Summer 2013

Angioma Alliance Newsletter

The DNA & Tissue Bank: Helping Researchers Tackle Tough Questions

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Important New Legislation Affecting Cavernous Angioma: We Need Your Help
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Note: In this newsletter, the terms "cavernous angioma," "cavernous malformation," and "CCM" are used interchangeably.

In recent years, researchers have made excellent animal- and cell-based models of the Cavernous Angioma to study this illness. But some questions can only be addressed by looking directly at diseased tissue: cavernous angioma lesions of the brain and spinal cord. These tissues are not readily available to all researchers, particularly those who are PhD scientists and do not treat patients or perform surgery.

In an effort to facilitate the research process and to speed the pace of discoveries, Angioma Alliance manages a DNA & Tissue Bank so researchers can get access to these crucially important samples.

Researchers use DNA extracted from blood samples, surgically removed cavernous angioma tissue, and medical and family histories to help answer key questions. By collecting these raw materials and distributing them to the research community, our DNA & Tissue Bank can help to advance research for a non-invasive treatment of cavernous angioma.

As of this writing, research projects at 10 different laboratories have taken advantage of this incredible resource; none of these projects would have been possible without the donations and generosity of our Angioma Alliance community. And you can help too. Here's how.

Who can participate?

Participation in the DNA/Tissue Bank is limited to individuals affected by cavernous angioma who:

- Have had surgery,
- Are scheduled to have surgery, or
- Who have multiple cavernous angiomas and/or a family history of the illness.

What is required of participants?

- Read and sign our information and consent form.
- Sign and return medical, imaging, and/or tissue release forms.
- Provide a blood sample.
- Complete a 90-minute phone interview with our nurse.
- Complete a 15-20 minute annual update phone interview with our nurse.

How can you sign up?

Complete and submit the interest form on the Angioma Alliance website at www.angioma.org/DNA. Amy Akers will then contact you to begin the enrollment process.

Current DNA & Tissue Bank Projects

The following summaries show the types of questions being investigated with the help of the DNA & Tissue Bank:

(Cont.)

Brigham and Women's Hospital and Harvard Medical School

Dr. Tanya Mayadas, PhD, describes her project (Note: endothelial cells are those that make up blood vessels):

> We are interested in endothelial-mediated permeability that is regulated by CCM proteins. Our recent work in zebrafish models and cell culture systems suggests that CCM2 may regulate a stress related pathway that is important in maintaining the integrity of the endothelium. We propose to determine whether markers of this pathway are present in the endothelium of human lesions.

UCSF & UNM – Brain Vascular Malformations Consortium

This study is ongoing and continues to recruit participants. According to Dr. Helen Kim, PhD:

> The goal of our research is to: (1) better understand the natural history of CCM1 by following a cohort of patients with the common Hispanic mutation (CHM) over a five-year period; and (2) identify factors explaining why CCM1-CHM patients have such a wide range in disease severity, even among members of the same family. This study will provide important information in this unique study population and serve as a baseline for future interventional studies of treatment for patients affected with this disease.

University of North Carolina at Chapel Hill

According to Dr. Gary L. Johnson, PhD:

> Endothelial cells, the cells that make up blood vessels, maintain vascular integrity through a complex balance of signals, ultimately resulting in appropriate shaping of the cytoskeleton: the network of fibers that gives a cell shape, adhesion, and motility. Recent research has shown that levels of RhoA, a protein responsible for cytoskeleton dynamics, is greatly increased in endothelial cells missing any of the three CCM proteins in vitro.
>
> Additionally, endothelial cells lacking the CCM proteins show a number of defects that are consistent with problems rearranging the cytoskeleton. Using tissue from patient samples, we hope to validate our in vitro findings in human [tissues]. This work will provide insight into the molecular mechanisms by which loss of CCM protein leads to the CCM clinical condition.

Max Delbruck Center for Molecular Medicine in Berlin

Dr. Salim Seyfried, PhD, describes his project:

> Our primary interest is to understand the role of the cerebral cavernous malformation (CCM) proteins in cardiac tissue. We use the embryonic zebrafish as a disease model to address this question. Zebrafish mutants that completely lack CCM proteins have ballooning and hypotrophic hearts that lack blood flow. Similar cardiac defects have also been described in CCM protein-deficient mice. Our studies in zebrafish have helped us to identify a molecular pathway that may also be relevant for defects that occur in cerebral blood vessels of CCM patients. We would now like to elucidate the potential relevance of this finding for patients.

Duke University Medical Center

Donated tissue to the Angioma Alliance DNA & Tissue Bank made possible the research by Amy Akers, while she was in Dr. Doug Marchuk's lab at Duke University. Dr. Akers describes her project:

> CCMs can develop sporadically, but the risk to develop CCMs can also be inherited by mutation in one of three recently identified genes. The presence of single lesions in sporadic cases, and multiple lesions in inherited cases, has led us to hypothesize that CCM lesion formation follows the Knudsonian two-hit mechanism. The two-hit mechanism occurs when a person has one inherited mutation in a CCM gene and then acquires another mutation in specific cells. We believe that acquiring the second mutation is necessary for lesion formation. We can test our hypothesis by analyzing human CCM lesion tissue for the presence of two mutations.
>
> This study has been completed and published results describing the two-hit mechanism for familial CCM are available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640209/ Additional studies on sporadic CCM are ongoing.

University of Michigan

Dr. Anuska Adjeckovic-Zochowska, PhD, describes her project:

> Normally the brain is protected from changes in the bloodstream by the blood-brain barrier situated at the brain blood vessels. Defects in that barrier may be important for developing stroke, epilepsy and other neurological diseases [including CCM].
>
> The purpose of this study is to highlight the molecular mechanisms underlying vessel hyperpermeability in this condition. In particular, the proposal will address how CCM3 protein affects the organization and stability of brain endothelial tight junction complex. This may provide a foundation for developing novel therapeutic strategies to lessen the impact of this disease as well as other neurological conditions that affect the blood brain barrier.

Thomas Jefferson University

Dr. Thomas Force, PhD, describes his project:

> We have been studying the mechanisms that lead to the generation of cavernous malformations. We have a great deal of evidence in cells about the way a mutation in PDCD10 [CCM3 gene] leads to the CCM3 malformations. However, this evidence is only in cultured cells and we need to determine if this could be the mechanism in patients. We can only accomplish this by directly studying tissue obtained from patients with malformations.
>
> As far as the proposal's significance, by identifying the mechanism by which PDCD10 mutations lead to malformations, and the specific proteins involved in the process, potential therapeutics could be generated to prevent the development and/or progression of CCMs.

Northwestern University

According to Dr. Issam Awad, MD:

> Cerebral cavernous malformations (CCMs) affect more than 1 million Americans, predisposing them to a lifetime risk of hemorrhagic stroke and epilepsy. Immunoglobulin and other related genes are markedly upregulated within human CCM lesions. Preliminary work suggests the infiltration of B-lymphocytes and plasma cells within the lesions.
>
> A potential role of the immune response in this disease has not been postulated previously, but would be compelling, given the unique antigenic milieu of CCM lesions with sequestered thrombi and leaky blood-brain barrier, and the numerous examples of immune modulation of angiogenesis in other disease states. It could explain, in part, why some CCM lesions remain biologically dormant, while other proliferate with serious clinical consequences.
>
> Immune response could play a role in, or represent, a potential marker of cerebral cavernous malformation lesion proliferation and hemorrhage. The proposed pilot studies will generate preliminary data for future research aimed at comparing the immune response in quiescent versus clinically aggressive CCM lesions and would stimulate future research to identity autoimmune or extrinsic antigenic triggers involved in CCM disease.

SickKids Hospital in Toronto, Canada

Dr. W. Brent Derry's Lab uses a worm model to study CCM and he describes his study below:

> Cerebral Cavernous Malformations (CCMs) are defects of the brain capillaries that can arise by inheritance of mutations in one of three 'familial' genes (CCM1, CCM2 or CCM3), or sporadically by unknown mechanisms.
>
> Our lab has developed a novel model of CCM in the genetically tractable roundworm Caenorhabditis elegans. The lab has discovered several genes that regulate the function of the familial CCM genes, and will sequence genomic DNA from CCM patients that do not have mutations in CCM1-3 to obtain a comprehensive understanding of the genetic basis of this disease.
>
> The ultimate goal of this work is to discover therapeutic targets that can be exploited for the clinical management of CCM in humans.

The University of Utah

This research team has worked to develop unique animal models for CCM and has utilized samples from Angioma Alliance's DNA & Tissue Bank to validate their work. According to Dr. Kevin Whitehead:

> One of the biggest obstacles to research into Cerebral Cavernous Malformations is our inability to study the physiology of the disease in a living organism. When CCMs occur in humans, we can only observe them; however, to truly understand this disease, we must be able to manipulate the malformations and try potential treatments under controlled conditions. Therefore, it is of paramount importance that we create an animal model of CCM disease. In order to be sure that the animal model is an accurate representation of the human disease, we must compare any animal tissue with actual human CCMs.

If you have participated in the DNA & Tissue Bank and/or have contributed to Angioma Alliance in another way, thank you! Your generosity has provided a tremendous resource to researchers who are using these precious samples to tackle some tough questions and make amazing advances in research.

To learn more about the DNA & Tissue Bank, please visit www.angioma.org/DNA

Amy Akers

9th annual CCM Scientific Meeting

The 9th annual CCM Scientific Meeting will be held on November 7-8, 2013, in Washington, DC. The CCM Meeting is a wonderful conference that attracts a broad range of researchers who present projects from distinct fields, all of which contribute to a more complete understanding of CCM disease biology. Because we encourage meeting attendees to openly share and discuss unpublished data, the Scientific Meeting is not open to the public.

It is the goal of Angioma Alliance to continue to host this annual series to help further scientific progress and drive research for a cure of CCM.

Five Years of the Brain Vascular Malformations Consortium

Ten years ago, the NIH Office of Rare Diseases Research launched a unique funding mechanism designed to connect scientists, clinicians and advocates to study rare diseases as a collaborative research team. Teams seeking funding under this cooperative design were required to include patient advocacy groups as research partners. This initiative is the first of its kind to require the participation of advocacy groups.

To take advantage of this great opportunity, Angioma Alliance worked with two other advocacy groups (The Sturge-Weber and HHT Foundations), fostered a collaboration, and encouraged our expert researchers to apply for this cooperative grant. Funding was awarded to the team, now called the Brain Vascular Malformations Consortium (BVMC), and we are nearing the end of the 5-year study. Dr. Amy Akers, our Chief Scientific Officer, is a member of the BVMC Executive Committee serving as Angioma Alliance's project representative.

The BVMC aims to study these three neurological and vascular disorders to better understand the biology, to improve patient treatment and clinical management, and to support clinical trials for a cure. These studies are continuing to enroll participants, and more information can be found at: http://rarediseasesnetwork.epi.usf.edu/BVMC/.

The project team members for the BVMC studies extend beyond researchers and advocates; the involvement of others has been critical to the success of these studies. Those include The National Institute of Neurological Disorders and Stroke (NINDS), The Data Management and Coordinating Center (DMCC), and patient participants.

We'd like to highlight some of the exciting discoveries and research advancements that have occurred thanks to this unique granting mechanism.

First Ever Clinical Trial for Cavernous Angioma!

Cavernous Angioma disease-causing genes have been previously identified; the BVMC studies for this illness are focused on treatment and better understanding of the wide range of clinical symptoms suffered by Cavernous Angioma patients.

Even among members of the same family, Cavernous Angioma symptoms vary greatly; BVMC

researchers are trying to understand this variability. The project team (including Dr. Leslie Morrison at the University of New Mexico and Dr. Helen Kim at the University of California at San Francisco) is collecting genetic, clinical and environmental information from 500 individuals with the Common Hispanic Mutation to investigate this. This lets them look at one huge family and investigate why some people have more lesions and/or more symptoms and may require more surgeries than others. This project is entering its final year of data collection.

Each BVMC project has multiple components. Last month, the University of New Mexico announced the enrollment of the first participant in the first-ever drug treatment trial for Cavernous Angioma. (See the sidebar below.) This small study of 30 participants is exploring the effects of statin drugs in humans. Mouse studies have shown that cavernous angioma lesions are permeable; these blood vessels allow blood to leak out into the surrounding tissue. Cholesterol-lowering medications called statins have been used to reverse the leakiness in mice. Now, using specialized MRI techniques, UNM researchers are measuring lesion leakiness before and after a 3-month regime of statin drug treatment. The goal of the study is to investigate whether statin drugs can reverse the leakiness in humans and to provide preliminary data for future large-scale studies including all genetic and sporadic forms of Cavernous Angioma.

Sturge-Weber Syndrome Gene Identified!

Like Cavernous Angioma, Sturge-Weber Syndrome (SWS) is a rare vascular and neurological disorder. Individuals with SWS are born with port-wine stain birthmarks on their face and often suffer symptoms such as seizures and glaucoma. Until this BVMC study, the cause of SWS was entirely unknown; no one knew whether this illness was caused by an environmental factor, a defective gene, or something else. This lack of fundamental biological knowledge made SWS very difficult to treat and discovering a cure even more challenging.

Last month, the BVMC research team proudly announced the discovery of a genetic mutation that causes SWS. Knowing the gene responsible for causing this illness paves the way for new research topics and study questions, and gives real hope to the SWS community to someday leverage this exciting finding to develop new treatments for the illness.

Moving forward

These BVMC studies have provided a unique opportunity for investigation and collaborative research that would not have been possible through traditional research strategies. The lessons learned from working together will help us better understand the Cavernous Angioma illness, and will enable us to perform better, more efficient large-scale clinical trials in the future.

Amy Akers

Maria Elena Alvarez is a retired mother of two and a resident of New Mexico. In 2007, at age 52, Alvarez suffered from abrupt partial seizures. Alvarez was taken to the hospital where a neurology expert, Dr. Morrison, found that Alvarez suffered from cavernous angiomas located towards the back of her brain. These cavernous angiomas are caused by a genetic trait shared among Hispanics in the New Mexico area. Among her family members who have shared the illness are Alvarez's nephew, first cousin, and her daughter, who recently underwent a successful craniotomy.

After suffering from partial seizures, Alvarez described feeling as if she had a "seizure hangover." She was constantly exhausted, and felt confused and paranoid. She began seeing a physical therapist 2-3 times a week and was monitored with an EEG for four days, three weeks after her seizure. Alvarez was prescribed Keppra, an anti-seizure medication, but suffered side effects including even more confusion and exhaustion. While under EEG monitoring, Alvarez suffered several more partial seizures. Even though her daughter had undergone a successful craniotomy, Alvarez was hesitant to have the procedure herself. She said she was thankful for that decision later, as an MRI showed that more malformations had formed in Alvarez's brain, making a craniotomy impossible.

Seven years after her first seizure, Alvarez is the first person to participate in the Statin Trial Study at the University of New Mexico. In this study, participants are given a cholesterol-lowering medication called Simvastin. Over a 3-month period, doctors will study the permeability of cavernous angioma lesions to see if Simvastin can control the leakiness of the lesion blood vessels. In studies with mice, the use of statin medications strengthened blood vessels and prevented leakiness. Alvarez has been participating in the study for six weeks now and is hopeful for successful results as the study progresses. She is "happy to be a part of this new study" that hopes to reduce the dangerous reactions that result from these cavernous angiomas bleeding.

News

New Legislation to Facilitate Cavernous Angioma Drug Trials Introduced

On June 26, the New Mexico delegation introduced The Cavernous Angioma Research and Treatment Act simultaneously in the US House of Representatives and Senate. Among other things, the bill calls for the establishment of a network of cavernous angioma clinical centers throughout the US to facilitate future clinical drug trials. This legislation is for everyone regardless of mutation status—the Centers would be located around the country serving anyone with a cavernous angioma. You can find more about the legislation including the entire text at www.angiomaalliance.org/pages.aspx?content=399.

This legislation was written with the assistance of Angioma Alliance, and we need everyone's help to move it through Congress. The House version of the bill, H.R. 2521, has been sent to the House Energy and Commerce Committee for review. The Senate version, S.1223, has been sent to the Senate Health, Education, Labor and Pensions Committee.

To get the legislation out of committee, we need co-sponsors in the House and Senate. Only you can make this happen. Senators, Representatives and their staffs typically spend August in their home districts. Please make an appointment with your Representative and Senators or their Health Liaison and explain to them what a drug treatment would mean for your family. Contact information and talking points are posted on our website at the link above to help you. If you are unable to get an appointment, please leave a detailed message asking your representative to co-sponsor the bill.

Passing this legislation will have a huge impact on the pace at which we can be prepared for drug trials. Thanks for your help!

4th Annual Dallas Fun Run Best Yet

The booming thunder and lightning that accompanied the torrential rains, only hours before the anticipated start time of 9 am, did not prevent the Angioma Awareness 5K Fun Run from being the most successful yet. Rachel Hart and Savannah Hollis, the co-organizers of the event, are patients themselves, as well as Angioma Alliance board members. They attribute the run's success to the overwhelming support and loyalty of family and friends, and to the increased visibility offered by social media.

The runners, walkers, and their cheerleaders huddled under the pavilion near the starting line at T.W. Richardson Grove Park in Irving, Texas, the morning of March 24, hoping the impressive storm would pass through without incident and the run could soon begin.

However, venue regulations required the event be called off if lightning persisted for more than 20 minutes after the start time. Raffle winners were announced as participants enjoyed their Starbucks coffee and generously donated bagels from Boopa's. Spirits remained high throughout the morning as introductions were made, and as old friends caught up on the events of the past year.

The weekend has become an unofficial assembly of patients and families affected by cavernous angioma. Savannah said, "So many of us had never met a person with cavernomas before Angioma Alliance. It is amazing to see more than 20 people diagnosed with the same condition along with their families and friends running the 5K or walking the one mile together, then swapping stories over dinner."

All the while, awareness for cavernous angioma was raised, along with the funding to support Angioma Alliance's quest for new treatment options for the condition and ultimately a cure.

Participants at the Dallas Fun Run.

CCM3 Action Updates

CCM3 Action is a working group of Angioma Alliance focused on individuals with a mutation on the CCM3 gene. This appears to be an ultra-rare condition that has features not found in other forms of CCM.

CCM3 Clinical Care and Research Center

In 2012, our first year of facilitating these visits, eleven of our members had MRIs and exams at Dr. Issam Awad's CCM3 Clinic at the University of Chicago. This year, we're pleased to be sending the eleven original members for a return visit, along with an additional six patients.

In just one year, we've seen important findings from the clinic. These findings are not yet published, so we're not at liberty to reveal specifics. However, we can say that they relate to permeability of CCM3-mutated lesions and surrounding brain tissue, and to additional, significant features of the illness not found in other forms of CCM mutation.

In one case, clinic visits have also provided an opportunity for CCM3 Action patients and their families to meet. On March 26, four girls between the ages of 10-14 with a CCM3 mutation were at clinic. They had an opportunity to spend time together the day before, and families filled the pediatric sedation unit waiting for and recovering from MRIs. We hope to organize a get-together of our entire membership in the future, but in the meantime, it's great that some of our kids will have real evidence they aren't alone.

Our celebrities – CCM3 in the news

Zane Smith is the 4-year-old son of Lee and Kim Smith, active members of Cavernoma Alliance UK. Lee and Kim are determined parents who wanted the best care for Zane, and this included a visit to the CCM3 Clinic in Chicago.

Since CCM3 Action didn't have enough funds to cover such a visit, Zane's parents made an appeal to the British public through the media. When the drive was over, they had raised $14,000, including a $1,500 donation from Darren Bent, a UK soccer superstar, to fund their trip and medical expenses and to support Cavernoma Alliance UK.

Zane was also featured in a story about Dr. Awad's CCM work at the University of Chicago: sciencelife.uchospitals.edu/2013/05/02/a-critical-mass-of-knowledge-on-ccm/

Our other celebrity, 16 year old Johanna Benthal, a member in Riverhead, New York, was featured in a multimedia piece on www.Riverheadlocal.com in which she described her experience of the illness. The piece is no longer available online, but was a touching testament to the strength of one special girl.

Etsy Store and Logo Items

The CCM3 Action Etsy Store is open featuring donated handcrafted items and, now, CCM3 Action logo gear. Stop by and check out the goods at www.etsy.com/shops/CCM3Action.

Join the 2nd Annual Zombie Run

Project A2 is hosting their second annual Zombie Run on August 24th, at Kensington Metro Parks in Milford, Michigan, to benefit Angioma Alliance.

All zombies are invited and encouraged to dress up! This is a 1 mile, 5K or 10K; you choose what you run or walk. Tickets are available online through August 15th at qrickets.com/event/index.do?event.id=9305 Even if you aren't able to get to Michigan, a general admission registration will get you a t-shirt in the mail. Show your support and help us raise funds for research!

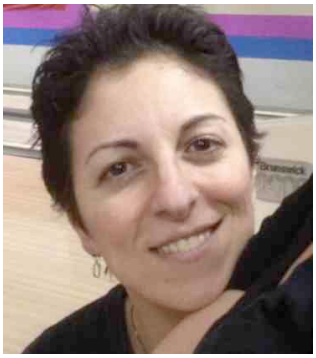
Dr. Issam Awad and Zane Smith.

MadoroM Charity Wine Auction

While the final figures aren't in as of publication time, this year's MadoroM Charity Wine Auction was a brilliant success. Liz Neuman's emotional presentation touched the hearts of attendees who responded with unbridled generosity. Several items were bid up to $25,000, including a Capitol Hill Experience with Representative Kevin McCarthy and two barrels of MadoroM 2010 Camouflage wine. First held in 2006, the MadoroM Charity Wine Auction is our largest fundraiser each year, and we are extremely grateful to the people of Bakersfield for their continuing support of our work to find a cure.

The MadoroM Charity Wine Auction team.

What Doesn't Kill You Has to Make You Stronger



Former board member Josephine Macaluso just celebrated the two-year anniversary of her brain surgery. She was asked to share her story last year and detailed her personal journey dealing with her cavernous malformation. The article can be viewed on the "Women You Should Know" website: http://www.womenyoushouldknow.net/what-doesnt-kill-you-has-to-make-you-stronger/

Jo wanted to tell her story to bring awareness and let others know they are not alone in their struggles. Jo says, "We just know we are different physically, mentally, emotionally… I guess that makes us special in some way."

Dylan Mayer Rock & Bowl for Angioma Alliance

On April 20, Cari and Tony Mayer hosted the Dylan Mayer Rock & Bowl fundraiser for Angioma Alliance. Last June, Tony and Cari's one-year old son Dylan suffered a seizure. A couple of weeks later, their son had surgery on his right frontal lobe to remove two Cavernous Angiomas that were bleeding. He fully recovered from his surgery and is doing well. They later found out that Dylan has the CCM1 genetic mutation and has other small Cavernous Angiomas. These are currently asymptomatic. They have also learned through genetic testing that Cari and her mother have the CCM1 mutation, though neither are currently presenting any symptoms.

Like many others affected with Cavernous Angiomas, Tony and Cari wanted to bring awareness and support to Angioma Alliance. With the help of family and friends, they hosted a Rock & Bowl in Cincinnati, Ohio, in their son's name, with all the proceeds going directly to Angioma Alliance. Nearly 200 people participated in bowling, raffles and a silent auction. It was a huge success that raised more than $11,000. Tony and Cari would like to again thank everyone who helped make their event possible. Look for the 2nd Annual Dylan Mayer Rock & Bowl for Angioma Alliance in the spring of 2014.

Dylan and his sister Kendall at the Rock & Bowl.

Cavernoma Alliance UK Update

"Transformational" was how one trustee of Cavernoma Alliance UK described the grant of nearly £200,000 ($300,000) upon hearing the news of our successful bid to the Big Lottery. (The UK Lottery provides funding for charities.) The award was a culmination of a year's hard work by the Board, David C. S. White, now Chair of the Trustees, Tim Millward (Treasurer), Frank Gent, and Mr. Ahmed Toma.

CA UK has set ambitious goals for the five-year project named Big Step (as it marks the transition from doing a lot with relatively little money, to doing even more with the Big Lottery funding).

Some of the aims of Big Step include the following goals: 120 new CA UK members a year, by the end of year three; 25 neurology departments and 50 GP surgeries providing information about CA UK to patients; 50 other medical professionals providing information about CA UK to patients; 50 consultants having information packs about CA UK; plus information packs for all newly diagnosed patients by the end of year two and in each subsequent year.

In addition, we aim to have 200 new users of social media - CaverChat, Facebook and Twitter - by the end of year five. By the end of the project, CA UK must have lobbied to ensure that cavernoma diagnosis, management and treatment is included in the training of medical students. We have our work cut out for us.

Cavernoma Alliance UK held its Seventh International Forum at the Grange Holborn Hotel, in London, on 16 June 2013 with a record attendance of 147 participants. CA UK organised a star-studded line-up of speakers. Professor Rustam Al-Shahi Salman spoke about the importance of establishing a randomized controlled trial regarding cavernoma treatment. Professor Dr Helmut Bertalanffy gave an exceptional talk entitled "Management of Cavernous Malformations of the Brain and Spinal Cord: Well-established and New Concepts."

Professor Dr Helmut Bertalanffy at the Cavernoma Alliance forum.

Sacha Bonsor, author of Dipped Into Oblivion, *spoke at this year's Cavernoma Alliance forum.*

After coffee, the CA UK Forum broke into six discussion groups dealing with: the psychological impact of having a cavernoma, living with a cavernoma, living with someone with a cavernoma, cavernoma and surgery, incidental and asymptomatic cavernoma, and spinal cavernoma.

The latter discussion group was well attended in a year dubbed "the year of the spinal cavernoma." Since Professor Bertalanffy's talk included his experience of spinal cavernoma, and there was a workshop on the subject, members with spinal cavernoma were well-informed.

In the afternoon, there was a talk by Dr Gordon Plant, a neurologist with a specialism in neuro-ophthamology. Dr Plant gave fascinating insights into some of the symptoms, such as double vision, that are a predominant feature of various cavernomas.

After a brief break, CA UK was lucky enough to have Sacha Bonsor join us in a discussion led by Emily Fletcher, a member and now a trustee of the Alliance. The Annual General Meeting followed which duly elected Professor David C. S. White CBE as chair of the trustee board.

I am often asked how and why I established a UK Alliance. Diagnosed with a left-sided midbrain cavernoma in 1987, I had no idea what a cavernoma was. Fifteen years later, finding myself back in the UK after teaching college in the USA, I became irritated at the lack of information available about the condition. This led me to the internet where I found Dr. Connie Lee. Connie sent me a "little red guy" pin and some leaflets about the condition. This resulted in the establishment of Angioma Alliance UK, and, in 2008, Cavernoma Alliance UK was born.

Little did I know that five years later, along with a Board of Trustees who run the charity with a commitment, energy and passion which never ceases to amaze me, our organization would be in the very fortunate position of helping over 600 others diagnosed with the condition.

So, thanks to the Lottery grant, I learn the difficult lesson of change. It is an exciting time of growth and development for both me and Cavernoma Alliance UK as we both accept this huge challenge.

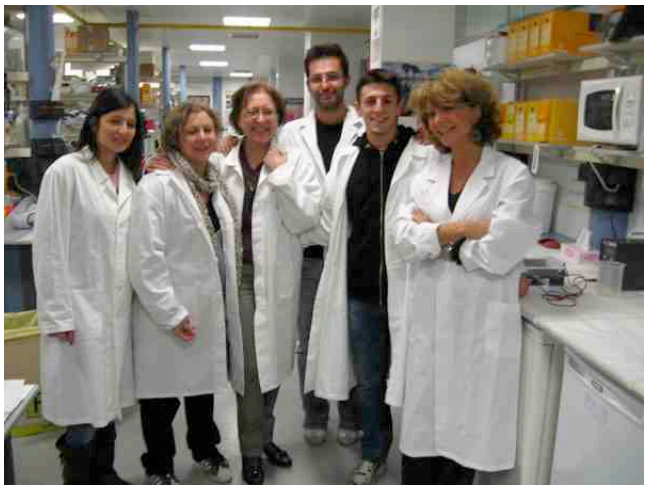
Ian Stuart

News from CCM Italia/AIAC

CCM Italia (www.ccmitalia.unito.it) and AIAC (www.ccmitalia.unito.it/aiac) initiatives are continuing to expand and strengthen cooperation among Italian institutions researching CCMs. Several new clinical and research units have recently joined the CCM Italia research network, including units from Padova, Udine, Ferrara, Ancona, and L'Aquila. Eleven Italian regions are currently represented in the network.

CCM Italia clinicians and researchers have begun joining their efforts in multidisciplinary approaches leading to novel perspectives on clinical management and basic mechanisms of CCM disease. (Guazzi P et al., PLoS One. 2012;7(9):e44705; Goitre L et al., J Signal Transduct. 2012;2012:807682; Bacigaluppi S et al., Clin Genet. 2013 Jan;83(1):7-14)

Furthermore, cooperation between two groups participating in the CCM Italia research network (the Dejana-Milano and Retta-Torino Units), plus the collaboration of a French group, have led to an important scientific discovery, recently published in Nature (Luigi Maddaluno, Noemi Rudini, et al., Nature. 2013 Jun 27;498(7455):492-6), which opens novel therapeutic perspectives for CCM disease.



Elisabetta Dejana's CCM Italia research unit.

Italian researchers identified the molecular and cellular mechanisms by which the loss of function of CCM genes, caused by mutations, determines the development of cerebral cavernous malformations. This demonstrates that the loss of function of CCM genes induces an event of "Endothelial-to-Mesenchymal Transition (EndMT)" through the activation of the Transforming Growth Factor-β (TGF-β) signaling pathway. EndMT is characterized by the loss of the blood-brain barrier function of endothelial cells that line brain capillaries and the acquisition by these cells of abnormal characteristics. These changes result in a weakening of the vessel walls and the consequent development of vascular malformations.

In the same paper, it is shown that inhibitors of the TGF-β signaling pathway are able to reduce the number and size of vascular lesions in animal models of the CCM disease, thus offering novel therapeutic opportunities for this disease.

CCM Italia has also recently organized a European research network focused on CCM (CCM Europe). This group is creating a unique European platform to facilitate the collaboration of a broad range of European fundamental and clinical research groups interested in the multifaceted aspects of the CCM disease. The goal is to integrate knowledge and experience in a multidisciplinary way "from bench to bedside."

Most of the main European clinical and research groups involved in CCM research issue have joined CCM Europe. To date, this network comprises research groups from 16 European countries, including Portugal, Spain, France, United Kingdom, Italy, Germany, The Netherlands, Belgium, Switzerland, Austria, Croatia, Poland, Romania, Sweden, Finland, and Lithuania.

Francesco Retta

About Angioma Alliance

Angioma Alliance is a non-profit, international, patient-directed health organization created by people affected by cerebral cavernous angiomas (also known as cavernous malformations or CCM). Our mission is to inform, support, and empower individuals affected by cavernous angioma and drive research for a cure. We are monitored closely in our educational efforts by a Scientific Advisory Board comprised of leading cerebrovascular neurosurgeons, neurogeneticists, and neurologists.

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www.angioma.org

How You Can Help

Your contributions help fund conferences and forums, increase research, and enhance outreach and support efforts. To donate to Angioma Alliance, send a check or money order (using the enclosed envelope) or visit www.angioma.org. You can also donate on line using a credit card with our Paypal connection.

Consider a sponsorship

Sponsorships can maintain essential programs or help us expand the ways that we support the cavernous angioma community. Please contact us at info@angioma.org to discuss these or other sponsorship opportunities.

Travel to Scientific Meeting: $1,500

Support the vital travel that allows Angioma Alliance to interface with governmental agencies and the scientific community on behalf of those with cavernous angiomas.

DNA/Tissue Bank Research Nurse: $6,000/year

Support the research nurse who gathers and maintains information for the DNA/Tissue Bank, which allows researchers to obtain material needed for projects that may one day lead to a cure for cavernous angioma.

Patient Registry: $8,500

Support the ongoing costs of the International Cavernous Angioma Patient Registry, which is an essential way to connect the patient and researcher communities in the shared goal of finding a cure.

Family Conference: $15,000

Support this important gathering of people with cavernous angiomas and those that care about them for a weekend of networking and education.

Seed grant: $35,000

Support a young researcher's pilot study that could be leveraged to obtain a $100,000+ NIH grant.

The Angioma Alliance Newsletter is a quarterly publication of Angioma Alliance
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