Pediatric Hydrocephalus Foundation (PHF) research and development funded grant: Inside the Harris Shunt lab & examining the fully funded MAG project. Interview date 2/7/17, publication date 5/11/17.

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Thanks to our generous donors, the Pediatric Hydrocephalus Foundation (PHF) has funded a grant for hydrocephalus research to the Harris Shunt laboratory. The research is for a new treatment for hydrocephalus that has potential to replace shunting. Micro-fabricated arachnoid granulations, or MAG, would mimic the brain's ability to transfer cerebral spinal fluid (CSF) to the sub-arachnoid space where it is then absorbed into the bloodstream.

Dr. Carolyn Harris submitted the grant request September 2016. The hydrocephalus community has not seen a breakthrough in treatment in over 50 years. The micro-fabricated arachnoid granulations (MAG), if proven viable, would provide a breakthrough in how hydrocephalus is treated; a breakthrough which would not rely on the problematic shunt system which fails most commonly due to obstruction.

"Despite our efforts for 50 years, shunts still have the highest failure rate of any neurological device: ***98% of all Shunts fail after ten years****" -Dr. Harris (Harris 2017)*

"I can attest to the fact that surgical interventions for the treatment of hydrocephalus have not improved outcomes as much as expected and the ***major obstacle to progress is the failure to prevent shunt obstruction****"*
- Dr. McAllister (MAG collaborator 2016)

The purpose of my interview with Dr. Harris was to better understand the project the Pediatric Hydrocephalus Foundation (PHF) is funding. We would also like to provide insight on how the funds are being utilized. The title of the project is "MAG for Treatment of Communicating Hydrocephalus."

The lab is located at the Detroit Children's Hospital of Michigan, part of the Detroit Medical Center (DMC). Walking into the DMC to conduct the interview brings back memories of the eight brain surgeries my son, Hawke, required when he was three years old during the summer of 2011. My wife and I were grateful Hawke survived the hydrocephalus complications which included multiple shunt failures over a three-month span in 2009. Without a breakthrough statistically, my son and thousands of hydrocephalic patients are nearly guaranteed to face additional brain surgeries as a result of shunt complications.

I met Dr. Harris along with Sulmaz Zahedi, who has a Bachelor's in Engineering and is obtaining a Master's of Health Science in Clinical Engineering, along with Prashant Hariharan, who has a Master's of Science Degree and Masters of Engineering Degree in Biomedical Engineering, and Ahmad Khasawneh, who is pursuing a Bachelor of Science in Biology while taking the pre-medical sciences track. After introductions, we headed to the shunt lab, taking two elevators and a few underground tunnels until we arrived at the labs. Several labs exist on the floor: the Harris lab is working on multiple shunt projects beyond the MAG project alone. I was thrilled to learn what the shunt lab was working on and how the MAG will be tested, trialed, and potentially validated.

One of the major focuses of the Harris shunt lab includes quantifying the cellular response to current hydrocephalus treatments and brain injury. Dr. Harris is nationally and internationally recognized as an expert in hydrocephalus due to her comprehension of the pathophysiology of the disorder and her investigation into shunt obstruction and shunt infection utilizing unique model systems. The Harris laboratory studies hydrocephalus with a prudent focus on bioengineering strategies that could improve treatment. They integrate experimental bench top data with translational studies involving patients to deepen our knowledge of this complex disorder. You can learn more regarding the Harris laboratory by visiting www.healinghydrocephalus.com.

Dr. Harris, would you mind telling us a little about yourself?

"I am an Assistant Professor in both the Department of Neurosurgery and Chemical Engineering and Material Science. I run a lab with great collaborators and fantastic students at Wayne State studying hydrocephalus with a focus on bioengineering strategies to improve treatment. I received my Bachelors of Science in Biomedical Engineering from Purdue University in 2006 and my Ph.D. from the University of Utah in 2011, also in Biomedical Engineering. I started working on hydrocephalus in 2004, and will not stop until treatment is dramatically improved. My husband, a software engineer, and I, are parents to two great kids."

What sparked your interest to pursue the study of the Brain, Neurosurgery, and the biomedical field?

"Predominately my mentor, James (Pat) McAllister, PhD, a Professor of Neurosurgery at Washington University in St. Louis. Dr. McAllister has been studying the pathophysiology of hydrocephalus for years and is an amazing asset to the hydrocephalus community. Even when I was a student, Dr. McAllister made my voice feel valued in his research lab. Predominately because of that positive mentorship, I believe, I am always trying to apply every engineering solution in medicine to hydrocephalus, to make treatment better. Personally, amidst my postdoctoral fellowship in Seattle, I delivered our first born ten weeks early. She spent six weeks in the NICU and had a few up and downs. Watching my daughter fight only made me want to fight harder for preemies and other patients, particularly those with hydrocephalus, especially because I know there is so much research we can do to help."

What is the leading cause of shunt failure?

"*Shunt obstruction. Shunts are great, until they're not. A shunt typically has 32 holes in the ventricular catheter which provide a path for CSF flow from inside the shunt to the abdomen region. Once many of these holes are blocked with the cells and tissues of the brain, drainage is slowed and pressures can rise. These shunt complications are alleviated by replacing the shunt and its catheters (brain surgery). Additional common failure modes include disconnected catheters, infection, and the shunt itself can exhibit a variety of problems.*

In your opinion, do you think the revenue generated in the biomedical (shunt) industry may create a financial environment which would decrease the industry's interest in investing in new treatment options? (Americans spend over two billion annually)

"*There is not much economic incentive for the biomedical industry to pursue new developments. Although there are certainly some advancements being made, we need basic science labs at universities to do some of the leg work that some big companies don't have time to do. In this way, amongst others, we can and will advance treatment in a significant way."*

Barometric pressure seems to impact most of the patients in the hydrocephalus community. Do you know of any scientific studies surrounding this phenomenon?

"At patient conferences everyone talks about the barometric pressure and its impact on the hydrocephalus community, but little hard data exists to explain this phenomenon, to my knowledge. We do have the technology to record the data in today's modern world."

Mrs. Zahedi, what are your thoughts on the modern-day shunt & what motivates you in this research?

"I have a problem with modern day shunts because they have such a high failure rate, the highest failure procedure in all neurosurgical procedures. It baffles me that the shunt system used to treat hydrocephalus has remained, essentially, unchanged since 1952. As an engineer, I know that we can certainly do better, and it's my mission to make that happen. Working in the field of hydrocephalus is often challenging, as there is so little that we know about its etiology, and the resulting pathophysiological changes that occur in the brain. Working under the mentorship of Dr. Harris has motivated me in many ways as she is a passionate and caring researcher, who has dedicated her career to furthering the understanding of hydrocephalus, and directly translating these findings into the clinic where they are needed the most. The Harris lab is a collaborative and open minded work space where we

not only run cutting edge research, but work directly with neurosurgical residents, mid-levels, neurosurgeons, and most importantly patients."

"Having the opportunity to directly interact with hydro patients and families through our shunt collection research has been a major and constant source of motivation and encouragement for me. Spending time with patients, and their families, listening to their journey with hydrocephalus, and explaining the research that we do in the Harris lab has not only sparked hope in patients, but brought up new ideas and potential avenues of research. I look forward to continuing to work towards a better hydrocephalus cure and am certain that we can achieve this goal within our life time."

Dr. Harris, how are the failure modes different in adults and children?

"The treatment of pediatric and adult hydrocephalus shares some similarities, but can be totally different. It all depends on the cause of hydrocephalus, and when it was diagnosed. In adults, particularly those with normal pressure hydrocephalus, the leading cause of failure is typically in the abdominal region. Compare this to the average pediatric patient, whose shunt usually fails at the ventricular catheter. The age this changes is not defined yet. It's perhaps something to do with ventricular size and the expandable skull in young children. When you shunt an adult, the ventricles don't change in size as much as they can in a child, so there's less chance for the location of the catheter in the ventricles to move around and become blocked. In an adult, there is often more fatty tissue in the abdomen than there is in kids. Failure from these tissues could accelerate problems in the peritoneal catheter of shunts in adults."

The PHF was able to fund a $20,000 grant due to the generosity of donors. The PHF is a non-profit made of all volunteer's (no-salaries paid) created and consisting of parents of children with hydrocephalus. The chase for a breakthrough in treatment and/or a cure is very intimate to us. Dr. Harris, can you explain to our readers how the experimental device called a MAG could provide a breakthrough in hydrocephalus treatment? What is the purpose of the MAG and how does it work?

"*First, thank you! This means so much to my lab. The MAG, if proven successful, will mimic arachnoid granulations. Arachnoid granulations are present and functional in most everyone without hydrocephalus. They act as one-way valves for CSF to travel from the brain to the sinuses, maintaining a balanced intracranial pressure. In patients with communicating (extra-ventricular) hydrocephalus, these arachnoid granulations can become blocked or may stop working efficiently. The MAG will mimic what already naturally occurs in patients without hydrocephalus by creating small, implantable one-way valves at the interface between the brain (sub-arachnoid space) and the blood (sinus) that will relieve CSF out of the brain so it can be absorbed. This premise is just like a shunt that diverts fluid out of the cranial space so it can be absorbed. We simply avoid using the tubing and mimic the natural bypass of fluid out. This concept is based on many previous iterations of mimicking the arachnoid granulations from some fantastic collaborators. The PHF funds allow us to merge our ideas with others, and test them in next generation systems to finally bring these concepts to fruition" (See MAG Illustration)*

What are arachnoid granulations?

"Arachnoid granulations are basically tiny one-way pressure regulated valves that allows CSF to pass out of the cranial space and be absorbed in the bloodstream. Anatomically, the arachnoid granulations are very close to the skull. Mrs. Zahedi believes the design of the MAG has great potential because it will function similar to natural arachnoid granulations"

Cerebrospinal Fluid (CSF) stops circulating properly and crushes the brain (increases intracranial pressure). Dr. Harris can you explain what CSF is & where it is created?

"In a person whom does not have hydrocephalus, CSF circulates around the brain to bathe it, protect it, and allow transportation of nutrients and waste byproducts. The scientific community is just learning of all the places CSF is absorbed, but one of these absorption sites is certainly at the arachnoid granulations as CSF comes up and around the outside of the brain to be absorbed. CSF is produced in the choroid plexus, which you can think of as a filter system: in the choroid plexus, blood is filtered into CSF."

Mrs. Zahedi, can you describe how the MAG system will work?

When a hydrocephalus patient has the most common form of hydrocephalus (communicating arachnoid granulations do not allow CSF to travel out of them. If arachnoid granulations are blocked, the MAG, if proven successful, will create an outflow pathway and mimic the arachnoid granulations which normally allow the CSF flow to exit. The MAG will have outflow pathway made of a needle valve. Each needle valve in the MAG represents 30-40 arachnoid granulations. The MAG is pressure controlled based on intracranial pressure (ICP). The MAG will poke through the dura. As we have studied in modern day shunts, we know the cells will also attack the MAG. In our research, we are working to learn how to mitigate the attacking cells to prevent blockage. Additionally, the use of hydrogels are being trialed and may prevent backflow and obstruction. We are partnering with a group in Arizona whom has developed these hydrogels. Hydrogels are similar to water, but breakdown at a very slow rate. It would take over 200 years for the gel to breakdown. Hydrogels breakdown, but at a rate that would only be evident over a 100-year period. I spent most of the 2016 summer to research and understand the mechanical properties of the dura, as the MAG will have to poke through the dura in order to transfer the CSF to the sub-arachnoid space. It's tough trying to understand the structural integrity required of a needle valve to poke through the dura without breaking the needle valve. Surprisingly, there are no papers on this topic. In my research, I found papers from 1950, 1951, 1872, and only one paper on arachnoid granulations."

Dr. Harris, do scientists in the community work together on research projects surrounding hydrocephalus?

"Scientists and researchers like to collaborate, especially in the study of hydrocephalus. It is common for us all to share information and work together with a common goal."

Dr. Harris, what about a Cure?

A cure is definitely needed. It has to be done. But in the meantime, surgical interventions are almost always necessary. What we're focusing on in this project is improving those interventions so we can, in a shorter term, improve daily life and attempt to eliminate guesswork from the parents.

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Author & Interviewee contributions: Jason Adams recorded and documented the interviews with Dr. Harris and Mrs. Zahedi. Dr. Harris and Mrs. Zahedi have read and approved the final version of this manuscript.

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References:

1. Adams, J. (2017, February 7). *Personal interview* with Harris, C.
2. Adams, J (2017, February 7). *Personal interview* with Zahedi, S.
3. Harris, C (2016, September 16). Dr. Harris, C. *PHF Grant application*. Research title "Micro-Fabricated Arachnoid Granulation (MAG) for treatment of communicating hydrocephalus".

Additional resources:

www.hydrokids.org
www.healinghydrocephalus.com

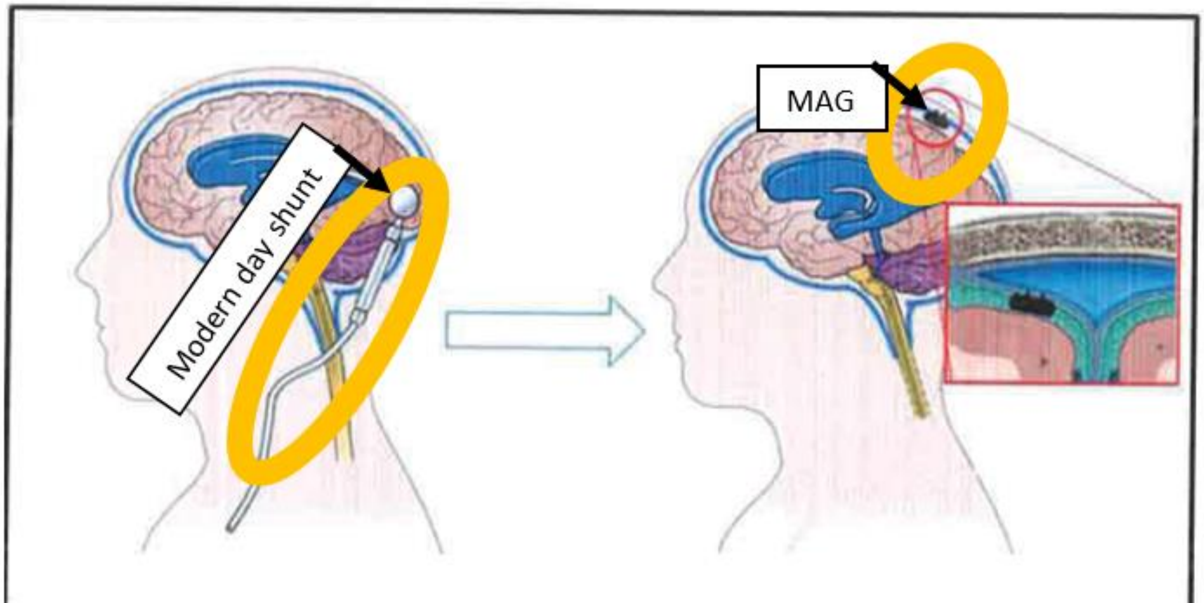

Figure 1. Comparison between traditional hydrocephalus treatment (left) and proposed MAG treatment (right). Bottom right: side view showing two valve connections.

Figure 1: Harris, C (2016, September 16). Dr. Harris, C. *PHF Grant application*. Research title "Micro-Fabricated Arachnoid Granulation (MAG) for treatment of communicating hydrocephalus".

Image 1: *2/27/17 Pictured left to right. Jason Adams (MI PHF Co-Director), Carolyn Harris (Assistant Professor of Neurosurgery, Adjunct appointment in Biomedical Engineering PhD),* Sulmaz Zahedi (Bachelor's in Engineering) and Prashant Hariharan (Masters of Science Degree & Masters of Engineering Degree in Biomedical Engineering).