2023

CURE CADASIL ANNUAL REPORT

HIGHLIGHTS – JANUARY 1, 2023 TO DECEMBER 31, 2023

CONTENTS

WHO WE ARE

Cure CADASIL is a 501(C)3 nonprofit organization incorporated in the US state or New Jersey. Our Board of Trustees are all volunteers who have CADASIL, or relatives and/or close personal ties to CADASIL.

Bertram Kasiske, President
Jane Gunther, Past-President & Science Officer
Debra Robinson, Treasurer
Pedro de Lencastre, Secretary
Sandra Talbird, Trustee
Vinita Bahl, Trustee

OUR VISION:

A world without CADASIL.

OUR MISSION:

Cure CADASIL is a patient-led organization committed to advancing CADASIL research through uniting patients, researchers, and clinicians to find a cure for CADASIL.

On March 6, 2024, the Cure CADASIL Board of Trustees approved a Strategic Plan for 2024 – 2026. Our Strategic Plan is significantly impacted by the Chan Zuckerberg Initiative grant awarded to Cure CADASIL in November of 2022, with funding through 2026 (see Financials page 14).

CZI PPC RARE NEURODEGENERATIVE DISEASES GRANT

Chan
Zuckerberg
Initiative

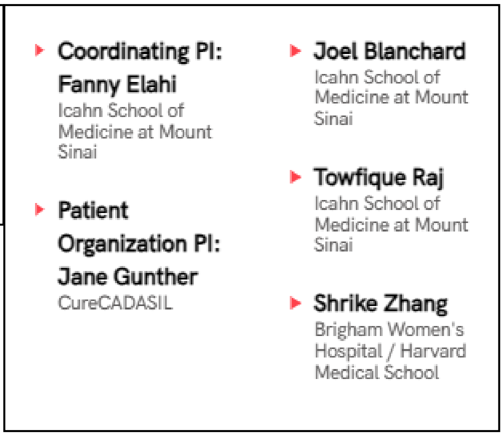
Patient-Partnered Collaborations for Rare Neurodegenerative Disease RFA Grantees

CZI invited applications from collaborative teams bringing together patient-led rare disease organizations and research teams for four-year research projects aimed at advancing our understanding of the fundamental biology underlying rare diseases. The Patient-Partnered Collaborations for Rare Neurodegenerative Disease RFA aims to advance the understanding of the pathophysiology and mechanistic underpinnings of rare neurodegenerative and neurological disorders. Patients are centered in this work. Each team is led by a Coordinating Primary Investigator (PI) and Patient Organization PI.

There were 5 grants awarded in 2022 and Cure CADASIL, teamed up with Mount Sinai, was fortunate to be awarded one of these grants.

CADASIL-centered Modeling of Immunovascular Neurodegenerative Disease

to reverse engineer CADASIL to discover therapeutic molecular targets using stem cell technologies in a deeply phenotyped cohort of patients



- **Coordinating PI: Fanny Elahi**
  Icahn School of Medicine at Mount Sinai
- **Patient Organization PI: Jane Gunther**
  CureCADASIL
- **Joel Blanchard**
  Icahn School of Medicine at Mount Sinai
- **Towfique Raj**
  Icahn School of Medicine at Mount Sinai
- **Shrike Zhang**
  Brigham Women's Hospital / Harvard Medical School

CZI NEURODEGENERATION CHALLENGE NETWORK MEETING

Co-PI's Fanny Elahi, MD, PhD, Mount Sinai and Jane Gunther, PhD, DABT, Cure CADASIL.

CZI offers a number of webinars and meetings that allow awardees to interact and learn from each other. One such meeting was held for investigators of grant recipients June 5-9, 2023, in San Diego, CA. The fifth annual meeting of the Neurodegeneration Challenge Network brought together (NDCN) 195 participants including NDCN investigators, collaborators, partners, alumni, project affiliates (students, postdocs, and staff scientists), and CZI program and Chan Zuckerberg Biohub staff. This 3.5-day event held in San Diego, California included a pre-meeting with two technology-focused tracks for investigators working on genetic engineering technologies, and advanced computational tools for neuroscience. The general meeting highlighted the strong collaborative spirit of the NDCN community through investigator talks and discussion, a panel highlighting the Network's patient-partnered research, a keynote on global science, and lightning talks and poster sessions aimed at providing an opportunity for NDCN trainees to present and network.

2023
5-9
JUN

Neurodegeneration Challenge Network 2023 Annual Meeting

Participants at CZI's Neurodegeneration Challenge Network 2023 Annual Meeting

DATE:
June 5-9, 2023

LOCATION:
Mission Bay Hotel, San Diego, CA

PROGRAM:
Neurodegeneration Challenge Network →

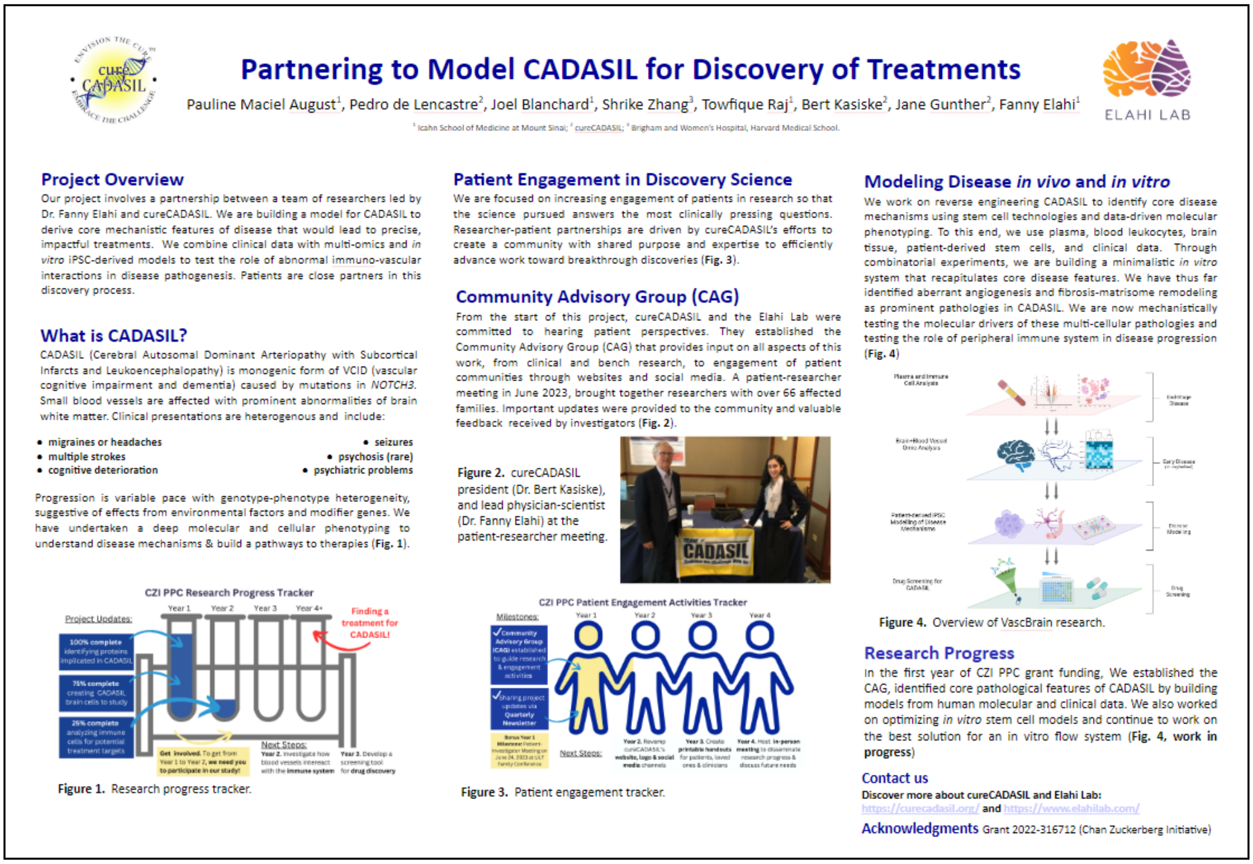
TYPE:
Investigator Meeting

CZI Science in Society Meeting

Newport Beach, CA, September 20-23, 2023

The CZI Science in Society Meeting is an annual event that brings together patient communities, scientists, policymakers, advocates, and philanthropic partners to foster meaningful integration of science and society. The meeting aims to support patient-driven research in rare diseases and to build public trust in science.

The meeting was attended by Pedro de Lencastre, in person, and Jane Gunther, virtually, representing Cure CADASIL. In addition, our research investigators team was represented by Pauline Maciel August, Icahn School of Medicine, Mount Sinai, New York.



Partnering to Model CADASIL for Discovery of Treatments

Pauline Maciel August[1], Pedro de Lencastre[2], Joel Blanchard[1], Shrike Zhang[3], Towfique Raj[1], Bert Kasiske[2], Jane Gunther[2], Fanny Elahi[1]

[1] Icahn School of Medicine at Mount Sinai; [2] cureCADASIL; [3] Brigham and Women's Hospital, Harvard Medical School.

Project Overview

Our project involves a partnership between a team of researchers led by Dr. Fanny Elahi and cureCADASIL. We are building a model for CADASIL to derive core mechanistic features of disease that would lead to precise, impactful treatments. We combine clinical data with multi-omics and *in vitro* iPSC-derived models to test the role of abnormal immuno-vascular interactions in disease pathogenesis. Patients are close partners in this discovery process.

What is CADASIL?

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is monogenic form of VCID (vascular cognitive impairment and dementia) caused by mutations in *NOTCH3*. Small blood vessels are affected with prominent abnormalities of brain white matter. Clinical presentations are heterogenous and include:

- **migraines or headaches**
- **multiple strokes**
- **cognitive deterioration**
- **seizures**
- **psychosis (rare)**
- **psychiatric problems**

Progression is variable pace with genotype-phenotype heterogeneity, suggestive of effects from environmental factors and modifier genes. We have undertaken a deep molecular and cellular phenotyping to understand disease mechanisms & build a pathways to therapies (**Fig. 1**).

Figure 1. Research progress tracker.

Patient Engagement in Discovery Science

We are focused on increasing engagement of patients in research so that the science pursued answers the most clinically pressing questions. Researcher-patient partnerships are driven by cureCADASIL's efforts to create a community with shared purpose and expertise to efficiently advance work toward breakthrough discoveries (**Fig. 3**).

Community Advisory Group (CAG)

From the start of this project, cureCADASIL and the Elahi Lab were committed to hearing patient perspectives. They established the Community Advisory Group (CAG) that provides input on all aspects of this work, from clinical and bench research, to engagement of patient communities through websites and social media. A patient-researcher meeting in June 2023, brought together researchers with over 66 affected families. Important updates were provided to the community and valuable feedback received by investigators (**Fig. 2**).

Figure 2. cureCADASIL president (Dr. Bert Kasiske), and lead physician-scientist (Dr. Fanny Elahi) at the patient-researcher meeting.

Figure 3. Patient engagement tracker.

Modeling Disease *in vivo* and *in vitro*

We work on reverse engineering CADASIL to identify core disease mechanisms using stem cell technologies and data-driven molecular phenotyping. To this end, we use plasma, blood leukocytes, brain tissue, patient-derived stem cells, and clinical data. Through combinatorial experiments, we are building a minimalistic *in vitro* system that recapitulates core disease features. We have thus far identified aberrant angiogenesis and fibrosis-matrisome remodeling as prominent pathologies in CADASIL. We are now mechanistically testing the molecular drivers of these multi-cellular pathologies and testing the role of peripheral immune system in disease progression (**Fig. 4**)

Figure 4. Overview of VascBrain research.

Research Progress

In the first year of CZI PPC grant funding, We established the CAG, identified core pathological features of CADASIL by building models from human molecular and clinical data. We also worked on optimizing *in vitro* stem cell models and continue to work on the best solution for an in vitro flow system (**Fig. 4, work in progress**)

Contact us

Discover more about cureCADASIL and Elahi Lab:
https://curecadasil.org/ **and** https://www.elahilab.com/

Acknowledgments Grant 2022-316712 (Chan Zuckerberg Initiative)

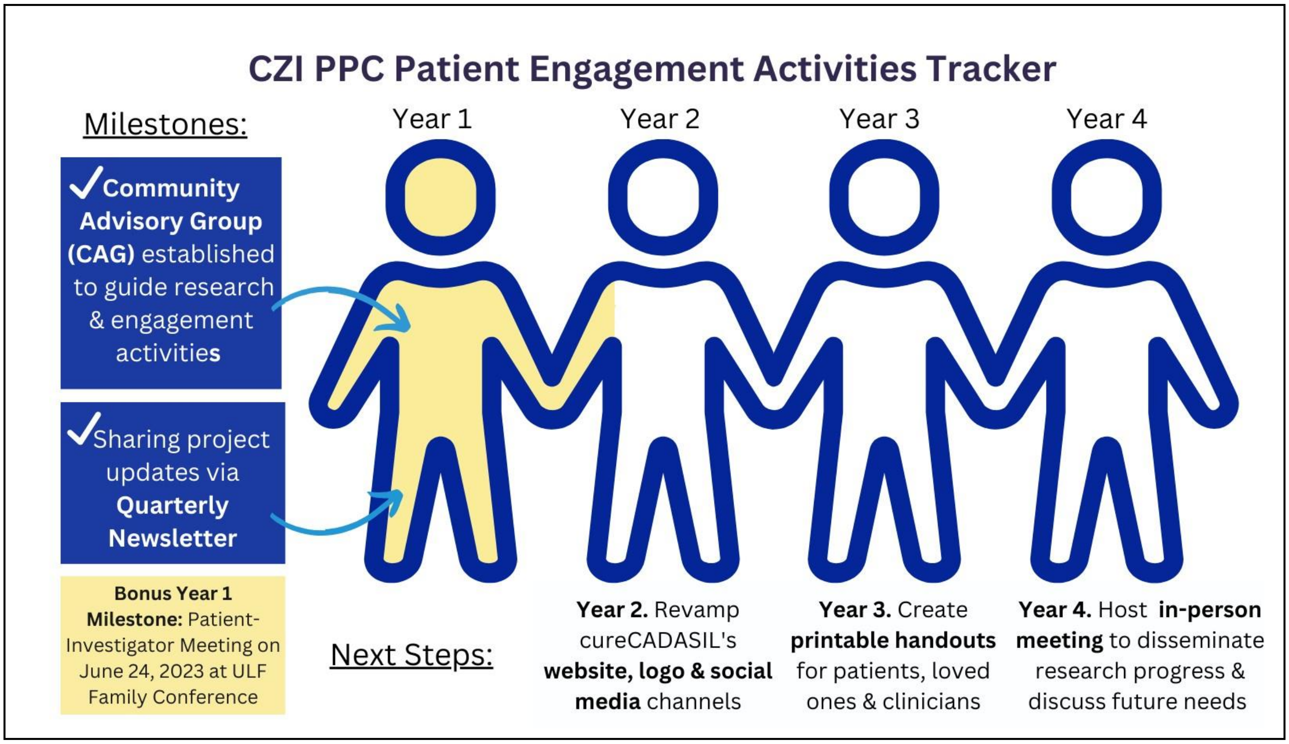
Cure CADASIL will continue to support the CZI grant initiative by helping to recruit patients, and provide a patient perspective for the investigators.

We need your help!

Join Our Study and Help Us Find a Cure for CADASIL!

cureCADASIL is collaborating with Dr. Fanny Elahi and a team of researchers to identify therapeutic targets for CADASIL

We are ahead of schedule! Many of the goals our organization set for this project have already been met. But the major challenge continues to be recruiting patients.



CZI PPC Patient Engagement Activities Tracker

Milestones:

✓**Community Advisory Group (CAG)** established to guide research & engagement activities

✓Sharing project updates via **Quarterly Newsletter**

Bonus Year 1 Milestone: Patient-Investigator Meeting on June 24, 2023 at ULF Family Conference

Next Steps:

Year 2. Revamp cureCADASIL's **website, logo & social media** channels

Year 3. Create **printable handouts** for patients, loved ones & clinicians

Year 4. Host **in-person meeting** to disseminate research progress & discuss future needs

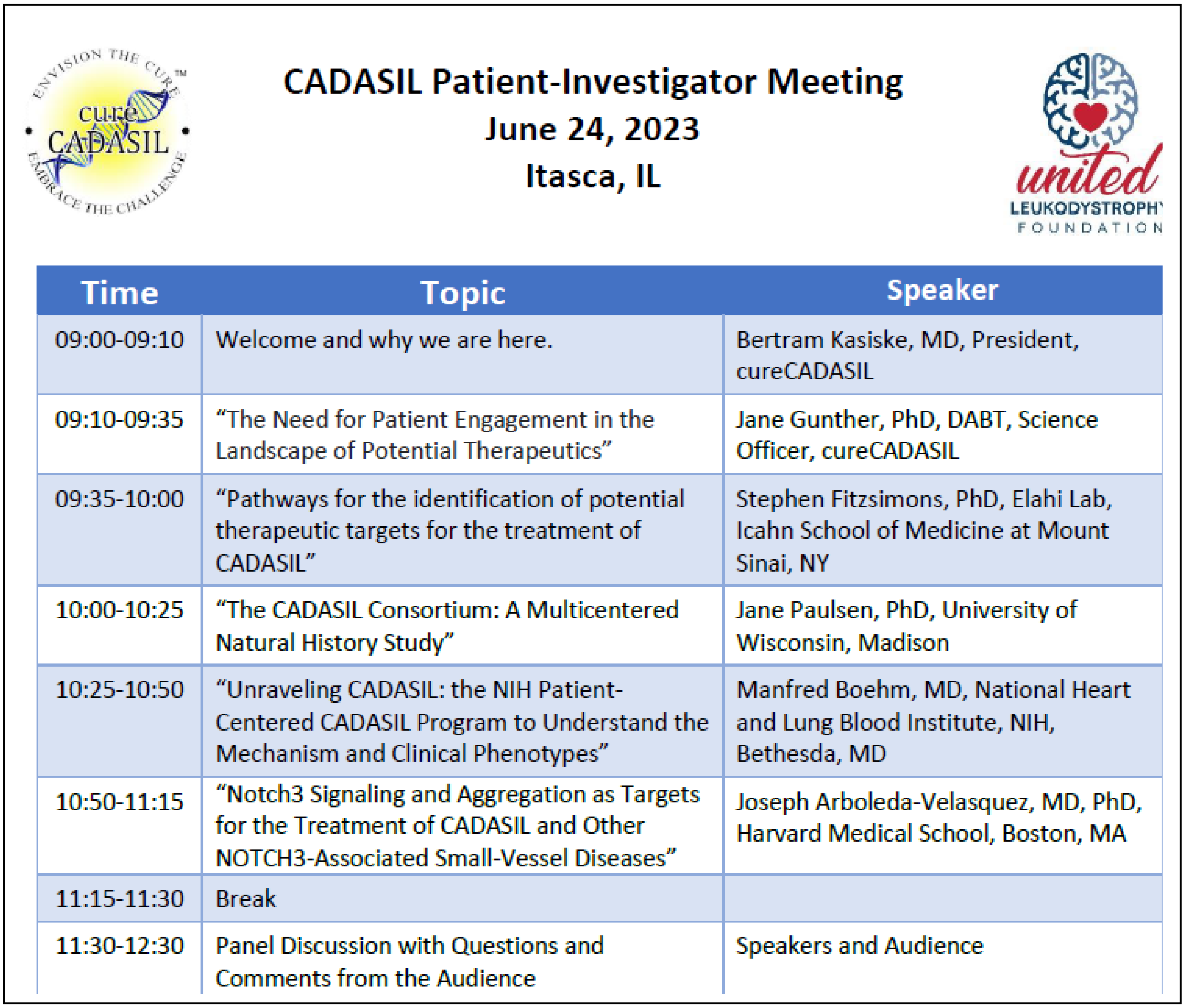
One of the Cure CADASIL goals for our CZI grant was to hold a Patient-Investigator Meeting. We did this by having a meeting held during the annual United Leukodystrophy Foundation’s Science Symposium & Family Conference, June 24, 2023, in Itasca, IL.

PATIENT-INVESTIGATOR MEETING 2023

UNITED LEUKODYSTROPHY FOUNDATION

Presents

2023 ULF Scientific Symposium & Family Conference

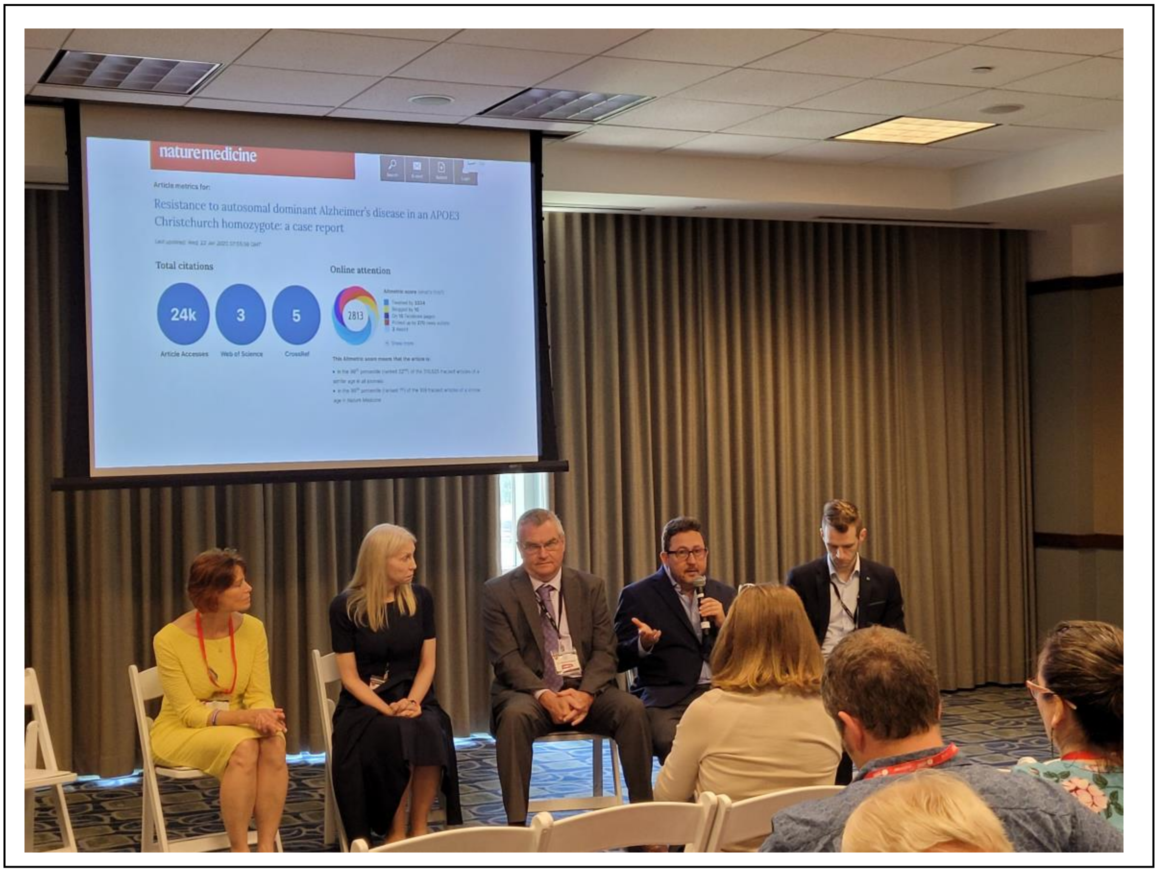


CADASIL Patient-Investigator Meeting

June 24, 2023

Itasca, IL

Time	Topic	Speaker
09:00-09:10	Welcome and why we are here.	Bertram Kasiske, MD, President, cureCADASIL
09:10-09:35	"The Need for Patient Engagement in the Landscape of Potential Therapeutics"	Jane Gunther, PhD, DABT, Science Officer, cureCADASIL
09:35-10:00	"Pathways for the identification of potential therapeutic targets for the treatment of CADASIL"	Stephen Fitzsimons, PhD, Elahi Lab, Icahn School of Medicine at Mount Sinai, NY
10:00-10:25	"The CADASIL Consortium: A Multicentered Natural History Study"	Jane Paulsen, PhD, University of Wisconsin, Madison
10:25-10:50	"Unraveling CADASIL: the NIH Patient-Centered CADASIL Program to Understand the Mechanism and Clinical Phenotypes"	Manfred Boehm, MD, National Heart and Lung Blood Institute, NIH, Bethesda, MD
10:50-11:15	"Notch3 Signaling and Aggregation as Targets for the Treatment of CADASIL and Other NOTCH3-Associated Small-Vessel Diseases"	Joseph Arboleda-Velasquez, MD, PhD, Harvard Medical School, Boston, MA
11:15-11:30	Break	
11:30-12:30	Panel Discussion with Questions and Comments from the Audience	Speakers and Audience



Panel discussion question and answer session during the Patient-Investigator meeting June 24, 2023. Shown from left to right, are Jane Gunther, Past President of Cure CADASI; Jane Paulsen, PI of the CADASIL Consortium Study; Manfred Boehm, National Heart Lung & Blood Institute; Joseph Arboleda-Velasquez, NIH Investigator from Harvard Medical School, and Stephen Fitzsimons, representing the Elahi Lab at Mt. Sinai School of Medicine CZI grant project.

From left to right: left
panel, Jane Gunther, Pedro de Lencastre, Bertram Kasiske; middle panel, Bertram Kasiske, Fanny Elahi; right panel, Jane Gunther, Fanny Elahi and Bertram Kasiske.

GLOBAL GENES MEETING SEPTEMBER 19-20, 2023

Global Genes®
Allies in Rare Disease

Arguably the most important and widely attended meeting of rare disease patient advocacy organizations is the annual Global Genes meeting. This year's meeting was held September 19-20, 2023, in San Diego, CA. Separate, parallel simultaneous sessions were designed for patients, family members, care givers and investigators. Cure CADASIL was represented by Bertram Kasiske, President, and Debra Robinson, Treasurer.

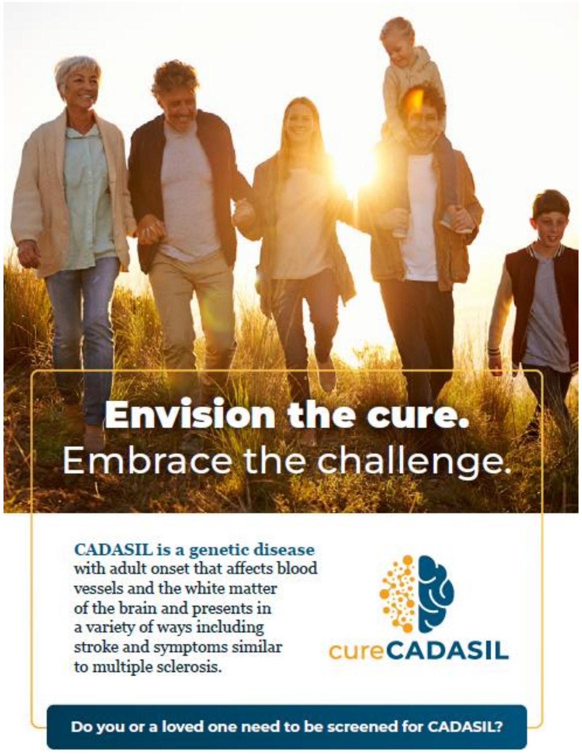
Bert Kasiske (Cure CADASIL Pres.) and Debra Robinson (Treasurer)

Left→Right are Chris Hopkins, Ray and Tracy Price, Bert and Jane Kasiske, and Debra Robinson.

Also attending and networking with other investigators was Chris Hopkins, Cure CADASIL Scientific Advisory Board member, and Ray Price a well know investigator in the rare disease community and participant in the Cure CADASIL Disease Modeling Group.

NATIONAL ORGANIZATION OF RARE DISEASES 2023

Cure CADASIL was invited by the United Leukodystrophy Foundation (ULF) to share their Table among the exhibits at the NORD meeting. Bertram Kasiske, President of Cure CADASIL joined with ULF and other patient advocacy groups meeting and networking at the ULF table during the NORD meeting. We used this opportunity to distribute the new Cure CADASIL brochure.



Envision the cure.
Embrace the challenge.

CADASIL is a genetic disease with adult onset that affects blood vessels and the white matter of the brain and presents in a variety of ways including stroke and symptoms similar to multiple sclerosis.

cureCADASIL

Do you or a loved one need to be screened for CADASIL?

To learn more about the **ongoing research studies you or your loved one can join**, see here:

Or join the cureCADASIL Family Registry to **help the medical community learn more about your and your loved ones' experience** with CADASIL.

cureCADASIL is a non-profit 501 (C)(3) organization **dedicated to CADASIL research, patients, and their families.**

cureCADASIL is a patient-led organization committed to advancing CADASIL research through uniting patients, researchers, and clinicians to find a cure for CADASIL.

We are dedicated to helping all touched by CADASIL, improving education available on CADASIL, and promote and support research for this rare disease.

Million Dollar Bike Ride Fundraiser

Once again, Cure CADASIL participated in the Orphan Disease Center’s Million Dollar Bike Ride fundraiser for research.

The 2023 Team CADASIL raised $109,856 for research.

Cure CADASIL invites recipients of the MDBR grants to present the results of research performed with the grant support. In 2023 we had two webinars describing research from the two grants awarded for the funding period Feb 1, 2022 – Jan 31, 2023.

"CADASIL vessel-on-chip for disease modeling and drug development."

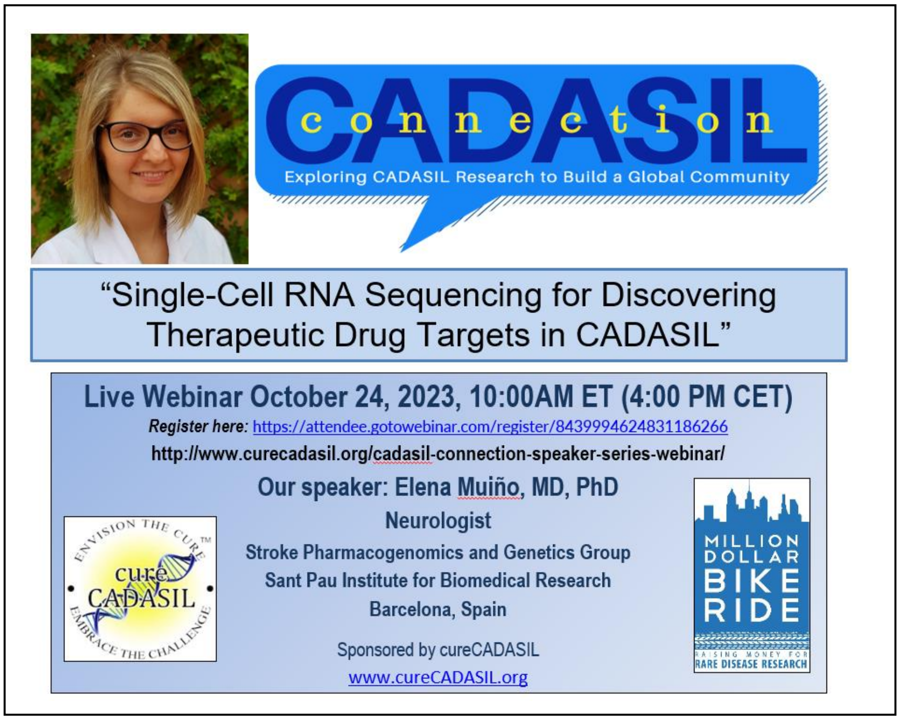
Live Webinar May 9, 2023, 10:00 ET (16:00 CET)

Register here: https://attendee.gotowebinar.com/register/8408116480666535002

http://www.curecadasil.org/cadasil-connection-speaker-series-webinar/

Our speaker: Marc Vila Cuenca, Ph.D.

Department of Anatomy and Embryology,
Leiden University Medical Center,
Leiden, The Netherlands
Sponsored by cureCADASIL
www.cureCADASIL.org



"Single-Cell RNA Sequencing for Discovering Therapeutic Drug Targets in CADASIL"

Live Webinar October 24, 2023, 10:00AM ET (4:00 PM CET)

Register here: https://attendee.gotowebinar.com/register/8439994624831186266

http://www.curecadasil.org/cadasil-connection-speaker-series-webinar/

Our speaker: Elena Muiño, MD, PhD

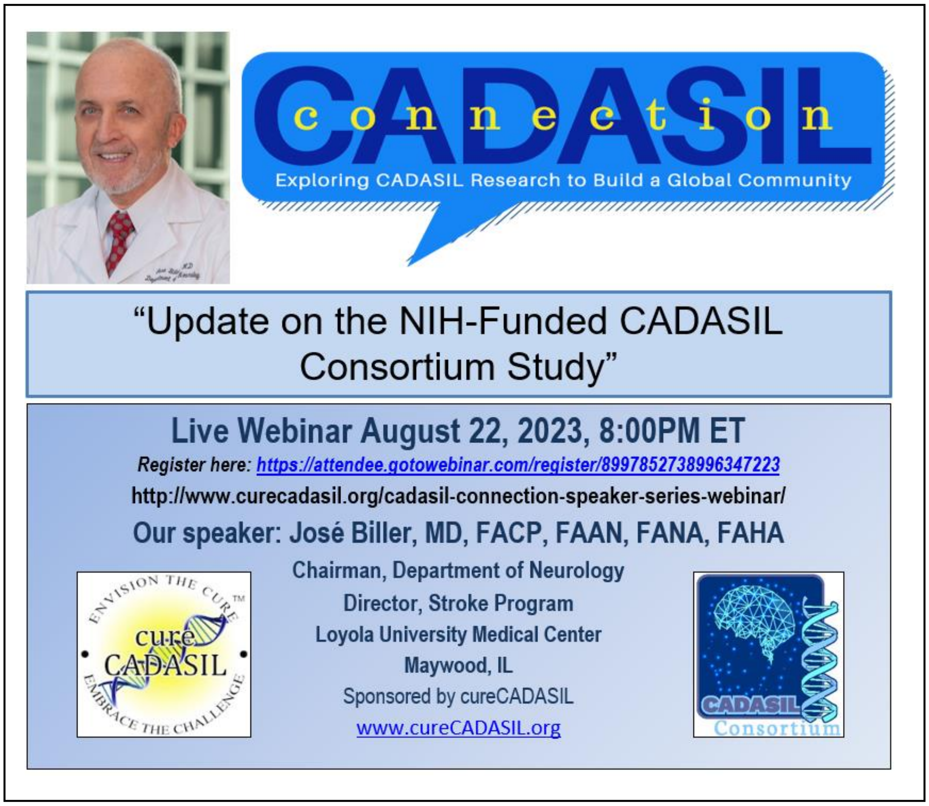
Neurologist
Stroke Pharmacogenomics and Genetics Group
Sant Pau Institute for Biomedical Research
Barcelona, Spain

Sponsored by cureCADASIL
www.cureCADASIL.org

SUPPORTING THE CADASIL CONSORTIUM STUDY

Cure CADASIL has encouraged participation in The CADASIL Consortium study (Home - CADASIL Consortium (cadasil-consortium.org)). This is a NIH-funded study with Jane Paulsen, PhD, University of Wisconsin and Michael Geschwind, MD, PhD, University of California at San Francisco, Co-PIs. There are 12 study sites in the US:

In 2023 Cure CADASIL sponsored a webinar to help encourage participation.



CADASIL connection

Exploring CADASIL Research to Build a Global Community

"Update on the NIH-Funded CADASIL Consortium Study"

Live Webinar August 22, 2023, 8:00PM ET

Register here: https://attendee.gotowebinar.com/register/8997852738996347223

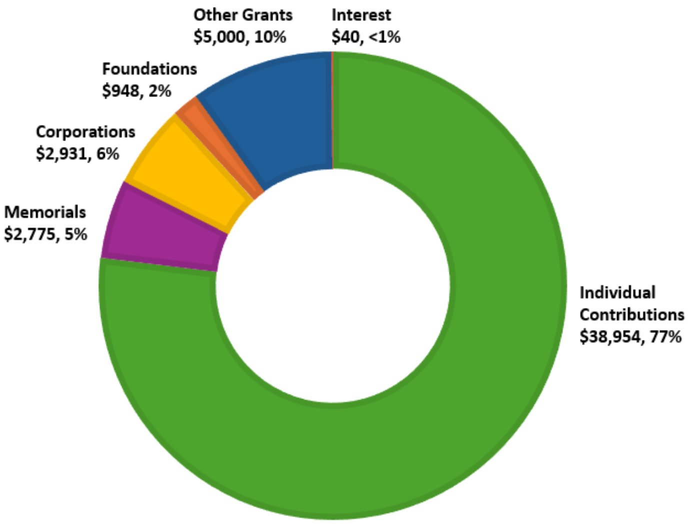
http://www.curecadasil.org/cadasil-connection-speaker-series-webinar/

Our speaker: José Biller, MD, FACP, FAAN, FANA, FAHA

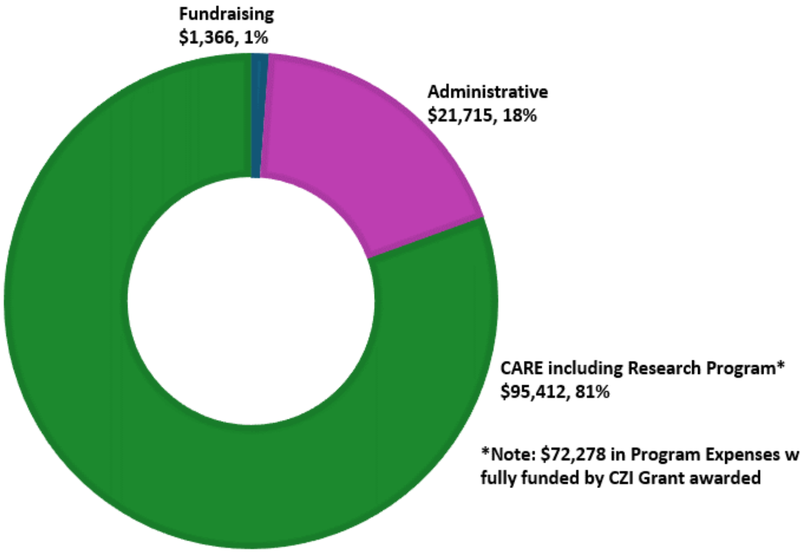
Chairman, Department of Neurology
Director, Stroke Program
Loyola University Medical Center
Maywood, IL
Sponsored by cureCADASIL
www.cureCADASIL.org

FINANCIALS

2023 CURECADASIL REVENUE BY SOURCE
TOTAL $50,649



2023 CURECADASIL EXPENSES
TOTAL $118,494



*Note: $72,278 in Program Expenses were fully funded by CZI Grant awarded

Expenses, excluding those funded by the CZI grant, were $46,216, i.e. less than the $50,649 revenue.