



Summer 2010

Angioma Alliance Newsletter

And Then There Were Three... Researchers identify two additional medications that may target cavernous angiomas

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

In the spring of 2009, we were very excited to announce the first published research indicating that a non-surgical treatment for cavernous angiomas might be on the horizon. Dr. Kevin Whitehead and his team at the University of Utah demonstrated that statin medications, specifically simvastatin, were effective in reducing the leakiness of blood vessels in mice that were bred to have the *Ccm2* genetic mutation (Whitehead, 2009).

Statin medications are already in widespread use to lower cholesterol. Right now, the group in Utah is performing a retrospective study using records from thousands of patients treated for cavernous angiomas in Utah. They are hoping to gather enough supporting information to apply for a major grant to perform a clinical drug trial to demonstrate the effectiveness of statin drugs in human cavernous angioma patients.

This spring, Rebecca Stockton, Dr. Mark Ginsberg, and the group at University of California at San Diego published research identifying another medication, generically known as fasudil, as being effective at reducing leaky blood vessels in mice bred with the *Ccm1* genetic mutation (Stockton, 2010). Fasudil is a "Rho Kinase inhibitor" and works on cavernous angiomas in a way that is similar to statins. Fasudil has been used in Japan

for more than 15 years to treat cerebral vasospasm. Currently, in the US, it is undergoing clinical trials to gain approval by the FDA to be used in the treatment of pulmonary hypertension and other conditions. At this time, the UCSD group is working with Dr. Issam Awad's group at the University of Chicago to continue to explore the effects of fasudil. There is not yet a clinical drug trial specifically for the treatment for cavernous angioma.

Finally, in July, Joycelyn Wüstehube in Dr. Andreas Fischer's lab in Heidelberg University, in Mannheim, Germany, published a paper documenting that yet another medication, sorafenib, is potentially effective in treating cavernous angioma (Wüstehube, 2010). Sorafenib was shown to shrink cavernous angiomas in mice bred without immune systems that had received a transplant of human CCM1-mutated endothelial cells. Sorafenib works by blocking the growth of new blood vessels, and it has been used to slow the spread of cancer in individuals with advanced primary kidney cancer and with advanced primary liver cancer.

A downside of sorafenib is its price; for example, it has been disallowed for use as a treatment for liver cancer by the United Kingdom National Health Service because treatment can cost more than \$4,500 per month.

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The identification of sorafenib, however, has opened the door to a different class of medications that can be explored.

The research above focused on the CCM1 and CCM2 genetic mutations. Does this mean that statins, fasudil and sorafenib are specific to these mutations, or will they work for all types of cavernous angiomas? This is a question without a solid *answer*. All of the CCM proteins (CCM1, CCM2, and *CCM3*) that cause the hereditary form of the illness have been shown to be part of the same system. Sporadic cavernous angioma lesions are indistinguishable from those in the inherited forms of the illness. It may be that a medication that works for CCM1 could also work for CCM2, CCM3 and sporadic cases. However, the more researchers learn about the function of the CCM proteins, the more they find that each has additional unique functions. How these functions affect the illness remains unknown. Additionally, what is not known is whether these effects would generalize from mice to humans.

It would be hard to exaggerate the amount of scientific progress in the research described in the three studies above and the work that led up to them (Borikova, Dibble, 2010). The next step, which is equally important, is to refine knowledge about the disease biology and move toward clinical trials. We are not there yet, but we're getting closer.

Right now, there is no reason to run out to get a prescription for any of these medications. We do not know whether they truly are helpful or harmful to humans with cavernous angiomas. If they are helpful, we don't know if this is the case for everyone with the illness or just those with specific mutations. We also do not have information on what dosages might be required to have an effect.

What this means is that increasing the size of the Angioma Alliance International Patient Registry is of critical importance. If we would like to see medication research in humans happen as quickly as possible, we need to provide researchers with an already organized group that has offered to participate in research studies. Since the three drugs identified so far are on the market and have already been proven safe and effective for other conditions, we could see a much shorter time to FDA-approved use for cavernous angiomas, if they are indeed helpful, if we can pull our resources together.

Help us move ahead by participating in the Angioma Alliance International Patient Registry; visit www.angioma.org/registry.

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*Connie Lee
President, Angioma Alliance*

Scientific Workshop To Place Focus on Sporadic Cavernous Angioma

The 6th Annual Angioma Alliance International Scientific Workshop will be held on November 1-2 in Washington, DC. In previous years, the Workshop has focused almost entirely on the genetic form of the illness. This year, Angioma Alliance has asked scientists to increase their focus on the sporadic form. One way that we hope to do this is by offering travel stipends to young investigators whose work is applicable to the sporadic form. We would like to award two domestic (\$1,000 each) and two international (\$1,500 each) stipends, and we would appreciate your help. If one person or a group of individuals donating together is able to sponsor an entire award, we will give you the right to name the award, e.g. The John and Jane Smith Young Investigator Travel Award. This is a wonderful opportunity to encourage the broadening of research to ensure that a cure is available for everyone.

What's in a number?

How often have you been asked “How common is cavernous angioma?” It's a hard question to answer because there are many different ways to calculate this, and none of them is perfect. We've been told the illness is common: 1 in 200, 1 in 300, or even 1 in 700 people is not a rare disease. Yet, unless we're involved in Angioma Alliance or live in New Mexico, most of us don't know another affected family. Where is everyone?

Let's see if we can pick this apart. There are a few ways we can count the number of people who have a cavernous angioma: by examining autopsy results, reading MRIs, or counting people who are diagnosed with symptoms.

Researchers have performed studies in which they counted the number of people who had cavernous angiomas by performing autopsies on series of cadavers. In a survey of 4,000 autopsies from Texas, every 1 in 250 people had a least one cavernous angioma (Sarwar and McCormick 1978). A French study that reviewed over 24,000 autopsies estimated the prevalence of cavernous angioma to be 1 in 190 of that population (Otten, Pizzolato et al. 1989). These numbers are close to each other and seem to indicate that cavernous angiomas are very common. The problem with autopsy studies is that the sample is somewhat biased. For various reasons, not everyone receives an autopsy at death. So, while 1 in 190-250 may be a good number, it's not a perfect number.

Three MRI studies have been performed which, taken together, provide us with a range, albeit a broad one, to use as another starting point. Two of the three studies were very similar. Over 14,000 MRI images generated between 1984 and 1989 at the Cleveland Clinic were analyzed to diagnose cavernous angioma. This study showed an estimated disease incidence of just under 1 in 200 (Robinson, Awad et al. 1991). In a similar study at the North Carolina Baptist hospital, a review of 8,000 MRI images estimated an incidence of 1 in 250 (Del Curling, Kelly et al. 1991). The problem with these studies is that the MRIs were being performed on individuals who were seeking treatment for symptoms that required an MRI. So, these folks were more likely than the average person to have some kind of neurological disorder, including, but not limited to, a cavernous angioma. The 1 in 200 figure is the most liberal estimate of how common it is to have a cavernous angioma, and it is probably an overestimate.

The third MRI study was a review of only healthy individuals. In this study, 7,300 healthy people (individuals without any neurological disease) underwent MRI. In this study, 1 in 670 people had a cavernous angioma (Al-Shahi Salman, Whiteley et al. 2007), whether or not they've been diagnosed.

Another thing we know is that 1 of every 400,000 people in Scotland is newly diagnosed with a cavernous angioma in a given year (Al-Shahi Salman, et al. 2003). That sounds like a really small number, but when you apply this to a population as large as the United States and add in the information about how often undiagnosed, asymptomatic people have a cavernous angioma, the numbers start to add up. If you never liked math class, feel free to skip past this series of bullets to find a conservative answer to “How common is it?”

- Based on a US population of 310 million and an annual diagnosis rate of 1 in 300,000 people, about 1,000 new cases should be diagnosed each year. (While 1 in 400,000 was getting diagnosed in Scotland at the time of their study, this number has likely improved, due to more sensitive diagnostic techniques and higher resolution MRIs. So, the 300,000 number is not perfect, but it's a place to start.)

- Assuming 20 years of diagnosis in the US, since the general availability of the MRI, there should be some 20,000 diagnosed cases in the US.

- So, there should be 465,000 asymptomatic, undiagnosed cases (1 in 670) walking around in the United States, and 20,000 diagnosed cases (1 in 300,000 x 20 years), for a total of 485,000 cases. This means only 4% of people with a cavernous angioma have been diagnosed.

- An additional complication in the US is that there are two founder mutations (the Common Hispanic Mutation and the CCM2 exon 2-10 deletion). These mutations dramatically increase the number of cases in the United States. For the Common Hispanic Mutation, there are likely 30,000-40,000 people in the United States. If 62% are symptomatic, as a French study of people with the CCM1 mutation would indicate (Denier, Labauge, et al., 2004), that would be an additional 20,000+ symptomatic cases. We don't know how many people with the CCM2 2-10 deletion there are, but it seems to be almost 10% of people with hereditary cavernous angiomas in the US.

- So, if we add in estimates of people with the two founder mutations (50,000 is a fair estimate), there should be about 535,000 people with cavernous angiomas who are either symptomatic or asymptomatic in the US today. Finally, there is an unknown number of misdiagnosed people, who present symptoms but have been diagnosed as having another illness.

Here's the bottom line. It would be safe to say that at least 1 in every 580 people in the United States (1 in 600 elsewhere) has a cavernous angioma, but only about 1 in 15,000 actually carries a diagnosis. Thus, cavernous angioma is a common blood vessel abnormality that, for a variety of reasons, is infrequently diagnosed.

Amy Akers & Connie Lee

See Amy Aker's more detailed version of this story on our website.

News

2011 Angioma Alliance Patient and Family Conference

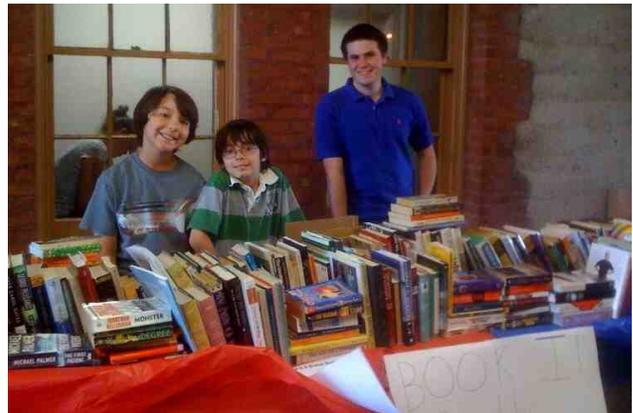
The next Angioma Alliance Patient and Family Conference will be held March 25-27, 2011, in Dallas, TX. The weekend will feature expert presentations by neurosurgeon Dr. Duke Samson, neurologist Dr. Jennifer Lee, and Angioma Alliance Chief Scientific Officer Dr. Amy Akers. There will be social time and small group time so that attendees will have a chance to spend time with each other. And, we will have a 5K Fun Run/Walk to spread awareness in the greater Dallas area. We will have more details in our next newsletter and on our website. We would love to have an estimate of how many people may be able to attend. If you think that you can be there, please email us at info@angioma.org or leave a message at 757-623-0615. This isn't a commitment, but is simply a way for us to plan.

Cinco de Mayo Dance

On May 8th, Kathy and Ronnie Bince held the 2nd Annual Blewer's Cinco de Mayo Dance for a Cure fundraiser in Alameda, CA. The event featured 4 DJs, lots of great Mexican food, and a raffle. It was a fun time for everyone who attended. Pictured below are: Larry Almeda, Dj Riktor, Deborah Porterfield, Zack Pieniasek, Kathy Bince, Adan Alonz, Brian Blewer, Alex Mejia.

Book it 4 Brains Book Sale

On April 8th, the Political Guild Club students of Flagler College in St. Augustine, Florida, sponsored a Book it 4 Brains Book Sale to benefit Angioma Alliance. The students raised \$320 from the sale of donated books. Pictured in the photo are, from left to right, Evan and Ethan Elfersy, and club President Frank Mahoney.



The students of the club are looking forward to holding another sale to benefit Angioma Alliance during the fall semester when the students return from summer break.



Angioma Awareness 5K Fun Run

On March 27, Rachel Hart and Savannah Hollis organized an Angioma Awareness 5K Fun Run in Irving, Texas. Over 80 registrants helped to raise funds and awareness in the Dallas area and beyond. The event will be repeated next year on March 26th in conjunction with an Angioma Alliance Family Conference.



Legislative Alert!

Senator Tom Udall will be introducing a bill to establish a Cavernous Angioma Clinical Care, Advocacy, Research and Education (CARE) at the University of New Mexico. Once the bill is introduced, we will be sending out an alert to our Community Forum, all members of our email mailing list, and our Facebook Group. At that time, we ask that you contact your Senators via fax or phone to ask for their support. The CARE Center at the University of New Mexico is intended to be our first of many CARE Centers throughout the country as we prepare for future clinical drug trials.

Upcoming Events

We are excited and grateful to announce four more upcoming awareness events in the right-hand column of this page. We would like to thank everyone who is taking the time to make "cavernous angioma" a household word in your community and helping to keep the work of Angioma Alliance going. We'd particularly like to thank Rachel Hart who has been putting in many hours supporting those who are organizing Fun Run/Walks. Please contact us at info@angioma.org if you would like to learn how to organize an event in your area.

Flapjack Fundraiser

Join the scarves4CCM1 girls at Cedar Crest Applebees for a flapjack breakfast and raffle to benefit Angioma Alliance. Tickets are \$5 and can be purchased by emailing scarves4CCM1@yahoo.com.

Scarves4CCM1 is a group of Springhouse Middle School girls who have been knitting and selling scarves to benefit Angioma Alliance. They are branching out into organizing events and this is their first! Come out and support Kylie, Alexis, Addie, Kamee, Val and Rebecca, and have a yummy breakfast, too!

The event will be held on Saturday, July 31, 2010, from 8 am to 10 am, at Applebees, 1510 Cedar Crest Blvd, Allentown, PA.

To learn more about the Scarves4CCM1 group, visit: <http://scarves4ccm1.piczo.com/?cr=2>

Party and Silent Auction

Join Allison and Ken Ruggles and friends for a fun night of dancing, food, and bidding to support cavernous angioma research and awareness!

The event will take place on Saturday, August 21, from 7 pm to 12 am, at Loring Center, 384 Court St, Plymouth, MA.

To RSVP, email info@angioma.org

Ogden 5K Angioma Awareness Fun Run/Walk

Brooke Mueller and her friends and family are organizing a 5K Fun Run/Walk to benefit Angioma Alliance in Ogden, Utah on September 11, starting at 8:30 am. The Run/Walk will take place on the trails of Mt. Ogden Park, providing a beautiful backdrop. Visit www.angiomaalliance5K.blogspot.com for complete information.

Angioma Awareness 5K Fun Run/Walk

Brought to you by Delia Candelaria and friends, this will not be your typical "walk in the park." We have recruited various sponsors and acquired generous donations to make the morning worth getting up so early! Reasons to come include door prizes, food & drinks, and lots of fun.

Participate in the Sabine-to-Bagby Promenade/ Buffalo Bayou Walk on Saturday, September 25, 9 am to 12 pm, at 150 Sabine Street/Parking Lot H, Houston, TX.

Registration is \$15 and includes a t-shirt. You can register by visiting www.awareness4life.myevent.com

Cavernoma Alliance UK Update



Since the last Spring newsletter, Cavernoma Alliance UK has been rather busy. As well as increasing our membership to 275, we have been successful in convincing the Neurological Alliance (the UK umbrella charity for neurological conditions) to list “cavernoma” on the NHS Choices website. This page can be viewed at <http://www.nhs.uk/conditions/cavernoma/Pages/Introduction.aspx>

Last year, Cavernoma Alliance UK established a successful series of CaverHubs funded by Awards for All. These CaverHubs are meetings held with neurosurgeons and neurologists in twelve centres of excellence throughout the UK. This infrastructure was very useful when Cavernoma Alliance UK participated in International Brain Awareness Week 2010. Please see: www.dana.org/brainweek.

Mr. Mohsen Javadpour (vascular neurosurgeon, The Walton Centre) gave a talk on cavernomas at NeuroSupport, Liverpool, in North-West England. And the internationally-known Mr. Andrew McEvoy spoke on epilepsy, cavernomas and awake craniotomy, introduced by former patient and indispensable Cavernoma Alliance UK board member, Tabitha Bushill, to a packed room at the National Hospital for Neurology and Neurosurgery, Queen Square, London (where Mr. McEvoy also works as consultant neurosurgeon.)

Tabitha Bushill made a valuable contribution to the CA UK display stand at the March meeting of the Society of British Neurosurgeons’ Conference in Cambridge. (The picture below shows Tabitha, myself, and the CA UK stand).



Frank Gent and my assistant, Iris Cassomini (both CA UK board members) joined me at the Association of British Neurologists’ Conference in Bournemouth, Dorset, on the UK’s South Coast.

These conferences were awareness-raising exercises for Cavernoma Alliance UK. Both conferences proved very successful with one neurosurgeon at Cambridge

begging not to receive any more information sheets. “I have got nine already.”

Dr Diana Dempster continues with her on-going attempt to secure funding for the Cavernoma Alliance UK project “psychological stress as the causative agent which induces symptomatic events in cavernomas.”

I cannot write without mentioning, and expressing our enormous gratitude to, CA UK’s Senior Medical Adviser for CA UK and consultant neurosurgeon at the National Hospital of Neurology and Neurosurgery, Queen Square, London, Mr. Neil Kitchen (pictured below) and his Herculean efforts at running the London Marathon raising over £6,000 (\$10,000) for our charity.



Finally, the International Cavernoma Alliance UK Forum took place at the Grange Holborn Hotel, London, on Saturday 5th June 2010. We had over eighty members present and our keynote speaker this year was Dr. Amy Akers, the Chief Scientific Officer for Angioma Alliance. Pictured below from left to right: Dr. Jonathan Berg, Dr. Rustam Al-Shahi Salman, medical adviser Cavernoma Alliance UK; and Mr. Neil Kitchen, Senior Medical Adviser Cavernoma Alliance UK, Dr. Amy Akers, and your humble servant.



Ian Stuart

Angioma Alliance Donors January 1, 2010 through March 31, 2010

In addition to all those who participated so generously in special events, Firstgiving and Network for Good, Angioma Alliance received:

Beacons (\$5000+)

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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.

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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

The Angioma Alliance Newsletter is a quarterly publication of Angioma Alliance

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