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(54) **Titre :** FORMULATIONS ET PROCEDES POUR LEUR UTILISATION DANS LE TRAITEMENT D'UNE NEUROPATHOLOGIE ET D'UNE NEURODEGENERATION EN RAISON D'UNE LESION TRAUMATIQUE

(54) **Title:** FORMULATIONS, AND METHODS FOR THEIR USE IN TREATMENT OF NEUROPATHOLOGY AND NEURODEGENERATION AS A RESULT OF TRAUMATIC INJURY

(57) **Abrégé/Abstract:**

The presently disclosed invention and particular invention embodiments relate to formulations, methods, procedures, and combinations thereof for treating numerous types of trauma-induced and other neurological disorders and injuries, such as but not exclusive to brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury. The formulations of the present invention comprising two, three or four biologically active compounds selected from:

- A. at least one biologically active compound selected from anticonvulsants and antiepileptics;
- B. at least one biologically active compound selected from neurosteroids and neuroactive steroids;
- C. at least one biologically active compound selected from NK-1 receptor antagonists; and
- D. at least one biologically active compound selected from lithium containing and lithium-related compounds.



ABSTRACT

The presently disclosed invention and particular invention embodiments relate to formulations, methods, procedures, and combinations thereof for treating numerous types of trauma-induced and other neurological disorders and injuries, such as but not exclusive to brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury. The formulations of the present invention comprising two, three or four biologically active compounds selected from:

- A. at least one biologically active compound selected from anticonvulsants and antiepileptics;
- B. at least one biologically active compound selected from neurosteroids and neuroactive steroids;
- C. at least one biologically active compound selected from NK-1 receptor antagonists; and
- D. at least one biologically active compound selected from lithium containing and lithium-related compounds.

**FORMULATIONS, AND METHODS FOR THEIR USE IN TREATMENT OF
NEUROPATHOLOGY AND NEURODEGENERATION AS A RESULT OF
TRAUMATIC INJURY**

FIELD OF THE INVENTION

[001] The presently disclosed invention and particular invention embodiments relate to formulations, methods, procedures, and combinations thereof for treating numerous types of trauma-induced and other neurological disorders and injuries, such as but not exclusive to brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury.

[002] The disclosed embodiments of the invention include, among other advantageous aspects, numerous formulations adapted and arranged for administration to a subject or patient in need thereof soon after that subject or patient has experienced a traumatic event; some particular disclosed embodiments include formulations that may be useful in preventative ways, such as when a traumatic event is possible, likely or anticipated as well as in prophylactic ways, such as when a procedure is known to produce neuropathology in some cases. The presently disclosed invention and its embodiments are thereby directed at preventing or reducing the development or the risk of development of secondary damage, or neuropathology and neurodegeneration, as a result of traumatic injury.

BACKGROUND OF THE INVENTION

[003] Trauma to neural tissue leads to injury, dysfunction or death of these cells, and thus to numerous adverse health conditions and disabilities. Trauma to neural tissue includes injury or damage to nerve cells or to cells that support the healthy, normal function and survival of neural tissue such as nerve cells.

[004] Injury to these cells typically occurs as a result of two factors. A first factor is the direct effect of the trauma itself. This is a primary type injury. The second factor results from biochemical cascades of cellular and metabolic processes that are activated or triggered directly or even indirectly by the trauma-induced tissue damage of the primary injury.

[005] Outcomes of primary traumatic damage to nerves or nerve cells differ significantly from the outcomes of primary traumatic damage to non-neural tissues. Non-neural tissues repair relatively rapidly compared to nerves or nerve cells, and that repair often results in a damage site restored to nearly identical condition to the original (pre-trauma) state of the tissue, especially with respect to function. In stark contrast, trauma to neural tissue, such as nerves, nerve cells or any of the neural support cells or neural support tissues, often results in

adverse health conditions that persist for days, weeks or permanently. It is this set of disadvantageous characteristics and events regarding neural tissues to which the present invention embodiments are targeted.

[006] The severity and duration of such adverse outcomes resulting from secondary neural tissue injury and cell death are governed by a balance of restorative and degenerative processes in those neural cells and tissues. In these target tissues, restorative processes drive toward recovery and repair, and the restoration of pre-trauma function. These are often considered to be adaptive processes. Degenerative processes drive toward loss of cell integrity and function, and often toward cell death. These are often considered to be maladaptive processes. Effective control of the balance of restorative and degenerative processes following trauma to neural tissue has proven to be difficult. It is noteworthy that this balance is often skewed toward the degenerative outcomes in neural tissue, such as cell or tissue death, and thus to permanent dysfunction. Conventional medical and therapeutic systems have shown little effectiveness in addressing these negative outcomes. There is therefore a significant clinical and societal need for new methods and formulations directed toward the treatment of secondary injury to neural tissues, such as nerve cells, neural support cells and neural support tissues that maintain the health and function of nerve cells. The scope and spirit of the many invention embodiments are directed toward addressing this clinical and societal unsolved need by promoting natural restorative processes and inhibiting intrinsic degenerative processes, thereby reducing or preventing the development, or the risk of development, of neuropathology as a result of traumatic injury.

[007] Conventional medical treatment tends to focus on acute treatment at the time of trauma, and on rehabilitative treatment for established disability or symptoms of injury that have become long-lasting or permanent. Thus, conventional medical treatment does not tend to focus on promoting restorative processes, recovery, regeneration, or restoration at the time of trauma. Conventional medical treatment also does not tend to focus at the time of trauma on inhibiting degenerative processes that lead to secondary injury and cell death. Such secondary injury can and often does contribute the greatest to permanent disability following a traumatic event.

[008] It is known that nerves and nerve cells in the central nervous system, that is the brain, the brain stem, the cerebellum and the spinal cord, lack the capacity to regenerate. This is in stark distinction to the healing and regenerative capacity of nerves and nerve cells in the periphery. Damage to the central nervous system can and often does lead to a loss of function and possibly cell death of neurones, neural support cells and neural support tissues, leading to long-term disability, whether by necrosis, apoptosis or other mechanisms. Once this damage has occurred there is no reparation.

[009] Nerves and nerve cells in the periphery can regenerate but do so more slowly than

other tissues. Furthermore, repair often fails to re-innervate the original peripheral target tissue. Repair also frequently fails to regain fully the extent of pre-injury function. Because of this, there is often a permanent dysfunction in excitability, or in activity discharge, in peripheral nerve cell function after repair. Nerves and nerve cells in the periphery maintain normal function through intrinsic homeostatic processes as well as through the normal function of healthy neural support cells and neural support tissues, which allow nerve cells to retain their function. There is a symbiotic relationship between nerve cells and neural support cells and tissues, where the health of each is interrelated with the health of the other. Damage or injury to a peripheral nerve can and often does lead to loss of function and possibly cell death of neurones, neural support cells and neural support tissues, leading to long-term or even permanent disability.

[0010] It is also known that that neural support cells, including glial cells, myelin cells and satellite cells, as well as neural support tissues, particularly but not exclusively vascular tissue, maintain the health and normal function of nerves and nerve cells in the periphery.

Nerves and nerve cells in the central nervous system are also dependent on neural support cells and neural support tissues to maintain their function; these neural support cells include but not exclusively microglia, astroglia, oligodendrocytes, myelin cells and satellite cells

[0011] Nerve cells in both the central nervous system and periphery require an adequate supply of oxygen and glucose in order to function properly. Because of these requirements, the health and effective functioning of nerve cells depends primarily on an adequate circulation of the local blood supply. Similarly, the full function of the endothelial cells of the vascular tissue that maintain the vasculature and the integrity of the blood-brain, blood-spinal and blood-nerve barriers also depend on an adequate local blood supply. Damage to or reduced function of the vasculature or the vascular supply to nerve cells and neural support cells can lead to loss of function or cell death of nerve cells and neural support cells, and thus to long-term or permanent disability.

[0012] Neural support tissues include the vasculature, and particularly, but not exclusively, the endothelial cells of the vasculature that prevent blood from leaking into nerve tissue while also providing the selective blood-nerve and blood-brain/spinal barriers that differentially permit the passage of certain supportive chemicals into nerve tissue as well as the passage of nerve tissue wastes out of nerve tissue into the blood.

Trauma and neuropathology

[0013] Evidence from studies in humans and in animal models indicates that the processes of secondary injury are activated immediately by a traumatic event. Evidence also indicates that each of these secondary processes can and often does continue over a prolonged and defined period of time, with some processes continuing for months (Bramlett and Dietrich, 2007). As a person of skill in the art will understand, the very biochemical nature of the

restorative and the degenerative processes triggered by trauma renders these processes amenable to therapeutic control or alteration, with potential, thereby, to promote restorative processes and to inhibit degenerative processes, with a resultant reduction or prevention of the development or the risk of development of neuropathology as a result of traumatic injury

[0014] Once the processes leading to secondary injury have proceeded beyond a certain threshold, any medical intervention directed toward treating the persisting adverse outcomes of trauma is almost always insufficient, inadequate or useless. In such circumstances, standard treatment can even be without any benefit whatsoever (Doppenberg *et al.*, 2004). As one with skill in the art will understand from the many conventional attempts to address these problems, time appears to be of critical importance, not only in terms of the start of medical intervention but also in terms of its duration or continuance.

[0015] The current state of knowledge suggests that there are multiple biochemical targets for promoting or interfering with specific cellular and metabolic processes for potential therapeutic approaches to prevent or reduce the development of the secondary injury that results from traumatic injury to nerve cells, neural support cells and neural support tissues. This knowledge, however, has thus far provided no adequate or effective treatment for such injuries.

[0016] An inference which might be made by a person of skill in the art, is that given the multiple processes that appear to be involved in causing this secondary injury, monotherapy that targets only a single process or pathway may be less effective than a polytherapy, or multi-drug therapy, that targets more than one, or even several, different processes or pathways.

[0017] Available literature in the field indicates that there have been many attempts to develop interventions to minimize secondary injury arising from brain injury. It is known, though, that these attempts have not yielded any effective products into the relevant therapeutic market for this use. Thus, despite intense efforts to develop therapeutic drugs for treatment for the persisting negative outcomes incident to brain injury, it has been stated that there is no new drug or drug combination has passed phase III clinical trials over the past 30 years (Doppenberg *et al.*, 2004).

FACTORS AND EVENTS THAT CAN INDUCE INJURY OR DAMAGE TO NERVE CELLS OR NEURAL SUPPORT CELLS OR NEURAL SUPPORT TISSUES OR THAT CAN ALTER NEURONE FUNCTION

[0018] Injury or damage to nerves or nerve cells can be the result of factors or events that are unanticipated or unexpected, while other factors or events can be anticipated. In either case, the present invention and its embodiments pertains to all event-triggered trauma, whether unanticipated, which is usually accidental, whether anticipated, which is often in cases of medical procedures, or whether preventive as described herein.

[0019] Trauma can be of many different types. For example, physical trauma to nerves or nerve cells, neural support cells or neural support tissues as described herein can occur, as examples, in vehicle accidents, in workplace accidents, sports accidents, on the battlefield, from falls, from assaults, from landmines, from explosive or other blasts, and the like but can also occur as a result of surgical or other medical procedures as described herein.

[0020] Chemical trauma to nerves or nerve cells or neural support cells or neural support tissues as described herein can occur, as examples, from alcohol overdose, drug abuse (such as methylenedioxyamphetamine, or MDMA, and the like), stimulant drugs such as pentylenetetrazol, carbon dioxide poisoning, acrylamide and related chemicals, overexposure to certain environmental chemicals such as copper or natural hazards such as scorpion venom toxin, herbicides, agricultural insecticides such as lindane, many industrial chemicals, neurotoxin bioterrorism chemicals such as soman and sarin, radiation bioterrorism chemicals such as polonium and strontium, and the like.

[0021] Medically-induced trauma to nerves or nerve cells or neural support cells or neural support tissues as described herein can occur as a result of surgery, amputation, injections, laparoscopy, implants, during a medical procedure that reduces or impedes the blood supply to any tissue containing nerve cells for any period of time as described herein, chemotherapy (for example from methotrexate, cisplatin, cytosine arabinose, carmustine, thiotepa among others), radiation therapy, immunosuppressants (such as tacrolimus) and the like.

[0022] Metabolic trauma to nerves or nerve cells or neural support cells or neural support tissues as described herein can occur as a result of many causes, including but not exclusive to cerebral ischemia, spinal cord ischemia, epileptic seizure, subacute posttraumatic ascending myelopathy and the like. Complex migraine, also termed complicated trauma, is associated with a high incidence of stroke or transient ischemic attack that can and often does occur during a migraine attack.

[0023] Beyond this, though, surgery in and of itself can produce other types of trauma that are injurious to nerves, nerve cells and nerve support cells and neural support tissues as described herein. For example, the life-saving benefits of cardiac surgery are frequently accompanied by trauma such as stroke, which remains a significant complication of cardiac surgery and occurs with an incidence of 2% to 13%, depending on the type of surgery.

[0024] Other events may also lead to epileptic seizures through secondary nerve injury processes, such as head trauma, tumors, status epilepticus and complex febrile seizures.

[0025] Other types of trauma that can lead to injury or damage to nerves, nerve cells and neural support cells and neural support tissues include, as examples, radiation, burns, hypoxia, and the like.

[0026] All tissues are impacted negatively by trauma, but nerve cells, neural support cells and neural support tissues are especially impacted by these factors as well as other events as

described in this document.

General perspective on trauma-induced neuropathology

[0027] Taking a broad perspective, event-triggered neurotrauma takes a heavy toll on those who are impacted by these events. Whether it is brain injury, central nervous system ischemia, spinal cord injury, enteric nerve injury or peripheral nerve injury, all share common properties, processes and mechanisms as described herein. All share mechanisms of secondary injury and cell death, as defined herein. Further, all share the capacity to be life changing.

[0028] With respect to brain injury, disability occurs to a large extent from the secondary injury that is triggered by the primary injury (Borgens and Liu-Snyder, 2012). Whether the numbers are large, as in the case of battlefield brain injury, or small, as with falls in the elderly, brain injury can be devastating to the individual.

[0029] With respect to central nervous system ischemia, whether the numbers are large, as in the case of stroke, or small, in the case of embolism from transcatheter aortic valve implantation, cerebral ischemia can be devastating to the individual. In fact, cerebral ischemia can occur in older persons, for example as a result of hypoperfusion during cardiac arrest, or in newborns, as a result of temporary or prolonged hypoperfusion due to complications at delivery. Ischemia can occur at the spinal level, for example during aortic clamp during surgery.

[0030] With respect to peripheral nervous system injury, whether the numbers are large, as those resulting from car accidents, or small, such as those resulting from laparoscopic surgery, the result of peripheral nerve injury can be a future of constant burning, debilitating neuropathic pain and other adverse health conditions caused by neuropathology or neurodegeneration.

[0031] With respect to enteric nervous system injury, whether the numbers are large, as with ischemic damage to enteric neurones, such as by hypovolemia, hypotension, sepsis, shock, vascular surgery, necrotising enterocolitis, intestinal obstruction and the like, or small, as with achalasia, damage to neurones in the enteric nervous system can be a precipitating cause of life-altering disability. Treatment to prevent the neuropathology and neurodegeneration processes leading to the need for rehabilitation is not addressed by current emergency or critical care standard practice.

[0032] Rehabilitation treatment for victims of trauma typically focusses on symptoms that are already established. Such treatment is usually initiated months or even years after a traumatic event, and is usually the result of patient requests for relief of debilitating symptoms that have become permanent.

PRIMARY VS. SECONDARY INJURY OR DAMAGE TO NERVES OR NERVE CELLS OR NEURAL SUPPORT CELLS OR INJURY THAT CAN ALTER

NEURONE FUNCTION

[0033] Damage or injury to nerves, nerve cells, neural support cells and neural support tissues can result from two types of injury. One is primary injury, the direct and immediate damage caused by the trauma, such as cutting, shearing, displacement, burning or other immediate destruction of tissue. This damage to nerves, nerve cells, glial cells and blood vessels and the associated haemorrhage and lacerations have immediate clinical effects. This injury is usually limited and focal.

[0034] The other is secondary injury (Borgens and Liu-Snyder, 2012), which is triggered immediately or within hours of the primary injury and can progress through cascades of metabolic and biochemical processes over a prolonged period of time. This secondary injury is caused by parallel or consecutive pathological processes initiated at the moment of the trauma, often with delayed clinical presentation. Secondary injury is the result of cellular, metabolic and neurochemical processes that are triggered by the primary injury but that continue over the hours, days, weeks and even months following trauma.

[0035] As described herein, this secondary injury can progress to nerve cells, neural support cells and neural support tissues beyond the locus of the primary injury and can include even areas remote from this primary injury.

[0036] Current standard practice at the time of trauma does not address prevention of neuropathology and neurodegeneration caused or triggered by trauma.

SECONDARY INJURY RESULTING FROM BRAIN INJURY

[0037] Brain injury is a major public health issue and a leading cause of disability and death, as summarized in a number of recent reviews in the scientific literature. Brain injury occurs most often from falls, motor vehicle accidents, workplace accidents, other accidents, and explosions, as well as in warfare, but damage to the brain can also be inflicted by chemical, surgical, metabolic and other types of trauma as described herein.

[0038] Brain injury results in the primary injury described above, a localized initial direct brain damage accompanied by impaired regulation of cerebral blood flow and metabolism, usually with an ensuing oedema swelling. Direct damage to nerve cells and glial cells results from tearing, shearing, stretching or compression of tissue in the brain. These events triggered directly by the traumatic event are usually treated clinically by hypothermia, cerebrospinal fluid drainage and efforts to reduce blood pressure as well as pharmacologically with drugs such as mannitol and barbiturates, largely to decrease mortality. Procedures to prevent neuropathology and neurodegeneration are not typically included in such treatments.

[0039] The changes in blood circulation and metabolism lead to a series of steps that also lead to further injury, including an accumulation of lactic acid due to anaerobic glycolysis, which causes depletion of energy-supplying ATP stores and failure of energy-dependent membrane ion pumps that are necessary to maintain health of nerve cells, neural support cells

and neural support tissues. Collectively, this further injury is included in 'secondary injury' (Borgens and Liu-Snyder, 2012).

[0040] The triggering event of brain injury is usually unanticipated by the victim. The trauma that induces brain injury is usually time-locked, so there is a specific time of occurrence that sets in place a starting point in time during which an early intervention is advised in order to maximize beneficial effects of therapeutic steps to mitigate the secondary injury and its sequelae of adverse health conditions or disability.

[0041] The triggering event of brain injury can also be anticipated. For example, brain injury is an important source of morbidity for patients with cancer receiving cancer drug therapies. Such complications include, among others, posterior reversible encephalopathy syndrome, cognitive dysfunction and others. Therapeutic radiation also can lead to brain injury; white matter necrosis occurs at doses of >60Gy, leading to functional deficits including impairments in memory, attention and executive function, with profound effects on quality of life.

[0042] Standard immediate treatment of brain injury does not typically include steps to reduce or prevent the plethora of secondary injury mechanisms that are triggered within minutes and hours of the traumatic event and that contribute to the cascades of metabolic and biochemical pathways that continue neuropathology and neurodegeneration development over the succeeding days, weeks, months and even years.

Pathophysiology of secondary injury from brain injury

[0043] The secondary injury that results from trauma to the head is brought about by a complex cascade of progressive processes. These processes include biochemical, metabolic and cellular changes triggered by a primary injury event. Processes leading to secondary brain injury begin within minutes and hours of the initial injury, yet may continue for months. Some of these processes may begin even weeks later..

[0044] These cascades of pathophysiological events lead to secondary injury not only at the site of the trauma but also more diffusely in neighbouring as well as more remote brain areas (Hartings *et al.*, 2009). The triggering events include depolarization of nerve terminal membrane and excessive release of excitatory neurotransmitters such as glutamate and aspartate. At high levels, these excitatory neurotransmitters become neurotoxic, triggering excessive influx of calcium and sodium, causing activation of intracellular self-digesting cascades. Lipid peroxidases, proteases and phospholipases are activated by the increased intracellular calcium, resulting in increased intracellular concentration of free fatty acids and free radicals. Activation of caspases, translocases and endonucleases initiates further progressive structural degeneration of membranes as well as fragmentation of DNA and inhibition of DNA repair. In particular, two pro-inflammatory cytokines are released after brain injury, tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). These cytokines

are increased rapidly after brain injury and act to stimulate inflammatory cells to release reactive oxygen and nitrogen species. They also lead to the release of excitotoxic glutamate, and impair glial cell buffering of extracellular potassium.

[0045] These inflammatory cascades become a toxic positive feedback loop, leading to further brain pathology. Over time, these changes lead to necrosis, largely due to ischemia and to degradative factors from neighbor cells or from the circulation. Programmed cell death, an auto-destruction of cells is of two types, termed autophagy and apoptosis.

[0046] Necrosis is characterized by a loss of integrity of cell membranes, intracellular organelle damage, flocculation of the nucleus, loss of the contents of lysosomes, swelling of the cell and cell lysis. Necrosis occurs in response to the direct damage as well as to the ischemia and hypoxia, the excessive release of excitatory amino acid transmitters and metabolic failure. Following somewhat later in the process is the release of phospholipases, proteases and lipid peroxidases that autolyse membranes, which are recognized as antigen material and removed by anti-inflammatory processes.

[0047] Apoptosis is characterized by a loss of cell volume, condensation of the cytoplasm and nucleus, bleb formation on otherwise intact cell membrane and preservation of organelle structure. In apoptosis the cell typically fragments into apoptotic bodies that are engulfed and degraded by neighbouring cells.

[0048] Neurones, neural support cells and neural support tissues undergoing apoptosis are morphologically intact during the immediate post-traumatic event, with adequate ATP-producing metabolism providing physiological survival. Activation and deactivation of interleukin-converting enzyme caspases are considered to be important mediators of programmed cell death. Apoptosis begins within hours of the primary damage and continues for days or weeks, due to translocation of phosphatidylserine that triggers progressive membrane disintegration along with lysis of nuclear membranes, chromatin condensation and DNA fragmentation. Apoptotic bodies, particles derived from condensed intracellular material, are removed from the shrinking cell by exocytotic mechanisms.

[0049] Ischemia may be due to hypoperfusion or hyperperfusion of brain areas, to local regulation of the cerebral vasculature, and to vasospasm. Necrosis may also arise from metabolic failure of nerve cells or neural support cells and neural support tissues and may be due to an imbalance of cerebral oxygen delivery and cerebral oxygen consumption, supply. Both primary and secondary injuries induce the release of cellular mediators such as proinflammatory cytokines, prostaglandins, free radicals and complement molecules. Chemokines and adhesion molecules are induced, which in turn mobilize immune cells and activated glial cells that infiltrate the injured tissue along with macrophages and T-cell lymphocytes. Proinflammatory enzymes such as tumor necrosis factor, interleukin 1 β and interleukin-6 are upregulated within hours.

[0050] In response to these inflammatory processes injured as well as adjacent tissues undergo necrosis and elimination, processes occurring within hours of the initial trauma as well as over the following days and weeks. Further secondary brain damage occurs as a result of the release of vasoconstrictors such as prostaglandins and leukotrienes, the obliteration of microvasculature through adhesion of leucocytes and platelets, lesions to the blood-brain barrier and oedema, and leakage of blood from the vasculature into brain tissue.

[0051] At the same time as some cascades of processes are driving toward loss of function and cell death, other, reparative, processes are triggered to restore cell health and function.

Times and mechanisms of secondary injury from brain injury

[0052] Evidence from human and animal studies suggests that the optimal window of time to intervene in these processes is minutes to hours. For example, IL-6 and IL-8 have been reported to peak in cerebrospinal fluid samples in human patients within 6 hours of brain injury. Other cytokines, specifically IL-1 β , TNF- α and IL-10, are elevated for 24 hours after injury, and gradually decrease after that time.

[0053] The complement system represents the first line of defense against microorganisms and tissue damage by sensing, targeting and clearing pathogen- and danger-associated molecules. In a study on 40 trauma patients, complement hemolytic activity was markedly reduced within 24 hours of injury while other markers showed varying levels. The authors concluded that there is a synchronously rapid activation and dysfunction of complement suggesting a trauma-induced pathology has developed rapidly after injury.

[0054] In a clinically relevant animal model of brain injury it has been reported that there are decreases in brain levels of cAMP and activation of its downstream target, protein kinase A, occurring as early as 15 minutes after moderate fluid-percussion brain injury.

[0055] Using a controlled cortical impact injury model in the rat there are observed changes in excitotoxic amino acid transmitters and microstructural changes ipsilaterally as early as 2 hours after injury as well as contralaterally as early as after 4 hours. The trend of the biochemical parameters to return toward normal levels at 4 hours prompted the authors to suggest that there may be an optimal temporal window of only 3 hours for interventions that might limit secondary injury due to excitotoxicity.

[0056] Specifically apoptotic mechanisms have been observed in a rat model of brain injury and observed DNA fragmentation in the injured cortex and ipsilateral hippocampus occurring as early as 4 hours after fluid percussion-induced injury and formation of apoptotic bodies developing as early as 6 hours. Caspases, which have been implicated in processes leading to apoptosis, are also increased in damaged cortex as early as 4 hours, but are also elevated in more remote brain areas at 24-72 hours. Maximum DNA fragmentation is observed 3 days after injury.

[0057] Infiltration of neutrophils, which are thought to be major contributors to secondary

injury, as measured by myeloperoxidase microassay, peaks at 24 hours after injury in the fluid percussion model.

[0058] Even structural changes are seen early after brain injury in rat models, including neuronal abnormalities as early as one hour after fluid percussion brain injury in the rat. After a mild injury to the cortex in the rat visible structural damage to axons was seen at three days, the earliest time sampled. Importantly, the changes were observed not only in the cortex but also in the thalamus, remote from the site of injury.

[0059] The evidence from these studies in humans and in animal models indicates that the processes of secondary injury are activated immediately by a traumatic event. The evidence also indicates that some processes progress over a limited period of time and then return to pre-injury levels, while other processes may continue for days, weeks or months. It is relevant to point out here, as elsewhere in this document, that once the initial processes have been completed medical interventions for the treatment of the persisting adverse outcomes of brain injury are largely without benefit (Doppenberg *et al.*, 2004).

Standard treatment following brain injury

[0060] Because of the severe impact of brain injury on individuals, families, the healthcare system and the economy, there is a voluminous literature pertaining to treatment strategies for brain injury, as summarized in recent reviews of approaches to management of brain injury (Loane and Faden, 2010; Tsang and Whitfield, 2011).

[0061] Unfortunately for those who are victims of brain injury standard immediate treatment strategies do not include neuroprotection. Immediate pre-hospital management of brain injury focusses on airway clearance, prevention of hypoxia, hypercapnia and hypotension, as well as rapid transport to a medical centre for detailed diagnosis and treatment. Actions to limit or prevent secondary injury to nerves, nerve cells or neural support cells or neural support tissues tends to be absent from standard practice. For example, in a recent review, while a stated purpose of the report was to focus on limiting secondary brain injury, there was no reference to direct approaches to limit neuropathology from secondary injury (Boer *et al.*, 2012); the focus was on emergency services without regard for neuroprotection.

[0062] Penetrating wounds can be broadly categorized into those caused by missiles (gunshot wounds, shrapnel, blast fragments, pellets, and the like) and those by stabs and lacerations (knives, axes, swords, tree branches and the like). Despite the recognition that penetrating trauma leads to secondary injury, treatments that limit such secondary injury are not practiced.

[0063] As further examples, in a recent report based on 119 cases of traumatic brain injury to 119 military personnel injured by anti-personnel devices or by vehicle landmines, specific recommendations were made based on the outcomes of various management approaches,

including immediate battlefield management as well as subsequent hospital management. There was no recommendation for any action or procedure to provide neuroprotection from secondary brain injury resulting from the trauma.

[0064] Similarly, recent recommendations for medical management following improvised explosive device accidents do not include any action or procedure to provide neuroprotection.

[0065] Clinical treatment of brain injury typically consists of reducing increased intracranial pressure and reducing brain oedema through surgical decompression, removal of any foreign bodies, administration of osmotic agents and reducing body temperature. Immediate treatment does not usually include any steps to reduce or prevent the developing secondary injury.

[0066] A number of early interventions have been introduced in animal models of brain injury as well as in human patients in efforts to improve outcomes, but these have not translated to successful phase III clinical trials. As one example of an effort to develop an effective compound, in an exploration of the potential therapeutic effects of inhibiting apoptotic processes, a peptide substrate for CPP32, a human apoptotic protein was administered intracerebroventricularly. The peptide reduced DNA cleavage in the injured cortex and improved motor recovery after the brain injury compared to controls that did not receive the peptide.

[0067] In another approach, focussed on an attempt to preserve mitochondrial integrity after brain injury, a single intravenous infusion of cyclosporin A was given within 12 hours of the traumatic event. At 5 mg/kg infused over 24 hours glucose, lactose and pyruvate measured by cerebral microdialysis were greater in treated compared to placebo control patients, indicating beneficial effects of treatment.

[0068] More recently, a cyclosporin A analogue has been run in a mouse model of brain injury and it was found that administration at 15 minutes and 24 hours after injury there was improved cognition and mitochondrial function, as well as reduced oxidative damage, and the efficacy and safety of cyclosporin A in human and animal studies on brain injury have been confirmed in a recent review (Lulic *et al.*, 2011).

[0069] Riluzole, which has been reported to be neuroprotective in models of cerebral ischemia has been studied in a rat model of brain injury and has been found to provide some protection as measured at one and three weeks after the induced injury. Riluzole is not listed among promising drugs in recent reviews of emerging therapeutic strategies (Tolias and Bullock, 2004; Loane and Faden, 2010).

[0070] Kabadi *et al.* (2012) targeted cell-cycle activation that leads to nerve cell death, microglial activation and neurological dysfunction by administration of roscovitine, an inhibitor of CDK1, CDK2, CDK5, and CDK7 kinase activity. At 3 hours after a controlled cortical impact in an animal model, they observed improved biochemical and functional

outcomes.

[0071] In another animal model of brain injury administration of rolipram, a selective phosphodiesterase IV antagonist, decreased contusion size, decreased the amount of neuronal death in the parietal cortex and hippocampus, and reduced beta-amyloid precursor protein deposits in the external capsule.

[0072] These and numerous other approaches have been taken to understand the variety of different mechanisms of secondary brain injury in both human and animal studies. With respect to drug therapy the literature contains several reviews of the area in the past few years (Loane and Faden, 2010; Bains and Hall, 2011; Ma *et al.*, 2011). However, a consensus in these reviews is that despite at least 20 compounds being tested in over 50 trials by the year 2004, and over 30 phase III prospective clinical trials by 2010 (Loane and Faden, 2010), significant endpoints have not been reached by any therapeutic intervention and no effective drug therapy is currently available.

SECONDARY INJURY RESULTING FROM CENTRAL NERVOUS SYSTEM ISCHEMIA

[0073] Cerebral ischemia is one of the leading causes of long-term disability; a recent review reports an estimated 700,000 cases of ischemic stroke in the US each year. The human central nervous system is heavily reliant upon a continuous and adequate supply of oxygen and of glucose and although the brain comprises only 2% of the body in terms of weight, it utilizes 20 % of the total oxygen consumption and 25 % of the total glucose consumption. This high energy-utilization tissue is surprisingly vulnerable to any compromise of the delivery of these metabolic substrates. Central nervous system ischemia occurs when the blood supply or circulation to the brain, the brain stem, the cerebellum or the spinal cord is reduced. Ischemia may result from any reduction, restriction, interference or slowing of the blood circulation. Central nervous system ischemia can be focal or global.

[0074] Global ischemia occurs when there is an overall reduction in the blood circulation. Global central nervous system ischemia can occur during events such as but not exclusive to asphyxiation, shock, prolonged systemic hypotension, brain injury, extracorporeal circulation, hypo-perfusion during even during transient cardiac arrest, drowning, as well as with acute spinal cord ischemic syndrome and acute respiratory distress syndrome, or even in perinatal hypoxia-ischemia. Global central nervous system ischemia can be anticipated in high-risk individuals as well as individuals treated for cancer with certain chemotherapeutic drugs. Global central nervous system ischemia can even occur during medical treatment or procedures such as thoracic aorta repair, repair of complex congenital heart lesions and during implantable cardiac defibrillator testing.

[0075] Cerebral ischemia can result from a number of causes. When a cerebral artery is occluded this is considered to be a focal ischemia. Global cerebral ischemia can occur as

above. While the insults may be different all trigger restorative and degenerative processes, with a net secondary damage or injury and the ensuing devastating effects on nerve cells, on neural support cells such as glia, or on neural support tissues such as the vascular endothelium, are mediated via the same mechanisms, and all lead to the same risk of mortality, adverse health conditions or disability.

[0076] Spinal ischemia can result from surgical procedures, for example by aortic cross clamping during cardiac surgery.

[0077] When the normal blood supply to central nervous system tissue is occluded, or blocked, by a clot this is called a thrombotic stroke. In cases where a clot has been dislodged or broken off elsewhere in the circulation this is called an embolic stroke, such as the cerebral injury that occurs, for example, during surgical transcatheter aortic valve implantation.

[0078] When the blood supply is reduced sufficiently cells in the immediate vascular bed begin to die, creating an infarct zone. Surrounding this infarct zone is mildly to moderately ischemic brain tissue. This surrounding area is termed the penumbra, which is supplied with collateral arteries that may remain viable for some time if reperfusion can begin early enough. This cerebral vasculature in the penumbra can buffer the pathophysiological changes that are triggered. Because of the buffering capacity and because any damage to the penumbra is due to secondary injury processes, this is often considered to be the salvageable neuropathology, or the salvageable ischemic penumbra. However, in this penumbra area the degree of ischemia and the timing of reperfusion govern the survival of the nerve cells, neural support cells and neural support tissues.

[0079] Central nervous system ischemia triggers both restorative and degenerative processes. Restorative processes are neurotrophic in nature, regenerative and reparative. These drive cells and tissues toward health and normal function. Degenerative processes lead to loss of function and cell death, and can spread from the area directly affected by the primary insult to more diffuse areas of the central nervous system. Following ischemic trauma to the central nervous system, degenerative processes tend to predominate, leading to progressive secondary damage or injury and its sequelae of adverse health conditions or disability. It has also been suggested that normally restorative processes may be altered in certain ways to become degenerative. Secondary injury is caused or brought about by cascades of cellular and metabolic processes. These secondary injury processes are spread over a space and time continuum. For example, after spinal cord injury changes can be observed in neuronal function even in remote areas of the central nervous system including the brain, and these processes follow time courses of hours, days, weeks and even months.

Pathophysiology of secondary injury from central nervous system ischemia

[0080] Due to its heavy reliance on a continuous and adequate supply of oxygen and glucose, cerebral ischemia can rapidly lead to cell death within the central nervous system.

Blockage or even an insufficient cerebral blood flow leads quickly to deprivation of oxygen and glucose delivery and to build-up of potentially toxic products of cell metabolism.

[0081] Loss of ionic balance is one of the immediate results of inadequate supply of oxygen and glucose to the central nervous system. This occurs within two minutes. Nerve cells do not store alternate sources of energy for cellular metabolism and therefore intracellular stores of adenosine triphosphate (ATP), the source of energy, become rapidly depleted. Oxygen is required to generate sufficient ATP by oxidative phosphorylation. In particular, the enzyme, sodium/potassium ATPase, in the membrane of nerve cells is estimated to consume 70% of the energy supplied to the brain. ATPase maintains the sodium/potassium pump that maintains high intracellular potassium and low intracellular sodium. ATP depletion leads to multiple cascades of metabolic and biochemical processes, each of which follows a specific time course, including release of toxic levels of excitatory amino acids, ionic imbalance and acidotoxicity, oxidative stress, nitrative stress, inflammation, apoptosis, nerve terminal depolarization and necrosis. All lead to cell death, including death of nerve cells, neural support cells and neural support tissues. Endothelial cells comprise the walls of the vasculature and their death can lead to subsequent loss of integrity of vessel wall, infiltration of degradative chemicals and immune cells, as well as bleeding into the brain.

[0082] When ATP is no longer available, the membrane polarization is lost and intracellularly stored transmitters exit along their concentration gradient. In particular, the excitatory amino acid transmitter, glutamate, is released at toxic levels, creating excitotoxicity. Among the receptors upon which glutamate acts is the N-methyl-D-aspartate (NMDA) receptor. Activation of this receptor leads to further depolarization through influx of sodium as well as calcium into the cell, and further calcium release from intracellular stores.

[0083] There is also a calcium pump in the neurone cell membrane that normally maintains low intracellular calcium. A calcium ATPase in neuronal cell membranes governs this calcium pump. When the calcium pump ceases due to insufficient ATP, intracellular calcium rises even further. As a result of the influx of calcium through the NMDA receptor as well as by loss of the calcium pump combined with the release of intracellular calcium there is a massive activation of calcium-dependent proteases, lipases and DNases, causing cells to die by their own catabolism.

[0084] It is this differential distribution of sodium and calcium as well as potassium ions that engenders the excitability nature of nerve cells, enabling them to be excited by synaptic input, conduct action potentials and release transmitters from their synaptic terminals. When the homeostatic processes end as a result of ischemia, depolarization of the membrane occurs and neurones lose their conductive properties.

[0085] Localized membrane depolarization of large numbers of cells leads to cortical spreading depression, which is a self-propagating slow wave of depolarization that

contributes to the spatial and temporal spread of ischemia-induced cell death beyond the core of an infarct.

[0086] Cerebral ischemia is also associated with acidosis, created by hyperglycemia, which decreases local pH by increasing lactate. This in turn activates sodium-selective acid sensing ion channels (ASICs) that allow further influx of sodium and calcium.

[0087] These high levels of sodium and calcium also stimulate mitochondria to produce high levels of reactive oxygen species, which are particularly damaging to nerve cells due to the relatively low levels of intracellular antioxidants in neurones. This oxidative stress contributes further to destruction of cell components and apoptotic cell death.

[0088] The enzyme nitric oxide synthase is also stimulated, resulting in excessive amounts of nitric oxide, which is labile and is rapidly combined with superoxide to form the highly potent oxidant peroxynitrite. Nitric oxide is also rapidly converted to other nitrates, the overall processes considered as nitrative stress.

[0089] Oxidative and nitrative stress spread from an infarct zone into surrounding and even remote central nervous system areas. Oxidative and nitrative stress are linked to activation of poly(ADP-ribose)polymerase, which, at high levels, impairs anaerobic glycolysis and mitochondrial respiration, leading to further exhaustion of ATP, energy failure and cell death.

[0090] Local superoxide, nitric acid and peroxynitrite also activate a family of metalloproteases that lead to degradation of structural components of the basal lamina with the result that the integrity of the vascular wall is compromised and the permeability of the blood-brain/spinal barrier is increased. Loss of integrity of the blood-brain/spinal barrier results in infiltration of neutrophils and other leukocytes into the central nervous system tissue. As a result of injury to endothelial cells and the loss of vascular integrity ischemic stroke may transform into central nervous system haemorrhage of blood into central nervous system tissue, which triggers further cascades leading to widespread cell death extending to surrounding and remote central nervous system areas.

[0091] Programmed cell death (types I, apoptosis, and II, autophagy), and necrosis are also observed as a result of the oxidative and nitrative stress and the release of proteases resulting from central nervous system ischemia. As a result, autolysis, blebbing, cell shrinkage, and fragmentation of DNA are seen in neurones and glial cells. The close association of apoptosis and necrosis has recently given rise to a concept of an apoptosis-necrosis cell-death continuum, to account for the complexity of the mechanisms leading to death of nerve cells, neural support cells and neural support tissues in the central nervous system.

[0092] Inflammation also results from cerebral ischemia and contributes to cell death, although the processes triggered differ somewhat between focal and global ischemia. Inflammatory changes that result from cerebral ischemia are delayed in comparison with metabolic failure and ionic disruption, thus providing inroads for therapeutic intervention at

different times. Inflammation-induced processes include release of inflammatory mediators and activation of several different types of inflammatory cell. In particular, central nervous system ischemia increases neutrophils and lymphocytes in central nervous system tissue and in the number of circulating monocytes.

[0093] Neutrophils are observed in the brain as early as 30 minutes after middle cerebral artery occlusion in an animal model. The process of migration of neutrophils from the vasculature to brain tissue is mediated by three classes of molecule termed 'cell adhesion molecules'; these include selectins, integrins and immunoglobulins. In brain tissue neutrophils release oxygen free radicals and proteolytic enzymes.

[0094] Lymphocytes, which are normally prevented from entering brain tissue access through the disrupted blood-brain/spinal barrier, appearing in brain within hours and leading to delayed tissue injury and cell loss in the central nervous system. These cells release reactive oxygen species and toxic enzymes, and further compromise blood flow through vascular stasis as well as activating platelets.

[0095] Nerve cells, glial cells, platelets, leukocytes and endothelial cells are stimulated to produce cytokines and chemokines, which are thus released in the central nervous system and contribute to cell death. Cytokines include IL-1, IL-6, TNF- α and TGF- β . Chemokines include primarily though not exclusively chemokine CXC ligand 12 (CXCL12) and monocyte chemoattractant protein-1 (MCP-1). Toll-like receptors (TLRs), which are expressed on neurones, microglia, astrocytes, oligodendrocytes and endothelial cells, recognize invading pathogens as a defense and lead to further release of cytokines and chemokines. TLRs are also activated by other components of the extracellular matrix associated with central nervous system tissue damage, including heat shock proteins, fibrinogen and DNA fragments.

Times and mechanisms of secondary injury from central nervous system ischemia

[0096] A person having ordinary skill in the art will understand that the processes involved in the spatial and temporal spread of injury from the core infarct are varied, some occurring as early as within minutes after the ischemic event yet others commencing hours and days later and extending for comparatively long periods of time (Brouns and De Deyne, 2009). A person having ordinary skill in the art will also understand that restorative and degenerative processes described here for cerebral ischemia apply also to ischemia in all other parts of the central nervous system.

[0097] Mechanisms of cell loss resulting from cerebral ischemia share similarities with those described herein that are triggered by brain injury, including particularly but not exclusively release of excitatory amino acids at levels that are excitotoxic, oxidative stress, release of free radicals, nitrative stress, necrosis, apoptosis and inflammation. These immediate changes are followed by processes that extend in time and space (Brouns and De Deyne, 2009).

Standard treatment following central nervous system ischemia

[0098] The National Brain Attack Initiative was launched as a recognition that cerebral ischemia can be responsive to medical intervention if therapeutic efforts are instituted in a timely manner. Current immediate treatment of focal ischemia involves removing the cause by dissolving the clot or by physically removing the clot. Immediate treatment for hypo-perfusion or global ischemia involves increasing arterial pressure with the aim of restoring adequate blood supply to the brain. Hypothermia is also recommended to treat global ischemia, although this approach is being used less frequently and opinion is that pharmacological neuroprotection remains the only option for treatment (Weigl *et al.*, 2005). Yet, despite the recognition that neurological effects result from global ischemia, pharmacological neuroprotection is seldom if ever included in any standard management approaches.

[0099] Unlike brain injury, a drug is available for immediate medical intervention for central nervous system ischemia. That drug is tissue plasminogen activator (tPA). While this is used extensively as an immediate intervention its use is limited to a narrow therapeutic window of only the first three hours after cerebral ischemia because after that time the risk of tPA-induced intracerebral haemorrhage limits its use for stroke. As a result, cerebral ischemia still lacks an effective medical intervention to reduce or prevent the development of the secondary changes in the brain that progress over the hours, days, weeks and even months following the ischemic event and that lead to long-term disability.

[00100] When taken together, available evidence indicates that despite standard practice for immediate or even long-term treatment of central nervous system ischemia, efforts to attain effective therapies have largely failed. There is compelling reason, then, to pursue innovative approaches to reduce or prevent the development or the risk of development of neuropathology as a result of central nervous system ischemia.

Clinical timelines for effective intervention following central nervous system ischemia

[00101] The consensus in reviews of the literature pertaining to cerebral ischemia is that the window of time for effective intervention begins immediately, yet spans days or weeks or even months.

[00102] If we might borrow from the issue of initiation of treatment raised earlier with respect to timelines for effective intervention following brain injury, it is important to point to an earlier study in which it was found that the median time to referral of 150 patients with subarachnoid haemorrhage was 3.6 days. The delay was due to physician diagnostic problems in 37% of these cases, delayed referral policy in 23%, unstable patient condition in 7%, failure of patients to recognize severity of illness in 8% and logistical complications in 12%. The point is raised again, then, as it was in the section on timelines for effective intervention in cases of brain injury, that patient outcome may be improved if the first encounter with a

health care professional includes immediate pharmaceutical intervention, and outcomes may be improved if procedures can be administered before a patient reaches a clinic or hospital..

SECONDARY INJURY RESULTING FROM SPINAL CORD TRAUMA

[00103] Epidemiological studies and professional reports emphasize the severe impact of spinal cord injury on individuals, on the healthcare system and on the economy. A recent systematic review indicated that an estimated 40 million people worldwide suffer a spinal cord injury every year, and that most are young men. Of the new cases of spinal cord injury each year in the U.S., it has been reported that motor vehicle crashes account for 40%, falls account for 28% and acts of violence such as gunshot wounds, account for 15%. Sports injuries account for 8%, with another 9% are of unreported or unknown causes.

[00104] Tetraplegia is due to injuries to cervical levels of the spinal cord while paraplegia is due to spinal injuries at the thoracic, lumbar or sacral level. Of cases reported in a national survey, 40% were incomplete tetraplegia, 22% were complete paraplegia, 22% were incomplete paraplegia and 16% were complete tetraplegia.

[00105] Another recent systematic review pointed out that priorities for people who live with injured spinal cord are improvements in motor function (including arm/hand function for individuals with tetraplegia and mobility for individuals with paraplegia), as well as bowel, bladder and sexual function.

[00106] Much of the current research on spinal cord injury is directed toward regeneration of spinal cord and restoration of function, or treatment of symptoms. Yet much of the disability that ensues after spinal cord injury arises from the secondary injury processes that are triggered by a primary trauma. As with other types of secondary injury, the cellular, biochemical and metabolic nature of these processes present opportunities for effective medical intervention. While it remains important to pursue medical approaches to regenerate pathways in the spinal cord, this does not obviate the need to minimize loss of cells and of function at the outset, by medical intervention at the time of the initiating trauma by targeting the processes that lead to secondary injury or the processes of recovery or restoration that are active over the minutes, hours, days and weeks following spinal cord injury. Yet, standard practice at the time of spinal cord injury does not encompass steps to treat or address such processes.

Pathophysiology of secondary injury from spinal cord trauma

[00107] Many of the pathophysiological mechanisms that lead to secondary spinal cord injury are the same as those described herein for brain injury and central nervous system ischemia. Direct tissue damage kills local nerve and glial cells, and produces an imbalance of ionic distribution across neurone cell membranes. This ionic imbalance causes excessive depolarization of these neurones, leading in turn to excessive release of excitatory amino acid transmitters, which is observed within 15 minutes of spinal injury; excitatory amino acids are

toxic to spinal cells at high concentrations. As a result, spinal cells undergo massive influxes of sodium and calcium.

[00108] Activation of N-methyl-D-aspartate glutamate receptors also leads to influx of calcium which leads in turn to a calcium-activated release of calcium from intracellular stores. The massive levels of intracellular calcium trigger a multitude of calcium-dependent metabolic pathways that can lethally alter cellular metabolism and health, and can lead to cell death. These pathways include activation of lytic kinases and transcription factors such as calpains, phospholipase A2, and lipoxygenase that contribute to cell death, as well as leading to increased excitability of more remote neurones. These calcium-dependent signaling proteins have been suggested to alter the properties not only of local neurones but also glial cells and contribute to the adverse health conditions or disability that typically accompany spinal cord injury.

[00109] Influx of sodium causes depolarization of the normally polarized neuronal membrane, which arrests action potential propagation and causes osmotic influx of water into axons, leading to cell swelling.

[00110] The influx of sodium and calcium also triggers oxidative stress due to excessive demands for and subsequent depletion of the energy-supplying ATP.

[00111] The combination of acidosis and oxidative stress, along with nitrative stress, leads to the temporal and spatial spread of cell death to spinal cord tissue beyond the site of primary injury, through apoptosis, autophagy and necrosis. Programmed cell death by apoptosis and autophagy involves shrinkage of the cell with intact organelles, activation of intracellular caspases and fragmentation into apoptotic bodies that are subsequently cleared by phagocytosis. Necrosis involves cell swelling, loss of the capacity to produce ATP, and disruption of cellular organelles as well as the cell membrane, releasing intracellular contents into the extracellular milieu, which in turn induces a local inflammatory response.

[00112] Oligodendrocytes are particularly susceptible to apoptosis and their loss contributes to demyelination of otherwise spared axons, thus contributing further to the spread of loss of neuronal function and cell death.

[00113] These processes eventually lead to activation of microglia and macrophages, as well as injury of endothelial cells of the spinal vasculature. Loss of vascular endothelial cells leads to local oedema and eventually to haemorrhage.

[00114] The local vasculature undergoes a number of additional changes that contribute to the temporal and spatial spread of secondary injury. Besides haemorrhage, local vasospasm and intravascular thrombosis contribute to local hypoperfusion and ischemia due to ionic imbalance and the release of large amounts of glutamate into spinal tissue with the ensuing excitotoxicity. The high metabolic needs of spinal tissue for oxygen are compounded by the loss of autoregulatory mechanisms of the spinal vasculature leading to further oxidative

stress.

[00115] When reperfusion of the local tissue occurs there is a major increase in local oxygen free radicals. These oxygen free radicals cause oxidation of fatty acids in cell membranes, the process of lipid peroxidation, leading to progressive disruption of cell membranes. This oxidative stress also disables enzymes in the mitochondrial respiratory chain, contributing to metabolic collapse and cell death by apoptosis, autophagy and necrosis.

[00116] With the loss of local vascular integrity, rapid infiltration of immune cells from the blood triggers a local inflammatory response that spreads from the site of the initial injury. This inflammatory response is carried out by neutrophils, macrophages and T lymphocytes, as well as locally-released cytokines, prostaglandins and complement, which cause further tissue injury and recruit other inflammatory cells. Monocytes/macrophages are activated along with local microglia, which together phagocytose injured tissue. Dying cells also release proinflammatory mediators locally that contribute to this local inflammatory response and to the spatial propagation of inflammation and cell death.

[00117] Reactive cells release cytokines that mediate the inflammatory response and can contribute to further tissue damage. Cytokines include TNF- α , interleukins and interferons. These induce further tissue injury, partly through the activation of cyclooxygenase to produce prostaglandins, prostacyclin and thromboxanes that promote loss of vascular integrity as well as inducing platelet aggregation.

[00118] Prostacyclin has vasodilatory properties that promote vascular permeability and oedema. Thromboxane A₂ worsens venous thrombosis and ischemia by promoting platelet aggregation and vasoconstriction.

[00119] Cytokines and chemokines are key mediators of this local inflammatory response. These include interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α (TNF- α), which are found within one hour after spinal trauma after spinal injury in humans but also appear to play a role in prolonging the inflammation and spreading tissue injury. It has been reported that the upregulation of these cytokines correlates with the severity of secondary injury in an animal model of spinal injury.

Times and mechanisms of secondary injury from spinal cord trauma

[00120] Most of the information regarding the timings of the different neuropathologies that develop as a result of spinal trauma is derived from animal studies. For example, glutamate levels increase several-fold within an hour following experimental spinal cord injury, a time point that is usually not accessible to therapeutic intervention at a hospital or clinic level. This means that the excitotoxic effects are manifest almost immediately, usually before access to appropriate medical treatment or intervention. Some of the earliest changes measured are in interleukin-1 β and tumor necrosis factor α , which appear rapidly within 5-15 minutes, but are

expressed only transiently. At 30-45 minutes after spinal trauma, IL-1 β and TNF α -positive cells are seen more extensively over more remote spinal cord segments. By 2 days after spinal injury mRNA signal for these cytokines has nearly disappeared. These times indicate that changes are initiated immediately by the trauma to the spinal cord. Importantly for the development of effective medical intervention, another wave of expression of IL-1 β and TNF α is observed at 14 days. Others have reported that TGF β 1 mRNA levels are maximum at 7 days.

[00121] Electron microscopic examination of spinal tissue reveals gross cell deformities with widespread oedema of all structures as well as severe oedema in the neuropil at 6 hours after spinal injury. Using a vascular tracer it has been observed that increases in permeability throughout the dorso-ventral axis of the spinal cord have developed by 3 days. By 7 days this had lessened, but there was a secondary increase in permeability at 14 to 28 days.

[00122] Inflammatory processes also appear early and persist. The appearance of neutrophils at the primary spinal lesion site has been seen within 4–6 hours, and these cells persist up to 5 days in animal models. At the site of injury, macrophages have been reported within 2 days, peak at 5–7 days, but persist for weeks to months. Astrocytes in the primary injury area alter their phenotype over the weeks that follow spinal trauma and these form a dense extracellular matrix that forms glial scars in the injured areas.

[00123] Chemokines and their receptors are upregulated in the spinal cord within 2 days of spinal injury and these levels continue to increase from 2 to 42 days.

[00124] Oligodendrocyte death appears maximal at 8 days indicating that loss of oligodendrocytes may result in demyelination of axons that have survived the initial trauma.

[00125] Programmed cell death and necrosis occur over extended periods of time after the initial trauma, and can be observed in remote parts of the spinal cord.

[00126] As a person having ordinary skill in the art will understand, the changes may be observed hours after a traumatic event, but in order to reach observable levels they would likely be triggered within a much shorter time. A person having ordinary skill in the art will also understand that the time to administer appropriate treatment would not be at the time of the peak change, or even at the time of the first observable change, but at the onset or initiation of the change. A person having ordinary skill in the art will also understand that to be most effective in reducing or preventing the temporal and spatial spread of neuropathology and cell death inhibition of expression of a biochemical or natural step at the initiation stage of a cascade of degenerative events, as described herein, would have to be administered immediately or as soon as possible after a traumatic event in order to offer the greatest effectiveness in reducing or preventing the development or the risk of development of neuropathology as a result of traumatic spinal cord injury.

Standard treatment following spinal cord trauma

[00127] Immediate clinical treatment for spinal injury includes surgical decompression and stabilization in order to reduce oedema and to prevent further primary injury (Kerwin *et al.*, 2008). However, a retrospective observational study concluded that surgical treatment has not resulted in improved hospital mortality or length of stay (Lenehan *et al.*, 2012) and a consensus meeting concluded that surgery does not improve neurological outcome following spinal cord injury (Albert and Kim, 2005).

[00128] Although there have been many studies investigating interventions to improve neurological and functional outcomes following spinal cord injury, there has been only one drug that has demonstrated beneficial effects, which is methylprednisolone, usually given as methylprednisolone sodium succinate (Bracken 2012). However, the benefit of methylprednisolone has been challenged through critical reviews of the literature by other groups (Sayer *et al.*, 2006).

[00129] Recent reviews of clinical trials on new drugs for early treatment of spinal cord injury have concluded that none of the emerging treatments has demonstrated efficacy (Gensel *et al.*, 2011; Rabchevsky *et al.*, 2011).

[00130] Yet, there are many leads coming from animal studies. Some of these have reported promising results with antioxidant therapy, anti-TNF- α therapy, inhibition of the estrogen receptor with tamoxifen, inhibition of the P2X7 receptor, inhibition of phosphodiesterase with rolipram, administration of progesterone, administration of bisperoxovanadium, administration of NSAIDs such as ibuprofen, and administration of progenitor cells. Other avenues to explore from animal studies include but are not limited to interfering with cytokine expression, inhibition of apoptosis and autophagy, inhibiting the inflammatory response and others.

[00131] However, a consensus remains that the results from animal studies have not translated into significant functional recovery or tissue sparing in humans (Curt, 2011; Rabchevsky *et al.*, 2011). This may be partly due to the fact that in the face of the complexity and multiplicity of the cascades of processes involved in causing secondary injury, most efforts remain with a single modality of treatment (Miller and Bai, 2012). A consensus is that a "magic bullet" approach will not succeed in reducing or preventing secondary spinal cord injury and that a combined treatment approach is necessary (Popovich *et al.*, 2011).

Clinical timelines for effective intervention for spinal cord injury

[00132] While immediate medical intervention is important to target the earliest of the pathophysiological mechanisms and processes that contribute to secondary spinal injury, it is important to recognize that some treatments that are initiated days after the traumatic event have also been reported to be at least somewhat effective in improving outcomes. For example, it has been reported that curcumin administration immediately after a spinal

hemisection in the rat, functional outcomes were improved compared to controls 24 hours after the primary injury was induced. Importantly, though, when curcumin was given to animals only 7 days after spinal cord hemisection, there was still an improvement in a functional outcome score, a reduction in neurone loss and apoptosis, as well as decreased astrocyte activation, indicating the persistence of mechanisms of secondary injury and therefore the importance of continuation of treatment.

[00133] A time-dependent multiphasic response of cellular inflammation has also been reported, comprised of an early phase of cellular inflammation, principally of neutrophils peaking 1 day after the primary injury, macrophages/microglia peaking 7 days after the primary injury, and T cells peaking 9 days after the primary injury. However, it has also been reported that a late phase of cellular inflammation can be detected after 14 days, which peaked after 60 days and remained detectable throughout the examination period, to 180 days for all three cell types.

[00134] Methylprednisolone sodium succinate is typically given in a dose regimen of an initial bolus of 30 mg/kg administered over 15 minutes, with a maintenance infusion of 5.4 mg/kg per hour infused for 23 hours. An additional benefit by extending the maintenance dose from 24 to 48 hours has been reported if start of treatment is delayed by between three and eight hours after injury. Walker *et al.* (2012) report efficacy of a clinically applicable pharmacological therapy for rapid initiation of neuroprotection post-spinal cord injury, and provide information on the signaling involved in its action..

SECONDARY INJURY RESULTING FROM PERIPHERAL NERVE TRAUMA

[00135] There are many outcomes of neuropathy of peripheral nerves. Neuropathic pain is perhaps the best documented, largely because of the enormous impact of chronic neuropathic pain on individuals and the fact that it tends to be refractory to medical treatment. However, other outcomes of secondary injury to peripheral nerves include, in terms of sensory disturbance, numbness, dysesthesia (an unpleasant abnormal sensation, whether spontaneous or evoked), paresthesia (an abnormal sensation, such as tingling, whether spontaneous or evoked), hypoesthesia (decreased sensitivity to stimulation, excluding the special senses) and loss of proprioception (possibly contributing to altered gait and to falls). In terms of motor control, peripheral neuropathy can lead to weakness, loss of movement, loss of corrective motor control and loss of muscle mass. Neuropathy of the autonomic nervous system can be manifest as orthostatic hypotension, dysautonomia, altered sudomotor function, and the like.

[00136] Peripheral nerve trauma causes injury and degeneration of nerve cells and neural support cells, such as the Schwann cells. Degeneration of axons or of neural support cells triggers a cascade of activated chemical pathways that lead to injury to otherwise intact nerve cells, Schwann cells, local vasculature and even more remote nerve cells by entry of degradation products into the blood circulation.

[00137] Much of the information available on the pathophysiology and treatment of peripheral neuropathy pertains to peripheral neuropathic pain, and, accordingly, this section will rely heavily on this literature, although evidence available regarding other outcomes of peripheral neuropathy will be cited where appropriate.

[00138] Neuropathic pain is defined as pain caused by damage, lesion, dysfunction or disease of the peripheral somatosensory nervous system and is characterized as a constant burning pain accompanied by hyperesthesia (increased sensitivity to stimulation, including the special senses). Hyperesthesia is usually clarified in clinical use as either hyperalgesia (increased pain from a stimulus that normally provokes pain) or allodynia (pain due to a stimulus that does not normally provoke pain). Neuropathic pain may also include periodic attacks of pain that feel like electric shocks or shooting pain.

[00139] In understanding mechanisms of peripheral neuropathic pain it is important to distinguish this type of pain from nociceptive pain and inflammatory pain. Nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors; nociceptive pain generally protects from potential tissue damage or from further tissue damage on a moment-to-moment basis, and triggers physiological and behavioral reflexes to avert damage. Inflammatory pain is pain that is triggered by tissue inflammation and serves to aid in healing and repair of injured non-neural tissue. Each type of pain is brought about by a particular set of mechanisms and each has a particular treatment algorithm. Neuropathic pain is different, not only with respect to underlying mechanisms and treatments, but it is considered to be a degenerative pain, as this type of pain neither protects nor supports healing and repair.

[00140] Neuropathic pain developing as a result of acquired or of hereditary causes is not the subject of the presently disclosed technology. In these cases the peripheral neuropathy is governed by mechanisms that are initiated at a time point that is not presently understood and would therefore require prolonged intervention. Acquired and metabolic peripheral neuropathy are due to, as examples, diabetes and chronic alcoholism. Hereditary peripheral neuropathy would include, as examples, Marie-Charcot-Tooth disease and Guillain-Barré syndrome.

Pathophysiology of injury from peripheral nerve trauma

[00141] There is a relative paucity of evidence on the pathophysiology of peripheral nerve injury compared to the evidence on the pathophysiology of brain injury, central nervous system ischemia and spinal cord injury. This may be at least partly due to the fact that there is no perceived immediacy to treatment of peripheral neuropathic pain because at the time of trauma the focus of medical attention is on immediate steps to control bleeding and other overt signs of primary injury. Prevention of secondary peripheral nerve injury is not currently a part of standard emergency treatment algorithms.

[00142] Fundamental and clinical research tends to focus on understanding peripheral neuropathy when it is clearly manifested in symptoms, and on developing approaches to treat an existing condition or existing symptoms.

[00143] Injury to peripheral nerves is not life threatening. As a result, there is relatively less drive for knowledge regarding the earliest processes and mechanisms activated by trauma to peripheral nerves compared to that for trauma to the central nervous system. The downside of this is that many victims of peripheral nerve injury are condemned to a lifetime of sensory, motor and autonomic dysfunction, whether due to an automotive accident, a battlefield incident, a sports injury, a workplace accident, or the like as described herein. In all cases, the outcome of secondary peripheral nerve injury can be devastating to the individual.

[00144] Trauma to a peripheral nerve has effects on sensory neurones, on motor neurones controlling skeletal muscle and on autonomic efferent neurones controlling the cardiovascular system and organs. This accounts for the range of outcomes of peripheral neurotrauma indicated above. As much of the research in this area is focussed on symptoms, available knowledge tends to be clearly fractionated into the bases of sensory loss, motor loss or autonomic dysfunction.

[00145] The overriding research on sensory loss pertains to peripheral neuropathic pain, which will be surveyed here to exemplify the pathophysiological changes that occur in peripheral nerves more generally. Even here, though, much attention is focussed on changes in the central nervous system, particularly at the level of the first sensory synapse in the spinal cord and in the brain stem. As a result treatment options tend to focus on targets within the central nervous system (Vorobeychik *et al.*, 2011). Research also tends to focus on the incidence of neuropathic pain rather than on underlying neuropathological processes. Notwithstanding this orientation, the first step here will be to examine the changes in peripheral nerves that result from neurotrauma.

[00146] Understanding pathophysiology arising from peripheral nerve trauma is further complicated by the various types of trauma, which consist largely of a total cut of a peripheral nerve, a partial cut, an event-triggered compression, a slowly-developing compression (such as from a tumor), and a degeneration of nerve cells or of neural support cells and neural support tissues. Total and partial cuts as well as event-triggered compression can occur as a result of an accident, a violent act or surgery. Degeneration can be induced, for example, by chemotherapy.

[00147] Multiple pathophysiological, neurochemical, and anatomical changes are triggered by peripheral nerve injury, whereby a simple focal peripheral nerve injury unleashes a range of peripheral and even central nervous system processes that contribute to persistent pain and abnormal sensation. Repair mechanisms of neural tissues in response to injury, and the reaction of adjacent tissues to injury lead to a state of hyperexcitability in primary sensory

nociceptors, a phenomenon termed peripheral sensitization. In turn, central neurones innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability, termed central sensitization.

[00148] Normally these sensitization phenomena extinguish as the tissue heals and inflammation subsides. However, when primary afferent function is altered in an enduring way by injury or disease of the peripheral nerves, these processes persist, become chronic and may be highly resistant to treatment.

[00149] Much of what has been learned regarding the pathophysiology of injury causing neuropathic pain has come from animal studies. Human laboratory studies, although limited in number, support the idea that the pathophysiological mechanisms discovered in animal models are valuable and relevant to our understanding of human neuropathic pain. There are several animal models of peripheral neuropathic pain, largely based on the types of primary injury or trauma that lead to peripheral neuropathic pain in humans.

[00150] Outcomes of peripheral nerve injury in these models include major changes in the properties of nerve cells and their support cells, including the Schwann cells. Changes in sensory nerve cells include spontaneous ectopic action potential generation, persisting sensitization of sensory nerve cell peripheral terminals, and increased release of excitatory neurotransmitters from their central nerve terminals. Other changes in sensory nerve cells include a change in function, changes in the expression of cell constituents such as sodium channels and changes in the expression of neurotransmitters, including de novo expression of substance P in large fibre, non-nociceptive sensory neurones.

[00151] Changes also occur in Schwann cells. Any changes in the supporting Schwann cells are important to understand because of their pivotal role in sustaining the physiological properties of peripheral nerve cells and because they are involved in degeneration and demyelination. Schwann cells are the glial cells of the peripheral nervous system, and include myelinating cells and non-myelinating satellite cells. Dysfunction of Schwann cells is at the basis of several peripheral nerve disorders, such as Guillain Barré disease and Charcot-Marie-Tooth disease.

[00152] Degeneration of an axon triggers a number of events in these neighbouring non-nerve cells in a degenerative process termed 'Wallerian degeneration'. As the Schwann cells decompose so do the myelin sheaths. The products of this decomposition trigger proliferation of new undifferentiated Schwann cells that align along the Büngner's bands that constitute the tubes within which the nerve bundles are contained, along with their support cells. Toll-like receptors are strongly induced by axotomy, they are involved in degeneration and they lie at the crossroads of peripheral nerve pathology and pain.

[00153] Changes also occur in other non-neuronal cells, affected by axonal degeneration and Wallerian degeneration of axons. Macrophages and lymphocytes as well as immune cells

from the blood infiltrate dorsal root ganglion cells and are attracted to the site of nerve damage. This chemical milieu contains many components that impact on all cell types, including neurotrophic factors (brain-derived neurotrophic factor, glial-derived neurotrophic factor, nerve growth factor and neurotrophin-3), pro- and anti-inflammatory cytokines (TNF- α , IL-1 α , IL-1 β , IL-6, IL-10 and leukemia inhibitory factor) and the chemokine monocyte chemoattractant protein-1. Axon-promoting chemicals are thought to provide support for regrowing axons. Some components are thought to cause increased excitability of undamaged axons as a cause of neuropathic pain. Even cutting ventral roots has been shown to lead to neuropathic pain behavior in rats, presumably due to the migration of chemicals from degenerating nerve and neural support cells associated with motor control to intact neighbouring sensory neurones.

[00154] Peripheral nerves travel alongside blood vessels and trauma to the nerve often physically disrupts the blood-nerve barrier, allowing the milieu of chemicals produced by axon and Schwann cell degeneration to enter the bloodstream, which then carries these chemicals to remote parts of the body, including direct access to uninjured dorsal root ganglia, the enteric nervous system and the central nervous system. This tends to carry peripheral nerve injury to remote sites beyond the site of primary injury.

[00155] As a result of acute peripheral nerve injury, discharge from both damaged and adjacent intact primary afferent fibres becomes abnormal. This modified afferent drive in turn has been reported to elevate the excitability and discharge of dorsal horn neurones and to induce changes in sensory processing at the level of the spinal dorsal horn including altered calcium-dependent signal transduction mechanisms, a shift in anion gradient, microglial activation, decreased inhibitory mechanisms, apoptosis and others. It is thought that this modified sensory processing at the level of the spinal dorsal horn, termed central sensitization or long term potentiation, contributes to neuropathic pain by exacerbating excitatory transmission to supraspinal structures.

Standard treatment following peripheral nerve trauma

[00156] For complete cut of a peripheral nerve a standard procedure is nerve repair or nerve grafting, but this approach remains suboptimal and is usually performed long after the cut has occurred. Axons have the capacity to regrow, but this is often incomplete or the regeneration misses the original tissue target. As a result there has been a wealth of research on mechanisms of regeneration and respective treatment modalities. Yet, outcome generally remains poor.

[00157] To make matters worse, leaders in the field of pain have suggested that there is little evidence that chronic postsurgical pain can be prevented. In fact, this assessment might just be correct, as the concept of 'prevention' of postsurgical chronic pain is usually embedded in the concept of peri-surgical anesthesia rather than control of the degenerative processes that

lead to secondary injury to nerve cells and Schwann cells in peripheral nerves. This latter approach is not included in treatments to prevent postsurgical pain, let alone a rationalized, combination therapy based on a timed sequence of pharmaceutical interventions aimed at reducing or preventing the secondary injury to these cells. The consensus therefore teaches away from this rationalized approach toward techniques that have been proven by evidence to be relatively ineffective, condemning multiples of thousands each year to a life of unending refractory pain, loss of motor function and autonomic dysfunction.

[00158] Numerous efforts have been made to treat neuropathic pain. Some treatments have been found to have beneficial effects. These include treatment with multimodal analgesics, botulinum toxin, peripheral nerve electrical stimulation, as have invasive approaches such as spinal cord stimulation and administration of stem cells. However, these are aimed at treating existing peripheral nerve dysfunction. What are not being explored are treatments to prevent the onset of neuropathic pain or any other of the sensory, motor or autonomic adverse sequelae of peripheral nerve injury.

[00159] Trauma to peripheral nerves is not considered life threatening, whether physical, chemical, metabolic or surgical. As a result there is limited incentive to pursuit of medical interventions, methods and procedures to reduce or prevent secondary peripheral nerve injury that results from trauma to peripheral nerves. For example, there is no appreciation of immediacy in medical intervention. Research on medical intervention for neuropathic pain focusses on treatment of an existing condition, once a complete diagnosis has been made. Complete or correct diagnosis can take weeks, months or even years. Standard treatment following peripheral nerve trauma typically involves drugs that reduce the acute pain intensity. Thus, in the pursuit of new drugs, neuropathic pain resulting from peripheral nerve trauma is becoming understood in terms of a static, or established, condition. The processes that are involved in the initial pathophysiology of peripheral nerve injury remain poorly understood and efforts to understand or to intervene in these early processes of secondary injury are few or nonexistent.

[00160] A second impediment to understanding the pathophysiology of peripheral nerves is that a major focus of research has been on the changes in the spinal cord and other central nervous system structures that result from peripheral nerve trauma. As a result, much of the research on the pathophysiology of neurones and neural support cells in neuropathic pain has focussed on changes in the spinal cord, where the predominant concepts are 'central sensitization' or 'long-term potentiation' and 'neuroplasticity', as mechanisms underlying the pain. While this is important, it has tended to shift focus away from the changes in peripheral nerves and the role of primary afferent drive in the mechanisms of neuropathic pain.

[00161] There is a rich literature pertaining to pharmacological treatments for peripheral neuropathic pain as an existing condition, summarized in a number of thorough reviews. This

abundant literature is largely due to the fact that neuropathic pain is a particularly debilitating type of chronic pain, yet it remains refractory to medical treatment in a large number of patients. However, despite this huge medical need, there is little information or drive with regard to reducing or preventing the development of peripheral neuropathic pain.

SECONDARY INJURY RESULTING FROM TRAUMA TO THE ENTERIC NERVOUS SYSTEM

[00162] The enteric nervous system is the interconnected network of neurones and glial cells intrinsic to the gastrointestinal tract. It is organized into ganglia located in two major nerve plexuses, Auerbach's myenteric plexus, in the muscularis propria, and Meissner's submucosal plexus, in the submucosal layer. Gut tissue is generally organized into layers, including the luminal mucosal layer, containing epithelium, lamina propria and muscularis mucosa. Next to this is the submucosa, then the muscularis propria and the outermost serosa or adventitia. Within the muscularis propria are also the layers of circular muscle and longitudinal muscle.

[00163] Cells of the enteric nervous system include neurones, progenitor cells, glial cells and the interstitial cells of Cajal that act as pacemaker cells. These are supported by the endothelial cells of the vasculature and circulating hormones. Function, survival and proliferation of cells of the enteric nervous system are regulated by a complex number of processes similar to those regulating nerve cells, neural support cells and neural support tissues elsewhere in the peripheral and central nervous systems, including neurotransmitter systems, secondary processes and intracellular mediators. Nerve cells also exist in a symbiotic relationship with local mast cells mediated largely by substance P.

[00164] The enteric nervous system is largely known for its control of coordinated smooth muscle contractile activity in the gut. However, it is also involved in regulation of the exchange of fluids across the mucosal layer, blood flow and secretion of gut hormones as well as regulation of the local inflammatory response. The enteric nervous system is capable of intrinsic activity, independent of control or regulation by other neurones. However, it also receives innervation from sympathetic and parasympathetic nerves of the autonomic nervous system. Sensory nerves are also found within the enteric nervous system, which convey information to spinal autonomic and sensory relay neurones.

Pathophysiology of injury from enteric nervous system trauma

[00165] The enteric nervous system is vulnerable to trauma, including ischemia, chemical and inflammatory trauma, physical trauma such as puncture wounds, parasitic and amoeboid infection, and radiation, among other types of neurotrauma. Many of the adverse health conditions and disability that result from enteric nervous system injury are due to secondary injury processes. Chemotherapy and radiation therapy can lead to dysfunction and even cell death of neurons in the gastrointestinal tract. Bariatric surgery is associated with a number of

neurological complications attributed to effector mechanisms besides changes in nutritional state, and may be associated with peripheral neuropathy, myelopathy, radiculoneuropathy and even encephalopathy. Many types of parasitic and amoeboid infiltrations, including salmonella, rotavirus, and many other bacterial, viral, and protozoan organisms, selectively produce neurotoxicity to enteric neurone cells, neural support cells and neural support tissues.

[00166] Pathologies of the enteric nervous system are reported to lead to spreading pathology to other parts of the gastrointestinal system through secondary injury neurodegenerative processes and mechanisms, including excitotoxicity from excitatory amino acid transmitter release.

[00167] Via similar processes, pathologies of the enteric nervous system are linked to central nervous system pathologies, as a multisystem interactive network involving chemical triggers, such that there is a high incidence of enteric neuropathies in people with Parkinson's disease and people with multiple sclerosis and it has been suggested that enteric pathologies are linked in a causative way more broadly to neurodegenerative diseases.

[00168] Pathologies of the enteric nervous system are also linked to other tissues of the body. For example, severe burn injury to the skin causes damage to gut tissue and increases intestinal permeability. *Campylobacter jejuni* infection can lead to a number of neurally-mediated gastrointestinal disorders such as inflammatory bowel disease, and irritable bowel syndrome, as well as systemic disorders, including Guillain Barré Syndrome, and reactive arthritis. Diverticular disease has also been traced to enteric neuropathology, as have intestinal motility abnormalities in diabetic patients.

Standard treatment following enteric nervous system trauma

[00169] Current standard treatments of gastrointestinal disorders typically do not include neuroprotective actions. Rather, current immediate steps of standard practice consist largely of stabilization of the victim. For example, treatment of acute radiation injury to the gastrointestinal tract largely consists of administration of fluids, anti-emetics, anti-diarrheal medications, antibiotics, blood transfusions, analgesics, and nutritional supplements, and in some cases transfusion of blood and platelets (Macvittie *et al.*, 2012). It has even been suggested that in the case of extreme radiation exposure medical management of immediate symptoms, such as administration of fluids, antibiotics, blood transfusions, analgesics and drugs to reduce diarrhea, is the only treatment administered (Farese *et al.*, 2012). There is little attention given to or even recognition of the importance of preventing damage or injury to nerve cells, neural support cells or neural support tissues in the enteric nervous system.

New approaches to minimize secondary injury resulting from enteric nervous system trauma

[00170] Animal studies have demonstrated promising data that neuroprotection from trauma to the enteric nervous system is possible, although these studies have not resulted in any

effective treatments for neurotrauma to enteric nerve cells, neural support cells or neural support tissues in humans (Gulbransen *et al.*, 2012). Some avenues to explore for protection from trauma include neuroprotective effects in the enteric nervous system of transmitters and other signal mediators (Voss *et al.*, 2012), the flavonoid antioxidant, quercetin, has been reported to have beneficial effects on the enteric nervous system in an animal model of diabetes (Lopez *et al.*, 2012) and other intrinsic factors implicated in central nervous system protection (Gulbransen *et al.*, 2012), probiotic *Lactobacillus acidophilus* and/or prebiotic inulin as well as other extrinsic factors have also been reported to have neuroprotective effects on the enteric nervous system. Cysteine protease inhibition has been reported to show effectiveness against this cytotoxicity in some cases.

[00171] Other avenues to explore in preventing trauma-induced damage or injury to nerve cells, neural support cells and neural support tissues in the enteric nervous system is through neurotrophic restorative processes, rather than neuroprotective mechanisms involved in degenerative processes, including growth factors and neurotrophic factors (Steinkamp *et al.*, 2012). Evidence also supports the involvement of glial factors in gut neuroprotection and this may be attributed to intrinsic neurotrophic factors in the gut (Abdo *et al.*, 2012).

[00172] In accordance with these and other objects, the present invention provides many embodiments of its formulations, methods, procedures and means for treating any neuropathological condition that is the result of, or incident to, at least partially, of trauma of any kind. The present formulations, methods and procedures advantageously affect cellular and tissue function, such as endogenous processes or biosynthetic and metabolic process pathways that govern, regulate or influence the health or function of nerves or nerve cells, or cells upon which nerves or nerve cells depend to maintain health and function. As an aspect of the presently disclosed technology, the formulations are preferably in forms and a dosages with respect to each of the respective components such that any of the formulations are adapted and arranged for administration to a mammal in need thereof, such that the development, or the risk of development, of neuropathology is reduced, lessened, attenuated or prevented.

SUMMARY OF THE INVENTION

Overview of the Invention

[00173] The presently disclosed many embodiments of the invention include formulations, methods, procedures and means for treating any neuropathological condition that is caused, at least partially, by trauma of any kind and involves endogenous processes or biosynthetic and metabolic pathways that govern, regulate or influence the health or function of nerves or nerve cells, or cells or tissues upon which nerves or nerve cells depend to maintain health and

function. Conditions of trauma are known to activate or trigger such processes and pathways that protect or restore health of nerves and nerve cells, as well as such processes and pathways that lead to loss of function, further damage and even cell death of nerves, nerve cells, neural support cells and neural support tissues. It is the balance of these restorative versus degenerative processes and pathways that governs and determines disability outcome.

[00174] Of the many variations and permutations of the multiple component formulations of the invention are two-component formulations. Included in the many two-component formulations of the invention are formulations adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulations comprising two biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compound. Such formulations comprise a pharmaceutically effective amount of: A. at least one biologically active compound from the group comprising anticonvulsants and antiepileptics; and B. at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids; and wherein the formulation is in a form and a dosage with respect to each of its components such that it is adapted and arranged for administration to a mammal in need thereof, such that the development, or the risk of development, of neuropathology and neurodegeneration is reduced, lessened, attenuated or prevented.

[00175] In some preferred embodiments, the component chosen from the group of anticonvulsants and antiepileptics is at least one form of gabapentin, and the component chosen from the group comprising neurosteroids and neuroactive steroids is at least one form of progesterone or synthetic progestin.

[00176] Particular compounds that comprise the formulation embodiments are any two of an anticonvulsant/antiepileptic/antiepileptic and a neurosteroid/neuroactive steroid or an analog, and these may be administered to or given to a subject in need in any combination or sequence. In some preferred embodiments of the invention the anticonvulsant/antiepileptic can be gabapentin and the neurosteroid/neuroactive steroid can be progesterone or synthetic progestin.

[00177] As one of ordinary skill in the art will comprehend, appropriate dosages of compounds according to the various embodiments of the invention can vary widely depending, inter alia, upon the type of trauma or condition to be treated, the route of treatment, the subject mammal, the sequelae of mechanisms and processes to be controlled, the compounds involved, the number of biologically active compounds involved, and the like. In a similar manner, dosage ranges can vary greatly. For example in two-drug formulations, between 10 nanograms and 60 grams of each of the biologically active components per kilogram of body weight of the individual mammal. Thus, some typical

ranges for the amount of gabapentin would, for example, include 5 to 9,600 mg as an acceptable range, 50 to 4,800 mg as a preferable range, 100 to 2,400 mg as a more preferable range and 200 to 600 mg as a most preferable range. Some typical ranges for the amount of progesterone or synthetic progestin would, for example, include 0.05 to 1,200 mg as an acceptable range, 5 to 600 mg as a preferable range, 50 to 450 mg as a more preferable range and 100 to 300 mg as a most preferable range. As a person of skill in the art will understand, respective dosages would be arranged and adapted depending on the need, the individual, the severity of the trauma, the response to administration of the formulation, the time to treatment before or after a traumatic event, the situation, whether in the field or in a hospital, and the like.

[00178] Of the many variations and permutations of the multiple component formulations of the invention are three-component formulations. Included in the many three-component formulations of the invention are formulations adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulations comprising three biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with two other biologically active compounds of the formulation. Such formulations comprise a pharmaceutically effective amount of: A. at least one biologically active compound from the group comprising anticonvulsants and antiepileptics; B. at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids; and C. at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds; and wherein the formulation is in a form and a dosage with respect to each of its components such that it is adapted and arranged for administration to a mammal in need thereof, such that the development, or the risk of development, of neuropathology and neurodegeneration is reduced, lessened, attenuated or prevented.

[00179] In some preferred embodiments, the component chosen from the group of anticonvulsants and antiepileptics is at least one form of gabapentin, the component chosen from the group comprising neurosteroids and neuroactive steroids is at least one form of progesterone or synthetic progestin and the component chosen from the group comprising lithium-containing and lithium-related compounds is lithium carbonate.

[00180] Particular compounds that comprise the formulation embodiments are any three of an anticonvulsant/antiepileptic/antiepileptic, a neurosteroid/neuroactive steroid and a lithium-containing/lithium-related compound or an analog, and these may be administered to or given to a subject in need in any combination or sequence. In some preferred embodiments of the invention the anticonvulsant/antiepileptic can be gabapentin, the neurosteroid/neuroactive steroid can be progesterone or synthetic progestin and the lithium-containing/lithium-related

compound is lithium carbonate.

[00181] As one of ordinary skill in the art will comprehend, appropriate dosages of compounds according to the various embodiments of the invention can vary widely depending, inter alia, upon the type of trauma or condition to be treated, the route of treatment, the subject mammal, the sequelae of mechanisms and processes to be controlled, the compounds involved, the number of biologically active compounds involved, and the like. In a similar manner, dosage ranges can vary greatly. For example in three-drug formulations, between 10 nanograms and 60 grams of each of the biologically active components per kilogram of body weight of the individual mammal. Thus, some typical ranges for the amount of gabapentin would, for example, include 5 to 9,600 mg as an acceptable range, 50 to 4,800 mg as a preferable range, 100 to 2,400 mg as a more preferable range and 200 to 600 mg as a most preferable range. Some typical ranges for the amount of progesterone or synthetic progestin would, for example, include 0.05 to 1,200 mg as an acceptable range, 5 to 600 mg as a preferable range, 50 to 450 mg as a more preferable range and 100 to 300 mg as a most preferable range. Some typical ranges for the amount of lithium, for example lithium carbonate, would, for example, include 0.5 to 3,600 mg as an acceptable range, 30 to 1,800 mg as a preferable range, 100 to 900 mg as a more preferable range and 200 to 600 mg as a most preferable range. As a person of skill in the art will understand, respective dosages would be arranged and adapted depending on the need, the individual, the severity of the trauma, the response to administration of the formulation, the time to treatment before or after a traumatic event, the situation, whether in the field or in a hospital, and the like.

[00182] Of the many variations and permutations of the multiple component formulations of the invention are four-component formulations. Included in the many four-component formulations of the invention are formulations adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulations comprising four biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with three other biologically active compounds of the formulation. Such formulations comprise a pharmaceutically effective amount of: A. at least one biologically active compound from the group comprising anticonvulsants and antiepileptics; B. at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids; C. at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds; and D. at least one biologically active compound from the group comprising NK-1 receptor antagonists; and wherein the formulation is in a form and a dosage with respect to each of its components such that it is adapted and arranged for administration to a mammal in need thereof, such that the

development, or the risk of development, of neuropathology and neurodegeneration is reduced, lessened, attenuated or prevented.

[00183] In some preferred embodiments, the component chosen from the group of anticonvulsants and antiepileptics is at least one form of gabapentin, the component chosen from the group comprising neurosteroids and neuroactive steroids is at least one form of progesterone or synthetic progestin, the component chosen from the group comprising lithium-containing and lithium-related compounds is lithium carbonate and the component chosen from the group comprising NK-1 receptor antagonists is aprepitant.

[00184] Particular compounds that comprise the formulation embodiments are any three of an anticonvulsant/antiepileptic/antiepileptic, a neurosteroid/neuroactive steroid and a lithium-containing/lithium-related compound or an analog, and these may be administered to or given to a subject in need in any combination or sequence. In some preferred embodiments of the invention the anticonvulsant/antiepileptic can be gabapentin, the neurosteroid/neuroactive steroid can be progesterone or synthetic progestin, the lithium-containing/lithium-related compound can be lithium carbonate and the NK-1 receptor antagonist can be aprepitant.

[00185] As one of ordinary skill in the art will comprehend, appropriate dosages of compounds according to the various embodiments of the invention can vary widely depending, inter alia, upon the type of trauma or condition to be treated, the route of treatment, the subject mammal, the sequelae of mechanisms and processes to be controlled, the compounds involved, the number of biologically active compounds involved, and the like. In a similar manner, dosage ranges can vary greatly. For example in four-drug formulations, between 10 nanograms and 60 grams of each of the biologically active components per kilogram of body weight of the individual mammal. Thus, some typical ranges for the amount of gabapentin would, for example, include 5 to 9,600 mg as an acceptable range, 50 to 4,800 mg as a preferable range, 100 to 2,400 mg as a more preferable range and 200 to 600 mg as a most preferable range. Some typical ranges for the amount of progesterone or synthetic progestin would, for example, include 0.05 to 1,200 mg as an acceptable range, 5 to 600 mg as a preferable range, 50 to 450 mg as a more preferable range and 100 to 300 mg as a most preferable range. Some typical ranges for the amount of lithium, for example lithium carbonate, would, for example, include 0.5 to 3,600 mg as an acceptable range, 30 to 1,800 mg as a preferable range, 100 to 900 mg as a more preferable range and 200 to 600 mg as a most preferable range. Some typical ranges for the amount of aprepitant would, for example, include 0.05 to about 750 mg as an acceptable range, 5 to about 375 mg as a preferable range, 20 to about 250 mg as a more preferable range and 40 to about 120 mg as a most preferable range. As a person of skill in the art will understand, respective dosages would be arranged and adapted depending on the need, the individual, the severity of the trauma, the response to administration of the formulation, the time to treatment before or after

a traumatic event, the situation, whether in the field or in a hospital, and the like.

[00186] An analog is a compound that has similar properties and can be a modification of the original drug or enhances the availability of the drug or provides a slow release, a delayed release or a controlled release of the drug for the target but still modifies the pathway similar to the parent compound. As a person having ordinary skill in the art will appreciate, any formulations of compounds that promote or inhibit endogenous processes that are activated by trauma and that are involved in the repair or in the injury to nerves or nerve cells are within the scope of the presently disclosed invention embodiments.

[00187] In the context of the presently disclosed technology the term “formulation” means a combination or mixture of pharmaceutically active or effective chemical entities in respective pharmaceutically effective doses, to create a desired end multi-drug product, in such a form that it can be safely administered to, given to, or taken by, a subject, and may include other ingredients or substances. Examples of such other ingredients or substances include, as examples, but not limited to, excipients, buffers, penetration enhancers, stabilizers, absorption enhancers and carriers.

[00188] Further, chemical entities in the formulations of the presently disclosed technology can include any pro-drug, derivative, metabolite, analog, salt or any other form including natural, standard or slow-, delayed-, sequential- or controlled-release forms.

[00189] Even further, the formulations may be delivered in any form, for example, as a tablet, capsule, pill, spray, solution, paste, cream or any standard way of administering a drug. Formulations may be delivered in any way that controls the release or availability of the formulation.

[00190] Components of the formulations can be given together as a single dose or sequentially in any order as needed or advisable for a particular trauma, a particular condition or to a particular subject, such as a particular human.

[00191] Components of the formulation can be given with respect to time in relation to one or more of the onset of a trauma, in anticipation of a trauma, during a trauma, during a period after a trauma and during a period of recovery from a trauma. Components of the formulation can be provided as an initial dose to a subject in accordance with a timing sequence whereby the timing sequence begins with the onset of trauma or before the onset of a procedure known to produce trauma in some cases.

[00192] In embodiments of the invention utilizing such two or more of compounds, the targets can include any target or targets that activate, enhance or facilitate processes or pathways that promote health and function of nerves and nerve cells, and the targets can include any target or targets that inhibit, attenuate or interfere with processes or pathways that lead to loss of function, injury, damage or death of nerves or nerve cells. Loss of function or injury, damage or cell death can also include that to neural support cells or neural support

tissues. Depending on the specific use and therapeutic context, analogues or modifications to the specific compounds included in embodiments of this invention can be tailored to target specific biological processes or pathways or to facilitate access of compounds to target sites in the central, peripheral or enteric nervous systems.

[00193] Delivery of compounds of embodiments of the invention, and in accordance with the methods and procedures described herein, can be effected in any manner that results in delivery of the compounds of embodiments of the invention such that positive or negative influence on the target pathway is accomplished. For example, the formulations can be administered by one or more routes such as, but not limited to oral, buccal, mucosal, parenteral, rectal, sub-cutaneous, transdermal, topical, intravenous, intrathecal, intravaginal, nasal, nasal inhalation, pulmonary inhalation, iontophoresis through the skin, iontophoresis through mucosal or buccal membranes, dermal patch, epidural, intracranial, intrapharyngeal, sublingual, intra-articular, intramuscular and subcutaneous.

[00194] In the context of invention embodiments, the term "neural support cell" is any cell that supports or could be considered to support the health, normal function, phenotype, gene expression and survival of nerves and nerve cells, and include, as examples but not exclusively, glial cells, microglia, myelin cells, astroglia, oligodendrocytes, satellite cells, Schwann cells, vascular endothelial cells, gastric epithelial cells, interstitial cells of Cajal, and the like.

[00195] In the context of invention embodiments, the term "neural support tissue" is any tissue that supports or could be considered to support the health, normal function, phenotype, normal gene expression or survival of nerves, nerve cells or neural support cells, and include, as examples but not exclusively, the vasculature or microvasculature, particularly the endothelial cells that prevent blood from leaking into nerve tissue and that provide the selective blood-nerve and blood-brain barrier that allows the passage of certain supportive chemicals into nerve tissue as well as the passage of nerve tissue wastes out of nerve tissue, as well as epithelial cells and interstitial cells of Cajal of the gut.

[00196] Preferably the administered compounds selected will facilitate, promote or potentiate restorative responses to trauma, and will interfere with, lessen or inhibit degenerative processes. This can occur, for example, by binding to an enzyme, receptor, allosteric site or other step of an endogenous biochemical or biosynthetic pathway to the extent that such pathway is altered, enabled, allowed or facilitated in its effective functioning, as in the case of restorative processes, or would prevent or lessen its effective functioning, as in the case of degenerative processes.

[00197] The presently disclosed invention and its embodiments are useful for strengthening or improving natural processes that help to restore the health and function of nerves, nerve cells, neural support cells and neural support tissues when compromised by trauma. Further,

the presently disclosed invention embodiments are also useful for lessening, diminishing or inhibiting natural processes that lead to loss of health and function of nerves, nerve cells, neural support cells and neural support tissues when caused by trauma.

[00198] In some embodiments of the invention, mammals, and especially humans, are suitable subjects. Of course, other mammals, such as cows, horses, cats, dogs, sheep, pigs and rodents, are suitable subjects for the presently disclosed invention embodiments.

[00199] The presently disclosed technology includes formulations, methods, procedures and combinations thereof directed toward reducing or preventing the development, or the risk of development, of neuropathology and neurodegeneration as a result of traumatic injury. Embodiments of the invention address heretofore unmet or unsolved medical needs including brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury, peripheral nerve injury and any other injury that can include or affect nerve cells, neural support cells or neural support tissues.

[00200] These unmet or unsolved medical needs share the common aspect of the potential for life-long adverse health conditions or disability. They also share the commonality of the void in current medical interventions that attempt to reduce or prevent these adverse health conditions or disabilities. These conditions also share common mechanisms of the secondary injury that develops following a primary injury or trauma, common mechanisms that trigger or govern this secondary injury. These conditions also share common possible therapeutic targets for inhibiting or promoting the cascades of mechanisms triggered by the primary injury. During the period that these processes continue appropriate medical treatment can reduce or prevent the neurological deficits that are the sequelae of these secondary injury processes. Due to the progressive nature of this cascades of events in secondary brain injury, these processes are accessible to and available for clinical intervention, and allow the development of new treatments to reduce or prevent the development of secondary brain injury triggered by traumatic events

[00201] As such mechanisms are triggered immediately by trauma, while others temporally downstream or spatially distant in the cascades of biochemical and metabolic pathways are engaged at different times and sites following trauma, it is necessary to administer the components comprising the formulation during the hours, days and in some cases, the weeks and months following trauma, with immediate or earliest possible initiation of treatment of paramount importance for the preventive measures to arrest the degenerative cascades and to promote the restorative cascades, as well as continuation of practice according to need.

[00202] Quite apart from the mechanisms involved in causing secondary injury is the issue of initiation of treatment. In a recent study on post-trauma health care for patients suffering severe traumatic brain injury, the median time to arrival of ambulance staff at the scene of a vehicle accident was 9 minutes (range 2-35 min), while the median time to arrival at a trauma

centre was 6 hours, suggesting that to achieve the earliest intervention to reduce or prevent secondary brain injury, the intervention should be administered by trained personnel at the site of accident or trauma. While the authors state that the effect of prolonged pre-hospital time on outcome from brain injury is unknown, they conclude that in their study patients did not seem to be harmed by a prolonged pre-hospital time; it is noteworthy in this respect that they did not include a long-term follow-up study in their report to support this statement. They did not compare pre-hospital time to functional or disability outcomes months later to substantiate their conclusion. The conclusion from this study is markedly different from the clinical consensus that early treatment reduces mortality after brain injury and the focus of the presently disclosed technology and its embodiments is therefore on a polypharmacy approach to immediate, sequential and timed methods and procedures, administering a formulation of neurotrophic and neuroprotective pharmaceuticals to reduce or prevent the development, or the risk of development, of secondary brain damage that results from trauma

[00203] Evidence indicates that once the secondary damage due to trauma has become entrenched, little can be done therapeutically other than attempts to manage symptoms.

[00204] A different rationale or approach to standard practice is thus justified and is critically needed, which is to intervene immediately in the processes governing, producing or developing secondary damage rather than only seeking later rehabilitation treatment for established symptoms. That is, in view of the evidence that current medical intervention fails to treat adverse health outcomes or disability resulting from brain injury an option of choice becomes developing a medical intervention to prevent the processes that lead to these adverse health outcomes and to promote natural restorative processes.

[00205] Trauma to the nervous system, or neurotrauma, often referred to as “acquired nerve injury,” is a catastrophic injury that imposes a number of negative outcomes that usually inflict one or more adverse health conditions or disabilities on its victims. These adverse health conditions and disabilities frequently place both short-term and long-term burdens on individuals, families, communities, the workplace, the health care system and economies in general. Few or no current practices are directed at attempts to lessen, prevent or ameliorate the effects of trauma on secondary injury. Until the presently disclosed formulations, methods and procedures, no satisfactory methods or pharmaceutical treatments have been successful at preventing or reducing the secondary injury, or neuropathology, associated with trauma and its sequelae.

[00206] The pathological changes, and the mechanisms or processes of secondary injury are shared by brain injury, central nervous system ischemia, spinal cord injury, peripheral nervous system injury and enteric nervous system injury. The many embodiments of the presently disclosed invention are directed at preventing or reducing the development of the sequelae of negative effects and symptoms that incidence studies indicate follow any of these

types of trauma, and that can continue for months or years, or even permanently.

[00207] Parenthetically, in the context of the presently disclosed invention embodiments, prevention does not imply avoidance. Prevention in the context of avoidance would be, as examples, avoiding falls, wearing body armor, wearing seat belts, wearing helmets while bicycling, and the like. Prevention in the context of the presently disclosed invention embodiments is administration of a pharmaceutically effective dose of a formulation of two or more chemical entities, following methods, procedures and practices, with the objective to reduce or prevent secondary injury by inhibiting or interfering with the natural degenerative processes triggered by trauma and to promote recovery and repair by enhancing or promoting the natural restorative processes triggered by this same trauma.

[00208] As a person having ordinary skill in the art will understand, pharmaceutical compositions, methods, procedures and means of administration of the presently disclosed invention are useful for treating or preventing any type of neuropathology such as, but not limited to, those characterized as brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury as described herein. Also included among the many conditions that can be treated or prevented by the pharmaceutical compositions, methods and procedures of the presently disclosed invention are disturbances of any etiology so long as involvement of any process or pathway is involved that can be modified or altered by an anticonvulsant/antiepileptic or neurosteroid/neuroactive steroid, or any analog, derivative or related compound.

[00209] The presently disclosed invention embodiments are based at least in some part upon Applicant's speculation that many of the negative outcomes and disabilities of trauma-induced neuropathology and neurodegeneration can be reduced in severity, or prevented altogether, by appropriate early intervention with one or more of the present methods, procedures and pharmaceutical formulations, especially when continued for a medically beneficial period of time. There are currently rehabilitation practices and interventions to treat or manage the disabilities that have resulted from a trauma to nerve cells and neural support cells once they have been established. Rehabilitation treatment for victims of trauma typically focuses on symptoms that are already established. Such treatment is usually initiated months or even years after a traumatic event, and is usually the result of patient requests for relief of debilitating symptoms that have become permanent. Applicant posits that in these cases long-term symptoms are preventable or can be reduced, if the appropriate medical intervention and procedure is applied and if this intervention is applied at the time when the processes that would culminate in disability are underway. However, immediate or early approaches targeted at the development phase of these outcomes are unknown, few or ineffective.

[00210] Illustrative of the failings of the current "conventional" treatments are those provided at the time of a traumatic event, whereby conventional medical attention focuses on

the treatment of immediate symptoms such as bleeding and maintaining adequate respiration, or to avoid or prevent infection, and do not even recognize the advantages of the present invention. Disadvantageously, currently conventional medical practice does not recognize the advantages of treatment to promote the cascades of restorative processes, as well as to prevent or reduce the cascades of degenerative processes, which result from trauma and that govern the prolonged or permanent adverse health conditions and disability that can and often do result from trauma. It is this latter treatment modality, i.e., effecting treatment to prevent or reduce damage from the secondary sequelae, that the presently disclosed technology is directed.

[00211] In the context of the presently disclosed invention embodiments prevention does not imply avoidance. Prevention in the context of avoidance would be, as examples, avoiding falls, wearing body armor, wearing seat belts, wearing helmets while bicycling, and the like. Prevention in the context of the presently disclosed invention embodiments is administration of a pharmaceutically effective dose of a formulation of two or more chemical entities, following methods, procedures and practices with the objective to reduce or prevent secondary injury by inhibiting or interfering with the natural degenerative processes triggered by trauma and to promote recovery and repair by enhancing or promoting the natural restorative processes triggered by this same trauma. Prevention in the context of the presently disclosed invention embodiments is inhibition of neurodegeneration processes and promotion of restorative processes.

[00212] There is an additional aspect, or advantage, of the present invention. For example, as trauma to the brain is known to increase the risk of the later development of some degenerative disorders, the presently disclosed technology is also directed at reducing or preventing the risk of longer-term neurodegeneration. Head trauma is a medically known risk factor for Parkinson's disease; stroke is a medically known risk factor for Alzheimer's disease. Further, slow degenerative disease is suspected in many athletes who have undergone multiple head traumas, such as in football, hockey and boxing; this manifests as mood swings, depression and forgetfulness that develop in athletes years after retirement from a sport, and also include Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, subacute posttraumatic ascending myelopathy and the like. Applicant posits that these manifestations of head trauma can be prevented or reduced by application or practice of the presently disclosed technology. Some victims of head trauma or repeated concussions or minor head injuries are driven to suicide. Applicant posits that at least some of these suicides may be prevented by application or practice of the presently disclosed technology, according to the methods and practices described herein.

[00213] Another striking example of progressive or developing neurodegeneration includes posttraumatic stress disorder that develops in soldiers weeks or even months after serving

active duty. In 2012 more US soldiers died from suicide than were killed in combat in Afghanistan: 349 died from suicide, 295 died in combat. Applicant posits as well that at least some suicides in soldiers may be prevented by application or practice of the presently disclosed technology, according to the methods and practices described herein.

Objects and Description of the Invention

[00214] It is therefore an object of the invention to provide formulations adapted and arranged for accomplishing one or more of preventing, ameliorating, lessening or eliminating the damages incident to many kinds and types of trauma to mammals, and especially to human beings.

[00215] It is another object of the invention to provide methods and means for administering formulations of the invention to accomplish these same goals and effects.

[00216] It is also an object of the invention to provide methods and means combined with formulations to be administered with respect to the time of the trauma, including beforehand, during, immediately afterward, and in a sustained manner for hours, days, weeks or months thereafter.

[00217] In accordance with these and other objects, formulations of the invention are adapted and provided for the prevention of the development of neuropathology and neurodegeneration, and for the amelioration of the effects caused by trauma to a subject, the formulation comprising two biologically active compounds. Preferably, the two biologically active compounds are provided in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compound. In some preferred embodiments of the invention, the two compounds comprise a pharmaceutically effective amount of A) at least one biologically active compound selected from the group comprising anticonvulsant and antiepileptics, wherein the anticonvulsant/antiepileptic is at least one form of gabapentin; B) at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, wherein the neurosteroid/neuroactive steroidal agent is at least one form of progesterone or synthetic progestin

[00218] In accordance with these and other objects, formulations of the invention are adapted and provided for the prevention of the development of neuropathology and neurodegeneration, and for the amelioration of the effects caused by trauma to a subject, the formulation comprising two or three biologically active compounds. Preferably, the two or three biologically active compounds are provided in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compounds. In some preferred embodiments of the invention, the three compounds comprise a pharmaceutically effective amount of A) at least one biologically

active compound selected from the group comprising anticonvulsant and antiepileptics, wherein the anticonvulsant/antiepileptic is at least one form of one or more of gabapentin; B) at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, wherein the neurosteroid/neuroactive steroidal agent is at least one form of one or more selected from the group comprising progesterone or synthetic progestin; C) at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds, wherein the lithium-containing/ lithium-related compound is at least one form of one or more of lithium carbonate.

[00219] Advantageously, the formulations of the invention are provided in a form and a dosage with respect to each of the formulations' components or compounds such that a formulation of the invention is adapted and arranged for administration to a mammal in need thereof, such as a human, so that the development, or the risk of development, of neuropathology and neurodegeneration is reduced, lessened, attenuated or prevented. The formulations and methods of the invention are particularly useful in the treatment of human beings.

Particular Embodiments

[00220] In accordance with these and other objects, the present invention provides many embodiments of its formulations, methods, procedures and means for treating any neuropathological condition that is the result of, or incident to, at least partially, trauma of any kind. The present formulations, methods and procedures advantageously affect cellular and tissue function, such as endogenous processes or biosynthetic and metabolic process pathways that govern, regulate or influence the health or function of nerves or nerve cells, or cells upon which nerves or nerve cells depend to maintain health and function. As an aspect of the presently disclosed technology, the formulations are preferably in forms and at dosages with respect to each of the respective components such that any of the formulations are adapted and arranged for administration to a mammal in need thereof, such that the development, or the risk of development, of neuropathology and neurodegeneration is reduced, lessened, attenuated or prevented.

[00221] In general, the presently disclosed technology comprises formulations adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulation comprising biologically active compounds from **three** groups of compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other two biologically active compounds.

[00222] In accordance with a key aspect of **three**-component embodiments of the invention, the formulation comprises, or consists essentially of, a pharmaceutically effective amount of

at least one biologically active compound from three groups of compounds. These three groups are A) anticonvulsants and antiepileptics, B) neurosteroids and neuroactive steroids, and C) lithium-containing and lithium-related compounds.

[00223] A formulation of the invention comprises, or consists essentially of, a pharmaceutically effective amount of at least one compound from the group consisting of anticonvulsants and antiepileptics, a pharmaceutically effective amount of at least one biologically active compound from the group consisting of neurosteroids and neuroactive steroids, and a pharmaceutically effective amount of at least one biologically active compound from the group consisting of lithium-containing and lithium-related compounds.

[00224] In accordance with other aspects of the invention, formulations of the invention are adapted for delivery to a mammal in need thereof with whatever delivery component, components or systems which are necessary to effect such delivery. Such components or systems include things such as excipients, buffers, penetration enhancers, stabilizers, absorption enhancers binders, coatings, transport enhancers, chelators, carriers, clearance modifiers, emulsifying agents, antioxidants, preservatives, sugars, salts, cellulose, dyes, flavoring agents and any other inactive ingredients that are considered generally recognized as safe.

[00225] The present invention is thus adapted and arranged to facilitate the treatment of cells, tissues, organs and combinations thereof that are affected or caused by trauma.

[00226] Formulations of the invention can thus be adapted and arranged to be directed toward any target or targets that activate, enhance or facilitate processes or pathways that promote health and function of nerves and nerve cells or that inhibit, attenuate or interfere with processes or pathways that lead to loss of function, injury, damage or death of nerves or nerve cells. Loss of function or injury, damage or cell death can also include the effects of trauma to nerve cells, neural support cells or neural support tissues.

[00227] In general, the presently disclosed technology comprises formulations, methods and procedures for administering to a mammal in need thereof, a therapeutically effective amount of three biologically active compounds which can be targeted to enhance or facilitate processes or pathways that promote health and function of nerves and nerve cells or that inhibit, attenuate or interfere with processes or pathways that lead to loss of function, injury, damage or death of nerves or nerve cells. Targeted functions can also be those that include loss of function, injury, and damage or cell death including that to nerve cells, neural support cells or neural support tissues.

[00228] In general, the presently disclosed technology comprises a two-component formulation adapted for the prevention of the development of neuropathology or neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulation comprising two biologically active compounds in amounts that are

pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compound, the formulation comprising at least one biologically active compound from the group comprising anticonvulsants and antiepileptics, wherein the anticonvulsant or antiepileptic is at least one form of gabapentin and at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, wherein the neurosteroid or neuroactive steroid is at least one form of progesterone or synthetic progestin.

[00229] In general, the presently disclosed technology comprises a three-component formulation adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulation comprising three biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other two biologically active compounds, the formulation comprising at least one biologically active compound from the group comprising anticonvulsants and antiepileptics, wherein the anticonvulsant or antiepileptic is at least one form of gabapentin, at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, wherein the neurosteroid or neuroactive steroid is at least one form of progesterone or synthetic progestin, and at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds wherein the lithium-containing or lithium-related compound is at least one form of lithium carbonate.

[00230] Many dosages, dosage ranges and combinations of the essential two components of the present formulations are within the scope of the invention. As one of many preferred embodiments, in a formulation of the invention, the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg.

[00231] Alternatively, in the formulation the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg. As a further alternative, in the formulation the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg.

[00232] In yet another preferred embodiment, some formulations of the invention include wherein the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg.

[00233] The present invention also includes methods, procedures and means which are adapted and arranged to utilize two-component formulations for one or more of preventing,

reducing the effects of, or reducing the risk of development of, neuropathology and neurodegeneration incident to trauma. In one significant aspect, a preferred method or procedure of the invention comprises the steps or actions of A) providing a formulation adapted for the prevention of the development of neuropathology, wherein the formulation comprises two biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compound, the two compounds respectively comprising i) a pharmaceutically effective amount of at least one biologically active compound from the group comprising anticonvulsants and antiepileptic drugs, and ii) a pharmaceutically effective amount of at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids; and then B) administering the formulation to a mammal in need thereof.

[00234] In a yet more specific embodiment, another preferred method or procedure of the invention comprises the steps or actions of A) providing a formulation adapted for the prevention of the development of neuropathology, wherein the formulation comprises two biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other biologically active compound, the two compounds respectively comprising i) a pharmaceutically effective amount of at least one biologically active compound from the group comprising anticonvulsants and antiepileptic drugs wherein the anticonvulsant/antiepileptic drug is gabapentin and ii) at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids wherein the neurosteroid or neuroactive steroid is progesterone; and then B) administering the formulation to a mammal in need thereof.

[00235] In the presently disclosed technology, administration in accordance with the present methods and procedures includes that for delivering a two-component formulation wherein the at least one anticonvulsant/antiepileptic is gabapentin and the at least one neurosteroid/neuroactive steroid is progesterone or synthetic progestin.

[00236] In the context of a preferred method or procedure of the present invention utilized to effect the administration of one of the two-component formulations, the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg.

[00237] In a similar context for a method or procedure for administration of a formulation of the invention, the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg. Even further, for administration of the formulation, the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to

about 450 mg.

[00238] Yet even further, for a method or procedure for administration of one of the present two-component formulations, the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg and the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg.

[00239] Many dosages, dosage ranges and combinations of the essential three components of the present formulations are within the scope of the invention. As one of many preferred embodiments, in a formulation of the invention, the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, and the lithium carbonate is provided in a dosage range of from about 0.5 mg to about 3,600 mg.

[00240] Alternatively, in the formulation the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg, and the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg. As a further alternative, in the formulation the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg, and the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg.

[00241] In yet another preferred embodiment, some formulations of the invention include wherein the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg, and the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.

[00242] The present invention also includes methods, procedures and means which are adapted and arranged to utilize three-component formulations for one or more of preventing, reducing the effects of, or reducing the risk of development of, neuropathology and neurodegeneration incident to trauma. In one significant aspect, a preferred method or procedure of the invention comprises the steps or actions of A) providing a formulation adapted for the prevention of the development of neuropathology and neurodegeneration, wherein the formulation comprises three biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other two biologically active compounds, the three compounds respectively comprising i) a pharmaceutically effective amount of at least one biologically active compound from the group comprising anticonvulsants and antiepileptic drugs, ii) a pharmaceutically effective amount of at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, and iii) at least one biologically

active compound from the group comprising lithium-containing and lithium-related drugs; and then B) administering the formulation to a mammal in need thereof.

[00243] In a more specific embodiment, another preferred method or procedure of the invention comprises the steps or actions of A) providing a formulation adapted for the prevention of the development of neuropathology and neurodegeneration, wherein the formulation comprises three biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other two biologically active compounds, the three compounds respectively comprising i) a pharmaceutically effective amount of at least one biologically active compound from the group comprising anticonvulsants and antiepileptic drugs wherein the anticonvulsant/antiepileptic drug is gabapentin, ii) at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids wherein the neurosteroid or neuroactive steroid is progesterone, and iii) at least one biologically active compound from the group comprising lithium-containing and lithium-related drugs wherein the lithium-containing or lithium-related drug is lithium carbonate; and then B) administering the formulation to a mammal in need thereof.

[00244] In the presently disclosed technology, administration in accordance with the present methods and procedures includes that for delivering a three-component formulation wherein the at least one anticonvulsant/antiepileptic is gabapentin, the at least one neurosteroid/neuroactive steroid is progesterone or synthetic progestin, and the at least one biologically lithium-containing/lithium-related compound is lithium carbonate.

[00245] In the context of a preferred method or procedure of the present invention utilized to effect the administration of one of the three-component formulations, the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, and the lithium carbonate is provided in a dosage range of from about 0.5 to about 3,600 mg.

[00246] In a similar context for a method or procedure for administration of a formulation of the invention, the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg, and the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg. Even further, for administration of the formulation, the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg, and the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg.

[00247] Yet even further, for a method or procedure for administration of one of the present three-component formulations, the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg, the progesterone or synthetic progestin is provided in a dosage

range of from about 100 mg to about 300 mg, and the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.

[00248] In general, the present invention comprises four-component formulations, methods and procedures adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulation comprising biologically active compounds from four groups in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other three biologically active compounds.

[00249] In accordance with a key aspect of a four-component embodiment of the invention, the formulation to be delivered by a method or procedure of the present technology comprises, or consists essentially of, a pharmaceutically effective amount of at least one biologically active compound selected from four groups of compounds. These four groups are A) anti-convulsants and antiepileptics, B) neurosteroids and neuroactive steroids, C) lithium-containing and lithium-related compounds, and D) a pharmaceutically effective amount of at least one biologically active compound from the group comprising substance P receptor (NK-1 receptor) antagonists. Thus, a formulation of the invention comprises, or consists essentially of, a pharmaceutically effective amount of at least one compound from the group consisting of anticonvulsants and antiepileptics, a pharmaceutically effective amount of at least one biologically active compound from the group consisting of neurosteroids and neuroactive steroids, a pharmaceutically effective amount of at least one biologically active compound from the group consisting of lithium-containing and lithium-related compounds, and a pharmaceutically effective amount of at least one biologically active compound from the group comprising substance P receptor (NK-1 receptor) antagonists.

[00250] In accordance with other aspects of the invention, formulations of the invention are adapted for delivery to a mammal in need thereof by way of methods and procedures of the invention with whatever delivery component, components or systems that are necessary to effect such delivery. Such components or systems include compounds or things such as excipients, buffers, penetration enhancers, stabilizers, absorption enhancers binders, coatings, transport enhancers, chelators, carriers, clearance modifiers, emulsifying agents, antioxidants, preservatives, sugars, salts, cellulose, dyes, flavoring agents and any other inactive ingredients that are considered generally recognized as safe. The present invention is thus adapted and arranged to facilitate the treatment of cells, tissues, organs and combinations thereof which are affected by neurotrauma. Formulations of the invention can thus be adapted and arranged to be directed toward any cellular, tissue or system target or targets that activate, enhance or facilitate processes or pathways that promote health and function of nerves and nerve cells or that inhibit, attenuate or interfere with processes or pathways that lead to loss of function, injury, damage or death of nerves or nerve cells. Loss of function or injury, damage

or cell death can also include the effects of trauma to neural support cells or neural support tissues.

[00251] In its many preferred four-component embodiments, the present invention comprises formulations adapted for the prevention of the development of neuropathology and neurodegeneration, or for the amelioration of the effects caused by trauma to a subject, the formulation comprising four biologically active compounds from four respective groups of compounds, in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other three biologically active compounds. Four-component formulations of the invention comprise at least one biologically active compound from the group comprising anticonvulsants and antiepileptics, wherein the anticonvulsant or antiepileptic is at least one form of gabapentin, at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, wherein the neurosteroid or neuroactive steroid is at least one form of progesterone or synthetic progestin, at least one biologically active compound from the group comprising NK-1 receptor antagonists wherein the NK-1 receptor antagonist is aprepitant, and at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds wherein the lithium-containing or lithium-related compound is at least one form of lithium carbonate.

[00252] Many dosages, dosage ranges and combinations of the essential four components of the present four-component formulations are within the scope of the invention. As one of many preferred embodiments, in a four-component formulation of the invention, the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, the aprepitant is provided in a dosage range of from about 0.05 to about 750 mg, and the lithium carbonate is provided in a dosage range of from about 0.5 mg to about 3,600 mg.

[00253] In another preferred embodiment of a four-component formulation for use with the methods and procedures of the invention, gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg, aprepitant is provided in a dosage range of from about 5 to about 375 mg, and lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg. As a further alternative preferred embodiment of the present methods and procedures, a four-component formulation consists essentially of gabapentin provided in a dosage range of from about 100 mg to about 2,400 mg, progesterone or synthetic progestin provided in a dosage range of from about 50 mg to about 450 mg, aprepitant provided in a dosage range of from about 20 to about 250 mg, and lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg.

[00254] As yet another preferred embodiment of the present four-component methods and

procedures, a formulation for use in the methods and procedures of the invention consists essentially of gabapentin provided in a dosage range of from about 200 mg to about 600 mg, progesterone or synthetic progestin provided in a dosage range of from about 100 mg to about 300 mg, aprepitant provided in a dosage range of from about 40 to about 120 mg, and lithium carbonate provided in a dosage range of from about 200 mg to about 600 mg.

[00255] Depending on the specific use and therapeutic context, analogues or modifications to the specific compounds included in embodiments of this invention can be tailored to target specific cells, tissues, organs, biological processes or pathways or to facilitate access of compounds to target sites in the central, peripheral or enteric nervous systems.

[00256] In accordance with yet other objects of the invention, a formulation of the invention may comprise a single dosage unit, or may be administered a plurality of times in a sequence, and to further achieve its objects, the formulation may be administered to a subject one or more dosage units per day. The present formulations, methods procedures and means are of the invention, the formulation is given to a subject mammal in need, wherein the subject is human.

[00257] As will be understood by one of ordinary skill in the art without undue experimentation, compounds in the formulations may be in the form of one or more of salts, prodrugs, hydrates, derivatives or metabolites of the compound itself, analogs, homologs, compounds acting on or through mechanisms that compounds can act on or through or compounds that modify, modulate or affect in any way pathways or processes affected by compounds or formulations of the invention.

[00258] One or more of the compounds in the formulation may be in a controlled release or slow release form, and formulations of the invention may be adapted and arranged to be administered as one or more sustaining doses. As yet another advantageous characteristic, formulations of the invention may be adapted and arranged to be administered before, during, or after a traumatic event or in anticipation of a possible traumatic event.

[00259] Also in accordance with the present invention, administration of the formulation to a mammal in need thereof can be effected with respect to time in order to advantageously intervene with negative processes or events triggered by the trauma, or in order to stimulate processes or events useful in correcting or ameliorating the damage triggered by the trauma. This timing can thus be in relation to one or more of i.) the onset of the trauma, ii.) in anticipation of a possible or potential trauma, iii.) during the trauma, and iv.) during a period of recovery from the trauma.

[00260] In one preferred embodiment, the presently disclosed formulations are first administered within two hours after the traumatic event. In alternative embodiments, the present formulations are first administered within 24 hours after the trauma. In yet another preferred embodiment, the presently disclosed formulations are first administered

preventively or prophylactically within 6 hours before the expected onset or the expected end of the trauma.

[00261] Moreover, formulations of the invention can be administered additionally one, or a plurality of, times after the formulation is first administered. In a similar manner, the present formulations can be administered one, or a plurality of times as a sustaining dose as needed.

Particular Advantages of Invention Embodiments

[00262] The present disclosed technology presents and illustrates at least four particular advantageous aspects of the invention embodiments, together comprising formulations, methods and procedures for reducing or preventing the development or the risk of development of neuropathology and neurodegeneration as a result of traumatic injury.

[00263] One particular advantageous aspect of embodiments of the invention includes the formulations of the presently disclosed technology, which formulations comprise two or more pharmaceutical compounds from four families of chemical compounds, administered together or sequentially at clinically effective doses. In general, each chemical compound, or entity, in the formulation is theorized to target a different biological process or different biological processes that is or are involved in governing the degree of secondary injury that follows a primary traumatic injury. Alternatively stated, some components of the formulations are directed at optimizing or facilitating the restorative processes that follow, or are triggered by, a primary traumatic injury. Some components of the formulation are directed at minimizing or inhibiting the degenerative processes that follow or are triggered by a primary traumatic injury. As described herein, restorative processes lead to recovery and, in contrast, degenerative processes lead to tissue damage and cell death. Applicant posits that optimal treatment to prevent or reduce secondary injury is best achieved by a multi-drug approach to include promotion of a number of different restorative processes and in addition inhibition of a number of different degenerative processes. The present disclosed technology and its embodiments are directed at maximizing control of the processes that govern eventual functional outcomes of trauma and neuropathology and neurodegeneration.

[00264] Before the present invention, the particular combinations of compounds described herein that make up or constitute the present formulations were unknown. Evidence of the efficaciousness of single-compound treatments for neurotrauma is spotty or contradictory. Hindsight with respect to the field of neurotrauma hints only generally toward single-component remedies, and not to any particular combination of drugs to possibly be selected from the various categories of pharmaceuticals and myriad permutations possibly selectable from them. Nonetheless, Applicant posits that the formulations, methods and procedures of the presently disclosed invention are effective in reducing or preventing the development of, or the degree of, or the risk of development of, neuropathology and neurodegeneration as a

result of trauma.

[00265] Despite the fact that single compound administrations in the art have had only limited, or no, beneficial effects, Applicant posits that a multi-drug approach that is directed at one or a plurality of restorative and degenerative processes, as is exemplified by the present formulations, may have greater beneficial effects than those deriving from a single-compound approach.

[00266] A second particular advantageous aspect of the invention embodiments is the specific treatment modality, wherein a formulation of the invention is given in temporal relation as a preventive, prophylactic or posttraumatic event treatment. The preventive practice aspects of the present invention is in cases where there is a high risk of trauma to an individual or there is planned entry into a condition, situation or place where such high risk may ensue. Prophylactic practice of the invention is in cases where incidence studies inform a known probability that that a procedure or practice results in neuropathology in a given number of subjects or patients. Posttraumatic event practice of the invention is in cases where a traumatic event has occurred or is occurring. In all cases, the presently disclosed technology is directed at preventing or reducing, or reducing the risk of, such neuropathology and neurodegeneration as a result of trauma.

[00267] A third particular advantageous aspect of the methods and formulations of the invention embodiments is the timing and route of administration, coupling the formulations and the delivery to the means of administering a formulation in a time-effective practice. Timing and route of administration of the formulations thus can be adapted and arranged to accommodate specific and unique conditions, situations, severity and type of trauma, and the status of the subject/recipient. As one example, in the event of unanticipated trauma, which may occur away from a hospital/clinic setting, at-site immediate or earliest possible administration of the formulation can be by nasal administration to provide a fast and effective intervention in an easily and socially acceptable format. Delivery by intranasal administration may also be by nasal spray, or by any effective means and methods effective to address the specific trauma, or class or class of trauma. In the context of an event of an anticipated trauma, for example, one that occurs in a hospital/clinic setting, treatment with a formulation can be intranasal administration but can alternatively be by oral, buccal, intravenous or even intramuscular routes.

[00268] A fourth particular advantageous aspect of the invention embodiments directs the formulations, the methods and the procedures specifically at secondary injury resulting from any and all types of trauma. This aspect of the invention is in contrast to the conventional view that the spectrum of types of trauma to the nervous system is not typically or usually considered as a single medical issue. To illustrate this point, standard emergency or immediate treatment of brain injury and stroke are different and follow different standard

protocols and procedures. However, while the primary trauma may be different, the processes and mechanisms of the secondary injury that can and often do ensue from both conditions are the same. Brain injury and stroke are thought to trigger the same, similar or overlapping restorative mechanisms and, similarly, they both trigger the same, similar or overlapping degenerative mechanisms. Advantageously, treatment by the present means and methods could be the same, similar or overlapping for both stroke and TBI. The present fourth particular advantageous aspect of the invention embodiments is in some respect that the formulations, methods and procedures can be applied universally or broadly for many types of trauma to the nervous system. As examples, practice of the invention is the same, similar or overlapping for metabolic trauma, such as from an epileptic seizure, and for impact or concussion trauma, such as from a penetrating head wound; similarly, trauma from chemotherapy or radiation therapy is believed to trigger the same, similar or overlapping neuropathological processes. Further, trauma is treated with the same practices of the invention whether trauma is to the periphery, to the enteric nervous system or to the central nervous system. Treating trauma-induced neuropathology as a single entity presents the framework, then, for practice of the present invention to fill the gap between standard emergency practice and standard rehabilitation practice, as described herein.

[00269] There is an additional aspect, or advantage, of the presently disclosed invention embodiments. Because trauma to the brain is known to increase the risk of the later development of some degenerative disorders, the presently disclosed technology is also directed at reducing or preventing the risk of longer-term neurodegeneration. To substantiate this point, head trauma is a risk factor for Parkinson's disease; stroke is a risk factor for Alzheimer's disease. As detailed herein, head trauma and stroke trigger the same, similar or overlapping cascades of progressing restorative and degenerative processes that alter the health, function and survival of nerves, nerve cells, neural support cells and neural support tissues, and, as these cascades are shared by trauma of different types the presently disclosed formulations, methods and procedures are useful in reducing risk factors for neurodegenerative diseases such as but not limited to Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, subacute posttraumatic ascending myelopathy and the like.

Addressing The Multiplicity Of Theorized Underlying Processes

[00270] In one aspect, the presently disclosed technology is based particularly on a polypharmacy, or a multi-drug, approach wherein delivery of beneficial chemical entities is given at specific times following or even before trauma. Current conventional approaches to treat trauma-induced neuropathology have heretofore focused exclusively on single drug approaches. Further, current approaches to treat trauma-induced neuropathology have focused

uniquely on either restorative processes or degenerative processes. Even further, there is reticence to initiate clinical trials due to the complexity and cost demanded by treating a number of independent injury factors simultaneously that occur over a prolonged period of time following trauma. Applicant posits that efforts to develop effective therapeutic approaches to minimize negative sequelae of trauma have failed because of failure to accommodate the multiplicity of the events triggered by trauma and a failure to match this multiplicity with appropriate additive or synergistic multi-drug approaches. The presently disclosed technology and its embodiments are directed to address this unsolved need by evidence-based potentially synergistic formulations that promote recovery and restoration and at the same time inhibit or prevent loss of cell function and cell death.

[00271] Applicant posits further that the progressive nature of these cascades of events in secondary injury may inform why conventional attempts to treat such injuries have failed to prevent the long-term adverse health sequelae of trauma-induced neuropathology and neurodegeneration. In contrast to conventional attempts, the present formulations are directed to addressing multiple underlying physiological mechanisms involved in the development of secondary injury triggered by traumatic events.

[00272] Any traumatic injury results in a localized initial direct damage accompanied by impaired regulation of blood flow and metabolism, usually with an ensuing edema swelling. Direct physical damage to nerve cells, neural support cells and neural support tissues can result, for example, from tearing, shearing, stretching or compression of nervous tissue. These events triggered directly by the traumatic event are usually treated clinically by hypothermia and efforts to reduce blood pressure as well as pharmacologically with drugs such as mannitol and barbiturates, largely to decrease mortality. What is not included in standard practice is effort or action to prevent or reduce the secondary injury resulting from the initial trauma even though long-term disability results mainly from secondary in many victims of trauma. Standard immediate treatment of traumatic injury does not typically include steps to reduce or prevent or alter the plethora of secondary injury mechanisms that are triggered within minutes and hours of a traumatic event.

[00273] Some processes of secondary injury are activated immediately by a traumatic event. Some progress over a limited period of time and then return to pre-injury levels, while other processes may continue for days, weeks or months. Some processes are cascades, one step triggering a subsequent step or subsequent steps in a myriad of metabolic and biochemical pathways. It is important to point out that once the initial processes have been completed any medical interventions for the treatment of the persisting adverse outcomes of traumatic injury are largely without benefit. As a result, from the time of a traumatic event there is a closing window of opportunity to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury and that there is a platinum hour, a golden day

and a silver week of opportunity to achieve optimal outcomes.

Secondary Injury As An Unaddressed Crisis

[00274] Unfortunately for those who are victims of trauma-induced neuropathology, standard immediate treatment strategies do not include neuroprotection. Immediate pre-hospital management of trauma focuses on such issues as airway clearance, prevention of hypoxia, hypercapnia and hypotension, as well as rapid transport to a medical center for detailed diagnosis and treatment. Actions to limit or prevent secondary injury to nerves, nerve cells or neural support cells or neural support tissues are absent from standard pre-hospital practice. As one example, in a recent review, while a stated purpose of the report was to focus on limiting secondary brain injury, there was no reference to direct approaches to limit neuropathology and neurodegeneration from secondary injury; in this case secondary brain injury had a different meaning from that used here and the focus was on emergency services without any regard for neuroprotection. Applicant posits that treatment with formulations given at doses shown to be safe for acute administration can be given at-site before complete diagnosis has been carried out. Applicant posits further that in some cases formulations given at doses shown to be safe for acute administration should be given immediately, without waiting for complete diagnosis to be carried out.

[00275] As a further example, in a recent report based on 119 cases of traumatic brain injury to military personnel injured by anti-personnel devices or by vehicle landmines, specific recommendations were made based on the outcomes of various management approaches, including immediate battlefield management as well as subsequent hospital management. There was no recommendation for any action or procedure to provide neuroprotection from secondary brain injury resulting from the trauma. Similarly, recent recommendations for medical management following improvised explosive device accidents did not include any action or procedure to provide neuroprotection from secondary injury.

[00276] Clinical treatment of penetrating brain injury, as yet another example, typically consists of reducing increased intracranial pressure and reducing brain edema through surgical decompression, removal of any foreign bodies, administration of osmotic agents and reducing body temperature. Immediate standard treatment does not include steps to reduce or prevent the developing secondary injury.

[00277] In the case of spinal injury, immediate medical practice includes surgical decompression and stabilization in order to reduce edema and to prevent further primary injury. However, a retrospective observational study concluded that surgical treatment has not resulted in improved hospital mortality or length of stay and a consensus meeting concluded that surgery does not improve neurological outcome. Clearly, current standard practice is not meeting need. With 1200 new cases of spinal cord injury in the US each year, there is an

urgent medical need to minimize the impact of injury on victims, on the healthcare system and on the economy.

[00278] Standard practice for trauma of any type, then, does not include steps or actions to minimize secondary injury. The result in many cases is unnecessary disability. Rehabilitation is the domain for management of disability. Applicant posits that secondary injury can be prevented or reduced. Further, Applicant posits that the incidence and the severity of disability can also be prevented or reduced by including in standard emergency practice application and practice of the presently disclosed technology.

Addressing Unsolved And Unaddressed Needs

[00279] Incidence studies indicate the number of people in a population who will go on to develop disability following trauma of any given type. Until the presently disclosed invention, these numbers have been accepted as being inevitable. There is a general acceptance that disability results from trauma. Applicant believes that this does not need to be the case. Medical attention has not typically been directed at reducing these numbers, especially preventing them altogether. Yet, as described herein much of the disability that ensues as a result of trauma is brought about by processes, largely biochemical, which can be modified by appropriate pharmaceutical intervention. Trauma-induced disability can thus be considered an unsolved need. Applicant posits that the number of people who go on to develop disability following trauma can be reduced. Further, Applicant posits that the severity of disability of those that do develop some level of disability can be reduced. The scope and the spirit of the presently disclosed invention embodiments are directed toward this unsolved need, both by reducing the number of victims of trauma that go on to develop adverse health conditions and disability, as well as by reducing the severity of disability in those who are left with trauma-induced negative or adverse health conditions. In accordance with this and other objects, the presently disclosed technology, in certain specific embodiments, aims to prevent or reduce the development, or the risk of development, of neuropathology that results from traumatic injury.

[00280] Numerous approaches have been taken to understand the variety of different mechanisms of secondary injury in both human and animal studies. With respect to drug therapy the literature contains several reviews of the area in the past few years. However, a consensus in these reviews is that despite at least 20 compounds being tested in over 50 trials by the year 2004, and over 30 phase III prospective clinical trials by 2010, significant endpoints have not been reached by any therapeutic intervention and no effective drug therapy is currently available. This failure can be attributed to a number of causes; even if a drug passes phase III clinical trials, full benefit may be elusive because all drugs currently in clinical trials II and III are monotherapies and do not address the consensus of the thought

leaders in the field that the multiplicity of mechanisms contributing to secondary injury require a polypharmacy, or multi-drug, approach. The critical literature attributes much of the failure to bring effective interventions forward from phase III clinical trials to the fact that most such trials, and their antecedent development strategies, are directed at a single factor or mechanism, despite the awareness of the plurality of the underlying mechanisms.

[00281] Further, mechanisms leading to this injury and its ensuing disability are complex and occur over a period of time extending up to months or even years after the traumatic event. Consensus opinion in the field is that a multi-mechanistic approach is needed, where multiple active compounds are given simultaneously or synchronously over specified respective periods of time. This is in stark contrast to the protocols of current clinical trials; these are based on monotherapies directed at only a limited number of the plethora of mechanisms that govern the severity of neuropathology and thereby the incidence and severity of the disability sequelae.

[00282] Applicant believes that at present, current drug development does not address the pluralities of treatment that are needed and, further, that standard practice that is immediate and even rehabilitation standard practice totally miss the underlying fact that there is a “platinum hour,” a “golden day” and a “silver week,” when the adverse health conditions, and the disability resulting from trauma-induced neuropathology and neurodegeneration, can be reduced or prevented and that a multi-drug approach is needed.

[00283] Unexpectedly, Applicant has recognized the significance of the heretofore unknown possible synergy of selected combinations of compounds that include formulations of two, three or four compounds from the four categories of anticonvulsant/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-containing/lithium-related compounds. These combinations are adapted and arranged, and adaptable and arrangeable, to facilitate, promote or potentiate the restorative processes that lead to neurological recovery, while at the same time lessening, or inhibiting, the degenerative processes that lead to secondary, progressive tissue damage and cell death.

[00284] While the bases for the possible synergistic advantages of the present formulations have been heretofore unknown, as have been the present combinations, the formulations are directed toward modifying both restorative and degenerative processes. Embodiments of the invention are directed with the proposition that improved neurological outcomes that are known to result from trauma can be reduced or prevented, or the risk of such outcomes, can be reduced or prevented by the administration of a formulation of possibly synergistic compounds that combine neurotrophic actions that repair and restore, as well as neuroprotective actions that prevent or reduce degenerative processes that lead to secondary injury or damage.

[00285] Applicant posits that three important issues need to be addressed in order to arrive

at effective medical intervention that will optimally reduce or prevent secondary brain injury resulting from brain or head trauma. One issue is the target or targets at which an intervention is aimed. Optimally, effective therapeutic intervention would promote, facilitate or potentiate restorative or regenerative targets and will also inhibit, lessen or block targets involved in further injury, loss of function and cell death. A second issue is that, given the multiplicity of the biochemical, metabolic and cellular mechanisms causing secondary brain injury, multiple targets need to be included in any effective therapeutic intervention. The third is that, given the temporal dispersal of the cascade of biochemical, metabolic and cellular events, the timing of various components of the intervention is critical, as well as the sequencing of the multiple therapeutic interventions. These three issues are addressed in the presently disclosed technology, which, along with its embodiments, includes evidence-based formulations, methods and procedures to reduce or prevent the development or the risk of development of neuropathology and neurodegeneration as a result of traumatic injury.

[00286] All types of trauma are known to activate secondary injury mechanisms. These secondary injury mechanisms are brought about as the outcome of a balance of restorative and degenerative biochemical and other processes triggered by trauma. The biochemical nature of these processes provides inroads to pharmaceutical intervention that can reduce or even prevent the alteration of function and even the death of nerve cells and their neural support cells and neural support tissues, alterations that can and often do ultimately lead to adverse health conditions or disability. The presently disclosed technology, in its numerous embodiments, is directed to promote these restorative processes and to inhibit these degenerative processes by specific pharmaceutical intervention at appropriate doses, with specific timings and sequences of intervention, using specific routes and modes of delivery.

[00287] Many traumatic events are unexpected and unanticipated such as sports concussions and battlefield injuries to the head. However, in many cases traumatic events can be anticipated, events that can and often do lead to adverse health conditions and disability. For example, clinical and incidence studies provide supportive evidence that as a result of certain procedures or events there is a high incidence of adverse health conditions and disability. A person having ordinary skill in the art will recognize that prophylactic measures can be taken in conditions where there is a high enough probability of neuropathology resulting from a clinical procedure. Further, in situations or conditions where a traumatic event may occur that can lead to damage or injury to nerve cells, to neural support cells or to neural support tissues, that precautionary or preventive measures are warranted, as described herein. The scope of the presently disclosed technology and its embodiments are directed toward both: unanticipated as well as anticipated traumatic injury.

[00288] Some examples are provided to illustrate what is meant as anticipated and unanticipated traumatic events. Minor head injury events are usually unanticipated, and have

been reported to lead to restrictions in lifestyle one year later in 47% of admissions to hospital. Chronic pain caused by surgery varies according to the type of surgery, but continuing pain one year after amputation has been reported in up to 85% of patients. Further, medically induced sensory, motor, autonomic or enteric nerve damage can and often does occur as a result of chemotherapy or radiation therapy. Spinal cord injury is usually unanticipated, and some survivors can be expected to have permanent physical disabilities, reduced independence, serious medical complications and enormous financial burden. Stroke is usually unanticipated, but in view of the fact that an estimated 44 million disability-adjusted life-years are lost by stroke survivors worldwide, many who have had a stroke know that they are at risk of a subsequent stroke or subsequent strokes. Applicant posits that much of the adverse health conditions and disability resulting from these and all traumas are amenable to therapeutic intervention.

[00289] As described herein, each of the chemical entities in a formulation of embodiments of the invention is theorized to target one or more biological processes or mechanisms.

Applicant theorizes that some of these mechanisms may sometimes be involved in governing the incidence and the degree or severity of secondary injury that follows the primary traumatic injury. It is at this secondary injury that the formulations of the invention embodiments are directed. A great amount of investigation regarding individual members of the categories of compounds has produced no efficacious formulations or methods. Indeed, a great amount of research in the field of neuropathology does not support aspects of Applicant's theory regarding the efficacy of particular combinations and dosages of these categories of compounds. This is so especially because, in some cases, administration of single compounds seldom produces adequate benefit, if any, and sometimes causes harm.

[00290] Despite this, Applicant presents novel formulations and methods having utility in treating various types and forms of neuropathology. In some sense, selected literature in the field might support the view that some of the individual compounds discussed herein, such as the neurosteroids/neuroactive steroids and lithium-containing/lithium-containing/lithium-related drugs, would be effective in promoting, facilitating or potentiating restorative processes due to, or resulting from, trauma.

[00291] In a similar sense, selected literature in the field might support the view that some anticonvulsant/antiepileptics and some lithium-containing/-lithium-containing/lithium-related drugs, might act to minimize or inhibit degenerative processes that follow or are triggered by a primary traumatic injury. Again, attempts at using these compounds have failed to provide sufficiently efficacious solutions to neuropathological conditions, although some single-compound attempts have shown some benefit.

[00292] Applicant has recognized the significance of the heretofore unknown complementarity of selected combinations of compounds that include formulations of two,

three or four compounds from the four categories of anticonvulsant/antiepileptics, neurosteroids/neuroactive steroids and lithium-containing/lithium-containing/lithium-related compounds and NK-1 receptor antagonists. These combinations are adapted and arranged, and adaptable and arrangeable, to facilitate, promote or potentiate the restorative processes that lead to neurological recovery, while at the same time lessening, or inhibiting, the degenerative processes that lead to secondary, progressive tissue damage and cell death.

[00293] While the bases for any possible synergistic advantages of the present formulations have been heretofore unknown, as have been the present combinations, the formulations are directed toward modifying both restorative and degenerative processes. Embodiments of the invention are directed with the proposition that neurological outcomes that result from trauma can be reduced or prevented, or the risk of such outcomes can be reduced or prevented, by the administration of a formulation of compounds that combine neurotrophic actions to repair and restore, as well as neuroprotective actions to prevent or reduce the incidence and severity of secondary injury or damage that results from trauma.

DETAILED DESCRIPTION OF THE INVENTION

[00294] In one significant aspect, disclosed formulations comprise two or more pharmaceutically effective compounds, administered to the subject or patient in accordance with the pharmaceutical effectiveness of the components and amounts to be administered. In some embodiments, the relative timing of the administrations of the formulations is keyed to the context of the actual, possible or likely nature of the injury. Regarding the timing aspects, the embodiments of the invention can be practiced with respect to the time that the injury or disorder has occurred, or with respect to a possibility, a probability or a likelihood that an injury will occur in the impending future. Thus, in one aspect of some embodiments can be adapted and arranged to preventative purposes, to curative as well as to ameliorative purposes.

[00295] Within the scope of the disclosed formulations, methods, and procedures are numerous embodiments. These embodiments include, as examples, those that involve administration of the formulations wherein both the composition of the formulations, and the timing of their respective administration, are adapted and arranged to a specific injurious event, or to a possible or likely future injurious event.

[00296] Embodiments of the invention can therefore be practiced within a rationalized earliest possible time frame following, or preceding, trauma, thereby to promote restorative processes and to inhibit degenerative processes activated by the trauma, or which are likely to be activated by the trauma. Thus, the formulations, methods, and procedures are all directed toward reducing or preventing the development, or the risk of development, of secondary nerve cell damage, loss of function, or cell death.

[00297] Disclosed formulations may be administered via any route or method, or via any means that results in delivery of effective amounts of the respective formulation components to target tissues in an efficacious and safe manner. In some method embodiments, a parenteral or alimentary route is advantageous. These routes are likely to reduce or prevent the development or the risk of development of secondary damage to neurones, neural support cells, neural support tissues or endothelial cells that can occur, or is likely to occur, as a result of traumatic injury.

[00298] In accordance with this and other objects, the presently disclosed invention and its embodiments provide methods, procedures and means for treating any neuropathological condition that is caused, at least partially, by trauma of any kind and involves endogenous processes or biochemical and metabolic pathways that govern, regulate or influence the health or function of nerves or nerve cells, or cells and tissues upon which nerves or nerve cells depend to maintain health and function. Conditions of trauma are likely to activate or trigger such processes and pathways that protect or restore health of nerves and nerve cells, as well as such processes and pathways that lead to loss of function, further damage and even cell death of nerves, nerve cells, neural support cells and neural support tissues. It is the balance of these processes and pathways that governs and determines disability outcome.

[00299] In general, the presently disclosed technology comprises methods and procedures for administering to a mammal in need thereof, a therapeutically effective amount of at least two biologically active compounds including an anticonvulsant/antiepileptic, a neurosteroid/neuroactive steroid, a substance P receptor (NK-1 receptor) antagonist or a lithium-related/lithium-containing compound. In embodiments of the invention utilizing two or more of such compounds the target can include any target or targets that activate, enhance or facilitate processes or pathways that promote health and function of nerves and nerve cells or any target or targets that inhibit, attenuate or interferes with processes or pathways that lead to loss of function, injury, damage or death of nerves or nerve cells. Loss of function or injury, damage or cell death can also include that to neural support cells or neural support tissues. Depending on the specific use and therapeutic context, analogues or modifications to the specific compounds included in embodiments of this invention can be tailored to target specific biological processes or pathways or to facilitate access of compounds to target sites in the central, peripheral or enteric nervous systems.

[00300] Preferably the administered compounds selected will facilitate, promote or potentiate restorative responses to trauma, or interfere with, lessen or inhibit degenerative processes, for example by binding to an enzyme, receptor, allosteric site or other step of an endogenous biochemical or biosynthetic pathway to the extent that such pathway is altered, enabled, allowed or facilitated its effective functioning, as in the case of a restorative process, or would prevent or lessen its effective functioning, as in the case of a degenerative process.

Examples of particular compounds are as described herein and include those identified in the listings described herein. As a person having ordinary skill in the art will appreciate, any formulations of compounds that promote or inhibit endogenous processes that are activated by trauma and that are involved in the repair or in the restoration of nerves or nerve cells are within the scope of the presently disclosed invention embodiments. Compounds that may be most effective for practicing embodiments of the invention include those that promote or interfere with at least a part of processes that are activated, induced or enhanced by trauma and that are involved in maintaining health and function or damaging nerves or nerve cells, or cells and tissues upon which the health and function of nerves and nerve cells depend.

[00301] The presently disclosed invention and its embodiments are useful for strengthening or improving natural processes that help to restore the health and function of nerves, nerve cells, neural support cells and neural support tissues when compromised by trauma. Further, the presently disclosed invention embodiments are also useful for lessening, diminishing or inhibiting natural processes that lead to loss of health and function of nerves, nerve cells, neural support cells and neural support tissues when caused by trauma.

[00302] In some embodiments of the invention, mammals, and especially humans, are suitable subjects. Of course, other mammals, such as cows, horses, cats, dogs, sheep, pigs and rodents, are suitable subjects for the presently disclosed invention embodiments.

[00303] Also in accordance with the objects of the invention, pharmaceutical preparations are provided. Pharmaceutical preparations according to embodiments of the invention comprise combinations of any two, any three or all four of at least one compound that is an antiepileptic drug, at least one compound that is a neurosteroid, at least one compound that is an NK-1 receptor antagonist and at least one compound that is a lithium drug, or an analog, and these may be administered to or given to a subject in need in any combination of two, three or all four of these classes of compound. An analogue is a compound that is a modification of the original drug or enhances the availability of the drug or provides a slow release of the drug for the target but still modifies the pathway similar to the parent compound.

[00304] Compounds of embodiments of the invention can be delivered in any manner consistent with their function and efficacy. For example, pharmaceutical preparations of the pharmaceutical compounds of the invention embodiments can be provided in admixture with at least one pharmaceutically acceptable substance that assists or enhances the delivery or effectiveness of the compounds or provides a controlled release of the compounds. Examples of such substances include, but are not limited to, excipients, penetration enhancers, stabilizers, absorption enhancers and carriers.

[00305] Delivery of compounds of embodiments of the invention, and in accordance with the methods and procedures described herein, can be effected in any manner that results in

delivery of the compounds of embodiments of the invention such that positive or negative influence on the target pathway is accomplished. For example, compounds such as antiepileptic drugs, neurosteroids, NK-1 receptor antagonists or lithium drugs, can be administered by one or more routes such as, but not limited to oral, buccal, mucosal, parenteral, rectal, sub-cutaneous, transdermal, topical, intravenous, intrathecal, intravaginal, nasal, nasal inhalation, pulmonary inhalation, iontophoresis through the skin, iontophoresis through mucosal or buccal membranes, dermal patch, epidural, intracranial, intrapharyngeal, sublingual, intra-articular, intramuscular and subcutaneous.

[00306] As one of ordinary skill in the art will comprehend, appropriate dosages of compounds according to the various embodiments of the invention can vary widely depending, inter alia, upon the type of trauma or condition to be treated, the route of treatment, the subject mammal, the sequelae of mechanisms and processes to be controlled, the compounds involved, and the like. Dosages range greatly, for example, between 10 nanograms and 60 grams per kilogram of body weight of the individual mammal. Some typical ranges for the amount of gabapentin, as one representative of the family of antiepileptic compounds, would include preferably from 50 to 4,800 mg per day for an individual human, or from 100 to 2,400 mg per day to an individual human, or from 200 to 600 mg per day to an individual, depending on the need, the individual, the severity of the neurotrauma, the response to administration of the formulation and the like. In some particular embodiments, the formulation is administered in a range of amounts from 5 to 600 mg per day of progesterone, as one representative of the family of neurosteroids. In other particular embodiments, the compound is administered in a range of amounts of 5 to 375 mg per day of aprepitant, as one representative of the family of NK-1 receptor antagonists. In further particular embodiments, the compound is administered in a range of amounts of 30 to 1,800 mg per day of lithium carbonate, as one representative of the family of lithium and related compounds.

[00307] As a person having ordinary skill in the art will understand pharmaceutical compositions, methods, procedures and means of administration of the presently disclosed invention are useful for treating or preventing any type of neuropathology such as, but not limited to, those characterized as brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury as described herein. Also included among the many conditions that can be treated or prevented by the pharmaceutical compositions, methods and procedures of the presently disclosed invention are disturbances of any etiology so long as involvement of any process or pathway that can be modified or altered by an anticonvulsant, a neurosteroid, an NK-1 receptor antagonist or lithium, or any analog, derivative or related compound is present.

[00308] In accordance with these aspects of embodiments of the invention, methods and

procedures are provided comprising administering to a mammal in need thereof, a therapeutically effective amount of at least two compounds that interfere with the function or process of endogenous pathways that can be modified or altered by an anticonvulsant, a neurosteroid, an NK-1 receptor antagonist or lithium, or any analog, derivative or related compound. Preferably, the compounds are at least two or more than two selected from the group comprising the family of anticonvulsants, the family of neurosteroids, the class of NK-1 receptor antagonists and lithium and related compounds. More specifically, particular groups of compounds include two or more selected from the groups described herein, including the families of anticonvulsants, neurosteroids, NK-1 receptor antagonists and lithium-related drugs.

[00309] The presently disclosed invention embodiments include also practices, kits and methods for treating or preventing any condition that is characterized at least partially by involvement of any process, pathway or mechanism involving a part that can be facilitated, promoted, potentiated, interfered with, lessened or inhibited by any of anticonvulsants, neurosteroids, NK-1 receptor antagonists or lithium-related compounds. A formulation includes, inter alia, a therapeutically effective amount of at least one compound that interacts with or interferes with a process, pathway or mechanism in which an anticonvulsant or antiepileptic or related compound can or does act. A formulation includes, inter alia, a therapeutically effective amount of at least one compound that promotes a process, pathway or mechanism in which progesterone or a related compound can or does act, or a compound that is a prodrug or metabolite of such a compound that promotes a process, pathway or mechanism in which progesterone or a related compound can or does act. A formulation includes, inter alia, a therapeutically effective amount of at least one compound that interacts with or interferes with a process, pathway or mechanism in which an NK-1 receptor antagonist or related compound can or does act. A formulation includes, inter alia, a therapeutically effective amount of at least one compound that promotes a process, pathway or mechanism in which lithium or related compounds can or do act. The formulation, methods and procedures of embodiments of the invention can be designed to target any neuropathological condition that involves brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury as described herein.

[00310] Incidence studies indicate the number of people in a population who will go on to develop disability following trauma of any given type. Until the presently disclosed invention and its embodiments, these numbers have been accepted as being inevitable. There is a general acceptance that disability results from trauma. Medical attention has not typically been directed at reducing these numbers, or preventing them altogether. Yet, as described in detail herein much of the disability that ensues as a result of trauma is brought about by

processes, largely biochemical, which can be modified by appropriate pharmaceutical intervention. Trauma-induced disability can thus be considered an unsolved need. Applicant posits that the number of people who go on to develop disability following trauma can be reduced. Further, the severity of disability of those that develop a disability can be reduced. The scope of the presently disclosed invention embodiments are directed toward this unsolved need, both by reducing the number of victims of trauma that go on to develop adverse health conditions and disability, as well as by reducing the severity of disability in those who are left with trauma-induced adverse health conditions. In accordance with this and other objects, the presently disclosed technology, in certain specific embodiments, aims to prevent or reduce the development, or the risk of development, of neuropathology that results from traumatic injury.

[00311] To illustrate, as one example, incidence studies inform that following surgery a certain number of patients are expected to be left with disabling chronic pain. Thus, from data gathered on the numbers of surgical operations performed in the USA and the UK, it has been reported that the incidence or probability of chronic pain following mastectomy is 20-50%, cardiac surgery is 30-55%, hernia repair is 5-35%, cholecystectomy is 5-50%. Similar numbers are available for other types of surgery.

[00312] Based on such reports and others as detailed herein, a person having ordinary skill in the art will understand that in the broadest terms trauma is expected to lead to disability in known percentages or probabilities, whether brain injury, central nervous system ischemia, spinal cord injury, enteric nerve injury or peripheral nerve injury. These disabilities constitute a major public health issue, affecting large numbers of patients or victims, having an enormous impact on the healthcare system, important economic consequences, and a significant effect on quality of life.

[00313] All types of trauma are known to activate secondary injury mechanisms. These secondary injury mechanisms are brought about as the outcome of a balance of restorative and degenerative biochemical and other processes triggered by trauma. The nature of these processes provides inroads to pharmaceutical intervention that can reduce or even prevent the alteration of function and even the death of nerve cells and their neural support cells and neural support tissues, alterations that can and often do ultimately lead to adverse health conditions or disability. The presently disclosed technology, in its numerous embodiments, is directed to promote these restorative processes and to inhibit these degenerative processes by specific pharmaceutical intervention at appropriate doses, with specific timings and sequences of intervention, using specific routes and modes of delivery.

[00314] Many traumatic events are unexpected and unanticipated. However, in many cases traumatic events can be anticipated, events that can and often do lead to adverse health conditions and disability. Clinical and incidence studies provide supportive evidence that as a

result of certain procedures or events there is a high incidence of such adverse health conditions and disability. A person having ordinary skill in the art will recognize that preventive measures can be taken in conditions where there is a high enough possibility of a traumatic event occurring that leads to damage or injury to nerve cells, to neural support cells or to neural support tissues, that precautionary or preventive measures are warranted, as described herein. The scope of the presently disclosed technology and its embodiments are directed toward at both: unanticipated as well as anticipated traumatic injury.

[00315] Some examples are provided to illustrate what is meant as anticipated and unanticipated traumatic events. Minor head injury events are usually unanticipated, but these have been reported to lead to restriction to lifestyle one year later in 47% of admissions to hospital. Post-surgical pain varies according to the type of surgery, but continuing pain one year after amputation has been reported in up to 85% of patients and thus pain can be anticipated in a certain percentage of amputees. Medically induced sensory, motor, autonomic or enteric nerve damage can and often does occur as a result of chemotherapy or radiation therapy. Spinal cord injury is usually unanticipated, and survivors can be expected to have permanent physical disabilities, reduced independence, serious medical complications and enormous financial burden. Stroke is also usually unanticipated, but in view of the fact that an estimated 44 million disability-adjusted life-years are lost by stroke survivors worldwide, many who have had a stroke know that they are at risk of a subsequent stroke or subsequent strokes. Applicant posits that much of the adverse health conditions and disability resulting from these and all traumas are amenable to therapeutic intervention. The presently disclosed invention embodiments are directed toward preventing or reducing these adverse health conditions and the disability that arise from these and other cases of trauma as described herein, by promoting restorative mechanisms and processes triggered by trauma as well as by inhibiting degenerative mechanisms and processes triggered by trauma.

[00316] Specifically, the presently disclosed invention and all its embodiments address the facts that damage or injury to nerves, nerve cells, neural support cells and neural support tissues can be a result of trauma, but such damage or injury can also be secondary, due to a complex series of events triggered by the direct injury. Disability arising from the primary injury occurring at the moment of the traumatic event, whether it is to brain, spinal cord, enteric nervous system or peripheral nervous system, is not preventable. However, disability resulting from the secondary injury is preventable, and this is the object of the presently disclosed invention embodiments. The presently disclosed invention and all its embodiments are an intervention with a pharmaceutically appropriate synergistic drug combination, given early following trauma or in advance of expected or potential trauma, and administered by a route that provides access under the circumstances of the traumatic event. The scope

of the presently disclosed technology and its embodiments are to promote the naturally-occurring restorative processes triggered by and resulting from the primary damage and to inhibit the naturally-occurring degenerative processes triggered by the primary damage. The expectation is that the formulation, the methods and the procedures of the presently disclosed technology will reduce or prevent the development, or the risk of development, of neuropathology as a result of traumatic injury.

[00317] Four particular aspects of embodiments of the invention are documented herein, together comprising formulations, methods and procedures for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury. One particular aspect, or advantage, of embodiments of the present invention is represented by the series of formulations that it provides. These formulations are compounded of selections from two, three or four categories of chemical entities. Each of the chemical entities is one of the pharmaceutically active compounds selected from one of four “categories.” These categories can also be described as “classes” or “families” of compounds. As utilized in the invention embodiments, the categories, classes or families are exemplified in the lists shown herein. Thus, two-component, three-component and four-component formulations are provided herein. Formulations therefore include two or more components from the four categories or classes of chemical entities, and can be administered together or sequentially as described herein, at clinically effective doses and in clinically effective preparations.

[00318] As described herein, each of the chemical entities in a formulation of embodiments of the invention is theorized to target one or more biological processes or mechanisms. Applicant theorizes that some of these mechanisms may sometimes be involved in governing the incidence and the degree or severity of secondary injury that follows a primary traumatic injury. It is at this secondary injury to which the formulations of the invention embodiments are directed. A great amount of investigation regarding individual members of these categories has produced no efficacious formulations or methods. Indeed, a great amount of research in the field of neuropathology does not support aspects of Applicant’s theory regarding the efficacy of particular combinations and dosages of these categories of compounds. This is so especially since in some cases administration of single compounds seldom produces adequate benefit, if any, and sometimes causes harm.

[00319] Despite this, Applicant presents inventive formulations as having utility in treating various types and forms of neuropathology. In some sense, selected literature in the field might support the view that some of the individual compounds discussed herein, such as the neurosteroids and lithium-containing drugs, would be effective in promoting, facilitating or potentiating restorative processes due to, or resulting from, trauma. In a similar sense, selected literature in the field might support the view that some anticonvulsants, some of the NK-1 receptor antagonists and some lithium-containing drugs, might act to minimize or

inhibit degenerative processes that follow or are triggered by a primary traumatic injury. Again, attempts at using these compounds have failed to provide sufficiently efficacious solutions to neuropathological conditions, although some single-compound attempts have shown some benefit.

[00320] Unexpectedly, Applicant has recognized the significance of the heretofore unknown synergy of selected combinations of compounds that include formulations of two, three or four compounds from the four categories of anticonvulsants, neurosteroids, NK-1 receptor antagonists and lithium-containing compounds. These combinations are adapted and arranged, and adaptable and arrangeable, to facilitate, promote or potentiate the restorative processes that lead to neurological recovery, while at the same time lessening, or inhibiting, the degenerative processes that lead to secondary, progressive tissue damage and cell death.

[00321] While the bases for the possible synergistic advantages of the present formulations have been heretofore unknown, as have been the present combinations, the formulations are directed toward modifying both restorative and degenerative processes. Embodiments of the invention are directed with the proposition that improved neurological outcomes that are known to result from trauma can be reduced or prevented, or the risk of such outcomes, can be reduced or prevented by the administration of a formulation of synergistic compounds that combine neurotrophic actions to repair and restore, as well as neuroprotective actions to prevent or reduce secondary injury or damage.

[00322] A second particular aspect, or advantage, of the presently disclosed technology and its embodiments is the specific practice modality of embodiments of the invention, as described herein, which, together with the other three particular aspects of the presently disclosed technology, as described herein, comprise formulations, methods and procedures for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury.

[00323] There are three types of practice modality described in this second particular aspect of invention embodiments: precautionary, prophylactic and posttraumatic event practices of the invention and its embodiments. One is a precautionary practice of invention embodiments in conditions where a subject is about to enter into a situation of high risk of trauma. In this case preventive practice of the invention embodiments refers to the administration of a formulation before an individual enters a situation where trauma may occur. This specific precautionary practice of invention embodiments fills a void that presently exists with respect to pharmaceutical protection from neuropathology resulting from a trauma that may or may not occur. Precautionary practice would be analogous to taking an anti-malarial medication when going into a malaria-infested area; it is not known that an individual will be exposed directly to malaria, but the medication is taken to avert disease.

[00324] Prophylactic practice of invention embodiments is a second specific practice

modality which is practiced in conditions where a procedure is about to take place wherein this procedure is known to result in damage to nerve cells or neural support cells or neural support tissues in some individuals. Prophylactic intervention refers to the administration of a formulation before a subject or patient is given a procedure where evidence indicates an incidence or probability of neuropathology and ensuing adverse health condition or disability. This specific prophylactic practice of invention embodiments fills a void that presently exists with respect to prevention of damage or injury to nerve cells, to neural support cells or to neural support tissues that may result from a procedure that is known to have an incidence or probability of adverse health conditions or disability.

[00325] Prophylactic practice of this second particular aspect of the invention embodiments would be analogous to a single combination tablet containing emtricitabine and tenofovir disoproxil fumarate (Truvada) to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who engage in sexual activity with HIV-infected partners. With respect to the presently disclosed invention embodiments, a prophylactic practice for reducing or preventing the development of injury would be in the case of anticipated trauma, as one case, which is a pre-exposure prophylaxis measure taken to reduce the risk of neuropathology in individuals who are about to undergo procedures where there is a risk of neuropathology. This would include but is not limited to such procedures as surgery, chemotherapy, radiation therapy and the like, where there is a known risk of damage to brain, brain stem, spinal cord, peripheral nerve or enteric nerve cells. Prophylaxis of trauma is different from pre- and post-surgical care, where steps are taken to ensure the patient's comfort and rapid recovery from the immediate condition.

[00326] Posttraumatic event practice of this second particular aspect, or advantage, of the invention and its embodiments is the third specific practice modality, which, together with the other three particular advantages of the presently disclosed technology comprise formulations, methods and procedures for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury. In this case, posttraumatic event practice of the invention and its embodiments applies in cases where a traumatic event has occurred, and this is different from precautionary and prophylactic practice. In many cases the traumatic event was unanticipated and unpredicted, differentiating this practice modality from precautionary and from prophylactic practices of invention embodiments. Posttraumatic event practice of invention embodiments refers to the administration of a formulation immediately following trauma, or as soon as possible following such trauma. This specific posttraumatic event practice of invention embodiments fills a void that presently exists with respect to the prevention of secondary injury or damage to nerve cells, to neural support cells or to neural support tissues; standard practice when a traumatic event has occurred typically treats events other than those involved in secondary injury or damage. As a

result, prevention or reduction of this secondary injury or damage remains an unsolved need.

[00327] Posttraumatic event practice of invention embodiments can be done in any appropriate setting, but immediacy of practice of invention embodiments is of importance, as many of the processes targeted by the formulations of invention embodiments are triggered in the minutes and hours following the traumatic event. For example, posttraumatic event practice of invention embodiments can be done in a home setting, in a pre-hospital setting or in a healthcare setting. A home setting refers to conditions where people well known to the victim of unanticipated trauma, such as a high risk individual for stroke as one example, or who are with the victim at the time of the trauma, are able to administer a formulation at the earliest possible time, including during the traumatic event. Pre-hospital setting refers to conditions where health care can be delivered by trained personnel, such as but not exclusively paramedics and emergency medical services personnel, military medics on or near a battlefield and the such. A healthcare setting or a hospital/clinical setting refers to a site that is equipped to dispense a range of health care and emergency medical care.

[00328] As examples, posttraumatic event practice of invention embodiments would include such conditions as motor vehicle accidents, battlefield injuries, sports injuries and the like, where there has been damage or injury to tissues, and where evidence indicates that there is a risk of damage to brain, spinal cord, enteric nervous system or peripheral nerve. Emergency treatment of secondary neuropathology is different from emergency treatment of trauma, where immediate steps are taken to prevent further injury, to stop bleeding, to take life-saving steps and the like. Emergency treatment specifically of secondary injury to nerve cells thus remains an unsolved need.

[00329] In all cases of practice modalities, administration of the formulation is to be continued as needed. A person having ordinary skill in the art will know that the cascades of mechanisms involved in the restorative and the degenerative processes triggered by trauma can and do continue over days, weeks and in some cases even months following trauma, and that optimal reduction or prevention of the development or the risk of development of neuropathology as a result of traumatic injury requires continuation of administration of the formulation of invention embodiments.

[00330] Practice modalities of the invention thus provide interventions that serve as protective, prophylactic or posttraumatic strategies to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury. In contrast to previous efforts to address neuropathologies of the type discussed herein, the present invention provides also a number of combinations of compounds that, in effect, address both the degenerative underlying mechanisms or processes, as well as the restorative mechanisms or processes. Applicant therefore believes that by addressing simultaneously both the degenerative and the restorative processes, the scope of the invention embodiments includes a

number of practice modalities and formulation combinations that minimize the adverse health conditions or the disability that would otherwise result from trauma that may occur, that does occur, or that has occurred.

[00331] The third particular aspect or advantage of invention embodiments is the timing and route of coupling of the formulations described in the first particular advantage of invention embodiments with the procedures of the second particular advantage of invention embodiments to methods of administration of the formulation, together also with the fourth particular advantage of invention embodiments for reducing or preventing the development or the risk of development of secondary neuropathology as a result of traumatic injury. With a few exceptions as cited, heretofore the compounds of the presently disclosed technology have not been administered in a time conscious practice or via routes intended for rapid access to the target tissue. As described herein, restorative and degenerative biochemical and other processes are activated immediately by traumatic events. Therefore, to optimize procedures for reducing or preventing the development or the risk of development of neuropathology as a result of trauma, time to treatment and route of treatment are important. Equally important is the duration of practice of invention embodiments, as described herein. Continuation of practice of invention embodiments beyond the initial practice at the time of trauma can be by any of the routes of administration described herein and can be by modifications of the formulations, methods and procedures to include any controlled release methods of delivery or administration.

[00332] With respect to this third particular aspect of invention embodiments, in the event of unanticipated trauma as an example, which usually occurs away from a hospital/clinic setting, at-site immediate or earliest possible administration of a formulation is by nasal administration. This would be administered optimally by first-on-scene personnel, such as a medic, a paramedic, emergency medical services personnel, or the like. This is to provide a fast and effective intervention in an easily and socially acceptable format. As other examples, in the event of an unanticipated trauma such as a stroke or other trauma that could occur with an individual with high risk or with a medical history, a formulation of the first particular advantage of invention embodiments would be administered optimally by at-present personnel, such as spouse or family member, or even a workplace colleague, or the like. As one example, the method of delivery of a formulation can be by intranasal administration, as this route provides rapid access to peripheral and central nerve cells, neural support cells and neural support tissues, and this method of administration is easily administered and is socially acceptable under such conditions. This example is provided to illustrate and is not intended to be limiting.

[00333] In the event of an anticipated trauma, which may occur in a controlled medical facility, such as a hospital or medical clinic setting, prophylactic intervention with the method

of administration of a formulation can be, as examples, by oral, buccal, intravenous or even intramuscular routes. Delivery of a formulation by intranasal administration will be by a nasal spray or other like medium. Delivery of a formulation by sublingual administration will be by a spray or other like medium. Delivery of a formulation by oral administration will be by tablet, capsule, pill or other like medium. Delivery of a formulation by intravenous or intramuscular administration will be by sterile injectable solution or other like medium of the formulation. A person having ordinary skill in the art will understand that this or other choice can be made without undue experimentation.

[00334] In the case of preventive practice of invention embodiments the method of self- or other administration of a formulation of the first particular advantage of invention embodiments would be by the easiest route of a stable formulation, such as a tablet, capsule or pill, although a nasal spray may be equally easy to administer and equally stable. A person having ordinary skill in the art will understand that this or other choice can be made without undue experimentation.

[00335] In another particular advantage, invention embodiments provide specific methods of administration of the formulations with respect to the relative time of the injury. Thus, both the formulations (combinations) and the present methods of invention embodiments regarding the timing and route of their administration, act to reduce or prevent the development, or the risk of development, of neuropathology as a result of traumatic injury.

[00336] In another advantageous and particular aspect, some of the individual formulations of invention embodiments can be administered orally, and some can be administered intranasally. This is so despite that fact that the individual compounds from the four categories, groups or families from which the compounds of the present formulations are drawn, have been used in these manners. Because a particular aspect of the methods of the invention in some embodiments or circumstances relates to the immediacy of treatment, the standard recommended or standard uses of the individual compounds are usually not suitable or appropriate for the immediate delivery aspects of the present methods. This is especially so when the immediacy of treatment in this particular aspect of the invention embodiments requires faster access to the target tissues than is possible by oral or other conventional administration.

[00337] The fourth particular aspect or advantage of invention embodiments is the application of the formulations, methods and procedures of the first, second and third particular aspects of invention embodiments described above, specifically to secondary injury resulting from types of trauma that are not typically or usually considered as a single factor. To illustrate using one example, in the case of the presently disclosed technology secondary injury from trauma can include that caused by an epileptic seizure. An epileptic seizure is not ordinarily caused by a physical insult. However, in the context of the presently disclosed

invention embodiments an epileptic seizure is itself a traumatic event. As a traumatic event an epileptic seizure, if severe enough, has the potential to activate the cascades of restorative and degenerative processes that are shared, for example, with physical trauma to the head. That is, an epileptic seizure activates the same or overlapping restorative processes and the same degenerative processes that are activated by a closed-head concussion or by a penetrating injury to the head. Thus, in this fourth particular aspect of invention embodiments, metabolic or intrinsic trauma is targeted in the same way as impact or concussion trauma to the head. Similarly, trauma from chemotherapy or radiation therapy triggers the same or at least overlapping restorative and degenerative processes that are triggered by impact or concussion trauma, and therefore medically-induced trauma is an object for therapy in this fourth particular aspect of invention embodiments. As described herein, this also applies equally whether the trauma is to neurones in the periphery, in the enteric nervous system or the central nervous system. In this fourth particular aspect of invention embodiments any and all types of trauma are targeted by the same formulations, methods and practices of the presently disclosed invention and its embodiments.

[00338] Formulations and methods of the invention embodiments provide heretofore unknown advantages with respect to treating some of the significant underlying mechanisms which are common to many types of trauma. The present invention embodiments addresses both restorative and degenerative processes, and not simply those which are believed to be damaging after a traumatic injury. Conventional practice provided before, or at the time of, trauma has not heretofore addressed the commonness of events, both those that are triggered by trauma, and those that govern, or influence, the incidence and severity of the adverse health conditions or disability that results from trauma of any type.

[00339] Standard practice has heretofore been based on separate and different strategies to treat brain injury vs. spinal cord injury vs. central or peripheral nervous system ischemia vs. peripheral nerve injury vs. enteric nervous system injury. In stark contrast, this fourth particular aspect of invention embodiments is particularly advantageous in that it addresses the commonness of the processes that are triggered or activated by trauma of all types and to any neurone, whether in the central nervous system, the enteric nervous system or the peripheral nervous system. Invention embodiments are thus directed toward the unsolved need to prevent or reduce the adverse health conditions or disabilities that result from, or that may result from, traumatic injury. In this aspect, the present methods and formulations are adapted and arranged as treatment for all types of trauma, irrespective of the cause of the trauma, the type of trauma, or the specific body parts injured.

[00340] Another particular aspect of invention embodiments can be understood in relation to conventional treatments for trauma. More specifically, conventional medical intervention or standard emergency practice does not include steps to reduce or prevent secondary injury

to nerve cells, neural support cells or neural support tissues. As one example, the immediate conventional medical approaches to stroke and to transcatheter aortic valve implantation bear few similarities in standard clinical practice, yet both can and often do cause the same functional neurological impairments, mediated via the same natural processes. Similarly, there is little or no similarity in conventional medical approaches to treat brain injury, spinal cord injury, injury to the enteric nervous system or injury to the peripheral nervous system. Indeed, standard medical practice sees these as separate and different emergencies or traumas, and the immediate treatment is different and unique to each of these cases. However, in part because Applicant theorizes that similar or overlapping restorative and degenerative processes are triggered by trauma irrespective of how and where this trauma occurs, the present invention in many of its embodiments treats both restorative and degenerative processes in any and all types of trauma.

[00341] Conventional evidence thus indicates that once the secondary damage due to nerve injury has become entrenched, little can be done therapeutically to reverse the resultant disability. In significant contrast to the failures of conventional, or current, standard approaches, the presently disclosed invention embodiments shift the focus from treatment of disability and symptoms that have developed as a result of trauma, to early treatment to prevent or reduce the development, and thus the incidence, of symptoms and disabilities caused by the secondary injury.

[00342] Incidence studies indicate the expectation or probability of disability and symptoms that result from the various types of trauma, and thereby exemplify the inadequacies of the current general medical approach of treating existing symptoms as they typically occur. In great contrast, the scope and spirit of the presently disclosed invention and of its many embodiments is that many of these heretofore untreated symptoms and much of the disability resulting from neural injury, can be reduced or prevented from occurring.

[00343] The presently disclosed invention embodiments are thus directed toward medical intervention before symptoms manifest, or medical intervention in the absence of symptoms in conditions where there is a known high incidence of symptoms and disability.

[00344] In one key aspect, the presently disclosed invention embodiments therefore present an intent-to-treat paradigm, not only as preparedness treatment or prophylactic treatment for anticipated or potential traumatic events, but also posttraumatic treatment for unanticipated events, for example by initiating key aspects of embodiments of the invention at the scene of accident or trauma, or as close in time to it as possible, within the shortest time following the trauma. Practice of embodiments of the invention, as illustrated herein with examples of particular embodiments, can be carried out by persons having ordinary skill in the art or are otherwise knowledgeable about the methods and procedures related to the present disclosure. Typically, methods and procedures of the presently disclosed invention embodiments are not

only to be initiated immediately, or as early as possible, but also include follow-up treatment with one or more of the formulations, methods and procedures that a person with skill in the art would carry out in a specialized health centre, such as a medical clinic or hospital.

[00345] As an example, one set of procedures or methods according to embodiments of the invention, is to arm first-on-scene healthcare professionals, such as but not limited to paramedics, emergency medical technicians, law enforcement personnel, military medic and the like, with formulations, methods and procedures to obtain consent and to administer the embodiments of invention within a hyper acute therapeutic window, with more specialized care to follow, as part of embodiments of the invention, at the site of trauma or in a clinical or hospital setting. This would be the case for brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury; in cases where the possibility of injury can be anticipated or is induced by a medical procedure, as described herein, initiation of embodiments of the invention would be before or during the traumatic event.

[00346] Neurotrauma, often referred to as acquired nerve injury, is a catastrophic injury that imposes a number of negative outcomes that usually inflict one or more adverse health conditions or disabilities on its victims. These adverse health conditions and disabilities frequently place both short-term and long-term burdens on individuals, families, communities, the workplace, the health care system and economies in general. Considerable money and effort have been expended on attempts to lessen, prevent or ameliorate the effects of neurotrauma. Until the presently disclosed formulations, methods and procedures, however, as described herein no satisfactory methods or pharmaceutical treatments have been successful at resolving the problems associated with neurotrauma and its aftermath.

[00347] The presently disclosed invention embodiments are based in part upon the conclusion that many of the negative outcomes and disabilities of neurotrauma can be reduced in severity, or prevented altogether, by appropriate early intervention with the appropriate methods, procedures and pharmaceutical formulations, continued for a medically-beneficial period of time. While there are currently practices and interventions to treat, manage or diminish the negative outcomes of neurotrauma once they have been established, immediate or early preventive approaches targeted at the development phase of these outcomes are nonexistent, few or ineffective. That is, at the time of a traumatic event medical attention focusses on treatment of immediate symptoms such as bleeding or to avoid infection, but medical attention does not typically address treatment to prevent the cascade of restorative and degenerative biochemical processes that result from neurotrauma and that lead to prolonged or permanent adverse health conditions and disability. It is this latter treatment, i.e. treatment to reduce or prevent, that this invention and its embodiments address.

[00348] The presently disclosed invention embodiments are directed at preventing or

reducing the development of the sequelae of negative effects and symptoms that incidence studies indicate follow trauma, and that can continue for months or years, or even permanently.

[00349] There is an additional aspect, or advantage, of the presently disclosed invention embodiments. For example, as injury to the brain is known to increase the risk of the later development of some degenerative disorders, the presently disclosed technology is also directed at reducing or preventing the risk of longer-term neurodegeneration. To substantiate this point, head trauma is a risk factor for Parkinson's disease; stroke is a risk factor for Alzheimer's disease. As detailed herein, head trauma and stroke trigger similar or overlapping cascades of progressing restorative and degenerative processes that alter the health, function and survival of nerves, nerve cells, neural support cells, and, as these cascades are shared by trauma of different types, the presently disclosed formulations, methods and procedures are useful in reducing risk factors for neurodegenerative diseases.

[00350] In the context of the presently disclosed invention embodiments, as described herein trauma includes physical, chemical, metabolic, surgical and other injury or damage to a nerve or nerve cell or support cell or support tissue, whether in the central nervous system or in the periphery. Neurotrauma is, then, trauma to nerves or nerve cells, or their supporting cells or their supporting tissues, whether in the brain or the brain stem or the cerebellum or the spinal cord, or the gut or in the periphery.

[00351] The symptoms of trauma and of neurodegeneration come about from pathophysiological changes in nerve cells, resulting in damaging effects commonly termed "neuropathology." As an example, brain insult produces morphological and functional alterations in the hippocampal formation, including neurodegeneration in CA1, CA3, and, most consistently, the dentate hilus. Most of these alterations develop gradually over several hours, days or weeks after the insult, providing a therapeutic window of opportunity for treatment with neurotrophic and neuroprotective agents in the immediate post-injury period. This window of opportunity slowly closes in time, however, and treatment is optimal when applied immediately, providing optimal benefit when applied during a platinum hour, a golden day and a silver week.

[00352] In the context of describing the invention, the terminology "neuropathology" includes neuropathy, neurodegeneration and other effects of trauma on nerve cells, neural support cells and neural support tissues as defined herein. Neuropathology following trauma can occur in the brain, brain stem, cerebellum or spinal cord, in enteric nerve cells of the gut or in peripheral nerves. Neuropathology is also influenced by events that impact neural support cells and neural support tissues, as neurone/glial interactions are important in brain homeostasis and are vital for survival of neurones in health as well as after injury. Further, nerve cells require an adequate supply of oxygen and glucose from the vascular supply, and

an adequate removal of cellular waste products by the vascular supply. As an example, injury-induced loss of glial cells or loss of glial function has been reported to have a negative outcome on injured neurones. Central nervous system neurotrauma can include brain injury, central nervous system ischemia (that is to brain, brain stem, cerebellum, spinal cord), and damage brought about by brain swelling or high cerebrospinal pressure. Spinal cord neurotrauma can include compression, vertebral collapse, wounds from cutting, puncture wounds, and the like. Injury or damage to the enteric nervous system and to the peripheral nervous system is similarly referenced herein.

[00353] Neurodegeneration can include brain changes that occur short-term, medium-term or long-term from any type of trauma. Examples of these include Alzheimer's disease, Parkinson's disease and other disorders where brain injury is a risk factor.

[00354] Parenthetically, in the context of the presently disclosed invention embodiments prevention does not imply avoidance. Prevention in the context of avoidance would be, as examples, avoiding falls, wearing body armor, wearing seat belts, wearing helmets while bicycling, and the like. Prevention in the context of the presently disclosed invention embodiments is administration of a pharmaceutically effective dose of a formulation of two or more chemical entities, following methods, procedures and practices with the objective to reduce or prevent secondary injury by inhibiting or interfering with the natural degenerative processes triggered by trauma and to promote recovery and repair by enhancing or promoting the natural restorative processes triggered by this same trauma. Prevention in the context of the presently disclosed invention embodiments is inhibition of neurodegeneration processes and promotion of restorative processes.

[00355] This presently disclosed invention embodiments aim to introduce a potentially symptom-sparing, pharmaceutical intervention coupled to the methods and procedures described herein that are rationalized temporally to reduce or prevent the onset of secondary cell and tissue damage caused by trauma. The strategy is to promote known restorative processes and inhibit known degenerative processes by administering a combination of chemical entities described herein. In the context of the presently disclosed technology and its embodiments administration of these chemical entities is at times during the progression of the cascades of biological effector pathways during the period that each is respectively called into play.

[00356] The presently disclosed invention embodiments aim to reduce or prevent the development, or the risk of development, of secondary injury resulting from brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury.

[00357] There are several other efforts to develop effective mechanism-based approaches to reduce or prevent secondary injury following trauma. The presently disclosed technology is

one of these efforts, and is based particularly on a polypharmacy approach where delivery of beneficial chemical entities is given at specific times following or even before trauma, as described herein. For example, Stoica *et al.* (2009) summarize biochemical processes triggered by neurotrauma and provide an overview of emerging treatments to lessen secondary injury, including cell cycle inhibitors and the brain hormone, thyrotropin releasing hormone. While they argue in favour of multifunctional drug treatment, their emphasis is only on inhibiting degenerative processes. They do not include in their treatment recommendations any approach to promote natural healing and restorative processes. Further, while they point out the fact that few victims of trauma have treatment initiated within six to eight hours, they do not report any emerging therapeutic approaches to introduce treatment before a victim reaches a medical facility. Even further, they conclude that the costs and methodological difficulties associated with clinical trials on multi-drug comparison studies in treating clinical neuropathology would likely prove prohibitive. The presently disclosed technology and its embodiments fill these gaps by evidence-based formulations, methods and procedures to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury.

[00358] The hurdles surveyed by Stoica *et al.* are also identified in a report by Vinck and Nimmo (2009), who provide an overview of the major secondary injury processes involved in brain injury and describe some of the new approaches emerging from animal studies that may provide new routes to explore by the pharmaceutical industry. Among the emerging therapeutic approaches they survey, none addresses promotion of repair or restorative processes that are triggered by trauma alongside those that drive toward neuropathology. Further, they point out that there is reticence on the part of this industry to initiate clinical trials of the complexity and cost demanded by treating a number of independent injury factors simultaneously that occur over a prolonged period of time following trauma.

[00359] Neuropathology resulting from traumatic injury is thus currently an unmet medical need and experts in the field are of the opinion that this situation will remain. The Applicant disagrees and has set forth a proposal including specific formulations, methods and procedures to address and meet this need.

[00360] A person having ordinary skill in the art will understand the progressive nature of the processes driving cells and tissues toward health and toward loss of function and cell death. A person having ordinary skill in the art will also understand that the outcome will be the result of a balance between these opposing processes. A person having ordinary skill in the art will also understand that appropriate therapeutic intervention to promote the restorative processes will tip this balance toward health and reduced adverse health conditions or disability. A person having ordinary skill in the art will also understand that optimal therapeutic intervention is necessary to stop or inhibit the degenerative cascades of processes

from developing farther toward adverse health conditions or disability. Immediate practice of the presently disclosed technology and its embodiments is advised to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury.

[00361] Taken together, the evidence suggests that these are multiple targets for potential therapeutic approaches to reduce or prevent the development, or the risk of development, of the secondary injury that results from trauma to the brain.

[00362] An important inference that can be made from this suggestion is that, given the multiple processes that are involved in causing this secondary injury, monotherapy that targets a single process or pathway will be less effective than a polytherapy or multi-drug approach that targets more than one, or several, different processes or pathways.

[00363] Together, the evidence suggests, and a person having ordinary skill in the art will understand, that from the time of trauma there is a closing window of opportunity to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury. Applicant suggests that there is a platinum hour, a golden day and a silver week of opportunity to achieve optimal outcomes.

[00364] The presently disclosed technology and its embodiments aim to meet this medical need by providing an evidence-based formulation of compounds, methods and procedures that, when given immediately or as early as possible after a brain injury, will reduce or prevent the development or the risk of development of neuropathology as a result of this traumatic injury.

[00365] There have been many drugs that have entered clinical trials for treatment of brain injury-induced secondary neuropathology, including calcium channel blockers, corticosteroids such as dexamethasone and methylprednisolone, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) such as rosuvastatin and atorvastatin, progesterone and its metabolite allopregnanolone, cyclosporin A and analogs, mannitol, magnesium sulfate (to block NMDA receptors), excitatory amino acid receptor antagonists, kinin receptor antagonists, barbiturates, monoaminergic agonists such as methylphenidate, free radical scavengers, cannabinoid receptor agonists and many others (Tolias and Bullock, 2004; Loane and Faden, 2010). The literature indicates that although there have been many attempts to develop interventions to minimize secondary injury arising from brain injury, these attempts have not yielded any new product onto the market for this use (Beauchamp *et al.*, 2008; Loane and Faden, 2010).

[00366] How is it that such extensive research has not yielded a clinically effective drug for the market? There are multiple levels of answer to this question. One is that even if a drug had passed phase III clinical trials, full benefit may have been elusive because all drugs currently in clinical trials II and III are monotherapies and do not address the consensus of the thought leaders in the field that the plurality of mechanisms contributing to secondary brain injury

requires a polypharmacy or multi-drug approach. The critical literature attributes much of the failure to bring effective interventions forward from phase III clinical trials to the fact that most such trials, and their antecedent development strategies, are directed at a single factor or mechanism, despite the awareness of the multiplicity of the underlying mechanisms.

[00367] At another level, a consensus that has emerged, and that is manifest in attempts to survey current and emerging medical interventions to reduce or prevent secondary brain injury, is that the mechanisms leading to this injury and its ensuing disability, are complex and occur over a period of time extending up to months after the traumatic event. As a result, recent opinion is that a multi-mechanistic approach is needed, where multiple active compounds are given simultaneously or synchronously over specified respective periods of time. This would result in reducing or preventing the expression of more than one of the mechanisms that would otherwise lead to secondary brain injury and disability (Tolias and Bullock, 2004; Loane and Faden, 2010).

[00368] As a person having ordinary skill in the art will understand, current standard practice attends to the immediate need to stop bleeding, to ensure adequate respiration and to ensure adequate and appropriate blood pressure. Protection or prevention of secondary damage or injury is not part of the immediate or early standard practice following brain injury. Any sequelae of this secondary damage or injury, that is the adverse health conditions or disability, are typically addressed later by rehabilitation. Standard practice to rehabilitate typically begins weeks or sometimes months after the brain injury. Applicant believes that as a result, standard practice that is immediate and rehabilitation standard practice totally miss the point that there is a platinum hour, a golden day and a silver week when the adverse health conditions or the disability resulting from secondary injury to the brain can be reduced or prevented.

[00369] Despite intense efforts to develop therapeutic drugs for the persisting outcomes of brain injury, there is no new drug that has passed phase III clinical trials over the past 30 years (Doppenberg *et al.*, 2004; Loane and Faden, 2010).

THE FORMULATION

ANTICONVULSANTS/ANTIEPILEPTICS

[00370] Anticonvulsant drugs, or antiepileptic drugs, are used, as the name indicates, to treat epilepsy. However, they are also used extensively off-label. For example, the broadest off-label use of gabapentin is to treat neuropathic pain. While anticonvulsant drugs are recommended as treatment of the outcomes of neuropathy they appear to not be used for prevention of neuropathy or protection from secondary injury that results from neurotrauma of any type.

[00371] Anticonvulsants are included in this invention to inhibit reported degenerative processes that trigger and are involved in pathophysiological changes in nerve cells, in neural

support cells and in neural support tissues, particularly endothelial cells, that result from trauma of any type. There is a wide range of different chemical entities in this class of drugs, as indicated herein. Most of these types of anticonvulsant have been implicated in pathophysiology or degenerative changes in nerve cells, neural support cells or neural support tissues and as a result the full class of anticonvulsants, including those known and unknown, is included in the presently disclosed technology and its embodiments.

[00372] Similarly, there is a wide range of downstream mechanisms that are inhibited by anticonvulsants, such as reducing or preventing calcium influx into cells and calcium release from intracellular stores that trigger activation of calcium-dependent catalytic enzymes, and other processes. As a result, this invention includes any chemical entity, known or unknown, that could act to inhibit or interfere with or reduce the activation of mechanisms upon which anticonvulsants do or can act.

[00373] As the degenerative processes that are inhibited or reduced by this class are triggered over the minutes and hours following trauma it is important to administer this class as rapidly as possible when trauma is expected or occurs unexpectedly. As an example, when a clinical trial is run, an anticonvulsant can be administered at a specified time before the traumatic (*e.g.* surgical) event. Selection of the specific time of administration will be governed by factors such as bioavailability of the particular anticonvulsant being run, as well as the type of trauma such as laparoscopic surgery vs. chemotherapy, or the like.

[00374] The class of anticonvulsants is rather broad in chemical composition. For example, anticonvulsants include the barbiturates (such as phenobarbital, methylphenobarbital, metharbital, barbexalone), benzodiazepines (such as clozapam, clonazepam, chlorazepate, diazepam, midazolam, lorazepam), bromides (such as potassium bromide), carbamates (such as felbamate), carboxamides (such as carbamazepine, oxcarbazepine, eslicarbazepine acetate), fatty acids (such as valproic acid, sodium valproate, divalproex sodium, vigabatrin, progabide, tiagabine), fructose derivatives (such as topiramate), GABA analogs (such as gabapentin, pregabalin), hydantoins (such as ethosin, phenytoin, mephentyoin, fosphenytoin), oxazolidinediones (such as paramethadione, trimethadione, ethadione), propionates (such as beclamide), pyrimidinediones (such as primidone), succinimides (such as acetazolamide, sultiamine, methazolamide, zonisamide), triazines (such as lamotrigine), ureas (such as pheneturide, phenacemide) and valproylamides (such as valpromide, valoctamide), and others.

[00375] As a result, irrespective of the mechanism of action of the various types of anticonvulsant, a wide range of different types has been demonstrated to have neuroprotective effects. As examples, these would include anticonvulsants that are generally held to express their effects through actions on voltage-gated membrane-bound sodium and calcium ion channels, such as gabapentin, pregabalin, carbamazepine, oxcarbazepine, lamotrigine and

valproate. They would include those acting on intracellular mechanisms, such as valproate, carbamazepine, lamotrigine. They would include those acting by enhancing GABAergic transmission, such as tiagabine, valproate, gabapentin and levetiracetam. They would include those that enhance GABAergic and reduce glutamatergic transmission, such as topiramate.

Why anticonvulsants/antiepileptics

[00376] The anticonvulsant, pregabalin, reduces negative functional outcome in an animal model, if drug administration is given early after neurotrauma and is continued daily over several days. In the nerve cuff model of peripheral nerve injury, where one or more thin polyethylene cuffs is inserted around one sciatic nerve, pain scores are measured using calibrated von Frey filaments as their effects on tactile withdraw threshold. Typically, in this model withdrawal threshold begins to decrease within 24 hours of model induction, the threshold continues to decrease over the following five to seven days and it remains lower, at a stable level, over the following weeks; the prolonged nature of the tactile hypersensitivity, which is an animal parallel to allodynia that typifies neuropathic pain in humans, provides a temporally stable model with which to study drug actions. As the early phase of this model can be reversed physiologically by removing the cuff at variable times (Dableh *et al.*, 2011), this model is particularly appropriate to study the early events triggered by neurotrauma that lead to adverse outcomes of neuropathology. Specifically, in heretofore unpublished studies, we have found in this animal model that when pregabalin is administered intraperitoneally on a daily basis during the first week the tactile hypersensitivity is reduced compared to a control group given vehicle on a daily basis during this first week. The study included a crossover, whereby the group that had received pregabalin during the first week received daily administrations of vehicle through the second week, and the group that had received vehicle during the first week received daily administrations of pregabalin through the second week. Importantly, the effect of pregabalin administration during the second week was significantly less than it had been in the other group during the first week. Further, during the second week the nociceptive scores in the group that had received pregabalin during the first week remained lower. Together the data suggest that administration of pregabalin during the first week had a greater effect than administration during the second week. The data also suggest that early administration of pregabalin has lasting beneficial effects that persist even after administration has ended. This in turn suggests that pregabalin interferes with very early changes triggered by peripheral nerve injury and it may also be interpreted that pregabalin acts early in these processes to prevent the initiation of at least some cascade of neuropathology or neurodegeneration triggered by the trauma. A person having ordinary skill in the art will understand that there may be permanent or long-lasting beneficial effects of administration of pregabalin, and possibly other anticonvulsants/antiepileptics, and that better outcomes are achieved with earlier administration following a traumatic injury.

[00377] There are several types of anticonvulsant, many of which have been implicated in inhibiting processes that are involved in producing secondary injury following trauma. As a result of the fact that many different anticonvulsants have been implicated for their neuroprotective role. A person having ordinary skill in the art will understand that neuroprotection is considered a class effect here. Some recent evidence suggests that the broad class of anticonvulsants may provide neuroprotection.

[00378] Anticonvulsants have been shown to have preventive effects in human studies. For example, Lapolla *et al.* (2011) have reported that when gabapentin is combined with valacyclovir in patients with acute herpes zoster the rate of postherpetic neuralgia at six months later is reduced. Thus, while it had acute effects, when administered during a phase when the processes leading to neuropathic pain were developing, the anticonvulsant was effective in reducing or preventing the adverse health conditions.

[00379] Animal studies have also provided evidence for preventive effects of a wide range of anticonvulsants on outcomes of neuropathology. This includes animal models of brain injury, where the barbiturates thiopental and pentobarbital were effective (Pérez-Bárcena *et al.*, 2008), glutamate excitotoxicity (lamotrigine; Leng *et al.*, 2012), cerebral ischemia (valproic acid; Liu XS, *et al.*, 2012), spinal cord ischemia (gabapentin; Kale *et al.*, 2011), spinal cord injury including contusion (pregabalin; Ha *et al.*, 2011) and compression (gabapentin; Emmez *et al.*, 2010) models, as well as our own evidence in an animal model of peripheral nerve injury, as indicated above. Treatment of acute seizures with gabapentin in a mouse model has also been shown to have beneficial effects on brain atrophy when measured even four weeks later (Traa *et al.*, 2008).

[00380] Stepień *et al.* (2005) provide a detailed overview of evidence implicating a neuroprotective role for a number of anticonvulsants in a variety of traumatic conditions. As one example, pregabalin has been shown to promote improved histological, biochemical and functional outcomes in a rat spinal injury model.

[00381] Valproic acid administration has been reported to reduce blood-brain barrier disruption in a model of cerebral ischemia (Wang ZF, *et al.*, 2011). Kouzounias *et al.* (2011) report improved neurological outcomes by topiramate administration 30 minutes after cortical contusion in the rat. Engel *et al.* (2012) report a sparing effect of inhibition of the purinergic P2X7 receptor on secondary brain injury following an induced status epilepticus seizure in mice. It has also been reported that neuroprotective effects of anticonvulsants can be increased by co-administration of other chemical entities (Liu Y, *et al.*, 2012).

Anticonvulsants have also been put forward as neuroprotection from excitotoxicity of spinal motor neurones in vitro (Chang *et al.*, 2010) as well as chemotherapy-induced peripheral neuropathy (Argyriou *et al.*, 2010). Pregabalin has been reported to protect from neurotoxic effects of copper (Marmolino and Manto, 2010). Diazepam and phenobarbital have been

reported to protect against scorpion venom toxin-induced epilepsy (Luongo *et al.*, 2009). Additional analogs and other follow-on anticonvulsants, which act via diverse mechanisms, are also entering the market for treatment of a wide range of traumatic events (Rogawski, 2006).

[00382] It is important to note that these different anticonvulsants act via different and diverse mechanisms of action. For example, felbamate is thought to negatively modulate the NMDA receptor through an action on the strychnine-sensitive site and positively modulate the GABAA receptor, as well as to induce cytochrome P450 and inhibit CYP2C19. Yet, others increase GABA levels in the brain, such as vigabatrin, which inhibits GABA-transaminase, and tiagabine, which inhibits GABA uptake into neurones and glial cells. Others have multiple actions, such as topiramate, which enhances GABA-mediated chloride influx into neurones, inhibits AMPA receptor conductance and modulates calcium-dependent action potential generation. Benzodiazepines are allosteric modulators of GABAA receptors. Others act by opening potassium channels.

[00383] As one with skill in the art will understand, the abundant evidence that a wide range of anticonvulsant and antiepileptic drugs, acting via a range of mechanisms, have neuroprotective effects in a wide range of types of neurotrauma indicates the importance of including these drugs as a class in the presently disclosed technology.

When to administer anticonvulsants/antiepileptics

[00384] Most of the scientific literature on anticonvulsants and antiepileptics pertains to acute administration, whether as treatment for seizures or for other purposes. With respect to the presently disclosed technology this reflects the usefulness of this class of compounds for rapid treatment.

[00385] Especially recently, this class of compounds has also been studied for its longer-term effects, particularly persisting effects including persisting effects in cases of trauma as described herein. A recent systematic review and meta-analysis concludes that there is sufficient evidence of beneficial effects of perioperative administration of gabapentin or of pregabalin in reducing the incidence of chronic post-surgical pain at two months or more after various types of surgery, including arthroplasty, thyroid surgery, breast surgery, cardiac surgery, hysterectomy surgery, inguinal herniorrhaphy and caesarian delivery.

[00386] A survey of the literature indicates a wide range of times used for administration of an anticonvulsant in clinical trials and in health care delivery. However, of particular relevance to the presently disclosed invention embodiments the recently published Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) demonstrates that the earlier anticonvulsant treatment is administered, the more effective it will be.

[00387] Pharmacokinetics and pharmacodynamics of anticonvulsants, especially to the target tissues involved in the presently disclosed technology, are rapid enough that this class of

compound is appropriate to meet the need for immediate effect, as part of a formulation to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury.

[00388] Anticonvulsants are included in the formulations, including when administered in a hospital or clinical setting before anticipated trauma. Anticonvulsants are also included in the formulations for administration in a hospital or clinic as an early treatment for unanticipated trauma. Anticonvulsants are effective in treating acute seizures and pain, consistent with their rapid absorption and distribution. However, as the processes of secondary injury progress over days into weeks, and as shown in animal neurotrauma models, daily administration of anticonvulsants should be continued as needed, for example for up to three weeks.

[00389] The data from human as well as animal studies suggest that the window of opportunity for optimal effective benefit from administration of an anticonvulsant for treatment of trauma to nerve cells, or neural support cells or neural support tissues is within a platinum hour, a golden day and a silver week.

[00390] A person having ordinary skill in the art will understand that anticonvulsants as a class of compound are effective when administered before or after a traumatic event, that anticonvulsants have been shown to be effective in reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury and that these compounds continued to be of benefit when administration is continue as needed.

Summary of anticonvulsants/antiepileptics

[00391] A person having ordinary skill in the art will understand that rather than considering each mechanism separately, anticonvulsants/antiepileptics share antiepileptic and brain-sparing neuroprotective properties as a class of compounds. A person having ordinary skill in the art will also understand that that this sharing of anti-seizure properties indicates that excessive neuronal activity can be reduced or prevented via a number of different mechanisms. It is this end result that is important. The presently disclosed invention embodiments propose evidence-based formulations, methods and procedures to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury. This applies specifically to reducing or preventing the secondary injury that occurs as a result of event-triggered trauma, whether physical, surgical, chemical, metabolic or other. This applies whether it is to the central nervous system, to the enteric nervous system or to the peripheral nervous system.

NEUROSTEROIDS/NEUROACTIVE STEROIDS

[00392] Neurosteroids, which are also called neuroactive steroids, include pregnenolone, progesterone and dehydroepiandrosterone, their metabolites and their sulfates and other derivatives as described herein. Neurosteroids are generally thought of as peripherally-acting steroids but they are also synthesized by nerve cells and glial cells in the central nervous

system. Neurosteroid receptors are also synthesized by nerve cells and support cells in the central nervous system and in the periphery. Enzymes are present in such neural tissue for the breakdown of neurosteroids to other metabolites.

[00393] Pregnenolone is derived from cholesterol and converted to progesterone and 17-hydroxy pregnenolone. Progesterone gives rise to mineralocorticoids and 17-hydroxy-progesterone. 17-Hydroxy-pregnenolone is also converted to 17-hydroxy-progesterone as well as glucocorticoids. Dehydroepiandrosterone is converted to androgens and estrogens. Cholesterol is transported from intracellular stores to the mitochondria by two transporter proteins, peripheral benzodiazepine receptor and steroidogenic acute regulatory protein. Within the mitochondria the cytochrome P450 side chain cleavage enzyme, P450_{scc}, converts cholesterol to pregnenolone. Progesterone itself is metabolized in one or more steps to active metabolites, including aldosterone, 5 α -dihydroprogesterone, 3 α ,5 α -tetrahydroprogesterone (called allopregnanolone), and others as described herein.

[00394] Neurosteroids are thought to act through a number of different mechanisms. For example, progesterone acts on progesterone receptors that are distributed throughout the central and peripheral nervous systems. Progesterone may also act through a diverse number of other mechanisms to protect neurones and glial cells from secondary injury, including acting on intracellular receptors, membrane ion channels and allosteric sites on membrane-bound receptors as described herein.

Why neurosteroids/neuroactive steroids

[00395] Neurosteroids, particularly progesterone, have been implicated in neurone-sparing roles throughout the central and peripheral nervous systems. While progesterone is the neurosteroid with most supportive evidence, the plethora of biosynthetic and metabolic pathways involved raise the possibility that beneficial effects may be due not only to the neurosteroid administered but also to downstream neurosteroid metabolites.

[00396] As one example, inhibition of intracellular and membrane calcium signaling is thought to be fundamental to a number of the neuroprotective effects of progesterone. It has been suggested that these beneficial effects of administered progesterone may be due to the parent steroid or to any of its active metabolites.

[00397] We have found that early administration of progesterone, as a representative of the class of neurosteroids, given intraperitoneally prevents the development of symptoms of peripheral nerve injury (Dableh and Henry, 2011). As described elsewhere, an animal model of peripheral neuropathy was used, in which a thin polyethylene cuff is inserted around the sciatic nerve. This typically induces a tactile hypersensitivity in the respective hind paw that begins to develop within 24 hours, reaches a maximum at five to seven days, and persists. When progesterone was given starting one hour after model induction, and was given daily for the subsequent 10 days tactile hypersensitivity developed over the first 20 days similar to

that in a control group given vehicle only. However, by 30 days the two groups were different, and the treatment group exhibited no tactile hypersensitivity. This effect of progesterone persisted to the end of the study period, which ended at day 85, even though the progesterone treatment ended on day 10.

[00398] Importantly, in another group, in which progesterone was given for 11 days, starting on day 20, there was no difference between this experimental group and the control group. The data from these animal studies suggest that early treatment with progesterone is effective in inhibiting mechanisms leading to the secondary injury that develops over the three weeks following peripheral nerve trauma. In another experiment, it was found that administration of progesterone starting one hour after model induction and given daily for the subsequent four days was less effective than it was when it was given early starting one hour after model induction and given daily for the subsequent 11 days. Here, the data suggest that the processes by which progesterone is acting are immediate but continue over a period of approximately three weeks, and that beneficial effects of progesterone are achieved by early and daily administration over a period of ten days.

[00399] Evidence from other studies suggests that neurosteroids, as a class of drugs (Sayeed *et al.*, 2009; Singh *et al.*, 2010), including metabolites and derivatives of neurosteroids, promote restorative processes, including those described in the sections on brain injury, on central nervous system ischemia, on spinal cord injury, on enteric nervous system injury and on peripheral nerve injury. As one example, in an animal model of peripheral nerve injury and chemotherapy-induced peripheral nerve injury, progesterone and dihydroprogesterone have been found to stimulate production of reelin, which is integral in neural repair. Similarly, in an animal model of spinal cord injury progesterone not only reduces degeneration of spinal motoneurons but also increases brain-derived neurotrophic factor, which is thought to provide a trophic environment to promote myelination.

[00400] In an NIH-NINDS contract undertaken to replicate the results from other studies, it was confirmed that pregnenolone, when administered along with lipopolysaccharide and indomethacin, improved myelin and axon sparing in an animal model of spinal cord injury, as well as promoting axonal sprouting. This study and others are leading to the concept that combination therapy that couples neurosteroid treatment with other active ingredients might yield improved outcomes over therapeutic interventions that target a single mechanism, gene or locus (Vinck and Nimmo, 2009; Stein and Wright, 2010); a rationalized approach to combination therapy is important, though, to optimize complementary mechanisms and to minimize co-administration with contraindicated approaches (Aguirre *et al.*, 2010).

[00401] Neurosteroids and related hormone therapy have been proposed to have positive outcomes in human clinical trials for traumatic brain injury (Stein and Wright, 2010), central nervous system ischemia (Gibson *et al.*, 2009), spinal cord injury (Popovic *et al.*, 2011) and

peripheral nerve injury (Roglio *et al.*, 2009). A consensus is that the area is in need of clinical trials, particularly phase III clinical trials (Vinck and Nimmo 2009; Stein, 2011). Xiao *et al.* (2008) have reported improved neurological outcomes in a prospective, randomized, placebo-controlled phase III clinical trial in approximately 80 patients who were treated within eight hours after brain injury. An NIH-sponsored trial is apparently on-going at present (Wright *et al.*, 2007). With the exception of combination therapy with vitamin D (Cekic *et al.*, 2009) what has not appeared to be considered strongly is the improved benefit of combination with other neuroprotective or neurone-sparing therapeutics, particularly a rationalized timed treatment with such combinations (Vinck and Nimmo, 2009).

[00402] A person having ordinary skill in the art will understand that neurosteroids have specific beneficial effects in sparing secondary injury from brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury.

When to administer neurosteroids/neuroactive steroids

[00403] Information regarding time of administration of neurosteroids derives from animal studies, and much of this information does not relate to the optimal time of administration over a range of different times. Most studies on neuroprotective effects of neurosteroids involve preadministration, which supports the precautionary and the prophylactic uses as described herein. However, given the rapid onset of the processes of secondary injury as described herein, a person having ordinary skill in the art will understand that immediate administration is advised for any and all therapeutic interventions to reduce or prevent the development or the risk of development of secondary neuropathology as a result of traumatic injury. Studies on the absorption, metabolism and clearance of neurosteroids, particularly of progesterone, report that after oral administration maximum concentrations in plasma occur within one to three hours.

[00404] Early beneficial effects of neurosteroids are supported by recent overviews of the neuroprotective effects of progesterone administration, which point out that progesterone over the short term reduces oedema and the production of inflammatory cytokines, and restores expression of beneficial local factors including those involved in the early stages of remyelination, with an overall improvement in functional outcomes (De Nicola *et al.*, 2009). In addition, more prolonged treatment with progesterone has been shown to promote recovery, by reducing motoneurone degeneration and stimulating remyelination (De Nicola *et al.*, 2009). This evidence suggests that progesterone has both neurotrophic as well as neuroprotective properties.

[00405] Neuroprotection by neurosteroids as a class, from early events in secondary injury, includes inhibition of excitotoxicity, inhibition of expression of inflammatory mediators and of glial cell activation, inhibition of expression of degradative enzymes. As a person having

ordinary skill in the art will understand that to optimize beneficial effects of administration of neurosteroids and given the relatively rapid rate of absorption matched with the rapid time course of development of secondary injury processes, the earliest possible administration of the formulations of the presently disclosed technology will offer the greatest possible benefit in reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury of any type. That is to say, that neurosteroid administration will be most effective when taken or given early during the platinum hour, as well as throughout the golden day and silver week.

[00406] Neurosteroids are included in the formulation, including when administered in a hospital or clinical setting before anticipated trauma. Neurosteroids are also included in the formulations for administration in a hospital or clinic as an early treatment for unanticipated trauma. As the processes of secondary injury progress over days into weeks, and as shown in animal neurotrauma models, daily administration of neurosteroids should be continued as needed, including for up to three weeks in the present application.

[00407] A person having ordinary skill in the art will understand that neurosteroids as a class of compound are effective when administered before or after a traumatic event, that neurosteroids have been shown to be effective in reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury and that neurosteroid compounds continue to be of benefit when administration is continued as needed.

5.2.3. Summary

[00408] Neurosteroids have thus been shown to be effective in humans for limited indications, and neurosteroids are also in use clinically. However, a review of the scientific literature indicates that neurosteroids have not been thoroughly investigated for promoting the natural restorative mechanisms triggered by trauma. Similarly, neurosteroids have not been thoroughly investigated for inhibiting natural degenerative mechanisms triggered by trauma. Research reports in the available literature are not directed at the objective of reducing or preventing secondary injury following event-triggered trauma, whether for brain injury, cerebral ischemia, spinal cord injury, enteric nervous system injury or peripheral nerve injury. A person having ordinary skill in the art will understand that there appears to be no current literature pertaining to the clinical or medical administration of neurosteroids as a restorative or preventive means of reducing the secondary injury sequelae that may occur. This is despite data from incidence studies on trauma-induced disability. Further, there appears to be no literature indicating that neurosteroids have been tested when administered at an early time before the manifestation of symptoms of these secondary injury processes. The presently disclosed technology and its embodiments include the neuroprotective effects that may derive from administration of a neurosteroid on neurones (Sayeed *et al.*, 2009), on glial support cells

(Jiang *et al.*, 2011) and on neural support tissues such as vascular or other endothelial cells (Wang *et al.*, 2009; Ishrat *et al.*, 2010). In the presently disclosed invention embodiments and its embodiments, administration of these compounds necessarily begins as soon as possible after trauma, and is administered for a period of at least several days in order to optimize benefit of promoting or potentiating restorative processes, in order to optimally reduce or prevent the development or the risk of development of neuropathology and secondary injury following trauma. Also, to optimize benefit, in this invention a neurosteroid is combined with one or more other preventive therapeutic compounds in the formulation, including those acting to promote, facilitate or potentiate the restorative processes that lead to cell and tissue function and health, as well as including those acting to inhibit degenerative processes that lead to this secondary injury.

TACHYKININS, RECEPTORS AND THEIR ANTAGONISTS

[00409] Substance P is an 11 amino acid peptide discovered first in 1932 as an unidentified gut extract that produced a rapid contraction of isolated gut tissue in vitro. The chemical structure was identified 40 years later and was the first neurotransmitter whose function was linked specifically to pain transmission (Henry, 1976). Since that time it has come to be implicated in a number of different neural functions in the central and peripheral nervous systems as well as a target for drug development.

[00410] Identified as a member of the kinin family, because of the rapid contraction of gut tissue it was classified as a tachykinin, a class mainly of three principle peptides, substance P, neurokinin A and neurokinin B; substance P and neurokinin A are encoded by the preprotachykinin TAC1 gene, neurokinin B by TAC3, with other less well-studied tachykinins by the TAC4 gene.

[00411] Each of these peptides acts preferentially on a receptor, NK-1, NK-2 and NK-3, respectively for substance P, neurokinin A and neurokinin B, although as a result of sharing a common terminal sequence there is cross-talk between the peptide ligands and these receptors. These receptors belong to the G protein-coupled receptor superfamily and are encoded by respective genes TACR1, TACR2 and TACR3. The human NK-1 receptor is a 407 amino acid protein coupled to G protein Gq and mediates signaling chiefly through calcium mobilization within the cell.

[00412] These receptors and their activation by a range of ligands are included in the presently disclosed technology, which is a rationalized, sequenced, polypharmacy approach to reducing or preventing trauma-induced neuropathology. It is important to point out, though, that these receptors and ligands acting on these receptors have been implicated more broadly in a range of biological functions and disorders governed by the central and peripheral nervous systems.

[00413] Neurokinin receptor isoforms have also been identified, and these may play unique

roles besides those filled by the full-length receptors. Due to the crosstalk between the various ligands and the various tachykinin receptors, the presently disclosed technology and its embodiments, as well as the range of potential mechanisms where the presently disclosed technology and its embodiments have the potential to reduce or prevent the development of secondary injury, the presently disclosed technology and its embodiments are intended to include all members of the family of tachykinin receptors, known or not known, including receptor isoforms, as well as any ligands, known or not known, that occupy, activate or deactivate, or in any way interact or interfere with these receptors.

Why tachykinin receptor antagonists

[00414] It has been reported that administration of an NK-1 receptor antagonist, CP-96,345, promotes the recovery from peripheral nerve injury in an animal model (Dableh *et al.*, 2011). A rat model of peripheral nerve injury was induced by placing a thin polyethylene cuff around one sciatic nerve in the rat. At the first reading of nociceptive scores, measured as withdrawal threshold from calibrated von Frey filaments, cuff-implanted rats demonstrated tactile hypersensitivity, the animal parallel to allodynia in humans. This effect became maximum at day three and persisted throughout the testing period, which ended 42 days after model induction. A physiological reversal of this tactile hypersensitivity was demonstrated in another group of rats by removing the cuff after 24 hours, and monitoring withdrawal threshold until 42 days after model induction. In this case, the tactile hypersensitivity developed only partially, and by day 18 it had reversed completely. In contrast, in a third group, when the cuff was removed on the fourth day recovery was delayed until day 25, and full recovery was never attained. This partial recovery indicated that between 24 hours and four days processes occur that result in prolonged, perhaps permanent, changes in nociceptive mechanisms, leading to tactile hypersensitivity.

[00415] Using this model of partial physiological reversal of tactile hypersensitivity, the effects of administration of the NK-1 receptor antagonist were tested during the period that the cuff was implanted, administering the antagonist on days 1, 2, 3 and 4. In this case, tactile sensitivity was reversed by day 10, and this remained on the last day of testing, which was on day 25 after model induction. This suggests that the processes that occur between 24 hours and four days after peripheral nerve injury and that lead to prolonged changes in nociceptive mechanisms, were prevented by administration of the NK-1 receptor antagonist and that upon peripheral nerve injury a window of opportunity for effective medical intervention may be open and, as time passes, the window closes progressively until, at some point, it is shut and the pain is entrenched as chronic neuropathic pain that is refractory to medical intervention. As a result, the earliest possible time of intervention is important, as the degenerative processes involving these mechanisms are progressing from the time of the trauma.

[00416] Other evidence implicates tachykinins and tachykinin receptors in secondary injury

resulting from trauma and leads to tachykinin receptor antagonists as promising therapeutic drugs to reduce or prevent the development, or the risk of development, of neuropathology as a result of traumatic injury. An analysis of post-mortem brains from patients who had succumbed to brain injury demonstrated that substance P is greater in brains that showed neuropathology compared to similar patients that did not show neuropathology. Animal studies have also provided a strong link between substance P in the brain and secondary injury. For example, in a recent review it was pointed out that substance P is released in the brain in animal models of brain injury, and facilitates the increase in permeability of the blood-brain/spinal barrier and the development of vasogenic oedema and cell death, and these effects are reduced by inhibition of substance P release and by the administration of NK-1 receptor antagonists.

[00417] As substance P is catalyzed by local enzymes it is important to point out that the administration of an angiotensin-converting-enzyme inhibitor has been reported to increase histological damage as well as motor deficits in an animal model of brain injury. This increase was attributed to inhibition of the breakdown of locally released substance P that normally occurs in brain tissue by angiotensin-converting-enzyme. This evidence supports the concept that substance P released as a result of traumatic injury to the nervous system plays a role in secondary injury to nerve cells and neural support cells. Recent reviews substantiate protective effects of tachykinin receptor antagonists in brain injury models as well as central nervous system ischemia models. With respect to ischemia, substance P has also been implicated in promoting clot formation through tachykinin receptors.

[00418] Substance P has also been shown to contribute to neurone cell death in other neurotoxic conditions. For example 6-hydroxydopamine has been shown to cause the release of substance P in cell culture and this release correlates with expression of a marker of cell death.

[00419] Beyond the involvement of substance P in processes leading to local pathology, the focus of much research, it is also relevant and important to point out the participation of substance P in more remote areas of the body. For example, it has been suggested that substance P, among other proinflammatory agents, may be responsible for distant organ damage and multiple organ dysfunction syndrome that follow traumatic burns. Substance P has also been implicated in tissue inflammation and oxidative stress after inhalation of oil smoke, also considered a traumatic event due to the adverse health outcomes.

[00420] The enteric nervous system can also be injured by trauma as described herein. Therefore, reducing or preventing development, or the risk of development, of neuropathology of neurones in the enteric nervous system is included in this invention. These neurones and their support cells and support tissues are at risk in a number of conditions. These conditions include, but are not exclusive to, radiation, where substance P is released

and has been implicated in nerve cell injury and generation of the inflammatory response.

[00421] NK-1 receptor antagonists have been the focus of intense research effort since the introduction of the first non-peptide antagonist CP-96,345 and its demonstrated biological effectiveness in vivo (Radhakrishnan and Henry, 1991). To date, over 300 patents have been filed for over 25 new chemical entities targeting this receptor. Among the reported beneficial outcomes of administration of NK-1 antagonists is neuroprotection in animal models. For example, in a recent review of the actions of substance P and potential therapeutic benefit of administration of NK-1 antagonists, Thornton *et al.* (2010) stress the potential benefit of these antagonists in prevention of secondary injury arising from brain injury, spinal cord injury and ischemic stroke. This extensive review did not, however, distinguish treatment of established symptoms or disorders from intervention to reduce or prevent secondary injury resulting from trauma. Pre-emptive administration of the NK-1 receptor antagonist, aprepitant (Emend, Ivermend) has been used as a preventive measure, but this administration was for acute effects on chemotherapy-induced nausea and vomiting, upon which the antagonist proved to be effective when administered in conjunction with another antiemetic drug. Aprepitant was not tested for effects on chemotherapy-induced cell death or on neuropathology or processes that lead to loss of function of nerve cells, neural support cells or neural support tissues.

[00422] Other NK-1 receptor antagonists that have reached clinical trials include fosaprepitant, the prodrug of aprepitant that is given intravenously, casopitant (Rezonic, Zunrisa), lanepitant (Eli Lilly), maropitant (Cerenia; marketed by Pfizer for treatment of acute vomiting in dogs), vestipitant (GSK) and vofopitant (GSK). Some NK-1 receptor antagonists have been withdrawn from clinical trials, including serlopitant and orvepitant.

[00423] Endpoints for treatment include mainly acute nausea and vomiting induced by chemotherapy. A few clinical trials have been run targeting acute treatment of tinnitus, insomnia, depression, anxiety and post-traumatic stress disorder, but these trials have not culminated in positive outcomes (Mathew *et al.*, 2011; Ratti *et al.*, 2011). In particular, despite stellar effects on acute nociception in animal models, clinical trials on NK-1 receptor antagonists have failed to demonstrate effectiveness in acute treatment of chronic pain in humans (Goldstein *et al.*, 2001; Diener, 2003).

[00424] Current clinical literature pertaining to human use of aprepitant, the subject of several recent reviews, recommends administering orally at an initial dose of 125 mg on day one of treatment, followed by a dose of 80 mg on each of days two and three of a three-day treatment. This regimen is for treatment of acute nausea and vomiting at the time of chemotherapy, an anticipated trauma, in a clinical setting. Aprepitant has also been reported to decrease post-operative nausea and vomiting in patients undergoing abdominal surgery; a

dose of 40 mg given before surgery was found to be effective. Similarly, when given 180 minutes before induction of surgery at a dose of 80 mg aprepitant has been reported to reduce post-operative nausea and vomiting after laparoscopic gynecological procedures. Recent reports substantiate the effectiveness of NK-1 receptor antagonists for surgically-induced post-operative and post-discharge nausea and vomiting.

[00425] As another example is typically administered intravenously. Current clinical literature recommends a bolus ranging from 115 to 150 mg of fosaprepitant followed by aprepitant orally on days two and three of a three-day regimen, for chemotherapy-induced nausea and vomiting.

[00426] Casopitant mesylate, another NK-1 receptor antagonist, has been tested in phase III international multicentre clinical trials also for its effects on chemotherapy-induced nausea and vomiting, at a single oral dose of 150 mg at an intravenous dose of 90 mg followed by daily oral doses of 50 mg on days two and three, in a three-day regimen.

[00427] A review of the literature did not find reports where long term outcomes of treatment with an NK-1 receptor antagonist were studied.

[00428] The duration of treatment with an orally administered NK-1 receptor antagonist will depend upon the specific trauma and on the specific clinical context, but it has been reported that aprepitant has been administered daily over a 14 day treatment regimen, with no adverse effects over an observation period of 42 days. Phase III clinical trials have also demonstrated aprepitant to be well tolerated through five cycles of treatment. As a result, administration of an NK-1 receptor antagonist can and should be continued as long as it is clinically beneficial.

[00429] In a phase IB safety study, aprepitant was well tolerated at a dose of 125 mg daily for 14 days. Casopitant mesylate, administered as 30 mg per day, as 80 mg per day or 120 mg per day, for eight weeks has also been found to be well tolerated.

[00430] Given even the limited literature that is presently available, it appears that it is not unreasonable to administer an NK-1 receptor antagonist for such an extended period of time as necessary to be clinically beneficial.

[00431] NK-2 receptors are also covered in this invention due to the cross-reactivity with substance P, which has been shown to contribute to degenerative responses to trauma, as outlined herein.

[00432] NK-3 receptor antagonists are included in the presently disclosed technology due to the cross-reactivity with substance P, which has been shown to contribute to degenerative responses to trauma, as outlined herein. Despite a number of patent applications on NK-3 receptor antagonists clinical trials have been disappointing so at present there are no available landmark data to define the optimum time and duration for administration of this class of antagonists.

When to administer tachykinin receptor antagonists

[00433] An NK-1 receptor antagonist is included in the presently disclosed technology and its embodiments in order to prevent activation of this receptor, whether by substance P or any other ligand, and to prevent downstream mechanisms, such as calcium influx into cells and calcium release from intracellular stores that trigger activation of calcium-dependent catalytic enzymes and other processes. With a surgical trauma such as orthopedic knee replacement surgery substance P is observed in spinal cerebrospinal fluid at the earliest time point of two hours (Buvanendran *et al.*, 2011). Thus, as these processes are triggered over the minutes, hours and days following trauma it is important to block NK-1 receptors as rapidly as possible when trauma is expected, as in the many cases described herein, or when it occurs unexpectedly or by accident.

[00434] With regard to the time of intervention with an NK-1 receptor antagonist, it can be administered at a specified time according to the nature of the injury or trauma.

Administration can be at the time of the traumatic event or at a specified time before the traumatic event. Selection of the timing will depend upon the particular indication, such as laparoscopic surgery or chemotherapy or the like, as well as the route of administration and the bioavailability of the given NK-1 receptor antagonist.

[00435] A survey of the literature did not find human clinical data indicating studies where the time of administration of a tachykinin receptor antagonist was assessed in terms of outcome against a known trauma. However, approval of NK-1 receptor antagonists for the treatment of acute nausea and vomiting supports early access to target tissues as well as efficacy for early interventions.

[00436] Current literature from animal studies supports beneficial effects of administration of NK-1 receptor antagonists within minutes or hours of trauma. For example, in a rat model of brain injury Donkin *et al.* (2009) have found that administration of N-acetyl-L-tryptophan, given as an NK-1 receptor antagonist 30 minutes after trauma, has beneficial effects on outcomes, such as reducing the increase in vascular permeability and the development of oedema that typically develop in this model. In a subsequent study Donkin *et al.* (2011) compared the benefits of N-acetyl-L-tryptophan with a more lipid-soluble analog, L-732,138 and found that whereas the parent compound had beneficial effects limited to five hours, the more lipid-soluble analogue had beneficial effects when given as late as 12 hours after trauma. This suggests that while immediate intervention is optimal, NK-1 receptor antagonism as late as 12 hours after trauma retains beneficial effects, at least in an animal model of brain injury. This in turn suggests that the processes that are inhibited by NK-1 receptor antagonism proceed from the time of trauma but at a rate where inhibition will still be effective if initiated as late as 12 hours after trauma.

[00437] Similar findings have been reported by Turner *et al.* (2011) when N-acetyl-L-

tryptophan was given as an NK-1 receptor antagonist two hours after reperfusion in a rat model of reversible cerebral ischemia. N-acetyl-L-tryptophan was effective in reducing cerebral oedema, loss of integrity of the blood-brain barrier and functional deficits.

[00438] The studies of Donkin *et al.* (2009, 2011) also suggest rapid absorption and bioavailability of aprepitant, properties also reported for casopitant mesylate (Pagiarusco *et al.*, 2011).

[00439] NK-2 receptors are also covered in this invention due to the cross-reactivity with substance P, which has been shown to contribute to degenerative responses to trauma, as outlined herein.

[00440] NK-3 receptors are also covered in this invention due to the cross-reactivity with substance P, which has been shown to contribute to degenerative responses to trauma, as outlined herein. Despite a number of patent applications on NK-3 receptor antagonists clinical trials have been disappointing so at present there are no available landmark data to define the optimum time and duration for administration of this class of antagonists (Malherbe *et al.*, 2011).

[00441] NK-1 receptor antagonists especially but not exclusively are included in the formulations, including when administered in a hospital or clinical setting before anticipated trauma. NK-1 receptor antagonists are also included in the formulations for administration in a hospital or clinic as an early treatment for unanticipated trauma. NK-1 receptor antagonists are effective in treating acute nausea and vomiting, consistent with their rapid absorption and distribution. However, as the processes of secondary injury progress over days into weeks, and as shown in animal neurotrauma models, daily administration of NK-1 receptor antagonists should be continued as needed.

[00442] The data from animal studies suggest that the window of opportunity for optimal effective benefit from administration of NK-1 receptor antagonists for treatment of trauma to nerve cells, or neural support cells or neural support tissues is within a platinum hour, a golden day and a silver week.

[00443] A person having ordinary skill in the art will understand that NK-1 receptor antagonists as a class of compound are effective when administered before or after a traumatic event such as chemotherapy and that these compounds continue to be of benefit when administration is continued as needed.

Summary on NK-1 receptor antagonists

[00444] NK-1 receptor antagonists have thus been shown to be effective in humans for limited indications, and some are marketed for human and animal use. Yet from a survey of the literature it appears that these antagonists have not been investigated for possible beneficial effects in reducing or preventing secondary injury following trauma, whether brain injury, cerebral ischemia, spinal cord injury, enteric nerve injury or peripheral nerve injury.

With the exception of preventing acute nausea and vomiting, there does not appear to be a literature pertaining to effectiveness or efficacy of NK-1 receptor antagonists in the absence of symptoms. The presently disclosed invention embodiments include the administration of an NK-1 receptor antagonist in the formulation given at the time of trauma or before a possible or probable trauma, to reduce or prevent the development of secondary injury following trauma.

LITHIUM-RELATED/LITHIUM-CONTAINING COMPOUNDS

[00445] Lithium is a monovalent cation that belongs to the group of alkali metals together with sodium, potassium and other elements, with which it shares some of its properties. Lithium carbonate, lithium citrate and lithium chloride have been approved for human use as prescription drugs. The most commonly prescribed lithium salt is the carbonate.

[00446] In terms of biological effects, lithium is best known as a mood stabilizer, prescribed for over 60 years for bipolar disorder, and to a lesser extent for depression. While the specific mechanisms by which mood is stabilized remain unclear, lithium has a broad range of actions and promotes restorative changes as well as inhibits degenerative changes triggered by trauma, through three principle actions. That is, lithium has both neurotrophic and neuroprotective properties.

[00447] In terms of promotion of restorative changes, one principal action of lithium-containing drugs is inhibition of glycogen synthase kinase-3 β , an enzyme that inhibits axon growth cone development and proliferation. Thus, one action of lithium-related drugs is to disinhibit a restorative process following trauma.

[00448] Another principal action of lithium-containing drugs is induction of cellular signaling by brain-derived neurotrophic factor (BDNF), which promotes pathways involved in cell survival, as well as upregulation of the BDNF receptor, tyrosine receptor kinase B. BDNF has a number of actions, including stimulation of cell-surface trophic factor receptors such as tyrosine receptor kinase B (TrkB), the receptor of brain-derived neurotrophic factor, insulin, and other growth factors. BDNF also activates multiple survival pathways including the phosphoinositide 3-kinases (PI3K)/Akt pathway and the MAP kinase kinase (MEK)/extracellular-signal regulated kinase (ERK) pathway. BDNF increases progenitor cell proliferation in brain and spinal cord following ischemia. Thus, another broad action of lithium-containing drugs is to promote cell-sparing trophic processes following trauma.

[00449] A third action is inhibition of calcium influx into neurones via the N-methyl-D-aspartate glutamate receptor. This action results from the attenuation of constitutive phosphorylation at Tyr1472 of the NR2B subunit of the NMDA receptor, which is catalyzed by Fyn, a member of the Src tyrosine kinase family. Neither total tyrosine protein kinase activity nor that of tyrosine protein phosphatase is affected by this drug, indicating the selectivity of the modulation of the NMDA receptor and its contribution to neuroprotection.

Thus, the third principal action of lithium- containing drugs is broadly to protect against calcium-dependent intracellular mechanisms that lead to loss of cell function or to cell death.

[00450] Additional actions have also been reported for lithium-related drugs that may impact on secondary injury to improve the functional outcomes from injury resulting from trauma. These include several actions that promote restorative processes, such as upregulation of anti-apoptotic pathways including those involving Bcl-2 and the cytoprotective protein, heat shock protein 60 as well as activation of the P13K/Akt cell survival pathway.

[00451] Lithium also inhibits degenerative processes, via several mechanisms. These include downregulation of apoptotic proteins, downregulation of the pro-apoptotic p42 pathway and inhibition of microglia activation, depletion of inositol that otherwise inhibits growth cones in cultured sensory neurones, as well as inhibition of phosphatases that interfere with the function of cell surface G protein-coupled receptor.

Why lithium

[00452] Widespread positive outcomes have been reported from lithium administration in animal models. These include improved return toward normal structural and functional measurements in animal models of brain ischemia and brain injury, and inhibition of oxidative stress in vitro and in vivo. Lithium has even been shown to produce inhibition of oxidative stress in healthy volunteer human subjects. Lithium brings about a decrease in excitotoxicity, as observed in neuronal cultured cells and in animal models of stroke, reduced numbers of neurone cell deaths following brain ischemia, activation of progenitor cells and restoration of blood circulation to the brain. Lithium leads to improved remyelination of injured axons and reduced volume of ischemic neuronal injury. Neuronal progenitor cell apoptosis induced by irradiation has also been reported to be reduced by administration of lithium chloride.

[00453] As a result of these reported neurotrophic as well as neuroprotective effects, lithium-related drugs can be seen as both promoting restorative processes and inhibiting degenerative processes in response to traumatic insults to nerves, nerve cells, neural support cells and neural support tissues. As an example, in a recent study of gene expression profiles of bipolar disorder responders vs. non-responders to lithium treatment, one month after treatment initiation several anti-apoptotic genes including Bcl2 and insulin receptor substrate 2 were up-regulated, while pro-apoptotic genes, including BCL2-antagonist/killer 1 and BCL2-associated agonist of cell death, were down-regulated.

[00454] This concept of neurotrophic as well as neuroprotective effects of lithium-related drugs has also been supported in a number of recent reviews. These diverse positive outcomes position lithium-related drugs uniquely among other therapeutic approaches because they possess actions that both promote cell survival as well as inhibit mechanisms that lead to loss of cell function or cell death. Lithium has been proposed as a multifunctional neuroprotectant.

[00455] Beyond the direct effects of lithium-related drugs on nerve cells, neural support cells and neural support tissues lithium has also been reported to improve oxygenation and vascularization of brain. This may be attributed to lithium's property of increasing protein levels of matrix metalloproteinase 9 (MMP9), essential in membrane structure, as well as vascular endothelial growth factor, which is involved in angiogenesis, neurogenesis and neuroprotection. Lithium has also been reported to increase progenitor cell proliferation in both ischemic and non-ischemic brain and spinal cord.

[00456] Lithium has been reported to have neurotrophic and neuroprotective effects when administered to animal models of neurotrauma. For example, in a rat cortical impact model of brain injury lithium chloride administration 30 minutes after injury and daily for five days reduced hippocampal neuronal cell loss and improved cognitive function measured as spatial learning and memory.

[00457] Lithium also improves spatial learning and memory in a mouse brain injury model. Given at 15 minutes as well as daily for three weeks, lithium chloride improved scores in the Y-maze test as well as in the Morris water maze test when measured ten to twenty days after model induction. Lithium chloride also decreased the trauma-induced expression of beta amyloid peptide and its cleaving enzyme BACE1 (beta amyloid precursor protein cleaving enzyme-1).

[00458] In another report on this mouse model of brain injury, lithium chloride was found to improve learning and memory, and to decrease neuronal cell death in the hippocampus.

[00459] In yet another mouse model of brain injury lithium chloride decreased neurone cell loss in cerebral cortex, reduced cerebral oedema and reduced the expression of the pro-inflammatory cytokine, interleukin-1 β .

[00460] Lithium chloride has been reported to have beneficial effects when administered to animal models of central nervous system ischemia. For example, with long term pre-treatment with lithium chloride a decrease in infarct volume and in neurological deficits has been observed in a permanent middle cerebral artery occlusion rat model as well as in a transient occlusion followed by reperfusion model. In a global brain ischemia model in the gerbil, seven-day pre-treatment with lithium chloride has been reported to lead to an increase in viable cells in the hippocampus and a decrease in the number of apoptotic cells. Functional benefits of treatment with lithium chloride include improved recovery of spatial learning, memory and behavioral deficits. Lithium chloride has been shown to reduce excitotoxicity-related brain damage following ischemic events, including brain ischemia-induced increases in Src-mediated tyrosine phosphorylation of NR2A, and the interaction of NR2A with Src and Fyn, which is mediated by postsynaptic density protein 95.

[00461] Lithium chloride has been reported to support regeneration of spinal neurones after spinal cord injury by inhibition of chondroitinase ABC in a rat model, suggesting a possible

role in restorative responses following nerve injury. Lithium chloride has also been reported to enhance proliferation and neuronal differentiation of neural progenitor cells in adult rat spinal cord and to reduce microglia and macrophage activation and thus the local immune response. Lithium chloride stimulates proliferation of neural stem cells, mesenchymal stem cells, hematopoietic stem cells and embryonic stem cells. It stimulates T cells and enhances survival of neural stem cells.

[00462] A phase I clinical trial examining the safety and pharmacokinetics in chronic spinal cord injury patients indicated that lithium carbonate is well tolerated over the first two weeks and that individual titration is essential to maintain optimal serum levels within the therapeutic range. Yet in a phase II clinical trial lithium carbonate was found to be without effect on neurological symptoms in spinal cord injury patients.

[00463] With regard to the presently disclosed invention embodiments, it is relevant that this phase II clinical trial was run only on patients with stable chronic spinal cord injury. It was not tested on patients immediately after, or even within days of spinal injury, and thus it is not known whether there could be beneficial effects of lithium carbonate administration on protecting against secondary nerve injury following spinal cord trauma. Applicant posits that benefit from lithium treatment would accrue from early administration after trauma or even administration before possible or probable trauma, or even during such trauma.

[00464] In a clinical study on patients with amyotrophic lateral sclerosis daily doses of oral lithium carbonate leading to 0.4-0.8 mmol/L plasma levels prevented death of 22 patients yet resulted in only minimal motor deterioration over 15 months, compared to a 29% mortality and significant motor deterioration in 22 patients that did not receive lithium. Thus, whether amyotrophic lateral sclerosis is considered to be due to a gene mutation, to excessive glutamate concentration or an autoimmune disease, it is nonetheless a result of motor neurone cell death in the spinal cord and periphery, and this beneficial effect of lithium treatment may reflect a broader neurone sparing effect.

[00465] In two peripheral nerve crush injury models in the mouse, a facial nerve injury model and a sciatic nerve injury model, lithium chloride was found to stimulate the expression of myelin genes, restore myelin structure and accelerate functional recovery; this effect was attributed to β -catenin binding to R-cell factor/lymphoid-enhancer factor response element identified in myelin genes. In a rat partial sciatic nerve ligation model lithium chloride administration reduced the nociceptive scores in response to tactile and thermal stimuli compared to controls.

[00466] In an in vitro study of chemotherapy-induced peripheral nerve damage, co-administration of lithium chloride to neuroblastoma cells reduced the adverse effects of paclitaxel (Taxol®) while sparing the therapeutic efficacy. In a mouse model of peripheral

nerve damage caused by treatment with paclitaxel, when co-administered with lithium chloride peripheral nerve damage was decreased without changing the antitumor effects of paclitaxel. Importantly, in this latter report the authors point out that co-administration of lithium with chemotherapy enables administration of higher doses of chemotherapeutic drugs, and may thereby enable patients to tolerate more aggressive treatment regimens, thus improving outcomes of chemotherapy.

When to administer lithium

[00467] Lithium is rapidly absorbed after oral administration, peaks at about two to three hours, and distributes readily throughout the body compartments. The half-life of lithium is 20 to 24 hours. It rapidly penetrates into brain, and after 24 hours it accumulates intracellularly in brain, with the result that serum levels are not representative of central nervous system effective levels.

[00468] While pretreatment for seven days with lithium has been shown to have beneficial effects in an animal model of brain ischemia, such as an increase in viable brain neurones and a decrease in apoptotic nerve cells in a stroke model, pretreatment for only two days has been reported to lack these beneficial effects, although three-day pretreatment has been found to have protective effects against haemorrhagic stroke in a rat model and two-day pretreatment has been reported to decrease excitotoxic damage, though to a lesser degree than six-day pretreatment. Continued lithium pre-treatment for several days appears to be necessary for optimal effectiveness, as protection has been reported in vitro as well as in vivo from MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic neurotoxicity in mice, which occurs with seven-day treatment but not with acute administration. Beneficial effects of lithium chloride administration at 24 hour intervals for seven weeks is reported to inhibit inflammation and to promote proliferation of neural progenitor cells in the brain in an animal model of hypoxia/ischemia.

[00469] Treatment following ischemia appears to be more effective than pre-treatment. Given at stroke onset, lithium has been shown to activate Akt, which promotes cell survival, and to inhibit GSK-3 β , which leads to cell death, in a rat model of permanent middle cerebral artery occlusion as well as a model that combines this occlusion with a bilateral common carotid artery occlusion with partial reperfusion. When administered up to three hours after the onset of ischemia and continued for several days in an animal model, treatment with therapeutic doses of lithium decreases infarct volume and decreases neurological deficits in sensory, motor and reflex tests. Even delayed administration of lithium, up to 12 hours after brain ischemia followed by daily administration for two weeks improved oxygenation of the brain and vascularization of the brain. Similar observations have been made in an animal model of peripheral nerve injury. A functional MRI study further showed that even delayed chronic lithium treatment, administered up to 12 hours after the onset of ischemia and

followed by daily injections for 2 weeks, significantly improved functional MRI response magnitude.

[00470] Lithium-related drugs and lithium-containing drugs are included in the formulation, including when administered in a hospital or clinical setting before anticipated trauma.

Lithium-related drugs and lithium-containing drugs are also included in the formulations for administration in a hospital or clinic as an early treatment for unanticipated trauma. Lithium is effective in treating acute manic attacks, consistent with its rapid absorption and distribution. However, as the processes of secondary injury progress over days into weeks, and as shown in animal neurotrauma models, daily administration of lithium should be continued for up to three weeks in the present application, coupled with careful monitoring of serum levels of lithium to ensure that levels remain within the narrow therapeutic range.

[00471] The data from human and animal studies suggest that the window of opportunity for optimal effective benefit from administration of lithium-related drugs for treatment of trauma to nerve cells, or neural support cells or neural support tissues is within a platinum hour, a golden day and a silver week.

[00472] A person having ordinary skill in the art will understand that lithium-containing and lithium-related drugs as a class of compound are effective when administered before or after a traumatic event and that these compounds continue to be of benefit when administration is continued as needed.

Summary on lithium

[00473] Lithium is a first line treatment for bipolar disorder. It is relatively unique among drugs for its neurotrophic as well as its neuroprotectant effects. These effects have been attributed to a wide range of actions, including principally inhibition of GSK-3 β , induction of BDNF expression as well as that of its receptor, inhibition of NMDA receptor-mediated signaling resulting in reduced glutamate-induced excitotoxicity and reduced influx of calcium into nerve cells. Lithium administration also leads to inhibition of mechanisms leading to apoptosis, inhibition of phosphoinositol phosphatases involved in inositol metabolism, inhibition of glutamate-induced downregulation of the protective Bcl-2 and upregulation of pro-apoptotic proteins such as p53 and Bax, inhibition of glial cell activation, and inhibition of other degenerative processes. Lithium is rapidly absorbed and penetrates rapidly into the central nervous system. Lithium has a narrow therapeutic window and there is wide inter-individual variability in its effective dose range. The neurotrophic and neuroprotectant effects of lithium-containing drugs place them as an important drug class for inclusion in the formulations of the present technology and its embodiments.

FORMULATIONS AS COMBINATIONS OF NEUROTROPHIC AND NEUROPROTECTIVE COMPOUNDS

[00474] The classes of compound, comprising anticonvulsants/antiepileptics,

neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds, each has supportive evidence in the scientific and clinical literature of neurotrophic or neuroprotective actions, or both, in vitro or in vivo, in animal models or in humans.

[00475] A person having ordinary skill in the art will understand that secondary injury or damage induced or triggered or caused by trauma, as described herein and as understood generally, occurs due to a wide variety of processes and biochemical pathways.

[00476] A person having ordinary skill in the art will also understand that the degree or severity of secondary injury or damage induced or triggered or caused by trauma is the result of a combination or balance of restorative processes or biochemical pathways and of degenerative processes or biochemical pathways.

[00477] A person having ordinary skill in the art will understand that any one target of anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds will have beneficial effects to a patient or a subject but that a single target approach will not have such optimal beneficial effects as may be achieved through administration of the formulations of the multi-drug presently disclosed technology.

[00478] A person having ordinary skill in the art will understand that each of any pairs of compounds from each of the classes of compounds comprising anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds may have beneficial effect greater than that of a single compound.

[00479] A person having ordinary skill in the art will understand that each of any triplets of compounds from each of the classes of comprising anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds may have beneficial effect greater than that of a single compound.

[00480] A person having ordinary skill in the art will understand that a combination of compounds from each of the four classes of compounds comprising anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds may have beneficial effect greater than that of a single compound.

[00481] It is the intent of the presently disclosed technology to prevent or reduce the development or the risk of development of neuropathology as a result of traumatic injury to a subject by administration of at least two biologically active compounds from the classes of compounds comprising anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds, each of the at least two compounds selected in accordance with their respective activities regarding at least two neurological mechanisms. One of skill in the art will understand that these compounds

may be given as any two compounds from these four classes.

[00482] One of skill in the art will understand that these compounds may be given as any three compounds from these classes.

[00483] One of skill in the art will understand that these compounds may be given as any four compounds from these classes.

[00484] Anticonvulsant/antiepileptic compounds suitable for use as components of invention embodiments include, but not exclusively, one or more from the group comprising gabapentin, pregabalin, barbiturates (such as phenobarbital, methylphenobarbital, metharbital, barbexalone and other central nervous system depressants), benzodiazepines (such as clozapam, clonazepam, chlorazepate, diazepam, midazolam, lorazepam, and other hypnotic, anxiolytic, anticonvulsant, amnesic compounds), bromides (such as potassium bromide,) carbamates (such as felbamate, fluorofelbamate), carboxamides (such as carbamazepine, oxcarbazepine, eslicarbazepine acetate), fatty acids (such as valproic acid, sodium valproate, divalproex sodium, vigabatrin, progabide, sec-butyl-propylacetamide), fructose derivatives (such as topiramate), hydantoins (such as ethotoin, phenytoin, mephentyoin, fosphenytoin), oxazolidinediones (such as paramethadione, trimethadione, ethadione), propionates (such as beclamide), pyrimidinediones (such as primidone), pyrrolidines (such as rivaracetam, levetiracetam, seletracetam), succinimides (such as ethosuximide, phensuximide, mesuximide), sulfonamides (such as acetazolamide, sultiame, methazolamide, zonisamide), triazines (such as lamotrigine), ureas (such as pheneturide, phenacemide) and valproyamides (such as valpromide, valoctamide) and others known and unknown, as well as any homolog or derivative or compound acting on or through a receptor, an enzyme or other mechanism upon which an anticonvulsive/antiepileptic can act, as well as any compound acting on or through mechanisms that would modify or affect in any way pathways or processes affected by one or more anticonvulsant/antiepileptic compounds, as well as any related slow-release compound.

[00485] Neurosteroid/neuroactive steroid compounds suitable for use as components of invention embodiments include, but not exclusively, one or more from the group comprising progesterone, progesterone prodrugs, progesterone derivatives, progesterone analogs, and other progesterone compounds such as but not exclusive to medroxyprogesterone acetate, megestrol acetate, 17a-hydroxyprogesterone, 5a-dihydroxyprogesterone, 3a,5a-trihydroxyprogesterone, 14b-hydroxy progesterone, 17a-hydroxyprogesterone caproate, 16-methyl-17-benzoyloxypregnen-4-en-3,20-dione, hydroxyprogesterone-3-O-carboxymethyloxime, 21-succinyloxy-6,19-epoxyprogesterone, 6,19-oxidoprogesterone, 17-p-bromopheny-lcarbamoyloxypregn-4-ene-3,20-dione, 17-phenylcarbamoyl-oxypregn-4-ene-3,20-dione, 4-pregnene-3,20-dione, 6,19-methanoprogesterone, 16,17-cyclohexano-4,5-dihydroprogesterone, nepapakistamine, vaganine D, Crinone, 18-oxo-18-vinylprogesterone,

16,17-cyclopropanoprogesterone, caproxyprogesterone, 21-hydroxy-6,19-oxidoprogesterone, 17-acetoxy-9-fluoro-6-methylprogesterone, ZK 136798, 3,17-dihydroxy-7-(4-methoxyphenyl)-androst-5-ene, 3,17-diacetate, progesterone-11HS-horseradish peroxidase, 21-hydroxy-11,19-oxidopregn-4-ene-3,20-dione, 21-hydroxy-6,19-oxidopregn-4-ene-3,20-dione, 4-cyanoprogesterone, 11,19-oxidoprogesterone, 6-fluoroprogesterone, 2-hydroxy-4-pregnene-3,20-dione, progesterone-3-(O-carboxymethyl oxime)-horseradish peroxidase, progesterone-11-hemisuccinyl-bovine serum albumin, pentarane B, pentarane A, progesterone 6-hemimaleate, progesterone 6-hemisuccinate, 7-(carboxyethylthio)progesterone, progesterone 3-(O-carboxymethyl)oxime-bovine serum albumin, 18-ethynylprogesterone, 18-vinylprogesterone, 6-methylprogesteron-17-pivalate, progesterone-11-bovine serum albumin, allylestriol, progesterone-3-ethanolimine, 3,20-dioxopregn-4-ene-18'-carboxaldehyde cyclic 18'-(1,2-ethandiylmercaptal), 18-ethylenedithioprogesterone, 17-acetoxy-6,16-dimethylene-4-pregnene-3,20-dione, 17-hydroxy-6-dehydroprogesterone, 2'-methyl-16,17-cyclohexaneprogesterone, 21,21-dichloroprogesterone, hydroxyprogesterone hemisuccinate bovine serum albumin tetramethylrhodamine isothiocyanate, 11-progesteryl-2-carboxymethyltyramine-4-(10-methyl)acridinium-9-carboxylate, progesterone 12-succinyltyrosine methyl ester, progesterone 11-succinyltyrosine methyl ester, 11-progesteryl-2-succinoyltyramine-4-(10-methyl)acridinium-9-carboxylate, 2-hydroxymethyleneprogesterone, 2-cyanoprogesterone, 17-(phenylseleno)progesterone, 21-(phenylseleno)progesterone and others known and unknown, and include other neurosteroids or neuroactive steroids such as, but not exclusive to prednisolone, methylprednisolone, alphaxolone, alphadolone, hydroxydone, minaxolone, ganaxolone, deoxycorticosterone, 3 alpha-hydroxy-5-alpha-pregnan-one (allopregnanolone), 3 alpha,21-dihydroxy-5 alpha-pregnan-20-one (allotetrahydro), as well as metabolites of neurosteroids and neuroactive steroids, and including any corticoid, glucocorticoid, estrogen compound or any such compound acting on or through a progesterone, corticosteroid, glucocorticoid, estrogen or other neurosteroid receptor or through any other mechanism upon which progesterone, a corticosteroid, a glucocorticoid, an estrogen or other neurosteroid does or can act, as well as any homolog or derivative or compound acting on or through mechanisms that would modify, modulate or affect in any way pathways or processes affected by progesterone, estrogen or any neurosteroid, as well as any related slow-release compound.

[00486] NK-1 receptor antagonist compounds suitable for use as components of invention embodiments include, but not exclusively, any biologically active compound of one or more from the group comprising aprepitant, fosaprepitant, casopitant, maropitant, vestipitant, CP-99,994, CP-122,721, MK 869, LY 303870, RPR 67580, RPR 100893, L 758298, L 365260, L 733060, GR 205171, CGP 49823, CJ 11974, and others known and unknown, and any compound acting on or through the NK-1 receptor or any other mechanism that involves

activation or involvement of the NK-1 receptor or its synthesis, and other chemical entities known and unknown, including any ligand or compound acting on or through an NK-1 receptor or other mechanism upon which substance P, an endogenous ligand for the NK-1 receptor, does or can act, as well as any compound acting on or through mechanisms that would modify or affect in any way pathways or processes affected by substance P or the NK-1 receptor, as well as any related slow-release compound. Further, in view of the evidence that some ligands and compounds can act through or by NK-2 or NK-3 receptors, any ligand or homolog or derivative or compound acting on or through an NK-1 or NK-2 or NK-3 receptor, including receptor isoforms, or related mechanism as well as any ligand that occupies, activates or deactivates these receptors, is included in the presently disclosed technology.

[00487] Lithium-related/lithium-containing compounds suitable for use as components of invention embodiments include, but not exclusively, any biologically active compound of one or more from the group comprising lithium citrate, lithium carbonate, lithium chloride, lithium bromatum and others known and unknown, as well as any compound acting on or through a lithium receptor or other mechanism upon which lithium does or can act, as well as any homolog or derivative or compound acting on or through mechanisms that would modify or affect in any way pathways or processes affected by lithium, as well as any related slow-release compound.

[00488] Numerous compounds can be administered to a subject in any combination or permutation of these classes of compound to practice this invention aimed to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury to a subject by administering to a subject in need thereof a multiplicity of compounds by such combinations of any two, any three or any four compounds from the classes of compounds comprising anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds. These combinations of above said compounds can be given by various routes of administration to treat any injury or damage that has resulted, will result or may result from trauma, and that injury or damage can be to any nerve cell or nerve cells, to any neural support cell as described herein, or to any neural support tissue as described herein. Injury or damage can be to the brain, the brain stem, the cerebellum, the spinal cord, the enteric nervous system and the peripheral nervous system or any other nerve cell. A subject in need of invention embodiments can be an individual who is at risk of injury or damage, an individual who is about to experience an event that has the potential to cause traumatic damage or injury, or an individual who has experienced a trauma as described herein.

CONCLUDING OVERVIEW ON FORMULATIONS

[00489] The presently disclosed technology contains formulations, methods and procedures

aimed at reducing or preventing the development, or the risk of development, of neuropathology as a result of traumatic injury. Embodiments of the invention address unmet or unsolved medical needs including brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury, peripheral nerve injury and any other injury that can include or affect nerve cells, neural support cells or neural support tissues. These unmet or unsolved medical needs share the commonness of the potential for life-long adverse health conditions or disability. They also share the commonness of the void in current medical interventions to reduce or prevent these adverse health conditions or disability. These conditions also share similar, common or overlapping mechanisms of the secondary injury that develops following a primary injury or trauma, common mechanisms that trigger or lead to this secondary injury and common possible therapeutic targets for inhibiting or promoting the cascades of mechanisms triggered by a primary injury. As such mechanisms are triggered immediately by trauma while others downstream in the cascades of biochemical and metabolic pathways are engaged at different times following trauma, it is necessary to administer components of the formulation through the hours, days and in some cases the weeks following trauma, with immediate initiation of treatment of paramount importance for the preventive measures to arrest the degenerative cascades and to promote the restorative cascades, as well as continuation of practice according to need.

[00490] The present Specification describes and documents four particular aspects of invention embodiments, together comprising formulations, methods and procedures for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury.

[00491] The formulations of the presently disclosed technology, consisting of two or more of four families of chemical entities, administered together or sequentially at clinically effective doses, constitutes one particular aspect of invention embodiments. Each chemical entity in the formulation targets a different biological process or different biological processes that is or are involved in governing the degree of secondary injury that follows a primary traumatic injury. That is, some components of the formulations target optimizing or facilitating the restorative processes that follow or are triggered by a primary traumatic injury, while others target minimizing or inhibiting degenerative processes that follow or are triggered by a primary traumatic injury. As described herein, restorative processes lead to recovery. Degenerative processes lead to tissue damage and cell death. The presently disclosed technology one is not obvious to do. Otherwise, the particular combination of compounds that make up or constitute the formulations of this invention would be practiced. However, the first particular aspect of invention embodiments is obvious to try, given the evidence that administration of a single compound from any of the four classes of compound has some benefit in some subjects when given after a traumatic event. This first particular

aspect of invention embodiments is also obvious to try because single compound administrations have had only limited beneficial effects, while targeting both restorative and degenerative processes, as with the proposed formulation, may have additive or synergistic beneficial effects than those deriving from a single compound approach.

[00492] The second particular aspect of invention embodiments is the specific treatment modality, where a formulation is given as a prophylactic intervention before the development of symptoms. This can apply to the home setting, or a community setting, a pre-hospital care setting and the hospital/clinic setting. Prophylactic intervention refers to the administration of a formulation in the first particular aspect of invention embodiments immediately following unanticipated trauma, or as soon as possible following such trauma, or before the trauma, as in the case of anticipated trauma. Home setting refers to conditions where people well known to the victim of unanticipated trauma, or who are with the victim at the time of the trauma, and are able to administer a formulation at the earliest possible time, including during the trauma. Pre-hospital setting refers to conditions where health care can be delivered by trained personnel, such as but not exclusively paramedics and emergency medical services personnel, medics on or near battlefield, and the such. Hospital/clinical setting refers to a site that is equipped to dispense the full range of health care and emergency care. Prophylactic intervention is differentiated from standard long-term treatment, which is administered to minimize the expression of established symptoms or acute flare-up of existing conditions.

[00493] The third particular aspect of invention embodiments is the timing and route of administration, coupling the formulations and the delivery to the means of administering a formulation in a time-effective practice. For example, delivery of a formulation can be by intranasal administration. In the event of unanticipated trauma, which usually occurs away from a hospital/clinic setting, at-site immediate or earliest possible administration of the formulation is by nasal administration. This is to provide a fast and effective intervention in an easily and socially acceptable format. In the event of an anticipated trauma, which usually occurs in a hospital/clinic setting, prophylactic intervention with a formulation can be by oral, buccal, intravenous or even intramuscular routes, as examples. Delivery by intranasal administration may be by nasal spray. Delivery by oral administration may be by tablet or capsule or pill. Delivery by intravenous administration may be by solution.

[00494] The fourth particular aspect of invention embodiments directs the formulations, the methods and the procedures specifically at secondary injury resulting from all types or any type of trauma. These are not typically or usually considered as a single medical issue. As one example, in the case of the present fourth particular aspect of invention embodiments, secondary injury from trauma includes that caused by an epileptic seizure. An epileptic seizure is not ordinarily caused by a physical insult, but it has the potential, nevertheless, to activate the cascades of restorative and degenerative processes that are shared with physical

trauma to the head. Thus, in the present fourth particular aspect of invention embodiments, metabolic or intrinsic trauma is targeted in the same way as impact or concussion trauma to the head. Similarly, neurotrauma from chemotherapy or radiation therapy, and whether to neurones in the periphery, in the enteric nervous system or the central nervous system, triggers similar restorative and degenerative processes as impact or concussion trauma, and therefore medically-induced trauma is an object for therapy in the presently disclosed technology.

CONTRIBUTIONS MADE BY THE INVENTION

[00495] The present provides heretofore unknown advantages in the treatment and prevention of trauma-induced damage and injury to nerve cells or neural support cells or neural support tissues.

[00496] The presently disclosed technology focusses on reducing the negative consequences that can and frequently do follow or ensue from trauma. In the context of invention embodiments, a traumatic event causes a primary injury to tissues including nerve cells, neural support cells or neural support tissues. Cell loss caused by this primary injury is not salvageable. However, the injury to neural tissues in the area of this primary injury spreads as a secondary injury or secondary damage or secondary neuropathology, which is salvageable. This spreads to neighbouring cells and tissues, including nerve cells, neural support cells and neural support tissues, that do not die from this primary injury. These cells and tissues undergo changes, whether due to the extracellular concentrations of cell-destructive byproducts of the primary cell death, due to loss of function of neural support cells in the direct area affected, to reduced circulatory supply of oxygen or glucose to the area or due to reduced clearance of damaging byproducts of cell metabolism as a result of reduced circulation of blood through this area, or due to the plethora of other cellular, biochemical or metabolic processes triggered by a primary injury as detailed herein. These changes trigger further cascades of cellular, biochemical and metabolic processes, some of which tend to return nerve cells, neural support cells and neural support tissues toward normal function and cell health. Some of the changes trigger further cascades of cellular, biochemical and metabolic processes, which tend to drive nerve cells, neural support cells and neural support tissues toward loss of cell function or cell death. The former group of processes is considered to be restorative processes. The latter group of processes is considered to be degenerative. The eventual outcome at the cellular and tissue levels is determined by or results from the balance of all the restorative and degenerative processes triggered by or resulting from the primary injury and its sequelae. Indeed, the damage caused by secondary processes can be as serious and extensive as, or even more serious and more extensive than, that caused by the primary trauma. Secondary processes also progress over time so that injury and damage can continue over the days, weeks and even months after the initial injury. Further, the secondary

processes can also progress to other areas so that injury and damage can spread spatially and manifest at sites remote from the site of the primary trauma, whether in the brain, brain stem, spinal cord, enteric nervous system or peripheral nerves.

[00497] This balance can be tipped toward normal function and health by appropriate pharmaceutical intervention at the appropriate time. This can be achieved because of the chemical nature or basis of the restorative and degenerative processes occurring at the cellular, biochemical and metabolic levels.

[00498] As detailed herein there are many targets or points of entry for pharmaceutical promotion, facilitation or potentiation of restorative processes to tip this balance toward function and health, in order to reduce or prevent the loss of function, the adverse health conditions or the disability that can and often do result from a traumatic event. The presently disclosed technology and its embodiments are based on a select few targets or points of entry, as represented in the formulations of the presently disclosed technology. This selection of specific, synergistic compounds of the formulations is based on fundamental and clinical evidence detailed herein and elsewhere.

[00499] As detailed herein there are many targets or points of entry for pharmaceutical inhibition, lessening or blocking degenerative processes. Such degenerative processes drive this balance away from function and health toward loss of function, adverse health conditions or disability. The presently disclosed technology and its embodiments includes a pharmaceutical approach taken in order to reduce or prevent the loss of function, the adverse health conditions or the disability that can and often do result from a traumatic event. The presently disclosed technology and its embodiments are based on a select few targets or points of entry to reduce the degenerative processes, as represented in the formulations of the presently disclosed technology. This selection of specific, synergistic compounds of the formulations is based on fundamental and clinical evidence detailed herein and elsewhere that is available and understood by a person having ordinary skill in the art.

[00500] More specifically, embodiments of the invention relate to reducing or preventing the secondary injury, or the damaging effects of the secondary injury, or the risk of secondary injury or its effects, that are triggered or caused by trauma. In most embodiments of the invention, this general post-trauma period includes the minutes, hours, days, weeks or months during which secondary damage or injury can occur.

[00501] Conventional or standard treatment of trauma typically consists of minimizing the symptoms of the immediate, or primary, traumatic injury. With conventional or standard methods and treatments, attempts are made to minimize these immediate symptoms. Standard treatment for any persisting loss of function or disability that results from the initial trauma is typically treated by rehabilitation, which is usually initiated after there has been overt recovery from the traumatic event itself. Initiation of rehabilitation typically comes weeks or

even months later, when the adverse health conditions or disability are clear and obvious.

[00502] In significant contrast, the primary aspect of the presently disclosed technology does not focus on either reducing the immediate trauma or rehabilitating long-term disability once this disability has been established. Instead, embodiments of the invention are directed toward reducing or preventing the sequelae of post-trauma effects that are an indirect result of the primary trauma.

[00503] That is, there is a gap in medical care between standard practice to treat a primary injury or damage at the time of trauma, and standard practice to rehabilitate. This gap represents an unsolved medical need. The presently disclosed technology and its embodiments address this unsolved medical need by filling this gap.

[00504] A rationale for the presently disclosed technology is that standard practice does not include specific steps to reduce or prevent adverse health conditions or disability that result from or may arise from secondary damage or injury. Secondary damage or injury can be and often is more severe and extensive than that arising from the primary damage itself. The presently disclosed technology and its embodiments are based on the evidence that the secondary damage or injury is mediated or brought about by cellular, biochemical or metabolic processes that can be modified or influenced pharmaceutically to reduce or prevent neuropathology as a result of traumatic injury.

[00505] Significantly, the point of differentiation between conventional or standard methods and the presently disclosed technology is the difference between the treatment of the symptoms of the primary injury, and formulations, methods and procedures taken at or about the time of trauma to prevent or lessen damage from the secondary sequelae that, without the benefit of the presently disclosed technology, may or are likely to develop. Thus, an important aspect of the presently disclosed technology is its usefulness in treating to prevent injuries that are expected or likely to occur, but that are not the damage caused immediately and directly by a traumatic event. Alternatively stated, the presently disclosed technology is distinguished by its prevention or amelioration of secondary sequelae versus the treatment of a primary injury.

[00506] As one example in the case of brain injury, as stated herein, "This cascade of pathophysiological events leads to secondary injury not only at the site of the trauma but also more diffusely in remote brain areas as well".

[00507] As another example in the case of brain injury, as stated herein, "Caspases, which have been implicated in processes leading to apoptosis, are also increased in damaged cortex as early as 4 hours, but are also elevated in more remote brain areas at 24-72 hours."

[00508] As yet another example in the case of brain injury, as stated herein, "After a mild injury to the cortex in the rat visible structural damage to axons was seen at three days, the earliest time sampled. Importantly, the changes were observed not only in the cortex but also

in the thalamus, remote from the site of injury."

[00509] In the case of central nervous system ischemia, it is stated herein, "These secondary injury processes are spread over a space and time continuum, whereby after spinal cord injury changes can be observed in neuronal function even in remote areas of the central nervous system including the brain".

[00510] In the case of spinal cord injury, an example cited herein, "These pathways include activation of lytic kinases and transcription factors such as calpains, phospholipase A2, and lipoxygenase that contribute to cell death, as well as leading to increased excitability of more remote neurones."

[00511] Further, examples are as follows, "At 30-45 minutes after spinal trauma, IL-1 β and TNF α -positive cells are seen more extensively over more remote spinal cord segments", and "Programmed cell death and necrosis occur over extended periods of time after the initial trauma, and can be observed in remote parts of the spinal cord".

[00512] With respect to secondary injury after peripheral nerve injury, one example is stated as, "Peripheral nerve trauma causes injury and degeneration of nerve cells and neural support cells, the Schwann cells. Degeneration of axons or of neural support cells triggers a cascade of activated chemical pathways that lead to injury to otherwise intact nerve cells, Schwann cells, local vasculature and even more remote nerve cells by entry of degradation products into the blood circulation".

[00513] As another example in the case of peripheral nerve injury, it is stated herein, "Peripheral nerves travel alongside blood vessels and trauma to the nerve often physically disrupts the blood-nerve barrier, allowing the milieu of chemicals produced by axon and Schwann cell degeneration to enter the bloodstream, which then carries these chemicals to remote parts of the body, including direct access to uninjured dorsal root ganglia, the enteric nervous system and the central nervous system. This tends to carry peripheral nerve injury to remote sites beyond the primary injury."

[00514] These examples indicate that secondary injury occurs at sites remote from the primary injury. However, the cascades of mechanisms leading to secondary injury at remote sites are also triggered locally at the site of the primary injury. The presently disclosed technology aims to reduce or prevent this secondary injury irrespective of whether this manifests locally or more remotely.

[00515] Conventional rehabilitation treatment is aimed at ameliorating existing symptoms, adverse health conditions or disability caused by a primary injury. These typical existing symptoms are easily recognized and can be measured. In significant contrast is the presently disclosed technology, where prevention is aimed at symptoms that are neither existent nor present at the time immediately following a traumatic event, but which have a likelihood or

probability to manifest if not reduced or prevented based on knowledge of their incidence with respect to the category of primary injury.

[00516] As indicated herein, the cascades of mechanisms leading to secondary injury are triggered within minutes and hours, yet continue to occur over the ensuing days, weeks and months. As a result, symptoms of secondary injury manifest over such periods, and the presently disclosed technology aims to reduce or prevent the manifestation or expression of these symptoms of secondary injury, which are known on the basis of incidence studies to occur. As a result, the presently disclosed technology addresses symptoms that are non-apparent, but that can be expected to occur with a known incidence or probability if not reduced or prevented by appropriate pharmaceutical intervention.

[00517] Despite this, it is known with certainty that trauma activates secondary injury mechanisms in a significant percentage of victims or patients. What can be measured with respect to these secondary injuries, then, is the incidence, measured at later time points after a category of traumatic events, by comparisons that can be made. Such comparisons are made, as examples, of the number of people who, after any given type of traumatic event, show symptoms that typically manifest long term in individuals that have been treated by standard procedures alone, with the number of people showing symptoms that are observed in individuals that have been treated by standard procedures along with the administration of formulations of the presently disclosed technology in accordance with embodiments of the presently disclosed technology.

[00518] Similarly, comparisons can be made of the severity of the symptoms that typically manifest after any given type of traumatic event in those individuals that have been treated with standard procedures alone, with those treated with standard procedures along with the practice of invention embodiments, including administration of formulations of the presently disclosed technology and the methods and procedures as described herein.

[00519] The presently disclosed technology and its particular embodiments provide numerous formulations that comprise synergistic combinations of existing chemical entities that have not been combined as in the presently disclosed technology. In one aspect, the specific chemical entities included in formulations of invention embodiments are selected along informed and rationalized lines of thought derived from an understanding of the intrinsic mechanisms that are triggered by primary injury and an understanding of the mechanisms of the secondary sequelae of this primary injury.

[00520] The biological targets of embodiments of formulations provided herein include mechanisms of the secondary sequelae that are restorative and function to save, rescue or restore neurones, neural support cells and neural support tissues toward their condition before the trauma and as well include mechanisms of the secondary sequelae that are degenerative processes, which drive neurones, neural support cells and neural support tissues toward

pathology, or loss of function or even cell death. Formulations of invention embodiments are therefore advantageous for the provided combination of specific chemical entities which, combined, reduce or prevent, or reduce the risk of, secondary damage resulting or developing from, or triggered by, any trauma event.

[00521] The present disclosure provides new uses of each of the chemical entities in the formulations of invention embodiments. Evidence is cited herein supporting the current uses of each of the families of chemical entity that are included in the formulation. There is some evidence that certain members of each of the four classes of chemical entity may have some neurone-sparing effect, but to date these have not been combined to reduce or prevent, or reduce the risk, of secondary injury to nerve cells, to neural support cells and neural support tissues and to endothelial cells resulting from trauma.

[00522] The formulations are advantageous also in that they are directed at maximizing, potentiating or facilitating naturally-occurring restorative mechanisms, while at the same time minimizing, reducing or inhibiting naturally-occurring degenerative processes. There is currently no medical intervention that purposefully targets both restorative as well as degenerative processes that are triggered by trauma and that govern, recover from or lead to secondary injury to nerve cells, neural support cells and neural support tissues or endothelial cells.

[00523] The presently disclosed technology is advantageous in that the formulations target trauma-induced secondary injury to nerve cells. The presently disclosed technology also targets trauma-induced secondary injury to neural support cells and neural support tissues. The presently disclosed technology also targets trauma-induced secondary injury to endothelial cells. As loss of function of neural support cells and neural support tissues and endothelial cells can contribute to overall secondary injury to nerve cells, protection of injury to neural support cells and neural support tissues and endothelial cells is also included in the presently disclosed technology.

[00524] The presently disclosed technology is advantageous in that it targets secondary injury to nerve cells, to neural support cells and neural support tissues, and to endothelial cells resulting from physical, chemical, metabolic, medical or other trauma. The presently disclosed technology outlines the various forms that each of these types of trauma manifests and the presently disclosed technology describes how the formulations, methods and procedures of the presently disclosed technology will prevent or reduce, or reduce the risk of, secondary injury to nerve cells, to neural support cells and neural support tissues, and to endothelial cells, that results from brain injury, ischemia of the central nervous system, spinal cord injury, enteric nervous system injury or peripheral nerve injury. It is the intent of the presently disclosed technology to include the full spectrum of trauma and traumatic events that lead to secondary injury to nerve cells, to neural support cells and neural support tissues,

and to endothelial cells inclusive of all parts of the body.

[00525] There is evidence from animal studies that early intervention at the time of trauma reduces the incidence as well as the severity of long term functional deficits. In one important aspect, the presently disclosed technology is advantageous in that it directs specific formulations to administration to humans.

[00526] The presently disclosed technology is advantageous in that a formulation is to be given beginning at specific times before, immediately, at the time of or following trauma.

[00527] The presently disclosed technology is advantageous in that it specifies that a formulation is to be given differently depending on the setting, which is described for purposes of illustration but not limitation, as the home setting, a community setting, the pre-hospital setting, or any setting outside the home and outside a hospital or sufficiently equipped clinical setting, where paramedic or pre-medic or medic intervention is possible, and a hospital or clinical setting that is fully staffed and equipped for the full range of healthcare.

[00528] The presently disclosed technology is advantageous in that it specifies the timing of administration of the formulation, depending upon the specific setting, as referred to in herein and as in examples of the particular embodiments.

[00529] The presently disclosed technology is advantageous in that the route of administration is dependent upon the specific setting, as defined herein and as in examples of the particular embodiments.

[00530] The presently disclosed technology is advantageous in that the formulations are applied differentially for unanticipated vs. anticipated trauma. Medical interventions or procedures, including those described herein, can lead to neuropathology. With respect to anticipated trauma, the presently disclosed technology is directed to reduce the known incidence of neuropathology as outlined herein, and thereby reduce the known long term disability and loss of function that result from the medical interventions described herein. The presently disclosed technology is advantageous in reducing or preventing, or reducing the risk, of injury to nerve cells, neural support cells and neural support tissues, and endothelial cells that occurs or can occur as a result of surgical or other medical interventions or procedures.

[00531] All types of neurotrauma, including those addressed in the presently disclosed technology extracts a heavy toll on individuals, on families, on the health care system and on the economy. These types of neurotrauma include, as examples, brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury. Primary injuries resulting from these types of neurotrauma are not amenable to reduction or prevention, but the secondary processes triggered by the primary trauma are, with the benefit of invention embodiments, amenable to medical intervention.

REASONS FOR THE INVENTION

[00532] The presently disclosed technology and its embodiments aim to fill a gap in standard practice for treating victims of trauma. This is the gap, as described herein, that exists between standard emergency practice and standard rehabilitation practice. Without the presently disclosed technology this gap represents an unsolved medical need because neither standard emergency practice nor standard rehabilitation practice are directed at preventing or reducing or decreasing the risk of neuropathology as a result of trauma.

[00533] The presently disclosed technology aims to rescue a subject in need, or potential need, from falling over a disability cliff by administering combinations of pharmaceutically effective doses of compounds selected from two, or three or all four classes of compound of the presently disclosed technology within the platinum hour, the golden day and the silver week after trauma, and continuing treatment as needed.

[00534] There is reasonable, and growing, evidence documenting the effectiveness of single compounds among anticonvulsants/antiepileptics, neurosteroids/neuroactive steroids, NK-1 receptor antagonists and lithium-related/lithium-containing compounds of the invention for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury. As a result, a person of skill in the art is capable of administering any combination of any two, any three or all four of the families of compounds of the invention to a subject in need.

[00535] However, this is not being practiced. A conclusion following an extensive review of the recent scientific and clinical literature, as well as the grey literature, is that combinations of these compounds are not presently being given as standard practice to subjects in need. Current standard emergency practices do not include formulations, methods or procedures as described in the presently disclosed technology, nor are there current practices that are similar to or resemble those described in the presently disclosed technology.

[00536] Further, a person of skill in the art will understand that it is unlikely that without the presently disclosed technology any combinations of any of these compounds will be given to subjects in need. Stated differently, a person of skill in the art will understand that there are presently no initiatives to develop formulations, methods and procedures to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury. A person of skill in the art will also understand that there are presently no initiatives to develop combinations of drugs that include neurotrophic drugs or neuroprotective drugs, not combinations thereof. This is largely due to current standard practice, which typically tends to pursue monotherapeutic approaches. With a limited number of exceptions as described herein, monopharmacy is entrenched in standard practice. A person of skill in the art will understand that without the presently disclosed technology it will be a years or perhaps decades before polypharmacy becomes standard practice for treating neuropathology resulting from trauma.

[00537] Even further, a person of skill in the art will understand that it will be years or even decades before combinations specifically of two, or three or all four classes of compound of the presently disclosed technology will be administered as standard practice to a subject in need.

[00538] Even further, a person of skill in the art will understand that in many cases the major cause of long-term or permanent disability is due to the secondary injury that follows an initial trauma, as detailed herein. A conclusion following an extensive review of the scientific and clinical literature, as well as the grey literature, is that following trauma standard practice is to treat the immediate damage, as described herein but not the processes that lead to progressive secondary injury or damage. The presently disclosed technology aims to provide to a subject in need, specific formulations, methods and procedures to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury. A person of skill in the art will understand that, with a few exceptions as described herein, standard practice does not typically focus on prevention of secondary injury. Rescue from injury, therefore remains an unaddressed need in research as well as in standard clinical practice.

[00539] Even further, a person of skill in the art will understand that standard practice does not typically focus on the urgency to treat secondary injury during the platinum hour, the golden day and the silver week. As described herein, restorative and degenerative processes triggered by trauma are initiated within minutes of a traumatic event and these processes proceed over the following hours, days, weeks and even months. As described herein, immediate standard practice at the time of a traumatic event aims to treat the primary damage and does not include those aimed at reducing or preventing secondary injury. With few exceptions as described herein, steps to reduce or prevent secondary injury are typically taken at a later time, beyond the critical minutes, hours and days after a traumatic event.

[00540] In cases where adverse health conditions or disability have resulted from trauma, standard practice is to rehabilitate the victim or patient. The presently disclosed technology aims to reduce the need for rehabilitation by reducing or preventing the development of such adverse health conditions or disability, or by reducing the severity of such adverse health conditions or disabilities that might result from trauma.

[00541] The presently disclosed technology includes specific formulations consisting of combinations of two, or three or four compounds from the four classes of compound described herein. The presently disclosed technology includes specific methods of administering the formulations. The presently disclosed technology includes specific procedures for administering the formulations and methods. As emphasized herein, the formulations, methods and procedures are to be practiced in a timely fashion, before an anticipated trauma, during an on-going trauma or within the critical time following trauma as

described herein, and continued as needed through the hours, days and even months following a traumatic event.

[00542] A person of skill in the art will understand that without the presently disclosed technology it will be years or decades before immediate treatment to reduce or prevent secondary injury as described herein becomes standard practice. The presently disclosed technology aims to rescue a subject in need from falling over a disability cliff by administering combinations of pharmaceutically effective doses of compounds selected from any two, any three or all four classes of compound of the invention, given or taken in a timely fashion, such as within the platinum hour, the golden day and the silver week, and continued as needed over the months following a traumatic event.

SOME REFERENCES MATERIAL TO THE FIELD AND BACKGROUND OF THE INVENTION

Anticonvulsants/antiepileptics:

[00543] Anticonvulsants/antiepileptics constitute a large number of compounds, in a large number of categories, as described herein. Many of these compounds are approved for human use and many have been marketed for several or many years. Neuroprotective effects have been reported for many of the categories of anticonvulsants/antiepileptics. From a vast scientific and clinical literature a few examples are presented.

Example 1 - Anticonvulsants/antiepileptics

[00544] Lapolla W, Digiorgio C, Haitz K, *et al.* Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: open-label study. Arch Dermatol. 147: 901-907, 2011. In this open-label clinical study, 133 adults presenting with shingles within 72 hours of vesicle formation were treated three times per day for seven days with the antiviral, valacyclovir HCl, and with gabapentin. Incidence of postherpetic neuralgia was determined 3, 4 and 6 months later; 15 of the 37 patients that were unavailable at the end of the study reported a pain level of 0 at their final study visit. The authors state that this combined therapy resulted in the lowest 6-month prevalence (9.8%) and the lowest incidence (6.8%) of postherpetic neuralgia "ever reported in a formal study", to their knowledge. The authors state that prior to this study only a few interventions have been proven to reduce the incidence of postherpetic neuralgia. The data from this study indicate that the use of gabapentin combined with valacyclovir during an episode of acute herpes zoster reduces the incidence of chronic postherpetic neuralgia and this study substantiates the neuroprotective effect of gabapentin and possibly other anticonvulsants against metabolically-induced neurotrauma.

Example 2 - Anticonvulsants/antiepileptics

[00545] White HS, Alex AB, Pollock A, *et al.* A new derivative of valproic acid amide possesses a broad-spectrum antiseizure profile and unique activity against status epilepticus

and organophosphate neuronal damage. *Epilepsia* 53: 134-146, 2012. In this experiment, sec-butyl-propylacetamide (SPD), a homolog of valnoctamide derivative of valproic acid was assessed for neuroprotective effects in animal models. SPD-treated rats that exhibited reduced pilocarpine-induced convulsive status epilepticus compared to controls, when examined 10-14 days later showed improved cognitive function using the Morris water maze test; similar results were observed with soman-induced seizures. These data demonstrate that a valproic acid derivative prevents cognitive disability resulting from seizure as well as that resulting from nerve gas poisoning, and this study substantiates a neuroprotective effect of this anticonvulsant, and possibly other anticonvulsants, against metabolically- as well as chemically-induced neurotrauma.

Example 3 - Anticonvulsants/antiepileptics

[00546] Stettner M, Dehmel T, Mausberg AK, Köhne A, Rose CR, Kieseier BC. Levetiracetam exhibits protective properties on rat Schwann cells in vitro. *J Periph Nerv Syst.* 16: 250-260, 2011. In this experiment, levetiracetam was tested for possible anti-inflammatory and anti-oxidative effects ex vivo on purified Schwann cells from neonatal rats and on dorsal root ganglion cells from rat embryos as models for Schwann cell proliferation and myelination. Lipopolysaccharide (LPS) was given as a pro-inflammatory agent ex vivo to model inflammation in the peripheral nerve. Administration of levetiracetam reduced the LPS-induced increase in markers TNF α and MMP-9. To model oxidative stress glutamate was administered; levetiracetam increased the survival of glial cells. The data from this study indicate that levetiracetam reduced injury to peripheral neural support cells and this study substantiates a neuroprotective role of levetiracetam and possibly other anticonvulsants against damage or injury to nerve cells and neural support cells from neurotrauma mediated via a number of different mechanisms of secondary injury.

Example 4 - Anticonvulsants/antiepileptics

[00547] Langer M, Brandt C, Zillinger C, Loscher W. Therapeutic window of opportunity for the neuroprotective effect of valproate versus the competitive AMPA receptor antagonist NS1209 following status epilepticus in rats. *Neuropharmacol* 6: 1033-1047, 2011.

[00548] In this experiment epileptic seizures were induced in the rat by electrical stimulation of the basolateral amygdala, as a model of temporal lobe epilepsy, and neurodegeneration was measured histologically in the hippocampal dentate hilus, the CA1 area and the CA3 area. Valproate or the glutamate receptor agonist AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) was given by continuous i.v. or intermittent i.p. administration for 24 hours after amygdala stimulation. The group treated with valproate, when compared to the group treated with AMPA demonstrated significantly less neuronal damage. The data from this study indicate that administration of valproic acid and perhaps other anticonvulsants prevent or reduce the secondary neural damage that occurs as a result of

seizures driven by intrinsic brain mechanisms. The data also demonstrate that there is a window of opportunity to protect brain nerve cells and that this window is minutes and hours after the onset of seizure-induced neurotrauma.

[00549] Several reviews also support the neuroprotective benefits of anticonvulsants/antiepileptics, of which the following is a representative example.

[00550] Clarke H, Bonin RP, Orser BA, Englesakis M, Wijesundera DN, Katz J. The Prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. *Anesth Analg*. 2012. This report reviews the literature on prevention of chronic postsurgical pain and concludes that these antiepileptic drugs are effective in reducing the incidence of this type of pain. This review of clinical literature supports the neuroprotective effects of antiepileptic drugs from disability due to surgical intervention, although as a person skilled in the art will understand the clinical literature tends not to address the urgency in administration of anticonvulsants/antiepileptics within the platinum hour, the golden day and the silver week.

Neurosteroids/neuroactive steroids:

[00551] Progesterone and many other neurosteroids/neuroactive steroids have been approved for human use in Canada, in the U.S.A., in Europe and elsewhere. These include but are not limited to progesterone, methoxypregnenolone, methylprogesterone, methylprednisolone and their derivatives or salts, and there may be others under development. However, while several neurosteroids/neuroactive steroids have been run in human clinical trials for neuroprotection, to date none has been approved for human use in neuroprotection. The following examples that teach toward neuroprotective effects of neurosteroids/neuroactive steroids have come from human studies. Further, the experiments and clinical studies that teach toward the beneficial effects of neurosteroids/neuroactive steroids to protect against neurotrauma are based on the use of several different neurosteroids/neuroactive steroids, and therefore neurosteroids/neuroactive steroids are considered as a class in the presently disclosed technology.

[00552] In the case of neurosteroids/neuroactive steroids, there is abundant evidence of neuroprotective effects in animal models. Over the past four years there has been a decreasing number of original peer-reviewed papers on neurosteroids and neuroprotection, yet there is a plethora of recent reviews. Some are indicated below. Much of the recent original literature has focussed on human clinical trials. Two phase 3 clinical trials currently underway are indicated below.

Example 1 - Neurosteroids/neuroactive steroids. -

[00553] Popovich PG, Tovar CA, Wei P, Fisher L, Jakeman LB, Basso DM. A reassessment of a classic neuroprotective combination therapy for spinal cord injured rats: LPS/pregnenolone/indomethacin. *Exp Neurol*. 233: 677-685, 2012. In this experiment spinal

cord injury was induced by a two second compression of the spinal cord using modified jewelers forceps. Following injury, a combination treatment of lipopolysaccharide, indomethacin and pregnenolone was given. Pregnenolone was given by implantable pellet; lipopolysaccharide and indomethacin were given by i.p. injection. This treatment was found to modestly improve myelin and axon sparing as well as axonal sprouting, while reducing lesion cavitation. The data from this experiment show that combination of a neurosteroid with two anti-inflammatory compounds provides neuroprotection in an animal model of spinal cord injury.

Example 2 - Neurosteroids/neuroactive steroids.

[00554] Dableh LJ, Henry JL. Progesterone prevents development of neuropathic pain in a rat model: timing and duration of treatment are critical. J Pain Res 4:91-101, 2011. In this experiment a peripheral nerve injury was induced by introduction of a thin polyethylene cuff around the sciatic nerve. This typically produces a marked decrease in nociceptive withdrawal threshold of the ipsilateral foot to light mechanical stimulation. When progesterone was administered one hour after cuff implantation and continued daily until day 10 the tactile hypersensitivity did not develop. When progesterone was administered starting on day 20 and continued for 11 days there was no change in sensitivity compared to control animals. The data from this experiment show that when progesterone is given early after trauma, beginning during the platinum hour, and continued for ten days, through the golden day and the silver week, the negative or adverse functional outcome of peripheral nerve damage was prevented.

Example 3 - Neurosteroids/neuroactive steroids.

[00555] Feeser VR, Loria RM. Modulation of traumatic brain injury using progesterone and the role of glial cells on its neuroprotective actions. J Neuroimmunol. 237:4 -12, 2011.

REVIEW. This report reviews the laboratory and clinical evidence for the use of progesterone in traumatic brain injury, describes the biology of progesterone, discusses the multiple mechanisms of action by which progesterone provides neuroprotection, discusses the role of biomarkers, and focusses on this hormone's target specific actions on glial cells of the central nervous system. The data reviewed in this report support neuroprotective effects of administration of progesterone for traumatic brain injury.

Example 4 - Neurosteroids/neuroactive steroids.

[00556] Singh S, Hota D, Prakash A, Khanduja KL, Arora SK, Chakrabarti A.

Allopregnanolone, the active metabolite of progesterone protects against neuronal damage in picrotoxin-induced seizure model in mice. Pharmacol Biochem Behav. 94: 416-422, 2010. In this experiment allopregnanolone demonstrated anti-seizure effects as well as protection against DNA fragmentation in this model. These effects were independent of binding to the progesterone receptor. The data from this experiment demonstrate neuroprotective effects of allopregnanolone and demonstrate further that these effects may be mediated via multiple

mechanisms over and above effects mediated via progesterone receptors.

Example 5 - Neurosteroids/neuroactive steroids.

[00557] Roglio I, Bianchi R, Camozzi F, *et al.* Docetaxel-induced peripheral neuropathy: protective effects of dihydroprogesterone and progesterone in an experimental model. *J Periph Nerv Syst* 14: 36-44, 2009. In this study, progesterone and its metabolite, dihydroprogesterone, were tested for potential beneficial effects in an experimental model of peripheral neuropathy. Rats received weekly injections of docetaxel, a chemotherapeutic agent that induces a peripheral neuropathy. In the groups treated with dihydroprogesterone or progesterone, when compared to a group given docetaxel only, both exhibited a reduced decrease in nerve conduction velocity, a reduced loss of innervation of the skin, less sensitivity to noxious heat and less interference with gene expression. The data from this experiment demonstrate protective effects of dihydroprogesterone and progesterone at biochemical, functional and morphological levels, supporting a neuroprotection effect from chemically-induced neurotrauma.

[00558] Two phase III clinical trials are currently underway testing progesterone in patients with severe traumatic brain injury.

[00559] NCT00822900 is a phase three clinical trial entitled “Phase 3 Clinical Trial to Determine if Progesterone Along With Standard Medical Care for Brain Injury is More Effective at Limiting the Amount of Damage Cause by a Traumatic Brain Injury Than Standard Medical Care Alone”.

[00560] NCT01143064 is a Phase 3 Clinical Trial, entitled “Efficacy and Safety Study of Intravenous Progesterone in Patients With Severe Traumatic Brain Injury (SyNAPSe)”.

NK-1 receptor antagonists:

[00561] A small number of NK-1 receptor antagonists has been approved for human use as acute antiemetics in the U.S.A. and Europe. These include aprepitant, fosaprepitant, vestipitant, maropitant and casopitant, and there may be others under development at present that will eventually be approved for human use. However, a review of the available literature reveals that to date none has reached a clinical trial for neuroprotection. Therefore the following examples that teach toward beneficial effects of NK-1 receptor antagonists as neuroprotectants have come from animal studies only.

Example 1 - NK-1 receptor antagonists

[00562] Turner RJ, Helps SC, Thornton E, Vink R. A substance P antagonist improves functional outcome when administered 4 h after onset of ischemic stroke. *Brain Res* 1393: 84-90, 2011. This study reports that the NK-1 receptor antagonist, N-acetyl-L-tryptophan, significantly reduced oedema formation and blood-brain barrier permeability at 24 h post-

ischemia and significantly improved functional outcome as assessed over 7 days in a rat model induced using a reversible thread model of middle cerebral artery occlusion where occlusion was maintained for 2 h and then released to allow reperfusion. The data from this experiment show that when administered within four hours of ischemic trauma a pharmaceutically effective dose of an NK-1 receptor antagonist reduces functional deficits in an animal model of cerebral ischemia.

NK Example 2 - NK-1 receptor antagonists

[00563] Donkin JJ, Cernak I, Blumbergs PC, Vink R. A substance P antagonist reduces axonal injury and improves neurologic outcome when administered up to 12 hours after traumatic brain injury. *J Neurotrauma*. 28: 217-224, 2011. This study reports that the NK-1 receptor antagonist, N-acetyl-L-tryptophan, improved cognitive outcome and motor performance in rats subjected to acceleration-induced brain injury even when administration was delayed by as much as 12 h. The data from this experiment show that an NK-1 receptor antagonist improves neurological outcome even when administered 12 hours after physical trauma to the head.

Example 3 - NK-1 receptor antagonists

[00564] Tatsushima Y, Egashira N, Kawashiri T, *et al.* Involvement of substance P in peripheral neuropathy induced by paclitaxel but not oxaliplatin. *J Pharmacol Exp Ther*. 337: 226-235, 2011. This study reports that a peptide NK-1 receptor antagonist, N-acetyl-L-tryptophan 3,5-bis(trifluoromethyl)benzylester (L-732,138), reduced the signs of peripheral neuropathy following repeated administration of the chemotherapeutic agent, paclitaxel (6 mg/kg i.p., once a week for 4 weeks) in the rat. The data from this experiment show protective effects of an NK-1 receptor antagonist from chemotherapy-induced trauma to peripheral nerves.

Example 4 - NK-1 receptor antagonists

[00565] Dableh LJ, Yashpal K, Henry JL. Neuropathic pain as a process: reversal of chronification in an animal model. *J Pain Res* 4: 315-323, 2011. This study reports that administration of the NK-1 receptor antagonist CP-96,345 to the rat on days 1, 2, 3 and 4 during induction of a sciatic nerve trauma-induced model of peripheral neuropathic pain resulted in a reversal of mechanical hypersensitivity. The data from this experiment show effectiveness of NK-1 receptor antagonism in reducing the negative functional outcomes as a result of a physical traumatic injury to a peripheral nerve.

[00566] Additional examples are as follows, but as a person of skill in the art will understand, with the exception of the study by Dableh (Example 4) clinical understanding of the impact or the importance of the timing of administration of NK-1 receptor antagonists, within the platinum hour, the golden day and the silver week, has not been a focus of research.

[00567] Donkin JJ, Nimmo AJ, Cernak I, Blumbergs PC, Vink R. Substance P is associated with the development of brain edema and functional deficits after traumatic brain injury. *J Cereb Blood Flow Metab.* 29: 1388-1398, 2009.

[00568] Thornton E, Ziebell JM, Leonard AV, Vink R. Kinin receptor antagonists as potential neuroprotective agents in central nervous system injury. REVIEW. *Molecules* 15:6598-6681, 2010.

[00569] Vink R, van den Heuvel C. Substance P antagonists as a therapeutic approach to improving outcome following traumatic brain injury. *Neurotherapeutics.* 7: 74-80, 2010.

Lithium-related/lithium-containing compounds

[00570] Several lithium-related/lithium-containing compounds are approved for human use and have been marketed for many years. While the most widespread use of lithium-related/lithium-containing compounds is for bipolar disorder and depression, neuroprotective effects have been reported. From a growing scientific literature on neuroprotective effects of lithium, a few examples are presented.

Example 1 - Lithium-related/lithium-containing compounds

[00571] Wong YW, Tam S, So KF, Chen JY, Cheng WS, Luk KD *et al.* A three-month, open-label, single-arm trial evaluating the safety and pharmacokinetics of oral lithium in patients with chronic spinal cord injury. *Spinal Cord* 49: 94-98, 2011. In this phase I clinical study 20 patients were recruited who met criteria of impairment due to spinal cord injury more than 12 months earlier. Each patient was given lithium carbonate at a daily dose of 500 mg, titrated upward by an additional 250 mg in steps to maintain a plasma lithium concentration of 0.6 to 1.2 mmol/L. The data from this clinical trial demonstrate that lithium is well tolerated by patients with spinal cord injury. However, as a phase I clinical trial, efficacy was not measured. In view of the descriptions of the time course of the changes triggered or caused by spinal cord injury lithium would be expected to have minimal beneficial neuroprotective effects in people with spinal cord injury of more than 12 months, as studied in this clinical study. This is because by 12 months most of these processes would have stopped. For future clinical trials in spinal injury patients it is imperative to provide lithium in a pharmaceutically effective dose, commencing within the platinum hour, golden day and silver week, and continuing as defined herein.

Example 2 - Lithium-related/lithium-containing compounds

[00572] Yang ML, Li JJ, So KF, Chen JY, Cheng WS, Wu J, Wang ZM, Gao F, Young W. Efficacy and safety of lithium carbonate treatment of chronic spinal cord injuries: a double-blind, randomized, placebo-controlled clinical trial. *Spinal Cord.* 50: 141-146, 2012. In this phase II, prospective, randomized, double-blind, placebo-controlled efficacy clinical trial, 40 stable chronic spinal cord injury patients, of more than 12 months, were recruited for a six week period; 20 were given lithium carbonate to achieve plasma lithium concentrations of 0.6

to 1.2 mmol/L; the remaining 20 patients received placebo. Baseline motor scores did not differ between treatment groups. Touch scores were also not different, until four subjects dropped out, when a small, statistically significant difference was observed. The authors concluded that lithium treatment did not change the neurological outcomes of patients with chronic spinal cord injury. Given the evidence described herein pertaining to the timing of interventions to treat victims of spinal cord injury, lithium would be expected to have minimal beneficial neuroprotective effects in people with spinal cord injury of more than 12 months, as studied in this phase II clinical trial. For future clinical trials in spinal injury patients it is imperative to provide lithium in a pharmaceutically effective dose, commencing within the platinum hour, golden day and silver week, as defined herein.

Example 3 - Lithium-related/lithium-containing compounds

[00573] van Erp TG, Thompson PM, Kieseppä T, *et al.* Hippocampal morphology in lithium and non-lithium-treated bipolar I disorder patients, non-bipolar co-twins, and control twins. *Hum Brain Mapp.* 33: 501-510, 2011. In this neuroimaging study hippocampal volume, area and length were compared between 10 lithium-treated bipolar I patients and 8 bipolar I patients that had not received lithium treatment, with the hypothesis that if lithium has neuroprotective effects the hippocampi of the lithium-treated group would be larger. The data demonstrated that patients treated with lithium long term showed trend-level larger volumes compared to those patients that did not receive lithium. Importantly, this study also compared hippocampal volume in twins given lithium and their control, matched twins that were not given lithium. The data from this study substantiate the neuroprotective effects of lithium, support the mechanisms described herein that lithium provides this neuroprotection possibly through neurotrophic and neurogenesis mechanisms, and indicates that lithium treatment protects against neuropathology that results from intrinsic or metabolic trauma as described herein.

Example 4 - Lithium-related/lithium-containing compounds

[00574] Dash PK, Johnson D, Clark J, *et al.* Involvement of the glycogen synthase kinase-3 signaling pathway in TBI pathology and neurocognitive outcome. *PLoS One.* 6(9):e24648, 2011. In this experiment, brain injury was induced in the rat by controlled cortical impact and animals were given lithium chloride or an equal volume of vehicle 30 minutes after injury, and each 24 hours afterward for five days. Compared to the control group, the lithium-treated group showed less neuronal cell death in the hippocampus, as well as better functional outcome measured as improved learning, memory and cognitive function in the Morris water maze task. The data demonstrate beneficial effects of early and sustained treatment with lithium following physical trauma to the head, including protection from cell death in the brain and protection from functional disability. The additional study groups comparing the GSK-3 selective inhibitor, SB-216763, with vehicle demonstrated that there was no difference

in neuroprotection between these groups. This indicates that the beneficial effects of lithium in this study were mediated by a mechanism or mechanisms besides inhibition of GSK-3. Further, this study substantiates the neuroprotective effects of early and continued administration of lithium during the platinum hour, golden day and silver week following trauma to protect structure and function of the nervous system.

Summary of references material to the invention:

[00575] References in the relevant art simply neither comprehend nor teach the synergistic compositions of the formulations of the presently disclosed technology. Before the present invention, there have been no combination drug formulations to reduce or prevent the secondary injury that results from trauma. The presently disclosed technology is a combination of pharmaceutical compounds. Those combinations have heretofore unknown additive or synergistic effects. Applicant theorizes that the effectiveness of the present formulations is at least partially due to the heretofore unknown additive or synergistic actions of drug compounds directed at multiple targets, including promoting multiple targets that function to restore or rescue cells from damage, as well as inhibiting multiple targets that function to drive cells toward loss of function and cell death.

[00576] Regarding of the underlying physiological and neurological mechanisms, until the presently disclosed formulations and methods, no effective combinations of compounds from the four groups herein have been known. Further, compounds selected from these groups have not been used in reducing or preventing secondary injury and its sequelae resulting from trauma. Therefore, the presently disclosed technology is advantageous in providing synergistic therapeutic formulations for preventing or reducing neuropathology which results from trauma.

DEFINITIONS, DELINEATIONS AND TERMINOLOGY

[00577] The purpose of the definitions, delineations and terminology is to explicate usages. Thus, while the definitions, delineations and terminology are intended to elucidate meanings, this is not intended to bind or limit by these definitions, delineations and terminology. Instead these definitions, delineations and terminology used herein have the same meanings as commonly understood by one of ordinary skill in the pharmaceutical or medical arts. Illustrations used are for purposes of clarity of understanding only and to remove any obscurity, and are not intended to be limiting. Various descriptions have been used to convey understanding of the definitions, delineations and terminology, and it will be understood that the meaning of these various definitions, delineations and terminologies extend to common linguistic or grammatical variations thereof. Further, the appended claims are not bound or limited by such definitions, delineations and terminologies.

[00578] FORMULATION - In the context of the presently disclosed technology the term “formulation” means a combination or mixture of pharmaceutically active or effective

chemical entities in respective pharmaceutically effective doses, to create a desired end drug product, in such a form that it can be safely administered to, or given to, or taken by a subject, and may include other ingredients or substances. Examples of such other ingredients or substances include, as examples but are not limited to, excipients, penetration enhancers, stabilizers, absorption enhancers and carriers. Further, chemical entities in the formulations of the presently disclosed technology can include any derivative, metabolite, analog, salt or any other form including natural, standard or slow-release forms. Even further, the formulations may be delivered in any form, for example, as a tablet, capsule, pill, spray, solution, paste, cream and any standard way of administering a drug, and may be delivered in any way that controls the release of the formulation.

[00579] PHARMACEUTICALLY EFFECTIVE - In the context of the presently disclosed technology the term "pharmaceutically effective" means an amount of one or more chemical entities that will alter, modify or promote restorative responses to trauma or interfere with, lessen or inhibit degenerative processes, for example by binding to an enzyme, receptor, allosteric site or other step of an endogenous biochemical, metabolic or biosynthetic pathway to the extent that the effective functioning of such pathway is altered, enabled, allowed or facilitated, as in the case of restorative processes, or would prevent, inhibit or lessen its effective functioning, as in the case of degenerative processes.

[00580] Compounds of invention embodiments that may be most effective for practicing invention embodiments include, but are not exclusively or limited to, those that promote or interfere with at least one or more parts of processes that are activated, induced or enhanced by trauma and that are involved in maintaining or damaging nerves or nerve cells, or cells upon which the health or function of nerves, nerve cells, neural support cells or neural support tissues, or cells or tissues upon which neurone cell function depend.

[00581] Included are pharmaceutical preparations of the drugs or analogs of invention embodiments that can be provided in admixture with at least one pharmaceutically acceptable substance that assists or enhances the delivery or effectiveness of the compound or compounds of invention embodiments. Examples of such substances include, as examples but are not limited to, excipients, penetration enhancers, stabilizers, absorption enhancers and carriers. Delivery of such compounds may include, but not exclusively, administration by one or more routes such as, but not limited to oral, buccal, mucosal, parenteral, rectal, subcutaneous, transdermal, topical, intravenous, intrathecal, intravaginal, nasal, nasal inhalation, pulmonary inhalation, iontophoresis through the skin, iontophoresis through mucosal or buccal membranes, dermal patch, epidural, intracranial, intrapharyngeal, sublingual, intra-articular, intramuscular and subcutaneous among others.

[00582] TRAUMA - In the context of the presently disclosed technology the term "trauma" means a wound, injury or damage to a mammalian body or body part, or an event or condition

resulting from such a wound or injury.

[00583] In one aspect, the presently disclosed technology is particularly applicable to a wound, injury or damage that includes, as examples, physical, chemical, metabolic, medical or surgical injury or damage to any tissue nerve or nerve cell, whether in the central nervous system or in the periphery, as described herein.

[00584] PHYSICAL TRAUMA - In another aspect, the presently disclosed technology is particularly applicable to physical trauma induced by, for example but not exclusively, vehicle accidents, workplace accidents, sports accidents, falls, burns, radiation, battlefield injuries such as but not exclusive to concussive blast injuries and injuries from landmines or improvised explosive devices (IED's), penetrating injuries and the like but can occur as a result of any traumatic event.

[00585] CHEMICAL TRAUMA - The presently disclosed technology is also particularly applicable to chemical trauma induced by, for example but not exclusively, medication or medication overdose, drug or drug overdose, drug abuse (such as methylenedioxyamphetamine, or MDMA, and the like), alcohol overdose, stimulant drugs such as pentylenetetrazol, carbon dioxide poisoning, heavy metals, acrylamide and related chemicals, overexposure to certain environmental chemicals such as copper or natural hazards such as scorpion venom toxin, herbicides, agricultural insecticides such as lindane, hazardous industrial chemicals, neurotoxin bioterrorism chemicals such as soman and sarin, radiation bioterrorism chemicals such as polonium and strontium, and the like.

[00586] METABOLIC TRAUMA - As an additional advantage, the presently disclosed technology is particularly applicable to metabolic trauma induced by, as examples but not exclusively, hypoxia, central nervous system ischemia, peripheral ischemia, enteric nervous system ischemia, hypoperfusion of nerve tissue, multiple sclerosis, shingles (herpes zoster), diabetes, diabetic shock, stroke, epileptic or other seizure, post-polio syndrome, HIV/AIDS peripheral neuropathic pain, subacute posttraumatic myelopathy, and other effects, syndromes and conditions following some type of trauma to the body or its nervous system. Metabolic trauma can also include but is not exclusive to hypoglycemia, hyperglycemia, ischemia, diabetic shock, epilepsy or seizure, hypoperfusion of nerve tissue during cardiac arrest, hypoperfusion in newborns resulting from complications at delivery and the like.

[00587] TRAUMA INDUCED BY MEDICAL TREATMENT OR PROCEDURE - As an additional advantage, the presently disclosed technology is similarly applicable to trauma induced by medical treatment or procedure, for example but not exclusively, injections, inoculation, implants, antibiotics, biologic drugs, antibodies, chemotherapy (for example but not exclusively with methotrexate, cisplatin, cytosine arabinose, carmustine, thiotepa among others), radiation therapy, immunosuppressants (for example tacrolimus), and the like, or during a medical procedure that can reduce or impede the blood supply for any period of time

and the like. Trauma from surgery includes, as examples, laparoscopy, amputation, mastectomy, cesarean section, cardiac surgery, hernia repair, cholecystectomy, joint replacement, thoracotomy, reparative surgery or any case, condition or situation where there is or might be detectable or undetectable cut, wound, injury or damage to nerves, nerve cells, neural support cells or neural support tissues or where long-term outcome from surgery can include adverse health conditions or disability as, for example, with failed back syndrome.

[00588] NEUROTRAUMA - In the context of the presently disclosed technology the term "neurotrauma" means a wound, injury or damage to nerves, to nerve cells, to neural support cells or to neural support tissues, as defined herein or any trauma that would or could alter the structure, phenotype, gene expression, function, survival or health of a nerve, a nerve cell, a neural support cell or a neural support tissue or any other property thereof. Trauma to neural tissue, such as nerve cells or to cells or tissues that support the structure, phenotype, gene expression, health, normal function or survival of neural tissue such as nerve cells, neural support cells and neural support tissues, can and often does lead to injury or dysfunction of these cells, and thus to numerous adverse health conditions and disabilities.

[00589] PATHOLOGY - In the context of the presently disclosed technology the term "pathology" means damage, injury or a change in cellular or tissue structure, function, phenotype, gene expression, survival or health, usually a detrimental change.

[00590] NEUROPATHOLOGY - In the context of the presently disclosed technology the term "neuropathology" means pathology of nerve cells, neural support cells or neural support tissue, neuropathy, neurodegeneration and the effects of neuropathology wherever these conditions are found. The neuropathology can occur in the brain, brain stem, cerebellum, spinal cord, enteric nervous system, peripheral nerves or any part of the body. Brain neuropathology can include, as examples, brain injury and ischemia. Spinal cord neuropathology includes, as examples, compression, vertebral collapse, cutting wounds, puncture wounds, ischemia, etc. Enteric nervous system neuropathology can include damage or injury to enteric nerve cells, progenitor cells, glial cells, interstitial cells of Cajal and any other cells and tissues upon which normal function and health are dependent. Injury to the enteric nervous system can include that resulting from chemotherapy, radiation therapy, ischemia, chemical and inflammatory trauma, physical trauma such as puncture wounds, parasitic and amoeboid infection, burns to the body, among other types of neurotrauma. Peripheral nervous system neuropathology can include damage or injury to nerve cells, nerve roots, ganglia, plexi, autonomic nerves or nerve cells, sensory nerves or nerve cells, motor nerves or nerve cells, or to any of the neural support cells or neural support tissues upon which these cells depend for normal function and health.

[00591] NEUROPATHY - In the context of the presently disclosed technology the term "neuropathy" means damage, disease or dysfunction of nerve cells, neural support cells or

neural support tissues.

[00592] NEURODEGENERATION - In the context of the presently disclosed technology the term "neurodegeneration" can include brain changes in nerve cells, neural support cells or neural support tissues resulting short-, medium- or long-term from trauma and can include Alzheimer's disease, Parkinson's disease and other disorders where brain trauma or injury is a risk factor.

[00593] NEUROTROPHIC - In the context of the presently disclosed technology the term, "neurotrophic", "neurotrophic mechanism" or "neurotrophic effect" or "neurotrophic action", terms that can be used interchangeably for the present context, encompass processes or mechanisms that augment, or therapeutic strategies intended to augment, survival, health, function, recovery, proliferation, differentiation, gene expression, growth, or regeneration of one or more cells or tissues.

[00594] NEUROPROTECTION - In the context of the presently disclosed technology the term "neuroprotection" or "neuroprotective" or "neuroprotective mechanism" or a "neuroprotective effect" or a "neuroprotective action", terms that can be used interchangeably for the present context, encompasses processes or mechanisms or therapeutic strategies intended to halt or slow the progression of secondary injury or damage, apoptosis, necrosis, excitotoxicity, nitrotoxicity, atrophy or cell death of one or more cells or tissues following the onset of insult or trauma.

[00595] NEURAL SUPPORT CELL - In the context of invention embodiments the term "neural support cell" is any cell that supports or could be considered to support the health, normal function and survival of nerves and nerve cells, and include, as examples but not exclusively, glial cells, microglia, myelin cells and satellite cells, astroglia, oligodendrocytes, satellite cells, Schwann cells, vascular endothelial cells, gastric epithelial cells, interstitial cells of Cajal, and the like.

[00596] NEURAL SUPPORT TISSUE - In the context of invention embodiments the term "neural support tissue" is any tissue that supports or could be considered to support the health, normal function, phenotype, gene expression or survival of nerves, nerve cells or support cells, and includes, as examples but not exclusively, cells of the vasculature or microvasculature, particularly the endothelial cells that prevent blood from leaking into nerve tissue and that provide the selective blood-nerve, blood-spinal cord and blood-brain barrier that allows the passage of certain supportive chemicals into nerve tissue as well as the passage of nerve tissue wastes out of nerve tissue, as well as epithelial cells and interstitial cells of Cajal of the gut.

[00597] RESTORATIVE - In the context of invention embodiments the term "restorative" means any biochemical, cellular, tissue or metabolic process that is activated by a traumatic event or the direct tissue damage from such event and that leads to or can lead to restoration,

recovery or repair of nerves, nerve cells, neural support cells or neural support tissue or that protects or restores or tends to restore normal function, gene expression and health of nerves, nerve cells, neural support cells or neural support tissues.

[00598] DEGENERATIVE - In the context of invention embodiments the term "degenerative" means any biochemical, cellular, tissue or metabolic process that is activated by a traumatic event or the direct tissue damage from such event and that leads to or can lead to loss of cell integrity, structure, function, gene expression or survival, or cell death. Such processes can or do lead to further damage or injury to such cells and tissues.

[00599] SECONDARY INJURY - In the context of invention embodiments the term "secondary injury" or "secondary damage", terms that can be used interchangeably for the present context, means any damage, injury, harm, loss, change in structure, change in phenotype, change in gene expression or change in function or survival of nerves, nerve cells, neural support cells or neural support tissue that occurs or can occur after or as a result of trauma and develops over the seconds, minutes, hours, days, weeks or months following such an event. Secondary injury or secondary damage is usually considered to result from biochemical cascades of cellular and metabolic processes that are activated or triggered by the trauma-induced direct tissue damage. Secondary injury or secondary damage is usually considered to involve endogenous processes or biosynthetic pathways that govern, regulate or influence the structure, health, function, gene expression or survival of nerves or nerve cells, or cells or tissues upon which nerves or nerve cells depend to maintain health and function, such as neural support cells and neural support tissues.

[00600] DISABILITY CLIFF - In the context of invention embodiments the term "disability cliff" means the condition, time or period where disability may develop or ensue as a result of trauma unless appropriate and timely medical or other intervention is initiated, whereas these adverse health conditions or disability can be prevented or the risk of these adverse health conditions or disability can be prevented by initiation of such intervention. Adverse health conditions or disability that can be reduced or prevented and that are due to secondary injury, as detailed herein, are the object of the presently disclosed technology, which includes formulations, methods and procedures to promote restorative processes and to inhibit degenerative processes. The presently disclosed technology aims to tip the balance away from falling over a cliff into disability, toward protection and regeneration of healthy cells and tissues. In the context of the presently disclosed technology, formulations, methods and procedures are formalized for reducing or preventing the development or the risk of development of neuropathology as a result of traumatic injury, saving or rescuing a subject from falling over the "disability cliff".

[00601] SALVAGEABLE NEUROPATHOLOGY - In the context of invention embodiments the term "salvageable neuropathology" means neuropathology that can be

reduced or prevented by appropriate and timely intervention, and includes damage to nerve cells, neural support cells and neural support tissues that ensues or can ensue from or results from secondary injury or secondary damage or injury. As a result of a traumatic injury or damage the condition of the subject is precarious, and appropriate intervention can prevent or rescue the subject, much the same for all neurotrauma as medical and therapeutic approaches to salvage the penumbra surrounding a stroke, or 'the salvageable penumbra'. Within the context of the presently disclosed technology, the neuropathology as a result of secondary traumatic injury is, broadly speaking, salvageable neuropathology.

[00602] PLATINUM HOUR - In the context of the presently disclosed technology the term "platinum hour" means the first hour beginning with a traumatic event as defined herein.

[00603] GOLDEN DAY - In the context of the presently disclosed technology the term "golden day" means the first day beginning with a traumatic event as defined herein.

[00604] SILVER WEEK - In the context of the presently disclosed technology the term "silver week" means the first week beginning with a traumatic event as defined herein.

PRACTICE EMBODIMENTS OF THE INVENTION

[00605] The present formulations, methods, procedures and systems of the presently disclosed technology provide a significant number of combinations of formulations, formulation components, dosages, administration sequences, patterns and combinations thereof to offer efficacious and safe anticipatory (pre-trauma) and posttrauma treatments for secondary damage or injury to nerve cells, neural support cells or neural support tissues.

[00606] To illustrate some of these permutations, Applicant presents herein some examples of the many particular embodiments of the invention, while noting that a person having ordinary skill in the art, armed with the present disclosure, would be able to comprehend and practice numerous forms of the formulations, methods, procedures and systems of invention embodiments, while adapting them to specific uses and circumstances and can do so without undue experimentation.

[00607] By way of scientific background, and as further described herein, all nerve cells, neural support cells and neural support tissues undergo similar, common or overlapping changes as a result of trauma, irrespective of whether these neurones are in the brain, the brain stem, the cerebellum, the spinal cord, or in the enteric nervous system or the periphery. The terminology "trauma" is broadly interpreted as explicated in its definitions and delineations as described herein.

[00608] The same or similar or overlapping restorative and degenerative processes, as defined herein, are triggered in nerve cells, neural support cells or neural support tissues, by trauma, irrespective of the site or the type of neurone or cell. While there may be some minor differences, such as the difference in sensitivity to excitotoxicity of neurones in the hippocampus vs. neurones in the cerebral cortex, the physiological processes triggered by

trauma are believed to be the same, or quite similar, in all neurones.

[00609] These physiological processes, including both the restorative and the degenerative processes, are activated within seconds or minutes by the traumatic event, and continue to develop over the hours, days, weeks and even months following the trauma. Each change that is activated or triggered by trauma sets off a process or cascade of biochemical and metabolic changes, as detailed herein. As a person having ordinary skill in the art will understand, as a result of the activation of degenerative processes, it is argued here that treatment be initiated at the earliest possible time in order to arrest or prevent further changes along the cascade. Similarly, it is advised that the restorative processes or cascades be facilitated or promoted to counteract the degenerative cascades and processes, and before irreparable damage can be done to the nerve cells, neural support cells or neural support tissues. The view of the Applicant is that there is a platinum hour, a golden day and a silver week within which optimal protection from trauma and neuropathology can be achieved, especially in the contexts of the presently disclosed technology and its embodiments. If allowed to progress, much of the neuropathology is entrenched and cannot be prevented or reversed, leading to permanent adverse health conditions or disability.

[00610] Whether the invention embodiments are practiced with respect to brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury or peripheral nerve injury practice of the invention, as indicated herein with examples of particular embodiments, occurs within the same or similar treatment parameters. As detailed herein, a key aspect of the invention in some particular embodiments relates to the timing of the administration of one or more of the present formulations. In accordance with this aspect, the timing of the administration of formulations of the invention is preferably adapted and arranged with respect to the traumatic event itself. Thus, the practice of the invention can be before a traumatic event has occurred or after a traumatic event has occurred. This timing aspect can be described generally with respect to three situations in which many embodiments of the invention are to be practiced: A) precautionary administration, B) prophylactic administration and C) posttraumatic event administration. Specific examples are provided herein to illustrate these three types of practice of invention embodiments, but are presented as examples only and do not exclude other practices of the invention.

[00611] Precautionary practice of invention embodiments includes, situations where an individual is about to enter into a high-risk situation or condition where trauma may occur. Precautionary practice would be an exigent practice, exigent circumstance practice, or contingency practice and is different from prophylactic practice or posttraumatic event practice.

[00612] Prophylactic practice of invention embodiments includes situations where a procedure, particularly a medical or surgical procedure, is about to take place wherein the

procedure is known to produce, or where evidence suggests it may produce, trauma, damage or injury to nerve cells or neural support cells or neural support tissues in some patients, whether in the central nervous system, the peripheral nervous system or the enteric nervous system. Prophylactic practice is thus distinguishable from precautionary practice or posttraumatic event practice.

[00613] Posttraumatic event practice of invention embodiments includes any situation or condition where a traumatic event is occurring or has occurred, and there is known, or there is reason to suspect, damage, injury or cell death to nerve cells, neural support cells and neural support tissues, whether in the central nervous system, the peripheral nervous system or the enteric nervous system. Posttraumatic practice is thus distinguished from precautionary practice or prophylactic practice.

PRECAUTIONARY PRACTICE OF THE INVENTION

[00614] Embodiments of the invention are useful also in circumstances where a trauma to nerve cells, neural support cells or neural support tissues is quite likely to occur, or whenever it is even anticipated. Embodiments of the invention that are precautionary in nature are quite useful, and fill a void which presently exists with respect to the treatment of such trauma in high risk conditions or situations.

[00615] In such cases of great likelihood of trauma being soon endured by one or more individuals, the presently disclosed technology is uniquely applicable. In such cases, no traumatic event has yet occurred at the time that a formulation of invention embodiments is taken by a subject or administered to a subject. In such precautionary embodiments of the methods, procedures, means and systems of embodiments of the invention, a formulation is administered prior to the highly expected trauma event or at the time of the pre-trauma awareness that a potential trauma exists.

[00616] In some embodiments lithium is not included in the usual four-component formulation because of its relatively narrow therapeutic dose range and the relatively low threshold for adverse effects. In other words, lithium is not included unless there is an actual traumatic event, in which case practice of the invention will follow the formulations methods and procedures represented herein as Posttraumatic Event practice embodiments.

Example 1 - A Military/Law Enforcement Precautionary Embodiment:

[00617] In one particular exemplary embodiment, the invention is adapted and arranged as part of the precautionary preparations in anticipation of subjects entering into a dangerous military or law enforcement operation or situation where a neurotrauma is specifically anticipated, and generally likely or suspected to occur, due to for example the surrounding circumstances in a military or law enforcement context.

[00618] In this type of example of a particular embodiment of the invention, a soldier or law enforcement officer subject is about to enter an area or situation where there is a high risk of

enemy combat or a high risk of the presence of live explosives (such as IEDs in a combat zone or booby traps set by domestic terrorists) or is a member of a team that dismantles explosive devices. In this scenario of applicability of invention embodiments, no traumatic event has occurred prior to administration of the formulation.

[00619] In this regard, Applicant notes that it is known that an explosive or percussive event can cause neurotrauma, particularly to but not necessarily only to the head of a victim. Thus, in precautionary embodiments of the methods, procedures, means and systems of embodiments of the invention, a formulation is administered (as a 2- or 3-component formulation) prior to the entry of each of one or more subjects into an area of high risk to thereby reduce the risk of development of neuropathology should the subject experience neurotrauma. The present example thus illustrates a circumstance where an individual is at high risk that a traumatic event will occur which event would likely adversely affect the head or other body parts, either directly or through a fall or impact, resulting in trauma to nerves, nerve cells, neural support cells and neural support tissues.

[00620] As an advantage of precautionary embodiments of the invention, an adequate supply of the formulation (as a 3-component formulation) in one or more appropriate forms, such as liquid, tablet, capsule or pill form adapted for oral administration is on hand for use by personnel in the military or law enforcement unit.

[00621] Thus, in some exemplary embodiments, from 20 to 90 minutes before the departure of the soldier or officer subjects into such an area, situation or scenario, the subject or subjects would self-administer or be given, as a precautionary action, one oral tablet, capsule or pill of the formulation.

[00622] To practice typical precautionary embodiments of the invention, the formulation would include sufficient amounts of any two or any three constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the any two or any three constituents preferably include Gabapentin, Progesterone and Aprepitant.

[00623] In this case, the individual, among other individuals, and among other actions to minimize risk, would have available the formulation (as a 2- or 3-component formulation) as tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone and from 5 to 375 mg of Aprepitant. These dosage ranges represent one particular embodiment of the invention.

[00624] More particularly, the three constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, and from 20 to 250 mg of Aprepitant. These dosage ranges represent one particular embodiment of the invention.

[00625] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg,

Progesterone at 100 to 300 mg and Aprepitant at 40 to 120 mg. These dosage ranges represent one particular embodiment of the invention.

[00626] To practice the invention in this case, the individual would self-administer or be administered three tablets, capsules or pills, each tablet, capsule or pill with the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg and Aprepitant at 40 mg.

[00627] As another advantage of the invention, in cases where a traumatic explosive or percussive event does not occur, there would be no adverse outcome expected of this type of embodiment of the invention or of this dose range of from 200 to 600 mg of Gabapentin, from 100 to 300 mg of Progesterone, and from 40 to 120 mg of Aprepitant.

[00628] In cases where a traumatic explosive or percussive event does occur, practice of the invention will follow formulations, methods and procedures described as Posttraumatic Event Embodiments of the invention.

Example 2 - A Civilian Precautionary Embodiment:

[00629] Embodiments of the invention are useful also as precautionary treatment in circumstances where a neurotrauma is specifically anticipated and generally likely or suspected in a civilian (non-military, non-law enforcement or the like) context.

[00630] In this type of use of particular exemplary embodiments of the invention, a person of importance, for example, in a governing role within a particular region or jurisdiction is alerted to impending danger in the form of a bioterrorism attack. There is thus a high risk of trauma from a neurotoxic substance, such as a botulinum toxin released from *Clostridium botulinum*, that is expected to be or to have been released locally into the environment, or to be released in some other way that could threaten the health or lives of individuals.

[00631] In this regard, Applicant notes that it is known that many of the chemical agents that can be released and disseminated in a bioterrorism attack have as their main target, nerve cells, neural support cells and neural support tissues, either in the central nervous system, in the enteric nervous system or in the peripheral nervous system, or all. Because of this, in addition to efforts to contain the spread of the neurotoxic substance, and efforts to move the persons of importance to a safe-room or safe condition, risk remains because what is not known, inter alia, are the specific active bioterrorism chemical or agent, the time when the substance was released, the spread of the substance, how persistent it is in the environment, how well it has been contained, its specific nature, whether there is an antidote to this substance. In this scenario, no symptoms have yet appeared.

[00632] This would be an example of a condition where there is a high potential that an individual, in this case someone important in the administration or governance of a region or jurisdiction, may have been exposed or may be exposed to sufficient amounts of the bioterrorism substance as to cause damage or injury to nerve cells, or neural support cells or neural support tissues. In this exemplary embodiment, the person would self-administer at the

earliest possible time, as a precautionary action, one oral tablet, capsule or pill of the formulation. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00633] To practice invention embodiments, the individual, among other individuals, and among other actions to minimize risk, would have available to self-administer or be administered the formulation (as a 2-, 3- or 4-component formulation) as three tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00634] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00635] Typically, an even more specific dose range comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00636] Practice of invention embodiments in this case would be for the individual to self-administer three tablets, capsules or pills, each tablet, capsule or pill with the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00637] In the event that symptoms of neurotoxicity begin to appear as a result of the bioterrorism act, in addition to the single dose of the formulation taken earlier, two tablets, capsules or pills of the formulation would be taken as a four-component formulation as soon as possible. In this event the subject would self-administer or be given to take two tablets, capsules or pills each comprising Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg, and Lithium carbonate at 200 mg.

[00638] Based on assessment of safety and risk as well as the presence of any symptoms of neurotoxicity as a result of the bioterrorism act, formulation administration would be continued or discontinued. If continued, the formulation would be taken as one pill, capsule or solution at eight-hour intervals, beginning 24 hours after the appearance of symptoms of neurotoxicity, each pill, capsule or solution comprising Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg, and Lithium carbonate at 200 mg. If formulation administration is continued beyond three days, the individual's serum levels of lithium would preferably be monitored professionally by qualified personnel to ensure they remain within

the therapeutic range. Typically, this range is believed to be 0.6 to 0.8 mEq/L; while intra-individual variability is limited, there is inter-individual variability and therefore serum levels are advantageously matched with effectiveness for each individual.

PROPHYLACTIC PRACTICE OF THE INVENTION

[00639] Embodiments of the invention are useful in medical circumstances where evidence from clinical studies indicates that damage to nerves or nerve cells, or neural support cells or neural support tissues may result from a medical procedure, such as surgery or other medical treatment or medical procedure. Embodiments of the invention that are prophylactic in nature are quite useful, and fill a void which presently exists with respect to the prevention of neuropathology that may result from surgery or medical treatment or medical procedure. The following examples of types of situations or scenarios where there is known or substantiated evidence that neurotrauma, or damage to nerve cells, or neural support cells or neural support tissues may be or will be an outcome of surgery or other medical treatment or medical procedure to a patient are therefore provided.

Example 3 - A Clinical Pre-surgical Embodiment:

[00640] In one particular exemplary embodiment, the invention is adapted and arranged as a prophylactic procedure to prevent or reduce the risk of neurotrauma to peripheral nerve cells, neural support cells and neural support tissues arising as a result of surgery. In this regard, Applicant notes that it is known that all major and even many moderate surgeries on a subject can and frequently do result in adverse health conditions, such as pain, persisting for months or even permanently. For example, as documented herein and in the available scientific and clinical literature, surgery leads to chronic pain in a known percentage of patients undergoing a particular type or class of surgery.

[00641] In this type of example of a particular embodiment of the invention, a 45-year-old woman is in hospital about to undergo a mastectomy. It is known that following this type of surgery 20-50% of patients end up with persistent neuropathic pain. It is unknown whether this particular patient will fall into this 20 or more percent. Thus the present example illustrates a case where it is unknown whether the surgery will cause neurotrauma, but clinical evidence indicates the possibility of persisting neuropathic pain resulting from this surgical procedure.

[00642] In this exemplary embodiment, the patient and her healthcare team would weigh the risks and benefits of taking prophylactic measures to limit the possibility of surgically induced chronic pain.

[00643] As yet another use and advantage of invention embodiments, an adequate supply of the formulation in tablet, capsule or pill form is available in the medical facility for use by the healthcare team.

[00644] To practice typical prophylactic embodiments of the invention, the formulation

would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00645] In this case, to practice invention embodiments the patient, among other actions to minimize risk, would have available to take or to be administered tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone and from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00646] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00647] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00648] If the patient and the healthcare team decide to reduce the risk of surgically induced neuropathic pain, to practice invention embodiments the subject would self-administer or be given the formulation as three single tablets, capsules or pills, each tablet, capsule or pill containing two, three or all four constituents (or their substitutes or equivalents) as Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00649] Following the surgery, in combination with standard postoperative care, beginning the following day the subject is given to take one tablet, capsule or pill each eight hours, in the doses prescribed herein or as prescribed by the attending physician, and continued afterward as needed. Typically continuation would be practiced as one tablet, capsule or pill each eight hours, each as Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. This continuation period will vary with the severity of the surgery and the known incidence of persistent pain, but would not usually need to exceed a total of three days.

[00650] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the subject's blood serum levels of lithium are advantageously monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the subject, the treatment protocol should be lessened to the administration of one tablet, capsule or pill each ten to twelve hours or as prescribed by the physician.

Example 4 - A Clinical Pre-radiation Therapy Embodiment:

[00651] In another particular exemplary embodiment, the intervention is adapted and arranged as a prophylactic procedure to prevent or reduce the risk of neurotrauma to peripheral nerves or to the enteric nervous system arising as a result of therapeutic radiation. In this type of example of a particular embodiment of the invention, a patient with cervical cancer is about to undergo external beam radiation therapy.

[00652] In this regard, Applicant notes that it is known that radiation therapy to a subject can and frequently does result in damage to nerves, nerve cells or neural support cells, with resulting long term or even permanent adverse health conditions or disability or other symptoms of neurotrauma. As documented herein and in the scientific literature, damage or injury to the enteric nervous system or the peripheral nervous system can lead to secondary damage to nearby nerve cells, neural support cells and neural support tissues, as well as spread to other nerve cells, neural support cells and neural support tissues more remotely in both the enteric nervous system and the peripheral nervous system. This secondary injury or damage to the peripheral nervous system can result in loss of sensation from the affected area, chronic neuropathic pain or loss of muscle control, or other symptoms of peripheral neuropathology. Such secondary damage or injury can also or otherwise be to the enteric nervous system in the gut; the disability ensuing from this type of secondary injury can include life-changing gastrointestinal complications or other autonomic dysfunction as described herein.

[00653] It is unknown whether this particular patient will develop pathological changes in nerve cells, neural support cells or neural support tissues in the enteric nervous system or in the peripheral nervous system as a result of this radiation therapy. The patient is given the option to take prophylactic measures to limit the possibility of radiation-induced neurotrauma to nerve cells, neural support cells or neural support tissues in the enteric nervous system or the peripheral nervous system.

[00654] The present example illustrates a case where it is unknown whether the radiation therapy will cause neurotrauma, but clinical evidence indicates the possibility of permanent numbness, pain, motor weakness, gastrointestinal disability, autonomic dysfunction or any combination of these or other symptoms as described herein.

[00655] In this exemplary embodiment, the patient and her healthcare team would weigh the risks and benefits of taking prophylactic measures to limit the possibility of symptoms of radiation induced neuropathology. If the patient decides to reduce the risk of neurotrauma resulting from the radiation treatment, among other actions to minimize risk the patient would self-administer or be given the formulation (as a two-, or three- or four-component formulation) 20 to 90 minutes before the beginning of radiation therapy.

[00656] As yet another use and advantage of invention embodiments, an adequate supply of

the formulation in tablet, capsule or pill form is available in the medical facility for use by the healthcare team.

[00657] To practice typical prophylactic embodiments of the invention, the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably any of Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00658] In this case, to practice invention embodiments the patient would have available to take or be administered tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00659] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00660] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00661] If the patient and the healthcare team decide to reduce the risk of radiation induced damage or injury to nerve cells, neural support cells or neural support tissues in the enteric nervous system or the peripheral nervous system, the subject would self-administer or be given the formulation as three single tablets, capsules or pills, each tablet, capsule or pill containing any two, any three or all four constituents (or their substitutes or equivalents) as Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00662] Following each radiation therapy session, in combination with standard post therapy care the subject is given one tablet, capsule or pill each eight hours, and continued afterward as needed. This period will vary with the intensity and extent of the radiation therapy, but would not normally need to exceed a total of three days. In the event that one or more radiation therapy sessions would be held, the treatment with the formulation would be adjusted according to the conditions as prescribed by a physician.

[00663] In a similar manner, in cases of other types of radiation therapy, the duration of continued eight-hour administration would vary depending on the known incidence of signs or symptoms of neuropathology outcomes, such as chronic pain or autonomic dysfunction, for each respective type of therapy. In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the

subject's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the subject, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours or as prescribed by her physician.

Example 5 - A Clinical Combination Chemotherapy Embodiment:

[00664] In another particular exemplary embodiment, the intervention is adapted and arranged as a prophylactic procedure to prevent or reduce the risk of neuropathology in the brain or other nerves, nerve cells, neural support cells or neural support tissues as a result of a combination of chemotherapy and radiation therapy. In this type of example of a particular embodiment of the invention, a patient with nasal cancer is about to undergo a combination of chemotherapy and external beam radiation therapy to treat the cancer in the head.

[00665] In this regard, Applicant notes that it is known that this type of combination therapy to a subject can and frequently does result in damage to nerves, nerve cells, neural support cells or neural support tissues of the brain, with resulting long term or even permanent disability or symptoms of neurotrauma. As documented herein and in the scientific and clinical literature, such combination therapy may cause neuropathology such as necrosis of nerve cells in the brain, as well as loss of function of peripheral nerve cells in the head, leading to blindness, loss of hearing, or other symptoms related to damage or death of nerve cells, neural support cells or neural support tissues.

[00666] The present example illustrates a case where it is not possible to predict ahead of the medical intervention whether the radiation therapy will cause neurotrauma, but clinical evidence indicates that risk is extended over a period of time including before and after radiation-induced trauma, as well as the extended period of the chemotherapy. The present example illustrates a case where it is unknown whether the combination of chemotherapy and radiation therapy will cause neurotrauma to this particular patient, or whether the patient will develop neuropathological changes in nerve cells, neural support cells or neural support tissues as a result of this combination of chemotherapy and radiation therapy. The patient and his/her healthcare team would weigh the risks and benefits of taking prophylactic measures to limit the possibility of early symptoms of radiation induced neuropathology as well as the possibility of symptoms developing that might result from the combination of radiation and chemotherapy, but in this exemplary embodiment the high level of risk coupled to the severity of the potential negative outcomes renders the patient and his/her healthcare team little option but to recommend preventive measures.

[00667] As yet another use and advantage of the invention, an adequate supply of the formulation in tablet, capsule or pill form is available in the medical facility for use by the healthcare team.

[00668] To practice typical prophylactic embodiments of the invention, the formulation would include sufficient amounts of two, three or four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the four constituents of the formulation are preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00669] In this case, to practice invention embodiments the patient, among other actions to minimize risk, would have available to take or be administered tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00670] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00671] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00672] To practice invention embodiments, the individual, among other actions to minimize risk, would self-administer or be given the formulation (as a 4-component formulation) as three single tablets, capsules or pills, each tablet, capsule or pill containing two, three or all four constituents (or their substitutes or equivalents) as Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00673] Beginning 24 hours following the therapeutic session, the patient will be maintained on a regimen of one single tablet, capsule or pill every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00674] In this or similar embodiments of the administration of the formulation, the period of continuation of treatment will exceed three days. As a result, the patient's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects of lithium begin to manifest in the patient, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours, as prescribed by a physician.

Example 6 - A Clinical Pre-cardiovascular Surgery Embodiment:

[00675] In another particular exemplary embodiment, the invention is adapted and arranged as a prophylactic procedure to prevent or reduce the risk of ischemic neurotrauma to the central nervous system as a result of cardiovascular implantation surgery. In this type of

example of a particular embodiment of the invention, an older patient is about to undergo transcatheter aortic valve implantation (TAVI) for severe aortic stenosis.

[00676] In this regard, Applicant notes that it is known that in patients undergoing TAVI surgery there is an incidence of stroke in 1.7 to 8.4% of such patients during or within hours of the TAVI surgery. As documented herein and in the scientific literature, such surgery may cause ischemia-induced neuropathy, and show negative symptoms and disability of TAVI-induced stroke.

[00677] In this case it is unknown whether this particular patient will develop central nervous system ischemia, but this patient would be considered at risk for embolic stroke during or immediately after the surgery. The patient and the healthcare team would consider the risks of TAVI surgery and would be given the option to take prophylactic treatment to reduce the risk of TAVI-induced stroke and its symptom sequelae. In such a prophylactic embodiment of the methods, means and systems of embodiments of the invention the formulation is administered before commencement of the surgery.

[00678] The present example illustrates a case where it is unknown whether the surgical intervention will cause neurotrauma to the brain, the brain stem, the cerebellum or the spinal cord, but clinical evidence indicates that permanent symptoms or death have resulted from TAVI-induced central nervous system embolic ischemia in some patients.

[00679] As yet another use and advantage of invention embodiments, an adequate supply of the formulation, in tablet, capsule or pill form, is available in the medical facility for use by the healthcare team. If the patient decides to reduce the risk of TAVI-induced embolic stroke, in this exemplary embodiment the patient will be given the formulation as tablets, capsules or pills to take 20 minutes to 90 minutes before the surgery, each tablet, capsule or pill, each comprising Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00680] To practice typical prophylactic embodiments of the invention, the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00681] In this case, to practice invention embodiments the patient, among other actions to minimize risk, would have available to take or be administered tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00682] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of

Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00683] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00684] To practice invention embodiments, the individual, among other actions to minimize risk, would self-administer or be given the formulation (as a 4-component formulation) as three single tablets, capsules or pills, each tablet, capsule or pill with the following constituents (or their substitutes or equivalents) as two, three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00685] In this or similar embodiments of the administration of the formulation, beginning 24 hours following the therapeutic session, the patient will be maintained on this regimen of one single tablet, capsule or pill every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg, as prescribed by a physician. The patient's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects of lithium begin to manifest in the patient, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours, as prescribed by a physician.

POSTTRAUMATIC EVENT PRACTICE OF THE INVENTION

[00686] Embodiments of the invention are useful in circumstances where a traumatic event has taken place and there is trauma or suspected trauma to the central nervous system, the peripheral nervous system or the enteric nervous system, comprising any neurone, set of neurones, nerve or nerve cell, or any cell or tissue that supports the health or survival of nerve cells directly or indirectly.

[00687] Embodiments of the invention that are posttraumatic in nature are quite useful, and fill a void which presently exists with respect to the treatment or prevention of neuropathology, or the risk of neuropathology that may result from a traumatic event.

[00688] In such posttraumatic embodiments of the methods, procedures, means and systems of embodiments of the invention, the formulation is administered as soon as possible after the traumatic event has occurred. In cases of an on-going or continuing traumatic event, the formulation is administered during the traumatic event or as soon afterward as possible.

Example 7 - A Seizure Embodiment:

[00689] In one particular exemplary embodiment, the invention is adapted and arranged to treat a seizure-type neurotraumatic event to the brain, to prevent, or reduce the risk of,

damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a seizure. In this type of example of a particular embodiment of the invention, a 35 year old male at high risk of recurrent epileptic seizures is at home with a spouse, and the spouse is knowledgeable about the aspects of the methods, procedures, means and systems of embodiments of the invention. The spouse becomes aware that a seizure is occurring.

[00690] The present example illustrates a case where a subject is known to be at risk for recurring seizures that can occur at any time. This would be a case of an unanticipated but not unexpected neurotrauma, such as an epileptic (or other neurologic) seizure where clinical evidence indicates a risk of further brain damage that could ensue from a seizure.

[00691] In this regard, Applicant notes that it is known that that an epileptic or other neurological seizure is associated with excessive release of excitatory amino acid transmitters that contribute to the seizure but also diffuse to other brain areas where they can cause excitotoxic neuropathology and death of nerve cells, neural support cells or neural support tissues in these other brain areas. As documented herein and in the scientific and clinical literature a seizure can and frequently does lead to neuropathology and sequelae of symptoms related to damage to the brain. In this case it is unknown whether this particular individual will develop neuropathological damage as a result of the seizure, but there is a risk of such neuropathological damage resulting from the seizure that is underway or has occurred.

[00692] In such a posttraumatic event exemplary embodiment, to practice invention embodiments, among other actions to minimize harm, the spouse would administer the formulation as soon as possible to prevent neuropathology resulting from the seizure. As yet another use and advantage of invention embodiments, an adequate supply of the formulation, in nasal spray form, is available in the home for use to be taken by the individual or administered by the spouse. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the four constituents of the formulation are preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00693] In this exemplary embodiment, each single spray would contain the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00694] More particularly, the four constituents (or their substitutes or equivalents) are provided as a single spray in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00695] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00696] In this case, to practice invention embodiments, among other actions to ensure the safety and comfort of the subject, upon the first sign of the beginning of a seizure, the subject undergoing or experiencing the seizure will self-administer, or if the subject is incapacitated or otherwise unable to do so, the spouse will administer to the subject, the formulation as a single nasal spray into one nostril, a single spray comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00697] As yet another use and advantage of invention embodiments, in case administration by nasal spray is not possible or practical, an adequate supply of the formulation, in tablet, capsule or pill form, is available in the home for use taken by the individual or given by the spouse. Each tablet capsule or pill would comprise two, three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg, and the subject would self-administer or be administered three such tablets, capsules or pills.

[00698] Once the seizure has dissipated there will be no further need for the subject to take or be given the formulation.

Example 8 - A Vehicular Accident Embodiment:

[00699] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma, or a possible or suspected neurotrauma, caused as a brain injury or a traumatic cord spinal injury or a traumatic injury to peripheral nerves resulting from a vehicular accident. Embodiments of the invention are adapted to prevent, or reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a vehicular accident. In this type of example of a particular embodiment of the invention, a 21 year old male is involved in an automobile accident and is awake, but has experienced a head impact against a part of the interior of the car at the time of collision of the vehicle with another car or with some other structure. The victim is awake but it is known that following this type of accident there is a possibility that some neurotrauma has occurred. The present example illustrates a case where there has been an unanticipated and unexpected traumatic event and where there has been or may have been damage to the brain or parts of the brain or the spinal cord or peripheral nerves that could lead to neuropathology and symptom sequelae.

[00700] In this regard, Applicant notes that it is known that an impact injury to the head can and often does cause a tearing, shearing or stretching of the brain or parts of the brain as well as spinal cord and peripheral nerves, and this can and often does lead to neuropathology in the parts of the brain, spinal cord or peripheral nerves that are directly traumatized as well as

more remote parts of the brain, spinal cord and peripheral nerves due to spreading secondary neuropathology as described herein. As documented herein and in the scientific and clinical literature, trauma to the head or body, can and frequently does lead to symptoms related to damage to nerve cells, neural support cells and neural support tissue in the brain, spinal cord and periphery. In this case it is unknown whether this particular individual has sustained or will develop neuropathological damage as a result of the trauma to the head and body, but there is a risk that such neuropathological damage resulting from the automobile accident is already underway or has occurred or will develop.

[00701] In such a posttraumatic event, to practice invention embodiments in this type of posttraumatic event embodiment includes administration of the formulation by a first-on-scene paramedic or emergency medical services personnel or other such qualified personnel, who would give the victim the formulation as tablets, capsules or pills immediately upon securing stabilization of the victim. Administration of a formulation would be part of standard practice. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00702] In this case, to practice invention embodiments the victim, being awake, among other actions to minimize risk, would have available to be given to take the formulation orally as tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00703] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00704] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00705] Practice of invention embodiments in this case would be for the individual to self-administer three tablets, capsules or pills, each tablet, capsule or pill with any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00706] As yet another use and advantage of invention embodiments, an adequate supply of the formulation, in tablet, capsule or pill form, is available with the paramedic or emergency medical services personnel or other qualified personnel for administration to one or more

victims in this or similar embodiments of the invention. In this exemplary embodiment, the rapid response paramedic or team, or other qualified personnel, as a complement of standard emergency procedures to stabilize the victim or victims of a vehicular accident, will administer to the victim or to each of the victims the formulation as three single tablets, capsules or pills, each comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00707] Practice of invention embodiments is incorporated with other emergency measures, such as transport of the victim or victims to the nearest healthcare facility for further emergency procedures, assessment, diagnosis and follow-up care. In such a posttraumatic embodiment of the methods, in follow-up care the methods, procedures, means and systems of embodiments of the invention will be employed so that a formulation is given or administered by the emergency clinic team, or other qualified personnel as prescribed by a physician.

[00708] If any signs or symptoms of neurotrauma begin to manifest, and especially if any such signs or symptoms show any signs of increasing, twenty-four hours after the initial dose of the formulation, the subject will be given one tablet, capsule or pill each eight hours, and continued afterward as needed. This period will vary with the severity of the injury to the head, but will not normally need to exceed a total of three days from the initial administration.

[00709] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days as determined by a physician, the subject's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the subject, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours as prescribed by a physician.

Example 9 - A Vehicular Accident with Unconsciousness Embodiment:

[00710] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma or a possible or suspected neurotrauma to the brain, to the spinal cord or to peripheral nerves, where an individual is unconscious, for example as a result of a serious vehicular accident where a victim is rendered unconscious. Embodiments of the invention are adapted to prevent, or to reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a serious vehicular or any such serious accident. In the present type of example of a particular embodiment, a subject is involved in an automobile accident and rendered unconscious in a remote area and the subject is not found, or does not recover enough to go for help, within 12 hours after the accident.

[00711] The present example illustrates a condition where there has been an unexpected, accidental neurotrauma, where the victim is unconscious or has been unconscious for some

minutes or hours, where the platinum hour has passed and the golden day of opportunity is passing or has passed, and where immediate rescue is imperative to prevent or reduce the risk of further damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a serious accident. If the party or parties that discover the victim do not have available an adequate supply of the formulations the victim needs to be transported as soon as possible to a nearby medical or hospital facility.

[00712] In this regard, Applicant notes that it is known that unconsciousness is rendered as a result of trauma to the head which can and often does cause a tearing, shearing or stretching of the brain or parts of the brain as well as spinal cord and peripheral nerves, and this can and often does lead to neuropathology in the parts of the brain, spinal cord and peripheral nerves that are directly traumatized as well as more remote parts of the brain, spinal cord and peripheral nerves due to spreading secondary neuropathology as described herein.

[00713] As documented herein and in the scientific literature, trauma to the head, particularly when the victim is rendered unconscious, can and frequently does lead to symptoms related to damage nerve cells, neural support cells and neural support tissue in the brain, spinal cord and periphery. In this case it is unknown whether this particular individual has sustained or will develop neuropathological damage as a result of trauma to the head and body, but there is a risk that such neuropathological damage resulting from the automobile accident is already underway or has occurred or will develop.

[00714] In such a posttraumatic event exemplary particular embodiment, to practice the invention includes administration of a formulation by a first-on-scene paramedic or emergency medical services personnel or other such qualified personnel, who arrives to transport the victim to the nearest medical or hospital facility. This paramedic or emergency medical services personnel would administer the formulation by nasal spray if the victim remains unconscious, or by tablet, capsule or pill if this is more practical. If the victim is transported by a passerby or other non-qualified personnel, the formulation would be administered by qualified personnel immediately upon arrival at the nearest healthcare clinic, centre or hospital. In this case, administration would be by nasal spray, or by tablet, capsule or pill if this method of administration is more practical.

[00715] In such a case, practice of invention embodiments requires serum levels of the constituents of the formulation to be established immediately or as soon as possible. The time course for these levels to reach the therapeutic range via the oral route is three to six hours. In this case further delay is allowing the degenerative processes to advance farther and some permanent neuropathology may have already occurred. The time to maximally enhance the restorative processes is also passing. The fastest route to achieve therapeutic serum levels of constituents of the formulation within the therapeutic range is via nasal spray.

[00716] Therefore, an emergency vehicle or a local medical or hospital facility is equipped

with an adequate supply to provide the formulation by nasal spray. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00717] To practice invention embodiments, the emergency services personnel or the local medical or hospital personnel would administer to the victim a single spray intranasally of the formulation with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00718] As yet another use and advantage of invention embodiments, an adequate supply of the formulation in the form of nasal spray, tablet, capsule or pill is available to the paramedic or to the medical or hospital facility for use by the healthcare team or by qualified personnel. In this exemplary embodiment, the qualified personnel, as a complement of standard emergency procedures to stabilize the victim, will administer to the victim the formulation, applying the methods and procedures of invention embodiments.

[00719] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00720] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00721] In this case, to practice invention embodiments the first healthcare professional available would administer to the victim one spray from a vaporizer into one nostril, with one spray containing any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00722] As yet another use and advantage of invention embodiments, in a case where administration by nasal spray is not possible due to injury to the nose or for any other reason, and if the victim has not regained consciousness or it is otherwise not possible or practical to administer the formulation in tablet, capsule or pill form, the same may be achieved via sublingual spray, although transit time via this route is slower. In this case, to practice this embodiment of the invention the sublingual spray of the formulation would be comprised of the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention. Alternatively, the constituents are provided in the ranges of from 100 to 2,400 mg of

Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention. An even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00723] As yet another use and advantage of invention embodiments, in a case where administration by nasal spray or by sublingual spray is not possible due to injury for any reason, the same may be achieved via an intramuscular or intravenous route. In this case, to practice this embodiment of the invention the intramuscular or intravenous solution of the formulation would be comprised of the following constituents in the ranges of from 200 to 600 mg of Gabapentin, from 100 to 300 mg of Progesterone, from 40 to 120 mg of Aprepitant and 200 to 600 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention. Alternatively, the constituents of the intramuscular or intravenous administration of the formulation are provided in the ranges of from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention. An even more specific dose comprises Gabapentin at 100 to 2,400 mg, Progesterone at 50 to 450 mg, Aprepitant at 20 to 250 mg and Lithium carbonate at 100 to 900 mg. These dosage ranges represent one particular embodiment of the invention.

[00724] In such a posttraumatic event exemplary embodiment of the methods, means and systems of embodiments of the invention the formulation is administered by the emergency clinic team, or other qualified personnel as prescribed by a physician. Twenty-four hours after the initial dose of the formulation, the subject will be given one tablet, capsule or pill each eight hours, and continued afterward as needed. This period will vary with the severity of the injuries suffered in the accident as well as the duration of the loss of consciousness, but will not normally need to exceed a total of three days. If the victim has regained consciousness the formulation (as a 4-component formulation) is given as one tablet, capsule or pill each eight hours, the formulation being with the any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00725] In such a posttraumatic event exemplary embodiment of the methods, means and systems of embodiments of the invention, if the victim has not regained consciousness the formulation (as a 4-component formulation) is given by intravenous administration with the following constituents: two, three or all four of Gabapentin at 600 mg, Progesterone at 100 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00726] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the subject's serum levels of

lithium are advisedly monitored professionally by qualified personnel to ensure they remain within the therapeutic range for the patient. In the event that adverse effects begin to manifest the treatment protocol should be lessened, for example to once each ten or twelve hours as prescribed by a physician.

Example 10 - An Explosive Device Embodiment:

[00727] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma, or a possible or suspected neurotrauma, caused as an explosive or percussive brain injury or to the spinal cord or to peripheral nerves resulting from close detonation of an explosive device, to prevent the development or the risk of development of neuropathology to the brain, the spinal cord or peripheral nerves, resulting from such detonation of an explosive device. Embodiments of the invention are adapted to prevent, or reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of trauma from an explosive device. In this type of example of a particular embodiment of the invention, a soldier is injured while on duty by a nearby explosion of an Improvised Explosive Device (IED).

[00728] In this type of example of a particular embodiment of the invention, a 26 year old soldier is on foot patrol in an enemy-threatened area and a companion soldier steps on a landmine and is killed instantly. However, the remaining soldier is thrown to the ground by the explosion and lands such that his helmeted head impacts on a protruding rock. Within a few moments the surviving soldier is able to get up and walk, though stunned, presumably by the explosion. His gait is unsteady, but he is able to return to a safe area where, after several minutes he is rescued by members of his team. The present example illustrates a case where there has been an unanticipated yet suspected traumatic event, with possible head injury, and it is unknown whether this surviving soldier has experienced or will develop neuropathological damage as a result of the explosion or as a result of the fall, to the head and body, but there is a risk that such neuropathological damage resulting from the explosion or from a head injury sustained from a fall is already underway or has occurred or will develop.

[00729] In this regard, Applicant notes that it is known that explosive and percussive trauma can, and in many cases does, lead to injury to nerves, nerve cells, support cells and support tissues in the central nervous system and the peripheral nervous system, and that such injury activates restorative and degenerative processes that limit or promote secondary neuropathology, locally to nerve cells, support cells and support tissues as well as in such cells in more remote areas of the central and peripheral nervous systems. Further, Applicant also notes that head injuries to soldiers in action who fall as a result of explosions or other cause, and who sustain a head injury or injury to the body can and in many cases does lead to injury to the brain, the spinal cord or the peripheral nervous system. As documented herein and in the scientific literature, trauma to the head or body, can and frequently does lead to

symptoms related to damage nerve cells, neural support cells and neural support tissue in the brain, spinal cord and periphery.

[00730] In such a posttraumatic event exemplary embodiment, to practice invention embodiments in this type of embodiment the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00731] In this case, to practice invention embodiments includes administration of the formulation by the unit medic or other such qualified personnel, who would ensure the safety of the situation, practice all immediate emergency standard practices and administer the formulation orally, as tablets, capsules or pills immediately upon securing stabilization of the wounded soldier. In this case each tablet, capsule or pill would be of the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00732] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00733] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00734] As yet another use and advantage of invention embodiments, an adequate supply of the formulation, in tablet, capsule or pill form, is available to the paramedic or emergency medical services personnel or other qualified personnel for administration to a wounded soldier in this or similar embodiments of the invention. In this exemplary embodiment of the invention, in combination with standard emergency measures the medic or other qualified personnel will administer to the wounded soldier the formulation as three single tablets, capsules or pills, each tablet, capsule or pill comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 300 mg, and Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00735] As yet another use and advantage of invention embodiments, in conditions or situations where it is not possible or practical to administer the formulation in tablet, capsule or pill form, an adequate supply of the formulation, in the form of a nasal spray is available to the medic or other qualified personnel for administration to a wounded soldier in this or similar embodiments of the invention. In this exemplary embodiment, the medic or qualified personnel, as a complement to standard emergency procedures to secure and stabilize a

wounded soldier, will administer to the soldier the formulation as a single nasal spray comprising Gabapentin at 600 mg, Progesterone at 300 mg, and Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00736] As yet another use and advantage of invention embodiments, in a case where administration by tablet, capsule or pill form or by nasal spray is not possible due to injury to the nose or for any other reason, the same may be achieved via sublingual spray, although transit time via this route is slower. In this case, to practice this embodiment of invention embodiments the sublingual spray of the formulation would be comprised of any two, any three or all four of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention. More particularly, the four constituents are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention. An even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00737] As yet another use and advantage of invention embodiments, in a case where administration by tablet, capsule or pill form, nasal spray or by sublingual spray is not possible due to injury to the face or for any reason, the same may be achieved via an intramuscular or intravenous route. In this case, to practice this embodiment of the invention the intramuscular or intravenous solution of the formulation would be comprised of the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention. Alternatively, the constituents of the intramuscular or intravenous administration of the formulation are provided in the ranges of from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention. An even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 3000 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00738] In such a posttraumatic event exemplary embodiment the wounded soldier is transported as immediately as is practically and safely possible to a nearby field hospital or to the nearest medical facility or health delivery facility where the methods, means and systems of embodiments of the invention are known and understood. A formulation is administered by the emergency clinic team, or other qualified personnel as prescribed by a physician. Twenty-

four hours after the initial dose of the formulation, the wounded soldier will be given one tablet, capsule or pill each eight hours, and continued afterward as needed. This period will vary with the severity of the injuries suffered in the accident as well as the duration of any loss of consciousness, but will not normally need to exceed a total of three days. In this case, the formulation (as a 2-, 3- or 4-component formulation) is given as tablets, capsules or pills, each tablet, capsule or pill with two, three or all four of the following constituents comprising Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00739] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the subject's serum levels of lithium are advisedly monitored professionally by qualified personnel to ensure they remain within the therapeutic range for the patient. In the event that adverse effects begin to manifest the treatment protocol should be lessened, for example to once each ten or twelve hours as prescribed by a physician.

Example 11 - A Stroke Embodiment:

[00740] In one particular exemplary embodiment, the invention is adapted and arranged to treat a stroke-type neurotraumatic event and to prevent or reduce the risk of damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of or resulting from the stroke. In this type of example of a particular embodiment of the invention a subject, a 76 year old male, who has a medical history of occasional ischemic strokes is in a shopping mall when a stroke occurs. This would be a case where a subject is known to be at risk for stroke and where evidence indicates a risk of brain damage that could ensue from the stroke. Immediate or earliest possible treatment is necessary to limit local and remote secondary brain damage. On the wrist, the individual wears an alert bracelet that explains that they need medication immediately when a stroke occurs. The bracelet explains that in their pocket is a brief set of instructions as well as a nasal spray container and that the subject needs a single spray into one nostril immediately if it appears to one or more passersby that a medical emergency situation has occurred. Instructions would also include contacting first-responders to provide such care as is needed immediately as well as to transport the victim to the nearest healthcare facility if the subject does not maintain consciousness or as assessed by an Emergency Medical Technician.

[00741] The present example illustrates a case where a subject has a history of recurrent ischemic strokes and the subject is aware that a stroke can occur at any time. The subject is also wearing bracelet and instructions to inform others who see the victim in distress as to what immediate actions to take.

[00742] In this regard, Applicant notes that an ischemic stroke activates a number of secondary injury and repair processes that, together, govern brain damage in the area of the

ischemia as well as brain damage in more remote brain areas that undergo neuropathological changes due to the secondary injury processes. As documented herein and in the scientific and clinical literature a stroke or other cause of insufficient blood circulation to the brain can and frequently does lead to symptoms related to damage to the brain. In this case it is unknown whether this particular individual will develop neuropathological damage as a result of the stroke, but there is a risk of such neuropathological damage resulting from the stroke that is underway or has occurred, and practice of this particular embodiment is to protect the brain as early as possible from damage from the stroke as well as to protect from any brain injury that might have occurred as a result of a fall caused by a loss of consciousness.

[00743] In such a post-traumatic event exemplary embodiment, to practice this embodiment of the invention, someone at the scene who is able to read and understand the explanation on the bracelet, in the set of instructions as well as on the nasal spray container, administers the formulation as one spray from the applicator into one nostril of the subject. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00744] In this exemplary embodiment, to practice the invention by someone who is not previously familiar with the invention, among other actions to ensure the safety and comfort of the subject, according to the instructions will immediately call emergency services or ask for a bystander to call for emergency services, and as well administer to the subject the formulation as a single nasal spray, the single spray containing the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00745] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00746] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00747] Practice of invention embodiments in this case would be for the passerby, understanding the instructions would administer one spray from the applicator into one nostril of the subject, the spray with any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00748] As yet another use and advantage of invention embodiments, an adequate supply of the formulation, in the form of a nasal spray is available on the stroke victim and is available for use by someone on the scene yet who is unfamiliar with embodiments of the invention methods or procedures, but who is able to follow written instructions concerning the method and procedure for administering the formulation.

[00749] Whether the subject would be transported to a medical facility or, upon recovery of consciousness, returned home, it is possible that further treatment with the formulation would not be required. However, if the stroke is severe and the stroke victim is showing signs of neuropathology, then eight hours after the initial dose of the formulation the stroke victim will take or be given the formulation as a single tablet, capsule or pill, each comprising two, three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg. This treatment will be continued every eight hours as needed.

[00750] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the stroke victim's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the subject, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours as prescribed by a physician.

Example 12 - A Chemotherapy with Central Nervous System Symptoms Embodiment:

[00751] In one particular exemplary embodiment, the invention is adapted and arranged to prevent or reduce the development of, or the risk of development of, neuropathology in the central nervous system that begins to appear during the early stages of chemotherapeutic treatment as a result of damage to or loss of function of nerve cells, neural support cells or neural support tissues. In this type of example of a particular embodiment of the invention a middle-aged woman is started on chemotherapy with methotrexate for breast cancer. After several days, the family notices that the patient is beginning to report dizziness and over the next few days speech becomes slurred, and the patient shows increasing drowsiness or fatigue and a lack of interest in eating.

[00752] The present example illustrates a case where signs and symptoms of the development of neuropathology, possibly as a result of continuing chemotherapy, begin to manifest. In this case, it is imperative that the subject receives medical attention as soon as possible. If medical opinion is that the signs and symptoms are or may be related to the chemotherapy, the subject and her healthcare providers will need to decide whether, among other standard practices, to practice the presently disclosed technology, in order to minimize the development or the risk of development of a medically related neurotoxic trauma that affects the brain and brain function.

[00753] In this regard, Applicant notes that it is known that this type of chemotherapy to a

subject can and frequently does result in damage to nerves, nerve cells, neural support cells or neural support tissues and that the symptoms expressed by this patient are typical of the result of dysfunction of the central nervous system and the peripheral nervous system. It is known and recognized, furthermore, that the developing symptoms such as these are typical of the neurotoxic effects of the chemotherapeutic drug, methotrexate. Taking methotrexate can then be considered to be causing neurotrauma by chemical toxicity and patient may be advised to have chemotherapy changed to a different cancer drug and, as well, started on the formulation. Thus, the present example also illustrates a case where symptoms begin to be expressed and clinical evidence indicates that risk is extended over a period of time through an extended period of chemotherapy.

[00754] To practice typical medically-related posttraumatic event embodiments of the invention, the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00755] To practice the invention, the subject, among other actions to minimize neurotrauma or the risk of neurotrauma resulting from continued chemotherapy, would have available to self-administer or be administered the formulation (as a 2-, 3- or 4-component formulation) as tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00756] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00757] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00758] Practice of the invention in this case would be for the individual, under medical advice and monitoring, to self-administer one tablet, capsule or pill, each tablet, capsule or pill with any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. The subject would take such one tablet, capsule or pill every eight hours, as needed, but most appropriately throughout the period of chemotherapy.

[00759] As yet another use and advantage of the invention, an adequate supply of the formulation, in tablet, capsule or pill form, is available in the medical facility for use by the

healthcare team and at home by the patient. In this exemplary embodiment of the invention the patient will continue taking the formulation as one single tablet, capsule or pill every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00760] Once the patient is rotated onto a different chemotherapeutic treatment, under medical supervision and monitoring administration of the formulation is continued as one tablet, capsule or pill each eight hours until the symptoms reverse or at least do not progress, and the patient is otherwise back to baseline. Once baseline has been achieved, the patient can be sustained on self-administration of one tablet, capsule or pill of the formulation each day as protection from possible neurotoxicity from the chemotherapy onto which the patient was rotated.

[00761] In this or similar embodiments of the administration of the formulation, the period of continuation of treatment will exceed three days. As a result, the patient's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the patient, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours, as prescribed by a physician.

Example 13 - A Chemotherapy with Peripheral Nervous System Symptoms Embodiment:

[00762] In one particular exemplary embodiment, the invention is adapted and arranged to prevent or reduce the development of, or the risk of development of, neuropathology in the peripheral nervous system that begins to appear during the early weeks of chemotherapeutic treatment as a result of damage to or loss of function of peripheral nerve cells, neural support cells or neural support tissues.

[00763] In this type of example of a particular embodiment of the invention a 73 year old male is started on cisplatin chemotherapy for bladder cancer. After several weeks the subject is beginning to experience changes in sensation in the hands and feet, motor weakness, loss of ankle reflexes and loss of vibration sense. Numbness and tingling in the hands and feet continue to increase and the subject asks his family what this means. The present example illustrates a case where practice of the invention is to minimize the risk of medically related neurotoxic trauma that affects peripheral nerve cells, neural support cells or neural support tissues and can and often does lead to permanent difficulties with activities of daily living requiring manual dexterity.

[00764] In this regard, Applicant notes that it is known that this type of chemotherapy to a subject can and frequently does result in axonal damage to peripheral nerves, and associated damage to nerve cells, neural support cells or neural support tissues, and that this damage can be irreversible. It is also known and recognized that the symptoms that are being experienced

by the subject are due to peripheral neuropathy from the neurotoxic effects of cisplatin, which is being taken to control the subject's bladder cancer. Cisplatin is thus considered to be the toxic chemical that is causing injury, damage of loss of function of nerves, nerve cells, neural support cells or neural support tissues in the periphery.

[00765] In this case the subject should obtain expert medical advice as soon as possible and, together with such advice, the subject should weigh the advantages of practicing the presently disclosed technology to reduce the risk of further damage to nerve, nerve cells, neural support cells and neural support tissues. The present example illustrates a case where practice of the invention is to minimize the risk of medically related neurotoxic trauma that can and often does lead to permanent difficulties with activities of daily living requiring manual dexterity. Cisplatin is thus considered to be the toxic chemical that is causing injury, damage of loss of function of nerves, nerve cells, neural support cells or neural support tissues in the periphery.

[00766] In this case, where symptoms of peripheral nerve injury begin to be expressed and clinical evidence indicates that risk is extended over a period of time through an extended period of cisplatin therapy, the presently disclosed technology can be practiced for minimizing risk of medically related neurotoxic trauma.

[00767] To practice typical medically-related posttraumatic event embodiments of the invention, the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00768] To practice the invention, the subject, among other actions to minimize neurotrauma or the risk of neurotrauma, would have available to self-administer or be administered the formulation (as a 4-component formulation) as tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00769] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00770] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00771] Practice of the invention in this case would be for the individual, under medical advice, to self-administer one tablet, capsule or pill, each tablet, capsule or pill with any two,

any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00772] As yet another use and advantage of the invention, an adequate supply of the formulation, in tablet, capsule or pill form, is available for use by the subject at home. In this exemplary particular embodiment of the invention the patient will continue taking the formulation as one single tablet, capsule or pill every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg. The patient will be maintained, as needed, on this regimen.

[00773] In this or similar embodiments of the administration of the formulation, the period of continuation of treatment will exceed three days. As a result, the patient's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the patient, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours, as prescribed by a physician.

[00774] Once the symptoms reverse or stabilize administration of the formulation, under medical guidance continuation of treatment may be stopped.

Example 14 - A Neonatal Embodiment:

[00775] In one particular exemplary embodiment, the invention is adapted and arranged to treat an ischemia-type neurotraumatic event in the foetus or neonate and to prevent or reduce the risk of damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues in the central nervous system, enteric nervous system and peripheral nervous system as a result of or resulting from insufficient circulation and supply of blood to the foetus due to umbilical cord blockage, obstruction or any other cause that would stop or reduce the supply of blood to the foetus.

[00776] In this type of example of a particular embodiment of the invention, a woman who is in the early stages of labor and is near delivery with her pregnancy is alerted to the umbilical cord protruding from her vagina. This is an emergency situation for the foetus due to the possibility of obstruction of the umbilical cord, which can lead to insufficient supply of oxygen to the foetus, and the woman needs to be rushed to the nearest hospital immediately. There is danger that the umbilical cord has become blocked and blood flow to the foetus is reduced or stopped. There are only a few critical minutes in order to save the foetus from lack of oxygen and the sequelae that lead to permanent brain and nerve damage.

[00777] In this regard, Applicant notes that it is known that severe central and peripheral neuropathology can result in cases where circulation of blood to a foetus is restricted by umbilical cord obstruction, folding or blockage. In this case, the global ischemia is the traumatic event that can result in long term or even permanent disability or symptoms of

ischemic neurotrauma. As documented herein and in the scientific literature, ischemia in a foetus can and frequently does cause permanent neuropathology and injury or death of nerve cells, neural support cells and neural support tissues in the central nervous system, the enteric nervous system or the peripheral nervous system. It is unknown whether in this particular case the foetus is rendered ischemic but clinical evidence indicates that risk is high that neuropathological damage may result from compromised blood supply to the foetus and practice of this particular embodiment is to protect the central nervous system, the enteric nervous system and the peripheral nervous system from ischemia that may be occurring as a result of the obstruction, folding or blockage of the protruding umbilical cord. The presently disclosed technology is to be practiced along with standard practice to provide emergency treatment and care.

[00778] The present example illustrates a case where the mother is aware of the possible danger of any prolonged interruption or restriction of blood supply to the foetus. This is an emergency situation requiring immediate or earliest possible protection from the risk of ischemia of the central nervous system, the enteric nervous system or the peripheral nervous system in the foetus. The mother immediately calls an ambulance to transport her to the nearest healthcare facility.

[00779] In such a traumatic event exemplary embodiment, to practice the invention in this type of embodiment includes administration of a formulation by a first-on-scene paramedic or emergency medical services personnel or other such qualified personnel, who, in combination with standard emergency procedures to protect the health of the mother and the foetus, would administer the formulation by nasal spray to the mother; this route may be advantageous because of the rapid absorption and distribution of the constituents of the formulation into the bloodstream of the mother and the rapid distribution across the placental barrier to the foetus.

[00780] The formulation (as a 2- or 3-component formulation) is given as nasal spray. In such a case, practice of the invention requires serum levels of the constituents of the formulation to be established immediately or as soon as possible. The time course for these levels to reach the therapeutic range via the oral route is three to six hours. In this case further delay is allowing the degenerative processes to advance farther and some permanent neuropathology may have already occurred. The time to maximally enhance the restorative processes is also passing. The fastest route to achieve serum levels within the therapeutic range is via nasal spray. Therefore, an emergency vehicle or a local medical or hospital facility is equipped with an adequate supply to provide the formulation by nasal spray in sufficient amounts of any two or all three constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, and Aprepitant.

[00781] To practice the invention the emergency personnel, among other actions to

minimize neurotrauma or the risk of neurotrauma to the foetus, would have available to administer the formulation (as a 2- or 3-component formulation) as nasal spray with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone and from 5 to 375 mg of Aprepitant. These dosage ranges represent one particular embodiment of the invention.

[00782] More particularly, the three constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone and from 20 to 250 mg of Aprepitant. These dosage ranges represent one particular embodiment of the invention.

[00783] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg and Aprepitant at 40 to 120 mg. These dosage ranges represent one particular embodiment of the invention.

[00784] After birth the newborn is to be monitored carefully for any signs or developing signs of neurological dysfunction and at the earliest signs of any such neurological dysfunction the baby should be administered the formulation at a reduced amount based on body weight, compared to 600 mg of Gabapentin, 300 mg of Progesterone, 120 mg of Aprepitant and 600 mg of Lithium carbonate in an average adult.

[00785] As yet another use and advantage of the invention, an adequate supply of the formulation, in the form of a nasal spray is available in the local medical or hospital facility for administration by qualified personnel to the newborn in this or similar embodiments of the invention, at the discretion of a physician and depending on the assessment of the health of the newborn. In this exemplary embodiment, the qualified personnel, as a complement of standard emergency procedures to stabilize the newborn, will administer to the newborn, the formulation as a single nasal spray comprising any two or all three of Gabapentin at 200 mg, Progesterone at 100 mg, and Aprepitant at 40 mg, or the formulation as a single nasal spray comprising Gabapentin at 600 mg, Progesterone at 100 mg and Aprepitant at 40 mg.

Example 15 - A Domestic Attack Wound Embodiment:

[00786] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma or a possible or suspected neurotrauma to the spinal cord or to peripheral nerves, where an individual has received penetrating wounds in the back with the possibility that these wounds have included injury to the spinal cord or peripheral nerves. The invention is adapted to prevent, or to reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a penetrating wound, such as from a knife, an axe or any other weapon or object that can penetrate the skin.

[00787] In the present example of a particular embodiment, an 18 year old teenage male victim suffers multiple knife wounds in the back during a street gang altercation in a downtown, largely ethnic section of a major city. The victim was unconscious and not

moving but breathing, and, being taken for nearly dead at the end of the altercation, is left in a dumpster. After several hours a passerby notices a weak groan coming from the dumpster, notices the victim inside and calls the police. When the police arrive they find that the victim cannot move his legs and they call an ambulance to take the victim to a nearby hospital. It appears to the officers on the scene that one or more knife punctures may have severed at least part of the spinal cord or damaged peripheral nerves.

[00788] In this regard, Applicant notes that it is known that unconsciousness or loss of movement is rendered as a result of trauma to the head, such as during a fall or having been thrown into the dumpster, or to loss of spinal cord function rendered as a result of injury to the spinal cord, or to injury to peripheral motor nerves innervating leg muscles, or to loss of blood and the ensuing ischemia of the brain, or the brain stem, or the spinal cord, and any and all of these conditions can and frequently do lead to loss of function, and can be due to neuropathology in the parts of the brain, spinal cord and peripheral nerves that are directly traumatized as well as more remote parts of the brain, spinal cord and peripheral nerves due to spreading secondary neuropathology that has developed from the time of the assault.

[00789] As documented herein and in the scientific and clinical literature, physical or ischemic trauma to the spinal cord can and frequently does lead to symptoms related to damage to nerve cells, neural support cells and neural support tissue in the spinal cord and periphery. As documented herein and in the scientific literature, trauma to the head, whether from a fall during the fight, from being thrown into a dumpster or from brain ischemia due to massive loss of blood, particularly when the victim is rendered unconscious, can and frequently does lead to symptoms related to damage to nerve cells, neural support cells and neural support tissue in the brain, spinal cord and periphery. In this case it is unknown whether this particular individual has developed or will develop secondary neuropathological damage or injury as a result of the physical or ischemic trauma to the head and body, but there is a risk that such neuropathological damage resulting from the penetrating knife wounds is already underway or has occurred or will develop.

[00790] The present example illustrates a condition where there has been an unexpected potential neurotrauma, where the platinum hour of opportunity is passing or has passed and where immediate rescue is imperative to prevent, or reduce the risk of, further damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of penetrating wounds to the back, where a victim is found unconscious at the scene at an undetermined time after the attack.

[00791] In such a posttraumatic event exemplary embodiment, the first emergency measures are to remove the victim to a safe area and to stabilize the victim according to standard emergency practices, and to transport the victim to a nearby medical centre or hospital as early as possible. To practice the invention in this type of embodiment includes

administration of a formulation by the first police officers on the scene or by a subsequently-arriving paramedic, emergency medical services personnel, police officer or other such qualified personnel, who would administer by nasal spray the formulation in sufficient amounts of any two, any three or all four of Gabapentin, Progesterone, Aprepitant and Lithium carbonate. This is to be done as part of standard immediate emergency practice.

[00792] The formulation (as a 2-, 3- or 4-component formulation) is given as nasal spray. In such a case, due to the severity of the wounds, the loss of consciousness and the time delay between the attack and discovery of the victim, practice of the invention requires serum levels of the constituents of the formulation to be established immediately or as soon as possible. The time course for these levels to reach the therapeutic range via the oral route is three to six hours. The platinum hour may have passed and the golden day is passing. In this case further delay is allowing the degenerative processes to advance farther and some permanent neuropathology may have already occurred. The time to maximally enhance or promote the restorative processes is also passing. The fastest route to achieve serum levels within the therapeutic range is via nasal spray. Therefore, a police cruiser, an ambulance, or other emergency vehicle is equipped with an adequate supply to provide the formulation by nasal spray. In some particular embodiments of the invention, the four constituents of the formulation are preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00793] As yet another use and advantage of the invention, an adequate supply of the formulation in the form of nasal spray, tablet, capsule or pill is available to the emergency services personnel or to the medical or hospital facility for use by qualified personnel. In this exemplary embodiment, the qualified personnel, as a complement of standard emergency procedures to stabilize the victim, will administer to the victim the formulation, applying the methods and procedures of the invention along with other standard procedures.

[00794] To practice the invention, the emergency services personnel or the local medical or hospital personnel would administer to the victim a single spray intranasally of the formulation with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00795] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00796] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00797] In this case, to practice the invention the first police officer on the scene or the first responder or the first healthcare professional available would administer to the victim one spray from a vaporizer into one nostril, with one spray containing any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00798] If the victim of the stabbing has not regained consciousness and it is not possible for any reason to administer the formulation at the scene by nasal spray, practice of the invention may be achieved via sublingual spray, although transit time via this route is slower. In this case, to practice this embodiment of the invention the sublingual spray of the formulation would be comprised of the following constituents in the ranges may be achieved via sublingual spray, although transit time via this route is slower. In this case, to practice this embodiment of the invention the sublingual spray of the formulation would be comprised of any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00799] If the victim of the stabbing has regained consciousness, then practice of the invention may be achieved by administration of the formulation in tablet, capsule or pill form, as three tablets, capsules or pills, each tablet, capsule or pill comprised of any two, any three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. As an alternative, practice of the invention may be achieved by administration of the formulation in injectable solution form, each injection comprised of Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00800] As yet another use and advantage of the invention, the police officers or other qualified personnel are knowledgeable about the particular aspects of the methods, procedures, means and systems of the invention in case of any traumatic event. Similarly, the ambulance which would arrive to transport the victim to a nearby medical centre or hospital would have an adequate supply of the formulation in tablet, capsule or pill form as well as in injectable solution form for intravenous or intramuscular administration, and the paramedic or emergency medical services personnel would also be knowledgeable about the particular aspects of the methods, procedures, means and systems of the invention in case of any traumatic event.

[00801] In such a posttraumatic event exemplary embodiment of the methods, means and systems of the invention, once the victim of the stabbing has been transferred to a medical centre or hospital, the initial standard emergency practices have been completed, continuing administration of the formulation can be done by the emergency clinic team, or other qualified personnel as prescribed by a physician. Twenty-four hours after the initial dose of the formulation, the subject, once having regained consciousness, will be given one tablet,

capsule or pill each eight hours, each tablet, capsule or pill containing any two, any three or all four of Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg, and this treatment will be continued afterward as needed. In the event that the victim has not regained consciousness administration of the formulation may be by daily intravenous or intramuscular injection, comprised of any two, any three or all four of Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg. The period of continued treatment with the formulation will vary with the severity of the injuries suffered in the attack as well as the duration of the loss of consciousness, but will not normally need to exceed a total of three days.

[00802] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the subject's serum levels of lithium are advisedly monitored professionally by qualified personnel to ensure they remain within the therapeutic range for the patient.

Example 16 - A Heart Attack Ischemia Embodiment:

[00803] In one particular embodiment, the invention is adapted and arranged to treat an ischemia-type neurotraumatic event due to insufficient supply of blood to the brain and spinal cord as a result of slowing or temporary stoppage of the heart during, for example, a heart attack, and to prevent the development or the risk of development of central nervous system neuropathology resulting from decreased blood supply to the central nervous system during the period that the heart is stopped or slowed as a result of a heart attack or any other cause. In this particular exemplary embodiment of the invention, an older person aged 82 years, with a history of heart attack, has a heart attack at home and loses consciousness. Several minutes later his spouse finds the individual unconscious on the floor. The subject has a medical history of heart attack and as a result the spouse is knowledgeable about actions to be taken in the event of such an attack as well as the particular aspects of the methods, procedures, means and systems of the invention in case of any signs of a heart attack as a traumatic event, and especially if the husband loses consciousness. She immediately phones for an ambulance and ensures that the airways of the heart attack victim are clear and that the victim is placed in a position where there is no danger to the victim.

[00804] In this regard, Applicant notes that it is known that global central nervous system ischemia, that can occur during heart attack, as well as by asphyxiation of any type, shock, extracorporeal circulation, cardiac arrest, drowning, as well as with acute spinal cord ischemic syndrome acute respiratory distress syndrome and other such conditions can and frequently does lead to ischemia-induced neuropathy that can lead to adverse health conditions or disability related to damage to the brain, brain stem, cerebellum or spinal cord. It is documented herein and in the scientific literature that any cause of insufficient blood circulation to the central nervous system, can result in such adverse health conditions or

disability.

[00805] In this case it is unknown whether this particular subject will develop central nervous system ischemia or the degree to which this might occur, but this subject would be considered at risk for global ischemia during or even immediately after the heart attack and clinical evidence indicates the possibility of permanent symptoms and disability or death resulting from ischemia-induced central nervous system neurotrauma.

[00806] The present example illustrates a case of an unanticipated but not unexpected neurotrauma, in this case a heart attack, in an individual with a history of heart attack, that compromises or limits circulation of the blood to the brain, brain stem, cerebellum or spinal cord. The loss of consciousness would be from insufficiency of blood supply to the brain. That is, an ischemic injury to the central nervous system. Loss of consciousness would result in a fall, which in turn could lead to a physical brain injury, and which would then be in addition to ischemic traumatic injury. This would be a case of an unanticipated but not unexpected neurotrauma, from global ischemic as well as physical traumatic brain injury, where clinical evidence indicates a risk of secondary brain damage that could ensue from the global ischemia or the physical brain injury.

[00807] In such a posttraumatic event exemplary embodiment, practice of the invention requires serum levels of the constituents of the formulation to be established immediately or as soon as possible and, practice the invention in this type of embodiment where the subject is unconscious as a result of a heart attack, includes administration of the formulation by the wife or by a first-on-scene paramedic or emergency medical services personnel or other such qualified personnel, who has responded to the call for an ambulance and who would administer the formulation by nasal spray. That is, if the heart attack victim is unconscious, an advantageous route of administration would be by nasal spray. If the heart attack victim has regained consciousness, then administration can alternatively be by tablet, capsule or pill if this is more practical.

[00808] As yet another use and advantage of the invention, an adequate supply of the formulation in the form of nasal spray, tablet, capsule or pill is available to the spouse as well as to the emergency services personnel.

[00809] To practice typical posttraumatic event embodiments of the invention in conditions of possible ischemia to the central nervous system, where there may also be or have been a period of insufficient blood supply to the enteric nervous system or the peripheral nervous system as a result of prolonged hypotension, for example as in this case, a prolonged stoppage of the heart, the formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00810] To practice the invention, the spouse or the emergency services personnel or the local medical or hospital personnel would have available a method or apparatus to administer to the victim a single spray intranasally of the formulation (as a 4-component formulation) with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00811] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00812] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00813] In the event that the heart attack victim is unconscious, practice of the invention in this case would be for the spouse, first responder or qualified personnel in a medical centre or hospital, as a complement to standard emergency procedures to stabilize the victim, to administer to the victim one spray from a vaporizer into one nostril, with one spray containing any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00814] In the event that the heart attack victim is conscious, practice of the invention in this case would be for the spouse, first responder or qualified personnel in a medical centre or hospital, as a complement to standard emergency procedures to stabilize the victim, to administer to the victim the formulation as three tablets, capsules or pills, each tablet, capsule or pill with any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. In this case, practice of the invention is to reduce or prevent the development or the risk of development of neuropathology as a result of traumatic injury from prolonged hypotension due to the heart attack or as a result of brain injury from fainting and a possible head injury.

[00815] Twenty-four hours after the initial dose, the subject will be maintained on a regimen of one single tablet, capsule or pill every eight hours as prescribed by a physician, each tablet, capsule or pill, comprising any two, any three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. This period of continued administration will vary with the severity of the injury to the head and with the incidence of any signs of neuropathology to the central nervous system, the enteric nervous system or the peripheral nervous system, but will not normally need to exceed a total of three days.

[00816] In this or similar embodiments of the administration of the formulation, when the

period of continuation of treatment is to exceed three days, the subject's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the subject, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours as prescribed by a physician.

Example 17 - A Penetrating Traumatic Brain Injury Embodiment:

[00817] In one particular embodiment, the invention is adapted and arranged to treat a neurotrauma or a possible or suspected neurotrauma to the brain, where an individual has received a penetrating wound or wounds to the head with the likelihood that this wound or wounds has caused injury to brain. The invention is adapted to prevent, or to reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a penetrating wound, such as from a bullet, a knife, an axe or any other weapon or object that can penetrate the skull. In the present exemplary embodiment of the invention, a police officer on duty is unexpectedly shot in the head and is rendered unconscious and is bleeding from the head. The officer's partner immediately ensures the safety of the fallen officer and calls for medical assistance and backup. The partner is knowledgeable about the particular aspects of the means, systems and methods of the invention in case of any traumatic event.

[00818] In this regard, Applicant notes that it is known that trauma to the head, such as a penetrating traumatic brain injury or as a result of an ensuing fall, any and all of these conditions can and frequently do lead to neuropathology in the brain that is directly traumatized as well as more remote parts of the brain due to spreading secondary neuropathology. Further, Applicant notes that it is known that direct brain damage from a penetrating projectile, passage of blood into brain tissue from ruptured cerebral vessels and lessening of the blood supply to otherwise healthy brain tissue due to general loss of blood and from brain swelling, secondary damage can spread extensively to areas of the brain remote from the site of the penetrating wound. Immediate medical attention is critical for survival and protection of the fallen officer from the direct brain damage as well as from the secondary brain damage described herein that results from such primary brain injury.

[00819] As documented herein and in the scientific and clinical literature, penetrating trauma to the head can and frequently does lead to symptoms related to damage to nerve cells, neural support cells and neural support tissue in the brain. In this case it is unknown whether the wounded officer will develop secondary neuropathological damage or injury as a result of the trauma to the head, but due to the penetrating injury there is a high risk that such neuropathological damage resulting from the penetrating bullet wound or from the fall is already underway or has occurred or will develop.

[00820] The present example illustrates a condition where there has been an unexpected,

accidental neurotrauma to the head, where, in addition to standard emergency practice to secure the victim, immediate practice of the invention is imperative to prevent or reduce the risk of further damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of the secondary damage processes triggered by the penetrating wound to the head or to the fall.

[00821] In such a posttraumatic brain injury event exemplary embodiment, to practice the invention in this type of embodiment includes administration of the formulation by the partner officer or by a first-on-scene paramedic or other such qualified personnel, who would administer the formulation by nasal spray. The formulation (as a 4-component formulation) is given as nasal spray. In such a case, due to the severity of the wound, the loss of consciousness, practice of the invention requires serum levels of the constituents of the formulation to be established immediately or as soon as possible. The time course for these levels to reach the therapeutic range via the oral route is three to six hours. In this case further delay is allowing the degenerative processes to advance farther and some permanent neuropathology may have already occurred. The time to maximally enhance or promote the restorative processes is also passing. The fastest route to achieve serum levels within the therapeutic range is via nasal spray.

[00822] Therefore, the police cruiser, an ambulance, or other emergency vehicle would be equipped with an adequate supply of the formulations available in sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00823] To practice the invention, the partner officer, a first responder or other qualified personnel would have available to administer to the fallen officer the formulation (as a 2-, 3- or 4-component formulation) as a single spray intranasally the formulation with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00824] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00825] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00826] Practice of the invention in this case would be for the partner officer, a first responder or another qualified personnel to administer to the fallen officer one spray from a

vaporizer into one nostril, with one spray containing any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00827] As yet another use and advantage of the invention, an adequate supply of the formulation, in the form of a nasal spray is available in the police cruiser or other emergency response vehicle, in tablet, capsule or pill form as well as in injectable solution form, and the partner officer or other qualified personnel are knowledgeable about the aspects of the methods, procedures, means and systems of the invention in case of any traumatic event.

[00828] As yet another use and advantage of the invention, in a case where administration by nasal spray is not possible due to injury to the nose or for any other reason, the same may be achieved via sublingual spray, although transit time via this route is slower. In this case, to practice this embodiment of the invention the sublingual spray of the formulation would be comprised of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00829] As yet another use and advantage of the invention, in a case where administration by nasal spray or by sublingual spray is not possible due to injury or for any reason, the same may be achieved via an intramuscular or intravenous route. In this case, to practice this embodiment of the invention the intramuscular or intravenous solution of the formulation would be comprised of any two, any three or all four of the following constituents: Gabapentin at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00830] In such a posttraumatic event exemplary embodiment of the methods, procedures, means and systems of the invention, twenty-four hours after the initial dose of the formulation, the subject, once having regained consciousness, will be given one tablet, capsule or pill each eight hours, and continued afterward as needed, each tablet, capsule or pill with any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. Practice of the invention will be continued as needed and this period will vary with the severity of the injuries suffered in the attack as well as the duration of the loss of consciousness, but will not normally need to exceed a total of three days.

[00831] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days, the subject's serum levels of lithium are advantageously monitored professionally by qualified personnel to ensure they remain within the therapeutic range for the patient. In the event that adverse effects begin to manifest the treatment protocol should be lessened, for example to once each ten or twelve hours as prescribed by a physician.

Example 18 - A Closed-head Traumatic Brain Injury Embodiment:

[00832] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma or a possible or suspected neurotrauma to the brain, where an individual is unconscious, for example as a result of a serious accident in a workplace, causing symptoms of closed-head brain injury, whether caused by a direct impact or by rapid acceleration/deceleration. The invention is adapted to prevent or to reduce the risk of damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a closed head brain injury, such as from a fall, an axe or any other object, projectile or weapon that does not penetrate the skull.

[00833] In the present example of a particular embodiment of the invention, a construction worker falls from a low scaffold and his head hits a cement block. There is no serious superficial laceration but after a few minutes the worker begins to complain of dizziness and his speech becomes slurred. The coworkers, seeing no external abrasions, think that the dizziness and slurred speech are simply because the injured worker was 'knocked out'. They return to their work. At the subsequent lunch break the coworkers notice that the injured worker shows no interest in lunch, he is not joining in conversation, he appears distanced from the group, staring emotionless. Finally, they realize that the injured worker needs medical attention and call an ambulance. The injured worker's coworkers are not knowledgeable about the possible consequences of an injury to the head and they are not knowledgeable about particular aspects of the methods, procedures, means and systems of the invention in case of any traumatic event in the workplace. Nor is any formulation available at the work site.

[00834] In this regard, Applicant notes that it is known that trauma to the head, including falls, sudden acceleration or deceleration and any and all possible conditions can and frequently does lead to neuropathology in the brain that are directly traumatized as well as more remote parts of the brain due to spreading secondary neuropathology. Applicant notes further that symptoms being exhibited and expressed by the injured worker are signs of brain injury and the worker needs immediate and appropriate medical care to prevent the development or the risk of development of neuropathology as a result of a traumatic injury to the head. As documented herein and in the scientific literature, trauma to the head, particularly when the victim is showing signs of dizziness, slurred speech, loss of affect, can and frequently does lead to symptoms resulting from secondary damage to nerve cells, neural support cells and neural support tissues in the brain. In this case it is unknown whether this particular individual has caused or will develop neuropathological damage as a result of the closed-head trauma, but there is a risk that such neuropathological damage resulting from the fall accident is already underway or has occurred or will develop.

[00835] The present example illustrates a condition where there has been an unexpected, accidental impact to the head, where signs and symptoms of altered neural function have

become evident, and where immediate medical attention is imperative to prevent, or reduce the risk of, damage or loss of function or cell death of nerve cells, neural support cells or neural support tissues as a result of a head injury.

[00836] In such a posttraumatic event exemplary embodiment, practice of the invention in this type of embodiment includes administration of a formulation by qualified personnel. Upon arrival at the scene a first responder or ambulance paramedic quickly ascertains that the worker has sustained a severe closed-head injury with symptoms of disorientation and signs of possible damage to the brain, and initiates practice of the invention. Due to the time that has elapsed from the head injury and the arrival of the paramedic, the paramedic decides that in such a case practice of the invention requires serum levels of the constituents of the formulation to be established immediately or as soon as possible. The time course for these levels to reach the therapeutic range via the oral route is three to six hours. In this case further delay is allowing the degenerative processes to advance farther and some permanent neuropathology may have already occurred. The time to maximally enhance the restorative processes is also passing. The fastest route to achieve serum levels within the therapeutic range is via nasal spray. Therefore, the emergency vehicle is equipped with an adequate supply to provide the formulation by nasal spray.

[00837] The first response vehicle or the ambulance is equipped with an adequate supply to provide the formulation by nasal spray. The formulation would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00838] To practice the invention, the first responder or ambulance personnel would administer to the victim a single spray intranasally of the formulation with the following constituents in the ranges of from 50 to 4,800 mg of Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00839] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium Carbonate. These dosage ranges represent one particular embodiment of the invention.

[00840] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00841] Practice of the invention in this case would be for the first responder or ambulance personnel to administer to the injured worker one spray from a vaporizer into one nostril, with one spray containing any two, any three or all four of the following constituents: Gabapentin

at 600 mg, Progesterone at 300 mg, Aprepitant at 120 mg and Lithium carbonate at 600 mg.

[00842] As yet another use and advantage of the invention, an adequate supply of the formulation, in the form of a nasal spray is available in the emergency response vehicle or ambulance, and also in tablet, capsule or pill form as well as in injectable solution form, and the first responder or paramedic or emergency medical services personnel are knowledgeable about the aspects of the means, systems and methods of the invention in case of any traumatic event.

[00843] The injured worker is taken to the nearest hospital for emergency attention, which consists of a thorough examination of neurological signs. This examination confirms possible brain injury. Being knowledgeable about aspects of the means, systems and methods of the invention the injured worker continues to be monitored by the hospital medical staff for signs or symptoms of brain injury. Eight hours after the initial nasal spray, the injured worker is given a tablet, capsule or pill comprised of any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg, and this is continued at eight-hour intervals as needed while the injured worker is monitored for signs of brain injury.

[00844] The period of continued practice of the invention will vary with the presence and severity of any signs or symptoms of neurotrauma or dizziness or slurred speech or loss of affect. In this case where administration is continued at eight hour intervals, each tablet, capsule or pill will be comprised of any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00845] In this or similar embodiments of the administration of the formulation, when the period of continuation of treatment is to exceed three days the subject's serum levels of lithium are advisedly monitored professionally by qualified personnel to ensure they remain within the therapeutic range for the patient. In the event that adverse effects begin to manifest the treatment protocol should be lessened, for example to once each ten or twelve hours.

Example 19 - A Toxic Chemical Embodiment:

[00846] In one particular exemplary embodiment, the invention is adapted and arranged to treat a neurotrauma or a possible or suspected neurotrauma where an individual or individuals are exposed to a neurotoxic chemical, for example in a chemical factory, chemical workplace or a chemical storage warehouse. In the present example of a particular embodiment, a leak of a neurotoxic chemical, methyl parathion, occurs in a chemical storage warehouse. It is only when the warehouse alarm sounds that six workers discover that they may have been exposed to dangerously high levels of the chemical. They immediately go to a safe area that is well ventilated and outside the area of the spill. They show no overt signs or symptoms of the exposure, yet these six workers are suspected of having been exposed to dangerous levels of

the chemical. It is known at the workplace that methyl parathion can produce damage to nerve cells, neural support cells or neural support tissues.

[00847] In this regard, Applicant notes that it is known that some toxic chemicals are particularly toxic to nerve cells, neural support cells or neural support tissues, and that exposure can lead to permanent loss of nerve cell function and nerve cell death. Signs and symptoms of exposure to toxic levels of the chemical spilled may not manifest for hours. Exposure of the workers to unsafe levels of a neurotoxic chemical constitutes a potentially traumatic event. As documented here and in the scientific literature, neurotoxic chemicals can cause acute as well as progressive trauma to nerve cells, neural support cells and neural support tissues in the central nervous system, the enteric nervous system and the peripheral nervous system, leading to symptoms related to injury, loss of function or death of these cells and tissues. It is unknown whether the affected workers have been exposed to levels of the chemical that are above safety standards, or whether the affected workers will develop neuropathological changes in nerve cells, neural support cells or neural support tissues as a result of this chemical exposure.

[00848] The present example illustrates a case where there has been an unexpected, accidental exposure to a potential chemical neurotrauma, and where it is not possible to predict whether the exposure to a neurotoxic chemical will cause activation of mechanisms of secondary damage or injury, but clinical evidence indicates that risk is extended over a period of time during and following such exposure. Immediate action is imperative.

[00849] If the assessment is that the workers have indeed been exposed to sufficiently high levels of the chemical that there is a risk of neurotrauma, to practice typical chemically-related posttraumatic event embodiments of the invention the exposed workers would self-administer the formulation that would include sufficient amounts of any two, any three or all four constituents (or their substitutes or equivalents). In some particular embodiments of the invention, the constituents of the formulation include preferably Gabapentin, Progesterone, Aprepitant and Lithium carbonate.

[00850] As the workplace routinely processes or handles quantities of neurotoxic chemicals, an adequate supply of the formulation in the form of nasal spray, tablet, capsule or pill is available in the workplace first-aid centre or infirmary. In this exemplary embodiment, the workers, their supervisor and any qualified personnel in attendance would weigh the level of exposure and the risk of neurotoxicity as well as the appearance of any neurological symptoms.

[00851] To practice the invention, the workers, among other actions to minimize neurotrauma or the risk of neurotrauma, would have available to self-administer the formulation (as a 2-, 3- or 4-component formulation) as tablets, capsules or pills, each tablet, capsule or pill with the following constituents in the ranges of from 50 to 4,800 mg of

Gabapentin, from 5 to 600 mg of Progesterone, from 5 to 375 mg of Aprepitant and from 30 to 1,800 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00852] More particularly, the four constituents (or their substitutes or equivalents) are provided in the following ranges: from 100 to 2,400 mg of Gabapentin, from 50 to 450 mg of Progesterone, from 20 to 250 mg of Aprepitant and from 100 to 900 mg of Lithium carbonate. These dosage ranges represent one particular embodiment of the invention.

[00853] Typically, an even more specific dose comprises Gabapentin at 200 to 600 mg, Progesterone at 100 to 300 mg, Aprepitant at 40 to 120 mg and Lithium carbonate at 200 to 600 mg. These dosage ranges represent one particular embodiment of the invention.

[00854] To practice the invention at the workplace, the workers would self-administer three tablets, capsules or pills, each tablet, capsule or pill with any two, any three or all four of the following constituents: Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. The first-aid or infirmary personnel would monitor the workers for any signs or symptoms of neurotrauma. In the event that any such signs or symptoms began to manifest the workers would be immediately transported to the nearest medical centre or hospital for thorough assessment and monitoring.

[00855] Nonetheless, even before the onset of any such signs or symptoms, the decision may be made to transport the exposed workers to a local hospital facility for further assessment, monitoring, diagnosis and treatment if needed. An adequate supply of the formulation, in tablet, capsule or pill form, is available in the medical facility for use by the healthcare team who are knowledgeable about the methods, procedures of the invention.

[00856] If neurological symptoms begin to appear or if the assessment of the exposed workers indicates further protection from neurotrauma is necessary the workers will be given the formulation as one single tablet, capsule or pill to take every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 200 mg, Progesterone at 100 mg, Aprepitant at 40 mg and Lithium carbonate at 200 mg. If deemed necessary by a physician, the workers will be maintained on this regimen of one single tablet, capsule or pill every eight hours, each tablet, capsule or pill, each comprising any two, any three or all four of Gabapentin at 600 mg, Progesterone at 100 mg, and Aprepitant at 40 mg and Lithium carbonate at 200 mg.

[00857] In this or similar embodiments of the administration of the formulation, the period of continuation of treatment will exceed three days. As a result, the patient's blood serum levels of lithium are advisedly monitored by qualified personnel to ensure they remain within the therapeutic range for that patient. In the event that adverse effects begin to manifest in the patient, the treatment protocol should be lessened, for example to the administration of one tablet, capsule or pill each ten to twelve hours, as prescribed by a physician.

SUMMARY OF EXEMPLARY PRACTICE OF THE INVENTION

[00858] Applicant has presented herein some examples of the many particular embodiments of the invention only as a means of illustrating some of the formulations, methods and procedures while noting that a person having ordinary skill in the art, armed with the present disclosure, would be able to comprehend and practice numerous forms of the formulations, methods, procedures and systems of invention embodiments, while adapting them to specific uses and circumstances and can do so without undue experimentation. The present formulations, methods, procedures and systems of the presently disclosed technology provide a significant number of combinations of formulations, formulation components, dosages, administration sequences, patterns and combinations thereof to offer efficacious and safe anticipatory (pre-trauma) and posttrauma treatments for secondary damage or injury to nerve cells, neural support cells or neural support tissues. In order to practice invention embodiments it is necessary for formulations to be readily available in areas, conditions, situations and proximities where its use is needed or may be needed, in order to practice the precautionary use, the prophylactic use and use during or after the time that a traumatic event has occurred or is occurring. The examples presented herein are presented as examples only as a means of illustrating.

PRECAUTIONARY PRACTICE OF THE INVENTION

[00859] To enable practice of invention embodiments the formulations should be in every police car, in every armored vehicle that is engaged in combat or warfare, in every military vehicle and personnel carrier that is engaged in combat or warfare, and in any condition or place where there is a high risk of trauma to an individual or a group of individuals or there is planned entry into any condition or place where there is a high risk of trauma to reduce the risk of development of damage to nerves or nerve cells as a result of a traumatic event that may occur or has a high possibility of occurring or will occur.

PROPHYLACTIC PRACTICE OF THE INVENTION

[00860] To enable practice of invention embodiments the formulations should be in every radiation therapy unit or centre, in every chemotherapy unit or centre and in every surgery unit or centre for administration before radiation therapy, chemotherapy or surgery is begun to reduce the development or reduce the risk of development of neurotrauma as a result of medical treatment.

POST TRAUMATIC EVENT PRACTICE OF THE INVENTION

[00861] To enable practice of invention embodiments, formulations are available in tablet, in nasal spray form and in injectable form in every ambulance, every police car, every fire department response vehicle, in every search and rescue vehicle, in every emergency response vehicle, with every battlefield medic, and with every security response team to initiate neuroprotective treatment during the platinum hour following trauma or as early as possible.

[00862] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every household where there is someone with a history or risk of stroke, epilepsy, to initiate neuroprotective treatment during a stroke or an epileptic seizure to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

[00863] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every nursing home, retirement home or other institution with high risk individuals, to initiate neuroprotective treatment as soon as possible after a fall or other accident or traumatic health event, to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

[00864] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every workplace, work area or other facility where there is risk of accident, to initiate neuroprotective treatment as early as possible after an injury where there may be damage to the head or other part of the body where there may be damage to nerves or nerve cells to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

[00865] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every industrial chemical factory, warehouse or other facility where there may be overexposure to potentially neurotoxic chemicals, to initiate neuroprotective treatment in the event of a chemical accident, to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

[00866] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every sports arena, gymnasium, sporting facility, high school, supervised public park where sport-related activities are carried out, to maximize benefit by treatment during the earliest phase of the platinum hour after a sports injury, concussion or other potentially harmful event has occurred, to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

[00867] To enable practice of invention embodiments, formulations are available in tablet and in nasal spray form in every emergency room, emergency clinic, field hospital, mobile health clinic to initiate neuroprotective treatment as soon as possible after any accident or traumatic health event, to maximize benefit by treatment during the earliest phase of the platinum hour or as early as possible.

THERAPEUTIC ADVANTAGES PARTICULARLY ASSOCIATED WITH THE DISCLOSED MULTI-DRUG FORMULATIONS

[00868] Applicant anticipates that multi-drug or multi-pharmaceutical formulations, as disclosed herein, will provide substantial therapeutic advantages over existing therapeutic formulations related to the drugs included in such formulations, which, so far as applicant is

aware, are single active drug formulations. Applicant anticipates that the coincident therapeutic use of multiple drugs as disclosed herein, with separate mechanisms of action, will provide therapeutic benefits for particular neurological conditions, as disclosed herein, that substantially exceed the benefits that could be ascribed to the use of any single drug alone. With reference to therapeutic benefits in excess of those that could be derived from any single drug, alone, the enhancement due to combination therapy could be additive or it could be synergistic. By additive, it is meant that the total benefit of a multi-drug formulation exceeds that which could be maximally achieved by any single drug as a monotherapy, regardless of the maximal effective dose of any single drug. By synergistic, it is meant that the total benefit of a multi-drug formulation exceeds even that which might be expected from adding the maximal therapeutic benefits from each of the drugs as a monotherapy.

[00869] Applicant further anticipates that the dosage-response profiles of individual drugs, when administered in multi-drug formulations as provided herein, and for the conditions as described herein, may be left-shifted. By left-shifted, it is meant that that maximal effective dosages of individual drugs in multi-drug formulations may be lower than dosages required for maximal therapeutic effect when the individual drugs as used as a monotherapy. The use of lower dosages of the individual drugs may advantageous in terms of minimizing unwanted side effects of the drugs that are associated with high dosages of the drug, particularly when used as a monotherapy. Lower dosages also provide a clear economic advantage to such multi-drug formulations.

[00870] Another aspect of therapeutic or safety advantages of the presently disclosed multi-drug formulations relates to minimizing the possibility of abusive uses of individual drugs. Anti-convulsants, such as Gabapentin, have a burden of being used as drugs of abuse or recreational use. In practical terms, including drugs of potential abuse within a multi-drug formulation tends to discourage its recreational or abusive use.

[00871] Coformulation of multiple drugs, as provided herein offers still further therapeutic advantages over monotherapy in that timed release strategies may be usefully applied to individual drugs within the multi-drug formulation. The many uses and advantages of timed-release formulations are discussed elsewhere in this disclosure. For example, it may be advantageous to stage the pharmacodynamics of drugs, as disclosed herein, independently of each other. By way of particular example, it may be advantageous to for the circulatory profiles of individual drugs by temporally staged with respect to each other (one drug having a circulatory profile that precedes the profile of a second drug). Such level of therapeutic choreography is significantly more controllable in multi-drug formulations delivered as a single pill, rather than multiple monotherapeutic formulations being delivered in separate pills.

SCOPE OF THE INVENTION

[00872] The foregoing detailed description sets forth various embodiments of formulations, methods, procedures and practices for reducing or preventing the development, or the risk of development, of neuropathology as a result of traumatic injury. Insofar as such formulations, methods, procedures and practices contain one or more functions or operations, it will be understood by those within the art that each formulation, method, procedure and practice can be implemented, individually or collectively, within a wide range of many combinations without undue experimentation.

[00873] A person having ordinary skill in the art will recognize that, in one significant aspect, the herein described formulations (*e.g.*, any combination of an anticonvulsant/antiepileptic, a neurosteroid/neuroactive steroid, an NK-1 receptor antagonist and a lithium-related/lithium-containing compound), methods, and procedures and practices, and the discussion accompanying them, are used as examples for the sake of conceptual clarity and that various methods, procedures and practices are within the skill of those in the art. Consequently, as used herein, the specific exemplars set forth and the accompanying discussion are intended to be representative of their more general classes. In general, use of any specific exemplar herein is also intended to be representative of its class, and the non-inclusion of such specific formulation components (*e.g.*, an anticonvulsant/antiepileptic, a neurosteroid/neuroactive steroid, an NK-1 receptor antagonist and a lithium-related/lithium-containing compound), methods, and procedures and practices herein should not be taken as indicating that limitation is desired.

[00874] It is generally contemplated that the formulations according to the inventive subject matter will be formulated for administration to a mammal, and especially to a human, having a condition that is responsive to the administration of such a formulation. Therefore, where contemplated formulation compounds are administered in a pharmacological composition, it is understood that contemplated compounds can be formulated in admixture with pharmaceutically acceptable carriers. As an example but not exclusively, contemplated compounds can be administered orally as pharmacologically acceptable salts, or intravenously in a physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration.

[00875] In particular, contemplated compounds may be modified to render them more soluble in water or other vehicle which, for example, may be easily accomplished with minor modifications (salt formulation, esterification, etc.) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound or formulation in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient or

subject.

[00876] In particular, contemplated compounds may be prepared for delivery in tablet, capsule, pill or solution form, including any delivery that can deliver a controlled release of these compounds.

[00877] Similarly, it should be appreciated that while some claims recite components of formulations of invention embodiments, one of skill in the art will comprehend that other constituents, while pharmacologically inactive or inert in the context of the presently disclosed technology, may be a part of the formulation. Such inactive constituents include, as examples, excipients, binders, coatings, absorption enhancers, penetration enhancers, transport enhancers, stabilizers, chelators, buffers, carriers, clearance modifiers, emulsifying agents, antioxidants, preservatives, sugars, salts, cellulose, dyes, flavoring agents and any other inactive ingredients that are considered generally recognized as safe.

[00878] In certain pharmaceutical dosage forms, prodrug and derivative forms of contemplated compounds may be formed for various purposes, including reduction of toxicity, increasing the organ or target cell specificity, etc. Among various prodrug and derivative forms, acylated (acetylated or other) derivatives, pyridine esters and various salt forms of the present compounds may be advantageous. One of ordinary skill in the art will recognize how to readily modify the present compounds to prodrug and other forms to facilitate delivery of active compounds to a target site within the host organism or patient. One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the prodrug and other forms, where applicable, in delivering the compounds to a targeted site within the host organism, subject or patient to maximize the intended effect of the formulation.

[00879] Similarly, it should be appreciated that contemplated compounds may also be metabolized to their biologically active form (*e.g.*, via hydroxylation, glycolsylation, oxidation etc.), and all metabolites of the compounds herein are therefore specifically contemplated. In addition, contemplated compounds (and combinations thereof) may be administered in combination with yet further antiviral and/or antibacterial agents. Suitable additional drugs therefore include various antibiotics (*e.g.*, beta-lactam antibiotics, tetracycline antibiotics, oxazine antibiotics, etc.), various antiviral compounds (*e.g.*, polymerase inhibitors), and/or compounds that stimulate the immune system.

[00880] With the presently disclosed technology described in detail herein, it is to be understood that the invention is not limited to the particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of only describing particular embodiments, and is not intended to be limiting, since the scope of the presently disclosed technology will be limited only by the appended claims or by a fair reading of the application as a whole.

[00881] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within embodiments of the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and this is also encompassed within embodiments of the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in embodiments of the invention.

[00882] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which embodiments of this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the presently disclosed technology, a limited number of the exemplary methods and materials are described herein.

[00883] All publications mentioned herein disclose and describe the methods and/or materials in connection with which the publications are cited, as well as the general background for the inventive subject matter disclosed herein. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the presently disclosed technology is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

[00884] The inventive technology described herein sometimes illustrates different components contained within, or connected with, different other components. It is to be understood that such descriptions or subject matter are merely exemplary, and that in fact many other descriptions, examples, methods, procedures and practices can be implemented which achieve the same functionality. In a conceptual sense, any arrangement of components to achieve the same functionality is effectively "associated" or "coupled" such that the desired functionality is achieved. Hence, any two or more methods, procedures or practices herein combined to achieve a particular functionality can be seen as "associated with" each other such that the desired functionality is achieved, irrespective of condition, event, injury, damage or pathology components. Likewise, any two or more components so associated can also be viewed as being "operably connected", or "operably coupled", to each other to achieve the desired functionality, and any two or more components capable of being so associated can also be viewed as being "operably couplable", to each other to achieve the desired functionality. Specific examples of operably couplable include but are not limited to practices

of embodiments of the invention required under different conditions, practices of embodiments of the invention requiring different routes or methods of administration, practices of embodiments of the invention requiring repeated administration for varying periods of time or logically interacting or logically interactable components to achieve the desired functionality.

[00885] In a general sense, those skilled in the art will recognize that the various aspects described herein which could be implemented, individually or collectively, by a wide range of methods, procedures or practices, or any combination thereof, can be viewed as being composed of various types of "formulation." Consequently, as used herein "formulation" includes, but is not limited to, two compounds representing two of the classes of an anticonvulsant/antiepileptic, a neurosteroid/neuroactive steroid, an NK-1 receptor antagonist and a lithium-related/lithium-containing compound, three compounds representing three of the classes of an anticonvulsant/antiepileptic, a neurosteroid/ neuroactive steroid, an NK-1 receptor antagonist and a lithium-related/lithium-containing compound, or four compounds representing the classes of an anticonvulsant/antiepileptic, a neurosteroid/neuroactive steroid, an NK-1 receptor antagonist and a lithium-related/lithium-containing compound. Those having skill in the art will recognize that the subject matter described herein may be implemented in a method, procedure or practice as described herein, or some combination thereof.

[00886] As examples, the one or more formulations, methods, procedures or practices of certain embodiments of the invention include many combinations and permutations thereof with respect to the nature of the individual formulations, and their relative methods, procedures or practices, can vary in operation by the relative methods, procedures or practices.

[00887] While particular aspects of the present subject matter described herein have been shown and described, it will be apparent to those skilled in the art that, based upon the embodiments herein, changes and modifications may be made without departing from the subject matter described herein and its broader aspects. The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

[00888] Those skilled in the art will recognize that it is common within the art to describe methods, procedures or practices in the fashion set forth herein, and thereafter use standard practices to integrate such described methods, processes or procedures to reduce or prevent the development or the risk of development of neuropathology as a result of trauma. That is, at least a portion of the methods, procedures or practices described herein can be integrated into reducing or preventing the development or the risk of development of neuropathology as a result of trauma via a reasonable amount of experimentation. Those having skill in the art

will recognize that typical methods, procedures or practices generally include those described herein. A typical method, procedure or practice may be implemented utilizing any suitable commercially available instrument, tool or device, such as any typically found in a medical facility or health delivery context or venue, and available to those typically familiar with methods, procedures or practices generally applied by those skilled in the art.

[00889] With respect to the use of substantially any plural or singular terms herein, those having skill in the art can translate from the plural to the singular or from the singular to the plural as is appropriate to the context or application. The various singular/plural permutations are not expressly set forth herein for sake of clarity.

[00890] Furthermore, it is to be understood that the invention is defined by the appended claims, and by the many claims that could be supported by the present specification. It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (*e.g.*, bodies of the appended claims) are generally intended as "open" terms (*e.g.*, the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to inventions containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (*e.g.*, "a" or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations.

[00891] In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (*e.g.*, the bare recitation of "two recitations," without other modifiers, typically means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least two of A, B, C and D, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.*, "a formulation having at least two of A, B, C and D" would include but not be limited to formulations that have A and B together, A and C together, A and D together, B and C together, B and D together, C and D together, A, B, and C together, A, B and D together, A, C and D together, B, C and D together, A, B, C and D

together, etc.). In those instances where a convention analogous to "at least two of A, B, C or D, etc.", or "at least three of A, B, C or D, etc.", or "at least four of A, B, C or D, etc.", is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.*, "a formulation having at least one of A, B, C or D" would include but not be limited to systems that have A and B together, A and C together, A and D together, B and C together, B and D together, C and D together, A, B, and C together, A, B and D together, A, C and D together, B, C and D together, A, B, C and D together, etc.).

[00892] It will be further understood by those within the art that virtually any disjunctive word or phrase presenting two or more alternative terms, whether in the description, claims, or practices, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. It is also to be understood that the terminology employed in the Background of the Invention, the Brief Description of the Invention and the Detailed Description of the Invention sections of this application is for the purpose of describing particular embodiments. It is also contemplated that any optional feature of the inventive variations described herein may be set forth and claimed independently, or in combination with any one or more of the features described herein. Moreover, in interpreting the disclosure, all terms should be interpreted in the broadest possible manner consistent with the context of the disclosed technology. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

[00893] Thus, specific compositions and methods of " FORMULATIONS AND METHODS FOR THEIR USE IN TREATMENT OF NEUROPATHOLOGY AND NEURODEGENERATION AS A RESULT OF TRAUMATIC INJURY" have been disclosed. It should be apparent, however, to those skilled in the art that the scope of the claims should not be limited by the specific emodiments set forth herein, but should be given the broadest interpretation consistent with the description as a whole.

Dose ranges of drug categories representing particular embodiments of the invention

Drug category	Exemplary Compound	Acceptable Range (mg)	Preferable Range (mg)	More Preferable Range (mg)	Most Preferable Range (mg)

A/A	Gabapentin	5-9,600	50-4,800	100-2,400	200-600
A/A	Pregabalin	0.5-2,400	15-1,200	25-60	50-150
A/A	Valproic acid	25-8,400	250-4,200	750-3,750	1,000-3,000
N/N	Progesterone	0.05-1,200	5-600	40-450	100-300
N/N	Methylprednisolone sodium succinate	0.02-500	2-250	10-80	15-45
N/N	Medroxyprogesterone acetate	0.001-400	0.5-200	1-50	2.5-7.5
N/K	Aprepitant	0.05-750	5-375	20-250	40-120
N/K	Vestipitant	0.001-200	1-100	1-60	5-15
N/K	Casopitant	0.005-1,000	0.5-500	10-300	50-150
L/L	Lithium carbonate	0.5-3,600	30-1,800	100-900	200-600
L/L	Lithium citrate	0.01-2,400	10-1,200	50-900	200-600
L/L	Lithium chloride	3-3,600	30-1,800	100-900	200-600

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What is claimed is:

1. A pharmaceutical composition comprising:
 - a) at least one anticonvulsant or antiepileptic selected from gabapentin, pregabalin and valproic acid;
 - b) at least one neurosteroid or neuroactive steroid selected from progesterone, methylprednisolone sodium succinate and medroxyprogesterone acetate;
 - c) at least one NK1 receptor antagonist selected from aprepitant, vestipitant and casopitant; and
 - d) at least one lithium compound selected from lithium carbonate, lithium citrate and lithium chloride.
2. The composition of claim 1, comprised of a single dosage unit.
3. The composition of claim 1, comprised of separate dosage units for each of a), b), c), and d).
4. The composition of any one of claims 1 to 3, wherein the anticonvulsant or antiepileptic is gabapentin.
5. The composition of claim 4, wherein the gabapentin is present in an amount of from about 5.0 mg to about 9600 mg.
6. The composition of claim 4, wherein the gabapentin is present in an amount of from about 50 mg to about 4800 mg.
7. The composition of claim 4, wherein the gabapentin is present in an amount of from about 100 mg to about 2400 mg.
8. The composition of claim 4, wherein the gabapentin is present in an amount of from about 200 mg to about 600 mg.
9. The composition of any one of claims 1 to 3, wherein the anticonvulsant or antiepileptic is pregabalin.
10. The composition of claim 9, wherein the pregabalin is present in an amount of from about 0.5 mg to about 2400 mg.
11. The composition of claim 9, wherein the pregabalin is present in an amount of from about 15 mg to about 1200 mg.
12. The composition of claim 9, wherein the pregabalin is present in an amount of from about 25 mg to about 600 mg.
13. The composition of claim 9, wherein the pregabalin is present in an amount of from about 50 mg to about 150 mg.
14. The composition of any one of claims 1 to 3, wherein the anticonvulsant or antiepileptic is

valproic acid.

15. The composition of claim 14, wherein the valproic acid is present in an amount of from about 25 mg to about 8400 mg.
16. The composition of claim 14, wherein the valproic acid is present in an amount of from about 250 mg to about 4200 mg.
17. The composition of claim 14, wherein the valproic acid is present in an amount of from about 750 mg to about 3750 mg.
18. The composition of claim 14, wherein the valproic acid is present in an amount of from about 100 mg to about 300 mg.
19. The composition of any one of claims 1 to 18, wherein the neurosteroid or neuroactive steroid is progesterone.
20. The composition of claim 19, wherein the progesterone is present in an amount of from about 0.05 mg to about 1200 mg.
21. The composition of claim 19, wherein the progesterone is present in an amount of from about 5 mg to about 600 mg.
22. The composition of claim 19, wherein the progesterone is present in an amount of from about 40 mg to about 450 mg.
23. The composition of claim 19, wherein the progesterone is present in an amount of from about 100 mg to about 300 mg.
24. The composition of any one of claims 1 to 18, wherein the neurosteroid or neuroactive steroid is methylprednisolone sodium succinate.
25. The composition of claim 24, wherein the methylprednisolone sodium succinate is present in an amount of from about 0.02 mg to about 500 mg.
26. The composition of claim 24, wherein the methylprednisolone sodium succinate is present in an amount of from about 2 mg to about 250 mg.
27. The composition of claim 24, wherein the methylprednisolone sodium succinate is present in an amount of from about 10 mg to about 80 mg.
28. The composition of claim 24, wherein the methylprednisolone sodium succinate is present in an amount of from about 15 mg to about 45 mg.
29. The composition of any one of claims 1 to 18, wherein the neurosteroid or neuroactive steroid is medroxyprogesterone acetate.
30. The composition of claim 29, wherein the medroxyprogesterone acetate is present in an amount of from about 0.001 mg to about 400 mg.
31. The composition of claim 29, wherein the medroxyprogesterone acetate is present in an

amount of from about 0.5 mg to about 200 mg.

32. The composition of claim 29, wherein the medroxyprogesterone acetate is present in an amount of from about 1 mg to about 50 mg.

33. The composition of claim 29, wherein the medroxyprogesterone acetate is present in an amount of from about 2.5 mg to about 7.5 mg.

34. The composition of any one of claims 1 to 33, wherein the NK-1 receptor antagonist is aprepitant.

35. The composition of claim 34, wherein the aprepitant is present in an amount of from about 0.05 mg to about 750 mg.

36. The composition of claim 34, wherein the aprepitant is present in an amount of from about 5 mg to about 375 mg.

37. The composition of claim 34, wherein the aprepitant is present in an amount of from about 20 mg to about 250 mg.

38. The composition of claim 34, wherein the aprepitant is present in an amount of from about 40 mg to about 120 mg.

39. The composition of any one of claims 1 to 33, wherein the NK-1 receptor antagonist is vestipitant.

40. The composition of claim 39, wherein the vestipitant is present in an amount of from about 0.001 mg to about 200 mg.

41. The composition of claim 39, wherein the vestipitant is present in an amount of from about 0.1 mg to about 100 mg.

42. The composition of claim 39, wherein the vestipitant is present in an amount of from about 1 mg to about 60 mg.

43. The composition of claim 39, wherein the vestipitant is present in an amount of from about 5 mg to about 15 mg.

44. The composition of any one of claims 1 to 33, wherein the NK-1 receptor antagonist is casopitant and the casopitant is present in an amount of from about 0.005 mg to about 1000 mg.

45. The composition of claim 44, wherein the casopitant is present in an amount of from about 0.5 mg to about 500 mg.

46. The composition of claim 44, wherein the casopitant is present in an amount of from about 10 mg to about 300 mg.

47. The composition of claim 44, wherein the casopitant is present in an amount of from about 50 mg to about 150 mg.

48. The composition of any one of claims 1 to 47, wherein the lithium compound is lithium

carbonate.

49. The composition of claim 48, wherein the lithium carbonate is present in an amount of from about 0.5 mg to about 3600 mg.
50. The composition of claim 48, wherein the lithium carbonate is present in an amount of from about 30 mg to about 1800 mg.
51. The composition of claim 48, wherein the lithium carbonate is present in an amount of from about 100 mg to about 900 mg.
52. The composition of claim 48, wherein the lithium carbonate is present in an amount of from about 200 mg to about 600 mg.
53. The composition of any one of claims 1 to 47, wherein the lithium compound is lithium citrate.
54. The composition of claim 53, wherein the lithium citrate is present in an amount of from about 0.01 mg to about 2400 mg.
55. The composition of claim 53, wherein the lithium citrate is present in an amount of from about 10 mg to about 1200 mg.
56. The composition of claim 53, wherein the lithium citrate is present in an amount of from about 50 mg to about 900 mg.
57. The composition of claim 53, wherein the lithium citrate is present in an amount of from about 200 mg to about 600 mg.
58. The composition of any one of claims 1 to 47, wherein the lithium compound is lithium chloride.
59. The composition of claim 58, wherein the lithium chloride is present in an amount of from about 3 mg to about 3600 mg.
60. The composition of claim 58, wherein the lithium chloride is present in an amount of from about 30 mg to about 1800 mg.
61. The composition of claim 58, wherein the lithium chloride is present in an amount of from about 100 mg to about 900 mg.
62. The composition of claim 58, wherein the lithium chloride is present in an amount of from about 200 mg to about 600 mg.
63. The composition of any one of claims 1 to 62, wherein one or more of a), b), c), and d) is in the form of one or more of pharmaceutically acceptable salts, prodrugs or hydrates.
64. The composition of any one of claims 1 to 62, wherein one or more of a), b), c), and d) are provided in a controlled release form.

65. A use of a composition of any one of claims 1 to 64 for reducing the effects of, or for reducing the risk of development of secondary injury caused by a trauma.
66. The use of claim 65, wherein the composition is formulated for use before the onset of the trauma, in anticipation of the trauma, during the trauma, or after the onset trauma.
67. The use of claim 65, wherein the composition is formulated for use within 2 hours after the onset or end of the trauma.
68. The use of claim 65, wherein the composition is formulated for use within 24 hours after the onset or end of the trauma.
69. The use of claim 65, wherein the composition is formulated for use within 6 hours before the expected onset or the expected end of the trauma.
70. The use of claim 65, wherein the composition is formulated for use one, or a plurality of times, after the formulation is first used.
71. The use of claim 65, wherein the composition is formulated for use one, or a plurality of times, as a sustaining dose.
72. A pharmaceutical composition comprising:
- a) at least one anticonvulsant or antiepileptic;
 - b) at least one neurosteroid or neuroactive steroid;
 - c) at least one NK1 receptor antagonist selected; and
 - d) at least one lithium compound,
- wherein the pharmaceutical composition is for use to reduce the effects of, or to reduce the risk of development of secondary injury caused by a trauma.