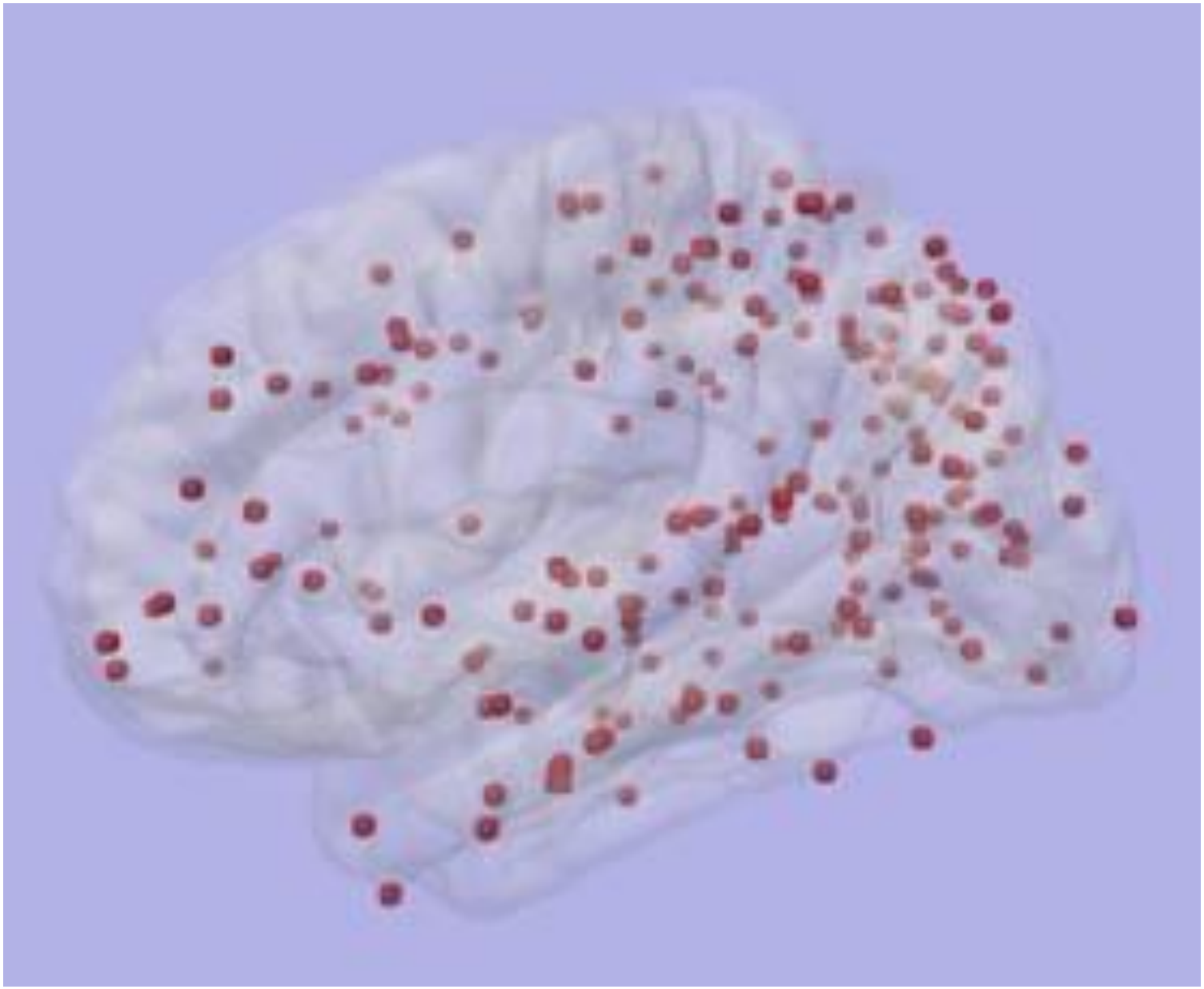


Mixed pattern

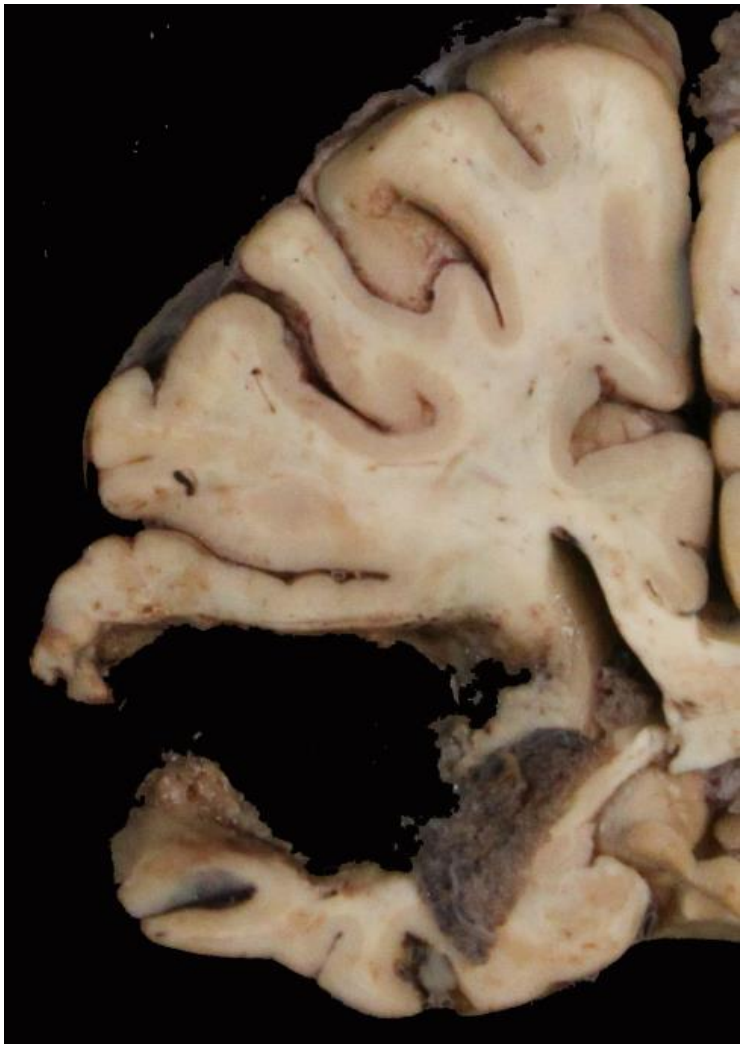
CAA

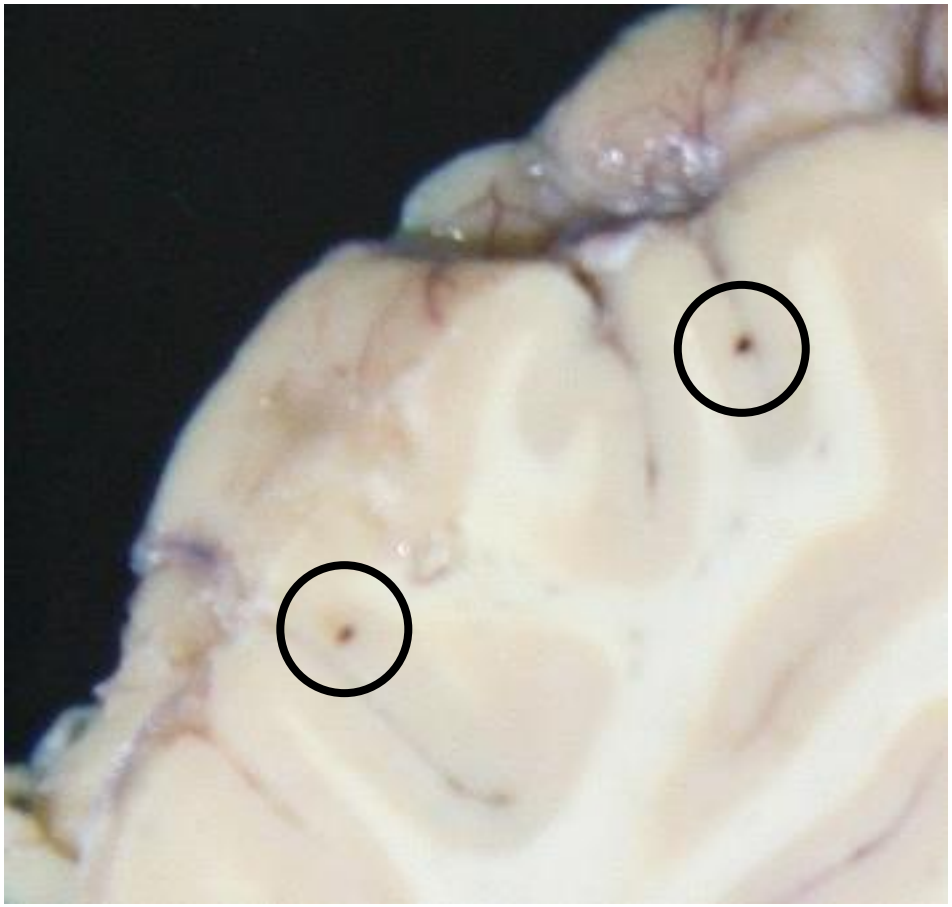




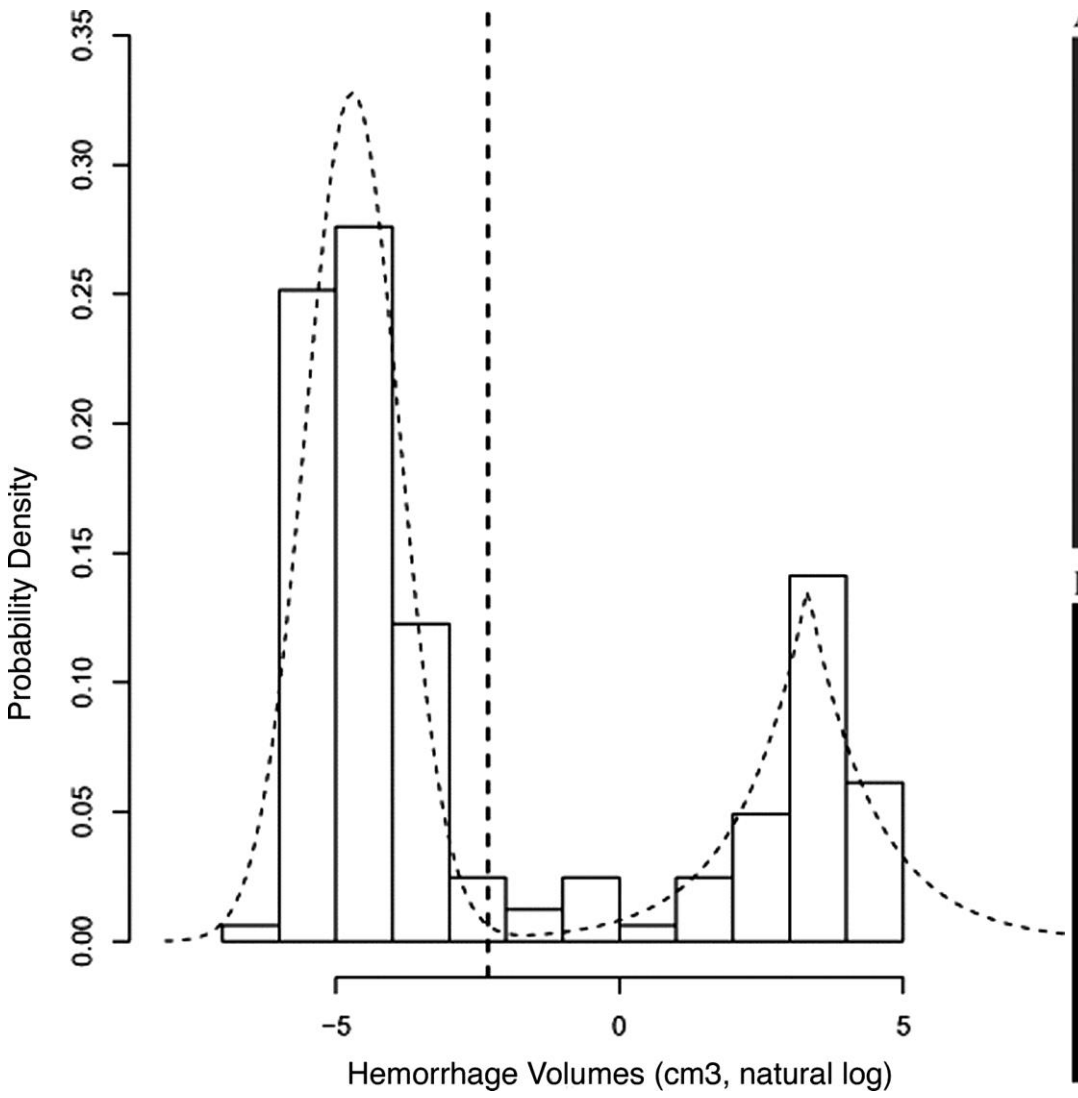


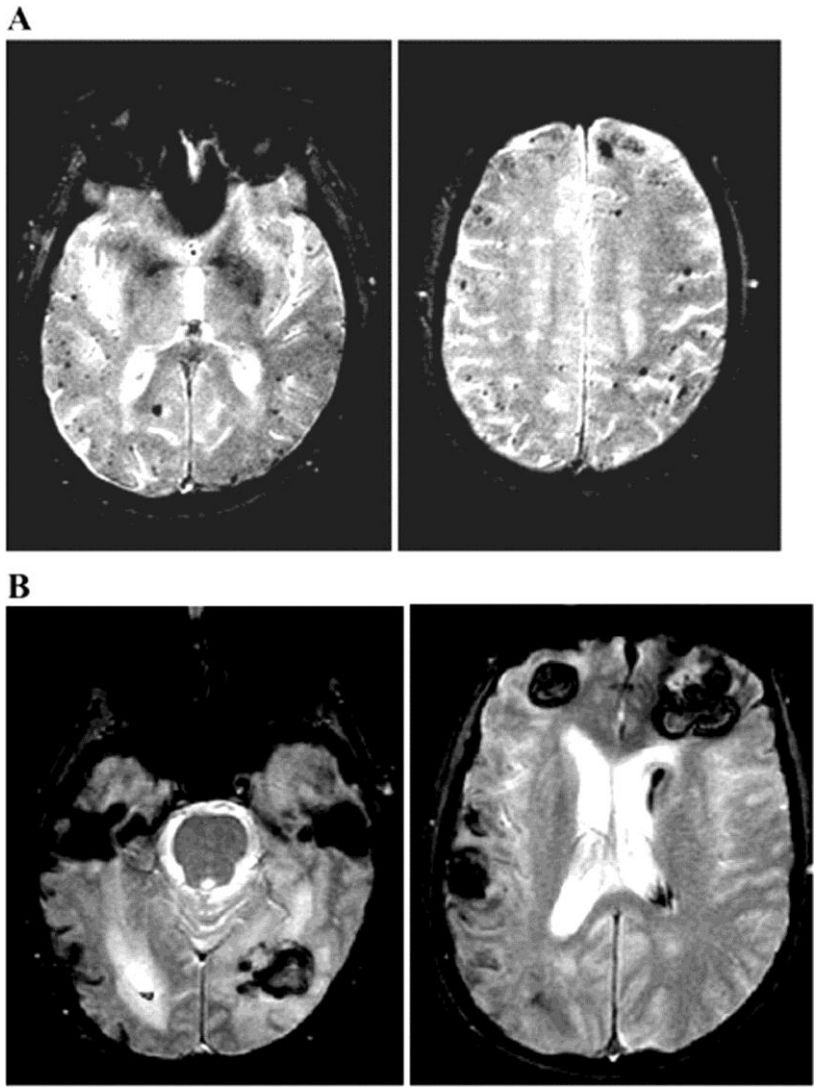
Macro vs micro





Macro vs micro





Macro vs. micro

	High burden of microbleeds (>50)	Low burden of microbleeds (<3)	p value
Proportion of vessel diameter of wall thickness for Aβ- laden vessels	0.53 ± 0.01	0.37 ± 0.01	<0.0001 (<0.005 adjusted for age and hypertension)
Proportion of vessel diameter of wall thickness for white matter vessels	0.40 ± 0.04	0.36 ± 0.04	0.45
Fraction of Aβ-laden vessels with circumferential involvement	>90%	>90%	0.19

Macro vs. micro

- Thicker deposits associated with higher burden of microbleeds
- Brain-by-brain rather than vessel-by-vessel
- Mixed cases can be observed

Cerebral amyloid angiopathy (CAA)

- Human studies
  - Types of bleeding
  - Inflammatory CAA
  - Impact of CAA on clinical trials for AD

Inflammatory CAA

- Long known as pattern with CAA

Journal of Neuropathology and Experimental Neurology
Copyright © 1986 by the American Association of Neuropathologists

Vol. 45, No. 1
January, 1986
pp. 79–90

Cerebral Amyloid Angiopathy: The Vascular Pathology and Complications

THADDEUS I. MANDYBUR, M.D., PH.D.

NEUROLOGY 29: 1336-1340, October 1979

Cerebral amyloid angiopathy: Possible relationship to rheumatoid vasculitis

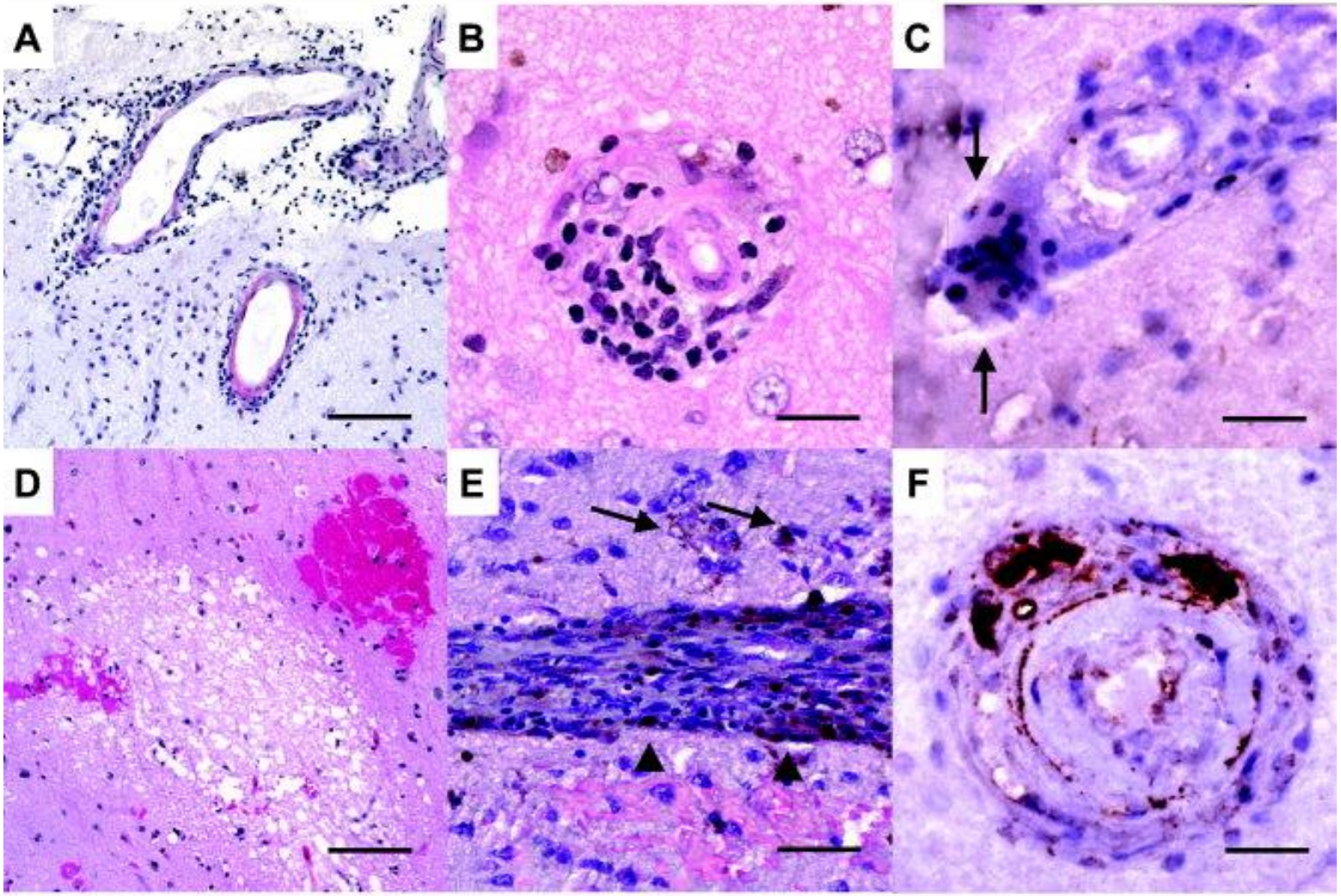
T. I. Mandybur, M.D., Ph.D.

- Are there distinct clinical consequences of inflammation associated with CAA?
  - Syndrome of cognitive impairment/seizure

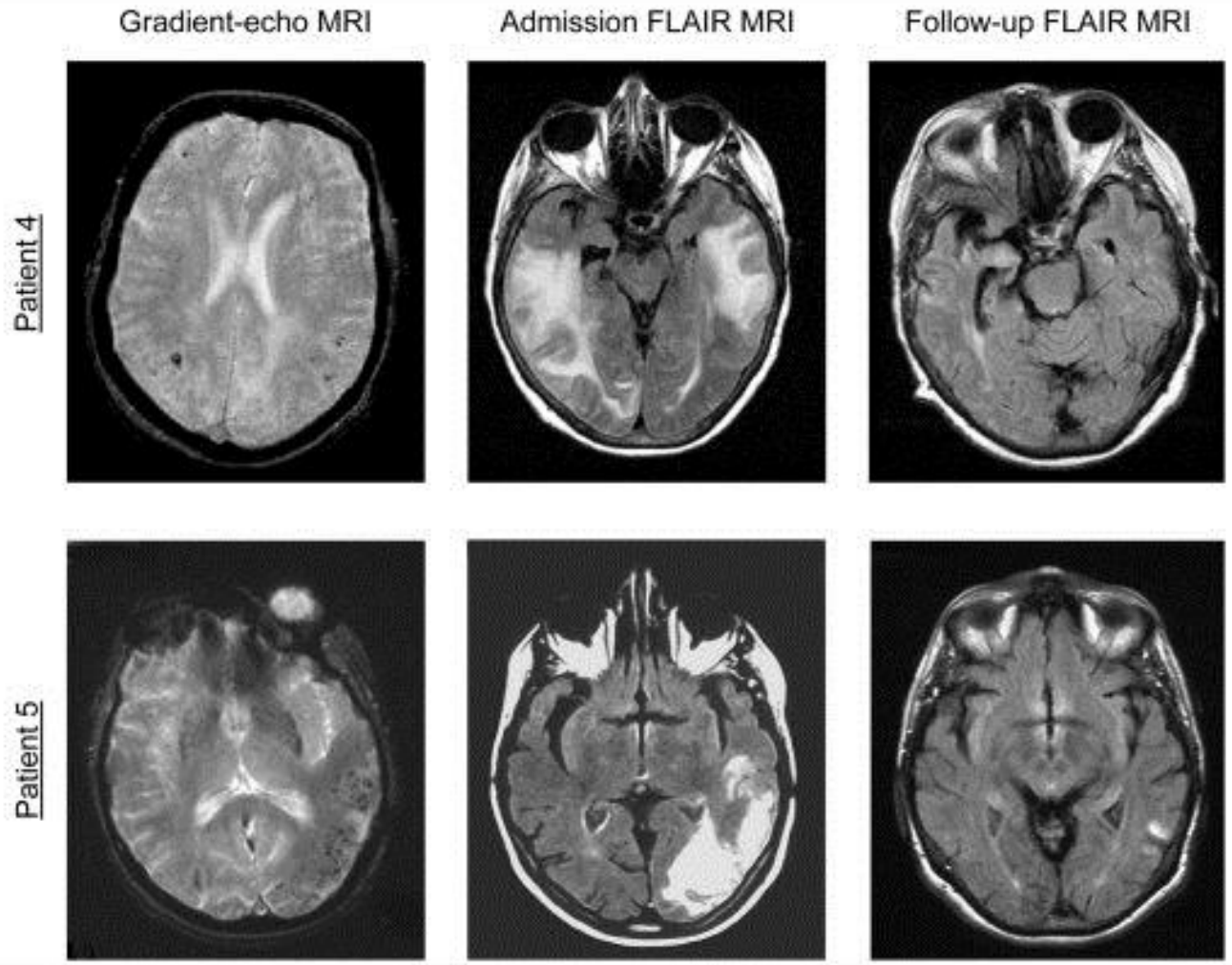
Inflammatory CAA

Characteristic	CAA with Inflammation (n = 7)	CAA without Inflammation (n = 35)
Age at presentation (yr ± SD)	68.3 ± 9.6[a]	75.8 ± 8.3
Sex (M/F)	3/4	10/25
Primary clinical presentation, n (%)		
Intracerebral hemorrhage	0 (0)[b]	33 (94)
Cognitive decline	3 (43)	1 (3)
Seizure	4 (57)	1 (3)
APOE genotype, n (%)[b]	n = 7 patients genotyped	n = 26 patients genotyped
ε4/ε4	5 (71)[b]	1 (4)
ε4/ε(2 or 3)	1 (14)	12 (46)
ε(2 or 3)/ε(2 or 3)	1 (14)	13 (50)

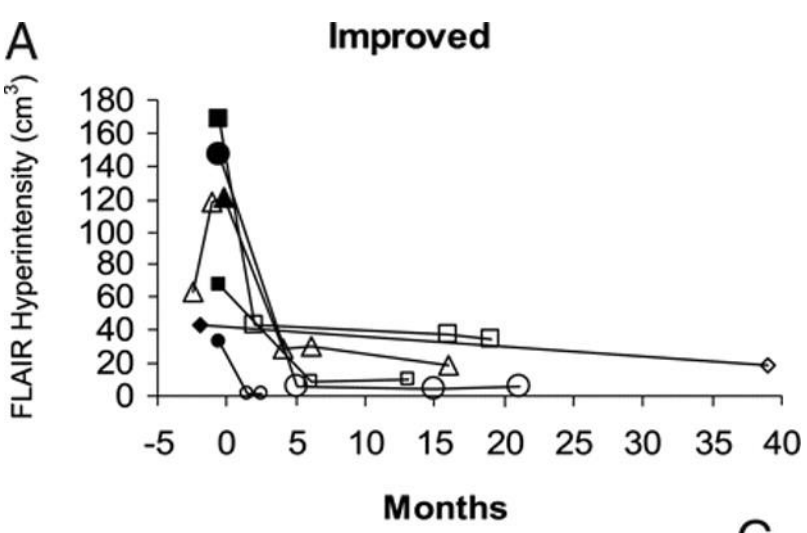
Inflammatory CAA

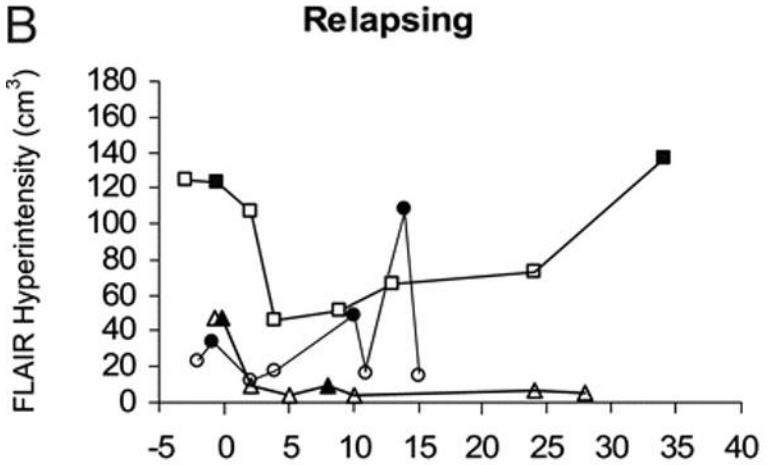


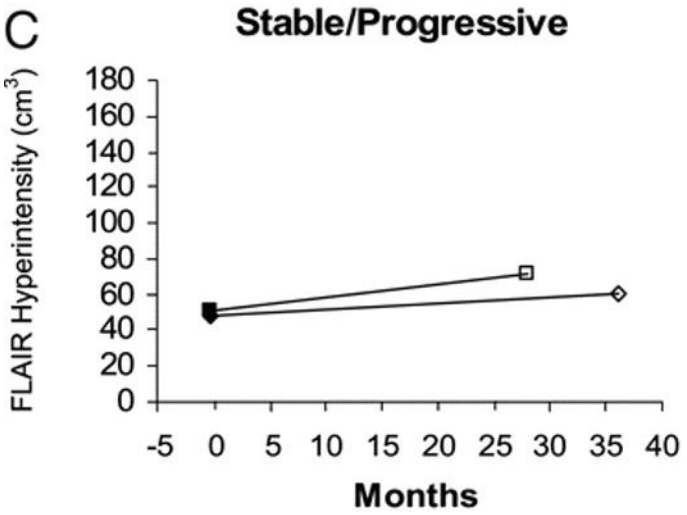
Inflammatory CAA



Inflammatory CAA

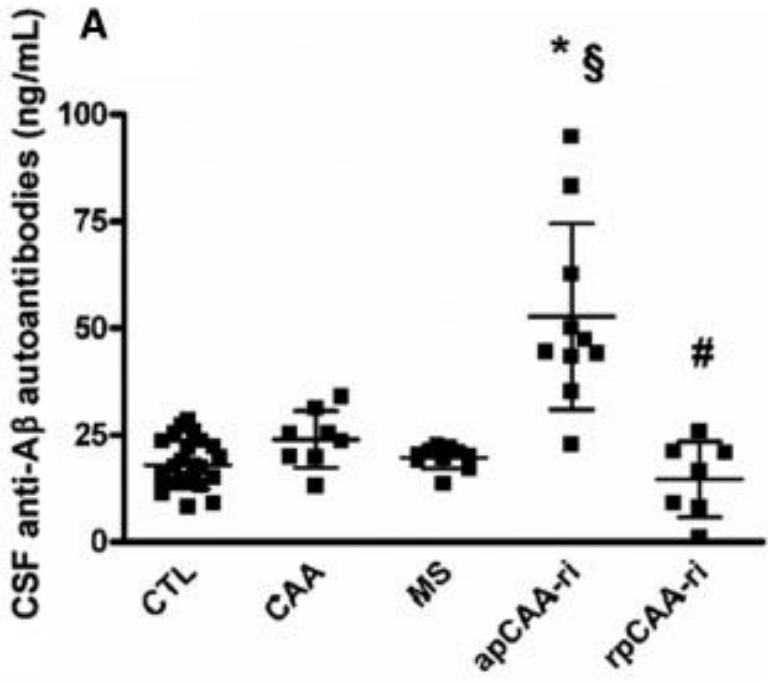






- Correlation between volume of FLAIR hyperintensity volume and clinical symptoms

Inflammatory CAA



- Appearance of anti-Aβ antibodies in CSF with active disease
- Drop in titer is associated with recovery

Piazza, et al (2013) Ann Neurol. 73:449-458

Aβ and antibodies

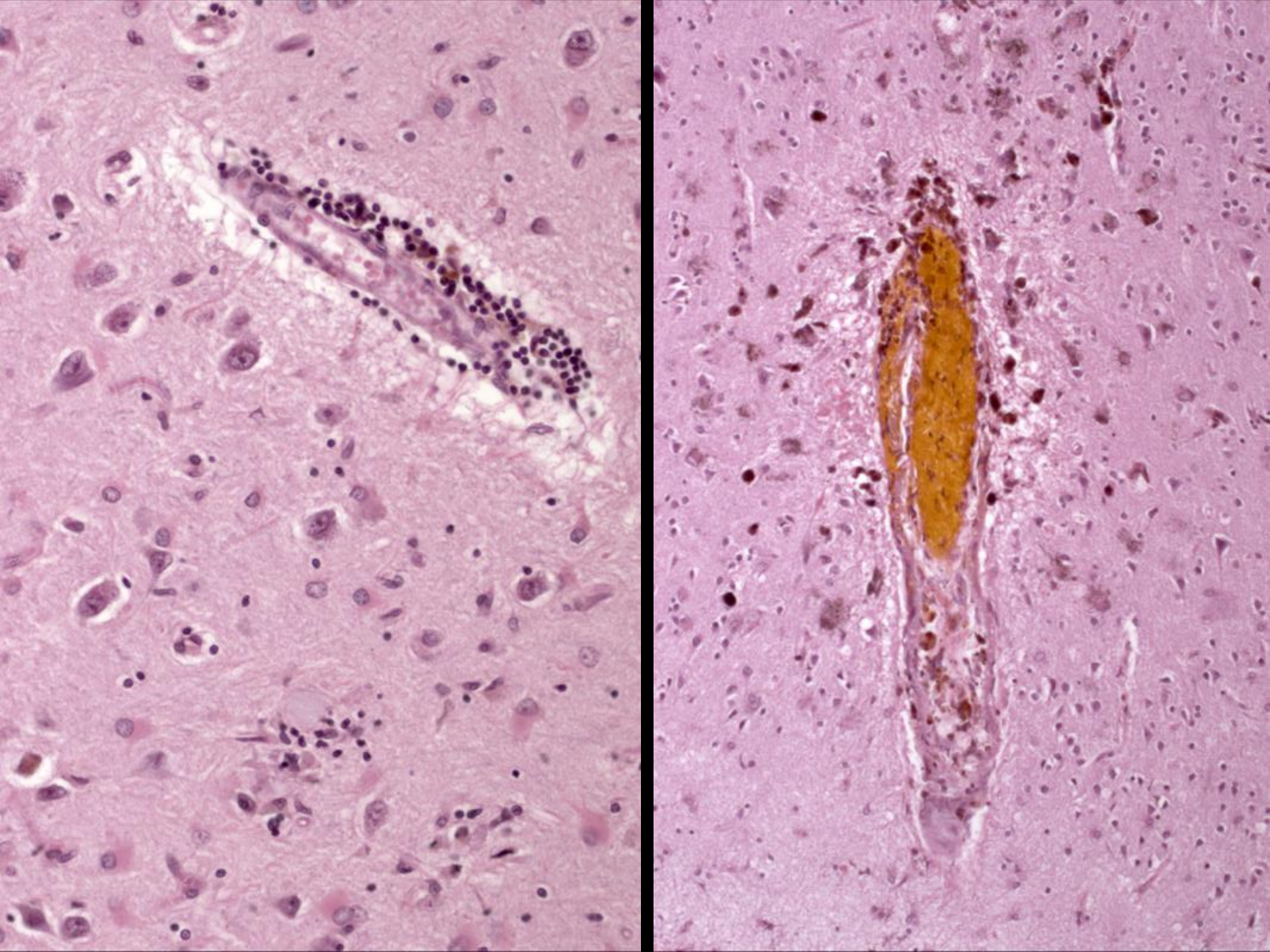
- Inflammatory CAA
  - Spontaneous subacute disorder with cognitive impairment & seizures
  - FLAIR signal changes
  - Presence of antibodies in CSF

Aβ and antibodies

- Inflammatory CAA
  - Spontaneous subacute disorder with cognitive impairment & seizures
  - FLAIR signal changes
  - Presence of antibodies in CSF
- Alzheimer disease
  - Slowly progressive disease with cognitive impairment
  - Immune therapies are being explored

Active immunization

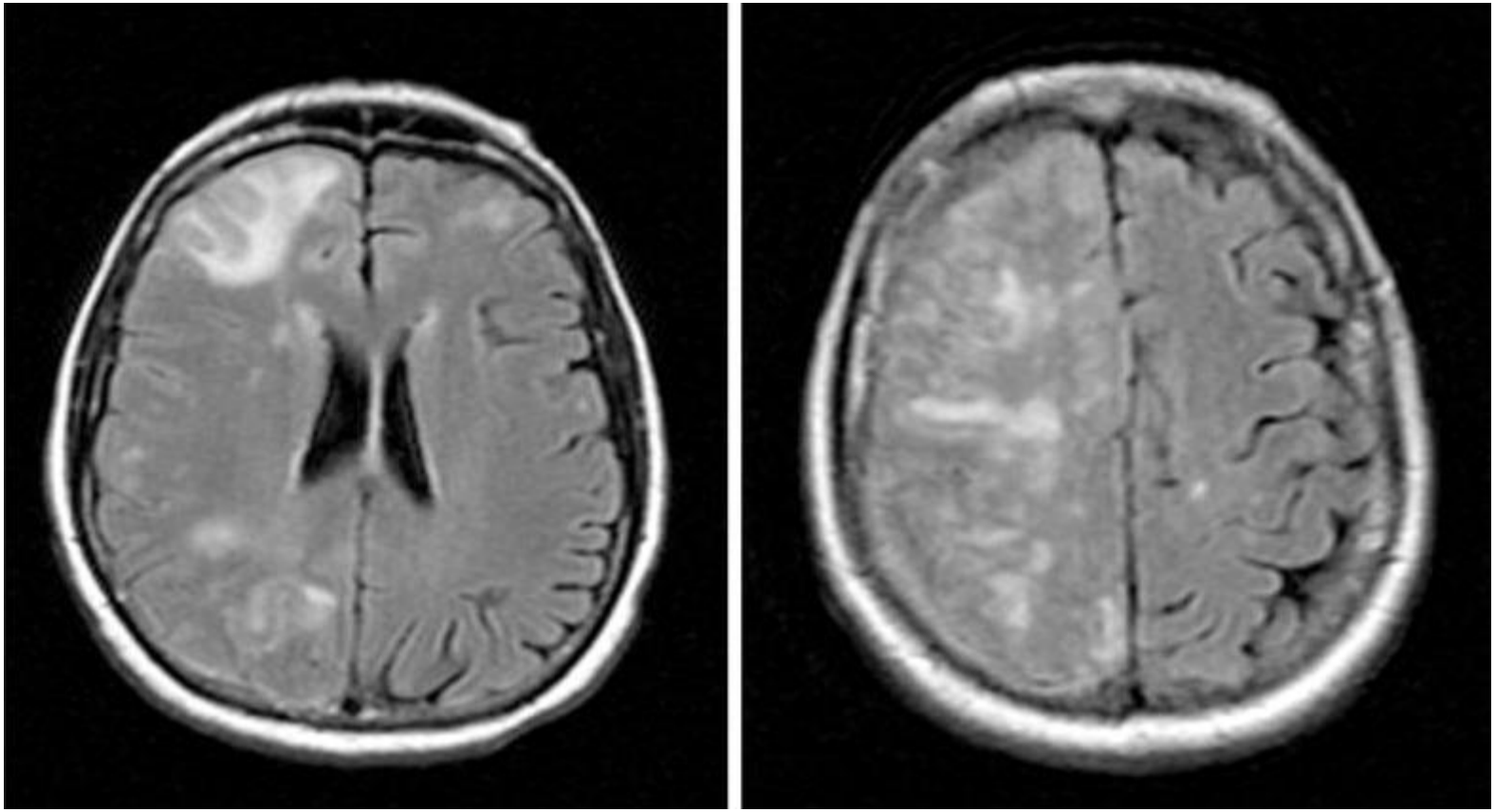
- AN1792 trial (only trial with any autopsy follow up)
- Strong suggestion that plaques were cleared
- Meningoencephalitis (some symptomatic)
- Suggestion that CAA burden might increase as plaques were being cleared



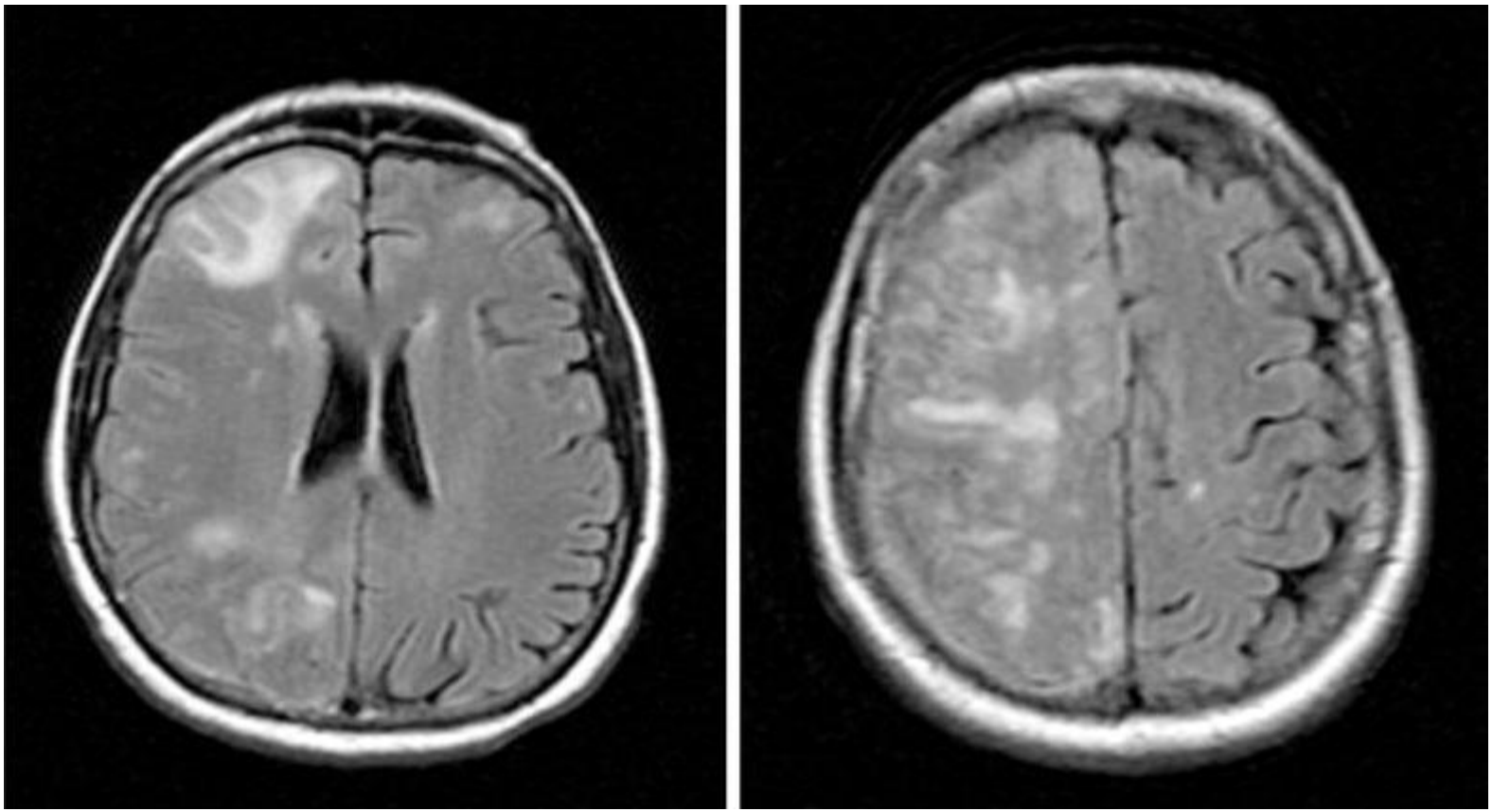
Immunotherapy for AD

- Active immunization trial:
  - Likely clearance of plaques and improvement with measures of neuronal injury
  - Concerns about lack of ability to control immune response (severity of response, epitopes)
- Shift to passive immunotherapy trials – several completed and others ongoing

Inflammatory CAA?



Passive immunotherapy trial



Amyloid related imaging abnormalities (ARIA)

- Relatively common event across trials
- Symptomatic and incidental
- Independent of antibody & epitope
- Two patterns:
  - FLAIR changes (ARIA-E)
  - Foci of susceptibility (ARIA-H)
- Both types of ARIA look like consequences of CAA

CAA and trials for AD

Adverse Event	Placebo	Bapineuzumab, 0.5 mg/kg	Bapineuzumab, 1.0 mg/kg	Bapineuzumab, 2.0 mg/kg
	number of patients (percent)			
Carrier study‡				
Amyloid-related imaging abnormalities with edema	1 (0.2)	103 (15.3)		
Fall	64 (14.3)	100 (14.9)		
Headache	48 (10.7)	78 (11.6)		
Noncarrier study‡				
Amyloid-related imaging abnormalities with edema	1 (0.2)	14 (4.2)	31 (9.4)	20 (14.2)
Fall	73 (13.9)	43 (12.8)	43 (13.1)	23 (16.3)
Urinary tract infection	59 (11.3)	40 (11.9)	42 (12.8)	15 (10.6)
Anxiety	43 (8.2)	19 (5.6)	39 (11.9)	11 (7.8)
Headache	49 (9.4)	30 (8.9)	34 (10.3)	16 (11.3)
Agitation	37 (7.1)	26 (7.7)	15 (4.6)	16 (11.3)

Event	Solanezumab (N=1027)	Placebo (N=1025)
	no. (%)	
Amyloid-related imaging abnormalities		
With edema	9 (0.9)	4 (0.4)
With hemorrhage	50 (4.9)	57 (5.6)

Also true in interim data of phase 3 trial with Aducanumab (AD/PD meeting, March 2015)

CAA and trials for AD

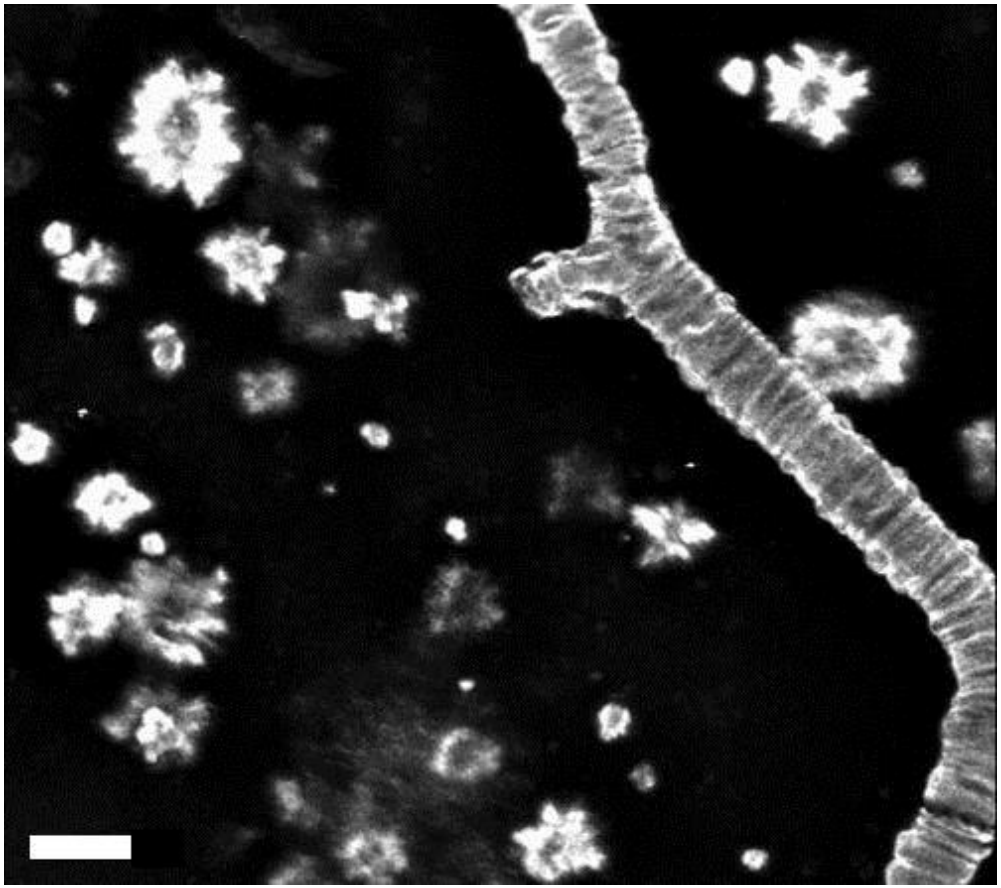
- Questions which remain about ARIA-E:
  - Does it have adverse effects if found incidentally?
  - Does it predict target engagement?
  - Can it be treated or prevented without impairing potential therapeutic effect of antibody treatment?
- No access to tissue during episodes (likely to remain true)

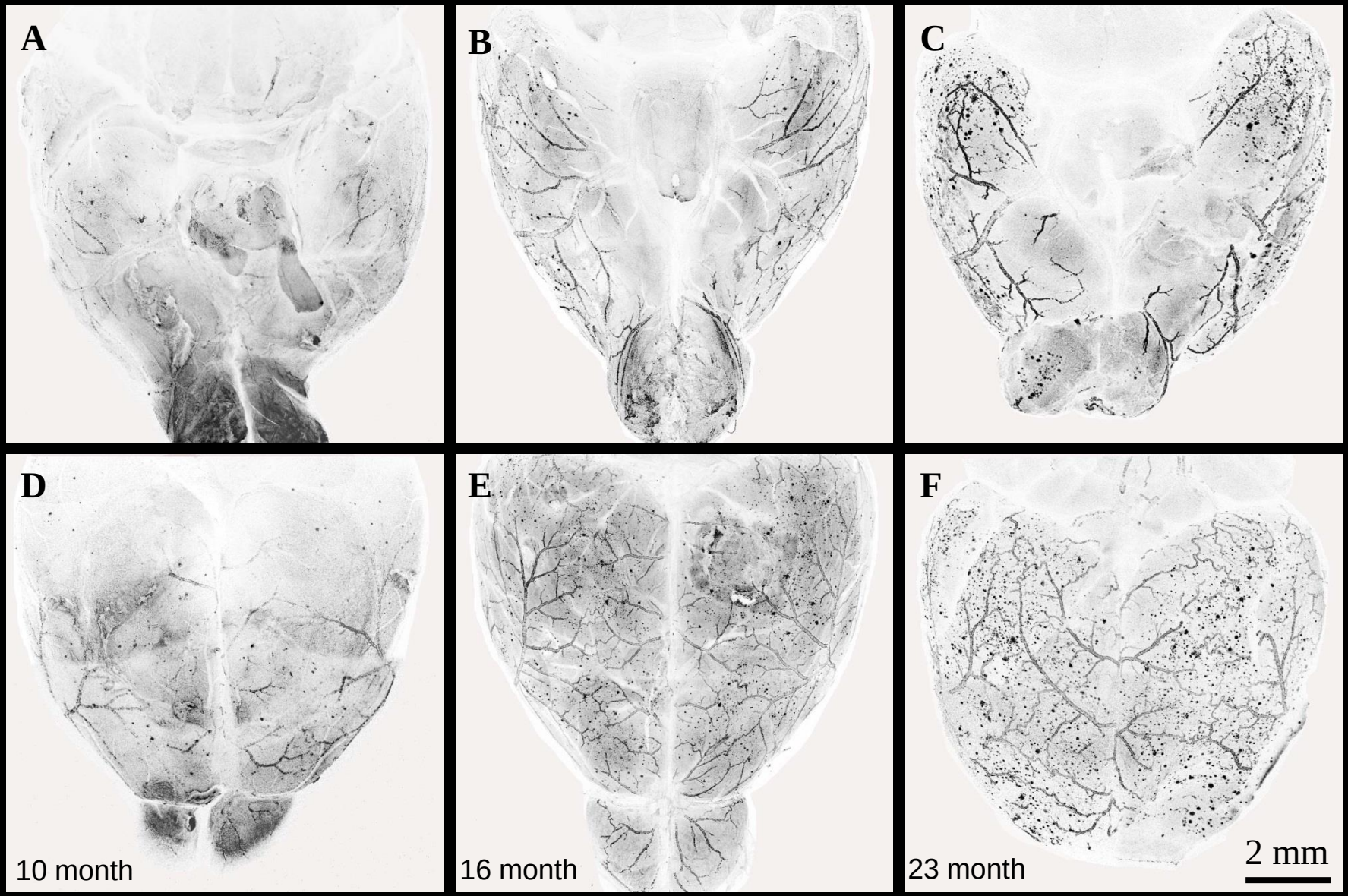
Cerebral amyloid angiopathy (CAA)

- Human studies
  - Types of bleeding
  - Inflammatory CAA
  - Impact of CAA on clinical trials for AD
- Animal models
  - Progression of CAA
  - Immune clearance of CAA
  - Perivascular efflux of Aβ

Animal models of CAA

- Transgenic models:
  - Tg2576 with hAPPswe (HaPrP)
  - hAPPswe:PS1dE9 (MoPrP promoter)
- Develop Aβ deposits as CAA and plaques
- Visualized with Methoxy-X04 (given i.p.)




A
B
C
D
E
F
10 month
16 month
23 month
2 mm

Kinetic vs end-point studies

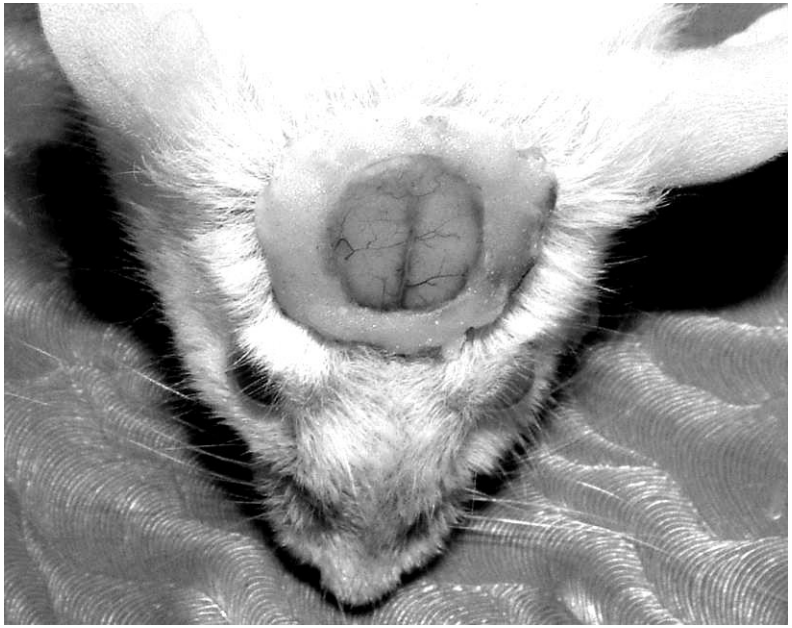
- Mouse-to-mouse variation in timing of CAA onset
- For a 20% effect in the face of a 30% S.D. need 50 animals per group
  - 100 mice @ 1 year = $36.5K
- If disease process has predictable kinetics but variable onset, then mouse-by-mouse measurements reduce sample size needs

Questions

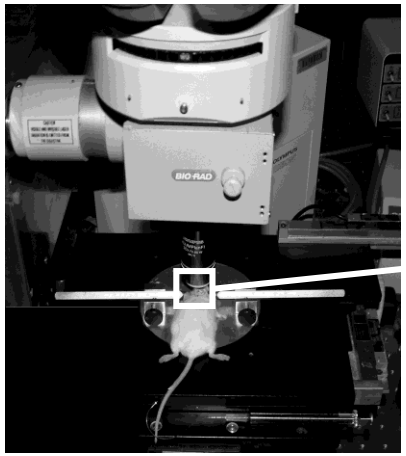
- What are the kinetics of CAA development?
- Can CAA be cleared by anti-Aβ therapies?
- How is the vessel wall injured?
- Why do vessels bleed?
- Why does Aβ deposit along the outside of arterial vessels?

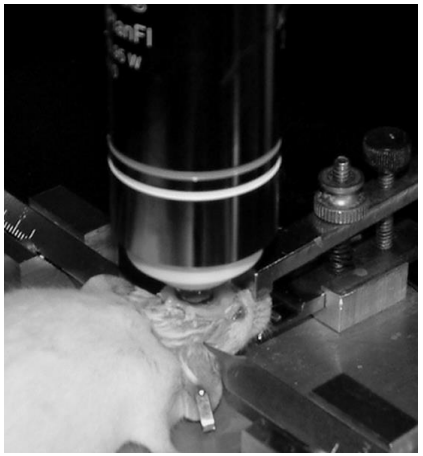
In vivo imaging of CAA

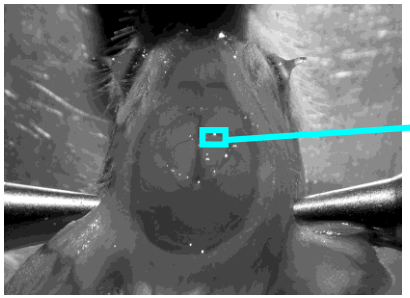
Mice are anesthetized, and prepared surgically for imaging:

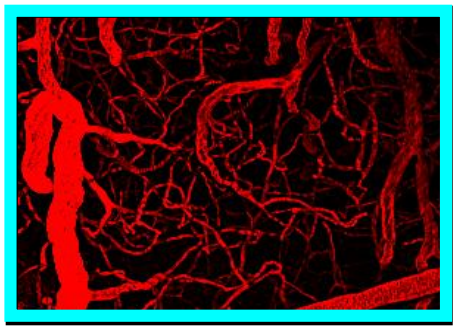


The mouse is immobilized and placed on the stage of a multiphoton microscope.



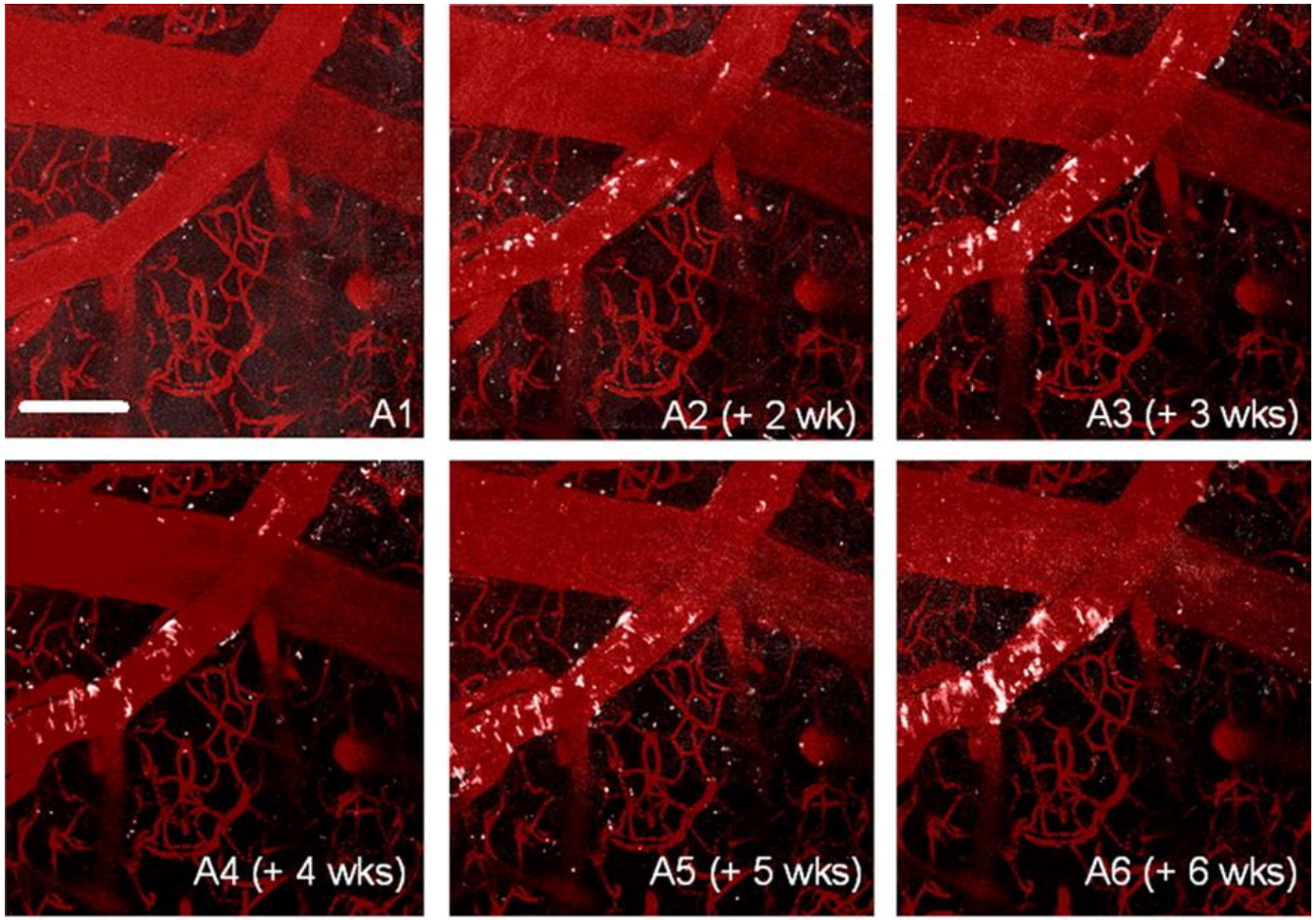


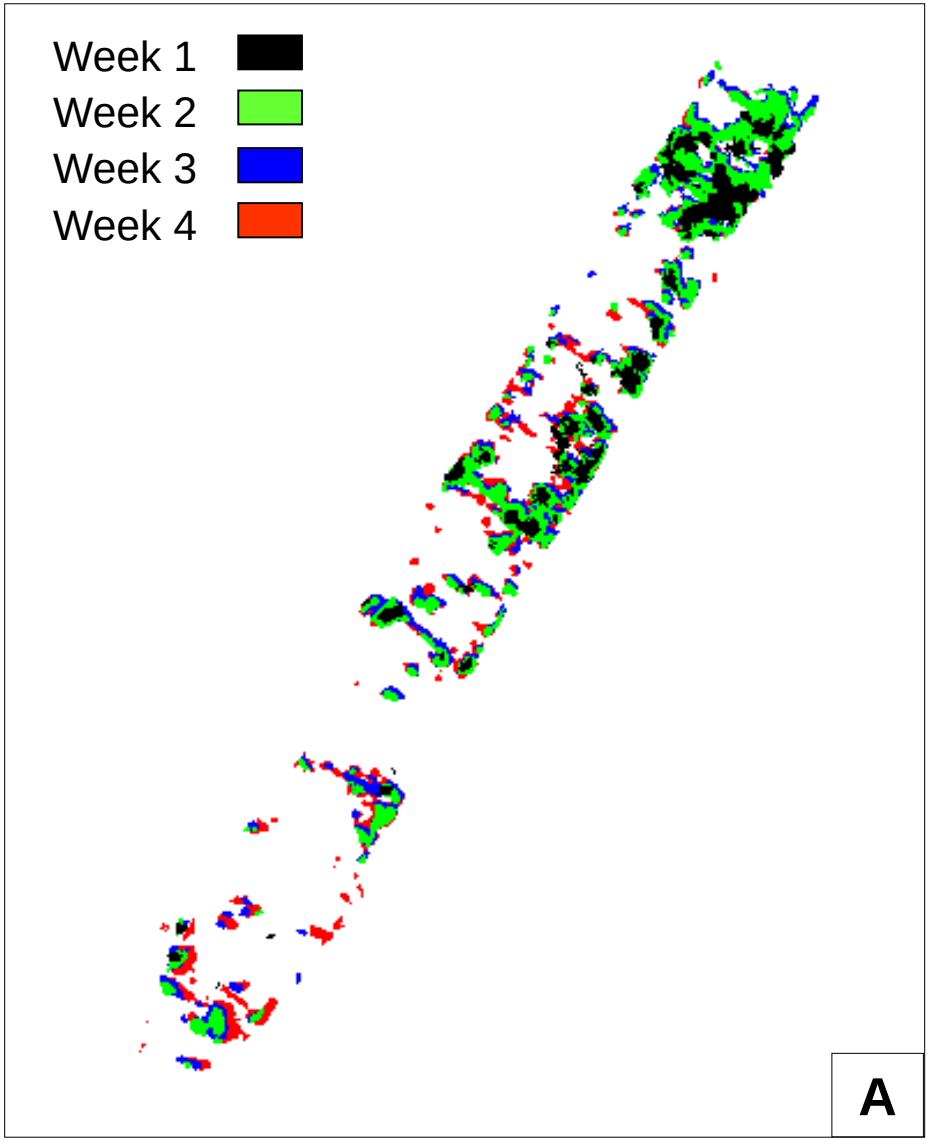


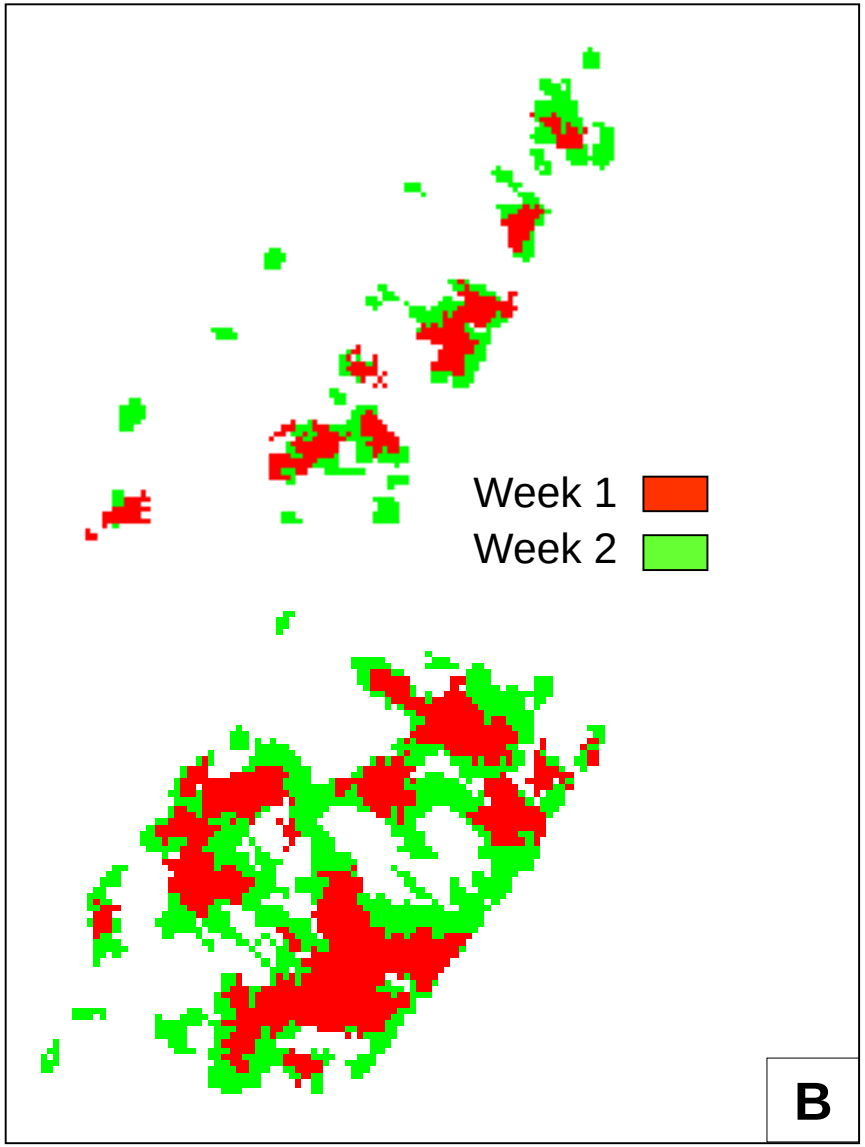


A “cranial window” is created by implanting a coverslip in place of the skull.

In vivo imaging of CAA

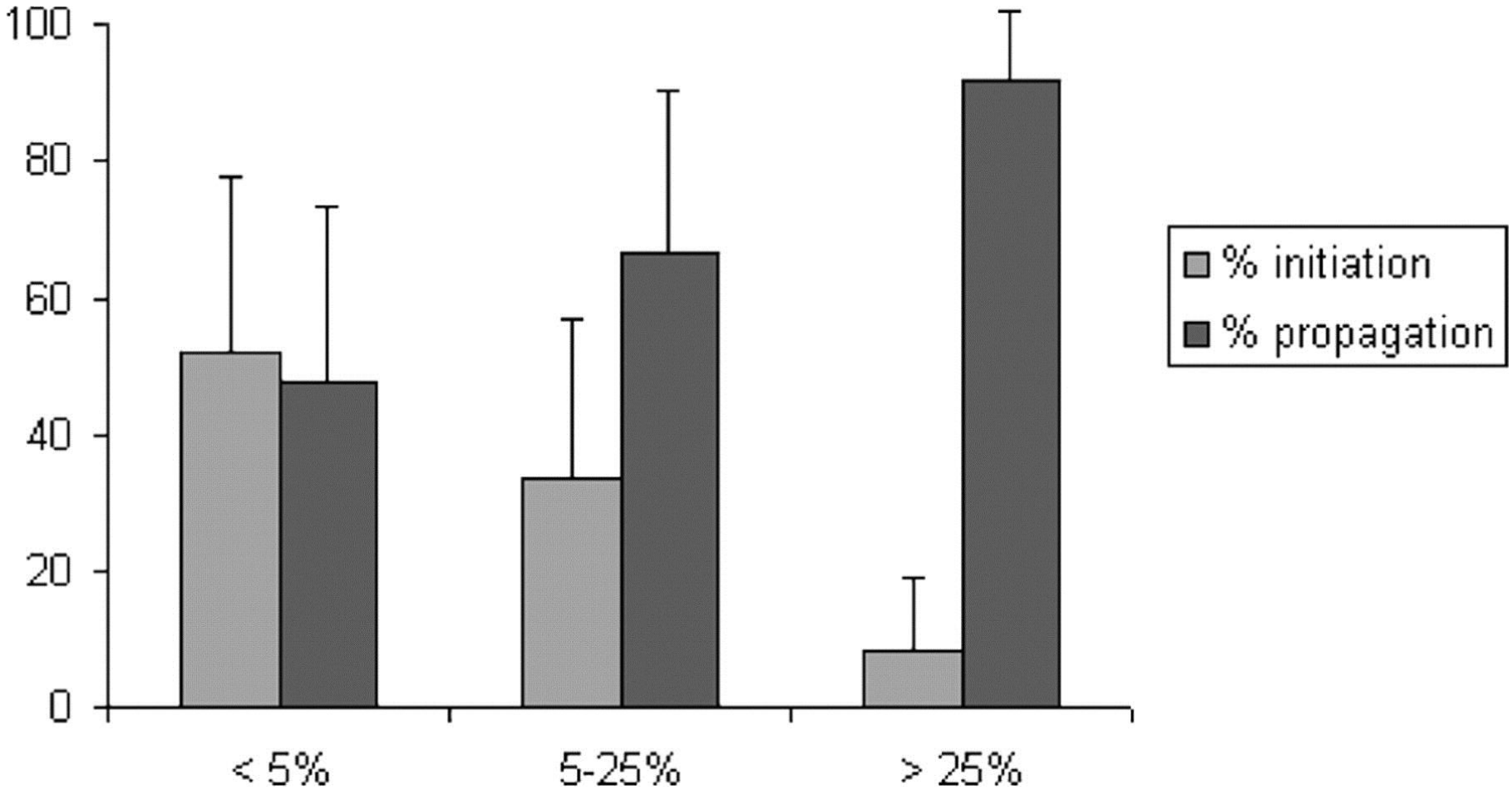



Week 1
Week 2
Week 3
Week 4
A


Week 1
Week 2
B

Analysis: from pictures to numbers

- Linear mixed effects model developed (similar to modeling done for human clinical data)
- Rate of progression of CAA burden differs by transgenic model:
  - Tg2576: 0.35% per day (95% C.I., 0.30 to 0.40)
  - APPsw/PS1dE9 : 0.17% per day
- But how does it progress?


100
80
60
40
20
0
< 5%
5-25%
> 25%
% initiation
% propagation

Questions

- What are the kinetics of CAA development?
- Can CAA be cleared by anti-Aβ therapies?
- How is the vessel wall injured?
- Why do vessels bleed?
- Why does Aβ deposit along the outside of arterial vessels?

Immunotherapy

- Mouse models provided basis for human trials in AD
- Suggestion that CAA increased as plaques were cleared and then was cleared itself (1792 trial autopsies)
- Examined effect of single does of anti-Aβ antibody on CAA progression kinetics

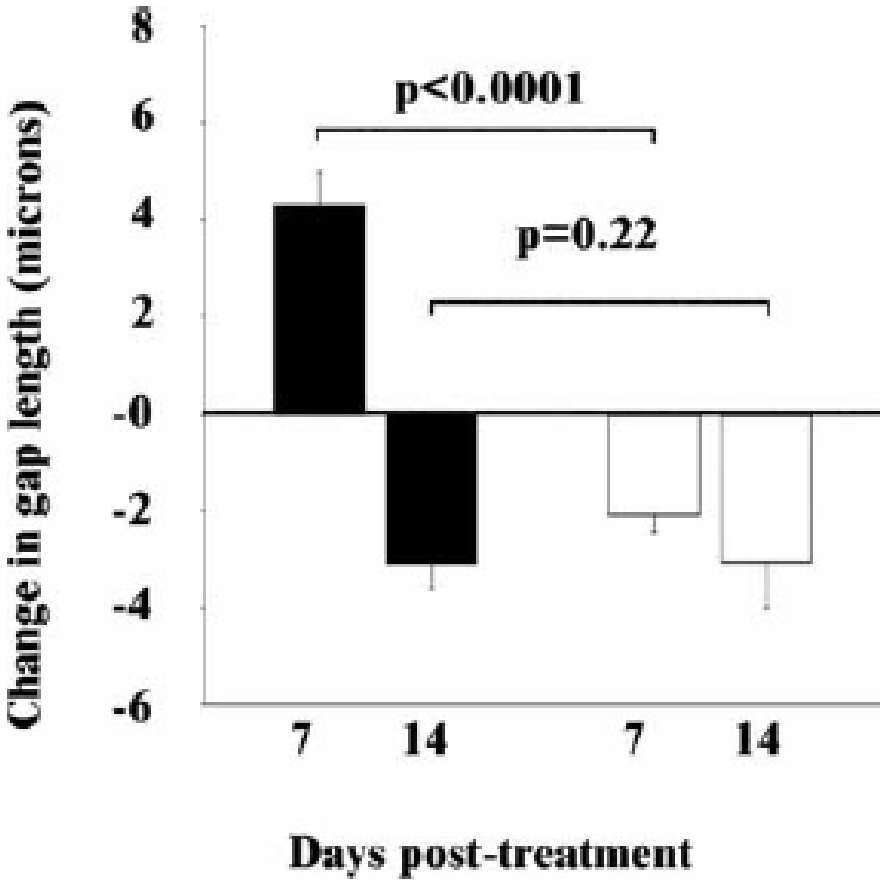
CAA clearance

SINGLE DOSE	**Anti-tau**	**Anti-Aβ**	***p***
Day 0 to Day 7	0.5 ± 0.20	*-0.49 ± 0.15*	<0.0001
Day 7 to Day 14	0.34 ± 0.20	0.84 ± 0.10	0.028

CONTINUED DOSE	**Anti-tau**	**Anti-Aβ**	***p***
Day 0 to Day 7	0.35 ± 0.17	*-0.6 ± 0.10*	<0.0001
Day 7 to Day 14	0.6 ± 0.13	*-0.23 ± 0.13*	<0.001

Positive slope = **PROGRESSION**
Negative slope = **REGRESSION**

Which CAA is cleared?



Gaps: spaces between confluent CAA deposits

CAA progresses mostly by propagation, which results in narrowing of gaps

“Youngest” deposits are at boundaries of gaps so clearance of this fraction will increase gap length

Immunotherapy

- Passive Aβ immunotherapy clears CAA without causing hemorrhages
- Newest deposits of CAA are the most susceptible to clearance
- Plaques are cleared in step-wise manner while CAA is cleared in a continuous manner

Questions

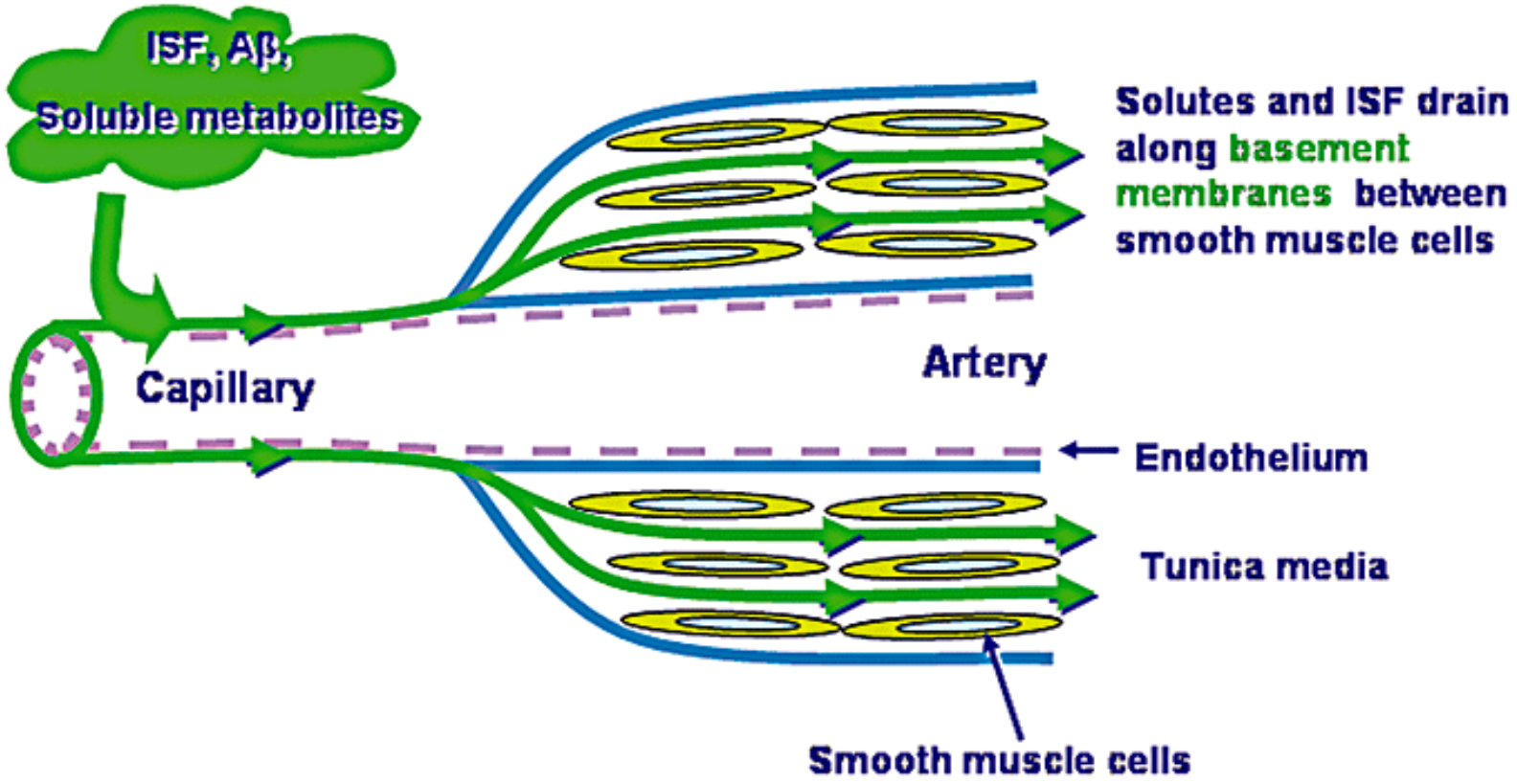
- What are the kinetics of CAA development?
- Can CAA be cleared by anti-Aβ therapies?
- How is the vessel wall injured?
- Why do vessels bleed?
- Why does Aβ deposit along the outside of arterial vessels?

What happens to Aβ in the brain?

- Deposition
- Degradation (IDE, neprilysin, etc)
- Cellular uptake by microglia, macrophages
- Transcytosis across the blood brain barrier via the low-density lipoprotein receptor (LRP1)
- Perivascular drainage along with the ISF

Aβ in CSF

- Measureable levels of Aβ40 and Aβ42
  - Aβ42 in the 100-250 pg/ml range
- Component of best established non-imaging biomarker for AD
  - ↑of p-tau & ↓ of Aβ42 (ratio used as measure)
- Why does CSF Aβ42 decline in AD?
  - Propensity to aggregate
  - Altered access to CSF



From Weller et al (2008) *Brain Pathology*, **18**: 253–266.

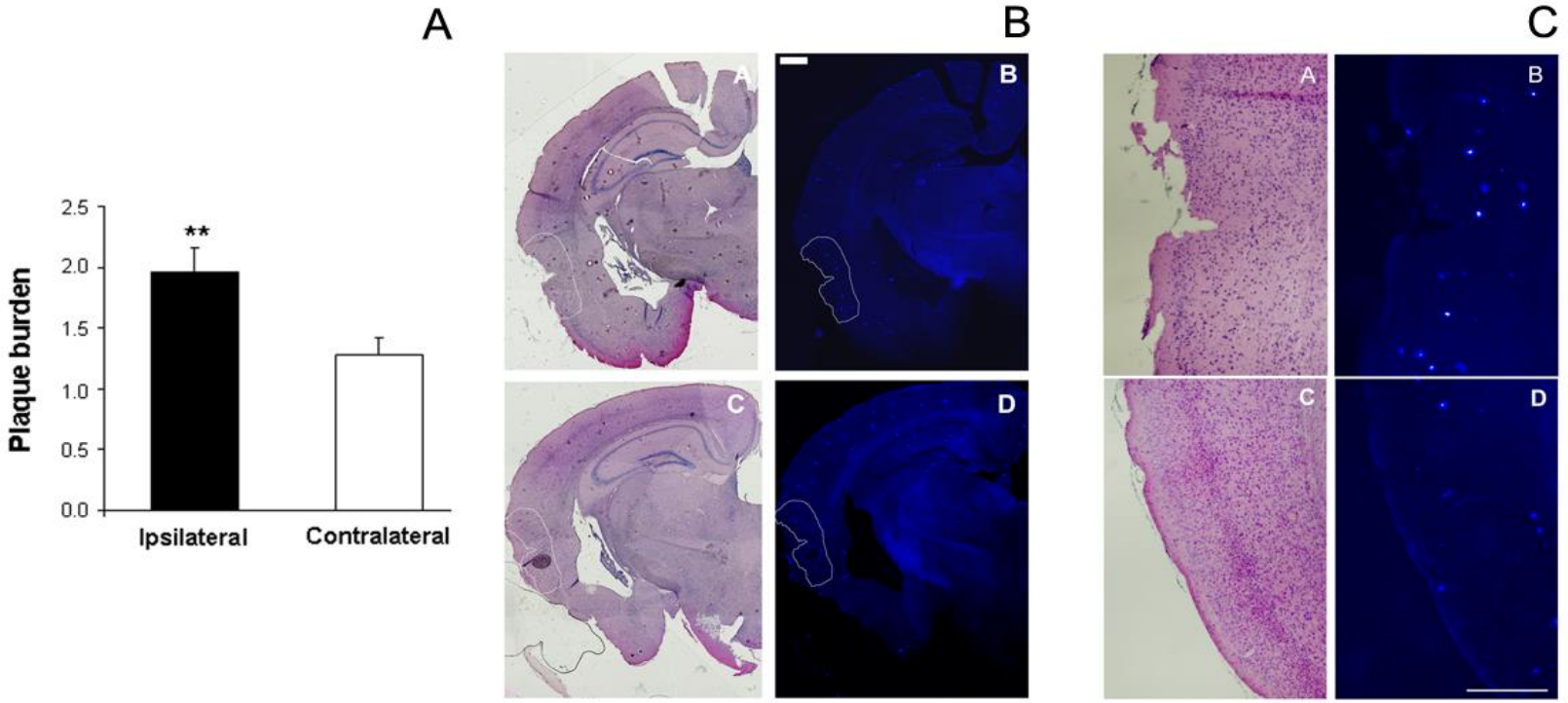
ISF Drainage

- Vessel pulsations proposed as motive force for perivascular drainage of ISF
- Loss of pulsations → loss of drainage
- Stiffening of arteries → reduced pulsation
- CAA will be a feed-forward process: increasing parenchymal and vascular Aβ deposition

Prediction

- If we decrease blood flow, we should see an increase in local Aβ deposition
- Fixed lesion: middle cerebral artery occlusion (MCAO)
- Transient lesion: Rose Bengal

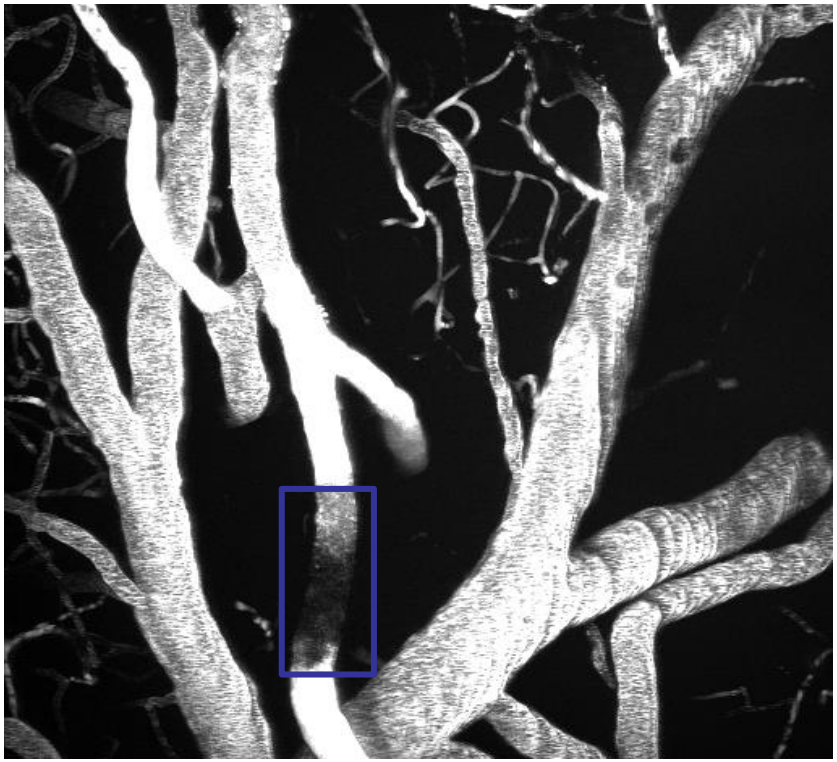
MCAO results in localized increase in plaque burden



Consequence of small vessel occlusion

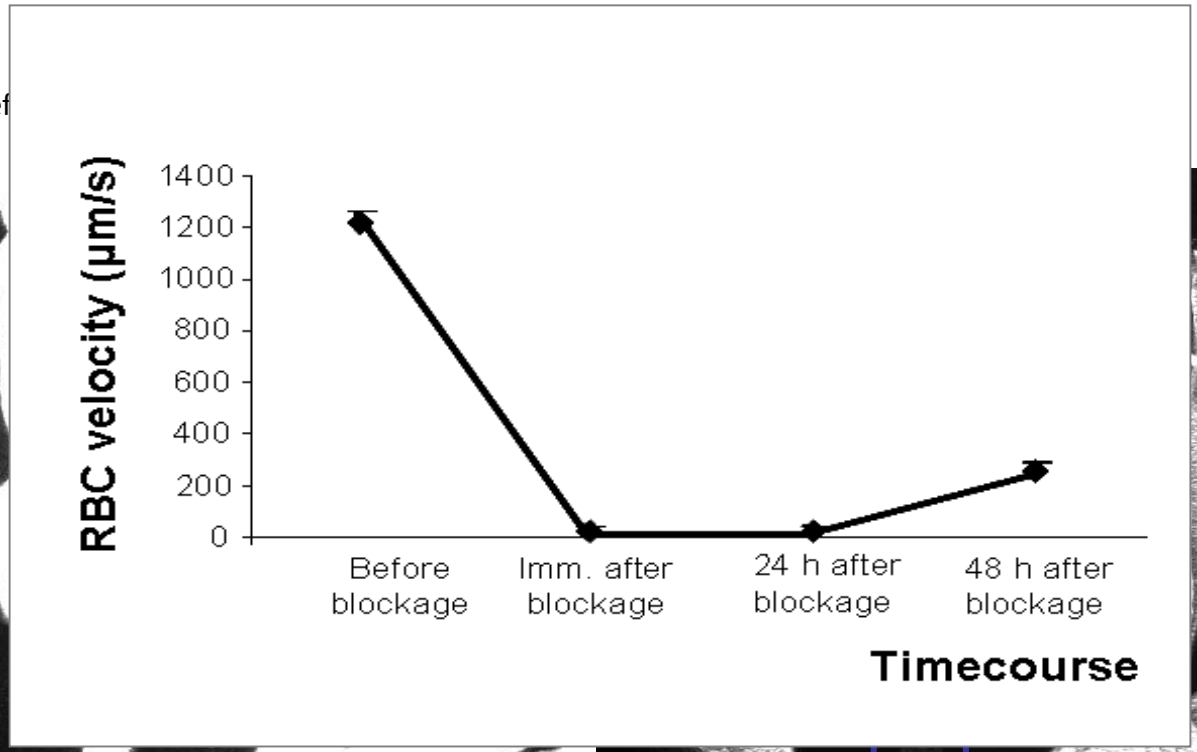
Angiogram before occlusion

Angiogram after occlusion

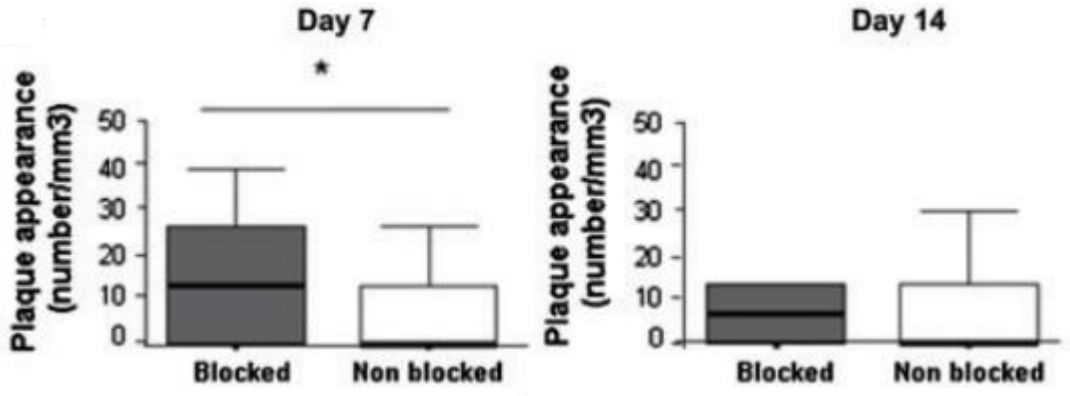


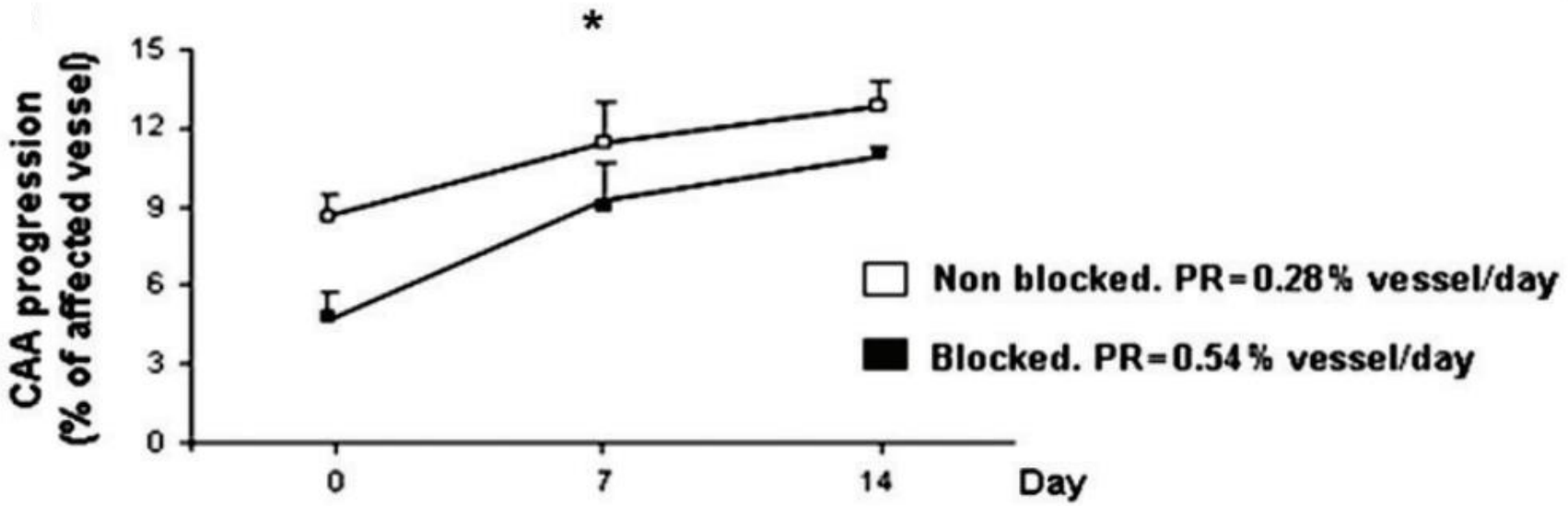
Consequence of small vessel occlusion

Angiogram bef



Consequence of small vessel occlusion

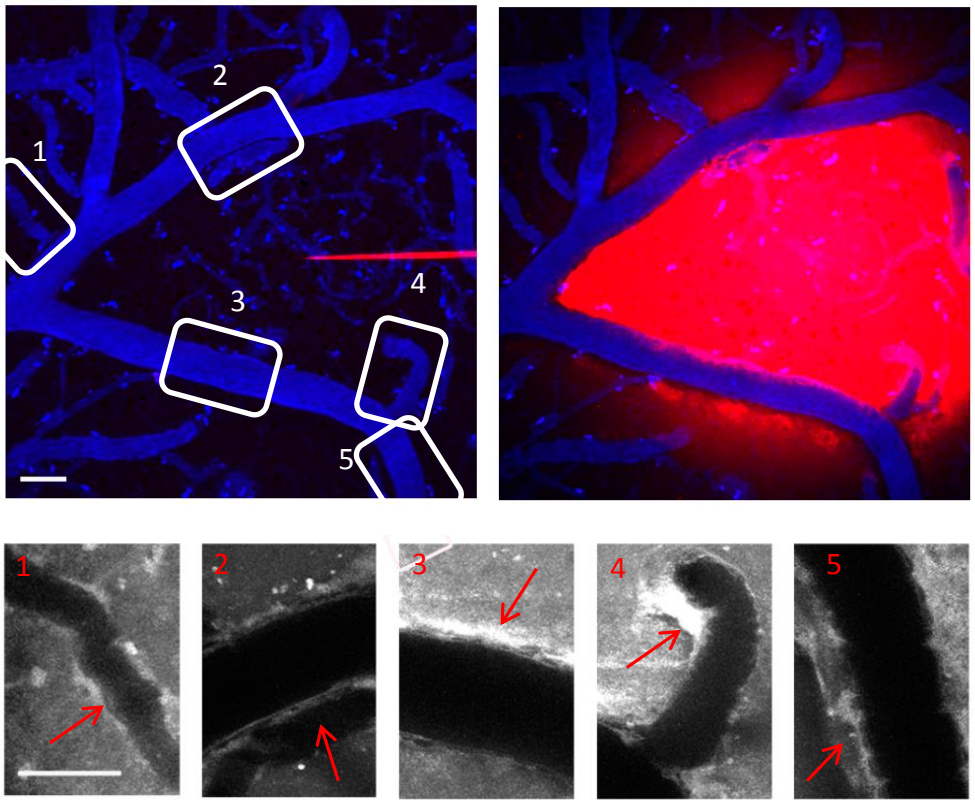




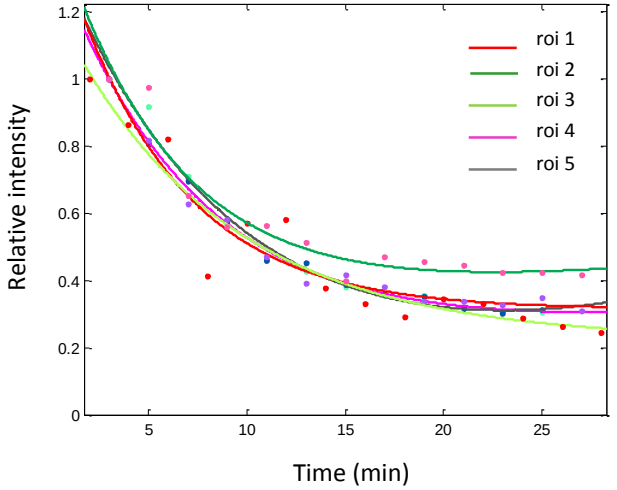
Quantifying perivascular efflux

Before injection

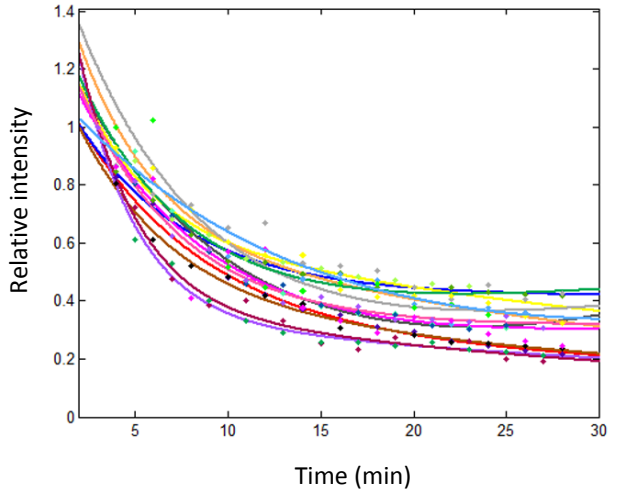
2min after bolus injection



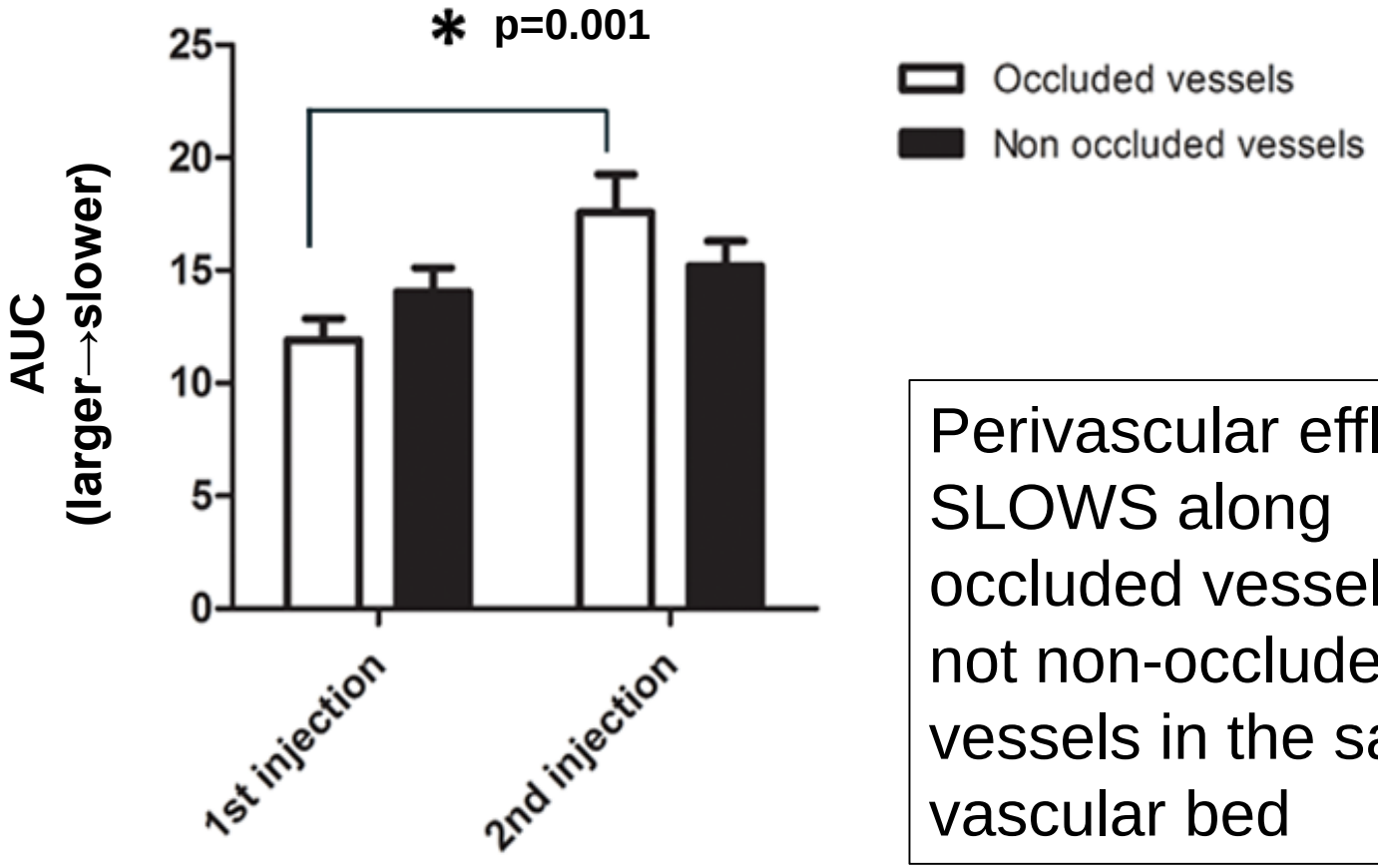
Vessels from the same brain



Vessels from 5 animals



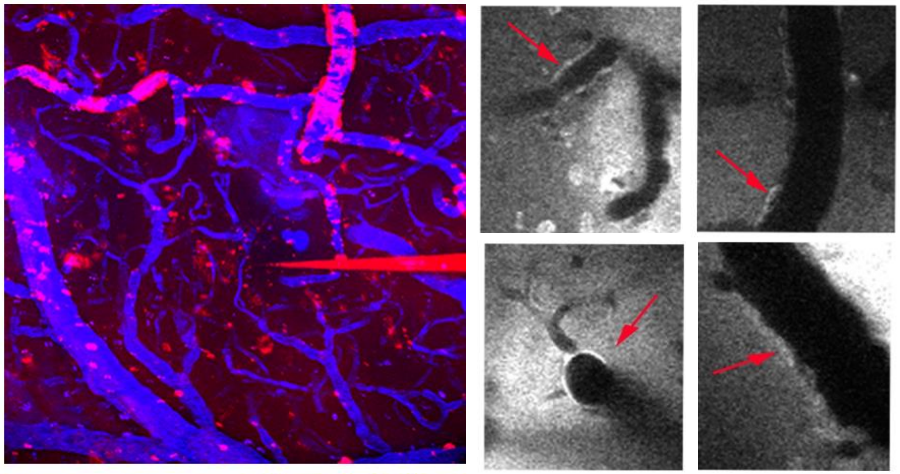
Quantifying perivascular efflux

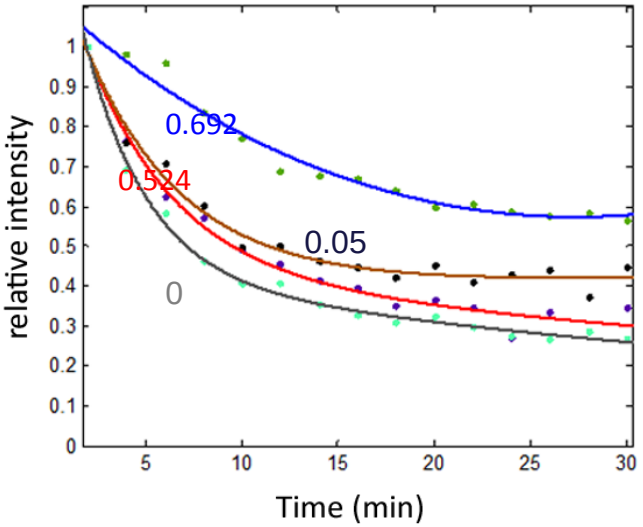


Perivascular efflux SLOWS along occluded vessels but not non-occluded vessels in the same vascular bed

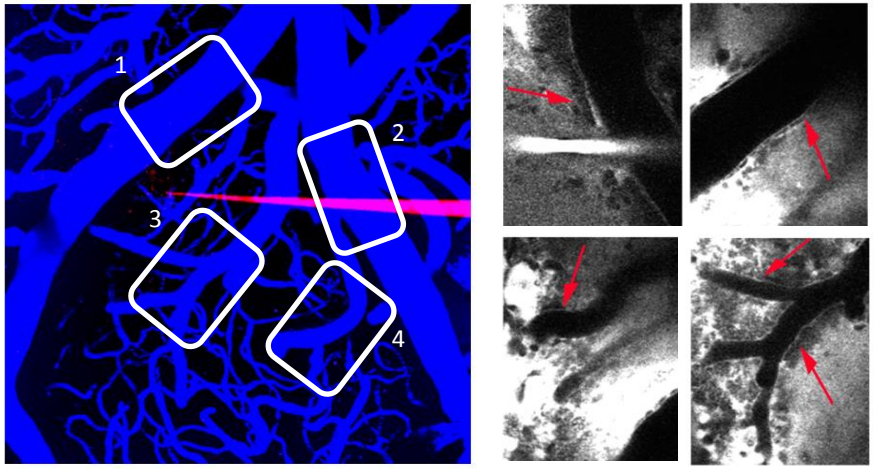
Quantifying perivascular efflux

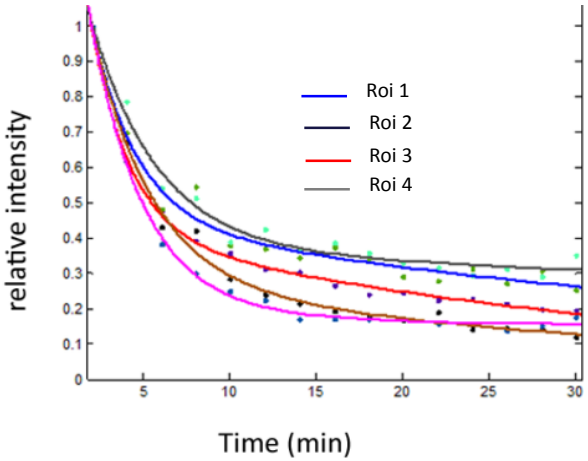
Tg



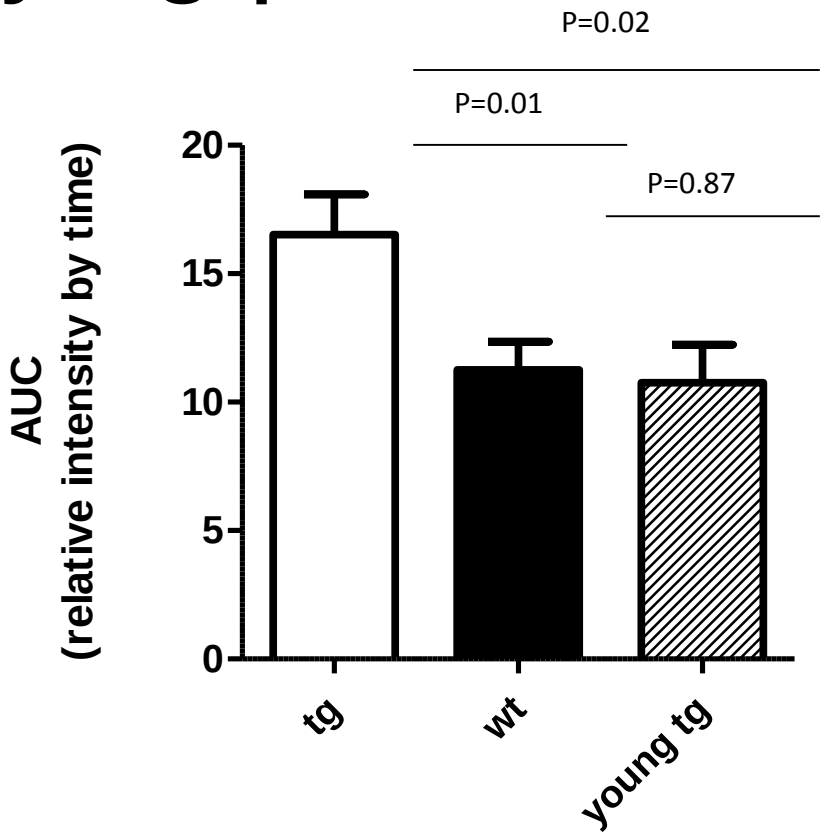


WT





Quantifying perivascular efflux



- Impaired perivascular effux in setting of CAA
- Depends on presence of CAA not on transgene status

Cerebral amyloid angiopathy (CAA)

- Clinicopathologic studies
  - Types of bleeding
  - Inflammatory CAA
  - Impact of CAA on clinical trials for AD
- Animal models
  - Progression of CAA
  - Immune clearance of CAA
  - Perivascular efflux of Aβ

Colleagues and collaborators

Rebecca Betensky, PhD

Brian Bacskai, PhD

Steve Greenberg, MD, PhD

Claudia Prada, MD, PhD

Julia Gregory, PhD

Monica Garcia-Alloza, PhD

Lingzhi Zhao, PhD

Michal Arbel-Ornath, PhD

Sarah Domnitz (PhD)

Elissa Robbins (PhD)

Sara Fine (MD)

Charles Greenberg (PhD)

Funding from NIA, NIBIB, Lefler Foundation, American Heart Association and Harvard NeuroDiscovery Center