參加國際幹細胞研究學會 2018 年會心得報告

錢宗良

本年度國際幹細胞研究學會 (International Society for the Stem Cell Research, ISSCR) 於 6 月 20 日至 23 日在澳大利亞墨爾本舉行。眾所皆知墨爾本是帶領澳大利亞醫療技術和藥品領先地位的城市。對全球生物技術關注的議題中，墨爾本因其在傳染病和免疫學領域居於世界領先地位，而再生醫學與幹細胞研究以及高質量的臨床試驗亦為其強項。本次國際幹細胞研究學會特別選定在南半球的墨爾本，有其特殊之用義。

作者第一天到達墨爾本大會地點 Melbourne Convention Center (圖一) ，已接近中午，在會場上碰到共同與會的台大醫院何弘能院長剛完成報到。緊接著準備參加下午的開幕儀式，第一次參加在澳洲舉辦的國際會議，充分感受到在真正是地大物博，即使是會議中心的建築規劃亦顯現出空間之寬闊與友善。本年度 ISSCR 正式開幕儀式在 20 日下午，由學會理事長 Dr. Hans Clever 致開幕詞，並邀請到澳大利亞當地首長 Governor of Victoria，Ms. Linda Dessau 以地主致歡迎詞。本年度 The ISSCR Tobias Award 頒獎給加拿大 Terry Fox Cancer Institute 的 Dr. Connie Eaves 並邀請她介紹畢生研究 “A Prospective Analysis of Human Leukemogenesis”。 她對於慢性白血病 (chronic myeloid leukemia) 研究貢獻了許多開創性的發現，包括血液中的幹細胞形成及其在正常和擾動狀態調節。很高興再次見到 Terry Fox Cancer Institute 這位資深的長者，能夠獲得國際幹細胞研究學會肯定。

大會本年度除提供許多鼓勵年輕研究者的獎項外，特別值得一提的是由華人 Zhongmei Chen Yong 提供贊助的 Travel Awards。此獎項持續鼓勵來自世界各地年輕學者，共同參與本年度在墨爾本舉行的年會。與去年在美國波士頓年會比較，本次參加的亞洲國家年輕學者更多，而澳大利亞本地的大學研究機構與生技產業亦有許多人積極參與。再次驗證亞太地區在幹細胞研究領域發展未來的世

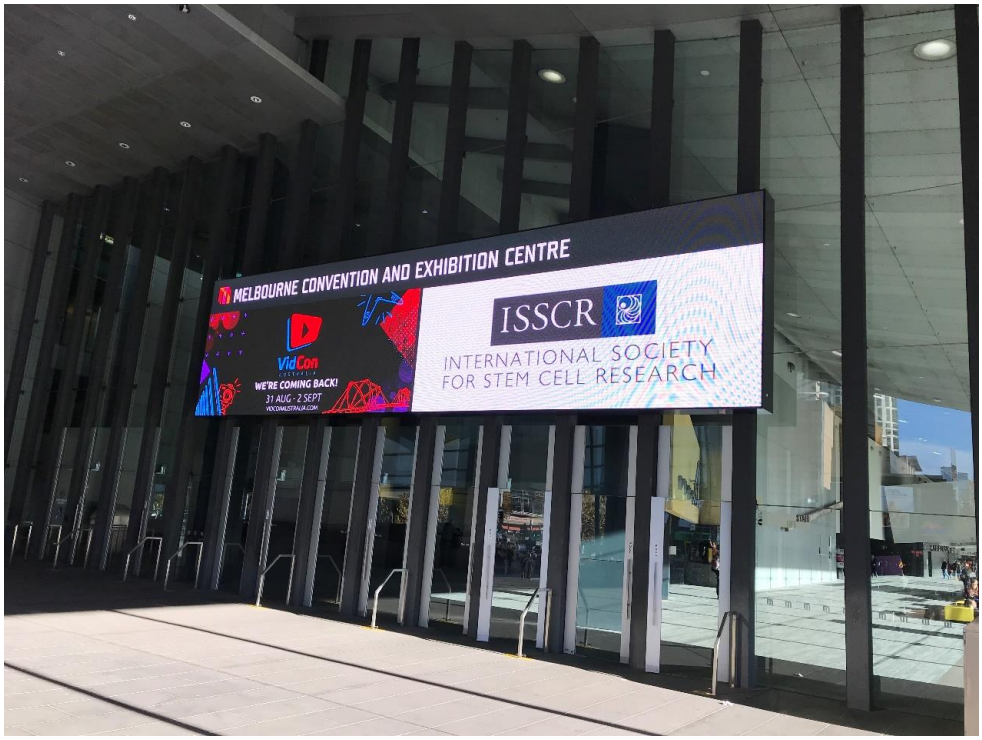
界主導力量。臺灣這次參加的人也不少，包括臺大、中研院、陽明大學、國防醫學院、國衛院等老師及研究生。

作者此次參加 ISSCR 年會第一天就遇到許多幹細胞領域研究的老師，包括台大的何弘能院長、陳佑宗老師、林泰元老師、林劭品老師等，北醫的黃彥華老師，中研院郭泓志老師，陽明大學王懷詩老師及國衛院邱英明老師等。本年度作者海報發表時段 (W2013)，依大會安排在第一天 20 日下午 6：30 發表研究成果 “Neural Regeneration of Rat Brain Injury Models via Cell Therapy” (圖二及圖三)。此部分是由碩士班畢業生周品同學的研究成果為主，從建立一個紅血球生成素過量表達 (erythropoietin-overexpressing) 3T3 細胞株，實驗證明利用 3T3 細胞分泌之紅血球生成素可保護神經退化，進而在腦損傷之大鼠實驗動物中協助神經再生，促成大鼠部分神經功能的恢復。此利用基因與細胞療法的策略，期望未來可運用在人類神經損傷疾病的新治療方法上(附件一)。巧合的是在第一天下午 7：30 偶數海報發表時段(W2014) 遇到相鄰海報發表的國衛院邱英明老師(圖四)，邱老師的研究發現細胞激素 IL12 可在神經再生上扮演積極的角色，特別建議邱英明老師可嘗試申請技術專利，對於國衛院法人機構研發成果將有莫大助益。

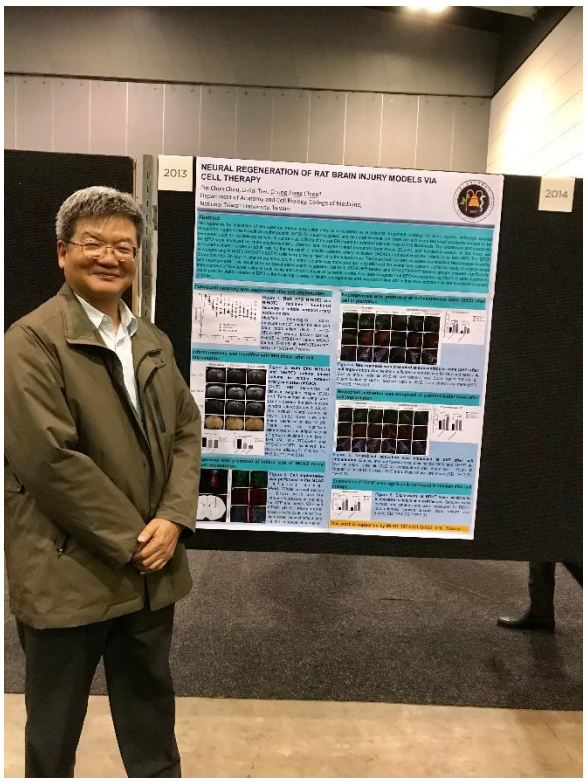
在第一天與連續幾天的會場展上，遇到多位臺灣來的學者及研究生，其中還包括陽明大學王懷詩老師與指導的研究生海報發表(圖五)，與台大陳佑宗老師游益興博士共同發表的海報(圖六)，藉由大家的研究內容詢答溝通瞭解，可觀察到臺灣目前在幹細胞研究的強項與國際發展的趨勢。而作者此次除以海報發表部分研究成果外，原本擔任臺灣幹細胞理事長已於去年交棒給中研院沈家寧老師，今年由沈家寧老師身分代表臺灣幹細胞研究學會參加國際幹細胞研究學會國際委員會舉辦的 Network Lunch Meeting。據沈老師的分享得知，今年國際幹細胞研究學會特別針對病人權益及治療同意書需告知事項進行會議討論，而 ISSCR 將於七月公佈同意書範本，醫生需要跟病人說明風險及治療內容外，對於長期的風險

及保險也要有所規範。這對於世界各國在執行細胞治療的法規制定，將有具體的參考價值。本年度除星期六最後一個專題演講：**Moving to the Clinic: Gene and Stem Cell Therapies** 中邀請上任主席 **Dr. Sally Temple** 主持外，特別安排下任學會主席 **Dr. Douglas Melton** 致詞。歡迎與會的國際學者專家明年年會在美國洛杉磯見。

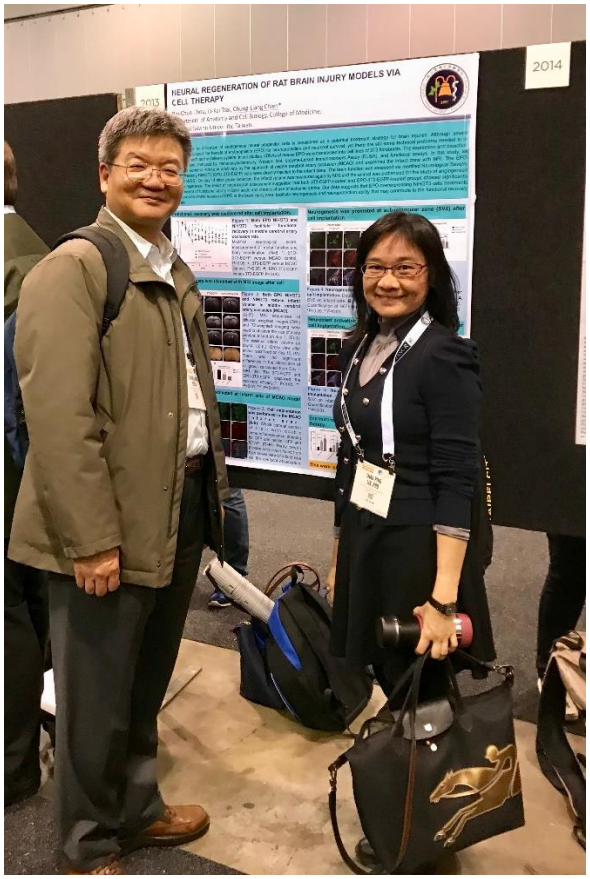
作者本年度能夠參加在美國墨爾本舉行的年會，要特別感謝科技部計畫的支持，與實驗室碩士班周品同學的努力及臺大神經科蔡力凱醫師的大力協助，得以具體研究成果發表。作者也藉此機會能與臺灣共同執行科技部再生醫學科技發展計畫的部分研究團隊交流溝通。順便瞭解各研究團隊目前可能之國際合作機會。作者連續兩年參加此學會舉辦之年會，發現此學會的發展不再僅限於幹細胞領域研究之主題，包括產業的未來發展、臨床運用法規的調適等均成為大會關切之主題，大會特別安排幹細胞領域年輕學者之聚會與討論，對於學會之永續發展具有前瞻之規劃，可預見不久之將來，國際幹細胞研究學會將持續蓬勃發展，協助科學界在國際社會作出更大的貢獻。



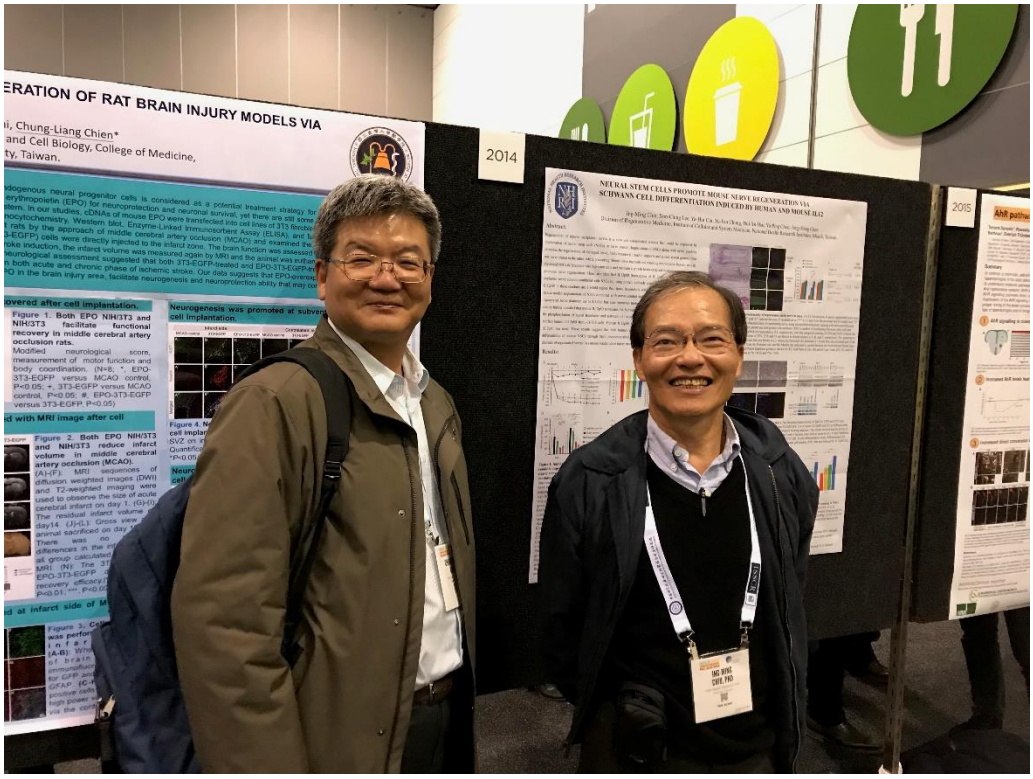
圖一、ISSCR 大會地點墨爾本 Melbourne Convention Center



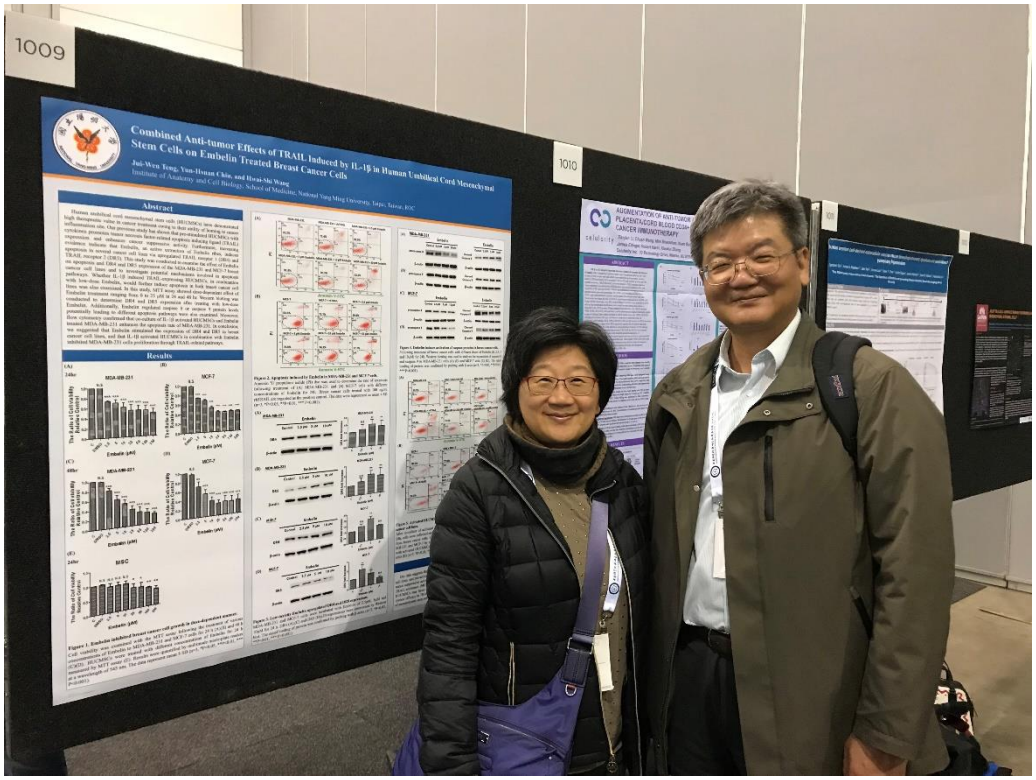
圖二、作者在海報張貼時留影。



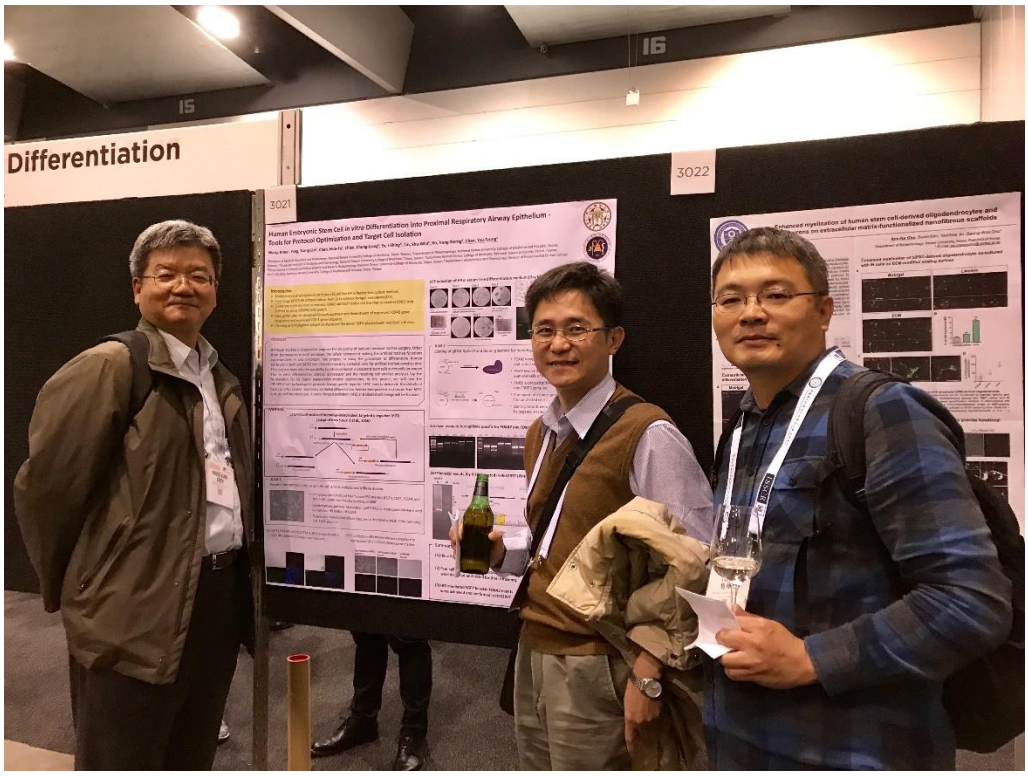
圖三、作者在海報發表時段與台大林劭品老師合影。



圖四、作者在海報發表時段與相鄰海報發表的國衛院邱英明老師合影。



圖五、作者在海報發表時段與陽明大學王懷詩老師發表海報前合影。



圖六、作者在海報發表時段與台大的陳佑宗老師、游益興博士發表海報前合影。

附件一、參加 2018ISSCR 海報

NEURAL REGENERATION OF RAT BRAIN INJURY MODELS VIA CELL THERAPY

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Abstract

Neurogenesis by activation of endogenous neural progenitor cells is considered as a potential treatment strategy for brain injuries. Although several researches support the benefit of erythropoietin (EPO) for neuroprotection and neuronal survival, yet there are still some technical problems needed to be overcome, such as the delivery system. In our studies, cDNAs of mouse EPO were transfected into cell lines of 3T3 fibroblasts. The expression and bioactivity for EPO were analyzed by immunocytochemistry, Western blot, Enzyme-Linked Immunosorbent Assay (ELISA), and functional assays. In this study, we produced ischemic stroke in adult rats by the approach of middle cerebral artery occlusion (MCAO) and examined the infarct zone with MRI. The EPO-overexpressing NIH/3T3 (EPO-3T3-EGFP) cells were directly injected to the infarct zone. The brain function was assessed via modified Neurological Severity Score (mNSS). On day 14 after stroke induction, the infarct volume was measured again by MRI and the animal was euthanized for the study of angiogenesis and neurogenesis. The result of neurological assessment suggested that both 3T3-EGFP-treated and EPO-3T3-EGFP-treated groups showed significantly improvement of functional ability in both acute and chronic phase of ischemic stroke. Our data suggests that EPO-overexpressing NIH/3T3 cells treatments could provide stable release of EPO in the brain injury area, facilitate neurogenesis and neuroprotection ability that may contribute to the functional recovery of brain.

Functional recovery was discovered after cell implantation.

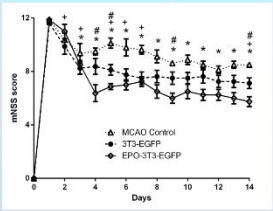

Figure 1. Both EPO NIH/3T3 and NIH/3T3 facilitate functional recovery in middle cerebral artery occlusion rats. Modified neurological score, measurement of motor function and body coordination. (N=8; *, EPO-3T3-EGFP versus MCAO control, P<0.05; +, 3T3-EGFP versus MCAO control, P<0.05; #, EPO-3T3-EGFP versus 3T3-EGFP, P<0.05)

Infarct recovery was identified with MRI image after cell implantation.

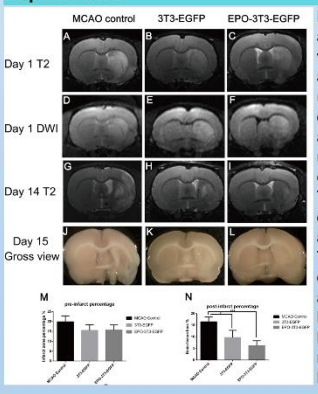

Figure 2. Both EPO NIH/3T3 and NIH/3T3 reduce infarct volume in middle cerebral artery occlusion (MCAO). (A)-(F): MRI sequences of diffusion weighted images (DWI) and T2-weighted imaging were used to observe the size of acute cerebral infarct on day 1. (G)-(I): The residual infarct volume on day14. (J)-(L): Gross view after animal sacrificed on day 15. (M): There was no significant differences in the infarct size of all group calculated from Day 1 MRI. (N): The 3T3-EGFP and EPO-3T3-EGFP displayed the recovery efficacy.(*, P<0.05; **, P<0.01; ***, P<0.001)

Neurogenesis was promoted at infarct side of MCAO model after cell implantation.

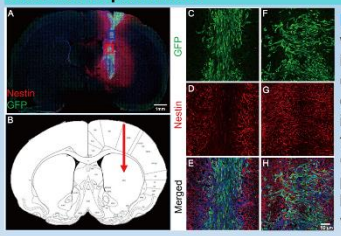

Figure 3. Cell implantation was performed in the MCAO infarct area. (A-B): Whole coronal section of brain with double immunofluorescence staining for GFP and nestin, GFP and GFAP. **(C-H)**: Many nestin positive cells could found from high power view of infarct side via the confocal observation.

Neurogenesis was promoted at subventricular zone (SVZ) after cell implantation.

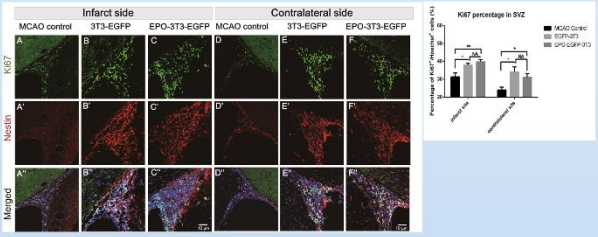

Figure 4. Neurogenesis was promoted at subventricular zone (SVZ) after cell implantation. Double immunofluorescence staining for ki67 and nestin. **A.** SVZ on infarct side. **B.** SVZ on contralateral site. Scale bar = 100μm. **C.** Quantification of ki67+/Hoechst+ cells in SVZ. Data shown are mean±SD. *P<0.05, **P<0.01.

Neuroblast activation was enhanced at subventricular zone after cell implantation.

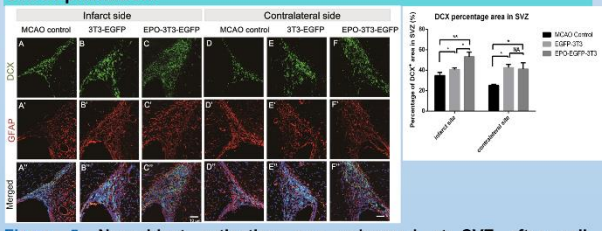

Figure 5. Neuroblast activation was enhanced at SVZ after cell implantation. Double immunofluorescence staining for DCX and GFAP. **A.** SVZ on infarct side. **B.** SVZ on contralateral site. Scale bar = 50μm. **C** Quantification of DCX area / SVZ area. Data shown are mean±SD; *P<0.05, **P<0.01.

Expressions of BDNF were significantly increased in striatum after cell therapy.

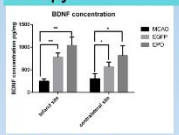

Figure 5. Expressions of BDNF were significantly increased in striatum after cell therapy. Samples were extract from striatum and were measured for BDNF (brain-derived growth factor) Data shown are mean±SD; *P<0.05; **P<0.01.

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