Interleukin-17A Induced Human Mesenchymal Stem Cells Are Superior Modulators Of Immunological Function

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Thesis submitted in fulfilment for the degree of

Doctor of Philosophy

In

The Department of Medicine

Faculty of Health Sciences

The University of Adelaide

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Table of Contents

Table of Figures

Table of Tables

Thesis Abstract

Interferon-gamma (IFN-γ) preactivated mesenchymal stem cells (MSC-γ) are highly immunosuppressive but immunogenic *in vivo* due to their inherent expression of major histocompatibility (MHC) molecules. This thesis presents an improved approach where human bone-marrow derived MSC were modified with IL-17A (MSC-17) to enhance T cell immunosuppression but not their immunogenicity. It was demonostrated in **CHAPTER 3** that MSC-17, unlike MSC-γ, showed no induction or upregulation of MHC class I, MHC class II and T cell co-stimulatory molecule CD40, but maintained normal MSC morphology and phenotypic marker expression. When co-cultured with phytohemagglutinin (PHA) activated human T cells, MSC-17 potently suppressed T cell proliferation, inhibited surface CD25 expression and suppressed the elaboration of Th1 cytokines IFN-γ, TNF-α and IL-2 when compared to untreated MSC (UT-MSC). T cell suppression by MSC-17 correlated with increased IL-6 but not indoleamine 2,3-dioxygenase 1, cyclooxygenase-1 and TGF-β. In **CHAPTER 4**, it was shown that MSC-17, but not MSC-γ consistently induced $CD4^{+}CD25^{high}CD127^{low}FoxP3^{+}$ regulatory T cells (iTregs) from PHA activated $CD4^{+}CD25^{-}$ T cells. MSC-induced iTregs expressed the functional Treg markers CD39, CD73, CD69, OX40, CTLA-4 and GITR. Functionally, FACS-sorted MSC- 17-induced-iTregs could suppress human T cell activation (CD154 suppression assay). **CHAPTER 5** was aimed at further dissecting mechanisms by which human MSC- 17 mediate their superior modulation of T cell responses. UT-MSC, MSC-γ and MSC-17 were assessed for their gene expression profile (microarray, 3 human MSC donors). Significantly regulated genes ($p<0.05$, fold change (FC) < -2 or >2) were identified for their biological functions (Database for Annotation, Visualisation and Integrated Discovery, DAVID). Microarray analysis revealed that 1278 differentially expressed genes (902 upregulated; 376 downregulated) were significantly regulated between MSC-γ and UT-MSC and only 67 genes (39 upregulated; 28 downregulated)

between MSC-17 and UT-MSC. Gene ontology analysis of upregulated MSC-γ genes uncovered significant enrichment of genes involved in immune response, antigen processing and presentation, humoral responses and complement activation (eg. HLA genes, complement components and CIITA). This data is consistent with the upregulation of MHC molecules and studies showing increased MSC-γ immunogenicity. MSC-17 upregulated genes were mainly associated with chemotaxis response. This may be essential for T cell recruitment for MSC-17 immunosuppression. MMP13 was highly expressed only in MSC-17 as determined by microarray (FC 15.6) and validated by real-time PCR, hence the potential involvement of MMP13 in the superior immunomodulatory function of MSC-17. The final results **CHAPTER 6** was to translate the findings with human MSC-17 to compact bone-derived mouse MSC (CB mMSC). Unexpectedly, CB mMSC-17 unlike human MSC-17 showed no enhancement of *in vitro* immunosuppression of allogeneically induced $CD4^+$ and $CD8^+$ T cell proliferation. Nevertheless, CB mMSC differ from bone marrow-derived mMSC and may represent a new source to isolate mouse MSC with high purity and potent immunosuppression properties that would be beneficial in a context of allotransplantation rejection. CB mMSC, without IL-17A preconditioning mediated potent *in vitro* suppression of T cells even when used at low doses. In conclusion, human MSC-17 are superior modulators of T cells and can engender Tregs to potently suppress T cell activation with minimal immunogenicity. MSC-17 represent a potential cell therapy to modulate T cell responses for clinical application.

Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (*as listed below) resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Kisha Nandini Sivanathan

Acknowledgements

Firstly, I would like to thank my supervisors Professor Toby Coates, Dr. Darling Rojas-Canales and Professor Stan Gronthos for their constant mentorship and support throughout my PhD. I would also like to thank my external supervisor Associate Professor Benjamin Thierry (University of South Australia) for his supervision at the early stages of my candidature.

I would especially like to sincerely thank my principal supervisor Professor Toby Coates for his excellent mentorship, support, and the opportunity to pursue a PhD in his laboratory. I would also like to express my sincere gratitude to you, Dr. Coates, for all the opportunities you have given to me - travelling nationally and internationally for conferences, meetings and networking. These travels were always very inspiring, recharging and on the personal level, changed my perspective and views about life and all the opportunities that is available ahead. I have always admired your optimism, positive thinking approach and enthusiasm.

I would also like to specially thank Dr. Darling Rojas-Canales, my co-supervisor, for her mentorship, patience, support, motivation, advice, time, laboratory assistance and great friendship! Thanks for helping me pull through those frustrating, difficult laboratory days with positive thoughts and different perspectives.

I thank Dr. Plinio Hurtado for his invaluable intellectual input and for always being my happy, excellent and amazing friend. I also thank Professor Shane Grey (Garvin Institute, Sydney) for his intellectual input and mentorship. I thank Daniella Penko for performing islet inflations, the islet transplant procedure, assistance with other animal work and for being an amazing friend. I also extend my sincere gratitude to Sharon Paton for teaching me mesenchymal stem cell isolations; Dr. Chris Hope for assistance and contributions in the regulatory T cell experiments; The Detmold facility and Ernesto Hurtado for flow sorting; Julie Johnston for her invaluable help in the laboratory and in proof-reading this thesis; Svjetlana Kireta for teaching laboratory techniques, support, advice and also for proof-reading this thesis; The Adelaide Microarray Centre for running the microarray samples; the Department of Histology (The Queen Elizabeth Hospital) and SA Pathology for tissue sectioning and histology staining; all the bone marrow donors and the Royal Adelaide Hospital; all the buffy coat donors and the Australian Red Cross Blood Service; Dr. Michelle Lorimer (Senior Statistician, Data Management and Analysis Centre, University of Adelaide) for statistics consultation; and ALL other individuals and organisations for their support throughout this research.

I would like to acknowledge the support from the University of Adelaide for awarding me the Adelaide Graduate Research Scholarship for 3.5 years and for travel grants; The Hospital Research Foundation for extending my PhD scholarship for 6 months; The Renal Department for supporting me as a student; The Robinson Research Institute, University of Adelaide for the high impact paper funding; and all travel grants awarded by the Royal Adelaide Hospital, The Transplantation Society of Australia and New Zealand, The Transplantation Society, The American Society of Transplantation and The American Society of Transplant Surgeons.

Thank you all, to the past and present members of the laboratory and the Renal Department for everything and for the great 4 years of my PhD. For all those who had been there from the start to the end of my PhD journey: Plinio, Ernesto, Darling, Daniella, Jodie, Julie, Svjetlana and Chris, I would like to specially thank you all for your many years of friendship, memories, laughter, parties, outings and being my laboratory/Australian family; while I was thousands of miles away from home. Thank you, especially to the Hurtado family who brought lots of smiles and happiness in my life! I also thank all my friends who have supported and been there for me, particularly A'fra Usman, Nurul Efifi and Dr. Umi Salleh.

Most importantly, I would like to thank my parents and family, who have continuously supported and helped me throughout my education. I am blessed to have such supportive and encouraging parents who gave me the opportunity to study at the University of Adelaide, to pursue my degree, honours and to the end of my PhD. They have always been open to set me free and find my life in a new country. A parent's love for their child is unconditional. I thank my mother for being by my side, in Australia at the final days of my PhD and for all the delicious healthy meals! I will always remember the "Tortoise and the Hare" story which my father reminded me of as a child.

Lastly, to my PhD, I am very thankful for all the opportunities and experiences I have learnt throughout this journey, especially at a young age. Reflecting on these 4 years, achievements have come way beyond what I have imagined at the start. I have gained wisdom, travelled around the world, learnt many things about myself and the people around me; all of which helped me grow as a person. For everything that failed, what I have learnt - don't be defeated, optimism, patience, dedication, determination and persistence. Essentially, your mind is the master of your success. "You can do it, if you put your mind into it." I would like to thank an individual, a significant person in my life for many years, who was essential for my growth. I was introduced to this book called "The Monk Who Sold His Ferrari" by Robin Sharma, that truly inspired me and was a guide that helped me pull through my PhD, especially

during the difficult times. As we move to the next-phase, we take with us all the lessons we learnt from the past to create a better future. Quoted from this book "The purpose of life is a life of purpose". The end of this PhD is a beginning of my lifelong commitment and dedication as a scientist. I truly enjoyed every step of my PhD journey and will continue to love science and research in the future. I would like to end with the most inspirational speech I have heard, back in October 2014, by Steve Jobs, while I tirelessly wished my experiments would work:

"Sometimes life hits you in the head with a brick. Don't lose faith. I'm convinced that the only thing that kept me going was that I loved what I did. You've got to find what you love. And that is as true for your work as it is for your lovers. Your work is going to fill a large part of your life, and the only way to be truly satisfied is to do what you believe is great work. And the only way to do great work is to love what you do. If you haven't found it yet, keep looking. Don't settle. As with all matters of the heart, you'll know when you find it. And like any great relationships, it just gets better and better as the years roll on. So keep looking until you find it. Don't settle…Your time is limited, so don't waste it living someone else's life. Don't be trapped by dogma – which is living with the results of other people's thinking. Don't let the noise of others' opinions drown out your own inner voice. And most important, have the courage to follow your heart and intuition. They somehow already know what you truly want to become. Everything else is secondary."

- Steve Jobs -

Publications

Sivanathan KN, Gronthos S, Rojas-Canales D, Thierry B, Coates PT. Interferon-gamma modification of mesenchymal stem cells: implications of autologous and allogeneic mesenchymal stem cell therapy in allotransplantation. *Stem Cell Rev.* 2014;10(3):351-375. – IF **3.214** Citations: **34** (**APPENDIX Published Paper 1**)

Lett B, **Sivanathan KN**, Coates PT. Mesenchymal stem cells for kidney transplantation. *World J Clin Urol.* 2014;3(2):87-95. (**APPENDIX Published Paper 2)**

Sivanathan KN, Rojas-Canales DM, Hope CM, et al. Interleukin-17A-Induced Human Mesenchymal Stem Cells Are Superior Modulators of Immunological Function. *Stem Cells.* 2015;33(9):2850-2863. – IF **6.523** Citations: **5** (**APPENDIX Published Paper 3**)
Press release: http://www.adelaide.edu.au/news/news79202.html
Stem Cell Video Highlight: (Invited) https://www.youtube.com/watch?v=gP6GONfRP80
Featured article in the Regenerative Medicine Weekly Newsletter (26 August 2015)

Sivanathan K.N., Rojas-Canales D, Gronthos S, Grey S.T., Coates P.T. Gene microarray comparative analysis of interferon-gamma and interleukin-17A preconditioned human Mesenchymal Stem Cells (**manuscript in preparation**)

Sivanathan K.N., Rojas-Canales D, Gronthos S, Grey S.T., Coates P.T. Immunodepletion and hypoxia preconditioning of mouse compact bone cells as a novel protocol to isolate highly immunosuppressive Mesenchymal Stem Cells (**manuscript in preparation**)

Sivanathan K.N., Rojas-Canales D, Coates P.T. Mesenchymal stem cells indirectly modulate T cell immunosuppression through the generation of regulatory T cells (**manuscript in preparation**)

Presentations

11th April 2016	Transplantation Society of Australia and New Zealand (TSANZ), Sydney, Australia **Sivanathan K.N., et al.** Microarray gene profiling of immunosuppressive interleukin-17A preactivated human bone marrow-derived Mesenchymal stem cells (MSC-17)
16th Nov 2015	IPITA-IXA-CTS Joint Congress, Melbourne, Australia **Sivanathan K.N., et al.** Gene microarray comparative analysis of interferon-gamma and interleukin-17A preconditioned human Mesenchymal Stem Cells (**oral presentation**)
16th Nov 2015	IPITA-IXA-CTS Joint Congress, Melbourne, Australia Bron Lett, **Sivanathan K.N., et al.** Imaging of Iron nano-particle labelled Mesenchymal Stem Cells in ovine heterotopic kidney transplantation (**oral presentation**)
13th Nov 2015	Transplantation Science Symposium, Lorne, Australia **Sivanathan K.N., et al.** Microarray gene profile study of immunosuppressive interleukin-17A preactivated human Mesenchymal Stem Cells (**oral presentation – Mentor-Mentee Award**)
22nd June 2015	Transplantation Society of Australia and New Zealand (TSANZ), Canberra, Australia **Sivanathan K.N., et al.** IL-17A modulated human Mesenchymal Stem Cells as a novel cell therapy to engender regulatory T cells (Tregs). (**President's Prize Symposium – oral presentation – Young Investigator Award**)
6th May 2015	Invited speaker, Athersys Inc., Cleveland, Ohio, U.S.A Interleukin-17A induced Mesenchymal Stem Cells are superior modulators of immunological function
3rd May 2015	American Transplant Congress, Philadelphia, U.S.A **Sivanathan K.N., et al.** Interleukin-17A induced Mesenchymal Stem Cells are superior modulators of immunological function. (**poster presentation – Poster of Distinction – Young Investigator Award**)
6th Nov 2014	Robinson Institute Research Symposium, University of Adelaide, Australia
14th Aug 2014	Invited speaker, The Karp Laboratory, Harvard Medical School Interferon-gamma (IFN-γ) and Interleukin-17 (IL-17) modification of Mesenchymal Stem Cells
11th Aug 2014	Invited speaker, The Thomas Startzl Institute, Pittsburgh Ex vivo modification of Mesenchymal Stem Cells in Allotransplantation

8th Aug 2014	Invited speaker, Professor Wang, Yi-Gang Lab, University of Cincinnati Ex vivo modification of Mesenchymal Stem Cells in Allotransplantation
July 2014	World Transplant Congress, Moscone West Convention Centre, San Francisco **Sivanathan K.N., et al.** Interferon-Gamma and onterleukin-17 modified Mesenchymal Stem Cells directly or indirectly modulate T cell responses by expressing inhibitory factors, downregulating T cell activation and inducing regulatory T cells (**oral presentation – Mentor-Mentee Award**)
June 2014	The Transplantation Society of Australia and New Zealand (TSANZ), Canberra, Australia **Sivanathan K.N., et al.** Interferon-Gamma and interleukin-17A enhance Mesenchymal Stem Cells (MSC) T cell suppressive function by mediating an increase and induction of $CD4^{+}CD25^{high}CD127^{low}FoxpP3^{+}$ regulatory T cells (**oral presentation – Young Investigator Award**)
11th Dec 2013	Centre for Stem Cell Research, The Robinson Institute, University of Adelaide Research Day, 2013, Australia **Sivanathan K.N., et al.** Mesenchymal Stem Cells preconditioned with proinflammatory cytokines enhance T cell inhibition by the downregulation of CD25 on activated T cells, expression of immunosuppressive factors and induction of regulatory T cells. (**poster presentation**)
17th July 2013	Invited speaker at Professor Dragun's Lab, Charite Hospital (Charité - Universitätsmedizin Berlin), Germany Ex vivo modification of Mesenchymal Stem Cells in Allotransplantation
7th -11th July 2013	12th Congress of the Cell Transplant Society, Milan, Italy **Sivanathan K.N., et al.** Mesenchymal Stem Cells preconditioned with proinflammatory cytokines enhance T cell inhibition by the downregulation of CD25 on activated T cells, expression of immunosuppressive factors and increase in regulatory T cells. (**oral presentation – Young Investigator Award**)
26th-28th June 2013	The Transplantation Society of Australia and New Zealand (TSANZ), Canberra, Australia **Sivanathan K.N., et al.** *Ex vivo* modified Mesenchymal Stem Cells (MSC) enhance T cell immunosuppression by the expression of inhibitory molecules, downregulation of CD25 on activated T cells and The increase in regulatory T cells. (**oral presentation – Young Investigator Award**)
5th June 2013	Australian Society for Medical Research (ASMR), Adelaide, Australia **Sivanathan K.N., et al.** Proinflammatory cytokine preactivated Mesenchymal Stem Cells suppress T cell proliferation by inhibiting T cell activation, increase in regulatory T cells and expression of immunosuppressive factors. (**oral presentation**)

21 May 2013	The Medical Staff Society Research Prize, Royal Adelaide Hospital, Adelaide, Australia (Finalist) **Sivanathan K.N., et al.** Interferon-Gamma preconditioned Mesenchymal Stem Cells enhance T cell immunosuppression via the expression of inhibitory molecules, downregulation of CD25 on activated $CD4^+$ or CD8+ T cells and increase in regulatory T cells. (**oral presentation**)
25th-28th Nov 2012	Australian Health and Medical Research Congress (AHMRC), Adelaide, Australia **Sivanathan K.N., et al.** Interferon-Gamma and interleukin-17A modification enhance the immunomodulatory function of Mesenchymal Stem Cells (**poster presentation**)
31 Aug 2012	Faculty of Health Sciences Postgraduate Research Conference, University of Adelaide, Australia **Sivanathan K.N., et al.** Real-Time magnetic resonance imaging localisation of superparamagnetic iron oxide nanoparticle-labelled Mesenchymal Stem Cells in ovine kidney autografts. (**poster presentation**)
2nd-6th June 2012	American Transplant Congress (ATC) International Conference The John B. Hynes Convention Centre, Boston, MA. **Sivanathan K.N., et al.** IFN-gamma preconditioning enhances the immunosuppressive properties of Mesenchymal Stem Cells to inhibit PHA-activated T cell proliferation (**poster presentation – presented by PT Coates**) Dyane A., Johnston J., **Sivanathan K.N., et al.** Magnetic resonance imaging cell tracking of Mesenchymal Stem Cells injected in kidney autografts of sheep. (**poster presentation – presented by PT Coates**)

Awards and Grants

19 Nov 2015	Royal Adelaide Hospital (RAH) Research Foundation 2016 Clinical Project Grant: "Interleukin-17A induced human Mesenchymal Stem Cells in improving transplant rejection outcomes in preclinical models of human islet transplantation – A proof-of-concept study" (**AUD 50 000**)
October 2015	The Hospital Research Foundation Grant Funded Scholarship **(AUD 25,849 / annum)**
August 2015	The International Transplantation Science Mentee-Mentor Travel Awards for the 2015 Transplantation Science Symposium, 11-13 Nov, 2015 Lorne, Australia **(USD 800)**
August 2015	The Robinson Research Institute High Impact Paper Funding, University of Adelaide **(AUD 2680.00)** (Sivanathan KN *et. al.*, 2015, Stem Cells)
June 2015	Travel grant for the Transplantation Science Symposium in Lorne, Victoria by TSANZ **(AUD 900)**
June 2015	TSANZ Young Investigator Award **(AUD 780.92)**
May 2015	Young Investigator Award, American Transplant Congress, Philadelphia, U.S.A. **(USD 1000)**
May 2015	Special Purpose Fund (to attend the American Transplant Congress), Royal Adelaide Hospital (**AUD 5000)**
May 2015	Poster of Distinction, American Transplant Congress, 2015, Philadelphia, U.S.A
June 2014	TSANZ Young Investigator award – at the 2014 TSANZ ASM (**AUD 701**)
June 2014	The Walter Dorothy Duncan Trust Fund, University of Adelaide – Travel Grant **(AUD 1500)**
25 April 2014	The International Transplantation Science Mentee-Mentor Travel Awards for the 2014 World Transplant Congress, 26-31, July, San Francisco CA, USA **(USD 2000)**
July 2013	The Transplantation Society Young Investigator Travel Award for the 12th Congress of the Cell Transplant Society, Milan, Italy, 2013 **(USD 2250)**
June 2013	TSANZ Young Investigator award – at the 2013 TSANZ ASM **(AUD 551.10)**
June 2013	The Walter Dorothy Duncan Trust Fund, University of Adelaide – Travel Grant **(AUD 2200)**
March 2012-Sept 2015	International Adelaide Graduate Research Scholarship (AGRS), The University of Adelaide (**full tuition and living allowances for 3.5 years**)

Scientific Community engagement

2014 – 2018 (current)	Cell Transplant and Regenerative Medicine (CTRMS) Society, Young Investigator Committee Member • organising the international IPITA-IXA-CTS Joint Congress (Melbourne, Nov 2015) • fundraising, awards and publicity (social) involvement • organising the upcoming CTS joint congress in Halifax, Canada • joint international publications – manuscript in preparation
18 Nov 2015	Women in Transplantation, Networking Breakfast at the International IPITA-IXA-CTS Joint Congress – invited speaker • only Australian representative in a panel of 5 female young investigators in the field of transplantation • discussed the role of women in the field of transplantation, challenges currently faced by women in this field of research and the future of women in research • primary focus of this event was to generate discussion and identify opportunities for women in transplantation and to support the next generation of woman leader
3rd July 2015	The University of Adelaide Press Release **http://www.adelaide.edu.au/news/news79202.html** (>5 million media views as reported on 23rd July 2015)
July 2015	Stem Cell Journal Video highlight (Sivanathan KN *et. al.* 2015) **https://www.youtube.com/watch?v=gP6GONfRP80**
2014 – current	Reviewer – active reviewer for: 1 Stem Cells (2015), 1 Kidney International (2014), 1 Nephrology (2014)
2014-2015	HDR student engagement team, School of Medicine, University of Adelaide • help design the future School of Medicine building space
2013	Committee Member of Health Science Postgraduate Association, University of Adelaide • publicity of the newly established association at the University of Adelaide Postgraduate Conference, National Wine Centre, 2013 • organising events for the association
12th Aug 2012	Science Alive, National Science Week, Representing the Robinson Institute (University of Adelaide) at the science exhibition • translating stem cell research to the society

Abbreviations

α-MEM - alpha Minimum Essential Medium

Ab – antibody

Ag – antigen

APC – antigen presenting cells

APC – allophycocyanin

AMR – antibody mediated rejection

ATP - adenosine triphosphate

ADP - adenosine diphosphate

AMP - adenosine monophosphate

AP-1 – activator protein 1

ANOVA – analysis of variance

AUC – area under the curve

bp – base pair

BM – bone marrow

BMMNC – bone marrow mononuclear cells

BGL – blood glucose levels

CEL – probe cell intensity files

CB – compact bones

CBA – cytokine bead array

cAMP - cyclic adenosine monophosphate

CD – cluster of differentiation

cpm – cell counts per minute

CTL – cytotoxic T cells

CTLA-4 – cytotoxic T-lymphocyte associated antigen-4

cDNA – complementary DNA

CFU-F – colony forming unit fibroblast

CMR – cell-mediated rejection

ConA – concavalin A

CXCL – chemokine C-X-C motif ligand

CXCR – C-X-C chemokine receptor

CCL – chemokine C-C motif ligand

CsA – cyclosporine A

CFSE – carboxyfluorescein succinimidyl ester

Cox – cyclooxygenase

DAVID – Database for Annotation, Visualization and Integrated Discovery

DC – dendritic cells

DMSO – dimethyl sulfoxide

DTH – delayed-type hypersensitivity

DNA – Deoxyribonucleic acid

$DiOC_{18}(3)$ – 3,3'-Dioctadecyloxacarbocyanine perchlorate

EAE – experimental autoimmune encephalomyelitis

EDTA – Ethylenediaminetetraacetic acid

ELISA – Enzyme-linked immunosorbant assay

ECM – extracellular matrix

ERK – extracellular signal-regulated kinases

FoxP3 – forkhead box P3

FACS – fluorescence-activated cell sorting

FBS – fetal bovine serum

FMO – fluorescence minus one

FSC – forward side scatter

FASL – FAS ligand

FITC – Fluorescein isothiocyanate

GITR – glucocorticoid-induced TNFR-related protein

GARP - glycoprotein A repetitions predominant, LLRC32, Garpin

GM-CSF – granulocyte-macrophage colony-stimulating factor

GvHD – graft versus host disease

GOTERM – gene ontology term

HBSS – Hank's Balanced Salt Solution

HO-1 – heme oxygenase-1

HLA-DR – human leukocyte antigen-DR

HPRT-1 – hypoxanthine phosphoribosyltransferase-1

H&E – Hematoxylin and eosin

HSC – haematopoietic stem cells

HGF –hepatocyte growth factor

IDO – indoleamine 2,3-dioxygenase

Ig – immunoglobulin

i.v. – intravenous

i.p. – intraperitoneal

IL - interleukin

iDC – immature DC

IPGTT – intraperitoneal glucose tolerance test

IL-17A – interleukin-17A

IFN-γ – interferon-gamma

IFNGR – interferon-gamma receptor

IGF-1 –insulin growth factor-1

iTreg – inducible regulatory T cells

JAK – Janus Kinase

LPS – Lipopolysaccharide

LAG-3 – lymphocyte-activation gene 3

LBP – lipopolysaccharide binding protein

LncRNA – long non-coding RNA

LAP - latent-associated peptide

mRNA – messenger RNA

MAPK – mitogen activated protein kinases

MSC – mesenchymal stem cells

MSC-17 – Interleukin-17A pre-treated MSC

MSC-γ – IFN-γ pre-treated MSC

mMSC – mouse MSC

mDC – mature DC

MMP – matrix metalloproteinase

MTI-MMP – membrane Type 1 MMP

MMF – mycophenolate mofetil

MFI – mean fluorescence intensity

MHC – major histocompatibility complex

MLR – mixed lymphocyte reaction

MDSC – myeloid derived suppressor cells

MST – mean survival times

miRNA – microRNA

NF-κB – nuclear factor kappa-light-chain-enhance of activated B cells

nTreg – natural regulatory T cells

NK – natural killer

PHA – phytohemagglutinin

PCA – principal component analysis

PBMC – peripheral blood mononuclear cells

PCR – polymerase chain reaction

PD-1 – programmed death-1

PBS – phosphate-buffered saline

PE – phycoerythrin

PE-Cy7 – phycoerythrin-Cy-7

PE-Cy5.5 – phycoerythrin-Cy-5.5

PD-L1 – programmed death ligand-1, B7-H1

PGE_2 –prostaglandin-E2

POD – post operative day

RNA – ribonucleic acid

RT-PCR – real-time PCR

RBC – red blood cells

RPMI – Roswell Park Memorial Institute Medium

RMA – robust multi-array analysis

SAA1 – serum amyloid A1

Sca-1 – stem cell antigen 1

SD – standard deviation

SDF-1 – stromal cell-derived factor-1

SEM – standard error of the mean

STAT – signal transducer and activator of transcription 5

STZ – Streptozotocin

STRO-1 – stromal precursor antigen-1

snoRNA – small nucleolar RNA

SSC – side scatter

TAC – transcriptome analysis console

Th – T helper

Treg – regulatory T cells

Tr1 – T regulatory 1

Tr3 – TGF-β expressing regulatory cells

TLR – Toll-like receptor

TGF-β1 – transforming growth factor beta 1

TCR – T cell receptors

TIMP – tissue-inhibitor of metalloproteinase

TNF-α – tumor necrosis factor-alpha

TRAF - TNF receptor-associated factors

T1D - Type 1 Diabetes

UT-MSC – untreated / unmodified MSC

VEGF – vascular endothelial growth factor

[^{3}H]-Thymidine – tritiated thymidine

γδ T cells – gamma delta T cells