Spring 2010

Angioma Alliance Newsletter

Angioma Alliance Launches International Patient Registry

IN THIS ISSUE

Note: In this newsletter, the terms "cavernous angioma," "cavernous malformation," and "CCM" are used interchangeably.

For several years, Angioma Alliance has operated a DNA/Tissue Bank with a corresponding clinical database. Because of funding restrictions, we have limited participation in this valuable resource to people who had a past surgery, who have a scheduled surgery, or those with a family history of cavernous angiomas. To date, our DNA/Tissue Bank has supported the work of six laboratories and led to the publication of several important papers.

THE INTERNATIONAL CAVERNOUS ANGIOMA PATIENT REGISTRY

Patients, Researchers, Advocates and Physicians Partnering for a Cure

Angioma Alliance
Striving for Answers

We are now ready to move ahead to the next step. We ask for your participation in the Angioma Alliance International Cavernous Angioma Patient Registry. We will use this resource two ways. First, the Patient Registry will provide a snapshot of the larger community of people affected by cavernous angiomas. Participants in the Patient Registry will be able to see this compiled information. Second, the Patient Registry will provide a way to contact affected individuals about opportunities for participation in research studies including clinical drug trials. Participants will have the opportunity to contact researchers themselves to let the researchers know that they are interested in participating in a particular study.

If you are already a member of the DNA/Tissue Bank, we encourage you to be part of the Patient Registry and vice versa. You will need to sign up for each separately. The purpose of the DNA/Tissue Bank is different from that of the International Patient Registry. With the DNA/Tissue Bank, Angioma Alliance collects biological samples and detailed, in-depth medical information. Researchers obtain the samples with no personal information from Angioma Alliance for use in their work. Participants in the DNA/Tissue Bank do not have direct contact with researchers.

In order to better clarify the differences between the DNA/Tissue Bank and the Patient Registry, a table on page 4 shows how each of these functions, the type of information they contain, and how that information is used.

We need everyone's participation to make this a valuable tool to help find a cure for cavernous angioma, so I hope you will all sign up for the International Cavernous Angioma Patient Registry.

Connie Lee
President, Angioma Alliance

News

Angioma Alliance Hires Robert Stowe as Fundraising Events Manager

The MadoroM Wine Auction marks the first event coordinated by Robert Stowe, our new Fundraising Events Manager. Robert will work with volunteers to plan and carry out awareness events and fundraisers throughout the United States.

"We are delighted to have Robert join our organization," said Angioma Alliance President Connie Lee. "His work will bring greater visibility to our efforts, and will enable us to expand our patient support and research efforts. I encourage our members to take advantage of his experience and assistance." Robert's email address is rstowe@angioma.org.

Before joining Angioma Alliance, Robert was a Community Manager for the American Cancer Society where, among his responsibilities, he managed the Relay for Life and other American Cancer Society events across a large section of south central Virginia. Before this, he was the Executive Director of the Murfreesboro, NC, Historical Association. He is a graduate of the Governor's School for Global Economics and Technology and of Averett University.

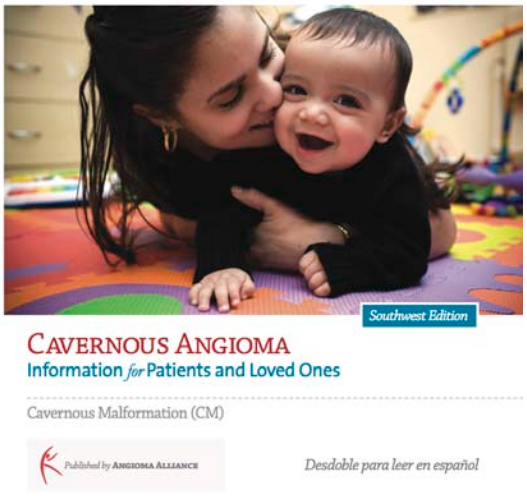
Robert said, "I am excited to be a part of Angioma Alliance and have enjoyed beginning my tenure with our largest fundraiser, the MadoroM Wine Release and Auction." (See below for more about the MadoroM event.)

New Mexico News

Individuals and family members in New Mexico are invited to attend a meeting of Angioma Alliance NM in Albuquerque on March 27th. For more information, contact Sarah Koster at skoster@salud.unm.edu or Joyce Gonzales at joyce@angioma.org.

This meeting follows our successful Santa Fe patient conference in November. Attendees learned about the illness, genealogy, and the latest University of New Mexico research study. Participants began brainstorming to identify specific needs for those with cavernous angiomas in New Mexico. Foremost was the need to raise awareness of the illness among the patient and healthcare provider population throughout the state. Several suggestions for addressing the need for increase awareness were generated including ideas such as providing information to school nurses who are likely to encounter undiagnosed families. We encourage everyone who is interested in meeting others with the illness in New Mexico and in working to address healthcare and research issues to attend the follow-up meeting on March 27th.

Angioma Alliance, with the support of the Con Alma Health Foundation, has produced a bilingual brochure specific to the Southwest area of the United States. The brochure provides general information about the illness, but also covers specifics of the Common Hispanic Mutation. It is being distributed through the University of New Mexico and in various locations in Santa Fe, and we expect it to spread throughout northern New Mexico over the next year.



Dallas Fun Run

Angioma Alliance members Rachel Hart and Savannah Hollis are organizing a Fun Run to benefit Angioma Alliance. The event will take place on March 27, 2010, at T.W. Richardson Grove in Irving, Texas. Everyone is invited!

Savannah Hollis, one of the Walk/Run organizers, was a college senior when a cavernous angioma hemorrhaged shortly after her 21st birthday. Because of her age, fitness, and lack of stroke risk factors, it was initially diagnosed as a migraine until a CT scan revealed blood pooling in her brainstem. Savannah's angioma and subsequent high risk brain surgery caused her to lose balance, vision, speech, and her ability to swallow. Through months of intensive therapy and hard work, she was able to return to college one year later. Savannah has been educating the public about this illness and has appeared in Cosmo magazine, on the television program "The Doctors," and in a feature article in the Dallas Fort Worth Star-Telegram.

At age 25, Rachel Hart, an elementary school teacher, experienced severe headaches and seizures. Initially, Rachel was diagnosed with an aneurysm until further testing showed otherwise. A month later, she underwent a successful brain surgery to remove the cavernous angioma. Since her surgery, Rachel and her husband have become the proud parents of Dane, their now 1-year-old son.

For more information about the event and to register, visit www.AwarenessFunRun.myevent.com.

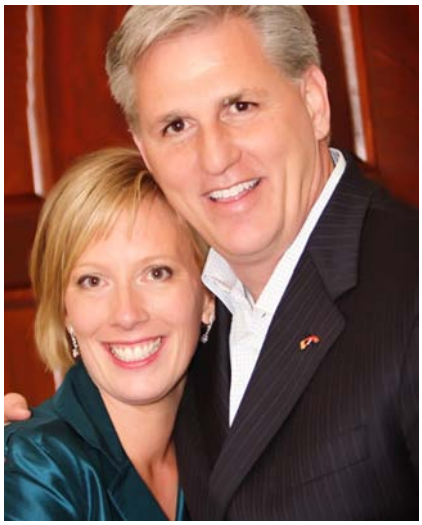
Another Successful MadoroM Wine Release and Auction

The 2010 MadoroM Charity Wine auction raised more than $55,000 for Angioma Alliance. Andy and Marissa Amador, and Shawn and Mike Blom, have turned what started as the auction of one 18-liter bottle of MadoroM wine during their wine release in 2007 into a major fundraiser and social event in Bakersfield, CA.

In addition to the traditional 18-liter bottle of MadoroM and other select items, this year's auction featured lunch for four with Congressman Kevin McCarthy. We are deeply grateful to the Amadors and Bloms, and to the people of Bakersfield for their ongoing generosity.

We cannot emphasize enough how important this annual fundraiser is in supporting the work we are doing. In past years, the event provided the funds we needed to begin our DNA/Tissue Bank and to host our family conferences. This year's fundraiser will support our growing research and awareness programs. We would also like to extend a special thanks to Liz Neuman and her children Jake and Sam who serve as an inspiration to this community.

Andy Amador (center) with Tiffany and Chad Manning and the 18-liter bottle of MadoroM they purchased.



Liz Neuman and Congressman Kevin McCarthy

Comparison of The DNA/Tissue Bank and the International Patient Registry

	DNA/Tissue Bank	International Patient Registry
Who can participate?	Those with past/future surgery or with multiple lesions.	All affected individuals, including those post-surgery.
Will I provide a blood sample to Angioma Alliance?	Yes.	No.
Will Angioma Alliance receive a tissue sample if one is available?	Yes.	No.
How much time should I expect to spend during the first year of my participation?	3 hours.	30 minutes.
How much time should I expect to spend in following years?	30 minutes.	20 minutes.
Can I withdraw from the project?	Yes.	Yes.
Will I complete an online questionnaire?	Yes, a short questionnaire for screening.	Yes, a more extensive questionnaire.
Will I participate in an interview with Angioma Alliance?	Yes.	No.
Will I complete medical record releases for Angioma Alliance?	Yes.	No.
How do researchers interact with me?	Researchers will not interact with you directly. Angioma Alliance will provide de-identified information to researchers.	Angioma Alliance will contact you if you match the criteria for a study. You will contact the researcher if you would like to participate.
Is there annual follow-up?	Yes, we would like you to participate in a 15-20 minute interview to update your information.	Yes, we will email you to remind you to update your online information.
Will my information remain confidential and anonymous?	Yes.	Yes, unless you choose to share your information and identity with a researcher.
How do I sign up?	Complete and submit the interest form at www.angioma.org/dna. Angioma Alliance will send you an Information and Consent document to review.	Visit www.angioma.org/registry. Read the Terms and Conditions, register, and complete your information online. (Note that the Patient Registry is not hosted on the Angioma Alliance web site, but rather by a company with whom we have contracted to manage this registry.)

International News

Cavernoma Alliance UK is proud to announce that it has a new Board. Members are Tabitha Bushill, Eliza Ellerby, Frank Gent, Iris Cassomini, and adjuncts Tim Millward and Dr Diana Dempster, who will be focusing on a special project for us from The Department of Health on cavernomas and stress. Completing the Board we have Mr. Kitchen's former registrar at the National Hospital for Neurology and Neurosurgery, Mr Ahmed Toma.

2009 saw the end (for the moment) of our CaverHub project which had been funded by the National Lottery. CaverHubs may be dead but they live in our latest venture which occurs in March: Brain Awareness Week. This international event is run by the DANA Centre of the Brain and details of two presentations which Cavernoma Alliance UK are making are available on their website www.dana.org/brainweek/. We are hosting Mr. Andrew McEvoy who operated on one of our members, Tabitha Bushill, in an awake craniotomy in November 2009. Tabitha will introduce Mr. McEvoy at the National Hospital for Neurology and Neurosurgery. The other event takes places in Liverpool with Mr. Javadpour, Consultant Neurosurgeon at the Walton Centre.

For the first time Cavernoma Alliance UK has a stand at the Spring Meeting of the Society of British Neurosurgeons which is being held in Queens' College, Cambridge. With a cost of over £2,500 ($4,000), Cavernoma Alliance UK will not be in attendance for the lecture series. However, Iris and I have done a major mailing to 42 Vascular Neurosurgeons in this "sceptered isle", who, I hope, will be present.

On 5 June we have our fourth international Cavernoma Alliance UK Forum with an impressive line-up of speakers, including a geneticist, neurologist and neurosurgeon, and your very own Chief Scientific Officer Dr Amy Akers. Dr Akers and her husband are making the trip especially for the London Forum. Described as "the one person in the world best able to present an overview of research developments across the spectrum," we are very excited to have her speak. The Forum will be held in its usual hotel, the Grange Holborn. The event is free and, with special prices for accommodation, worthy of American support!

More information about the Forum is available on our web site, http://cavernoma.org.uk. I do hope that our friends from across the pond will attend.

A note for our international readers: it is not a sign of disrespect that we refer to our eminent neurosurgeons as "Mister." Like everything else in the UK, this practice is bathed in tradition. In the UK people who have an MD (or a Ph.D.) but who are *not* surgeons—neurologists are often a case in point—usually call themselves "doctor." Surgeons, who call themselves "Mr", obviously have an MD. But therein lies the distinction. They are surgeons. Those who cut open the human body were, in the past, less skilled than doctors. This novelty (sorry, I mean tradition) has been retained to the present.

Ian Stuart

Author Alex Lemon Discusses his Brainstem Bleed and Surgery

In an interview on the Leonard Lopate Show, originally broadcast on WNYC radio, author Alex Lemon talks about the debilitating strokes that interrupted his hard-partying college days. In *Happy: A Memoir,* he recounts coping with strokes, brain bleeds, and depression by sinking deeper into drug and alcohol abuse, and how his mother nursed him back to health after brain surgery.

You can listen to the interview at this URL: http://www.wnyc.org/shows/lopate/episodes/2010/02/04

Find out more about the book at: http://www.alexlemon.com

Pathobiology of CCM Scientific Workshop Summary

The 2009 Pathobiology of CCM Scientific Workshop was held on November 12th and 13th in Santa Fe, New Mexico. This meeting was planned in conjunction with Cavernous Angioma Awareness week and it preceded the annual New Mexico patient meeting that was held on Saturday November 14th. The disease-specific format of this meeting enabled researchers from distinct fields and geographic locations to interact with one another. This year, 40 researchers traveled from across the United States, Canada and Europe to participate in the workshop. Scientific fields represented included Neurology, Dermatology, Surgery, Radiology, Biochemistry, Molecular Biology and Genetics. Thirteen scientific presentations launched into lively discussion, which enabled idea sharing, and fostering of continued and new research collaborations. The Pathobiology of CCM Scientific Workshop is a meeting where participants typically share unpublished data with their colleagues—this practice is not common at all meetings, and is an example of the enthusiasm and commitment of Cavernous Angioma (CCM) researchers.

Session I: Clinical And Lesion Studies: In the first session, presentations and discussions focused on the nature and behavior of cavernous angioma lesions. A lengthy discussion ensued comparing and contrasting two commonly used magnetic resonance imaging technologies: Gradient Echo (GRE) and Susceptibility Weighted Imaging (SWI). Both of these technologies display positive attributes, and while SWI typically shows enhanced sensitivity in detection of small lesions, the general consensus is that GRE is sufficient to determine if a patient has single or multiple lesions.

Additionally, in this session there were presentations on lesion biology. One presentation focused on the inflammatory response around brain lesions, and concluded with hypothesis generation on how such inflammation may affect the clinical course of the disease. A presentation on lesion genetics updated the research community with current studies of the molecular genetic mechanism that is believed to be the cause of lesion development.

Session II: Basic Science - Molecular And Animal Studies: This year the meeting had researchers using mice, fish, worms, and humans as study organisms; each model provides researchers with unique tools and experimental techniques for research studies. This basic science session focused on the molecular biology of the CCM gene products (proteins). Each talk provided new insight to the nature of these proteins and how they function in a wildtype (non-diseased) state to maintain proper vascular structure and integrity.

Increasing amounts of evidence demonstrate that the three CCM proteins have distinct functions but work together in a cooperative pathway to maintain the structure of blood vessels. In the disease state, when one of the CCM genes is mutated, vascular integrity is lost and blood vessels of the lesion are leaky, resulting in clinical symptoms associated with Cavernous Angioma. There are numerous studies underway to determine the precise molecular pathways involved in maintaining non-leaky vessels. One such pathway has been identified. This discovery identified a future potential point for pharmacological intervention, and perhaps a treatment for Cavernous Angioma. Current studies of this pathway are being conducted in mice that carry mutations for the CCM genes.

The basic science session concluded with a discussion of the CCM3 protein. Past research data suggested that the CCM3 protein functions along similar

Amy Akers, the Angioma Alliance Chief Scientific Officer; Dave McDonald from the Marchuk Lab; Doug Marchuk, who runs the Molecular Genetics & Microbiology lab at Duke University; Changbin Shi from the Feinberg School of Medicine at Northwestern University.

pathways as the other two CCM proteins; however, there is new evidence for additional functions of CCM3. These data are beginning to explain why patients who carry CCM3 mutations typically suffer a more severe disease course. This session provided a lot of insight and generated a lot of hypotheses for future studies into the fundamental mechanisms underlying Cavernous Angioma biology.

Session III: Clinical Studies And Human Genetics: In this final session there was considerable discussion between the conference attendees and presenters. First discussed was the current genetic testing techniques and the need for standardizing radiology reports among clinicians. To close the meeting, there was a discussion of the statin drug trial including the rationale for using statin drugs to treat CCM.

Statins are a class of drug that includes Crestor, Lipitor and Zocor. These drugs are currently approved to be used in the treatment of high cholesterol. The interest in using these drugs to treat CCM came following a study at the University of Utah in mice in which a statin drug was used to stop blood vessel leakage that is caused by Cavernous Angioma disease mutations.

Before clinicians are advised to prescribe statins to all of their Cavernous Angioma patients, a clinical trial must be conducted on human patients to determine if statins have the same affect on the human condition as they do in mice. Currently, a retrospective trial is being conducted in Utah in which researchers are assessing the patient population through review of medical records. These researchers aim to determine how many people with Cavernous Angioma have taken statin drug versus those who have not; this is an important step toward beginning a clinical trial. If all of the patients in Utah, where the study will be conducted, are already taking a statin drug, then there will be no way to determine the effect of the drug on the disease. For a proper trial there must be a control group of individuals who have not had statin treatment.

The most up-to-date information about opportunities to participate in research will be available on the International Cavernous Angioma Patient Registry website: www.angioma.org/registry. If you are interested in participating in future research studies or clinical trials please visit the registry website and complete the online profile. The purpose of the registry is to collect enough information from people who are interested in research so that we at Angioma Alliance can help researchers identify a group of participants who are qualified and interested in study participation. Identifying study participants can be the most difficult part of beginning a clinical trial. Our goal is to establish a robust patient registry so that Cavernous Angioma researchers are able to conduct their studies in timely and effective ways.

Amy Akers

Research Update: Cavernous Angioma and Cancer

Historically, physical defects of the blood vessel system have been classified into one of two distinct categories: tumors or malformations. Vascular tumors are rapidly growing cell masses that display high rates of endothelial cell proliferation. Conversely, vascular malformations are typically present at birth and grow proportionally with the host individual, without cell proliferation. The primary biological difference between these types of lesions is the growth or proliferative capabilities of the cells (endothelial cells) from which the vascular lesion is formed (Mulliken, Zetter et al. 1982).

In contrast to these distinct categories, cavernous angioma lesions display characteristics of both types of vascular anomalies. Historically, cavernous angioma lesions were described as being stagnant; they were all believed to be present at birth and able to increase in size only due to remodeling and increasing body size (Del Curling, Kelly et al. 1991; Robinson, Awad et al. 1991). However, advances in magnetic resonance imaging technology have shown that cavernous angioma lesions are often dynamic in nature—their cellular structure is able to proliferate, new lesions may develop through time, and lesion size may increase with increasing patient age (Labauge, Brunereau et al. 2000; Zhao, Tan et al. 2007).

The dual nature of the cavernous angioma lesion is exemplified by the common inconsistency in naming these lesions and the vascular disorder of the same name. Some investigators refer to the lesions as cavernous malformations, emphasizing the malformation-like qualities of the lesions, and others as cavernous angiomas, emphasizing the tumor-like characteristics. This inconsistency is reflective of the way lesions grow both by remodeling and through endothelial cell proliferation (Sure, Butz et al. 2001; Uranishi, Baev et al. 2001; Shenkar, Sarin et al. 2005). Consistent with the tumor-like qualities of CCM lesions, multiple labs have shown that the molecular mechanism that causes the formation of familial cavernous angioma lesions is analogous to a common mechanism for many cancerous tumors (this topic was discussed in the September 2009 Newsletter). As a continuation of this

cancer-related research, the following is an overview of three scientific papers published in recent months describing the functions of the proteins responsible for causing the onset of Cavernous Angioma.

By way of a brief background, three genes have been identified, that when mutated cause onset of Cavernous Angioma. These genes are termed *CCM1*, *CCM2*, and *CCM3* (named after Cerebral Cavernous Malformations). When these were first identified as disease genes, the normal function of the resulting proteins was entirely unknown. While their functions are beginning to be uncovered, this is an active area of research for many labs throughout the US and the world.

Two recent publications describe new functions for the CCM1 protein. Past studies have shown that the CCM1 protein is involved in a variety of processes, the end result of which is to maintain the integrity of the cellular junctions between neighboring endothelial cells (these are the cells that make up blood vessels). Interestingly, the CCM proteins are present throughout the entire body. This observation suggests they have additional properties and functions that have yet to be uncovered.

Since the discovery of the disease-causing genes for Cavernous Angioma (*CCM1*, *CCM2*, and *CCM3*), researchers have focused on learning the functions of proteins that are made from these genes. The purpose of this line of investigation is to understand the basic biological mechanisms that cause cavernous angioma lesions to develop.

Cavernous Angioma is a disorder that affects the blood vessel system. However, the CCM1, CCM2, and CCM3 proteins are found all throughout the body, not just in blood vessels. Recent research shows that these proteins work in other types of tissue to control cell replication and death. Controlling these processes is critical for healthy living. For example, uncontrolled cell replication can lead to tumor formation in cancer.

Researchers are now working to determine how these processes affect the Cavernous Angioma disease in human patients. By better understanding the functions of these genes, researchers may be able to discover a way to treat all types of Cavernous Angioma, including sporadic and inherited cases.

CCM1 as a Regulator for Programmed Cell Death

In a study from a group in Toronto, Canada, researchers used an animal model to study the function of the CCM1 protein. These researchers did not use mice, or another commonly known laboratory animal; instead they used C. elegans for their studies. C. elegans are nematode worms that have transparent bodies and are only 1 millimeter long when fully grown. These worms have become an excellent model organism to use in the laboratory; they are cheap and easy to propagate, they eat bacteria (which allows for lots of unique genetic experiments that cannot be done in other organisms), and they have many of the same basic biological mechanisms as higher organisms, including humans. This lab uses C. elegans to study apoptosis, which is the process of programmed cell death. Having regulated cell death in any organism is essential for development and healthy living. In many cases, unregulated cell death leads to excessive cellular proliferation—a hallmark of cancer and early stage tumors.

In this publication, researchers specifically investigated the regulation of cell death of the germ cells (sperm and eggs) within the worms. These cells will undergo cell death if they are damaged and unfit for reproductive purposes. These researchers discovered that when germ cells are damaged by ionizing radiation, the CCM1 protein is required to initiate the death-signaling pathway. Interestingly, through this line of investigation, a novel pathway was discovered in which CCM1 functions in a cross-tissue signaling mechanism. Classically, death signaling is initiated within the cell that is going to die. However, a new mechanism was identified in which CCM1 signals from a non-dying cell in response to radiation and instigates the death of the damaged cell. These results have defined a new mechanism for CCM1 and its multiple functions outside of vascular tissue (Ito, Greiss et al.).

CCM1 Regulates Tumor Progression in a Mouse Model

Another study from the University of California at San Diego also investigated the function of the CCM1 protein and its behavior outside of endothelial cells. In this report, researchers used a mouse model for intestinal cancer to investigate the role of CCM1 in the initiation of tumor development. Prior to this line of investigation, these researchers discovered that within endothelial cells, CCM1 works with another protein called β-catenin to stabilize the junctions between endothelial cells (Glading, Han et al. 2007). This process is essential to the normal function of blood vessels to prevent blood from leaking through vascular structures.

Similar to the previous line of investigation, these researchers wanted to determine the roles of CCM1 and β-catenin in tissue types other than those of the vascular

system. β-catenin is a multi-functional protein that is responsible for the regulation of processes that lead to the development and progression of cancerous tumors. In a mouse that has been bred to develop intestinal cancer, tumors develop because of the dysregulation of β-catenin (Solanas, Porta-de-la-Riva et al. 2008; Taddei, Giampietro et al. 2008).

These researchers discovered that CCM1 is a major contributor to the regulation of β-catenin. By extension, they showed that when CCM1 is mutated, the resulting effect is uncontrolled β-catenin function and onset of intestinal tumors (Glading and Ginsberg). Thus, CCM1 and β-catenin have multiple functions, apparently dependent on the tissue type in which they are located. Within the blood vessels, these molecules are required to maintain vascular integrity. When the CCM1 protein is non-functional due to mutations, as in the Cavernous Angioma disease condition, blood vessel structure is weakened and shows the hallmark features of this disorder. These results also show that CCM1 and β-catenin have important maintenance and structural roles in other tissues, which, when mutated, may result in other disorders.

Novel Function Of CCM2 Protein

The final study involves investigation of the cell death pathway in a cancer model for neuroblastoma (cells within this type of tumor are derived from neuronal cells). This study explored the role of the CCM2 protein related to tumor progression. Previously, CCM2 had been described as a scaffolding protein; that is, CCM2 binds to other proteins to provide support and compartmental localization of its binding partners. Localization within cells is a common method to control regulation of a wide range of cellular processes. In this study, researchers identified a novel mechanism for CCM2: it binds to a protein called TrkA and works in conjunction with that molecule to regulate cell death within neuroblastoma tumors. These researchers showed that in neuroblastoma tumors, if there was a high level of CCM2 protein, the clinical course of the tumor was better, as CCM2 regulated the cell death process to control growth of the tumor. Conversely, a low level of CCM2 leads to uncontrolled proliferation and growth of the tumor (Harel, Costa et al. 2009).

Summing Up

Each of these studies adds another piece to the puzzle of CCM pathogenesis. The more that is understood about the fundamental biological processes of these molecules, the better we will be able to develop drugs to treat Cavernous Angioma. It should be mentioned that the above-described research does not argue that Cavernous Angioma is a cancer, but rather that the underlying biology of the disease follows a cancer-like mechanism. By investigating the normal functions of the proteins that are mutated in the familial form of the disease, researchers are working to identify chemical pathways that may give insight to future drug trials and treatments for all forms of the disorder.

Amy Akers

References:

Del Curling, O., Jr., D. L. Kelly, Jr., et al. (1991). "An analysis of the natural history of cavernous angiomas." J Neurosurg 75(5): 702-8.

Glading, A., J. Han, et al. (2007). "KRIT-1/CCM1 is a Rap1 effector that regulates endothelial cell cell junctions." J Cell Biol 179(2): 247-54.

Glading, A. J. and M. H. Ginsberg (2010) "Rap1 and its effector KRIT1/CCM1 regulate beta-catenin signaling." Dis Model Mech 3(1-2): 73-83.

Harel, L., B. Costa, et al. (2009). "CCM2 mediates death signaling by the TrkA receptor tyrosine kinase." Neuron 63(5): 585-91.

Ito, S., S. Greiss, et al. "Cell-Nonautonomous Regulation of C. elegans Germ Cell Death by kri-1." Curr Biol.

Labauge, P., L. Brunereau, et al. (2000). "The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients." Neuroradiology 42(5): 327-32.

Mulliken, J. B., B. R. Zetter, et al. (1982). "In vitro characteristics of endothelium from hemangiomas and vascular malformations." Surgery 92(2): 348-53.

Robinson, J. R., I. A. Awad, et al. (1991). "Natural history of the cavernous angioma." J Neurosurg 75: 709-714.

Shenkar, R., H. Sarin, et al. (2005). "Variations in structural protein expression and endothelial cell proliferation in relation to clinical manifestations of cerebral cavernous malformations." Neurosurgery 56(2): 343-54.

Solanas, G., M. Porta-de-la-Riva, et al. (2008). "E-cadherin controls beta-catenin and NF-kappaB transcriptional activity in mesenchymal gene expression." J Cell Sci 121(Pt 13): 2224-34.

Sure, U., N. Butz, et al. (2001). "Endothelial proliferation, neoangiogenesis, and potential de novo generation of cerebrovascular malformations." J Neurosurg 94(6): 972-7.

Taddei, A., C. Giampietro, et al. (2008). "Endothelial adherens junctions control tight junctions by VE-cadherin-mediated upregulation of claudin-5." Nat Cell Biol 10(8): 923-34.

Uranishi, R., N. I. Baev, et al. (2001). "Expression of endothelial cell angiogenesis receptors in human cerebrovascular malformations." Neurosurgery 48(2): 359-67; discussion 367-8.

Zhao, Y., Y. Z. Tan, et al. (2007). "Morphological Observation and In Vitro Angiogenesis Assay of Endothelial Cells Isolated From Human Cerebral Cavernous Malformations." Stroke 38:1313-1319.

Angioma Alliance Financial Statements - Year Ending Sept. 30, 2009

Angioma Alliance's financial year is from October 1, 2008 through September 30, 2009. The information on this page is a summary of our financial position at fiscal year-end.

Because of your very generous contributions and the energy you have put into special events, Angioma Alliance has continued to grow despite what has been a difficult economic year around the globe. While we've hired two employees in the last seven months, it is clear that our members are the heart of our organization.

Thank you for all that you do in helping Angioma Alliance to achieve our vision of a cure for cavernous angioma.

Karen Asbury
Treasurer

STATEMENT OF FINANCIAL POSITION
SEPTEMBER 30, 2009

ASSETS	
Cash	67,133
Accounts Receivable - Pledge	5,500
Equipment, Furniture & Registry Database	166,520
Less Accumulated Depreciation	(56,813)
Security Deposit	700
TOTAL ASSETS	$ 183,040
LIABILITIES AND NET ASSETS	
Accounts Payable and Accrued Liabilities	2,374
TOTAL LIABILITIES	2,374
NET ASSETS	
Unrestricted	159,706
Total Unrestricted Net Assets	159,706
Temporarily Restricted	20,960
Total Net Assets	180,666
TOTAL LIABILITIES AND NET ASSETS	$ 183,040

STATEMENT OF ACTIVITIES
For the Year Ended September 30, 2009

	Unrestricted	Temporarily Restricted	Total
PUBLIC SUPPORT AND REVENUE			
Contributions	57,732		57,732
Conference Registration Fees	4,025		4,025
Family Health History Project			- 0
Grants and Contracts	38,370	2,500	40,870
In-Kind Contributions	19,097		19,097
Special Events	34,693	31,858	66,550
Miscellaneous	455		455
TOTAL PUBLIC SUPPORT AND REVENUE	154,371	34,358	188,729
EXPENSES			
Program Services	121,106	1,025	122,131
General and Administrative	17,172		17,172
Fund Development	44,414	12,373	56,787
TOTAL EXPENSES	182,692	13,398	196,090
CHANGE IN NET ASSETS	(28,321)	20,960	(7,361)
NET ASSETS AT BEGINNING OF YEAR	35,562	152,465	188,027
NET ASSETS AT END OF YEAR	$ 7,241	173,425	$ 180,666

Angioma Alliance Donors July 1, 2009 – December 31, 2009

Beacons ($5000+)

Capital Group Companies Charitable Foundation
John and Connie Lee
Charmean and Robert Neithart
Roger Peters and Lorna Reichl

Leaders ($1000-$4999)

David Asofsky, Asofsky Family Foundation
Friends and Family of Max Grubisic – Forever 6
The Rashkind Family Foundation
William and Kristi Reyneveld

Benefactors ($500-$999)

Libby and Mel Davis
Daniel Engle
Merritt and DeeDee Hayslett
Maureen Heath *in honor of Lisle Cohen*
Donald and Patty Houchin
Helaine Hudson
Heather and John Kurpiewski
Tom and Nancy McHugh
Barbara and Charles Moore
Edward and Rita Mullin
Lee and Michael Rashkind *in honor of the Grady family and in loving memory of Marsha Garofalo*
Susan and Paul Sukalich *in honor of Sara and Susan Sukalich*
Wert Family Foundation
Erik Young and Derry Dental Associates

Community Builders ($250-$499)

Batesville Products *in honor of Samantha Weber*
Colleen Benthal *in memory of Donald S. Benthal*
The Binding Source
Jerry and Charlene Bowlin *in honor of Bettina Charlene Bendzlowicz*
Donations through Firstgiving
Diana and James George
Tony Gussio
Laura Hebard
Marc and Jane Kirshner
Douglas and Christina Martin
Raquel Silva
Ron and Amy Schechter
Catherine Smith

Partners ($100-$249)

Donald and Linda Adams
American Express
Ray and Joyce Asbury *in honor of Mitch Asbury*
Jonas and Lisa Batten
Janeen Carlo *in honor of Lisle Cohen*
Janice Cerabona *in honor of Riley Cerabona*
Lisle Cohen
Kathleen Connelly *in honor of Norma Villa*
Christopher and Taraline Coughlin
Thomas and Rose Cox
Sally and Mike Derrig *in honor of Julia Lee*
Ted and Paula Driscoll *in honor of Heather Kurpiewski*
Tom and Robin Feher
Joseph and Anna Ferrando *in memory of Shirley Ferrando*
Diana and Joseph Gonzales *in memory of Blue Haven Gonzales*
Vicky Gonzales *in honor of the Fred A. Gonzales family*
Eugene and Mary Grady *in honor of Lee Grady Rashkind*
Charles and Rosemarie Hall
Ronald Harrington
Rachel Hart
George and Kathleen Hildum
Michelle and Steve Hnath
Carol Hoffman
Alan and Sharon Horton *in honor of Sharon Horton*
Lee and Paula Hougen
Jean and John Jacon
Molly Lee and Jeff Kaban *in honor of Julia Lee*
Tammy and Joe Lovrich
Erin McRoberts *in honor of Glenn Babich*
Donations through Network for Good
James and Helen Neuman *in honor of Jake and Sam Neuman*
David Nii and Pamela Brunner
Roger and Josephine Palutsis
Virginia Peter
Gretchen and Scott Poole *in honor of Parker Poole*
Kimberly Randall
Shirley and David Ray *in honor of Jonathan Ray and Dr. Lara Vaughn*
Ken and Mary Reeb
Stephen and Barbara Rich
Diana Rodionov
Allison and Ken Ruggles
Mary Ellen Schraven
Scott and Amy Stier *in honor of Ryan and Samantha Stier*
Maggie Sukalich
John and Eunice Wiley
Robin Zingone

Supporters ($50-$99)

AnyDoc Software
Carl and Chelsea Beffa
Richard and Barbara Bodson
Edmundo and Cynthia Carrillo
Theresa and Corey Countryman
Randall and Anna Crawford
Jessica Franzini *in honor of Evan Elfersy*
Gary Fuller
Thomas and Joan Graney
Marie and Robert Gussio
Karen Heldmeyer
Lindsay and Robert Hood
David and Ruth Hopkinson
Tom Hoyt and Carolyn Zawacki
Brandon Hildum
Brad and Rebecca Hogue *in honor of Jake and Sam Neuman*
Patrick and Trudy Hoover
Debra and Michael Jett *in memory of George E. Brown*
Jeffrey Jin
Lawrence Marino
Jennifer and Doug Martindale
Kari McDonald
Microsoft Giving Campaign
Ronald and Katherine Miller
Sheri and Pat Moore
Daniel and Joann Passeri *in honor of Allison Ruggles*
Tony Pino
Gary Pleason
Billie Roach
Mike and Cathy Ryan *in memory of Shirley Ferrando*
David and Lisa Sicker
Karen Smith and Paul DeMarco *in honor of Catherine Smith*
Nancy Taylor
Bill and Irene Thomas *in honor of Ronnie Bince*
Mary and Wallace Varonko
Kandance Weems Norris
Tom and Laura White *in honor of Joyce and Greg Gonzales*

Friends ($1-$49)

Abbott Laboratories
Fred and Joan Adair
Candace and Eduardo Alamilla
Imelda Basada
William Calloway *in honor of Mark Seymour*
Mary Jane Cartmill
CJ Coughlin
Kelsey Coughlin
Sylvia and Anthony Diaz *in honor of Heather Kurpiewski*
Henry and Roberta Gallegos
Bill and Susan Geary
Kim and Rick Gerdes
Julie Gernert
Herbert and Clara Hagen
Donations through igive.com
Kathy Immer
Sandi Johnson
Kevin and Lori Langan *in honor of Evan Elfersy*
Diane and Howard Lawrence *in honor of Diane Lawrence*
Rick and Kathi Moore
Janice Nott
Ned and Margaret Perry *in honor of Connie Lee*
Charlotte Petersen
Melanie Pistiolas
June Rochedieu *in memory of Bebe Simon*
Eric and Heather Ryan
Eric and Heather Ryan *in memory of Shirley Ferrando*
Mike and Kathy Ryan *in memory of Ernest Lyons*
A.T. and Kansadie Weems *in honor of Kandance Weems Norris*
Tom and Laura White *in honor of Nina Gonzales*

In Kind Gifts

Christine Castellano
Sandy and Ron Kauffman
Ronald and Amy Schechter
Mark Seymour
Maureen Kehner and Mark Spade
Joan Davis and Greg Wissman

Who We Are

Angioma Alliance is a non-profit, international, patient-directed health organization created by people affected by cerebral cavernous malformations (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.

Angioma Alliance
520 W 21st Street, Suite G2-411
Norfolk, Virginia 23517

866-HEAL-CCM (Toll free)
757-623-0615
info@angioma.org
www.angioma.org

How You Can Help

Your contributions will help fund conferences and forums, increase research, and enhance outreach and support efforts. Our pins, car decals and wristbands support the mission and growth of Angioma Alliance. Share these meaningful gifts with your friends and family.

Each donation of $10 or more will come with a CCM lapel pin thank you gift. Our "little red guy" pin is a wonderful way to increase awareness of cerebral cavernous malformation (CCM). Increasing public awareness can go a long way toward increasing research funding and improving quality of life for those with cavernous angioma. Each pin comes with cavernous angioma business-size information cards that can be handed to anyone who might have questions.

Angioma Alliance also offers a wide range of apparel and other items featuring the Angioma Alliance logo. There are t-shirts, sweatshirts, hoodies, mugs, stickers and much more available. You can find these items in our Café Press store. To purchase Angioma Alliance merchandise, go to our web site and click the Store link at the top of the page.

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.

We Need You: Angioma Alliance needs volunteers in many areas. If you have time to give, please visit www.angioma.org/volunteer.htm.

The Angioma Alliance Newsletter is a quarterly publication of Angioma Alliance

Editor: Kirk McElhearn, kirk@mcelhearn.com

Photo credit: bottom of page 3: Anita Matejka Photography, Bakersfield, CA.