



The Research Initiative – Delivering on a Promise

Research Initiative Report for 2009-2011



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The Hydrocephalus Association Research Initiative Report

Hydrocephalus Association (HA) Research Mission

At HA, we are dedicated to the advancement of promising research with the potential to promote the understanding, diagnosis, treatment and, ultimately, the prevention of hydrocephalus. Since the first National Institutes of Health (NIH)-sponsored workshop on hydrocephalus in 2005, in which HA played an instrumental role, the increase in research on hydrocephalus has been a cause for hope for the hydrocephalus community. Since HA launched its Research Initiative in 2009, the Association has directly funded both basic and clinical research which is advancing the knowledge base on hydrocephalus and is leading to improvements in diagnosis and treatment. HA remains committed to stimulating and funding research which improves the quality of life for people living with hydrocephalus, while encouraging more scientists – both junior and senior -- to focus on this condition, so we may better understand, diagnose, treat, and eventually cure it.

Outstanding Challenges in Hydrocephalus Research

The hydrocephalus research community has made much progress, but substantial and critical barriers exist to reaching our research goals. The most immediate barrier is the inadequacy of resources devoted to studying hydrocephalus. To significantly advance this research effort, HA needs:

- a substantial funding increase from public and private sources
- people and infrastructure dedicated to the research mission of improving care and quality of life.

The complexity of hydrocephalus itself, including multiple etiologies, symptoms, and abnormal consequences, is another key barrier. For example:

- There is no consensus on treatments, clinical outcome measures, or quality of life measurements.
- Substantial improvements are needed in patient safety, clinical outcomes, and cost of treatment.
- A paucity of basic science exists about the brain injury mechanisms related to hydrocephalus.

The final and long-standing problem facing hydrocephalus patients relates to the shunts (ventricular and lumbar) used to treat the condition. An unacceptably high complication and failure rate is associated with these devices, and more research is needed to improve them and the techniques related to their implantation. Ideally, we will find alternative treatments and preventive mechanisms.

Research Initiative Yields Priorities for a Five-Year Research Plan

In 2011, HA unveiled a specific research plan to address the aforementioned problems. The board of directors established three priorities for the use of research dollars:

- 1) Stimulate the research ecosystem by continuing to fund collaborative research efforts, such as research conferences, to encourage pilot studies that will ultimately garner NIH and other funding. These efforts also identify promising young scientists and support their mentoring by senior scientists in the field.
- 2) Identify and improve clinical practices, reduce shunting complications, and develop consensus in the scientific and clinical community on clinical assessments and outcome measures. To address this goal, HA funds research networks and studies devoted to understanding shunt failure and reducing practice variation.
- 3) Improve the understanding of the causes of hydrocephalus to aid in the diagnosis and treatment of the condition and to improve patient quality of life. HA is and plans to continue devoting funding to the identification of biomarkers, the understanding of cerebrospinal fluid regulation, and the genetic basis of hydrocephalus. Findings in these areas should enable the discovery of pharmacological interventions, among other possible innovative treatments. HA also aims to support key infrastructure initiatives, including tissue banks, animal model development, and image databanks to test various hypotheses relevant to the physiology of hydrocephalus.



Stimulating Researchers to Apply to NIH – Significantly More Public Funding is Required

To address all of these priorities, HA and the hydrocephalus community needs to work diligently to stimulate the hydrocephalus research ecosystem. A strong ecosystem should consist of:

- all of the institutions that fund and conduct research, both public and private,
- individuals studying (and potentially studying) the condition, and
- patients and families involved in clinical studies.

Due in large part to HA's concerted efforts to raise funds and awareness for research, the current research environment is far more robust than it was at the time of that first NIH-sponsored workshop seven years ago. However, significant attention and effort is still required to maintain and improve upon the progress made. Public investments in hydrocephalus research totaled only \$6.4 million in 2011 – a 25% decrease from the average of the prior two years. HA is committed to taking the steps necessary to stimulate the research ecosystem and to drive more attention and funding towards that end. Our long-term vision is a dramatically improved landscape for hydrocephalus research and treatment by the end of this decade. We believe that an influx of new researchers and an environment that encourages interdisciplinary and cross-institutional collaboration will produce promising findings in basic science that will point the field towards improved treatment options and, eventually, a cure. We are confident that such stimulation of the research ecosystem can lead to more publicly- and privately- funded grants. Furthermore, we are confident that this research will lead to:

- standardized neurosurgical practices that will reduce shunt revision and infection rates;
- advances in proteomic and genomics findings that will lead to pharmaceutical treatments;
- and, new insights into the complex brain dynamics underlying hydrocephalus that will enable better clinical practice, improved quality of life, and progress towards a cure.



Hydrocephalus Associated Sponsored Research

Starting in 2009, HA began to devote significant resources to funding both basic and clinical research aligned with what has become our first priority: stimulating the hydrocephalus research ecosystem. We co-sponsored the second NIH Workshop on hydrocephalus, attracting 80 investigators to the event held in Baltimore, Maryland. We initiated our first of two grant cycles dedicated to Mentored Young Investigators (MYI's) to attract young researchers to the field of hydrocephalus, while fostering a relationship with their experienced research mentors.

In 2011, HA developed a partnership with the Hydrocephalus Clinical Research Network (HCRN), to accelerate progress on our clinical research priorities. HA supports the HCRN network and its investigation of clinical practice and outcomes in pediatric hydrocephalus neurosurgery. To date, the research conducted by HCRN includes seven studies into the improved treatment of hydrocephalus.

After helping initiate the first NIH-sponsored workshop on hydrocephalus in 2005, HA discovered that conferences were a very effective way to increase collaboration among researchers in a way that resulted in more public funding of hydrocephalus research. Since that time, HA has established that a bedrock of its Research Initiative would be to sponsor or facilitate a conference or workshop of hydrocephalus researchers bi-annually.

Hydrocephalus Research Conferences and Workshops Sponsorships

Year	Grant	Institution	Title	Investigator	Amount
2009	Workshop	NIH	Improving Outcomes In Hydrocephalus: Bridging the Gap Between Basic Science and Clinical Practice	Pat McAllister	\$15,000
2012	Conference	Seattle Children's	Opportunities in Hydrocephalus Research: Pathways to Better Outcomes (Basic & Clinical)	Sam Browd, MD, PhD	\$87,000

Mentored Young Investigator Program

Our Mentored Young Investigators (MYIs) program targets researchers who typically have recently completed their doctorate or are in the final stages in their specialization in neurosurgery and are being coached by an experienced researcher often with a track record in hydrocephalus research. The goal of this program is to increase the number of young researchers that commit to a career in hydrocephalus research and to increase the likelihood of their success through mentorship. The program provides \$55,000 per year of salary support for each of two years which is sufficient to sustain a post doctorate fellowship in an establish laboratory. For a neurosurgeon, it provides the protected time necessary to conduct research in the face of a busy clinical schedule. Successful MYI grantees will go on to receive grant funding from the NIH for career awards or research grants.

Hydrocephalus Associated Sponsored Research



Mentored Young Investigator Program

The table below provides brief description of our MYI grantees since the launch of the program in 2009.

Year	Grant	Institution	Title	Investigator	Amount
2009 - 2010	Mentored Young Investigator	Harvard	The role of angiogenesis in hydrocephalus (Basic)	Joon Shim, PhD	\$110,000
2009 - 2010	Mentored Young Investigator	Cleveland Clinic	Effects of VEGF agonist (rVEGF) and VEGF antagonist (Bevacizumab) treatment on cerebrovascular density and permeability, and learning in a kaolin model of hydrocephalus	Abhishek Deshpande, MD, PhD	\$110,000
2009 - 2010	Mentored Young Investigator	Cornell Medical College	Quantitative measurement of ventricular volume and cortical atrophy to improve diagnosis of normal pressure hydrocephalus (Clinical)	Dana Moore, PhD	\$ 110,000
2009 - 2010	Mentored Young Investigator	University of Utah	Early versus late CSF drainage treatment in experimental neonatal hydrocephalus (Basic)	Ramin Eskandari, MD	\$ 110,000
2009 - 2010	Mentored Young Investigator	Scripps Research Institute	Lysophosphatidic acid (LPA) signaling in hydrocephalus (Basic)	Yun Yung	\$ 110,000
2010 - 2011	Mentored Young Investigator	University of California San Diego	Study of Augurin, a novel choroid plexus-derived peptide hormone that regulates CSF formation by controlling epithelial cell homeostasis (Basic)	Sandra Podvin, PhD	\$ 110,000
2010 - 2011	Mentored Young Investigator	University of Utah	Study of ventricular size associated with neuropsychological outcome in children presenting with new diagnoses of hydrocephalus at 6 months. (a phase II clinical study)	Jay Riva-Cambrin, MD MSc	\$ 110,000



Hydrocephalus Associated Sponsored Research

Hydrocephalus Clinical Research Network Partnership

The Hydrocephalus Clinical Research Network (HCRN) grew out of the frustration of parents and doctors struggling to save children from a sentence of life-long disability. A collaboration of multiple research institutions, HCRN's mission is to overcome the obstacles that have stymied previous research efforts: too few patients to study in any one hospital, uncoordinated research, and under-staffed/under-funded studies. HCRN's current organization consists of a central data coordinating center, and seven (7) research centers at high-patient-volume pediatric hospitals in North America. Principal investigators at member institutions each lead an important study designed to yield results for improving hydrocephalus treatment. All centers enroll eligible patients in all appropriate studies concurrently. This model makes sure the studies are both adequately powered by sufficient sample sizes and are appropriately staffed, while also ensuring data is collected quickly and professionally.

HCRN Research Team Members



The Hydrocephalus Association has committed to sustaining the research of HCRN through philanthropic funding. The table below describes the current research efforts of HCRN. It is noteworthy and exciting that the first study has already published results reducing post operative infection rates for shunt surgery by more than 35% at the participating centers.

Hydrocephalus Associated Sponsored Research



Hydrocephalus Clinical Research Network Partnership

HCRN Partnership -- Active Studies

Year	Grant	Institution	Title	Investigator
2012 - 2014	Partnership	HCRN	Quality improvement: shunt infection protocol (Clinical)	John Kestle, MD, MSc
2012 - 2014	Partnership	HCRN	Shunting outcomes in post hemorrhagic hydrocephalus (Clinical)	Jay Wellons
2012 - 2014	Partnership	HCRN	Shunt Registry (Clinical)	Jay Riva-Cambrin
2012 - 2014	Partnership	HCRN	ETV Registry (Clinical)	Abhaya Kulkarni
2012 - 2014	Partnership	HCRN	Infection Registry (Clinical)	Tamara Simon
2012 - 2014	Partnership	HCRN	Biomarkers in Post Hemorrhagic Hydrocephalus (Basic & Clinical)	David Limbrick

An Adult Hydrocephalus Clinical Research Network

While HCRN's focus is on pediatric hydrocephalus, a number of their studies should improve treatment overall for hydrocephalus patients. That said, the Hydrocephalus Association is committed to seeing the infrastructure of HCRN extended to support research into the adult population. In 2012, HA launched an initiative to form an Adult Hydrocephalus Clinical Research Network ("AHCRN"). Five sites have been selected and are participating in the creation of a registry to track essential information for people who suffer from hydrocephalus in adulthood. The goal of this group is to launch "AHCRN" in 2013.



Hydrocephalus Associated Sponsored Research

Established Investigator Grants in Basic Science

HA's priority in research to understand the etiology of hydrocephalus has been supported by our most recent request for applications in 2011. The goals of these grants are to provide sufficient funding for an established investigator to make meaningful progress on an important research area on our priority list. A successful grant would allow the investigator to develop sufficient pilot data to pursue sustained funding through the NIH or another granting agency. Our 2011 RFA focused on the dynamics of Cerebrospinal Fluid (CSF) in the hopes of finding a mechanism to regulate its production or resorption to relieve intracranial pressure that is common with hydrocephalus.

Established Investigator Grantees

Year	Grant	Institution	Title	Investigator	Amount
2012	Request for Applications	University of Toronto	Hydrocephalus and lymphatic cerebrospinal fluid absorption (Basic)	Miles Johnston, BSc, PhD	\$ 83,000
2012 - 2013	Request for Applications	University of Utah	Novel neurobiological interventions for the treatment of hydrocephalus (Basic)	Pat McAllister, PhD	\$ 317,000

Outcomes and Measurements of Success



Research only benefits our constituents if it produces better outcomes – improved treatments, improved quality of life, better therapeutic interventions and, eventually, cures and prevention. These outcomes occur through a lengthy and careful process of research dissemination, adoption of evidence-based practice by practitioners, testing of new inventions through randomized control trials, approval of new technologies and therapies by the FDA, and circulation and distribution to patients with hydrocephalus.

The engine driving this process is career development, training, collaboration and the very critical step of public research funding. It is a very difficult funding environment for all investigators, especially young investigators, so we must take a long-term perspective. In the early phases of our Research Initiative, HA is measuring success based on career development and the number of research grants made by NIH. In the long term, the Association will follow all phases of these grants – HA's grants as well as subsequent NIH grants -- through to publication of research outcomes, and will track adoption of improved treatments and the approval of therapeutic interventions by the FDA. Ultimately, HA will measure quality of life of our constituents as the end goal of all research programs.

Early returns on HA's Research Initiative show promise. Three of the Mentored Young Investigators have gone on to apply for NIH grants (both career development and research grants) and four additional grants being developed though not yet submitted. HA-funded research has resulted in 20 presentations at professional meetings, four publications in peer reviewed journals and an additional three manuscripts have been submitted for publication. Evidence produced and disseminated by HA's research partners at HCRN has reduced post-surgical shunt infections by more than 35% across their institutions. We are encouraged to report that more than 20 medical institutions have requested this protocol to reduce shunt infections. If this protocol were adopted nationwide, we estimate that there would be 2500 fewer infections related to shunt surgeries, and a savings of \$74 million, over a five year period alone.



The Horizon

The current economic environment has proved challenging to all those interested in seeing an expansion of research around diseases, chronic conditions and rare disorders. As public policy makers in the United States wrestle with burgeoning health care costs and the need to increase patient safety, there is a compelling argument to be made for fostering research around hydrocephalus. Better, safer treatments hold the promise of fewer complications and shunt revisions – and subsequently less recurring costs for medical interventions.

Equally promising, recent advances in the study of genomics have the potential to turn upside-down the current model for the delivery of healthcare. When a simple and inexpensive gene test can provide to a medical practitioner and the patient some previously-unavailable information about the likelihood of a set of symptoms being associated with a condition, then the world of diagnostic testing as we know it today will be forever changed.

As already noted, an increase in research on hydrocephalus was a cause for hope for the hydrocephalus community but has been dampened by recent declines in public funding. The prior increase only happened because the hydrocephalus community joined forces to make sure it happened. In an era of diminishing federal budgets and dwindling foundation grants, it is all the more important that the patient community redouble its efforts to motivate public policy makers to commit scarce resources to improving the standard of care and knowledge base around hydrocephalus. The Hydrocephalus Association stands committed to lead that effort on behalf of hydrocephalus patients, no matter their age, wherever they might be.

You Can Help

We have donor opportunities at many financial levels. Your investment will make a direct impact on moving us closer to the day when we can proudly say we've eliminated the challenges of hydrocephalus!

To learn more about how you can help, contact the Hydrocephalus Association's development office at 888-598-3789 .



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