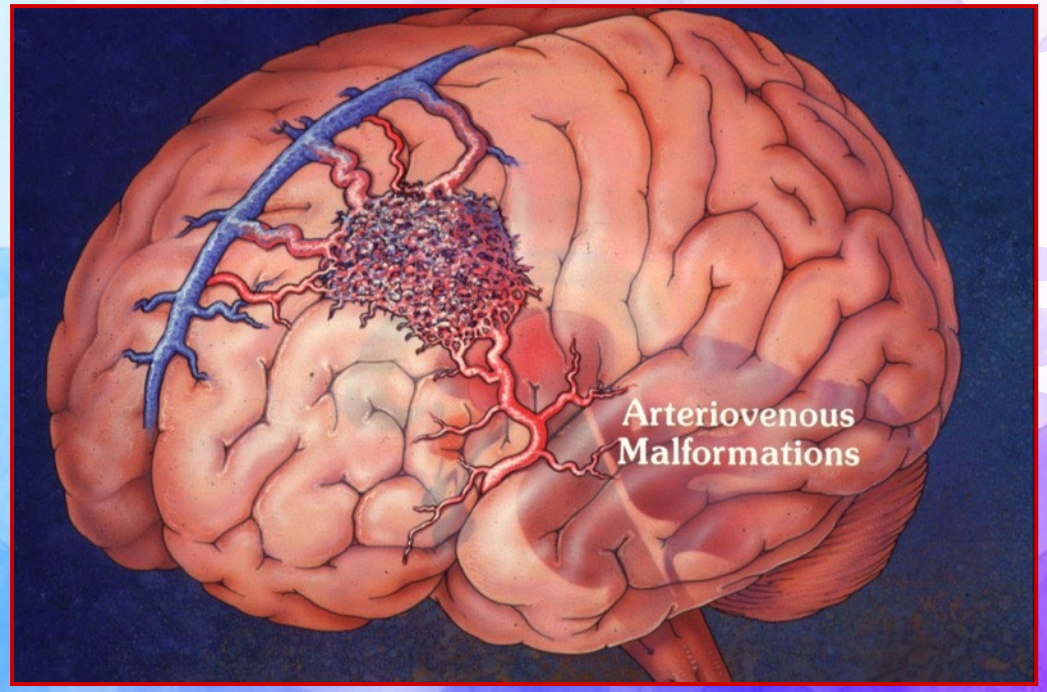
Brain Arteriovenous Malformation: Opening up the Pandora's Box

Unlocking new Possibilities



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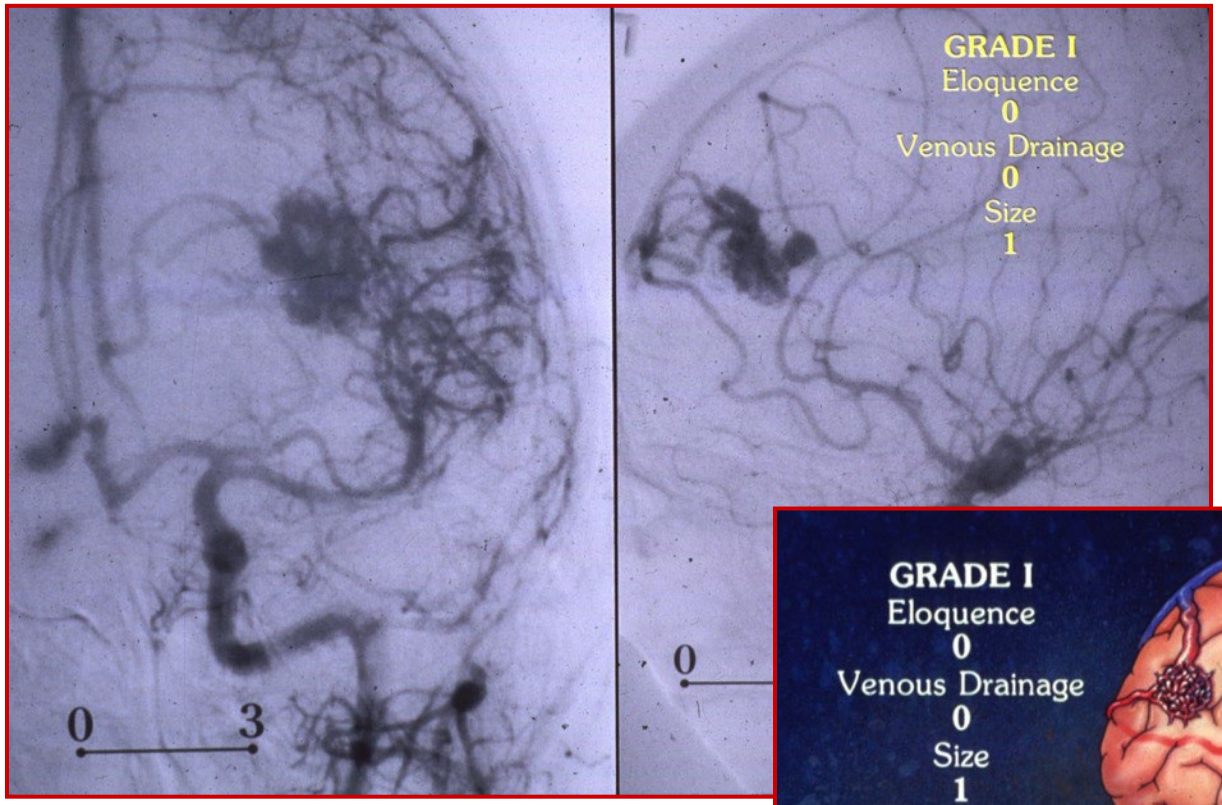
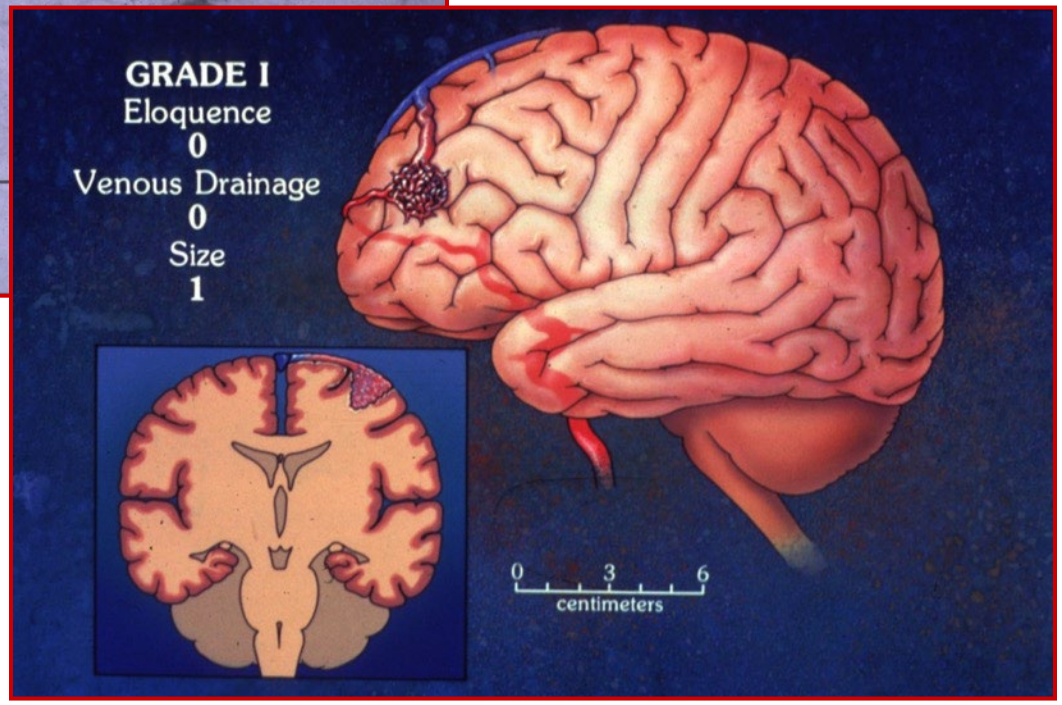
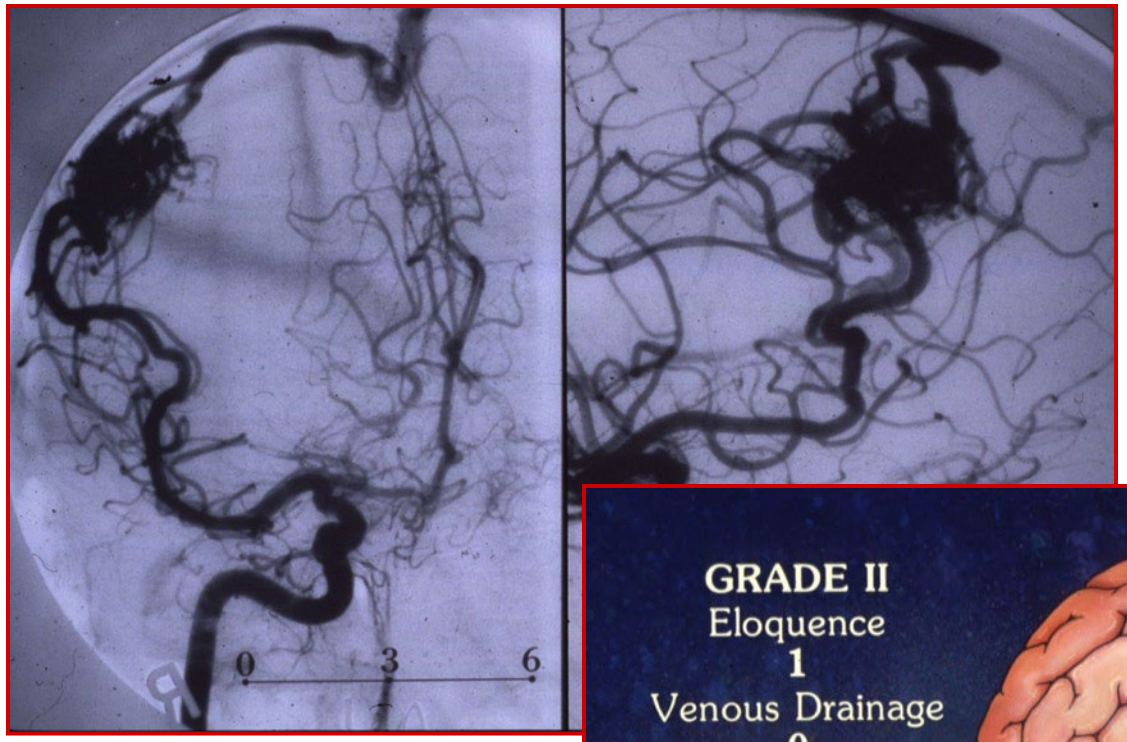
Disclosure

- Stryker Research Grant (Unrelated to this research)
- Balt Neurovascular Research Grant (Unrelated to this research)
- NIH Grant

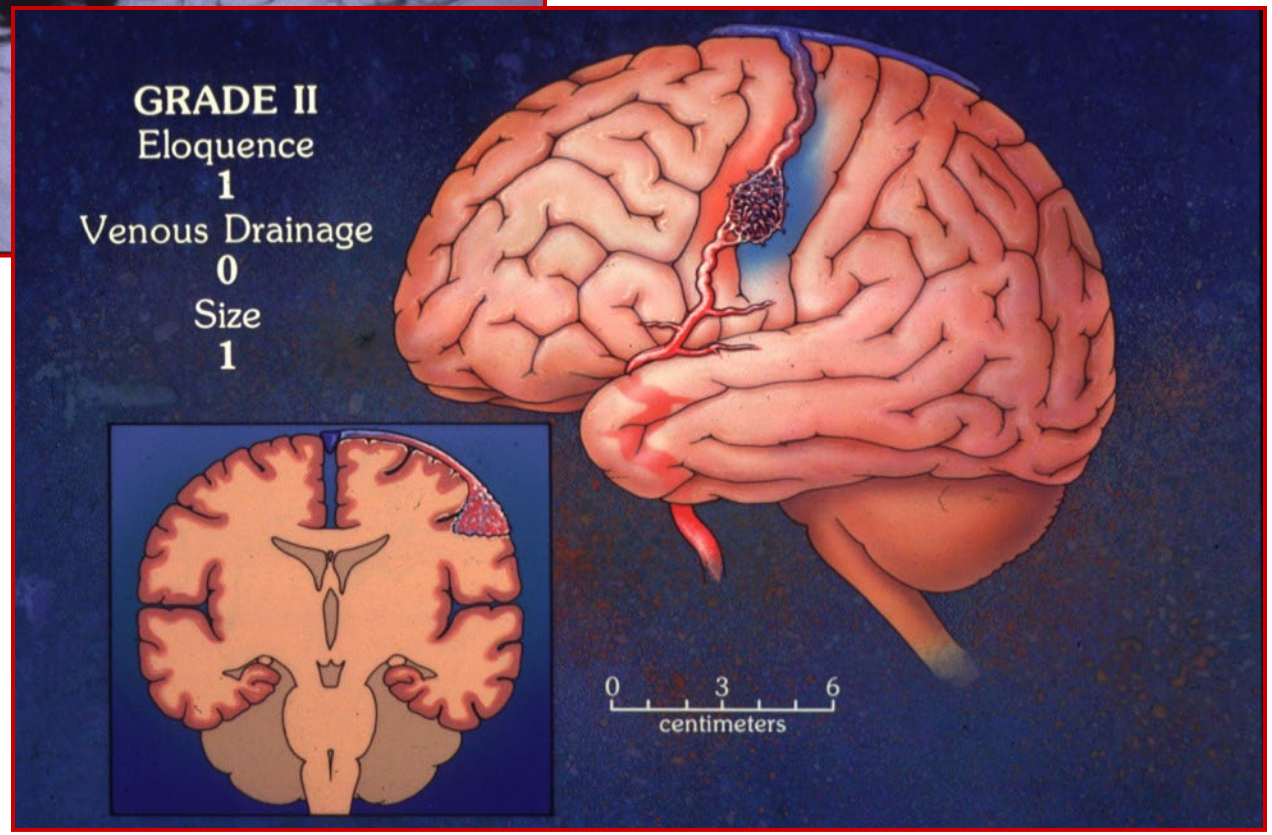
bAVM with Spetzler-Martin Grading



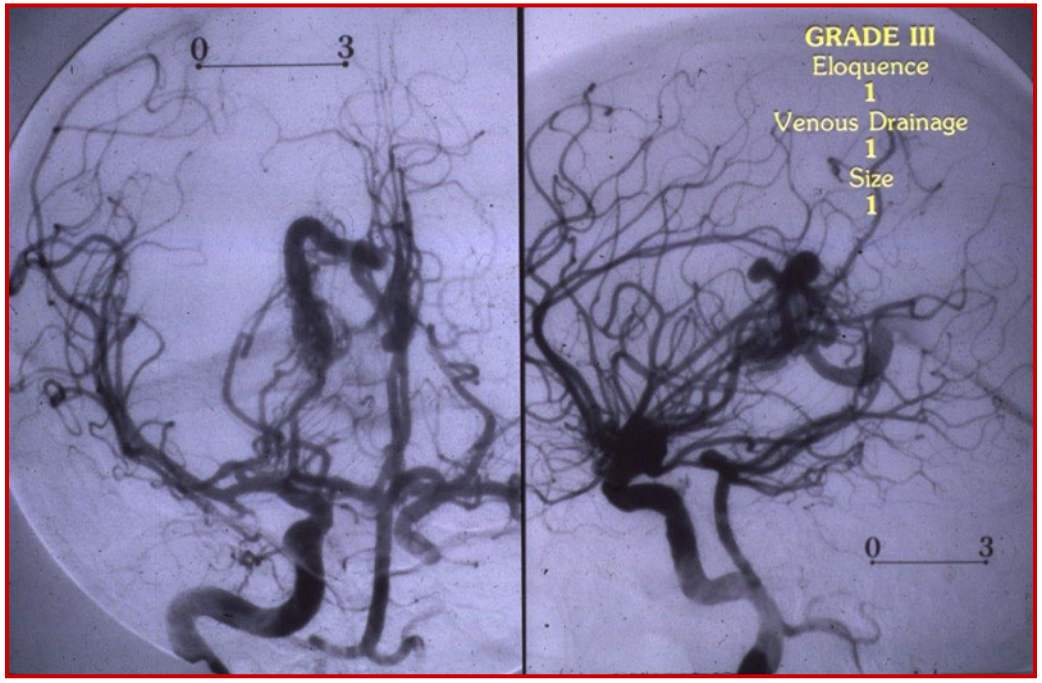


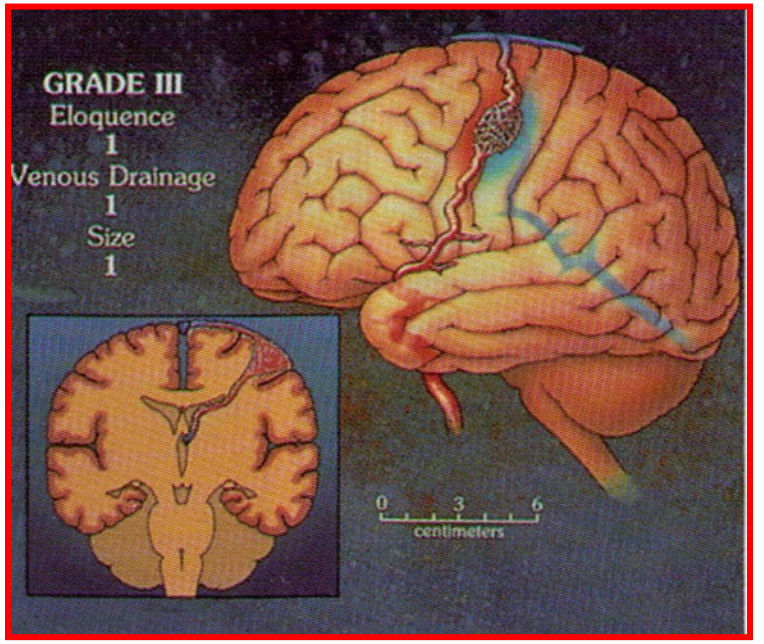


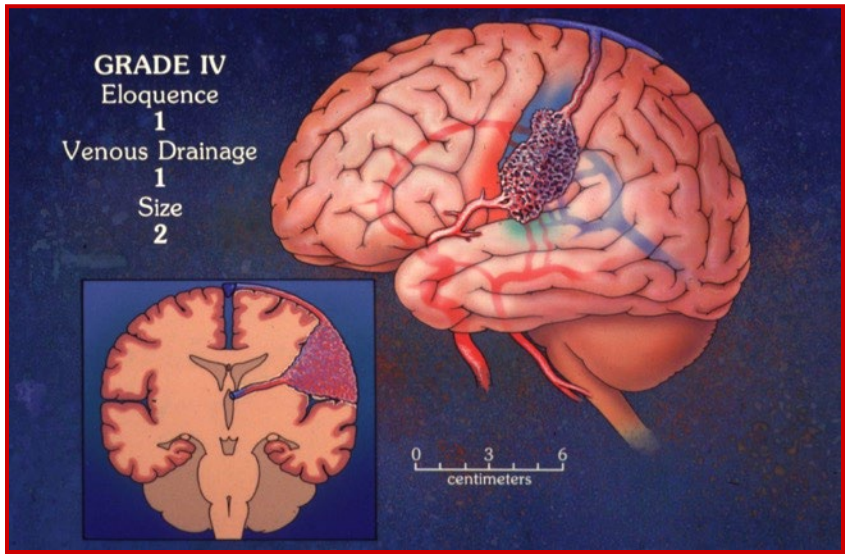
bAVM with Spetzler-Martin Grading

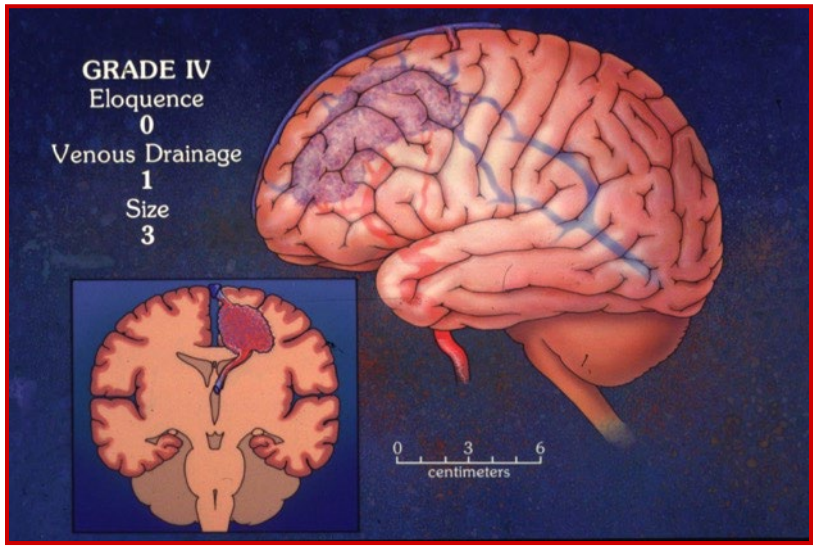


bAVM with Spetzler-Martin Grading

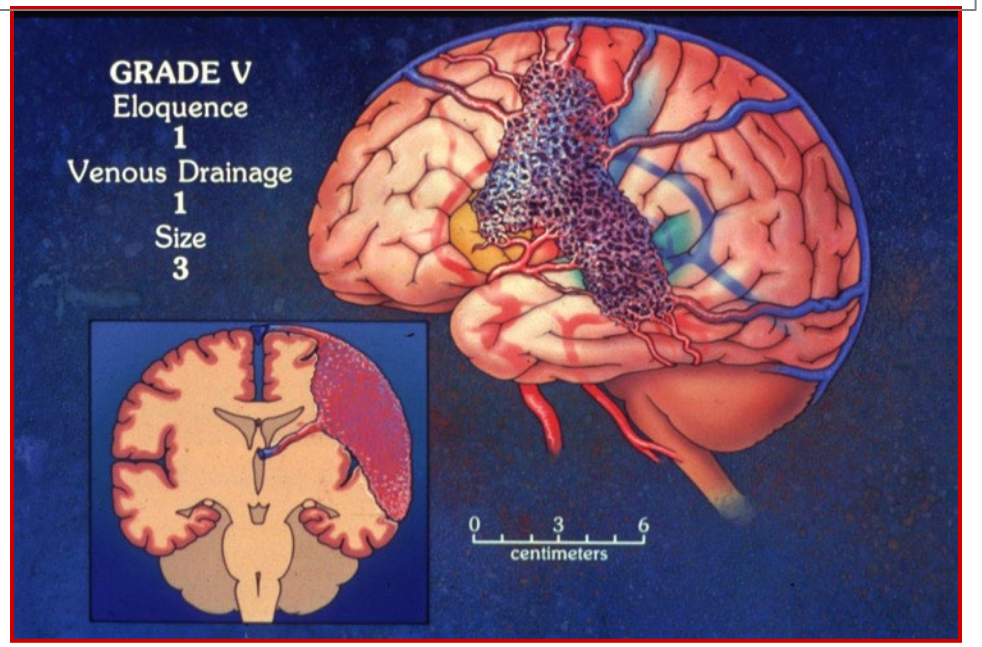


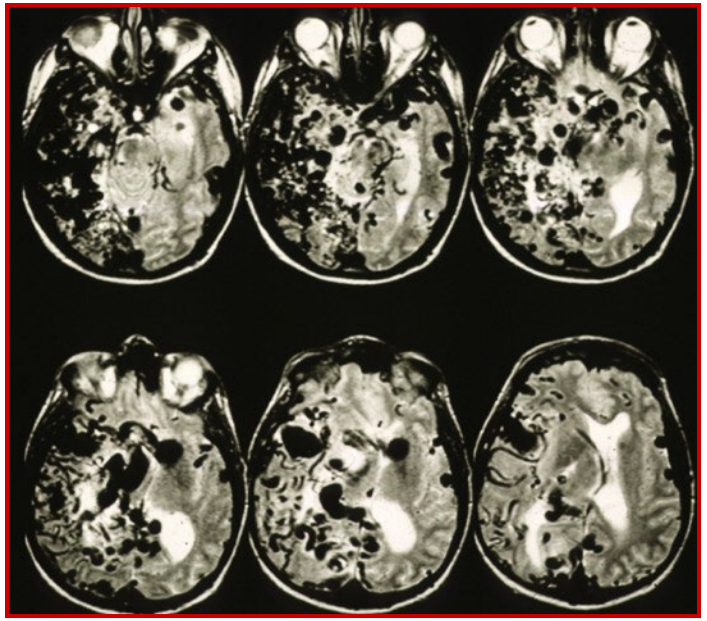






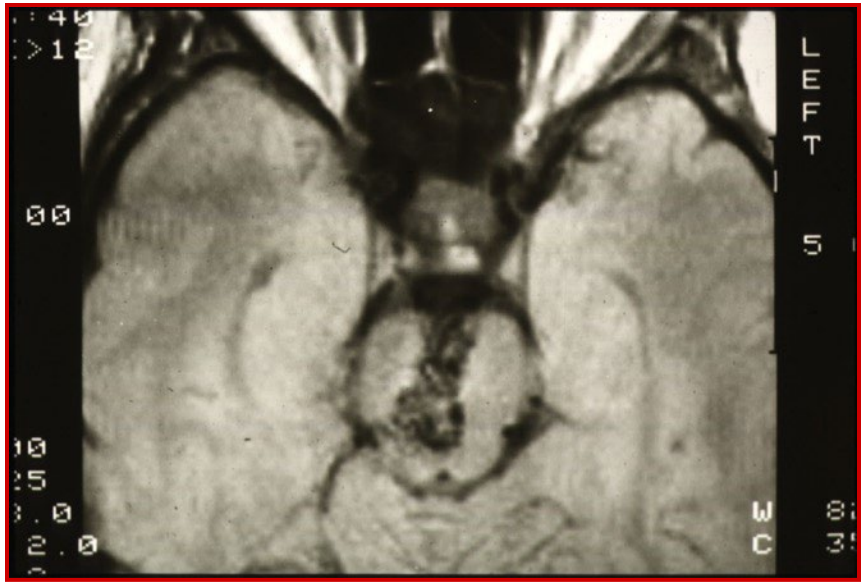
bAVM with Spetzler-Martin Grading





Grade V

“Grade VI” = inoperable



Natual History of bAVM

- Ondra et al. (J Neurosurg 1990)
- Hemorrhage: 4% /yr
- Major Morbidity: 1.7% /yr
- Mortality: 1% / yr
- Combined M & M 2.7% /yr

Previous ruptured AVM

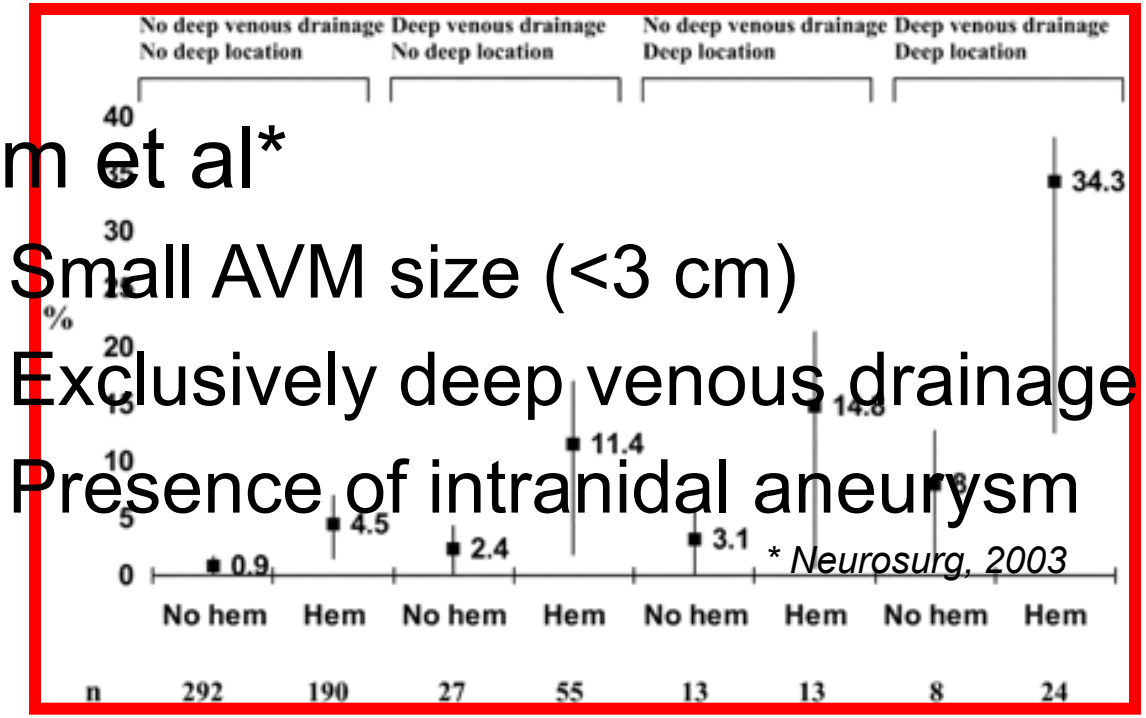
- Stapf et al. 6% /yr
- Pollock et al. 7.45%/yr

Predictors of bAVM Hemorrhage

- Initial hemorrhagic presentation
- Deep brain location
- Exclusive deep venous drainage

Stapf et al, 2006, stroke

- Kim et al*
  - Small AVM size (<3 cm)
  - Exclusively deep venous drainage
  - Presence of intranidal aneurysm



** Neurosurg, 2003*

Clinical Management

1. Observation
2. Therapeutic interventions:
   - Endovascular embolization (less likely curative, particularly for the large bAVM)
   - Stereotactic radiosurgery (curative for bAVM < 3 cm)
   - Microsurgery (curative for grade 1- 3, and most of 4)

- **All treatment modalities have their own M & M**
- Management decision making is based on risks of interventions vs risk of natural history of bAVM

Current Recommendation for bAVM treatment based on Spetzler-Martin Grade

- Grade I: Microsurgical Resection
- Grade II: Microsurgical Resection
- Grade III: case by case.
  - Microsurgery, Embolization + microsurgery, Embolization, Radiosurgery, Embolization + Radiosurgery.
- Grade IV and V: Observation.
  - Multimodality treatment Only repetitive hemorrhage or significant hemorrhage or progressive neurological disability.

Complications rate associated to bAVM treatment

- Grade I:
- Grade II:
- Grade III:
- Grade IV:
- Grade V:

So, It's time to think differently

Recommendations for AVM treatment

- ** Unruptured Grade IV and V AVM
  - seems to have lower risk of hemorrhage, 1%/yr
  - Partially treated, 10.5%/yr risk of hemorrhage.

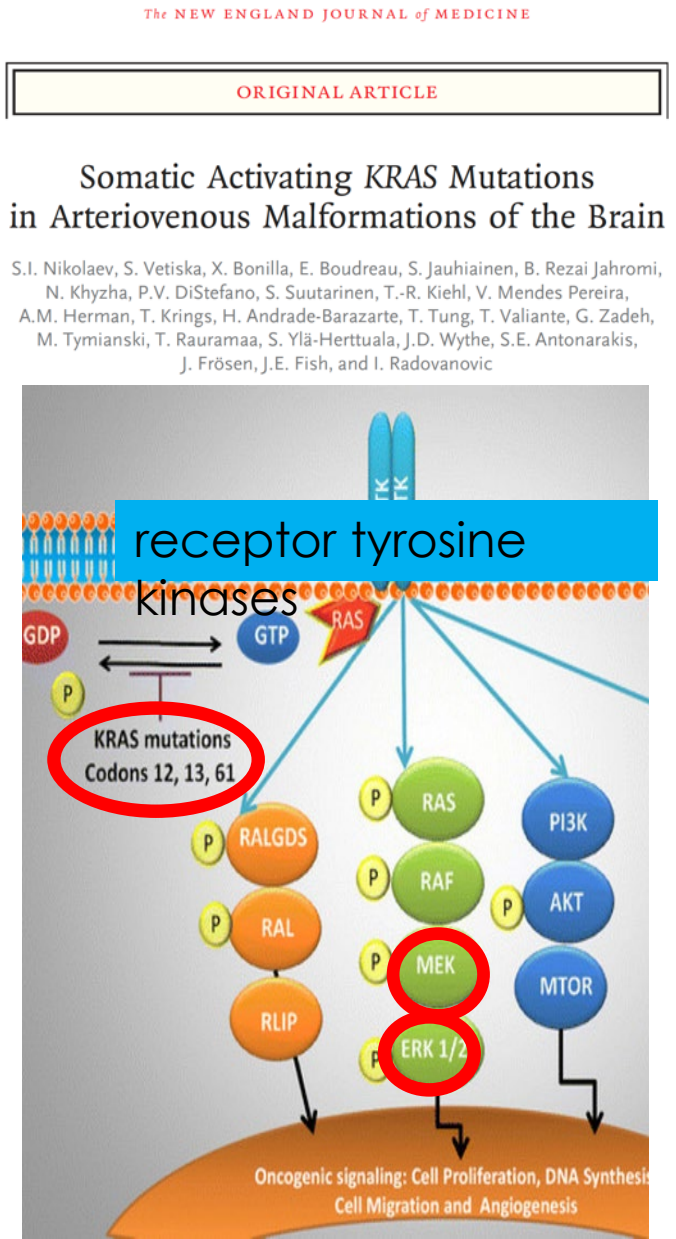
- Observation is Recommended

***Han et al, J Neurosurg 2003*

KRAS Mutations and bAVM

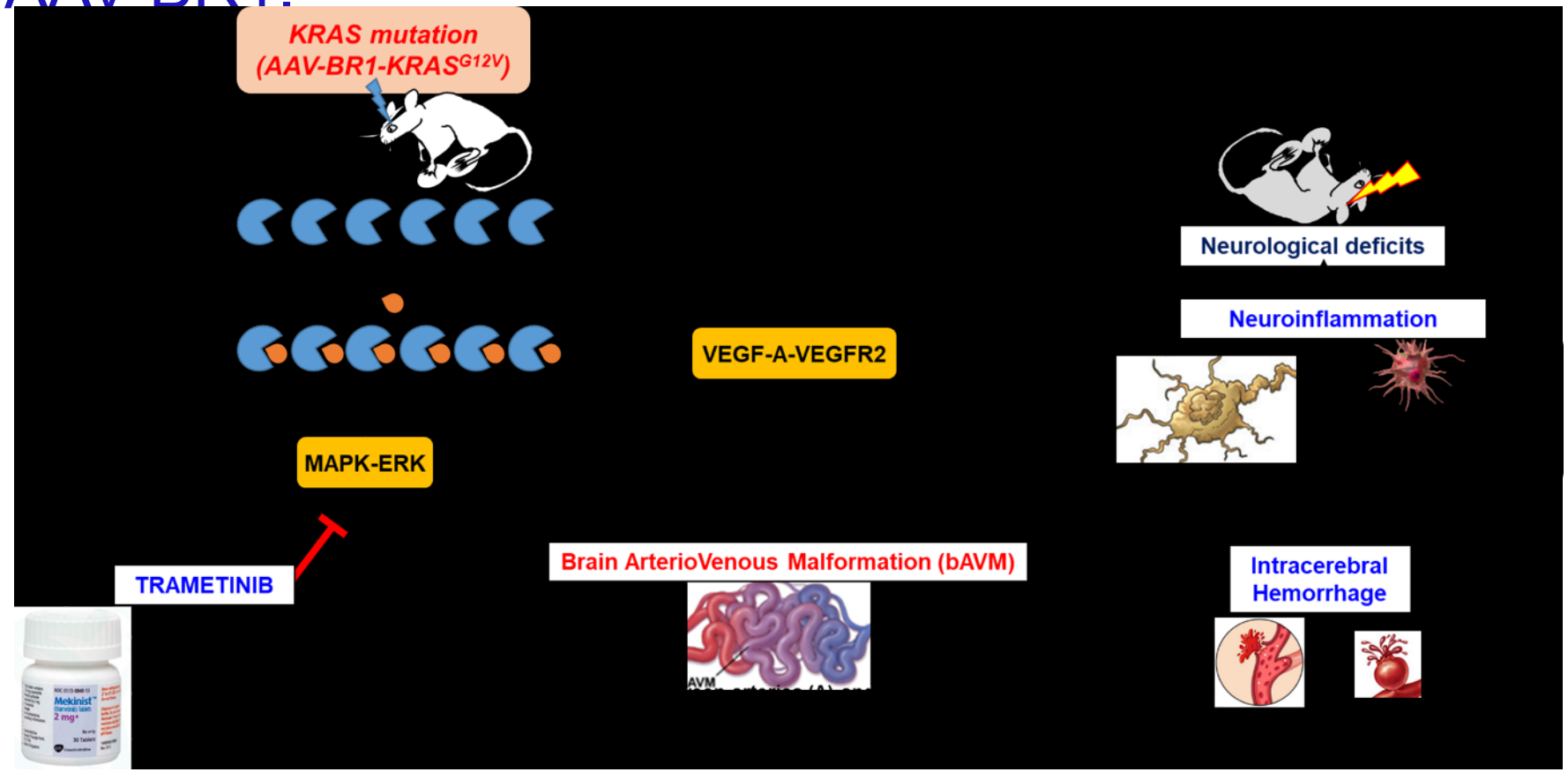
- Over 95% of bAVM cases are sporadic
- Previous bAVM researches largely in the setting of hereditary hemorrhagic telangiectasia (HHT).
- KRAS mutations are frequently observed in cancers, and a recent unprecedented finding of these mutations in human sporadic bAVMs offers a new direction in the bAVM research
- 60 – 70% of patients with sporadic bAVMs displayed somatic *KRAS* mutations in the endothelial cells of human bAVM samples.*
- *KRAS* mutations, including c.35G→A (*p.Gly12Val, i.e. $KRAS^{G12V}$), or c.35G→T (p.Gly12Asp, i.e. $KRAS^{G12A}$)*
- Endothelial cells isolated from human bAVMs displaying KRAS mutations showed significantly increased downstream ERK phosphorylation and reversed by MEK/ERK inhibition.

*Nikolaev *et al*, 2018; Oka *et al*, 2019; Priemer *et al*, 2019; Hong *et al*, 2019



What is the role of KRAS^{G12V} mutation in sporadic bAVM pathogenesis?

In this study, we investigate whether bAVMs are induced by overexpression of *KRAS^{G12V}* in brain endothelial cells in mice using AAV-BR1.



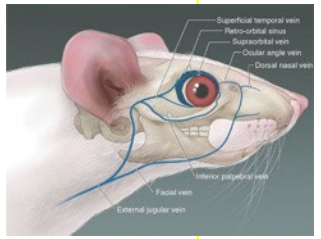
Method

*Adeno-associate virus with NRGTEWD peptide , AAV-BR1, has high specificity in brain endothelial cells with minimal off-target affinity after systemic administration

- Animals: Total 65 mice
- 46 for bAVM characterization studies, and 19 for MEK/ERK inhibition study
- 15 subjected to MRI/MRA scans, to collect bAVM tissue or to determine the effect of MEK/ERK inhibition

1. AAV-BR1 injection:

- AAV-BR1-KRAS^{G12V} and AAV-BR1-GFP
  (University Medical Center Hanburg-Eppendorf and Vector Biolabs, Malvern, PA, USA)
- 5-6 wks old mice given 100ul PBS containing 5 x 10^{10} genome copies/mouse of AAV-BR1-KRAS^{g12v} or -GFP (control) through retro-orbital venous sinus injection



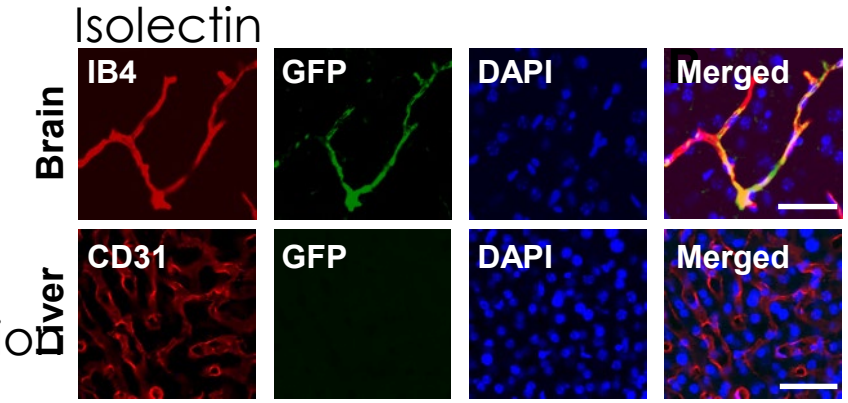
2. Trametinib Treatment:

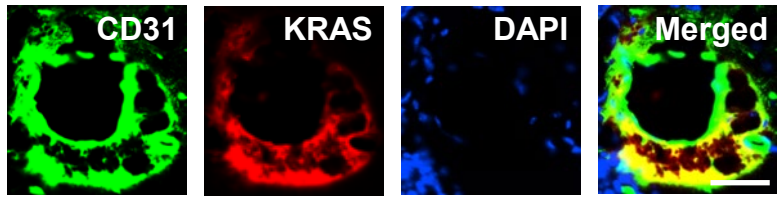
- starting 1 day after KRAS^{G12V} injection, for 6 weeks (1 mg/kg) or vehicle (0.5% [hydroxypropyl]methyl cellulose and 0.2% Tween-80)

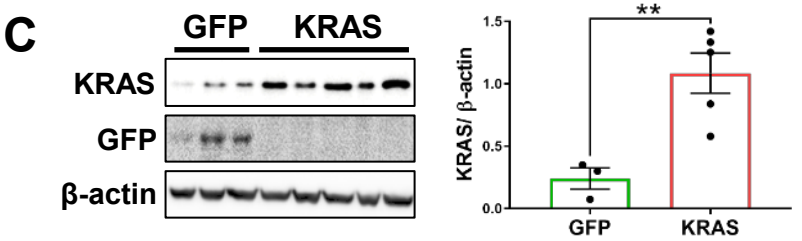
Results

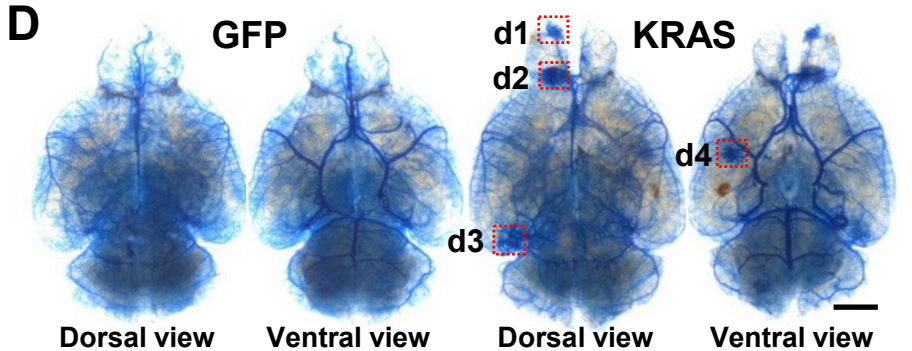
At 9 weeks after the injection

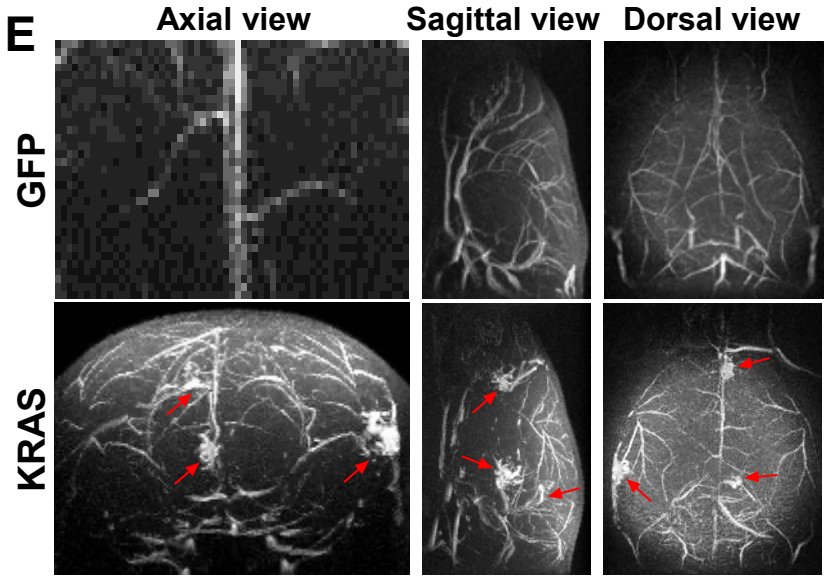
Viral-mediated brain endothelial Specific $KRAS^{G12V}$ overexpression induces bAVMs in mice

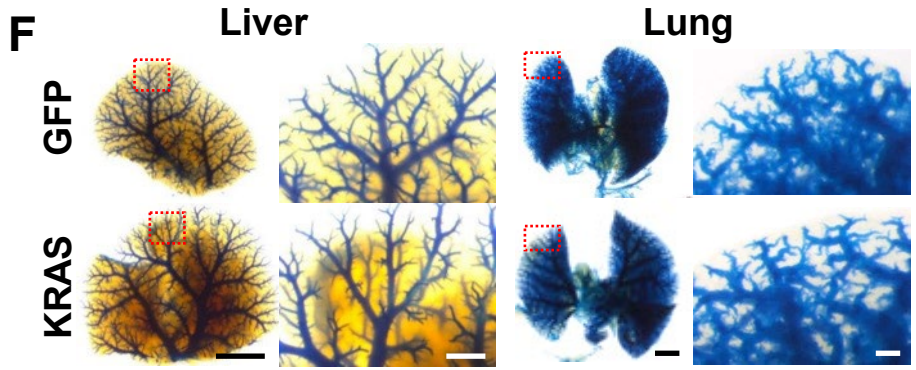


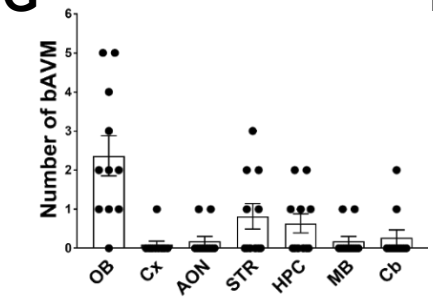


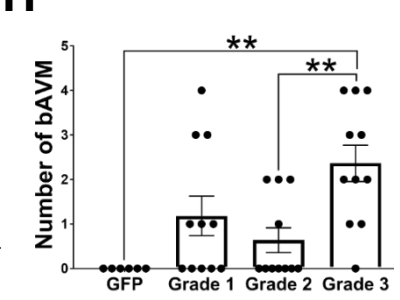








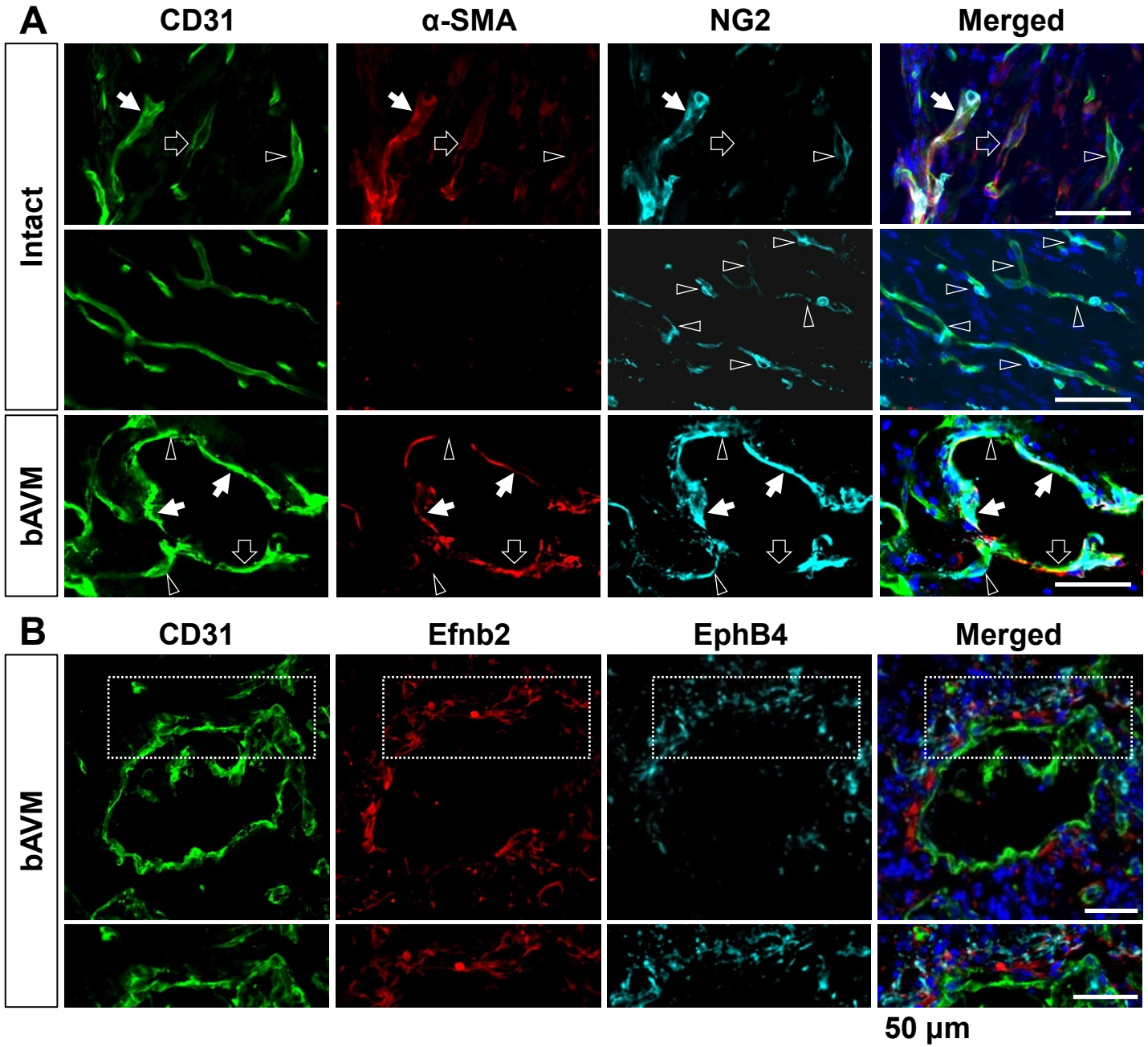




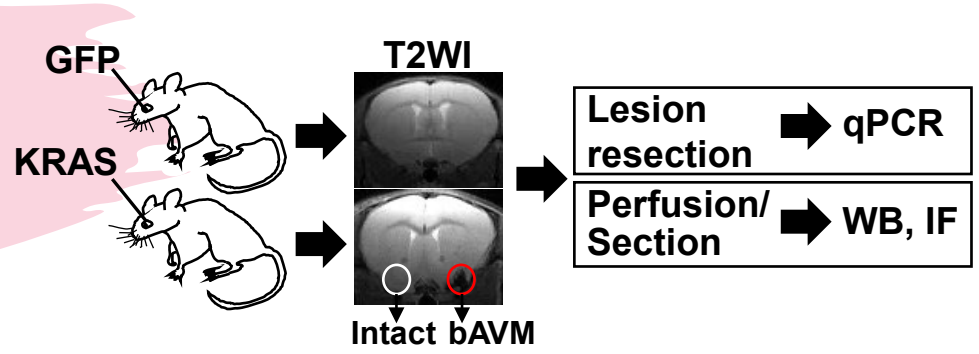
Results

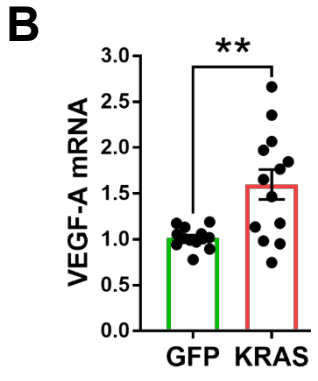
Vessels in bAVMs were characterized by immunohistochemistry using markers:

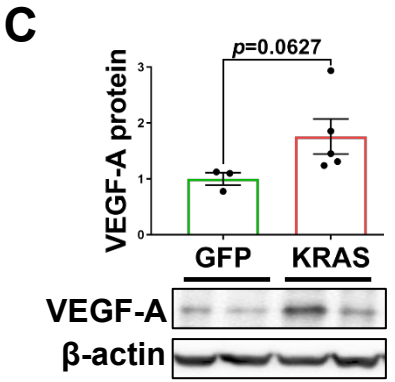
Smooth muscle cells: a-SMA,
Pericytes: NG2,
Artery: Efnb2,
Vein: EphB4

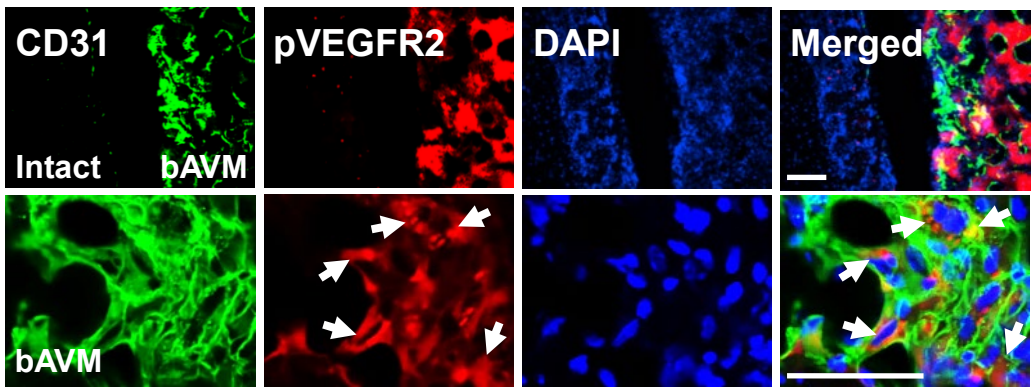


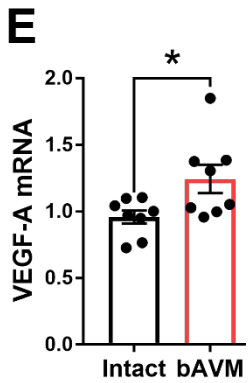
Results

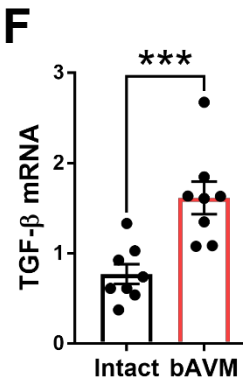

A
GFP
KRAS
T2WI
Intact
bAVM
Lesion resection
qPCR
Perfusion/ Section
WB, IF

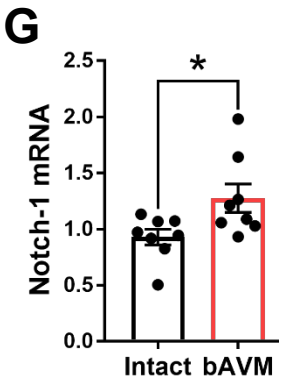

B
VEGF-A mRNA
**
GFP
KRAS

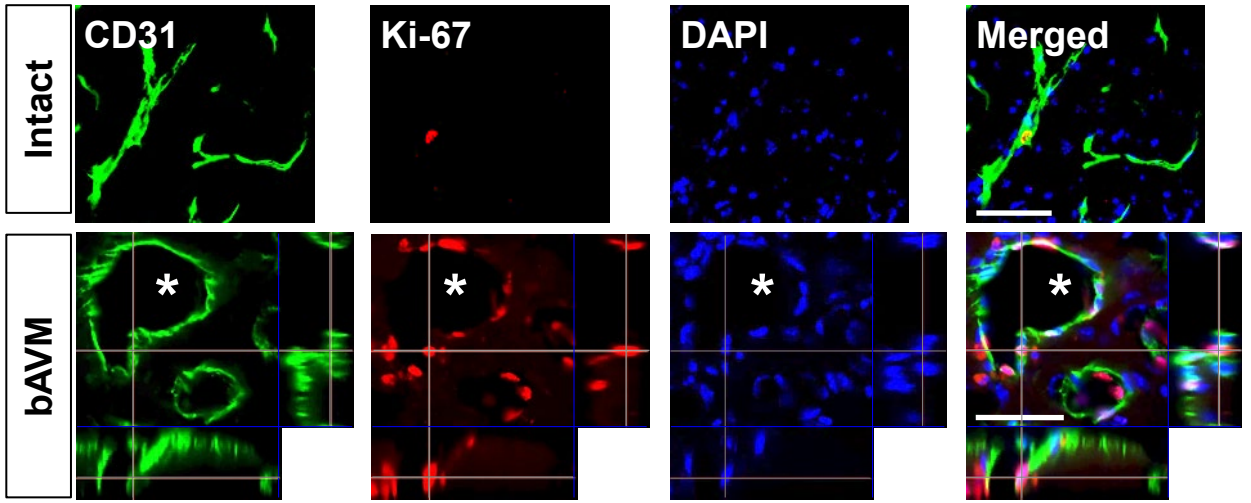

C
VEGF-A protein
p=0.0627
GFP
KRAS
VEGF-A
β-actin

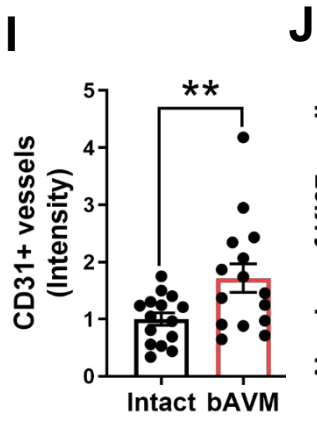

D
CD31
pVEGFR2
DAPI
Merged
Intact
bAVM
bAVM

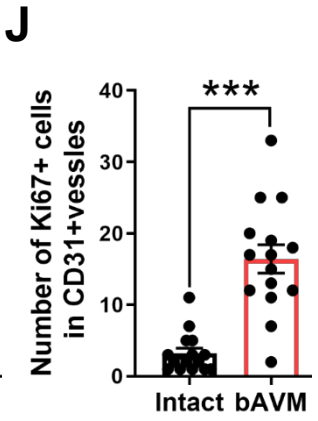

E
VEGF-A mRNA
*
Intact
bAVM


F
TGF-β mRNA
***
Intact
bAVM


G
Notch-1 mRNA
*
Intact
bAVM

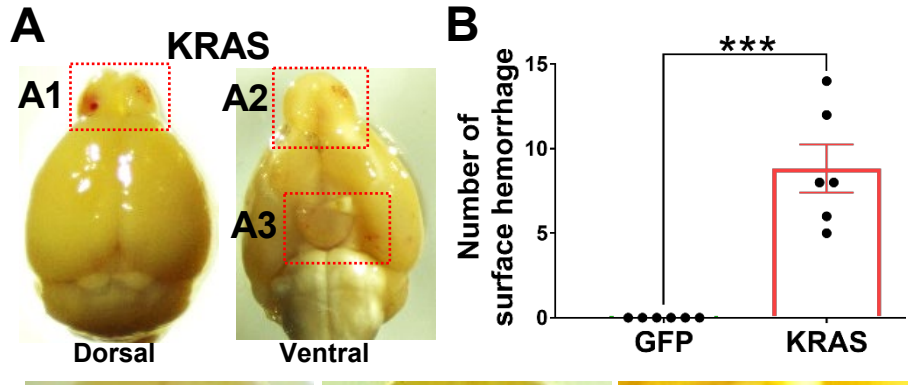

H
Intact
bAVM
CD31
Ki-67
DAPI
Merged

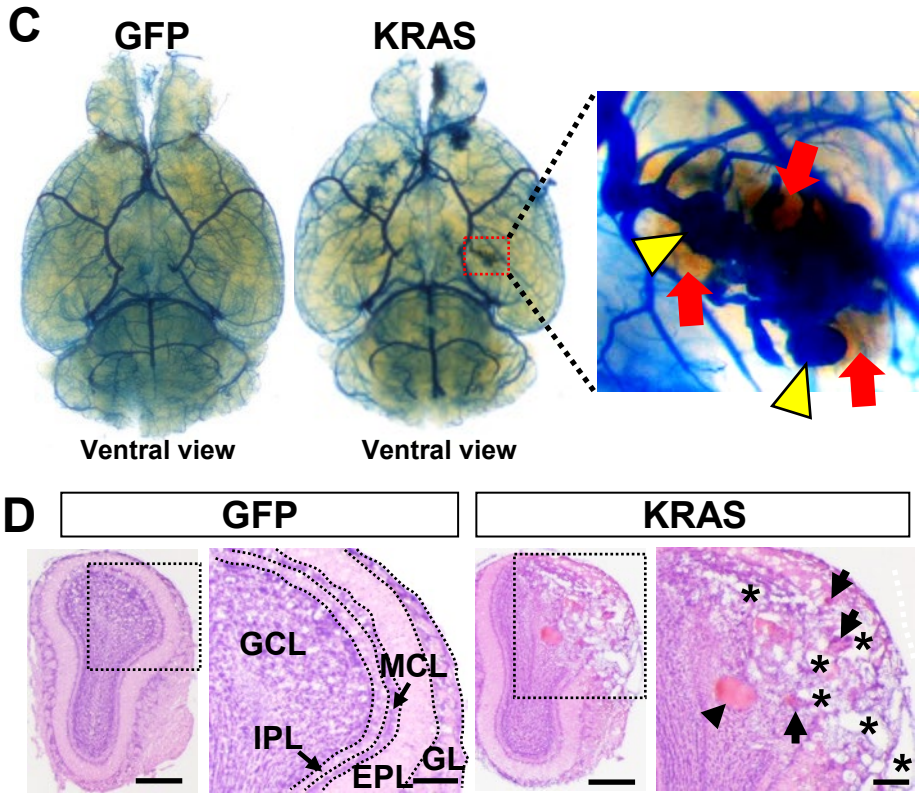

I
CD31+ vessels (Intensity)
**
Intact
bAVM

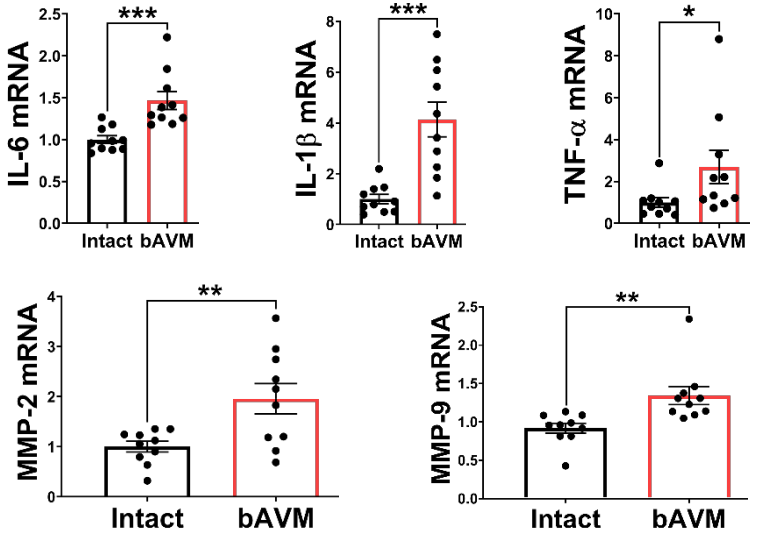

J
Number of Ki67+ cells in CD31+vessles
***
Intact
bAVM

Results

Spontaneous Intracerebral Hemorrhage and Neuroinflammation Occur in KRASG12V-Induced AVMs

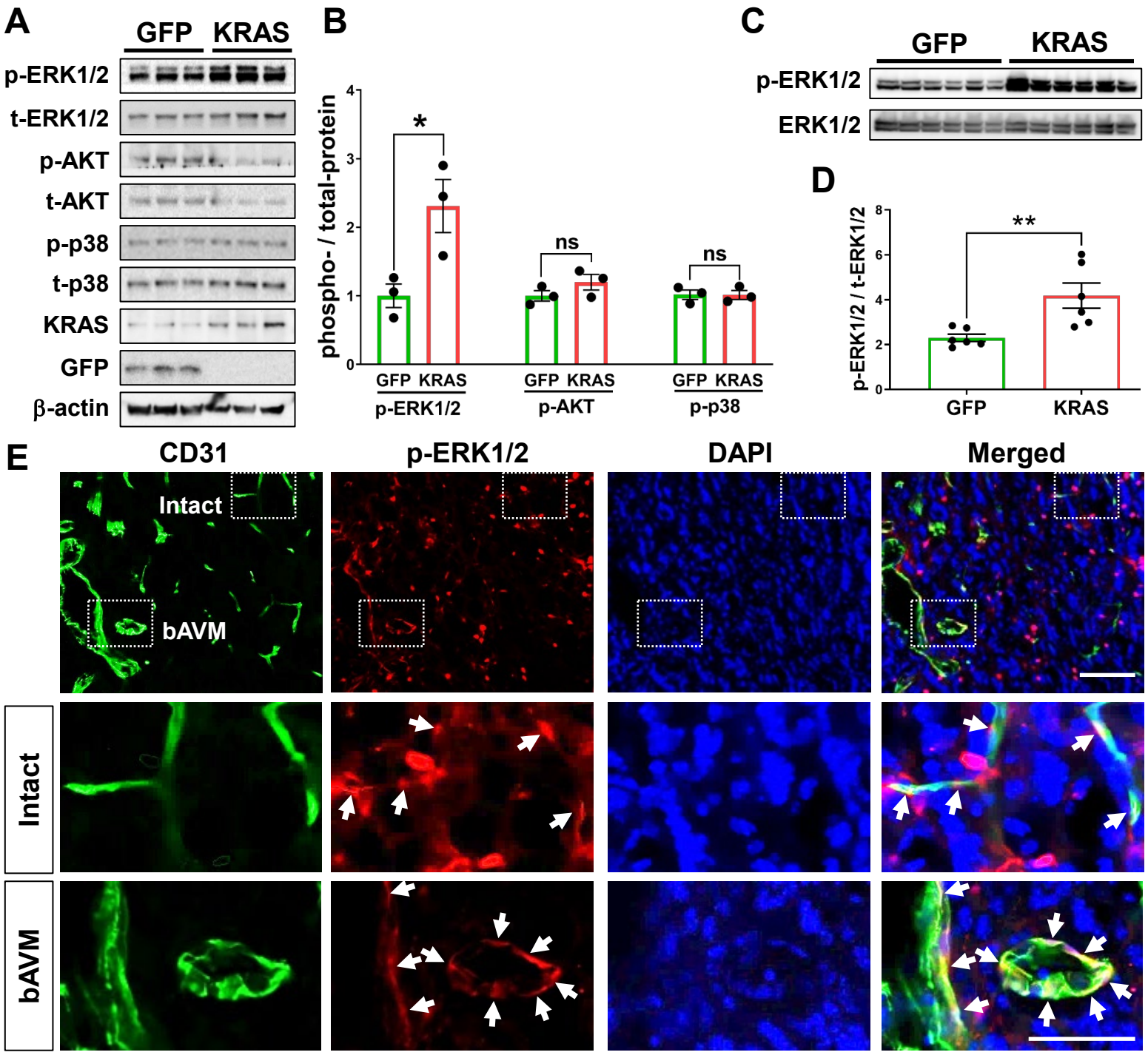






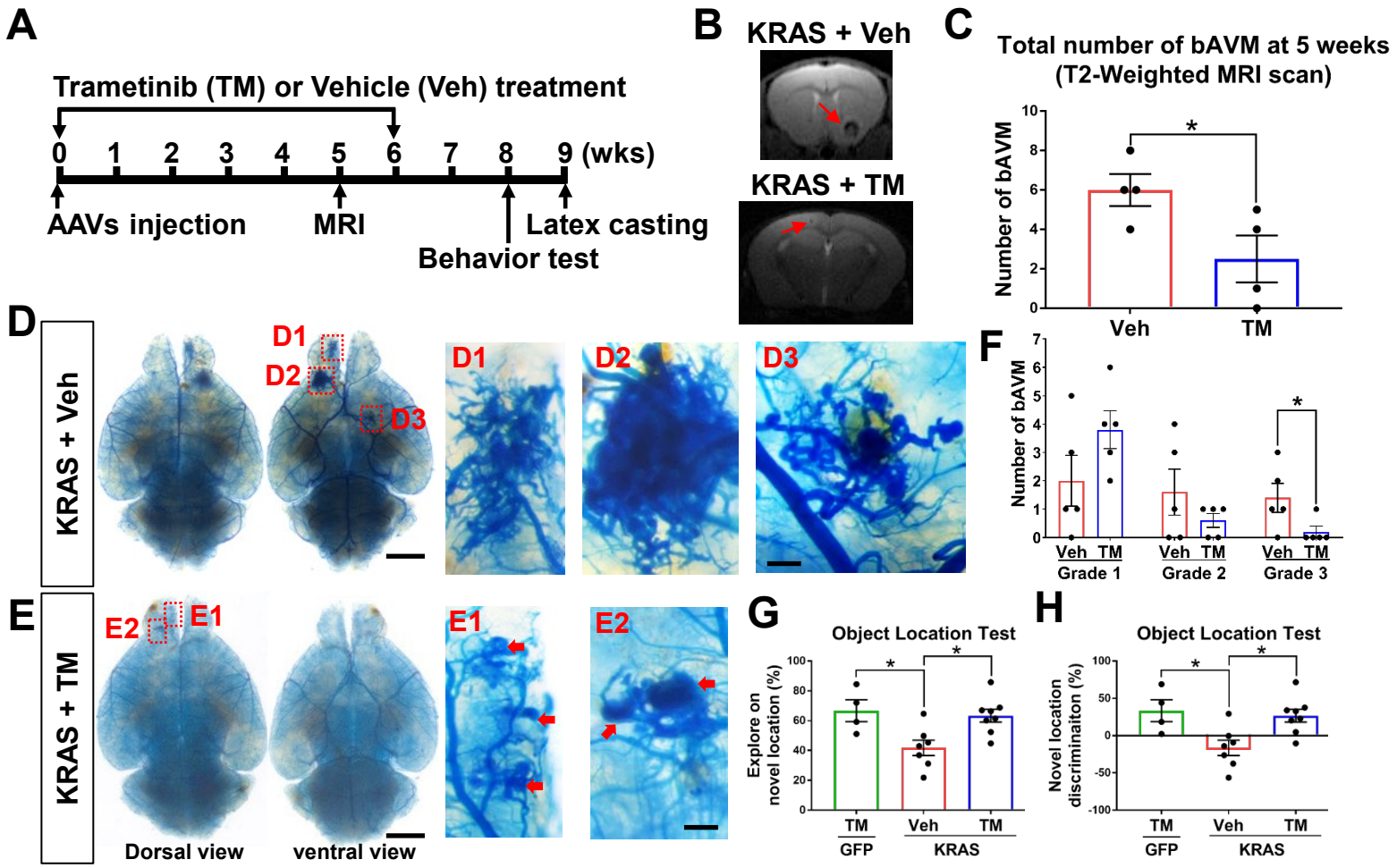
Results

MEK/ERK signaling is activated in cerebral microvascular endothelial cells and $KRAS^{G12V}$-induced bAVMs.



Results

Pharmacological MEK/ERK Inhibition Attenuates Mutant KRASG12V-Induced bAVM Growth



Summary

1. Viral mediated brain endothelial $KRAS^{G12V}$ overexpression induces sporadic bAVMs in a mouse model.
2. This study support the conclusion of KRAS mutations play an important role in human sporadic bAVMs.
3. bAVMs are accompanied by several pathological events, such as focal angiogenesis, hemorrhages, and neuroinflammation.
4. $KRAS^{G12V}$ – induced bAVM growth is attenuated by the inhibition of MEK/ERK signaling (using an FDA approved agent, trametinib).
5. Using our novel animal model of bAVMs will provide new insights into the underlying pathophysiology of sporadic bAVMs and develop new therapeutic strategies for patients with bAVM.

Funding support: Weatherhead Foundation
AVM Research Foundation