# DOWNLOAD PDF NOVEL THERAPIES FOR CNS INJURIES

## Chapter 1 : NOVEL TREATMENT FOR CNS INJURIES - Patent - Europe PMC

*Summary This book provides reviews of the epidemiology, evaluation, and patient management of central nervous system (CNS) injuries. Internationally recognized clinicians and basic scientists discuss recent research that has significantly advanced the understanding of the pathophysiology of neuronal death and facilitated development of new therapeutic approaches.*

The observed increase in cytokine production offers an attractive target for novel cell therapies. An increase in the proportion of T regulatory cells with MSC coculture was also observed [ 20 ]. These promising preliminary studies have shown that modulation of the locoregional postinjury proinflammatory environment could afford neuroprotection. Modulation of the Systemic Immunologic Response Recent work completed in the Pennypacker laboratory has shown that the adrenergic output associated with rodent ischemic stroke leads to the release of immunologic cells T cells from the spleen into the systemic circulation causing a reduction in splenic mass and an increase in cavity volume. Treatment with the panadrenergic blocker carvediol prevented the loss of splenic mass and decreased cavity volume [ 23 ]. Using a similar model, Verdrame et al. Additional research investigating the potential interaction between transplanted progenitor cells and lung immunologic cells is currently underway. Using a murine sepsis model, the Mezey laboratory has shown that the intravenous injection of MSCs is associated with decreased mortality and improved organ function. The observed benefit was derived from interactions between the injected MSCs and lung macrophages leading to increased IL production via a prostaglandin E2-dependent mechanism. Furthermore, the beneficial effect was eliminated by the administration of antibodies to either IL or the IL receptor thereby confirming the importance of anti inflammatory cytokine production in therapeutic efficacy [ 25 ]. There is limited data on the interaction of implanted adult progenitor cells with other organ systems in the setting of neurologic injury. Distribution studies have demonstrated localization of implanted cells to liver and kidney in addition to the more commonly described spleen and lung after intravenous or intra-arterial administration [ 26 â€” 29 ]. Preliminary preclinical work investigating the potential role of progenitor cell therapeutics for CNS injury has shown promise. The mechanism of the observed benefit remains controversial; however, more recent data questions the frequency and clinical significance of transdifferentiation as well as the volume of cells reaching the injury site due to a significant pulmonary first-pass effect [ 30 ]. Progenitor cells could interact with resident lung macrophages and splenic T cells leading to an increase in anti inflammatory cytokine production. The observed increase in systemic anti inflammatory cytokine concentrations may affect the resident brain microglia accounting for the observed therapeutic benefit. Clinical Trials The growing amount of preclinical data showing the potential benefit associated with progenitor cell therapy warrants the development of well-controlled clinical trials to investigate therapeutic safety and efficacy for central nervous system insults such as ischemic stroke, SCI, and TBI. Below we review the preliminary clinical trials investigating progenitor cell therapy for CNS insults completed to date. Ischemic Stroke Stroke is a leading cause of long-term disability in the United States [ 31 ]. Intravenous tissue plasminogen activator tPA is the only proven treatment for acute ischemic stroke within the first three hours of symptom onset [ 32 ]. Cell-based therapies have emerged as a novel and highly promising investigational approach to enhance recovery after stroke in animal models [ 33 â€” 37 ]. The encouraging preliminary results have led several investigators to launch clinical trials evaluating the safety of cell-based therapies in stroke patients. The safety, feasibility, ideal cell type, optimal dosage, and most favorable delivery method of cells are currently unknown. NCT evaluating the safety of bone marrow aspiration and infusion of bone marrow mononuclear cells BMMCs in adults within 24â€”72 hours of ischemic stroke. Primary outcome measures include a series of short- and long-term safety assessments with a secondary evaluation of neurological function as measured up to 90 days after injury. Autologous BMMCs are administered via peripheral intravenous injection followed by serial measurements of hemodynamic variables to assess immediate postinfusion safety. The investigators plan to enroll 60 patients and is currently underway. Cellular harvest and injection occurs between 5 and 9 days after the onset of stroke symptoms. Patient hemodynamics and neurologic status are monitored in the acute setting

with follow up exams up to 6 months after treatment. Adverse events are classified as any worsening of the neurologic exam. Therapeutic efficacy is determined via serial physical, laboratory, and radiographic exams. Selected inclusion criteria are symptoms and signs of clinically definite MCA acute stroke http: Federal University of Rio de Janeiro, Rio de Janeiro, Brazil are conducting a Phase 1 clinical trial investigating the intravenous and intra arterial injection of the autologous bone marrow-derived mononuclear cell fraction within 90 days of MCA stroke. Patients will be monitored with serial physical and radiographic exams up to 4 months after treatment. Adverse events will be recorded as any worsening in neurologic exam. Transcranial doppler will be used during intra arterial injection to ensure adequate blood flow in the middle cerebral artery. Improvement in neurologic deficits and neuroimaging will be recorded as secondary outcome measures during the study time period. Safety is to be assessed by physical exam and laboratory parameters. Selected inclusion criteria include a clinically definite acute stroke with known onset time, ability to start treatment within 7 days of onset, and patients between 30 and 80 years old. Data collection for the trial is set to be completed in May http: Preliminary clinical trials investigating the role of cell therapeutics for ischemic stroke have been limited to date and powered only to evaluate safety Table 1. The majority of these studies are restricting enrollment to patients with MCA infarcts territory and do not assess the role of these cells in other areas of the brain. No optimal method of delivery has been established, and it is unclear whether intravenous, intra-arterial, or other approaches may be safer and lead to better outcomes. Additionally, the studies employ different outcome measures limiting the ability to compare results among trials. While these preliminary studies have yielded some data to support the safety of cellular transplantation, additional trials need to be completed prior to controlled multicenter trials. The consensus highlighted the need for well-designed clinical trials with cell therapy being an excellent candidate [ 38 ]. Listing of location and details of current clinical trials being completed to investigate the potential role of bone marrow-derived progenitor cell therapeutics for the treatment of ischemic stroke. Traumatic Brain Injury A search of the Clinicaltrials. The treatments were focused on both acute therapy, as well as ongoing or chronic therapy, and included but were not limited to medications i. A single Phase I study using bone marrow-derived mononuclear cells in children after isolated TBI has recently been completed. To determine the safety of administration, systemic and cerebral hemodynamics, laboratory parameters, chest radiographs, and serial clinical assessments were monitored. Additionally, serial cerebral magnetic resonance imaging, neuropsychologic evaluation, and functional outcome measures were obtained as preliminary measures of efficacy. There were no identifiable adverse events with close monitoring of the neurologic, pulmonary, renal, hepatic, and hematologic systems. Functional and neuropsychological testing, including the Glasgow Outcome Scale, the Pediatric Injury Functional Outcome Scale, and the Wechsler Abbreviated Scale of Intelligence, revealed recovery consistent with or improved from expected baselines. Magnetic resonance imaging volumetric data revealed no significant change in grey matter, white matter, intracranial volume, or CSF space at 1 and 6 months as measured relative to expected norms [ 39 ]. This study should open the door for translation of cell therapies, particularly among patients with neurologic diseases and among pediatric patients. Given the apparent safety of this study, the development of larger, multicenter studies to further assess dosing and efficacy of autologous cell therapy for TBI is underway. Additionally, similar more dispensable progenitor cell populations, such as cord blood cells, may be safe and efficacious as well and warrant further study. Spinal Cord Injury 3. No outcomes data has been published on this trial. In the first group subacute group , cell therapy was delivered between 10 and 33 days following SCI. The second group chronic group was treated between 2 and 18 months after SCI. Of the eight subacute patients, four were treated intravenously and four via an intra-arterial route. Two of the chronic patients were treated intra-arterially and the remaining ten patients were treated intravenously. Patients were evaluated 3, 6, and 12 months post BMMC treatment. All four of the subacute patients treated via the intra-arterial route and one of the four treated intravenously experienced improvement in the American Spinal Injury Association ASIA score. One of two chronic patients treated via an intra-arterial route experienced an improvement in ASIA score, but none of the remaining 10 chronic patients treated with intravenous administration of BMMCs improved [ 40 ]. The patients all had complete SCI of two or more years duration. Cells were delivered intra-arterially into the anterior spinal artery at or near the level of their

SCI. Patients were followed with serial somatosensory-evoked potential SSEP testing over 30 months. No difference in response rates was identified between paraplegic or quadriplegic patients [ 41 ]. Our group has recently obtained an investigational new drug IND application to treat chronic greater than 6 months post injury pediatric SCI with autologous BMMC via intravenous infusion. We expect to begin enrolling patients by late summer  Patients underwent repeat LP 7 days posttreatment and the repeat LPs were reported to be normal. No mention of functional outcome was reported [ 42 ]. Serial magnetic resonance imaging scans performed following treatment demonstrated cell migration to the edges of the SCI in 5 of the cell-treated patients but none of the nano-particles only treated patients [ 43 ]. Cells were delivered by intravenous infusion, direct injection into the spinal cord above and below the injury site, and by a cell-infused matrix implanted surgically into the injury site. Patients were divided into acute treated within 2 weeks of injury , subacute treated between 2 and 8 weeks from injury , and chronic treated greater than 8 weeks from injury treatment groups. Neurologic improvements were greater in patients with the greatest leukocytosis following GM-CSF treatment. Neuropathic pain occurred in a third of the subacute and chronically treated patients but in only one of sixteen acutely treated patients. One control group patient developed neuropathic pain [ 45 ]. Human Trials Using Embryonically Derived Stem Cell Products Considerable regulatory caution has been exercised when human trials using embryonically or fetally derived stem cell products are proposed. Although these more immature cell types have the theoretical advantage of pluripotency, they have also been associated with tumor formation. A case report from Israel describing the development of multifocal CNS glioneuronal tumors following treatment of a child with ataxia telangiectasia using fetal neural stem cells obtained from multiple human fetuses has caused researchers and regulators to move cautiously in this area. The tumors were shown to have developed from the transplanted fetal tissue Figure 1 [ 46 ]. The cell preparations are injected directly into the spinal cords at the lesion site. Patients must undergo treatment within 7 to14 days following injury. Geron and the FDA have reached an agreement to allow the trail to move forward if subsequent preclinical studies provide satisfactory outcome. Conclusions Prior to large, multicenter clinical trials investigating the potential efficacy of progenitor cell therapies for CNS insults, a number of issues need to be addressed. Further research into optimal cell dosing, cell delivery method, and techniques for in vivo cell tracking need to be completed to ensure the safety of potential trials while affording them the best possible chance at success. Additional preclinical work to more clearly delineate the progenitor cell mechanism of action would also aid in the planning of quality-controlled clinical studies. Overall, while the very preliminary clinical trials reviewed in this paper offer novel data supporting the potential efficacy of cell therapeutics for CNS injury, a great deal of additional work is needed to ensure the safety and efficacy of progenitor cell therapy prior to widespread clinical trials. Acknowledgments This work was supported by Grants nos. Diaz Paredes et al. View at Google Scholar N. View at Google Scholar H.

## Chapter 2 : Novel Therapies for CNS Injuries: Rationales and Results - CRC Press Book

*Offers reviews of the epidemiology, evaluation, and patient management of central nervous system (CNS) injuries. This book discusses research that has developed the understanding of the.*

Injectable drug delivery to the intrathecal space. When injected into the intrathecal space, a hydrogel can localize and modulate drug release at the site of injury. This route is preferred over epidural delivery when the diffusive barrier presented by more Cell Delivery to the Injured CNS for Neuroprotection and Neuroregeneration Exploiting cells for transplantation offers great potential, with cells functioning as biologically active systems to produce specific beneficial factors or to replace lost cells and tissue. Though this section will focus on the use of donor cells, it should be noted that treatment strategies are also being developed to stimulate and augment endogenous stem cell populations. This strategy has shown promise following TBI [ 94 ], but this has not demonstrated functional benefit in SCI to date. Advantages of transplanting cells include the ability to target multiple neuroprotective and neuroregenerative mechanisms and the ability to provide a sustained treatment. Furthermore, cells, particularly stem cells, can adapt to their environment and are thus able to evolve with the pathology of the brain and spinal cord. Options for the choice of cell type and source are extensive, each with distinct advantages and disadvantages. Exhaustive reviews of the different cell types and sources used experimentally following TBI and SCI were recently completed [ 95 , 96 ]. Stem cells are being investigated for transplantation, owing largely to their proliferative and pluri- and multipotent nature. Though transplantation of stem cells at various points along the differentiation continuum of both neural and nonneural lineages has been investigated, implantation of primed stem cells is a common method of current investigation because of the risk of tumorigenesis of undifferentiated stem cells and the desire to control stem cell fate. In addition to being a great source of trophic support for the rescue of host cells after CNS trauma, stem cells have the potential to directly replace the cells of the CNS, that is, neurons, astrocytes, and oligodendrocytes, all of which are damaged by the traumatic insult [ 97â€” ]. The fate of donor stem cells is dictated by both in vitro preparation and the host environment [ ]. Neural stem cells NSCs are multipotent stem cells with the capacity to differentiate into the major cells of the CNS and have many potential applications in transplantation. NSCs persist in the adult brain [ 56 , ] and contribute to neurogenesis that occurs throughout adult mammalian life in the olfactory and hippocampal regions [ 56â€”58 , ]. The rate of neuro- and gliogenesis increases following TBI [ 56â€”58 , ] and is thought to be an attempt at self-repair and plasticity. Transplanting NSCs into the injured brain may augment the neuro- and gliogenic environment that the brain inherently attempts to create following injury. NSCs transplanted after experimental TBI have been shown to promote motor and cognitive recovery [ 96 , â€” ]. In addition to fetal or adult sources, NSCs may be derived from embryonic- [ â€” ], skin- [ ], or bone-marrow-derived stem cells [ , ], offering promising alternative cell sources. Transplantation of cells derived from fetal nervous and hematopoietic tissue has already shown promise in the clinic for treating severe TBI [ ]. For SCI, transplantation of embryonic stem cellâ€derived oligodendrocyte precursors is being pursued for clinical trials [ ], where the resulting oligodendrocytes are expected to myelinate degenerated fibers, thereby providing a neuroprotective effect against degeneration. Olfactory ensheathing glia OEG , currently in clinical trials, have been shown to guide axon regeneration and to myelinate these axons [ ]. A common problem with cell transplants is their limited survival and interaction with host tissue, particularly compared to fetal tissue grafts. Transplantation of fetal tissue has been shown to promote recovery after CNS injury as well as combat neurodegenerative diseases for reviews, see [ , ]. Studies that directly compare cells in suspension with tissue transplants have shown that donor cells in the tissue had significantly improved survival; furthermore, animals receiving intact tissue had significantly better functional outcome compared to those treated with cell suspension grafts [ â€” ]. The enhanced donor cell survival observed for transplantations of intact tissue may be due to the presence of three-dimensional architecture and a higher accessibility of extracellular adhesive proteins to which the donor cells can attach. Thus, tissue engineering approaches that emulate tissue transplants are being explored. While cell transplantation has already demonstrated promise in the clinic for both TBI and SCI, it is important to

enhance survival and integration of donor cells in host tissue to further advance cell transplantation therapy. Other hurdles associated with translating cell transplantation to the clinic include the host immune response to the cells or shed antigens [ ] and other associated risks. The choice of cell type and source is critical in addressing these issues. For example, autologous stem cells e. Embryonic stem cells have relatively low levels of major histocompatibility complex, thus minimizing the immune response, yet, as discussed above, priming embryonic stem cells is desirable for control toward specific cell lineages. Stimulation of endogenous stem cells could overcome hurdles associated with stem cell transplantation. In addition to determining the optimal cell type and source, the delivery time, location, and method e. All of these factors will affect the efficacy of the treatment, and it is likely that multiple combinations of these parameters will prove to be beneficial at promoting functional recovery. Tissue Engineering and Biomaterial Strategies in the Injured CNS Tissue engineering strategies include the introduction of natural or synthetic biomaterial- based interventions as well as combinations of cells and biomaterial scaffolds. Biomaterial-based strategies include those where the biomaterial itself has some therapeutic benefit or serves as a delivery vehicle for growth factors and extracellular matrix proteins, with the goal of recruiting host cells or enhancing axonal growth. When used as a delivery vehicle for cells, biomaterials must provide a suitable microenvironment for cell survival, tissue regeneration, and host tissue integration. Unlike polymer scaffolds that are molded into a particular shape prior to implantation, the irregularly shaped cavity resulting from traumatic injury requires a scaffold that can conform to its shape. An attractive approach is a hydrogel system injected in liquid form into the lesion cavity, which then forms a three-dimensional scaffold in situ, allowing for minimally invasive delivery into the lesion as shown in Figure 8. To this end, several thermosensitive polymeric systems such as poly N-isopropylacrylamide [ ], agarose [ ], methylcellulose [ ], and poly ethylene glycol -poly lactic acid -poly ethylene glycol tri-block polymer [ ] have been investigated. Hyaluronic acid hydrogels modified with laminin have been shown to encourage cell infiltration and angiogenesis, reduce glial scar formation, and promote neurite extension when implanted into a brain lesion [ ]. In addition, injection of a hyaluronanâ€”methylcellulose blend into the intrathecal cavity that surrounds the spinal cord tissue has been shown to promote functional recovery in experimental models of SCI [ 91 ]. Hydrogels injected into a lesion after TBI conform to the cavity and can be rendered bioactive by tethering adhesive ligands or other molecules. When used as a drug delivery vehicle, drugs and therapeutic more Regenerative strategies often look to developmental biology as a basis for design and incorporation of specific signaling molecules that are important to cell and axonal guidance in the brain and spinal cord. Permissive scaffolds can be tailored to mimic the developing brain by promoting migration of endogenous stem cells and enhancing plasticity and redevelopment following TBI. During development, axon guidance results from a combination of attractive and repulsive, long-range and short-range cues [ ], and these have been incorporated into biomimetic strategies in vitro [ â€” ] but have yet to be translated to in vivo preparations. Hollow fiber membranes filled with brain-derived neurotrophic factor but not presented in a gradient have promoted axonal regeneration in vivo [ ]. Tissue engineering strategies often include implanting of constructs containing exogenous cells in a bioactive scaffold. Specific combinations of cells and scaffolds can be designed to meet the needs of the physiologic and pathologic system of interest. Cell-seeded polymer scaffolds have been shown to increase cell adhesion, survival, and host-implant integration in many physiological systems, including the CNS [ 72 , â€” ]. NSCs have also been used in combination with biomaterial scaffolds for enhanced delivery of cells following TBI [ ] and enhanced regeneration following SCI [ 72 , ]. In SCI, several studies have focused on creating a permissive environment for regeneration using either peripheral nerve grafts or biomimetic nerve guidance channels. Nerve guidance channels, or nerve cuffs, are used clinically to repair peripheral nerve injuries, providing a permissive pathway through which severed axons regrow. Some interesting results in SCI repair have been obtained using peripheral nerve grafts, where Schwann cells likely contribute by cleaning up the degenerative debris that follows injury [ â€” ]. Furthermore, connecting gray and white matter with a series of intercostal peripheral nerve grafts has shown promising results [ ]; however, these results have been difficult to replicate. The challenge with this biomimetic approach is to stimulate a sufficient number of axons to regenerate within the defined environment. Hollow fiber membranes composed of either synthetic or

naturally derived polymers have been evaluated for transected SCI models [ ], and synthetic scaffolds have been tested in hemi-section models for a similar purpose [ 72 ]. Alone, the hollow fiber membranes or scaffolds are insufficient for repair, but when they are combined with regenerative factors, matrices, cells, or other drug molecules, greater regeneration has been observed. Peripheral intercostal nerves [ ] and peripheral Schwann cells [ , ] have been incorporated into synthetic guidance channels or scaffolds and have demonstrated enhanced axon regeneration when combined with neurotrophic factors or hormones [ , , ]. Another strategy is to combine the permissive channel environment with an enzyme, such as chondroitinase ABC, which has been shown to degrade the glial scar [ 50 ], thereby improving the physical pathway for regeneration [ ]. In addition to using biomaterials and tissue engineering approaches to guide axon growth in the spinal cord, these strategies can be employed to improve survival and integration of cells transplanted into the traumatically injured brain or spinal cord. As noted previously, fetal tissue grafted into the injured brain has shown promising results, likely because the grafts are less vulnerable to cell death and more effectively promote repair. However, limitations to fetal tissue transplants include inadequate availability and ethical concerns, technical difficulties keeping tissues viable in vitro, and a potentially invasive delivery strategy required of a three-dimensional implant. These limitations can be overcome by engineering a tissue-like construct based on core components of the developing fetal brain tissue, such as NSCs, extracellular matrix proteins, and in situâ€”forming three-dimensional structures. Tethering bioactive ligands, such as extracellular matrix motifs, to scaffold materials may positively influence cell behavior of transplanted cells. For example, NSCs transplanted in animal models after TBI within a matrix-based scaffold have been shown to exhibit improved survival and migration [ ] over cells transplanted in the absence of the scaffold, perhaps because of the antiapoptotic properties of matrix proteins such as laminin and fibronectin [ â€” ]. A tissue engineering approach to neural transplantation may combine the benefits of whole tissue grafts e. Numerous promising clinical trials are currently underway or planned for SCI, including the delivery of neutralizing molecules, cells stem and olfactory ensheathing glia , and even biomaterials i. While the scientific and medical community is excited by these clinical trials, a commitment has been made to combination strategies that include the use of cells, materials, and proteins. There is a strong sense that multiple pathways will have to be targeted for a substantive functional benefit to be realized. For example, cell delivery holds great promise, but technical difficulties are associated with their survival. The delivery of cells in suitable biomaterials may lead to greater donor cell survival and thus greater benefit. Future strategies will likely include factors that both promote neuroprotection and provide a suitable environment for regeneration. In addition to the challenges facing treatment of acute injury, even greater challenges exist in treatment of chronic injury, where degeneration has persisted, muscle tissue has atrophied, cysts have formed, and the glial scar is well formed. While neuroprotective strategies may be appropriate for acute injury, regenerative strategies will be required for treatment of chronic injury. Some of the advances in tissue engineering and biomaterials may provide the underlying scaffold required to promote regeneration in the hostile environment that follows traumatic injury. For TBI, the goal of regeneration is not necessarily recreating previous circuitry, but rather, enhancing neuroplasticity i. Neuroplasticity is also important for SCI where axonal regeneration is required beyond the glial scar and to the target organs for restoration of the neuronal circuitry and functional improvement. Connecting the appropriate tracts poses an even greater challenge, and thus plasticity in the spinal cord and brain are critical. To date, regeneration along the same tracts has largely been ignored since the focus has been on the intermediate goal of encouraging sufficient axons to grow across the glial scar. Because of the increased scale and scope of clinical CNS injuries, translation to human therapies is technically challenging, requiring significant amounts of cells and scaffold materials. Considerations such as scale-up, shelf-life of treatment, and invasiveness of transplant procedure are important when moving toward clinical treatments. Despite the many challenges, the future has never been so promising, with more clinical trials planned for traumatic CNS injuries than ever before and new developments in research laboratories paving the way for future combination strategies. MSS is grateful to the following agencies for funding: MCL acknowledges contributions from the following agencies for funding: Long-term dysfunction following diffuse traumatic brain injury in the immature rat. Quantitative structural changes in white and gray matter 1 year following

traumatic brain injury in rats. Hippocampally dependent and independent chronic spatial navigational deficits following parasagittal fluid percussion brain injury in the rat. The hippocampal laminin matrix is dynamic and critical for neuronal survival. PMC ] [ PubMed: Hall ED, et al. Spatial and temporal characteristics of neurodegeneration after controlled cortical impact in mice: Levin HS, et al. Neurobehavioral outcome 1 year after severe head injury. Experience of the Traumatic Coma Data Bank. Update of neuropathology and neurological recovery after traumatic brain injury.

## Chapter 3 : - NLM Catalog Result

*This book provides reviews of the epidemiology, evaluation, and patient management of central nervous system (CNS) injuries. Internationally recognized clinicians and basic scientists discuss recent research that has significantly advanced the understanding of the pathophysiology of neuronal death and facilitated development of new therapeutic approaches.*

LL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e. The myriad of known biological activities of IL- 1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels. It should be noted that some of these effects have been described by others as indirect effects of IL- 1. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. Interleukin-8 IL-8 is a chemotactic factor first identified and characterized in  IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Many different names have been applied to 1L-8, such as neutrophil attractant activation protein- 1 NAP-1 , monocyte derived neutrophil chemotactic factor MDNCF , neutrophil activating factor NAF , and T-cell lymphocyte chemotactic factor. IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. Many diseases are characterized by massive neutrophil infiltration. IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states. There remains a need for the treatment, and for the prevention of CNS injuries which are related to the ability of compounds which are cytokine suppressive, i. The preferred compounds for use as cytokine inhibitors are those compounds of Formula I as noted herein. A preferred group of these cytokine suppressive compounds are described herein as compounds of Formula I. CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area. Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this are has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu et al. Treatment which reduced edema formation was found to improve functional outcome in those animals treated. Preferred compounds for use as cytokine inhibitors are those compounds of Formula I noted below. Synthetic chemistry and methods of pharmaceutical formulations thereof are also contained within each noted patent application. Accordingly, the present invention provides for use of a compound of Formula I: Suitably, Rl is 4-pyridyl, pyrimidinyl, quinolyl, isoquinohnyl, quinazolinyl, 1- imidazolyl or 1 -benzimidazolyl. Suitably Y is X 1 -Ra wherein X 1 is oxygen or sulfur, preferably oxygen. A preferred ring placement of the Rl substituent on the 4-pyridyl derivative is the 2-position, such as 2-methoxypyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-methoxy-pyrimidinyl. When the substituent is Y, and Ra is aryl, it is preferably phenyl or naphthyl. When Ra is aryl alkyl, it is preferably benzyl or napthylmethyl. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring. Suitably Rc is optionally substituted Ci-6

alkyl, C cycloalkyl, aryl, arylCi-4 alkyl, heteroaryl, heteroarylC 1 -4alkyl, heterocyclyl, or heterocyclylC 1. Preferably, when the substituent is NHRa then Ra is aryl, arylalkyl, halosubstituted arylalkyl, halosubstituted aryl, heterocyclic alkyl, hydroxy alkyl, alkyl- 1 -piperidine - carboxylate, heterocyclic, alkyl substituted heterocyclic, halosubstituted heterocyclic, or aryl substituted heterocyclic. Preferably, such Ri substituents are tertbutylaminoethoxy, or hydroxyethoxy. Preferably, the R4 moiety is an unsubstituted or substituted phenyl moiety. Most preferably, R4 is 4-fluorophenyl. In Formula I , Z is suitably oxygen or sulfur. More preferably R2 is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC l-io alkyl, an optionally substituted Ccycloalkyl, or an optionally substituted Ccycloalkyl Ci-io alkyl. When the ring is optionally substituted, the substituents may be directly attached to the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2- or 6- position or both, such as 2,2,6,6-tetramethylpiperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are all directly on the available nitrogen. Preferably this alkyl moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. The heterocyclic ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl. Suitably R is hydrogen, a pharmaceutically acceptable cation, aroyl or a Ci-io alkanoyl group. Suitably Re is a 1,3-dioxyalkylene group of the formula -O- CH2 s-O-, wherein s is 1 to 3, preferably s is 2 yielding a 1,3-dioxyethylene moiety, or ketal functionality. The ring may be saturated or contain more than one unsaturated bond. When the cycloalkyl ring is di-substituted it is preferably di-substituted at the 4 position, such as in: In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula I may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. The following terms, as used herein, refer to: For the purposes herein the "core" 4-pyrimidinyl moiety for Rj is referred to as the formula: The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention. Exemplified compounds of Formula I include: The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states. Preferably, the cytokine inhibitor is a compound of Formula I , or a pharmaceutically acceptable salt thereof. As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula I which will cause a decrease in the in vivo levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin- 1 and tumor necrosis factor. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In order to use a compound of Formula I or a pharmaceutically acceptable salt thereof in therapy, it will normally be Formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula I and a pharmaceutically acceptable carrier or diluent. The compounds of Formula I may be administered in conventional dosage forms prepared by combining a compound of Formula I with standard pharmaceutical carriers according to

conventional procedures. The compounds of Formula I may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier s must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof. The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax. A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension. Compounds of Formula I may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula I externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0. Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Creams, ointments or pastes according to the present invention are semi-solid Formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate 0. Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol. Compounds of Formula I may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula I may also be administered by inhalation, that is by intranasal and oral inhalation administration.

## Chapter 4 : WOA1 - Novel treatment for cns injuries - Google Patents

*CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.*

Increase font size Developing Novel Strategies for CNS Repair and Protection We are actively exploring a broad range of treatment strategies for the protection and repair of the central nervous system in spinal cord injury, multiple sclerosis, and stroke. These strategies include cell transplantation approaches, as well as delivery of cell products, antibodies, small molecules, and biomaterials. Using our expertise in cell isolation, transplantation, behavioral recovery assessment, and quantitative morphological analysis of tissues, are rigorously analyzing the therapeutic potentials and risks of different treatment approaches. Many of these studies are being carried out in collaborations around the world. Our emphasis has been on preclinical studies designed to provide the kinds of information necessary for assessing the feasibility of producing clinically significant improvements in patient function and for choosing the appropriate treatment parameters for clinical trials if the data suggests they are warranted. We are investigating transplantation of myelin-forming cells into the site of injury as an approach to induce remyelination of demyelinated axons and thereby restore impulse conduction. We are also exploring the use of human mesenchymal stem cells, derived from the adult bone marrow, as an approach to repair of the injured brain and spinal cord. For example, we have shown that these autologous cellsâ€”administered intravenouslyâ€”can limit the damage to brain or spinal cord tissue in animal models of stroke or contusive spinal cord injury. Of ongoing interest, we are evaluating the relative therapeutic effectiveness of different cell types with similar overall properties and to identify parameters most important for transplant success. These recently characterized particles are produced by all cell types and are believed to play important roles in cell-cell communication in both health and disease. Our recent work suggests that exosomes produced by mesenchymal stem cells may be responsible for the therapeutic effects in CNS injury. Exosomes are far more stable and easy to store compared to cells. They are less likely to induce immune rejection, and amenable to large-scale production. Exosomes therefore represent a more practical alternative to some cell based therapies. In collaboration with researches in the laboratory of Philip Askenase Dept. Focus on CNS Vasculature We and others have recently highlighted the importance of the blood-brain and blood-spinal-cord barrier integrity in protecting the CNS from damage. Our studies in a rat model of MS showed that transient disruption of the blood spinal cord barrier alone is sufficient to induce a demyelinating lesion as the site of disruption in animals which had been immune sensitized, but which had been previously free of lesions. This observation suggested that increasing the stability of the blood-brain and blood-spinal cord barriers could represent a novel target for preventing the progression of MS. Similarly, our investigations into the mechanisms of therapeutic efficacy of intravenous MSCs for promoting recovery after contusive spinal cord injury showed that the rapid improvement in functional recovery correlated closely with a rapid restoration of BSCB integrity, implying that the ongoing vascular leakage after CNS trauma contributes significantly to poor outcomes. Anti-Nogo Antibodies -- Inhibiting the Inhibitors Although axons can regenerate after peripheral nerve injury, the environment of the central nervous system is not conducive to long distance axon growth. This poor regeneration is due in large part to the presence of molecules such as NOGO, which inhibit regeneration. In collaboration with the Strittmatter laboratory Dept. Targeting Serotonin to Improve Motor Control After Spinal Cord Injury Fibers descending from the brain through the raphe spinal tract make synaptic connections with motor neurons in the spinal cord, which allow individuals to control the movement of their arms or legs. Cells of the raphe spinal tract use the neurotransmitter serotonin to control the motor neurons. We have shown that raphe spinal tract axons which are spared after a spinal cord injury can sprout many new connections synaptic terminals over a period of several months after injury and that the appearance of these new synaptic terminals correlates with improved control over the limb. Furthermore, drugs which affect the serotonin system can reversibly affect limb control. These data suggest that medications, which enhance communication at serotonergic terminals, may improve muscle control for

individuals with incomplete spinal cord injuries. Collaborating on Clinical Trials Our preclinical studies have played an important role in establishing the safety profile of human bone marrow mesenchymal stem cells for treatment of stroke and spinal cord injury. We maintain a close relationship with colleagues in Sapporo, Japan Drs. Osamu Honmou and Masanori Sasaki who are conducting Phase I Clinical trials of autologous human bone marrow mesenchymal stem cells for the treatment of stroke and spinal cord injury. Collaboration between our two groups has been important for continuously assessing safety risks and refining treatment protocols.

## Chapter 5 : EPA4 - Novel treatment for cns injuries - Google Patents

*Use of 2,4,5-substituted imidazole compounds and compositions in the treatment of CNS injuries to the brain.*

## Chapter 6 : Clinical Development Of Multistem? For Treatment Of CNS Injury And Disease |

*Offers reviews of the epidemiology, evaluation, and patient management of central nervous system (CNS) injuries. This book discusses research that has developed the understanding of the pathophysiology of neuronal death and facilitated development of various therapeutic approaches.*

## Chapter 7 : NOVEL TREATMENT FOR CNS INJURIES - SMITHKLINE BEECHAM CORP

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