



**UNIVERSITY OF
TECHNOLOGY SYDNEY**

**An Examination of the Cellular and Inflammatory
Response in Rats After Spinal Cord Injury;
the Effects of Age and Survival Time**

A thesis submitted in fulfilment of the requirements of the degree of

Doctor of Philosophy

By

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DECLARATION OF AUTHORSHIP/ORIGINATLITY

I, Theresa Sutherland, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Life Sciences at the University of Technology Sydney. This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

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- Mao, Y., Nguyen, T., Sutherland, TC., and Gorrie, CA. (2016) ***Endogenous neural progenitor cells in the repair of the spinal cord.*** *Neural Regeneration Research* 11(7): 1075-1076

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- **Neuroscience 2016**
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- **New Horizons Conference 2014**
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ABBREVIATIONS

AD.....	Alzheimer's disease
ANOVA.....	Analysis of variance (statistic)
ASIA.....	American spinal injury association (impairment scale)
BBB.....	Blood brain barrier
BBB.....	Basso, Beattie and Bresnahan (behavioural score)
BDNF.....	Brain derived neurotrophic factor
BMDM.....	Bone marrow derived macrophages
BMP.....	Bone morphogenic protein
BMSC.....	Bone marrow stromal cells
BSCB.....	Blood spinal cord barrier
CBS.....	Combined behavioural score
CNS.....	Central nervous system
CNTF.....	Ciliary neurotrophic factor
CXCL.....	(C-X-C motif) ligand
EAE.....	Experimental autoimmune encephalomyelitis
ELISA.....	Enzyme-linked immunosorbent assay
eNPC.....	Endogenous neural progenitor cell
GDNF.....	Glial derived neurotrophic factor
GFAP.....	Glial fibrillary acidic protein
hECS.....	Human embryonic stem cells
IGF-1.....	Insulin-like growth factor-1
IFN- γ	Interferon-gamma

IL.....Interleukin-
 INC.....Intermediate nucleus of Cajal
 IRLS.....Infant rat locomotor score
 M1.....Pro-inflammatory macrophage/monocyte
 M2.....Anti-inflammatory macrophage/monocyte
 MBP.....Myelin basic protein
 MDM.....Monocyte-derived macrophages
 MS.....Multiple Sclerosis
 MSC.....Mesenchymal Stem Cells
 MVA.....Motor vehicle accident
 NGF.....Nerve growth factor
 NPC.....Neural progenitor cells
 NSPC.....Neural stem/progenitor cell
 NT-3.....Neurotrophin 3
 NTF.....Neurotrophic Factors
 OEC.....Olfactory ensheathing cells
 OPC.....Oligodendrocyte progenitor cells
 P7.....Post-natal day 7
 P10.....Post-natal day 10
 PD.....Parkinson’s disease
 PNS.....Peripheral nervous system
 RT-PCR.....Reverse transcription polymerase chain reaction
 ROS.....Reactive oxygen species
 RNS.....Reactive nitrogen species
 SCI.....Spinal cord injury
 SCIWORA.....Spinal cord injury without radiographic anomaly

SEM.....	Standard error of the mean
SEZ.....	Subependymal zone
SNI.....	Spinal nerve injury
SPC.....	Stem/progenitor cell
SVZ.....	Subventricular zone
T10.....	10 th thoracic vertebral level
TBI.....	Traumatic brain injury
TGF- β	Transforming growth factor-beta
TNF- α	Tumour necrosis factor-alpha
TNF-R.....	Tumour necrosis factor receptor
TLR.....	Toll-like receptor
TSCI.....	Traumatic spinal cord injury

ABSTRACT

Spinal cord injury (SCI) is a complex and devastating condition that has a life-long effect on patients' quality of life, their family, carers and society. Currently there is no cure for SCI, and no proven treatment in the acute phases of SCI. Tissue loss and varying degrees of functional impairment result from a SCI, and only limited repair is exhibited. A great deal of research has focused on reducing the degenerative effects that occur during the secondary injury phase of injury to order to promote tissue repair and regeneration. The immune and inflammatory response is thought to play a significant role in this process, albeit with both beneficial and detrimental responses reported. Most research to date has concentrated on adult SCI, yet it has been suggested that the young show better functional recovery compared to adults both for humans and in a variety of animal models.

The current research project used an animal model of contusive SCI to compare adult (9wk), juvenile (5wk) and infant (P7) Sprague-Dawley rats. One cohort (n=108) was assessed over a 6 week post-injury period for 1) locomotor function using established and newly developed scoring systems, 2) injury progression using histology, and 3) inflammatory cell changes using immunohistochemistry. A second cohort (n=97) was assessed acutely (1h, 24h and 1wk post-injury) for inflammatory mediators using flow cytometry on the injured tissue homogenate and multiplex cytokine ELISA on the tissue supernatant. Finally, an in vitro study was conducted to

explore the possibility of modulating different macrophage populations using conditioned media to create a more anti-inflammatory microenvironment.

The results described in this thesis show that following a SCI of comparative severity there were significant differences between adult and infant injury progression and presentation, inflammatory responses, and behavioural recovery. This research reinforced the inherent difficulties in modelling infant conditions for comparative studies, but it has also highlighted two important avenues of research to be pursued. 1) A better understanding of SCI progression in the young is needed to inform how paediatric SCI is treated and managed, and 2) targeted modulation of the inflammatory response in adult SCI patients may be a promising avenue for better functional recovery.