1. **Motor and cognitive recovery from severe stroke: Do covert lesions impact outcome?**
Top ranked grant & winner of Dr. Hakim Stroke Research Award

Principal Investigator: **Dr. Lara Boyd, *University of British Columbia***
Co-investigators: Dr. Sandra Black (*Sunnybrook Research Institute*), Dr. Gail Eskes (*Dalhousie University*), Dr. Angela Auriat (*University of British Columbia*), Dr. Kathryn Hayward (*University of British Columbia*)

Brief Project Description: This study will assess the impact that covert lesions (tiny difficult to see lesions that can accumulate) have on motor and cognitive recovery from severe stroke over time.

Project Summary: Every year, over 62,000 Canadians have a stroke. Recent advances in acute care have increased the likelihood of surviving a large stroke and have resulted in up to 30% of all stroke survivors living with severe arm impairments. While some people with severe impairment attain little recovery, others show substantial gains. Because even partial recovery of function can be meaningful for individuals with severe arm impairment, it is critical to be able to identify who has the most potential for improvements. In addition, 30-100% of individuals with stroke also have small, covert lesions (lesions that are so small they are difficult to see) in the brain. It is possible that the total volume of covert lesions may help to explain who shows partial recovery of motor and/or cognitive function after severe stroke. However, no work has considered whether the presence of these very small lesions in the acute stage predicts recovery in these areas at 3- and/or 6-months post-stroke.

Thus, the main aims of the proposed research are to: 1) track individuals with severe arm impairment across the first 6-months post-stroke to determine which factors best predict motor and cognitive recovery of function; 2) to see if the volume of covert lesions changes in the first 6-months after stroke; and 3) to establish how the presence of covert lesions acutely impacts cognitive and motor recovery of function after stroke. Determining reasons why someone with severe arm impairment achieves partial recovery after stroke is an important question; this information may be used to advocate for improved rehabilitation for this growing and under-served group of Canadians.

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2. **Engaging skeletal muscle and vascular plasticity to promote hindlimb functional recovery in a rat model of ischemic stroke**

Principal Investigator: **Drs. Dale Corbett & Baptiste Lacoste, *University of Ottawa***
Co-investigators: Dr. Bernard Jasmin (*University of Ottawa*), Dr. Susan Marzolini (*Toronto Rehabilitation Institute – University Health Network*)

Brief Project Description: This study will assess whether the benefits of exercise can be augmented when combined with metformin, an FDA-approved anti-diabetic drug that produces changes in muscles similar to exercise in a rodent stroke model.

Project Summary: Many stroke survivors have reduced ability to move their limbs, thereby greatly limiting their activities of daily living. Researchers are testing new approaches to improve stroke recovery, including combining rehabilitation with other interventions. A promising intervention is exercise that improves stroke recovery in animal and human studies. However, a major barrier to widespread implementation of exercise into stroke rehabilitation is the rapid deterioration in cardiovascular fitness and muscle strength following a stroke, superimposed on an inactive lifestyle prior to the stroke. This makes it difficult for individuals to exercise at intensity sufficient to restore and improve physical fitness levels.

To address this problem, we will use an exercise program (similar to that used in humans) in rats that have stroke-induced hindlimb deficits reducing (but not preventing) their ability to walk and climb. Exercise (both aerobic and strength training) will be preceded by dosing with metformin (MET), an FDA-approved anti-diabetic drug that produces changes in muscles similar to exercise and thus considered an "exercise mimetic". Exercise with and without MET will be used to determine if impairments in hindlimb function (assessed by sensitive behavioral tests) can be reduced. The impact of the exercise and/or MET treatments on the fitness level of the rats will be measured in the same way as in humans (maximal oxygen consumption), to facilitate translation of our findings to the clinic. Finally, in organs important for stroke recovery (muscle and brain) we will investigate changes in the density of blood vessels and in different molecular pathways that affect vascular remodeling and inflammation. The proposed experimental approach has a high translational potential to significantly increase both the rate and level of motor recovery in stroke patients.

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3. Increasing access to fitness in early stages of stroke rehab: Determining safe participation through a graded submaximal exercise test

Principal Investigator: **Dr. Elizabeth Inness, *Toronto Rehabilitation Institute – University Health Network (TRI-UHN)***
Co-investigators: Dr. Mark Bayley (*TRI-UHN)*, Louis Biasin (*University of Toronto*), Dr. Dina Brooks (*University of Toronto & TRI-UHN*), Dr. Avril Mansfield (*Sunnybrook Research Institute & TRI-UHN*), Dr. Susan Marzolini (TRI-UHN), Viven Poon (*University of Toronto)*, Dr. Ada Tang (*McMaster University*)

Brief Project Description: This study will use physiological data collected on 350 stroke patients to identify the prevalence and severity of abnormal signs or symptoms in order to establish profiles of those who can safely participate in a fitness exercise program.

Project Summary: Poor aerobic fitness is common post-stroke, contributes to functional disability and increases the risk of recurrent stroke. Aerobic exercise can have many benefits for people with stroke and is, therefore, a part of best practice recommendations for rehabilitation. However, there are challenges to implementing these recommendations that can present barriers to exercise participation. For example, heart disease is common in people with stroke so exercise stress testing with electrocardiographic (ECG) monitoring is recommended. However, the trained personnel and special equipment required for this testing is not readily accessible at most stroke rehabilitation centres and this test might not be feasible for people with low levels of physical ability. If less intense exercise is planned, a submaximal exercise test may be performed but the research to support this recommendation is much less clear. It is

critical to gain a better understanding of the risks involved in exercise and remove barriers to exercise participation among those with stroke who are at risk for inactivity-related health problems.

In 2010, we implemented fitness programming as part of routine clinical practice within a stroke rehabilitation setting. Since then, we have accumulated a rich dataset of submaximal exercise test results and ECG recordings from approximately 350 individuals with stroke. We propose to review these data to identify the prevalence and severity of abnormal signs or symptoms that occurred during testing. The results of this study will more clearly establish the profiles of those who can safely participate in fitness programming informed by a submaximal exercise test. This information can then be used to modify current clinical guidelines, which will *promote early access to fitness for more people after stroke*, and inform future studies evaluating the benefits of early exposure to exercise on long-term exercise behavior, recovery and health.

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4. Web-based goal management training® in stroke patients with executive deficits: A randomized-controlled trial examining feasibility and efficacy

Principal Investigator: **Dr. Brian Levine, *Rotman Research Institute, Baycrest***
Co-investigators: Dr. Sandra Black (*Sunnybrook Health Sciences Centre*), Dr. Vessela Stamenova (*Rotman Research Institute, Baycrest*)
Collaborators: Ron Riesenbach (*Baycrest*), Michael Meagher (*Cognicity*), Dr. Zindel Segal (*University of Toronto*)

Brief Project Description: The goal of the proposed research is to design an automated, web-based Goal Management Training® (GMT) program that can be delivered remotely and that is specifically geared towards patients with stroke.

Project Summary: Patients with overt strokes often show deficits in executive functioning: deficits of planning, organization, multitasking, and sustained attention. All of these functions are critical for the performance of daily activities, such as shopping, cooking, and financial management and as a result have a direct impact on one's ability to maintain functional independence. Unfortunately, there are few validated rehabilitation approaches for executive deficits.

One rehabilitation approach, Goal Management Training® (GMT), has shown promise in patients with various neurological problems including overt stroke. In its standard implementation, GMT is led in small groups. Although this approach is effective, it has significant practical limitations. Some patients have limited mobility and others may live in remote areas. In addition, leading group-based studies is difficult to organize and expensive.

The goal of the proposed research is to design an automated, web-based GMT training program that can be delivered remotely and that is specifically geared towards patients with stroke. Patients will still have access to a therapist, but their time will be limited to focused interactive online sessions. We plan to assess its feasibility in patients with overt strokes. We will compare its efficacy to an active control group that would participate in a commercially available online "brain training" program that we do not expect to improve cognition (although it is widely used and promoted as effective). Efficacy will be examined by comparing performance

on a series of cognitive assessments and questionnaires that will be administered before and after the training is complete. We would also conduct surveys and interviews at the end of training to obtain patient feedback on their experiences using the web-based training.

We expect that the patients who complete the web-based training program will show improvement on cognitive tasks not directly trained through the program and in self-reports, whereas patients who belong to the active control group will show no such improvement. This program is part of a larger, independently funded collaborative knowledge translation effort for GMT. Funding from this catalyst project would allow us to leverage existing funding to tailor the web-based implementation to stroke patients, and to test its efficacy in stroke survivors. The translation of GMT to a web-based format will greatly increase its accessibility to stroke survivors throughout Canada and beyond, with significant downstream impacts on their quality of life and ability to maintain functional independence.

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5. A cognitive-augmented mobility program (CAMP): Combining cognitive strategy training and best evidence mobility training to optimize long-term meaningful living for people with stroke

Principal Investigator: **Dr. Sara McEwen, *Sunnybrook Research Institute***
Co-investigators: Dr. Joyce Chen (*Sunnybrook Research Institute*), Elizabeth Inness (*University Health Network - Toronto Rehab*), Elizabeth Linkewich (*Sunnybrook Health Sciences Centre*), Jennifer Shaffer (*Sunnybrook Health Sciences Centre - St. John's Rehab*), Dr. Ada Tang (*McMaster University*)

Brief Project Description: This study will combine best evidence for mobility interventions with best evidence for cognitive strategy training to develop and evaluate a new intervention to optimize long-term functional mobility outcomes for those living with stroke.

Project Summary: Difficulty walking is a leading cause of activity restriction in survivors of stroke. It is directly related to important functional issues, such as challenges in crossing a street in time, difficulty walking to a bus stop and increased risk of falls. These functional issues can then impact a person's confidence to move around their community, ultimately leading to lower levels of physical activity and potential negative health consequences. The best way to optimize recovery in walking and mobility is not yet known, and there are critical gaps in existing treatments. While some approaches are effective in the short term, strategies to promote the maintenance of improvements are not well established, benefits are usually not transferred beyond the specific skills trained and the specific context in which they were learned, few interventions impact community participation, and cost effectiveness has rarely been investigated.

A potential solution exists in combining best-evidence interventions: *task-specific gait and mobility training* to improve skill quality, *cardiorespiratory and strength exercises* to improve endurance and speed, and *cognitive strategy training* to teach problem solving, improve confidence and to ensure long-term maintenance and transfer of skills to home and community settings. We will combine best evidence mobility interventions with best evidence cognitive strategy training to develop and evaluate a new intervention to optimize long-term functional mobility outcomes for those living with stroke.

The project consists of two sequential stages: 1) intervention development through literature synthesis; face validity testing using focus groups with patients, family members and expert stroke rehabilitation clinicians; and intervention refinement; followed by 2) feasibility/pilot testing with 10 people more than 6 months post stroke. Anticipated outcomes include a fully developed intervention with the potential to optimize mobility rehabilitation and effect size estimates to permit the design of a future, appropriately-powered randomized controlled trial.

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6. Effects of noninvasive brain stimulation on pathological perilesional activity in stroke

Principal Investigator: **Dr. Jed Meltzer*, Rotman Research Institute, Baycrest***
Co-investigators: Dr. Regina Jokel (*Rotman Research Institute, Baycrest*), Dr. Paul Verhoeff (*Baycrest*)
Collaborator: Dr. Elizabeth Rochon (*Toronto Rehabilitation Institute – University Health Network & University of Toronto*)

Brief Project Description: This project will measure brain waves in stroke patients immediately before and after receiving a brain stimulation intervention, testing whether activity can in fact be improved (normalized).

Project Summary: 40% of stroke survivors have speech and language problems, affecting their independence and ability to work. Although some interventions have shown promise for improving recovery even years after stroke, none have become routinely used, and few patients have access to them outside of research studies. Large clinical trials are seldom performed, as the high individual variability between stroke patients makes it difficult to see a consistent effect.

Our project aims to assess the effectiveness of interventions in the short-term, by testing their effect on the brain's electrical activity. Using magnetic measurements of brain waves, we have shown that function is disrupted in brain areas that were affected by a stroke but not destroyed by it. We suspect that some interventions can restore normal activity to these areas, and that is why they are effective. Our project will measure brain waves in stroke patients immediately before and after receiving an intervention, testing whether activity can in fact be normalized.

Our ultimate goal will be to develop a general platform for fast evaluation of biological interventions, including drugs, brain stimulation, and behavioural therapy. For the catalyst project, we will first test electrical stimulation of the brain areas surrounding the stroke lesion. We hypothesize that electrical stimulation can increase neural activity in this kind of brain tissue, resulting in a temporary reversal of the abnormal signals seen there.

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7. Higher intensity interval training for people with stroke deficits: Optimizing the exercise intervention (The HIT - Stroke Study)

Principal Investigator: **Drs. Susan Marzolini & Paul Oh, *Toronto Rehabilitation Institute – University Health Network***

Brief Project Description: This study will directly compare the effects on cardiovascular fitness, walking function and cognition of higher-intensity interval training vs. conventional moderate-intensity continuous exercise in stroke patients.

Project Summary: Studies provide convincing evidence that exercise such as walking can improve cardiovascular fitness, cognition and result in better walking function in those recovering from stroke. More recently, studies conducted in healthy populations have shown that intensity of exercise (how hard a person is exercising) may play a role in optimizing fitness, walking function, and brain health. There is a well-established evidence base that suggests that greater gains in cardiovascular fitness are possible with higher intensity exercise.

Optimizing cardiovascular fitness is important as higher fitness may be associated with lower stroke risk, and is now established as a strong predictor of a longer life span. Increasing exercise capacity by higher intensity training may also have implications for activity of daily living function in people following stroke. For example, cardiovascular fitness requirements for carrying out day-to-day activities like dressing, getting across an intersection before the light turns red, or making the bed may have been completed with ease prior to a stroke, but become difficult post stroke due to the maximal strain that may be imposed on the cardiovascular system. Improvements as a result of higher intensity exercise would likely elevate the threshold of tolerance for completion of some activities required for living. Also, although we do not have a good understanding of why intensity is important for cognition, one study showed that a growth factor in the blood that helps to improve cognition (like fertilizer for the brain) increased immediately after high intensity exercise but not after low intensity exercise. Our group has also shown that higher intensity exercise results in greater blood flow to parts of the brain that affect walking function than lower intensity exercise. Thus, higher intensity exercise may also result in augmented improvements in walking function.

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8. An investigation of the feasibility of a group and home video dance (GROOVE-D) program to improve gait, balance and mood post-stroke

Principal Investigator: **Dr. Kara Patterson, *Toronto Rehabilitation Institute – University Health Network (TRI-UHN)***
Co-investigator: Dr. Dina Brooks (*University of Toronto)*
Collaborators: Miriam Schacter (danceABILITIES™), Louis Biasin (TRI-UHN)

Brief Project Description: This study will investigate the effects on gait, balance and mood in stroke patients who participate in the GROOVE-D program (**gro**up and h**o**me v**i**d**e**o **d**ance), which involves an initial phase of group dance classes, followed by a maintenance phase of home sessions with instructional videos and monthly group "check-ups".

Project Summary: Stroke negatively impacts many aspects of life including mood, social integration and mobility. Dancing is a fun, social activity that has physical and psychological benefits similar to more traditional exercise. Our ongoing pilot work suggests that a group dance program for people with stroke is feasible and satisfaction with the program is high. Our systematic review found emerging evidence of improved gait, balance and mobility with dance for people with neurological conditions including stroke. In addition, studies of dance for people

with Parkinson's disease report good adherence and many participants express a desire to continue with dance classes after the study has ended. Long term maintenance is important because in order for any type of exercise to have a benefit, it must be sustainable.

Unfortunately, providing dance classes to people with stroke indefinitely is impractical in terms of cost, facilities and human resources. A home dance program may address these issues, but is unlikely to provide the same psychological and mood benefits since these benefits are partly derived from the social interaction in a group class format. We are proposing the GROOVE-D program (**gr**oup and h**o**me **v**id**e**o **d**ance), which involves an initial phase of group classes, followed by a maintenance phase of home sessions with instructional videos and monthly group "check-ups".

This study aims to: 1) consult with stakeholders (individuals with stroke, physiotherapists, dance instructors) to develop and deliver GROOVE-D; 2) assess the effects of GROOVE-D on gait, balance and mood in individuals with chronic stroke; and 3) determine safety and feasibility of GROOVE-D for individuals with stroke. We will then run a pre-post intervention study to assess the feasibility and effects of GROOVE-D. The results will inform design and funding applications for a randomized controlled trial of GROOVE-D.

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9. Exosome-mediated delivery of a potent neural stem cells inducing factor into the post-stroke brain *in vivo*

Principal Investigator: **Dr. William Stanford, *Ottawa Hospital Research Institute***
Co-investigators: Dr. Lisa Julian *(Ottawa Hospital Research Institute)*
Collaborators: Dr. Diane Lagace *(University of Ottawa)*, Dr. Derrick Gibbings *(University of Ottawa)*

Brief Description: This study will investigate new methods to substantially enhance the activation of stem cells in the brain to promote recovery in a mouse model of stroke.

Project Summary: This application builds off of our promising preliminary findings from our current CPSR catalyst grant, whose objective is to generate autologous neural stem cells (NSCs) rapidly and efficiently via novel cellular reprogramming approaches, enabling NSCs transplantation as quickly as possible post-stroke. Our preliminary findings have revealed that reprogramming of human fibroblasts to NSCs is greatly accelerated when the fibroblasts are engineered for deficiency in the *TSC2* gene. Strikingly, *TSC2*-deficient fibroblasts give rise to neurospheres 2 days after initiation of reprogramming, much more quickly than current protocols in which neurospheres take 1.5-2 weeks to arise. Furthermore, as *TSC2* is a key regulator of cell proliferation, survival and differentiation, we anticipate that transplantation of transiently *TSC2*-deficient NSCs will provide enhanced therapeutic benefit.

To build on these exciting results, we now propose to translate our findings to enhance the survival and regenerative properties of *endogenous* NSCs following stroke, using our ischemic mouse model. Given our recent findings, we anticipate that delivery of *TSC2* inhibitory RNA molecules into the post-ischemic brain will substantially enhance the activation of endogenous NSCs and lead to improved structural and functional recovery. We will employ purified exosomes, natural cellular vesicles that transport RNA and protein molecules, and can easily

access brain tissue, to deliver *TSC2* shRNA molecules into endogenous NSCs. We will ultimately assess the efficacy of this approach to promote structural and functional recovery after ischemic stroke in our established mouse model. If this approach is effective it will drive further discovery to determine: 1) the best therapeutic time points post-stroke for delivery of the *TSC2*-shRNA containing exosomes; and 2) the *in vivo* mechanisms through which this *TSC2*-mediated recovery is achieved. We believe that this novel genetic and technical approach will greatly enhance the regenerative capacity of endogenous NSCs following stroke and thereby drive significant recovery.

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10. Addressing comorbidities to improve independence after stroke in Ontario

Principal Investigator: **Dr. Walter Swardfager, *Sunnybrook Research Institute***
Co-investigators: Dr. Bradley MacIntosh (*Sunnybrook Research Institute*), Dr. Jodi Edwards (*Sunnybrook Research Institute*), Dr. Richard Swartz (*Sunnybrook Research Institute*), Dr. Nathan Herrmann (*Sunnybrook Research Institute*), Dr. Moira Kapral (ICES Central)

Brief Project Description: This project will use public health records to investigate the incremental burden of comorbid conditions, such as depression and diabetes, on those recovering from stroke, and investigate differences in outcomes based on the medications used to treat them.

Project Summary: As more Canadians live with the effects of stroke, barriers to recovering independence are increasingly important public health concerns. Diabetes and depression are common in stroke and they impact outcomes, but the extent of this burden remains unknown. The prevalence of diabetes in Canada will increase 41% by 2025, contributing to more strokes. Thirty percent of stroke survivors experience depression. This CPSR catalyst grant will use public health records to show the incremental burden of these comorbid conditions on those recovering from stroke, and investigate differences in outcomes based on the medications used to treat them.

We will quantify the impact of these comorbidities, alone and in combination, on stroke survivors in two ways. First, we will estimate the increased risk of being institutionalized over 3 years following stroke. Second, we will quantify health services used (e.g. procedures, diagnostics, medications, hospital stays). We will use the Ontario Stroke Registry to identify all patients with first-ever ischemic stroke, and determine differences in these outcomes between people who have diabetes, depression, both, or neither. We will also determine if specific medications used to treat these conditions initiated either before or after stroke are associated with better outcomes.

Previously, we demonstrated that having one of these comorbidities doubled the risk of cognitive impairment after stroke, while having both tripled the risk, with a similar additive burden on walking ability. Showing that these comorbidities threaten independence will inform resource allocation towards initiatives that optimize recovery for the 62% of survivors who suffer from one or both comorbidities. Demonstrating potential benefits of certain medications will inform intervention trials to determine optimal treatment regimens for patients with multiple chronic conditions, and lead to economic studies to estimate associated costs. The proposed

study represents a critical first step towards improved systems planning and individualized care for stroke patients with multiple comorbidities.

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11. Stem cell-based therapy for post-stroke neurovascular regeneration and functional recovery

Principal Investigator: **Dr. Jing Wang, *Ottawa Hospital Research Institute***
Co-investigators: Dr Dale Corbett (*University of Ottawa*), Dr. William Stanford (*Ottawa Hospital Research Institute*), Dr. Marjorie Brand (*University of Ottawa*)

Brief Description: This study will use a combination stem cell-based therapy (neural and vascular stem cells) to augment brain repair and enhance functional recovery in a rodent stroke model.

Project Summary: Stroke-related brain injury results in loss of both neural and vascular cells. The extent of regeneration of both neurons and micro-vessels may limit the level of functional recovery after stroke. Therefore, long-term neuroreparative therapies need to repair the two types of cells to restore cerebral blood flow and promote neural regeneration for stroke recovery.

Hereby, we propose a combination stem cell-based therapy by co-transplantation of both neural and vascular stem cells to augment brain repair and enhance functional recovery. The beneficial reciprocal interaction between neural and vascular components facilitates the regeneration of both neurons and blood vessels following stroke. To avoid ethical and immunosuppression issues for future clinical translation, we propose to use autologous human induced pluripotent stem cell (iPSC)-derived neural stem cells and human blood-derived blood vessel stem cells that can be derived from stroke patients' own body for the co-transplantation. We expect that co-transplantation of both human neural and blood vessel stem cells following stroke will provide sufficient quantities of all major brain cell types to efficiently regenerate neurovascular units in the damaged brain and improve neurobehavioral recovery, leading to better therapeutic outcomes for the treatment of ischemic stroke.
