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MOLECULAR AND CELLULAR ANALYSIS OF MSC-EPO-MEDIATED PROTECTION OF DEGENERATING RETINAS

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By

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MOLECULAR AND CELLULAR ANALYSIS OF MSC-EPO-MEDIATED PROTECTION OF DEGENERATING RETINAS

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September 2021

Chair : Mok Pooi Ling, PhD
Faculty : Medicine and Health Sciences

The retina is a multi-layered tissue that functions to provide vision. Because of its complexity, a dysfunction in any layer can lead to retinal degeneration and various degrees of visual impairment. Such cases are imminent, and current treatments can only delay the disease onset. In order to restore the degenerating retina, stem cells can be introduced. Mesenchymal stem cells (MSC) have been heralded as a potential cure due to its multipotent differentiation and cellular reparative capabilities, as shown in numerous clinical studies. However, there were also contradicting findings that revealed a worse prognosis for blindness after MSC transplantation. Such variable results are due to the limitations of MSC therapy. For example, donor cell heterogeneity, epigenetic modifications, and health status can have a huge impact on MSC efficacy. These limitations can be tackled by genetically-modifying MSCs to express exogenous growth factors that enhance the survivability of transplanted MSCs and the surrounding tissue. Erythropoietin (EPO) is a potential enhancer. Apart from being involved in erythropoiesis, EPO plays another role in anti-apoptosis and neuroregeneration by binding to EPO-receptors on non-erythroid cells like the retina. In this study, the novel synergistic interactions between MSC and EPO were explored in the form of human EPO-expressing MSCs ($MSCs^{EPO}$) to evaluate its therapeutic potential in recovering the retina of a rodent model of retinal degeneration. Firstly, this was tested in an *in vitro* model of retinal cell toxicity. ARPE-19 cytotoxicity was induced with a retinotoxin known as sodium iodate ($NaIO_3$) and treated with conditioned media (CM) from MSCs or $MSCs^{EPO}$. Subsequent cell viability assays performed using MTT and flow cytometry revealed statistically significant increases in ARPE-19 survivability at 24 h and 48 h post-treatment ($P < 0.05$). Furthermore, MSC^{EPO}-CM treatment was shown to be statistically significant in the early phase of the treatment (24 h). However, both MSC and MSC^{EPO}-CM treatments were comparable at 48 h. After performing the proof of concept study *in vitro*, the study proceeded to *in vivo* experimentation. After an initial optimization with various doses of systemically-administered $NaIO_3$ (20 – 80

mg/kg) in Sprague-Dawley rats, it was found that 40 mg/kg was the ideal dose to trigger moderate retinal degeneration (around 50%). This was assessed using histo-anatomical methods and electroretinography (ERG), which revealed the degenerated retinal layers and attenuated ERG graphs. After successfully developing the model, an intravitreal transplantation of MSCs^{EPO} was performed, and the model was assessed using similar techniques. The results showed that after day 30, both the MSC and MSC^{EPO} treatment groups exhibited improved visual functions compared to the sham control ($P < 0.05$). Although MSCs were able to protect visual function, MSCs^{EPO} showed comparable results with MSCs. A further in-depth investigation using RNA sequencing revealed a set of pro-survival gene expressions. Most notably, MSC^{EPO} was found to activate the phototransduction pathway. The PI3K-Akt signaling pathway, a downstream EPO activator, was also significantly activated by MSC^{EPO}. The transcriptomics profile showed a clear, positive correlation with the functional data from the treated groups. Interestingly, several immune response pathways were upregulated in the MSC group but not MSCs^{EPO}. Further studies are required to investigate the functional implications of this expression profile on immunomodulation. Taken together, this study has shown that treatment with MSCs conferred pro-survival benefits to retinal cells as well as protection against retinal degeneration. On the other hand, MSCs^{EPO} showed comparable results with MSCs and hence, was not significantly better. Still, these results may be utilized in future studies to further investigate MSC^{EPO} therapy for retinal diseases.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

ANALISIS MOLEKUL DAN SEL DALAM PERLINDUNGAN BERANTARAKAN MSC-EPO PADA RETINA ROSOT

Oleh

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Retina adalah tisu berlapis-lapis yang terlibat dalam penglihatan. Kekompleksan retina menyebabkan disfungsi pada mana-mana lapisan akan mengakibatkan kemerosotan retina dan kecacatan penglihatan. Kecacatan ini tidak boleh disembuhkan dan rawatan yang sedia ada hanya melambatkan kemerosotan. Untuk memulihkan retina yang rosot, sel puncak digunakan. Sel punca mesenkima (MSC) dilihat sebagai penyembuh yang berpotensi disebabkan kebolehan pembezaan multipoten dan pembaikan sel oleh sel punca ini, seperti yang ditunjukkan dalam banyak kajian klinikal. Namun, terdapat beberapa dapatan di mana MSC mengakibatkan kemerosotan retina yang lebih serius. Keputusan yang pelbagai ini disebabkan oleh had terapi MSC. Sebagai contoh, keheterogenan, pengubahsuaian epigenetik, dan kesihatan sel penderma mempunyai pengaruh yang besar pada keberkesanan rawatan MSC. Had ini boleh diatasi dengan mengubah MSC secara genetik untuk mengekspres faktor-faktor pertumbuhan eksogenus bagi meningkatkan kemandirian MSC yang dipindahkan dan tisu di sekeliling. Eritropoietin (EPO) adalah penggalak yang berpotensi. Selain terlibat dalam eritropoiesis, EPO juga memainkan peranan dalam proses anti-apoptosis dan penjanaan semula sel neuron secara mengikat kepada reseptor EPO pada sel-sel bukan eritrosit seperti retina. Dalam kajian ini, interaksi bersinergi antara MSC dan EPO dikaji dalam bentuk MSC manusia yang mengekspresi EPO (MSC^{EPO}) untuk menilai potensi terapeutik bagi pemulihan retina dalam model tikus dengan retina rosot. Pertama sekali, kajian dilakukan ke atas model ketoksikan sel retina in vitro. Kesitotoksikan ARPE-19 dicetuskan menggunakan sodium iodat ($NaIO_3$) dan dirawat dengan medium terlazim (CM) daripada MSC atau MSC^{EPO}. Ujian MTT dan sitometri aliran menunjukkan peningkatan kadar kemandirian sel ARPE-19 yang signifikan secara statistik dalam rawatan 24 dan 48 jam ($P<0.05$). Malah, rawatan MSC^{EPO}-CM menunjukkan keberkesanan yang signifikan pada fasa awal rawatan (24 jam). Namun, keberkesanan rawatan MSC dan MSC^{EPO}-CM adalah setara pada 48 jam. Selepas pembuktian konsep kajian secara in vitro, kajian diteruskan secara in vivo. Selepas pengoptimuman awal dengan pelbagai dos

$NaIO_3$ (20 – 80 mg/kg) yang diberi secara sipuncaik kepada tikus Sprague-Dawley, ditemui bahawa 40 mg/kg adalah dos yang ideal untuk mencetuskan kadar kemerosotan retina yang sederhana (sekitar 50%). Ujian histologi dan elektoretinograf (ERG) digunakan untuk mengesahkan lapisan-lapisan retina yang merosot dan graf ERG yang terjejas. Selepas model berjaya dibentuk, pemindahan MSC^{EPO} secara intravitreus dilakukan dan model dinilai menggunakan teknik-teknik yang sama. Selepas 30 hari, keputusan menunjukkan bahawa kumpulan rawatan MSC dan MSC^{EPO} menunjukkan penglihatan yang lebih baik berbanding dengan kawalan palsu (P<0.05). Walaupun rawatan MSCs dan $MSCs^{EPO}$ berkesan bagi mengekalkan fungsi penglihatan dan menunjukkan kesan yang setara, namun rawatan MSC^{EPO} tidak menunjukkan kerbekesanan yang lebih baik. Kajian yang lebih mendalam menggunakan penjujukan RNA mendedahkan pengekspresan gen-gen yang menyokong kemandirian sel. Paling ketara, MSC^{EPO} didapati mengaktifkan jejak laluan proses penglihatan (phototransduction). Jejak laluan pengisyaratan PI3K-Akt, salah satu pengaktif hiliran EPO, juga diaktifkan oleh MSC^{EPO}. Profil transkriptom menunjukkan hubungan positif yang jelas dengan data kumpulan dirawat. Di samping itu, terdapat jejak-jejak laluan pengisyaratan gerak balas imun yang boleh dikesan selepas rawatan MSC tetapi tidak bagi MSC^{EPO}. Kajian lanjut diperlukan untuk menyiasat kesan profil ekspresi ini ke atas mekanisme immunomodulasi. Secara keseluruhan, kajian ini telah menunjukan bahawa rawatan dengan MSC memberikan perlindungan serta kebaikan bagi kemandirian sel-sel retina yang menunjukkan tanda-tanda kemerosotan. Namun, kerberkesanan rawatan MSC^{EPO} dalam kajian ini adalah setara dengan MSC. Pada masa yang sama, dapatan ini boleh digunakan untuk kajian lanjut bagi membangunkan terapi MSC^{EPO} bagi penyakit retina.

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Thank you, everyone, I am signing out.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AAV	Adeno-associated viruses
AMD	Age-related macular degeneration
ANG-1	Angiopoietin-1
ARR3	Arrestin
ATCC	American Type Culture Collection
BAX	Bcl-2-associated X protein
BCL2	B-cell lymphoma 2
BP	Biological processes
CC	Cellular components
CCND	Cyclins
CDK6	Cell division protein kinase
CM	Conditioned medium
CNS	Central nervous system
CRX	Cone-rod homeobox
CT	Cycle threshold
DEGS	Differentially expressed genes
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetraacetic acid
EPHB4	Ephrin-type B receptor 4
EPO	Erythropoietin
EPOR	Erythropoietin receptor
ERG	Electroretinography
ESC	Embryonic stem cells

EVS	Extracellular vesicles
FECH	Ferrochelatase
FGF	Fibroblast growth factors
GFP	Green fluorescent protein
GO	Gene ontology
GRK1	Rhodopsin kinases
GSEA	Gene set enrichment analysis
HBSS	Hank's balanced salt solution
HEBP1	Heme-binding protein 1
HMOX1	Heme oxygenase 1
HSPB1	Heat shock protein family B member 1
IC50	Half maximal inhibitory concentration
IGF-1	insulin-like growth factor
INL	Inner nuclear layer
IPL	Inner plexiform layer
IPSCS	Induced-pluripotent stem cell
JAK-STAT	Janus kinases-signal transducer and activator of transcription proteins
JC-1	Tetraethylbenzimidazolylcarbocyanine iodide
KEGG	Kyoto Encylopedia of Genes and Genomes
MAPK	Mitogen-activated protein kinase
MF	Molecular functions
MSC	Mesenchymal stem cells
MSCEPO	Erythropoietin-expressing mesenchymal stem cells

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NFATC1	Nuclear factor of activated T-cell
NF-KB	Nuclear factor kappa B
NGS	Next-generation sequencing
NRF2	Nuclear factor erythroid 2-related factor 2
ONL	Outer nuclear layer
OPL	Outer plexiform layer
ORA	Over-representation analysis
PBS	Phosphate buffered saline
PCA	Principal component analysis
PI3K/AKT	phosphatidylinositol 3-kinase/protein kinase B
PLAU	Plasminogen activator urokinase
PLCE1	1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase
PR	Layer or rods and cons/ photoreceptor layer
QPCR	Quantitative polymerase chain reaction
RAP1	Ras-related protein 1
RAS	Rat sarcoma
RDH5	Retinol dehydrogenase
RGC	Retinal ganglion cell
RHO	Rhodopsin
RNA	Ribonucleic acid
RNA-SEQ	RNA sequencing
ROS	Reactive oxygen species
RPE	Retinal pigment epithelium

SPIA	Signaling Pathway Impact Analysis
TCA	Tricarboxylic acid cycle
TERT	Telomerase reverse transcriptase
TGFB	Transforming growth factor β1
TH	T helper
TNF	Tumor necrosis family
VEGF	vascular endothelial growth factor
WNT	Wingless-related integration site
AAV	Adeno-associated viruses
AMD	Age-related macular degeneration

LIST OF SYMBOLS

$NaIO_3$	Sodium iodate
CO_2	Carbon dioxide

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CHAPTER 1

INTRODUCTION

1.1 Background of the study

The visual system is a complex sensory feature that involves many components. The retina is the first component that is involved in visual processing. This multi-layered neural tissue, which is situated in the eye, is an outer extension of the central nervous system (Siegel, Sapru and Siegel, 2006). Because of its critical involvement in processing light stimuli, our vision is immediately affected when retinal degeneration occurs. The causes are highly varied and can be due to inherited disorders (e.g. retinal dystrophies), infections (e.g. by varicella zoster virus, cytomegalovirus) and other disorders like age-related macular degeneration (Margalit and Sadda, 2003). Although these retinal degenerative disorders represent only a portion of ocular disorders (i.e. 24%), it is among those of higher prevalence in Malaysia (Zainal, 2002; Patel et al., 2011).

To date, there are a number of treatments available to patients who intend to improve their ailing eyesight; however, the emerging applications of stem cell therapy as an alternative approach makes it particularly promising as these cells hold the ability to divide and form specialized cells, replacing those that have been damaged and lost (Wei et al., 2013). Mesenchymal stem cells are one such example that have been widely used in cellular regeneration studies. Current literature has shown that apart from differentiation, tissue repair can occur with the transfer of MSC-secreted exosomes/microvesicles that contain protein factors and RNA (Rani et al., 2015). However, donor heterogeneity, such as age and health status, can result in varied therapeutic efficacy Furthermore, MSC therapy can be improved by combining them with recombinant proteins that confer tissue protective and anti-apoptotic effects (Lombardero, Kovacs and Scheithauer, 2011).

In order to improve the chances of success for MSC therapy, several strategies have been employed. Most notably, MSCs were enhanced with the expression of cell stimulating growth factors through genetic modification as a synergistic approach to improve donor cell survivability and regenerative potential (Chan et al., 2005; Kavanagh et al., 2015; Park et al., 2015). Erythropoietin (EPO) is a potential growth factor due to its neuroprotective and anti-apoptotic effects (Maiese, 2016; Wang et al., 2015). These therapeutic effects have been shown to benefit retinal cells, whereby studies have demonstrated that EPO could attenuate the inflammatory response (Chang et al. 2013) and protect retinal cells from oxidative stress-induced damage such as in cases of macular degeneration (Wang et al. 2009). Most importantly, EPO demonstrated retinal protective effects in animal models after a number of insults, including optic nerve crush (Sullivan et al., 2011), light-induced photoreceptor damage (Colella et al., 2011), as well as genetic photoreceptor degeneration (Colella et al., 2011).

These effects were exhibited due to the presence of EPO receptors in the retina where, when activated, leads to the expression of a number of pathways involved in pro-survival, including JAK-STAT (Galal, Abdel-Rafei, & Hasan, 2018), MAPK (Yuen et al., 2011), NF-κB (Zhang et al., 2018), and PI3k/Akt (Rong & Xijun, 2015). However, systemic administration of EPO in humans could lead to complications, especially an increased risk of blood clots/thrombovascular events (Singh et al., 2006). Repeated intraocular injections of EPO may also pose a surgical risk. Hence, bringing MSCs into the picture could potentially make EPO a possible treatment solution for retinal degeneration.

By modifying MSCs to express EPO (MSC^{EPO}), researchers have found that a single transplant could rescue the retina from degeneration in an animal model by prolonging the presence of MSC^{EPO} and enhancing its therapeutic effect (Guan et al., 2013). Hence, utilizing transplanted $MSCs^{EPO}$ could act as a lasting treatment that benefits those who suffer from this debilitating affliction. However, the effectiveness of $MSCs^{EPO}$ and their influence on the genetic expression of the local tissue has not been well studied. Hence, this study aimed to understand this stem cell-host tissue interaction and exploit this unique approach in treating retinal dystrophies.

1.2 Hypothesis

Erythropoietin-expressing mesenchymal stem cells enhance retinal regeneration through the influence of erythropoietin and mesenchymal stem cells on the retinal transcriptome.

1.3 Research Objectives

This study has one main general objective that is supported by four specific objectives.

General Objective:

To investigate the protective role of erythropoietin-expressing mesenchymal stem cells in a prophylaxis model of sodium iodate-induced retinal degeneration.

Specific Objectives:

i. To characterize culture-expanded erythropoietin-expressing mesenchymal stem cells and evaluate its rescue potential in the survivability of a sodium iodate-induced ARPE-19 retinal cells *in vitro*

ii. To develop an *in vivo* retinal degeneration model by using sodium iodate as a retinotoxin, and characterize the model using electrophysiological and histopathological analysis

iii. To evaluate the degree of visual improvement in the *in vivo* model on a functional and cellular level after intravitreal stem cell transplantation by using comparative electrophysiological and histopathological analysis

iv. To elucidate the protective and prophylactic role of transplanted erythropoietin-expressing mesenchymal stem cells against retinal degeneration in the *in vivo* model on a molecular level by using differential gene expression and topology-based analyses in an RNA-Seq approach

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APPENDICES

Appendix 1: Animal ethics approval for conducting the present study.

UNIVERSITI KEBANGSAAN MALAYSIA

Jawatankuasa Etika Penggunaan Haiwan (UKMAEC) *UKM Animal Ethics Co*

UKM 1.5.24/138/61/2
17hb. Oktober, 2014

UKMAEC
d/a
Unit Sumber Haiwan Makmal
Fakulti Perubatan
Universiti Kebangsaan Malaysia
Jalan Raja Muda Abdul Aziz
50300 Kuala Lumpur.

Profesor Madya Dr. Mae-Lynn Catherine Bastion,
Jabatan Oftalmologi,
Fakulti Perubatan,
Universiti Kebangsaan Malaysia,
Jalan Yaacob Latiff, Bandar Tun Razak,
Cheras, 56000 Kuala Lumpur.

Puan,

Kelulusan Dari Jawatankuasa Etika Penggunaan Haiwan (UKMAEC) Untuk Tajuk: "Rescue of phtoreceptors degeneration by human mesenchymal stem cells expressing erythropoietin in a rat model of retinitis pigmentosa."

Dalam mesyuarat UKMAEC pada 24hb. September, 2014 telah memutuskan bahawa permohonan puan diluluskan. Nombor kelulusan adalah seperti berikut:

FP/OPHTAL/2014/MAE-LYNN/24-SEPT./605-OCT.-2014-SEPT.-2016

Bersama surat ini kami lampirkan sijil kelulusan dengan butiran penyelidikan yang berkaitan. Diharap sijil ini dapat dimanfaatkan pada masa hadapan.

Sekian, terima kasih.

Yang benar,

PROFESOR MADYA DR. KAMISAH YUSOF
Pengerusi UKMAEC
Universiti Kebangsaan Malaysia

s.k. - Pengarah CRIM

d/a Unit Sumber Haiwan Makmal, Fakulti Perubatan, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur
Telefon: +603-9289 5086 / 5091 Faksimili: +603-2698 3743 E-mel: kuhaiwan@medic.ukm.my Laman Web: http://www.medic.ukm.my/laru

Appendix 2: Extension of animal ethics approval for the present study.

UNIVERSITI KEBANGSAAN MALAYSIA
The National University of Malaysia

Pusat Perubatan UKM | ***UKM Medical Centre***

Rujukan : UKM FPR.4/244/ FF-2014-376
Tarikh : 21 Julai 2016

Profesor Dr. Mae-Lynn Catherine Bastion
Jabatan Oftalmologi
Pusat Perubatan UKM

YBhg. Profesor/Datuk/Dato'/Datin/Tuan/Puan,

KELULUSAN PERMOHONAN TAMBAHAN MASA DAN PERUNTUKAN PENYELIDIKAN

Tajuk Penyelidikan : *Rescue of Photoreceptors Degeneration by Human Mesenchymal Stem Cells Expressing Erythropoetin in a Rat Model of Retinitis Pigmentosa*

Kod Projek : FF-2014-376

Dengan hormatnya merujuk kepada perkara di atas.

Adalah dimaklumkan bahawa Jawatankuasa Penyelidikan Perubatan, Pusat Perubatan UKM bertarikh 19 Julai 2016 telah memutuskan bahawa permohonan tambahan masa dan peruntukan bagi penyelidikan di atas diluluskan seperti butiran berikut:

1. Kelulusan Tempoh Kajian (Asal) : 31 Oktober 2014 – 30 Oktober 2016
   Kelulusan Tambahan Masa : 31 Oktober 2016 – 30 Mei 2018

2. Bantuan kewangan (Asal) : Tanpa Bantuan
   Bantuan kewangan (Baru) : RM10,000.00 (Kategori B) daripada Dana Fundamental PPUKM

Bersama-sama ini dilampirkan senarai perincian perbelanjaan yang diluluskan untuk tindakan selanjutnya.

Sekian, terima kasih.

Yang benar,

PROFESOR DR. IMA NIRWANA SOELAIMAN
Timbalan Dekan (Penyelidikan dan Inovasi)
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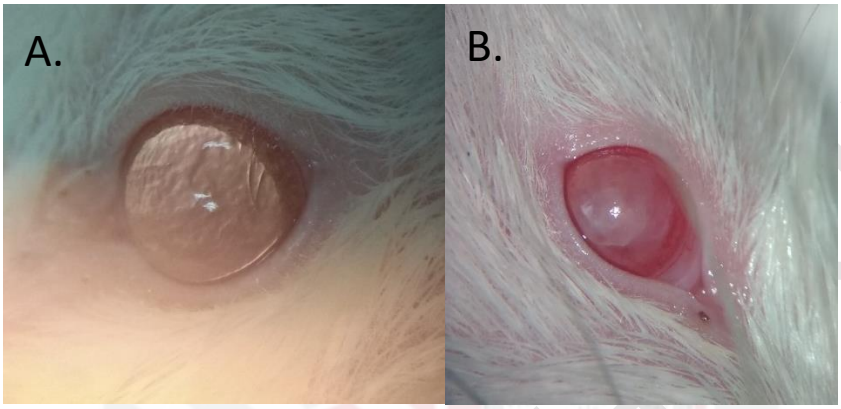
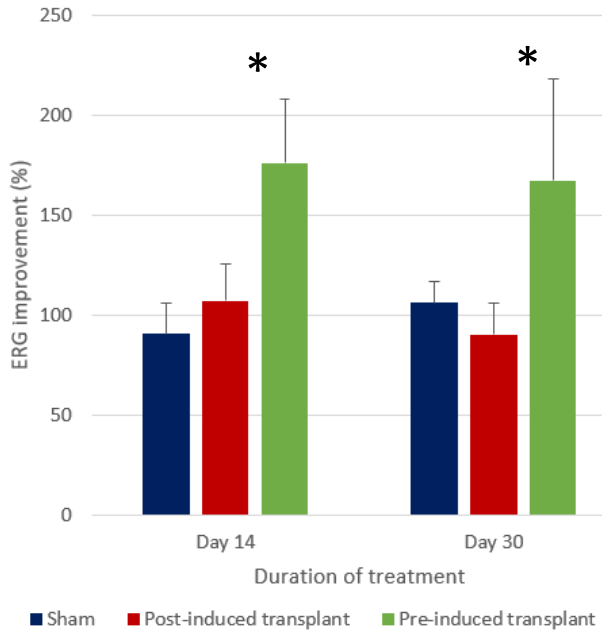
Appendix 3: Formation of cataracts or lens scarring after intravitreal transplantation of stem cells. This may occur if the injecting needle damages the lens, but it has also been reported that intravitreally transplanted MSCs may also cause cataracts (Huang et al., 2019). A. Left eye without transplant. B. Right eye one week after MSC transplant.



Appendix 4: Optimizing MSC transplantation for the present study. Transplanting MSCs four days after $NaIO_3$ administration did not result in any improvements in visual function. Conversely, transplanting MSCs 4 days before $NaIO_3$ administration resulted in a statistically significant improvement in ERG b wave response. The results were presented as mean ± SEM, where *P* values were obtained using two-way ANOVA, followed by Tukey's multiple comparisons test post-hoc where sham was used as the reference (*$P < 0.05$). Sham, degenerated control; Post-induced transplant, MSCs transplanted after $NaIO_3$ administration; Pre-induced transplant, MSCs transplanted before $NAIO_3$ administration.



Appendix 5: Command lines/scripts used in NGS selective alignment and transcript quantification with the Salmon tool. Selective alignment and transcript quantification were then performed in Salmon's mapping-based mode using both the generated reference index and the RNA-Seq FASTQ files. The output files containing the transcript abundance were then stored. A representative example (using the MSCEPO ID) of the command used in Salmon are as follows:

```
# denotes a description and is not a command
$ denotes a command input in Ubuntu

# the Salmon program was invoked
$ salmon activate
# the reference index for Rattus norvegicus was generated
$ cat Rattus_norvegicus.Rnor_6.0.cdna.all.fa Rattus_norvegicus.Rnor_
6.0.dna.toplevel.fa > gentrome.fa
$ salmon index -t gentrome.fa -i r.norv_index --decoys decoys.txt -k 31
# Selective alignment and quantification were performed
$ salmon quant -i r.norv_index -l A -1 EPO1_R1.fastq EPO2_R1.fastq
EPO3_R1.fastq -2 EPO1_R2.fastq EPO2_R2.fastq EPO3_R2.fastq -p
8 --validateMappings -o EPO_quant
```

Appendix 6: Command lines/scripts used for differential gene expression analysis and visualization of transcripts with the DESeq2 tool. The DESeq2 tool was used to perform differential gene expression analysis. The normalized count data was then exported and stored. Visualization of the data was done in Rstudio. The commands used in Tximport and DESeq2 in Rstudio are as follows:

```
# denotes a description and is not a command
> denotes a command input in RStudio

# running tximport, setting the directory, and converting transcript
files > library(tximport)
> library(readr)
> dir <- "C:/Avin/UPM/Thesis/Results/NGS/DeSeq2ShamRef"
> samples <- read.table(file.path(dir,"samples.txt"), header=TRUE)
> files <- file.path(dir, "salmon", samples$run, "quant.sf")
> names(files) <- paste0("sample", 1:12)
> library(GenomicFeatures)
> txdb <- makeTxDbFromGFF("Rattus_norvegicus.Rnor_6.0.98.gtf")
> k <- keys(txdb, keytype = "TXNAME")
> tx2gene <- select(txdb, k, "GENEID", "TXNAME")
> txi <- tximport(files, type = "salmon", tx2gene = tx2gene,
ignoreTxVersion = TRUE)
> sampleTable <- data.frame(condition = factor(rep(c("NTD", "Sham",
"MSC", "EPO"), each = 3)))
> rownames(sampleTable) <- colnames(txi$counts)
# running DESeq2 and differential gene expression analysis
> library(DESeq2)
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> dds <- DESeqDataSetFromTximport(txi, sampleTable, ~condition)
> dds$condition <- relevel(dds$condition, ref = "Sham")
> dds <- DESeq(dds)
> keep <- rowSums(counts(dds)) > 1
> dds <- dds[keep,]
> rld <- rlog(dds, blind=F)
# extracting transformed differentially expressed genes (e.g. MSCEPO)
> resLFC_MSC_EPO <- lfcShrink(dds,
coef="condition_EPO_vs_NTD", type="apeglm")
# annotating data with gene symbols and function (e.g. MSCEPO)
> library(Rattus.norvegicus)
> ens.str <- substr(rownames(resLFC_EPO_Sham), 1, 18)
> resLFC_EPO_Sham$symbol <- mapIds(Rattus.norvegicus, keys=en
s.str, column="SYMBOL", keytype="ENSEMBL", multiVals="first")
> resLFC_EPO_Sham$description <- mapIds(Rattus.norvegicus,
keys= ens.str, column="TERM", keytype="ENSEMBL",
multiVals="first")
# Visualization of differentially expressed genes in RStudio (e.g.
MSCEPO)
> library(EnhancedVolcano)
> EnhancedVolcano(resLFC_EPO_Sham, lab = NA, x = 'log2FoldCha
nge', y = 'padj', xlim = c(-12, 12), ylim = c(0, -log10(10e-20)), xlab =
bquote(~Log[2]~ 'fold change'), ylab = bquote(~-
```

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Log[10]~adjusted~italic(P)), title = 'EPO', subtitle = 'vs Sham' , pCutoff = 0.05, FCcutoff = 2, legend=c('NS','Log2 FC','Adjusted p-value','Adjusted p-value & Log2 FC'), legendPosition = 'right', legendVisible = FALSE, gridlines.major = FALSE,gridlines.minor = FALSE, captionLabSize = 0)

```
> library(pheatmap)
> library(dplyr)
> library(viridis)
> library(gplots)
> library(dendsort)
> topVarianceGenes <- head(order(rowVars(assay(rld)), decreasing= T),500)
> matrix <- assay(rld)[topVarianceGenes,]
> matrix <- matrix - rowMeans (matrix) dend = dendsort(hclust (dist(matrix)))
> pheatmap(matrix, annotation_col=annotation_data, cluster_rows= dend, show_rownames=TRUE, cluster_cols=TRUE, show_colnames = F, color = greenred(20), border_color = "NA", main = "Differentially expressed genes in the stem cell-treated sodium iodate rat models", fontsize_col = 4, fontsize_row = 2.5)
```

Appendix 7: Command lines/scripts used for Topology-based pathway analysis and visualization of differentially expressed genes with the Signaling Pathway Impact Analysis tool. Firstly, the present list of KEGG pathways were downloaded using Ubuntu and stored in the SPIA directory file. After that, the SPIA tool was activated in RStudio, and the expression dataset file was loaded. Once the data was generated, Graphpad Prism (https://www.graphpad.com/ scientific-software/prism/) was used to construct the bar plots. The commands used in SPIA and Rstudio are as follows:

```
# denotes a description and is not a command
$ denotes a command input in Ubuntu
> denotes a command input in RStudio

# downloading the list of KEGG kgml pathway maps
$ curl "http://rest.kegg.jp/list/pathway/rno" | cut -f 1 | while read A ; do
curl -o "${A}.xml" "http://rest.kegg.jp/get/${A}/kgml" ; done
# Activating and running SPIA (e.g. MSCEPO)
> library(SPIA)
> mydir=system.file("extdata/keggxml/rno",package="SPIA")
> makeSPIAdata(kgml.path=mydir,organism="rno",out.path="./")
> EPOsham_spia <-read.csv("EPOsham_spia.csv", row.names = 1)
> EPOsham_spia<
EPOsham_spia[!duplicated(EPOsham_spia$entrez),]
> tg1<-EPOsham_spia[EPOsham_spia$padj<0.1,]
> DE_EPOsham=tg1$log2FoldChange
> names(DE_EPOsham)<-as.vector(tg1$entrez)
> ALL_EPOsham=EPOsham_spia$entrez
> res=spia(de=DE_EPOsham,all=ALL_EPOsham,organism
="rno",data.
dir="./",nB=2000,plots=FALSE,beta=NULL,combine="fisher",verbose=
FALSE)
> res_EPOsham_spia <- res
```

BIODATA OF STUDENT

Avin Koh Ee Hwan was born in Ipoh, but moved back to Kuala Lumpur with his family before kindergarten. He studied in a local secondary school and then took up STPM in Tunku Abdul Rahman College as his Pre-U certification. He later on pursued Biomedical Science as his Bachelor of Science degree in Universiti Tunku Abdul Rahman. After that, he initially pursued a Master's degree in Universiti Putra Malaysia, but was converted to a PhD program in light of his achievements. His project revolves around the application of genetically modified mesenchymal stem cells expressing erythropoietin in a model of retinal degeneration. His expertise spans many aspects of *in vitro*, *in vivo*, and *in silico* research. This includes, but is not limited to, stem cell biology, molecular biology, microscopy, flow cytometry, gene expression study, transplantation study, and also bioinformatics. Throughout his study, he has already published more than 10 papers, including those not strictly related to his research study.

LIST OF PUBLICATIONS

Koh, A. E.-H.*, Kumar, S. S., Farhana, A., Alam, M. K., Mok, P. L. (2021) Mitigation of sodium iodate-induced cytotoxicity in retinal pigment epithelial cells in vitro by transgenic erythropoietin-expressing mesenchymal stem cells. Front Cell Dev Biol. 2021 Mar 15. doi: 10.3389/fcell.2021.652065.

Alsaeedi, H. A., **Koh, A. E.-H.***, Lam, C., Rashid, M. B. A., Harun, M. H. N., Saleh, M. F. B. M., Teh, S. W., Luu, C. D., Ng, M. H., Isa, H. M., Leow, S. N. Then, K. Y., Bastion, M. C., Mok, P. L., Muthuvenkatachalam, B. S. Samrot, A., Swamy, K. B., Nandakumar, J., Kumar, S. S. (2019). Dental pulp stem cells therapy overcome photoreceptor cell death and protects the retina in a rat model of sodium iodate-induced retinal degeneration. Journal of Photochemistry and Photobiology B: Biology, 198. https://doi.org/10.1016 /j.jphotobiol.2019.111561

Koh, A. E.-H.*, Alsaeedi, H. A., Rashid, M. binti A., Lam, C., Harun, M. H. N., Saleh, M. F. bin M., Luu, C. D., Ng, M. H., Isa, H. M., Leow, S. N. Then, K. Y., Bastion, M. C., Kumar, S. S., Khan, M. S. A., Mok, P. L. (2019). Retinal degeneration rat model: A study on the structural and functional changes in the retina following injection of sodium iodate. Journal of Photochemistry and Photobiology B: Biology, 111514. https://doi.org/10.1016/J.JPHOTO BIOL.2019.111514

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*First and equally contributing first author in the related study only

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