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Review Article

Arteriovenous Malformations: An Update on Models and Therapeutic Targets

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Abstract

Arteriovenous malformations (AVMs) are an anomaly of the vascular system where feeding arteries are directly connected to the venous drainage network. While AVMs can arise anywhere in the body and have been described in most tissues, brain AVMs are of significant concern because of the risk of hemorrhage which carries significant morbidity and mortality. The prevalence of AVM's and the mechanisms underlying their formation are not well understood. For this reason, patients who undergo treatment for symptomatic AVM's remain at increased risk of subsequent bleeds and adverse outcomes. The cerebrovascular network is delicate and novel animal models continue to provide insight into its dynamics in the context of AVM's. As the molecular players in the formation of familial and sporadic AVM's are better understood, novel therapeutic approaches have been developed to mitigate their associated risks. Here we discuss the current literature surrounding AVM's including the development of models and therapeutic targets which are currently being investigated.

Key words: spontaneous intracranial hypotension ; bibliometric ; research progress ; cite space

Introduction

A brain arteriovenous malformation (bAVM) is a disordered mass of blood vessels in the brain. Vascular lesions are formed where feeding cerebral arteries are directly connected to draining veins with no capillary bed between them [1]. An AVM can occur anywhere in the body; however symptomatic presentation usually occurs due to AVMs that have formed in or near the brain or spinal cord[2].

Prevelence

While it is understood that the rate of cerebral AVM occurrence is similar in males and females, the exact prevalence in the general population is unknown [3, 4]. Studies that have attempted to estimate a population-based AVM prevalence have either suffered from small population size or biased reporting techniques [3, 5]. An inference from the incidence data reported in the New York Island AVM Study estimates the AVM prevalence to be less than 10.3 per 100,000[3]. It is however likely that the prevalence and incidence of AVMs are different in other populations around the world [6-8]. AVM prevalence data is further complicated due to increased incidental detection of asymptomatic AVMs after unrelated brain imaging [9, 10]. This has led researchers to believe that the actual prevalence of AVM is much higher in the general population [2]. A 1978 autopsy study estimated that only 12% of AVMs become symptomatic, but no recent studies have corroborated this finding [11].

Diagnosis and Presentation

Depending on size and location, the risk of cerebral AVM rupture could be high, resulting in intraventricular or intracerebral hemorrhage, and subsequent symptoms such as seizures, cephalalgia, and myasthenia [12]. AVM rupture is the most common cause of hemorrhagic stroke in children and young adults [13, 14]. Meta-analysis and natural history studies have reported an annual hemorrhage rate of 2% - 4%, and an annual mortality rate of about 1% for AVMs of all sizes [15-17]. An unruptured AVM can also cause symptoms due to mass effect or cerebral ischemia of surrounding tissues [18]. AVMs are found in all age groups. However, on average, symptomatic presentation occurs in young adults in their third or fourth decades of life [19].Besides brain hemorrhages, other symptoms associated with AVMs include headaches, seizures, focal neurological signs, and spontaneous intracerebral or subarachnoid hemorrhages [20]. While patients with AVMs may present with a wide variety of symptoms, overall, an estimated 88% of AVM patients are asymptomatic, making identifying AVMs challenging [21]. Previously, the gold standard for diagnosing AVMs was with angiography [22]. With advancements in radiologic technology, MRI and especially CT have

become the gold standard for identifying, visualizing, and diagnosing AVMs in patients [23, 24].

Etiology

The pathogenic mechanisms surrounding the development and rupture of cerebral AVMs are also not yet fully understood. Historically, AVM formation was considered to be solely the result of a congenital abnormality [25]. Recent studies have however revealed AVM formation and rupture to be dynamic and multifactorial processes in which genetic factors may play a small role [26]. The majority of familial AVM cases (about 5% of all AVM cases) are associated with hereditary hemorrhagic telangiectasia (HHT) and capillary malformation–arteriovenous malformation syndrome, both of which are autosomal dominant inherited genetic conditions. [27, 28]) Preclinical investigations have attempted to isolate the genes that lead to cerebral AVM in these diseases. It has been shown that congenital mutations in the TGF-β and RAS vascular signaling pathways result in an increased risk of cerebral AVM formation [29, 30]. This research has primarily been focused on the genes that code for Endoglin (ENG) and Activin A receptor type II-like 1 (ALK1) [27, 28, 31].

About 95% of AVM cases are not related to familial conditions [32]. The causative agents for these de-novo AVMs are also largely unknown. Recent studies have linked somatic mutations in the RAS-MAPK pathway to sporadic AVM development [33, 34].Additionally, abnormal endothelial and mural cells have been found in ruptured AVM vasculature [35, 36]]. As further discussed here, researchers are characterizing various vascular findings such as endothelial hyperplasia, cellular involvement in the breakdown of the blood-brain barrier, and reduction in pericyte and smooth muscle cell populations to potentially elucidate mechanisms leading to AVM formation, and to create therapies for the prevention of AVM rupture[37-40]].

Treatment and management

Currently, multiple therapies are available to treat AVMs, such as neurosurgery, embolization, or stereotactic radiosurgery (SRS). Even with the multiple treatment options currently available to treat AVMs, some studies have suggested that medical management alone can provide better outcomes for patients than those that received intervention prior to AVM ruptures[21, 41]. The study most cited in favor of conservative treatment is the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformation) trial completed with published short-term [42]and long-term [41]results. Researchers showed both a clinical and significant decrease in the risk of stroke and death in patients who received medical management alone compared to those who underwent prophylactic interventional therapy to treat unruptured AVMs. A follow-up study done in 2022 challenged these findings and suggested that conservative approaches to AVM treatment following the results of the ARUBA trial created a higher rate of AVM rupture and mortality. Researchers compared the AVM rupture and mortality rates in patients before and after the ARUBA trial. The study showed a 3-fold increase in both AVM rupture and mortality rate [DOI:10.1161/SVIN.122.000442]. Regardless of whether conservative treatment is the best option for patients, there remains a need for novel treatments for AVMs as our current therapies still have poor outcomes. Studies have shown that endovascular embolization increased the number of complications from surgery compared to the curative goal [43]. Stereotactic radiosurgery has been shown to be effective, but total AVM obliteration can take as long as two years post-surgery [44]. In addition to the lag time between treatment and desired results, patients often develop seizures post-treatment, of which the etiology is not entirely understood [45]. What complicates AVM treatment further is that there are no established guidelines for treatment [46]. There is a great need for not only novel treatment strategies for AVMs but also established and universal treatment guidelines.

Pre-clinical models of brain arteriovenous malformations

Models of bAVM have undergone significant evolution over the past 50 years driven by scientific and clinical need for models that accurately and consistently replicate human bAVM. Initially, models of bAVM pathophysiology relied upon surgical creation of arteriovenous fistulas and shunts to evaluate alterations in hemodynamics in various animal models **[47]**. Creation of arteriovenous fistulas and shunts often relied upon extracranial anastomosis of carotid-jugular vessels. This technique was first described in 1948 when it was applied towards studying patterns of hemodynamic alterations related to elucidating the pathophysiology of seizure disorders and mental disability [48]. Decades later, this technique was used in a different context towards understanding hemodynamics of bAVM. One of the first models attempting to replicate bAVM pathophysiology *in vivo* implemented an arteriovenous fistula to shunt blood from the Circle of Willis to the internal jugular vein in rhesus monkeys to evaluate changes in hemodynamics [49, 50]. Adoption of this technique expanded to other model systems, namely murine, feline, and large animal models such as sheep, to simulate the physiology of bAVM and to evaluate safety and efficacy of therapies such as endovascular embolotherapy and radiosurgery [50-54]. Morgan et al 1989 developed a rat model of bAVM using carotid-jugular anastomosis which yielded hemodynamic results that were similar to clinical observations in humans [51]. However, limitations exist for any model system. Surgical introduction of a fistula or shunt may aid in “simulating” hemodynamics of bAVMs but are markedly limited in answering fundamental questions related to the biology of bAVM development.

Important to the history of bAVM modeling, swine were observed to possess an anatomical feature known as a rete mirabile. This structure is defined as a plexiform network of interconnected microarteries and angiographically resembles features of human bAVM [55-57]. Pertinent to bAVM biology, this structure lacks arteriovenous communication and to achieve this, surgical puncturing of the rete mirabile is required to divert blood to the cavernous sinus [55]. Anatomically, this structure is also located extracranially. This swine-based model demonstrated fundamental features of human bAVM such as similar hemodynamics but has several limitations. Not only does the model rely upon surgical modification of the rete mirabile, but this structure is also not intimately involved with cerebral microcirculation [55, 57]. Surgical puncture led to proptosis, chemosis, and sub-conjunctival hemorrhage in the ipsilateral eye and occlusion of the shunt within 5-7 days in swine models [55, 57]. Given the time to vessel occlusion, this model is suitable for short-term investigation of bAVM biology. A chronic model of bAVM was developed using the rete mirabile to study mechanisms of vascular remodeling and liquid embolization efficacy [56, 58, 59]. Increased chronicity was achieved by delaying the time to vessel occlusion and creating a fistula large enough to remain patent and allow vascular remodeling of the rete mirabile to occur [56-58]. Safety and efficacy of liquid embolization compounds such as copolymer ethylene vinyl alcohol, n-butyl cyanoacrylate and other novel agents were evaluated using swine-based bAVM models with results demonstrating favorable biocompatibility and effective embolization of surgically induced bAVMs in the rete mirabile[56, 58-60].

Alluded to earlier, swine, feline, murine and large animal models such as sheep utilized extracranial shunts and fistulas to study bAVM biology and therapeutic efficacy. This fails to directly assess the biology of intracranial bAVMs and interactions with cerebral microvasculature. Motivated by this gap in the literature, Pietila et al 2000 developed a canine model of bAVM that depicted angiographic and histopathologic findings comparable to intracerebral bAVMs seen in humans [61]. The design of this canine model relied upon several prerequisites model to best replicate human bAVM biology which include intermediate to large-sized cerebral vessels, similar cerebral angioarchitecture and hemodynamics to

humans, and stimulation of angiogenesis demonstrating abnormal wall structures around the bAVM [61].

Genetically engineered mouse models are ubiquitous in basic and translational research and have offered insight into the molecular and genetic basis of bAVMs, especially in regard to HHT [62, 63]. Aimed at studying the etiology of HHT1, a mouse model was developed harboring a heterozygous knockout of endoglin ($Eng^{+/-}$) to evaluate changes in cerebral vasculature [62]. Compared to wild-type, heterozygotes demonstrated vasculature anomalies including bAVMs. Within the heterozygous group, only 30% of mice demonstrated vascular anomalies, while the homozygous group displayed no vascular anomalies. These results suggest a potential contributory role of endoglin towards the development of bAVMs, but other factors are likely needed given that less than a third of heterozygotes developed bAVMs. Similar to constitutive endoglin knockout, another study utilized a transgenic Cre-recombinase inducible endoglin knockout [64]. 90% of postnatal mice developed a bAVM phenotype when endoglin was knocked out in vascular smooth muscle cells following tamoxifen administration [64]. Other studies have evaluated this murine model of HHT1 with administration of vascular endothelial growth factor (VEGF). When VEGF was administered to heterozygous mice, 8 of the 9 mice developed abnormal cerebral vasculature including bAVMs while homozygous controls did not develop abnormal vasculature [65]. This study provides evidence of synergy between knockout status of endoglin and VEGF, however further study is necessary to elucidate molecular interactions driving these vascular phenomena. As previously referred to, another gene implicated in HHT is activin receptor-like kinase 1 (*Alk1*) [66]. A Cre-recombinase model that conditionally knocks out *Alk1* resulted in 3 phenotypic groups: group 1 with no detectable lesions, group 2 with arteriovenous fistulae and group 3 with AVMs [67]. While conditional knockout resulted in a population of mice that develop AVMs, a limitation of GEMMs is that there is often a lack of consistency of the disease phenotype in mice expressing the genetic alteration [34740197]. Other studies have utilized this conditional knockout model to study hemorrhagic stroke and hemorrhaging from AVMs and these models replicate the AVM phenotype seen with loss of function in *Alk1* [68, 69]].

Transforming growth factor beta has been implicated in the development of neurovasculature [70]. An inducible Cre-recombinase conditional knockout model of *itgb8* and *smad4* evaluated the role of integrin-8-mediated TGF-β activation in cerebral neoangiogenesis [71]. Vascular morphological alterations consistent with capillary dysplasia and bAVM arose in the context of VEGF-induced angiogenesis when TGF-β signaling was disrupted [71]. This study provides evidence that integrin 8 is an important regulator of TGF-β activation in the setting of cerebral angiogenesis and that disruption of this signaling axis could result in the development of an AVM-like phenotype [71]. Of note, in mutants with disrupted TGF-β signaling, vascular density was not significantly different from controls, indicating that other regulators may be influencing capillary densities [71]. Another regulator of AVM formation is matrix Gla protein (MGP). Homozygous knockout ($Mgp^{-/-}$) in a murine model resulted in a robust AVM phenotype characterized by abnormal and enlarged vessels [72]. Mechanistic evaluation revealed that the AVM phenotype in $Mgp^{-/-}$ mice was driven by upregulated Jagged 1 and 2[72]. Abrogation of these two proteins prevented the development of cerebral AVMs in the knockout model [72].

Other genetic studies examined gain-of-function mutations in *Kras* (G12D or G12V) *in vivo* in postnatal and adult mice, and zebrafish [33, 73, 74]. Using a tamoxifen-inducible Cre-recombinase transgenic system, both mutations of *Kras* alone induced bAVMs in mice and zebrafish [73]. Other activating mutations that are associated with the development of an AVM-like phenotype in mice include constitutively active Notch4 (*int3*) [75]. In mice with tetracycline-induced expression of Notch4, mutants demonstrated vascular abnormalities resembling bAVMs as well as evidence of arteriovenous shunting which mimicked the principal defect of human bAVMs [75]. Related to canonical Notch1 signaling, a conditional knockout of *Rbpj*, a gene that encodes a mediator of Notch1 signaling, in cerebral endothelium generated arteriovenous shunting, increased vessel density, irregular vascular morphology and abnormalities consistent with AVM in early postnatal mice [76].

While *in vivo* models offer extensive insight into the pathophysiology of bAVMs, various *in vitro* models have been developed to evaluate therapeutic efficacy, imaging, treatment materials, and other aspects of the disease[77-79]. *In vitro* models often lack the ability to recapitulate anatomic features of bAVMs, but to overcome some of these limitations, Kaneko et al 2020 manufactured a three-dimensional (3D)-printed model of bAVM using images from patient angiography. This model was successfully used to simulate endovascular procedures to treat bAVMs and mimicked vascular geometry from actual patient data, the first model of its class to incorporate hollow nidus channels within the model's internal structure [80]. Recently, an AVM-on-a-chip model was developed to replicate hallmarks of AVM using human endothelial cells (ECs) harboring KRAS mutations [81]. Cell lines of immortalized human umbilical vein endothelial cells (HUVEC) expressing either wild-type or doxycycline-inducible mutant KRAS were cultured with fibroblasts in fibrin hydrogels on a microfluidics device [81]. Mutant ECs demonstrated significantly greater vessel enlargement, greater number of branches at junctions, and increased permeability consistent with AVM biology [81]. Barrier integrity deficits in the mutant ECs were corrected after administration of a MEK inhibitor, which impaired signaling through mutant KRAS [81].

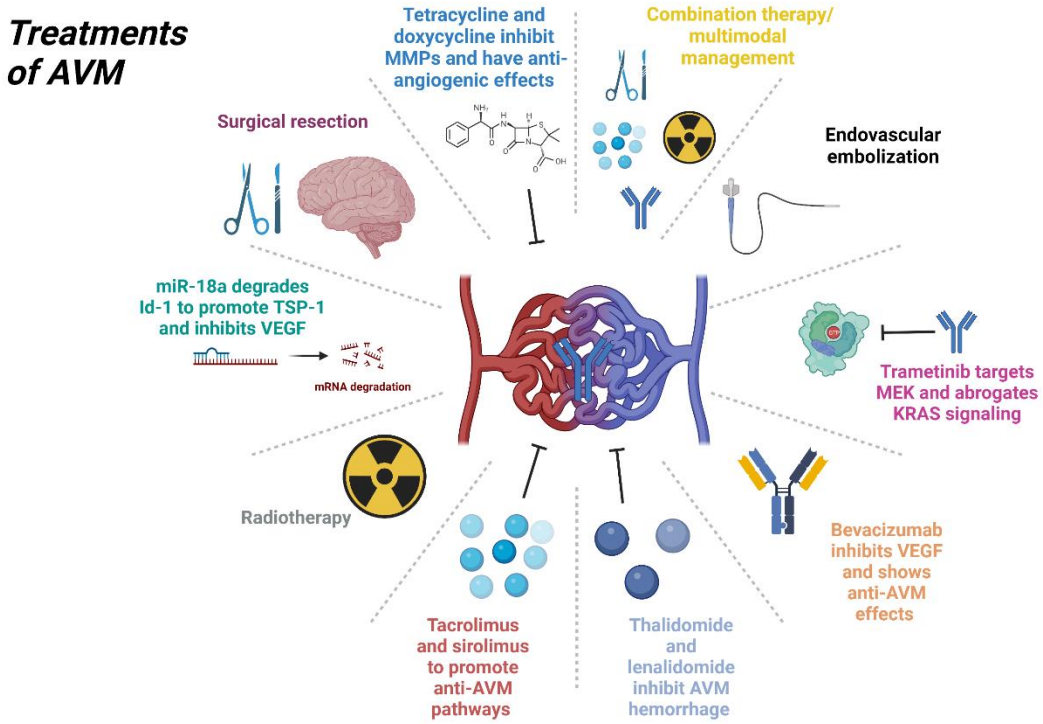
Preclinical analysis of bAVMs provide insight on potential therapeutic targets to ameliorate and reverse progression of AVMs. Evidence *in vivo* of constitutively active Notch4 and mutant KRAS (G12D or G12V) suggests contributory roles of these mutations toward generation of bAVM phenotype likely through pro-angiogenic pathways[33, 73-75]]. Small molecules that inhibit these proteins offer therapeutic potential towards reversing morphological and architectural changes of the endothelium away from AVM features. Repression of constitutive signaling in Notch4 and mutant KRAS rescues mice from progression of the disease and significantly increases survival [75]. Of note, inhibition of PI3K, a mediator downstream of KRAS, did not ameliorate and reverse features of AVM. Rather, inhibition of mitogen activated protein kinase kinase 1 (MEK), an upstream KRAS mediator, abolished mutant KRAS signaling and highlighted the reversible nature of the disease upon MEK inhibition [73]. A phase II clinical trial is presently recruiting for patients with extracranial AVMs to undergo treatment with trametinb, a MEK inhibitor, with the primary outcome listed as disease response rate NCT04258046. This is the first phase II trial to evaluate use of a MEK inhibitor in treating AVM. Evidence also suggests a contributory role of VEGF towards the development of an AVM, especially in the context of knockout models related to endoglin and integrin 8 [65, 71]. Inhibitors of VEGF, including bevacizumab, are being studied in clinical trials as part of treatment for bAVMs. The primary outcome of a phase 1 trial assessing the use of bevacizumab is change in bAVM volume compared to pre-treatment MRI. Despite trial completion, the results have not been published NCT02314377. While small molecule inhibitors and monoclonal antibodies can target gain-of-function mutations and constitutively active proteins, restoring loss-of-function mutations as well as agonizing disrupted pathways may require the development of novel gene therapies, improved drug delivery and tissue specificity. Introduction of functional *Eng*, *Alk1*, or *Mgp* genes in addition to agonism of TGF-β and Notch1 signaling may offer novel solutions toward decreasing AVM size and progression [62, 67, 71, 72, 76].

Presently, the foundation of bAVM treatment guidelines is centered around conservative management, surgical removal, stereotactic surgery, endovascular therapy, or combinatorial therapy [82]. Exciting innovations directed at novel targets offer a potential glimpse at the future therapeutic landscape of bAVMs. Some studies have undertaken analysis of gene expression genes in endothelial cells before and after stereotactic radiosurgery (SRS) to discover new targets. Proteomics and mass spectrometry of membrane proteins in ECs following SRS at different time points revealed differential membrane protein upregulation [83]. Specifically in comparing cells 24 and 48 hours post SRS, significant upregulation of PECAM-1, Cadherin 5, integrin beta 1, EPCR, and Multimerin 2 was demonstrated along with changes in cell morphology [83]. These observations are clinically interesting given the role of these membrane proteins in cell signaling and potential for targeting with small molecules or immunotherapy to induce efficient thrombosis [83]. Like this study, comparative proteomics analysis was used following gamma knife surgery in an *in vivo* model of bAVM and revealed upregulation of a CRYAB, a heat shock protein involved in cellular survival, radio-resistance, and possible role in tumor angiogenesis [84]. While unvalidated as a target, CRYAB may have therapeutic potential against bAVMs given its potential role in promoting angiogenesis and high level of upregulation following SRS. *In vitro* evaluation of thrombin conjugated to an anti-CRYAB antibody resulted in robust thrombus formation following irradiation of cerebral microvascular endothelial cells [85]. Other upregulated adhesion molecules in endothelial cells following irradiation include E-selectin, P-selectin, ICAM-1, and ET-1 which may serve as targetable proteins for inducing thrombosis [86]. Radiotherapy-induced changes to levels of membrane proteins and intracellular localization of proteins may suggest that adaptive cellular responses to radiation could involve differential protein splicing, and post-translational processing leading to the production of targetable neoantigens and induction of thrombosis [87].

Combining radiotherapy with lipopolysaccharide and soluble tissue factor conjugate (LPS/sTF) produced significant increases in thrombosis with minimal systemic effects in a rat model of AVM, but these interpretations may be constrained towards treating small-vessel AVMs [88]. Other innovative, but experimental therapies involve the use of tetracycline and doxycycline given their anti-angiogenic effects and inhibitory activity of matrix metalloproteases (MMPs), proteins implicated in the pathophysiology of AVMs [89-91].

Targeting of VEGF is being explored through use of thrombospondin-1 (TSP-1) and microRNA-18a (miR-18a)[92]. TSP-1 is an antagonist of VEGF-A and miR-18a increases levels of TSP-1 RNA by inhibiting Id-1, an inhibitor of TSP-1 [93, 94]. VEGF activity is also suppressed by various tyrosine kinase inhibitors that target downstream mediators of VEGF signaling such as sorafenib, pazopanib, and nintedanib [95]. Lastly, soluble FMS-related tyrosine kinase binds to the extracellular domain of VEGF and reduced vessel dysplasia and AVM growth in an in vivo mouse model deficient in endoglin[95]. Thalidomide and lenalidomide may have clinically significant anti-bleeding properties and offers benefits to prevent hemorrhage from AVM, potentially mediated by upregulation of platelet-derived growth factor (PDGFB) [95]. While unknown, thalidomide may interact and inhibit VEGF, given its anti-bleeding effects *in vivo*, with modulatory effects on inflammation and vascular reorganization [96, 97]].

Various genetic deficiencies, such as loss of function *ENG*, *Alk1*, and *Mgp*, promote the development of bAVMs. Promotion of pathways affected by these genetic losses through use of tacrolimus and sirolimus has been shown in preclinical studies to reverse formation of AVMs [95, 98, 99].



Discussion

While several therapeutic drug targets in AVM seem promising, they remain in early preclinical studies. Ultimately, there is still no truly analogous animal model of AVM, bringing in to question the implications of there early findings. However, the limited data showing success of existing repurposed drugs in AVM lends to the validity of the previously mentioned target pathways. Medications such as bevacizumab and thalidomide which are implicated in inhibiting angiogenesis and inflammation are well studied in oncology and have seen off label use for symptomatic AVMs, but the adverse effects of these drugs may prevent there use outside of the highest risk patients**[100].**Currently, clinical management of AVM's depends on age, with invasive management being recommended younger patients with high-risk features and medical management being recommended for older adults [101]. Current medical management of bAVM primarily involves managing neurological symptoms secondary to mass effect [101]. While invasive management to obliterate the arteriovenous shunt is the definitive treatment for bAVM, previously mentioned clinical studies have shown that for unruptured bAVM this management leads to more adverse outcomes than medical management alone [41, 42, 82]. The sheer lack of options for conservative and post-op medical management demonstrates the need for novel therapeutics. Although the use of novel or repurposed therapeutics to directly mitigate the pathophysiology of AVM's is appealing, it is important that they do not contribute to adverse outcomes and that long-term therapy is tolerable. Heterogeneity among bAVM patients in grade, genetic, and environmental risk factors, makes assessing the efficacy of targeted drug therapies difficult. The successful development of a risk modifying drug therapy would fill an important gap in the treatment of bAVM's and contribute to our understanding of vasculopathies broadly.

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