

Hemangiomas & Vascular Malformations

Research Update 2017

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National Leadership

The Hemangioma and Vascular Malformation Center (HVMC) is a leader within the International Society for the Study of Vascular Anomalies (ISSVA) and a regular presenter at ISSVA conferences. At ISSVA's 21st annual meeting in April 2016 in Buenos Aires, Argentina, the HVMC team members described their research.

ISSVA 21st Annual Meeting Presentations by HVMC

Lead	Study
Paula Mobberley-Schuman, MS	The mTOR Inhibitor Sirolimus for the Treatment of Complicated Vascular Anomalies: A Retrospective Review of Medical Records
Adrienne Hammill, MD, PhD	Zometa and sirolimus
Adrienne Hammill, MD, PhD	HHT in Children: Symptomatic pediatric presentations of arteriovenous malformations (AVMs) in previously undiagnosed families
Tomoyuki Mizuno, PhD	Developmental Pharmacokinetics of Sirolimus: Implications for dosing in neonates and infants with vascular anomalies
Kiersten Ricci, MD	GLA and Gorhams from Retrospective Sirolimus study and SIR-DA-0901
Belinda HsiDickie, MD, PhD	Evidence For Somatic Mutations that Complement Activating PIK3CA Alleles in Determining the Growth and Metabolism of Lymphatic Malformation-Derived Endothelial Cells
Tim LeCras, PhD	Biomarkers from SIR-DA-0901
Denise Adams, MD	Clinical case series of Hepatic Angiosarcoma
Jennifer Davis, Do	SIR-DA-0901 Long term follow up of patients
Anita Gupta, MD	Seven-year-old male with a PTEN hamartoma of soft tissue (PHOST) arising in the stomach:
Roshni Dasgupta, MD	Propranolol versus Steroids for the Treatment of Ulcerated Hemangiomas

Adrienne Hammill, MD, PhD	Sirolimus for the treatment of Juvenile Nasopharyngeal Angiofibroma
Miho Watanabe, MD	A single center experience of prenatal diagnosed lymphatic malformation

Dr. Hammill chairs the Practice Committee of American Society of Pediatric Hematology- Oncology (ASPHO) Vascular Anomalies Special Interest Group (SIG). The goal of SIG is to teach other doctors and to provide groundwork for the development of a combined group to study vascular anomalies. Collaboration is important for rare diagnoses to ensure enough patient numbers be pooled to provide meaningful data.

Clinical Research Highlights

HVMC provides excellent multidisciplinary care for infants, children and young adults. Clinical care improves by a mixture of clinical research, new drug investigation and discoveries in the understanding of vascular biology. Scientific study of vascular tumors and vascular malformations is an important and growing area of research. HVMC team researchers in the laboratory help the medical community better understand the conditions, develop new treatments and improve quality of life for our patients.

Current studies enrolling at this time include:

- [Registry for Sturge Weber Syndrome](#)
- [Urine Biomarkers for Sturge Weber Syndrome](#)
- Lymphatic Anomalies Registry
- Rare Benign Tumor Registry
- HVMC Tissue Repository
- [A Prospective Study evaluating the use of Spinal Angiography prior to Indirect De-tethering in Patients with Recurrent Tethered Cord](#)
- [Identification of Biomarkers for Patients with Vascular Anomalies](#)

Translational Research Highlights

Laboratory research at Cincinnati Children's provides the foundation for original treatments. This has become a major goal for HVMC.

Greater understanding of vascular development



Knowing how genes regulate normal development of the vascular system will help us to understand genetic causes and possible treatments for human vascular disorders. Researcher Saulius Sumanas, PhD uses zebrafish embryos as a model system to study how vascular systems develop. He is among a very few scientists in the world studying this key process. Similar genes control both

human and zebrafish vascular development. Dr. Sumanas is studying detailed mechanisms of blood vessel formation and identifying new genes participating in these processes. In the end, he hopes to find new genes that can be targeted for treatment of vascular disorders.

Venous Malformations

Vascular anomalies are birthmarks caused by defects in the vascular system affecting capillaries, arteries, veins or lymphatics (or a combination of these) and involve increased number of vessels and/or vessels that are enlarged and twisting. Elisa Boscolo, PhD is investigating venous malformations (VM). VMs are slow-flow lesions composed of twisting veins with irregular smooth muscle cell coverage. VMs cause defects, pain, localized intravascular coagulopathy, and they expand with time. Activating mutations in the endothelial cell tyrosine kinase receptor TIE2 and PIK3CA genes are a common cause of these lesions.



Dr. Boscolo's lab recently made a mouse model of VM expressing the most frequent VM-causing TIE2 mutation TIE2-L914F to test possible drugs for their ability in stopping lesion growth. The mTOR pathway inhibitor sirolimus successfully prevented VM growth through its ability to reduce mutant TIE2-induced AKT signaling. An HVMC clinical pilot study showed clinical improvement in sirolimus treated patients with venous malformation, measured by decreases in pain, bleeding, lesion size, function, appearance and coagulopathy. Currently Dr. Boscolo's lab is testing an array of FDA-approved drugs for their effects on TIE2 mutant endothelial cells and on murine VM growth and regression to identify a drug that can be used alone, or in combination with sirolimus, to increase clinical improvement in patients.

Biomarker and Therapeutic Targets

Vascular malformations and tumors can significantly impact the well-being of affected children causing long-term health problems and even death. Final diagnosis of these diseases is challenging and usually requires a biopsy which can worsen the disease and cause severe problems. One major goal of Tim Le Cras' (PhD) laboratory is to detect biomarkers for vascular malformations and tumors.

Mechanisms driving lymphangiogenesis in these patients are unclear and therapeutic options are limited. A second goal for his laboratory is to gain insights into the mechanisms and causes of these diseases so that new therapeutic targets can be identified.

Le Cras' laboratory is based in the Pulmonary Biology Division but he has established far-reaching collaborations with physicians in the HVMC. Since these are rare but devastating diseases he collaborates with other vascular anomaly centers as well as patient advocacy groups around the U.S. to include more patients in his studies and also spread the findings beyond Cincinnati Children's. The lab actively encourages other physicians, investigators and patients to contact us if they are interested in participating in any of our studies.



Projects:

- 1) Biomarker analysis
- 2) Human cell xenograft models
- 3) Mouse models of vascular anomalies
- 4) Therapeutic targeting of vascular anomalies

Diseases under active investigation:

- 1) Generalized lymphatic anomaly (GLA)
- 2) Kaposiform lymphangiomatosis (KLA)
- 3) Kaposiform Hemangioendothelioma (KHE)
- 4) Micro and microcystic lymphatic anomalies

Pharmacokinetics of Sirolimus Dosing



Alexander A. Vinks, PharmD, PhD, FCP is the Cincinnati Children's Research Foundation Endowed Chair and Professor of Pediatrics and Pharmacology at the University of Cincinnati, College of Medicine.

Exact dosing of mTOR inhibitors in the treatment of Hemangioma and Vascular Malformations.

Complicated vascular anomalies have limited therapeutic options and cause significant morbidity and mortality. Sirolimus (rapamycin) is the first drug to show efficacy in the treatment of complicated vascular anomalies. Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) targeting the cellular signaling pathway involved in the occurrence and progression of vascular anomalies. Sirolimus is approved for use in pediatric kidney transplantation in patients aged 13 years. Dosing information for other indications is limited and no dosing guidance is available for younger children such as infants and newborns. In addition, as sirolimus exhibits large between patient variability in its pharmacokinetics (PK), a precision dosing strategy to ensure effectiveness and safety is necessary.

As part of ongoing studies we have studied sirolimus pharmacokinetics at length in pediatric patients including our population of pediatric patients with complicated vascular anomalies. Our data also include a large number of very young patients (infants and neonates) as age of initiation of sirolimus treatment may be influential in its efficacy with younger patients having a more substantial response. This has allowed us to develop PK models that predict the effects of growth and maturation on sirolimus pharmacokinetics. The sirolimus maturation model is now integrated as part of a pharmacokinetically-guided precision dosing strategy that generates dosing recommendations in real time to rapidly achieve and maintain the desired target trough concentration ranges across the different age ranges. This PK model-based approach in combination with sirolimus concentration measurements (Bayesian feedback) enables sirolimus precision dosing in children, infants and newborns with vascular anomalies. A prospective study is being planned.

First FDA-Funded Study for Complicated Vascular Anomalies:

The Phase II study, Sirolimus for the treatment of complicated anomalies completed and was published in the Journal Pediatric Blood Cancer, Volume 137: 2 in February of 2016. This study showed sirolimus to be safe and effective in the majority of patients after 12 months of treatment with minimal side effects. Further study is needed to evaluate specific disease phenotypes and to understand mechanism of action. These study participants continue to be followed for 5 years after study end to follow for possible late effects and long-term treatment effects. The plan is to use this platform for other investigational drug studies.

Recent Publications:

Beverly A. Schaefer, Dehua Wang, Arnold C. Merrow, Belinda H. Dickie, Denise M. Adams. Long-term outcome for kaposiform hemangioendothelioma: A report of two cases. *Pediatr Blood Cancer*. Oct. 2016 epub ahead of print

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