Hayley Antczak

Final Project Rough Draft

7 August 2020

**The Efficacy of Human Induced Pluripotent Stem Cells (hiPSCs) in Modeling Neurodegenerative Diseases: A Qualitative Review**

**Abstract**

Debilitating millions worldwide, neurodegenerative diseases are among the most prevalent and difficult-to-study conditions. Thorough, accurate modeling of neurodegenerative diseases in-vitro can provide valuable insight related to disease pathophysiology and drug discovery. For decades, animal models and immortalized cell lines have been well-established tools in modeling of neurodegenerative diseases. However, limitations involving ethical dilemmas and disparities in characteristics among animal cells, immortalized cell lines, and human neurons have barred the scientific community from preciseness in the modeling and treating of neurodegenerative diseases. With the induction of human induced pluripotent stem cells (hiPSCs) by Nobel Prize winner Shinya Yamanaka in 2006 came a promising tool that bypassed these limitations, the first ever man-made stem cell. This review will examine the efficacy of human induced pluripotent stem cells in modeling and intervention development for Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS).

**Introduction**

Human induced pluripotent stem cells are a fairly new yet promising contribution to medicine that can help bypass many ethical and biological dilemmas. The discovery and induction of induced pluripotent stem cells by Shinya Yamanaka in 2006 prompted major advancements in regenerative medicine, disease modeling, and drug discovery. For the first time, somatic cells could be reprogrammed back to a pluripotent state, similar to that of human embryonic stem cells, and then differentiated back into specialized cells. Yamanaka accomplished this feat via the transforming factors protein Oct3/4, transcription factor Sox2, transcription factor Klf4, and gene c-Myc. These four “Yamanaka factors” are highly prevalent in human embryonic stem cells, and when applied to human somatic cells, they reprogram them to possess the highly sought-after characteristic of pluripotency (Takahashi & Yamanaka, 2006).

Human induced pluripotent stem cells are especially useful in modeling rare diseases, polygenic diseases such as Alzheimer’s, Parkinson’s, and ALS, and diseases of difficult-to-obtain tissues, such as neurons (Wang et al., 2013). Because neurons are difficult to obtain and can’t survive for long periods of time in-vitro, induced pluripotent stem cells have proven to be a novel, unlimited source for modeling neurodegenerative diseases. Human induced pluripotent stem cells have already contributed to the creation of novel drug therapies, as well as the confirmation of disease mechanisms and pathophysiology, enhancing our understanding of neurodegenerative diseases and their origins. (Ko & Gelb, 2014). If human induced pluripotent stem cells yield successful results in clinical applications, it is possible that they will become the new “gold standard” for disease modeling and drug development, as they bypass many of the microbiological and ethical issues that plague scientists. This study was developed based on the research question: What is the efficacy of human induced pluripotent stem cells in modeling and developing intervention for neurodegenerative diseases? The purpose of this research paper is to provide a comprehensive review of the literature and data surrounding human induced pluripotent stem cell neurodegenerative disease modeling and drug discovery.

**Methods**

These studies were gathered by using the Brown University Library and Google Scholar to search for meta-analyses and studies related to induced pluripotent stem cell neurodegenerative disease modeling using the keywords and phrases, “induced pluripotent stem cell neurodegenerative disease modeling,” “neurodegenerative disease modeling,” “induced pluripotent stem cell uses and limitations,” “medical advancements as a result of iPSCs,” and “stem cell disease modeling.” The search results yielded information concerning newfound disease mechanisms and drug therapies as a result of induced pluripotent stem cell disease modeling, as well as the benefits and limitations of the technique. The following data were selected based on the criteria that the induced pluripotent stem cells were derived from humans, not animal models; that the research was peer-reviewed and/or backed by a reputable institution or publisher; and that the neurodegenerative diseases modeled were limited to Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis for the sake of conciseness. The sources were organized according to which of the three selected neurodegenerative disease they focused on. No obvious discrepancies or unexpected trends were found when scanning and cleaning the data. No literature or values within the data were dismissed for being disreputable or missing. However, it should be noted that due to authors’ and publishers’ tendencies not to report or publish unsuccessful or ambiguous results, it is possible that not all information on this topic was able to be collected due to these biases. Taking a qualitative analytical approach, the efficacy of induced pluripotent stem cell neurodegenerative disease modeling in this study is based on the following variables: whether the disease mechanism was found, and whether a personalized intervention or drug therapy was developed for patients following the hiPSC modeling. The data that contributed to this study were selected on the assumptions that no other modeling techniques and/or interventions were involved and that the efficacy of the modeling had nothing to do with failures or mistakes in the initial engineering of the induced pluripotent stem cells. These assumptions were checked by reviewing all of the documents for information related to the aforementioned abnormalities. Searching and screening for these criterion yielded twelve studies that met them, four of which concerned Alzheimer’s disease, four of which that concerned amyotrophic lateral sclerosis, and four of which that concerned Parkinson’s disease.

**Results**

**Alzheimer’s Disease**

|  |  |  |
| --- | --- | --- |
| **Methodology of Study** | **Study Results** | **Reference** |
| This study was designed to observe the pathophysiological differences between amyloid-beta oligomer accumulation in patients with sporadic Alzheimer’s patients and familial Alzheimer’s patients using human induced pluripotent stem cells. | Patients suffering from familial Alzheimer’s had a far-larger presence of amyloid-beta oligomer build-up than patients suffering from sporadic Alzheimer’s disease. Familial Alzheimer’s patients presented an abundance of the amyloid precursor protein, the gene that provides instruction for amyloid-beta oligomer production, while only one sporadic Alzheimer’s patient showed these pathophysiological markers. | (Israel et al., 2012) |
| This study was designed to test the efficacy of the drug therapy docosahexaenoic acid (DHA) in relieving stress on the endoplasmic reticulum due to amyloid-beta oligomer accumulation in neurons. The drug was tested on human induced pluripotent stem cells that had been differentiated into an Alzheimer’s-diseased neurons. | Docosahexaenoic acid (DHA) proved to be therapeutic in relieving stress on the endoplasmic reticulum due to amyloid-oligomer accumulation and is recommended to continue into more clinical testing. | (Kondo et al., 2013) |
| This study was designed to observe the efficacy of sulindac sulfide in treating the symptoms of Alzheimer’s disease by inhibiting amyloid-beta oligomer production and build-up. The drug was tested by being applied to human induced pluripotent stem cells that had been differentiated into Alzheimer’s- diseased neurons. | Sulindac sulfide proved to be an effective intervention in preventing amyloid-beta oligomer accumulation and has been recommended for further clinical study and testing. | (Kondo et al., 2013) |
| The purpose of this study was to test the effectiveness of dual antiplatelet therapy (DAPT) on early-onset Alzheimer’s in adults with Down syndrome. Dual antiplatelet therapy was applied to human induced pluripotent stem cells that were reprogrammed into Alzheimer’s-diseased neurons. | Dual antiplatelet therapy proved to be a novel therapeutic source for managing symptoms of early-onset Alzheimer’s in adults with Down syndrome. The therapy has been recommended for further study because of its initial success in this trial. | (Shi et al., 2012) |

**Parkinson’s disease**

**Methodology Results Resource**

|  |  |  |
| --- | --- | --- |
| This study was intended to model the late stages of Parkinson’s diseases using human induced pluripotent stem cells that had been reprogrammed back into neurons. | This study yielded information regarding the limitations of induced pluripotent stem cell neurodegenerative disease modeling. Because of the thorough reprogramming process that somatic cells have to go through before induction into a stem cell-like state, they exhibit epigenetic changes. This means that at some point during the reprogramming process, genes of the Parkinson’s disease patients’ somatic cells were changed or lost along the way. Because of this, it is difficult to study age-related and progressive disorders, as the induced pluripotent stem cells have been reprogrammed. | (Kim, 2014) |
| The purpose of this study was to search for unknown pathophysiological mechanisms of Parkinson’s disease using human induced pluripotent stem cells that had been reprogrammed back into neurons. | Modeling Parkinson’s disease with induced pluripotent stem cells showed a neurotoxic ratio of alpha-synuclein tetramers to monomers. It is still unknown as to what specific mechanism causes this dangerous ratio/ | (Dettmer et al., 2015) |
| The purpose of this study was to identify pathophysiological components of Parkinson’s disease by modeling it via human induced pluripotent stem cells that had been reprogrammed into cortical neurons. | The human induced pluripotent stem cell cortical neurons exhibited cell atrophy. Upon closer observation, this was found to be due to swelling and stress on the neurons’ mitochondrion, furthering the understanding of how cell stress and death occur in Parkinson’s disease. | (Ludtmann et al., 2018) |
| This study was intended to explore the role of the LRRK2 mutation and its suspected role in Parkinson’s disease. Human induced pluripotent stem cells were reprogrammed into neural stem cells with the LRRK2 mutation. | When applied to induced pluripotent stem cell neurons, the LRRK2 mutation resulted in cell atrophy similar to that of Parkinson’s disease, insinuating that LRRK2 is a component of the disease’s pathophysiology as many neuroscientists suspected. Furthermore, researchers were able to genetically modify and correct the LRRK2 gene in human induced pluripotent stem cells, which inhibited Parkinsonian cell death. | (Reinhardt et al., 2013) |

**Amyotrophic Lateral Sclerosis (ALS)**

|  |  |  |
| --- | --- | --- |
| **Methodology** | **Results** | **Reference** |
| This study was designed to observe the role that the SOD1 gene is suspected to play in ALS. It achieved this by observing the microbiology of human induced pluripotent stem cells that were differentiated into motor neurons. | The results of this study revealed that the SOD1 gene caused stress and swelling in the induced pluripotent stem cell motor neurons’ endoplasmic reticulums and mitochondrion. This revealed the physiology behind how the SOD1 gene causes neurodegeneration. | (Kiskinis et al., 2014) |
| This study was designed to prove that the SOD1 gene is a cause of ALS. The study involved induced pluripotent stem cells that had been reprogrammed into non-motor neuron cells and induced pluripotent stem cells that had been reprogrammed into motor neurons. | The reprogrammed non-motor neuron cells showed no sign of the SOD1 gene. However, the motor neuron cells contained the SOD1 gene. This proves that the SOD1 gene is specifically a neurodegenerative mechanism. | **(**Chen et al., 2014) |
| This study was designed to test the efficacy of the drug kenpaullone in blocking the SOD1 gene and its effects. Kenpaullone was tested on induced pluripotent stem cells that had been reprogrammed into motor neurons with ALS. | Kenpaullone proved to be an effective novel therapy for inhibiting the SOD1 gene and its neurotoxic effects. It has been recommended for further clinical study. | (Yang et al., 2013) |
| This study was designed to test the efficacy of the anacardic acid in inhibiting the debilitating effects of certain mutations linked to ALS. Anacardic acid was tested on induced pluripotent stem cells that had been reprogrammed into motor neurons with ALS. | Anacardic acid proved to inhibit neurotoxic effects as a result of ALS-linked mutations. It has been recommended for further study beyond in-vitro modeling. | (Egawa et al., 2012) |

**Conclusion, Limitations, and Opportunities**

Although fairly new to medicine, human induced pluripotent stem cells are an already-successful and promising tool for modeling neurodegenerative diseases. However, the time-consuming and costly stem cell induction process, coupled with epigenetic changes as a result of the somatic cell being reprogrammed, remain obstacles that regenerative medicine researchers are working to overcome. Induced pluripotent stem cells’ versatility, unlimited supply, opportunity for patient-specific intervention and modeling, presents the opportunity to make great strides in neurodegenerative disease pathophysiology and treatment. Seen by many as the future of regenerative medicine, these highly sought-after characteristics open up countless opportunities for induced pluripotent stem cell use in neuroscience, including using them in the development of three-dimensional organoids, which can further-advance our knowledge of neurodegenerative diseases and their pathophysiological mechanisms.

**References**

Chen, H., Qian, K., Du, Z., Cao, J., Petersen, A., Liu, H., Blackbourn, L. W., Huang, C.-L., Errigo, A., Yin, Y., Lu, J., Ayala, M., & Zhang, S.-C. (2014). Modeling ALS with iPSCs Reveals that Mutant SOD1 Misregulates Neurofilament Balance in Motor Neurons. *Cell Stem Cell*, *14*(6), 796–809. https://doi.org/10.1016/j.stem.2014.02.004

Dettmer, U., Newman, A. J., Soldner, F., Luth, E. S., Kim, N. C., von Saucken, V. E., Sanderson, J. B., Jaenisch, R., Bartels, T., & Selkoe, D. (2015). Parkinson-causing α-synuclein missense mutations shift native tetramers to monomers as a mechanism for disease initiation. *Nature Communications*, *6*. https://doi.org/10.1038/ncomms8314

Egawa, N., Kitaoka, S., Tsukita, K., Naitoh, M., Takahashi, K., Yamamoto, T., Adachi, F., Kondo, T., Okita, K., Asaka, I., Aoi, T., Watanabe, A., Yamada, Y., Morizane, A., Takahashi, J., Ayaki, T., Ito, H., Yoshikawa, K., Yamawaki, S., … Inoue, H. (2012). Drug screening for ALS using patient-specific induced pluripotent stem cells. *Science Translational Medicine*, *4*(145), 145ra104. https://doi.org/10.1126/scitranslmed.3004052

Kim, C. (2014). Disease modeling and cell based therapy with iPSC: Future therapeutic option with fast and safe application. *Blood Research*, *49*(1), 7–14. https://doi.org/10.5045/br.2014.49.1.7

Kiskinis, E., Sandoe, J., Williams, L. A., Boulting, G. L., Moccia, R., Wainger, B. J., Han, S., Peng, T., Thams, S., Mikkilineni, S., Mellin, C., Merkle, F. T., Davis-Dusenbery, B. N., Ziller, M., Oakley, D., Ichida, J., Dicostanza, S., Atwater, N., Maeder, M. L., … Eggan, K. (2014). Pathways Disrupted in Human ALS Motor Neurons Identified Through Genetic Correction of Mutant SOD1. *Cell Stem Cell*, *14*(6), 781–795. https://doi.org/10.1016/j.stem.2014.03.004

Ko, H. C., & Gelb, B. D. (2014). Concise Review: Drug Discovery in the Age of the Induced Pluripotent Stem Cell. *Stem Cells Translational Medicine*, *3*(4), 500–509. https://doi.org/10.5966/sctm.2013-0162

Kondo, T., Asai, M., Tsukita, K., Kutoku, Y., Ohsawa, Y., Sunada, Y., Imamura, K., Egawa, N., Yahata, N., Okita, K., Takahashi, K., Asaka, I., Aoi, T., Watanabe, A., Watanabe, K., Kadoya, C., Nakano, R., Watanabe, D., Maruyama, K., … Inoue, H. (2013). Modeling Alzheimer’s disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. *Cell Stem Cell*, *12*(4), 487–496. https://doi.org/10.1016/j.stem.2013.01.009

Ludtmann, M. H. R., Angelova, P. R., Horrocks, M. H., Choi, M. L., Rodrigues, M., Baev, A. Y., Berezhnov, A. V., Yao, Z., Little, D., Banushi, B., Al-Menhali, A. S., Ranasinghe, R. T., Whiten, D. R., Yapom, R., Dolt, K. S., Devine, M. J., Gissen, P., Kunath, T., Jaganjac, M., … Gandhi, S. (2018). α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson’s disease. *Nature Communications*, *9*(1), 2293. https://doi.org/10.1038/s41467-018-04422-2

*Probing sporadic and familial Alzheimer’s disease using induced pluripotent stem cells*. (n.d.). Retrieved August 12, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3338985/

Reinhardt, P., Schmid, B., Burbulla, L. F., Schöndorf, D. C., Wagner, L., Glatza, M., Höing, S., Hargus, G., Heck, S. A., Dhingra, A., Wu, G., Müller, S., Brockmann, K., Kluba, T., Maisel, M., Krüger, R., Berg, D., Tsytsyura, Y., Thiel, C. S., … Sterneckert, J. (2013). Genetic Correction of a LRRK2 Mutation in Human iPSCs Links Parkinsonian Neurodegeneration to ERK-Dependent Changes in Gene Expression. *Cell Stem Cell*, *12*(3), 354–367. https://doi.org/10.1016/j.stem.2013.01.008

Takahashi, K., & Yamanaka, S. (2006). Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, *126*(4), 663–676. https://doi.org/10.1016/j.cell.2006.07.024

Yang, Y. M., Gupta, S. K., Kim, K. J., Powers, B. E., Cerqueira, A., Wainger, B. J., Ngo, H. D., Rosowski, K. A., Schein, P. A., Ackeifi, C. A., Arvanites, A. C., Davidow, L. S., Woolf, C. J., & Rubin, L. L. (2013). A Small Molecule Screen in Stem Cell-derived Motor Neurons Identifies a Kinase Inhibitor as a Candidate Therapeutic for ALS. *Cell Stem Cell*, *12*(6), 713–726. https://doi.org/10.1016/j.stem.2013.04.003

Amin, Nashwa, Xiaoning Tan, Qiannan Ren, Ning Zhu, Benson O. A. Botchway, Zhiying Hu, and Marong Fang. “Recent Advances of Induced Pluripotent Stem Cells Application in Neurodegenerative Diseases.” *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 95 (December 20, 2019): 109674. https://doi.org/10.1016/j.pnpbp.2019.109674.

Cao, Lei, Lan Tan, Teng Jiang, Xi-Chen Zhu, and Jin-Tai Yu. “Induced Pluripotent Stem Cells for Disease Modeling and Drug Discovery in Neurodegenerative Diseases.” *Molecular Neurobiology* 52, no. 1 (August 2015): 244–55. https://doi.org/10.1007/s12035-014-8867-6.

Doss, Michael Xavier, and Agapios Sachinidis. “Current Challenges of IPSC-Based Disease Modeling and Therapeutic Implications.” *Cells* 8, no. 5 (April 30, 2019). https://doi.org/10.3390/cells8050403.

Ebert, Antje D., Ping Liang, and Joseph C. Wu. “Induced Pluripotent Stem Cells as a Disease Modeling and Drug Screening Platform.” *Journal of Cardiovascular Pharmacology* 60, no. 4 (October 2012): 408–16. https://doi.org/10.1097/FJC.0b013e318247f642.

Garcia-Leon, Juan Antonio, Javier Vitorica, and Antonia Gutierrez. “Use of Human Pluripotent Stem Cell-Derived Cells for Neurodegenerative Disease Modeling and Drug Screening Platform.” *Future Medicinal Chemistry* 11, no. 11 (June 1, 2019): 1305–22. https://doi.org/10.4155/fmc-2018-0520.

Jung, Yong Wook, Eriona Hysolli, Kun-Yong Kim, Yoshiaki Tanaka, and In-Hyun Park. “Human Induced Pluripotent Stem Cells and Neurodegenerative Disease: Prospects for Novel Therapies.” *Current Opinion in Neurology* 25, no. 2 (April 2012): 125–30. https://doi.org/10.1097/WCO.0b013e3283518226.

Kim, Changsung. “Disease Modeling and Cell Based Therapy with IPSC: Future Therapeutic Option with Fast and Safe Application.” *Blood Research* 49, no. 1 (March 1, 2014): 7–14. https://doi.org/10.5045/br.2014.49.1.7.

———. “IPSC Technology-Powerful Hand for Disease Modeling and Therapeutic Screen.” *BMB Reports* 48, no. 5 (May 2015): 256–65. https://doi.org/10.5483/BMBRep.2015.48.5.100.

Ko, Huaising C., and Bruce D. Gelb. “Concise Review: Drug Discovery in the Age of the Induced Pluripotent Stem Cell.” *Stem Cells Translational Medicine* 3, no. 4 (April 2014): 500–509. https://doi.org/10.5966/sctm.2013-0162.

Mohamet, Lisa, Natalie J Miazga, and Christopher M Ward. “Familial Alzheimer’s Disease Modelling Using Induced Pluripotent Stem Cell Technology.” *World Journal of Stem Cells* 6, no. 2 (April 26, 2014): 239–47. https://doi.org/10.4252/wjsc.v6.i2.239.

Orack, Joshua C., Michela Deleidi, David Pitt, Kedar Mahajan, Jacqueline A. Nicholas, Aaron L. Boster, Michael K. Racke, Manuel Comabella, Fumihiro Watanabe, and Jaime Imitola. “Concise Review: Modeling Multiple Sclerosis With Stem Cell Biological Platforms: Toward Functional Validation of Cellular and Molecular Phenotypes in Inflammation-Induced Neurodegeneration.” *Stem Cells Translational Medicine* 4, no. 3 (March 2015): 252–60. https://doi.org/10.5966/sctm.2014-0133.

Reinhardt, Peter, Benjamin Schmid, Lena F. Burbulla, David C. Schöndorf, Lydia Wagner, Michael Glatza, Susanne Höing, et al. “Genetic Correction of a LRRK2 Mutation in Human IPSCs Links Parkinsonian Neurodegeneration to ERK-Dependent Changes in Gene Expression.” *Cell Stem Cell* 12, no. 3 (March 7, 2013): 354–67. https://doi.org/10.1016/j.stem.2013.01.008.

Schlachetzki, Johannes C. M., Soraya Wilke Saliba, Antonio Carlos Pinheiro de Oliveira, Johannes C. M. Schlachetzki, Soraya Wilke Saliba, and Antonio Carlos Pinheiro de Oliveira. “Studying Neurodegenerative Diseases in Culture Models.” *Brazilian Journal of Psychiatry* 35 (2013): S92–100. https://doi.org/10.1590/1516-4446-Amin, Nashwa, Xiaoning Tan, Qiannan Ren, Ning Zhu, Benson O. A. Botchway, Zhiying Hu, and Marong Fang. “Recent Advances of Induced Pluripotent Stem Cells Application in Neurodegenerative Diseases.” *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 95 (December 20, 2019): 109674. https://doi.org/10.1016/j.pnpbp.2019.109674.

Cao, Lei, Lan Tan, Teng Jiang, Xi-Chen Zhu, and Jin-Tai Yu. “Induced Pluripotent Stem Cells for Disease Modeling and Drug Discovery in Neurodegenerative Diseases.” *Molecular Neurobiology* 52, no. 1 (August 2015): 244–55. https://doi.org/10.1007/s12035-014-8867-6.

Doss, Michael Xavier, and Agapios Sachinidis. “Current Challenges of IPSC-Based Disease Modeling and Therapeutic Implications.” *Cells* 8, no. 5 (April 30, 2019). https://doi.org/10.3390/cells8050403.

Ebert, Antje D., Ping Liang, and Joseph C. Wu. “Induced Pluripotent Stem Cells as a Disease Modeling and Drug Screening Platform.” *Journal of Cardiovascular Pharmacology* 60, no. 4 (October 2012): 408–16. https://doi.org/10.1097/FJC.0b013e318247f642.

Garcia-Leon, Juan Antonio, Javier Vitorica, and Antonia Gutierrez. “Use of Human Pluripotent Stem Cell-Derived Cells for Neurodegenerative Disease Modeling and Drug Screening Platform.” *Future Medicinal Chemistry* 11, no. 11 (June 1, 2019): 1305–22. https://doi.org/10.4155/fmc-2018-0520.

Jung, Yong Wook, Eriona Hysolli, Kun-Yong Kim, Yoshiaki Tanaka, and In-Hyun Park. “Human Induced Pluripotent Stem Cells and Neurodegenerative Disease: Prospects for Novel Therapies.” *Current Opinion in Neurology* 25, no. 2 (April 2012): 125–30. https://doi.org/10.1097/WCO.0b013e3283518226.

Kim, Changsung. “Disease Modeling and Cell Based Therapy with IPSC: Future Therapeutic Option with Fast and Safe Application.” *Blood Research* 49, no. 1 (March 1, 2014): 7–14. https://doi.org/10.5045/br.2014.49.1.7.

“IPSC Technology-Powerful Hand for Disease Modeling and Therapeutic Screen.” *BMB Reports* 48, no. 5 (May 2015): 256–65. https://doi.org/10.5483/BMBRep.2015.48.5.100.

Ko, Huaising C., and Bruce D. Gelb. “Concise Review: Drug Discovery in the Age of the Induced Pluripotent Stem Cell.” *Stem Cells Translational Medicine* 3, no. 4 (April 2014): 500–509. https://doi.org/10.5966/sctm.2013-0162.

Mohamet, Lisa, Natalie J Miazga, and Christopher M Ward. “Familial Alzheimer’s Disease Modelling Using Induced Pluripotent Stem Cell Technology.” *World Journal of Stem Cells* 6, no. 2 (April 26, 2014): 239–47. https://doi.org/10.4252/wjsc.v6.i2.239.

Orack, Joshua C., Michela Deleidi, David Pitt, Kedar Mahajan, Jacqueline A. Nicholas, Aaron L. Boster, Michael K. Racke, Manuel Comabella, Fumihiro Watanabe, and Jaime Imitola. “Concise Review: Modeling Multiple Sclerosis With Stem Cell Biological Platforms: Toward Functional Validation of Cellular and Molecular Phenotypes in Inflammation-Induced Neurodegeneration.” *Stem Cells Translational Medicine* 4, no. 3 (March 2015): 252–60. https://doi.org/10.5966/sctm.2014-0133.

Reinhardt, Peter, Benjamin Schmid, Lena F. Burbulla, David C. Schöndorf, Lydia Wagner, Michael Glatza, Susanne Höing, et al. “Genetic Correction of a LRRK2 Mutation in Human IPSCs Links Parkinsonian Neurodegeneration to ERK-Dependent Changes in Gene Expression.” *Cell Stem Cell* 12, no. 3 (March 7, 2013): 354–67. https://doi.org/10.1016/j.stem.2013.01.008.

Schlachetzki, Johannes C. M., Soraya Wilke Saliba, Antonio Carlos Pinheiro de Oliveira, Johannes C. M. Schlachetzki, Soraya Wilke Saliba, and Antonio Carlos Pinheiro de Oliveira. “Studying Neurodegenerative Diseases in Culture Models.” *Brazilian Journal of Psychiatry* 35 (2013): S92–100. https://doi.org/10.1590/1516-4446-2013-1159.

Slanzi, Anna, Giulia Iannoto, Barbara Rossi, Elena Zenaro, and Gabriela Constantin. “In Vitro Models of Neurodegenerative Diseases.” *Frontiers in Cell and Developmental Biology* 8 (May 13, 2020). https://doi.org/10.3389/fcell.2020.00328.

Wang, Hansen, and Laurie Doering. “Induced Pluripotent Stem Cells to Model and Treat Neurogenetic Disorders.” *Neural Plasticity* 2012 (July 19, 2012): 346053. https://doi.org/10.1155/2012/346053.

Wu, Yi-Ying, Feng-Lan Chiu, Chan-Shien Yeh, and Hung-Chih Kuo. “Opportunities and Challenges for the Use of Induced Pluripotent Stem Cells in Modelling Neurodegenerative Disease.” *Open Biology* 9, no. 1 (January 9, 2019). https://doi.org/10.1098/rsob.180177.