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Angioma Alliance

Chief Scientific Officer

Cavernous Angioma 2019
A Scientific Summary

ANGIOMA ALLIANCE

because brains shouldn't bleed

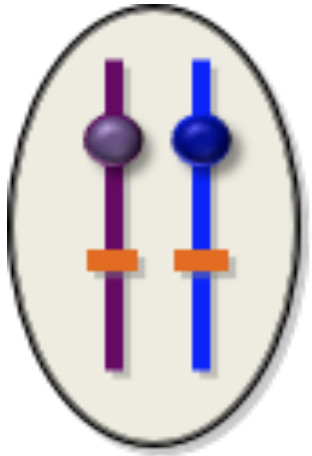
Genetics of Cavernous Angioma

Sporadic and Inherited Forms

- Solitary vs multiple lesions

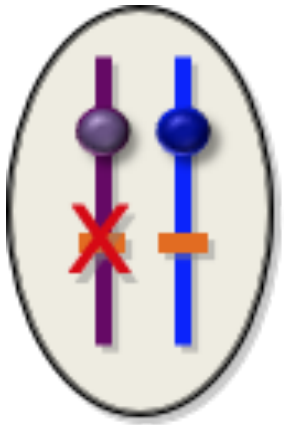
3 Genes for Cavernous Angioma

- ***CCM1*** (1999)
- ***CCM2*** (2003)
- ***CCM3***(2005)

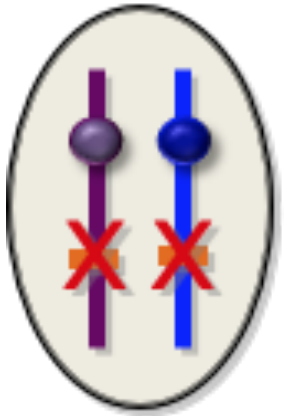


Wildtype

1 Mutant Copy



2 Mutant Copies



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 activatio…ous malformation signaling pathways (Gamble group, November 2019)
- Long-term antithrombotic therapy and risk of intracrania…m cerebral cavernous malformations: a populations-based coho…ly, systematic review, and meta analysis (Flemming & Salman, October 2019)
- Bl…cular anomalies in a zebrafish model of cerebral cavernous malformations (Rodel et al, September …
- Ph…ntitative susceptibi…rast-enhanced permeability MR sequences across i…019)
- A…ailable ROCK2 inh… Aggressive Cavernous Angioma Disease (BioAxone August 2019)
- Transcriptome clarifies mechanisms of lesio…sion in models of Ccm3 cerebral cavernous malformations (Awad Group, August 2019)
- Biomarkers of cavernous angioma with sym…wad group June 2019)
- Endothelial cell clonal expansion in the development of cerebral cavernous malfo… 2019)
- Precise CCM1 gen…activation in patient-derived endothelial ce… hypothesis in vitro (Felbor group, May 2019)
- Systems-wide a…w roles of CCM signal complex (CSC) (Zhang C…)
- A conserved CC…poptosis non-autonomously by regulating zinc homeostasis (Derry Group, April 2019)
- Postzygotic mosai…vernous malformation (Felbor gr… 2019)
- Rho Kinase Inhibition Blunts Lesion Development and H…ssive Pdcd10/Ccm3 Disease (Awad & Marchuk, February 2019)
- Plasma Biomarkers of Cavernous Angioma with Sympto…up January 2019)
- Cerebral cavernous malformations form an anticoagulant vascular do…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 (…18)
- Ponatinib (AP24534) inhibits MEKK3-KLF signaling and prevents formation and progression of cerebral caverno…vember 2018)

Fluid Stress

Biomarkers

Anti-thrombotics

BA-1049 in Mice

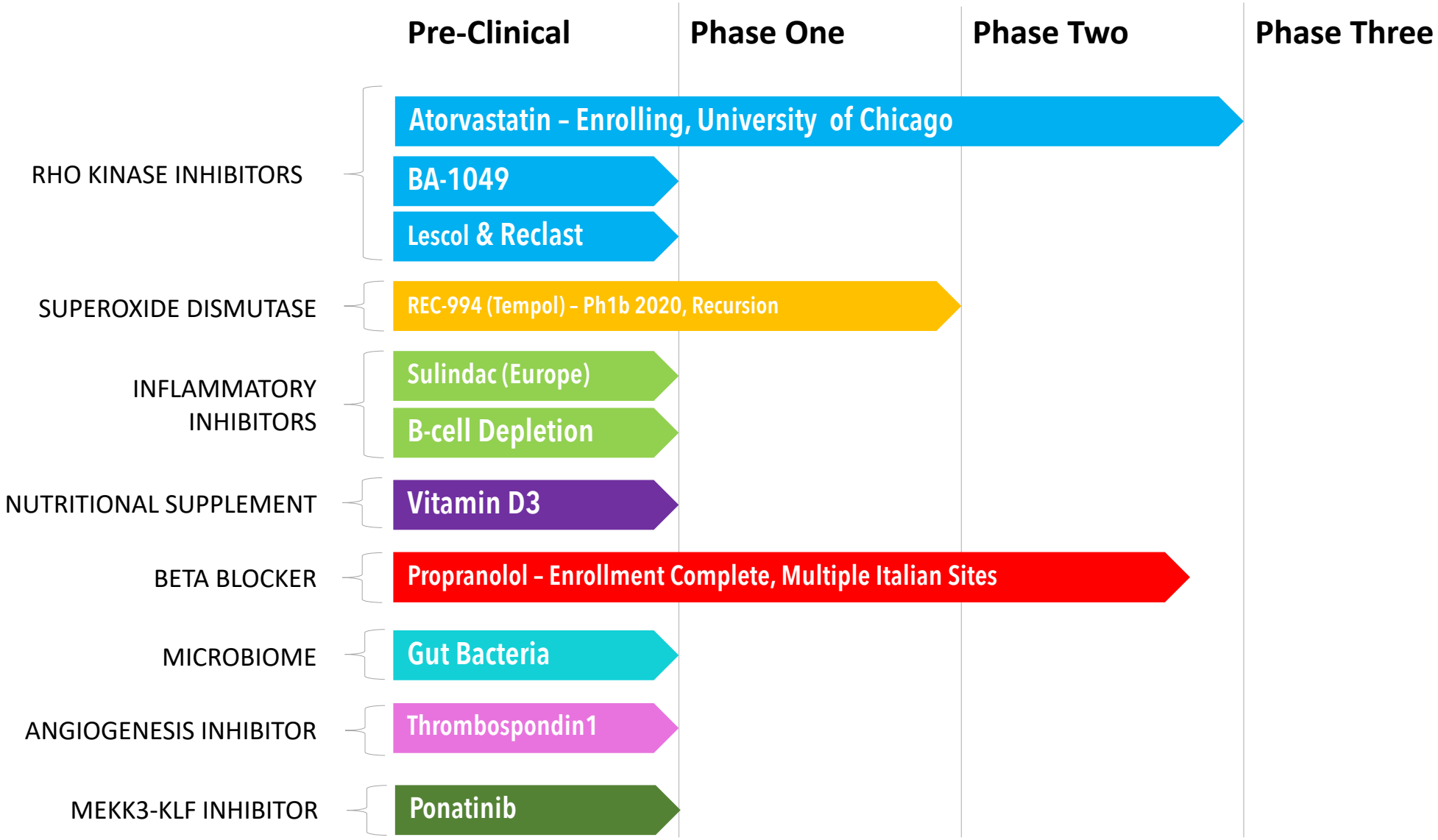
Clonal Expansion

Gene Therapy

Transcriptome

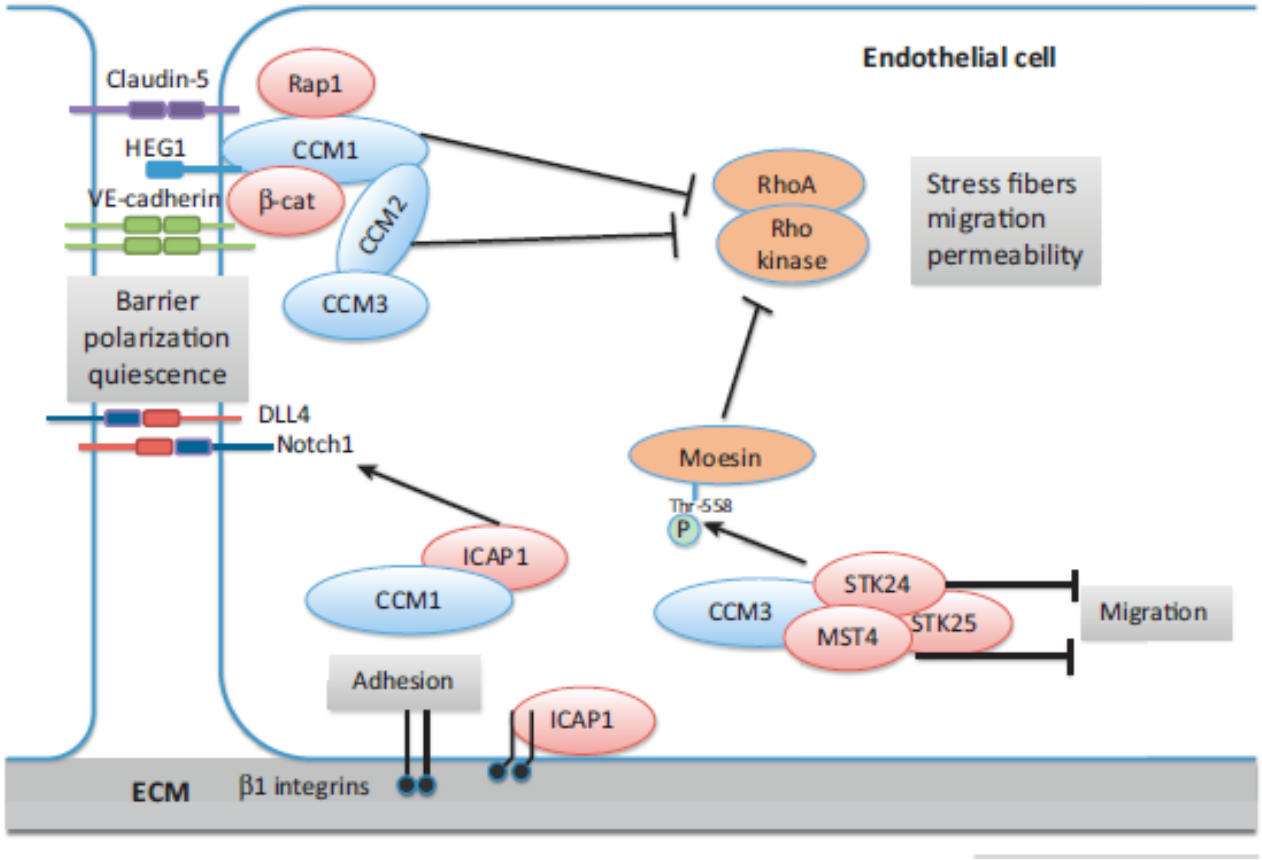
Atorva & Ponatinib in Mice

CCM Treatment Pipeline



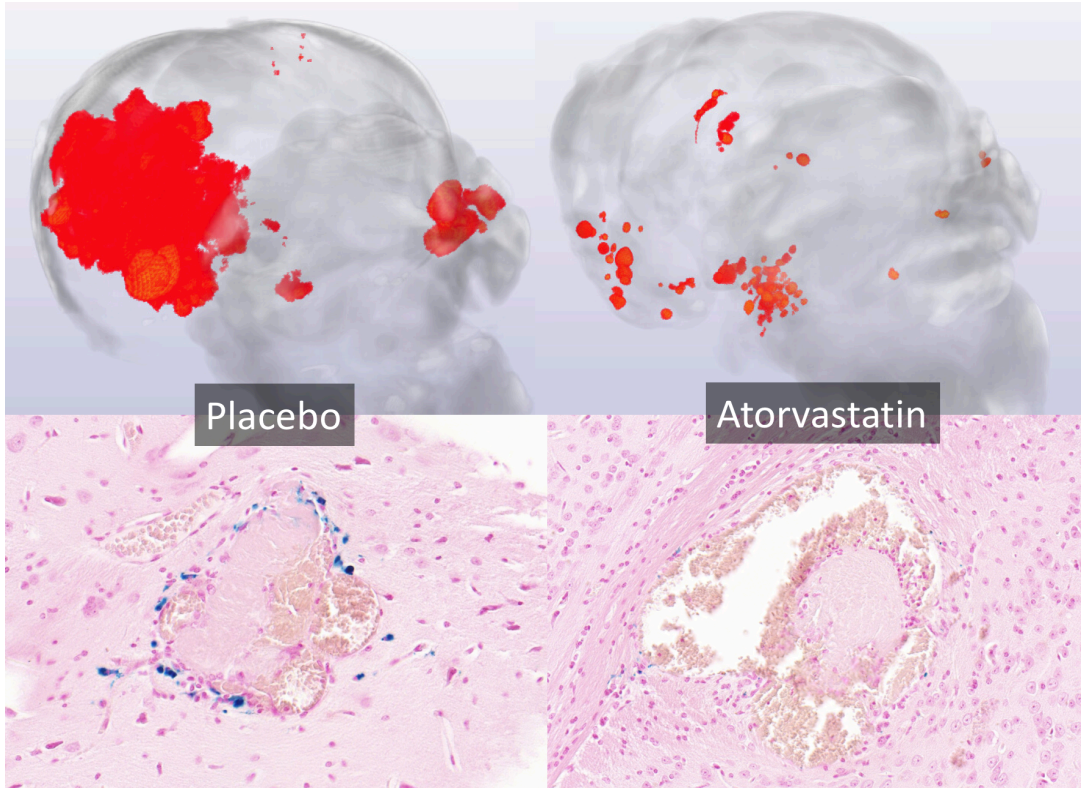
Rho Kinase Inhibitors Target Cell Junctions

From Fischer et al, 2013. Trends in Molecular Medicine



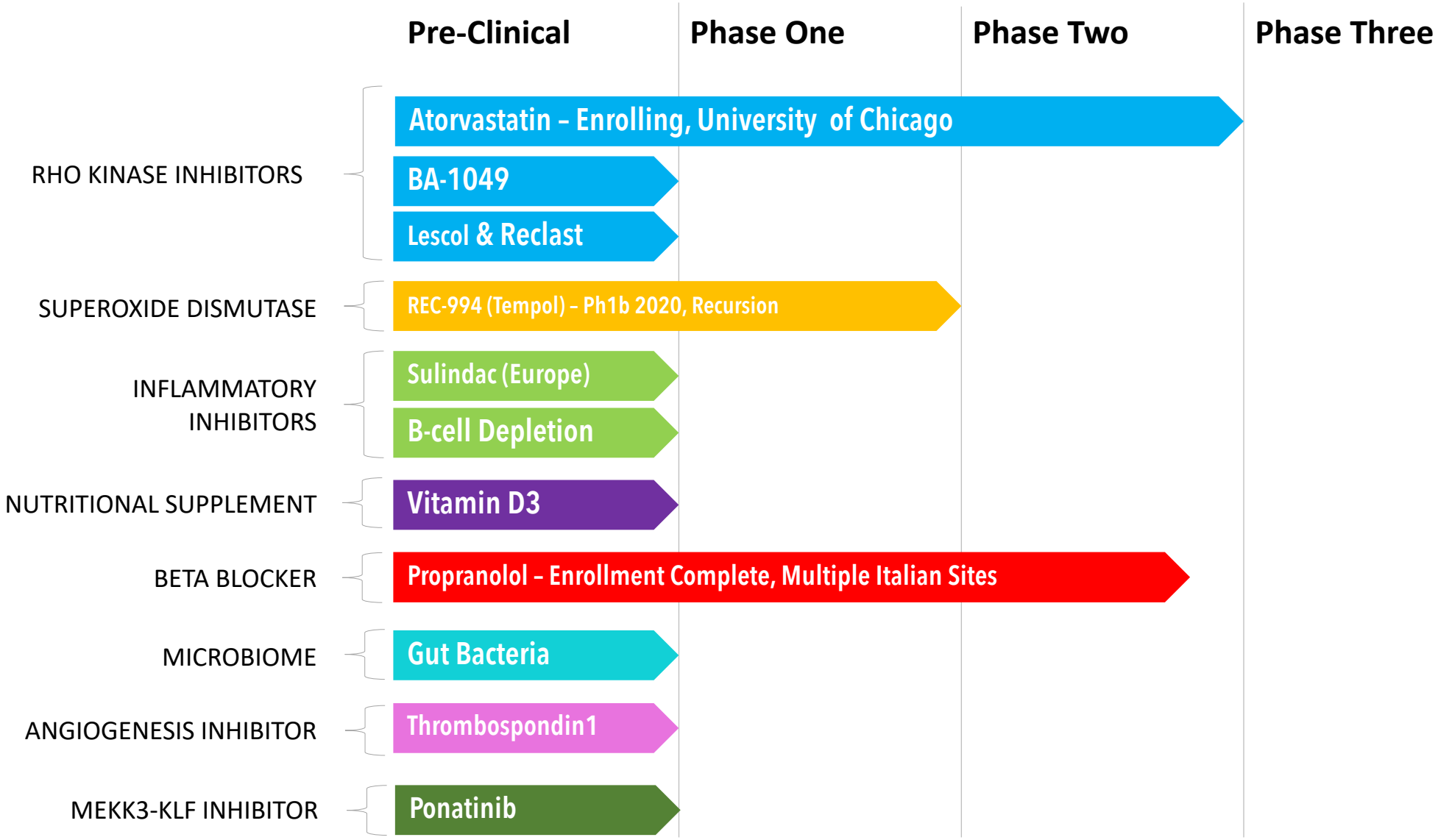
Why study atorvastatin?

- 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)

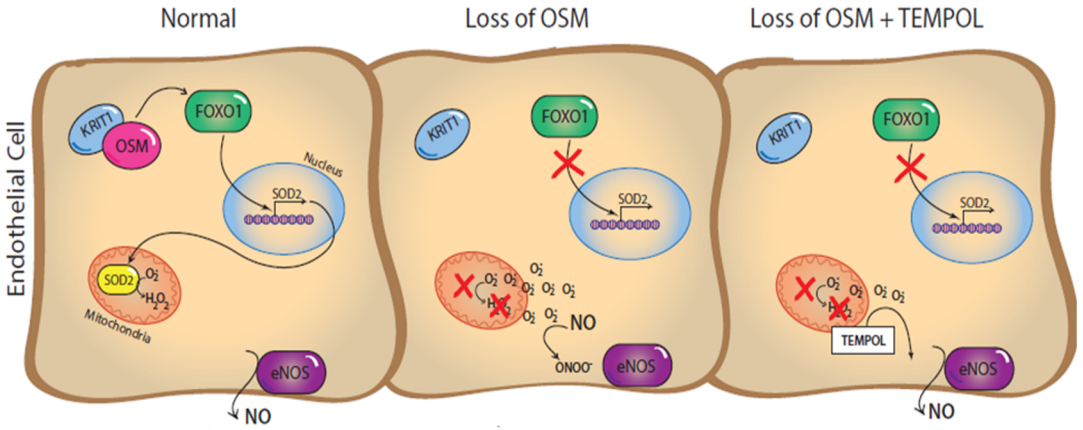


(Awad, U Chicago)

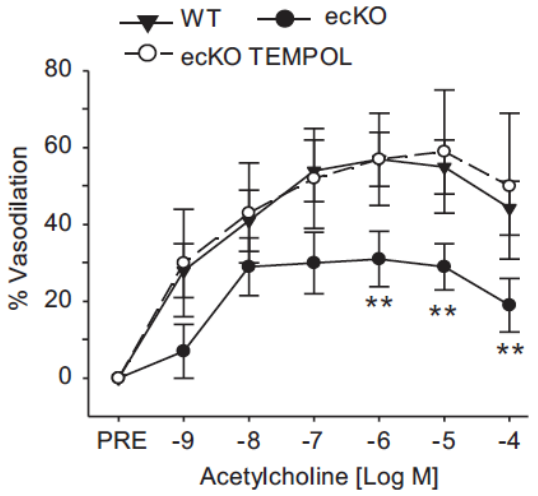
CCM Treatment Pipeline



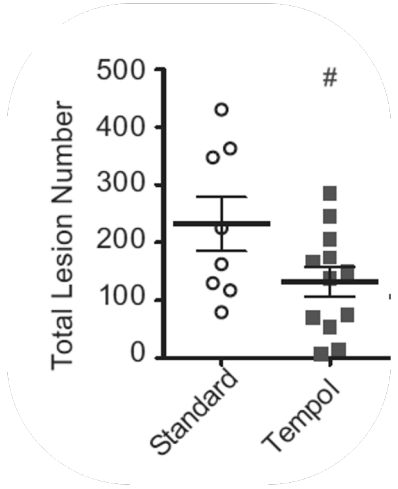
Tempol/REC-994 restores the balance of reactive free oxygen species



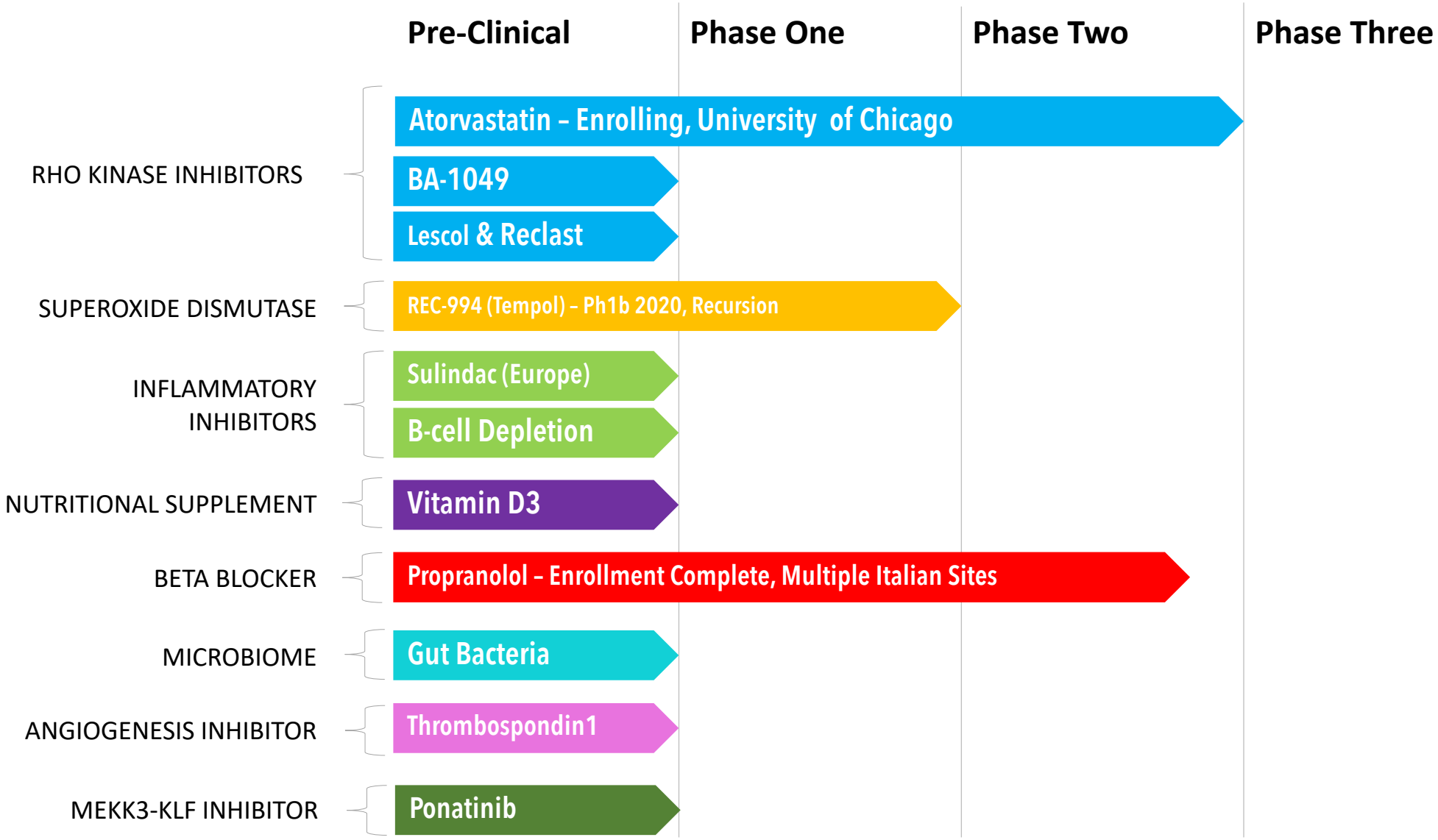
Tempol treatment rescues vasodilation defect



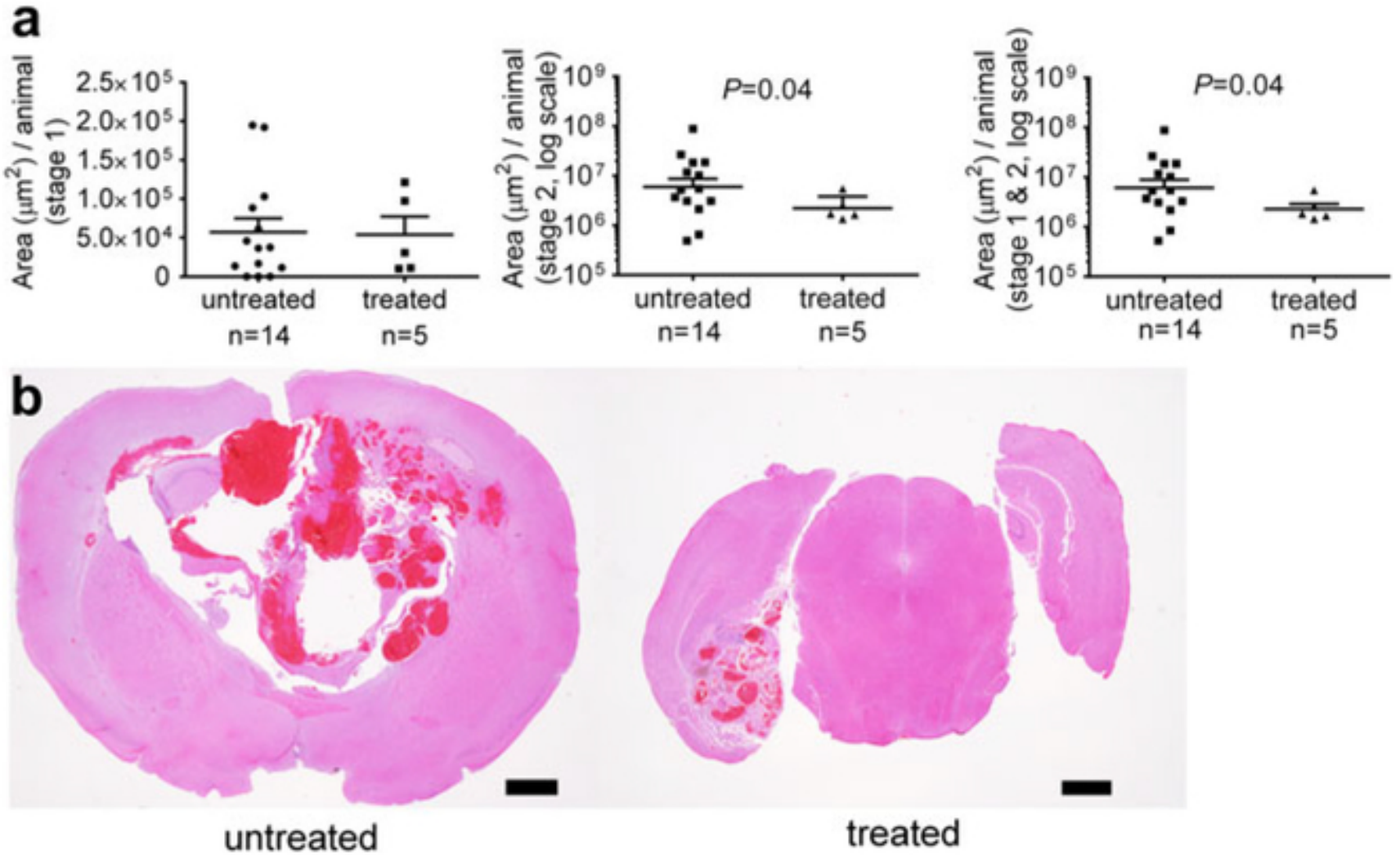
Tempol treatment reduces CCM Lesion Number



CCM Treatment Pipeline

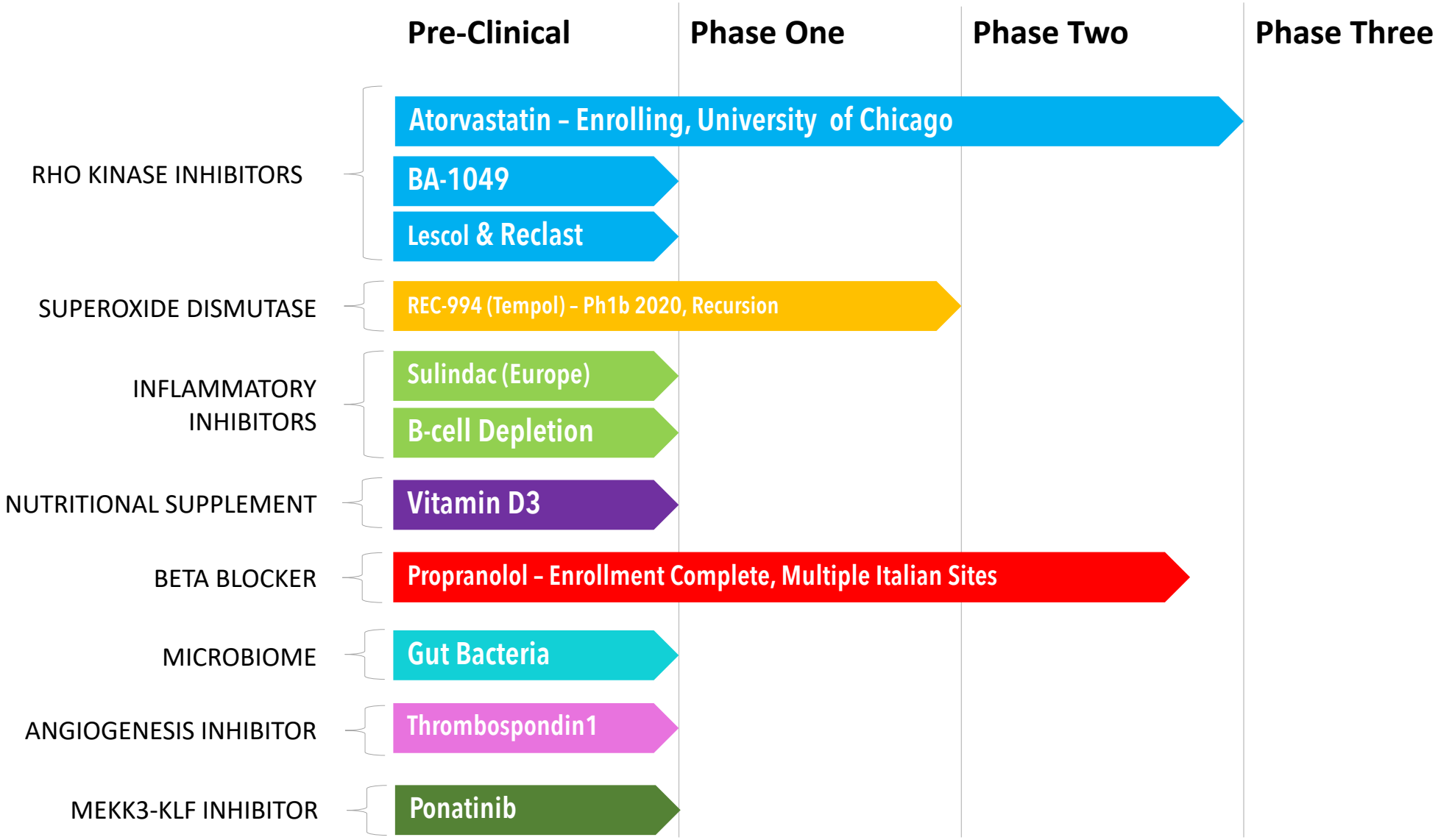


B-cell depletion therapy reduces mature lesions



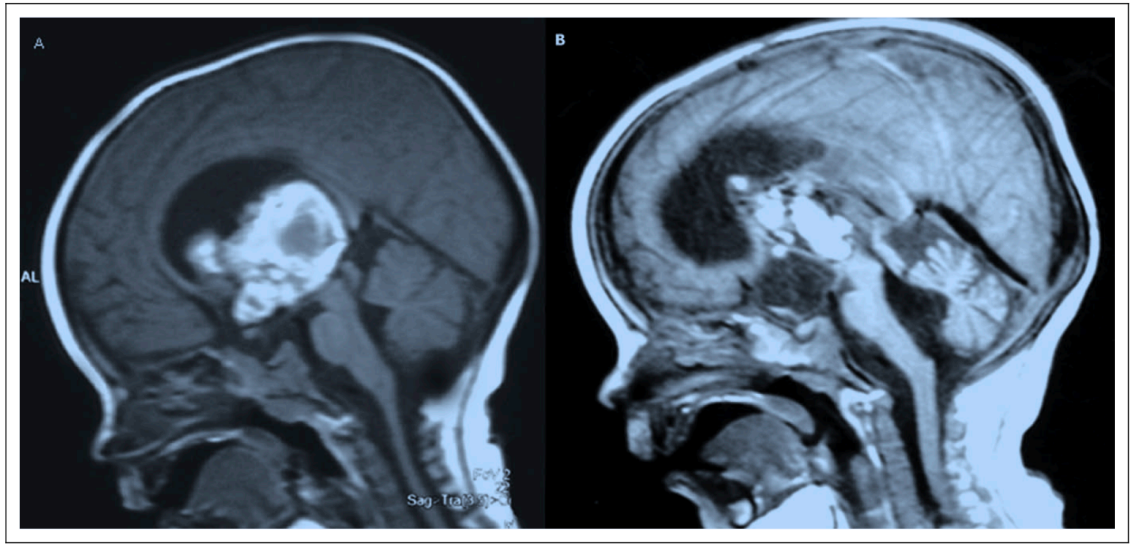
Awad 2016

CCM Treatment Pipeline

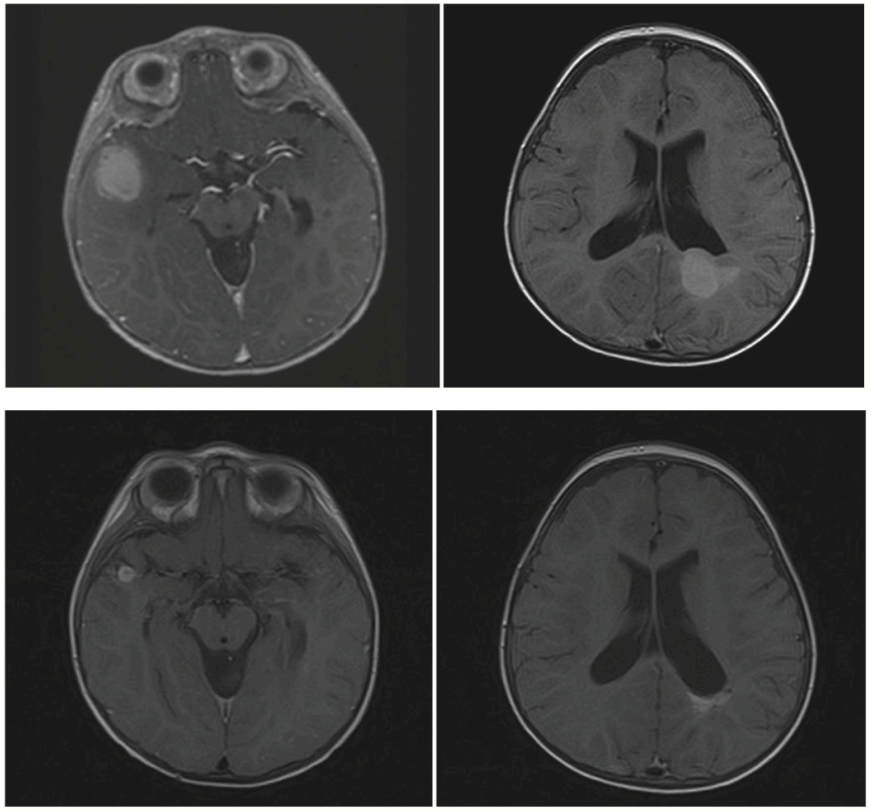


Prior Therapeutic Use - Propranolol

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

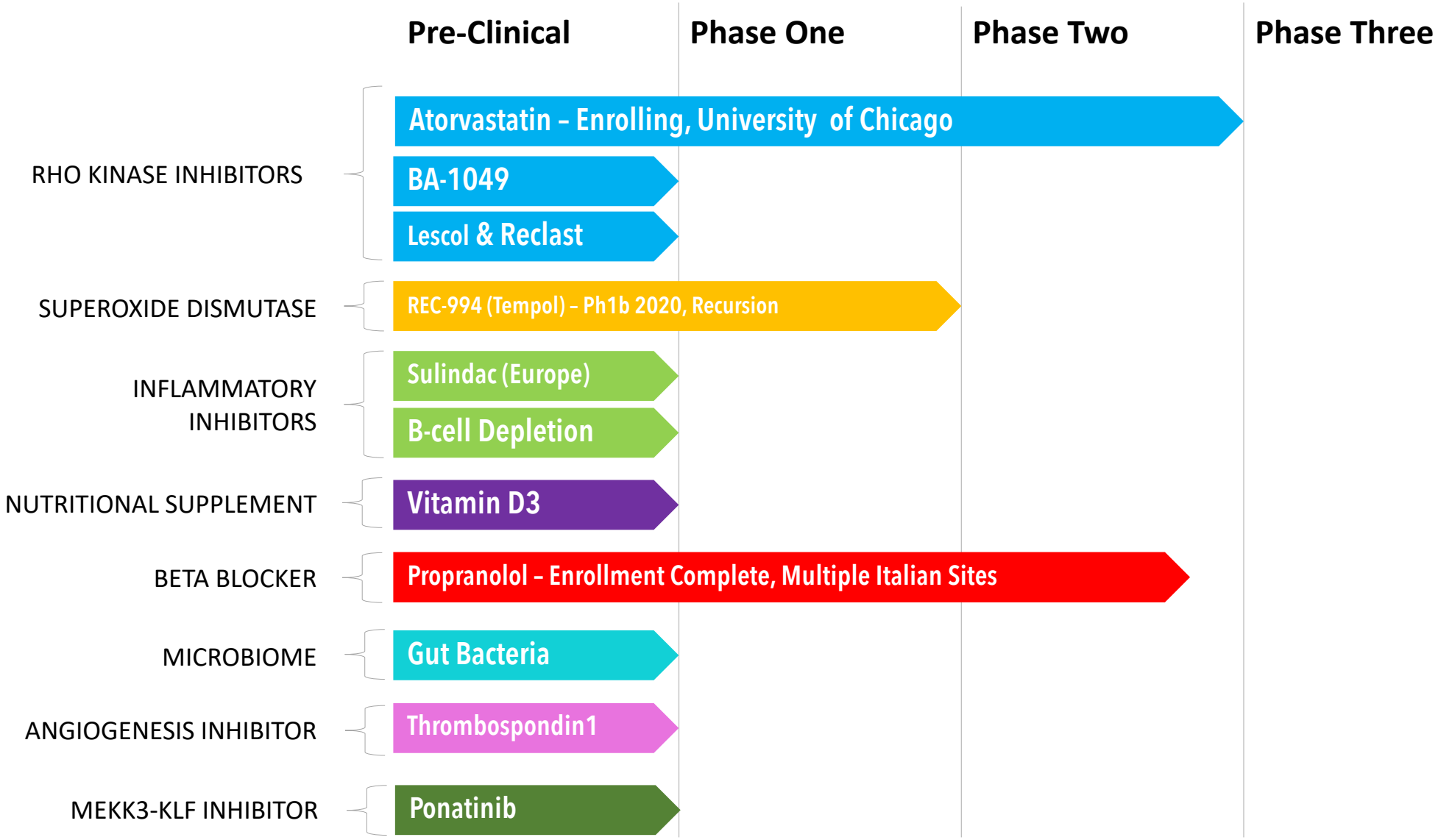


J Child Neurology. 2010. 25(5) 653-655.



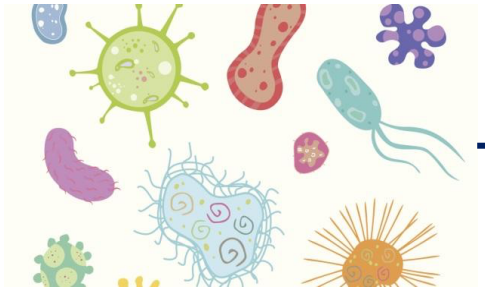
Clin Pediatr. 2014 Feb;53(2): 189-90.

CCM Treatment Pipeline



Gut-Brain Axis & CCM Lesion Development

Bacteria Signals travel through blood stream

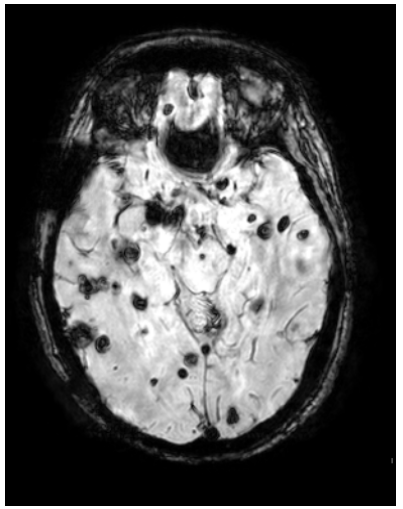


→

TLR4 Receives Signal

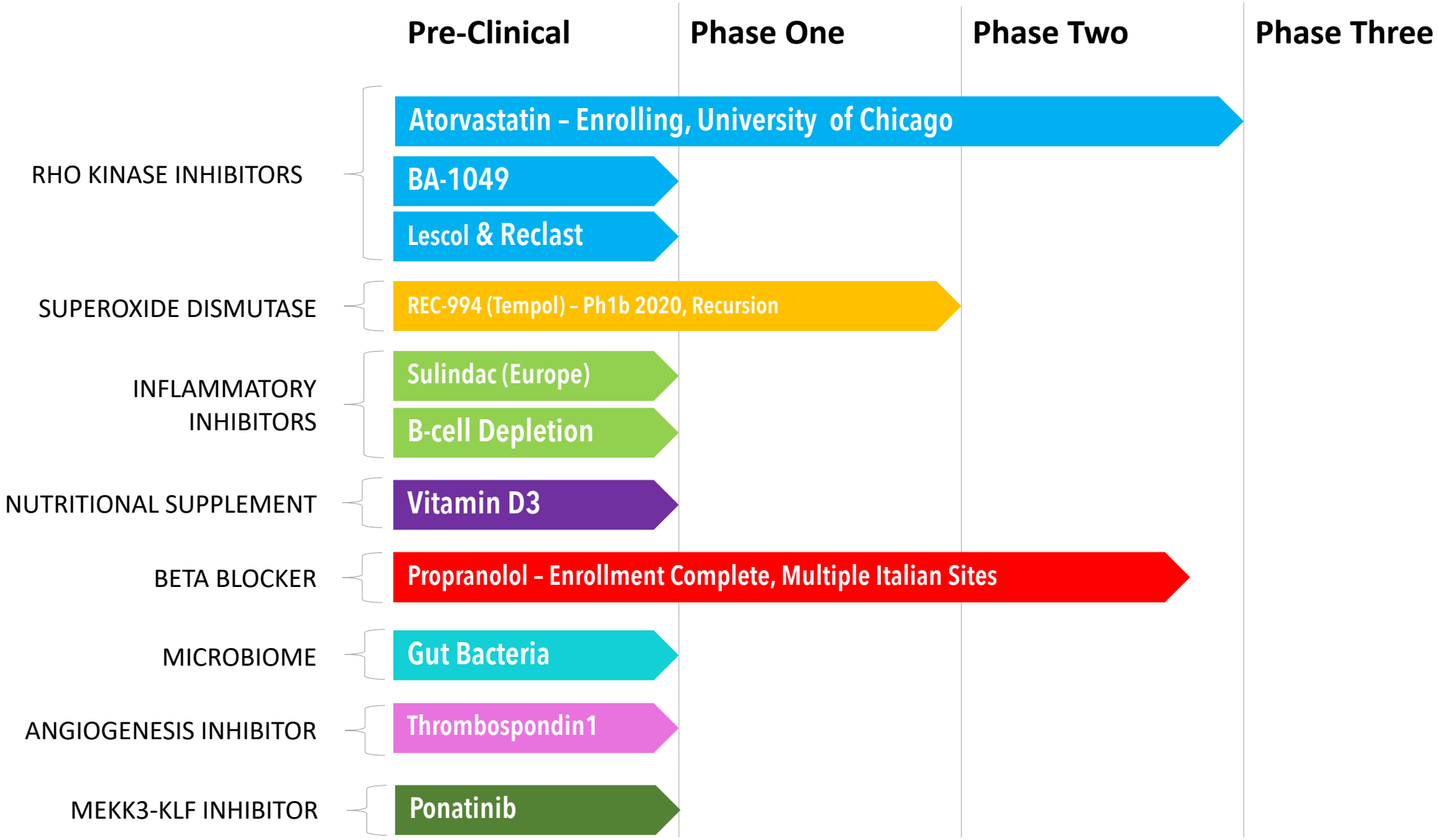
→

Stimulates MEKK3-KLF2/4 Signaling & **Lesion Development**



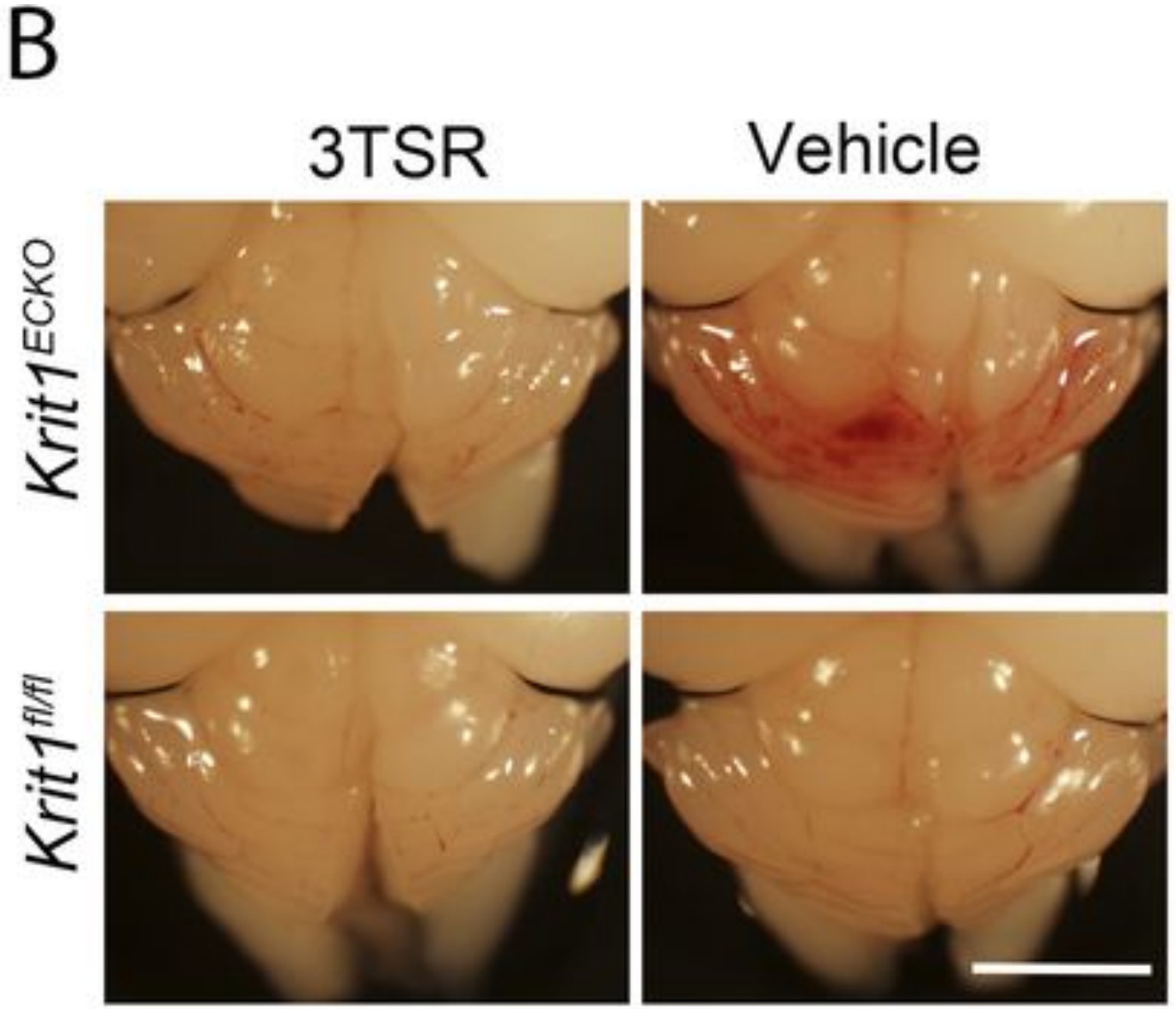
Drug Hypothesis: Change bacteria in gut, or block TRL4 to **prevent lesion development**

CCM Treatment Pipeline

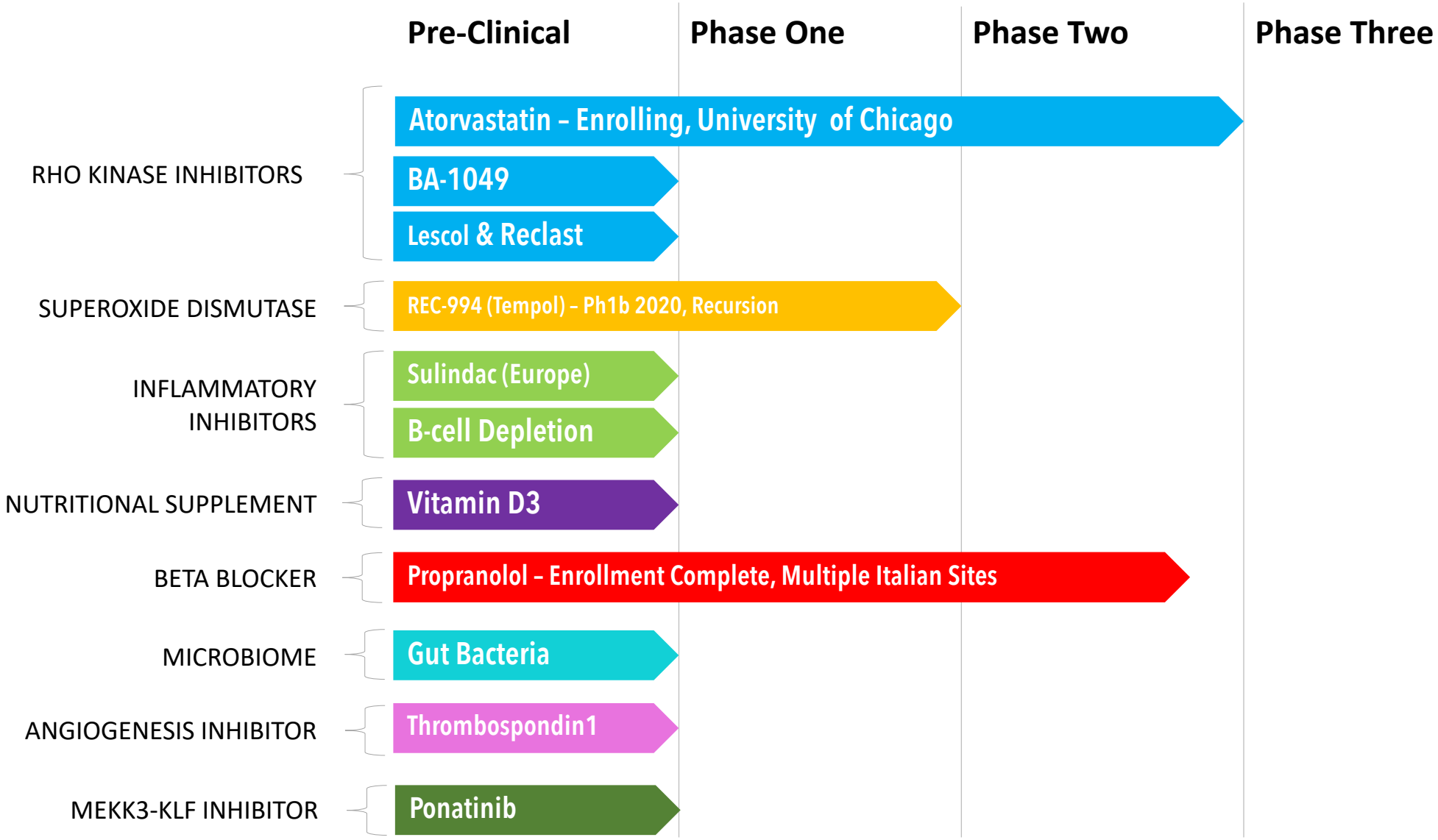


Anti-Angiogenic Molecules rescues tight junction defects and inhibits lesion development

Miguel Alejandro Lopez-Ramirez et al. J Exp Med 2017;214:3331-3346

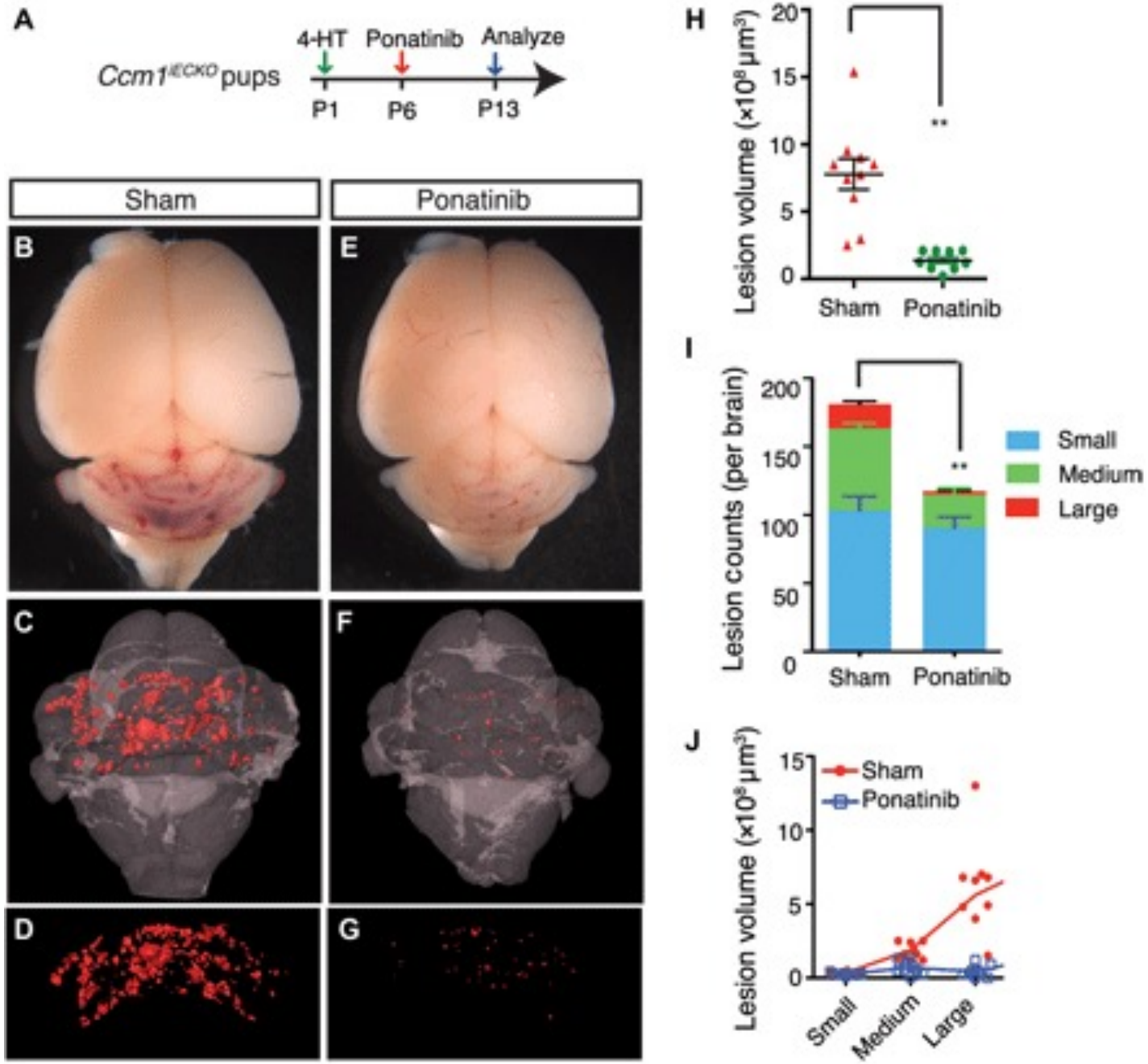


CCM Treatment Pipeline

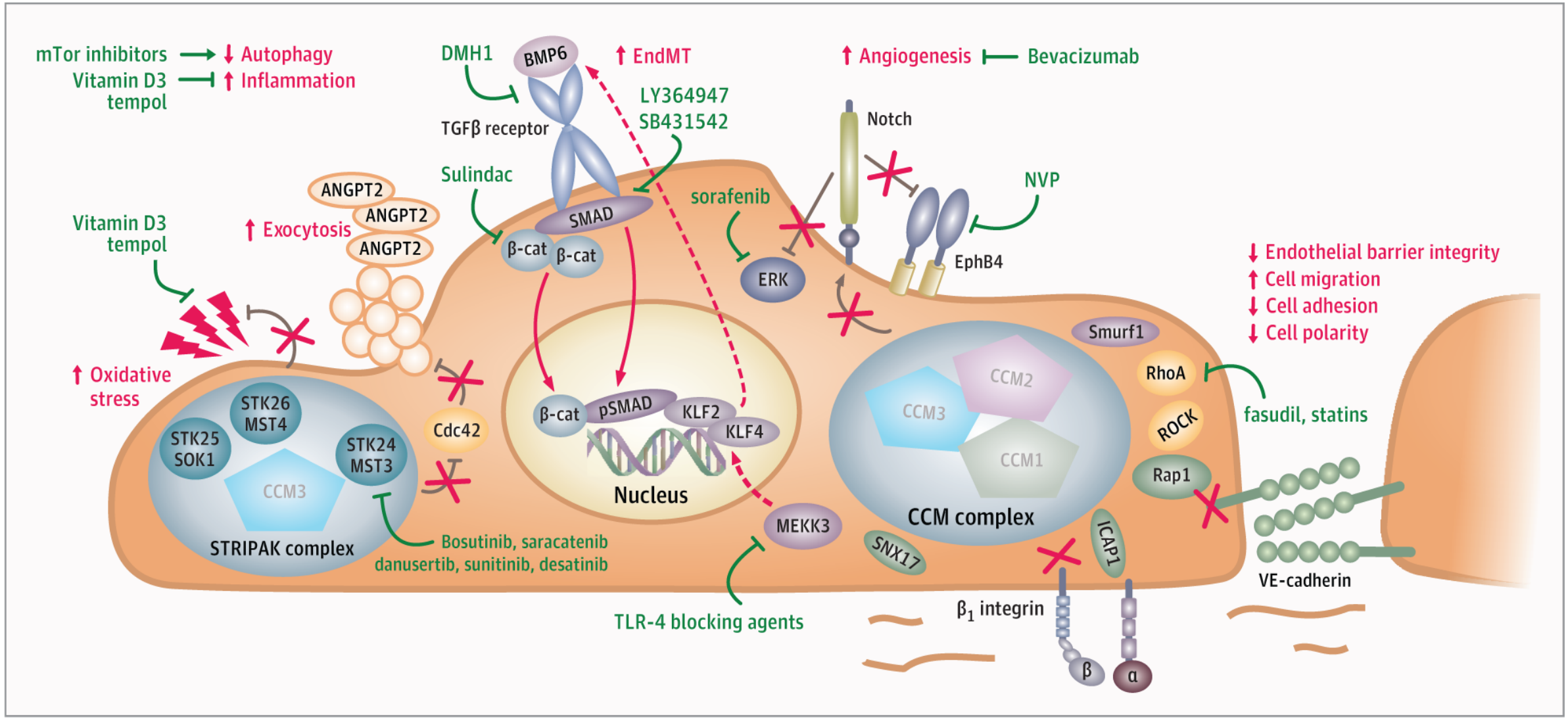


MEKK3 inhibitor, Ponatinib, inhibits lesion formation in *Ccm1* mice

Choi et al, 2018



B CCM EC and proposed pharmacologic approaches



Chohan et al, 2019