Why are lesions multifocal?

Inherited Genetic Causes of Vascular Anomalies

Cutaneous Venous Malformation (VMCM): <1%

Variable expressivity within family members

Activating inherited TIE2/TEK mutation

• Autosomal-dominant
• Multiple, small VMs, more with time
• Variable presentation
• High penetrance: 98%
• D-dimers often elevated

Activating inherited TIE2/TEK mutation

Cutaneomucosal Venous Malformation (VMCM); <1%

Variable expressivity within family members

Multifocal CMs (25) with halo and AVM in left hand. Tortuous arteries on T1-weighted MRI

RASA1: c.2035C>T; p.Arg679X

Variable expressivity within family members

Central AVM on T2 weighted MRI (pial arterial aneurysm and draining vein)
Variable expressivity within family members

- Germline predisposing mutation
- Somatic second-hit (double-hit)

VMCM-TIE2
GVM-glomulin
CM-AVM1–RASA1

Variable expressivity, lesions multifocal and small, increase in number with time, penetrance < 100%

- Role of somatic mutations in sporadically occurring malformations?

Venous malformation

- Somatic activating PIK3CA mutations cause venous malformation

50% somatic, activating TIE2 mutation

- 20% Activating somatic PIK3CA mutation

Capillary Malformation (CM) & Sturge-Weber Syndrome (SWS)

- Activating somatic GNAQ, GNA11 mutation

Activating somatic PIK3CA mutation

Lymphatic Malformation (LM)

- Sporadically occurring
**PIK3CA-Related Overgrowth Syndromes (PROS)**

Sporadically occurring

Activating somatic PIK3CA mutation

**Arteriovenous malformation (AVM)**

Sporadically occurring

Activating somatic RAS/MAPK mutation

**Signaling Pathways in Vascular Anomalies**

**Preclinical Models: in vivo**

Venous Malformation Mouse Model

**Venous Malformation Mouse Model: effect of rapamycin**

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**Inhibitors?**

**Lesion area (mm²)**

*F* *p* = 0.007

Boscolo et al., J Clin Invest 2015

**Lesion area (mm²)**

Boscolo et al., J Clin Invest 2015
First Molecular Therapy for VM

Boscolo et al, J Clin Invest 2015

Rapamycin for Lymphatic Malformations

Adams et al, Pediatrics 2016

CR= complete response
PR=partial response
PD=progressive disease
SD=stable disease

Patients with vascular anomalies
1mois – 70 years
Ineffective or unfeasible conventional R/Sirolimus (Rapamycin) 2mg daily in adult or 0.8mg/m² twice daily in children

MRI
Primary endpoint
- Safety
- Efficacy
- Clinical and radiological size
- Symptoms: pain, functional limitation
- Quality of life

STOP Sirolimus

MRI

Phase III Clinical Trial: Vascular Anomaly - Sirolimus – Europe (VASE)

Coordinating Center: CUSL Brussels, Prof L Boon

Percentage of patients with Pain improvement (MMPI)

No response
1-25% improvement
26-75% improvement
>75% improvement

Percentage of patients with Functional limitation improvement (MMPI)

No response
1-25% improvement
26-75% improvement
>75% improvement

Boon and Seront et al, unpublished

https://www.clinicaltrialsregister.eu/
EudraCT Number: 2015-001703-32

Boon and Seront et al, unpublished

Abstract

Background
Sporadic vascular malformations (VMs) are complex congenital anomalies of blood vessels that lead to stroke, life-threatening bleeds, disfigurement, overgrowth, and/or pain. Therapeutic options are severely limited and multi-disciplinary management remains challenging, particularly for high-flow arteriovenous malformations (AVM).

Methods
To investigate the pathogenesis of sporadic intracranial and extracranial VMs in 160 children in which known genetic causes had been excluded, we sequenced DNA from affected tissue and optimised analysis for detection of low mutant allele frequency.

Results
We discovered multiple mosaic activating variants in four genes of the RAS-MAPK pathway, KRAS, NRAS, BRAF and MAP2K1, a pathway commonly activated in cancer and responsible for the germ-line RASopathies. These variants were more frequent in high-flow than low-flow VMs.

In vitro characterisation and two transgenic zebrafish AVM models which recapitulated the human phenotype validated the pathogenesis of the mutant alleles. Importantly, treatment of AVM-BRAF mutant zebrafish with the BRAF inhibitor, Vemurafenib, restored blood flow in AVM.

Conclusions
Our findings uncover a major cause of sporadic vascular malformations of different clinical types, and thereby offer the potential of personalised medical treatment by repurposing existing licensed cancer therapies.
After 2 years of thalidomide (50 mg/day)

CONCLUSIONS

* ISSVA classification is essential to speak a common language to get the proper diagnosis (www.ISSVA.org)

* Vascular Anomalies are caused by genetic alterations
  1) inherited forms: LOF+2nd hit
  2) sporadic forms: somatic activating mutation
  3) slow-flow vascular anomalies: PIK3CA/AKT/mTor signaling
  4) fast-flow vascular anomalies: RAS-MAPK signaling
  5) Inhibitors!

Patients organization www.vascapa.org

Collaborative prospective studies European Reference Networks VASCERN — Vascular Diseases

Translational research

Thank you!

Human Molecular Genetics Center for Vascular Anomalies, Saint-Luc Clinics