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(72) Inventor; and

(71) Applicant : HENRY, James, Lorne [CA/CA]; 132 North Shore Boulevard East, Burlington, Ontario L7T 1W4 (CA).

(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).

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(54) Title: THREE-COMPONENT FORMULATIONS, METHODS AND PROCEDURES, AND COMBINATIONS THEREOF, FOR REDUCING OR PREVENTING THE DEVELOPMENT, OR THE RISK OF DEVELOPMENT, OF NEUROPATHOLOGY RESULTING FROM TRAUMA

(57) Abstract: Novel three-component formulations, procedures and methods for use in treating neuropathology incident to trauma are provided. Three-component formulations of the invention comprise biologically active forms of at least one neurosteroid, at least one anti-epileptic or anticonvulsant, and at least one lithium-containing or lithium-related compound. The provided formulations are configured or adapted to prevent or reduce the incidence and severity of neurological damage caused by neurotrauma. Formulations, procedures and methods of the invention advantageously effect both neuroprotective actions to prevent or reduce secondary injuries, and neurotrophic actions to repair and restore cells and tissues affected by the trauma, and are especially useful in treating neurological trauma, such as those caused by sports injuries, chemical weapons, vehicle collisions and improvised explosive devices in combat.



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THREE-COMPONENT FORMULATIONS, METHODS AND
PROCEDURES, AND COMBINATIONS THEREOF, FOR REDUCING OR
PREVENTING THE DEVELOPMENT, OR THE RISK OF DEVELOPMENT,
OF NEUROPATHOLOGY RESULTING FROM TRAUMA

RELATED APPLICATION AND PRIORITY

[001] This Utility Patent Application claims the priority and benefit of commonly owned U.S. Provisional Patent Application Serial No. 61/750,745 of James L. Henry, as filed 9 January 2013, and as entitled “Formulations, Methods And Procedures For Reducing Or Preventing The Development Or The Risk Of Development Of Neuropathology As A Result Of Traumatic Injury” which provisional patent application is hereby incorporated by reference in its entirety into the present patent application. Also hereby incorporated by reference in their entireties are each of the references cited herein, as well as those cited in Provisional Patent Application Serial No. 61/750,745.

FIELD OF THE INVENTION

[002] The presently disclosed invention, and the many particular embodiments of the invention, relate to multiple-component formulations, the use of such formulations, and to methods, procedures and combinations thereof to prevent, eliminate, or reduce, or to reduce the risk of, the damage that can otherwise lead to numerous types of neuropathology as a result of trauma.

BACKGROUND OF THE INVENTION

Clinical Context and Terminology

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

and tissues.

[004] Injury to these cells and tissues typically occurs as a result of two factors. The 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 by the trauma-induced tissue damage of the primary injury. The direct, or “primary,” damage (such as physical disruption) is not salvageable once it has developed. However, in accordance with the presently disclosed novel formulations, procedures and methods, the indirect damage, which is typically considered a “secondary injury”, or “secondary damage”, by nature of the biochemical and metabolic pathways governing this secondary injury, can be reduced, ameliorated or prevented by the present therapeutic treatment, intervention and formulations, and is therefore regarded as a salvageable neuropathology.

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

[006] 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 injuries and 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.

[007] 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), streptozotocin, 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.

[008] 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.

[009] 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.

[0010] 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.

[0011] Trauma, or "neurotrauma", to nerve cells, to neural support cells or to neural support tissues, can be, for example but not exclusively, brain injury that would include traumatic brain injury (TBI), central nervous system ischemia, spinal cord injury, enteric nervous system injury, peripheral nerve injury or other type of injury to nerve cells.

[0012] Outcomes of traumatic damage to nerve cells or tissues differ significantly from the outcomes of traumatic damage to non-neural tissues and cells. 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 or outcomes that persist for days, weeks or permanently. It is this set of disadvantageous characteristics and events regarding neural tissues to which the present invention is directed.

[0013] The severity and duration of such adverse outcomes resulting from neural tissue injury and cell death are governed by a balance of restorative and degenerative processes in those neural cells and tissues. In such injured cells and tissues, restorative processes drive cells and tissues toward recovery and repair, and the restoration of pre-trauma function. During the same period, degenerative processes drive cells and tissues toward loss of cell integrity and function, and even toward cell death. 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 and disability. Conventional medical and therapeutic systems and processes 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 present invention embodiments are directed toward addressing this clinical and societal heretofore unsolved need by promoting natural restorative processes while inhibiting intrinsic degenerative processes, thereby reducing or preventing the development, or the risk of development, of neuropathology as a result of traumatic injury.

Neuropathology and Manifestations Thereof

[0014] In the context of the disclosure, 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, brainstem, cerebellum or spinal cord, in the enteric nervous system and in peripheral sensory, motor and autonomic nerves. Neuropathology is also influenced by events that impact neural support cells and neural support tissues, as neuron/glia interactions are important in brain homeostasis and are vital for survival of neurons in health as well as after brain injury and 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 one example, injury-induced loss of glial cells or loss of glial function has been reported to have a negative outcome on injured neurons.

[0015] 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 gabapentin, progesterone or synthetic progestin or lithium, or any analog, derivative or related compound is present.

[0016] Brain injury is a major public health issue, inter alia, because it is a leading cause of disability. Brain injury occurs commonly from falls, motor vehicle accidents, sports injuries and 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. Repeated minor symptomatic or asymptomatic concussions and injuries to the brain have a cumulative effect that can be expressed as recurring headaches, periods of short term memory loss, depression, and appear, for example, as dementia pugilistica, posttraumatic stress disorder, chronic traumatic encephalopathy and similar disorders. Brain injury, or neuropathology more broadly, can also be caused, as one example, in patients with cancer who receive cancer drug therapies, which can result in complications including, among others, posterior reversible encephalopathy syndrome, cognitive dysfunction, and the like. As another example, therapeutic radiation also can lead to brain injury; white matter necrosis has been shown to occur at doses of >60Gy, leading to functional deficits including impairments in memory, attention and executive function, with profound effects on quality of life. 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 and life-changing to the individual.

[0017] Central nervous system ischemia is that condition when the blood supply or circulation to the brain, the brainstem, the cerebellum or the spinal cord is reduced. CNS ischemia may result from any reduction, restriction, interference or slowing of the blood circulation. Central nervous system ischemia can be focal or global. Cerebral ischemia alone 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. 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. Brainstem, or cerebellar or spinal ischemia can result from surgical procedures, for example by aortic cross clamping during cardiac surgery, or as a result of hypoperfusion during cardiac arrest, or in

newborns, as a result of temporary or prolonged hypoperfusion due to complications at delivery. Whether the numbers are large, as in the case of stroke, or small, as in the case of embolism from transcatheter aortic valve implantation, cerebral ischemia can have devastating and life-changing outcomes for the individual.

[0018] Spinal cord injury has a severe impact on individual victims, on the healthcare system and on the economy, as evidenced from epidemiological studies and professional reports. A recent systematic review indicated that an estimated 40 million people worldwide incur 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% of spinal injuries, falls account for 28% and acts of violence such as gunshot or other wounds account for 15%. Sports injuries account for 8%, with another 9% of unreported or unknown causes. Whether the numbers are large, as in the case of vehicular accidents, or small, as in the case of many of the unreported cases, spinal cord injury can have a damaging and life-changing outcome for the individual.

[0019] 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 trauma. Many of the adverse health conditions and disability that result from enteric nervous system injury are due to secondary injury processes. As examples, 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 neuron cells, neural support cells and neural support tissues. Secondary injury to the enteric nervous system can have disabling and life-changing effects on the individual victim.

[0020] Neuropathology or neuropathy of peripheral nerves results in a myriad of adverse health conditions and disability. 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 can be similarly devastating, including, 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, including the special senses) and loss of proprioception (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 manifest as orthostatic hypotension, dysautonomia, altered sudomotor function, and the like. 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 any of these other adverse health conditions and disabilities described herein.

[0021] 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. 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.

[0022] 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.

Mechanisms of Secondary Injury

[0023] 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.

[0024] 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.

[0025] Secondary injury is triggered immediately or within hours, days, weeks, or even months, of the primary injury and can continue and progress over a prolonged period of time. This secondary injury is caused or brought about by cascades of parallel as well as consecutive pathogenic processes initiated at the moment of the trauma, often or usually with delayed clinical presentation. Secondary injury is the result of cellular, metabolic and neurochemical processes that are triggered by a primary injury but that continue over the hours, days, weeks and even months following trauma. In the context of the present invention embodiments injury processes are targets for pharmaceutical intervention with the formulations of the presently disclosed technology.

[0026] In addition to any physical damage, trauma also compromises the normal supply of oxygen and glucose to the nervous system. In turn, this causes a loss of ionic balance. These typically occur within several minutes of a primary injury.

[0027] Nerve cells do not store alternate sources of energy for cellular metabolism and therefore intracellular stores of adenosine triphosphate (ATP), the source of cellular 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. ATPase maintains the sodium/potassium pump that maintains high intracellular potassium and low intracellular sodium. Among other actions, ATP depletion leads to multiple cascades of progressive 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 into neural tissue, as well as bleeding into the extravascular space.

[0028] 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. Increased intracellular calcium leads to a further calcium release from intracellular stores.

[0029] There is also a calcium pump in the neuron cell membrane that normally maintains physiologically appropriate levels of 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.

[0030] Oxidative and nitrative stress spread from an injury zone into surrounding and even remote brain 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. As a result, 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 the site of this primary injury, whether in the central nervous system, the enteric nervous system or the peripheral nervous system.

[0031] Secondary injury thus spreads both temporally and spatially. The negative sequelae may not manifest for weeks, months or years; suicide in athletes and soldiers years after trauma is one example. However, the optimal time to treat is as soon as possible or even before, around the time of trauma as described herein. Much of the neuropathology that is allowed to develop after the first few days may be refractory to any later medical treatment.

SUMMARY OF THE INVENTION

Overview of the Invention

[0032] 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.

[0033] Particular compounds that comprise the formulation embodiments are any two, or all three of an anticonvulsant/antiepileptic/antiepileptic, a neurosteroid/neuroactive steroid and a lithium drug 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 drug can be lithium carbonate. 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 spirit and scope of the presently disclosed invention embodiments.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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 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 after a traumatic event, the situation, whether in the field or in a hospital, and the like.

[0045] 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.

[0046] 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 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.

[0047] 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. 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.

[0048] 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.

[0049] 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 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. However, immediate or early approaches targeted at the development phase of these outcomes are unknown, few or ineffective. 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, or to prevent or reduce the cascades of degenerative processes, which result from trauma and that lead to prolonged or permanent adverse health conditions and disability. 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.

Objects and Description of the Invention

[0050] 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.

[0051] It is another object of the invention to provide means and methods for administering formulations of the invention to accomplish these same goals and effects.

[0052] 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.

[0053] In accordance with these and other objects, formulations of the invention are adapted and provided for the prevention of the development of neuropathology, and for the amelioration of the effects caused by trauma to a subject, the formulation comprising two or three or four biologically active compounds. Preferably, the two or three or four biologically active compounds are provided

in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other three biologically active compounds. In some preferred embodiments of the invention, the four compounds comprise a pharmaceutically effective amount of A) at least one biologically active compound selected from the group comprising anticonvulsant/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/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/lithium-containing/lithium-related compounds, wherein the lithium-containing/lithium-containing/lithium-related compound is at least one form of one or more of lithium carbonate.

[0054] 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 is reduced, lessened, attenuated or prevented. The formulations and methods of the invention are particularly useful in the treatment of human beings.

Particular Embodiments

[0055] 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.

[0056] In general, the presently disclosed technology comprises formulations adapted for the prevention of the development of neuropathology, 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.

[0057] 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. 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, and a pharmaceutically effective amount of at least one biologically active compound from the group consisting of lithium-containing and lithium-related compounds.

[0058] 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. 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 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.

[0059] 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 neural support cells or neural support tissues.

[0060] In general, the presently disclosed technology comprises a three-component formulation adapted for the prevention of the development of neuropathology, 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.

[0061] Many dosages, dosage ranges and combinations of the essential three components of the present formulations are within the scope and spirit 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.

[0062] 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.

[0063] 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.

[0064] 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 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 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.

[0065] 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, 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] In general, the present invention comprises four-component formulations, methods and procedures adapted for the prevention of the development of neuropathology, 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.

[0071] 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.

[0072] 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 which 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.

[0073] In its many preferred four-component embodiments, the present invention comprises formulations adapted for the prevention of the development of neuropathology, 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.

[0074] Many dosages, dosage ranges and combinations of the essential four components of the present four-component formulations are within the scope and spirit 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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

[0084] 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 as a result of traumatic injury.

[0085] 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.

[0086] 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 as a result of trauma.

[0087] 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, have greater beneficial effects than those deriving from a single-compound approach.

[0088] 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 as a result of trauma.

[0089] 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. 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. 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.

[0090] 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.

[0091] 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.

Need: To Address The Multiplicity Of Theorized Underlying Processes

[0092] 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.

[0093] 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. In contrast to conventional attempts, the present formulations are directed to addressing the multiple underlying physiological mechanisms involved in the development of secondary injury triggered by traumatic events.

[0094] 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.

[0095] 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

[0096] 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. 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; 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.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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

[00101] 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 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.

[00102] 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.

[00103] 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.

[00104] 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, can be reduced or prevented and that a multi-drug approach is needed.

[00105] 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.

[00106] 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.

[00107] 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 as a result of traumatic injury.

[00108] 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.

[00109] 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 and spirit of the presently disclosed technology and its embodiments are directed toward both: unanticipated as well as anticipated traumatic injury.

[00110] 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 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.

[00111] 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.

[00112] 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. 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.

[00113] 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. 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.

[00114] 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

[00115] Numerous combinations, variations and permutations of preferred formulations of the invention can be provided while remaining within the scope, spirit, function and effectiveness of the invention. Among the many preferred four-component formulations are those wherein the anticonvulsant/antiepileptic is gabapentin, the neurosteroid/neuroactive steroidal agent is progesterone or synthetic progestin, the NK-1 receptor antagonist is aprepitant and the lithium-containing/lithium-containing/lithium-related compound is lithium carbonate.

[00116] Preferred dosages of the respective compounds are many, and include any that produce the required or desired effect with respect to the particular trauma or traumas. As one of skill in the art can appreciate, such dosages can be tailored with respect to many factors. Exemplary of these factors are the nature and extent of the trauma, the cause of the trauma, the tissues affected by the trauma, the time since the traumatic event, whether the traumatic event is continuing or ongoing, the current medications being taken by the subject, if any, the standard or other emergency medical procedures being applied to the subject at the time, the proximity to, need for, and range of care of a

specialized healthcare facility, such as a hospital or emergency clinic, as well as the size, gender, race, ethnicity, age and physical condition of the subject mammal, especially humans.

[00117] As one of skill in the art will comprehend, the formulations of the invention described herein include those wherein one of the four compounds can be provided in a number of ranges, while the relative amounts the remaining three components of the invention in the specified ranges can be determined by methods known generally in the pharmaceutical art.

[00118] Among these formulations, wherein the range amount of one component is defined, are those wherein the gabapentin is provided in specified dosage ranges. As examples of preferred ranges of gabapentin, a dosage range of from about 5.0 mg to about 9,600 mg. is provided. Similarly, a preferred dosage range of the gabapentin component can be provided in a dosage range of from about 50 mg to about 4,800 mg. A more preferred dosage range is where the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg. In a most preferred dosage range the gabapentin can be provided in a dosage range of from about 200 mg to about 600 mg.

[00119] Similarly, among these formulations are those wherein the progesterone or synthetic progestin is provided in set dosage ranges while the amounts of the other components are determined relative to those ranges. Exemplary of these are wherein the progesterone or synthetic progestin is provided in amounts of from about 0.05 mg to about 1,200 mg. In another preferred dosage range, the progesterone or synthetic progestin is provided in a range of from about 5 mg to about 600 mg. A more preferred dosage range is where the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg. In a most preferred dosage range the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg.

[00120] With respect to lithium-containing/lithium-related compounds, among the formulations that are initially defined by one component are those wherein the lithium carbonate is provided in a preferred dosage range of from about 0.5 to about 3,600 mg. In a more preferred dosage range the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg. A more preferred dosage range is where the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg. In a most preferred dosage range the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.

Particular four-component formulations

[00121] As yet another advantage of the invention, many preferred four-component formulations of the invention are provided wherein each of the four components is provided in a specified range.

Among these preferred formulations are those wherein the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, and wherein the lithium carbonate is provided in a dosage range of from about 3.0 to about 3,600 mg. Another preferred formulation comprises wherein the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg, and wherein the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg.

[00122] Other preferred formulations of the invention include wherein the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg, and wherein the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg; and wherein the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg, and wherein the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.

[00123] Formulations of the invention can be provided in many types of dosages, and in many types of dosage units, including those in which the release of the individual compounds is controlled, slowed, delayed or sequenced in accordance with the desired delivery dynamics of the formulation with respect to many factors as known in the art. The many formulations of the invention can thus be adapted and arranged with respect to, as examples, the characteristics and circumstances of the subject, the nature and extent of the trauma, and the nature and extent of the overall injury. These factors include, as additional examples, the environment in which they are intended to be used, the intended users, the liquid, solid or other form in which the formulation is provided, the intended subjects or recipients, the type of trauma, the proximity and need for specialized healthcare such as a hospital or emergency clinic, the age, body weight and gender of the subject, and other medications the subject may be receiving.

[00124] In some preferred embodiments, a formulation of the invention comprises a single dosage unit. In other preferred embodiments, two, or a plurality, of dosages are provided over time with respect to the onset, or with respect to the anticipated onset, of the traumatic event. Formulations of the invention can be provided also in many types of controlled release forms adapted for providing effective amounts of each of the compounds of the formulations at appropriate times.

[00125] The various dosing regimens and timing sequences with respect to administration of the formulation can be configured such that an effective treatment for the prevention, amelioration, or post-traumatic management, of the neuropathological sequelae associated with trauma to a subject comprises the administration of one or more dosage units per day. As examples of factors to be considered in this regard, are the subject's vital signs, the subject's state of consciousness, the severity of the trauma, and other medications the subject may be taking.

[00126] In other advantageous aspects of the invention, formulations of the invention can be developed, titrated, configured, adapted and arranged with respect to one or more sets of dosage ranges for one or all of the four components or compounds of the formulation. As one example, the anticonvulsant/antiepileptic, such as gabapentin, can be provided in a dosage range of from about 5.0 mg to about 9,600. Mg. The dosages and dosage ranges of the other three biologically active compounds can then be adapted to correspond to the chosen dosage level of the gabapentin. Thus, by using a set range for one, two or three of the four compounds of a formulation of the invention, the effectiveness of the overall formulation can be determined with respect to the chosen one, two or three compounds.

[00127] Thus, in a similar manner, the neurosteroid/neuroactive steroid compound, such as progesterone or synthetic progestin, can be provided in a dosage range, for example, of from about 50 mg to about 450 mg. in order to accomplish a similar evaluation. Moreover, the Lithium-containing/lithium-containing/lithium-related compound of the formulation, such as lithium carbonate, can provided in a dosage range of from about 100 mg to about 900 mg.

[00128] Formulations of the invention can be provided in any effective form. As examples, formulations of the invention can be provided wherein one or more of the compounds is in the form of one or more of salts, prodrugs, hydrates, derivatives or metabolites of a 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.

[00129] Moreover, formulations of the invention can be provided wherein one or more of the biologically active compounds are provided in at least one controlled release form. In addition, formulations of the invention can also be adapted and arranged to be administered as one or more sustaining doses. Similarly, the disclosed formulations can be adapted and arranged to be administered before a possible or an anticipated traumatic event.

[00130] While not intending to be bound by any one theory or set of theories, in one underlying

aspect, Applicant speculates that the formulations of the invention possess unexpected advantages in part because they do not rely on affecting just one neurological mechanism. Instead, Applicant believes that the present formulations are adapted and arranged to affect several restorative, as well as several degenerative, underlying mechanisms. Alternatively stated, some of the components of the present formulations are selected to maximize the recovery processes initiated by the trauma, while other components are selected to minimize or prevent the destructive processes initiated by that same trauma. In doing so, formulations of the invention are believed to achieve complementary positive effects that would not be achieved by formulations that affect only one of the involved mechanisms. Moreover, Applicant speculates that the specific formulations disclosed herein are especially effective when compared to other multiple-drug approaches.

Particular Method Embodiments

[00131] In accordance with similar and parallel objectives of the invention, a method for the prevention of, for reducing the effects of, or for reducing the risk of development of neuropathology incident to trauma, is provided.

[00132] In one preferred embodiment, a method of the invention comprises the steps or actions of Step A) providing a formulation adapted for the prevention of the development of neuropathology, wherein the formulation comprises four biologically active compounds in amounts that are pharmaceutically effective for each compound, respectively, when administered in combination with the other three biologically active compounds, the four compounds comprising a pharmaceutically effective amount of: i) at least one biologically active compound from the group comprising anticonvulsant and antiepileptic drugs, ii) at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids, iii) at least one biologically active compound from the group comprising NK-1 receptor antagonists, and iv) at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds, and wherein the formulation is in a form 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; and Step B) administering the formulation to a mammal in need thereof.

[00133] In accordance with a particularly advantageous aspect of the invention, Step B of the method is preferably effected with respect to time in relation to one or more of i) the onset of the trauma, ii) in anticipation of the trauma, iii) during the trauma, and iv) during a period after the trauma. A method of the invention thus affords wide choices with respect to adapting and arranging

the administration of a formulation of the invention with respect to the time of the onset and duration of the trauma, as well as with respect to a possible or an expected trauma.

[00134] A method of the invention thus encompasses wherein the formulation is first administered posttraumatic event within one hour after the onset of the trauma, or within two hours after the onset of the trauma, or within three hours after the onset of the trauma, or within six hours after the onset of the trauma, or within 8 hours after the onset of the trauma, or within 12 hours after the onset of the trauma, or within 18 hours after the onset of the trauma, or within 24 hours after the onset of the trauma or within two days, or within three, four, five, six or seven days or any time thereafter.

[00135] In some preferred embodiments, the method of the invention includes also wherein the formulation is administered at least once when a subject is about to enter into a situation, condition or scenario where trauma may occur, in which case this is a preventive measure as described herein. Examples of such preventive administration include within 10 hours before the possible onset of the trauma, within 8 hours before the possible onset of the trauma, or within 6 hours before the possible onset of the trauma, or within 4 hours before the possible onset of the trauma, or within 2 hours before the possible onset of the trauma or at the time of onset of the trauma.

[00136] In some preferred embodiments, the method of the invention includes also wherein the formulation is administered at least once in anticipation or expectation of trauma, or prophylactically as described herein. Examples of such prophylactic administration, include within 10 hours before the expected onset or the expected end of the trauma within 8 hours before the expected onset or the expected end of the trauma, or within 6 hours before the expected onset or the expected end of the trauma, or within 4 hours before the expected onset or the expected end of the trauma, or within 2 hours before the expected onset or the expected end of the trauma or at the time of onset of the expected or possible trauma.

[00137] As an additional advantageous aspect of the method of the invention, formulations of the invention can be administered more than one time. Additional administrations can be provided one or a plurality of times after the formulation is first administered regardless of whether a formulation is first administered before, during or after the trauma. In a similar manner, formulations of the invention can be administered one, or a plurality of times as desired or needed, as one or more sustaining doses in order to provide desired physiological or pharmacological levels in the subject of the several compounds of the formulations.

[00138] As a particularly preferred aspect of the present method, the formulation is configured

such that 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 lithium-containing/lithium-containing/lithium-related compound is lithium carbonate.

[00139] Preferred dosages of the respective formulations and compounds to be used in the present method are many, and include any that produce the required or desired effect with respect to the particular trauma or traumas. As one of skill in the art can appreciate, such dosages can be tailored with respect to many factors. Exemplary of these factors are the nature and extent of the trauma, the cause of the trauma, the tissues affected by the trauma, the time since the traumatic event, whether the traumatic event is continuing or ongoing, the current medications being taken by the subject, if any, the standard or other emergency medical procedures being applied to the subject at the time, the proximity to, need for, and range of care of a specialized healthcare facility, such as a hospital or emergency clinic, as well as the size, gender, race, ethnicity, age and physical condition of the subject mammal, especially humans.

[00140] Among these formulations are those wherein the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg. In a preferred dosage range the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg.

[00141] Among these formulations are those wherein the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg. In a preferred dosage range the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg.

[00142] Among these formulations are those wherein the lithium carbonate is provided in a dosage range of from about 0.5 to about 3,600 mg. In a preferred dosage range the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg.

[00143] Other preferred dosages of compounds and formulations suitable for use in effecting the method of the invention are listed elsewhere in the present disclosed invention and its embodiments, both textually and in the Tables presented elsewhere in this disclosed invention and its embodiments. As one of skill in the art can appreciate, any of the present formulations can be configured, adapted or arranged for use with the present method in conjunction with any of the dosage ranges of any or all of the other constituents of the formulations.

Scope of the invention

[00144] 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.

[00145] The present invention provides heretofore unknown advantages in the treatment and prevention and reduction of trauma-induced damage and injury to nerve cells or neural support cells or neural support tissues. 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. This gap represents an unsolved medical need. The presently disclosed technology aims to fill this gap.

[00146] The presently disclosed technology focuses 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 beyond treatment. However, the injury to neural tissues in the area of this primary injury spreads through secondary injury mechanisms in time as well as to neighboring and even remote cells and tissues, including nerve cells, neural support cells and neural support tissues, that do not die from this primary injury. Indeed, the damage caused by these secondary processes can be as serious and extensive as, or even more serious and 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 spatially so that injury and damage can spread to other parts of the body and manifest at sites remote from the site of the primary trauma, whether in the brain, brainstem, spinal cord, enteric nervous system or peripheral nervous system.

[00147] 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.

[00148] Restorative mechanisms: 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, additive or 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.

[00149] Degenerative mechanisms: as detailed herein there are many targets or points of entry for pharmaceutical inhibition, lessening or blocking the degenerative processes that tip this balance away from function and health toward loss of function, adverse health conditions or disability. Such an approach is 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, additive or 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.

[00150] Conventional or standard immediate or emergency treatment of trauma typically consists of minimizing the symptoms of the immediate, or primary, traumatic injury. 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 the sequelae of post-trauma effects that are an indirect result of the primary trauma. The aim is to incorporate the presently disclosed technology into standard emergency health care, as well as to practice the presently disclosed invention as standard preventive and prophylactic practice.

[00151] Significantly, a 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 occur. 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 the secondary sequelae versus the treatment of the primary injury.

[00152] Secondary injury spreads to sites remote from the primary injury. In fact, 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.

[00153] Conventional rehabilitation treatment is aimed at ameliorating existing symptoms, adverse health conditions or disability caused by the 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 to manifest if not reduced or prevented based on knowledge of their incidence with respect to the category of primary injury.

[00154] As indicated herein, the cascades of mechanisms leading to secondary injury are triggered within 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 if not reduced or prevented by appropriate pharmaceutical intervention.

[00155] 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 a category of traumatic events, 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.

[00156] Similarly, comparisons can be made of the severity of the symptoms that typically manifest after a category of traumatic event in those individuals that have been treated with standard procedures alone, with the severity of symptoms in 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.

[00157] (i) The presently disclosed technology and its particular embodiments provide numerous formulations that comprise combinations of complementary 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.

[00158] (ii) The biological targets of embodiments of formulations provided herein include mechanisms of the secondary sequelae that are restorative and function to restore neurons, 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 neurons, 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 that, combined, reduce or prevent, or reduce the risk of, secondary damage indirectly resulting from, or triggered by, the trauma event.

[00159] (iii) The present disclosure provides new uses of each of the chemical entities in the formulations of invention embodiments. Evidence is cited in the description of the invention 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 neuron-sparing effect, but to date these have not been used 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.

[00160] (iv) 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 and 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.

[00161] (v) The presently disclosed technology is advantageous in that the formulations target trauma-induced secondary injury to nerve cells. Further, the presently disclosed technology also targets trauma-induced secondary injury to neural support cells and neural support tissues. Even further, 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.

[00162] (vi) 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, surgical 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.

[00163] (vii) 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.

[00164] (viii) The presently disclosed technology is advantageous in that a formulation is to be given beginning at specific times before, at the time of or immediately following trauma, and continued as needed.

[00165] (ix) 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, the pre-hospital setting, or any setting outside the home and outside a hospital or sufficiently equipped clinical setting, where pre-medication or medication intervention is possible, and a hospital or clinical setting that is fully staffed and equipped for the full range of healthcare.

[00166] (x) 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 herein.

[00167] (xi) 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.

[00168] (xii) The presently disclosed technology is advantageous in that the formulations are applied differentially for unanticipated vs. anticipated trauma as described herein. 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.

[00169] All types of trauma, including those addressed in the presently disclosed technology extract a heavy toll on individuals, on families, on the health care system and on the economy. These types of trauma include, as examples but are not limited to, brain injury, central nervous system ischemia, spinal cord injury, enteric nervous system injury and peripheral nerve injury. Primary injuries resulting from these types of trauma are not amenable to prevention or reduction, but the secondary processes triggered by the primary trauma are, with the benefit of the presently disclosed technology and its embodiments, amenable to medical intervention.

Exemplary Practice Embodiments Of The Invention

[00170] The 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.

[00171] 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.

[00172] By way of scientific background, and as further described herein, all nerve cells, neural support cells and neural support tissues undergo similar or overlapping changes as a result of trauma, irrespective of whether these neurons are in the brain, the brainstem, 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.

[00173] 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 neuron or cell. While there may be some minor differences, such as the difference in sensitivity to excitotoxicity of neurons in the hippocampus vs. neurons in the cerebral cortex, the physiological processes triggered by trauma are believed to be the same, or quite similar or overlapping, in all neurons.

[00174] These physiological processes, including both the restorative and the degenerative processes, are activated within seconds or minutes by a traumatic event, and continue to develop over the hours and days 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 advised 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.

[00175] 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.

[00176] 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.

[00177] Embodiments of the invention are useful also in circumstances where a trauma 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 or prevention of trauma-induced neuropathology in high risk conditions or situations.

[00178] 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 before the highly expected trauma event or at the time of the pre-trauma awareness that a potential trauma exists.

[00179] 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

[00180] Prophylactic practice of invention embodiments includes situations where a procedure, particularly a medical procedure, is about to take place wherein the procedure is known to produce, or where evidence indicates a certain probability that 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.

[00181] Embodiments of the invention are useful in medical circumstances where evidence from clinical studies indicates a certain probability 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, for example but not exclusive to chemotherapy or radiation therapy. 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 of medical procedure. Embodiments of the invention include types of situations or scenarios where there is known or substantiated evidence that neuropathology, 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 in some patients.

[00182] 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.

[00183] 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 neuron, set of neurons, nerve or nerve cell, or any cell or tissue that supports the health or survival of nerve cells directly or indirectly.

[00184] 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.

[00185] 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. Administration of the formulation is continued as needed.

Therapeutic Advantages Particularly Associated With The Disclosed Multi-Agent Formulations

[00186] Applicant anticipates that multi-agent formulations, as disclosed herein, will provide substantial therapeutic advantages over existing therapeutic formulations related to the agents included in such formulations, which, so far as applicant is aware, are single active agent formulations. Applicant anticipates that the coincident therapeutic use of multiple agents as disclosed herein, covering a range of 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 agent alone. With reference to therapeutic benefits in

excess of those that could be derived from any single agent, 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-agent formulation exceeds that which could be maximally achieved by any single agent as a monotherapy, regardless of the maximal effective dose of any single agent. By synergistic, it is meant that the total benefit of a multi-agent formulation exceeds even that which might be expected from adding the maximal therapeutic benefits from each of the agents as a monotherapy.

[00187] Applicant further anticipates that the dosage-response profiles of individual agents, when administered in multi-agent 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 agents in multi-agent formulations may be lower than dosages required for maximal therapeutic effect when the individual agents as used as a monotherapy. The use of lower dosages of the individual agents may advantageous in terms of minimizing unwanted side effects of the agents that are associated with high dosages of the agent, particularly when used as a monotherapy. Lower dosages also provide a clear economic advantage to such multi-agent formulations.

[00188] Another aspect of therapeutic or safety advantages of the presently disclosed multi-agent formulations relates to minimizing the possibility of abusive uses of individual agents. Some anti-convulsants, such as barbiturates and benzodiazepines, have a burden of being used as drugs of abuse or recreational use. In practical terms, including drugs of potential abuse within a multi-agent formulation tends to discourage its recreational or abusive use.

[00189] Coformulation of multiple agents, as provided herein offers still further therapeutic advantages over monotherapy in that sequential and timed release strategies may be usefully applied to individual agents within the multi-agent formulation. The many uses and advantages of sequential or timed-release formulations are discussed elsewhere in this disclosure. For example, it may be advantageous to stage the pharmacodynamics of agents, as disclosed herein, independently of each other. By way of particular example, it may be advantageous for the circulatory profiles of individual agents to be temporally staged with respect to each other (one agent having a circulatory profile that precedes the profile of a second agent). Such level of therapeutic choreography is significantly more controllable in multi-agent formulations delivered as a single pill, rather than multiple monotherapeutic formulations being delivered in separate pills.

Table 1: Dose Ranges Of Constituents Of Formulations Representing Particular Embodiments Of The Invention

Compound	Acceptable Range (mg)	Preferable Range (mg)	More Preferable Range (mg)	Most Preferable Range (mg)
Gabapentin	5 - 9,600	50 - 4,800	100 - 2,400	200 - 600
Progesterone	0.02 - 600	0.2 - 300	2 - 100	100 - 300
Lithium Carbonate	0.5 - 3,600	30 - 1,800	100 - 900	200 - 600

[00190] Dose ranges for constituents of formulations are based to some extent on ranges of standard practice and are intended as exemplary, and not limiting. Instead, they are provided as additional guidance with respect to the invention embodiments, although those of skill in the art will comprehend with certainty that specific dosages, or specific dosage ranges, can be determined with respect to many other combinations and permutations with the assistance of the present Specification and procedures known in the art which can be adapted without undue experimentation.

[00191] A person having ordinary skill in the art will recognize that, in one significant aspect, the herein described formulations (e.g., any combination of any two or all three of gabapentin, progesterone or synthetic progestin and lithium), 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., gabapentin, progesterone or synthetic progestin and lithium), methods, and procedures and practices herein should not be taken as indicating that limitation is desired.

[00192] 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 an appropriate pH such as 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 present disclosure to provide numerous formulations for a particular route of administration.

[00193] In particular, contemplated compounds may be modified to render them more soluble in water or other vehicle that, for example, may be easily accomplished with minor modifications (e.g. 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.

[00194] In particular, contemplated compounds may be prepared for delivery in tablet, capsule, pill or solution form, including any form that can deliver a controlled release of these compounds.

[00195] 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, might 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.

[00196] 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 present compounds to a targeted site within the host organism, subject or patient to maximize the intended effect of the formulation.

[00197] 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 but are not limited to 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.

[00198] 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 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.

[00199] 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 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.

[00200] 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.

[00201] All publications mentioned herein are hereby incorporated by reference to 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 might be different from the actual publication dates, which may need

to be independently confirmed.

[00202] 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 invention requiring repeated administration for varying periods of time or logically interacting or logically interactable components to achieve the desired functionality.

[00203] 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 selected from gabapentin, progesterone or synthetic progestin and lithium, three compounds selected from gabapentin, progesterone or synthetic progestin and lithium or all four compounds selected from gabapentin, progesterone or synthetic progestin and lithium. 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.

[00204] As examples, the 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.

[00205] 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 and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of the subject matter described herein.

[00206] 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 traumatic injury. 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 traumatic injury 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.

[00207] 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 set forth herein for sake of clarity.

[00208] 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.

[00209] 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 Detailed Description 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.

[00210] Thus, specific compositions and methods of "Three-Component Formulations, Methods And Procedures, And Combinations Thereof, For Reducing Or Preventing The Development, Or The Risk Of Development, Of Neuropathology Resulting From Trauma" have been disclosed and exemplified. It should be apparent, however, to those skilled in the art that many more variations, permutations and modifications besides those already described are possible without departing from the inventive concepts herein, or from the spirit of the invention. The inventive subject matter, therefore, is not to be restricted except in the spirit of the disclosure.

What is claimed is:

1. A formulation adapted for the prevention of the development of neuropathology, 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 a pharmaceutically effective amount of:

- A. 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;
- B. 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;
- C. 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;

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 is reduced, lessened, attenuated or prevented.

2. The formulation of claim 1, wherein the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, and wherein the lithium carbonate is provided in a dosage range of from about 0.5 mg to about 3,600 mg.

3. The formulation of claim 1, wherein the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600

mg, and wherein the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg.

4. The formulation of claim **1**, wherein the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg, and wherein the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg.

5. The formulation of claim **1**, wherein the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg, and wherein the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.

6. The formulation of claim **1**, wherein the formulation comprises a single dosage unit.

7. The formulation of claim **1**, wherein the formulation is adapted and arranged to be administered a plurality of times in a sequence.

8. The formulation of claim **6**, wherein an effective treatment level for the prevention or treatment of neuropathological sequelae associated with trauma to a subject comprises an administration of one or more dosage units per day.

9. The formulation of claim **1**, wherein the subject for which the treatment is effective is human.

10. The formulation of claim **1**, wherein the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg.

11. The formulation of claim 1, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg.
12. The formulation of claim 1, wherein the lithium carbonate is provided in a dosage range of from about 0.05 mg to about 3,600 mg.
13. The formulation of claim 1, wherein one or more of the compounds is 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.
14. The formulation of claim 1, wherein one or more of the biologically active compounds are provided in a controlled release form.
15. The formulation of claim 1, adapted and arranged to be administered as one or more sustaining doses.
16. The formulation of claim 1, adapted and arranged to be administered before, during or after a traumatic event or a possible traumatic event.
17. A method for one or more of preventing, reducing the effects of, or reducing the risk of development of, neuropathology incident to trauma, the method comprising the steps or actions of
 - A. providing a formulation adapted for the prevention of the development of neuro-pathology, 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 a pharmaceutically effective amount of:

- i. at least one biologically active compound from the group comprising anticonvulsants and antiepileptic drugs;
 - ii. at least one biologically active compound from the group comprising neurosteroids and neuroactive steroids;
 - iii. at least one biologically active compound from the group comprising lithium-containing and lithium-related compounds,
- wherein the formulation is in a form 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, and
- B. administering the formulation to a mammal in need thereof.

- 18.** The method of claim **17**, wherein Step B is effected with respect to time 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.
- 19.** The method of claim **17**, 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.
- 20.** The method of claim **18**, wherein the formulation is first administered within two hours after the trauma.
- 21.** The method of claim **18**, wherein the formulation is first administered within 24 hours after the onset of the trauma.
- 22.** The method of claim **18**, wherein the formulation is first administered preventively or prophylactically within 6 hours before the expected onset or the expected end of the trauma.

- 23.** The method of claim **18**, wherein the formulation is administered additionally one, or a plurality of, times after the formulation is first administered.
- 24.** The method of claim **18**, wherein the formulation is administered one, or a plurality of times as a sustaining dose as needed.
- 25.** The method of claim **17**, wherein the gabapentin is provided in a dosage range of from about 5.0 mg to about 9,600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 0.05 mg to about 1,200 mg, and wherein the lithium carbonate is provided in a dosage range of from about 0.5 to about 3,600 mg.
- 26.** The method of claim **17**, wherein the gabapentin is provided in a dosage range of from about 50 mg to about 4,800 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 5 mg to about 600 mg, and wherein the lithium carbonate is provided in a dosage range of from about 30 mg to about 1,800 mg.
- 27.** The method of claim **17**, wherein the gabapentin is provided in a dosage range of from about 100 mg to about 2,400 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 50 mg to about 450 mg, and wherein the lithium carbonate is provided in a dosage range of from about 100 mg to about 900 mg.
- 28.** The method of claim **17**, wherein the gabapentin is provided in a dosage range of from about 200 mg to about 600 mg, wherein the progesterone or synthetic progestin is provided in a dosage range of from about 100 mg to about 300 mg, and wherein the lithium carbonate is provided in a dosage range of from about 200 mg to about 600 mg.