

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

William H. Frey II

Center for Memory & Aging (Alzheimer's Research Center), Regions Hospital, 640 Jackson St., St. Paul, MN 55101, Department of Pharmaceutics, Neurology and Neuroscience, University of Minnesota.

Together with my collaborators in Germany, especially Lusine Danielyan M.D., we discovered and patented (1) that therapeutic cells, including adult stem cells and genetically-engineered cells, can be non-invasively delivered to the CNS using the noninvasive intranasal delivery method that I developed (2). The first of our scientific papers on this new discovery describes this successful method of delivery and proprietary formulations that enhance delivery (3). The second of our papers describes the successful treatment of Parkinson's disease in an animal model with intranasal adult bone marrow derived mesenchymal stem cells (4).

Intranasal stem cells bypass the blood-brain barrier 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 (4). Researchers at University Medical Center Utrecht in the Netherlands have demonstrated the effectiveness of intranasal stem cell treatment technology in an animal model of neonatal cerebral ischemia (5) and also in animals with neonatal brain damage (6) and subarachnoid hemorrhage (6a).

Researchers at Emory University have used our intranasal stem cell treatment successfully in an animal model of stroke (7), and researchers at 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 an EAE model of multiple sclerosis leading to reduced disease symptoms (8). Intranasal adult neural stem cells have also been shown to improve the EAE model of MS (9) as have intranasal mesenchymal stromal cells (10).

Other researchers have reported that intranasal stem cells target and treat brain tumors (11, 12). This intranasal delivery, targeting and treatment technology can make stem cell treatments practical for CNS disorders by eliminating the need for invasive neurosurgical implantation of cells and by eliminating the need for intravenous delivery that disperses cells throughout the body resulting in unwanted systemic exposure. This delivery and treatment method can facilitate the development of stem cell and genetically-engineered cell therapies for Parkinson's, PSP, Huntington's, Alzheimer's, MS, epilepsy, stroke, neonatal ischemia, brain tumors, traumatic brain injury (TBI), spinal cord (SCI) injury, etc.

In humans, GnRH neurons or Gonadotropin-releasing hormone expressing neurons are known to reach the brain by using this same olfactory neural pathway during development. In addition, pathologic cells, such as the amoeba *Naegleria fowleri*, are known to enter the brains of humans by this same pathway and cause amoebic infection of the brain. We have discovered how to use this pathway to deliver therapeutic cells, including stem cells, to the brain to treat disorders of the central nervous system. This intranasal therapeutic cell delivery, targeting and treatment technology is available for licensing.

References:

1. Frey, Danielyan and Gleiter (2012). Methods, pharmaceutical

- compositions and articles of manufacture for administering therapeutic cells to the animal central nervous system. U.S. Patent 8283160 B2 filed 2009 and issued October 9, 2012.
2. Frey, W.H. 2nd (1997). Method of administering neurologic agents to the brain. US Patent 5,624,898 filed 1989 and issued April 29, 1997.
3. Danielyan, L., et al., Intranasal delivery of cells to the brain. *Eur J Cell Biol*, 2009. 88(6): p. 315-24.
4. Danielyan, L., et al., Therapeutic efficacy of intranasally delivered mesenchymal stem cells in a rat model of Parkinson disease. *Rejuvenation Res*, 2011. 14(1): p. 3-16.
5. van Velthoven, C. et al. Nasal administration of stem cells: a promising novel route to treat neonatal ischemic brain damage. *Pediatr Res* 2010. 68(5): p. 419-422.
6. Donega, V., et al., The endogenous regenerative capacity of the damaged newborn brain: boosting neurogenesis with mesenchymal stem cell treatment. *J Cereb Blood Flow Metab*, 2013. 33(5): p. 625-34.
- 6a. Kooijman, E., et al., Intranasal Mesenchymal stem cell transplantation restores brain damage, improves sensori-motor function and reverses depressive-like behavior in a model of subarachnoid hemorrhage in rats. *Brain, Behavior, and Immunity*. 2013, 32 (Supplement):e38.
7. Wei N., et al. Delayed intranasal delivery of hypoxic-preconditioned bone marrow mesenchymal stem cells enhanced cell homing and therapeutic benefits after ischemic stroke in mice. *Cell Transplantation*, 2013. 22(6) p. 977-991.
8. Fransson M., et al. CAR/FoxP3-engineered T regulatory cells target the CNS and suppress EAE upon intranasal delivery. *J Neuroinflammation*, 2012. 9:112.
9. Wu, S., et al., Intranasal Delivery of Neural Stem Cells: A CNS-specific, Non-invasive Cell-based Therapy for Experimental Autoimmune Encephalomyelitis. *J Clin Cell Immunol*, 2013. 4:310.
10. Fransson, M., et al., Intranasal delivery of central nervous system-retargeted human mesenchymal stromal cells prolongs treatment efficacy of Immunology, 2014. 142: p. 431-441.;
11. Reitz, M., et al. Intranasal delivery of neural stem/progenitor cells: A noninvasive passage to target intracerebral glioma. *Stem Cells Trans Med*, 2012. 1(12): p. 866-73.
12. Balyasnikova, I., et al., Intranasal Delivery of Mesenchymal Stem Cells Significantly Extends Survival of Irradiated Mice with Experimental Brain Tumors. *Molecular Therapy: the Journal of the American Society of Gene Therapy* 2014 22(1):140-8.

Corresponding Author: William H. Frey II, Ph.D.
Center for Memory & Aging (Alzheimer's Research Center)
Regions Hospital, 640 Jackson St., St. Paul, MN 55101
Professor of Pharmaceutics, Neurology and Neuroscience
University of Minnesota. alzheimr@umn.edu.
Cell phone: 651-261-1998
© 2015 by the Journal of Nature and Science (JNSCI).