

Making an Impact

Research Initiative Report

2018-2020



Letter from the CEO and Chair

In 2009, the Hydrocephalus Association launched a research initiative with aggressive goals of stimulating the research ecosystem, identifying the causes of hydrocephalus, and improving the lives of those living with the condition.

Today, we are happy to say that our investments are paying off in a big way. Over the past three years, we have seen significant advances in understanding how altered brain development can lead to congenital hydrocephalus, we have seen multiple drug therapies move towards clinical use, and we have seen our clinical research networks change the way hydrocephalus research is conducted.

Since the start of our research program, we've awarded 43 grants to brilliant scientists who are exploring innovative new treatments and pathways to a cure. Our strategy is to grow our support of scientists with cutting edge ideas to advance hydrocephalus research and bring real progress to patients.

We have forged partnerships with the Rudi Schulte Research Institute and the National Institutes of Health in order to expand funding opportunities for hydrocephalus researchers and are working with many companies to improve the treatment and management of hydrocephalus.

Together, we are experiencing the expansion of hydrocephalus research in ways that we could not have foreseen, driven by the Hydrocephalus Association's support of innovative, ground-breaking research. It is an exciting and promising time for hydrocephalus research, with results that could impact our community for years to come.



Diana Gray, MA

*President & CEO
Hydrocephalus Association*

A handwritten signature in black ink that reads "Diana Gray".



Brett Weitz

*Chair, Board of Directors
Hydrocephalus Association*

A handwritten signature in black ink consisting of the initials "BW".

Hydrocephalus Association

The mission of the Hydrocephalus Association is to find a cure for hydrocephalus and improve the lives of those impacted by the condition.

HA Research Program

The strategic goal of the Research Program is to fund and promote high impact research to advance care, treatments, prevention, and ultimately a cure for hydrocephalus.

To accomplish this, we are working to:

- Incorporate the patient voice into all we do
- Leverage and coordinate the research networks
- Grow the research community
- Advocate for outside research funding

The **drivers** of our Research Program are our patient registry and three research networks. Together, these programs encompass an extensive range of research from identifying new causes of hydrocephalus and testing novel treatments to optimizing current treatments and improving long-term outcomes and quality of life.



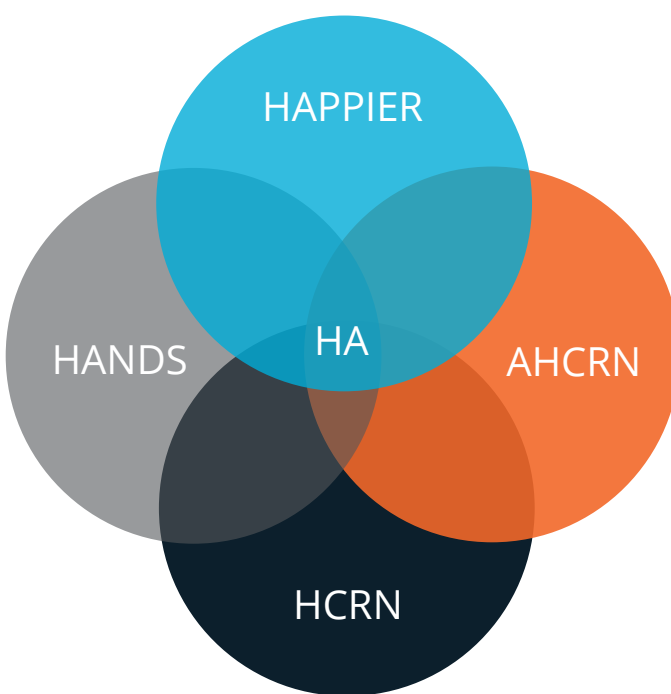
HAPPIER

HA Patient-Powered Interactive Engagement Registry (HAPPIER) is an online survey-based registry created to bring the patient perspective to hydrocephalus research.



HANDS

HA Network for Discovery Science (HANDS) is an online platform for basic and translational scientists to interact, collaborate, and apply for grants.



HCRN

Hydrocephalus Clinical Research Network (HCRN) is a network of fourteen children's hospitals focused on improving outcomes for children with hydrocephalus.



AHCRN

Adult Hydrocephalus Clinical Research Network (AHCRN) is a network of eight hospitals focused on improving the lives of adults with hydrocephalus.

The Big Picture

Since 2009, the Hydrocephalus Association has invested over **\$12 million** on our Research Program. Our grantees and clinical networks have then gone on to secure over **\$35 million** in additional funding.

“The funding I received from the Hydrocephalus Association Innovator Award allowed my research team to generate substantial preliminary data that supported my recently funded NIH R01 application.”

– Joanne Conover, PhD, University of Connecticut



By the Numbers

Since the start of our Research Initiative in 2009, HA has:

Invested over \$12M on our Research Program

Awarded 43 Grants

Sponsored 7 Research Workshops

Supported 3 Research Networks & 2 Biobanks

Developed the 1st Hydrocephalus Patient-Powered Registry

HA funded Grantees and Clinical Networks have gone on to:

Secure over \$35M in Additional Grants

Publish 85 Peer-Reviewed Studies

Decrease Shunt Infection Rates by 36%

Test 10 Preclinical Drug Therapies

Secure 1 New Patent for a Drug Target

Submit 1 FDA Investigational New Drug application

The Impact

We are learning that hydrocephalus is not “just a plumbing problem.”

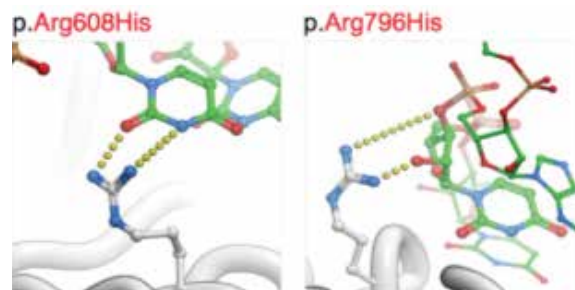
HA has funded **18 mechanistic studies** focused on understanding why hydrocephalus develops and has supported patient **recruitment for 1 large scale genetic study**. These studies have opened the door for us to understand hydrocephalus as a neurological condition and to broaden the scope of research into new therapies.

We are turning new therapies to prevent and treat hydrocephalus into a reality.

HA has funded **10 preclinical drug studies**, which have resulted in **1 new patent** and **1 Investigational New Drug submission** to the FDA. One drug combination is moving towards a clinical trial aimed at **preventing posthemorrhagic hydrocephalus** of prematurity.

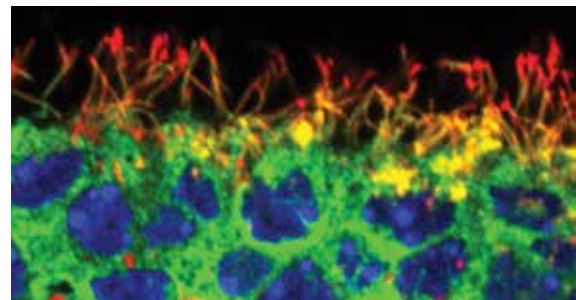
We are improving lives now by changing the landscape of hydrocephalus clinical research.

The HCRN and AHCRN have become the **gold standard** for hydrocephalus clinical research. Combined, the networks have secured funding for **3 randomized control trials** to compare treatment options, and the HCRN has led the way in understanding and **reducing shunt infections by 36%**.



A mutation in the TRIM1 gene, found in some infants with congenital hydrocephalus, causes the TRIM1 protein to fold incorrectly.

Image courtesy of Dr. Kristopher Kahle, Yale University (reprinted with permission)



Ependymal cells (blue/green) with cilia (red).

Image courtesy of Dr. June Goto, Cincinnati Children's Hospital (reprinted with permission)

“Our family believes that HA’s research is truly making a difference. The outcomes have not only resulted in additional funding of the scientists from other sources, but they’ve also generated more interest in the field, and will attract more urgent attention to the need for a cure for our son and others living with hydrocephalus.”

– John Devlin, parent of a child with hydrocephalus

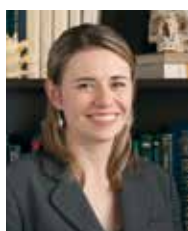


Funding the Best Research

In total, HA has funded **43 grants** to individual researchers through the HA Network for Discovery Science (HANDS).

Over the past three years, HA has awarded **15 grants** to individual researchers with 3 additional grants being funded through our partnership with the Rudi Schulte Research Institute (RSRI).

Meet the Newest Grantees



Carolyn Harris, PhD

Wayne State University

Supported by Team Hydro

Preventing shunt occlusion

Dr. Harris is focused on understanding the differences in how immune cells in the brain

react after a shunt is placed. This information will shed light on why some people are more likely to experience shunt blockages than others and direct new therapies to prevent shunt blockages.



Jose Peiro, MD, PhD

University of Cincinnati

Funded by RSRI

Treating congenital hydrocephalus prior to birth

Dr. Peiro is developing a technique to treat congenital hydrocephalus

by performing an endoscopic third ventriculostomy (ETV) *in utero*. Early treatment may improve cognitive outcomes and negate the need of a shunt.



Aditya Pandey, MD

University of Michigan

Preventing hydrocephalus after a stroke

Dr. Pandey aims to test if acetazolamide (Diamox), when

put directly into the ventricles, can block the activity of a protein in blood and prevent hydrocephalus after a stroke. Although acetazolamide has been tested before, this is the first time intraventricular administration will be attempted.



Stavros Taraviras, PhD

University of Patras

Supported by Team Hydro

Turning scar tissue into functioning cells

Dr. Taraviras is working to reprogram scar tissue into

functioning ependyma, the cells that line the ventricles. In many forms of hydrocephalus, ependyma are damaged and fall into the cerebrospinal fluid (CSF). Scar tissue replaces the ependyma. This treatment could reduce ventricle size and improve CSF movement, brain development, and brain health.



HANDS
Hydrocephalus Association
Network for Discovery Science
Collaboration • Innovation • Impact

297 Members | **37** Countries | **7** Databases | **2** Biobanks

Growing the Research Enterprise

\$3 MILLION Posthemorrhagic Hydrocephalus Campaign

In 2018 we reached our goal of raising \$3 million for the Posthemorrhagic Hydrocephalus (PHH) Campaign. This successful campaign would not have been possible without the Vision Dinner events, which were generously underwritten by Craig and Vicki Brown. These events inspired giving and served as a platform for supporters to hear directly from scientists about the impact of their contributions. **Through the campaign, HA was able to fund amazing research to improve outcomes and prevent PHH, including:**

- Using noninvasive focused ultrasound to dissolve blood clots after a brain bleed in preterm infants
- Determining the role of the glymphatic system in CSF absorption after a brain bleed
- Predicting the delayed development of hydrocephalus after a subarachnoid hemorrhage in adults
- Delineating the role of the choroid plexus and CSF overproduction in the development of hydrocephalus after a brain bleed
- Understanding the role of motile cilia in hydrocephalus development after a traumatic brain injury and in PHH of prematurity

6 PHH studies directly tested drugs to prevent or minimize the impact of hydrocephalus after a brain bleed. One drug combination is now moving towards a clinical trial.

“Vicki and I firmly believe that supporting HA research is our promise for the future. Our Vision Dinner Campaign built awareness of the condition and provided initial funding for treatments to improve lives and ultimately find a cure for those who have been suffering with hydrocephalus.”

– Craig Brown, longtime benefactor of the Hydrocephalus Association

Magnifying the Impact of our PHH Campaign

Driving Common Pathways: Extending insights from posthemorrhagic hydrocephalus
Washington University, St. Louis, Missouri

On November 4-5, 2019, HA brought together a diverse group of researchers to discuss their current research on PHH and other forms of hydrocephalus. The goal of the workshop was to explore areas of potential overlap between hydrocephalus etiologies with a focus on identifying drug targets that could positively impact multiple etiologies of hydrocephalus.



The workshop spurred 12 new collaborations

NEW TECHNOLOGY*

To name a few:

- **Aesculap Inc., in partnership with MIETHKE, launched a new shunt valve called the M.blue™ valve.** M.blue™ valve is the first programmable valve with an integrated fixed differential pressure unit.
- **Anuncia, Inc. received FDA clearance for its Alivio ReFlow™ Ventricular System** which flushes CSF backward through the proximal catheter to unblock occluded holes or open a new hole to allow CSF flow.
- **brain4care**, developer of a non-invasive way to indirectly measure changes in intracranial pressure (ICP), received **ANVISA certification for the commercial use of the product** in Brazil.
- **CereVasc™, developer of an alternative CSF drainage solution**, is beginning its first-in-human trials in Argentina.
- **Cerovations, LLC** was accepted to participate in the NIH I-Corps program to assess market fit for two shunt technologies.
- **Rhaeos, developer of FlowSense, a shunt flow monitor, won MedTech Innovator's 2020 Global Competition.** MedTech Innovator is the largest accelerator of medical devices in the world.
- **Longeviti Neuro Solutions developed, InvisiShunt®**, a cranial implant that houses the shunt valve and restores the skull's natural contour. The first-in-human experience was published in 2019.

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HIGHLIGHTS IN Hydrocephalus Etiologies

Congenital Hydrocephalus

- New genes have been identified as possible causes of congenital hydrocephalus and indicate that impaired brain development may be to blame.
- Altered brain development, CSF absorption, and CSF movement are all implicated as having a role in one genetic form of hydrocephalus.
- After five years, there were no differences in overall health or quality of life for children with hydrocephalus caused by aqueductal stenosis and treated with shunt or ETV, according to the International Infant Hydrocephalus Study.

Acquired Hydrocephalus

- New research is identifying common mechanisms, such as CSF overproduction and ependymal cell loss, in the development of multiple types of acquired hydrocephalus.
- Live imaging of the translucent tadpole is being used to understand the role of cilia and CSF flow in the development of hydrocephalus after a traumatic brain injury (TBI).
- Combined melatonin and erythropoietin may prevent posthemorrhagic hydrocephalus of prematurity. The treatment is also being tested in models of postinfectious hydrocephalus (PIH) and TBI.

Normal Pressure Hydrocephalus

- Work is underway to study genetic mutations that may play a role in the development of NPH. Early gene candidates appear to affect CSF movement and CSF production.
- Impairment in the glymphatic system, an alternative route for CSF absorption, is now being implicated in the development of NPH.
- A large number of patients with NPH also have pathological markers of Alzheimer's disease (AD). However, it is unclear if the presence of AD pathology diminishes the benefits of shunt treatment.

HIGHLIGHTS IN Research Programs

HAPPIER

HA Patient-Powered Interactive Engagement Registry

- HAPPIER launched in 2018 as the first patient-powered hydrocephalus registry.
- HAPPIER now has almost 700 participants ranging in age from 0-86 years old.
- HAPPIER launched a new annual survey to simplify longitudinal data collection.

HANDS

HA Network for Discovery Science

- Over the past three years HA has awarded 15 grants to individual researchers through HANDS. Six have already gone on to receive funding from the NIH.
- HANDS membership has continued to grow with 297 members from 37 countries.
- HANDS organized a research workshop and supported one NIH workshop over the past three years. In 2020, HANDS held its first webinar featuring NIH Program Director, Dr. Jill Morris.

HCRN

Hydrocephalus Clinical Research Network

- The HCRN published eight papers over the past three years primarily focused on shunt infection, risk factors of fast and ultra-fast shunt failures, and ETV with choroid plexus cauterization (CPC).
- The network completed a randomized control trial (RCT) comparing shunt failure rates when the shunt enters at the front or back of the head.
- The network received a \$10 million NIH grant to run a RCT comparing shunt to ETV with CPC in children under two years old.

AHCRN

Adult Hydrocephalus Clinical Research Network

- The AHCRN published a seminal paper describing four groups of adult hydrocephalus patients ranging from adults treated in childhood to those diagnosed with NPH.
- The network completed a pilot study to test the efficacy of shunting in the NPH population.
- The network used the pilot data to apply for a multi-site award from the National Institutes of Health to run a full RCT.

Other Notable HA-funded Studies

Linking NPH symptoms to changes in brain anatomy

*Joel Geerling, MD, PhD
University of Iowa*

Is altered sugar metabolism a risk factor for congenital hydrocephalus and NPH?

*Bernadette Holdener, PhD
Stony Brook University*

Testing a new shunt coating that resists occlusion

*Carolyn Harris, PhD
Wayne State University*

Stopping acute CSF overproduction in postinfectious hydrocephalus

*Kristopher Kahle, MD, PhD
Yale University*

Understanding the brain's gene response in postinfectious hydrocephalus

*R. Reid Townsend, MD, PhD
Washington University*

Determining how the choroid plexus responds to preterm hemorrhage

*Maria Lehtinen, PhD
Boston Children's Hospital*

Looking toward the future

Incorporating **YOU** in all we do! Putting patients in the forefront of our research.



This year, HA began our Community Research Priority Assessment.

What's that you say? We want your priorities to guide our Research Agenda. This year we launched the first survey to gather input from our community. The response was tremendous with over 1,000 individuals providing over 4,800 responses. Over the next year, we will refine these priorities and finalize our top 10 list during a workshop that engages a wide range of hydrocephalus stakeholders.

Introducing our inaugural Scientific Advisory Board



Guy Fish, MD (Chair)

HA Board Member, former CEO Cellanox

Expertise in life sciences and health care innovation, development, and commercialization



Jill Morris, PhD

National Institutes of Health

Expertise in neurological disorders, glial biology, neural crest cells, and genetics



Richard Keep, PhD (Vice Chair)

University of Michigan

Expertise in blood-brain and blood-CSF barriers, hemorrhage, and inflammation



Mike Siegel, PhD

Pediatric Dermatology Research Alliance

Expertise in scientific programs and bioengineering, living with hydrocephalus



Issac (Zak) Kohane, MD, PhD

Harvard Medical School

Expertise in genomics, precision diagnoses, technology, and big data

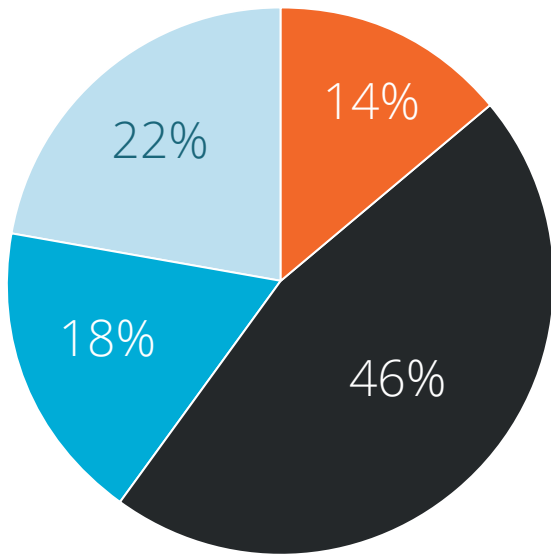


Mark Wallace, PhD

Vanderbilt University

Expertise in sensory motor integration, developmental conditions, and electrophysiology

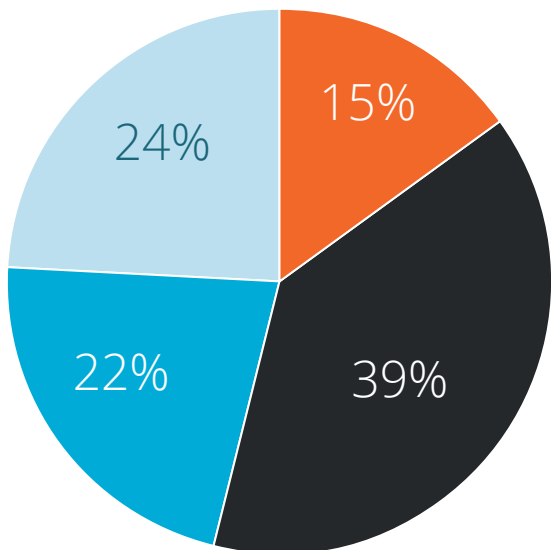
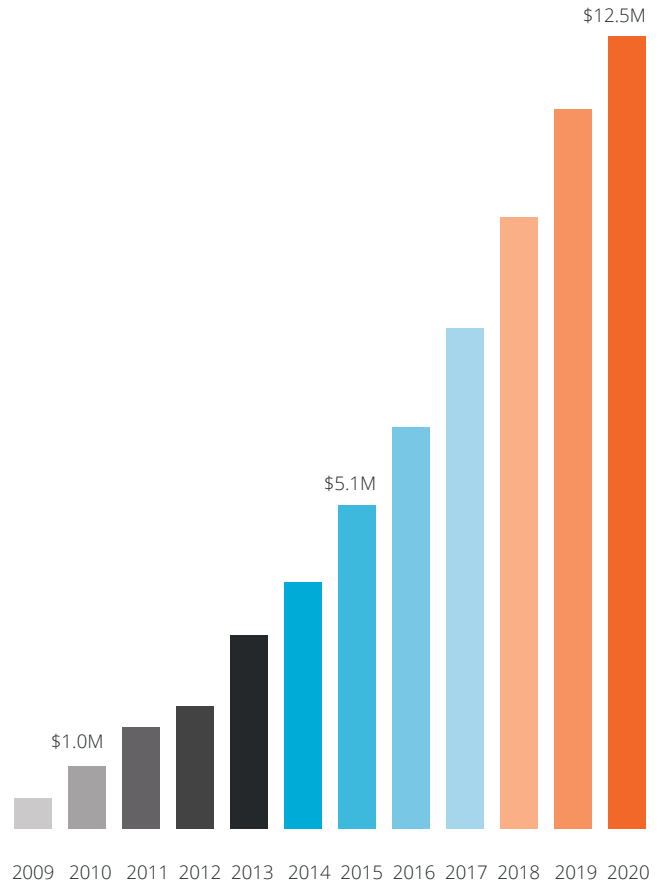
Research Investment



2018-2020
Priority Area Investment

- Stimulate Research Ecosystem
- Understand Root Causes
- Improve Clinical Outcomes - Pediatric
- Improve Clinical Outcomes - Adult

Cumulative Research Spending



2009-2020
Total Priority Area Investment

- Stimulate Research Ecosystem
- Understand Root Causes
- Improve Clinical Outcomes - Pediatric
- Improve Clinical Outcomes - Adult



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