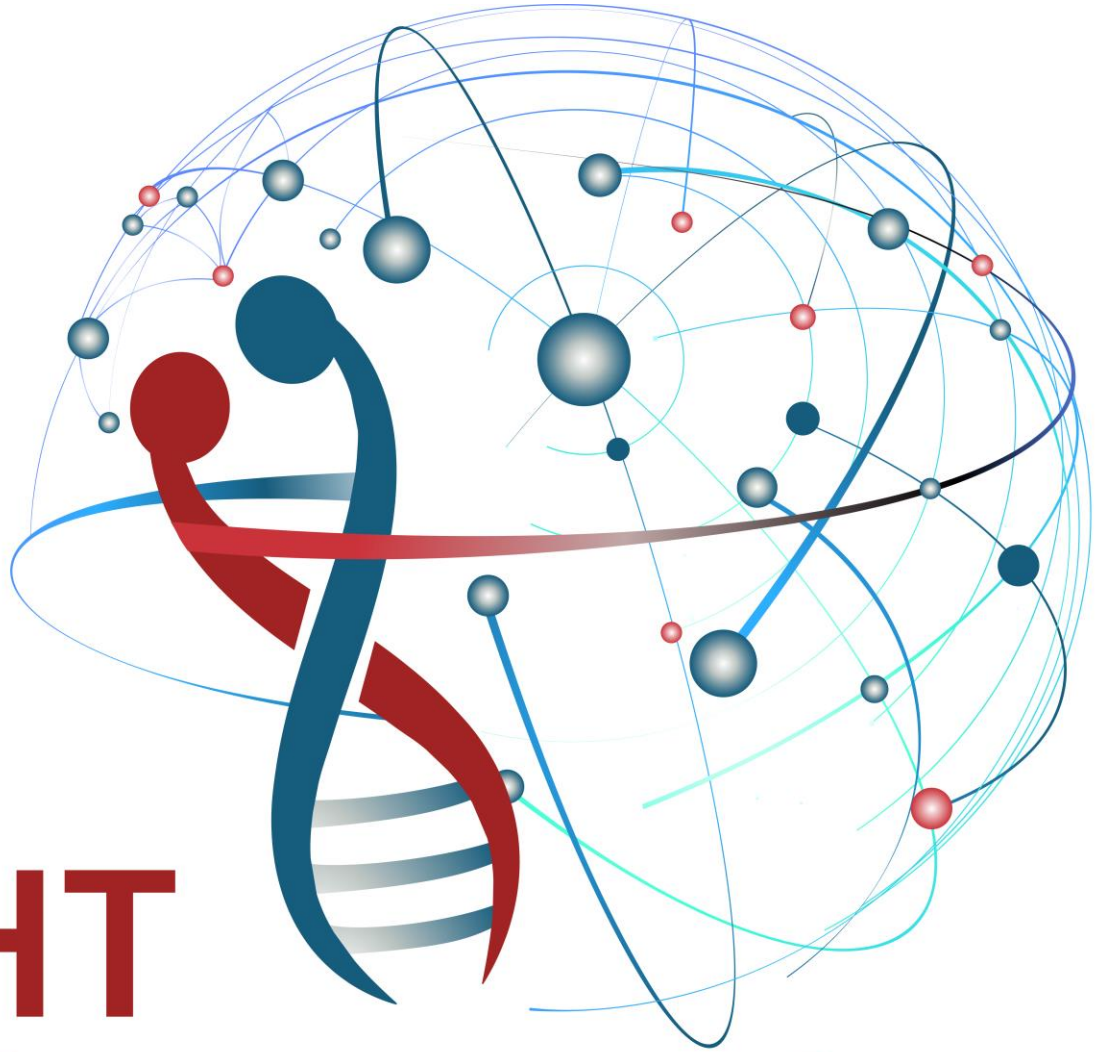


CURE HHT RESEARCH NETWORK

Overview of the Cure HHT Research Network (CHRN)

- Launched in 2020
- CHRN is a patient-led, collaborative research network that encourages the sharing of ideas among patients, scientists, and physicians.
- Aims to bring safe, effective treatments to patients more quickly by prioritizing research based on patient needs, broadening the HHT scientific community, encouraging global collaboration, and facilitating HHT research.

Goals of the Patient-Driven Research Network

1. Establish a large, collaborative scientific and patient community
   - Encourage and facilitate collaborations between basic scientists and clinicians
   - Promote data sharing and sample sharing
   - Expand to underserved areas
2. Incorporate the patient voice to drive basic science research and ultimately clinical outcomes
3. Develop approved treatments for HHT

Prioritizing and Driving HHT Research: An iterative process

1. Review the current state of HHT research (clinical and basic science)
2. Identify gaps in research (from perspective of patients, clinicians, and researchers)
3. Prioritize most important next steps in research
4. Identify best professionals to pursue prioritized research (both inside and outside HHT community)

Expected Outcomes of the CHRN

- Community participation (meeting attendance; project participation; forum participation)
- Collaboration between basic scientists and clinicians (moving experimental drugs into the clinic; sample sharing) and patients with HHT
- Shared research tools are established (biobank; shared data repository; e-PRO tool; quality of life tool)
- Approved therapies are developed
- Patient priorities are addressed and met

The first project of the CHRN: Creating a Research Roadmap

Objectives

- Identify patient outcomes priorities that are most important to patients
- Identify HHT research that is most important from perspective of patients, clinicians, and scientists, respectively
- Bring together patients, clinicians, and scientists to discuss patient outcomes, the state of HHT science, and the future of HHT research
- Bring together patients, clinicians, and scientists to prioritize HHT research that can contribute toward improvement of the patient outcomes that are most important to patients

Methods

1. Survey the HHT communities at large to identify priority topics areas/gaps in knowledge
2. Host virtual workshops to discuss identified topic areas
3. Host in-person working meeting (with alternative virtual streaming option) to prioritize research topics and establish an HHT Research Roadmap

Accomplishments of the CHRN

- ✓ Established an Executive Team to set goals and milestones
- ✓ Created and disseminated surveys to identify gaps in knowledge and resources and identify opportunities for collaboration and support
- ✓ Established workstream topics based on survey results
- ✓ Recruited a diverse team of basic scientists, clinicians, patients and outside experts to participate in Workstreams aimed at establishment of research priorities
- ✓ Identified a date & location for the Cure HHT Research Network International Conference: March 19-20, 2022, Boston, MA
- ✓ Established online Research Forum Hub for repository of documents and intrateam collaboration and communications

Survey Results

Patient Perspective on HHT Research Gaps

- 49 Question Survey was created by Cure HHT and distributed to the community
- 1204 HHT patients and caregivers answered
- Survey topics:
  - History of HHT (symptoms, age of onset, treatments received, personal view of treatment success, quality of life)
- Opinion of research/knowledge gaps in HHT
  - Barriers to access of care for HHT

Survey: HHT Patients

- A cure
- Stop nose bleeding completely
- Women's issues (uterine bleeding, pregnancy, hormones)
- Gene therapy
- Dietary impacts on HHT severity
- Improve quality of life

EDUCATION FOR HEALTHCARE PROVIDERS ABOUT HHT

Survey: HHT Scientists

- 17 Question Survey was created by Cure HHT and distributed to the community
- 42 HHT scientists answered
- Survey topics:
  - Area of HHT research
  - Barriers to achieve more successful research (lack of collaboration, lack of resources, etc.)
  - Perceived gaps in HHT research to improve patient outcomes
  - Ability to share/collaborate with other scientists and clinicians

Scientists identify several areas with knowledge gaps (ranked order)

- Mechanistic basis for fragile vessels/differences in propensity to bleed in different vascular beds
- Preclinical models for drug discovery
- Cellular origins of AVMs
- Role of hemodynamic force in AVM development
- BMP/ALK1/ENG signaling

- Cellular origins of AVMs
- Role of hemodynamic force in AVM development
- Genetic and epigenetic mechanisms of disease (including genetic modifiers of disease)
- Biomarkers of disease
- Other signaling pathways: VEGF, PI3K/AKT/mTOR, ANG/TIE2
- Environmental modifiers of disease
- Utility of patient-derived iPSC lines
- Genotype/phenotype correlations

Scientist survey results

Scientists agree HHT research needs:

- Biobank or access to patient samples
- Better imaging techniques
- Bioinformatics support
- More funding
- More collaboration with clinicians
- Better models of disease

Survey: HHT Clinicians

- 25 Question Survey was created by Cure HHT and distributed to the community
- 96 HHT clinicians answered
- Survey topics:
  - Perceived gaps in HHT research to improve patient outcomes
  - Collaborative ability/status among HHT Centers of Excellence
  - Patient priority areas to improve outcomes
  - Views on Curacao criteria for diagnosing HHT

Clinician Survey Responses

60% of clinicians say office management of epistaxis is a top area needing more research to achieve a positive impact on HHT patient outcomes

The second area of research need to achieve better patient outcomes is in standardization of protocols for management of anemia

- 96 Clinicians surveyed
- 65% located in US
- 57% treat at an HHT COE

CURE HHT RESEARCHNETWORK

Clinicians rank top areas of HHT research focus areas needed to impact clinical outcomes with little consensus

1. HHT signaling pathways
2. Impact of HHT genotype on response to therapeutic agents
3. Pathophysiological basis for HHT-1 & HHT-2 phenotypic differences
4. Genotype-phenotype correlation
5. Phenotypic mimics of HHT
6. Pathophysiological basis for ‘classic’ HHT findings in patients with negative HHT gene testing

Clinician survey results

Based on Survey Results:

7 Topic Areas were developed as a guideline for discussion

1. Bleeding
2. AVM Progression
3. Drug Therapies/Discovery
4. Unresolved Topics in Lung AVMs
5. Genetic Considerations in HHT Diagnosis
6. Somatic Mutations and Genetic Mechanisms of Disease
7. Unresolved Topics in Brain AVMs

Each topic represents a Workstream of dedicated clinicians, scientists, and patient leaders who work within the topic areas to understand the landscape of each problem and find opportunities to study these topics to impact HHT patients

Workstreams

Work Stream 1: Bleeding

Co-Chairs: Franck Lebrin PhD, Raj Kasthuri MD, Hanny Al-Samkari MD

- **Problem Statement:**
  - Individual HHT patients have a wide disparity in bleeding severity without obvious explanations.
  - Tools are missing to measure severity and response to therapy.

- **Subtopics:**
  - Understanding factors that influence epistaxis (frequency, severity, variation between patients; nasal airflow and nasal inflammation)
  - Understanding GI bleeding severity amongst patients

Work Stream 2: AVM Progression

Co-Chairs: Paul Oh PhD, Kevin Whitehead MD

- **Problem Statement:**
  - Natural history and the factors influencing growth and development of AVMs is unknown
  - Tools are missing to measure growth and response (routine imaging sensitivity may not be sufficient to measure in real-time)

- **Subtopics:**
  - Mechanistic basis of telangiectasia/AVM enlargement over life (disease progression with age)
  - Predicting liver VM progression and shunt progression (factors leading to high output heart failure)

Work Stream 3: Drug Therapies/Drug Discovery

Co-Chairs:Phillipe Marambaud PhD, Christine Mummery PhD, Vivek Iyer MD

- **Problem Statement:**
  - There are no FDA approved therapies for HHT patients

- **Subtopics:**
  - Resistance to anti-angiogenics
  - Enhancing BMP/ENG/ALK1 signaling
  - Drug repurposing and high throughput screening

Work Stream 4: Unresolved Topics in Lung AVMs

Co-Leaders: Marie Faughnan MD MMSc, Miles Conrad MD

- **Problem Statement:**
  - There is little information on effective treatments to prevent complications of diffuse pulmonary AVMs
  - There is a need to understand determinants of PAVM complications
  - Pathophysiology and risk factors for embolic complications (migraines with aura; infections; stroke)

- **Subtopics:**
  - Diffuse PAVMs
  - Mechanisms and research pathway to better understand the embolic potential of PAVMs

Work Stream 5: Genetic Considerations and HHT Diagnosis

Co-Chairs: Mikka Vikulla PhD, Jamie McDonald MS LGC

- **Problem Statement:**
  - There is a significant proportion of HHT patients in whom we cannot confirm genetic diagnosis

- **Subtopics:**
  - Noncoding variants in known HHT genes versus new genes
  - Updating Curacao diagnostic criteria (improve criteria; to include genetic testing)
  - Clinical manifestations of HHT with negative genetic testing and HHT-like syndromes

Work Stream 6: Somatic Mutations and Genetic Mechanisms of Disease

Chair: Doug Marchuk PhD

- **Problem Statement:**
  - There is a need to understand the balance between primary and any secondary mutations that contribute to the HHT phenotype

- **Subtopics:**
  - Role of somatic mutations in visceral organ involvement (how does this role vary between organs?)
  - Mosaicism in AVMs

Work Stream 7: Unresolved Topics in Brain AVMs

Co-*Chairs:Helen Kim MPH PhD, Steve Hetts MD, Timo Krings MD PhD FRCS*

- **Problem Statement:**
  - There is insufficient knowledge/information available to classify brain VMs as high risk vs low risk, to identify those who need preventive treatment
  - Could there be a role for medical therapy for brain VMs
- **Subtopics:**
  - Risk factors of intracranial hemorrhage and other brain outcomes
  - Outcomes of endovascular, radiotherapy and radiotherapy in HHT
  - Determine lifetime protocols

Workstream Members Commitment

Preconference

- Review and summarize the current state of research in the topic area
- Identify research priorities and opportunities based on evidence or lack of evidence
- Generate a prioritized list of research/research questions within the topic area by order of impact, importance, feasibility, and rational order [Zuccatto et al., 2019]

Workstream Process

- Zoom meetings twice per month for 1 hour
- Co-Leaders from each group will lead team and process
- Hara Levy, MD MMsc, Chris Hughes PhD, Beth Roman PhD, and Vivek Iyer MD will provide facilitation assistance for each group
- Schedule first meeting by November 23rd, 2021
- Define process and determine assignments for each team member

Workstream Outcome

Develop a plan that includes the areas of consensus, areas that lack evidence or data, and a path forward to address the gaps in scientific understanding of their specific topic within HHT research.

All workstreams come together to build a **Research Roadmap** to drive HHT research.

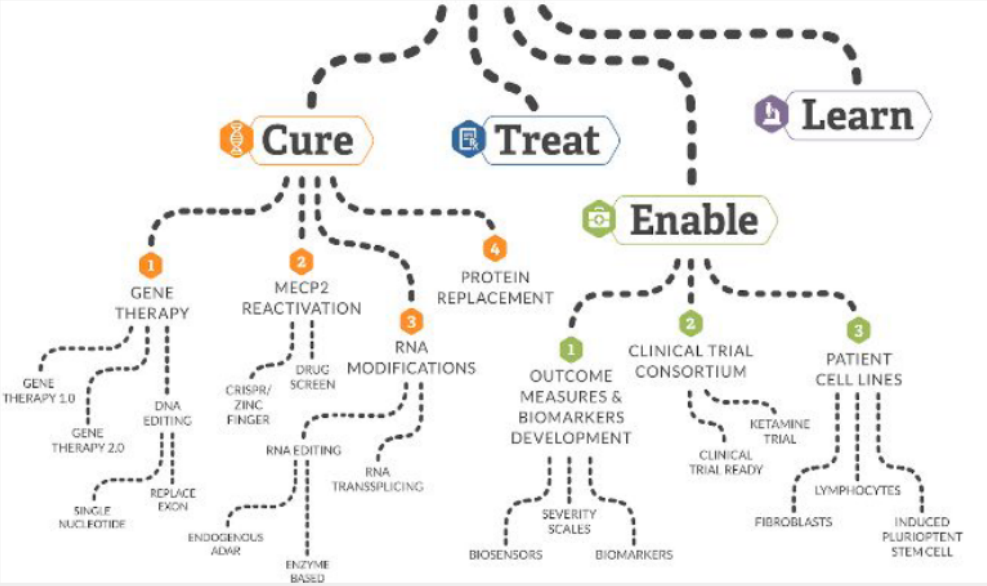
Workstream Members Commitment

Conference (in-person) with your workstream group

- Each workstream will arrive with a final draft of prioritized research gaps with recommendations for:
  - research questions to be addressed
  - tools needed
  - suggested collaborations/consortia
  - funding needed
  - timeline
- Each workstream will present their specific recommendations of research priorities
- The entire group will come to consensus on top research priorities
- Priorities will be fitted to a Research Strategic Roadmap that will be used to guide development of RFAs funded by Cure HHT and advocated by Cure HHT to NIH, DOD and private foundations

EXAMPLE OF RESEARCH ROADMAP GENERATION

A framework for understanding the research landscape, gaps, generating a roadmap



Learn	Patients and Families - Disease Journey, Unmet Needs Clinicians - Diagnosis and Treatment Researchers - State of discovery, translational, clinical research
Enable	Where are the gaps across the continuum How can patient groups enable the bridging of those gaps
Treat	Are there current treatments? How can they be improved? Leveraged? How are current treatments approved? How does this need to be modified?
Cure	What is the state of R&D towards the mechanism of the disease?

https://reverserett.org/cure/

rett syndrome research trust

Slide from CZI presentation.

Framework/image developed by rett syndrome research trust.

Long-Term Goals

- Develop robust HHT research collaborations for funding & investment
- Establish research tools (biobank, tissue repository, shared data repository, e-PRO tool, quality of life tool)
- Gain approval for new and effective therapies from the FDA
- Expand the Cure HHT footprint into large underserved populations in South and Central America, Asia-China and India and Africa

Next Steps

- Register on www.HHThub.org
- Set meeting schedule twice per month via Zoom
- Assign group responsibilities
- Complete workstream milestones
  - Summarize current state of science per topic area
  - Identify and prioritize gaps in knowledge and/or research opportunities
  - Attend in person meeting to gain consensus of priorities, build research roadmap and timeline

- Preview Research Hub