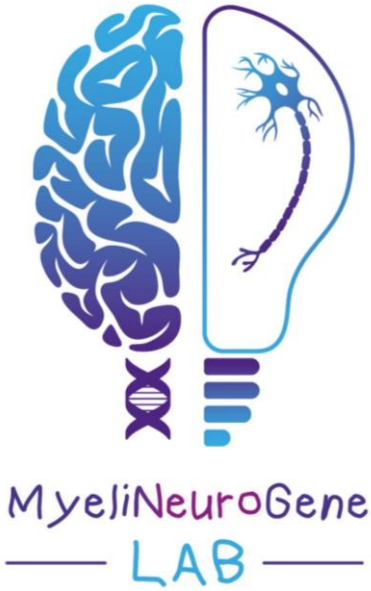
MyeliNeuroGene Lab

2023 REPORT

Dr. Geneviève Bernard



la fondation de l'hôpital de montréal pour enfants
the montreal children's hospital foundation

Dr. Geneviève Bernard

Dr. Geneviève Bernard is a pediatric neurologist and scientist at the Research Institute of the McGill University Health Centre.

Twelve years ago, Dr. Bernard established the MyeliNeuroGene lab research group and devoted herself to the study of rare neurodegenerative disorders. Within a short span of time, Dr. Bernard was recognized internationally as one of the leading experts on leukodystrophies, both in the clinic and the laboratory. Since its inception in 2011, the MyeliNeuroGene lab has pushed the rare childhood disease field forward and remains committed to unraveling the mysteries behind myelin biology and disease processes. Dr. Bernard has built a successful research program with a multitude of international and national collaborations, more than 140 published manuscripts, several consensus statements, book chapters and abstracts and has been invited as a keynote speaker at over 145 international, national, and provincial conferences.

Dr. Bernard is this year's recipient of the 2023 Pfizer Research Award of Excellence from the Montreal Children's Hospital Foundation, which recognizes a researcher from the Montreal Children's Hospital whose initiatives have made significant contributions to pediatric care. She is also this year's recipient of the Moser Service Award from the United Leukodystrophy Foundation, which recognizes outstanding service and commitment to the lives of people with leukodystrophies and their families. McGill University awarded Dr. Bernard the 2020 Maude Abbott Prize, a distinction reserved for outstanding female faculty that have excelled and demonstrated great leadership in research and the Royal College of Physicians and Surgeons named her the recipient of the 2019 Specialist of the Year Award – Regional "Prix d'Excellence".

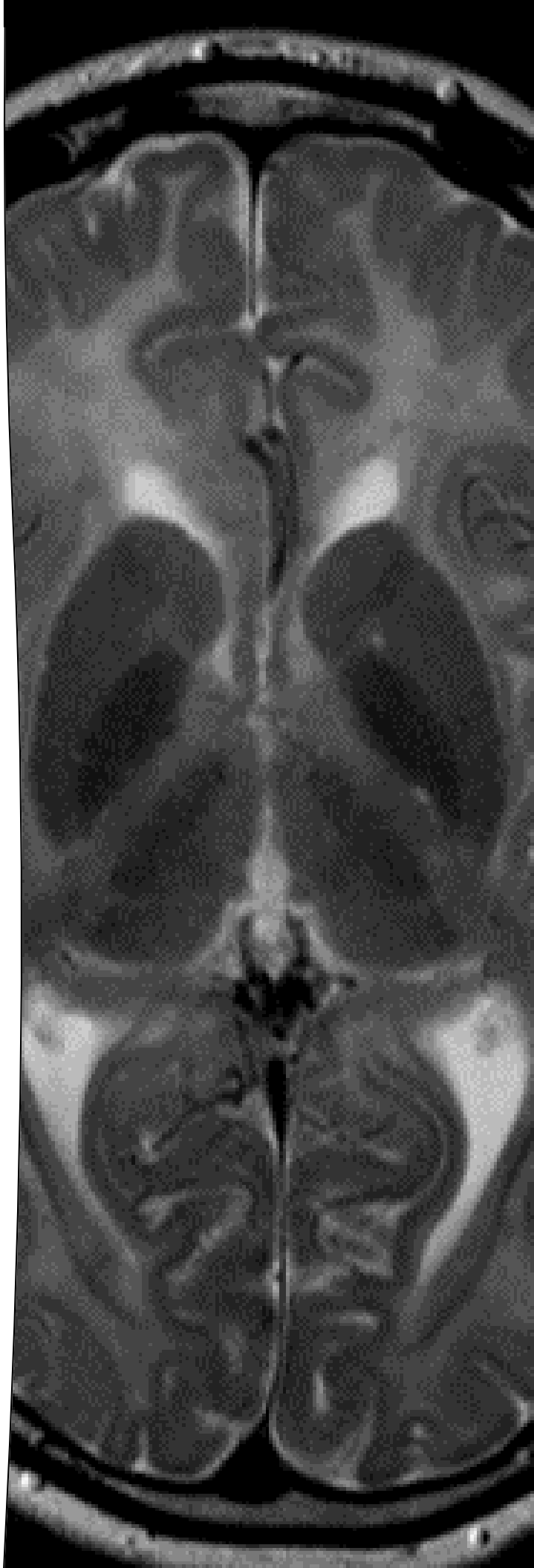
Supporting patients and their families has always been a priority for Dr. Bernard, as exemplified by her high degree of involvement in various foundations, patient advocacy groups and international consortia. Most notably, Dr. Bernard is the first woman, first Canadian and youngest individual to be selected as Chair of the Medical and Scientific Advisory Board of the United Leukodystrophy Foundation, one of the largest leukodystrophy foundations in the world, founded in 1982.

Leukodystrophies

Dr. Bernard and her MyeliNeuroGene Research team study leukodystrophies, a group of inherited white matter disorders. White matter, or myelin, is the part of the brain that insulates and protects nerve fibers. Neurons signal to each other via these nerve fibers, which can be thought of as electrical wires, and myelin acts as the coating surrounding the wire. Myelin is critical for making sure the brain can send signals to different parts of the brain, or to muscles in the body like the arms or legs. When this myelin is not present or is damaged, the brain can't send these signals as effectively.

Leukodystrophies are genetically determined disorders whereby errors (i.e., genetic variants) are inherited from parent(s) to child. While children with leukodystrophies are often born healthy, these diseases eventually cause a progressive disease and often, early death.

Leukodystrophies can be split into 2 groups - hypomyelinating (when myelin doesn't form normally during development) and non-hypomyelinating leukodystrophies (where myelination occurs normally in development, but the myelin then gets sick). While Dr. Bernard's lab investigates both categories of leukodystrophies, the main focus of the MyeliNeuroGene lab is hypomyelinating leukodystrophies. There are many kinds of leukodystrophies caused by mutations in different genes and while each form is individually rare, collectively leukodystrophies are quite common. In fact, recent estimates suggest leukodystrophies affect 1 in 4733 live births.



CLINICAL RESEARCH

Ongoing Research Projects

Qualitative study exploring the experience of parents of children with POLR3-related leukodystrophy navigating the healthcare system

- We believe that parents of children with 4H leukodystrophy experience extensive burden including time, travel and financial challenges when navigating the healthcare system
- We aim to understand the first-hand experience of parents of children with 4H leukodystrophy navigating the healthcare system

Stress and Quality of Life of Parents of Children with POLR3-related Leukodystrophy

- Caring for a child with 4H leukodystrophy can be a challenging experience
- The goal of this project is to explore the quality of life and stress of parents of children with 4H leukodystrophy

Natural History Studies of POLR3-related Leukodystrophy

- There is an urgent need to collect long-term data on disease progression in individuals with 4H to better understand the disease, provide anticipatory guidance and prepare for forthcoming clinical trials. Indeed, it is crucial to conduct natural history studies to pinpoint suitable endpoints and validate novel biomarkers to stratify patient cohorts.

Exploring the impact of rare disease support interventions for patients and their families

- This project aims to determine how support interventions, such as providing educational materials or attending a rare disease conference, may improve quality of life of patients and their families

Explore our recent publication!

We recently published our study examining craniofacial features in POLR3-related leukodystrophy in the Journal of Medical Genetics!

J Med Genet. 2023 Oct;60(10):1026-1034. doi: 10.1136/jmg-2023-109223. Epub 2023 May 16.

Craniofacial features of POLR3-related leukodystrophy caused by biallelic variants in *POLR3A*, *POLR3B* and *POLR1C*

WET LAB RESEARCH

Ongoing Research Projects

Polr1c Mouse Model Development

- Following the generation and characterization of our *Polr3b* mouse model (publication below), our lab is employing the same methods to develop a *Polr1c* mouse model

Preclinical Therapy Testing in Animal models

- This project aims to test novel therapeutics using our recently generated mouse models
- Preclinical testing of gene therapy and FDA approved drug Riluzole are already in progress!

Induced Pluripotent Stem Cell (iPSC) Disease Modeling

- Our lab has developed iPSCs from patients with POLR3- and EPRS1-related leukodystrophies
- The goal of this project is to use the patient iPSCs to generate neurological cell types such as oligodendrocytes and neurons, as well as 3D 'mini-brains' called organoids, to better understand how these disorders impact the brain

Explore our recent publications!

Our *Polr3b* mouse model was just published in the prestigious journal Brain! This is the first *Polr3b* disease model and the first POLR3-related leukodystrophy model to mimic common symptoms seen in patients.

> Brain. 2023 Aug 28:awad249. doi: 10.1093/brain/awad249. Online ahead of print.

Hypomyelination, hypodontia and craniofacial abnormalities in a Polr3b mouse model of leukodystrophy

> MethodsX. 2023 Feb 2:10:102051. doi: 10.1016/j.mex.2023.102051. eCollection 2023.

An optimized and validated protocol for the purification of PDGFRα+ oligodendrocyte precursor cells from mouse brain tissue via immunopanning

We optimized and published a protocol to isolate oligodendrocyte progenitor cells, the main cells affected in POLR3-related leukodystrophy.

This paper examined how oligodendrocytes, the major myelin producing cells of the brain, are affected in POLR3-related leukodystrophy.

> Front Neurosci. 2023 Apr 25:17:1167047. doi: 10.3389/fnins.2023.1167047. eCollection 2023.

Decreased RNA polymerase III subunit expression leads to defects in oligodendrocyte development

MEET THE TEAM

MyeliNeuroGene LAB

GRADUATE STUDENTS

- Alexandra Chapleau, PhD candidate

Project: *EPRS1*-related leukodystrophy: genetic, clinical and pathophysiological characterization using patient-derived iPSCs

- Mackenzie Michell-Robinson, MD-PhD candidate

Project: Investigating the role of RNA polymerase III subunit mutations in the development of hypomyelinating leukodystrophy and genetically related disorders

- Adam Le, Master's student

Project: Qualitative interviews with families of patients affected by POLR3-related leukodystrophy

- Samuel Gauthier, Master's student

Project: Preclinical evaluation of antisense oligonucleotide therapeutics for the severe striatal form of RNA polymerase III-related leukodystrophy using brain organoids

- Batool Hassan, Master's student

Project: Preclinical testing of Riluzole therapy in RNA polymerase III-related leukodystrophy

MEDICAL RESIDENTS

- Amytice Mirchi MD

Projects: Leukodystrophy natural history studies; Craniofacial features of POLR3-related leukodystrophy caused by biallelic variants in *POLR3A*, *POLR3B* and *POLR1C*

- Gabrielle Lambert MD

Projects: Leukodystrophies genotype-phenotype correlation studies; Natural history study of the mild and severe striatal forms of POLR3-related leukodystrophy

MEDICAL STUDENTS

- Kelly-Ann Thibault

Projects: Qualitative interviews with families of patients affected by POLR3-related leukodystrophy; Exploring the impact of rare disease support interventions for patients and their families

RESEARCH STAFF

- Clinical research: Luan Tran MSc, Laura Lentini MSc
- Wet lab: Xiaoru Chen PhD, Chia-Lun Wu PhD

AWARDS:
CONGRATULATIONS DR. BERNARD!

Pfizer Research Award of Excellence

Awarded by The Montreal Children's Hospital Foundation
to a researcher whose initiatives have made significant contributions to pediatric care.

Moser Service Award

Recognized by the United Leukodystrophy Foundation for outstanding service and commitment to the lives of people with leukodystrophies and their families.

Congratulations to the 2022 and 2023 Graduates!

Stefanie Perrier
PhD

Julia Macintosh
MSc

Neeti Jain
MSc

Helia Toutounchi
MSc

Laura Lentini
MSc

Congratulations to the Bernard Team for their 2023 Accomplishments

Julia Macintosh, MSc Student

- Invited to speak at the United Leukodystrophy Foundation Scientific Conference

Julia presenting at the United Leukodystrophy Conference, June 2023

Adam Le, MSc Student

- Received the RI-MUHC Desjardins Studentship Award in Child Health Research
- Awarded the IPN Internal Student Award

Neeti Jain, MSc Student

- Won best oral work in progress seminar in the Child Health and Human Development program

Alexandra and fellow poster winners at the United Leukodystrophy Conference, June 2023

Alexandra Chapleau, PhD Student

- Awarded 1st prize for poster at Congrès Mère-Enfant Conference
- Awarded 3rd prize for poster at the United Leukodystrophy Foundation Scientific Conference
- Recipient of Stem Cell Travel Award, awarded to a student with exceptional promise in the stem cell field

Selected Bernard Lab Publications of 2023

> J Child Neurol. 2023 Apr;38(5):329-335. doi: 10.1177/08830738231176672. Epub 2023 May 24.

The Experience of Parents of Children With Genetically Determined Leukoencephalopathies With the Health Care System: A Qualitative Study

Pouneh Amir Yazdani [1 2 3 4], Marie-Lou St-Jean [1 2 3 5], Sara Matovic [1 2 3], Aaron Spahr [1 2], Luan T Tran [1 2], Renée-Myriam Boucher [6], Chantal Poulin [2 3], Bradley Osterman [2 3], Myriam Srour [1 2 3], Bernard Rosenblatt [2 3], Sébastien Chénier [7], Jean-Francois Soucy [8 9], Anne-Marie Laberge [8 9], Maria Daniela D'Agostino [10 11], Cam-Tu Emilie Nguyen [12], Maxime Morsa [5 13], Geneviève Bernard [1 2 3 10 11]

> MethodsX. 2023 Feb 2:10:102051. doi: 10.1016/j.mex.2023.102051. eCollection 2023.

An optimized and validated protocol for the purification of PDGFRα+ oligodendrocyte precursor cells from mouse brain tissue via immunopanning

Julia Macintosh [1 2], Mackenzie A Michell-Robinson [1 2], Xiaoru Chen [1 2], Daryan Chitsaz [1 3], Timothy E Kennedy [1 3], Geneviève Bernard [1 2 4 5 6]

> J Med Genet. 2023 Oct;60(10):1026-1034. doi: 10.1136/jmg-2023-109223. Epub 2023 May 16.

Craniofacial features of POLR3-related leukodystrophy caused by biallelic variants in *POLR3A*, *POLR3B* and *POLR1C*

Amytice Mirchi [# 1 2 3], Simon-Pierre Guay [# 4 5], Luan T Tran [1 3], Nicole I Wolf [6], Adeline Vanderver [7 8], Bernard Brais [1 4 9], Michel Sylvain [10], Daniela Pohl [11], Elsa Rossignol [12], Michael Saito [13], Sebastien Moutton [14], Luis González-Gutiérrez-Solana [15], Isabelle Thiffault [16 17], Michael C Kruer [18 19 20], Dolores Gonzales Moron [21], Marcelo Kauffman [22], Cyril Goizet [23 24], László Sztriha [25], Emma Glamuzina [26], Serge B Melançon [27], Sakkubai Naidu [28], Jean-Marc Retrouvey [29], Suzanne Lacombe [29], Beatriz Bernardino-Cuesta [30], Isabelle De Bie [# 4 5 31], Geneviève Bernard [# 32 2 3 4 5]

Case Reports > Child Neurol Open. 2023 May 29:10:2329048X231176673. doi: 10.1177/2329048X231176673. eCollection 2023 Jan-Dec.

A Recurrent *De Novo* Variant in *EIF2AK2* Causes a Hypomyelinating Leukodystrophy

Julia Macintosh [1 2], Isabelle Thiffault [3 4 5], Tomi Pastinen [3 4 6], László Sztriha [7], Geneviève Bernard [1 2 8 9 10]

Case Reports > Front Cell Neurosci. 2023 Aug 4:17:1216487. doi: 10.3389/fncel.2023.1216487. eCollection 2023.

Neuropathological characterization of the cavitating leukoencephalopathy caused by COA8 cytochrome *c* oxidase deficiency: a case report

Alexandra Chapleau [1 2], Renée-Myriam Boucher [3], Tomi Pastinen [4 5], Isabelle Thiffault [4 5 6], Peter V Gould [7], Geneviève Bernard [1 2 8 9 10]

> Front Neurosci. 2023 Apr 25:17:1167047. doi: 10.3389/fnins.2023.1167047. eCollection 2023.

Decreased RNA polymerase III subunit expression leads to defects in oligodendrocyte development

Julia Macintosh [1 2], Mackenzie Michell-Robinson [1 2], Xiaoru Chen [1 2], Geneviève Bernard [1 2 3 4 5]

> Brain. 2023 Aug 28:awad249. doi: 10.1093/brain/awad249. Online ahead of print.

Hypomyelination, hypodontia and craniofacial abnormalities in a Polr3b mouse model of leukodystrophy

Mackenzie A Michell-Robinson [1 2], Kristin E N Watt [3], Vladimir Grouza [1 4], Julia Macintosh [1 2], Maxime Pinard [5], Marius Tuznik [1 4], Xiaoru Chen [1 2], Lama Darbelli [1 2], Chia-Lun Wu [1 2], Stefanie Perrier [1 2], Daryan Chitsaz [1], Nonthué A Uccelli [1], Hanwen Liu [1 4], Timothy C Cox [6], Christoph W Müller [7], Timothy E Kennedy [1], Benoit Coulombe [5 8], David A Rudko [1 4 9], Paul A Trainor [3 10], Geneviève Bernard [1 2 11 12 13]

Review > Orphanet J Rare Dis. 2023 Jul 13;18(1):187. doi: 10.1186/s13023-023-02802-6.

Hypomyelination caused by a novel homozygous pathogenic variant in FOLR1: complete clinical and radiological recovery with oral folinic acid therapy and review of the literature

Ana Potic [1], Stefanie Perrier [2 3], Tijana Radovic [4], Svetlana Gavrilovic [5], Jelena Ostojic [6], Luan T Tran [2 3], Isabelle Thiffault [7 8 9], Tomi Pastinen [7 8], Raphael Schiffmann [10], Geneviève Bernard [2 3 11 12]

> Front Neurol. 2023 Apr 3:14:1148377. doi: 10.3389/fneur.2023.1148377. eCollection 2023.

Solving inherited white matter disorder etiologies in the neurology clinic: Challenges and lessons learned using next-generation sequencing

Stefanie Perrier [1 2], Kether Guerrero [1 2], Luan T Tran [1 2], Mackenzie A Michell-Robinson [1 2], Geneviève Legault [1 2 3], Bernard Brais [1 4 5], Michel Sylvain [6], James Dorman [7 8], Michelle Demos [9], Wolfgang Köhler [10], Tomi Pastinen [11 12], Isabelle Thiffault [11 12 13], Geneviève Bernard [1 2 3 5 14]

> Pediatr Neurol. 2023 Nov:148:133-137. doi: 10.1016/j.pediatrneurol.2023.08.013. Epub 2023 Aug 19.

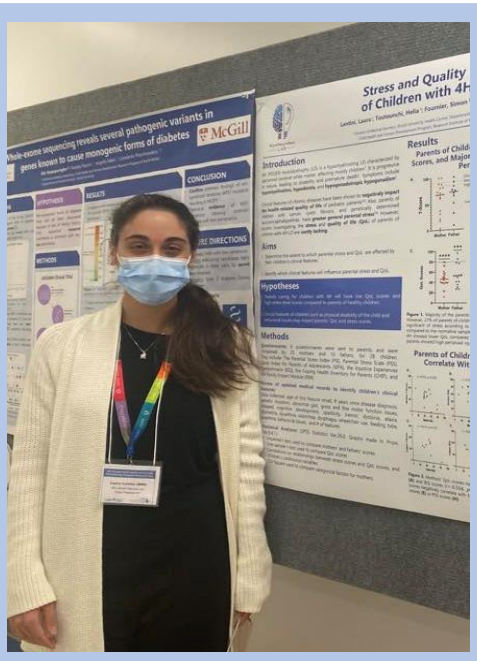
Longitudinal Characterization of the Clinical Course of Intermediate-Severe Salla Disease

Alexandra Chapleau [1], Amytice Mirchi [2], Luan T Tran [1], Chantal Poulin [3], Geneviève Bernard [4]

For a more comprehensive review of Dr. Bernard's publications, please see the following link!

The Bernard Lab Out and About!

The team at the Awards of Excellence 2023 award ceremony, May 2023.

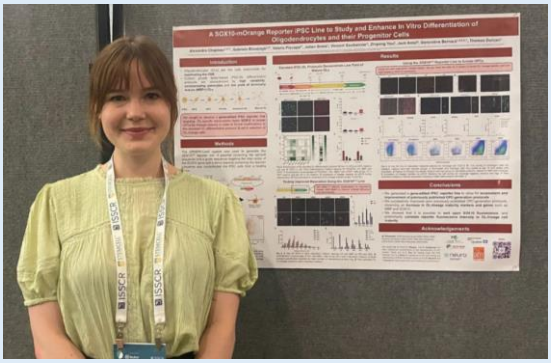


Laura presenting her research at the Child Health and Human Development Research Day, Nov 2022.

Julia, Neeti, Laura and Alex after their presentations at the rareDIG conference for rare disease research, March 2023.

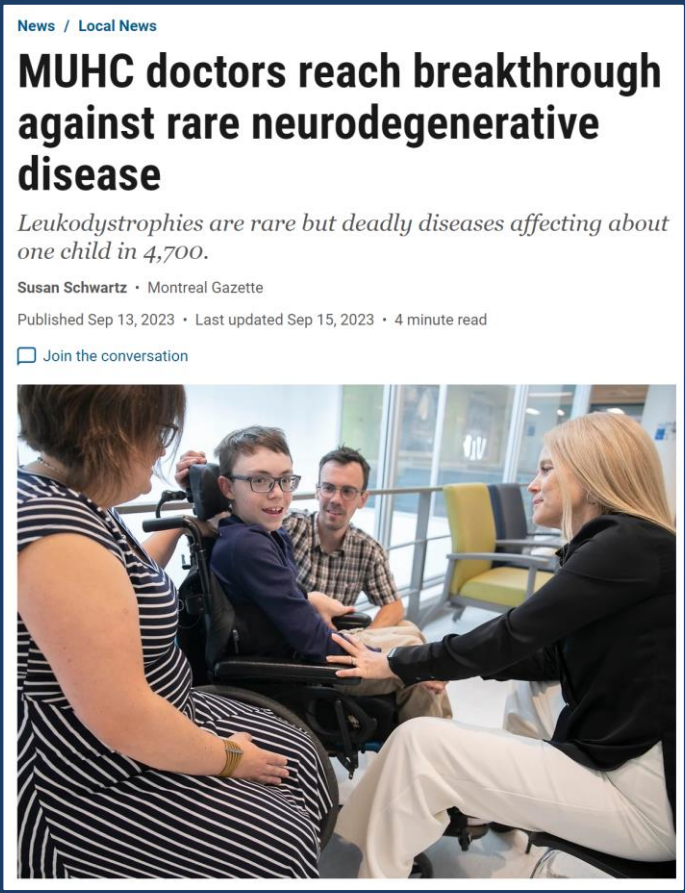
Alex giving an oral presentation on her PhD work at the Neuroscience Program Scientific Retreat, September 2022.

Neeti presenting her work on severe forms of POLR3-HLD at the Child Health and Human Development Research Day, November 2022.



Alex in front of the poster she presented at the International Society for Stem Cell Research in Boston, June 2023.

Featured Bernard Lab Media



News / Local News

MUHC doctors reach breakthrough against rare neurodegenerative disease

Leukodystrophies are rare but deadly diseases affecting about one child in 4,700.

Susan Schwartz · Montreal Gazette

Published Sep 13, 2023 · Last updated Sep 15, 2023 · 4 minute read

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Percée à McGill dans le traitement des leucodystrophies

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Bernard lab student prepping a Western Blot!

MyeliNeuroGene

LAB

THANK YOU FOR YOUR SUPPORT!

For more information, please contact
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