

# Driving Common Pathways Workshop



## Extending Insights from Posthemorrhagic Hydrocephalus

Monday, November 4, 2019  
7:30 am - 5:00 pm

Tuesday, November 5, 2019  
7:00 am - 3:00 pm

Washington University in St. Louis  
Charles F. Knight Center  
Executive Education & Conference Center  
Throop Drive and Snow Way Washington,  
St. Louis, MO 63130





## Welcome Letter: From President and CEO Diana Gray

Welcome to the Hydrocephalus Association (HA) workshop, Driving Common Pathways: Extending Insights from Posthemorrhagic Hydrocephalus. Over the past four years, HA has committed significant resources to posthemorrhagic hydrocephalus (PHH) research, and we plan to continue these efforts in the near future. However, we are now seeing significant overlap between the mechanisms implicated in PHH and other forms of hydrocephalus, such as postinfectious hydrocephalus (PIH).

Our task over this two-day workshop is to explore these areas of overlap and determine which hold the most promise for new therapy development and improved outcomes for our community. We anticipate active discussion and debate throughout the two days, and expect the proceedings from this workshop to be presented in a white paper and published in a peer-reviewed journal. Insights from this workshop will help guide HA in our mission to find a cure for hydrocephalus and improve the lives of those affected by the condition.

The workshop is being funded through the \$3MM Vision Dinner PHH Campaign led by Vicki and Craig Brown. We are extremely grateful to the Browns and all of the donors who contributed to this successful campaign, enabling HA to provide new research opportunities and to bring the research community together to collaborate at this important meeting.

Thank you for your participation and for sharing your expertise through this collaborative workshop!

Sincerely,

A handwritten signature in black ink that reads "Diana Gray". The signature is fluid and cursive.

Diana Gray, MA

President and Chief Executive Officer  
Hydrocephalus Association

### Planning Committee

**Lauren Jantzie, PhD**

Johns Hopkins University

**Jason K. Karimy, MS**

Yale School of Medicine

**Jenna Koschnitzky, PhD**

Hydrocephalus Association

**Maria Lehtinen, PhD**

Boston Children's Hospital

**David Limbrick, MD, PhD**

Washington University  
School of Medicine

**James P. (Pat) McAllister, PhD**

Washington University  
School of Medicine

**Jill Morris, PhD**

National Institutes of Health

# Diving Common Pathways Workshop Agenda

Monday, November 4, 2019

7:30-8:30 **REGISTRATION** Room 200, 2<sup>nd</sup> Floor  
**BREAKFAST** Anheuser-Busch Dining Room,  
3<sup>rd</sup> Floor

## INTRODUCTION

### Welcome:

8:30-8:40 **Welcome | Framework and Goals of Workshop**  
*Ms. Diana Gray, MA, President & CEO,  
Hydrocephalus Association*

### Overviews:

8:40-9:10 **Clinical Overview**  
*Dr. Shenandoah Robinson, Johns Hopkins  
University*

9:10-9:30 **Linking Mechanisms Across Hydrocephalus  
Etiologies**  
*Dr. David Limbrick, Washington University  
School of Medicine*

9:30-9:55 **BREAK**

## SESSION 1

### Role of the Choroid Plexus

#### Perspective:

10:00-10:30 **CSF Production - Now With Cotransport of  
Water**  
*Dr. Nanna MacAulay, University of Copenhagen*

#### Short Talks:

10:30-10:45 **Pediatric Intraventricular Hemorrhage Induces  
Rapid Intracellular Calcium Signaling in the  
Choroid Plexus and Chronic Changes in CSF  
Reabsorption**  
*Dr. Cameron Sadegh, Harvard University*

10:45-11:00 **A Role for Inflammation: TLR-4-mediated  
Cerebrospinal Fluid Hypersecretion in  
Post-hemorrhagic and Post-infectious  
Hydrocephalus**  
*Mr. Jason K. Karimy, Yale University*

11:00-11:15 **Role of TRPV4 in CSF Production: In Vivo  
and In Vitro Mechanistic Studies**  
*Ms. Makenna Reed, Indiana University -  
Purdue University Indianapolis*

11:15-11:40 **Discussion:**  
*Moderator: Dr. Kristopher Kahle, Yale School of  
Medicine*

11:40-12:50 **LUNCH: Anheuser-Busch Dining Room,  
3<sup>rd</sup> Floor**

## SESSION 2

### Role of Cilia

#### Perspectives:

1:00-1:30 **The Role of Motile Cilia in the Nervous  
System, What the Zebrafish Can Teach Us**  
*Dr. Nathalie Jurisch-Yaksi, Norwegian University of  
Science & Technology*

1:30-2:00 **The Response of Developing (and Diseased)  
Ciliated Epithelia to Mechanical Strain**  
*Dr. Chris Kintner, Salk Institute*

2:00-2:30 **Panel:**  
*Moderator: Dr. Lauren Jantzie, Johns Hopkins  
University*  
*Dr. June Goto, Cincinnati Children's  
Hospital Medical Center*  
*Dr. Jennifer Strahle, Washington University  
School of Medicine*  
*Dr. Nathalie Jurisch-Yaksi, Norwegian  
University of Science & Technology*  
*Dr. Chris Kintner, Salk Institute*

2:30-2:55 **BREAK**

## SESSION 3

### Brain Development and Microglia

#### Perspectives:

3:00-3:30 **Development of Human Germinal Matrix  
and Its Implications in Neurodevelopmental  
Disorders**  
*Dr. Eric Huang, University of California San  
Francisco*

3:30-4:00 **Microglial Remodeling of Brain Circuits and  
Implications for Hydrocephalus**  
*Dr. Dorothy Schafer, University of  
Massachusetts Medical School*

4:00-4:35 **Response and Discussion:**  
*Moderator: Dr. Marc Del Bigio, University of  
Manitoba*

## CLOSE OF DAY ONE

4:35-5:00 **HA Programs and Closing Remarks**  
*Ms. Diana Gray, MA, President & CEO,  
Hydrocephalus Association*

6:00-9:00 **Dinner: Anheuser-Busch Dining Room,  
3<sup>rd</sup> Floor**

# Tuesday, November 5, 2019

7:30-8:30 **REGISTRATION** Room 200, 2<sup>nd</sup> Floor  
**BREAKFAST** Anheuser-Busch Dining Room,  
3<sup>rd</sup> Floor

## INTRODUCTION

### Welcome:

8:00-8:05 **Welcome**  
*Ms. Diana Gray, MA, President & CEO,  
Hydrocephalus Association*

### The NIH and Hydrocephalus

8:05-8:35 **NIH Funding Opportunities for Hydrocephalus  
Research**  
*Dr. Jill Morris, National Institutes of Health*

### Perspective:

8:35-9:05 **Neuroinflammation and Drug Targets**  
*Dr. John Zhang, Loma Linda University*

9:05-9:20 **BREAK**

## SESSION 4

## Role of Ependyma

### Perspectives:

9:25-9:55 **Development and Plasticity of Multiciliated  
Ependyma**  
*Dr. Chay Kuo, Duke University*

9:55-10:25 **The Role of Hippo-Yap Pathway in PHH  
Pathogenesis**  
*Dr. Seonhee Kim, Temple University*

### Short Talks:

10:25-10:40 **ADAM10 Inhibitor: A Novel Therapeutic  
Strategy for PHH and PIH**  
*Dr. Albert Isaacs, Washington University School of  
Medicine*

10:40-10:55 **PI3K-Yap Activity - A Common Mechanism  
For Congenital and Posthemorrhagic  
Hydrocephalus?**  
*Dr. Achira Roy, Seattle Children's Hospital  
Research Institute*

10:55-11:10 **Injury and Repair of Ependymal Motile Cilia in  
a Preclinical Model of Posthemorrhagic  
Hydrocephalus of Prematurity**  
*Ms. Jessie Neville, Johns Hopkins University*

11:10-11:35 **Discussion:**  
*Moderator: Dr. James P. (Pat) McAllister,  
Washington University School of Medicine*

11:35-12:45 **LUNCH: Anheuser-Busch Dining Room,  
3<sup>rd</sup> Floor**

## SESSION 5

## Opportunities in Cell Therapies

### Perspective:

12:50-1:20 **iPSC-based Regenerative Medicine For  
Human Disease and Hydrocephalus**  
*Dr. Edwin Monuki, University of California Irvine*

### Short Talk:

1:20-1:40 **Reverting Astrocytes to Ependymal Cells for  
Treatment of Hydrocephalus**  
*Dr. Stavros Taraviras, University of Patras*

### Perspective:

1:40-2:05 **The Challenges of Personalized and Precision  
Medicine**  
*Dr. Evan Y. Snyder, Sanford Prebys Medical  
Discovery Institute*

2:05-2:30 **Discussion:**  
*Moderator: Dr. Evan Y. Snyder, Sanford Prebys  
Medical Discovery Institute*

## CLOSE OF DAY TWO

2:30-2:55 **The Workshop in Review: Opportunities and  
Next Steps**  
*Dr. Richard Keep, University of Michigan*

2:55-3:00 **Closing Remarks:**  
*Ms. Diana Gray, MA, President & CEO,  
Hydrocephalus Association*

# Workshop Attendees

🔊 Denotes Speaker

## **Khadar Abdi, PhD**

**Duke University**  
Durham, NC  
kma9@duke.edu

Multiciliated ependymal cells line brain ventricles to promote cerebrospinal fluid flow. Most ependymal cells are generated from radial glial progenitors in the final gestational week in humans and the first postnatal week in mice. The inability to differentiate these cells during development consistently leads to hydrocephalus in various mutant mouse models. In my recent publication, we show that radial glial progenitors express EGFRs and that suppression of EGFR signaling allows the ependymal differentiation program to engage. We found that blood serum contains enough EGFR to suppress ependymal maturation in vitro. Control of EGFR signaling in ependymal radial progenitors effectively takes place through the exclusion of receptors from their apical plasma membrane domains. We uncovered the endocytic protein Numb as an important mediator in EGFR trafficking. Mice with conditional loss of Numb through Foxj1-Cre mediated deletion develop lethal hydrocephalus by 4-5 weeks of age. These results provide insight into how local growth factor microenvironments can affect differentiation of multiciliated ependymal cells and lead to hydrocephalus.

## **Bonnie Blazer-Yost, PhD**

**Indiana University Purdue University Indianapolis**  
Indianapolis, IN  
bblazer@iupui.edu

The Blazer-Yost laboratory is studying transepithelial electrolyte and water

transport to understand the role of the choroid plexus epithelial cells in the production and maintenance of the unique composition of the CSF in both health and disease. Currently the laboratory is using a rat model of hydrocephalus to test several ion transport modulatory reagents that alter disease severity. Our group is also developing additional animal models for proof-of-principle testing of promising drug candidates. For mechanistic studies, we are using a porcine choroid plexus cell line that exhibits the characteristics of the native tissue including a high transepithelial resistance indicating a barrier epithelium as well as correctly polarized transport proteins. Electrophysiological studies combined with immunohistochemistry and specific ionic dye tracers are providing crucial information regarding the nature of key transport proteins as well as the intracellular mediators that regulate their activity.

## **Marc Del Bigio, MD, PhD, FRCPC**

**University of Manitoba**  
Winnipeg, Canada  
marc.delbigio@umanitoba.ca

I have been doing hydrocephalus related research on human tissue and animal models since 1983. I can contribute meaningfully to discussions about: human brain development, animal models of neurological disease, causes of hydrocephalus, pathophysiology of brain damage caused by hydrocephalus, brain damage due to premature birth (including hemorrhage), drug treatment of experimental hydrocephalus, and tissue contributions to shunt failure.

## **Hannah Botfield, PhD**

**University of Birmingham**  
Edgbaston, United Kingdom  
h.botfield@bham.ac.uk

My research focusses on the cerebrospinal fluid (CSF) dynamics system in the brain and its dysfunction in diseases including hemorrhagic stroke, idiopathic intracranial hypertension and hydrocephalus. I work on all aspects of the CSF dynamics system from investigating molecules that target the choroid plexus to reduce CSF secretion, to exploring the role of inflammation and fibrosis in reducing CSF clearance and drainage from the brain. This research aims to advance our understanding of pathological mechanisms underlying CSF dynamics dysfunction and to develop alternative therapies that reduce brain injury, manage intracranial pressure and promote a better outcome for patients.

## **June Goto, PhD**

**Cincinnati Children's Hospital Medical Center**  
Cincinnati, OH  
june.goto@cchmc.org

Our lab's interest is on functions of CSF circulation in neonatal brain development. We use genetic mouse and rat models of neonatal hydrocephalus to investigate the development and function of ependymal motile cilia that are essential for creating uni-directional CSF flow within the ventricular system. We use mouse and rat genetics, high-speed video camera recording of ependymal cilia motility and CSF flow ex vivo, adeno-associated virus, and various surgical techniques to model neonatal hydrocephalus development and

## Workshop Attendees (cont.)

surgical treatment options for this condition.

👉 **Diana Gray, MA**  
**President and CEO,**  
**Hydrocephalus Association**  
**Bethesda, MD**  
[diana@hydroassoc.org](mailto:diana@hydroassoc.org)

As President and CEO, Diana is responsible for leading the Hydrocephalus Association (HA), fulfilling its strategic vision, implementing its core values, accomplishing its mission and executing its strategic plan. Diana manages the overall operations, staff and resources, and in partnership with the staff and Board of Directors, continually seeks to grow and develop the organization's programs, supporters, volunteers and mission impact. Diana has been working in the public health and nonprofit sectors for more than 30 years and began her tenure with HA in November 2015. Prior to joining HA, Diana served in Vice President roles for the Juvenile Diabetes Research Foundation Int'l (JDRF) and the Lupus Foundation of America, Inc. In her early career, Diana devoted 14 years serving in the HIV/AIDS arena. After working on the public health side of HIV/AIDS, she closed out her tenure in this field as the Executive Director of The Damien Center, the largest AIDS services organization in Indiana. Upon her departure she was honored by the Governor of Indiana with the highest civilian award, the Sagamore of the Wabash, for her distinguished service. In December 2017, Diana was elected to the National Health Council (NHC) Board of Directors and is thrilled to be representing the Hydrocephalus Association along with 133 million Americans living with a chronic disease or disability through

the work of the Council. In addition, Diana was honored to join the Board of Directors for the Rudi Schulte Research Institute in May 2019.

👉 **Carolyn Harris, PhD**  
**Wayne State University**  
**Detroit, MI**  
[caharris@wayne.edu](mailto:caharris@wayne.edu)

Dr. Harris and her research group at Wayne State investigate cell-biomaterial interactions to shunts. Using translational research, bench-top 3D culture models, and high-throughput microfluidic models, she works to understand how local environments impact CSF dynamics and how and why shunts obstruct. With this data and the help of the HA Innovator Award, Dr. Harris develops novel, biologically inspired shunt coatings to inhibit cell attachment and shunt obstruction.

👉 **Maxwell Heiman, PhD**  
**Boston Children's Hospital,**  
**Harvard Medical School**  
**Boston, MA**  
[heiman@genetics.med.harvard.edu](mailto:heiman@genetics.med.harvard.edu)

There is a major bottleneck in hydrocephalus research between gene discovery in patients and identifying molecular mechanisms in animal models, which are typically expensive and cumbersome. Establishing simpler animal models will allow more rapid determination of molecular mechanisms, an essential step toward development of better therapies. Recently, while investigating glia-dendrite interactions in *C. elegans*, we discovered a pathway that involves three of the key factors implicated in congenital hydrocephalus – homologs of L1CAM and CCDC88C, called SAX-7 and GRDN-1 respectively, as well as an

MPDZ-like protein called MAGI-1. We found that each of these factors acts in glia to shape the morphology of two specific sensory dendrites. This suggests that, remarkably, despite studying a phenotype with no obvious relationship to hydrocephalus, we unexpectedly uncovered a developmental pathway that uses the same fundamental cellular mechanisms. In addition to providing insights into the molecular mechanisms by which these genes act, this innovative *C. elegans* platform will allow large-scale functional screening of candidate variants from patients and will open the door to whole animal drug screens in this powerful model.

👉 **Eric Huang, MD, PhD**  
**University of California San Francisco**  
**San Francisco, CA**  
[eric.huang2@ucsf.edu](mailto:eric.huang2@ucsf.edu)

The human ganglionic eminences (GEs) contain a large number of neural progenitors that give rise to diverse subtypes of cortical interneurons and oligodendroglia. Hemorrhages in these regions are common in premature infants, but the cause(s) for hemorrhages in these regions and their ensuing consequences remain poorly understood. My presentation will focus on our recent work on the organization and development of GEs during mid-late gestation and early postnatal life. I will discuss our results that reveal the molecular properties of neural progenitors and their interactions with the nascent vasculature in the human medial ganglionic eminence (hMGE) and lateral ganglionic eminence (hLGE). Together, these multi-disciplinary approaches establish the

spatiotemporal development of interneurons and key vascular cell types in the human brain, and provide the fundamental knowledge needed to understand their contributions to neurodevelopmental diseases, including hydrocephalus.

👉 **Albert Isaacs, MD**  
**Washington University School of Medicine**  
**St. Louis, MO**  
[albert.isaacs@wustl.edu](mailto:albert.isaacs@wustl.edu)

The metalloprotease ADAM10, can be activated independently by blood and by microbial toxins. While ADAM10 is ubiquitous in the human body, one of its major mechanisms of action is disruption of epithelial barriers through cleavage of cell junction molecules such as N-cadherin. Since N-cadherin maintains adherens junctions in the ventricular zone and ependymal barrier, we hypothesized that PHH and PIH result from ventricular zone disruption through ADAM10-mediated cleavage of N-cadherin. Utilizing experimental models of intraventricular hemorrhage (PHH, from whole blood injection) and ventriculitis (PIH, from alpha toxin inoculation) we performed several studies that demonstrated ventricular zone disruption and reactive periventricular gliosis are associated with N-cadherin cleavage, which likely heralds PHH and PIH development. Further, pharmacological inhibition of ADAM10 abrogated the ventricular zone disruption, suggesting that an ADAM10-N-cadherin pathway can be defined as a modifiable mechanism to prevent the development of PHH and PIH.

**Lauren Jantzie, PhD**  
**Johns Hopkins University**  
**Baltimore, MD**  
[ljantzie@jhmi.edu](mailto:ljantzie@jhmi.edu)

The Jantzie lab is dedicated to understanding the pathophysiology of hydrocephalus acquired in utero, and/or in early life through hemorrhage, infection or trauma. A main component of our work is aimed at discovering non-surgical therapies directed at preventing and treating hydrocephalus. We focus on improved ependymal cilia health and development, as well as neurorepair, and neurorestoration in the context of neonatal and pediatric neuroscience.

**Mark Johnson, MD, PhD**  
**University of Massachusetts Medical School**  
**Worcester, MA**  
[mark.johnson3@umassmemorial.org](mailto:mark.johnson3@umassmemorial.org)

Idiopathic normal pressure hydrocephalus is a neurological disorder of aging that is characterized by walking difficulty, incontinence and cognitive impairment. The cause of iNPH is unclear, although published reports suggest that it can be familial. We have performed high throughput sequencing of DNA obtained from iNPH patients to look for genetic alterations that are associated with the development of iNPH.

👉 **Nathalie Jurisch-Yaksi, PhD**  
**Norwegian University of Science and Technology**  
**Trondheim, Norway**  
[nathalie.jurisch-yaksi@ntnu.no](mailto:nathalie.jurisch-yaksi@ntnu.no)

Coordinated beating of motile cilia leads to a directional fluid flow, which is important for various biological processes from respiration to reproduction. In the nervous system,

motile ciliary beating of ependymal cells allows the cerebrospinal fluid (CSF) to flow through the ventricular system. Such flow plays a central role in the nervous system as human patients or animal models with ciliary defects develop neurological features including hydrocephalus and spine curvature. Still, very little is known about how the nervous system generates and regulates specific flow patterns and how flow controls neural activity and animal behavior. Here, I will discuss how motile cilia and other physiological factors act jointly to regulate CSF flow dynamics and distribution in the brain ventricles using the zebrafish as model system. I will also describe the importance of ciliary beating during brain development and homeostasis. Altogether, our long-term goal is to understand the role of cilia-mediated flow at the brain-CSF interface in the context of brain physiology and diseases.

**Kristopher Kahle, MD, PhD**  
**Yale School of Medicine**  
**New Haven, CT**  
[kristopher.kahle@yale.edu](mailto:kristopher.kahle@yale.edu)

The primary focus of the Kahle Laboratory is investigating the genetic determinants of pediatric neurodevelopmental disorders, such as congenital hydrocephalus, Chiari malformation, Vein of Galen malformation, congenital scoliosis, and arachnoid cysts. This is accomplished by coupling trio-based recruitment (i.e. affected individual and both parents) with Whole-Exome Sequencing, which allows for the identification of de novo and inherited mutations that may contribute to disease pathology. The pathogenicity of these candidate

## Workshop Attendees (cont.)

genes is screened and confirmed using genetically altered xenopus, zebrafish or murine models. The Kahle lab also specializes in the molecular pathophysiology of post-hemorrhagic and post-infectious hydrocephalus. Here, we utilize novel rodent models to study CSF dynamics responding to hemorrhage or bacterial infection as well as genetic and pharmacological therapeutics to attenuate hydrocephalus following acute insult. Our overall goal is to understand the genetic and molecular physiology underlying diseases that are otherwise only treatable using invasive neurosurgical techniques. Using this knowledge base, we hope to find new methods to treat these neurological disorders and improve patient quality of life.

🔊 **Jason K. Karimy, MS**  
**Yale University**  
**New Haven, CT**  
[jason.karimy@yale.edu](mailto:jason.karimy@yale.edu)

A fundamental obstacle in developing novel therapeutics for hydrocephalus has been a relative lack in our understanding of the pathophysiology of the choroid plexus epithelium (CPE) following IVH and bacterial meningitis. Both post-hemorrhagic and post-infectious hydrocephalus (PHH; PIH) exhibit non-obstructive ventriculomegaly and CPE inflammation. Recently, we demonstrated that TLR-4-SPAK-dependent inflammation caused CSF hypersecretion and PHH. LPS, the canonical TLR4 ligand, is a component of many PIH-causing bacteria. Thus, we hypothesized that IVH and bacterial meningitis share a common pathogenic mechanism of TLR4-dependent CSF hypersecretion. We developed a

novel rat model of PIH via the continuous intracerebroventricular infusion of LPS. In vivo CSF secretion measurements and MRI imaging evaluated the impact of LPS on CSF dynamics. RNAseq and LC-MS/MS phospho-proteomics assessed changes in the CPE transcriptome/ phospho-proteome in response to IVH and LPS. Immunoblotting evaluated the functional expression of specific TLR4- and SPAK-kinase-associated molecules in the CPE. ICV-LPS infusion triggered a striking increase in CSF secretion (~3.5-fold;  $p < 0.01$ ) and ventriculomegaly (>300%;  $p < 0.01$ ). IVH and LPS induced a shared signature of TLR4-dependent signal transduction mediators and SPAK-regulated ion transporters in the CPE. LPS stimulated the activating phosphorylation of TLR4-NF- $\kappa$ B-mediated SPAK-NKCC1 ion-transport pathways greater than IVH (>450%;  $p < 0.01$ ). IVH metabolites and bacteria-derived LPS similarly promote TLR-4-SPAK-dependent CSF hypersecretion and acute hydrocephalus via up-regulation of a SPAK-regulated network of ion transporters in the inflamed CP. Non-surgical modulation of CPE immuno-secretory function with drugs targeting TLR4 or SPAK could create a breakthrough for patients in the hydrocephalus community and ultimately improve overall quality of life.

🔊 **Richard F. Keep, PhD**  
**University of Michigan**  
**Ann Arbor, MI**  
[rkeep@umich.edu](mailto:rkeep@umich.edu)

I have a long-standing interest in the impact of clot-derived 'neurotoxic' factors (e.g. hemoglobin, iron, thrombin) and their role in brain injury

after cerebral hemorrhage (intracerebral, intraventricular, subarachnoid). I also work on the blood-brain and blood-CSF (choroid plexus) barriers in health and disease - primarily ischemic and hemorrhagic stroke.

🔊 **Seonhee Kim, PhD**  
**Lewis Katz School of Medicine**  
**in Temple University**  
**Philadelphia, PA**  
[seonhee.kim@temple.edu](mailto:seonhee.kim@temple.edu)

The absence of Yap, a downstream effector in the Hippo pathway, in neural progenitors lining the aqueduct of Sylvius causes hydrocephalus due to decreased proliferation, disruption of cellular junctions, and failure to generate ependymal cells. Previous studies showed that administration of the blood lipid lysophosphatidic acid (LPA) into the CSF causes hydrocephalus which mimics posthemorrhagic hydrocephalus (PHH). This LPA-induced hydrocephalus is remarkably similar to the Yap mutant phenotype. To study the role of the Hippo-Yap pathway in PHH pathogenesis, we examined the alteration of Hippo-Yap signaling components when LPA is introduced into the CSF. We found that LPA reduces phosphorylated Yap (at S112) and activated Lats1, a major kinase responsible for the serine 112, in both ependymal cells and neural progenitors. Therefore, because we previously showed that phosphomimetic Yap (S112D; serine to aspartic acid substitution) promotes epithelial integrity by causing N-Cadherin to be retained, it is plausible that increasing pYap production will prevent or ameliorate PHH induced by LPA. Alternatively,



because Yap phosphorylation inhibits nuclear translocation by promoting cytoplasmic retention, it is also possible that decreased transcription cofactor function of Yap will have a therapeutic effect. Importantly, we found that fingolimod increases levels of activated Lats1 kinase and pYap in normal cerebellum and LPA-treated cortex, and reduces the degree of hydrocephalus induced by LPA. Fingolimod, which is approved by the FDA to treat relapsing multiple sclerosis, decreases sphingosine 1-phosphate (S1P) receptors on the cell surface and thereby act as a functional antagonist. It is also known to suppress responses to LPA in other disease processes, including demyelination, and to promote recovery from spinal cord and traumatic brain injury. We are currently investigating whether fingolimod acts therapeutically on cellular defects such as ependymal cell loss caused by LPA. We are also comparing the effects of fingolimod to the outcomes of treatments with a Yap nuclear function inhibitor such as Verteporfin and with other pharmacological agents such as ROCK inhibitors.

👉 **Chris Kintner, PhD**  
**The Salk Institute for Biological Studies**  
**La Jolla, CA**  
kintner@salk.edu

Epithelia use motile cilia to produce directed fluid flow in a number of organ systems, including within the ependymal layer and choroid plexus of the brain. My laboratory studies the developmental mechanisms that enable epithelia to form motile cilia and to orient these cilia along a common planar axis. Recently, we

have focused on the role of mechanical strain as a developmental cue in ciliated epithelia differentiation. I will present evidence that mechanical strain can have a profound affect on the formation of a planar axis, which in turn can affect how epithelial cells respond to strain. I will also present evidence that mechanical strain can alter cilia differentiation. In sum, these studies emphasize the role of mechanical strain as a developmental cue that can act rapidly and over long distances to coordinate the properties of ciliated epithelia. In this light, I will also discuss how mechanical strain could be an important factor in altering the ependymal layer of the brain during hydrocephalus.

👉 **Jenna Koschnitzky, PhD**  
**Hydrocephalus Association**  
**Bethesda, MD**  
research@hydroassoc.org

As the Director of Research Programs, I am responsible for planning, managing, implementing, and evaluating all aspects of the research program for the Hydrocephalus Association. I joined HA in July 2014 after completing a Postdoctoral Fellowship at Seattle Children's Hospital Research Institute where I studied maternal health and preterm birth. In 2011, I received my Doctorate of Philosophy with a concentration in Neuroscience from Northwestern University. My dissertation was focused on the electrical properties of motor neurons in a mouse model of Amyotrophic Lateral Sclerosis.

👉 **Chay T. Kuo, MD, PhD**  
**Duke University**  
**Durham, NC**  
chay.kuo@duke.edu

As a primary cell type lining the adult brain ventricles, multiciliated ependymal cells form an integral part of the postnatal lateral ventricular neurogenic niche, important for new neuron production from stem cells. A specialized glial cell type with multiple motile cilia, we know relatively little about basic ependymal biology beyond ciliary movements mediating cerebrospinal fluid flow. We showed previously that disruption of neural progenitor maturation to multiciliated ependymal cells can lead to dramatic ventriculomegaly. Through a chemical screen, we have uncovered surprising cellular instability in mature ependymal cells, resulting in rapid de-differentiation of their multiciliated phenotype and ventricular wall disorganization. Using a combination of mouse genetics, biochemistry, and cellular imaging, we are elucidating the steps necessary to induce and control ependymal cellular plasticity. The goal of our research is to unravel the poorly understood neural developmental mechanisms regulating ependymal cell formation, maturation, and functional stability.

**Maria Lehtinen, PhD**  
**Boston Children's Hospital**  
**Boston, MA**  
maria.lehtinen@childrens.harvard.edu

Our goal is to improve the understanding of the mechanisms regulating human brain development and health. We focus on the choroid plexus (ChP)-cerebrospinal fluid (CSF) system, and have found that it distributes secreted signals to

## Workshop Attendees (cont.)

regulate neurogenesis and health. The ChP is regionalized across brain ventricles, and as such, contributes to region- and age-specific secretion of factors into the CSF. We are investigating mechanisms regulating secretion into the CSF, and in the context of hydrocephalus, we are testing how the ChP senses and responds to intraventricular hemorrhage in the developing brain. Identification of the molecular mechanisms affected by hemorrhage during the early, vulnerable time of brain development should open avenues to new therapies for this condition.

👉 **David Limbrick, MD, PhD**  
**Washington University School of Medicine**  
**St. Louis, MO**  
limbrickd@wustl.edu

Hydrocephalus may result from various pathological triggers initiated by a myriad of etiologies. This presentation explores common pathways in the pathogenesis of pediatric hydrocephalus using post-hemorrhagic, post-infectious, and developmental hydrocephalus as models. The effect of these three etiologies on ventricular/subventricular zone biology, neuro-inflammation, and developmental pathways in experimental and human hydrocephalus will be examined.

👉 **Nanna MacAulay, MSc, PhD**  
**University of Copenhagen**  
**Copenhagen, Denmark**  
macaulay@sund.ku.dk

The mammalian brain is bathed in cerebrospinal fluid (CSF), which is continuously secreted by the choroid

plexus located in each of the four ventricles. CSF production was generally assumed to take place by transepithelial transport of ions followed by osmotically obliged, passive movement of water, partly via the water channel aquaporin 1 (AQP1) expressed at the luminal membrane of the choroid plexus. The limitations of such a conventional osmotic model for CSF production are apparent from the minimal effects of genetic deletion of AQP1 and the ability of the choroid plexus epithelium to transport water uphill against a transepithelial osmotic gradient. A number of cotransporter proteins have the inherent ability to cotransport water along with the ions/solutes in the translocation mechanism in a manner that permits water to be transported independently of an osmotic gradient. This talk will introduce the water-translocating Na<sup>+</sup>,K<sup>+</sup>,2Cl<sup>-</sup> cotransporter, NKCC1, as a key contributor to CSF production in the murine choroid plexus. The NKCC1 cotransport protein is located in the luminal membrane of the choroid plexus and is poised for ion and water transport from the choroid plexus epithelial cell to the ventricle. With its inherent ability to transport water along with the ion translocation, NKCC1 is able to move water independently of the osmotic gradient and in this manner contribute approximately half of the CSF secretion across the luminal membrane.

**James P. (Pat) McAllister II, PhD**  
**Washington University School of Medicine**  
**St. Louis, MO**  
pat.mcallister@wustl.edu

For many years I have been involved in comprehensive interdisciplinary research programs with the ultimate goal of improving clinical treatments for hydrocephalus. I continue to explore the cellular and physiological neuropathology associated with pediatric hydrocephalus and employ various in vivo and in vitro models to focus on neuroinflammation, non-invasive neuroimaging (MRI, diffusion tensor imaging, and MR elastography), pharmacological strategies for neuroprotection and recovery of function, and the development and testing of novel surgical and bioengineering approaches for new treatment applications. Our recent initiation of infant/juvenile piglet models of post-inflammatory and post-hemorrhagic hydrocephalus have set the stage for a wide variety of experimental and surgical studies on these clinically-relevant models, including (but not limited to) systematic evaluations of novel CSF drainage systems (shunt catheters and valves) and two popular but controversial surgical treatments: endoscopic third ventriculostomy and choroid plexus cauterization.

**Kathleen Millen, PhD**  
**Seattle Children's Research Institute/University of Washington**  
**Seattle, WA**  
kathleen.millen@seattlechildrens.org

The long-term goal of my research program is to understand the developmental biology and genetic basis of developmental brain disorders combining the strengths of human and mouse genetics. Much of my work has focused on cerebellar disorders including Dandy-Walker malformation, associated with a

dramatically enlarged fourth ventricle. We also study disorders of human cortical development including brain growth disorders, hydrocephalus and epilepsy. My lab has made foundational discoveries regarding the genetic and developmental causes of numerous human and mouse brain malformations, defining multiple novel and central regulators of brain development. Functional analyses of gene function in my lab have focused primarily on studies in mouse models. Recently, while modeling human PI3K-pathway developmental brain overgrowth disorders in mice, Achira Roy, an accomplished post-doctoral fellow in my group, determined that highly-regulated PI3K-YAP signaling at the apical surface of neural stem cells is essential for normal ependymal development and regulates cortical neurogenesis. Disruption causes congenital hydrocephalus which can be reversed by administration of the nuclear YAP inhibitor verteporfin. Our data suggests that there are convergent mechanisms between common forms of congenital hydrocephalus and post-hemorrhagic hydrocephalus that represent novel therapeutic targets.

👉 **Edwin Monuki, MD, PhD**  
**University of California Irvine**  
Irvine, CA  
emonuki@uci.edu

Induced pluripotent stem cells (iPSCs) hold tremendous promise for regenerative medicine. As a living and readily expandable source of patient-specific material, iPSCs provide for unique opportunities in disease modeling, diagnostics, drug screening, and cell-based therapies that lie in “sweet spots” between medicinal molecules and organ transplants. In this talk, I will reflect on

the current state of iPSC-based regenerative medicine and highlight opportunities in hydrocephalus, including work from my laboratory aimed at a choroid plexus-based regenerative medicine.

👉 **Jill Morris, PhD**  
**NIH National Institutes of Neurological Disorders and Stroke**  
Bethesda, MD  
jill.morris@nih.gov

I am a Program Director at the National Institute of Neurological Disorders and Stroke (NINDS). My grant portfolio consists of multiple neurological disorders including hydrocephalus. As a Program Director, I assist grant applicants, develop initiatives, review progress reports, and facilitate funding. In addition, I work to identify gaps and solutions in a research area by speaking with researchers in a field, collaborating with advocacy groups, attending conferences and organizing workshops. My presentation will provide an update on the current status of hydrocephalus research at NIH. In addition, I will describe funding opportunities for hydrocephalus research.

👉 **Jessie Newville, BS**  
**Johns Hopkins University**  
Baltimore, MD  
jessien@salud.unm.edu

The coordinated beating of ependymal motile cilia on the apical surface of ependymal cells creates organized flow patterns of cerebral spinal fluid within the ventricular system. Here, we investigated whether ependymal motile cilia function and structure are disrupted

in an established preclinical model of PHHP. Using live cell and confocal imaging we uncovered altered cilia generated flow patterns in PHHP animals, and found that PHHP resulted in disrupted planar polarity of neighboring ependymal cells. Importantly, we also show that administration of erythropoietin plus melatonin mitigated the PHHP-induced functional and structural deficits observed. Taken together, our data supports the involvement of ependymal motile cilia injury in the evolution of PHHP, and indicate that early therapeutic administration of erythropoietin plus melatonin can modulate this injury.

👉 **Makenna Reed, BA**  
**Indiana University Purdue University Indianapolis**  
Indianapolis, IN  
reedmak@iu.edu

The Blazer-Yost laboratory is using congenital rodent models of hydrocephalus in preclinical drug testing studies. This research is complemented using a porcine choroid plexus epithelial cell line (PCP-R) to examine the mechanism of action of the potential drug compounds and to determine the rate-limiting steps in CSF production. The primary in vivo model is the Tmem67<sup>-/-</sup> rat model, which is a ciliopathy that is orthologous to human Meckel Gruber Syndrome 3. The homozygous animals have severe hydrocephalus and polycystic kidney disease that causes them to die by postnatal day 18-21. Treatment of the Tmem67<sup>-/-</sup> rat pups with a TRPV4 (transient receptor potential, vanilloid 4) antagonist (RN1734, i.p. daily) from postnatal day 7 to 15 ameliorated the ventricular enlargement measured by MRI before

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and after treatment. To further understand the TRPV4 mechanism of action, the PCP-R cell line is being used in Ussing-style electrophysiology experiments. This cell line forms a barrier epithelium in culture and expresses the major electrolyte transporters that have been identified in the native choroid plexus epithelial cells including TRPV4, a non-specific cation channel. Electrophysiological experiments using the PCP-R cell line indicate that TRPV4 agonists stimulate transepithelial electrogenic ion flux that can be blocked by preincubation with TRPV4 antagonists, including RN1734. The transepithelial ion flux is, in part, due to K<sup>+</sup> secretion via the Ca<sup>2+</sup>-sensitive intermediate conductance K<sup>+</sup> channel (IK). Interestingly, stimulation with a TRPV4 agonist causes a substantial increase in the conductance of the tissue, indicating a change in the barrier function of the epithelium. Ongoing studies are directed toward the intracellular signaling mechanisms as well as a more complete characterization of the electrolyte and fluid flux that is stimulated in response to TRPV4 activation. Combining these techniques our laboratory hopes to make advances in the understanding and treatment of hydrocephalus.

### **Shenandoah Robinson, MD**

**Johns Hopkins University  
Baltimore, MD**  
srobin81@jhmi.edu

From a clinical perspective, different etiologies of hydrocephalus share common themes, but also have unique characteristics. The similarities and differences influence how we approach surgical treatment,

as well as underlying mechanisms and novel therapies. We will review the common causes of hydrocephalus across the lifespan, how etiology affects presentation and current clinical management. We will also discuss the optimal timing and duration for novel interventions, clinically-viable options for drug delivery in different types of patients, and clinically important research outcomes. The focus will be on the important questions and nuances that impact basic and translational research approaches.

### **Achira Roy, PhD** **Seattle Children's Research Institute** **Seattle, WA** achira.roy@seattlechildrens.org

Hydrocephalus is among the most common neurodevelopmental disorders with often devastating outcomes. Genetic/developmental and environmental causes, including intra-ventricular hemorrhage, are being identified behind different types of hydrocephalus. Yet the underlying cellular and molecular mechanisms remain largely unknown. Moreover, new therapeutic approaches are urgently needed since current treatment requires invasive surgeries with associated significant complications. Activating mutations in the phosphoinositide 3-kinase (PI3K) signaling pathway result in a broad spectrum of brain disorders in human patients, including severe brain overgrowth and cortical dysplasia, often associated with intractable epilepsy, intellectual disability, ventriculomegaly and developmental hydrocephalus. Using related mouse models, we previously recapitulated this entire phenotypic spectrum and also identified underlying cellular and

molecular mechanisms behind some of these malformations. Recently, I identified that PI3K-related ventriculomegaly, followed by hydrocephalus, develops only when the PI3K mutation is specifically acquired during embryogenesis in our mouse models. We demonstrated that abnormal PI3K-Yap pathway activity caused dysregulated cell adhesion among neural progenitors during early ependymal fate allocation, eventually leading to hydrocephalus. Intriguingly, administration of Yap inhibitor attenuated these phenotypes by rescuing cell-cell adhesion deficits. Our findings, combined with previous studies from other labs, suggest that altered cell adhesion caused by dysregulated YAP signaling may be a common underlying mechanism for congenital and post-hemorrhagic hydrocephalus. By demonstrating that small-molecule regulation of Yap function can rescue early hydrocephalus, our data provides the promise of molecularly rational therapy in this important patient population.

### **Cameron Sadegh, MD, PhD**

**Harvard University**  
**Boston, MA**  
cameron.sadegh@childrens.harvard.edu

Intraventricular hemorrhage (IVH) leads to ventriculomegaly or symptomatic hydrocephalus in a subset of preterm infants by unclear mechanisms that potentially include increased CSF production by the choroid plexus (ChP), based on recent work in adult rats (Karimy et al., 2017). The earliest physiologic changes within ChP epithelial cells likely involve calcium signaling, which is a critical intracellular messenger in

other secretory epithelial cell populations. Using a genetically encoded calcium reporter in transgenic mice (FoxJ1::Gcamp6f), we visualized calcium signaling in embryonic day 14.5 lateral ventricle ChP explants. Focal plasma exposure rapidly triggered a robust calcium response in a majority of epithelial cells. Following an initial wave of activity, spontaneous calcium activity returned with a more pronounced magnitude of calcium events in individual cells and persisted for minutes. Using different conditions of calcium blockade, we identify endoplasmic reticulum storage as the primary source of intracellular calcium release. More than one month after embryonic or early post-natal IVH, we subsequently measured an increase in the capacity for CSF reabsorption, using a modification of the constant-rate infusion test (Marmarou et al., 1975). Together, we found that IVH leads to choroid plexus epithelial cell responses on timescales faster than the initiation of an inflammatory response and also leads to chronic compensation for the increased intraventricular CSF volume. These data highlight both rapid and chronic changes in the intraventricular compartment and contribute to our understanding of IVH-induced hydrocephalus pathophysiology in infants and children.

📍 **Dorothy Schafer, PhD**  
**University of Massachusetts  
Medical School**  
Worcester, MA  
dorothy.schafer@umassmed.edu

Microglia are resident macrophages of the central nervous system. Beyond their role in inflammatory processes, they are becoming increasingly appreciated as dynamic

sensors of their extracellular environment and regulators of synaptic connectivity. Our previous work has demonstrated a role for microglia in developmental synaptic remodeling, in which microglia engulf and prune away synapses via complement-dependent phagocytic signaling. We are now also applying these mechanisms to uncover how microglia contribute to changes in synaptic connectivity in disease, and we have identified a new role for microglia-mediated synapse elimination in the context of demyelinating disease. We identify in postmortem human multiple sclerosis tissue and in nonhuman primate and mouse models of demyelination, profound synapse loss and microglial synaptic engulfment. This is accompanied by increased localization of complement component C3, but not C1q, at synapses. Finally, we use an AAV approach to specifically inhibit C3 at synapses and demonstrate robust protection of structural and functional synaptic connectivity. Together, these data provide novel insight into how synaptic connectivity is modified in demyelinating disease. Importantly, this work could have important implications for elucidating synaptic changes in other diseases with disruptions in the myelin sheath. This includes hydrocephalus where disruptions in the myelin sheath have been described as a core underlying feature, leading to long-term disability.

📍 **Evan Y. Snyder, MD,  
PhD**  
**Sanford Burnham Prebys  
Medical Discovery Institute**  
La Jolla, CA  
esnyder@sbp.edu

The launch of this project was catalyzed by the realization that it remains unknown which premature newborns will develop intraventricular hemorrhage (IVH) and post-hemorrhagic hydrocephalus (PHH). We propose to generate what this field desperately needs: a database of functional (via human induced pluripotent stem cells [hiPSCs] and their derivatives) and molecular (whole genome sequencing [WGS], proteomic, metabolomic) profiles of relevant cells from a large cohort of newborns. We propose 100=27 weeks gestation over 5 years in an unbiased prospective fashion, correlating these metrics with clinical outcome to derive informative biomarkers and predictors, with an eye also to giving us new insight into PHH pathophysiology and, therefore, novel drug targets and, perhaps, drugs. Although non-hypothesis-driven (other than that PHH could be the “poster child” for personalized/precision medicine), novel hypotheses inevitably will emerge from this unique database which will prove to be a valuable resource to be mined by all investigators of newborn (especially if pre-term) development and disease of all organs, but particularly the brain with a focus on hydrocephalus. The cells themselves can then be used for testing informative responses (both functional and molecular) to various interventions. This presentation will not only discuss the rationale, vision, and methods of this project, but will also point out that neonatology is in a position to be the bellwether of how proper personalized/precision medicine (with an eye to discovery) should be done in general -- prospective, unbiased, wide-capture, non-selective, with long-term

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longitudinal follow-up and clinical correlation. It will also discuss some unexpected hurdles (not insurmountable but time-consuming) to this approach which are a product of our modern-day (legitimate) concern for patient confidentiality; ownership of biological material, data, and commercial products derived from that material; biosafety; misuse, appropriation, and unauthorized dissemination of patient data; consent for the under-aged; “learning personal genetic facts that may not want to be known”.

### **Jennifer Strahle, MD**

**Washington University School of Medicine**  
St. Louis, MO  
strahlej@wustl.edu

Our lab studies how intraventricular hemorrhage results in brain injury and hydrocephalus. Cilia have been implicated in the pathogenesis of hydrocephalus in genetic models, but their role in post-hemorrhagic hydrocephalus is not well known. We specifically study how iron and hemoglobin alter cilia function and well as downstream regional and global cerebrospinal fluid flow in PHH.

**☞ Stavros Taraviras, PhD**  
**University of Patras**  
Patras, Greece  
taraviras@med.upatras.gr

Hydrocephalus is a clinical entity involving abnormal circulation/accumulation of CSF in the brain ventricles, commonly leading to elevated intracranial pressure. Loss of ependymal cells is an important component of hydrocephalus pathogenesis. Current therapeutic

schemes for hydrocephalus provide only temporary relief to patients and usually require surgery revisions with high risk of infections, highlighting the necessity of novel effective treatments. Our research team has recently shown that GemC1 and MclDas, members of the Geminin superfamily, are implicated in fate decisions and cellular differentiation events of neural stem cells. We have shown that their expression is sufficient to convert embryonic radial glial cells to the ependymal lineage. GemC1 and MclDas expression is necessary to transcriptionally activate c-Myb, Foxj1 and p73, well-established modulators of initial steps of multiciliogenesis, and initiate the differentiation program leading to ependymal cells. Direct lineage reprogramming is a novel approach that utilizes the cellular plasticity of differentiated cells to convert them into desired target cell types for disease modeling and tissue repair. We have examined whether overexpression of GemC1 or MclDas can program normal astrocytes into ependymal cells. In addition, we have also tested whether GemC1 or MclDas can have a similar effect when they are overexpressed in vivo in a mouse model of human hydrocephalus. Our study serves as a pilot study examining whether cellular reprogramming for the generation of ependymal cells is feasible, with potential application on the development of novel therapeutic approaches for treating hydrocephalus in the future.

**☞ R. Reid Townsend, MD, PhD**  
**Washington University School of Medicine**  
St. Louis, MO

**rtownsend@wustl.edu**


Ependymal gliosis, arachnoiditis, and multi-loculated infiltrates that typically characterize postinfectious hydrocephalus (PIH) suggests that PIH may be propagated by host-immune responses that scars and obstructs cerebrospinal fluid (CSF) pathways. Defining the PIH host-immune response is imperative for defining disease pathophysiology, defining CSF biomarkers, and ultimately developing adjunct strategies to prevent hydrocephalus during treatment of infection. With a central hypothesis that PIH host-immune response is mediated by specific activated gene pathways, we utilized proteogenomics, an innovative approach that integrates deep-scale proteomics with next-generation transcriptomics to define critical network and pathway level linkages to probe the molecular mechanisms of this disease. These experiments were done as part of the multi-institutional CONSHA consortium led by Dr. Steven Schiff (Penn State). Proteomics and RNA-seq transcriptomics were concurrently performed on intraoperative CSF samples of sub-Saharan Africa infants under 3 months of age with PIH (n=64) and hydrocephalus not attributed to PIH (NPIH, n=36). PIH infants were sub-categorized based on CSF 16S rRNA sequence analysis consistent with *Paenibacillus* infection status. Abundance and differential expression analyses identified between-group variations. Gene ontology, ingenuity pathway and gene-set enrichment analyses parsed the omics' data into biological functions. Integrating proteomic and RNA-seq data we were able to define specifically activated pathways within our cohort

of PIH patients. Of 616 proteins and 10622 genes identified by proteomics and RNA-seq respectively, there was enrichment for leukocyte extravasation, antigen presentation, macrophage phagocytosis and neuroinflammation expressomes in PIH compared to non-PIH. Paenibacillus status correlated with expressomes related to neutrophil activation and extracellular matrix organization. Proteogenomic integration yielded candidate biomarkers of PIH at the time of surgery. In conclusion, PIH host-immune expressomes in this cohort were identified and proteogenomic integration facilitated identification of activated pathways with higher predictive values for combined RNA and protein data compared to either approach alone. Candidate neuroinflammation biomarkers identified for Paenibacillus-related PIH can be cross-validated with targeted assays and further evaluated for monitoring and pharmacological therapies to treat neonatal meningitis and ventriculitis to prevent PIH.

**Yun Yung, PhD**  
**Scintillon Institute**  
**San Diego, CA**  
[yyung@scintillon.org](mailto:yyung@scintillon.org)

There has been much recent progress in understanding the etiologies and downstream sequelae of post-hemorrhagic hydrocephalus (PHH) through identification of blood-derived factors, involved genes and pathways. However, their interactions and potential synergy in PHH remain unknown. Another challenge for the field is identifying and optimizing drug delivery and compounds for non-surgical PHH treatment. Some promising approaches include opening blood

brain barriers using physicochemical methods, as well as permeant, target factor-specific nano-antibodies, which confer distinct advantages over traditional antibody-based medicines. I am studying the potential cross-talk between lysophosphatidic acid (LPA) and blood components such as erythrocytes; the role of LPA signaling in brain barrier changes to improve drug accessibility; and the therapeutic potential of nanoantibodies to modulate neuroinflammation using our established preclinical hydrocephalus mouse models.

 **John Zhang, MD, PhD**  
**Loma Linda University**  
**Loma Linda, CA**  
[johnzhang3910@yahoo.com](mailto:johnzhang3910@yahoo.com)

This presentation will summarize the current status of a role of neuroinflammation in the development of post hemorrhagic hydrocephalus (PHH) in a neonatal brain hemorrhage animal model. The brain is an immunologic privileged site, without peripheral immune cell infiltrations, however, after a severe brain injury such as PHH, the blood brain barrier is compromised which allows peripheral immune cells to enter into brain tissues. In the meantime brain injuries activate microglia which releases cytokines and other inflammatory molecules. Neuroinflammation has been identified as a major factor in the development of PHH and aggravates brain injuries. Three strategies have been employed in the experimental studies of PHH, the first target is “blood clot” and a potential treatment using chemical removal of blood, one of the major sources of neuroinflammation; the second target is “brain tissues that mediates the toxic effect” that intervention of the

downstream factors of blood and iron in the brain tissues; and the last is an overall anti-neuroinflammation approach. Some of the experimental studies demonstrated beneficial effects of these above mentioned strategies.



4340 East West Highway, Suite 905, Bethesda, MD 20814-4447  
(888) 598-3789 | [info@hydroassoc.org](mailto:info@hydroassoc.org) | [www.hydroassoc.org](http://www.hydroassoc.org)

