

2018 CCM Scientific Meeting – Summary and Overview

Specialized scientific conferences are held all over the world, each uniquely focused on a specific research topic or strategy. The American Society for Human Genetics; Society for Neuroscience; and International C. elegans (worm) Meetings are just a few examples of those attended by our CCM researchers. However, as the names imply, they each draw a subset of our research whole. The CCM Scientific Meeting is unique in that it draws together scientists and clinicians who otherwise would not interact with one another. This interaction of diverse scientific thinkers is critical for advancing our science and driving research for a cure.

The 2018 CCM Meeting continued on a great tradition of success – for the first time, we had over 100 attendees with representatives from five continents, five drug companies, three advocacy organizations, government officials and an international consortium of clinicians and scientists. (Pictured below is almost all of us...our group grew so big, we couldn't all squeeze into this large stairwell!) There were two other landmarks. First, we now have more presentations dedicated to CCM clinical research than to animal models of the illness or basic biological building blocks. This allowed us to dedicate an entire meeting day to topics focused on treatments and on understanding the impact of the illness in humans. Also, for the first time, we held a concurrent national patient conference that allowed researchers and patients to meet each other over lunch and attend a joint session. The shared time was appreciated by both groups and may be included again as our budget allows.



A unique feature of this meeting is our focus on unpublished research and lively discussion. With a strong privacy policy in place, our researchers feel comfortable sharing with one another, engaging in discussion and developing new hypotheses and collaborations. These collaborative efforts have led us to where we are today - recruiting for our first clinical trial for hemorrhage, our first Phase I trial for safety, and with a whole host of new drugs and druggable targets.

With respect to our privacy policy, the following summary is an overview of the meeting proceedings. As each new study is peer-reviewed and published, we will share the details through my Facebook page ([facebook.com/AmyAkersPhD](https://www.facebook.com/AmyAkersPhD)) and Angioma Alliance's newsletters.

New Drug Targets

Basic science continues to charge forward, uncovering new druggable pathways, identifying currently approved drugs that might be repurposed for CCM, and bringing hope for translation from the lab to clinic. Bringing together so many scientists from different backgrounds draws out unique perspectives and leads to exciting discussion. Each model system provides information about the functional biology of the CCM proteins (those that are disrupted and no longer function in the cavernous angioma lesions). Zebrafish models are great for studying vessel biology - baby fish develop in clear eggs and have transparent bodies making them uniquely suited for studies that fluorescently label cells to track the development of vascular systems with advanced microscopy. We also heard from worm and fly research teams. Rapid growth and short generation time are features that make these systems ideal for quickly screening large drug libraries and studying the biology of tube formation.

Several academic labs have developed genetic models for all familial forms of CCM in mice. Mouse studies help us learn about lesion formation and are the model used for drug treatment studies. At the meeting we heard from two groups who looked closely at the lesion to investigate their cancer-like nature. In recently published work, the team at Duke University used advanced microscopy and a fluorescent tracking system to show that from the very earliest stage of development, CCM lesions (in the familial form) start with an inherited plus a random (somatic) mutation. In combination, these two mutations completely destroy the function of one of the CCM genes in a brain blood vessel cell. These mutational events change the cell such that it starts to grow, and grow, and grow like a cancer. As it becomes a mature multi-cavernous large lesion, those mutant cells also recruit non-mutated blood vessel cells into the lesion. How the recruitment occurs remains unknown.

Over the past few years, there has been a lot of work on the Rho Kinase (ROCK) signaling pathway and how the molecules of that pathway are involved in CCM lesion development. From this research, ROCK inhibitors emerged as leading candidates for drug therapy. Atorvastatin (a ROCK inhibitor) is currently in clinical trial for hemorrhage of cavernous angioma (more on that later...).

ROCK may be only one piece of the CCM puzzle; there are many other signaling pathways involved in a complex regulatory network. For the first time, we heard about the new (just published the week of the meeting) work out of Centenary Institute in Australia that showed a leukemia drug, Ponatinib, is able to prevent lesion formation in CCM mice by disrupting a critical (MEKK3-KLF) signaling pathway. Adding yet another possible drug target to the growing list for CCM, Ponatinib is approved by the

FDA as a cancer drug. However, this drug targets more than just MEKK3-KLF and is known to have negative side effects, which may make it inappropriate for cavernous angioma treatment. Further studies may determine whether Ponatinib, or perhaps a new generation of this drug, or a new MEKK3-KLF inhibitor might be best suited for human study.

What does all this mean for treating people?

Now, on to human research...the business end of all this work and why we do what we do - driving research to develop a non-surgical treatment for cavernous angioma.

Natural History & Biomarkers - Studies to Prepare for Large Clinical Trials.

When we use the term, natural history, we are referring to the typical clinical course of an illness to describe its progression through time. In particular, the term refers to what happens when an affected person is left untreated by drugs or surgical intervention. We are beginning to understand better the natural history of cavernous angioma, but one of the major challenges we face is to truly understand the variability between patients, particularly those within families who carry the exact same disease-causing mutation. Major questions include what risk factors or other medical conditions may be associated with future hemorrhage and/or lesion development. The [Brain Vascular Malformations Consortium](#) study is focused on studying variation of familial cavernous angioma. We heard talks and viewed poster presentations from this project team related to studies of spinal lesions, hemorrhagic risk factors and causes of death. Investigating the microbiome in all patients (sporadic and familial) is another ongoing study related to variation and natural history, for which we discussed preliminary data. Another active area of investigation is on quality of life - the team from the Mayo Clinic is currently recruiting for an [online survey-based study](#) to learn about the quality of life for folks with brainstem lesions. The importance of understanding natural history relates to clinical management and also clinical trials. By knowing what outcome to expect over time, one can thoughtfully predict drug effects and design clinical trials that enroll the right number of people to prove a drug's efficacy.

According to the FDA, a biomarker is something that is measured either as an indicator of disease course or response to a drug or surgical intervention. Biomarkers can be relevant in the clinic to predict future disease state, for example. Or, during clinical trials to measure the effect of the drug treatment under study. Previously, Dr. Awad's team at the University of Chicago had identified a series of chemical biomarkers measured from blood plasma that are predictive of future hemorrhage. We heard about the latest findings as his team continues to expand the biomarker set and refine the use of this tool. Future FDA qualification can move plasma biomarkers into everyday clinical practice.

Another biomarker type of keen interest for clinical trial, particularly trials of symptomatic hemorrhage, is imaging. Specialized MRI techniques to measure permeability and iron leak (surrogate for hemorrhage) are developed and in use at the University of Chicago for research and the atorvastatin trial. A new study, the CASH (Cavernous Angioma of Symptomatic Hemorrhage) [Clinical Trials Readiness Project](#), brings together six clinical sites (Universities of Chicago, New Mexico, California San Francisco, and Utah, as well as the Mayo Clinic and Barrow Neurological Institute) to validate use

of the imaging biomarkers at partnering institutions and to understand better the potential pool of study participants at each site. As the name implies, the purpose of project is preparation of future large-scale multi-center clinical trials.

Clinical Trials

It was exciting to learn about the projects of our clinical research groups. BioAxone BioSciences continues progress with safety and animal studies to prepare for human studies. For the first time, we have a new chemical entity being tested for safety as Recursion Pharmaceuticals announced it has moved their drug REC-994 (tempol) to a Phase I trial. Phase I studies are for new drugs and aim to determine whether the drug is safe for human use. Phase I trials involve healthy volunteers, not cavernous angioma patients. With positive safety results, Rec-994's next step will be Phase II to determine whether the drug is effective in treating CCM patients. Representatives from both BioAxone and Recursion presented at the family conference held jointly with the scientific meeting. Their presentations can be viewed on the [Angioma Alliance YouTube channel](#).

Throughout the course of the meeting, we also heard presentations on two trials for drugs currently approved for use in other indications - atorvastatin and propranolol. In Italy, a multi-center trial is recruiting for [treatment with propranolol](#), a beta-blocker commonly prescribed to control blood pressure and tremors. The study is designed to investigate the effects of long-term propranolol treatment on clinical symptoms and/or changes to lesion size or number.

Atorvastatin is a cholesterol lowering medication that is being studied at the University of Chicago, with a specific focus on cavernous angioma patients with recent symptomatic hemorrhage. The study is seeking to recruit those who have experienced hemorrhage within the last 12 months. This one-year window is important as the year following a previous hemorrhage is the time when you are most likely to hemorrhage again - and thus, a critical window for potential therapeutic treatment. Enrolling individuals who have recently hemorrhaged allows the trial to be shorter but does not reduce its generalizability to others with CCM.

In summary, cavernous angioma research is active at all levels. It is thrilling to begin our first clinical trials, and also, hopefully, to continue finding new possible ways to treat the illness. In the coming years we expect to have more trials and more clinical studies that need cavernous angioma patient participation. Stay tuned and remember, *without you, there can be no cure!*

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