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# **Report on Research Activities in the Adult Neurosurgery Program supported by the Division's Clinical Research Coordinator**

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# Table of Contents:

<b>1. INTRODUCTION.....</b>	<b>3</b>
<b>2. ONGOING PROSPECTIVE STUDIES .....</b>	<b>4</b>
<b>3. ONGOING RETROSPECTIVE STUDIES .....</b>	<b>12</b>
<b>4. INACTIVE OR COMPLETE STUDIES .....</b>	<b>17</b>

***\*\*This report only includes research supported by the Division's Clinical Research Coordinator. It does not include an exhaustive list of all of the projects being conducted by the Division of Neurosurgery faculty.***

# 1. INTRODUCTION

This report contains up to date information on the ongoing research projects that are supported by the Clinical Research Coordinators (CRC) of the University of British Columbia's (UBC's) Division of Neurosurgery at the Clinical Academic Campus of Vancouver General Hospital (VGH).

<i>Number of Ongoing Studies</i>			
Prospective	Retrospective	Inactive or Complete Studies	Total
12(1 new this quarter)	10	6	28

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

\*\*This report does not encompass research projects in the Division's paediatric neurosurgery, functional neurosurgery and spine neurosurgery programs.

## 2. ONGOING PROSPECTIVE STUDIES

### 1. Timing of Mobilization After Burr Hole Drainage of cSDH:

PI: Dr. Akagami; Co-I: Drs. Tu, Chang, Honey, Makarenko, Fatehi, Sadr.

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	Sep 2014 - Sep 2019	100	92	Yes	Active	N/A

This is a two treatment arm, randomized, prospective study to minimize re-do burr-hole drainage procedures and any other associated complications in patients with chronic subdural haematomas.

Primary Outcomes:

- Recurrence requiring re-do drainage within the 1<sup>st</sup> month post-operatively
- Recurrence requiring re-do drainage between the 1<sup>st</sup> and 3<sup>rd</sup> months post-operatively

The timing of when to mobilize patients after burr-hole drainage of chronic subdural haematomas remains controversial. Traditionally, patients have been subjected to delayed mobilization in order to allow for the theoretical re-expansion of the brain and to decrease recurrence. Timing of bed rest is not consistent among centres and varies from immediately after to 7 days after surgery.

The objective is to determine optimal timing of mobilization in CSDH patients following a burr-hole drainage.

*Enrolment has ended. A total of 92 participants were enrolled. Manuscript preparation is in progress.*

### 2. Adult Hydrocephalus Clinical Research Network (AHCNRN):

PI: Dr. Zwimpfer

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	Nov 2014 -	perpetual	493	Yes	Active	N/A

A multi-centre and multinational registry that collects data on adult hydrocephalus patients to characterize the etiology, understand variability, progression, and current treatment practices for hydrocephalus patients.

The overall purpose of the Registry is to establish and maintain a hydrocephalus patient event database for the Clinical Centres of the AHCNRN, a research network newly established to investigate clinical management of adult hydrocephalus.

Primary Objectives:

- To describe the natural history and treatment response for adults with previously untreated congenital hydrocephalus
- To describe the assessment and treatment of patients with Normal Pressure Hydrocephalus (NPH)
- To describe the complications associated with shunt surgery

- To determine the role for treatment with Endoscopic Third Ventriculostomy (ETV)

The Registry will provide previously unavailable epidemiological information about hydrocephalus patients seen throughout the participating Clinical Centers. This information will provide the basis for multi-institutional studies to be carried out by the AHCRN that may ultimately improve the clinical care for adults with hydrocephalus throughout the world. The continuing collection of such information serves to provide data necessary for hypothesis generation and study design. Examples of preliminary study designs include, but are not limited to, the following: preliminary power analysis, sample size determination, and recruitment projections. Radiologic imaging data will provide a unique opportunity to assess aspects of adult hydrocephalus diagnosis, management, and outcomes.

*There are 1875 participants enrolled in the AHCRN Registry at all participating sites. Of those, 499 are from the VGH site with 6 patients enrolled in the last quarter.*

### **3. Quality of Life in Patients Diagnosed with Unruptured Cerebral Aneurysms Prospective Single-Centre Series:**

PI: Dr. Gooderham; Co-PI: Drs. Dandurand, Redekop, Haw

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	TAAF (NGO)	Jan 2016 - Dec 2019	150	150	Yes	Active	N/A

Aneurysms may require endovascular or microsurgical treatment if ruptured, growing, symptomatic or of significant size. The goal of prophylactic treatment of an aneurysm is to increase the number of years with good quality of life.

The main goal of the present study is to identify how does the diagnosis of an unruptured cerebral aneurysm and its subsequent treatment impact quality of life as measured by SF-36 and EQ5D in patients. We aim to quantify if the impact in quality of life varies overtime. We aim to verify if the choice of technique (endovascular vs microsurgical) has an impact on quality of life in the short and long term. We will explore the relationship with other variables such as gender, medical comorbidities, aneurysm location, and postoperative complications.

Quality of life will be assessed via the SF-36 and the EQ5D tool at time 0 (time of diagnosis) and at 1 year for patients with an untreated cerebral aneurysm. Quality of life will be assessed via the SF-36 tool at time 0 (time of diagnosis), 6-8 weeks postoperative follow-up and at 1-year postoperative follow-up in the patients who have been treated. The latter group will be divided in 2 sub-groups: endovascular and microsurgical (clipping).

*Data analysis and manuscript preparation is ongoing for this study.*

#### **4. Quality of Life in Patients Diagnosed with Moyamoya Disease: Cross-Sectional Study:**

PI: Dr. Gooderham; Co-PI: Drs. Dandurand, Yip

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Rare Diseases Foundation	May 2017 – May 2019	100	28	Yes	Active	N/A

#### **Purpose**

Moyamoya disease is a rare and chronic disease characterized by the progressive occlusion of intracranial vessels. The supraclinoid carotid arteries are the first arteries affected. It rarely affects the posterior circulation. Small collateral vessels begin to form at the base of the brain as the larger vessels become occluded giving it the characteristic appearance of a «puff of smoke» on angiographic radiological studies. This disease can present with ischemic stroke or intracranial hemorrhage depending on the age of the patient.

#### **Objectives**

The main goal of the present study is to identify how does the diagnosis of Moyamoya disease, its different clinical presentations and its subsequent treatment impact quality of life as measured by SF-36, EQ5D and 49-item Stroke-Specific Quality of Life Scale (SSQOL) in patients. We aim to verify if the choice of technique (direct or indirect bypass) has an impact on quality of life. We will explore other variables such as clinical presentation (incidental, ischemic or hemorrhagic), radiological features (cerebrovascular reserve and evidence of ischemic stroke), gender, medical comorbidities, postoperative complications and length of time after diagnosis and treatment.

*There are 37 participants currently enrolled in the study, 0 participants were enrolled during the last quarter. Enrolment has ended.*

#### **5. EVD Complications in Canada:**

PI: Dr. Ryoko Akagami; Co-PI: Dr. Makarenko

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	Jan 2018 –	500 (across Canada) 50 (VGH)	50	Yes	Approved	N/A

#### **Context**

Placement of external ventricular drain (EVD) catheters is a common neurosurgical procedure typically performed in emergent situations for the treatment of hydrocephalus and raised intracranial pressure (ICP). The procedure is associated with a number of complications resulting in significant morbidity. Comprehensive, prospective studies are lacking in describing the

incidence of these complications and associated risk factors. A multi-centre prospective study is required in order to adequately investigate the complication profile of EVD catheter placement.

### **Design**

This is a prospective multi-centre observational study to be conducted at 12 Canadian neurosurgical centres forming part of the Canadian Neurosurgery Research Collaborative (CNRC). The CNRC is a Canadian research network made up of 12 neurosurgery residents representing the participating sites, and supported by attending neurosurgeons. The CNRC is bound by an agreement signed by all residents to protect the confidentiality of data and privacy of patients.

### **Hypothesis**

This study hypothesizes that in patients with EVD-catheters placed urgently (e.g. in the setting of intracranial hemorrhage or traumatic brain injury), the rates of EVD catheter-related complications including EVD catheter infection, hemorrhage and misplacement are influenced by patient, catheter and operator-related factors as described above.

*There are 50 participants enrolled. Data collection has been completed across all Canadian sites. Manuscript has been submitted to the Journal of Neurosurgery.*

## **6. Meningioma QOL Electronic Patient Reported Outcomes:**

PI: Dr. Ryojo Akagami

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	Jan 2018 – ongoing	Perpetual	20	Yes	Active	N/A

### **Purpose**

This is a prospective study to collect information on quality of life before and after treatment for patients with meningioma. Knowing the expected quality of life associated with this diagnosis in the short and long term will not only help physicians and patients make a decision regarding treatment, but also, prepare the patient for the upcoming hardship. The goal of our study is to identify ways we can improve patient quality of life while they are undergoing treatment (surgery, radiation, or observation under the care of a neurosurgeon) for meningioma.

### **Objectives**

The main goal of the study is to identify how does the diagnosis of meningioma and its subsequent treatment impact quality of life as measured by FACT-MNG in patients. We aim to establish a baseline for pre-operative quality of life in patients with meningioma and to determine the impact of surgical treatment and/or subsequent interventions on patient reported quality of life outcomes.

### **Hypothesis**

Our hypotheses are the following: 1) we hypothesize that patient quality of life will improve after surgery for resection of meningioma compared to the observational group; 2) we hypothesize that VisionTree will be a feasible, well-tolerate and efficient tool for measuring objective and patient reported quality of life outcomes after meningioma treatment.

*There are 21 participants currently enrolled in this study. None enrolled during the last quarter.*

**7. Next Generation Sequencing for Rare Variants in Familial Intracranial Aneurysms:**

PI: Dr. William Gibson (UBC Medical Genetics; BCCHR), Co-I's: Drs. Redekop, Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	HSFC	Aug 2019 – ongoing	Perpetual	146	Yes	Approved	N/A

**Purpose**

Several genes that predispose to aneurysms of the large blood vessels like the aorta are already known, and there are some rare genetic syndromes that predispose to brain aneurysms when other medical features (such as kidney cysts) are also present. However, there are no genes yet known that cause non-syndromic brain aneurysms. Our goal is to identify the first human gene(s) for isolated intracranial berry aneurysms.

**Objectives**

Our two specific aims are to catalogue the spectrum of rare coding variants in families diagnosed with intracranial aneurysms, and to validate functional effects of the most promising variant(s) on cerebral vasculature using animal models.

*There are 175 participants currently enrolled in this study. 13 were enrolled this quarter. Manuscript preparation is in progress*

**8. Study of Biomarkers in the Blood and Cerebral Spinal Fluid of Aneurysmal Subarachnoid Hemorrhage Patients**

PI: Drs. Redekop, Hanafy (Beth Israel Deaconess Medical Center), Co-I's: Drs. Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Aug 2019 – ongoing	250	0	Yes	Approved	N/A

**Purpose**

The aim of this protocol is to study the biomarkers involved in the clinical consequences of aneurysmal subarachnoid hemorrhage (aSAH) in human subjects. The hypothesis is that a study of inflammatory biomarkers such as Toll-like receptor 4 (TLR4) and heme oxygenase (HO)-1 in aSAH patients, will allow for better prognostication following aSAH.



## Objectives

The overall objective of this study is to collect blood and CSF samples from human subjects in order to study the biomarkers involved in the clinical consequences of patients who have been diagnosed with aneurysmal subarachnoid hemorrhage (aSAH). Samples will be studied using lab techniques such as molecular diagnostics, gene expression profiling, and blotting of factors that have been experimentally shown to have involvement in the clinical occurrences of aSAH. An attempt will be made to correlate results with the clinical time course of SAH. The long-term goal of this study is to increase management options for the clinical consequences of aSAH such as inflammation, vasospasm, and EBI, and work towards treatments that improve chronic aSAH neurological outcome.

*Approvals for this study have been obtained, recruitment will commence in the near future.*

### 9. The genetic and epigenetic basis of intracerebral aneurysms

PI: Drs. Redekop, Hanafy (Beth Israel Deaconess Medical Center), Co-I's: Drs. Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Aug 2019 – ongoing	250	0	Yes	Approved	N/A

## Purpose

The goal of this study is to delineate the underlying mechanism leading to aneurysm development, progression, rupture and vasospasm, which will help in identifying targets which are amenable to intervention.

We are aiming to discover genes and epigenetic influences on genes. Part of the project will be to identify these specific genes and epigenetic phenomena involved in the progression and rupture of aneurysms. There is no work to date on the epigenetic regulation of genes involved in these processes.

## Objectives

The objective is to identify the biological functional pathways that were significantly over-represented by differentially expressed genes between aneurysm and control tissue samples as well as between ruptured and unruptured aneurysm samples

### 10. Variability in the concentration of antiepileptic agents in the cerebrospinal fluid of critically ill patients

PI: Dr. Farzad Moien-Afshari (Neurology) Co-I's: Drs. Griesdale, Agha Khani, Redekop, Fatehi

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Nov 2019 – ongoing	100	0	Yes	Approved	N/A

### **Purpose**

Patients who are critically ill receive a multitude of medications, have metabolic disturbances and may also have renal or hepatic dysfunction. These factors influence the pharmacokinetics and pharmacodynamics of medications including AEDs. Consequently, previous studies have recommended using AEDs with easily measurable levels in the ICU. Again however, there is a paucity of studies that have addressed the CSF levels of these medications. Hence, there is a clear impetus to determine whether the serum level of AEDs is an effective surrogate of CSF concentrations and also to determine whether medications such as verapamil do in fact increase CSF levels.

### **Objectives**

The main goal of this study is to determine whether the concentration of phenytoin, levetiracetam, carbamazepine, lacosamide, and valproic acid remain therapeutic in critically ill patients. We propose a single-center study of patients admitted to the Vancouver General Hospital (VGH) ICU.

## **11. Identification of blood and cerebral spinal fluid factors involved in aneurysmal subarachnoid haemorrhage**

PI: Dr. Haw Co-I's: Drs. Sadr, Bernie, MacVicar

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Nov 2019 – ongoing	100	0	Yes	Approved	N/A

### **Purpose**

Ruptured intracranial aneurysms lead to subarachnoid haemorrhage (SAH), a form of intracranial bleed that is often associated with severe morbidity and mortality. One of the most feared complications of aneurysmal SAH (aSAH) patients is cerebral vascular constriction, or vasospasm. This vasoconstriction leads to decreased cerebral tissue perfusion and ischemic strokes, causing significant neurological sequelae and potentially lethal complications.

The current standard of care for aSAH patients in vasospasm include the administration of vasodilators such as intra-arterial verapamil and intra-venous milrinone. However, such treatments require invasive and highly specialised tools and personnel, are costly, and have limited efficacy.

The molecular mechanisms leading to post-aSAH vasospasm remain elusive. Therefore, better characterising such mechanisms could provide new avenues into tackling its devastating consequences.

### **Objectives**

The aim of our research is to identify blood and cerebrospinal fluid factors that are involved in aneurysmal vasospasm. Characterising those molecular triggers of vasospasm would improve our understanding of the underlying pathophysiology. Ultimately, our goal is to predict and prevent vasospasm, or at least developing novel targets to manage it and prevent its devastating neuro-pathological manifestations.

**12. Neuroscience of the human brain in health and disorder (new this quarter)**

PI: Dr. Mark Cembrowski (UBC Dept. Cellular and Physiological Sciences); Co-I: Dr. Redekop

Funding	Source	Study period	# of subjects enrolled	Approvals	Status
No	-	Nov 2020 – ongoing	1	Yes	Recruitment ongoing

**Purpose**

(1) Understand organization and function of the healthy (i.e., pathologically unremarkable) human brain at molecular, cellular, and circuit levels; (2) use this understanding of the healthy brain to interpret dysregulation during epilepsy.

**Objectives**

(1) Characterize the molecular, cellular, and circuit properties of surgically resected discard human brain tissue in healthy cortex, (2) Compare this to analogous characterizations in brain tissue from epileptic foci to identify molecular, cellular, and circuit dysregulation in epilepsy.

**Research design**

Non-diagnostic discard brain tissue from Dr. Redekop and his staff, obtained via standard surgical resections from informed consenting participants, will be de-identified by Dr. Redekop or a member of VGH research staff, and via Dr. Hirsch- Reinshagen and VGH pathology, received by Dr. Cembrowski to be used in neuroscientific research examining molecular, cellular, and circuit properties. Acute experiments will involve:

- transcriptomics and epigenomics (tissue from n=12 participants needed for each of epileptic and non-epileptic datasets, in order to acquire sufficient statistical power based upon previously published results)
- whole-cell patch-clamp electrophysiology and morphological reconstructions (n=50 neurons needed for each of epileptic and non-epileptic datasets, likely requiring tissue from ~10 participants, in order to acquire sufficient statistical power based upon previously published results)

### 3. ONGOING RETROSPECTIVE STUDIES

#### 1. Quality of Life after Surgery in Patients with Pituitary Tumors and Acromegaly:

PI: Dr. Akagami; Co-PI: Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Dec 2015 Dec 2018	Yes	63	Active	Published in the Journal of Neurological Surgery (2017)	N/A

Patients with pituitary tumors have been previously noted to report decreased quality of life (QoL). These studies have used a variety of validated questionnaires (such as SF36 and AcroQoL) to assess the physical, cognitive and psychological well-being of patients affected by functional and non-functional tumors. Predictably, QoL is variably affected by different types and extents of tumor. Studies which have focused on patients with acromegaly have generally shown improvement of QoL after treatment (GH<2ng/ml). However, it is not clear whether the improvement of QoL is primarily driven by the correction of hormonal imbalances.

This is a retrospective review of QoL after pituitary surgery in patients with acromegaly. Any patient that lacks the SF36 questionnaire will be contacted, consented and given a copy to complete. All charts of patients who have previously undergone this procedure with Dr. Akagami shall be assessed. Multivariate analysis will be used to determine the factors which most impact QoL improvement post-operatively. The chart reviews have been completed.

#### 2. Computational 3D Segmentation of Cerebral Vasculature for Evaluation of Cerebral Aneurysms:

PI: Dr. Gooderham; Co-PI: Drs. Hamarneh, Chew, Mendelsohn

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jan 2010 Dec 2018	Yes	500	Active	N/A	None

The primary objective of this study is to develop computer software using advanced imaging analysis techniques that can accurately detect cerebral aneurysms on CTA scans. The secondary objective of this study is to develop computer software that can detect changes in the size and shape of aneurysms over time in the same patient.

We hypothesize that advanced imaging analysis techniques will be able to be applied to CTA scans to successfully and accurately detect cerebral aneurysms and compare their size and shape at different points in time in the same patient. The chart reviews have been completed.

#### 3. Trigeminal Schwannoma Study:

PI: Dr Akagami; Co-PI: Dr. Makarenko

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Mar 2016 Feb 2017	Yes	30	Active	Published in the Journal of Neurological Surgery Part B: Skull Base (2017)	N/A

This is a retrospective review of trigeminal schwannomas that were operated on by Dr. R. Akagami with an open craniotomy approach between 2001-2015 at Vancouver General Hospital. Our aim is to characterize the clinical presentation against imaging findings, and document the natural history of the TS tumours with respect to management strategy that includes surgical resection, radiotherapy, and observation.

We have two objectives. First, we will attempt to characterize the patients' trigeminal schwannoma anatomy with respect to location in middle and posterior cranial fossae, and then investigate their outcomes following transcranial resection of tumour by Dr. R. Akagami. We hope to correlate the patient's clinical presentation with the tumour anatomy with respect to sensory and motor symptoms, and then compare these against those of the findings in literature. The chart reviews have been complete

4. **Reliability of the Unified Visual Fields Scale (UVFS) Study:**

PI: Dr. Ryogo Akagami; Co-PI: Drs. Gooderham, Makarenko

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jun 2017- Jun 2019	No	30	Approved	In preparation	N/A

**Purpose**

This is a study in inter- and intra-observer reliability. We will select 30 de-identified patients with pituitary lesions affecting vision. We will obtain their last visual acuity and visual fields assessments (Goldmann's visual fields) following surgical resection, and a UVFS score will be assigned as a consensus decision by the study investigators. We will then perform additional individualized assessments done by two neurosurgeons, two neurosurgery residents, and two medical student trainees. The reviewers will be presented with a formal visual field assessment as well as visual acuity scores and asked to assign the UVFS score. These will be presented 3 different times to limit recall bias (total of 90 scores will be applied).

**Analysis**

We will use three statistical tests to assess inter- and intra-observer reliability. The interclass correlation coefficient (ICC) will be used to measure both inter-and intra-observer agreement for total UVFS scores (two-way mixed effect model, in which people effects are random, and measures effects are fixed). Fleiss's kappa will be used for multiple raters to measure interobserver agreement, and Cohen's kappa will be used to evaluate intra-observer agreement.

5. **PICA Aneurysm Study:**

PI: Dr. Gary Redekop; Co-PI: Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jan 2017 – Ongoing	Yes	53	Approved	In preparation	N/A

## Purpose

Aneurysms found in the posterior inferior cerebellar artery (PICA) are a rare cause of subarachnoid hemorrhage. Treatment for this type of aneurysm may be microsurgical or endovascular. This decision is based on patient characteristics, aneurysm location and dimensions along with surgical/institutional experience. Knowing how patient outcomes are affected by the different treatments of PICA aneurysms would help physicians and patients in their decision regarding treatment options.

## Objectives

The main goal of this study is to determine whether there are outcome differences between surgically and endovascular treatment. We aim to determine whether patient characteristics or aneurysm features predict treatment choice and subsequently patient outcome.

### 6. Surgical epilepsy: complications and long-term outcomes:

PI: Dr. Redekop; Co-I: Dr. Ayling.

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jun 2018 –Jun 2019	Yes	500	Approved	N/A	N/A

## Objectives

To document our rates of complications and results of seizure status in patients that have undergone surgery for epilepsy at Vancouver General Hospital since 2000.

## Hypothesis

Specific patient and surgical factors will be associated with peri-procedural complications as well as long-term seizure outcomes.

## Research Design

This will be a retrospective review of patients diagnosed with epilepsy and that have undergone a surgical procedure. Charts of patients who have been managed at VGH will be reviewed for demographic, treatment strategies, and imaging data.

### 7. Pituitary Adenoma Resection and Post-Operative Diabetes Insipidus:

PI: Dr. Gooderham; Co-I's: Dr. Akagami, Makarenko.

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jun 2018 – Ongoing	Approved	300	Not started	N/A	N/A

## Objectives

Our main objective is to characterize the rate of diabetes insipidus following endoscopic transsphenoidal resection of pituitary tumours and to analyze the amount of pituitary gland translation in the post-operative period. As our secondary objectives, we will assess clinical features and surgical outcomes among the cohort.

## Hypothesis

We hypothesize the rate of diabetes insipidus following transsphenoidal pituitary surgery can be correlated with the distance travelled by the pituitary gland and subsequently the pituitary stalk following resection.

## Research Design

This is a retrospective chart review of endoscopic transsphenoidal pituitary tumour resections by Drs. P. Gooderham and R. Akagami between January 1st 2010 and December 31st 2017 at Vancouver General Hospital. There is expected to be approximately 300 patient charts to be reviewed.

### 8. Presentations of Ischemic Pituitary Apoplexy: A Case Series

PI: Dr. Akagami

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
2009 - 2019	Obtained	5	Active	N/A	N/A

## Research Objective

This case series aims to illustrate and discuss five unique presentations of macroadenoma ischemic pituitary apoplexy, and direct physician attention towards specific symptoms that may warrant urgent surgical decompression despite little to no mass effect or changes on imaging.

## Research Design

Charts from 01-January 2009 to 24-February-2019 will be reviewed. The collected data will be reported on for each case of ischemic pituitary apoplexy, describing salient and unique features of the history of presenting illness, imaging findings, lab results and management. A discussion section will summarize important learning points for clinicians and detail appropriate management in the context described.

### 9. Milrinone for the Treatment of Cerebral Vasospasm Secondary to Aneurysmal Subarachnoid Hemorrhage

PI: Dr. Gooderham; Co-I's: Drs. Sekhon, Griesdale, and Ms. Caelie Stewart

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
2012 - 2019	In progress	170	Active	N/A	N/A

## Purpose of Research

Cerebral vasospasm (CVS) is the leading cause of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (aSAH). Various protocols exist to treat CVS with variable profiles of adverse outcomes. Vancouver General Hospital (VGH) follows the Montreal Neurological Hospital protocol for treatment of CVS, utilizing milrinone to reverse vasospasm. Knowing the spectrum of patient outcomes and adverse events with milrinone treatment will help physicians anticipate complications and make informed patient management plans.

## Objectives

The primary objective of this work is to evaluate the neurological outcomes and adverse reaction profile of patients with aSAH complicated by CVS and treated with milrinone. This will be done through a single-center retrospective chart review of all patients admitted to VGH for aSAH who secondarily suffered CVS and were treated with milrinone. Data will be collected on patient demographics, clinical presentation, diagnosis, treatment, complications and outcome measures.

## Hypothesis

Our hypothesis is that milrinone is associated with good neurological outcomes and minimal adverse reactions to treatment

### 10. Exploration of Potential Benefits to Radiation Therapy in Grade 2 Meningiomas

PI: Dr. Makarenko; Co-I: Dr. Rebchuk

Study period	Approvals UBC CREB/VCHRI	Anticipated number of patients reviewed	Status	Abstract/Paper/ Manuscript	Funding
Oct 2020- ongoing	Approved	800	Not started	N/A	N/A

## Purpose of research

In this study, we will explore whether adjuvant radiation therapy (RT) provides overall survival (OS) and progression-free survival (PFS) benefit following resection of grade II meningioma in our local cohort. We will perform subgroup analysis to compare whether the extent of resection and timing of RT have a modifying effect on OS and PFS in this cohort. We also hope with subgroup analysis, to clarify if specific pathologic features of atypical meningiomas affect outcomes. Furthermore, we will explore whether the 2016 diagnostic change to grade II meningioma has affected the prevalence rate of these diagnoses. These results will guide local practice patterns in patients with grade II meningiomas.

## Research Aims

- 1) Explore whether adjuvant RT following operative resection of grade II meningioma has an effect on PFS and OS
  - a) Explore any modifying effect by Simpson grade (Grade 1 v Grade 2-3)
  - b) Explore any modifying effect of RT timing (early [ $<6$ wks] v late [ $>6$ wks])
- 2) Determine whether grade of resection predicts OS or PFS in grade II meningiomas
- 3) Explore clinical and histopathological predictors of OS and PFS, and tumour recurrence in grade II meningiomas
- 4) Explore whether recent changes to histopathological diagnosis of meningiomas has affected prevalence rate
- 5) If possible, explore the effect of watch and wait versus operative +/- RT treatment for asymptomatic grade II meningiomas



## Design

We will perform a single center retrospective chart review. Patient level data will be obtained from Vancouver General Hospital and BC Cancer Agency database between October 2007 and December 2020.

## 4. INACTIVE OR COMPLETE STUDIES

### 1. Resident Activity Tracker Evaluation (RATE) Study:

PI: Dr. Toyota; Co-PI: Drs. Mendelsohn, Redekop, Singhal, Gooderham

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/Paper/Manuscript
Yes	RDBC (NGO) BCSPQC (NGO) MD Financial (NGO)	Sep 2015 - Aug 2017	60	59	Yes	Completed	In submission

Medical resident work hour restrictions remains a large topic of debate in the Accreditation Council for Graduate Medical Education; and more importantly, also in the Royal College of Physicians and Surgeons of Canada.

An adequate number of hours of sleep play an important role in medical residents' performance, and quality of life. Formal changes to resident work-hours regulation have not been imposed for Canadian medical residents. On-call duties vary substantially across medical specialties further complicating the issue. The actual physical demands of resident on-call duties and the impact on sleep duration and number of interruptions have not been comprehensively investigated to date.

This study will be the first in literature to measure average and maximum heart rate, sleep duration and interruptions, and number of steps taken per day in medical resident trainees, across non-surgical and surgical specialties and when the residents are on or off call. Such novel results will help advance and guide current discussion on resident work hour restriction towards a more comprehensive conclusion.

*There are 59 residents currently enrolled in the RATE Study. The enrolment has been completed. The manuscript has been submitted.*

### 1. Current Glioblastoma Outcomes in BC:

PI: Dr. Toyota; Co-PI: Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/Manuscript	Funding
Jul 2016 – Dec 2017	Yes	200	Active	Published	N/A

Glioblastoma remains a lethal diagnosis with well-recognized failures in truly effective curative strategies. However there have been incremental improvements over the past decade that has

predicted 2.5-fold improvements in 2-year survival. This prediction was based on a handful of studies describing new treatment strategies and bio-marker revelations. Our study seeks to document the actual 'real-world' change in glioblastoma outcomes. The objective is to establish the overall and median survival of a current cohort of patients treated for glioblastoma in B.C. undergoing standard treatment algorithms. The chart reviews have been completed.

*This study has published.*

**2. Basilar Tip Aneurysm Study: Case series, systematic review and meta-analysis:**

PI: Dr. Gooderham; Co-I: Dr. Dandurand

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jan 2018 –Jan 2019	Yes	150	Active	Manuscript in progress	N/A

**Objectives**

This investigation aims at characterizing 1) radiological outcome stratified per treatment technique 2) clinical outcome per treatment technique 3) rate of retreatment per treatment technique 4) risk factors for retreatment 4) create a large pool of patients to characterize rare phenomenon such as progressive growth of basilar aneurysm despite adequate occlusion at first treatment.

**Hypothesis**

Our hypothesis is the following: 1) radiological outcome will be better with the use of stent-assisted coiling vs coiling alone 2) Perioperative complications may be higher in the stent-assisted group, but the retreatment rate and rehemorrhage rate will be lower.

**Outcomes**

We will assess the relationship between radiological and clinical outcomes with each endovascular and surgical technique. Relationship between covariates and outcomes such as, patient’s demographics, clinical presentation, size and features of aneurysms, radiological characteristics, and postoperative complications.

*This study has published.*

**3. TOCA 511 Study - A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma:**

PI: Dr. Toyota; Co-PI: Dr. Yip

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Tocagen (Industry)	Apr 2016 - Dec 2019	200 in Phase 3	0	Yes	Inactive	N/A

Name of Investigational Product: Toca 511, a retroviral replicating vector (RRV) expressing a yeast-derived, codon-optimized cytosine deaminase (CD) prodrug-activator gene, in combination with Toca FC (flucytosine) extended-release tablets.

Primary Objective: To compare the overall survival (OS) of subjects treated with Toca 511 combined with Toca FC to subjects treated according to standard of care after tumor resection for recurrence of glioblastoma or anaplastic astrocytoma.

Methodology: This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus standard of care (SOC) that comprises Investigator's choice of either single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of glioblastoma or anaplastic astrocytoma. Subjects will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC or control. Repeat scans will be obtained every 6 weeks for the first year and every 3 months after that.

Subjects may receive any standard of care treatment following progression or discontinuation from study due to toxicity. Crossover to the Experimental arm is not allowed, unless the primary endpoint is met and the Sponsor notifies the sites.

*This study has completed recruitment worldwide.*

#### 4. LAANTERN Registry:

PI: Dr. Toyota; Co-PI: N/A

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	Monteris (Industry)	Jan 2016 - Dec 2019	150 (all sites)	15	Yes	Active	N/A

The NeuroBlate® System (NBS) is a minimally invasive robotic laser thermotherapy tool that is being manufactured by Monteris Medical. It employs a pulsed surgical laser to deliver targeted energy to abnormal brain tissue. To further understand performance and utilization of NBS in current standard of care, post-market multi-center registry called LAANTERN (Laser Ablation of Abnormal Neurological Tissue using Robotic Neuroblate system) is designed to collect baseline, procedural and follow-up data on patients that are already scheduled to be treated with NBS in observational manner for publication purposes.

This is a multi-center registry that will include data collection at baseline (prior to NeuroBlate® procedure, which is also referred as the index procedure), during index procedure, discharge and up to 24-month follow-up. Up to 1,000 patients may be enrolled at up to 50 study sites. Most of the Enrolment will occur prospectively; however, the data collection for patients who already

underwent a procedure with NBS may also take place retrospectively. For example, if the patient already had a NBS procedure, he/she may be approached about study participation. If the patient agrees to participate in the study, the data collection will be initiated once Informed Consent Form (ICF) is signed (e.g., demographics, procedure, and discharge data will be collected retrospectively and future follow-up visits collected prospectively).

*Enrolment and follow-up have been completed. There were 15 participants enrolled in the LAANTERN Registry.*

**5. Biomarkers in Malignant Brain Tumors Study:**

PI: Dr Toyota

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /Sample Size	Status	Abstract/Paper/ Manuscript	Funding
Jun 2015 Aug 2018	Yes	151/151	Active	N/A	N/A

To conduct a retrospective clinical chart review of our institution’s glioblastoma cases to compare the predictive and prognostic value of molecular markers to that of traditional histological diagnoses.

This is a retrospective chart review involving charts of patients with glioblastoma treated at VGH from 2010-2014. We have created a database to register basic patient demographics, treatment protocols and outcome. Specific to our study, we classified the tumors by classic histologic description and grading as well as new cutting edge diagnostic molecular and genetic analysis.

Based on this database, we will stratify the patients into outcome categories based on classical grading and newer molecular markers. A statistical analysis of this data will then be conducted in order to compare the predictive value of these classic histologic methods with the newer methods for patient outcomes. Quinn Parker was a summer student who had obtained UBC SSRP funding for the summer. The chart review has been completed, and we await statistical analysis.

**6. Operative Cerebrovascular Exposure by Canadian Neurosurgery Residents:**

PI: Dr. Toyota, Co-I’s: Drs. Gooderham, Makarenko

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	None	March 2018 – August 2018	Residents and PDs from every neurosurgical centre in Canada		Yes	Approved	N/A

**Purpose**

Given this rapid changing landscape of cerebrovascular neurosurgery, the training of a new generation of neurosurgeons has also evolved. The extent of these changes however has not been well documented, and the expectation of graduating neurosurgical programs across Canada and North America still reflect the management paradigm of past decades. With this survey we hope

to characterize the resident experience and exposure with open cerebrovascular neurosurgery, predominantly the treatment of intracranial aneurysms. We hope by gaining this insight we can provide feedback as well as steer the development of training curriculum to account for the shift in cerebral aneurysm management.

**Objectives**

We have two objectives. First, we will attempt to characterize the overall operative exposure of Canadian neurosurgery residents to treatment of cerebral aneurysms. Second, we will contrast the extent of the volume of open vascular and endovascular cases at each major Canadian neurosurgical centre by surveying program directors at the respective institutions.

**Hypothesis**

We suspect that while it will vary across the country, with emerging emphasis on endovascular management of cerebrovascular conditions, the exposure of residents will be limited to open surgical cases.

*30 residents and 10 program directors have responded to the survey. Data collection has been completed.*

**7. Image Analysis and Machine Learning for the Evaluation of Brain Tumours:**

PI: Dr. Toyota; Co-I: Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
Jan 2018 –Jan 2020	Yes	300	Active	N/A	N/A

**Objective**

The primary objective of this study is to develop computer software that can accurately compare images from various time-points. Specifically, this software will be used to assess changes in tumors over time. The secondary objective of this study is to develop a computer software that can stratify tumor type and patient prognosis based upon radiologic features. In order to develop the automated computer software, imaging analysis of 300 brain MRI scans will be necessary.

**Hypothesis**

We hypothesize that advanced imaging analysis techniques may be applied to MRI and CT scans to accurately assess the size and growth of brain tumors at different points in time in the same patient.

Tumor characteristics on imaging will correspond with and ultimately help predict patient survival.

**8. Evaluation of Quality of Life of Patients with Lesions Affecting the Optic Apparatus and Comparison with Unified Visual Outcome Scale (UVFS):**

PI: Dr. Ryojo Akagami; Co-PI: Drs. Gooderham, Makarenko

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	May 2017 – May 2019	60	27	Yes	Approved	N/A

### **Purpose**

We have designed a Unified Visual Function Scale (UVFS) based on the definition of legal blindness and the fitness to drive as a quick, accurate, and easy-to-use tool for evaluating visual outcomes (Makarenko et al. 2017, in print). UVFS needs to be tested for inter- and intra-observer reliability, as well as its correlation to be able to reflect quality of life impact. Other scales such as Visual Function Questionnaire (VFQ-25) or Activities of Daily Vision Scale (ADVS) have been used in attempts to correlate visual function to quality of life, but these are also unsuitable for routine clinical use. This study hopes to correlate UVFS to these scales, as well as establish its reliability for capturing quality of life assessments.

### **Objective**

We have two objectives. First, we will attempt to characterize visual outcomes of patients with lesions affecting the optic apparatus, and then investigate the accuracy of our new Unified Visual Function Scale to correlate with the visual quality of life data. We hope to demonstrate that the Unified Visual Function Scale is able to not only provide clinically useful information, but also reflect impact of vision on patient quality of life.

*This study has been published.*