UNIVERSITI SAINS MALAYSIA
GERAN PENYELIDIKAN UNIVERSITI PENYELIDIKAN
LAPORAN AKHIR

IMATINAB MESYLATE TREATMENT IN CHRONIC MYELOID LEUKEMIA (CML) – UNDERSTANDING THE FUNDAMENTAL PHARMACOKINETIC AND PHARMACOGENETIC MECHANISMS FOR VARIATION IN RESPONSE

PENYELIDIK

PROF. DR. RAVINDRAN ANKATHIL

PENYELIDIK BERSAMA

PROF. DR. ABDUL AZIZ BABA
PROF. DR. ROSLINE HASSAN
PROF. DR. GAN SIEW HUA
DR. AZLAN HUSIN

2016

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RU GRANT
FINAL REPORT FORM

Please email a softcopy of this report to rcmo@usm.my

A	**PROJECT DETAILS**
i	**Title of Research:** Imatinib Mesylate Treatment in Chronic Myeloid Leukemia (CML)-Understanding the Fundamental Pharmacokinetic and Pharmacogenetic Mechanisms for Variaton in Response.
ii	**Account Number:**
iii	**Name of Research Leader:** Prof. Dr. Ravindran Ankathil
iv	**Name of Co-Researcher:** 1. Prof. Dr. Abdul Aziz Baba 2. Prof. Dr. Rosline Hassan 3. Prof. Dr. Gan Siew Hua 4. Dr. Azlan Husin
v	**Duration of this research:** a) **Start Date** : 1 October 2012 b) **Completion Date** : 31 March 2016 c) **Duration** : 42 months d) **Revised Date** (*if any*) : .....

B 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 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)

Although Imatinib mesylate (IM) is the gold standard drug for chronic myeloid leukemia (CML) treatment, resistance to IM emerges in a significant number of patients. Resistance could be due to several factors. Pharmacokinetic variability as a result of genetic polymorphisms in IM metabolizing genes could be a potential factor. This study was undertaken to investigate the genotype frequencies and the impact of *ORM1* 520G>A, *PXR* 1792A>G, *CAR* 540C>T, *CYP3A4* 878T>C and *CYP3A5* 6986A>G polymorphisms towards CML susceptibility risk and IM response. A total of 540 subjects (270 CML patients and 250 normal healthy controls) have been recruited in this study. Genotyping was performed and the association between allelic variants and CML susceptibility risk and response to IM treatment were assessed by means of odds ratio (OR) with 95% confident intervals calculated by logistic regression. Results showed that *PXR* 1792A>G, *CAR* 540C>T and *CYP3A5* 6986A>G were significantly associated with IM responses and *CAR* 540C>T, *CYP3A4* 878T>C and *CYP3A5* 6986A>G were significantly associated with CML susceptibility risk. Further study should be done on a larger scale to validate whether this polymorphism can be used as a predictive biomarker for identifying resistance development among CML patients undergoing IM treatment.

Walaupun imatinib mesylate (IM) telah menjadi ubat utama dalam rawatan kronik leukemia mieloid

(CML), sejumlah besar pesakit telah menunjuk rintangan kepada IM. Rintangan ini mungkin disebabkan oleh beberapa faktor. Salah satu faktor yang berpotensi menyebabkan rintangan ini adalah akibat daripada kepelbagaian farmakokinetik yang terhasil daripada polimorfisme genetik dalam IM metabolisme gen. Kajian ini dijalankan untuk mengkaji frekuensi genotip dan kesan polimorfisme *ORM1* 520G>A, *PXR* 1792A>G, *CAR* 540C>T, *CYP3A4* 878T>C and *CYP3A5* 6986A>G terhadap risiko kecenderungan CML dan tindak balas IM. Seramai 540 subjek (270 pesakit CML dan 250 individu sihat) telah terlibat dalam kajian ini. Penjenisan gen telah dilakukan dan asosiasi diantara alel variasi dan kecenderungan risiko CML dan tindak balas terhadap rawatan IM telah dinilai dengan menggunakan nisbah kemungkinan (OR) dengan 95% selang keyakinan yang dikira menggunakan regresi logistik. Hasil kajian menunjukkan bahawa *PXR* 1792A>G, *CAR* 540C>T dan *CYP3A5* 6986A>G telah nyata berkaitan dengan tindak balas IM dan *CAR* 540C>T, *CYP3A4* 878T>C and *CYP3A5* 6986A>G telah nyata berkaitan dengan kecenderungan risiko CML. Kajian lanjut perlu dilakukan pada skala yang lebih besar bagi mengesahkan samada polimorfisme ini boleh digunakan sebagai penanda bio prediktif untuk mengenal pasti pembangunan rintangan dikalangan pesakit CML yang menjalani rawatan IM.

C BUDGET & EXPENDITURE

i

Total Approved Budget :

Total Expenditure :

Balance :

Percentage of Amount Spent (%) :

 # Please attach final account statement (eStatement) to indicate the project expenditure

ii **Equipment Purchased Under Vot 35000**

No.	Name of Equipment	Amount (RM)	Location	Status

 # Please attach the Asset/Inventory Return Form (Borang Penyerahan Aset/Inventori) – Appendix 1

D RESEARCH ACHIEVEMENTS

i **Project Objectives** *(as stated/approved in the project proposal)*

No.	Project Objectives	Achievement