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# Commentary

## Neurorestoratology: A Concept and Emerging Discipline in the Treatment of Neurological Disorders

"*Logic will get you from A to B. Imagination will take you everywhere*".
Albert Einstein

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Restoration of neurological function as a consequence of disease or traumatic insult is one of the major challenges facing neuroscience today. In its broadest terms, we refer to strategies for achieving this goal as Neurorestoratology. As a discipline, Neurorestoratology has evolved from early practice to formal theory and finally a discipline.

Efforts to explore neurorestorative methods have necessarily explored also potential restorative mechanisms, including neurostimulation, neuromodulation, neuroprotection, neuroregeneration, neurorepair, neuroreplacement, and neuroplasticity - among others. However, due to limitations in understanding and/or interest in a given specialty, most investigators have generally focused on their own particular research area(s) or a single neurorestorative mechanism.

Our research group carried out the first study 15 years ago in which olfactory ensheathing cells (OECs) were used to treat patients with chronic complete spinal cord injury. The findings were unexpectedly surprising: not only we observed recovery of some CNS neurological functions, but also improvement in patient's quality of life several days after cell therapy [1-3]. These results attracted much attention from the international scientific community [4, 5] and encouraged us to propose and actively promote the discipline of Neurorestoratology, together with its theories and comprehensive neurorestorative therapies [6-9]. Its development has gone through five steps, which we should like to outline in this commentary.

### 1. Proposing and Creation of the CNS Neurorestoratology Theory

The ability to restore loss of neurological function in patients with chronic complete spinal cord injury remains a point of controversy in medical circles [10-12]. Initial reported findings met, perhaps not surprisingly, with a good dose of skepticism among basic and clinical investigators in the neurological sciences. Such resistance may have its foundations in the long-held basic concept that CNS damage and chronic neurodegenerative disease sequelae cannot be restored or regenerated [10, 13]. We believe that this core concept is not immutable, as emerging studies now indicate. In the beginning we also had doubts whether the reported observations of functional recovery were merely the result of chance, or rather an actual consequence from cell therapy. Not until over 100 patients had undergone OEC therapy with a positive outcome, and based on these clinical results, we did propose the theory of CNS neurorestoratology.

### 2. Neurorestoration as a Mechanism for Neural Function and Structural Recovery

Prior to our findings with OEC therapy we also supported the mainstream view of the neuroscience community that neurological functional recovery was through neuroregeneration. The appearance of functional recovery after several days of OEC transplantation in patients with chronic complete spinal cord injury could not be due to neuroregeneration. Rather, we propose that secretion or release of factors after OEC therapy may change the microenvironment of the injury area and induce stimulating or protective mechanisms in surviving (but functionally 'dormant') neurons [1-3, 8, 14]. In this sense, the mechanism for restoring neural structure and function should be neurorestoration, which includes neuroregenerative processes, and is broader in scope. Neurorestorative mechanisms include also neurostimulation or neuromodulation, neuroprotection, neuroplasticity, neuroreplacement, loop reconstruction, remyelination, immunoregulation, angiogenesis, and others [8]. The ability of this concept to

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bring about a gradual change in the research direction of neuroscience and medicine should evolve, we believe, into the creation of Neurorestoratology as a discipline.

### 3. Neurorestoratology as a Discipline

Historically, mainstream thought has held that the sequelae of CNS damage or the consequences of late-stage chronic neurodegenerative diseases were not therapeutically amenable, although this view has been continually challenged [7]. A variety of approaches have been tried in the attempt to open the door for neural functional and structure recovery, by means of stimulation or modulation of electromagnetic or chemical factors, neural tissue or cell transplantation, biological engineering and tissue engineering, neurotrophic factors or drugs, interventional surgery, nerve bridging or other strategies [7, 15]. Even though viewed as sub-disciplines (e.g., restorative neurology, restorative neurosurgery, restorative neuroscience, neural transplantation and repair), their ultimate goal is neurorestoration. At that time, however, there was no common platform for the exchange of information between basic scientists and clinicians related to neurorestoration. With this in mind we first proposed the concept of Neurorestoratology as a discipline in its own right [16, 17]. Working closely with leading worldwide experts, the International Association of Neurorestoratology (IANR) was founded in late 2007. In 2009, the IANR released the "Beijing Declaration of IANR", which formally gave definition to Neurorestoratology, and laid out its purpose and range of treatments, and therapeutic methods [18]. This Declaration, revised in 2015, clearly states that "functional recovery is possible after CNS injury and neurodegeneration"; and that "cell therapies may become a key clinical therapeutic option for acute, subacute, and/or chronic CNS disease or damage" [19]. Our team, together with Chinese investigators began publishing a book "***CNS Neurorestoratology***" in 2009 in Chinese [20], and formulated "standard recommendations for the application of Chinese clinical cell therapy for neurorestoration" in 2012 [21]. Working with an international team of experts "Neurorestoratology" debuted in English in 2015 [22]. In addition, the IANR in 2013 launched its official journal "***Journal of Neurorestoratology***". Collectively these efforts provide a platform for recognition of the discipline of Neurorestoratology.

### 4. Cell-Based Clinical Comprehensive Neurorestorative Therapies

Our initial positive clinical results with OEC therapy have been confirmed in a number of laboratories worldwide related to cell therapy using OECs, as well as neural stem/progenitor cells, Schwann cells, mononuclear cells, and stromal cells to treat CNS damage and diseases [23-28]. In addition to cell therapy, electromagnetic or chemical factor stimulation or modulation, bioengineering and tissue engineering, neurotrophic factors or drugs, or bridging nerve grafting surgery have also been reported to yield positive results for Alzheimer disease [29], traumatic brain injury [30], stroke [31], multiple sclerosis [32], Parkinson's disease [33], and amyotrophic lateral sclerosis/motor neuron disease [34]. Our studies and those of other teams found that integrated or combined treatment was more effective than using only one method [35] or cell type [36]. As such, we propose that cell-based comprehensive neurorestorative therapies should be a guiding basic principle in treatment. This principle is the fourth step underlying Neurorestoratology, namely, that existing findings point to future therapeutic directions.

### 5. Improving the Framework Underlying Neurorestoratology

In order to maintain the integrity of neural structure and function when faced with insult or damage from within or without, nature has endowed us with the capability to react through various neurorestorative mechanisms. These neurorestorative mechanisms may differ depending on the injury, and work also through multiple mechanisms. Clearly, there will be a delicate balance between the insult and neurorestorative mechanism(s) as a function of each one's strength. Undoubtedly there will be instances where the body's self-restoring mechanism(s) cannot compete with the insult/injury, leading to a pathological state [8] (Fig. **1A**). At this point a neurorestorative intervention is appropriate to enhance endogenous neurorestorative capacities, and halt and/or reverse loss or damage of neural function/structure (Fig. **1B**) which would otherwise progress (Fig. **1C**).

Based on these principles, we propose the theory of an integrated neurorestorative process that melds interaction between neural insults and restorative mechanisms [8]. Further, this theory leads to what may be described as an inherent law of neurorestoration, that is, "while a degree of self-restoration always occurs by nature in the face of insults, appropriate medical intervention serves to optimize restoration of functions and/or structures" [8]. The above concept, we believe, has much improved the theoretical system of the discipline of Neurorestoratology.

### 6. Perspective

Neurorestoratology should be viewed today an important discipline across preclinical and clinical neuroscience which, we hope, will serve as a common platform to promote greater interactions between basic scientists and physicians. This discipline can serve as 'clearing house' to encourage the collection of new knowledge relating to neurorestoration; to probe into new neurorestorative mechanisms; to explore the most effective neurorestorative therapies. Now those cell-based neurorestorative therapies are beginning to yield benefit to patients. The ultimate goal of Neurorestoratology is, of course, the pursuit of optimizing benefit to patients with neurological disorders or injury such as dementia, stroke, Parkinson's disease, motor neuron disease, neurotrauma, and cerebral palsy, among others. Today we are seeking regions hitherto well unexplored. Let us seize it, not in fear, but in gladness.

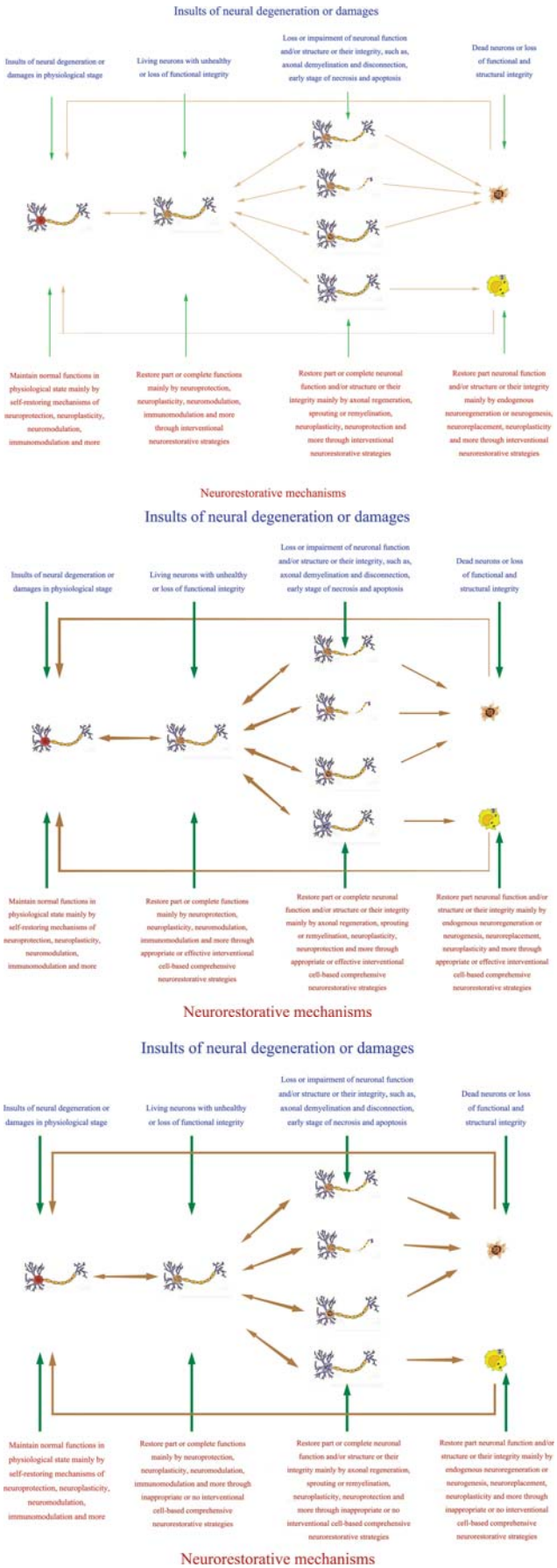


**Fig. (1).** The dynamic relationship between insults and neurorestorative mechanisms.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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## REFERENCES

[1] Huang H, Wang H, Xiu B, *et al.* Preliminary report of clinical trial for olfactory ensheathing cell transplantation treating the spinal cord injury. J Naval General Hospital 2002; 15: 18-21.
[2] Huang H. Basic and clinical research of olfactory ensheathing cell transplantation for spinal cord injury. Chin J Clin Rehabil 2002; 6: 2027-9.
[3] Huang H, Chen L, Wang H, *et al.* Influence of patients' age on functional recovery after transplantation of olfactory ensheathing cells into injured spinal cord injury. Chin Med J 2003; 116: 1488-91.
[4] Cyranoski D. Fetal-cell therapy: paper chase. Nature 2005; 437: 80-1.
[5] Watts J. Controversy in China. Lancet 2005; 365: 109-10.
[6] Huang H, Sharma H. Neurorestoratology: One of the most promising new disciplines at the forefront of neuroscience and medicine. J Neurorestoratol 2013; 1: 37-41.
[7] Huang H, Chen L, Sanberg PR. Developmental history of neurorestoratology. J Neurorestoratol 2015; 3: 31-8.
[8] Huang H, Chen L. Neurorestorative process, law, and mechanisms. J Neurorestoratol 2015; 3: 23-30.
[9] Huang H, Mao G, Chen L, Liu A. Progress and challenges with clinical cell therapy in neurorestoratology. J Neurorestoratol 2015; 3: 91-5.
[10] Anderberg L, Aldskogius H, Holtz A. Spinal cord injury – scientific challenges for the unknown future. Ups J Med Sci 2007; 112: 259-88.
[11] Tator CH. Review of treatment trials in human spinal cord injury: issues, difficulties, and recommendations. Neurosurgery 2006; 59: 957-82.
[12] Mothe AJ, Tator CH. Advances in stem cell therapy for spinal cord injury. J Clin Invest 2012; 122: 3824-34.
[13] Cajal SRY. Degeneration and regeneration of the nervous system. London: Oxford University Press; 1928.
[14] Huang H, Chen L, Sanberg PR. Cell therapy from bench to bedside translation in CNS Neurorestoratology era. Cell Med 2010; 1: 15-46.
[15] Huang H, Chen L, Sanberg PR. Clinical achievements, obstacles, falsehoods, and future directions of cell–based neurorestoratology. Cell Transplant 2012; 21(S1): S3-11.
[16] Huang H, Chen L. Neurorestoratology-new subject, new principle, new field in 21st century. Chin. J Repar Reconstr Surg 2008; 22: 439-45.
[17] Chen L, Huang H. Neurorestoratology: new concept and bridge from bench to bedside. Chin J Repar Reconstr Surg 2009; 23: 366-70.
[18] IANR (International Association of Neurorestoratology). Beijing declaration of international association of neurorestoratology (IANR). Cell Transplant 2009; 18: 487.
[19] Young W, AlZoubi ZM, Saberi H, *et al.* Beijing Declaration of International Association of Neurorestoratology. J Neurorestoratol 2015; 3: 121-2.
[20] Huang H. CNS Neurorestoratology. Beijing, Science Press, 2009.
[21] Chinese Branch of the International Association of Neurorestoratology; Preparatory Committee of Chinese Association of Neurorestoratology. Standard recommendation for theapplication of Chinese clinical cell therapy for neurorestoration. Cell Transplant 2013; 22(S1): S5-10.
[22] Huang H, Raisman G, Sanberg PR, Sharma H, Chen L. Neurorestoratology. New York, Nova Biomedical, 2015.
[23] Huang H, Mao G, Chen L, Liu A. Progress and challenges with clinical cell therapy in neurorestoratology. J Neurorestoratol 2015; 3: 91-5.
[24] Sharma A, Gokulchandran N, Sane H, *et al.* Detailed analysis of the clinical effects of cell therapy for thoracolumbar spinal cord injury: an original study. J Neurorestoratology 2013; 1: 13-22.
[25] Gong D, Yu H, Wang W, Yang H, Han F. Human umbilical cord blood mononuclear cell transplantation for delayed encephalopathy after carbon monoxide intoxication. J Neurorestoratol 2013; 1: 23-9.
[26] Sych N, Klunnik M, Ivankova O, *et al.* Efficacy of fetal stem cells in Duchenne muscular dystrophy therapy. J Neurorestoratology 2014; 2: 37-46.
[27] Tsolaki M, Zygouris S, Tsoutsikas V, Anestakis D, Koliakos G. Treatment with adipose stem cells in a patient with moderate Alzheimer's disease: case report. J Neurorestoratol 2015; 3: 115-20.
[28] Huang H, Sun T, Chen L, *et al.* Consensus of clinical neurorestorative progress in patients with complete chronic spinal cord injury. Cell Transplant 2014; 23(Suppl 1): S5-17.
[29] Qiao L, Huang H, Muresanu DF. Clinical neurorestorative progress in Alzheimer's disease. J Neurorestoratol 2015; 3: 1-9.
[30] Huang H, Chen L, Huang H. Clinical neurorestorative progress in traumatic brain injury. J Neurorestoratol 2015; 3: 57-62.
[31] Qiao L, Lu J, Huang H. Clinical neurorestorative progress in stroke. J Neurorestoratol 2015; 3; 63-71.
[32] Geng TC, Mark VW. Clinical neurorestorative progress in multiple sclerosis. J Neurorestoratol 2015; 3: 83-90.
[33] Chen L, Huang H, Duan WM, Mao GS. Clinical neurorestorative progress in Parkinson's disease. J Neurorestoratol 2015; 3: 101-7.
[34] Chen L, Huang H, Xi H, Mao G. Clinical neurorestorative progress in amyotrophic lateral sclerosis. J Neurorestoratol 2015; 3: 109-14.
[35] Moviglia GA, Moviglia-Brandolino MT. Varela GS, *et al.* Feasibility, safety, and preliminary proof of principles of autologous neural stem cell treatment combined with T-cell vaccination for ALS patients. Cell Transplant 2012; 21(Suppl 1): S57-63.
[36] Huang H, Xi H, Chen L, Zhang F, Liu Y. Long-term outcome of olfactory ensheathing cell therapy for patients with complete chronic spinal cord injury. Cell Transplant 2012; 21(Suppl 1): S23-31.

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