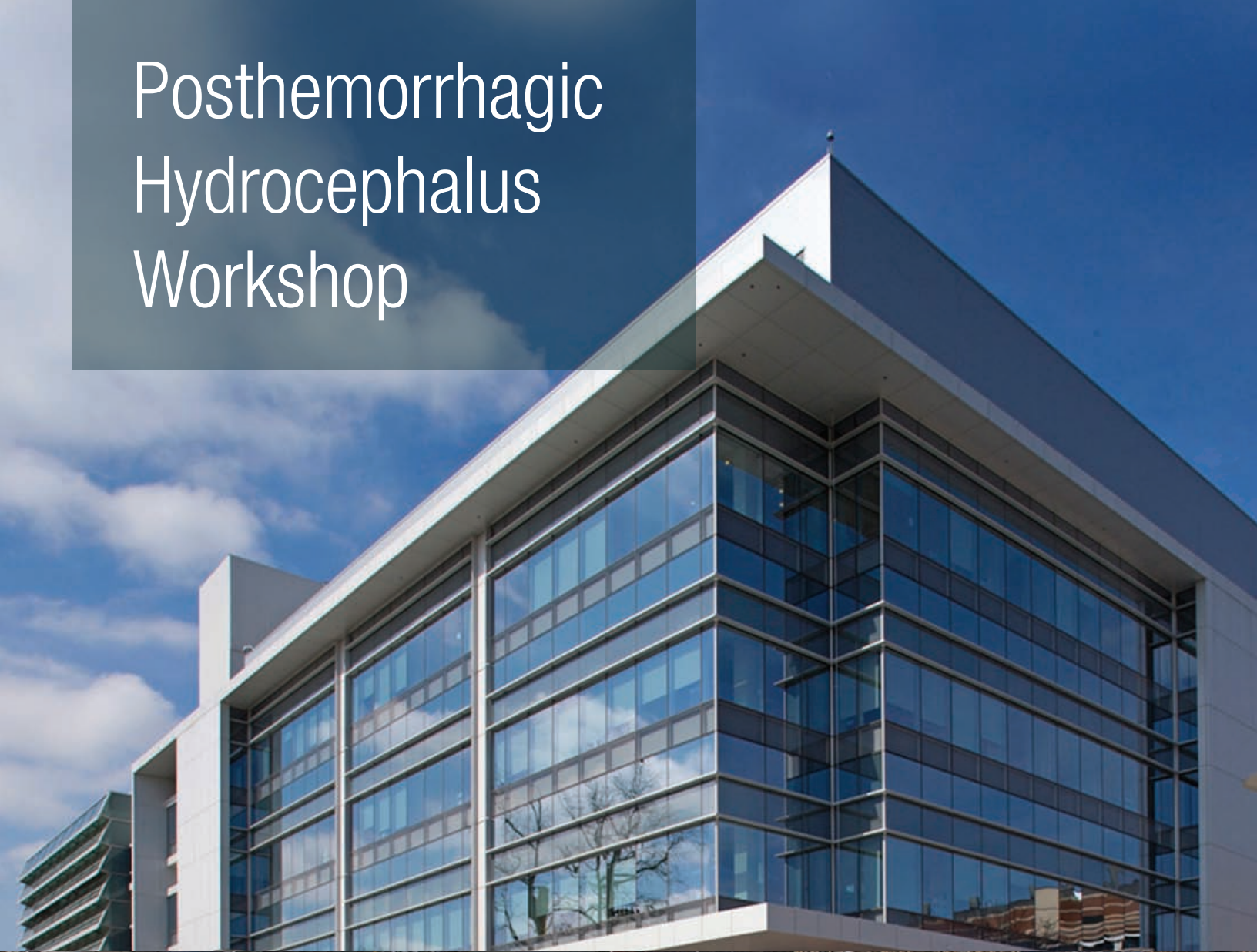


Posthemorrhagic Hydrocephalus Workshop



Monday, July 25, 2016
8:00 am - 5:30 pm

Tuesday, July 26, 2016
8:00 am - 5:30 pm



NIH Neuroscience Center Building
6001 Executive Boulevard
Rockville, MD 20852



Welcome Letter: From CEO Diana Gray

Welcome to the Hydrocephalus Association (HA) Posthemorrhagic Hydrocephalus (PHH) Workshop. As the most prevalent form of pediatric hydrocephalus in the United States, HA has identified PHH as a significant research problem. It is one of the most insidious forms of hydrocephalus, leading to the likelihood of children to suffer from intellectual disabilities and the coexistence of epilepsy and cerebral palsy.

Planning Committee

Paul Gross

Hydrocephalus Association

Terrie Inder, MD

Harvard Medical School

Richard Keep, PhD

University of Michigan

Jenna Koschnitzky, PhD

Hydrocephalus Association

David Limbrick, MD, PhD

Washington University
School of Medicine

James P. (Pat) McAllister, PhD

Washington University
School of Medicine

Lyna Merzoug

Hydrocephalus Association

Jill Morris, PhD

National Institute of Neurological
Disorders and Stroke

Yun Yung, PhD

The Scripps Research Institute

Our task over this two-day workshop is to utilize the expertise of our presenters and participants to identify and prioritize research areas that hold promise related to PHH. We expect these priorities to be presented in a white paper and published in a peer-reviewed journal. The insights from this workshop will guide and inform the areas of research HA will fund through its 2016 Innovator Awards.

I would like to acknowledge the generosity of our workshop benefactors, Vicki and Craig Brown, Paul Gross and Lori Poliski. Our investors are true partners and their participation in this workshop is reflective of our commitment to engaging thought leaders from our diverse base as we tackle issues like PHH.

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

Sincerely,

Diana Gray, MA
Chief Executive Officer
Hydrocephalus Association

Posthemorrhagic Hydrocephalus Workshop Agenda

Monday, July 25, 2016

8:00-8:30 BREAKFAST

SESSION 1

Introduction and Clinical Presentation

- 8:30-8:50 **Welcome: Framework**
Dr. Jenna Koschnitzky, Hydrocephalus Association
- 8:50-9:25 **PHH: Clinical Progression**
Dr. David Limbrick, Washington University School of Medicine
- 9:25-10:00 **PHH: Neurodevelopmental Outcomes**
Dr. Hudson G. Taylor, Rainbow Babies & Children's Hospital
- 10:00-10:15 BREAK

SESSION 2

Review: Learning from Past Clinical Trials

- 10:15-10:45 **Overview of Clinical Trials in PHH**
Dr. Andrew Whitelaw, University of Bristol
- 10:45-11:15 **Overview of Clinical Trials in Adult Hemorrhage**
Dr. Wendy Ziai, Johns Hopkins University
- 11:15-12:00 **Discussion**
Moderator: Dr. Laura Ment, Yale School of Medicine
- 12:00-12:45 LUNCH

SESSION 3

Outside Perspective: Cell Therapy

- 1:00-1:30 **Overview of PHH and Cell Therapy**
Dr. Shenandoah Robinson, Johns Hopkins University
- 1:30-2:00 **Stem Cells and Stroke Recovery**
Dr. Evan Snyder, Sanford Burnham Prebys Medical Discovery Institute
- 2:00-2:20 **Discussion**
Moderator: Dr. James P. (Pat) McAllister, Washington University School of Medicine

SESSION 4

Genetic Risk Factors

- 2:20-2:45 **Genetic Risk Factors for IVH**
Dr. Laura Ment, Yale School of Medicine
- 2:45-3:05 BREAK

SESSION 5

Barriers and CSF

- 3:05-3:35 **Breakdowns: The interaction between Blood and CSF Composition and Regulation**
Dr. Richard Keep, University of Michigan
- 3:35-3:55 **Brain/CSF Barrier**
Dr. Joanne Conover, University of Connecticut
- 3:55-4:15 **Choroid Plexus/CSF Barrier**
Dr. Adam Chodobski, Warren Alpert Medical School of Brown University
- 4:15-4:35 **Diffusion and fluid flow within the brain: relevance for drug delivery**
Dr. Robert Thorne, University of Wisconsin-Madison School of Pharmacy
- 4:40-5:30 **Discussion**
Moderator: Dr. Richard Keep, University of Michigan
- 5:30 CLOSE OF DAY 1

Tuesday, July 26, 2016

8:00-8:30 Breakfast

8:30-8:35 Welcome and Overview of Day
*Dr. Jenna Koschnitzky,
Hydrocephalus Association*

SESSION 6

Brain Development and Susceptibility

8:35-9:05 Critical Timing: The Interaction between Brain Development and IVH
Dr. Terrie Inder, Harvard Medical School

9:05-9:25 Intrinsic Vulnerability of Germinal Matrix Vasculature to Hemorrhage in Premature Infants
Dr. Praveen Ballabh, New York Medical College

9:25-9:45 Discussion
Moderator: Dr. Terrie Inder, Harvard Medical School

9:45-10:05 BREAK

SESSION 7

Quick Looks: Mechanisms and Therapeutic Targets

10:10-10:35 Iron and PHH
Dr. Guohua Xi, University of Michigan

10:35-11:00 LPA and PHH
Dr. Yun Yung, The Scripps Research Institute

11:00-11:25 TGF-beta and PHH
Dr. James P. (Pat) McAllister, Washington University School of Medicine

11:25-12:00 Injury, Immunity and Infection: The Contribution of Uniquely Human Genes to Uniquely Human Disease
Dr. Andrew Baird, University of California San Diego

12:00-12:45 LUNCH

SESSION 8

Critical Review of Current Models

12:45-1:25 Critical Review of Current Models
Dr. John Zhang, Loma Linda University

1:25-2:00 Mechanisms and Models Panel Discussion
*Moderator: Dr. John Zhang, Loma Linda University
Panelists: Dr. Hudson G. Taylor, Dr. James P. (Pat) McAllister, Dr. Andrew Baird, and Dr. Marc Del Bigio*

SESSION 9

Outside Perspective: White Matter Repair

2:00-2:30 White Matter Injury: Strategies for Regeneration and Repair
Dr. Stephen Back, Oregon Health Science University

2:30-3:00 Encouraging Remyelination
Dr. Joseph Scafidi, Children's National Medical Center

3:00-3:20 Discussion
Moderator: Dr. James P. (Pat) McAllister, Washington University School of Medicine

3:20-3:40 BREAK

SESSION 10

Recap and Next Steps

3:40-4:00 Interaction with NIH
Dr. Jill Morris, NIH NINDS

4:00-5:15 Recap of Workshop and Final Discussion
Moderator: Dr. Jenna Koschnitzky, Hydrocephalus Association

Areas of Promise
Areas for Collaboration
Opportunities for Shared Resources

Closing Remarks

5:15-5:30 Closing Remarks
Paul Gross, Hydrocephalus Association

PHH Speaker Abstracts

Andrew Baird, PhD

**University of
California San Diego
San Diego, CA**

The laboratories of Andrew Baird, PhD, study the molecular processes that govern resolution phase of the injury response that ultimately defines the extent of recovery. The overall objective is to apply the knowledge acquired to: (1) improve outcome after injury; and (2) identify new therapeutic approaches for peripheral tissue and central nervous system injury.

It is obvious that the presence of taxonomically-restricted genes in the genomes of different species, makes those genomes unique. It is completely unknown however, how these unique genes confer species-specific biological responsiveness. They hypothesize that the emergence of uniquely human genes in the hominid genome may contribute to the appearance and progression of complex human inflammatory disease. First, there was a recongition that in humans, uniquely-human genes are over-represented in immune cells like monocytes, lymphocytes and even progenitor bone marrow cells. Second, there was a finding that the open reading frames of these genes, once thought to be "pseudogenes", often encode ligands (e.g. c2orf40TRG), receptors (e.g. CHRFBAM7A), signal transduction molecules (e.g. TBC1D3) and even candidate transcription factors (e.g. TPTEP1). In addition, it is shown that each can be implicated in human inflammation. As expected, these uniquely human genes emerged into the human genome through

processes that are common to all species like: (1) mutagenesis, (2) partial duplication and gene fusion, (3) differential mRNA splicing; and (4) the endogenization of foreign DNA. Moreover, it is shown that these genes can have new biological activities, gauge the activities of known genes or compensate for the activity of the parental gene(s). In this way, they affect the fundamental biology of human cells in processes like migration, trafficking, the altered responsiveness of cells to secretogogues and/or drug sensitivity and, affecting the ability of cells to grow in colonies.

Because uniquely-human genes have the potential to create uniquely human signaling pathways that, by definition are absent in other species, we propose that their identity, their expression and their roles in human disease needs to be better understood, so as to fully understand their role(s) in the development, progression and resolution of human (inflammatory) disease.

Praveen Ballabh, MD **New York Medical College** **New York, NY**

Praveen Ballabh, MD, is a professor at New York Medical College. His lab studies the pathogenesis of intraventricular hemorrhage (IVH) and evaluates neuro-protective strategies to prevent brain damage after IVH in premature infants. They have used rabbit pups to develop a model of IVH similar to human preterm survivors whereby hemorrhage results in periventricular white matter injury and posthemorrhagic hydrocephalus. They have found that celecoxib,

thyroxine, or Bone morphogenetic protein inhibition restores neurologic recovery in preterm rabbits with brain hemorrhage. Dr. Ballabh is also researching the neurogenesis in human brain from fetuses and preterm infants in late pregnancy.

Marc Del Bigio, MD, PhD, FRCPC

University of Manitoba
Winnipeg, Canada

Marc Del Bigio, MD, run's an animal model research lab. Since 1983, he has conducted experimental studies on animal models of hydrocephalus at various ages, (including mice, rats, rabbits, ferrets, cats, and sheep). The lab has mainly used kaolin to induce hydrocephalus, but also has experience with other agents (silicone oil, Matrigel, type 1 collagen, fibrin glue, n-butyl-cyanoacrylate, and ethylene vinyl alcohol copolymer). Dr. Del Bigio has been exploring drug interventions to modify hydrocephalus-associated brain damage. Since 2000, he has been using newborn mice and rats to study the pathogenesis of brain damage associated with germinal matrix hemorrhage, in particular trying to understand how blood interferes with proliferation in the subventricular zone. He uses behavioral testing, magnetic resonance imaging, histopathology, and biochemical / molecular assays to evaluate the models. He has also been studying the mechanical properties of brain tissue and intracranial components in a variety of disease models.

Dr. Del Bigio is a clinical / diagnostic neuropathologist with a particular interest in disorders of the developing

PHH Speaker Abstracts (cont.)

human nervous system. His main research areas using human autopsy material are: (1) brain damage due to hydrocephalus; (2) brain damage associated with prematurity especially periventricular / germinal matrix hemorrhage; and (3) brain damage associated with substance abuse (including fetal alcohol spectrum disorder). In addition, he has also done a variety of small projects exploring the pathogenesis of brain damage in rare genetic disorders.

Stephen A. Back, MD, PhD
Oregon Health & Science University
Portland, OR

With advances in neonatal care, preterm survivors are sustaining an evolving constellation of motor and cognitive disabilities related to diffuse non-cystic white matter injury (WMI). The studies of Stephen A. Back, MD, PhD, support that these milder forms of WMI involve disturbances in maturation of late oligodendrocyte progenitors (preOLs) and chronic disturbances in white matter regeneration and repair. The pathological hallmark of cerebral white matter injury (WMI) is myelination disturbances that coincide with diffuse reactive astrogliosis. Myelination disturbances are initiated by acute selective degeneration of preOLs, but are sustained by persistent preOL maturation arrest. Dr. Back has identified that preOL maturation arrest is mediated in part by specific inhibitory forms of hyaluronic acid that accumulate at sites of WMI. These bioactive forms of hyaluronic acid are generated hyaluronidases including a CNS-enriched hyaluronidase, PH20.

A novel selective PH20 inhibitor promotes preOL maturation. Bioactive forms of HA act via a heteromeric complex of CD44 and Toll-like receptors. Recent studies have identified a novel signaling pathways that displays tolerance-like features to mediate myelination failure.

Adam Chodobski, PhD
Warren Alpert Medical School of Brown University
Providence, RI

Adam Chodobski, PhD, has a long-standing interest in translational research on traumatic brain injury. The areas of his research encompass the molecular and cellular aspects of the blood-brain barrier and blood-CSF barrier function in the context of neurotrauma, and he currently serves as the Director of Neurotrauma and Brain Barriers Research Laboratory in the Department of Emergency Medicine at the Alpert Medical School of Brown University. The primary focus of investigations conducted in Dr. Chodobski's laboratory is on the mechanisms underlying the brain inflammatory response to injury and on therapies directed to limit post-traumatic neuroinflammation and improve functional outcome after neurotrauma. His laboratory also conducts clinical studies on blood biomarkers for the diagnosis of concussion.

Joanne Conover, PhD
University of Connecticut
Storrs, CT

In fetal development, neuroepithelial stem cells generate ependymal cells to cover the entire ventricular

surface of the brain. Ependymal cells function as both a barrier and a transport system for exchange of solutes and toxins between the cerebrospinal fluid and the interstitial fluid. Hydrocephalus, an abnormal enlargement of the ventricles, places extraordinary demands on the stem cell population to provide adequate ependymal cell coverage of the ventricle surface. The studies of Joanne Conover, PhD, involve 4D mapping of stem cell-mediated ependymal cell generation during normal fetal development and in hydrocephalic brain tissue, and examination of how the stem cell niche, neurogenesis and the ependyma are adversely affected in hydrocephalus. Her aim is to determine the limitations of stem cell-mediated ependymal cell generation, explore consequences of inadequate ependymal cell coverage, and investigate the downstream neurodevelopmental consequences of a depleted neural stem cell pool.

Terrie E. Inder, MD, PhD, MBChB
Harvard Medical School
Boston, MA

Terrie E. Inder, MD, PhD, MBChB, is the first appointed chair of the newly transitioned Department of Pediatric Newborn Medicine at Brigham and Women's Hospital in Boston. As a dual boarded child neurologist and neonatologist, her major discoveries have been in clinical and translational research into the nature and timing of brain injury in preterm and high-risk term born infants. She has utilized both magnetic resonance

imaging and bedside monitoring techniques to define the impact of clinical exposures and conditions in the high risk infant on brain injury and brain development.

Dr. Inder, a native New Zealander, received her education and training at the University of Otago, Dunedin, where she also completed her residency in Pediatrics and fellowship in Newborn Medicine. She then went on to complete a fellowship in Pediatric Neurology at Boston Children's Hospital. Her first faculty appointment was at the University of Melbourne, Royal Children's Hospital in 2001 before moving to St. Louis Children's Hospital at Washington University in St. Louis as a Professor in 2005.

Richard F. Keep, PhD
University of Michigan
Ann Arbor, MI

Richard F. Keep, PhD, primarily works on preclinical models of cerebrovascular disease and normal cerebrovascular function. Current areas of research focus include: (1) Mechanisms of brain injury and therapeutic interventions for intracerebral, intraventricular and subarachnoid hemorrhage; (2) cerebral ischemia; (3) normal blood-brain barrier and blood-CSF barrier function; (4) mechanisms of barrier injury; (5) cerebral cavernous malformations; (6) diabetic ketoacidosis; and (7) development of blood-brain barrier penetrant therapeutics for lysosomal storage disorders, neurotropic viruses, toxoplasmosis and pain.

Jenna Koschnitzky, PhD
Hydrocephalus Association
Bethesda, MD

As the Director of Research Programs, Jenna Koschnitzky, PhD, is responsible for planning, managing, implementing, and evaluating all aspects of a research program for the Hydrocephalus Association. Dr. Koschnitzky joined HA in July 2014, after completing a Postdoctoral Fellowship at Seattle Children's Hospital Research Institute where she studied maternal health and preterm birth. Dr. Koschnitzky has presented her research at 15 international conferences and currently has published 12 primary and review articles in peer-reviewed journals. During her research career, Dr. Koschnitzky has been awarded 6 grants to fund her research including the National Institutes of Health's Ruth L. Kirschstein National Research Service Award as a graduate student. She is also a member of the Society for Neuroscience and American Physiological Society.

David D. Limbrick, Jr., MD, PhD
Washington University School of Medicine
St. Louis, MO

David D. Limbrick, Jr., MD, PhD, is Associate Professor in the Department of Neurosurgery and Chief of the Division of Pediatric Neurosurgery at the St. Louis Children's Hospital. His broad clinical and basic translational research is focused on the development of diagnostic markers of hydrocephalus and associated neurological disability. He is completing a K23 Career

Development Award from the NIH/NINDS investigating cerebrospinal fluid (CSF) proteins in post-hemorrhagic hydrocephalus of prematurity (PHH) and the implications of these proteins in long-term neurodevelopment. He serves as the Washington University Site Investigator for the Hydrocephalus Clinical Research Network (HCRN), is the Principal Investigator for the HCRN's CSF Biomarkers study line, and has established a HCRN CSF Repository in order to investigate candidate CSF biomarkers of hydrocephalus. In addition to Dr. Limbrick's work in hydrocephalus, he is also the PI and Associate Director of the Park-Reeves Syringomyelia Research Consortium, a 34-center platform for clinical studies in Chiari-associated syringomyelia and related disorders, as well as the PI on a \$2.8 million grant from the Patient-Centered Outcomes Research Institute (PCORI) titled "Posterior Fossa Decompression with or without Duraplasty for Chiari Type I Malformation with Syringomyelia". His ongoing collaborations have also allowed development of MR diffusion tensor imaging (DTI), MR elastography, and MR resting state functional connectivity to investigate the effects of hydrocephalus on white matter integrity, brain stiffness/ventricular compliance, and neural networks, respectively.

James P. (Pat) McAllister II, PhD
Washington University School of Medicine
St. Louis, MO

James P. (Pat) McAllister II, PhD, is a Professor in the Department of

PHH Speaker Abstracts (cont.)

Neurosurgery at the Washington University School of Medicine in St. Louis. His interdisciplinary approach includes a variety of translational research initiatives to advance understanding of the pathophysiology of hydrocephalus and develop improved treatments for this disorder. His shunting experiments and pharmacological interventions in various animal models have contributed to what is known about the potential for neuroprotection and neuronal recovery. His collaborations also explore the pathogenesis of congenital hydrocephalus, novel surgical approaches, and the development of shunt systems that resist cellular obstruction. Current research involves analyzing brain compliance using magnetic resonance elastography in patients and animal models, testing the effects of anti-inflammatory agents, and determining the pathophysiology of posthemorrhagic hydrocephalus in gyrencephalic animals.

Laura Ment, MD **Yale School of Medicine** **New Haven, CT**

Emerging data suggest intraventricular hemorrhage (IVH) of the preterm neonate is a complex disorder with contributions from both the environment and the genome. Environmental analyses suggest factors mediating both cerebral blood flow and angiogenesis contribute to IVH, while candidate gene studies report variants in angiogenesis, inflammation and vascular pathways. Gene-by-environment interactions demonstrate the interaction between the environment and the genome,

and a non-replicated genome-wide association study suggests that both environmental and genetic factors contribute to the risk for severe IVH in very low birth weight preterm neonates.

Jill Morris, PhD **NIH National Institute** **of Neurological Disorders** **and Stroke** **Bethesda, MD**

Jill Morris, PhD, oversees a grant portfolio that consists of multiple neurological disorders, including hydrocephalus. As a Program Director, she assists grant applicants, develops initiatives, reviews progress reports, and facilitates funding. In addition, she works to identify gaps in the research by working with leaders in the field, attending conferences and organizing workshops. Furthermore, she works with advocacy groups to make sure that research progress is being made in their disease area toward therapeutics. Prior to coming to the NIH, she was an Assistant Professor in the Department of Pediatrics in the Feinberg School of Medicine at Northwestern University and Children's Memorial Research Center. Her laboratory studied in depth and published multiple papers on the function of DISC1, a schizophrenia susceptibility gene. Previously, she was Senior Research Biologist in the Department of Neuroscience at Merck Research Laboratories where she directed research projects relating to bipolar affective disorder, schizophrenia, Alzheimer's disease and Parkinson's disease. Prior to Merck, she was

a Senior Staff Fellow in the Unit of Molecular Neurogenetics at the National Institutes of Health where her research led to the identification and characterization of the gene responsible for the autosomal recessive neurodegenerative disorder called Niemann-Pick type C disease.

Shenandoah Robinson, MD, **FAAP, FACS** **Johns Hopkins University** **Baltimore, MD**

Shenandoah "Dody" Robinson, MD, FAAP, FACS, is a Professor of Neurosurgery and Neurology (PAR) at Johns Hopkins University School of Medicine. In her clinical practice as a pediatric neurosurgeon, she treats children, adolescents and young adults who experience consequences of perinatal brain injury including hydrocephalus, cerebral palsy and epilepsy. She also conducts basic, translational and clinical research to develop better preclinical models of early CNS injury, clarify mechanisms of perinatal brain injury and repair, discover predictive serum and imaging biomarkers, and optimize clinical outcomes for this population.

Joseph Scafidi, DO **Children's National** **Medical Center** **Washington D.C.**

There are no clinically relevant treatments available that improve function in the growing population of children with neonatal brain injury. Diffuse white matter injury and decreased gray matter volumes are a common finding on advanced magnetic resonance imaging

obtained from recent graduates of the neonatal intensive care units. These findings are associated with long-term neurological impairments. In recent studies, we have found that enhanced epidermal growth factor signaling during a critical period after injury promotes cellular, metabolic and ultrastructural improvements - ultimately resulting in functional recovery. Targeting the epidermal growth factor receptor is a potentially applicable treatment that may improve endogenous recovery after neonatal brain injury.

**Evan Y. Snyder, MD,
PhD, FAAP**

**Sanford Burnham Prebys
Medical Discovery Institute
La Jolla, CA**

The therapeutic utility of stem cells is rooted in an understanding -- and exploitation -- of their natural role from earliest development to life's end. Their "job" is first to participate in organogenesis and then to maintain homeostasis of that organ (e.g., the nervous system) in the face of perturbations. Accomplishment of these goals requires numerous actions, cell replacement representing but one. The tasks, in fact, require extensive cross-talk between multiple cell types (including stem cell-derived progeny themselves) and the unfolding of complex developmental programs. This complexity actually enriches the therapeutic potential of the stem cell.

The lab of Evan Y. Snyder, MD, PhD, FAAP, studies the behavior of neural stem cells (NSCs) in various models of injury and degeneration, particularly

in the pediatric population. During neurodegeneration and inflammation, factors are transiently elaborated which draw NSCs (even over great distances) to engage the "niche" and attempt restoration of equipoise by a variety of mechanisms. These actions include differentiating towards the replacement of impaired neural cells, both neurons and non-neuronal "chaperone" cells, all of which are essential for restitution of function. NSCs elaborate factors that promote neuroprotection, trophic support, differentiation, neurogenesis, connectivity, angiogenesis, inhibition of inflammation and scarring. In addition to producing diffusible factors, NSCs communicate via gap junctions to re-equilibrate the intracellular metabolism of endangered neurons or via exosomes. NSCs may serve as vehicles for protein delivery enabling simultaneous cell and gene therapy. NSCs synergize with biomaterials to "re-engineer" damaged regions. Multimodal approaches are likely required for most neurological conditions; NSCs may serve as the "glue".

When studied in vitro ("development- or disease-in-a-dish"), NSCs may help identify novel mechanisms, drug targets, and the drugs themselves. Furthermore, induced pluripotent stem cells (iPSCs) derived from patients and studied/profiled in vitro may provide a launching pad for true personalized/ precision medicine -- i.e., individualized therapies.

While repair may entail recapitulating developmental programs, pathology may represent the perversion of

such programs. Thwarting such pathology, may involve the pharmacological re-establishment of the "proper" program.

H. Gerry Taylor, PhD
**Rainbow Babies
& Children's Hospital
Cleveland, OH**

H. Gerry Taylor, PhD, is a pediatric neuropsychologist and Professor of Pediatrics at Case Western Reserve University and Rainbow Babies & Children's Hospital, University Hospitals Case Medical Center, Cleveland, Ohio. His research has focused on neurodevelopment outcomes of early brain-related conditions, including meningitis, preterm birth, and traumatic brain injury (TBI). Findings from his studies have enhanced understanding of the cognitive, behavior, and family consequences of these conditions, as well as the medical and environmental factors that predict how well the children will do with advancing age. More broadly, his research aims to inform more effective approaches to identification and treatment of learning and behavior problems in children at risk for early brain insults. He has also participated in research on genetic influences on speech-language disorders in children and in clinical trials of behavioral interventions to reduce problems in family and child functioning following pediatric TBI and of adenotonsillectomy to improve neurobehavioral outcomes of childhood sleep disorders.

PHH Speaker Abstracts (cont.)

Robert Thorne, PhD
**University of Wisconsin-
Madison School of Pharmacy**
Madison, WI

The research of Robert Thorne, PhD, focuses on the study of diffusive and convective transport within the extracellular and perivascular spaces of the central nervous system and the development, refinement, and optimization of strategies for delivering large molecule biologics into the brain. His laboratory aims to leverage knowledge of physiology and central nervous system structure with state-of-the-art in vivo imaging methods in order to identify new ways to effectively deliver peptides, proteins, oligonucleotides, and gene therapy vectors to the brain and spinal cord. Recent findings related to intranasal and intrathecal delivery of macromolecules will be presented, highlighting the distribution pathways and mechanisms taken by labeled tracers to reach diverse target sites within the central nervous system. In particular, the talk will emphasize the importance of fluid flow within the perivascular spaces of cerebral blood vessels for widespread brain distribution of tracers administered to the nasal passages or directly to the cerebrospinal fluid.

Andrew Whitelaw, MD
University of Bristol
Bristol UK

Andrew Whitelaw, MD, is a clinical neonatologist whose research has concentrated on diagnosis, mechanisms and treatment of perinatal brain injury. He has been lead investigator on two randomized clinical trials of posthemorrhagic

ventricular dilatation (Ventriculomegaly and DRIFT), was co-investigator on the PHVD Drug Trial and is currently co-investigator in the ELVIS Trial. Recent research has addressed how treatment trials need to quantify development in severely damaged young children who cannot complete the conventional developmental tests. The last two years he has been working on neurodevelopmental assessment of the children in the DRIFT trial at the age of 10 years.

Guohua Xi, MD
University of Michigan
Ann Arbor, MI

Guohua Xi, MD, received his medical degree from Zhejiang Medical University, China, and had his postdoctoral training at the University of Cincinnati and the University of Michigan. He is currently a Richard C. Schneider Research Professor and Professor of Neurosurgery at the University of Michigan. His research interests are: (1) the mechanisms of brain injury after intracerebral hemorrhage and subarachnoid hemorrhage; (2) iron chelation therapy for intracerebral hemorrhage; and (3) the mechanisms of hydrocephalus development following brain hemorrhage.

Yun C. Yung, PhD
The Scripps Research Institute
La Jolla, CA

Yun C. Yung, PhD, is a postdoctoral research scientist at The Scripps Research Institute in La Jolla, California. His interests include understanding mechanisms of hemorrhage and inflammation in

hydrocephalus and other related neurodevelopmental conditions as well as basic transcriptomic and genomic variations within the normal and diseased brain.

Posthemorrhagic hydrocephalus (PHH) is a common neurological condition that can affect neonates and infants. PHH is characterized by increased calvarial size, cerebrospinal fluid (CSF) accumulation, and CNS disability. Multiple methods to modulate excessive CSF offer only palliative treatment, and thus there is pressing need to both understand underlying mechanisms and to develop novel preventative and therapeutic strategies. Our studies explore a new mechanism in the etiology of PHH through the actions of lysophospholipids that occur during prenatal or premature life. These small, membrane-derived lipids include lysophosphatidic acid (LPA) that can be present at high levels in blood and hemorrhagic fluids. LPA activates a family of 6 LPA receptors, and data demonstrate the involvement of at least one G protein-coupled receptor, LPA1, in mediating the actions of blood and LPA in promoting PHH in a mouse model. This model recapitulates multiple comorbid brain changes that are associated with yet differ between prenatal and preterm PHH in humans: LPA or blood exposure alters cortical neuroprogenitor development, neural cell migration, cell adhesion, ependymal cell and attendant cilia function, ventricular patency, and subsequent intracranial pressure. Interim data support the involvement of additional LPA receptors and LPA-related lipid

pathways that may be attractive pharmacological targets for treatment.

**John H. Zhang, MD,
PhD, FAHA**

**Loma Linda University
Loma Linda, CA**

The main research direction in the Zhang Laboratory is focused on the ischemic and hemorrhagic stroke, as well as global cerebral ischemia, neonatal hypoxia, and neurological complications of neurosurgery and anesthesia. Animal models of above mentioned neurological disorders are currently employed in the studies of cerebral physiology including blood-brain barrier, brain edema, cerebral blood flow and intracranial pressure, cerebral morphology, especially immunohistochemistry, molecular biology, neuro-imaging, neurological and neurobehavioral

functional testing. The main focus of research interests is cerebral vascular biology, neuroprotective strategies, gene therapy, signaling pathways, apoptosis, and hyperbaric medicine.

Since late 1970s, animal models of GMH have been established in sheep, rabbits, beagles, mice and rats. Methods to establish those animal models include hypoxia and intracranial hypertension, hemorrhage, intraperitoneal glycerol injection, and periventricular injection of autologous blood or collagenase. Large animal models are complicated, need surgical experiences and facilities, and expensive, even though they are closer to human. Rodents are easier to handle, cheaper, less white matter, but genetic altered strains are available. The overall to suggest is similar to other stroke fields, to test in rodents, if promising move to large animals, before clinical trials.

**Wendy Ziai, MD,
MPH, FAHA**

**Johns Hopkins University
Baltimore, MD**

Intraventricular extension of spontaneous intracerebral hemorrhage in adults is a particularly poor prognostic sign, with expected mortality between 50-80%. Mechanisms of how IVH contributes to morbidity and mortality will be discussed, in particular key candidate pathogenic factors analyzed in the recently completed CLEAR III (Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage) clinical trial and prior clinical trials of acute intraventricular hemorrhage. Evidence for an effect size using clot mitigation techniques such as intraventricular drainage and thrombolytics will be discussed.



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