Cavernous Angioma 2019
A Scientific Summary

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Angioma Alliance
Chief Scientific Officer
Genetics of Cavernous Angioma

Sporadic and Inherited Forms
- Solitary vs multiple lesions

3 Genes for Cavernous Angioma
- *CCM1* (1999)
- *CCM3* (2005)

Determining the function of these gene products is a major focus of research related to drug development for both sporadic and familial CCM.
A year in basic research – published studies

- Low fluid shear stress conditions contribute to activation of cerebral cavernous malformation signaling pathways (Gamble group, November 2019)
- Long-term antithrombotic therapy and risk of intracranial hemorrhage from cerebral cavernous malformations: a populations-based cohort study, systematic review, and meta analysis (Flemming & Salman, October 2019)
- Blood flow vascular anomalies in a zebrafish model of cerebral cavernous malformations (Rodel et al, September 2019)
- Phenotypic evaluation of quantitative susceptibility and contrast-enhanced permeability MR sequences across patient data sets (Awad group September 2019)
- A Brain Targeted Orally Available ROCK2 inhibitor Benefits Mild and Aggressive Cavernous Angioma Disease (BioAxone August 2019)
- Transcriptome clarifies mechanisms of lesion genesis versus progression in models of Ccm3 cerebral cavernous malformations (Awad Group, August 2019)
- Biomarkers of cavernous angioma with symptomatic hemorrhage (Awad group June 2019)
- Endothelial cell clonal expansion in the development of cerebral cavernous malformations (Dejana group, June 2019)
- Precise CCM1 gene correction and inactivation in patient-derived endothelial cells: Modeling Knudson's two hit hypothesis in vitro (Felbor group, May 2019)
- Systems-wide analysis reveals new roles of CCM signal complex (CSC) (Zhang Group, May 2019)
- A conserved CCM complex promotes apoptosis non-autonomously by regulating zinc homeostasis (Derry Group, April 2019)
- Postzygotic mosaic in cerebral cavernous malformation (Felbor group March 2019)
- Rho Kinase Inhibition Blunts Lesion Development and Hemorrhage in Aggressive Pdcd10/Ccm3 Disease (Awad & Marchuk, February 2019)
- Plasma Biomarkers of Cavernous Angioma with Symptomatic Hemorrhage (CASH) (Awad group January 2019)
- Cerebral cavernous malformations form an anticoagulant vascular domain in humans and mice (Lopez & Ginsberg, January 2019)
- Biallelic CCM3 mutations cause a clonogenic survival advantage and endothelial cell stiffening (Felbor & Rath, December 2018)
- Atorvastatin Treatment of Cavernous Angiomas with Symptomatic Hemorrhage Exploratory Proof of Concept (Atorva & Ponatinib in Mice, November 2018)
### CCM Treatment Pipeline

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<tr>
<th>Pre-Clinical</th>
<th>Phase One</th>
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Rho Kinase Inhibitors Target Cell Junctions

From Fischer et al, 2013. Trends in Molecular Medicine
Why study atorvastatin?

• Treated mice show fewer lesions and less bleeding
• Expect statin therapy to restore junctions and to see a decrease in QSM signal (iron on the brain)

(Awad, U Chicago)
Tempol/REC-994 restores the balance of reactive free oxygen species.
CCM Treatment Pipeline

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B-cell depletion therapy reduces mature lesions

Awad 2016
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Prior Therapeutic Use - Propranolol

- Case reports successful treatment
  - Child with giant infantile cavernous
  - Adult females (2) with symptomatic hemorrhage


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Gut-Brain Axis & CCM Lesion Development

**Bacteria** Signals travel through blood stream

TLR4 Receives Signal

Stimulates MEKK3-KLF2/4 Signaling & Lesion Development

Drug Hypothesis: Change bacteria in gut, or block TLR4 to prevent lesion development
Anti-Angiogenic Molecules rescues tight junction defects and inhibits lesion development

MEKK3 inhibitor, Ponatinib, inhibits lesion formation in Ccm1 mice

Choi et al, 2018