ONGOING RESEARCH STUDIES IN THE DIVISION OF PEDIATRIC NEUROLOGY

JULY 1, 2023 TO DECEMBER 31, 2023

Prepared by

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Our Vision:

To become a national and international leader in the provision of leading edge care for children and youth with neurological disorders, conducting research, applying technology to improve patient care, obtaining superior clinical outcomes and sharing information through peer reviewed publications and educational programs.

Our Mission:

To improve the neurological health of children and youth in B.C. through compassionate, leading edge care, education and research, and to implement advances in pediatric neuroscience, particularly those that significantly improve patient outcomes.

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1. INTRODUCTION

This report contains up to date information on the ongoing research projects in the Division of Pediatric Neurology for the period of July 1, 2023 to December 31, 2023. The main objective of the report is to familiarize the members of Pediatric Neurology with the current research activities. The studies presented in the report are divided into two major categories: ongoing prospective studies and retrospective studies. Each study category is further divided in 4 subcategories: Epilepsy, Brain Injuries / Inflammation, Developmental Malformation / Neuromuscular Diseases and Neuro-oncology. The number of studies per category and subcategory is presented in the table below.

Number of Ongoing Studies in the Divisions of Pediatric Neurology			
Category	Prospective	Retrospective	Total
Epilepsy	38 (5 new, 2 closed)	21 (2 new, 2 closed)	59
Brain Injuries/Inflammation	6 (1 new)	0	6
Developmental Malformations/ Neuromuscular Diseases	13 (1 new, 3 closed)	5	18
Neuro-oncology	0	6 (2 new)	6
QA projects	1	0	1
Total	58	32	90

Detailed description of the purpose, objectives, budget and sample size of each study is presented in the next two sections of this report.

Dr Alex Rauscher and Dr Alex Weber are PhD scientists with their academic positions in Neurology at UBC. Their amazing work and accomplishments have not been captured in this report due to the size of this report. We also welcomed Dr Thiviya Selvanathan, a clinician scientist who is an outstanding addition to the Neurology division.

2. ONGOING PROSPECTIVE STUDIES

2.1. EPILEPSY

1. fMRI Study - PI: Dr. Bjornson

Multi-Site Pediatric Network for fMRI Mapping in Childhood Epilepsy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	2006 ongoing	200	175	yes	active	multiple abstracts

The purpose of this study is to establish the utility of functional Magnetic Resonance Imaging (fMRI) to identify atypical language in childhood localization related epilepsy, by using a variety of language paradigms that have already been tested in normal children and patients with epilepsy.

The study objectives include:

- To establish the network infrastructure for multi-site collection and management of functional imaging data linked to a database of common assessments and measures;
- To establish the feasibility of conducting multi-site fMRI by identifying patients with atypical language, and to provide pilot data necessary to conduct a large scale study to compare fMRI findings to invasive methods (IAT, ECS, surgical outcome).

To achieve our goals, we will establish an imaging consortium with web based access and central data storage. A multi-centre, cross sectional prospective study will use fMRI to study patients undergoing epilepsy surgery. A web based system will be established that will allow entry of clinical variables and imaging data. Clinical data will be collected as part of routine evaluation for chronic epilepsy in children considered for epilepsy surgery. The Inclusion Criteria are:

- Patients undergoing comprehensive epilepsy evaluation;
- Children between 3-19 years of age.

There are 175 subjects enrolled in the study, with 2 enrolments in the last 6 months period.

2. EEG-MEG/EEG-fMRI Epilepsy Study – PI: Dr Bjornson

Pediatric Integrating Neurophysiology with Neuroimaging for Pediatric Epilepsy Connectomics

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Internal funds	60K	2018 2025	10	7	yes	active	N/A

The aim of the study is to establish the feasibility of using EEG-MEG and EEG-fMRI to localize inter-ictal spike related activity. We will begin data collection with data obtained from prescribed protocols. We will assess the applicability of multimodal imaging methods using standard study paradigms already tested in clinical practice. Studies will be performed with children and adolescents (7 to 17 years and verbal) with specific epilepsy clinical profiles determined as part of routine clinical care. As a consequence, all children will have clinical, EEG, structural MRI and neuropsychological assessments. Children will be excluded if they have contraindications to MR scanning or are unable to cooperate and complete study tasks.

MEG and EEG-fMRI literatures suggest that both methods may make positive contributions to the pre-surgical work-up; however, it remains unclear as to why the findings remain so mixed. Only testing both the MEG and EEG-fMRI paradigms with representative groups drawn from the population of pediatric epilepsy patients at BCCH will determine the utility of both methodologies for children with medication-resistant epilepsies in the province of British Columbia.

The study has been approved and is active. ***Two adult control subjects and five children have been enrolled in the study. There were no enrolments in the last term.***

3. GTX-102 Angelman Syndrome Study – PI: Dr. Boelman

A Phase 1/2 Open-label, Multiple-dose, Dose-escalating Clinical Trial of the Safety and Tolerability of GTX-102 in Pediatric Patients with Angelman Syndrome (AS)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Ultragenyx	130K/ pt 19K site fees	2023-2026	3@ BCCH	1	yes	active	

This is a first in humans, open-label, multiple-dose study to evaluate the safety and tolerability of new study drug called GTX-102 in pediatric patients who have Angelman Syndrome.

Objectives:

Primary: To evaluate the safety and tolerability of multiple-ascending doses of GTX-102 administered by intrathecal (IT) injection to patients with AS.

Secondary: To evaluate the pharmacokinetics (PK) of GTX-102 in plasma and cerebrospinal fluid (CSF) of patients with AS.

Exploratory:

- To explore the pharmacodynamic (PD) effects of treatment with GTX-102 in patients with AS.
- To investigate the potential efficacy of treatment with GTX-102 based on various clinical outcome measures.

Investigational Product/Route/Regimen:

Patients will receive a total of 3 or 4 IT injections of GTX-102 administered at monthly intervals (ie, every 28 days) during the Monthly Dosing phase of the study and then once every 3 months (ie, 84 days) during the Maintenance phase of the study.

Study Duration:

The Monthly Dosing phase of the study is up to approximately 22 weeks and includes a ≤ 4-week Screening period, an 8 to 12-week Treatment period, and 6-week Follow Up period. Patients may continue on GTX-102 during the Maintenance phase of the study until GTX-102 is commercially available, intolerable toxicity occurs, the parent/legal guardian withdraws consent, or the study is terminated.

There was one enrolment during the last term. The enrolment has been completed at all participating sites.

4. Lorcaserin Dravet Syndrome Study – PI: Dr. Boelman

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Eisai	29K/pt 19K site fees	2021-2024	3-5 @ BCCH	0	yes	active	

This is a multicenter, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group adjunctive therapy study in subjects with Dravet syndrome. The study will consist of a Core Study and open-label Extension Phase.

Core Study

Primary Objective

- The primary objective of the study is to demonstrate that lorcaserin has superior efficacy compared to placebo on percent change in frequency of convulsive seizures per 28 days in subjects with Dravet syndrome.

Secondary Objectives

- To evaluate whether lorcaserin has superior efficacy compared to placebo on the 50% responder rate (percent of subjects with at least 50% reduction in frequency of convulsive seizures per 28 days compared to baseline)
- To evaluate whether lorcaserin has superior efficacy compared to placebo on the proportion of subjects who are free from convulsive seizures
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To evaluate the safety and tolerability of lorcaserin in subjects with Dravet syndrome

Extension Phase:

- To evaluate the safety and tolerability of lorcaserin
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of convulsive seizures
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of each type of seizure
- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are free from convulsive seizures
- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are seizure-free
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of clusters
- To summarize the efficacy of lorcaserin as measured by CGIC
- To summarize the efficacy of lorcaserin as measured by on quality of life

There are no enrolments yet in this clinical trial. The enrolment period has been extended until March 31, 2024 for all sites.

5. Lorcaserin Extended Access Program Study – PI: Dr. Boelman

Extended Access Program and Retrospective Chart Review for Lorcaserin in Dravet Syndrome and Other Refractory Epilepsies

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Eisai	19K/pt 18K site fees	2022-2028	5 @ BCCH	0	yes	active	

This protocol includes an Extended Access Program (EAP) for patients who have completed the Lorcaserin Dravet Sy study described above, and who, based on the treating physician's judgment, had a clinical benefit.

The primary objective is to provide continued access of lorcaserin to patients with Dravet syndrome and other refractory epilepsies.

Secondary Objectives:

- To summarize the efficacy of lorcaserin as measured by percent change in frequency of convulsive seizures
- To summarize the efficacy of lorcaserin as measured by the 50% responder rate (percent of patients with at least 50% reduction in frequency of convulsive seizures per 28 days) compared to baseline
- To summarize the efficacy of lorcaserin as measured by the proportion of patients who are free from convulsive seizures
- To summarize the efficacy of lorcaserin as measured by percent change in total seizure frequency
- To summarize the efficacy of lorcaserin as measured by the 50% responder rate (percent of patients with at least 50% reduction in total seizure frequency per 28 days) compared to baseline
- To summarize the efficacy of lorcaserin as measured by the proportion of patients who are seizure-free
- To summarize the retention rate of patients started on lorcaserin
- To evaluate the safety and tolerability of lorcaserin

The study is active with no patients enrolled yet.

6. TAK-935-3001-Dravet Syndrome: SKYLINE Study – PI: Dr. Boelman

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects with Dravet Syndrome (DS)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Takeda	22K/pt 23K site fees	2022-2028	3-5 @ BCCH	2	yes	active	

The purpose of this Phase 3 clinical trial is to evaluate the safety, tolerability, and efficacy of soticlestat as an adjunctive therapy in pediatric patients and young adults with Dravet Syndrome (DS).

Soticlestat is a first-in-class small molecule inhibitor of cholesterol-24-hydroxylase (CH24H) in the brain. Soticlestat has shown antiseizure efficacy in nonclinical studies, including models relevant to the rare developmental epileptic encephalopathies (DEEs) that are inadequately treated by current adjunctive antiepileptic drugs.

Primary Objectives:

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).
- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.

Research Design:

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and young adult subjects with DS. The treatment period is approximately 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.

This study consists of the following periods:

- 4- to 6-week screening/baseline period.
- 16-week treatment period (4-week titration period and 12-week maintenance period)
- 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow- up visit or phone call.

The study is active. There are 2 enrolled participants in this study. One participant completed the study and transitioned to the TAK 3003 extension study. There was one enrolment in the past 6 month period at BCCH site.

7. <u>TAK-935-3002-LGS-SKYWAY Study</u> – PI: Dr. Boelman

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Adult Subjects with Lennox-Gastaut Syndrome (LGS)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Takeda	22K/pt 23K site fees	2022-2028	3-5 @ BCCH	3	yes	Active Completed enrollment	

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and adult subjects with Lennox-Gastaut Syndrome (LGS).

The purpose of this Phase 3 clinical trial is to evaluate the safety, tolerability, and efficacy of soticlestat as an adjunctivetherapy in pediatric patients and young adults with Lennox-Gastaut syndrome (LGS).

Primary Objective is to assess the efficacy of soticlestat in reducing major motor drop (MMD) seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).

Secondary Objectives:

- To assess the following in subjects taking soticlestat as compared with placebo during the full treatment period, unless otherwise noted:
- Proportion of treatment responders defined as those with ≥50% reduction in MMD seizures from baseline during the maintenance period and the full treatment period.
- Effect on total seizure frequency of all seizure types during the maintenance period and the full treatment period.
- Change from baseline in proportion of MMD seizure-free days.
- Longest MMD seizure-free interval.
- Number of days when rescue antiseizure medications (ASMs) are used.
- Effect on the Clinical Global Impression of Improvement (CGI-I); (clinician) and Caregiver Global Impression of Improvement (Care GI-I).
- Effect on CGI-I Seizure Intensity and Duration.
- Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers.
- Effect on Quality of Life Inventory-Disability (QI-Disability).

Exploratory Objectives are to assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period:

- Seizure frequency of each seizure type per 28 days.
- Health care resource utilization including but not limited to emergency room visits and hospitalizations.
- Population pharmacokinetic (PK) and correlation of the population PK exposure parameters with pharmacodynamic (PD) (plasma 24S-hydroxycholesterol [24HC] levels) in subjects receiving soticlestat.
- Correlation of change in PD (24HC) exposure and efficacy (change in MMD seizure over the full treatment period).
- Effect on EuroQol 5 Dimension 5 Level (EQ-5D-5L) Quality of Life scale.

Safety Objectives:

- To assess the incidence of treatment-emergent adverse events (TEAEs).
- To assess the incidence of abnormal values and change for clinical laboratory evaluations, vital signs, electrocardiogram (ECG) parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS) parameters.
- To assess the incidence of new seizure types arising during soticlestat treatment that are not identified at the time of screening (by history) or during prospective baseline.

The enrolment has been closed for all participating sites. There were no enrolments in the last 6 months period. All 3 enrolled participants completed the study and transitioned to the TAK 3003 extension study.

8. TAK-935-3003 ENDYMION Study – PI: Dr. Boelman

A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies to Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects with Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Takeda	22K/pt 23K site fees	2022-2028	3-5 @ BCCH	4	yes	active	

This open-label extension (OLE) study is designed to obtain additional safety, tolerability, efficacy, PK, and PD data related to soticlestat administered long-term in subjects who participated in either of the phase 3 clinical studies, TAK-935-3001 (subjects with DS) or TAK-935-3002 (subjects with LGS) and continue to be treated with standard-of-care (SOC) anti-seizure therapy.

Primary Objectives:
To assess the long-term safety and tolerability of soticlestat when administered as adjunctive therapy to SOC (eg, ASMs, vagus nerve stimulation, ketogenic diet, modified Atkins diet) in subjects with DS or LGS.

Secondary Objectives:

- To assess the effect of soticlestat on seizure frequency (convulsive seizures for the DS cohort, MMD seizures for the LGS cohort, and total seizure count for each cohort).
- To assess the effect of soticlestat on the Clinical Global Impression of Improvement (CGI-I) (clinician) and Caregiver Global Impression of Improvement (Care GI-I).
- To assess the effect of soticlestat on CGI-I Seizure Intensity and Duration.
- To assess the effect of soticlestat on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.
- To assess the effect on Quality of Life Inventory-Disability (QI-Disability).

Exploratory Objectives:

- Health care resource utilization including but not limited to emergency room visits and hospitalizations.
- Number of days when rescue ASMs are used.
- Effect on caregiver's quality of life and time spent providing care.
- Correlation of PK or PD (24HC) exposure and efficacy.
- Characterization of subject and caregiver study experience (selected sites only).

There were 4 enrolments in the past 6 months.

9. STXBP1 Registry – PI: Dr. Boelman

A National STXBP1 Registry and Family Resource

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no			2018 2025	50	26	yes	active	N/A

We wish to establish a secure Canadian registry & family resource for patients who are affected by STXBP1 gene mutations. These mutations cause a rare neurodevelopmental disorder that starts

in early childhood with drug-resistant epilepsy, a movement disorder, intellectual disability & autism spectrum disorder. With very few patients known to us across the country, we do not have a complete characterization of this disorder, nor are there any personalized treatments or any family support or patient advocacy groups in Canada.

The registry will facilitate a better understanding of how we can make the greatest impact on the patients' quality of life by understanding the experiences across the lifespan from the patients, their families & clinicians. We hope to facilitate a sense of belonging for patients & their caregivers that may foster them reaching out to each other for support, advocacy & the sharing of ideas. ***There are 26 enrolments, with 3 enrolments in the last 6 months period.***

10. Angelman Syndrome Study - PI: Dr. Boelman

A Prospective Natural History Study of Angelman Syndrome for Therapeutic Development

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCH	10,000	2020 2026	250 total 15 @ BCCH	20	yes	active	N/A

The purpose of the study is to increase our understanding of the long-term natural history of Angelman Syndrome (AS) and obtain AS-specific norms for outcome measures that can be used in AS clinical trials, ultimately improving the care of individuals with AS.

We hypothesize that through this study, we will collect data so as to better determine appropriate outcome measures and endpoints for clinical trials.

Primary objective: To analyze the changes over time in sleep disturbance, adaptive functioning, maladaptive behaviors, and anxiety in a cohort of children and adults with AS.

Secondary objectives include, but are not limited to, the analyses of the prevalence of medical complications such as seizures, ages at which specific developmental milestones are achieved, prevalence of behavioral traits that are not necessarily maladaptive at different ages, changes in facial characteristics over time, as well as changes in levels of parental stress and quality of life for the family over time.

This is a longitudinal observational investigation into the natural history, morbidities, and mortality of Angelman syndrome (AS).

There are 20 subjects enrolled in the study, with 5 enrolments in the last term. One subject withdrew from the study.

11. Black Light Study – PI: Dr. Connolly

Commercial Hand-held Black Light to Facilitate Screening for Neurocutaneous Disorders

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
No			2021 - 2024	75	16	yes	active	N/A

The purpose of this pilot study is to show that a commercial hand-held black light is non-inferior to a Wood's lamp to identify hypomelanotic lesions in fair skin patients with known neurocutaneous disorders.

The primary hypothesis is that a commercial hand-held black light is non-inferior to a Wood's lamp to identify hypomelanotic lesions in light skin patients with known neurocutaneous disorders. The secondary hypothesis is that a commercial hand-held black light is equivalent to a Wood's lamp to identify hypomelanotic lesions in fair skin patients with known neurocutaneous disorder.

The primary objective is to identify if a commercial hand-held black light can identify all the hypomelanotic lesions identified with a Wood's lamp to demonstrate non-inferiority of commercial hand-held black light to Wood's lamp. The second objective is to demonstrate the equivalence of commercial hand-held black light to Wood's lamp. The third objective is to report descriptive epidemiological data about hypomelanotic lesions in TSC patients. The primary end points will be the skin tone and the number and size of hypomelanotic lesions identified under normal lighting and with a Wood's lamp and a commercial hand-held black light. Secondary end points will include age, pre or post puberty status, sex, diagnosis and if there is a genetic confirmation of diagnosis.

This will be a comparative randomized descriptive pilot study where each patient will be his/her own control. Since TSC is a neurocutaneous disease with hypomelanotic lesions, we will recruit patients attending the TSC Clinic at BC Children's Hospital.

There are 16 subjects enrolled in the study, with two enrolments in the past 6 months.

12. BBD in Epilepsy Study – PI: Dr. Afshar/Dr. Connolly

Prevalence of Bladder and Bowel Dysfunction (BBD) in pediatric patients with Epilepsy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
no			2021 - 2024	50	45	Yes	active	N/A

Functional disorders of the lower urinary tract and bowel known as Bladder and Bowel Dysfunction (BBD) are one of the most common reasons for outpatient referrals to pediatric urologists. Diagnosis and management of BBD in a timely manner is important to prevent future complications such as recurrent urinary tract infections and renal failure and to improve the quality of life of the affected children and their families. It is suggested that the neurological pathways that regulate bladder and bowel control might be disturbed in children with epilepsy. Based on this, we expect the frequency of BBD in children with epilepsy to be higher than the general population (2-20%). However, overlapping presentation between epilepsy and BBD (e.g., urinary incontinence around the time of epilepsy or urinary problems associated with anti-seizure medications) makes the diagnosis of BBD in this group of pediatric patients more challenging. This study is the first to use a validated tool to determine what percentage of children with epilepsy are affected by BBD at the same time.

Purpose: To improve the diagnosis and management of BBD in children with epilepsy.

Hypothesis:

- The prevalence of BBD in children with epilepsy is higher than 20%
- There is an association between BBD and anti-seizure medications.

Objective: To determine the prevalence of BBD in pediatric patients with epilepsy

Specific Aims:

- To determine the prevalence of BBD based on the type of epilepsy.
- To determine the association of anti-seizure medications and prevalence of BBD.

The enrolment has been completed. The Urology team is finalizing the data analysis.

13. RAD-GRIN-101 study – PI: Dr. Connolly – *new study this period*

A Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effect on Seizures and Behavioral Symptoms of Multiple Individually Titrated Doses of Radiprodil in Children with GRIN-related Disorder

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	GRIN Therapeutics	75K/pt, 36.6K start up fees	2024 2033	2-3	0	pending	not started yet	N/A

The study will consist of 2 parts; a dose escalation part (Part A) to determine the safety, tolerability, and PK (pharmacokinetics) of multiple individually titrated doses of Radiprodil, and a long-term follow-up period (Part B) to assess the treatment effect on seizures and behavioural symptoms. A safe and well tolerated dose after 8 weeks of continuous treatment during Part A will be established, and initial signs of efficacy and changes in quality of life will be evaluated. The study will further evaluate the long-term safety and tolerability of Radiprodil and assess the maintenance of the treatment effect during Part B.

The study aims at establishing a safe and well tolerated dose after 8 weeks of continuous treatment in Part A as well as assessing the safety, tolerability, and PK of multiple Radiprodil doses in a pediatric population, together with evaluating the long-term safety and tolerability and the maintenance of the treatment effect.

Primary Objectives:

- To determine the long-term safety and tolerability of multiple individually titrated doses of Radiprodil as an add-on therapy to standard of care (SOC) in pediatric participants.
- To establish a safe and well tolerated dose after 8 weeks of continuous treatment in Part A.
- To determine the PK and plasma exposure of Radiprodil.

Secondary Objectives:

- To evaluate initial signs of efficacy on frequency and severity of epileptic seizures in those participants with seizures.
- To evaluate initial signs of efficacy of Radiprodil on additional CNS features including behavior, motor symptoms, sleep, and quality of life and the maintenance of the treatment effect.

Exploratory Objective is to determine the PK and the plasma exposure of Radiprodil major metabolites obtained at different doses in Part A.

The study is under REB review, and the CTA is being negotiated at present.

14. RAD-GRIN-201 study – PI: Dr. Connolly – *new study this period*

A Multicenter, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effect on Seizures and Behavioral Symptoms of Radiprodil in Patients with Tuberous Sclerosis Complex (TSC) or Focal Cortical Dysplasia (FCD) Type II

Fundin g	Source	Amount $	Study period	Anticipated enrolment	# of subjects consented	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	GRIN Therapeu tics	TBD	2024 2034	2-3	0	pending	not started yet	N/A

This is an open-label, multicenter, phase 1B/2A study in participants with TSC or FCD Type II. The study will consist of 2 parts; a dose escalation/maintenance period (Part A) to determine the safety, tolerability, and PK of multiple individually titrated doses of radiprodil, and a long-term follow-up period (Part B) to assess the treatment effect on seizures and behavioral symptoms. A safe and well tolerated dose after approximately 16 weeks of continuous treatment during Part A will be established, and initial signs of efficacy and changes in quality of life will be evaluated. The study will further evaluate the long-term safety and tolerability of radiprodil and assess the maintenance of the treatment effect during Part B.

Primary objectives:

- To determine the safety and tolerability of multiple individually titrated doses of radiprodil in TSC and FCD Type II patients.
- To determine the pharmacokinetics (PK) and plasma exposure of radiprodil

Secondary Objectives:

- To evaluate initial signs of efficacy on frequency and severity of epileptic seizures in those participants with seizures
- To evaluate initial signs of efficacy of radiprodil on additional central nervous system (CNS) features including behavior and quality of life The budget negotiation process is underway. The study hasn't been approved at BCCH site yet.

15. ARGUS Trial – PI: Dr. Connolly

A 20-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of EPX-100 (Clemizole Hydrochloride) as Adjunctive Therapy in Patients with Dravet Syndrome

Fundin g	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Epygenix Therapeu tics	86.4K/pt, 36K start up	2022 2026	2-3	3	yes	active	N/A

This is a 20-Week Multicenter, randomized, double-blind, placebo-controlled, dose escalation design of EPX-100 (Clemizole HCl) as adjunctive therapy in Patients with Dravet Syndrome.

The primary objective is to evaluate the efficacy of EPX-100 orally in divided doses as adjunctive therapy compared with placebo in participants with Dravet Syndrome, in terms of the mean percent change in countable convulsive seizure frequency (CCSF1) in the Titration and Maintenance (T+M) periods relative to baseline.

Secondary Objectives:

- To evaluate the difference between EPX-100 vs placebo in proportion of participants with >50% reduction in the median countable convulsive seizure frequency between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week maintenance Period.
- To evaluate the difference between EPX-100 vs placebo in proportion of participants with >25% reduction in the median countable convulsive seizure frequency between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week Maintenance Period.
- To compare the difference between EPX-100 vs placebo in the number of countable convulsive seizure-free days during the final 4-week Maintenance Phase vs the Observational Phase.
- To describe the difference between EPX-100 vs placebo in the reduction in episodes of status epilepticus1, between 4-week Baseline period (Observational Phase) and final 4-week period of the 12-week maintenance Phase.
- To evaluate the median difference between EPX-100 vs placebo in the percent change per 28-day frequency of all seizures I the final 4-weeks of the 12-week treatment period (Maintenance Phase) relative to the baseline (4-week Observational Phase).
- To compare the incidence of rescue antiepileptic drug (AED) use between treatment arms, as measured by the number of days on rescue AEDs during the 12-week Maintenance Phase as compared with the 4-week Observational Phase.
- To describe improvement in Clinical Global Impression (CGI).
- To describe changes in Quality of Life in Childhood Epilepsy short form (QOLCE-55).
- To describe changes in Targeted Behavior using Visual Analog Scales (VAS).
- To describe change in the Sleep Disturbance Scale for Children (SDSC) by treatment arm and by each scheduled visit.
- To evaluate the safety of EPX-100 orally in divided doses as adjunctive therapy compared with placebo.
- To determine the PK profile of EPX-100 in plasma during the Titration Phase, Maintenance Phase and Open-Label Extension Phase.

The study is active, with 3 enrolments in the last 6 months period. Two participants withdrew from the study, and there is one active participant.

16. EMCADS Study Study – PI: Dr. Connolly – *new study this period*

Extended Monitoring for Cardiac Arrhythmias in Dravet Syndrome (EMCADS)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Dravet Foundation	250K USD	2024-2028	20	0	pending	not started yet	N/A

The purpose of this study is to understand the role of the cardiac system in DS in order to save lives of children with DS. Specifically, through the following two objectives, we plan to comprehensively evaluate the cardiac symptoms preceding and during seizures in children with DS:

Objectives:

- To monitor prevalence of cardiac arrhythmias in pediatric patients diagnosed with Dravet syndrome using subcutaneous implantable cardiac monitors (ICM) over a 2-year period.
- To identify whether cardiac arrhythmias occur during the ictal or post-ictal phases of seizures in patients with Dravet syndrome.

Hypotheses

- Cardiac arrhythmias will be detected in 20% of patients with Dravet Syndrome by use of subcutaneous ICMs.
- The devices will be safe and well-tolerated by patients and care providers.

Research Design

This is a single-centre, pilot study that will aim to evaluate the potential connection between cardiac arrhythmias and seizures in patients with DS. Each participant will be in the study for two years. Approximately 20 participants are expected to enroll over the course of the study. Recruitment will begin as soon as the application has been reviewed and approved by the Research Ethics Board. Study design follows as such:

- A screening window (up to 30 days), which includes the confirmation of the inclusion/exclusion criteria by Neurology and Cardiology, a baseline Cardiology visit, and a 24h Holter monitor recording and review.
- Baseline visit: device implantation once eligibility is confirmed.
- In-person/tele-health visits with Neurology and Cardiology every 3 months. Phone calls with the Research Coordinator in-between those visits (every 6 weeks).
- Device extraction at 24 months.

The study is under REB review. The funding of 250K USD has been obtained by the Dravet Foundation. Additional funding application has been submitted to Epilepsy Canada for 100K CAD.

17. TSC Database – PI: Dr. Connolly/Dr Horvath

Translational collaborative informatics platform for Precision Health (Pilot)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	BB&D BCCH	95K	2022-2024	All eligible 100	31	yes	active	N/A

The purpose of this pilot study is to link four large datasets stored by the Pediatric Neurology Clinic, Neuropsychology Clinic and Mental Health Data Access Working Group at BC Children's Hospital to study a group of patients with Tuberous Sclerosis Complex (TSC).

Development of a central database for Precision Health, which merges data from multiple databases/datasets across various clinics and research groups is needed to better understand and precisely address the health needs of people with rare diseases in British Columbia.

Tuberous Sclerosis Complex (TSC) is a rare genetic disorder characterized by a variety of neuropsychiatric conditions such as drug-resistant epilepsy, autism spectrum disorder, intellectual disability, global developmental delay and mood and behavior disorders. People living with TSC in British Columbia represent a small and specific patient population who are regularly cared for by multiple departments at BC Children's Hospital, including neurology and psychiatry. As a result, large datasets relating to TSC patients exist across multiple clinical and research platforms.

The datasets to be linked include: The Epilepsy Database (CEDAR Database), The Neurology TSC Database, the Neuropsychology Registry and The Mental Health Dataset. These datasets will be linked to create a central database. The central database or 'translational informatics platform' will then be used to characterize seizures, clinical characteristics, as well as disease traits of people living with TSC and cross-reference this information with TSC patients' mental health, behavioral, and psychological assessments to answer the following research questions:

- Are early onset (beginning at less than 2 years of age) epilepsy and severe epilepsy associated with an increased risk of long term mental health conditions in patients with TSC?
- Are there aspects of social determinants of health (place of residence (urban vs. rural), schools, family components, access to clinical and mental health resources) which are associated with the outcome of TSC patients?

This study aims to ultimately demonstrate the feasibility of a translational informatics platform for Precision Health at BC Children's Hospital and facilitate further large scale research to support precision health within British Columbia.

The study is active, with 31 enrolments up to date. Eleven participants have been enrolled in the last term.

18. Complex movement disorders tool – PI: Dr Horvath/ Dr. Connolly –*New study this term*

Validation of a clinical and deep learning-base tool for recognition, assessment, and monitoring of complex movement disorders in dystonia patients

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A		2023-2026	50 25@BCCH		yes	active	N/A

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements, postures, or both. It includes abnormal tone, posture, or hyperkinetic movement disorders. However, dystonia relates to both symptom, and underlying conditions. As a disease, it is described in two ways: i) clinical features: age at onset, body distribution, temporal pattern, co-occurrence of other movement disorders and other neurological manifestations and, ii) etiology-presence of radiological alterations, static or progressive disorder and inheritance.

The specific aims of this project are:

- The development and validation of an easy-to-use grid allowing identification and monitoring of dystonia and associated motor phenomenology. The present study is to assess the reliability of the grid, specifically inter-rater, intra-rater, and test–retest reliability, and the effects of training on reliability.
- The development of a deep learning-based library designed for training models from clinical video recordings already published to perform video-based classification and body key points estimation (movement, amplitude, deformation, etc.) to classify movement disorders.
- Additional validation of the grid and deep learning tool by quantitative measurements of movements

Methods

i) Development and validation of the grid

As a first step, we propose a multiple point-in-time evaluation using a motor phenotype assessment grid we developed to capture the occurrence and persistence of associated movement and tone disorders together with dystonia, during disease progression, in combined and complex dystonia. The grid includes different type of movement disorders: dystonia, associated hyperkinetic movement disorders (chorea, athetosis, ballismus, myoclonus, tremor, tics, stereotypies) and associated neurological signs (ataxia, bradykinesia, hypotonia, pyramidal signs and dysarthria).

The grid is used to list all the motor symptoms presented by the patients and their persistence, occurrence, or disappearance during follow-up. The core and necessary motor phenomenology for inclusion is dystonia. The grid is filled out for each video-recorded follow-up time points selected for assessment in the study.

Expected outcomes

As outcome of the current project, we expect a better characterization of the motor phenomenology in combined and complex dystonias and their monitoring following different therapeutical interventions, both pharmacological agents and advanced therapies such as deep brain stimulation.

The study has been REB approved and will be initiated in the New Year.

19. Dravet Syndrome & LGS Study (1900) – PI: Dr. Connolly

An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Zogenix	25K start-up funds 32K/pt	2019-2024	8@ BCCH	7	yes	active	N/A

This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with rare seizure disorders, epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with LGS who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time.

Objectives:
The primary objective of the study is to assess the long-term safety and tolerability of ZX008.

The key secondary objectives of the study are:

- To assess the effect of ZX008 on the following effectiveness measures:
- Investigator assessment of convulsive seizure response
- Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the investigator
- CGI-I rating, as assessed by the parent/caregiver

- Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by the investigator - Symptomatic CGI-I for cognition, behavior, motor abilities, as assessed by the parent/caregiver

Subject will be eligible to participate in this trial for up to 36-months, or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary. Thus, the maximum duration for participation is 36 months. ***Seven subjects have been enrolled in the study.*** The enrolment has been completed globally. At BCCH site, 4 participants completed the study, and 3 participants terminated the study early due to side effects. The sponsor plans to close the study in 2024, and all participants will be able to access the study drug via Special Access Program.

20. QOL Study - SickKids – PI: Dr. Connolly

Efficacy Impact of Pediatric Epilepsy Surgery on Health-Related Quality of Life

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	CIHR	270/study visit	2014-2024	50@ BCCH	29	Yes	completed enrolment	N/A

Epilepsy in children often has catastrophic consequences on multiple domains of health-related quality of life (HRQL). Medically refractory epilepsy refers to poorly controlled epilepsy in spite of treatment with two or more antiepileptic drugs. The two main treatments for medically refractory epilepsy are medical treatment with antiepileptic drugs or surgery.

Primary Objectives:

- To assess HRQL over two years in children with medically refractory epilepsy, comparing two treatment groups: surgery and medical therapy.
- To evaluate the mediating and moderating factors for changes in HRQL following treatment.
- To identify the baseline characteristics predicting HRQL in children at two years after surgery.

Secondary Objective is to assess whether changes in the children's HRQL following epilepsy surgery will be associated with changes in family factors.

Inclusion criteria

- Age 4 – 18 years (the HRQL instrument has been validated in this age range)
- Medically refractory localization-related epilepsy (assessed by clinical semiology and/or electroencephalography)

There are 29 subjects enrolled at BCCH, with no enrolments in the last quarter. There are 20 active subjects, and 9 subjects withdrew from the study. The enrolment has been completed and closed. The active subjects have been completing the questionnaires as per protocol.

21. ANAVEX2-73-RS-003 Rett Syndrome Study – PI: Dr. Datta

A Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of ANAVEX2-73 in Patients with Rett Sy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript

yes	Anavex Life Sciences Corp.	30K/pt 26K site fees	2021-2024	5 @ BCCH	5	yes	active	

This international Phase 2 efficacy, tolerability, and safety study design is a double-blind, randomized, placebo-controlled, 12-week dose titration study of ANAVEX2-73 oral solution in the treatment of patients with RTT between 5 and 17 years of age. Approximately 84 participants of the study with a voluntary option for all patients to continue in a 48-week open-label extension.

Primary Endpoints

- Recording of Adverse Events (AEs); graded AEs according to common Terminology Criteria for Adverse Events (CTCAE) V5.0.
- Physical and neurological examination.
- Vital signs (heart rate, respiratory rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], and oral body temperature).
- 12-lead ECG; three consecutive ECGs where participants should be in a resting position for ≥ 5 minutes prior to each ECG evaluation.
- Clinical laboratory tests (hematology including routine clotting tests; clinical chemistry including full liver function tests and lipid panel; CYP polymorphisms; and urinalysis).
- Concomitant medication log.
- PK of ANAVEX2-73 and ANAVEX19-144.

Co-Primary Efficacy Endpoints:

The co-primary efficacy endpoints will be the change from baseline to End of Treatment (EOT) in the modified intent-to-treat (mITT) population in the following measures:

- Rett Syndrome Behaviour Questionnaire (RSBQ) total score, and
- Clinical Global Impression - Improvement Scale (CGI-I) score

The mITT population is defined as all randomized patients who receive at least 1 dose of study medication.

Secondary endpoints include a range of efficacy (clinical, quality of life) and PK measures.

- RSBQ Emotional Factor-Pediatric (subset of the RSBQ)
- Clinical Global Impression - Improvement Scale (CGI-I
- Anxiety, Depression, and Mood Scale (ADAMS)
- Children's Sleep Habits Questionnaire (CSHQ)
- Seizure frequency via seizure diary
- Motor Behavioral Assessment-7 dynamic pediatric items (MBA-Ped7)
- Visual Analog Scale (VAS) of the top three concerns a family has for their daughter
- Rett Syndrome Caregiver Inventory Assessment (RTT CIA)
- Child Health Questionnaire-Parent Form 50 (CHQ-PF50)
- Population PK of ANAVEX2-73 and its active metabolite, ANAVEX19-144, integrated to safety, tolerability and efficacy assessments.

Exploratory endpoints include a variety of genomic and biochemical measures and analyses of relevance to safety and efficacy.

- Glutamate plasma concentration.
- GABA plasma concentration.
- Other Amino Acid plasma concentrations.

- Exploratory DNA and RNA profiles.
- Analyses of efficacy endpoints in the subgroups of subjects without the SIGMAR1 (rs1800866) or COMT (rs113895332/rs61143203) sequence variations.
- Pharmacodynamics (PD); PK-PD relationships will be explored for safety, tolerability, and efficacy endpoints.

Patients will be randomized into 2 arms to receive placebo or ANVEX2-73 for a total of 12 weeks during the period of blinded titration and safety monitoring. Upon completion, all patients will be offered the option of participating in an additional 48-week OLE. Study drug will be provided to the patients/caregivers in 120 ml bottles that are labelled in a blinded fashion, containing a solution of either Placebo or 5 mg/ml ANAVEX2-73. Open-label product will be provided for the OLE study. Safety Reviews will occur on site or at home at Weeks 0, 4 and 12 during the 12-week double-blind period, and at Weeks 0, 12, 24, 36 and 48 during the OLE, and any other time, if medically indicated.

There are 5 enrolled subjects, with 2 active subjects, 3 subjects completed the study, and 2 subjects withdrew from the study. The global enrolment has been completed.

22. <u>Trust TSC Study 1042-TSC-3001</u> - PI: Dr. Datta

A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Marinus Pharmaceuticals	29K/pt 22K start-up fees	2022-2027	2	1	yes	active	

Purpose: To assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults.
Hypothesis: Patients treated with GNX will demonstrate a decrease from baseline in the frequency of countable major motor and focal seizures (primary endpoint seizures) during the double-blind phase compared to patients treated with placebo.

Objectives:

Primary:

- To assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults as assessed by the change from baseline in the frequency of countable major motor and focal seizures (primary endpoint seizures) during the double-blind phase.

Secondary:

- To determine the percentage of change from baseline in 28-day primary endpoint seizure frequency during the maintenance period.
- To assess the change in focal seizure frequency from baseline during the double-blind phase.
- To assess changes in mood, behavior, and quality of life using the following:

    - ADAMS
    - Peds-QL-FIM
    - SF-36
    - ELDQOL
- To assess overall clinical outcome using the CGI-I scores by the clinician and the parent/caregiver.
- To evaluate the changes in seizure intensity and duration using the CGI-CSID.

Exploratory:

- To evaluate other seizure outcomes such as change in other seizure types and changes in seizure-free days.
- To evaluate changes in sleep using the CSHQ for children or adolescents or SQS for adults.
- To evaluate rescue medicine utilization in participants.
- To assess PK parameters in participants receiving GNX doses up to 63 mg/kg/day (1800 mg/day maximum).

Safety:

- To assess the safety and tolerability of GNX compared with placebo as adjunctive therapy.

Study Design: This is a Phase 3, global, double-blind, randomized, placebo-controlled study of adjunctive GNX treatment in children and adults with TSC-related epilepsy. The study consists of a 4-week prospective baseline phase, defined as the first 28 days following screening, followed by a double-blind phase consisting of a 4-week titration period and a 12-week maintenance period.

The study is active with 1 enrolment in the last 6 month period.

23. <u>Trust TSC OLE Study 1042-TSC-3002-</u> - PI: Dr. Datta

A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Marinus Pharmaceuticals	10K/pt 22K start-up fees	2023-2028	2	0	yes	active	

Purpose: To assess the long-term safety and tolerability of GNX as adjunctive therapy for seizures associated with TSC in children and adults.

Hypothesis: It is hypothesized that the augmentation of GABAA-receptor mediated signalling with GNX treatment will reduce seizures in patients with TSC. Changes in neurobehavioral symptoms, mood, sleep, and quality of life will also be assessed.

Objectives:

Primary: To assess the long-term safety and tolerability of GNX as adjunctive therapy for seizures associated with TSC in children and adults.

Secondary

- To determine the percentage of change from baseline in 28-day seizure frequency during open-label treatment.

- To assess the change in frequency of countable focal seizures frequency from baseline during open-label treatment.
- To assess changes in mood, behavior, and quality of life using SF-36.
- To assess overall clinical outcome using CGI-I scores by the clinician and the parent(s)/caregiver(s)/LAR(s).
- To evaluate the changes in seizure intensity and duration using the CGI-CSID.

Exploratory: To evaluate the long-term effects of GNX as add-on therapy to antiepileptic medications.

Research Design: This is a Phase 3, global, OLE study of adjunctive GNX treatment in children and adults with TSC-related epilepsy who previously participated in either Study 1042-TSC-3001 or Study 1042-TSC-2001.

The study has been approved, and there are no eligible participants yet.

24. <u>mTOR Study</u> - PI: Dr. Datta

Treatment of Medically Refractory Epilepsy due to Focal Cortical Dysplasia with mTOR inhibitors

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	RDF BCCHF	3,500 20K	2019-2024	6	2	yes	active	

Summary: We are proposing an open-label pilot study looking at the efficacy of mammalian target of rapamycin (mTOR) inhitibor, sirolimus, for the treatment of acute seizure exacerbation secondary to a focal cortical dysplasia in children who are awaiting imminent epilepsy surgery.

Purpose: The purpose of this study is to measure if mTOR inhibitor, sirolimus reduces seizure frequency by effecting mTOR signalling (an electrical activity signal in the brain) in patients with Focal Cortical Dysplasia (FCD) with treatment resistant epilepsy (TRE) who will be undergoing respective epilepsy surgery.

Hypothesis: Since patients with FCD have been shown to have excess mTOR signalling brain activity, and it has been shown to be effective in patients with TSC, mTOR inhibitors may be useful in reducing seizure frequency in patients with FCD who are admitted to hospital with extreme TRE prior to surgery.

Methods: This is a single center open-label pilot study of patients with FCD and TRE over 1 year. Patients 5 months to 6 years, with FCD, which is confirmed on MRI, who are undergoing pre-surgical investigations, not responding to AEDs (failed >6) and requiring admission for seizure control will be included.

The study is active with total of two enrolled participants, with no enrolments in the last 6 months period.

25. <u>Eating Disorders & Keto Diet Study</u> - PI: Dr. Coelho/Dr. Datta

Ketogenic diets for children and youth with epilepsy: Long-term impact on eating behaviour and quality of life

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCCHRI	10,000	2022-2024	24 cases & 24 controls Total 48	27 cases & 16 controls total 43	yes	active	

The purpose of the study is examining the impact of a time-limited dietary intervention for drug-resistant epilepsy on eating behavior and quality of life.
Hypothesis: We expect that patients treated with a dietary intervention (ketogenic diet or similar dietary intervention) for management of drug-resistant epilepsy (DRE) are at higher risk of developing disordered eating after discontinuation of the diet than those with DRE who do not have treatment with a dietary intervention.

Objectives:

- Compare eating pathology, somatic symptoms and quality of life in a group of youth with DRE who did not have a dietary intervention with a group of youth who did not engage in a dietary intervention for their seizures.
- Compare dietary intake of youth who engaged in a dietary intervention for DRE after the diet using a 3-day food diary, which will be compared to the food diary maintained by families just prior to commencing the diet.
- Explore families experiences while supporting their child with a dietary intervention for DRE (e.g., aspects that they found challenging) to examine potential barriers and facilitators to this intervention.

This is a single center study of cross-sectional design, which will include 24 patients who previously were treated with a dietary intervention for DRE. They will be identified from the clinic database from 2005 to 2020. A comparison group of patients with DRE who never tried the KD (n=24) will also be recruited. The study will comprise of a within-subjects comparison of changes to dietary intake from pre- to post-diet, and a between-subjects comparison between youth with DRE epilepsy who were on the KD, with those who did not undergo the diet as part of their treatment.

The study update is the following:

For the Keto (KD) group: 30 families have been invited to participate, 15 families consented (total participants=27). Of those, 18 completed questionnaires (12 parents and 6 children), and 6 completed and uploaded the food diaries.

For the Clinical Comparison group: 82 families have been invited to participate, 12 families consented (total participants=16), completed questionnaires=14 (11 Parents, 2 Youth (19+) and 1 child).
There has been no change in number of enrolled participants during the last term. Some of the families who consented to participate did not complete the questionnaires, but did not request to withdraw consent for the study.

26. <u>Brain Differences in Children with Rett Syndrome</u> - PI: Dr Weber/Dr Datta

Functional, Metabolic, and Structural MRI Findings in Rett Syndrome

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Catalist grant	20K	2021 2024	20	2	yes	active	

Background: Rett Syndrome (RTT) is a severe genetic brain disorder that typically manifests in females due to de novo mutations in the methyl-CpG-binding protein 2 gene (MECP2). Patients usually have normal early growth and development until 6 to 18 months of age, followed by a slowing of development, loss of purposeful hand movements, distinctive hand movements and deceleration of brain and head growth. Although there is a spectrum of clinical severity, common symptoms involve neurologic (seizures, movement disorders), cardiac (arrhythmias), gastrointestinal (poor feeding, gastroparesis), orthopaedic (scoliosis) and autonomic systems. Further research is necessary to understand anatomical, metabolic, and functional changes in the brains of children with RTT, and to link these changes with measures of genetics, disease progression and clinical features.

The primary aim of this study will be to investigate WM architectural and metabolic differences between girls with RTT (aged 5-12 years; n = 10) compared to healthy age-matched girls (aged 5-12 years; n = 5-10), as well as explore the relationship between these WM measures and RTT clinical severity scores, age, genetic MECP2 mutations, and seizures. Secondary aims will explore novel functional abnormalities in RTT and its association with severity, age, genetic mutations, and seizures.

Hypothesis 1: Reductions in fractional anisotropy (FA), as measured using DTI, in the genu and splenium of the corpus callosum and external capsule will be found in girls with RTT compared to controls. FA will be found to decrease with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

Hypothesis 2: Single voxel spectroscopy measures of NAA will be reduced in frontal lobe white matter, while mI and Glx will be increased. NAA, mI and Glx will be found to be correlated with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

Hypothesis 3: Resting state blood oxygen level dependent (BOLD) MRI measures of functional connectivity and brain dynamics complexity (Hurst exponent) will reveal reduced connectivity and efficiency of information processing (respectively) with age, clinical severity, and will be linked to specific MECP2 mutations and seizures.

This research will help identify the structural, metabolic and functional differences between girls with RTT and their healthy counterparts. These findings will be linked to specific MECP2 mutations and clinical severity, allowing for a greater understanding of the specific causes of RTT, and paving the way for future targeted therapies.

The Rett Sy patients (cases for the study) will undergo General Anesthesia for the MRI. We have included co-investigators from the Department of Anesthesia. ***The study is active with no enrolments in the last 6 months period.*** Due to difficult enrolment, the inclusion criteria have been modified and REB approved accordingly.

27. tDCS Study - PI: Dr. Datta

Transcranial direct current stimulation (tDCS) for treatment of pediatric focal refractory epilepsy not amenable to epilepsy surgery: a feasibility pilot study at BCCH

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A	0	2018-2024	6	6	yes	completed enrolment	

Summary: This is an open-label pilot study to investigate the feasibility of transcranial direct current stimulation (tDCS) in the pediatric population at BC Children's Hospital with treatment resistant focal seizures, who have been evaluated for epilepsy surgery and are deemed not to be epilepsy surgery candidates. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that has been shown to suppress regional cortical excitability, using electrodes through the scalp to stimulate the nervous system. It has also been shown to reduce inter-ictal epileptiform discharges (IEDs) and frequency of seizures in some clinical studies, including pediatric studies.

Method: We will include 6 children, adolescents and young adults, aged 6-21 years, with focal treatment resistant epilepsy, who are not amenable to epilepsy surgery.

There are 6 subjects enrolled so far. Five subjects have completed the treatment; one subject withdrew from the study. It was decided to wrap up the enrolment and perform the analyses of the already enrolled participants.

28. NIH Toolbox Study - PI: Dr. Datta/Dr Panenka

Determining Associations between Epileptiform Discharges, Cognition, and Emotional Functioning in Children with Epilepsy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Catalist Grant	22K	2018-2024	210	113	yes	completed enrollment	

Overview: Early detection of cognitive and emotional dysfunction in pediatric epilepsy is critical for improving outcomes. The proposed study aims to use a novel assessment tool, the 'National Institutes of Health Toolbox', to characterize cognitive functioning in pediatric idiopathic epilepsy and to investigate how cognitive and emotional functioning are impacted by inter-ictal seizure activity.

Study Goals and Objectives: This study will systematically screen children with idiopathic epilepsies (IE) for cognitive and emotional deficits using the NIH Toolbox and standardized psychological screening tools. Our goal is to investigate the impact of inter-ictal epileptiform discharges (IEDs) features on cognitive and emotional functioning in patients with IGE. Based on the above reviewed evidence, we hypothesize:

- Children with IE will exhibit global and domain-specific cognitive impairments compared to same-aged peers.
- A higher frequency of IEDs will be associated with poorer global cognitive functioning (i.e., cognitive composite score) and increased symptoms of depression and anxiety.
- Location of IEDs will be associated with different profiles of cognitive functioning.

Implications: If practicality and feasibility are demonstrated, this project will immediately change care for children in the BC epilepsy service as the NIH Toolbox is then likely to be adopted into clinical care. This study will also increase our understanding of how IEDs contribute to cognitive and emotional dysfunction in epilepsy, and has the potential to inform therapies that will ultimately improve outcomes for affected children.

There are 113 subjects enrolled in the study, with completed enrolment. The data analysis is underway.

29. Alexander Disease study - PI: Dr. Demos – *closed this term*

A Phase 1-3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ION373 in Patients with Alexander Disease

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Ionis Pharmaceuticals	62K/pt 19K start-ups	2021 2026	2-4	0	yes	active	

This is a registration supporting (Phase 1-3), double-blind, randomized, placebo-controlled study conducted at multiple centers.

The primary objective is to evaluate the efficacy of ION373 in improving or stabilizing gross motor function in patients with Alexander disease.

The secondary objective is to further evaluate the efficacy of ION373 in improving or stabilizing disease manifestations across the full range of affected domains (gross and fine motor, communication, swallowing, autonomic and/or other gastrointestinal functions, nutritional/growth status) in patients with Alexander disease.

The exploratory efficacy objective is to explore the effects of ION373 in additional disease specific clinical manifestations, such as orthostatic hypotension (OH) and macrocephaly, and in exploratory disease progression biomarkers.

The pharmacokinetic objective is to characterize the pharmacokinetics (PK) of ION373 in cerebrospinal fluid (CSF), plasma and urine in patients with Alexander disease.

The safety objective is to evaluate the safety and tolerability of ION373 in patients with Alexander disease.

This study is composed of 2 periods – a Double-Blind Treatment Period and an Open-Label Treatment Period – each with a duration of 60 weeks.

The study has been closed.

30. Epilepsy & Genomics study - PI: Dr. Demos

Pediatric Epilepsy: Using Genomics to Improve Patient Care and Outcomes

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript

Yes	Alva Foundation UBC Vancouver Foundation	100,000 45,000 50,000	2014 ongoing	300	266	yes	active	multiple abstracts, papers

Current methods of genetic testing in Canada limit doctors' ability to identify genetic disorders implicated in epilepsy in a timely fashion, and it's likely that some go undiagnosed. Modern genomic technologies such as next-generation sequencing (NGS), specifically whole exome sequencing (WES), allows for simultaneous sequencing of many genes or exons (coding region of DNA) all at one time. Compared to current standards of genetic testing in Canada, the use of whole exome sequencing would allow for earlier diagnosis of single gene disorders causing epilepsy and thus earlier institution of appropriate treatment which could have a positive impact on outcome.

Overall Objectives

Performing WES technology in infants and young children with epilepsy of unknown cause will likely increase numbers identified to have a single gene disorder causing epilepsy and allow for more rapid diagnosis of a single gene disorder which in turn will allow for earlier intervention with a specific treatment plan based on genetic cause. The latter will likely lead to better outcomes for children and their families. WES may also reduce costs associated with current testing strategies which often involve extensive investigations in children with epilepsy of unknown cause.

A total of 160 eligible patients (and their parents) between the ages of 0 and 18 years attending the Pediatric Neurology Clinic at BC Children's Hospital or admitted to BC Children's Hospital will be invited to participate in this study. Genetic counselling will be offered to all families, both pre- and post-testing. In this study, new genetic technologies will efficiently analyse the genes of participating children to learn more about the cause of their epilepsy and how it can be treated.

There are 266 subjects enrolled in the main study, including 7 siblings. This main study is no longer enrolling. The 17 trios for Whole Genome Sequencing are being analysed with a collaboration with the Rare Disease Discovery Hub at BCCHRI.

There are two sub-studies associated with this study. Both sub-studies have been REB approved. Sub-study 1 named: "Clinical Whole Exome Sequencing" is focused on identifying gene variants and gene candidates associated with epilepsy in children who have seizures and epilepsy and have undergone whole exome sequencing through clinical investigations. ***There are 42 subjects currently enrolled in sub-study 1, with no enrollements in the last period, and the sub-study is actively enrolling.*** Sub-study 2 is named "Parents of Children Who Have Undergone Genetic Testing for Epilepsy" and is focused on interviewing parents of participants in the main study who have been told their child's WES results, to determine the importance of genetic testing in parents' decision-making regarding their children's epilepsy treatment, and care. ***There are 28 subjects currently enrolled in sub-study 2, with no enrolments in the last period, and the sub-study 2 is closed to enrollment.***

Exome re-analysis: Re-analyzing research exome sequencing data in unsolved cases to identify candidate genetic variants responsible for patient's phenotype. These patients are recruited under EPGEN study and have undergone exome sequencing on research basis.

We have started a regular Genomics rounds every month to discuss genetic causes of epilepsy in our patients.

31. <u>IDIC 15 Registry</u> - PI: Dr. Demos – *closed this term*

The Isodicentric chromosome 15 (Idic (15)) registry of British Columbia, Canada

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A		2015 2025	50	0	yes	closed	N/A

Current Isodicentric chromosome 15 (Idic(15)) is a rare chromosomal disorder in which affected people have additional genetic material derived from chromosome 15.

Hypothesis: The development of a provincial Idic(15) registry will provide the patient numbers and clinical data necessary to facilitate research, including potentially breakthrough therapeutic translational research, and will allow for ongoing accurate education of affected patients/families and medical professionals on this disorder.

Objective: The purpose of this registry is to learn more about the rare chromosomal disorder Isodicentric chromosome 15 with the goal of improving the future for patients with Idic(15) through the enablement and support of research. The registry will compile de-identified clinical data that will further researchers understanding of the disorder, enabling the identification of important research questions and the planning of future studies.

The study has been dormant for few years, and was closed this term.

32. <u>IDIC 15 Registry</u> - PI: Dr. Demos – ***new study this term***

The Isodicentric chromosome 15 (Idic (15)) registry of British Columbia, Canada

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A		2024 No end	All eligible	0	yes	active	N/A

The protocol of the recently closed study was re-worked and the new study initiated this term. Isodicentric chromosome 15 (Idic(15)) is a rare chromosomal disorder in which affected people have additional genetic material derived from chromosome 15. An affected child typically has developmental delay/intellectual disability, seizures and autistic behavior. The seizures can be severe and difficult to treat and affected children and adults are at increased risk of sudden, unexpected and unexplained death. There are no specific guidelines for treatment and research is limited by small numbers of identified affected individuals and amount of accurate information available on them. Rare disease registries are vital for collecting accurate information and facilitating research which has significant impact on care. The development of a provincial Idic(15) registry will provide the patient numbers and clinical data necessary to facilitate local research, including potentially breakthrough therapeutic translational research, and will allow for ongoing accurate education of affected patients/families and medical professionals on this disorder.

The registry will collect the data on ongoing basis. The intention for this registry is to improve outcome of affected individuals by capturing information that will allow for earlier diagnoses and interventions, more effective research, and improved access for patients and clinicians to accurate and up-to-date information on this disorder. We will be collecting data from participants' medical charts. This data may be collected retrospectively by accessing participants' health records. Therefore, the data will be collected over the time frame of the participants' lives.

The study was approved in December 2023, and is open for enrolment. ***There are no participants enrolled yet.***

33. CAE- Pharmacogenomics-PI: Dr. Demos

Investigating Treatment-Resistance to Ethosuximide in Childhood Absence Epilepsy by Genome-Wide Association Study

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCCHRI Seed grants		2020 2024	250-300	55	yes	active	

Purpose: In this study, we would like to investigate clinical and contributing genomic factors that may influence treatment response to ethosuximide in patients with childhood absence epilepsy.

Hypothesis: Common polymorphisms in genes directly or indirectly associated with etiology, pathogenesis, and drug metabolism of ethosuximide, along with clinical features manifesting in childhood absence epilepsy could be associated with variable treatment response and seizure outcome.

Objectives:

1. Evaluate clinical factors associated with treatment response to ethosuximide in patients with childhood absence epilepsy treated with ethosuximide.

2. To compare common genomic polymorphisms in childhood absence epilepsy patients who respond to ethosuximide versus non-responders.

Sample size: Our hospital records from 2018 to 2020 (2 years) revealed a total of 159 documented cases of typical absence seizures. This number is expected to be lower than the reality as the software often overlooks the actual clinical data. We consulted a statistician for sample size calculation. The sample size of 289 is calculated based on the main outcome of treatment resistance with an anticipated rate of 15% to ethosuximide. Based on these two indications, we estimate that 270-300 patients will meet the inclusion and exclusion criteria.

Analysis of results: We will perform Chi-Square and Fisher's exact tests for group comparisons. A p–value less than 0.05 will be considered significant. Relations between outcomes and variables will be analyzed by using the multivariate logistic regression model. GWAS specific statistical analysis will be carried out for genomic data analysis.

There are 55 subjects enrolled in the study, with 6 enrolments in last period. There are saliva samples collected from 48 participants so far.

34. CARE-E Study – PI: Dr. Huh

Cannabidiol in Children with Refractory Epileptic Encephalopathy: A Phase 1 Open Label Dose Escalation Study (CARE-E).

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Saskatchewan Health Research	$4,500 start-up $4,000/patient	2016 – 2024	7	7	yes	completed	N/A

	Foundation							

This is an open label dose escalation study. The overall study is being conducted and sponsored by the University of Saskatchewan. The medical marijuana (Cannabis) Herbal Extract used in this study will be produced from the CanniMed® brand of Marijuana for Medical Purposes Regulations (MMPR) product produced by Prairie Plant Systems Inc. (PPS) who are based in Saskatoon, Saskatchewan. PPS is providing technical assistance with the production of the Cannabis Herbal Extract, but is not providing financial assistance to perform this study.

The purpose of this research study is to assess the safety and tolerability (how well a person deals with side effects) of a CBD-enriched Cannabis Herbal Extract (the study drug) in a small group of children with refractory epileptic encephalopathy. This is a pilot study, which means that it is a small-scale preliminary study. Because of the small number of participants in this pilot study, this study will not be able to determine the effectiveness of the study drug. Instead, it is hoped that the results of this study will allow us to determine appropriate dosage regimens for children, and to allow for larger clinical trials to take place.

This study will also look at:

1. The pharmacokinetics (what the body does to a drug) of the study drug;
2. How effective the study drug is at decreasing the number and duration of seizures;
3. The effect of the study drug on developmental functioning of study participants;
4. Measuring the general well-being of study participants using quality of life questionnaires.

The study was expected to enrol approximately 30 participants from 5 Canadian sites (University of Saskatchewan, University of Alberta, University of Manitoba, Universite de Montreal and the University of British Columbia).

There are 7 subjects enrolled at BCCH, all of them completed the study visits according to the protocol. The data cleaning and monitoring is still underway.

35. CEEG Consortium - PI: Dr. Huh

A Critical Care EEG Monitoring Research Consortium

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A	N/A	2016 2025	All eligible	0	yes	active	N/A

The goal of this project is to collect and analyze de-identified clinical and EEG data obtained as part of routine clinical care at each center. This information will serve as preliminary data and inform the design of future studies with the following aims over the next 10 years. This is a non-interventional, observational study of patients who are undergoing cEEG monitoring in the ICU. Patients receiving video-EEG monitoring for non-emergent or non-acute reasons (e.g. characterization of chronic seizures) will be excluded from the study. ICU cEEG monitoring will be performed as clinically indicated and patients will be treated according to local standards of care at the discretion of the clinical care team. This study makes use of data already being collected as part of routine clinical care and does not involve patient or family contact. The study involves critically ill patients most of whom will not be capable of giving informed consent during their acute illness. ***The study is active, without pediatric reports available so far.***

36. EPBiome Study – PI: Dr. Huh

Leveraging the gut microbiota in pediatric refractory epilepsy: Safety and feasibility of oligofructose-enriched inulin supplementation for dysbiosis and seizure control

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Garfield Weston	149,206	2019-2024	75	26	yes	active	N/A

This is a two parts study: (A) Randomized, open-label, pilot study, and (B) randomized double-blind. Primary objectives include:

- To evaluate inter- and intra-patient variability in gut microbiome in epilepsy patients
- To evaluate the tolerability of inulin administration alone or in combination with the KD in patients with epilepsy
- To assess the feasibility of sample collection in this population

Secondary objectives include:

- Effects of inulin on the GM of children on KD
- Effects of inulin on seizure frequency in children with refractory epilepsy

Randomized 1:1 to receive inulin while on KD, or proceed with KD alone. The treatment duration will be 3 months, and the sample size is 75. REB submission was made to amend the study visits to be virtual instead of on site visits. ***There are 26 subjects enrolled in the study, 3 in the KD arm, 11 in the epilepsy arm, 10 controls and 2 withdrawn subjects. There were no enrolments during the last period.***

37. <u>VNS study</u> - PI: Dr. Dewi Schrader; Co-PI: Dr. Connolly

Predicting Seizure Responsiveness to Neuromodulation Using Connectomic Profiling (Vagus Nerve Stimulation [VNS] Study)

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	SickKids/ CIHR	2020-2025	10	2	Yes	active	N/A

Medically intractable epilepsy is a form of epilepsy that does not get better with medication. Children with poorly controlled epilepsy may be treated with a surgical procedure called vagal nerve stimulation (VNS). VNS involves putting a device called a pulse generator inside the body which sends regular mild electrical pulses to calm down irregular brain activity that leads to seizures. The study aims to look at how VNS therapy affects seizures and health-related quality of life – quality of life questionnaires will be administered to both parents and patient, and MRI imaging will be used to quantify the effects of VNS. ***There were no enrolments in the last period.***

38. In Silico Study - PI: Dr. Schrader

Connectome-informed simulations of pediatric epilepsy surgery

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	SickKids Foundation	295K	2017-2024	50 (35 cases, 15 controls)	25 cases 9 controls	Yes	Active	

Overall hypothesis is that preoperative MRI markers alone are not sufficient to predict outcome of childhood epilepsy surgery, which is *per se* an invasive procedure that induces a cascade of degenerative and plastic brain changes. Instead, preoperative indicators of outcome should be combined with models that simulate consequences of a given surgical approach based on empirical data.

Objective 1 will integrate preoperative markers and data on the actual surgery (resection extent obtained from postoperative MRI). Multi-parameter MRI will map atrophy, gliosis, and myelin changes, directly testing whether anomalies outside the resected area predict seizure relapse. Conversely, pattern analysis of memory and language fMRI will localize regions critical for performance, and test whether their resection relates to postoperative cognitive decline.

Objective 2 will longitudinally analyze feature change from pre- to postoperative MRI, mapping degeneration and functional reorganization in non-resected areas. We will develop a connectome-based framework that simulates postsurgical brain reorganization. Simulations of surgical effects are expected to improve predictive models developed in *Objective 1*.

There are 9 controls and 25 cases enrolled at BCCH, with two case enrolments in the last period.

2.2. BRAIN INJURIES/INFLAMMATION

1. Advanced neuroimaging in pediatric stroke study - PI: Dr. Bjornson

Advanced neuroimaging in Pediatric Stroke, Pathophysiology of injury and repair in children with focal brain ischemia

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Brain Canada	27,000	2017-2024	90 total, 15/BCCH	19	yes	active	

Research in pediatric stroke has lagged far behind adult stroke due to a lack of use of advanced brain imaging including MRI. Post-stroke recovery is much better in the developing brain (infants and children) compared with the mature brain (adults). Insights from MRI and other brain imaging have a tremendous ability to inform us on the reasons and mechanisms for the increased recovery in the developing child's brain. Tracking the brain's anatomic and functional changes from the time of acute stroke during the first year of recovery in children suffering stroke will allow us to better understand the mechanisms of stroke injury and repair, predict outcome, and develop new strategies for brain protection and rehabilitation.

The purpose of this study is to discover mechanisms of injury and repair in children with stroke and correlate these with better and worse neurodevelopmental outcomes. The overall objective of this study is to discover mechanisms of injury and repair in children with stroke and correlate these with better and worse neurodevelopmental outcomes. Study design:

This is a prospective observational study. Each case participant will undergo MR imaging 4 times over 12 months. Each control participant will be undergo 2 hours of MR scanning, as either one or two scan sessions. The total number of study participants is 90. At BCCH, we aim for 15 study participants. ***There are 16 adult controls and 3 cases enrolled in the study, with no enrolments in the last period.***

2. IPSS Study - International Paediatric Stroke Study; PI: Dr. Bjornson

International Pediatric Stroke Study

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	N/A	2006 ongoing	100	79	Yes	Active	N/A

The purpose of this study is to obtain preliminary data from large multi-center studies assessing sub-types, outcomes and current treatments for newborns and children with stroke. Due to the relative rarity of childhood stoke, sufficient numbers of patients to provide the necessary power can only be achieved with multi-center and multi-national approaches.

The overall objective is to develop and conduct clinical trials in childhood stroke.

The specific aims are:

Objective 1: To ascertain in a prospective cohort study the numbers of newborns and children with ischemic stroke, their stroke sub-types and risk factors, their current treatments and outcomes within the participating centers. These data will provide the rationale and feasibility data for the study group to design and implement the initial RCT's in paediatric stroke as well as other fundable grant proposals.

Objective 2: To develop and institute standardized protocols for (1) diagnosis, (2) investigation of risk factors, (3) antithrombotic therapies and (4) outcome assessment of neonates and children with arterial ischemic stroke and sinovenous thrombosis

Objective 3: To develop standardized data forms and an appropriate database with web-based data entry from multiple study sites.

Objective 4: Submit successful grant applications for additional funding of IPSS multi-centre studies.

This prospective study will enrol newborns and children with ischemic stroke born at or referred to BC Children's Hospital. This study will then follow these newborns at 3 and 12 months post stroke. ***There are 79 subjects enrolled in the study so far, with no enrolments in the last period.***

3. CFRIF Scans for Protocol Development - PI: Dr. Bjornson

Child & Family Research Imaging Facility - Scans for Protocol Development

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	N/A	2012 - 2024	200	62	Yes	Active	N/A

The purpose of this study is to develop and optimize magnetic resonance (MR) imaging protocols for the 3.0 Tesla scanner located on the UBC Oak Street campus at the Children's & Women's Health Centre of BC.

Hypothesis: After optimization, we expect that the CFRIF will be able to safely and efficiently supply high-quality MR data for individual research studies.

Justification: MRI studies will enhance quantitative and dynamic assessments of tissue structure, microstructure, metabolism and function which ultimately improve early diagnosis and provide new information for treatment. Thus sequences need to be optimized and equipment tested and calibrated. We therefore require practice scans on volunteers to establish appropriate MRI scan protocols and computational approaches before we can host research studies.

Objectives: To maintain a high standard of quality, ensure safety and efficiency by developing and optimizing magnetic resonance (MR) imaging protocols for the new 3.0 Tesla scanner located on the UBC Oak Street campus at the Children's & Women's Health Centre of BC.

The study is active with 61 subjects enrolled, with one enrolment during the last period.

4. Biohaven Migraine Study – PI: Dr. Lee *–new study this period*

A A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Migraine Prevention in Children and Adolescents ≥ 6 to <18 years of age

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript

Yes	Pfizer/ Biohaven	54K/pt 32K start up fees	2024-2028	3	0	pending	not started yet	N/A

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention in children and adolescents ≥ 6 to < 18 years of age with episodic migraine. There is an optional open-label, extension phase following the double-blind, treatment phase.

Primary Objective is to compare the efficacy of rimegepant to placebo as a preventive treatment for migraine in adolescents (>12 to <18 years of age) with episodic migraine, as measured by the reduction from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase. (A month is defined as 4 weeks for the purpose of this protocol.)

Secondary Objectives:

Key Secondary Objectives:

- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month over the entire course of the double-blind treatment phase in adolescents with episodic migraine.
- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month in the first 4 weeks of the double-blind treatment phase in adolescents with episodic migraine.
- To compare the change from baseline in the Pediatric Quality of Life (PedsQL™) 4.0 Generic Core Scales total score at Week 12 of the doubleblind treatment phase between rimegepant and placebo in adolescents with episodic migraine.

Other Secondary Objectives:

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month over the entire course of the double-blind treatment phase in children (≥ 6 to <12 years of age) and children and adolescents combined (≥ 6 to <18 years of age) with episodic migraine.
- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 50% reduction from baseline in the mean number of moderate to severe migraine days per month over the entire course of the double-blind treatment phase in children, and children and adolescents combined with episodic migraine.
- To compare the use of acute migraine-specific medications (triptans) between rimegepant and placebo based on the change from baseline in monthly acute migraine specific medication days in each month and over the entire course of the double-blind treatment phase in adolescents, children, and children and adolescents combined.
- To evaluate the safety and tolerability of rimegepant as a preventive treatment for migraine in children and adolescents.
- To evaluate the frequency of hepatic-related adverse events (AEs) and the frequency of hepatic-related treatment discontinuations in subjects treated with rimegepant.

Exploratory Objectives:

- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the double-blind treatment phase in adolescents, children, and children and adolescents combined with episodic migraine.

- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 50% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the double-blind treatment phase in adolescents, children, and children and adolescents combined with episodic migraine.
- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have at least a 75% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the double-blind treatment phase in adolescents, children, and children and adolescents combined with episodic migraine.
- To compare the efficacy of rimegepant to placebo on the proportion of subjects that have a 100% reduction from baseline in the mean number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the double-blind treatment phase in adolescents, children, and children and adolescents combined with episodic migraine.
- To compare the efficacy of rimegepant to placebo on the reduction from baseline in the mean number of migraine days per week by severity (total; moderate or severe) in the first week of the double-blind treatment phase in adolescents, children, and children and adolescents combined with episodic migraine.
- To evaluate the reduction in the number of migraine days per month by severity (total; moderate or severe) in each month and the entire course of the open-label extension phase in adolescents, children, and children and adolescents combined.
- To evaluate the frequency of ALT or AST > 3x ULN with concurrent elevations in bilirubin > 2x ULN in subjects treated with rimegepant.
- To evaluate the frequency of elevated liver function tests (AST, ALT, or total bilirubin) in subjects treated with rimegepant.
- To evaluate the frequency of subjects with ALT or AST elevations > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with rimegepant.
- To evaluate the effect of rimegepant treatment on Pediatric Quality of Life (PedsQL™) domain scores in adolescents, children, and children and adolescents combined.
- To compare the change from baseline in the Pediatric Migraine Disability Assessment (PedMIDAS) total score at Week 12 of the double-blind treatment phase between rimegepant and placebo in adolescents, children, and children and adolescents combined.

The study will recruit male and female subjects, who are at least 6 years of age and less than 18 years of age at the time of signing consent/assent with at least a 6 month history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition.1

This protocol will initiate with enrollment of subjects who are ≥12 to <18 years of age; enrollment of subjects > 6 to <12 years of age will initiate at a later date, pending additional clinical pharmacology data from an ongoing Phase 1 study in this patient population.

Number of Subjects:

Approximately 1100 subjects will be screened to randomize approximately 640 subjects with episodic migraine, to rimegepant or placebo, of which approximately 160 will be children (>6 to < 12 years of age) and 480 will be adolescents (>12 to <18 years of age). It is also expected that there will be a similar number of subjects enrolled in the >12 to <16-year age range and the >16 to <18 year age range. It is estimated that approximately 510 subjects may enter the open-label,

extension phase; to ensure adequate information on safety, at least 200 subjects will be treated with rimegepant for up to 1 year.

The study is under REB review, and the CTA is currently being negotiated..

5. PIBD (Pediatric Inflammatory Brain Disease) database – PI: Dr Schrader

Cerebral Brain inflammation in pediatric diseases: Development of a cross-specialty collaborative research program

Funding	Source	Amount $	Study period	Approvals	Status	Abstract/ Paper/ Manuscript
yes	BCCHRI infrastructure award	65K	2022 - 2024	QI/QA No approvals needed	active	N/A

This pilot study will develop a cross-disciplinary research approach at BCCH for the study of patients with pediatric inflammatory brain diseases (PIBD). It will benchmark the scope of the problem of PIBD across our campus and demonstrate in a pilot cohort the feasibility of patient recruitment to a centralized research registry. Participants with diagnoses of systemic lupus erythematosus, systemic autoinflammatory diseases, central inflammatory or autoimmune diseases, and obsessive-compulsive disorder will be recruited to this registry over the funding period. Cross-sectional assessments will include (a) clinician-reported disease activity or severity; (b) screening for emotional and behavioural problems and executive dysfunction; (c) patient-reported outcome measures for anxiety, depressive symptoms, stress, cognitive function, fatigue, mobility, sleep, and pain; (d) health-related quality of life; and (e) screening for adversity and resilience factors. Scores for validated outcome measures will be compared to normative population data. Exploratory analyses will evaluate associations among outcome measures. Patient/family perspectives on registry participation as well as future linked biological sample collection and neuroimaging will be determined by a study-specific questionnaire. This study will demonstrate proof-of-principle in the development of clinical and translational research capacity across pediatric subspecialties, with the goal of catalyzing new research and improving care for children with diseases affecting the brain with an inflammatory background.

The QI/QA RedCap database has been developed. ***The data for 14 subjects has been entered into the database, with no new entries in the last quarter.***

6. <u>PIBD pilot study</u> - PI: Dr. Dewi Schrader

Brain inflammation in pediatric diseases: Prospective cross-specialty collaborative cohort study

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Catalyst grant BCCHRI	2023-2025	45	2	yes	active	N/A

This pilot study will assess the feasibility of a centralized registry incorporating standardized patient- and clinician-reported measures of mental and physical health in patients and their families

with inflammatory brain diseases, specific primary inflammatory or autoimmune brain diseases, SLE, and OCD associated with a suspected immune-related syndrome. We will also assess patients' and families' interest in participating in future linked biomarker and neuroimaging studies.

This is a cross-sectional observational pilot study in which participants recruited from each of the three clinics/services (Rheumatology, Neurology, Psychiatry) will be enrolled over a 12-month period. Target sample size is at least 15 participants per clinic based on preliminary data regarding number of patients seen at BCCH within each diagnostic group over the past three years.

Objective 1: To assess the feasibility of recruitment to and participation in a centralized pediatric inflammatory brain diseases (PIBD) registry, either for clinical purposes only, or for clinical purposes and research. The registry will include standardized patient- and clinician-reported measures of mental and physical health for patients and their families presenting to BCCH with the following diagnoses:
1) Primary inflammatory or autoimmune brain disease
2) Systemic lupus erythematosus
3) Obsessive-compulsive disorder with PANS/PANDAS syndrome or significant immune-related comorbidity

Objective 2: In exploratory analyses, to compare patient-/parent-reported outcome measures (PROMs) across diagnostic categories. Standardized physical, cognitive, and mental health outcome measures will be collected as listed in Table 1 of the protocol.

Objective 3: To assess patients' and families' interest in participating in future linked biomarker and neuroimaging studies.

We expect that implementation of this pilot registry will be feasible (based on acceptability to patients, demand for the program among clinicians and patients, implementation, and practicality of integration with clinical care) and generate pilot descriptive data characterizing a spectrum of cross-sectional cognitive and mental health outcomes across the three disease groups included in the study. We anticipate that this pilot study will demonstrate proof-of-principle in the development of clinical and translational research capacity across pediatric subspecialties, with the goal of catalyzing new research and improving care for children with diseases affecting the brain with an inflammatory background. Comparison of patient-reported outcome measures (PROMs) relative to standardized norms and between groups will be exploratory rather than hypothesis-driven.

There are 2 participants enrolled in the study, both of them during the last term.

2.3. DEVELOPMENTAL MALFORMATION / NEUROMUSCULAR DISEASES

1. CNDR Registry - The Canadian Neuromuscular Disease Registry - PI: Dr. Selby

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Marigold Foundation, Jesse's Journey.	9,000/year	2011 ongoing	400 @ BCCH	409	yes	active	N/A

Neuromuscular Diseases (NMDs) are comprised of a group of disorders involving the central and peripheral nervous systems (brain, spinal cord, nerve roots, plexi, peripheral nerves, etc.) and smooth and/or skeletal muscle. Lack of epidemiologic data on NMDs in Canada, combined with the recognition that small, single-centre clinical studies provide inadequate sample sizes to study NMDs, and the growing international interest in NMD registries, suggest that a new, more comprehensive approach is needed in Canada. The CNDR will create a national framework to provide mutual accessibility between patients and medical scientists to facilitate clinical studies on a national level while providing access to patients from all across Canada including those in remote areas with limited access to specialized neurologic care.

The primary objective of this study is to improve the future for Neuromuscular Disease (NMD) patients through the enablement and support of research into potential treatments.

Secondary Objectives include:

- Enhancing the understanding of NMD epidemiology in Canada
- To understand variations in disease management in Canada
- Foster collaborative research initiatives amongst Canadian investigators
- Identify important research questions
- Create a tool for clinical knowledge translation allowing more uniform standards of care in Canada
- Attract international trial opportunities by making Canada more congruent with the international neuromuscular (NM) community

There are 409 subjects enrolled at BCCH site in this registry, with 1 enrolment in the last 6 months period.

2. DELIVER Study (Dyne DMD) - PI: Dr Selby

A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study Assessing Safety, Tolerability, Pharmacodynamics, Efficacy, and Pharmacokinetics of DYNE-251 Administered to Participants with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping (DELIVER Study)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Dyne	112K/pt 24.5K start-up	2022 2027	4 @ BCCH	0	pending	Not started yet	N/A

Dyne Therapeutics, Inc (Dyne) is focused on delivering disease-modifying therapeutics for genetically driven muscle disease. DYNE-251 is an antigen-binding fragment (Fab)-drug conjugate (FDC) designed to efficiently deliver an exon 51 skipping PMO therapeutic to muscle tissue for the treatment of DMD, a rare, X linked progressive neuromuscular disease.

The purpose of this first-in-human study is to evaluate the safety, tolerability, PD, efficacy, and PK of multiple ascending doses of DYNE-251 administered IV to participants with DMD caused by mutations amenable to exon 51 skipping. This study is designed to identify the therapeutic dose, which may be used in future studies.

Primary Objectives:
1. To evaluate the safety and tolerability of multiple IV doses of DYNE-251 administered to participants with DMD
2. To evaluate dystrophin protein levels in muscle tissue following multiple IV doses of DYNE-251 administered to participants with DMD

Secondary Objectives:
1. To evaluate the effects on muscle tissue exon skipping, percent dystrophin-positive fibers (PDPFs), and blood creatine kinase (CK) following multiple IV doses of DYNE-251 administered to participants with DMD
2. To evaluate muscle function following multiple IV doses of DYNE-251 administered to participants with DMD
3. To evaluate plasma and muscle tissue PK following multiple IV doses of DYNE 251 administered to participants with DMD
4. To evaluate the immunogenicity of multiple IV doses of DYNE-251 administered to participants with DMD

Exploratory Objectives:
1. To explore muscle function following multiple IV doses of DYNE-251 administered to participants with DMD
2. To explore patient-reported outcomes (PRO) following multiple IV doses of DYNE 251 administered to participants with DMD

This is a multiple ascending dose (MAD) study with a double-blinded, placebo-controlled component to assess the safety, tolerability, PD, efficacy, and PK of DYNE-251 administered IV to participants with DMD caused by mutations amenable to exon 51 skipping. Twenty-eight participants (20 on active treatment, 8 on placebo) will be enrolled across number of sites across the globe.

REB review is underway, and the contract has been fully executed.

3. ARGX-113-2006 (ADAPT JR) Study - PI: Dr Selby

An Open-label Uncontrolled Trial to Evaluate Pharmacokinetics, Pharmacodynamics, Safety, and Activity of Efgartigimod in Children From 2 to Less Than 18 Years of Age With Generalized Myasthenia Gravis

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Argenx BV	12K/pt 25K start-up fees	2023 2028	2	0	yes	active	N/A

The aim of this trial is to investigate the pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, immunogenicity, and activity of efgartigimod administered intravenously (IV) in pediatric participants from 2 to less than 18 years of age with generalized myasthenia gravis (gMG).

Objectives:

Primary Objective: To confirm an age-adjusted optimum dose of efgartigimod IV and provide (model-predicted) evidence for a treatment response.

Secondary Objectives:

- To evaluate the safety and tolerability of efgartigimod IV
- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of efgartigimod IV
- To evaluate the immunogenicity of efgartigimod IV
- To evaluate the activity and impact on quality of life of efgartigimod IV
- To evaluate the effect of efgartigimod treatment on antibody response to vaccines

Research Design:

ARGX-113-2006 is an, open-label, multicenter uncontrolled trial in pediatric participants with gMG. Before starting the trial, the appropriate dose for the age range of 12 to less than 18 years will be predicted based upon adult-exposure modeling. The trial is comprised of a single dose-confirmatory part (Part A), followed by a multiple-dose treatment response-confirmatory part (Part B). At least 12 evaluable participants for the primary analysis will be enrolled in the trial with at least 6 evaluable participants per age group (age groups 12 to less than 18 years and 2 to less than 12 years).

There are no participants enrolled in the study yet.

4. ARGX-113-2008 Study - PI: Dr Selby

A Long-term, Single-Arm, Open-label, Multicenter, Follow-on Trial of ARGX-113-2006 to Evaluate Safety of Efgartigimod Administered Intravenously in Children with Generalized Myasthenia Gravis

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Argenx BV	12K/pt 25K start-up fees	2023 2028	2	0	yes	active	N/A

The aim of this trial is to investigate the long-term safety, tolerability, and immunogenicity of efgartigimod administered intravenously (IV) in pediatric participants ages 2 to less than 18 years with gMG rolling over from the ARGX-113-2006 trial and to ensure access to the drug before commercial availability or until another option to access efgartigimod is available.

Objectives:

Primary Objective: To evaluate the safety and tolerability of efgartigimod IV

Secondary Objective: To evaluate the immunogenicity of efgartigimod IV

Exploratory Objective: To evaluate the activity and impact on daily activities of efgartigimod IV in participants

Research Design: ARGX-113-2008 is a long-term, single-arm, open-label, multicenter, follow-on trial of ARGX-113-2006 to evaluate the safety of efgartigimod administered intravenously in pediatric participants ages 2 to less than 18 years with gMG.

The study is REB approved. There are no enrolments yet.

5. WVE-N531 DMD Study - PI: Dr Selby - *study closed this term*

An Open-label Phase 1b/2a Study of WVE-N531 in Patients with Duchenne Muscular Dystrophy)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Wave	53K/pt 26K start-up fees	2022 2027	1-2	0	no	closed	N/A

Purpose: This is a first-in-human Phase 1b/2a open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), Pharmacodynamics (PD), and clinical effects of intravenous (IV) WVE-N531 in patients with Duchenne Muscular Dystrophy (DMD) amenable to exon 53 skipping intervention.

Hypothesis: WVE-N531 administered intravenously at 1 mg/kg will be safe and well-tolerated, and will result in exon skipping in patients with DMD. Skipping Exon 53 will allow participants bodies to produce a shortened, but still working, form of the dystrophin protein; which may result in improved muscle function in people with DMD.

Objectives:

Primary Objective: To evaluate the safety and tolerability of WVE-N531 in patients with DMD amenable to exon 53 skipping intervention.

Secondary Objective(s):

- To determine the concentration of WVE-N531 in muscle tissue.
- To evaluate the PD effect of WVE-N531 by assessing changes in dystrophin levels in deltoid muscle tissue.
- To characterize the PK of WVE-N531.

Exploratory Objective(s): To evaluate the clinical effects of WVE-N531 by assessing changes in muscle function, muscle strength, and pulmonary function.

Study Design: This is a Phase 1b/2a open-label study to evaluate the safety, tolerability, PK, PD, and clinical effects of intravenous (IV) WVE-N531 in patients with DMD. To participate in the study, patients must have a documented mutation of the DMD gene that is amenable to exon 53 skipping intervention.

The sponsor decided to walk away.

6. SMA Exergame Study - PI: Dr Selby

Patient centred trial promoting physical activity and participation in children with SMA

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	CIHR	15,955	2022 2024	7 @ BCCH 15 in total	4	yes	active	N/A

Our overall objective is to improve motor outcome for children with SMA, using an evidence-based approach, and building on our expertise in patient registries and common data elements. The SMA research program is embedded in INFORM RARE, an innovative clinical trials initiative funded (2020-2025) by the Canadian Institutes of Health Research (CIHR) Strategy for Patient Oriented Research (SPOR) co-designed by patients and families, health care providers, policymakers, methodologists, and experts in research ethics. INFORM RARE addresses a recognized need for innovation in rare disease, using patient registries as platforms for trials to facilitate timely and robust evidence generation in support of the decision needs of stakeholders.

Specific Aims:

- To develop the exergaming intervention using an iterative process with feedback from a multidisciplinary team including co-investigator parents
- To assess the feasibility & usability of the exergaming intervention
- To assess the feasibility of using the Syde© device as an outcome measure

Inclusion Criteria for Children with SMA

- Participants enrolled in the Canadian Neuromuscular Disease Registry;
- Confirmed genetic diagnosis of 5q SMA;
- Aged 6-18 years old;
- Able to stay seated independently for at least 10 seconds;
- A score of at least 2 points in entry item A of the RULM (i.e., “Can raise 1 or 2 hands to the mouth but cannot raise a 200 g weight in it to the mouth”);
- Treated with disease-modifying therapy;
- Receiving care the INFORM Rare pediatric centers from Quebec and British Columbia. Exclusion criteria:

There will be no exclusion based on SMN2 copy number.

Inclusion Criteria for Healthy Controls: Aged 6-18 years old.

Exclusion criteria for healthy controls: Any neuromuscular disorder or other disorder deemed to affect motor function according to investigator.

Setting: A total of 22 subjects will be recruited in the study at 2 participating sites. Fifteen subjects from the McGill University Health Center (8 cases & 5 controls), and 7 subjects from BC Children’s Hospital (5 cases and 2 controls).

There are 4 subjects (3 cases and 1 control patient) enrolled at BCCH site. Two subjects (1 case and 1 control patient) withdrew from the study. The pilot study has been completed.

7. Biogen CS11 Study - PI: Dr. Selby - *Closed this term*

An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443

Fundin g	Source	Amount $	Study perio d	Anticipate d enrolment	# of subject s	Approvals	Status	Abstract / Paper/

					enrolled			Manuscript
yes	Biogen	75K/pt 29K start-up fees	2016 2023	5 @ BCCH	4	yes	active	N/A

This randomized, double-blind, sham-procedure controlled study will test the clinical efficacy, safety, tolerability, and pharmacokinetics of intrathecal ISIS 396443 over 13 months.

The primary objective is to evaluate the long-term safety and tolerability of ISIS 396443 administered intrathecally (IT) to patients with SMA who previously participated in investigational studies of ISIS 396443. The secondary objective is to examine the long-term efficacy of ISIS 396443 administered intrathecally to patients with SMA who previously participated in investigational studies of ISIS 396443. The tertiary objective is to examine the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ISIS 396443 administered intrathecally to patients with SMA who previously participated in investigational studies of ISIS 396443.
The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of ISIS 396443 (12 mg) administered as intrathecal injections by lumbar puncture (LP) in subjects who previously participated in investigational studies of ISIS 396443. Up to 274 subjects who previously participated in investigational studies may be eligible to enroll into this study. The sample size is based solely on the number of subjects enrolled in ISIS 396443-CS3B, ISIS 396443-CS4 and ISIS 396443-CS12 studies who may be eligible for participation in this study. ***There are 4 subjects enrolled in the study.*** One subject has been transferred to BCCH from another site. The enrolment has been completed. All patients have completed their study visits. ***The study has been closed this term.***

8. Biogen DEVOTE Study - PI: Dr. Selby – ***closed this term***

An Escalating Dose and Randomized, Controlled Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Biogen	49K/patient 20K start-up fees	2021 2025	3 @ BCCH	0	yes	active	N/A

This is a 3-part (Parts A, B, and C) study in which participants will be followed for approximately 10 months after the first dose of study treatment. Following the completion of this study, all eligible participants may elect to enroll in a separate open-label long-term extension study, pending study approval by ethics committees and the appropriate regulatory authorities. In regards to participants rolling over from Part B, this will be done without unblinding the participant's treatment group.

Part A will be conducted in participants with later-onset SMA who are 2 to 15 years of age, inclusive, for the purpose of evaluating adverse events (AEs). Part B will include participants with both infantile-onset SMA (≤ 7 months of age) and later-onset SMA (2 to < 10 years of age). Part C will enrol participants of all ages with SMA who have been receiving nusinersen treatment for at least 1 year prior to entry in this study. This part is designed to evaluate the safety of transitioning

participants from the currently approved dosing regimen to the high dosing regimen in a representative patient population.

Primary Objective: To examine the clinical efficacy of nusinersen administered intrathecally at higher and less frequent doses to participants with SMAPrimary Objective is to evaluate the efficacy of eculizumab in the treatment of pediatric refractory generalized myasthenia gravis (gMG) based on change from Baseline in the Quantitative Myasthenia Gravis score for disease severity (QMG).

Secondary Objectives:

- To examine the safety and tolerability of nusinersen administered intrathecally at higher and less frequent doses to participants with SMA
- To examine the effect of nusinersen administered at higher and less frequent doses compared to the currently approved dose in participants with SMA.

The study has been closed this term.

9. Italfarmaco Ulysses Study – PI: Dr. Selby – *new study this term*

Randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy, safety and tolerability of givinostat in non-ambulant patients with Duchenne Muscular Dystrophy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Italfarmaco	15.5K/patient 35K start-up fees	2024 2029	3-5 @ BCCH	0	pending	Not started yet	N/A

The purpose of the study is to find out about the safety and efficacy of givinostat for the treatment of DMD. Givinostat is an experimental drug which is not approved by Health Canada for the treatment of DMD. Approximately 138 males between the ages 9 to 18 will take part in this study.

Justification: Givinostat is a HDAC (histone deacetylases) inhibitor developed for the treatment of DMD based on the role that increased HDAC activity is thought to exert in contributing to DMD pathogenesis. It has shown to contribute to the preservation of physical function and muscles as demonstrated by clinically meaningful and statistically significant differences in Study DSC/14/2357/48.

Objectives:

Primary Objective is to demonstrate the efficacy of givinostat in reducing muscle decline in non-ambulant DND patients.

Secondary Objectives:

- To evaluate the safety and tolerability of givinostat in non-ambulant DMD patients.
- To further explore the efficacy of givinostat in non-ambulant DMD patients.

Exploratory Objectives:

- To evaluate the quality of life and activities of daily living (ADL) following givinostat treatment in non-ambulant DMD patients.
- To evaluate the PK/pharmacodynamics (PD) of givinostat.

This is a randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy, safety, and tolerability of givinostat in non-ambulant male pediatric (aged 9 to less than 18 years) patients with DMD. Patients will be randomized 2:1 to givinostat or placebo and will be treated for 18 months with an oral suspension of study drug twice daily (bid) in a fed state.

The study is in REB submission stage. The contract is being negotiated with TDO.

10. Italfarmaco Open Label Study – PI: Dr. Selby

Open label, long-term safety, tolerability, and efficacy study of GIVINOSTAT in all DMD patients who have been previously treated in one of the GIVINOSTAT studies

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	Italfarmaco	18K/patient 50K start-up fees	2020 2025	5 @ BCCH	4	yes	active	N/A

The Primary objective:

- To assess the long-term safety and tolerability of GIVINOSTAT in patients with DMD following core protocols program and with naïve GIVINOSTAT DMD subjects, i.e. subjects screened in study DSC/14/2357/48 who met:
    - all the inclusion criteria and none of the exclusion criteria, and
    - never been randomized because the enrolment in the off-target group was completed.

Secondary objectives:

- To evaluate the effects of long-term administration of GIVINOSTAT on muscular function and strength;
- To evaluate the effects of long-term administration of GIVINOSTAT on respiratory function;
- To evaluate the impact on daily activities and quality of life following longterm administration of GIVINOSTAT.

There are 4 subjects enrolled in the study. The enrolment has been completed. The study patients are followed up according to the protocol.

11. VBP15-006 Study - PI: Dr. Selby

A Phase II Open-Label, Multiple Dose Study to Assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys ages 2 to <4 years and 7 to <18 years with Duchenne Muscular Dystrophy (DMD)

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	ReveraGen.	13K/pt 13K start-ups	2022 2025	17	15	yes	active	N/A

This Phase II study is an open-label, multiple dose study to evaluate the safety, tolerability, PK, PD, clinical efficacy, behavior and neuropsychology, physical functioning, and sleep-wake activity of vamorolone over a treatment period of 12 weeks in steroid-naïve boys ages 2 to <4 years, and glucocorticoid-treated and currently untreated boys ages 7 to <18 years with DMD.

Primary Objective: To evaluate the safety and tolerability of vamorolone administered orally at daily doses of 2.0 mg/kg and 6.0 mg/kg over a 3-month treatment period in boys ages 2 to <4 and 7 to <18 years with DMD.

Secondary Objectives:
1. To evaluate the pharmacokinetics (PK) of vamorolone administered orally in boys ages 2 to <4 and 7 to <18 years with DMD.
2. To confirm the vamorolone exposure in boys ages 2 to < 4 and 7 to 18 years with DMD at 2.0 and 6.0 mg/kg and to adjust the doses if appropriate to achieve similar vamorolone AUCs across the entire pediatric age range.

Research design: The study is comprised of a 5-week Pretreatment Screening Period; a 1-day Pretreatment Baseline Period; a 3-month open-label Treatment Period (Weeks 1-12); and a 4-week open-label Dose-tapering Period (Weeks 13-16) for subjects who will not transition directly to further vamorolone or standard of care (SoC) glucocorticoid treatment at the end of the study.
The study has been approved by REB, and is currently opened for enrolment. ***There are 15 subjects enrolled in the study, 3 of them enrolled last 6 months period.*** Thirteen subjects completed the study and transitioned to the Vamorolone Extended Access Study.

12. Vamorolone OL Expanded Access Study - PI: Dr. Selby

An Open-Label, Expanded Access Protocol for Boys with Duchenne Muscular Dystrophy who have Completed the Long-Term Extension (VBP15-LTE) or VBP15-004 Studies

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	ReveraGen.	10K	2019 2025	24	20	yes	active	N/A

The intent of this protocol is to provide continued access to vamorolone for subjects who have completed the VBP15-004 protocol during the time that VBP15-004 is ongoing, and while a new drug application for vamorolone is under preparation and review. The patients will receive standard of care treatment and procedures for management of DMD. The condition of the subjects will be monitored by their treating physician, according to standard of care clinical practice. Adverse events (AEs) and Serious adverse events (SAEs) must be reported in the OpenClinica eCRF. Approximately 30-40 subjects in Canada will be eligible for enrolment, 4-5 of them at BCCH.

There are 15 subjects enrolled so far, 5 of them transitioned from the Vision DMD study, 2 subjects got transferred from Calgary, and 8 transitioned from the VBP15-006 Study. ***There were 5 enrolments in the last period.*** The study patients are being followed up according to the protocol.

13. PTC-016 Study – PI: Dr. Selby

An open-label, safety study for previously treated ataluren (ptc124) patients with nonsense mutation dystrophinopathy

Funding	Source	Amount $	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
yes	PTC Therapeutics Inc.	19,485 start-up 3,556/subject	2017 2027	160 total 5 @ BCCH	5	yes	active	N/A

The objective of this study is to assess the safety and tolerability of 10, 10, 20 mg/kg ataluren in subjects with nmDBMD who had prior exposure to ataluren in a PTC sponsored clinical trial or treatment plan.

The patient is required to complete a visit at the clinical research facility every 48 weeks. Every 24 weeks the patient is required to visit their local PCP for a weight check. A study drug shipment will be sent to the patient/caregiver's home every 12 weeks. Phone conversations by the investigator site will be conducted every 12 weeks (post-drug dispensing) to confirm drug receipt and to monitor and capture adverse events and use of concomitant medications

There are 5 subjects enrolled in this study. One of them withdrew from the study. The enrolment has been completed. Four active subjects are being followed according to the study protocol.

2.4. NEURO-ONCOLOGY

3. ONGOING RETROSPECTIVE STUDIES

3.1. EPILEPSY

1. ShutEye study - PI: Dr. Boelman/Dr Jeffers

Eye-Closure Induced Paroxysms on First EEG as Diagnostic for Eyelid Myoclonia with Absences and Pharmacoresistant Epilepsy.

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2015-2025	yes	100	active	N/A	N/A

The purpose of this study is to identify, via retrospective review of charts and EEG reports, ECP as a sensitive and specific EEG feature of EMA which can be identified on the first EEG study of children presenting with CAE-like epilepsy. This information will inform future designation of epilepsies presenting as either EMA or CAE. The utility of this information lies in the circumvention of pharmacoresistance.

The primary hypothesis of this study is that ECP is a sensitive and specific EEG feature of EMA that can be identified in the first EEG study of children presenting with CAE-like epilepsy. The secondary hypothesis is that ECP predicts pharmacoresistance.

This study is a retrospective chart and EEG review of cases of EMA diagnosed between 2005-2015, compared with a matched control group of patients diagnosed with childhood absence epilepsy on their first EEG study at BC Children's Hospital. ***The study is active.***

2. CC following VNS in children with LGS study - PI: Dr Connolly

The added value of Corpus Callosotomy (CC) following Vagal Nerve Stimulator (VNS) implantation in children with Lennox-Gastaut Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021- 2025	yes	5-6	active	N/A	N/A

Goals:

- The primary goal is to assess the efficacy of CC following prior VNS in children with LGS.
- The secondary goal is to assess the safety of CC following prior VNS.

Study design: This is a multicenter, multinational retrospective study. All LGS patients who had VNS procedure performed followed by CC between January 1, 1990 to August 18, 2021 at BC Children's Hospital (BCCH) will be identified. Epidemiological and clinical data will be collected by review of patient records by the study investigators and the study coordinator. ***The chart review has been completed at this site.***

3. Breath Holding Spells Study- PI: Dr. Datta

Breath holding spells followed by prolonged seizures: clinical outcome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding

2023-2025	no	100	active	N/A	N/A

Background: Breath holding spells (BHS) are common non-epileptic paroxysmal behavioral involuntary episodes occurring in up to 5.9% of healthy children. The attacks occur in early childhood (0.5-3 years) but are self-limited by school age (4-5 years old) (90%). Classically, BHS were classified as cyanotic (blue), pallid (pale), and mixed based on the color change of the child during the spell. In general, cyanotic spells have been classically described in a toddler with excessive temper tantrums (stubborn, easily frustration or annoyed. The mechanisms of BHS are controversial. The long-term prognosis for BHS is good. There is no definite therapy for BHS. In children with low frequency spells, parental reassurance are just enough; however, high frequency spells may result in anxiety to the parents or fear from sudden death of the child or development delay. Treatment with iron has been reported to result in reduction of the frequency of spells or its stoppage. Reflex anoxic seizures can occur, associated with stiffening or alteration in consciousness, however these usually last for less than 30 seconds and are not considered epileptic seizures.

However, in rare cases the spells might be followed by some myoclonic jerks or even by generalized tonic-clonic (GTC) seizures lasting longer than 30 seconds, and rarely, status epilepticus (longer than 5 minutes). There are also limited data in the literature regarding long-term outcome of children with longer seizure events. In this study, we would like to review patients at BCCH with prolonged seizures after breath holding spells over the past 31 years to determine treatment response, duration of treatment required and outcomes at least two years after diagnosis. We will compare long term outcomes to patients without longer reflex anoxic seizures and those who had an EEG for other paroxysmal episodes that are not seizures.

Purpose: The purpose of the study is to determine the clinical features, treatments, neuro-development, EEG findings and long-term outcome of children with prolonged seizures (>30 seconds) associated with breath holding spells.

Hypothesis: We hypothesize that BHS triggering seizures greater than 30 seconds are not common. Many children may have associated iron deficiency anemia. Treatment with various ASMs can result in reduction or cessation of the seizures. These children will have good long-term seizure outcome. They may have a higher risk of syncope when older, anxiety or psychiatric co-morbidities in the future.

Methods: A retrospective EEG, database and chart review of children who had an EEG for breath holding spells. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. We estimate 50 patients with breath holding spells inducing seizures longer than 30 seconds.

The study was approved, and the chart review is in progress.

4. ALL Study - PI: Dr. Datta - ***new study this term***

Significance of frontal rhythmic delta activity (FIRDA) on EEG in the pediatric population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2023-2026	yes	4	active	N/A	N/A

Purpose: This proposal aims to conduct a case studies report to describe the clinical course of four (4) patients with childhood leukemia (T-cell and B-cell ALL) who subsequently

developed treatment-resistant epilepsy, exploring risk factors, including an ethnic, genetic or autoimmune predisposition, neurodevelopmental outcomes and prognosis of epilepsy treatment.

Hypothesis: In pediatric patients with childhood leukemia, risk factors for developing epileptic encephalopathy and treatment-resistant epilepsy due to probable drug-induced leukoencephalopathy may include prior developmental delay or concerns, treatment protocol, medication dosages and risk severity, and genetics. Further long-term neurodevelopmental outcomes for this subset of patients include regression in skills, cognitive and behavioral conditions.

Objectives

- To explore potential risk factors associated with the development of treatment-resistant epilepsy in patients treated for childhood leukemia and presumed methotrexate toxicity.
- To assess the seizure characteristics, including seizure types, age of onset, and electrographic data.
- To describe the associated neuroimaging findings, and results of autoimmune and genetic investigations.
- To investigate the impact of treatment-resistant epilepsy on the neurodevelopmental long-term outcomes of these patients.
- To evaluate current management strategies for treatment-resistant epilepsy in patients with a history of childhood leukemia and their efficacy, including epilepsy surgery modalities.

Research Design: Study Design: This case studies report will utilize a retrospective design, analyzing medical records and clinical data of patients who have been managed for childhood leukemia and subsequently developed treatment-resistant epilepsy.

Sample Selection: The study will include patients diagnosed with childhood leukemia who later developed treatment-resistant epilepsy. These patients are identified at BCCH by the attending neurologist. The investigators will obtain consent.

The study has been approved by REB, and will be initiated in the New Year.

5. Positive Spikes Study - PI: Dr. Datta - ***new study this term***

Prevalence of positive interictal epileptiform discharges in children and its clinical significance

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2024-2026	yes	1200	active	N/A	N/A

The purpose of the study is to determine the significance of focal positive interictal epileptiform discharges in pediatric EEG to predict the risk of epilepsy, neuro-imaging abnormalities, seizure etiology, and epilepsy co-morbidities, such as developmental delay and difficulties with school performance.

Hypothesis: Negative polarity spikes or sharp waves are recognized as the common form of epileptiform discharges. The significance of positive spikes needs to be recognized more.

Although EEG findings of negative polarity epileptiform abnormalities relative to the reference electrodes may be necessary for children to predict subsequent epilepsy after a first unprovoked

seizure, the detection of positive spikes is equally important and has been identified in multiple conditions.

We anticipate a high degree of parenchymal injuries and increased risk of epilepsy in patients with focal positive spikes.

Methodology: A retrospective EEG, database and chart review will be performed for children with isolated focal positive spikes on EEG at BCCH from January 1, 1992 to December 31, 2023. The EEG records were part of the indicated clinical assessment for patients being investigated for seizures or epilepsy. In addition, patients with focal positive spikes will be compared to a random group of patients that had EEGs in our lab during the same time frame that are age and sex matched.
We anticipate 600 patients with positive waves on EEG.
We anticipate 600 control patients.
Total study number (N): 1200 patients.
The study is REB approved, and the chart review has been initiated.

6. FIRDA Study - PI: Dr. Datta

Significance of frontal rhythmic delta activity (FIRDA) on EEG in the pediatric population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2023-2025	no	100	active	N/A	N/A

Background: Frontal intermittent rhythmic delta activity (FIRDA) is a transient EEG pattern reported mostly in adults. FIRDA also occurs in children. However, there are few studies attempting to establish the clinical significance of frontal intermittent rhythmic delta activity in the pediatric population.

Purpose: The purpose of the study is to determine the frequency and significance of FIRDA on EEG in the pediatric population.

Hypothesis: We hypothesize that FIRDA is not common in the pediatric population. It is not as frequently associated with encephalopathy of deep midline lesions in children, as it is in the adult population. We hypothesize that it has similar significance as intermittent frontal slowing in the pediatric population and is not necessarily associated with epilepsy.

Methods: A retrospective EEG, database and chart review of children who had an EEG with FIRDA and subsequent follow up EEG between 12-24 months. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. We estimate 100 patients with FIRDA.

The chart review is in progress.

7. Clinical experience with Briv. at BCCH study - PI: Dr. Datta

Clinical Experience with Brivaracetam in the Pediatric Population at BC Children's Hospital

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	10	active	N/A	N/A

The safety and efficacy of brivaracetam has not been established in patients younger than 16 years of age. However, as with many new anti-seizure drugs on the market, it is often used off-label in

children, especially in those with treatment resistant epilepsy who have not responded to other medications. Open-label post-marketing studies can be very important to clinicians by providing additional information on efficacy and safety of the newer drugs in the "everyday" clinical setting. In addition, children are a unique population that may respond differently to a drug than adults. Therefore, we would like to review the experience with this new anti-seizure medication for pediatric patients treated at BC Children's Hospital. All patients prescribed Brivateracetam between July, 2018 and June 2020 at BC Children's Hospital (BCCH) will be identified. A retrospective case series will be performed. Responder rate will be defined as the proportion of patients who experience a 50% reduction in seizure frequency, retention on treatment and adverse effects leading to withdrawal. All patients treated with brivateracetam at BCCH from July 1, 2018 to June 1 2020. There will be approximately 10 patients included in the study. ***The study is active.***

8. CBD Postal Code Study - PI: Dr. Datta

The socio-demographic impact on the use of CBD for pediatric epilepsy in British Columbia

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2024	yes	131	active	N/A	N/A

Purpose: Although there is recent evidence that CBD can be effective for the treatment of seizures, at present, the cost in not covered for patients, unlike other anti-seizure medications. The purpose of this study is to determine if CBD use, including duration of use, dosage (mg/kg), the formulation, and benefit from CBD for pediatric epilepsy varies among different socio-demographic areas. This will be determined by correlating clinical data with postal codes linked to census data, using Statistic Canada's Postal Code Conversion File.

Hypothesis: The use of good formulation of CBD, longer duration of use and sustained benefit of CBD will be more prevalent in more affluent neighbourhoods, as at present, the cost is not covered for families, unlike other anti-seizure medications.

A retrospective chart review of children with epilepsy who are on CBD or have trialled CBD from 2014 to June 1, 2021. Patients will be identified from the EEG database. We anticipate to include 131 patients in this study. ***The chart review is in progress.***

9. Trisomy 21 patients multicentre study - PI: Dr. Datta

Multi-centre study retrospective study: Comparison of treatment-response of Trisomy 21 patients with infantile spasms to first-line vigabatrin or hormonal therapies

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2024	pending	100 25@ BCCH	active	N/A	N/A

Purpose: In this retrospective study, patients with Trisomy 21 syndrome with infantile spasms will be reviewed from the time frame of January 1, 2000 to June 1, 2021. The purpose of this study will be to compare the treatment response of first-line vigabatrin to first-line hormonal therapy for patients with Trisomy 21 and infantile spasms.

Hypothesis: T21 patients treated with hormonal therapy first-line for infantile spasms will have a better treatment response than patients treated with vigabatrin first-line. Better treatment response

includes: 1) shorter time frame for clinical and EEG resolution of infantile spasms, 2) reduced occurrence of infantile spasm relapse, and 3) less subsequent epilepsy.

Methodology: A retrospective multi-center chart review of children with T21 and infantile spasms from January 1, 2000 to June 1, 2021. Including all centers, we anticipate to include 100 patients in this study; 50 treated with first-line hormonal therapy and 50 treated with first-line vigabatrin. Specifically, from BC Children's Hospital (BCCH), we anticipate 25 children. ***The study is active.***

10. Five Year JAE Study - PI: Dr. Datta

Five year follow up of patients with juvenile absence epilepsy and EEG prognostic features

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	1000	active	N/A	N/A

The purpose of the study is to determine if there are clinical and EEG predictors to determine the prognosis of patients with juvenile absence epilepsy 5 years after diagnosis.

We hypothesize that most patients with juvenile JAE will require anti-seizure medications for seizure-control at 5 years. Approximately half will have good seizure control with medication. Those that had a trial of weaning off medications will have a high risk of seizure relapse and may not have the same response to an anti-seizure medication after re-initiation. A small percentage will be seizure free after weaning medications.

The outcome measures at 5 years will include: 1) number of patients requiring seizure medications, 2) number of patients who are seizure-free on medication, 3) number of patients who are seizure-free off medication, 4) number of patients continuing medication after an attempted wean off medication, and 5) number of patients who are treatment-resistant. ***The chart review is in progress.***

11. Pooled Perampanel Analysis study - PI: Dr. Datta –*closed this term*

Global pooled analysis of perampanel real-world data

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2023	yes	30	active	N/A	N/A

The purpose of the pooled analysis will be to evaluate the effectiveness and safety/tolerability of perampanel in patients with epilepsy. The primary endpoints include:

- 1-year retention rate
- 1-year seizure-freedom rate (≥6 months)
- Incidence and types of adverse events (adverse events will be categorized using MEdDRA classification)

The study population includes patients treated with PER at BCCH and ACH from July, 2014 to February 2015. There will be approximately 30 patients included in the study. ***The chart review is in progress.***

12. Focal Spikes Study - PI: Dr. Datta

The location of focal spikes on EEG to predict epilepsy and neuro-development

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	1000	active	N/A	N/A

A retrospective chart review and analysis of existing EEG data available at BC Children's Hospital (BCCH).

Purpose: The purpose of the study is to determine the significance of focal pediatric EEG spikes in various localizations (frontal, temporal, midline, parietal and occipital lobes) to predict the risk of epilepsy, neuro-imaging abnormalities, and neuropsychiatric co-morbidities, such as developmental delay and difficulties with school performance.

Hypothesis: Patients with frontal spikes will have a significantly higher risk of developing epilepsy than those with focal spikes in other regions.

Although EEG findings may be important in children to predict subsequent epilepsy after a first unprovoked seizure, their significance can be improved when associated with imaging findings. We anticipate more focal lesion in the frontal and temporal lobe and more diffuse or non-localized imaging abnormalities in other lobes.

We anticipate a high degree of neuro-psychiatric co-morbidities in patients with focal spikes, especially frontal and temporal spikes (due to connections with the pre-frontal cortex and limbic systems), including in those without seizures. ***The chart review is in progress.***

13. ESL Study - PI: Dr.Datta

Clinical experience with eslicarbazepine after trials of carbamazepine and oxcarbazepine in children in two Canadian centers

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	30	active	N/A	N/A

Purpose: The purpose of the study is to assess the efficacy, safety and tolerability of ESL in patients transitioning from CBZ or OXC to ESL due to lack of efficacy, poor tolerability or poor compliance, by performing a retrospective chart review of children treated with ESL in two Canadian Pediatric tertiary care centers.

Hypothesis: ESL will be efficacious and generally well tolerated in pediatric patients transitioning from CBZ or OXC in clinical practice due to inadequate seizure control or intolerable AEs with these agents.

Population: All patients treated with ESL at BCCH and Children's Hospital of Winnipeg will be included. There will be approximately 30 patients included in the study. The date range of the charts to be included in this research proposal is from 1999 to 2020. ***The chart review is in progress.***

14. LKS & ESES Study - PI: Dr. Datta –new ESES component added to this study

Long-term follow up of electro-clinical features of patients with Landau-Kleffner Syndrome

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding

2020-2024	yes	30	active	N/A	N/A

Purpose: The aim of the study is to retrospectively analyze the electro-clinical features, etiology, treatment, and prognosis of patients with Landau–Kleffner syndrome (LKS) and ESES with a long-term follow-up from 2-20 years.

Hypothesis: Patients treated with LKS and ESES will likely good have good prognosis regarding seizure control and improvements on EEG at follow-up. However, despite seizure control, they may continue to have language, behavioral, sleep and cognitive issues long-term. Adequate and early treatment may reduce or prevent some of the language and cognitive deterioration.

Methodology: A retrospective EEG, database and chart review of children with LKS and ESES who had an EEG at BCCH from 1992 to January 2020. ***The study is active.***

15. EEG Hydrocephalus study - PI: Dr. Datta

The association of epilepsy, EEG abnormalities and Hydrocephalus

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2022-2024	yes	200	active	N/A	N/A

The purpose of this study is to determine clinical features that are associated with epilepsy in patients with hydrocephalus, including age of onset of hydrocephalus, neuro-imaging findings, presence of shunt and age of shunt placement, shunt complications and EEG findings. We want to determine if any electro-clinical features predict more refractory seizures, development delay or behavioral problems in patients with hydrocephalus.

Hypothesis: Patients with hydrocephalus and seizures are more likely to have:

- Congenital hydrocephalus due to perinatal insult to the brain, including hemorrhage, and infection
- Young age of onset (<2 years of age)
- More developmental delay, ASD, ADHD, psychiatric diagnoses
- Parenchymal brain abnormalities
- History of shunt malfunction, infection, or a combination of these

A subgroup of these patients will have very frequent or nearly continuous epileptiform discharges on EEG during; increasing the risk of treatment resistant seizures, developmental delay, and behavioral issues.

Patient Population

A retrospective EEG, database and chart review of children who had an EEG at BCCH from 1992 to April, 2022 and a diagnosis of hydrocephalus. Patients will be identified by searching the EEG database, which has a specific code for hydrocephalus.

Inclusion Criteria

- Adequate technical EEG recordings
- Confirmed hydrocephalus by chart review
- Availability of the clinical information in medical records
- Availability of clinical data at 2-4 years of follow-up data after diagnosis of hydrocephalus

Exclusion Criteria

- Inadequate clinical data

- Hydrocephalus not confirmed on chart review
- Lack of 2-4 year follow-up data after diagnosis of hydrocephalus
- No available EEG data

Data Analysis and Collection

All EEG's done at BCCH are entered in an EEG database which includes the EEG interpretation and additional clinical data. All patients with an EEG from 1992 to April, 2022 and a code for hydrocephalus in the EEG database will be identified in this database. Detailed chart reviews of the entire medical record will be performed on all patients meeting inclusion criteria.

The chart review is ongoing.

16. SUDEP 2019 study - PI: Dr. Datta

The relationships of Spike wave index count on EEG and Sudden Unexpected Death in Epilepsy

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	60	active	N/A	N/A

This study is a retrospective chart review and analysis of existing EEG data available at BC Children's Hospital. The purpose of the is to determine if the quantity of inter-ictal spikes on EEG can be predictive of Sudden Unexpected Death in Epilepsy (SUDEP). Inter-ictal spikes are brief paroxysmal electrographic discharges observed between spontaneous recurrent seizures in epileptic patients. They provide information about localization of seizures and a high number of spikes can be suggestive of sub-optimal seizure control.

We hypothesize that patients with SUDEP will have a significantly higher quantity of inter-ictal spikes, (SWI) in comparison to control patients with treatment resistant epilepsy who did not die of SUDEP, as in increased quantity of inter-ictal spikes can be suggestive of sub-optimal seizure control In addition, as previously reported by some, we expect post-ictal suppression (voltage attenuation on the EEG after a seizure lasting for 1 second or more) will correlate with an increased incidence of SUDEP.

The results from this study will provide additional risk factors or predictors for SUDEP, a condition where little is still known, especially in the pediatric population. ***The chart review is in progress.***

17. KD Age Spasms Study - PI: Dr. Datta

Response to the Ketogenic Diet in refractory infantile/epileptic spasms

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2018 - 2024	yes		active	N/A	N/A

Retrospective chart review of patients with infantile/epileptic spasms treated with the ketogenic diet at BC Children's Hospital (BCCH). No patient contact.

The purpose of the study is to determine if the efficacy of the ketogenic diet (KD) in refractory infantile/epileptic spasms (IS/ES) varies depending on the age the KD is initiated and if hypsarrythmia is present on EEG or not. We will identify all patients with refractory IS/ES treated with the KD at BCCH from January 1, 2012 to September 15, 2018, to determine if the age at

initiation of KD and presence of hysparrythmia will predict the degree of response in reducing or eliminating seizures.

Hypothesis

Based on our clinical experience and review of the literature, we hypothesize that in IS/ES refractory to first line therapies, the KD is not as effective when initiated under the age of 12 months, regardless of etiology. However, if the diet is initiated in patients older than 12 months, there will be better response with seizure freedom or >50% reduction in seizures.

Research Design & Methodology

A retrospective chart review for all patients with infantile or epileptic spasms treated with the ketogenic diet by the BC Children's Epilepsy Service from January 2012 - September 2018 will be performed. ***The chart review is in progress.***

18. School Study - PI: Dr. Datta – *closed this term*

School Performance at the time of the first EEG and Follow-up

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2024	yes		active		N/A

Purpose: The purpose of the study is to determine if there are differences in school performance difficulties between patients with seizures and patients without seizures at the time of a first EEG. For patients with 2 to 4 year follow-up at BCCH, we also aim to determine if school performance changes over time and if school difficulties are more prevalent in patients with seizures compared to children without seizures (with other chronic medical conditions). Finally, we want to compare children with seizures and children without seizures, but psychiatric disorders with 2-4 years of follow-up at BCCH to see determine if there is a difference in school performance difficulties at baseline and follow-up between these two groups. Chronic psychiatric disorders include mood, psychotic, eating disorders, etc.

Hypothesis: Approximately 30% of patients who have a first EEG will have confirmed seizures. The remainder of patients will not have seizures, but will have an EEG to characterize various paroxysmal events, such as headaches, movement disorders, psychiatric conditions or to assess level of consciousness.

At the time of the EEG, it is hypothesized that approximately a third of children with and without seizures will have difficulties with school performance. However, at 2-4 years, children with seizures with seizures will have significantly more school performance difficulties, related to various aspects, including ongoing seizures, seizure medications and missed school days than children without seizures, but other chronic medical conditions. Subsequently, children with seizures and children with psychiatric disorders that are followed at BC Children's Hospital for 2-4 years will be compared. It is hypothesized that children with seizures and chronic psychiatric disorders will have similar levels of difficulties with school performance at baseline and follow-up.

A retrospective EEG, database and chart review of children who had a first EEG at BCCH from 2015 to 2017 who are of school age. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. ***The study is active.***

19. Parietal Spikes Study - PI: Dr. Datta

Predictive Value of Parietal Spikes on EEG in the Pediatric Population

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021 - 2024	yes	400	active		N/A

The purpose of the study is to determine the frequency and predictive value of parietal spikes on EEG in the pediatric population. There is currently little data on the significance of parietal spikes on EEG. We will identify EEG's of pediatric patients with isolated parietal spikes over 20 years at BCCH and compare them to a control group (a random sample of patients who had an EEG at BCCH) to determine if isolated parietal spikes can help to predict clinical, seizure and developmental outcome.

A retrospective EEG, database and chart review of children who had an EEG with isolated parietal spikes. The EEG records were part of indicated clinical assessment for patients being investigated for seizures or epilepsy. We will include 200 study patients and 200 control patients. ***The chart review is in progress.***

20. Brivateracetam Study - PI: Dr. Datta

Clinical Experience with Brivateracetam in the Pediatric Population in two Canadian Centers

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2018 - 2024	yes	4	active		N/A

Brivaracetam was granted FDA approval as an add-on therapy in February 2016. It is indicated as adjunctive therapy for treating adults and adolescents 16 years of age or older with epilepsy. The safety and efficacy of brivaracetam has not been established in patients younger than 16 years of age. We would like to review the experience with this new anti-seizure medication for pediatric patients treated at BC Children's Hospital and Alberta Children's Hospital. All patients prescribed Brivateracetam between February, 2016 and July, 2018 at BC Children's Hospital (BCCH) and Alberta Children's Hospital (ACH) will be identified. A retrospective case series will be performed. ***The chart review is underway.***

21. MRI FCD Epilepsy Study – PI: Dr Schrader

The use of advanced MRI analysis techniques to improve the detection of focal cortical dysplasia in children with partial epilepsy on clinical scans.

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2020-2024	yes	200	active	N/A	N/A

The purpose of this study is to improve the detection of FCD in children with pharmacoresistant epilepsy using advanced image processing techniques. We anticipate that these techniques will improve FCD detection, particularly in "MRI-negative" cases. We hypothesize that FCD's that are missed on visual inspection of MRI of the developing brain will be detected by advanced MRI analysis techniques.

The specific aims include:

- To determine if the advanced automated MRI techniques designed for the detection of focal cortical dysplasia in adults can be applied to the developing brain by testing them on MRI-positive cases of histopathologically-proven focal cortical dysplasia in children.To determine if these advanced MRI techniques can be used to identify histopathologically proven areas of focal cortical dysplasia that were previously missed on visual inspection of conventional MRI.
- To determine if the application of these advanced MRI techniques to new cases of refractory partial epilepsy improves the detection of focal cortical dysplasia.

Research design: We will apply methods that were previously developed in the Neuroimaging of Epilepsy Laboratory to existing clinical MRI scans. ***The study is active.***

3.2. BRAIN INJURIES/INFLAMMATION

3.3. DEVELOPMENTAL MALFORMATION / NEUROMUSCULAR DISEASES

1. Muscle Gene Panel Testing Study – PI: Dr Selby

Retrospective analysis of diagnostic outcome of muscle gene panel testing in children presenting with suspected neuromuscular disease at BCCH

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2019 - 2024	yes	150	active	N/A	N/A

The purpose of this study is to examine the diagnostic outcome of muscle gene panel testing and determine the associated impacts on clinical management for children presenting with a possible neuromuscular disease at BCCH.

We hypothesize that the introduction of muscle gene panel testing has increased the proportion of patients with a definitive genetic molecular diagnosis and that identification of new genetic diagnoses has altered clinical management.

The objectives are to quantify the proportion of patients for which muscle gene panel testing provided a definitive diagnosis and to determine whether early genetic testing shortens the diagnostic process and/or changes management in patients presenting with suspected neuromuscular disease.

Analysis of Data: Genetic testing results will be categorized based on whether they provide definitive causal mutations, variants of unknown significance, non-causal (benign) mutations or no abnormality found. The genetic results will then be incorporated into the clinical context where we will determine whether the genetic diagnosis is congruent with the clinical phenotype. We will also review the sequence of diagnostic investigations to determine when in the diagnostic process the patient received genetic testing, and if genetic testing altered clinical management. ***The study is active.***

2. Impact of Genetic Testing Study – PI: Dr Selby

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2020 - 2024	yes	180	active	N/A	N/A

The purpose of this study is to examine the impact of genetic testing on the diagnosis and further investigations completed in children with suspected neuromuscular disorders who have presented at BCCH between 01 May 2017 and 20 May 2020.

We hypothesize that the introduction of genetic testing early on in the diagnostic odyssey increases the proportion of patients who can be given a definitive diagnoses, improves our understanding of the expanded phenotype and genotype in neuromuscular diseases in childhood and allows for improved management and clinical care.

This study serves as a retrospective analysis in patients presenting at BCCH with a suspected neuromuscular disorder, including a review of their diagnostic journey and the rate of positive diagnosis that the muscle gene panel performed at Sherbrooke Genomic Medicine has allowed, and also the additional ability to get whole exome sequencing and in some cases whole genome

sequencing and how this has also further expanded our understanding and contributed to our interpretation of the pathological findings on muscle biopsy. We also understand that due to limitations in our current knowledge base, genetic testing will yield variants of uncertain significance (VUS), which currently have unknown pathogenicity. The diagnostic yield of these variants will need to be reviewed over time as our collective knowledge base expands.

Primary outcome measure: Determining the diagnostic yield of the gene panel testing (i.e. the percentage of patients for which a definitive diagnosis was reached after genetic testing).

Secondary outcome measures:
1) time taken to reach diagnosis
2) investigations required to reach diagnosis
3) outcomes of diagnosis in terms of changes in clinical management. ***The study is active.***

3. AFP Study – PI: Dr Selby

Acute Flaccid Paralysis in Canadian Children: Evaluation of etiological factors and response to therapy

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2018-2024	yes	6	active	N/A	N/A

Between the months of August and October 2014, a cluster of children suffering from acute onset flaccid paresis was identified in North America, all with MRI findings suggestive of poliomyelitis. Despite the relatively uniform clinical presentation and MRI findings, no single specific pathogen has been implicated. Because of the uncertainty regarding pathogenesis, the optimal treatment in the acute phase remains unknown. To identify the clinical features and characteristics of the non-polio/enterovirus-associated acute flaccid limb weakness cases in Canada in 2014, we conducted a comprehensive chart review study and reported the clinical spectrum and neuroimaging findings, treatments and clinical outcomes in children presenting to participating Canadian institutions with this clinical phenomenon. After their initial episode, a majority of the patients had recovered completely by the time of their last clinic follow-up but a few still had persistent deficits or disability.

Since the late summer of 2018, there has been an apparent increase in the number of children presenting with acute limb weakness in several Canadian provinces, including Ontario, Quebec and Manitoba. To extend our previous study of enterovirus associated-AFP, we will conduct a retrospective chart review of patients in the AFP cohort in 2014 as well as the recent AFP cases in Canada. Findings from this study will help provide insights into the epidemiology and clinical implications of enterovirus infection in pediatric AFP.

The aim of the study is:

- To perform detailed clinical review of a large cohort of well characterized, geographically diverse pediatric patients with non-polio AFP.
- To perform detailed assessments of demographic and clinical information.
- To establish a detailed demographic and clinical patient database. ***The study is active.***

4. Nusinersen respiratory outcomes study – PI: Dr. Wright/Dr. Selby

Respiratory outcomes in children with 5q Spinal Muscular Atrophy types 1 and 2 treated with nusinersen

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2020-2024	yes	23	active	N/A	N/A

The aim of the study is to determine whether respiratory health is improved in patients with SMA treated with nusinersen. As nusinersen therapy has been found to result in significantly improved motor function, we hypothesise that its use will also be associated with improvement in markers of respiratory health, and hospitalization for respiratory illness. This will be a retrospective observational chart review of children <18 years of age diagnosed with SMA managed at BCCH and treated with nusinersen from January 1st 2016 to April 30th 2020. ***The study is active.***

5. <u>Lipids study</u> – PI: Dr Selby

Abnormal lipids in Children with Duchenne Muscular Dystrophy: A contributing factor to muscle weakness

Study period	Approvals UBC/C&W	Sample size	Status	Abstract/Paper/ Manuscript	Funding
2021-2024	yes	70	active	N/A	N/A

The purpose of this retrospective study is to characterize the frequency and type of dyslipidemia in a cohort of children in British Columbia with DMD and to determine the relationship with DMD disease severity, specific genetic mutation and treatment received. We will also review markers of liver function and liver ultrasound findings where available.

Hypothesis: We hypothesize that children with DMD will have high rates of dyslipidemia and demonstrate evidence of a primary dyslipidemia.

Objectives:

- To describe the frequency and type of dyslipidemia at presentation and during treatment in children with DMD.
- To describe markers of fatty liver disease (liver enzymes, liver ultrasound findings) in children with DMD.
- To explore the relationship between the observed genetic mutations in these children with DMD, level of physical ability and any observed lipid abnormalities.

This study is a retrospective chart review of all patients with DMD followed in the BCCH neuromuscular diseases program at BC Children's Hospital that have had a lipid panel performed as part of their care. ***The study is active.***

3.4. **NEURO-ONCOLOGY**

1. High-Grade Glioma (HGG) study – PI: Dr. Hukin-*new study this term*

Molecular testing and clinical outcome of pediatric patients diagnosed with high-grade glioma, high-grade neuroepithelial tumors, and high-grade glioneuronal tumors who were treated with radiation sparing approach

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2024-2026	yes	15	active	N/A	N/A

Brain tumors constitute 20% of cancer in children, which mean they are the second most common malignacy in pediatric population. Unfortunately, they are the leading cause of death due to cancer in children. Given these are rare tumors in children, we are proposing to retrospectively collect a group of patients with HGG and describe their clinical presentation, pathology and molecular testing with the aim of having better understanding of clinical and molecular characteristics that may have impacted the outcome in these patients.

Purpose and Objectives:
To retrospectively collect cases diagnosed with high-grade glioma, high-grade neuroepithelial tumors, and high-grade glioneuronal tumors who were treated with radiation sparing approach, and describe their clinical presentation, imaging, histology, and treatments received. In addition, we will include RNA sequencing and methylation profiling results.

The study is REB approved. The chart review is in progress.

2. Choroid plexus carcinoma study – PI: Dr. Hukin-*new study this term*

Can Evaluation of the prognostic impact of TP53 germline and somatic mutations in newly diagnosed children with choroid plexus carcinoma in the context of initial therapeutic approach

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2024-2026	yes	27 in total 2 @ BCCH	active	N/A	N/A

This is a retrospective multicentre review of patients treated with a radiation sparing approach with intensive chemotherapy for choroid plexus carcinoma. We have 2 patients who are eligible, both of whom have sadly passed away from this disease. The review is retrospective of clinical data available in the BC Children's hospital records, oncology clinic chart or hospital electronic chart only. New therapeutic strategies are desperately needed in this aggressive malignant brain cancer affecting primarily young children.

This study is to provide background data ultimately for the development of an international prospective therapeutic and biological trial for children newly-diagnosed with CPC.

Hypothesis: This is a descriptive study evaluating the response of choroid plexus carcinoma to intensive chemotherapy. Evaluation of the prognostic impact of TP53 germline and somatic mutations in newly diagnosed children with choroid plexus carcinoma in the context of initial therapeutic approach: correlation of outcomes.

Methodology: Retrospective clinical, genetic (TP53 tumor and germline mutations), primary therapy and outcomes data on children with choroid plexus carcinoma will be analyzed to justify

the use of marrow ablative consolidation with the upfront treatment of high risk choroid plexus carcinoma children with TP53 mutations (germline or somatic).

The study is REB approved, and the chart review will be initiated in the New Year.

3. Infant relapse medulloblastoma study – PI: Dr. Hukin

Can we salvage young children with relapse medulloblastoma after initial radiation sparing approaches?

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2020-2024	yes	70 total 10 @ BCCH	active	N/A	N/A

Background and Rationale: The management of medulloblastoma in very young children remains a challenge for neuro-oncologists in large part because of the greater vulnerability of the developing brain to radiotherapy related toxicity. Innovative strategies based on high dose chemotherapy, use of intrathecal chemotherapy, modified field or dose of adjuvant radiation have been used to delay or avoid craniospinal irradiation to minimize the risk of deleterious neurocognitive impairment in survivors.

Objectives: By assembling a large cohort of young children with relapsed medulloblastoma following initial radiation sparing approach, we aim:

Primary objectives:

- To describe their progression-free survival and overall survival following salvage therapies
- To describe the potential prognostic factors (clinical, therapeutics, pathology and molecular) associated with successful salvage therapy

Secondary objectives:

- To describe the pattern of relapse after initial radiation sparing strategies
- To report the rate of palliative management without any cancer-directed therapy at time of relapse in this young age group
- To report on the toxicity profile of these salvage therapies focusing on the neurocognitive outcome and hearing toxicity.

Study population

We will take advantage of our Canadian Pediatric Brain Tumor Consortium which includes 16 Canadian pediatric centers with pediatric oncologists involved in pediatric neuro-oncology research to undertake the study at the national level. While Johnston et al previously described 96 cases of infant with medulloblastoma diagnosed in Canada between 1990 and 2005(10), and knowing that approximately half of them relapsed, we estimated we could collect information on 40 Canadian young patients with relapse medulloblastoma for the period of 1995-2017. We estimate based on preliminary contact we could gather an additional 30 patients for a total expected 70 patients meeting our study criteria described below:

- Patient aged between 0 to 6 years at time initial diagnosis of medulloblastoma
- Primary diagnosis of medulloblastoma between 1995 and 2017
- Radiological evidence of relapse medulloblastoma, with or without pathology proven diagnosis of relapse
- Patient treated with infant brain tumor strategies defined by any upfront therapies with the exception of those including upfront craniospinal irradiation. ***The study is active.***

4. NF1-retrospective chart review study – PI: Dr. Hukin

A Real-World Assessment of the Paediatric Neurofibromatosis Type 1 Patient Journey in Canada: Evidence From a Retrospective Medical Record Review

Funding	Source	Amount $	Study period	Sample size	# of charts reviewed	Approvals	Status	Abstract/ Paper/ Manuscript
yes	AstraZeneca	54K	2022-2024	26	26	yes	active	N/A

Background: Neurofibromatosis type 1 (NF1) is a progressive genetic condition reported in approximately 1 in 2,000 to 1 in 5,000 individuals, regardless of sex, race, or ethnicity. It is characterized by changes in skin pigmentation and diverse skin, neurological, and musculoskeletal manifestations. Signs and symptoms of NF1 often begin during early childhood and can vary substantially between patients and within families. NF1 can manifest in myriad cutaneous, neurological, skeletal, and neoplastic complications across patients, resulting in learning disabilities, visual impairment, twisting and curvature of the spine, high blood pressure, malignancies, and epilepsy.

Aim: The aim of this study is to describe the journey of patients diagnosed with NF1 who developed 1 or more inoperable Plexiform Neurofibromas (PNs), with a primary focus on those who developed 1 or more symptomatic, inoperable PNs, from a medical care perspective, including clinical characteristics at diagnosis, treatment, healthcare utilization among multispecialty providers, surgeries performed for symptom and pain management, and clinical outcomes in Canada.

Objectives:

- To describe demographic and clinical characteristics of paediatric patients diagnosed with NF1 and who develop inoperable PNs at ≤ 18 years of age
- To characterize clinical signs and symptoms of NF1 that lead to the initial diagnosis and the diagnostic procedures and/or tests used to establish or differentiate the diagnosis
- To describe treatment modalities used in the management of inoperable PNs, including surgeries, pain management, radiation therapy, and/or chemotherapy; diagnostic procedures used to assess disease progression (e.g., MRI scans to monitor tumour growth after surgery); and clinical outcomes (e.g., medical events of interest after treatment, surgery outcomes, tumour recurrence, progression, and mortality)
- To describe characteristics of inoperable PNs such as size, changes in size (assessed qualitatively by clinician), progression, location, and associated symptoms
- To document healthcare resource utilization related to the management of NF1 and inoperable PNs, including inpatient and outpatient visits and specialty care encounters (e.g., surgery, oncology, ophthalmology, orthopaedics, physiotherapy, behavioural health, cardiology)

Results from this study may aid in the following:

- Depicting characteristics of patients with NF1 who develop inoperable PNs
- Understanding the multidisciplinary management of inoperable PNs, and defining the patient journey
- Gaining insight into clinical characteristics of paediatric patients with NF1-related inoperable PNs and identifying characteristics of patients with poor outcomes and substantial unmet treatment need

- Providing real-world descriptions of current treatments, outcomes, and resource use to which the value of alternative therapeutic options may be compared, which can be used to inform health economic models
- Understanding the drivers of the direct economic burden of NF1 and inoperable PNs

The chart review has been completed and data submitted to the sponsor for review.

5. Male βHCG study – PI: Dr. Hukin

Testosterone Levels in βHCG-secreting CNS Germ Cell Tumors

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/ Paper/Manuscript	Funding
2021-2024	yes	35 total 2-5 @ BCCH	active	N/A	N/A

Background: Central nervous system (CNS) germ cell tumors are a subset of brain tumors classified on the basis of histological and immunohistochemical features. 'Secreting' germ cell tumors are characterized by elevated levels of alpha-fetoprotein (AFP) or beta-human chorionic gonadotrophin (beta-HCG) secreted into the serum and/or cerebral spinal fluid. Despite the histologically malignant nature of CNS germ cell tumors, symptoms may be present for many months or, at times, years prior to diagnosis.

Purpose & Objectives: To retrospectively collect cases of beta-HCG-secreting CNS germ cell tumors in males that presented with precocious puberty and/or had inappropriately elevated testosterone levels at presentation for their level of puberty.

We are proposing to retrospectively collect and publish a case series of male patients with beta-HCG-secreting CNS germ cell tumors that presented with precocious puberty and/or had inappropriately elevated testosterone levels at presentation for their level of puberty. As this is a rare tumor, we anticipate no more than 35 relevant patients to be identified for this case series from all collaborators. The main PI is Dr Holly Lindsay from Baylor College of Medicine in Houston, Texas. ***The study is active.***

6. Molecular Profiling of Ependymoma Study - PI. Dr. Hukin

Molecular Profiling of Ependymoma: Identification and Characterization of Candidate Biomarkers and Regulatory Genes

Study period	Approvals UBC/C&W	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
2017-2024	yes	sample size will be determined based on tissue availability	active		

The objective of this study is to retrospectively determine the prevalence of visual disturbances (eye movement, pupillary, and visual field), due to pineal lesions and their treatments in the pediatric population. The manuscript has been accepted in the Journal of Neurosurgery Pediatrics. ***The study is active.***

3.5. QUALITY ASSURANCE PROJECTS

1. Biobanking study - PI: Dr. Vercauteren/ Co-investigators Dr. Demos, Dr. Connolly

Collection and banking of biological specimens and collection of clinical data from children with neurological disorders

Funding	Source	Amount ($)	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
no	N/A		2014 ongoing	All eligible	397	yes	active	N/A

BCCH Pediatric Neurology BioBank supports procedures related to the collection of biological specimens (biospecimens) and patient clinical information for research purposes. Both biospecimens and clinical information will be collected from patients who are referred to or regularly attend the C&W Pediatric Neurology clinic. In most cases patients will only be approached once regarding the donation of biospecimens to the C&W Neurology BioBank, however there is the possibility that patients could be asked at other time points throughout their treatment. Participants will always be informed about the collection of biospecimens for BioBanking purposes and can refuse further donations or withdrawal from the BioBank at anytime. In addition patients will be asked to give their permission to be contacted in the future regarding other research that may involve filling out questionnaires or the collection of additional biospecimens. Physicians and scientists of C&W and CFRI/other institutions may use biospecimens from the BCCH Pediatric Neurology BioBank after approval of their research project by the C&W Pediatric Neurology BioBank Scientific Committee, ECMO and CW REB

There are 397 subjects from Pediatric Neurology who consented to have their biospecimens banked, three of them in the last 6 months period.