Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease, and amyotrophic lateral sclerosis (ALS) are characterized by progressive loss of neurons (Bossy-Wetzel et al., 2004). The number of AD patients in the United States in 2012 was approximately 5.4 million, while that of PD patients in 2010 was roughly 630,000 (Kowal et al., 2013). However, currently there is no pharmacological agent that cures neurodegenerative diseases.

Neural stem cells (NSCs) can self-renew and possess the ability to differentiate into neurons, astrocytes, and oligodendrocytes (Gage, 2000). NSCs are present not only in the developing central nervous system (CNS) but also in the adult CNS (Gage, 2000). NSCs in the adult CNS are known to produce new neurons throughout the subventricular zone and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Taupin and Gage, 2002). Thus, small molecules that can modulate the promotion of neurogenesis from endogenous NSCs may be considered as novel drug candidates for the treatment of these diseases.

Small molecules that increase neurogenesis from NSCs have recently been reported, however, the underlying mechanisms behind neuron generation have not yet been fully identified. A natural product, forskolin (FSK) was found to increase neuronal differentiation of NSCs (Lairson et al., 2013). FSK enhanced neurogenesis by stimulating adenylyl cyclase and resulted in an increase in the concentration of intracellular cyclic adenosine monophosphate. In addition, NSCs were synergistically differentiated into neurons upon treatment with FSK in combination with retinoic acid. Another synthetic molecule, neuropathiazol, has been reported to increase neuronal differentiation by inducing the mRNA expression of neuroD, while suppressing astrocytogenesis in NSCs (Lairson et al., 2013). Sertraline, an antidepressant drug, was found to increase neurogenesis through the glucocorticoid receptor in neural progenitor cells (NPCs) (Anacker et al., 2011; Peng et al., 2012). Sodium butyrate, a histone deacetylase inhibitor, was also shown to promote neurogenesis (Kim et al., 2009a).

Key Words: Neurodegenerative diseases, Neural stem cells, Neurogenesis, Final cell division, Aminopropyl carbazoles

INTRODUCTION

Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease, and amyotrophic lateral sclerosis (ALS) are characterized by progressive loss of neurons (Bossy-Wetzel et al., 2004). The number of AD patients in the United States in 2012 was approximately 5.4 million, while that of PD patients in 2010 was roughly 630,000 (Kowal et al., 2013). However, currently there is no pharmacological agent that cures neurodegenerative diseases.

Neural stem cells (NSCs) can self-renew and possess the ability to differentiate into neurons, astrocytes, and oligodendrocytes (Gage, 2000). NSCs are present not only in the developing central nervous system (CNS) but also in the adult CNS (Gage, 2000). NSCs in the adult CNS are known to produce new neurons throughout the subventricular zone and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Taupin and Gage, 2002). Thus, small molecules that can modulate the promotion of neurogenesis from endogenous NSCs may be considered as novel drug candidates for the treatment of these diseases.

Small molecules that increase neurogenesis from NSCs have recently been reported, however, the underlying mechanisms behind neuron generation have not yet been fully identified. A natural product, forskolin (FSK) was found to increase neuronal differentiation of NSCs (Lairson et al., 2013). FSK enhanced neurogenesis by stimulating adenylyl cyclase and resulted in an increase in the concentration of intracellular cyclic adenosine monophosphate. In addition, NSCs were synergistically differentiated into neurons upon treatment with FSK in combination with retinoic acid. Another synthetic molecule, neuropathiazol, has been reported to increase neuronal differentiation by inducing the mRNA expression of neuroD, while suppressing astrocytogenesis in NSCs (Lairson et al., 2013). Sertraline, an antidepressant drug, was found to increase neurogenesis through the glucocorticoid receptor in neural progenitor cells (NPCs) (Anacker et al., 2011; Peng et al., 2012). Sodium butyrate, a histone deacetylase inhibitor, was also shown to promote neurogenesis (Kim et al., 2009a).
Sodium butyrate treatment resulted in the sprouting of dendrites, an increase in the number of synapses, and up-regulation of neuroD expression (Fischer et al., 2007). We have also recently reported that a phytochemical, kuwanon V, induced neurogenesis not only in the absence of but also in the presence of mitogens such as epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2) (Kong et al., 2015).

Recently, a synthetic molecule, an aminopropyl carbazole, termed P7C3, was reported to increase neurogenesis in the mouse SGZ of the dentate gyrus, and improved the cognition of aged rats (Pieper et al., 2010). In addition, P7C3 derivatives had effects on PD and ALS in animal models (De Jesus-Cortes et al., 2012; Tesla et al., 2012). It has been reported that P7C3 exerted its proneurogenic activity by protecting newborn neurons from apoptosis but not by promoting the proliferation of mice hippocampal NPCs (MacMillan et al., 2011). The neuroprotection exerted by P7C3 is through the targeting of nicotinamide phosphoribosyltransferase (NAMPT) to produce nicotinamide adenine dinucleotide (NAD) (Wang et al., 2013). Brieﬂy, NSCs were plated onto 48-well plates (Corning, Corn ing, NY, USA) at a density of 3×10⁴ cells/well and treated with different concentrations of 1 or 0.1% dimethyl sulfoxide (DMSO; Sigma-Aldrich) as a vehicle for 2 days. The cells were incubated with MITT solution (1 mg/ml) for 2 hours at 37°C. Formazan crystals that formed in the NSCs were solubilized with 20% sodium dodecyl sulfate (Amresco, Solon, OH, USA) in 50% aqueous N,N-dimethylformamide (Sigma-Aldrich). Ly sates were transferred to 96-well plates (Corning) and the absorbance was measured at 550 nm using the Synergy H1 Hybrid Multi-Mode Microplate Reader (Biotek, Winooski, VT, USA).

**Cell viability assay**

Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma-Aldrich) assay. NSCs were plated onto 48-well plates (Corning, Corning, NY, USA) at a density of 3×10⁴ cells/well and treated with different concentrations of 1 or 0.1% dimethyl sulfoxide (DMSO; Sigma-Aldrich) as a vehicle for 2 days. The cells were incubated with MITT solution (1 mg/ml) for 2 hours at 37°C. Formazan crystals that formed in the NSCs were solubilized with 20% sodium dodecyl sulfate (Amresco, Solon, OH, USA) in 50% aqueous N,N-dimethylformamide (Sigma-Aldrich). Lysates were transferred to 96-well plates (Corning) and the absorbance was measured at 550 nm using the Synergy H1 Hybrid Multi-Mode Microplate Reader (Biotek, Winooski, VT, USA).

**Immunocytochemistry and cell counting**

Immunocytochemical examination was performed as previously described (Kim et al., 2007). Cell cultures were fixed with 4% paraformaldehyde (PFA; USB Products, Cleveland, OH, USA) for 30 minutes and washed with phosphate-buff ered saline (PBS). Fixed cells were blocked with 5% normal goat serum (Millipore, Temecula, CA, USA) and 0.2% Triton X-100 (Amresco) in PBS for 30 minutes and incubated with primary antibodies against cleaved caspase-3 (rabbit monoclonal antibody, 1:400; Cell Signaling), glial fibrillary acidic protein (GFAP, rabbit polyclonal antibody, 1:1000; Dako, Denmark), and βIII Tubulin (TuJ1, mouse monoclonal antibody, 1:1000; Sigma-Aldrich) for 1 hour. After rinsing with PBS, the cells were incubated for 30 minutes with secondary antibodies conjugated to Cy3 (goat anti-rabbit immunoglobulin G [IgG], 1:1000; Jackson ImmunoResearch, West Grove, PA, USA) or Alexa Fluor 488 (goat anti-mouse IgG, 1:1000; Invitrogen) followed by 5 minutes in 4',6-diamidino-2-phenylindole (DAPI, 1:10,000 in PBS; Sigma-Aldrich) to stain the nuclei. Images were obtained using an inverse fluorescence microscope (DML; Leica, Wetzlar, Hesse, Germany). Cleaved cas-

**Fig. 1.** Chemical structures of P7C3 and 1-3.

---

**MATERIALS AND METHODS**

**Cell culture**

NSCs were cultured as previously described (Kim et al., 2013). Briefly, NSCs isolated from the cortex of E14 Sprague-Dawley rat embryos were dissociated, seeded onto tissue culture flasks (200,000 cells/ml), and expanded as neurospheres for 7 days in Dulbecco's modified Eagle's medium/F12 supplemented with 1% (v/v) PSA, 2% (v/v) B27 (all from Gibco, Grand Island, NY, USA), 20 ng/ml EGF and 20 ng/ml FGF2 (both from Chemicon, Temecula, CA, USA). The medium was replaced every 2 days. Neurospheres were dispersed into a single-cell suspension with accutase (Chemicon), and dissociated cells were seeded onto tissue culture plates pre-coated sequentially with 0.01% poly-D-lysine (Sigma-Aldrich, St. Louis, MO, USA) and 10 μg/ml laminin (Invitrogen, Grand Island, NY, USA). The cells were maintained at 37°C in 5% CO₂.

**MATERIALS AND METHODS**

**Cell culture**

NSCs were cultured as previously described (Kim et al., 2013). Briefly, NSCs isolated from the cortex of E14 Sprague-Dawley rat embryos were dissociated, seeded onto tissue culture flasks (200,000 cells/ml), and expanded as neurospheres for 7 days in Dulbecco's modified Eagle's medium/F12 supplemented with 1% (v/v) PSA, 2% (v/v) B27 (all from Gibco, Grand Island, NY, USA), 20 ng/ml EGF and 20 ng/ml FGF2 (both from Chemicon, Temecula, CA, USA). The medium was replaced every 2 days. Neurospheres were dispersed into a single-cell suspension with accutase (Chemicon), and dissociated cells were seeded onto tissue culture plates pre-coated sequentially with 0.01% poly-D-lysine (Sigma-Aldrich, St. Louis, MO, USA) and 10 μg/ml laminin (Invitrogen, Grand Island, NY, USA). The cells were maintained at 37°C in 5% CO₂.

**Cell viability assay**

Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma-Aldrich) assay. NSCs were plated onto 48-well plates (Corning, Corning, NY, USA) at a density of 3×10⁴ cells/well and treated with different concentrations of 1 or 0.1% dimethyl sulfoxide (DMSO; Sigma-Aldrich) as a vehicle for 2 days. The cells were incubated with MITT solution (1 mg/ml) for 2 hours at 37°C. Formazan crystals that formed in the NSCs were solubilized with 20% sodium dodecyl sulfate (Amresco, Solon, OH, USA) in 50% aqueous N,N-dimethylformamide (Sigma-Aldrich). Lysates were transferred to 96-well plates (Corning) and the absorbance was measured at 550 nm using the Synergy H1 Hybrid Multi-Mode Microplate Reader (Biotek, Winooski, VT, USA).

**Immunocytochemistry and cell counting**

Immunocytochemical examination was performed as previously described (Kim et al., 2007). Cell cultures were fixed with 4% paraformaldehyde (PFA; USB Products, Cleveland, OH, USA) for 30 minutes and washed with phosphate-buffered saline (PBS). Fixed cells were blocked with 5% normal goat serum (Millipore, Temecula, CA, USA) and 0.2% Triton X-100 (Amresco) in PBS for 30 minutes and incubated with primary antibodies against cleaved caspase-3 (rabbit monoclonal antibody, 1:400; Cell Signaling), glial fibrillary acidic protein (GFAP, rabbit polyclonal antibody, 1:1000; Dako, Denmark), and βIII Tubulin (TuJ1, mouse monoclonal antibody, 1:1000; Sigma-Aldrich) for 1 hour. After rinsing with PBS, the cells were incubated for 30 minutes with secondary antibodies conjugated to Cy3 (goat anti-rabbit immunoglobulin G [IgG], 1:1000; Jackson ImmunoResearch, West Grove, PA, USA) or Alexa Fluor 488 (goat anti-mouse IgG, 1:1000; Invitrogen) followed by 5 minutes in 4',6-diamidino-2-phenylindole (DAPI, 1:10,000 in PBS; Sigma-Aldrich) to stain the nuclei. Images were obtained using an inverse fluorescence microscope (DML; Leica, Wetzlar, Hesse, Germany). Cleaved cas-

**Fig. 1.** Chemical structures of P7C3 and 1-3.
Neurosphere growth rate

Neurosphere growth was measured as previously described (Gamm et al., 2008; Kim et al., 2009b). Briefly, individual spheres (approximately 100-200 μm in diameter) were transferred to single wells of 96-well plates containing 200 μl growth media with 1 or DMSO (n≥4, for each treatment). The diameter of the spheres was measured daily using a lens-mounted microscope (Leica). The volume of the neurospheres was calculated by the equation \( V = \frac{4}{3} \pi r^3 \), where \( r = 1/2 \) diameter. Neurosphere volume on each day (day 0-3) was divided by the volume at day 0 and then multiplied by 100 to obtain the percentage increase in sphere volume.

Neurosphere formation assay

NSCs expanded as neurospheres in the presence of EGF and FGF2 for 1 week were dissociated and plated as single cells onto uncoated 48-well plates at clonal density (1 cell/μl) in 250 μl media in each well (Coles-Takabe et al., 2008). The cells were grown as floating cell aggregates (neurospheres) for 7 days in the presence of mitogens added with 5.0 μM compound 1 or DMSO. The number of neurospheres was counted from 3 independent fields photographed using the JULI-Digital Bio (NanoEnTek, Seoul, Korea).

Statistical analysis

Data were expressed as the mean ± standard error of the mean (S.E.M.) or the mean ± standard deviation (S.D.), and statistical significance was determined using Student's t-test (*p<0.05, **p<0.01, and ***p<0.001).

RESULTS

Increased cell viability by compound 1 during NSC differentiation

NSCs proliferate in the presence of EGF and FGF2, and differentiate into neurons or glia in the absence of mitogens. It was previously reported that 5.0 μM of 1 increased neurogenesis compared to DMSO-treated control during differentiation (Yoon et al., 2013). To investigate the mode of action of 1, we first tested whether 1 affected the cell viability in the absence of growth factors. NSCs were isolated from the cortex of E14 rat embryos, dispersed into a single cell suspension, and expanded in tissue culture flasks as neurospheres for 6 days in the presence of EGF and FGF2. Neurons were dissociated into single cells, seeded onto 48-well plates, and treated with various concentrations (2.5, 5.0, 6.0, 7.5, and 10.0 μM) of 1 or DMSO as a vehicle for 2 days in the absence of mitogens. Subsequently, cell viability was assessed by an MTT assay. Treatment with 1 significantly increased the cell viability by 22.79, 44.44, 52.00, 30.64, and 53.63% at 2.5, 5.0, 6.0, 7.5, and 10.0 μM, respectively, compared with the DMSO-treated control (Fig. 2). These data suggest that 1 enhances cell viability/numbers during NSC differentiation.

Fig. 2. 1 increases cell viability during NSC differentiation. NSCs were treated with various concentrations (2.5, 5.0, 6.0, 7.5, and 10.0 μM) of 1 or DMSO for 2 days in the absence of EGF and FGF2. Cell viability was assessed by an MTT assay. The values are presented as the mean ± S.D. (n=7, **p<0.01 and ***p<0.001). Statistical analysis was performed using Student’s t-test.
Facilitation of final cell division by compound 1 during NSC differentiation

To test whether the increased cell viability/number by 1 in the absence of EGF and FGF2 was due to increased cell survival, we examined the levels of cleaved caspase-3, an apoptosis marker, by immunocytochemistry. NSCs were treated with 5.0 μM compound 1 or DMSO for 4 days in the absence of growth factors, and apoptotic cells were immunostained with an anti-cleaved caspase-3 antibody. However, there was no significant difference in the number of cleaved caspase-3-positive cells between the 1- and DMSO-treated groups (Fig. 3). These data suggest that 1 does not affect cell survival during differentiation.

We then performed BrdU pulsing experiments to investigate whether the increased cell viability/number was a result of the stimulated proliferation during NSC differentiation. When BrdU, a thymidine analog that incorporates into the DNA of proliferating cells in the S-phase, was pulsed during the first 12 hours of differentiation, the number of BrdU-positive cells in the 1-treated group was not significantly different from the DMSO-treated control (Fig. 4B[a,b], 4C). However, when BrdU was added during the next 12 hours of differentiation, the number of BrdU-positive cells in the 1-treated group was significantly increased compared with that of cells treated with DMSO (Fig. 4B[c,d], 4D). Moreover, 1 markedly increased the number of BrdU/TuJ1 double-positive cells compared with the DMSO control when BrdU was added for both the first 12 hours and the next 12 hours of differentiation (Fig. 4E-4G). These data suggest that 1 promotes final cell division to generate neurons during NSC differentiation.

Compound 1 does not affect NSC proliferation in the presence of mitogens

We next examined whether 1 affected NSC proliferation in the presence of EGF and FGF2. Firstly, we performed a neurosphere growth assay. The sizes of the neurospheres treated with 5.0 μM compound 1 or DMSO in the presence of growth factors were measured daily for 4 days (day 0-3). As shown in Fig. 5A, the sizes of the neurospheres became bigger in a time-dependent manner. To evaluate the effect of 1 on NSC proliferation, we measured the diameters of neurospheres and calculated the volumes of spheres using the equation \( V = \frac{4}{3} \pi r^3 \), where \( r = \frac{1}{2} \) diameter. Neurosphere volume on each day was divided by the volume on day 0 and then multiplied by 100 to obtain the percentage increase in sphere volume. However, there was no significant difference in the volume increase of the neurospheres between the two groups (Fig. 5B). Furthermore, when we dissociated, plated NSCs at clonal density (1 cell/μl), and cultured for 7 days in the absence of mitogens with 5.0 μM compound 1 or DMSO to determine neurosphere formation ability, we observed no significant difference between the two groups (Fig. 5C, 5D). Taken together, these data suggest that 1 does not change the proliferation or neurosphere formation ability of NSCs in the presence of growth factors.

Induction of neurogenesis but no significant changes in astrogliogenesis by compound 1 during NSC differentiation

In order to investigate whether 1 has effects on the astroglial differentiation of NSCs, NSCs were treated with either 5.0 μM compound 1 or DMSO for 4 days in the absence of EGF and FGF2. Astroglia and neurons were detected using antibodies against GFAP and TuJ1, respectively. Immunocytochemistry results showed that there was no significant difference in the number of GFAP-expressing astrocytes between the 1-treated group and the DMSO-treated control group (Fig. 6A-6C). Conversely, we confirmed the neurogenic effects of 1 that had been reported in our previous study (Yoon et al., 2015).
As shown in Fig. 6D-6F, 1 significantly increased the percentage of neurons by 1.90-fold, compared to the DMSO-treated control. These data suggest that 1 promotes neurogenesis but does not affect astroglial differentiation in NSCs.
aminopropyl carbazoles. However, treatment with 1 did not change the number of cleaved caspase-3-positive cells compared with the DMSO-treated control, suggesting that 1 may act differently to P7C3.

Interestingly, it was shown that 1 promoted cell division during NSC differentiation. When BrdU was pulsed during 12-24 hours of differentiation, 1 significantly increased the number of proliferating cells compared with the DMSO-treated control. Moreover, 1 considerably increased the number of BrdU/Thy1 double-positive cells within 24 hours of differentiation. During neurogenesis, neural progenitor cells undergo symmetric or asymmetric divisions (Noctor et al., 2004). A time-lapse and immunocytochemistry study revealed that just before neurogenesis NSCs do not transform to neurons but undergo final cell division (Kim et al., 2007). Thus, data obtained in the current study suggest that compound 1 may facilitate final cell division to produce daughter neurons during NSC differentiation. Similar to compound 1, kuwanon V, a phenolic compound isolated from the Morus bombycis bark, increased neurogenesis and final cell division in early NSC differentiation (Kong et al., 2015). Insulin-like growth factor-1 is also known to induce neurogenesis by stimulating cell division of granule cell precursors (Lin and Bulleit, 1997).

Although the detailed mechanisms involved in increased neurogenesis by aminopropyl carbazole derivatives should be investigated in further studies, our results provide another underlying neurogenic mechanism of aminopropyl carbazole derivatives that is different from those reported with P7C3 and its other derivatives (Yoon et al., 2013; Wang et al., 2014; Yin et al., 2014). P7C3 was found to increase neurogenesis by increasing survival of newborn neurons but not by promoting proliferation of neural precursor cells, and 2 was also shown to enhance neurogenesis by boosting cell survival during NSC differentiation (MacMillan et al., 2011; Yoon et al., 2013). In contrast, 1 did not show protective effects but increased neurogenesis by the facilitation of final cell division during NSC differentiation. Identification of P7C3 derivatives or variants may provide not only neuroprotective but also neuroproducing agents for neurodegenerative diseases.

ACKNOWLEDGMENTS

This work was supported by the Chung-Ang University Excellent Student Scholarship, the National Research Foundation (NRF-2014R1A1A1002607) and the Ministry of Knowledge Economy [No. 10041913, Development of stem cell culture system based on surface-nano-structure control].

REFERENCES

Anacker, C., Zunszain, P. A., Cattaneo, A., Carvalho, L. A., Garabedian, M. J., Thuret, S., Price, J. and Pariante, C. M. (2011) Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. Mol. Psychiatry 16, 738-750.

Bossy-Wetzel, E., Schwarzzenbacher, R. and Lipton, S. A. (2004) Molecular pathways to neurodegeneration. Nat. Med. 10 Suppl, S2-9.

Coles-Takabe, B. L., Brain, I., Purpura, K. A., Karpowicz, P., Zandstra, P. W., Morshhead, C. M. and van der Kooy, D. (2008) Don’t look: growing clonal versus nonclonal neural stem cell colonies. Stem Cells 26, 2938-2944.

De Jesus-Cortes, H., Xu, P., Drawbridge, J., Estill, S. J., Huntington, P., Tran, S., Britt, J., Teslia, R., Morlock, L., Naidoo, J., Melito, L. M., Wang, G., Williams, N. S., Ready, J. M., McKnight, S. L. and Pieper, A. A. (2012) Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of Parkinson disease. Proc. Natl. Acad. Sci. U.S.A. 109, 1710-1715.

Fischer, A., Sananbenesi, F., Wang, X., Dobbin, M. and Tsai, L. H. (2007) Recovery of learning and memory is associated with chromatin remodelling. Nature 447, 178-182.

Gage, F. H. (2000) Mammalian neural stem cells. Science 287, 1433-1438.

Gamm, D. M., Wright, L. S., Capowski, E. E., Shearer, R. L., Meyer, J. S., Kim, H. J., Schneider, B. L., Melvan, J. N. and Svendsen, C. N. (2008) Regulation of prenatal human retinal neurosphere growth and cell fate potential by retinal pigment epithelium and MASH1. Stem Cells 26, 3182-3193.

Kim, H. J. and Jin, C. Y. (2012) Stem cells in drug screening for neurodegenerative disease. Korean J. Physiol. Pharmacol. 16, 1-9.

Kim, H. J., Leeds, P. and Chuang, D. M. (2009a) The HDAC inhibitor, sodium butyrate, stimulates neurogenesis in the ischemic brain. J. Neurochem. 110, 1226-1240.

Kim, H. J., McMillan, E., Han, F. and Svendsen, C. N. (2009b) Regionally specified human neural progenitor cells derived from the mesencephalon and forebrain undergo increased neurogenesis following overexpression of ASCL1. Stem Cells 27, 390-398.

Kim, H. J., Sugimori, M., Nakafuku, M. and Svendsen, C. N. (2007) Control of neurogenesis and tyrosine hydroxylase expression in neural progenitor cells through bHLH proteins and Nurt1. Exp. Neurol. 203, 394-405.

Kim, W., Kim, J. H., Kong, S. Y., Park, M. H., Sohn, U. D. and Kim, H. J. (2013) Comparison of ectopic gene expression methods in rat neural stem cells. Korean J. Physiol. Pharmacol. 17, 23-30.

Kong, S. Y., Park, M. H., Lee, M., Kim, J. O., Lee, H. R., Han, B. W., Svendsen, C. N., Sung, S. H. and Kim, H. J. (2015) Kuwanon V inhibits proliferation, promotes cell survival and increases neurogenesis of neural stem cells. PloS one 10, e0118188.

Kowal, S. L., Dall, T. M., Chakrabarti, R., Storm, M. V. and Jain, A. (2013) The current and projected economic burden of Parkinson’s disease in the United States. Mov. Disord. 28, 311-318.

Lairson, L. L., Lyssiotis, C. A., Zhu, S. and Schultz, P. G. (2013) Small molecule-based approaches to adult stem cell therapies. Annu. Rev. Pharmacol. Toxicol. 53, 107-125.

Lin, X. and Bulleit, R. F. (1997) Insulin-like growth factor I (IGF-I) is a critical trophic factor for developing cerebellar granule cells. Brain Res. Dev. Brain Res. 99, 234-242.

MacMillan, K. S., Naidoo, J., Liang, J., Melito, L., Williams, N. S., Morlock, L., Huntington, P. J., Estill, S. J., Longgood, J., Becker, G. L., McKnight, S. J., Pieper, A. A., De Brabander, J. and Ready, J. M. (2011) Development of prionogenic, neuroprotective small molecules. J. Am. Chem. Soc. 133, 1428-1437.

Noctor, S. C., Martinez-Cerdeño, V., Ivic, L. and Kriegstein, A. R. (2004) Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nat. Neurosci. 7, 136-144.

Peng, Z. W., Xue, Y. Y., Wang, H. N., Wang, H. H., Xue, F., Kuang, F., Wang, B. R., Chen, Y. C., Zhang, L. Y. and Tan, Q. R. (2012) Sertraline promotes hippocampus-derived neural stem cells differentiating into neurons but not glia and attenuates LPS-induced cellular damage. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 36, 183-188.

Pieper, A. A., Xie, S., Capota, E., Estill, S. J., Zhong, J., Long, J. M., Becker, G. L., Huntington, P., Goldman, S. E., Shen, C. H., Capota, M., Britt, J. K., Kotti, T., Ure, K., Brat, D. J., Williams, N. S., MacMillan, K. S., Naidoo, J., Melito, L., Hsieh, J., De Brabander, J., Ready, J. M. and McKnight, S. L. (2010) Discovery of a prionogenic, neuroprotective chemical. Cell 142, 39-51.

Taupin, P. and Gage, F. H. (2002) Adult neurogenesis and neural stem cells of the central nervous system in mammals. J. Neurosci. Res. 69, 745-749.

Teslia, R., Wolf, H. P., Xu, P., Drawbridge, J., Estill, S. J., Huntington, P., McDaniel, L., Knobbe, W., Burket, A., Tran, S., Starwall, R., Morlock, L., Naidoo, J., Williams, N. S., Ready, J. M., McKnight, S. L. and Pieper, A. A. (2012) Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of amyotrophic lateral sclerosis.
Proc. Natl. Acad. Sci. U.S.A. 109, 17016-17021.
Wang, G., Han, T., Nijhawan, D., Theodoropoulos, P., Naidoo, J., Yadavalli, S., Mirzaei, H., Pieper, A. A., Ready, J. M. and McKnight, S. L. (2014) P7C3 neuroprotective chemicals function by activating the rate-limiting enzyme in NAD salvage. Cell 158, 1324-1334.
Warashina, M., Min, K. H., Kuwabara, T., Huynh, A., Gage, F. H., Schultz, P. G. and Ding, S. (2006) A synthetic small molecule that induces neuronal differentiation of adult hippocampal neural progenitor cells. Angew. Chem., Int. Ed. Engl. 45, 591-593.
Yin, T. C., Britt, J. K., De Jesus-Cortes, H., Lu, Y., Genova, R. M., Khan, M. Z., Voorhees, J. R., Shao, J., Katzman, A. C., Huntington, P. J., Wassink, C., McDaniel, L., Newell, E. A., Dutca, L. M., Naidoo, J., Cui, H., Bassuk, A. G., Harper, M. M., McKnight, S. L., Ready, J. M. and Pieper, A. A. (2014) P7C3 neuroprotective chemicals block axonal degeneration and preserve function after traumatic brain injury. Cell Rep. 8, 1731-1740.
Yoon, H. J., Kong, S. Y., Park, M. H., Cho, Y., Kim, S. E., Shin, J. Y., Jung, S., Lee, J., Farhanullah and Kim, H. J. (2013) Amino- propyl carbazole analogues as potent enhancers of neurogenesis. Bioorg. Med. Chem. 21, 7165-7174.