



## Alzheimer's Disease: A Special Collection

STUART P. ATKINSON

Stuart P. Atkinson, M.D.

Centro de Investigación Príncipe Felipe, Valencia, Spain

September 26, 2017.

A special collection of articles on Alzheimer's disease (AD), previously published in **STEM CELLS** and **STEM CELLS Translational Medicine**, comes hot on the heels of new figures from the Centers for Disease Control and Prevention that indicate that the death rate from AD in the United States is slowly creeping up. The rise from 29 to 31 deaths per 100,000 people this past year will translate to thousands more deaths and vast amounts of additional health care costs with each passing year [1]. Furthermore, it is likely that statistics from other countries around the world will also display this same unfortunate trend.

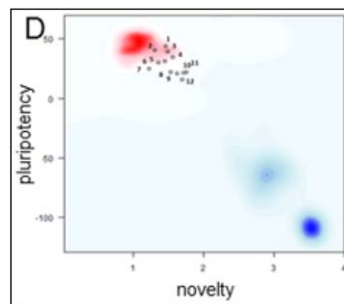
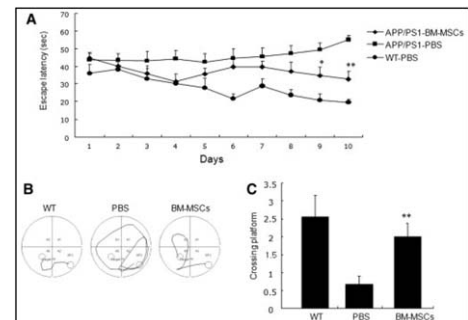
However, as can be appreciated by the sheer number of high-quality studies, stem cell therapy may represent an important treatment option for AD and other dementia-related diseases and disorders. **STEM CELLS** and **STEM CELLS Translational Medicine** have held a long interest in potential stem cell therapies for AD, and we hope that you enjoy reading the excellent collection of 11 well-cited recent articles that encompass the breadth of research performed by stem cell scientists in the field.

We thank all of the authors for their commitment to their research and the Journals and look forward to publishing new research on furthering this progress.

### FEATURED ARTICLES

#### BM-MSC Rescues Memory Deficits in AD Mice

Research from the group of Hee Kyung Jin and Jaesung Bae at Kyungpook National University, South Korea, demonstrates that bone marrow-derived mesenchymal stem cell (BM-MSC) treatment may represent an exciting new therapy for AD [2]. Amyloid- $\beta$  peptide ( $A\beta$ ) plaques and the formation of neurofibrillary tangles characterize AD; however, Lee et al. discovered that intracerebral transplantation of BM-MSCs into AD model mice reduces  $A\beta$  deposition, modulates immune/inflammatory responses, ameliorates pathophysiology, and improves associated cognitive decline.



#### C9orf72 Neurons Recapitulate Features of ALS/FTD

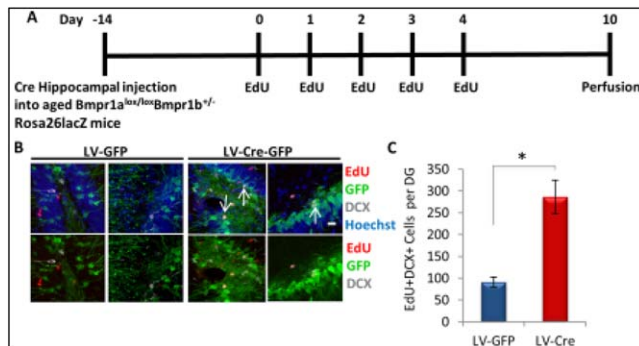
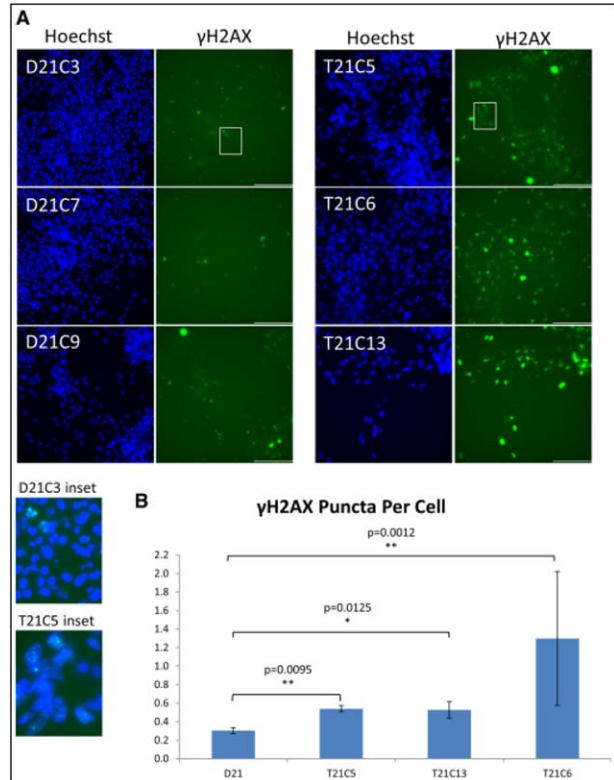
Researchers working for Kevin Talbot (John Radcliffe Hospital, Oxford, UK) and Sally A. Cowley (University of Oxford, UK) sought to understand just how alterations to the *C9orf72* gene lead to the development of two common neurodegenerative diseases (frontotemporal dementia and amyotrophic lateral sclerosis). To do this, Dafinca et al. created induced pluripotent stem cells (iPSCs) from patient samples and differentiated them into motor neurons and cortical neurons finding multiple interesting disease-specific alterations and providing potential pharmacological targets for the treatment of neurodegenerative diseases related to AD [3].

<http://dx.doi.org/10.1002/sctm.12217>

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

### Isogenic iPSC Model of Mosaic Down Syndrome

Induced pluripotent stem cells (iPSCs) generation also plays a role in a study from Dean Nizetic (Nanyang Technological University, Singapore) and Jurgen Groet (The Blizard Institute, Barts & The London School of Medicine, UK) concentrating on Down syndrome, the most common genetic cause of dementia and intellectual disability [4]. Murray et al. created and neuronally differentiated non-integration-reprogrammed isogenic human iPSCs in the hope of modeling mechanisms of developmental, accelerated ageing, and neurodegenerative pathologies.

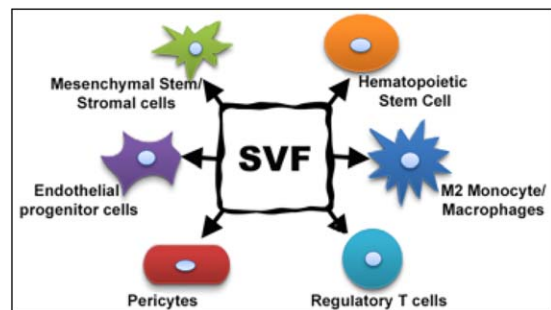


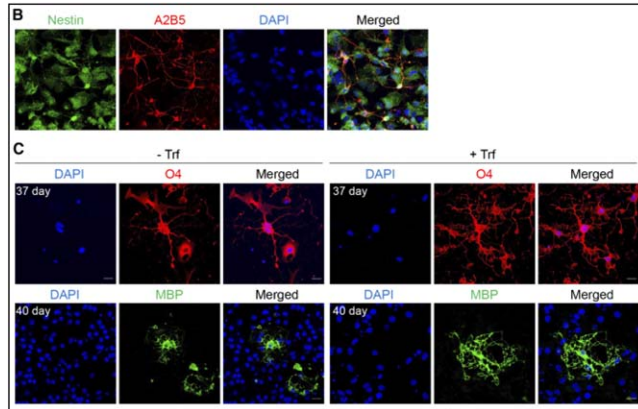
### Increased BMP Signaling Inhibits Neurogenesis with Aging

A decline in hippocampal neurogenesis, mediated by resident neural stem cell proliferation and differentiation, may contribute to age-related decline in cognitive function and dementia, and a team from the group of David V. Schaffer (University of California Berkeley, USA) sought to tease apart why this decline transpires [5]. Yousef et al. suggest that increased BMP signaling may be behind reduced neural stem cell proliferation in mice, and more interestingly, the team discovered that the in vivo attenuation of BMP signaling increases neurogenesis in old mouse hippocampi. The authors note that this may serve as the starting point for a treatment for age-related cognitive decline.

### Regenerative Potential of Adipose-Derived SVF

Treatment with the stem-cell enriched stromal vascular fraction of human adipose tissue has garnered attention as a regenerative therapy, given its ability to secrete paracrine factors that accelerate endogenous repair, the ease of accessibility, and the lack of identified major adverse effects. The therapeutic potential of these cells includes the treatment of neurodegenerative diseases such as AD. A review article from the laboratory of Daniel J. Kota (Sanford Research, South Dakota, USA) provides an overview of the current knowledge driving this phenomenon and its regulatory issues and existing studies and proposes potential unmapped applications [6].



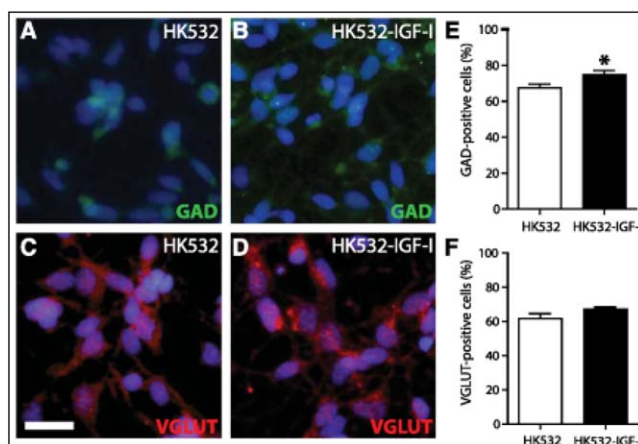
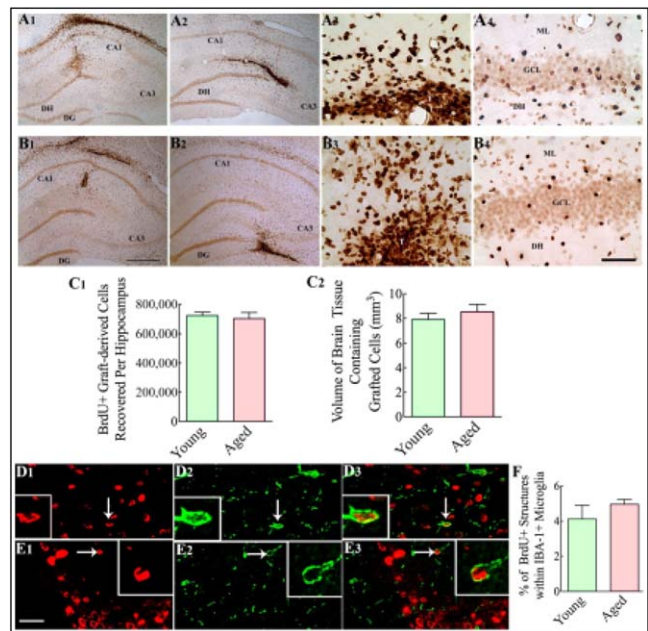


### Effects of Protein-iPSCs on AD Pathogenesis

Cha et al. report that treatment with iPSCs generated via the exposure of mouse skin fibroblasts to protein extracts of embryonic stem cells may also represent a relevant therapeutic option for AD [7]. In this study, from Inhee Mook-Jung and Hyo-Soo Kim (Seoul National University Hospital, Republic of Korea), the authors demonstrate that iPSCs transplanted into a mouse AD model differentiate into glial cells, reduce plaque depositions, and mitigate observed cognitive dysfunction.

### Neural Stem Cell Grafts and Aged Hippocampus

Research from Ashok K. Shetty and Hattiangady Bharathi (Texas A&M Health Science Center College of Medicine, Temple, Texas, USA) assessed the capability of neural stem cells (NSCs) to graft and survive in the aged hippocampus as a possible means to treat neurodegenerative disorders. They discovered that both young and aged hippocampi permitted NSC engraftment, migration, and differentiation and that NSCs established new neurogenic niches. This research suggests that the hippocampi of elderly patients are receptive to NSCs transplants, so providing encouragement for the demographic most likely to suffer from neurodegenerative disorders [8].

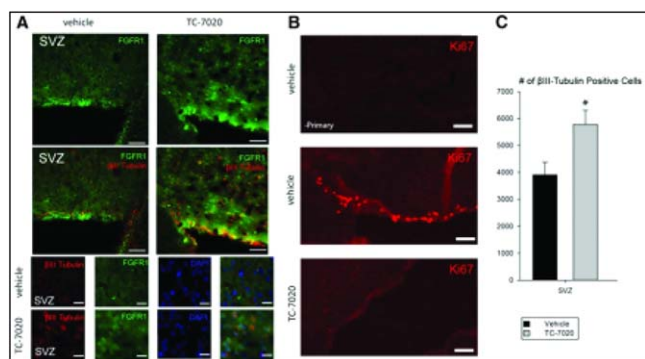
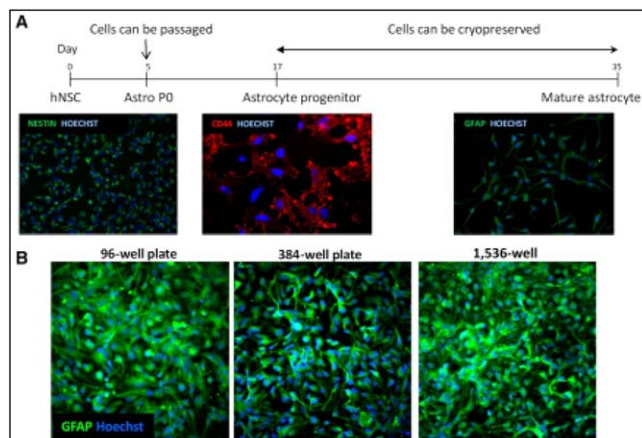


### Neural Stem Cells and Induced IGF-I Expression

Previous studies from Eva L. Feldman (University of Michigan, Ann Arbor, Michigan, USA) had demonstrated the potential for NSCs for the treatment of the neurodegenerative disease ALS. As a means to extend this strategy to treat AD, McGinley et al. modified NSCs to overexpress insulin-like growth factor-I (IGF-I) to promote neurogenesis and synaptogenesis in vivo [9]. Interestingly, this study suggests that IGF-I promotes differentiation of NSCs to the neuronal cell types dysregulated in AD and enhances neuroprotection and so may represent a disease-modifying intervention for AD.

## Phenotypic Screening of Human Astrocytes

Astrocyte dysfunction has been implicated in the pathogenesis of many neurodegenerative diseases, including Alzheimer's disease, and so glia represent an attractive new target for drug discovery. Researchers from the laboratories of Natasha Thorn and Zheng Wei (National Institutes of Health, Bethesda, Maryland, USA) differentiated embryonic stem cells (ESCs) into vast amounts of astrocytes for drug screening purposes. Thorne et al. identified 22 compounds that support cytoprotection of astrocytes in a large-scale high-throughput screen, so demonstrating the relevancy and utility of employing astrocytes differentiated from ESCs as a disease model for drug discovery and development [10].



## Activation of Neurogenesis by Nicotinic Agonist

The reactivation of neurogenesis by endogenous neural progenitor and stem cells (NSPCs) in the brain and spinal cord may represent an alternative strategy to combat neurodegenerative disorders. Research from the laboratory of Michal K. Stachowiak (State University of New York at Buffalo, USA) indicates that targeting the  $\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7$ nAChRs) activates integrative nuclear fibroblast growth factor receptor 1 (FGFR1) signaling and promotes the differentiation of NSPCs of the subventricular zone (SVZ) into new neurons. Narla et al. suggest that targeting  $\alpha 7$ nAChR may offer a new strategy to treat brain injuries, neurodegenerative diseases, and neurodevelopmental diseases [11].

## Defeating Dementia through Research

Alzheimer's Research U.K. has focused on defeating dementia through research for over 20 years, and in this final manuscript, Dr. Eric Karran, the director of research for the charity, shares the organization's accomplishments to date and future goals [12].

The Alzheimer's disease virtual issue is available online at [www.Alzheimers.StemCellsJournals.com](http://www.Alzheimers.StemCellsJournals.com)

## REFERENCES

- Thielking M. Morning Rounds Tuesday, August 8, 2017: Alzheimer's deaths are creeping up in number. Available at <http://us11.campaign-archive2.com/?u=f8609630ae206654824f897b6&id=6711a0ccd0>. Accessed August 22, 2017.
- Lee JK, Jin HK, Endo S et al. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. *STEM CELLS* 2010;28:329–343.
- Dafinca R, Scaber J, Ababneh Na et al. *C9orf72* hexanucleotide expansions are associated with altered endoplasmic reticulum calcium homeostasis and stress granule formation in induced pluripotent stem cell-derived neurons from patients with amyotrophic lateral sclerosis and frontotemporal dementia. *STEM CELLS* 2016;34:2063–2078.
- Murray A, Letourneau A, Canzonetta C et al. Brief Report: Isogenic induced pluripotent stem cell lines from an adult with Mosaic Down Syndrome Model accelerated neuronal ageing and neurodegeneration. *STEM CELLS* 2015;33:2077–2084.
- Yousef H, Morgenthaler A, Schlesinger C et al. Age-associated increase in BMP signaling inhibits hippocampal neurogenesis. *STEM CELLS* 2015;33:1577–1588.
- Dykstra JA, Facile T, Patrick RJ et al. Concise Review: Fat and furious: Harnessing the full potential of adipose-derived stromal vascular fraction. *STEM CELLS TRANSLATIONAL MEDICINE* 2017;6:1096–1108.
- Cha MY, Kwon YW, Ahn HS et al. Protein-induced pluripotent stem cells ameliorate cognitive dysfunction and reduce A $\beta$  deposition in a mouse model of Alzheimer's disease. *STEM CELLS TRANSLATIONAL MEDICINE* 2017;6:293–305.
- Shetty AK, Hattiangady B. Grafted subventricular zone neural stem cells display robust engraftment and similar differentiation properties and form new neurogenic niches in the young and aged hippocampus. *STEM CELLS TRANSLATIONAL MEDICINE* 2016;5:1204–1215.
- McGinley LM, Sims E, Lunn JS et al. Human cortical neural stem cells expressing insulin-like growth factor-I: A novel cellular

therapy for Alzheimer's disease. *STEM CELLS TRANSLATIONAL MEDICINE* 2016;5:379–391.

**10** Thorne N, Malik N, Shah S et al. High-throughput phenotypic screening of human astrocytes to identify compounds that protect against oxidative stress. *STEM CELLS TRANSLATIONAL MEDICINE* 2016;5:613–627.

**11** Narla ST, Klejbor I, Birkaya B et al. Activation of developmental nuclear fibroblast growth factor receptor 1 signaling and neurogenesis in adult brain by  $\alpha 7$  nicotinic receptor agonist. *STEM CELLS TRANSLATIONAL MEDICINE* 2013;2:776–788.

**12** Karran E. Alzheimer's research U.K.: Defeating dementia through research. *STEM CELLS TRANSLATIONAL MEDICINE* 2012;1:449–450.



## Alzheimer's Disease CALL FOR PAPERS

This fast-paced stem and regenerative medicine field calls for more pioneering progress. We invite authors to submit their original research papers on stem cell treatments for Alzheimer's disease and other related neurodegenerative disorders that may lead us closer to bona fide treatments and their clinical application. All articles are subject to peer review.

Anthony Atala, MD



Submit your paper today at  
<http://mc.manuscriptcentral.com/stemcellstm>

