UNIVERSITI SAINS MALAYSIA
GERAN PENYELIDIKAN UNIVERSITI
PENYELIDIKAN
LAPORAN AKHIR

REGULATORY ROLE OF T HELPER 17 (TH17) CELLS IN AUTOIMMUNE DIABETES
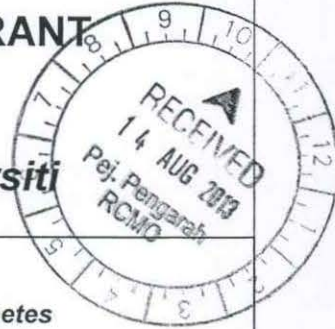
PENYELIDIK

PROF. DR. NORAZMI MOHD NOR

PENYELIDIK BERSAMA

PROF. DR. NIK SORIANI YAACOB
DR. NURUL ASMA ABDULLAH

2013

RESEARCH UNIVERSITY GRANT
FINAL REPORT
Laporan Akhir
Geran Penyelidikan Universiti

UNIVERSITI SAINS MALAYSIA

A.	**TITLE OF RESEARCH:** *Tajuk penyelidikan:* **Regulatory Role Of T Helper 17 (Th17) Cells In Autoimmune Diabetes**
B.	**DETAILS OF RESEARCHER** / *MAKLUMAT PENYELIDIK*
(i)	**Name of Research Leader** *Nama Ketua Penyelidik* **Prof. Dr. Norazmi Mohd Nor**
	Name of Co-Researchers *Nama Penyelidik Bersama* **Prof. Dr. Nik Soriani Yaacob; Dr. Nurul Asma Abdullah**
(ii)	**School/Institute/Centre/Unit :** *Pusat Pengajian /Institut/Pusat/Unit :* **Pusat Pengajian Sains Kesihatan**

C. **Research Platform (Please check for appropriate box):**
Pelantar Penyelidikan (Sila tanda kotak berkenaan):

- [ ] **A. Life Sciences**
  Sains Hayat

- [ ] **B. Fundamental**
  Fundamental

- [ ] **C. Engineering & Technology**
  Kejuruteraan & Teknologi

- [ ] **D. Social Transformation**
  Transformasi Sosial

- [ ] **E. Information & Communication Technology (ICT)**
  Teknologi Maklumat & Komunikasi

- [ ] **F. Clinical Sciences**
  Sains Klinikal

- [x] **G. Biomedical & Health Sciences**
  Sains Kesihatan & Bioperubatan

D. **Duration of this research :**
Tempoh masa penyelidikan ini :

  *Duration : 36 bulan
  Tempoh :

  From   : 01 Mei 2010   To   : 30 April 2013
  Dari: Ke :

E. ABSTRACT OF RESEARCH

(An abstract of between 100 and 200 words must be prepared in Bahasa Malaysia and in English. This abstract will be included in the Annual Report of the Research and Innovation Section at a later date as a means of presenting the project findings of the researcher/s to the University and the community at large)

Abstrak Penyelidikan

(Perlu disediakan di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan juga Bahasa Ingge** Abstrak ini akan dimuatkan dalam Laporan Tahunan Bahagian Penyelidikan & Inovasi sebagai satu cå untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti & masyarakat luar).

Th17 cells are thought to be involved in various autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and experimental autoimmune encephalomyelitis. The role of Th17 cells in the pathogenesis of autoimmune or type I diabetes (T1D) was thus investigated using the non-obese diabetic (NOD) and the non-obese diabetic resistant (NOR) control mouse models. The expression of various cytokines in the Th17 cells was assessed using flow cytometry following incubation with the peroxisome proliferator activated receptor gamma (PPARγ) agonists, ciglitazone and 15-prostagalndin J2, and the PPARγ antagonist, GW9662 to further delineate the influence of this immunoregulatory nuclear receptor on the Th17 cell function. Basically, the constitutive level of the signature IL17A expression by Th17 cells in NOD mice was more than that of NOR mice and that ciglitazone enhanced the expression of this cytokine in NOD mice whereas 15-PGJ2 and GW9662 had no effect. Interestingly, despite eliminating IFNγ-expressing cells (Th1) at the start of culture, Th17 cells of NOD mice expressed high levels of this cytokine upon culture with ciglitazone suggesting that Th17 may convert to Th1-like cells in T1D in the presence of this PPARγ agonist and may contribute to the pathogenesis of this autoimmune disease.

Sel Th17 dipercayai terlibat dalam pelbagai penyakit autoimun seperti skelosis berbilang, reumatoid artritis dan enkefalomilitis autoimun experimental. Oleh itu peranan sel Th17 dalam patogenesis diabetes autoimun atau diabtes jenis 1 (T1D) telah dikaji menggunakan model mencit diabetik tak obes (NOD) dan model mencit rintang diabetik tak obes (NOR) sebagai kontrol. Pengekspresian pelbagai sitokin oleh sel Th17 diukur menggunakan flow sitometri setelah sel-sel tersebut dieram dengan agonis reseptor teraktif proliferator peroksisom gama (PPARγ), iaitu siglitazon dan 15-prostagalndin J2, serta antagonis PPARγ, iaitu GW9662, untuk meneliti pengaruh reseptor ini terhadap fungsi sel Th17. Secara dasarnya aras konstitutif sitokin penanda sel Th17, iaitu IL17A, lebih tinggi pada mencit NOD berbanding mencit NOR. Tambahan pula siglitazon meningkatkan ekspresi sitokin ini dalam mencit NOD manakala 15-PGJ2 dan GW9662 tidak mempunyai kesan terhadap sel Th17. Apa yang menarik adalah walaupun sel-sel yang mengekspres IFNγ (sel Th1) telah dimusnahkan pada awal kajian, sel Th17 daripada mencit NOD mampu mengekspres sitokin ini apabila dikultur dengan siglitazon. Ini mencadangkan bahawa sel Th17 daripada mencit NOD boleh bertukar menjadi seperti sel Th1 apabila ditindak oleh agonis PPARγ dan ini mencadangkan sel tersebut mungkin berperanan dalam patogenesis penyakit autoimun ini.

F.	SUMMARY OF RESEARCH FINDINGS Ringkasan Penemuan Projek Penyelidikan

SUMMARY OF RESEARCH FINDINGS
Ringkasan Penemuan Projek Penyelidikan

1. The constitutive level of the signature IL17A expression by Th17 cells in NOD mice was more than that of NOR mice

2. The PPARγ agonist, ciglitazone, enhanced the expression of IL17A cytokine in NOD mice

3. Th17 cells of NOD mice expressed high levels of the pathogenic cytokine, IFNγ, upon culture with ciglitazone

4. Th17 cell control may be dysregulated in NOD mice and may contribute to the pathogenesis of type 1 diabetes

G. COMPREHENSIVE TECHNICAL REPORT

Applicant are required to prepare a Comprehensive Technical Report explaning the project.
(This report must be appended separately)
Sila sediakan laporan teknikal lengkap yang menerangkan keseluruhan projek ini.
[Sila gunakan kertas berasingan]

Sila lihat Lampiran

List the key words that reflects your research:
Senaraikan kata kunci yang mencerminkan penyelidikan anda:

English	Bahasa Malaysia
Autoimmune diabetes	Diabetes autoimun
Th17 cells	Sel Th17
PPARγ	PPARγ

H.

a) Results/Benefits from this research
Hasil Penyelidikan

No. *Bil:*	Category/Number: *Kategori/ Bilangan:*	Promised	Achieved
1.	**Research Publications** (Specify target journals) ***Penerbitan Penyelidikan*** *(Nyatakan sasaran jurnal)*	1	**Finalising draft**
2.	**Human Capital Development**		
	a. **Phd Students**		
	b. **Master Students**	1	**1 (writing thesis)**
	c. **Undergraduate Final Year Project**		
	d. **Research Officer**		
	e. **Research Assisstant**		
	f. **Others: Please Specify**		
3.	**Patents** *Paten*		
4.	**Specific @ Potential Applications** *Spesifik/Potensi Permohonan*		
5.	**Networking & Linkages** *Jaringan & Jalinan*		
6.	**Possible External Research Grants to be Acquired** *Jangkaan Geran Penyelidikan Luar Dipohon*		

- Kindly provide copies/evidence for Category 1 to 6.

b) Equipments used for this research.
Peralatan yang telah digunakan dalam penyelidikan ini.

Items *Perkara*	Approved Equipment	Approved Requested Equipment	Location
Specialized Equipment Peralatan khusus			
Facility Kemudahan			
Infrastructure Infrastruktur			

- Please use additional appendix

I.   BUDGET / *BAJET*

Perbelanjaan :: Expenditure
Project Account No.   : 1001 / PPSK/813029

Total Approved Budget   : RM 249,620
Total Additional Budget   : RM 0
Grand Total Approved Budget   : RM 249,620

                                                        Yearly Budget Distributed
                                                        Year 1   2010   : RM 96,940
                                                        Year 2   2011   : RM 79,440
                                                        Year 3   2012   : RM73,240

                                                        Additional Budget Approved
                                                        Year 1   2010   : RM 96,940
                                                        Year 2   2011   : RM 79,440
                                                        Year 3   2012   : RM73,240
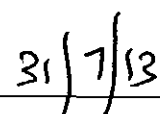**Total Expenditure**   : RM 249,527.87
Balance   : RM 92.13

- **Please attach final account statement from Treasury**

Signature of Researcher
Tandatangan Penyelidik

31/7/13

Date
Tarikh

Pejabat Pelantar Penyelidikan 2009

H.	RESEARCH COMMITTEE COMMENTS *KOMEN JAWATANKUASA PENYELIDIKAN PERINGKAT PTJ*

General Comments:
Ulasan Umum:

....

....

....

....

....

Signature and Stamp of Chairperson of PTJ's Evaluation Committee
Tandatangan dan Cop Pengerusi Jawatankuasa Penilaian PTJ

Date   : ....
Tarikh :

sufficient output .

Signature and Stamp of Dean/ Director of PTJ's
Tandatangan dan Cop Dekan/ Pengarah PTJ

Date   : ...4.../...8.../..13......
Tarikh :

PROFESOR AHMAD HJ. ZAKARIA
Dekan
Pusat Pengajian Sains Kesihatan
Kampus Kesihatan
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan

UNIVERSITI SAINS MALAYSIA
JABATAN BENDAHARI
KUMPULAN WANG UNIVERSITI PENYELIDIKAN (RU)
PENYATA PERBELANJAAN SEHINGGA 31 JULAI 2013

	RM	
Jumlah Geran :	249,620.00	Ketua Projek : PROF NORAZMI MOHD NOR
Peruntukan MEI 2010 : (Tahun 1)	96,940.00	Tajuk Projek: Regulatory Role Of T Helper 17 (Th17) Cells In Autoimmune Diabete
Peruntukan MEI 2011 : (Tahun 2)	79,440.00	Tempoh : 36 Bulan (01/05/2010-30/04/2013)
Peruntukan MEI 2012 : (Tahun 3)	73,240.00	No. Akaun : 1001/PPSK/813029

Kwgan	Akaun	PTJ	Projek	Peruntukan Projek	Perbelanjaan Terkumpul sehingga Tahun lalu	Peruntukan Semasa	Tanggungan Semasa	Bayaran Tahun Semasa	Belanja Tahun Semasa	Baki Projek
1001	11000	PPSK	813029	107,820.00	14,744.90	93,075.10	-	-	-	93,075.10
1001	14000	PPSK	813029	-	674.95	(674.95)	-	-	-	(674.95)
1001	15000	PPSK	813029	-	500.00	(500.00)	-	-	-	(500.00)
1001	21000	PPSK	813029	10,000.00	33,168.41	(23,168.41)	-	5,446.90	5,446.90	(28,615.31)
1001	22000	PPSK	813029	-	200.00	(200.00)	-	-	-	(200.00)
1001	23000	PPSK	813029	-	965.50	(965.50)	-	-	-	(965.50)
1001	24000	PPSK	813029	-	-	-	-	-	-	-
1001	25000	PPSK	813029	-	-	-	-	-	-	-
1001	26000	PPSK	813029	-	-	-	-	1,185.00	1,185.00	(1,185.00)
1001	27000	PPSK	813029	129,300.00	179,104.34	(49,804.34)	1,442.75	8,503.00	9,945.75	(59,750.09)
1001	28000	PPSK	813029	-	-	-	-	-	-	-
1001	29000	PPSK	813029	2,500.00	3,592.12	(1,092.12)	-	-	-	(1,092.12)
1001	32000	PPSK	813029	-	-	-	-	-	-	-
1001	35000	PPSK	813029	-	-	-	-	-	-	-
				249,620.00	232,950.22	16,669.78	1,442.75	15,134.90	16,577.65	92.13

Regulatory Role of T helper 17 (Th17) cells in Autoimmune Diabetes

Mohd Khairi CHE PA[1]; Nik Soriani YAACOB[2]; Mohd Nor NORAZMI[1*];

Schools of [1]Health, and [2]Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

* Corresponding Author (norazmi@kb.usm.my)

ABSTRACT

Th17 cells are thought to be involved in various autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and experimental autoimmune encephalomyelitis. The role of Th17 cells in the pathogenesis of autoimmune or type I diabetes (T1D) was thus investigated using the non-obese diabetic (NOD) and the non-obese diabetic resistant (NOR) control mouse models. The expression of various cytokines in the Th17 cells was assessed using flow cytometry following incubation with the peroxisome proliferator activated receptor gamma (PPARγ) agonists, ciglitazone and 15-prostagalndin J2, and the PPARγ antagonist, GW9662 to further delineate the influence of this immunoregulatory nuclear receptor on the Th17 cell function. Basically, the constitutive level of the signature IL17A expression by Th17 cells in NOD mice was more than that of NOR mice and that ciglitazone enhanced the expression of this cytokine in NOD mice whereas 15-PGJ2 and GW9662 had no effect. Interestingly, despite eliminating IFNγ-expressing cells (Th1) at the start of culture, Th17 cells of NOD mice expressed high levels of this cytokine upon culture with ciglitazone suggesting that Th17 may convert to Th1-like cells in T1D in the presence of this PPARγ agonist and may contribute to the pathogenesis of this autoimmune disease

1