# FORMULATING CURES WITH FRAGMENTS OF LIFE

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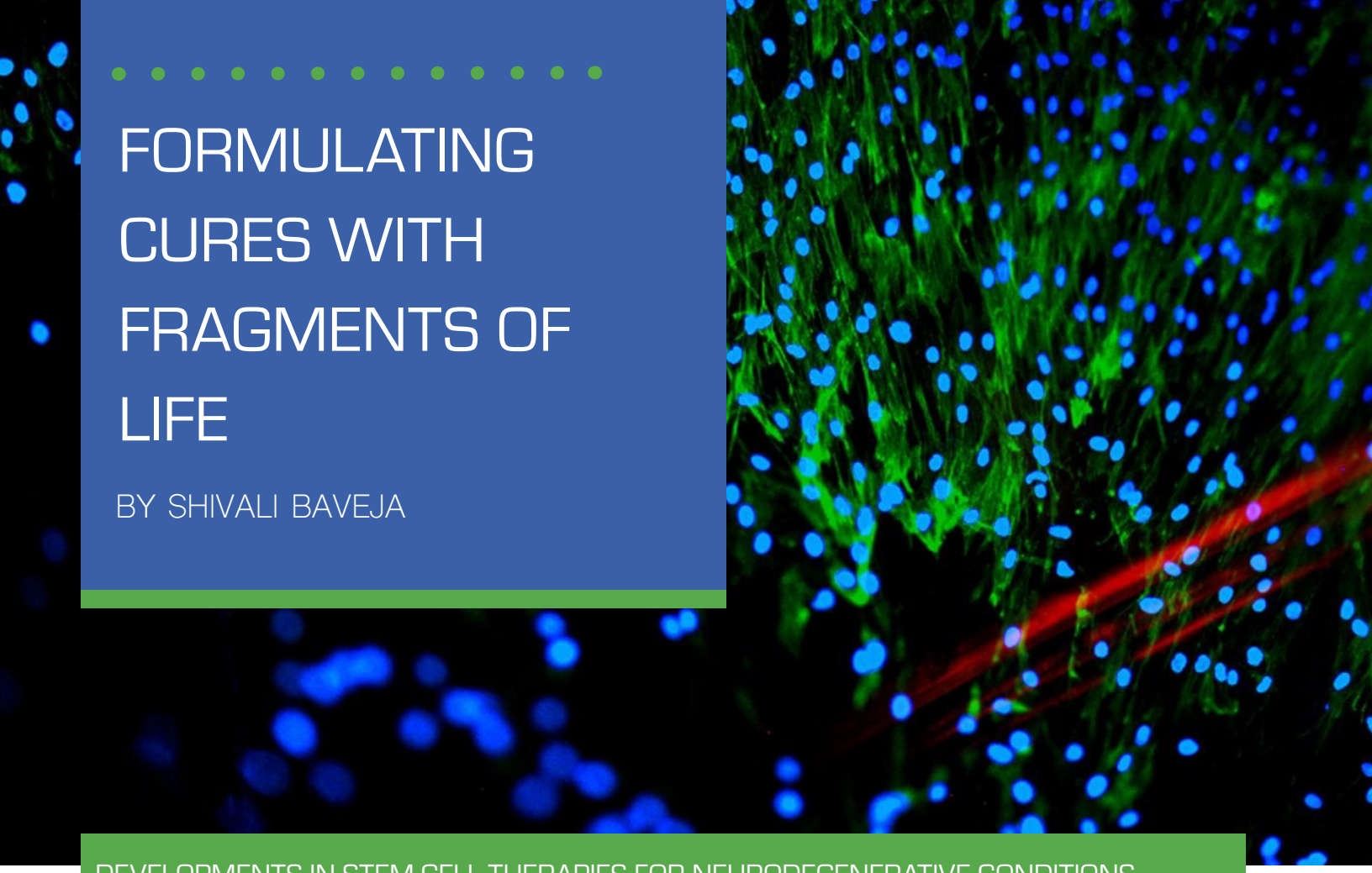

## DEVELOPMENTS IN STEM CELL THERAPIES FOR NEURODEGENERATIVE CONDITIONS

Most know the famed stem cell, a simple yet immensely powerful unit of life, via the rather bombastic rhetoric in the media today. Stem cells are highly promising as a means to regenerate tissue—perhaps even entire organs—and the quest to effectively manipulate them remains further underway than often meets the eye. As our body of knowledge surrounding these cells slowly grows, we progressively develop our ability to utilize stem cells in improving the state of disease. Just as a tool's properties must be understood before it can be used, researchers are only now beginning to develop promising stem cell therapies in order to combat a vast array of conditions.

One of the many areas in which stem cells show promise is neurodegenerative conditions, a class of diseases that affect the proper functioning of neurons in the brain. Over time, neurons degenerate and become unable to effectively pass messages, leading to problems in cognition, memory, and movement of the patient. As the disease progressively worsens, neurodegenerative conditions can impair the most basic functions of survival and lead to death.[1]

As investigation continues, manipulation of stem cells through the process of differentiation may allow for treatment of neurodegenerative conditions. Diseases for which stem cell therapies are being currently designed include Parkinson's Disease (PD), Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS). These three diseases each affect the neurons in the brain in distinctly different ways. PD affects a subtype of neurons in the midbrain called dopaminergic neurons, whose breakdown results in a lack of motor control and coordination.[2] HD is similar to Parkinson's in that it affects motor control, but Huntington's affects the basal ganglia in the brain and thus causes cognitive problems as well.[3] ALS is another condition causing gradual degradation of motor functioning and is eventually fatal, leading to the shutdown of crucial bodily systems.[4]

BY DEFINITION, STEM CELL THERAPIES ARE A MEANS OF UTILIZING STEM CELLS TO ALLEVIATE SYMPTOMS OF A CONDITION.

Currently, these therapies exist in two categories; namely, endogenous therapies which use a patient's own cells, and transplantation therapies which construct tissues with other cells. Through use of these strategies, stem cell therapies may allow for neuronal replacement as a means of counteracting neurodegenerative conditions.[5]

In endogenous stem cell therapy, stem cells within one's own body are manipulated and directed to areas of damage within the brain. Since endogenous stem cells do not exist in large populations, it may be worth investigating anti-apoptotic genes which inhibit stem cell death. By prolonging the life spans of these cells, researchers are given the advantage of being able to experiment on and influence cell development

for longer periods of time. Understanding these genes may allow researchers to prevent cell death and generate more efficient endogenous stem cell therapies.[5] Another area of exploration is induced pluripotent stem cells (iPSCs), adult cells which have been converted back into an undifferentiated state. The process of differentiation is what causes a stem cell to develop into a particular cellular subtype which then retains a specific function. By understanding how cells transition between differentiated and undifferentiated states, more types of endogenous stem cell populations can be developed for use in therapies.[6]

ON THE OTHER HAND, TRANSPLANTATION STEM CELL THERAPIES DIFFERENTIATE EXTERNAL STEM CELLS AND DEVELOP THEM INTO TISSUES MADE TO MATCH THE RECIPIENT.

Thus far, research has been done on transplantation of various types of stem cells, including mesenchymal and neural stem cells (MSCs and NSCs respectively). MSC have been seen to be very effective at shielding themselves from the immune system, thus decreasing chances of the host rejecting them once transplanted. In fact, studies using fetal MSCs in models for HD saw a decrease in the rate of the condition's development and onset.[7] In trials like these, the transplanted stem cells increased the rate of growth and thus the rate of recovery of damaged neurons. Further research on NSCs has shown similar improvements. When tested in mice, transplanted NSCs resulted in reduced symptoms of Sandhoff Disease, a disease similar to ALS in its effects on motor neurons. Continued trials have shown improvement in symptoms for PD patients with NSC transplantations as well.[8]

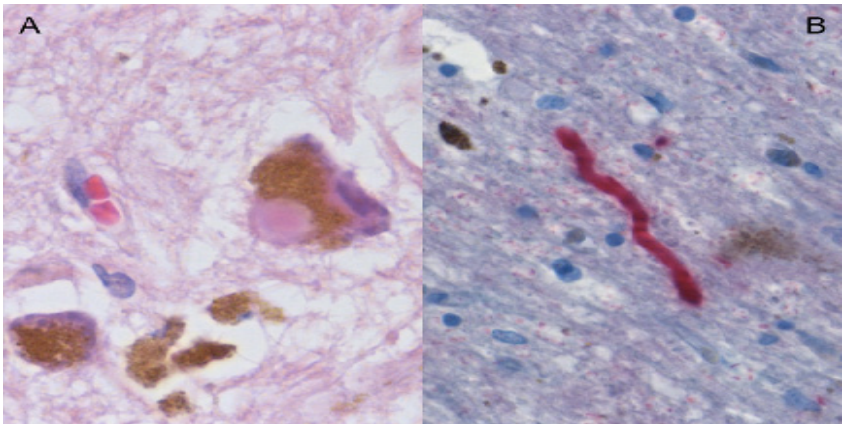


Figure 1: Lewy Bodies (a) and Lewy Neurites (b) are indicators of neurodegeneration particularly as seen in Parkinson's Disease.[16]

Despite the small-scale successes of transplantation therapies, running clinical trials for them has proven to be difficult. Ethical concerns surrounding the source of stem cells are often difficult to overcome for potential participants in stem cells therapies. Increasing awareness about stem cell research—the vast majority of which does not involve embryonic stem cells at all—would greatly increase the feasibility of clinical trials.

Scientists have broken down the areas in which growth is necessary for stem cell trials to develop. First, within animal models, there is a need for greater proof of the potential of integrating stem cells into the larger neuronal system. Second, a means to expand the lifespan of transplanted stem cells would also be greatly beneficial in tissue testing and development. Third, for application to trials, further analysis of how different patients are affected by individual therapies would allow for more personalized trials to be run.[10]

BEYOND THE GENERIC AREAS OF DEVELOPMENT, THERE IS SCOPE TO EXPERIMENT WITH DIFFERENT TYPES OF STEM CELLS.

As bone marrow-derived stem cells continue to be explored, other types of cells being investigated include endothelial and neural stem cells. Amniotic fluid stem cells have also been seen to be very promising, although the procedure of amniocentesis necessary to harvest the cells can be rather risky. Finding means to extract these cells may also be an avenue to explore further.[11]

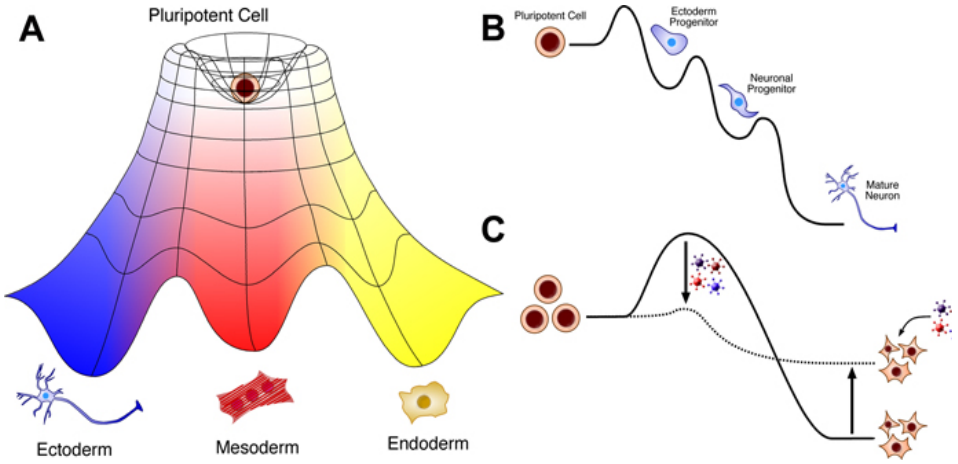


Figure 2: (a) Pluripotent stem cells can differentiate into one of three larger categories of which the ectoderm includes neuronal subtypes. (b) There exist several distinct progenitor states for cells as they differentiate from their initial pluripotent states to neurons.[17]

## "Researchers are also growing cells in 3D structures to better mimic the actual bodily conditions, allowing development of transplantation and endogenous therapies."

As researchers work with these cells, tools for differentiating them are being created and discovered. Genetic manipulation is one way this can be accomplished, as RNA sequencing for singular cells currently allows us to control neuronal development. This technique allows us to observe and manipulate the biological makeup of a cell through gene transcription, a process which indirectly determines a cell's identity and behavior. One gene being targeted via RNA sequencing is WNT7A, a gene controlling progenitor cell replication, which if successfully modified would allow us to build frameworks for cell implantation.[12] Physical tools can also be used to construct structures for cells. An example of this is a cellular bio-bridge, which is being used to guide the development and migration of endogenous stem cells.[13] Researchers are also growing cells in 3D structures to better mimic the actual bodily conditions, allowing development of transplantation and endogenous therapies.[14]

Developments in stem cell therapy are burgeoning as different types of cells and tools emerge from the accumulating body of research. The use of both transplantation and endogenous therapies provide paths to bettering the lives of those facing neurodegenerative conditions. Although we continue to learn more about the stem cell, there is ever more left to explore in order to develop effective therapies such that these fragments of life can better our lives.

## REFERENCES


1. "What Is Neurodegenerative Disease." JPND, www.neurodegenerationresearch.eu/about/what/.
2. "Parkinson's Disease." Mayo Clinic, Mayo Foundation for Medical Education and Research, 7 July 2015, www.mayoclinic.org/diseases-conditions/parkinsons-disease/basics/definition/con-20028488.
3. "Huntington's Disease." Mayo Clinic, Mayo Foundation for Medical Education and Research, 13 June 2017, www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20356117.
4. "Amyotrophic Lateral Sclerosis." Mayo Clinic, Mayo Foundation for Medical Education and Research, 12 May 2017, www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022.
5. Kishk, N., & Abokrysh, N. (2011). Stem Cell in Neurological Disorders. Stem Cells in Clinic and Research. doi:10.5772/21408
6. Lindvall, O., & Kokaia, Z. (2010). Stem cells in human neurodegenerative disorders — time for clinical translation? Journal of Clinical Investigation, 120(1), 29-40. doi:10.1172/jci40543.
7. Scuteri, A. (2012). Treatment of Neurodegenerative Pathologies Using Undifferentiated Mesenchymal Stem Cells. Stem Cells and Cancer Stem Cells, Volume 6, 185-195. doi:10.1007/978-94-007-2993-3_16.
8. Lee, J., Jeyakumar, M., Gonzalez, R., Takahashi, H., Lee, P., Baek, R. C., . . . Snyder, E. Y. (2007). Stem cells act through multiple mechanisms to benefit mice with neurodegenerative metabolic disease. Nature Medicine,13(4), 439-447. doi:10.1038/nm1548.
9. Aked, J., Delavaran, H., Lindval, O., Norrving, B., Kokaia, Z., & Lindgern, A. (2017). Attitudes to Stem Cell Therapy Among Ischemic Stroke Survivors in the Lund Stroke Recovery Study. Stem Cells and Development, 26(8). doi:10.1089/scd.2016.0343.
10. Lindvall, O., Kokaia, Z., & Martinez-Serrano, A. (2004). Stem cell therapy for human neurodegenerative disorders–how to make it work. Nature Medicine, 10(7). doi:10.1038/nm1064.
11. Corey, S., Ghanekar, S., Sokol, J., Zhang, J., & Borlongan, C. (2017). An update on stem cell therapy for neurological disorders: cell death pathways as therapeutic targets. Chinese Neurological Journal, 3(4). doi:10.1186/s41016-016-0071-2.
12. Toledo, E. M., Gyllborg, D., & Arenas, E. (2017). Translation of WNT developmental programs into stem cell replacement strategies for the treatment of Parkinsons disease. British Journal of Pharmacology. doi:10.1111/bph.13871
13. Napoli, E., & Borlongan, C. V. (2017). Cell Therapy in Parkinsons Disease: Host Brain Repair Machinery Gets a Boost From Stem Cell Grafts. Stem Cells, 35(6), 1443-1445. doi:10.1002/stem.2636.
14. Correia, C., Koshkin, A., Duarte, P., Carido, M., Lima, P., Teixeira, A., . . . Serra, M. (2017). Novel Strategies for Generation and Hypothermic Storage of the Human Pluripotent Stem Cell-Derived Cariomyocytes for Cell Therapy Applications. Cytotherapy,19(5). http://dx.doi.org/10.1016/j.jcyt.2017.03.040ylene terephthalate) Science 1196-11.


## IMAGE SOURCES


15. https://www.flickr.com/photos/cambridgeuniversity-engineering/14310429488/in/photostream/.
16. By Werner CJ., Heyny-von Haussen R., Mall G., Wolf S. - Werner CJ., Heyny-von Haussen R., Mall G., Wolf S. Proteome analysis of human substantia nigra in Parkinson's disease.. Proteome Sci. 6, 8. 2008. doi:10.1186/1477-5956-6-8. PMID 18275612., CC BY 2.0, https://commons.wikimedia.org/w/index.php?curid=3946973.
17. By Rodolfa, K.T., Inducing pluripotency (September 30, 2008), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.22.1.