Intranasal Stem Cells
New Developments on the Frontier

• Charles F Mahl MD FACS FICS
• GenLife Regenerative Medicine
• GenStem Prolotherapy and Stem Cell Institute
• 2333 Ponce De Leon Blvd Suite 302
• Coral Gables, Miami, Florida 33134
• drmahl@genlifemed.com
Intranasal Stem Cells

- Bypass the blood-brain barrier.
- Is non-invasive.
- Reduces or eliminates systemic exposure.
- Does not require modification of the therapeutic agent.
- Works best for potent therapeutics.

- Targets the CNS. Results in rapid extracellular delivery to the brain and spinal cord along both the olfactory and trigeminal pathways.

Robert Thorne first demonstrated the trigeminal pathway for drug delivery to the CNS.

Treat Parkinson’s Disease, Multiple Sclerosis, Brain Tumors, TBI, Alzheimer’s, Hemorrhage, Ischemia and other CNS Disorders

Charles F. Mahl MD FACS FICS
William Frey PhD & Lusine Danielyan MD

- Discovered and patented that therapeutic cells, including adult stem cells and genetically engineered cells, can be non-invasively delivered to the brain via an intranasal delivery method.
Intranasal Stem Cells

- From Bone Marrow
  Allogeneic vs Autologous
- From Peripheral Blood
  Allogeneic vs Autologous

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Invasive and Noninvasive Routes To Overcome the Blood-Brain Barrier.

Clinical Indications

- Intranasal and pluripotent stem cells derived from peripheral blood, after activation, have been shown in case studies, to positively address post concussive symptoms secondary to TBI: memory, sleep, mental fatigue, mental clarity, libido, motor function and balance.
Intranasal Treatment References

- Noninvasive intranasal stem cells bypass the blood brain barrier to target the brain to treat Parkinson’s disease, stroke, MS, brain tumors, cerebral ischemia, Alzheimer’s and other CNS disorders. Frey, WH 2nd. 2015 Journal of Nature and Science, Vol. 1 No. 1 e23 (Neuroscience)

- Johnson NJ, Hanson LR et al June 2010 Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. 7(7) 884-93
How does Intranasal Delivery work?

• Intranasal stem cells bypass the bbb to target the brain by traveling extracellularly along the olfactory neural pathway with minimal delivery to other organs.

• Once in the brain, adult stem cells target the damaged areas of the brain, specifically to treat the underlying disease.

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Researchers have demonstrated the effectiveness of intranasal stem cell treatment technology in an animal models of neonatal ischemia, neonatal brain damage and subarachnoid hemorrhage.
Emory University, Atlanta, GA

• Researchers here have used intranasal stem cells on the animal model of stroke
Uppsala University in Sweden

- Have demonstrated that intranasal T regulatory cell therapy delivered and targeted the cells to the brain and efficiently suppressed ongoing inflammation in a model of sclerosis leading to reduced disease symptoms.
Intranasal Adult Neural Stem Cells

- Have also been shown to improve the model of MS as having intranasal mesenchymal stromal cells.

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Intranasal Stem Cell Delivery

• Eliminates the need for invasive neurosurgical implantation of cells and by eliminating the need for intravenous delivery that disperses cells throughout the body resulting in an unwanted systemic exposure.

• This delivery and treatment can facilitate the development of stem cell and genetically engineered cell therapies for Parkinson’s, PSP, Huntington’s, Alzheimer’s, MS, Stroke, TBI, SCI (Spinal Cord Injury), etc.
Alzheimer’s Patients’ Brains Do Not Take Up Glucose Properly.

Glucose Uptake & Utilization (FDG-PET)

Alzheimer’s Patient

Normal Elderly Adult

Papers

Alzheimer’s Disease & New Approaches to Treatment and Prevention

- William H. Frey II, Ph.D. St. Paul, MN
- Health Partners Center for Memory and Aging
- Alzheimer’s – loss of short term memory, confusion and disorientation, 65% of dementia cases, deficiencies of Vitamin B12, Vitamin D and Thyroid hormone.

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Stem Cell Nasal Spray for Parkinson’s Disease

• Successful intranasal delivery of stem cells to the brains of rats with Parkinson’s Disease yielded significant improvement in motor function and reversed the dopamine deficiency characteristic of the disease.

• Rejuvenation Research journal published by Mary Ann Liebert
Intranasal Stem Cells

- Clinical Trials on Retinal and Optic Nerve Diseases  
  Charles F Mahl MD

- Ischemic Optic Neuropathy
- Traumatic Optic Neuropathy
- Retinitis Pigmentosa
- Macular Degeneration

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Intranasal Delivery Methods to the Retina and Optic Nerve

• Investigation of the Intranasal Delivery Method as a Means of Targeting Therapeutic Agents to the Injured Retina and Optic Nerve
• A DISSERTATION
• THE UNIVERSITY OF MINNESOTA
• Sandra R. Alcalá September 2009
Iron accumulates abnormally in the brains of patients with Neurodegenerative disorders including Alzheimer’s, Parkinson’s, Stroke, hemorrhage, TBI, Huntington’s and ALS.

Iron is a potent promoter of oxidative and free radical damage which inactivates the human brain receptor required for memory and other key brain functions required for movement and function.

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Intranasal Insulin for Alzheimer’s Disease

- Brains do not take up glucose properly
- Amount of insulin (insulin gene expression) in brain is reduced
- Insulin signaling is reduced - insulin resistance
- Diabetes of the Brain “Type 3”
- Brain cells are starved for energy and thus cannot function.
- Diabetes doubles the risk of Alzheimer’s Disease

William Frey Ph.D. 1989 and 1999 patents
Charles F Mahl MD FACS FICS
Quercetin

- Penetrates cell membranes via glucose transport proteins and chelates intracellular iron.
- Can be used to bind and transport iron out of brain cells
- The combination of Quercetin and DFO is more effective than either treatment alone.
- For Parkinson’s and Alzheimer’s

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Intranasal Stem Cells

- Bypass the bbb
- Specifically target the damaged areas of brain
- Are anti-inflammatory and can produce therapeutic proteins needed by the brain to promote repair and treat neurodegenerative disorders.

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Intranasal Stem Cells

- Questions to be answered—
  - Use alone?
  - Use with Insulin?
  - Use with DFO?
  - Use with DFO and Quercetin?
• Danielyan L. Beer-Hammer S et al. Intranasal Delivery of Bone Marrow-Derived Mesenchymal Stem Cells, Macrophages, and Microglia to the Brain in Mouse Models of Alzheimer's and Parkinson's Disease
2014 Cell Transplantation Vol. 23 (1) 123-39

• Frey II W. H. Intranasal Stem Cells and T Cells Bypass the Blood-Brain Barrier to Treat CNS Disorders while Reducing Systemic Exposure
CellR4 2015; 3 (5): e1646
Intranasal
Intranasal Delivery of Umbilical Cord-Derived Mesenchymal Stem Cells Preserves Myelination in Perinatal Brain Damage


- Studied the remyelinating potential of human Wharton’s jelly mesenchymal stem cells (hWJ-MSCs) after intranasal delivery.

- Wistar rat pups, previously brain-damaged by a combined hypoxic-ischemic and inflammatory insult, received hWJ-MSC (150,000 cells in 3 μL) that were intranasally delivered twice to each nostril (600,000 cells total). WMI was assessed by immunohistochemistry and western blot for myelination, astrogliosis, and microgliosis. The expression of preoligodendrocyte markers, and neurotrophic factors, was analyzed by real-time polymerase chain reaction.

- Animals treated with intranasally delivered hWJ-MSC showed increased myelination and decreased gliosis compared to untreated animals.

- hWJ-MSC may, therefore, modulate the activation of microglia and astrocytes, resulting in a change of the brain microenvironment, which facilitates the maturation of oligodendrocyte lineage cells.

- This is the first study to show that intranasal delivery of hWJ-MSC in rats prevented hypomyelination and microgliosis in a model of WMI in the premature rat brain. Further studies should address the dose and frequency of administration.
The researchers at University of Minnesota discovered that when suspended in fluid and snorted, stem cells migrate quickly to the brain, arriving within an hour in most cases.

Researchers initially tested the procedure on mice, having them sniff adult rat stem cells suspended in solution. An hour later, the inhaled stem cells were visible within the brain. Testing a second time using stem cells from a human tumor, the cells again migrated quickly and reached the brain within an hour.
How long do they last?

In rats that received the **stem cells** intranasally it was possible to find **stem cells** in the olfactory bulb, cortex, hippocampus, striatum, cerebellum, brainstem, and spinal cord. Out of \(1 \times 10^6\) MSCs applied intranasally, 24% of the **stem cells** could be detected for at least 4.5 months in the brains of 6-OHDA rats.
Intranasal Delivery

- Stem cells are administered through the nose using an aspirator nozzle to spray the cells in the nose. The nasal cavity has two primary functions, olfaction (sense of smell) and warming, humidifying and filtering air we breathe.
- Inside the nasal cavities are turbinates, which are highly vascular and convoluted passageways lined with a warm, moist mucosal layer. These highly vascular turbinates allow for rapid absorption into the bloodstream.
Frey’s Research

• According to Frey, "When you cut into the brain, that leads to an inflammatory response.

• We’re hoping this will help. We didn’t see evidence that intranasal stem cell treatment caused inflammation. Intranasal delivery of therapeutic cells could potentially benefit the treatment of head injury, stroke, Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, and so on. One of the best ways to treat patients may be with their own cells. For example, the patient’s own bone marrow-derived stem cells could be delivered to produce dopamine, the missing chemical messenger in Parkinson’s disease. Therefore, we are also looking into the use of antibiotics, anti-inflammatories, and immunosuppressants that may further facilitate the safe delivery of therapeutic cells. 

Charles F. Mah, MD, FACS, FICS
For treating traumatic brain injury (TBI), PRP and insulin are employed as regenerative injection therapy.

At TBI Therapy, these adult stem cells are infused into the brain, typically while the patient is in the middle of receiving other regenerative therapies and adjunctive treatments. To promote regeneration in the brain, stem cell injections are usually paired with hyperbaric oxygen therapy (HBOT) sessions after TBI patients have completed an intranasal platelet rich plasma (PRP) infusion.
Publications

- Published online 2013 Sep 19. doi: 10.1371/journal.pone.0073118
- PMCID: PMC3777974
- Intranasal Delivery of Plasma and Platelet Growth Factors Using PRGF-Endoret System Enhances Neurogenesis in a Mouse Model of Alzheimer’s Disease
- Eduardo Anitua,1 Consuelo Pascual,2,3

- doi: 10.4103/1673-5374.198973
- PMCID: PMC5319232
- Platelet-rich plasma, an adjuvant biological therapy to assist peripheral nerve repair
- Mikel Sánchez,1,2 Ane Garate,2 Diego Delgado, Ph.D.,2,* and Sabino Padilla, M.D., Ph.D.3,*

Charles F. Marx, MD FACS FICS
Dementia

- Dementia is a general term describing degenerative brain disorders characterized by loss of short term memory, confusion and disorientation.

- Alzheimer’s disease accounts for about 65% of dementia cases with the rest being due to Lewy Body Dementia, vascular dementia, Frontotemporal dementia and other disorders.

- Diagnosis requires a neurologic exam, neuropsychometric testing, brain imaging and blood tests to eliminate deficiencies of B12, thyroid hormone (and vitamin D).

Charles E Mahl MD FACS FICS
Intranasal Delivery to the Brain

- Is non-invasive.
- Bypasses the blood-brain barrier.
- Results in rapid extracellular delivery to the brain and spinal cord along both the olfactory and trigeminal pathways involving perineural and perivascular channels.
- Reduces or eliminates systemic exposure.
- Does not require modification of the therapeutic agent.

Robert Thorne first demonstrated the trigeminal pathway for drug delivery to the CNS.

Charles F Mahl MD FACS FICS
Iron

• Iron accumulates abnormally in the brain in virtually all neurodegenerative disorders including: Alzheimer’s, Parkinson’s, stroke, hemorrhage, Traumatic Brain Injury, Huntington’s Disease and ALS.

• Iron is a potent promoter of oxidative and free radical damage which inactivates the human brain receptor required for memory and other key brain components required for movement and function.  Charles F Mahl MD FACS FICS
Deferoxamine (DFO) is a generic drug that binds iron with exceptionally high affinity \(10^{31}\), that has been used to treat iron overload in the blood in humans for decades.

Intramuscular DFO has been shown in a two year clinical trial in patients with Alzheimer’s to reduce cognitive decline by 50% but has significant side effects, and does not cross the blood-brain barrier well.

Consequently, we have developed and patented intranasal DFO to treat Alzheimer’s, Parkinson’s, Stroke, and Traumatic Brain Injury.


Charles E Mahl MD FACS FICS
DFO

- Intranasal (I.N.) DFO protects dopamine nerve cells and improves movement in animals with Parkinson’s disease in both the genetic and the neurotoxin models of Parkinson’s.
- Just a few nose drops of DFO given before or after a stroke, reduces brain damage in rats by 55%.
Insulin

- Both the amount of insulin (insulin gene expression) and insulin signaling are reduced in the brains of Alzheimer’s patients causing a metabolic disorder “type 3 diabetes” or “diabetes of the brain” which leaves brain cells starved for energy and unable to function normally.

- Insulin resistance characterizes the insulin signaling deficit in Alzheimer’s brain.

Charles F Mahl MD FACS FICS
The issuing of my 1989 and 1999 patent filings claiming direct intranasal delivery of insulin to the brain to treat Alzheimer’s disease and Parkinson’s disease have been followed by a number of human clinical trials by ourselves and others.

Five trials in Alzheimer’s patients and five trials in normal human adults demonstrated improved memory following intranasal insulin treatment.

Charles F. Mahl MD FACS FICS
Intranasal Insulin

- A single intranasal insulin treatment acutely improved verbal memory for adults with Alzheimer’s disease within 15 minutes at doses that did not alter blood levels of insulin or glucose.1

- Intranasal insulin (20 IU bid) for 21 days enhanced delayed recall (memory) compared to placebo (p = .03) and significantly improved attention (p = .01) and functional status (p = .04).

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Insulin

- Insulin can provide energy needed to prevent brain degeneration and replace worn out parts of brain cells.
- Insulin increases Insulin Degrading Enzyme, the enzyme that degrades beta amyloid, and reduces GSK3beta that phosphorylates tau to form Alzheimer’s tangles.
- Insulin maintains synaptic density.
- If humans are given intranasal insulin at the first sign of a deficiency of insulin in the brain, it may be able to delay or prevent the onset and progression of the disease.
Quercetin

- Quercetin decreased beta amyloid, tauopathy, astrogliosis and microgliosis in the brain.
- Quercetin improved performance on learning and spatial memory tasks.
- Quercetin reverses the pathology of Alzheimer’s disease and protects cognitive and emotional function in this aged triple transgenic mouse model of Alzheimer’s disease.

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Sabogal Guaqueta et al. Neuropharmacology

- Free brain iron, elevated in Alzheimer’s disease and other brain disorders, generates free radicals that inactivate the memory receptor.
- Iron removal from cells is enhanced by deferoxamine.
- Quercetin penetrates cell membranes via glucose transport.

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Intranasal Stem Cells for Pain?

- Pain Center of the brain: the parietal lobe is involved in interpreting pain and touch, the dorsal posterior insula seems to be specific to the “actual” hurt level of pain itself.

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Charles F Mahl MD FACS
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Dorsal Posterior Insula
Amplified Musculoskeletal Pain Syndrome (AMPS)

- Amplified musculoskeletal pain syndrome (AMPS) is a very painful medical condition that can cause pain anywhere in the body. These episodes of pain can be intermittent or constant, can affect the whole body or be localized to one area of the body or affect just a limb. Whenever it occurs, the degree of pain children or adults with AMPS experience is more intense than one would normally expect.

Charles F Mahl MD FACS FICS
Forms of Amplified Pain

- Diffuse amplified pain – also called total body pain or pediatric fibromyalgia
- Intermittent amplified pain
- Complex regional pain syndrome (CRPS) with autonomic changes
- Localized amplified pain without autonomic changes (autonomic changes include color and temperature changes - for example, cold and blue - as well as swelling and sweating
The Future

- Intranasal stem cell technology doesn't cause any inflammation or infection of brain tissue, or precipitate any autoimmune response. Even so, the right cocktail of stem cells and anti-inflammatory or antibiotics could mean the next generation of neuro-treatments could be administered as easily as over-the-counter nasal decongestants.

Charles F Mahl MD FACS FICS
Intranasal Therapies

• Basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF) infusion enhances injury-induced cell proliferation in the dentate gyrus (DG) and improves cognitive function in rats following fluid percussive injury (Sun, 2014).

• Other studies have found that infusion of VEGF can also enhance neurogenesis in the hippocampus and improve the functional recovery of animals following TBI (Kleindienst et al, 2005; Lee and Agoston, 2010; Thau-Zuchman et al, 2010 cited from Sun, 2014).
Intranasal Stem Cells

- Peripheral blood derived pluripotent stem cells that are released from the bone marrow are used.
- Plasma contains hundreds of thousands of these cells per ml in peripheral blood depending on age.
Totipotent Stem Cells

- TSCs are delivered intranasal (1-2 microns)
- Not PSCs or MSCs