**Purpose of review**
Recently, it has been discovered that a subset of vascular malformations, of the lymphatic and venous type, are caused by oncogenic mutations in the **PIK3CA** gene. Now, efforts have been focused in the understanding of the molecular and cellular consequences of these mutations and the opportunities for novel-targeted therapies for these diseases.

**Recent findings**
Here, we review the latest findings in the biology of oncogenic **PIK3CA** mutations in the pathogenesis of vascular malformations. We focus on the recent development of in-vitro and in-vivo tools for the study of **PIK3CA**-mutant vascular malformations with special interest in preclinical models for drug testing. Also, we review the latest advances in phosphoinositide 3-kinase (PI3K) inhibitors in the clinic and their repurposing for the treatment of lymphatic malformations and venous malformations.

**Summary**
Oncogenic mutations on **PIK3CA** causing lymphatic malformations and venous malformations are also frequently found in epithelial cancer. Thus, fundamental research done in the cancer field during the past decades might be applied to the understanding of lymphatic malformations and venous malformations. Likewise, repurposing PI3K pathway inhibitors that are currently in cancer clinical trials can be used as a novel strategy for the treatment of these diseases. Here, we also open a debate for the consideration of lymphatic malformations and venous malformations as developmental tumours.

**Keywords**
lymphatic malformations, phosphoinositide 3-kinase, **PIK3CA**, venous malformations

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**INTRODUCTION**
Vascular malformations are a heterogeneous group of diseases affecting a large population (one in 100 individuals) [1] for whom limited treatment options exist. These lesions appear during embryonic development and are manifested at birth (congenital) or throughout the life of affected individuals [2]. Vascular malformations are classified according to their histological appearance in different categories that include low-flow lesions: capillary, venous, and lymphatic; and fast-flow arteriovenous malformations. Specifically, venous malformations are localized collections of abnormal and tortuous venous channels. Venous malformations have a major impact on the quality of life of patients; they are painful and disfiguring, and many lead to bleeding, recurrent infections, thrombosis, organ dysfunction, and even death. Similarly, lymphatic malformations are congenital lesions occurring as a result of a defect in the development of the lymphatic system. These lesions are composed by dilated lymphatic channels and can occur anywhere in the body [3]. Venous malformations and lymphatic malformations do not regress but expand proportionally with the growth of the child. Current standard of care includes compression, surgical excision, and/or sclerotherapy [4]. However, these treatment strategies are likely to be insufficient and patients commonly experience a high risk of recurrence and progression. In both types of malformations, the blood and lymphatic vessels are dedifferentiated, immature, and most likely occur as a consequence of an abnormal hyperproliferation of endothelial cells during development.

With the emergence of high-throughput and ultra-deep sequencing technologies, the genetic landscape of vascular malformations has undergone a great progress. A decade ago, it was determined...
that around half of sporadic venous malformations are caused by somatic gain-of-function mutations in the TEK gene which codes for the endothelial tyrosine-protein kinase receptor TIE-2 [5]. In 2015, it was discovered that most lymphatic malformations were caused by somatic oncogenic mutations in the PIK3CA gene [coding for the p110α isoform of phosphoinositide 3-kinase (PI3K) lipid kinases] [6], and, a year later, it was demonstrated that around 25–30% of venous malformations are also caused by these oncogenic PIK3CA mutations [7,8,9]. In most venous malformations, PIK3CA and TEK mutations are mutually exclusive, all triggering an overactivation of the PI3K signalling pathway. An unusual case has been recently reported in which both PIK3CA and TEK mutations have been found in endothelial cells derived from same venous malformations [10**]. Of note, in this specific case, neither PIK3CA nor TEK mutations are hotspots mutations of the disease.

Despite the discovery of the genetic cause of venous and lymphatic malformations, it is still unclear how these mutations change the cellular phenotype and how the molecular mechanisms driven by these mutations lead to the pathogenesis of these diseases. Here, we review the most recent advances in the biological effects of PIK3CA mutations in venous malformation and lymphatic malformation pathogenesis towards the implementation of new targeted therapies for these diseases. Also, we propose lymphatic malformations and venous malformations to be considered as developmental tumours considering their genetics and biology.

**PIK3CA SIGNALLING IN VASCULAR BIOLOGY**

PIK3CA encodes for the p110α lipid kinase protein, one of the four p110 catalytic subunits of the class I PI3Ks [11]. In cells, p110 isoforms exist in a heterodimeric complex with a regulatory subunit.

Based on the regulatory subunit binding preferences, they are grouped in class IA (p110α, β and δ) and class IB (p110γ). Class IA isoforms bind to a p85 regulatory subunit (there are five variants: p85α, p55α, p50α, p85β, and p55γ), while class IB isoform binds either to p84 or p101 regulatory subunits. The regulatory subunits prevent from p110s protein degradation, but also, the p85 subunits keep p110α, β and δ in an inactive cytosolic state. Activation of class IA PI3Ks can occur by three modes, all of which start with binding of a ligand to receptor tyrosine kinases (RTKs). First mode of activation occurs through a direct binding of p85 to RTKs allowing conformation change and activation of the p110 subunits. Another way of activation occurs through adaptor proteins such as the GRB2/GAB complex which bind p85 upon being recruited to RTKs. Finally, the small GTPases may also activate class I PI3Ks by interacting with the so called RAS binding domain contained in the p110 catalytic subunits. In addition, the p110β subunits can be activated by G protein-coupled receptors [12].

Class I PI3Ks activation generates the lipid phosphatidylinositol-3,4,5-triphosphate [PI(3,4,5)P3], which may be metabolised to PI(3,4)P2 by 5-phosphatases such as SHIP (SH2 Domain-Containing Inositol 5’-Phosphatase 1). Both, PI(3,4,5)P3 and PI(3,4)P2 act as second messengers by interacting with lipid-binding pleckstrin homology domains in a variety of protein effectors and regulating their localization and/or activity. The main PI3K effector proteins include protein kinases (being the serine/threonine kinase AKT the most well known), regulators of GTPases and scaffolding proteins [13]. This plethora of downstream mediators allows PI3Ks to regulate cell growth, metabolism, survival, and proliferation in physiology and disease [11,13]. The 3-phosphatase PTEN (Phosphatase and Tensin Homolog) inhibits class I PI3K signalling by dephosphorylating PI(3,4,5)P3 and PI(3,4)P2.

All class I PI3K isoforms produce the same lipid but they regulate distinct physiological functions. This is partially explained by their relative expression levels in different cell types and by their mode of activation by upstream signals [11]. In agreement with the presence of activating mutations of PIK3CA in venous malformations and lymphatic malformations, and not yet identified other mutant PI3K isoforms, p110α is the sole isoform required for blood and lymphatic vascular development [14–16]. The catalytic domain of p110α has been reported to be necessary for angiogenesis and lymphangiogenesis [14,15]. In contrast, blocking the ability of p110α to bind RAS impairs lymphatic vascular development only [16]. This indicates that
p110α capacity to respond to upstream signals is different in blood and in lymphatic vessels’ endothelial cells. Understanding how this occurs might shed light into the pathogenic mechanisms of \( PIK3CA \) mutations in venous malformations and lymphatic malformations.

An interesting observation from mouse gene targeting studies (including ubiquitous and endothelial cell-specific models) is that too much and too little activation of p110α leads to embryonic lethality due to incomplete development of blood vessels [9*,14,17,18]. This suggests that endothelial cells are extremely sensitive to PIP₃ fluctuations, and that its levels need to be tightly regulated for an adequate formation of the vascular plexus. This might also explain why activating mutations in \( PIK3CA \) have only been identified somatically and in a mosaic fashion as the presence of activating mutations in the germline is incompatible with life (Fig. 1). From a biological perspective, the study of loss-of-function genetic models have unravelled that p110α signalling critically regulates collective cell migration during angiogenesis. Specifically, p110α signalling prevents NUAK1-dependent phosphorylation of the myosin phosphatase targeting-1 protein. This allows myosin light chain phosphatase activity which reduces actomyosin contractility [19*]. It remains to be unravelled whether these biological processes are also relevant in the pathogenic endothelium upon expression of activating mutations of \( PIK3CA \). In line with this, defective cell migration cause capillary-venous malformations when endothelial cells are unable to redistribute within the vascular network [20]. Taken together, it is tempting to speculate that aberrant endothelial cell migration also accounts for the pathogenic mechanism induced by activating mutations in \( PIK3CA \) in lymphatic malformations and venous malformations.

### Oncogenic \( PIK3CA \) Mutations in Lymphatic Malformations and Venous Malformations

\( PIK3CA \) mutations occur in most lymphatic malformations patients [21*] whereas \( PIK3CA \)-mutations in venous malformations are less common, being present in 25–30% of the cases [7,8*,9*]. These discoveries are in line with previous and consequent findings of oncogenic \( PIK3CA \) mutations in the so-called PROS (\( PIK3CA \)-Related Overgrowth Spectrum) which also present vascular malformations [22]. This suggests that \( PIK3CA \) mutations appear at different stages during embryonic development affecting different cell types and in a mosaic fashion which leads to the broad spectrum of syndromes caused by these mutations [23]. Since isolated lymphatic malformations and venous malformations are usually localized lesions, it is tempting to speculate that, in these cases, mutations occur late during development, affecting a single clone of endothelial cells (Fig. 1). However, the cell of origin of these malformations is still a mystery; whether they come from an endothelial cell progenitor or an already venous/lymphatic-committed endothelial cell remains unknown. In fact, since lymphatic vessels arise from primitive lymph sacs within veins [24], lymphatic malformations and venous malformations might arise from the same cell lineage at different embryonic stages. This is

![PIK3CA MUTATIONS](image)

**FIGURE 1.** Effect of germline and somatic \( PIK3CA \) mutations during embryonic development and adulthood.
plausible since very often lymphatic malformations and venous malformations are mixed malformations with the presence of abnormal lymphatic and blood vessels within the lesion. Furthermore, lymphatic malformations appear filled with both lymphatic fluids and blood. This speculation highlights that single cell-tracing in-vivo studies might be of the utmost importance to reveal the cellular origin of lymphatic malformations and venous malformations and better understand their pathogenesis.

Like in epithelial cancer, the most common mutations found in lymphatic malformations and venous malformations are activating mutations in the helical (E542K, E542K) and kinase (H1047R, H1047L) domains of PIK3CA [25]. In fact, these are the so-called oncogenic mutations in PIK3CA. These two types of mutations lead to a constitutive binding of p110α to the plasma membrane by two different and independent gain-of-function mechanisms both of which trigger an overactivation of the PI3K signalling pathway [26,27]. It is still unclear whether helical or kinase mutations prevail one over the other in these lesions. Other less studied activating mutations in PIK3CA have been also found in lymphatic malformations and venous malformations [10**,21*,28,29**]. To date, there is no well known correlation between any particular PIK3CA mutation and phenotype. However, a recent study including data from sixteen institutions has given valuable information about the genetic landscape of vascular anomalies with broad phenotypic severity [29**]. A critical question is whether higher activation (helical and kinase mutations) leads to more aggressive phenotypes in lymphatic malformations and venous malformations.

BIOLOGY OF PIK3CA MUTATIONS IN LYMPHATIC MALFORMATIONS AND VENOUS MALFORMATIONS

With the discovery of PIK3CA mutations in lymphatic malformations and venous malformations, the next required step for fundamental researchers in the field is to understand their biological effect in the pathogenesis of these diseases. For this, there has been developed a wide spectrum of in-vitro and in-vivo models of lymphatic malformations and venous malformations: from cell lines ectopically expressing the mutations to sophisticated genetic mouse models of the diseases (Table 1). By

Table 1. Experimental in-vitro and in-vivo models of PIK3CA-driven lymphatic malformations and venous malformations

| Disease | Model | Molecular mechanism | Organismal phenotype and cellular mechanism | Ref. |
|---------|-------|---------------------|------------------------------------------|------|
| LM | Lymphatic endothelial cells from human LMs | Uptregulation of VEGFR3 and neuropilin-2 | Increased cell proliferation | [6] |
| LM | Lymphatic endothelial cells from human LMs | Uptregulation of VEGF-C and CXR2, Downregulation of ANG-2 and CCR4 | Increased sprouting; reduced doubling time | [30] |
| LM-GLA | Mouse model of adult LM-GLA: lymphatic endothelial cell expression of mutant Pik3ca | na | Hyperplastic lymphatic network. Functional impairment of lymphatic vessels. Increased cell proliferation | [32] |
| VM | HUVECs with ectopic expression of mutant PIK3CA | Downregulation of ANG-2 and PDGFB | Abnormal morphology of endothelial cells. Loss of ECM fibronectin | [7] |
| VM | Mouse model of congenital VMs: mosaic expression of mutant Pik3ca in the embryonic mesoderm under its endogenous promoter | Downregulation of Pdgfb and arteriovenous specification markers | Congenital VMs (cutaneous and internal). Systemic effects: phlebectasia of internal veins, bleedings Endothelial cell hyperproliferation; loss of mural cell coverage | [8**] |
| VM | Mouse model of adult VMs: ubiquitous expression of mutant Pik3ca | Downregulation of ANG-2 | Adult VMs (cutaneous and internal). Systemic effects: increased α-dimer levels Endothelial cell hyperproliferation. Aberrant tube formation | [9**] |
| VM | Patient-derived VM-endothelial cell mouse xenograft model | na | Scarce mural cell coverage | [10**] |
| VM | Mouse model of VMs: endothelial-specific expression of mutant Pik3ca | Uptregulation of VEGFR3 and neuropilin-2 | Adult internal VMs. Recruitment of inflammatory cells to the VM. Increased cell proliferation and senescence. Enhanced angiogenic sprouting | [33] |

ANG-2, angiopoietin-2; COX2, cyclooxygenase 2; CXR4, C-X-C motif chemokine receptor 4; ECM, extra-cellular matrix; GLA, generalized lymphatic anomaly; HUVECs, human umbilical vein endothelial cells; LMs, lymphatic malformations; na, not applicable; PDGFB, platelet derived growth factor subunit B; VEGF-C, vascular endothelial growth factor C; VEGFR3, vascular endothelial growth factor receptor 3; VMs, venous malformations.
integrating these very recent studies we have gained an extensive molecular and cellular insight into the pathogenesis of lymphatic malformations and venous malformations. Importantly, these studies have served as critical proof-of-concept for the use of targeted therapies in these diseases. However, these are still very early days for a comprehensive and deep understanding of the pathogenesis of lymphatic malformations and venous malformations and many questions are still unanswered since their genetic cause was only recently discovered. Yet, great advances in the molecular and cellular processes underlying the pathogenesis of lymphatic malformations and venous malformations have been made (Fig. 2). Most of the fundamental and preclinical studies in lymphatic malformations have been made using human lymphatic malformation-derived endothelial cells [6,21,28,30–32]. These works, apart from discovering PIK3CA onco-
genic mutations in lymphatic malformations, have demonstrated that PIK3CA-mutant lymphatic endothelial cells show enhanced proliferation and sprouting capacity. Also, in-vitro preclinical studies reveal that PI3K pathway inhibitors effectively block PI3K pathway overactivation and proliferation. However, the inhibitors tested (mostly pan-PI3K and PI3K downstream pathway inhibitors) are not specifically targeting mutant cells since they also impaired cell growth in normal lymphatic endothelial cells. At the molecular level, these studies assess the expression of lymphangiogenic factors on PIK3CA-mutant cells. They show that vascular endothelial growth factor C, vascular endothelial growth factor receptor 3, and neuropilin-2 are over-
expressed in these cells, while angiopoietin-2 (ANG-2) and C-X-C motif chemokine receptor 4 are down-regulated, leading to proangiogenic properties of these cells [6,30]. Even though these studies have much helped in the understanding of lymphatic malformation pathogenesis, yet, unbiased, high-

**FIGURE 2.** Molecular and cellular mechanisms driven by PIK3CA mutations in the pathogenesis of lymphatic malformations and venous malformations.
throughput molecular approaches will allow to decipher new key players in the generation and maintenance of lymphatic malformations. Moreover, genetically engineered animal models of this disease (such as mice or zebrafish) will strongly benefit the field by providing highly valuable preclinical tools to test potential molecular therapies for lymphatic malformations. This will also generate crucial knowledge in its pathogenesis, such as deciphering the cell origin, mutant-cell dynamics or the involvement of other cell types. A very recent study has provided the first PIK3CA-driven mouse model of lymphatic malformations [32]. Although this mouse model resembles generalized lymphatic anomaly (GLA), where the lymphatic malformations are diffuse or multifocal, it serves as a preclinical model of lymphatic malformations. Indeed, the authors show clinical improvement in these mice when treated with the mammalian target of rapamycin inhibitor rapamycin and this was further supported in a pilot clinical assay. Still, this model expresses the mutant form of Pik3ca under the Rosa26 locus which might lead to nonphysiological expression levels of Pik3ca. It is possible then that some of the biological effects occurring in these mice are caused by abnormal mutant Pik3ca overexpression; this might be overcome by using a mouse model expressing mutant Pik3ca under its endogenous promoter.

Biological research on PIK3CA-driven venous malformations is a step further compared with lymphatic malformations, probably due to the development of xenograft and genetic mouse models of this disease [8*,9*,10**,33]. Critically, when the transgenic mouse model finely reproduces the cause of venous malformations (Pik3ca mutation expressed under its endogenous promoter in a mosaic fashion within the embryonic mesoderm) these lesions fully recapitulate the systemic effects occurring in humans with isolated venous malformations such as intravascular coagulopathy (high p110α-dimer levels) or phlebectasias of the main internal veins [8*]. This highlights the need to use accurate preclinical models to assess therapy efficacy. Venous malformations mouse models have further demonstrated the exceptional sensitivity of endothelial cells for Pik3ca alterations since ubiquitous and nonendothelial specific expression of mutant Pik3ca leads to the development of venous malformations. The cellular phenotype triggered by oncogenic PIK3CA mutations in venous malformations is similar to lymphatic malformations, where endothelial cells show enhanced proliferation [8*,9*,10**,33]. Also, Pik3ca-driven venous malformations in mice show scarce mural cell coverage, a feature typically observed in human venous malformations [8*]. At the molecular level, targeted approaches have shown that platelet derived growth factor subunit B and ANG-2 expression is reduced in PIK3CA mutant endothelial cells, which could contribute to the poor mural cell coverage in these lesions [8*,9*]. Arteriovenous specification markers are also reduced in these mutant cells, supporting the idea of a dedifferentiated or progenitor-like state of these cells. In-vivo preclinical studies for venous malformations have demonstrated that rapamycin and the p110α-specific inhibitor BYL719 are effective in reducing venous malformation lesions as well as limiting the systemic effects of these malformations [8*,9*]. These drugs reduce PIK3CA-mutant endothelial cell proliferation; however, for already-established venous malformations which are low proliferative the mechanism of action of these inhibitors in still unclear.

**ARE LYMPHATIC MALFORMATIONS AND VENOUS MALFORMATIONS DEVELOPMENTAL TUMOURS?**

Lymphatic malformations and venous malformations are a collection of abnormal and nonfunctional vascular channels in which the vascular vessels are dedifferentiated and immature, and they lack mural cell coverage. Lymphatic malformations and venous malformations have long been considered ‘vascular malformations’ but not ‘vascular tumours’. This is partially based on the observation that in adults these vascular malformations are relatively static [34,35]; hence these lesions are considered slow proliferative malformations. This is compatible with the fact that the vasculature primarily expands during embryonic development and remains quiescent in adulthood. Furthermore, it suggests that the presence of the mutation in only endothelial cells is not sufficient to result in high proliferative vascular lesions, and thereby growth factor signals are required to promote proliferation. In line with this, endothelial cell hyperproliferation during vasculogenesis has previously been shown to give rise to vessel hyperfusion and to result in dilated, dysfunctional vessels, similar to those found in venous malformations [36]. Yet, it should be taken into consideration that PIK3CA-driven lymphatic malformations and venous malformations do share most of the typical characteristics of the so-called childhood solid tumours or developmental solid tumours [37,38]. Lymphatic malformations and venous malformations are rare congenital entities: they arise as a consequence of genetic errors during development. The cell of origin of lymphatic malformations and venous malformations is mesodermal, as mainly occurs in paediatric tumours. In
paediatric tumours, often, a single, specific driver alteration might promote cancer development in certain cell lineages during a crucial developmental period. In lymphatic malformations and venous malformations, a single PIK3CA activating mutation is sufficient to develop the lesion when affecting endothelial cells, a cell type that has been proven to be extremely sensitive to PIK3CA alterations. In addition, the same PIK3CA mutations occurring in lymphatic malformations and venous malformations are frequently found in adult epithelial tumours such as breast or colon [39]. However, in contrast to lymphatic malformations and venous malformations, epithelial adult tumours bearing PIK3CA mutations need a multiple-hit process in which genetic alterations accumulate before the onset of the tumour. The current paradigm posits that lymphatic malformations and venous malformations do not metastasize which fits with the fact that most of these malformations are presented as isolated lesions. However, occasionally there are patients in which the disease is manifested as multifocal. This has been described for venous malformations carrying mutations in the TEK gene [39], an upstream activator of p110α, and for GLA carrying mutations in PIK3CA [32]. Yet, it is not known whether these multifocal lesions within the patient have arisen from the same early precursor or the lesions derive from others through dissemination or metastasis. Although the current studies provide valuable insights, much work on clonal evolution is still required to complete this picture. With these premises, the current classification of lymphatic malformations and venous malformations calls for a debate.

**FUTURE PERSPECTIVES AND THERAPEUTIC OPPORTUNITIES**

The discovery of oncogenic PIK3CA mutations as drivers of lymphatic malformations and venous malformations has opened an enormous window of opportunities for the fundamental understanding of the pathogenesis of these malformations as well as of the role of this key gene in the disease. There is no doubt that this has also had an invaluable impact on the way these patients are managed; from diagnostic approaches to therapeutic opportunities. To optimize efforts in the path to discover new molecular players and cellular processes driven by PIK3CA mutations in lymphatic malformations and venous malformations, we advise to always keep in mind the ‘oncogenic’ nature of these mutations. Indeed, most of the functional research done so far has been focused on assessing the proliferative and growth capacity of mutant cells. In line with this, findings made in the cellular and molecular mechanisms driven by oncogenic PIK3CA mutations in a cancer context might be applied to understand the pathogenesis of these vascular malformations. For instance, it has been shown that oncogenic PIK3CA leads to centrosome amplification and tolerance to spontaneous genome doubling, which might account for irreversible genetic changes in tumours with these mutations [18]. Another example of the biological impact of these mutations in epithelial cancer is the switch on cellular metabolic requirements [40]. Might these mechanisms be also applied to PIK3CA-driven lymphatic malformations and venous malformations? Also, the experimental approaches to assess the molecular mechanisms triggered by PIK3CA mutations in lymphatic malformations and venous malformations have been mostly biased, based in the canonical PI3K signalling pathway where activation of AKT is at the core of the pathway. Therefore, a holistic approach using a combination of high throughput technologies will be very valuable to decipher new molecular players involved in the pathogenesis of these diseases. This will impact in the development of novel therapies in combination with PI3K inhibitors.

At present, lymphatic malformations and venous malformations are often treated with rapamycin or rapamycin analogues such as everolimus or sirolimus with success in the improvement of lesions and quality of life of patients [41]. However, these malformations do not significantly regress or disappear upon rapamycin treatment [41]. The use of p110α-specific inhibitors, which are currently on clinical trials for cancer [42,43], might be a better option for lymphatic malformations and venous malformations caused by PIK3CA mutations. Still these inhibitors are currently used at maximum-tolerated doses in cancer patients making these drugs poorly tolerated by the patients. Also, when used at high concentrations, they induce signalling feedback loops that can block their effect. A recent successful study treating PROS patients with the p110α-specific inhibitor BYL719 has given new hope for venous malformations and lymphatic malformations patients [44**]. Thus, long-term treatment with low-dose of p110α inhibitor could normalize aberrant PI3K signalling avoiding systemic toxicity and be effective in reducing or eliminating PIK3CA-driven vascular malformations. The efficacy of these drugs at low doses is crucial taking into account that these are congenital diseases and most patients are paediatric. Similar to developmental tumours, lymphatic malformations and venous malformations carrying a single mutation might be much more sensitive to targeted therapies than...
CONCLUSION

Since the discovery of PIK3CA mutations in lymphatic malformations and venous malformations, not other genetic alteration has been found in these diseases. Yet, the genetic causes of all lymphatic malformations and venous malformations cases have not been identified; thus, the discovery of new genetic events in these diseases will be crucial to apply targeted therapies. In line with this, the comprehensive genetic landscape of lymphatic malformations and venous malformations will lead to an accurate stratification of these patients. Likewise, unbiased molecular approaches might shed light on unexpected roles of PIK3CA mutations in the pathogenesis of these vascular malformations which might lead to the development of novel therapeutic strategies. Lastly, we open a debate for the consideration of lymphatic malformations and venous malformations as developmental tumours; this might have a positive impact in the clinical management of these diseases.

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Conflicts of interest

There are no conflicts of interest.

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