Advisory Board for Lived Experience of Stroke, Epilepsy & Dementia (ABLE)

iNeuron Guidebook

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Introduction

This Guidebook is intended to support ABLE members to participate in the iNeuron project. It includes an overview of the iNeuron aims, descriptions of each pillar and cross-cutting theme, including the researchers involved in each component, and a glossary that provides plain language definitions of relevant scientific terms. Please note - this Guidebook is intended to be a living document, meaning it will continue to be updated as the iNeuron project progresses. Feedback on the Guidebook is welcomed!

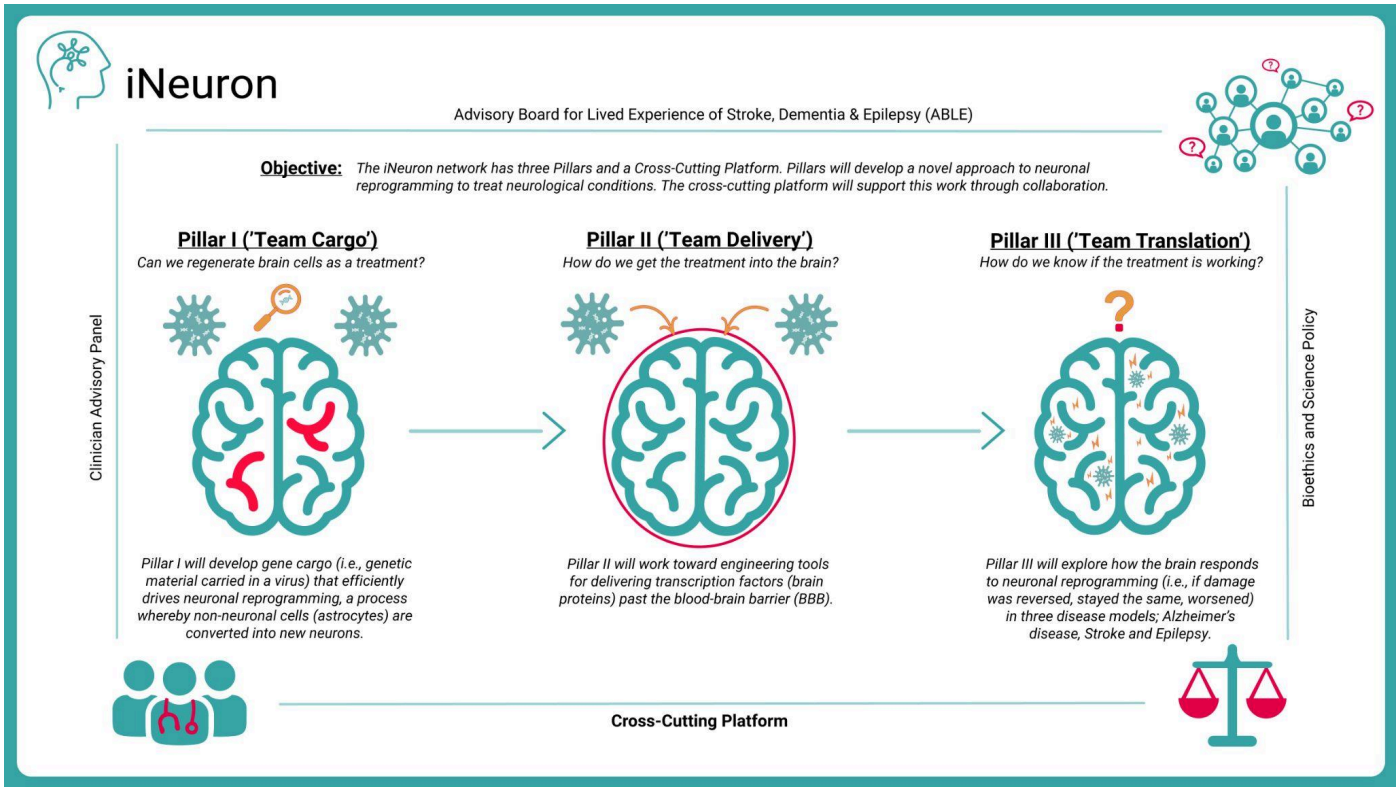
Contact

Please email ABLE manager at ellen.snowball@uhn.ca if you have any questions.

iNeuron

Overall objective: The iNeuron team is structured around three core pillars and a cross-functional platform. The pillars will develop a novel approach to neuronal reprogramming to treat neurological conditions. The platform includes ABLE members, a bioethicist, and a clinician advisory panel who will collaborate to support the efforts of the pillars.

What is neuronal reprogramming? a process whereby non-neuronal cells (astrocytes) are converted into new neurons.



Pillar I

("Team Cargo"/Can we regenerate brain cells?): How do transcription factors (TFs; proteins that help turn specific genes "on" or "off" by binding to nearby DNA) interact with deoxyribonucleic acid (DNA) to create messenger ribonucleic acid (mRNA)? Pillar I will develop gene cargo (i.e., genetic material carried in a virus) that efficiently drives neuronal reprogramming, a process whereby non-neuronal cells (astrocytes) are converted into new neurons.

Approaches: Pillar I will iteratively combine computer-based methods, empirical tests (testing a hypothesis through real-world observation) and computer and laboratory methods, including using genomic engineering that can change or "edit" pieces of a cell's DNA and working with rodent and human cells.

Team Members:

- **Dr. Antonio del Sol**: will study how transcription factors (TFs; proteins that help turn specific genes "on" or "off") interact with groups of genes and identify which pairings work best for neuronal reprogramming. His lab will use computer-based methods.

- **Dr. Magdalena Gotz:** will use rodent and human astrocytes (non-neuronal cells in the brain) to test how they can be converted into new neurons using transcription factors (TFs; proteins that help turn specific genes "on" or "off").

- **Dr. Janelle Drouin-Ouellet:** will use human brain tissue (non-neuronal cells) to test how they can be converted into iNeurons (new neurons). Her lab will look at how cells affect different brain regions, considering brain age and sex.

- **Dr. Diogo Castro:** will analyze chromatin (DNA and proteins that make up chromosomes) to study how transcription factors (TFs; brain proteins) reprogram cells in the targeted brain areas. His lab will work with live mice and human astrocytes (non-neuronal cells).

- **Dr. Pierre Mattar**: will examine how nucleosomes (DNA that is wrapped around protein) and enzymes (a substance that brings about biochemical reactions) can be influenced to turn genes "on" or "off".

- **Dr. Guang Yang:** will study how transcription factors (TFs; proteins that help turn specific genes "on" or "off") interact with new neurons to make them more efficient.

- **Dr. Carol Schuurmans:** will study the impact of phosphorylation (a process that affects how proteins function) on transcription factors (TFs; brain proteins) and their ability to create new neurons. She will work with live mice and cells in a lab.

- **Dr. Stefan Stricker:** will examine how transcription factors (TFs; brain proteins) turn genes “on” or “off”. His lab will examine how this affects neuronal reprogramming. He will use Clustered Regularly Interspaced Short Palindromic Repeats (i.e. CRISPR; a tool used to change or “edit” pieces of a cell's DNA) with live mice and cells in a lab.

Pillar II

("Team Delivery"/How do we get the treatment into the brain?):
How can the reprogrammed transcription factors (TFs; brain proteins) be deposited into the brain so they can convert astrocytes (non-neuronal cells) to new neurons? Pillar II will engineer tools for delivering gene cargo (i.e., genetic material carried in a virus) past the blood-brain barrier (a membrane that keeps harmful substances out of the brain).

Approaches: Pillar II will test different types of delivery systems (e.g., nanoparticles, focused ultrasound) to see which best targets astrocytes (non-neuronal cells) in the brain, while carrying the gene cargo (i.e., genetic material carried in a virus or other molecular carrier) necessary for neuronal reprogramming.

Team Members:

- **Dr. Anna Blakney**: will utilize ribonucleic acid (RNA; a molecule with similarities to DNA) to deliver transcription factor (TFs; brain proteins) mixtures to mouse and human astrocytes (non-neuronal cells) in a lab. She will use micro ribonucleic acid (miRNA; RNA regulating gene expression) to regulate gene expression.

- **Dr. Ildiko Badea:** will use nanoparticles (a small particle) to "capture" RNA (saRNA; self-replicating RNA) to test neuronal conversion (turning non-neuronal cells to new neurons) in astrocytes (non-neuronal cells) in a lab.

- **Dr. Derrick Gibbings**: will look at the stem-loop structure (a pattern of strands) of micro ribonucleic acid (miRNA; a class of sRNA that regulates gene expression) and insert activating ribonucleic acids (saRNAs; cells that activate gene expression) into small extracellular vesicles (sEVs; particles released from cells).

- **Dr. Roderick Slavcev:** will use glial fibrillary acidic protein (GFAP; found inside of non-neuronal cells) and micro ribonucleic acid (miRNA; RNA that regulates gene expression) for neuronal reprogramming (turning non-neuronal cells to new neurons) in human astrocytes (non-neuronal cells) in live mice within a lab.

- **Dr. Isabelle Aubert, Dr. Kullervo Hynynen:** will use focused ultrasound (FUS) to get around the blood-brain-barrier (a membrane that keeps harmful substances out of the brain) to deliver transcription factor (definition) cargo

(definition). They will also use the delivery systems of other researchers, such as nanoparticles (an assembly of molecules or atoms) and bacteriophages (viruses that infect and replicate only in bacterial cells) to deliver the cargo.

Pillar III

(“Team Translation”/How do we know if the treatment is working?): How do the damaged neurons respond to the new transcription factors (TFs; brain proteins)? Pillar III will explore how the brain responds to neuronal reprogramming (i.e., if damage was reversed, stayed the same, worsened) in three disease models; Alzheimer’s disease, Stroke and Epilepsy.

Approaches: Pillar III will test the effectiveness of reprogramming using tools to assess the ability of new neurons to integrate at the cellular and whole animal level. Since human brain tissue cannot be used, Pillar III will develop non-invasive imaging (e.g., positron emission tomography (PET) scan; measures blood flow to show how organs and tissues are functioning) methods and analyze neurochemical tests (magnetic resonance spectroscopy; studying the chemical makeup and activities of nervous tissue).

Team Members:

- **Dr. JoAnne McLaurin:** will utilize rodents with Alzheimer’s disease pathology to study the impact of various genes and measure cognitive function using the maze test.
- **Dr. Cindi Morshead:** will study the impact of stroke on motor function by utilizing endothelin-1 (ET-1; a peptide vasoconstrictor that regulates physiological responses) to induce strokes in a lab environment and then test motor function (using gait analysis, grip strength tests).
- **Dr. Deborah Kurrasch:** will study how gene mutations that cause epilepsy can be stabilized with new iNeurons, and how Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR; a tool used to change or “edit” pieces of a cell's DNA) can further perfect/optimize new neurons (iNeurons).
- **Dr. Jamie Near:** will use magnetic resonance imagery (MRS; technique used to measure concentrations of various compounds in the brain such as lipids/fatty compounds) to see if iNeurons are functioning properly, and develop specific tests for Alzheimer’s, Epilepsy and Stroke.
- **Dr. Hon Leong:** will use biomarkers (biological measure of how something is functioning) to determine how iNeurons are negatively or positively impacting the brain with Alzheimer’s, Epilepsy, or Stroke pathology.

Cross-Cutting Platform

Advisory Board for Lived Experience of Stroke, Epilepsy & Dementia (ABLE): ABLE is an Advisory Group composed of people with lived experience of stroke, epilepsy and dementia (i.e., people with the condition, caregivers/care partners, family and friends). The program will integrate lived experience with biomedical research to ensure that treatments address the priorities of people living with these conditions as well as provide education to researchers, the public and healthcare providers about experiences of stroke, epilepsy and dementia.

Approaches: ABLE Advisory Group members actively and meaningfully collaborate in iNeuron activities, including governance, priority setting, research, and knowledge translation. Their contributions include the development of educational materials for healthcare providers, researchers, and others living with these conditions about the benefits of including people with lived experience in research, and how to address barriers to engagement.

Dr. Carrie McAiney, Dr. Jennifer Bethell, Dr. Julia Jacobs Levan: will facilitate engagement between people with lived experience, researchers, and clinicians to develop research priorities, educational materials, and address perspectives on new biological treatments for Alzheimer's, Epilepsy, and Stroke.

Bioethics and Science Policy: This team will address ethical concerns about new treatment options, such as availability, cost, and risks and benefits to people living with these conditions.

Approaches: This team will target specific issues regarding the use/application of potential treatments resulting from iNeuron research in the general population such as mistrust (i.e. population views and trust of science and medicine), and regulatory and ethical issues (i.e. accessibility, affordability). Lastly, protecting and sharing intellectual property will be addressed so that iNeuron research can be shared to help people with stroke, epilepsy and dementia globally.

Dr. Ubaka Ogbogu: will examine ethical issues related to the accessibility, affordability, and the use/sharing of new treatments while protecting the intellectual property of the iNeuron team.

Clinician Advisory Panel: This team is composed of clinicians who serve as advisors on current patient needs for each disease model (Alzheimer's, Stroke, Epilepsy).

Plain Language Glossary

Pillar 1 – Team Cargo	
Term	**Definition**
Astrocyte	A large, star-shaped cell in the brain that holds nerve cells in place and helps them develop and work the way they should. An astrocyte is a type of glial cell (*Astrocyte*).
Chromatin	A mixture of DNA and proteins that form the chromosomes found in the cells of humans and other higher organisms (*Chromatin*).
CRISPR	It's a way of finding a specific bit of DNA inside a cell … the next step in CRISPR gene editing is usually to alter that piece of DNA. However, CRISPR has also been adapted to do other things too, such as turning genes on or off without changing their sequence (*CRISPR*).
Deoxyribonucleic acid (DNA)	A molecule that carries genetic information for the development and functioning of an organism (*DNA*).
Endogenous	Produced inside an organism or cell (*Endogenous*).
Exogenous	Introduced from or produced outside the organism or system (*Exogenous*).
Genes	Genes carry the information that determines your traits … which are features or characteristics that are passed on to you — or inherited — from your parents (*Genes*).
Glial cell	Cells that hold nerve cells in place and help them work the way they should (*Glial cell*). E.g., astrocyte
Histone Proteins	A type of protein found in chromosomes. Histones bind to DNA and help give chromosomes their shape, and control the activity of genes (*Histone*).
Induced Neurons (iNeurons; iNs)	Non-neuronal cells that can be transformed into neurons using transcription factors (*Team iNeuron Definition*).
In vitro	In the laboratory (outside the body) (*In vitro*).
In vivo	In the body (*In vivo*).
Messenger RNA (mRNA)	A molecule that contains the instructions or a recipe that directs the cells to make a protein using its natural machinery. It is crucial in transcribing genetic information from DNA to protein factories within cells (*mRNA*).

Neuron	A cell that carries information between the brain and other parts of the body (*Neuron*).
Neuronal Reprogramming	Neuronal reprogramming converts non-neuronal cells to neurons (*Neuronal Reprogramming*).
Nucleosome	A nucleosome is a section of DNA that is wrapped around a core of proteins (*Nucleosome*).
Nucleosome Remodeling	Nucleosome remodeling involves changing histone–DNA interactions as a means of disrupting, assembling or moving nucleosomes. (*Nucleosome Remodeling*)
Protein	Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs (*Protein*).
Ribonucleic acid (RNA)	A molecule present in all living cells that has structural similarities to DNA (*RNA*).
Traits	Any characteristic of a living thing. It can be physical (like nose shape), a behavior (like language), or internal (like the ability to digest milk) (*Traits*).
Transcription Factors (TF)	Transcription factors are proteins that help turn specific genes "on" or "off" by binding to nearby DNA (*Transcription Factors*), determining if a function is present or not.
Transcription Factor (TF) Cargo	A package of transcription factors (TFs) (*Team iNeuron Definition*).

Pillar 2 – Team Delivery - Delivery Models	
Term	**Definition**
Bacteriophage	Viruses that infect and replicate only in bacterial cells (*Bacteriophage*).
Blood-brain barrier (BBB)	A tightly locked layer of cells that defend your brain from harmful substances, germs and other things that could cause damage (*Blood-Brain Barrier*).
Extracellular Vesicles (EVs)	Small, membrane-bound structures that are released from cells into the surrounding environment (*Extracellular Vesicles*).
High Intensity Focused Ultrasound (HIFU)	A minimally invasive medical procedure that uses ultrasound waves to treat certain conditions. The very high-intensity and highly focused sound waves interact with targeted tissues in your body to modify or destroy them (*HIFU*).

Nanoparticle	A particle that is smaller than 100 nanometers (one-billionth of a meter). In medicine, nanoparticles can be used to carry substances to certain parts of the body (*Nanoparticle*).
Self-amplifying RNA (saRNA)	Self-amplifying RNA can be regarded as “disabled” virus that is capable of amplifying within cells for a prolonged period (*saRNA*).
Virus	In medicine, a very simple microorganism that infects cells and may cause disease. Because viruses can multiply only inside infected cells, they are not considered to be alive (*Virus*).
Virus (Viral) Vector	A form of a virus used to deliver genetic material into a cell (*Viral Vector*). Viral vectors do not cause disease in humans.

Pillar 3 – Team Translation	
Term	**Definition**
Advanced Magnetic Resonance Spectroscopy (MRS)	Noninvasive diagnostic test compares the chemical composition of normal brain tissue with abnormal tissue. This test can also be used to detect tissue changes in stroke and epilepsy (*MRS*).
Alzheimer’s Disease	A brain disorder that usually starts in older age adults that progressively declines over time (*Alzheimer’s Disease*). It is a type of dementia that affects functions such as memory, thinking, behaviour, and language. Loss of these functions vary differently in patients (*Alzheimer’s Disease*).
Biomarkers	A measurable marker or sign that shows what is taking place inside a person's body (*Biomarkers*).
Corticospinal Neurons (CSN+)	Specific neurons (called upper motor neurons) that travel in the corticospinal tract and connect to skeletal muscle, causing muscle contractions (*Corticospinal Neurons*).
Corticospinal Tract	The corticospinal tract is the major neuronal pathway that provides voluntary motor function (*Corticospinal Tract*).
Epilepsy	A brain disease where nerve cells don't signal properly, causing seizures (*Epilepsy*).
Functional Magnetic Resonance Imaging (fMRI)	An imaging scan that shows activity in specific areas of the brain (*fMRI*).
High Density Electrophysiological	Electrophysiology techniques are used to record the electrical activity of neurons (*Electrophysiology Techniques*).

Recording Techniques	
Neurodegeneration (Neurodegenerative Disorder)	A type of disease in which cells of the central nervous system stop working or die (*Neurodegenerative Disorder*).
Neuronal Conversion Cargo	A package of transcription factors (TFs) used to convert non-neuronal cells into neurons (*Team iNeuron Definition*).
Parvalbumin (PA; PVALB+)	A calcium-binding protein thought to be involved in the regulation of calcium levels in various parts of the body from neurons to muscle (*PA*). Is involved in the inhibition of neuronal activity (*Parvalbumin*).
Seizures	Uncontrolled bursts of electrical activities that change sensations, behaviors, awareness and muscle movements (*Epilepsy*).
Somatostatin (SOM+)	An important hormone that works to inhibit the release of other hormones (*Somatostatin*).
Stroke	When a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot or bursts (*Stroke*).

General Terms	
Term	**Definition**
Action Potentials (APs)	Nerve signals generated by neurons (*APs*) to transmit information from one place to another (APs).
Adeno-associated Viruses (AAVs)	Is a viral vector that acts as a delivery mechanism for gene therapy (*AAVs*).
Antibody	A protein made by plasma cells (a type of white blood cell) in response to an antigen (a substance that causes the body to make a specific immune response). Each antibody can bind to only one specific antigen. The purpose of this binding is to help destroy the antigen (*Antibody*).
Assays	A laboratory test used to find and measure the amount of a specific substance (*Assays*).
Brain Organoids	Human neural tissues that have brain-like morphology than can be used to represent certain areas of the brain (*Team iNeuron Definition*).
Cell	The smallest unit that can live on its own and that makes up all living organisms and the tissues of the body (*Cell*).

Cell Membrane	Found in all cells and separates the interior of the cell from the outside environment (*Cell Membrane*).
Cellular Reprogramming	The process in which cells are converted (or reprogrammed) into an earlier stage of development, changing the fate of the cell (*Cellular Reprogramming*).
Cell Culture	The growth of microorganisms such as bacteria and yeast, or human, plant, or animal cells in the laboratory (*Cell Culture*).
Cognitive Impairment (Deficit)	Problems with a person's ability to think, learn, remember, use judgment, and make decisions (*Cognitive Impairment*).
Differentiation	The processes by which immature cells become mature cells with specific functions (*Differentiation*).
Electroencephalogram (EEG)	A recording of brain activity. A painless test, where small sensors are attached to the scalp to pick up the electrical signals produced by the brain. These signals are recorded by a machine and are looked at by a professional (*EEG*).
Embryonic Stem Cell	These stem cells come from embryos that are 3 to 5 days old. These are pluripotent stem cells, meaning they can divide into more stem cells or can become any type of cell in the body (*Embryonic Stem Cells*).
Excitatory Neurons	Neurons that prompt one neuron to share information with the next (*Excitatory neurons*).
Excitatory Neurotransmitter	Neurotransmitters that "Excite" the neuron and cause it to "fire off the message." The message continues to be passed along to the next cell (*Excitatory neurotransmitter*).
Gland	An organ that makes one or more substances, such as hormones, digestive juices, sweat, tears, saliva, or milk (*Gland*).
Hormone	One of many substances made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs (*Hormones*).
Hypersynchrony	Large numbers of neurons firing action potentials (nerve signals) in unison (*Synchrony*). This causes seizures due to the high influx in action potentials.
Hypertrophy	Describes exaggerated growth or complexity (*Hypertrophy*).
Induced Pluripotent Stem Cells	A cell taken from any tissue (usually skin or blood) and is genetically modified to form any type of adult cell type (*Induced Pluripotent Stem Cells*).
Inhibitory Neurons	Neurons that have reduced capacity for transferring information (*Inhibitory neurons*).

Inhibitory Neurotransmitter	Neurotransmitters that block or prevent the chemical message from being passed along (*Inhibitory neurotransmitter*).
Lipid	Fatty compounds that perform a variety of functions in your body. They help with moving and storing energy, absorbing vitamins and making hormones (*Lipids*).
Magnetic Resonance Imaging (MRI)	A safe and painless test that uses magnets and radio waves to make detailed pictures of the body's organs, muscles, soft tissues, and structures (*MRI*).
Neurotransmitter	Chemical messengers that your body can't function without. Their job is to carry chemical signals ("messages") from one neuron (nerve cell) to the next target cell (*Neurotransmitter*).
Organ	In medicine, a part of the body that is made up of cells and tissues that perform a specific function (*Organ*).
Pathogen	Any organism that causes disease (*Pathogen*).
Pluripotent Stem Cells	A cell that is able to develop into many different types of cells or tissues in the body (*Pluripotent Stem Cells*).
Positron Emission Tomography (PET) Scan	A type of imaging test that uses a radioactive substance called a tracer to look for disease in the body. It shows how organs and tissues work (*PET Scan*).
Quantitative Polymerase Chain Reactions (qPCR)	A technology used for measuring DNA (*qPCR*). It enables the determination of exact amounts of amplified DNA in samples (*qPCR*).
Reprogramming Factors	Factors (substance; components) that work very closely together (often as a multiprotein complex) to change the state of the cell (*Reprogramming Factors*).
Stem Cell	A cell that has the potential to turn into any other type of cell (*Stem Cell*).
Synapse	Synapses connect neurons and help transmit information from one neuron to the next (*Synapse*).
Transduce	To convert into another form (*Transduce*).
Vesicles	A self-contained structure consisting of fluid or gas surrounded and enclosed by an outer membrane called the lipid bilayer. It can help transport materials that an organism needs to survive and recycle waste materials (*Vesicles*).
Video Electroencephalography (video EEG)	Records what you are doing or experiencing on video while an EEG test records the electrical activity of the brain or brainwaves (*Video EEG Test*).