Theranostic Advances in Vascular Malformations



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Vascular malformations are subdivided into capillary, lymphatic, venous, arteriovenous, and mixed malformations, according to the type of affected vessels. Until a few years ago, treatment options were limited to sclerotherapy and/or surgery. Since, it has been demonstrated that the majority of vascular malformations are caused by inherited or somatic mutations in various genes. These mutations lead to hyperactivity of two major signaling pathways: the RAS/ mitogen-activated protein kinase and the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathways. These discoveries paved the way for the development and testing of targeted molecular inhibitors as therapies for vascular anomalies via repurposing of anticancer drugs.

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INTRODUCTION

Vascular anomalies are classified into vascular tumors and vascular malformations (Mulliken and Glowacki, 1982). This classification was opted in 1996 by the International Society for the Study of Vascular Anomalies and is regularly updated (Wassef et al., 2015). Vascular malformations are most often congenital, even if they are discovered later in life.

Most vascular malformations occur sporadically (Nguyen et al., 2017). Some occur in multiple family members and were logically first studied by geneticists. These include hereditary hemorrhagic telangiectasia (HHT), cerebral

Correspondence: Miikka Vikkula, Human Molecular Genetics, de Duve Institute, University of Louvain, Avenue Hippocrate 74, Brussels B-1200, Belgium. E-mail: miikka.vikkula@uclouvain.be cavernous malformation, mucocutaneous venous malformation (VM), glomuvenous malformation, capillary malformation (CM)-arteriovenous malformation (AVM), and PTEN hamartoma tumor syndrome. Mutations were identified in 11 different genes. They cause loss of function of the encoded protein in 10/11, often leading to increased downstream signaling. It was also demonstrated that lesions in inherited forms need a second-hit mutation. This led to study somatic mutations as the cause of sporadic malformations (Queisser et al., 2018). The first somatic mutations that were shown to be associated with sporadic VMs occurred in *TIE2/TEK* (Limaye et al., 2009). Since then, genetic causes have been identified for numerous vascular anomalies (Figure 1).

Genes implicated in the familial forms are relatively vascular cell-type specific (Queisser et al., 2018). *EPHB4*, *RASA1*, and *glomulin* expression is enriched in blood vessels and *TIE2/TEK* on endothelial cells (ECs) (Uebelhoer et al., 2012). In contrast, many of the genes implicated in sporadic vascular malformations are ubiquitously expressed and encode proteins acting in major signaling pathways. Yet, they are common downstream effectors of the proteins mutated in inherited forms, making a functional link between the two.

The two major activated signaling pathways are the RAS/ mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway (Figure 2) (Nguyen et al., 2017; Queisser et al., 2018). They are important regulators of cellular growth, proliferation, migration, apoptosis, and often implicated in cancers. The fact that similar mutations are observed in vascular anomalies may be explained by the occurrence of second-hits and somatic mutations in ECs and in the context of a stable genome, whereas in cancers other cell types are affected, and commonly an accumulation of somatic mutations occur (Osborn et al., 2015; Samuels et al., 2004). More extensive mosaicism can be seen in syndromic forms of vascular anomalies, such as Klippel-Trénaunay syndrome (capillary-lymphatico-VM with overgrowth), congenital lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis syndrome, or macrocephaly-CM (Nguyen et al., 2017); yet, these forms are without malignant transformation. These discoveries have led to test small molecule inhibitors (anticancer drugs) as repurposed targeted molecular therapies for vascular malformations (Boon et al., 2019; Nguyen et al., 2017; Queisser et al., 2018).

Vascular malformations involving the PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR pathway is often called the "antiapoptosis pathway" (Nguyen et al., 2017; Queisser et al., 2018). *PIK3CA* encodes the catalytic subunit alpha of PI3K.

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Abbreviations: AE, adverse event; AKT, protein kinase B; AVM, arteriovenous malformation; CM, capillary malformation; EC, endothelial cell; ERK, extracellular signal—regulated kinase; HHT, hereditary hemorrhagic telangiectasia; LM, lymphatic malformation; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; PROS, PIK3CA-related overgrowth spectrum; VM, venous malformation

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Figure 1. Clinical aspects of different vascular malformations in correlation with the genotype. (a) CM with overgrowth: somatic *GNAQ* mutation. (b) Verrucous venous malformation: somatic *MAP3K3* mutation. (c) VM: somatic *TIE2* mutation. (d) LM: somatic *PIK3CA* mutation. (e) CLOVES syndrome: somatic *PIK3CA* mutation. The patients or their parent or guardian consented to the publication of these images. CLOVES, congenital lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis; CM, capillary malformation; LM, lymphatic malformation; VM, venous malformation.

PI3K is part of the signaling pathway downstream of several tyrosine kinase receptors present on cell membranes, such as TIE2/TEK and the vascular endothelial growth factor receptor 2. PI3K activates AKT (among which AKT1) and thereby mTOR and regulates cell growth, apoptosis, proliferation, migration, and angiogenesis (Schlögel et al., 2018).

The majority of all four classes of VMs are caused by mutations in the endothelial receptor tyrosine kinase TIE2, encoded by the *TEK* gene. In familial cutaneomucosal VM, the most common mutation is R849W (Boon and Vikkula, 2008), and a second hit that is always somatic is needed to develop the multiple small-sized VMs. Patients with sporadically occurring multiple VMs tend to be mosaic for the first mutation (R915C), and they also generate intriguingly the same second hit (Y897C) (Soblet et al., 2017). Sporadic unifocal VMs are most frequently (> 60%) caused by somatic L914F mutation (Limaye et al., 2009), whereas in the blue rubber bleb nevus syndrome, somatic *TEK*double-mutations are observed, including T1105N-T1106P and Y897F-R915L (Soblet et al., 2017).

A somatic mutation in *PIK3CA* can be found in half of the patients with sporadic *TIE2*-negative VM (20% of all VMs; Limaye et al., 2015). Somatic *PIK3CA* mutations are also found in lymphatic malformations (LMs) (Boon et al., 2019; Luks et al., 2015). Mutations occur particularly in "hot spots" (the same as in cancers), such as p.E542K and p.E545K or H1047R (Schlögel et al., 2018), and the phenotype likely depends on the affected cell-type: venous versus lymphatic ECs (Schlögel et al., 2018). Both the *TIE2* and *PIK3CA* mutations lead to constitutive activation of the PI3K/AKT/mTOR pathway. The inherited *TIE2* mutations have a weaker effect than the somatic mutations. This activation is responsible for accumulation of ECs owing to reduced apoptosis and defective recruitment of vascular smooth muscle cells, resulting in the formation of abnormal vascular channels.

In segmental overgrowth syndromes such as Klippel-Trénaunay, congenital lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis syndrome, and megalencephaly-CM (Kurek et al., 2012; Keppler-Noreuil et al., 2015; Rivière et al., 2012), mosaic mutations in *PIK3CA* have also been discovered. The same is true for overgrowth phenotypes without lymphatic or vascular malformations. The term PROS was therefore coined to refer, though not specifically, to *PIK3CA*-related overgrowth spectrum (Keppler-Noreuil et al., 2015). The differences in time points of occurrence of the postzygotic mutations likely explain this phenomenon (Nguyen et al., 2017). Recently, somatic activating *PIK3CA* mutations were identified in nine patients with generalized lymphatic anomaly (Rodriguez-Laguna et al., 2019), increasing the phenotypic spectrum.

The inherited PTEN hamartoma tumor syndrome (Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome) and the sporadically occurring Proteus syndrome also involve activation of the PI3K/AKT/mTOR pathway. PTEN inhibits PI3K signaling. It converts phosphatidylinositol (3,4,5)-triphosphate into phosphatidylinositol (4,5)-bisphosphate (Delannoy et al., 2017). In PTEN hamartoma tumor syndrome, germline PTEN mutations lead to loss of its inhibitory activity. These patients are predisposed to malignancies and also to vascular malformations. In the rare Proteus syndrome, activating mosaic gain-of-function mutations occur in AKT1 (Lindhurst et al., 2011). The PI3K/AKT/mTOR pathway may also play a role in HHT, with mutations in ENG, ACVRL1, or BMP9/10 (Queisser et al., 2018). Endoglin and ACVRL1 are type III and type I transforming growth factor-ß receptors and wellexpressed on vascular ECs. A loss of function of this signaling concomitantly increases PI3K-AKT signaling (Ola et al., 2016).

Another inherited venous-type malformation is glomuvenous malformation. More than 40 different germline mutations in *glomulin* have been identified (Brouillard et al., 2002; Queisser et al., 2018). Glomulin seems to be expressed in ECs and in vascular smooth muscle cells, and earlier data suggest that it is involved in hepatocyte growth factor/cMet signaling via PI3K (Queisser et al., 2018). This suggests a link between pathophysiology and PI3K/AKT/ mTOR signaling.

Vascular malformations involving the RAS/MAPK/ERK signaling pathway

The RAS/MAPK/ERK pathway is often called the proliferation pathway; it plays a role in cell cycle regulation, proliferation,

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Figure 2. The RAS/MAPK/ERK and PI3K/AKT/mTOR pathways hyperactivated in vascular malformations. RAS/MAPK/ERK pathway hyperactivated when mutations arise in *GNAQ/GNA11*, *EPHB4*, *RASA1*, *ARAF*, *BRAF*, *KRAS*, *MAP2K1*, *MAP3K3*, and *KRIT1*. PI3K/AKT/mTOR pathway hyperactivated when mutations arise in *TIE2*, *PIK3CA*, *PTEN*, *AKT*, *endoglin*, *ACVRL1*, or *BMP9/10*. Targeted treatments noted in blue.

and migration. The pathway is activated when a growth factor binds to a receptor tyrosine kinase. This interaction causes the recruitment of adaptor proteins, such as growth factor receptor-bound protein-2. Growth factor receptor-bound protein-2 is bound to a nucleotide exchange factor, son-ofsevenless, which is subsequently recruited to the plasma membrane. Son-of-sevenless proteins are guanosine nucleotide exchange factors that induce activation of green fluorescent protein—bound RAS with activation of Raf phosphorylation. Phosphorylated Raf activates MAPK/ERK kinase (MEK), which in turn phosphorylates and activates ERK. ERK regulates multiple functions of downstream cytosolic and nuclear molecules (Nguyen et al., 2017; Tidyman and Rauen, 2009).

Rasopathies are caused by activating mutations in different genes of the RAS/MAPK/ERK pathway. In these diseases, vascular malformations can also arise, for example, in Noonan syndrome or cardio-facio-cutaneous syndrome (Tidyman and Rauen, 2009). Various isolated vascular malformations should now also be included in rasopathies because their underlying cause is activation of this pathway (Aoki et al., 2016; Nguyen et al., 2017) (Figures 1 and 2).

CM-AVM1 and CM-AVM2 are caused by inherited loss-offunction mutations in *RASA1* and *EPHB4*, respectively (Amyere et al., 2017; Eerola et al., 2003). *RASA1* encodes RASp21 protein activator 1 (p120RasGAP), which induces intrinsic GTPase activity of RAS thereby increasing the conversion of GTP-RAS to GDP-RAS. This suppresses RAS activity. p120RasGAP plays an important role in the organization of EC networks, cellular growth, differentiation, and proliferation. EPHB4 is preferentially expressed in venous ECs during vascular development, whereas its ligand EPHRINB2 is expressed on arterial ECs. This ligand-receptor system is important for establishing arteriovenous entity and thereby separation of arteries from veins. EPHB4 represses RAS/MAPK/ERK signaling in venous ECs through interaction with p120RasGAP (Xiao et al., 2012). Therefore, *RASA1* and *EPHB4* loss-of-function mutations cause inadequate activation of the pathway in ECs.

This pathway is also implicated in sporadically occurring, isolated fast-flow vascular anomalies. Somatic activating *MAP2K1* "hot spot" mutations (encoding MEK1) were identified in extracranial AVMs (Couto et al., 2017b) and *KRAS* and *BRAF* mutations in intracranial AVMs (Al-Olabi et al., 2018; Nikolaev et al., 2018). Common vascular tumors, such as pyogenic granulomas, are associated with activating "hot spot" mutations in *KRAS* (Lim et al., 2015).

A special germline *EPHB4* mutation was recently identified as a cause of central conducting lymphatic anomaly in one family (Li et al., 2018). In two other unrelated sporadic patients with central conducting lymphatic anomaly, a mosaicactivating*ARAF* mutation was identified. *ARAF* encodes for serine/threonine-protein kinase A-Raf, an integral member of the MAPK pathway (Li, 2019). These data associate central conducting lymphatic anomaly with RAS/MAPK/ERK activation, likely in ECs of lymphatic conduits. Furthermore, a somatic activating mutation in *N-RAS* was discovered in several patients with kaposiform lymphangiomatosis (Barclay et al., 2019; Manevitz-Mendelson et al., 2018).

Isolated CMs and Sturge-Weber syndrome are associated with somatic activating p.R183Q *GNAQ* mutations (Shirley et al., 2013). Diffuse CM with overgrowth is associated with somatic p.R183C *GNA11* mutation (Couto et al., 2017a). These mutations partially inactivate the

corresponding GNAQ or GNA11 guanosine triphosphatase activity. This results in constitutive activation of the MAPK pathway, at least in some cancer cells (Van Raamsdonk et al., 2010). There is controversy whether this happens also in ECs.

Another entity that seems to link to increased RAS/MAPK signaling is vertucous VM owing to somatic gain-of-function mutations in *MAP3K3* (Couto et al., 2015). Similar cutaneous lesions called hyperkeratotic cutaneous capillary-VMs are seen in some patients with inherited cerebral cavernomas. Hyperkeratotic cutaneous capillary-VMs are due to a combination of a loss-of-function germline *KRIT1* mutation with a somatic second hit (Eerola et al., 2000; Toll et al., 2009). The loss of KRIT1 causes activation of MAP3K3, and thereby activation of the RAS/MAPK/ERK pathway (Zhou et al., 2016).

Targeted treatments in vascular malformations

Until now, treatment options for vascular malformations were limited to conventional local treatments (sclerotherapy, laser, embolization, and surgery). Since most vascular malformations are caused by genetic mutations responsible for hyperactivation of the two major signaling pathways, the use of targeted molecules has become an interesting new noninvasive possibility. Various small molecule inhibitors have been developed to regulate these pathways because they are frequently involved in cancers.

Slow-flow malformations

An animal model of VM was developed in 2015 (Boscolo et al., 2015). This was based on the subcutaneous injection of ECs highly overexpressing mutant TIE2. These human cells were able to generate vascular lumens and to connect with the murine vasculature. Macroscopically and histologically, the lesions mimicked human VMs. This provided the possibility to test drugs in vivo. Treatment with rapamycin reduced EC accumulation and development of VMs (Boscolo et al., 2015). Two other VM models were subsequently developed using murine lines generated to conditionally express mutant PIK3CA (H1047R) in murine ECs. In the first model, rapamycin treatment resulted in a 25% reduction in VM volume (Castillo et al., 2016) and in the second model, everolimus treatment resulted in a halted progression of VMs and reduction of vessel anomalies (di Blasio et al., 2018). Yet another model was generated by injection of PIK3CA (H1047R)-expressing cells into mice, with formation of highly vascularized and proliferative masses. Again, everolimus led to a reduction of VM size, but the PI3K inhibitor, alpelisib (BYL719), resulted in a greater response (Castel et al., 2016). These preclinical studies demonstrated that an activating TIE2 or PIK3CA mutation in vascular ECs is sufficient to generate a VM and that inhibition of the PI3K/AKT/ mTOR pathway can stop the development and diminish the size of VMs (Seront et al., 2019).

mTOR inhibitor. Rapamycin (sirolimus) is an mTOR inhibitor traditionally used as an immunosuppressive agent for organ transplantation. Sirolimus has now been used in a small number of clinical trials to treat slow-flow vascular malformations (Adams et al., 2016; Boscolo et al., 2015). In these studies, the mTOR inhibitor was used to treat LMs, painful extensive VMs, Klippel-Trénaunay syndrome, kaposiform hemangioendotheliomas, microcystic LMs,

generalized lymphatic anomaly, and PTEN hamartoma tumor syndrome. More recently, in a phase 2B study, 19 patients (adults and children) with VM, LM, and/or complex malformations refractory to standard treatment were studied (Hammer et al., 2018). All patients had a significant and rapid improvement of their symptoms and quality of life (Hammer et al., 2018; Seront et al., 2019). Similar encouraging results have been reported in case studies and retrospective off-label series (Curry et al., 2019; Hammill et al., 2011; Lackner et al., 2015; Ogu et al., 2018; Ricci et al., 2019; Triana et al., 2017; Triana et al., 2019; Zhang et al., 2019). Three clinical trials are ongoing for the use of sirolimus in complicated slow-flow vascular malformations (VASE, see below; Maruani et al., 2018; Ozeki et al., 2019).

In VMs, patients experienced reduction of pain, bleeding, and lesional volume (Hammer et al., 2018; Seront et al., 2019). Sirolimus also had a beneficial effect on coagulation abnormalities (Boscolo et al., 2015; Hammer et al., 2018; Seront et al., 2019). In LMs, several patients experienced fewer infections, reduction in lymphatic leakage or oozing, and reduction of lesional volume (Adams et al., 2016; Hammill et al., 2011). Sirolimus treatment made some lesions amenable to sclerotherapy or surgical resection, suggesting an adjuvant role in the treatment of LMs. (Hammer et al., 2018).

A prospective multicentric single-arm phase 3 trial (VASE) is ongoing to evaluate rapamycin efficacy in pediatric and adult patients with various slow-flow vascular malformations (EudraCT number: 2015-001703-32). All patients are being treated with rapamycin for 2 years. The preliminary results are encouraging (Seront et al., 2019).

In the majority of these studies, sirolimus was well tolerated. In the phase 2B trial, headache (58%), fatigue (48%), skin rash (37%), mucositis (37%), and diarrhea (37%) were the most frequent grade 1-2 adverse events (AEs) (Hammer et al., 2018). Eleven percent of patients had AE grade 3 mucositis. These AEs were relatively easily managed with dose reduction or temporary interruption of treatment (Hammer et al., 2018). One patient with a previous history of skin cancer developed a basal cell carcinoma one year after the introduction of rapamycin. A girl aged 11 years was diagnosed with large B-cell lymphoma 34 months after initiation of rapamycin for a LM extending from the suprahyoideal region to the clavicular area. This lymphoma was non-Epstein-Barr virus-related (Hammer et al., 2018). Another girl aged 4 years with an unusual primary upper extremity lymphedema with severe pleural effusion developed a lymphangiosarcoma 3 months after the initiation of rapamycin (Janssens et al., 2018). In all these cases, a causal relationship with rapamycin treatment could not be established.

Adams et al. (2016) evaluated rapamycin in 60 children and young adults with LMs. They observed grade 3 bone marrow toxicity in 27%. A recent study using low-dose sirolimus in 39 patients (children and adults) with PROS showed a slight reduction in overgrowth but with a high rate of AEs: grade \geq 3 AEs in 37% of patients, 18% of which led to discontinuation of treatment, and grade \geq 2 infection-related AEs in 41% of patients. Only 5% of hematological AEs were Theranostics in Vascular Malformations

reported in this study (Parker et al., 2019). The reasons for the higher hematological toxicity observed by Adams et al. (2016) and the higher infection rate observed by Parker et al. (2019) are not known. It may be related to the type of vascular anomalies and/or various concomitant (environmental) factors.

PIK3CA inhibitor. A mouse model of the PROS/congenital lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis syndrome spectrum was generated by expressing mutant PIK3CA in mice. These models were subsequently treated with a PIK3CA inhibitor BYL719 (alpelisib), which prevented and improved organ dysfunction; BYL719 early-treated mice had preserved tissues and normal vessels (Venot et al., 2018). Alpelisib seemed to be more effective than rapamycin when mice were treated after apparition of organ anomalies (scoliosis, muscle hypertrophy, and vessel malformation). On the basis of these results, 19 patients with PROS (15 children and 4 adults) were treated with alpelisib at the dose of 250 mg per day for adults and 50 mg per day for children; in advanced PIK3CA mutated breast cancer, alpelisib is used at a dose of 300 mg per day, in combination with fulvestrant (André et al., 2019). Eight patients with congenital lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis syndrome, two with megalencephaly-CM, and nine with localized overgrowth syndrome were included. Alpelisib treatment resulted in volume reduction of the vascular lesions and in improvement of congestive heart failure, hemihypertrophy, scoliosis, and pain. Alpelisib was well tolerated with transient hyperglycemia (n = 3 of 19) and discrete transient mouth ulcerations (grade I) (n = 3 of 19) as the most common AEs in the short follow-up period (6 to 12 months).

AKT inhibitor. Miransertib (ARQ 092), an experimental orally bioavailable selective AKT inhibitor, was used in a phase 0/1 pilot study that included six patients with Proteus syndrome. A seven-fold lower dose than that used to treat cancer was shown to be sufficient to treat these patients, with good tolerance (Keppler-Noreuil et al., 2019). Miransertib is currently being evaluated in phase 1 and 2 studies for Proteus syndrome and for patients with PROS.

MEK inhibitor. A zebrafish model of EPHB4 dysfunction resulted in deformities in lymphatic vessel development and vessel misbranching. The mTOR inhibitor (rapamycin) and MEK inhibitor (cobimetinib) rescued the distorted vessels (Li, 2019). Moreover, one patient with an activating somatic *ARAF* mutation with central conducting lymphatic anomaly was treated with an MEK inhibitor with clinical improvement of lymphatic edema and pulmonary function tests (Li, 2019), suggesting a better response for MEK inhibitors in some patients with central conducting lymphatic anomaly.

Fast-flow malformations

BRAF inhibitors. Various mosaic-activating variants in the RAS/MAPK/ERK pathway have been identified in fast-flow malformations. These include activating *BRAF* (V600E) and *MAP2K1* (Q58del) mutations. For both of these, zebrafish models demonstrated abnormal tail vasculature. Treatment of

the mutant zebrafish with vemurafenib (an approved anticancer BRAF inhibitor) increased the number of fish with normal blood flow (Al-Olabi et al., 2018).

MEK inhibitors. Intracerebral AVMs were associated with somatic gain-of-function mutations in *KRAS* (Nikolaev et al., 2018). In vitro studies showed that MEK inhibition decreased ERK phosphorylation and angiogenic gene expression in ECs derived from such KRAS-mutant AVMs (Nikolaev et al., 2018). In a case report on off-label use of the MEK inhibitor, trametinib, reduced activity and size of a *MAP2K1*-mutated AVM was observed in a girl aged 11 years (Lekwuttikarn et al., 2019). These findings suggest a possible role for RAS/MAPK inhibition in fast-flow malformations.

Antiangiogenic drugs

Bevacizumab. Bevacizumab, a recombinant full-length humanized vascular endothelial growth factor-A antibody, is a potent antiangiogenic agent. It was used intravenously in HHT patients for high output cardiac failure in severe hepatic form and for severe epistaxis with encouraging results. However, relapses occurred when treatment was stopped, and intravenous use needs good compliance and close monitoring of toxicity. Topical and submucosal bevacizumab does not seem to be efficient for HHT (Dupuis-Girod et al., 2012; Halderman et al., 2018; Stokes et al., 2018).

Thalidomide. Thalidomide is another potent antiangiogenic agent. It reduces efficiently the frequency and duration of nose bleeds and gastrointestinal bleeding in HHT (Buscarini et al., 2019; Harrison et al., 2018; Lebrin et al., 2010). Thus, it may have a wider application in vascular malformations with important angiogenic activity. In a recent mouse model, thalidomide reduced hemorrhage of brain AVM (Zhu et al., 2018).

CONCLUSIONS

The groundbreaking discoveries that were made through genetic analyses of vascular malformations have transformed the way we think of our options for their management. The identification of somatic mutations as the culprit of sporadically occurring VMs led to the discovery of gain-of-function mutations as the cause of most vascular malformations. This uncovered the hyperactivation of the RAS/MAPK/ERK and/or the PI3K/AKT/mTOR pathway underlying most vascular malformations.

The development of the VM mouse model by Boscolo et al. (2015) paved the way for preclinical in vivo therapeutic studies. This was strengthened by the most encouraging results obtained in patients with the use of molecular therapies. Numerous research groups are now interested in unraveling in detail the molecular pathophysiologic mechanisms and generation of variable in vivo models. This will enable screening of a number of drugs and evaluating cross-talks between signaling pathways.

In parallel, an increasing number of specialized multidisciplinary centers for the treatment of vascular anomalies are being established. Thus, we expect to see a surge in clinical trials and off-label use of the various molecules that are available for repurposing. Theranostics, the use of genetic testing for choosing the precision drug, is likely to become mainstream in the management of vascular anomalies.

Despite the excitement and hope these developments have generated for patients with vascular anomalies, we also need to stay cautious. The novel anticancer drugs have never been used for long periods of time, and consequently the AEs after long-term use are unknown. It also remains to be seen, how these drugs can be used in the context of other, classical therapies and at which dose, and whether lifelong or shorter administration is useful. Definition of clinical outcome measures is also urgently needed allowing comparisons among studies. This is particularly difficult for internal lesions, for example, for those in the central nervous system. The development of local delivery systems will also be of interest, eventually allowing to reduce AEs.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

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