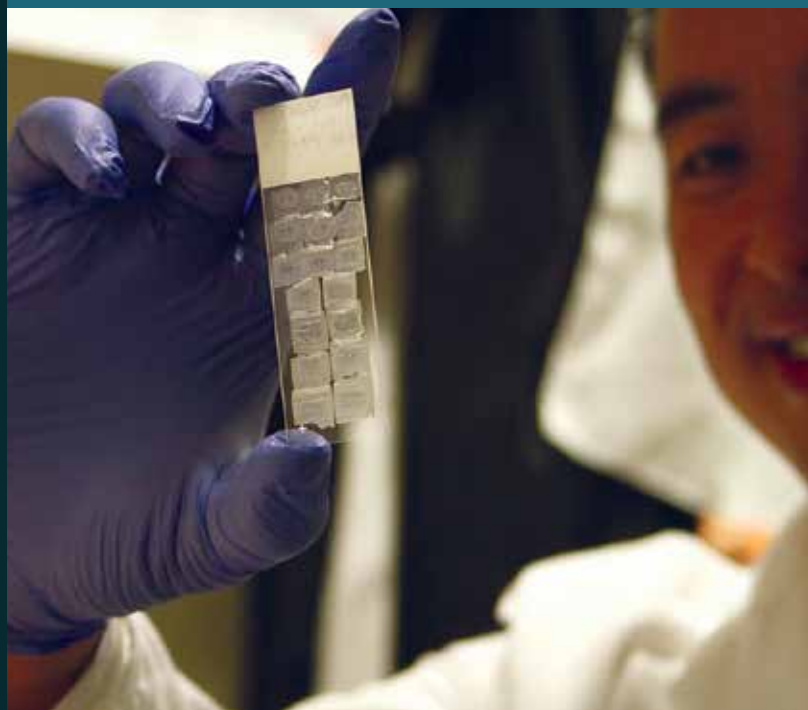
Hydrocephalus Association

Research Initiative Report 2012-2014

Creating a Cure-Focused Research Ecosystem



Letter from the Chairman

This is an exciting time for the hydrocephalus community. After years of stagnation, hydrocephalus research is picking up steam. The hydrocephalus research ecosystem is expanding, bringing in new expertise, innovative approaches, and productive collaborations. As old theories are being questioned, new lines of research are being explored that highlight the complexity, but also the opportunity, inherent in hydrocephalus research. Through discovery, understanding and innovation, science holds the promise of novel treatments and therapies for those affected by hydrocephalus.

The Hydrocephalus Association is proud of the role we have played thus far in supporting hydrocephalus research efforts. Since the start of our Research Initiative in 2009, the Hydrocephalus Association has sponsored one conference and two workshops and has supported the research of four hydrocephalus principal investigators, the careers of seven early career investigators, the work of the Hydrocephalus Clinical Research Network, and the development of the Adult Hydrocephalus Clinical Research Network. Our work, however, is not done. We are developing new initiatives and leveraging our resources to create a unified hydrocephalus research community that is prepared to quickly capitalize on new discoveries and innovations, and, in late 2014, committed funding the development of the Hydrocephalus Association Network for Discovery Science.

It is impossible to tell where the next scientific breakthrough for hydrocephalus will come from. It could be from a new and innovative shunt design, a better understanding of CSF production, absorption, or pulsatility, identification of a new biomarker, or a way to stop the downstream effects of a subarachnoid hemorrhage. By funding innovative projects, bridging the gap between basic and clinical research, and growing the hydrocephalus research community, the Hydrocephalus Association's Research Initiative is accelerating discovery and advancing hydrocephalus research on all fronts.

Aseem Chandra
Chairman of the Board

The Hydrocephalus Association

Today the Hydrocephalus Association is the leading private funder of hydrocephalus research and has made significant gains in each priority area.

Who We Are

The Hydrocephalus Association is an agile team focused on Support, Education, Advocacy, and Research. The mission of the Hydrocephalus Association is to promote a cure for hydrocephalus and improve the lives of those affected by the condition. We strive to accomplish these goals by collaborating with patients, caregivers, researchers and industry, raising awareness, and funding innovative, high-impact research to prevent, treat, and ultimately cure hydrocephalus.

The Evolution of the Association

Since our initial gathering in San Francisco, CA, in 1983, as a parent support group, the Hydrocephalus Association has significantly impacted the health care and scientific communities as well as the lives of individuals affected by the condition. In 2009, the Hydrocephalus Association solidified its commitment to research through the launch of the Research Initiative. The mission of this initiative is to fund research that improves the quality of life for people living with hydrocephalus, and ultimately to find a cure. To accomplish this mission, the Board of Directors established three priority areas:

1. Stimulate the Research Ecosystem
2. Improve Clinical Outcomes and Quality of Life
3. Advance the Study of Root Causes

THANK YOU

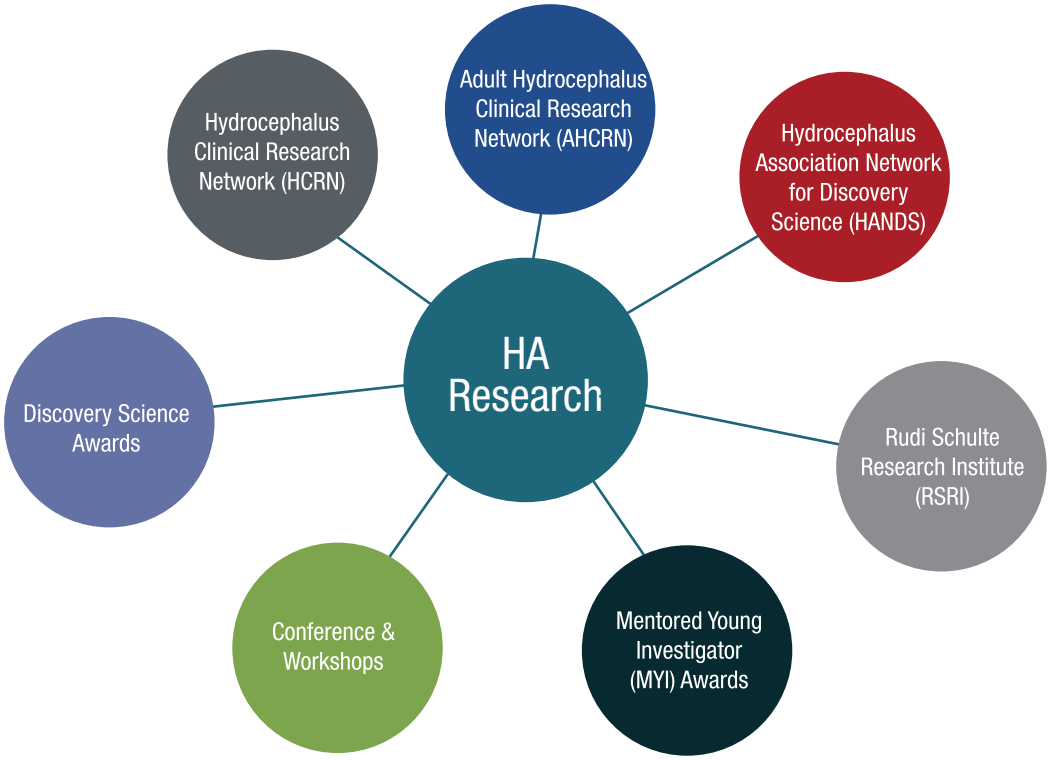
Thank You for Helping Us Exceed Our Goal!

Thank you for helping us exceed our $3 million funding goal for the Reason for Hope research campaign! The campaign (2009-2013) was launched in order to support the Hydrocephalus Association Research Initiative. With your support, the Hydrocephalus Association was able to fund research that advanced all three priority areas – stimulating the research ecosystem, improving clinical outcomes and quality of life, advancing the study of root causes – and established the Hydrocephalus Association as a trusted resource and partner in the advancement of hydrocephalus research.

Paul Gross
CEO and Research Committee Co-chair

Our Research Program

Our research program spans clinical, translational, and basic research. The relationships and partnerships we forge through this program help us to effectively move hydrocephalus research forward.



What We Do

The Hydrocephalus Association Research Initiative is focused on advancing all promising avenues of hydrocephalus research and building a committed and connected hydrocephalus research community.

Research Networks

We support three networks that accelerate high quality, high-impact hydrocephalus research.

- **Hydrocephalus Clinical Research Network (HCRN)**
  A network of nine children's hospitals that conduct clinical research on hydrocephalus.
- **Adult Hydrocephalus Clinical Research Network (AHCRN)**
  Modeled after the HCRN and launched in late 2014, the AHCRN is a clinical network of four hospitals focused on adult hydrocephalus patients.
- **Hydrocephalus Association Network for Discovery Science (HANDS)**
  Although still in development, HANDS is a platform for both communication and collaboration among hydrocephalus basic and translational researchers with a focus on mentorship, innovation, and shared infrastructure.

Research Awards

We award research grants to individual researchers conducting innovative research and support the career development of young hydrocephalus researchers.

- **Mentored Young Investigator (MYI) Awards**
  The MYI Award provides salary support and requires active mentorship for early-career investigators. Seven awards have been granted since 2009.
- **Discovery Science Awards**
  The Discovery Science Awards fund topic-specific basic and translational research projects. Four awards have been granted since 2011.

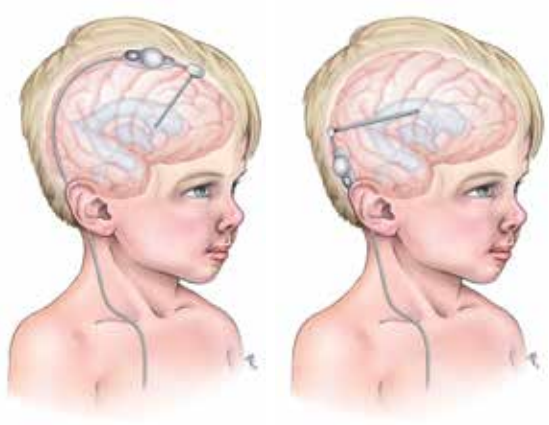
Conferences and Workshops

HA-sponsored research conferences and workshops are designed to promote collaboration, review the current state of research, and identify promising new opportunities. Since 2005, HA has supported five conferences and workshops.

2012-2014 Highlights

Networks

HA-HCRN partnership results in $2.5 million grant to conduct a randomized control trial



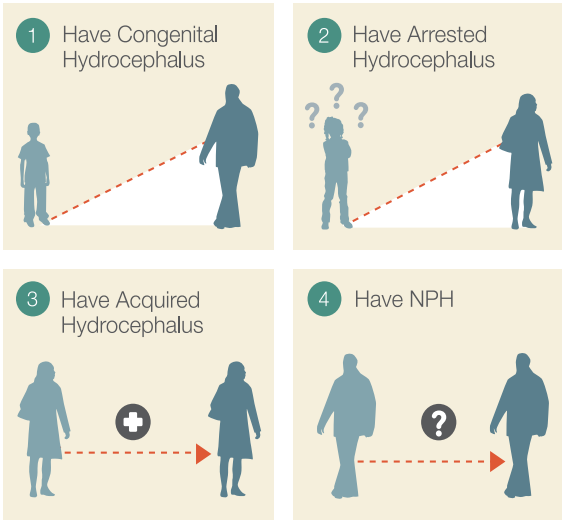
ANTERIOR ENTRY SITE* POSTERIOR ENTRY SITE*

In 2014, The Patient-Centered Outcomes Research Institute (PCORI) awarded a $2.5 million grant in support of a Hydrocephalus Clinical Research Network (HCRN) study. The randomized control trial will determine if failure rates are lower when an anterior or posterior shunt entry site is used. The Hydrocephalus Association partnered with HCRN to involve patients and caregivers in the initial study selection and development, and, now, in the continued execution and results dissemination.

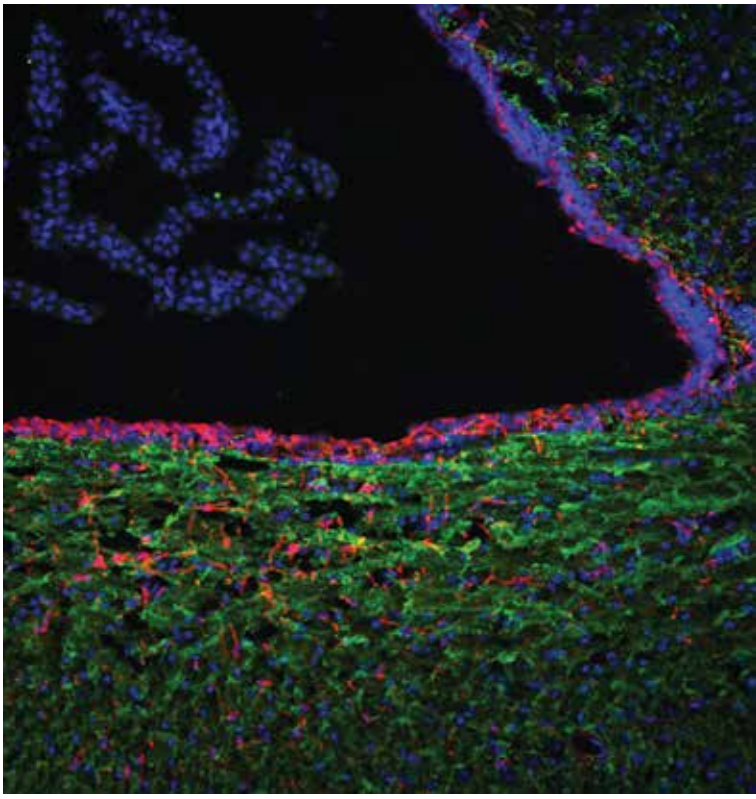
AHCRN launches the Core Data Project

In late 2014, the Adult Hydrocephalus Clinical Research Network (ACHRN) officially launched. The initial focus is on a core data project that will collect patient demographics, hydrocephalus cause, diagnosis information, surgical and medical management information, images, and cerebrospinal fluid (CSF) samples for biobanking. This initial data will be used to understand the variability, progression, and current treatment practices and inform the development of hypothesis-driven research. The creation of a CSF biobank and image database will help fast track research, enabling basic, translational, and clinical research to move forward in parallel.

CORE DATA PROJECT PATIENT GROUPS



Research Awards



HA and Partners award $1,000,000 directly to basic science researchers

In 2013, the Hydrocephalus Association partnered with the Rudi Schulte Research Institute (RSRI) to award two grants, totaling $1 million, to basic science researchers.

Dr. Timothy Vogel from Cincinnati Children's Hospital Medical Center was awarded $400 thousand over three years for his study focused on brain development in neonatal hydrocephalus.

Dr. Mark Wagshul from the Albert Einstein College of Medicine, Bronx, NY, was awarded $600 thousand over three years for his study focused on how brain compliance relates to slit ventricle syndrome and headaches in hydrocephalus patients.

Hydrocephalus research now eligible for $247 million in DOD funding

HA, working in conjunction with our allies on Capitol Hill, earned a huge victory for our community in 2014 when President Obama signed into law H.R. 83, the Omnibus and Continuing Resolutions Act of 2015, which, for the first time, made hydrocephalus a condition eligible to receive funding through the congressionally directed Peer Reviewed Medical Research Program (PRMRP). In 2015, the PRMRP will award $247 million to projects solicited from 41 eligible conditions. HA is fully committed to supporting researchers who are interested in applying for this funding and will continue to monitor and track the progress of this program.

2014

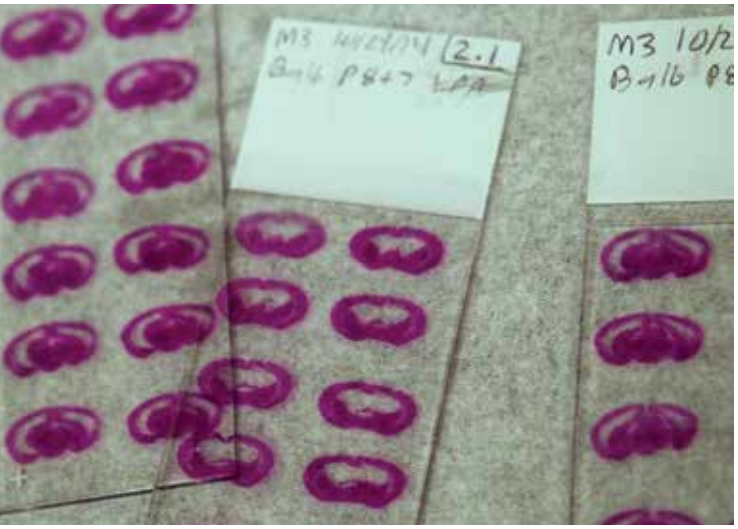
- Gerber Foundation Awards $100K to HCRN Investigator
- Biomarkers in Hydrocephalus Workshop, St. Louis, MO
- PCORI Awards $2.5M to HCRN & HA
- NIH Midbrain/Hindbrain Malformations and Hydrocephalus Workshop, Bethesda, MD
- Hydrocephalus eligible for $247M from DOD
- AHCRN Launches Core Data Project

2012-2014 Updates

Mentored Young Investigators (MYI)

Under Pressure: Brain Injury and Repair

The brain is resilient, but repeated cycling between high and low pressures takes its toll. Dr. Ramin Eskandari (MYI 2010) is focused on how pressure affects different areas in the brain and how brain cells react to pressure. In his new position as an Assistant Professor at the Medical University of South Carolina, Dr. Eskandari is continuing his research efforts to improve the lives of those living with hydrocephalus.



Preventing Post-Hemorrhagic Hydrocephalus

The prevention of post-hemorrhagic hydrocephalus (PHH) may be on the horizon. At the Scripps Research Institute, Dr. Yun Yung (MYI 2010) is now testing drugs that target a molecular pathway involved in the development of PHH. By blocking the activity of a specific compound found in blood, Dr. Yung hopes to stop the downstream effects of a brain bleed and prevent PHH. The MYI Award provided Dr. Yung with the initial funding for this project. Dr. Yung's research is now being supported by a large National Institutes of Health (NIH) grant.

Non-Invasive CSF Regulation

After completing his MYI Award, Dr. Simon Shim (MYI 2010) became a Visiting Professor at the Indiana University-Purdue University Indianapolis. In collaboration with Dr. Bonnie Blazer-Yost, Dr. Shim is testing a group of drugs that decrease ventriculomegaly in an animal model by altering fluid regulation in the brain. Potentially, these drugs will be a non-invasive, pharmaceutical therapy for CSF modulation in hydrocephalus patients.

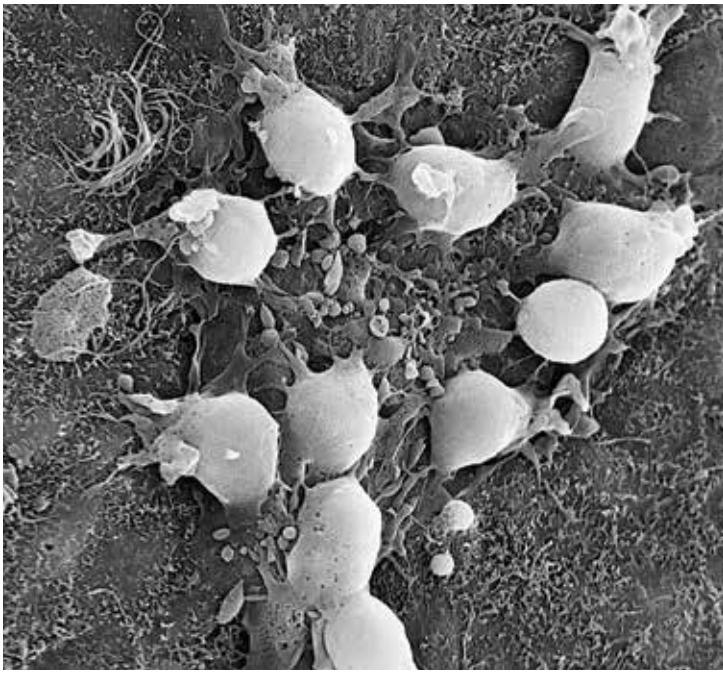
MYIs Since the Award

- 73 peer-reviewed papers; 18 focused on hydrocephalus
- 41 presentations
- 5 of 7 still actively conducting hydrocephalus research

Discovery Science Awards

Conquering Fetal-Onset Hydrocephalus

Dr. James 'Pat' McAllister from Washington University in St. Louis, in collaboration with Dr. Esteban Rodriguez from the Universidad Austral de Chile, are unlocking the causes of fetal-onset hydrocephalus. Their research, supported by HA, revealed that a primary defect in the junctions, or connections, between cells lining the ventricles cause ventriculomegaly and abnormal brain development in a model of communicating hydrocephalus. These results have been published in the 2012 paper, "A cell junction pathology of neural stem cells leads to abnormal neurogenesis in hydrocephalus." They are now working on ways to prevent and arrest the development of hydrocephalus by strengthening these weak connections.



Alternative Routes: CSF Reabsorption

In 2014, Dr. Miles Johnston published the paper, "Potential for intranasal drug delivery to alter cerebrospinal fluid outflow via the nasal turbinate lymphatics," which showed that two drugs known to modulate lymphatic vessel contractility could increase CSF outflow rates at high intracranial pressures. Although in its early stages, this is promising HA-sponsored research that may lead to a non-invasive way to help manage hydrocephalus.

2012-2014 HA-Sponsored Publications

- 2014 "Hydrocephalus research funding from the National Institutes of Health: a 10-year perspective," *Journal of Neurosurgery: Pediatrics*
- 2014 "Pediatric Hydrocephalus: systematic literature review and evidence-based guidelines," *Journal of Neurosurgery: Pediatrics*

Hydrocephalus Clinical Research Network

Finding Focus: HCRN's Dr. Tamara Simon targets repeated CSF shunt infections

Dr. Tamara Simon, Seattle Children's Hospital, is focused on factors related to repeated cerebrospinal fluid (CSF) infections. Shunt infections are a major problem for hydrocephalus patients resulting in up to 2,400 admissions and 59,000 hospitals days each year in the United States. In 2014, Dr. Simon published the paper, "Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort." Using the HCRN patient registry, the paper found that CSF shunt infections occurred in 11% of patients and almost all occurred within six months of initial shunt placement. Patients who had undergone just one shunt revision were three times more likely to develop a shunt infection than patients who did not have a shunt revision. If a patient underwent two or more shunt revisions, the risk of CSF shunt infection jumped to 14 fold greater risk. Dr. Simon's study underscores the urgent need for new ways to prevent shunt infections, and decrease shunt failure rates.

Making the Grade: HCRN's Dr. Abhaya Kulkarni tests the utility of the ETV-CPC

Dr. Abhaya Kulkarni, Hospital for Sick Children in Toronto, was involved in the development of the endoscopic third ventriculostomy (ETV) success score, a measure that predicts ETV success for individual patients. Now the ETV has been paired with choroid plexus cauterization (ETV-CPC) and, unlike the ETV alone, the combined ETV-CPC procedure appears to have low failure rates in children younger than two years old. Utilizing the HCRN patient registry, Dr. Kulkarni was able to analyze the ETV-CPC procedure. Published in 2014, Dr. Kulkarni showed that ETV-CPC failure in children under two was near 50% at 12 months, slightly worse than shunt failure rates. However, if greater than 90% of the choroid plexus was removed, ETV-CPC failure was closer to 20%. Dr. Kulkarni will continue this work and begin to look at longer term outcomes.

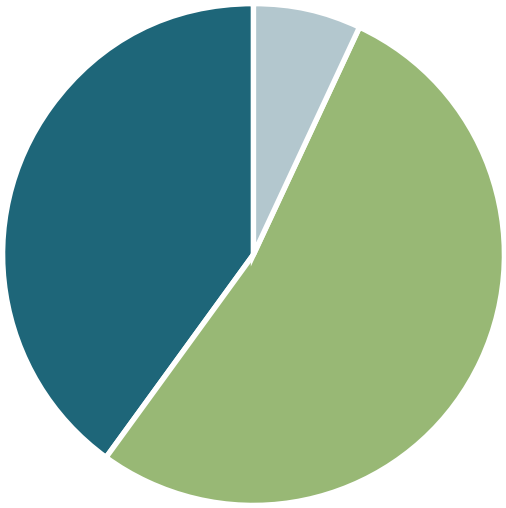
2012-2014 Hydrocephalus Clinical Research Network (HCRN)

- $3.4 million in new grants - HCRN has leveraged your support 6:1
- 5 new studies underway - HCRN is testing treatment options and improving clinical outcomes
- 7 new studies published for a total of 12 publications - HCRN is sharing protocols and study results to improve patient care at non-HCRN centers
- 20 invited presentations - HCRN Investigators are leaders in conducting quality hydrocephalus clinical research

Research Spending

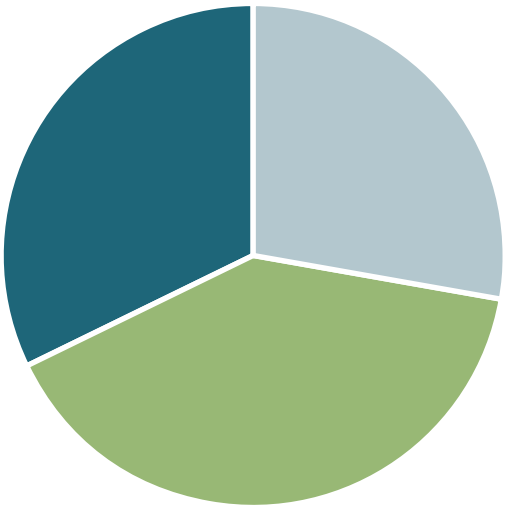
PRIORITY AREA SPENDING (2012-2014)

- Ecosystem: 7%
- Clinical Research: 53%
- Basic Research: 40%



TOTAL PRIORITY AREA SPENDING (2009-2014)

- Ecosystem: 28%
- Clinical Research: 40%
- Basic Research: 32%



Priority Area Spending 2012-2014

STIMULATE RESEARCH ECOSYSTEM

Conference & Workshops	$139,143
Mentored Young Investigator Award	$0
TOTAL ECOSYSTEM	$139,143

IMPROVE CLINICAL OUTCOMES

HCRN	$544,858
AHCRN	$591,721
TOTAL CLINICAL RESEARCH	$1,136,579

UNDERSTAND ROOT CAUSES

Discovery Science Awards	$866,000*
TOTAL BASIC RESEARCH	$866,000
TOTAL RESEARCH INITIATIVE SPENDING	$2,141,722

*Includes HA/Rudi Schulte Research Institute Award

Total Priority Area Spending 2009-2014

STIMULATE RESEARCH ECOSYSTEM

Conference & Workshops	$139,023
Mentored Young Investigator Award	$770,000
TOTAL ECOSYSTEM	$909,023

IMPROVE CLINICAL OUTCOMES

HCRN	$745,684
AHCRN	$591,691
TOTAL CLINICAL RESEARCH	$1,337,375

UNDERSTAND ROOT CAUSES

Discovery Science Awards	$1,066,000*
TOTAL BASIC RESEARCH	$1,066,000
TOTAL RESEARCH INITIATIVE SPENDING	$3,312,398

*Includes HA/Rudi Schulte Research Institute Award

Looking Forward

2015 and Beyond

This year the Hydrocephalus Association finalized a new five-year Strategic Plan. Once again, the focus is firmly placed on supporting hydrocephalus research efforts. Strategic Objective #1 is to increase the amount of high-quality, high impact research being conducted on hydrocephalus. With this in mind, the research goals over the next five years are focused on the hydrocephalus research ecosystem, clinical treatment outcomes, and advancing the development of treatments and cures.

Research Goals

1. Grow and broaden the hydrocephalus research community
2. Improve treatment outcomes by supporting research focused on targets such as reducing revision rates.
3. Advance the development of preventions and cures.

Creating a Cure-Focused Research Ecosystem

Since the start of the Research Initiative in 2009, HA has focused on creating a research ecosystem primed to find a cure for hydrocephalus. Through conferences and workshops, individual grant awards, and the Mentored Young Investigator program, HA has supported the research ecosystem and basic science efforts while the HCRN and AHCRN provide the structure and expertise necessary to efficiently and thoroughly test new technology, therapies, and preventions with the highest clinical standards. What we are still missing is a unified basic research community committed to developing these breakthroughs. To fill this gap, this year, HA is starting the Hydrocephalus Association Network for Discovery Science.

HA Network for Discovery Science (HANDS)

Developed out of discussions from HA- and NIH-sponsored workshops, HANDS will be a platform for both communication and collaboration among hydrocephalus basic and translational researchers with a focus on mentorship, innovation, and shared infrastructure to support high-quality, high impact research.

To accelerate the development and implementation of innovative, cure-focused ideas, researchers need access to the tools, the specimens, and the expertise of scientists and clinicians around the globe. In its current state, the field of hydrocephalus research is small and scattered. Ideas with potentially field-altering implications are being left on the table because researchers do not have the necessary tools to perform the studies and collaborations are slow to form. HA is centralizing and solidifying the field by bringing together the brightest minds into a single virtual center – Hydrocephalus

Association Network for Discovery Science. Utilizing shared infrastructure from top institutions around the country, forward-thinking researchers will be able to test their hypotheses at an accelerated pace

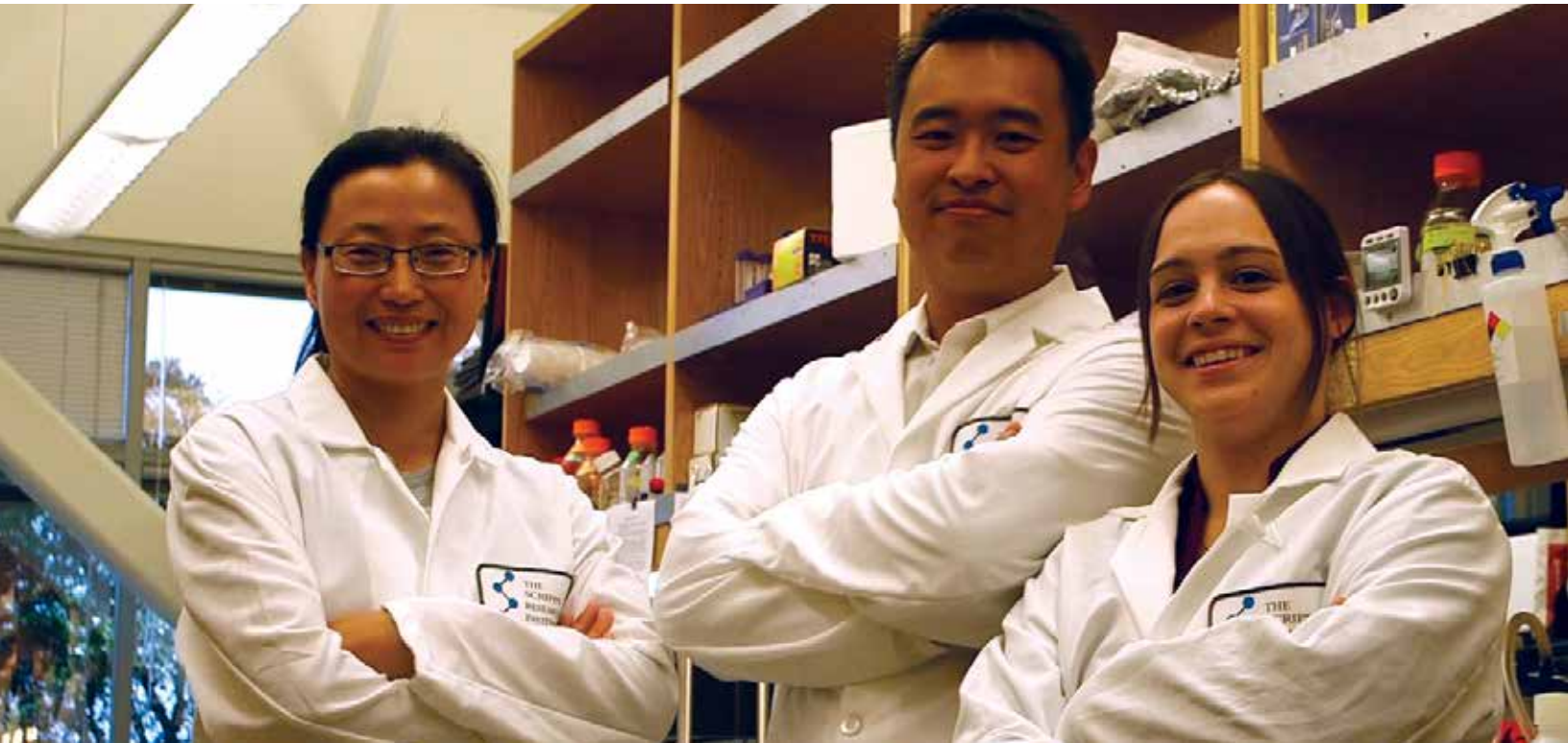
HA Network for Discovery Science

- Dynamic collaborations to tackle new ideas
- Central bio-repositories to accelerate experimentation
- Rapid animal model development to catalyze genetic discoveries
- High-powered imaging tools and image databases to visualize brain function and recovery
- Key scientific databases to engage and connect investigators
- Public and private funding opportunities to execute the research country, forward-thinking researchers will be able to test their hypotheses at an accelerated pace.

Funding Cure-Focused Research

This summer, HA launched the 2015 Innovator Award for Investigators in Hydrocephalus Therapeutics Research. The goal of this initiative is to provide seed funding for bold and innovative research with the potential to transform the field of hydrocephalus through the understanding of disease mechanisms and the development of novel therapies. New 2015 Innovator Award:

- $200 thousand in available funding
- Awards at $25 or $50 thousand level
- 12 month maximum time frame



Vision of a Healthy Research Ecosystem

IMAGINE that by 2025, the landscape of hydrocephalus research and treatment has dramatically improved. An influx of new researchers and the collaborative environment of the prior decade has produced promising findings in basic science that have an immediate and direct impact for people with hydrocephalus.

IMAGINE that the development of standardized treatments, through the process of evidence-based medicine, has led to better outcomes for patients. For example, the infection rate for shunt surgeries (currently approximately 10%) drops by 50% nationwide as neurosurgeons adopt proven techniques. The HCRN has already dropped infection rates by 30% at participating HCRN hospitals.

IMAGINE that a deep understanding of the complex brain dynamics of hydrocephalus has led to research that translates directly into improved treatments and cures.

IMAGINE having the confidence that you are receiving medical advice and treatment that conforms to a standard of care based on the highest understanding of hydrocephalus.

And finally, IMAGINE that we have a way to reduce or eliminate the need for shunt revisions... Or that we have a pill that alleviates intracranial pressure, memory loss and imbalance... Or even that shunts are unnecessary because hydrocephalus can be detected and cured at its onset, or prevented altogether.

The Hydrocephalus Association is committed to making all of this a reality.

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