UNIVERSITI SAINS MALAYSIA
GERAN PENYELIDIKAN UNIVERSITI
PENYELIDIKAN
LAPORAN AKHIR

MOLECULAR BASIS OF PRIMARY AND SECONDARY RESISTANCE TO IMATINIB MESYLATE

PENYELIDIK

PROFESOR DR. ABDUL AZIZ BABA

PENYELIDIK BERSAMA

PROFESOR RAVINDRAN ANKATHIL
PROF. MADYA DR. ROSLINE
DR. ABU DZARR
MARJANU HIKMAH ELIAS

2012

FINAL REPORT
FUNDAMENTAL RESEARCH GRANT SCHEME (FRGS)

Laporan Akhir Skim Geran Penyelidikan Asas (FRGS) IPT
Pindaan 1/2010

A

RESEARCH TITLE : **Molecular basis of primary and secondary resistance to IMATINIB MESYLATE**

Tajuk Penyelidikan **treatment in Chronic Myeloid Leukemia patients**

PROJECT LEADER : **PROF (DR) ABDUL AZIZ BABA**
Ketua Projek

PROJECT MEMBERS (including GRA) :
Ahli Projek
1. **PROF RAVINDRAN ANKATHIL**
2. ASSOCIATE PROF (DR) ROSLINE
3. DR ABU DZARR
4. MARJANU HIKMAH BINTI ELIAS

PROJECT ACHIEVEMENT *(Prestasi Projek)*

B

ACHIEVEMENT PERCENTAGE			
Project progress according to milestones achieved up to this period	**0 - 50%**	**51 - 75%**	**76 - 100%**
Percentage			√

RESEARCH OUTPUT		
Number of articles/ manuscripts/ books *(Please attach the First Page of Publication)*	**Indexed Journal**	***Non-Indexed Journal***
Conference Proceeding *(Please attach the First Page of Publication)*	**International**	***National***
Intellectual Property *(Please specify)*		

HUMAN CAPITAL DEVELOPMENT √

Human Capital	**Number**				**Others** (please specify)
	On-going		**Graduated**		
Citizen	Malaysian	Non Malaysian	Malaysian	Non Malaysian	
PhD Student	√				
Master Student					
Undergraduate Student					
Total	1				

EXPENDITURE *(Perbelanjaan)*

Budget Approved *(Peruntukan diluluskan)*	: **RM 146,000.00**
Amount Spent *(Jumlah Perbelanjaan)*	: **RM 145,959.46**
Balance *(Baki)*	: **RM 40.54**
Percentage of Amount Spent *(Peratusan Belanja)*	: 99.97 %

ADDITIONAL RESEARCH ACTIVITIES THAT CONTRIBUTE TOWARDS DEVELOPING SOFT AND HARD SKILLS
(Aktiviti Penyelidikan Sampingan yang menyumbang kepada pembangunan kemahiran insaniah)

D

International

Activity	Date (Month, Year)	Organizer
1) 8th International Conference of Anticancer Research	17-22 October, 2008	International Journal of Cancer Research and Treatment.
2) 9th Asia Pacific Conference on Human Genetics	30-3 December, 2010	Asia Pacific Society of Human Genetics.

National

Activity	Date (Month, Year)	Organizer
1) 14th National Conference on Medical and Health Sciences	21-22 May, 2009	Universiti Sains Malaysia
2) 8th Malaysia Genetics Congress	4-6 August, 2009	Persatuan Genetik Malaysia
3) The IXth Malaysian National Haematology Scientific Meeting	29 April -1 May, 2011	Persatuan Hematologi Malaysia
4) The IXth Malaysian National Haematology Scientific Meeting	29 April -1 May, 2011	Persatuan Hematologi Malaysia
5) Intensive Fluorescence and Confocal Microscopy Course	12-13 April, 2011	Department of Neurosciences, USM.
(e.g : Course/ Seminar/ Symposium/ Conference/ Workshop/ Site Visit)		

PROBLEMS / CONSTRAINTS IF ANY *(Masalah/ Kekangan sekiranya ada)*	
RECOMMENDATION (*Cadangan Penambahbaikan*)	
F	
RESEARCH ABSTRACT – Not More Than 200 Words (*Abstrak Penyelidikan – Tidak Melebihi 200 patah perkataan*) ✓	
G	Recently, IMATINIB MESYLATE (IM), a selective Tyrosine Kinase inhibitor, is widely used as a frontline therapy for Chronic Myeloid Leukemia (CML). However, development of resistance to IM either primary or secondary, has emerged as a major obstacle in the successful management of CML patients. Development of resistance is a multifunctional phenomenon in patients with CML and is mediated by diversity of mechanisms which could be classified under BCR-ABL dependent or BCR-ABL independent pathways. BCR-ABL dependent mechanisms are most frequently associated with point mutations in tyrosine kinase domain (TKD) of BCR-ABL1 and BCR-ABL gene amplification. The types and frequencies of mutation reported in different studies have shown wide variability probably due to different composition of cohorts. But no reports are available from Malaysia. So, this study was undertaken to investigate the frequency and pattern of BCR-ABL kinase domain mutations utilizing dHPLC, followed by direct sequencing and BCR-ABL gene amplification using FISH on 92 CML patients who showed resistance to IM. Mutations were detected in 20 patients (21.7%). Nine different types of mutations consisting of T315I (n=9), E255K (n=2), M351T (n=2), G250E (n=2), E355G (n=1), Y253H (n=1), G251E (n=1), V289F (n=1) and N368S (n=1) mutation(s) respectively were discovered in these patients. The T315I mutation appeared to be the most predominant type of mutation among Malaysian CML patients. Interestingly, the G251E and N368S were novel mutations which have not been reported from elsewhere. In the rest 72 IM resistant CML patients, contribution of BCR-ABL gene amplification was investigated, but none of them showed BCR-ABL gene amplification. It is presumed that the mechanisms of resistance in these 72 patients might be due to BCR-ABL independent pathways for which we are probing various candidate mechanisms, utilizing other grants. Different mutations confer different levels of resistance and hence detection as well as characterization of TKD mutations is highly relevant to guide therapy in CML patients. Furthermore we also tried to associate all the factors with the overall survival among the CML patients treated with IM. The CML stage along with the presence of additional chromosomal abnormalities (ACA) showed the most significant association with the overall survival of the patients. Thus, performing conventional cytogenetics is still very crucial in identifying the presence of ACA and consequently help in predicting the prognosis of the patients.

Date : *Tarikh*	**Project Leader's Signature:** *Tandatangan Ketua Projek*

COMMENTS, IF ANY/ ENDORSEMENT BY RESEARCH MANAGEMENT CENTER (RMC)
(Komen, sekiranya ada/ Pengesahan oleh Pusat Pengurusan Penyelidikan)

Health Campus
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan

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Name:
Nama:

Signature:
Tandatangan:

Date:
Tarikh: