

UNIVERSITI SAINS MALAYSIA  
GERAN PENYELIDIKAN UNIVERSITI PENYELIDIKAN  
LAPORAN AKHIR

THE ROLE OF HYPOXIA IN CONTROLLING VOLTAGE-  
GATED SODIUM CHANNELS (VGSCS) INDUCED BREAST  
CANCER INVASIVENESS

PENYELIDIK

DR. NOOR FATMAWATI MAKHTAR

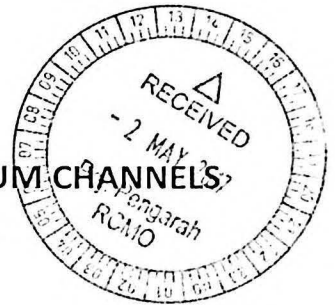
PENYELIDIK BERSAMA

PROF. NIK SORIANI YAACOB

2017

LAPORAN AKHIR GERAN UNIVERSITI PENYELIDIKAN (RUI)

THE ROLE OF HYPOXIA IN CONTROLLING VOLATAGE-GATED SODIUM CHANNELS?  
(VGSCS) INDUCED BREAST CANCER INVASIVENESS



NO. AKAUN : 1001/CIPPM/813060

TEMPOH : 15/07/2012 - 14/07/2016

NOOR FATMAWATI MOKHTAR

INSTITUT PENYELIDIKAN PERUBATAN MOLEKUL (INFORMM)

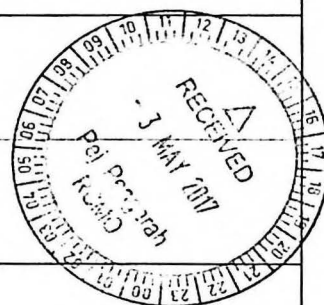
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## RU GRANT FINAL REPORT FORM

Please email a softcopy of this report to [rcmo@usm.my](mailto:rcmo@usm.my)

<b>A</b>	<b>PROJECT DETAILS</b>
<b>i</b>	<b>Title of Research:</b> The role of hypoxia in controlling voltage-gated sodium channels (VGSCs)-induced breast cancer invasiveness
<b>ii</b>	<b>Account Number:</b> 1001/CIPPM/813060
<b>iii</b>	<b>Name of Research Leader:</b> Noor Fatmawati Mokhtar (Dr)
<b>iv</b>	<b>Name of Co-Researcher:</b> Nik Soriani Yaacob (Prof)
<b>v</b>	<b>Duration of this research:</b> <ul style="list-style-type: none"> <li>a) Start Date : 15 July 2012</li> <li>b) Completion Date : 14 July 2015</li> <li>c) Duration : 3 years (36 months)</li> <li>d) Revised Date (if any) : July 2016 (48 months)</li> </ul>
<b>B</b>	<b>ABSTRACT OF RESEARCH</b>
	<p><i>(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)</i></p> <p>English</p> <p>This study was designed mainly to investigate the role of transcription factor, hypoxia inducible factor-1<math>\alpha</math> (HIF-1<math>\alpha</math>) in enhancing Nav1.5 and nNav1.5 expression in breast cancer that transforms it to become aggressive. siRNA was conducted to knockdown HIF-1<math>\alpha</math> expression in the aggressive MDA-MB-231 cells whilst hypoxia-mimetic agent, cobalt chloride (CoCl<sub>2</sub>) was used to stabilize HIF-1<math>\alpha</math> in the less aggressive MCF-7 cells. Total RNA and protein were extracted and subjected to real-time PCR and Western blotting. Migration and motility assays were carried out to study effect of treatments (siRNA and CoCl<sub>2</sub>) on metastatic cell behaviours. Nav1.5, nNav1.5, HIF-1<math>\alpha</math> and CA9 expression were all highly expressed in MDA-MB-231 cells. siRNA caused a significant decreased in HIF-1<math>\alpha</math></p>



expression (mRNA and protein) and HIF-1 $\alpha$ -common target gene, CA9. mRNA expression of Nav1.5 but not nNav1.5 was significantly downregulated by siRNA-HIF-1 $\alpha$  followed by suppression of migration. When MCF-7 cells were treated with CoCl<sub>2</sub>, HIF-1 $\alpha$  protein, CA9 and Nav1.5mRNA expression was increased significantly but not nNav1.5 followed by enhanced motility and migration. In conclusion, transcription factor, HIF-1 $\alpha$  able to regulate Nav1.5 (but not nNav1.5) in breast cancer to promote its aggressiveness.

Bahasa Malaysia

Kajian ini dilakukan terutamanya untuk mengkaji peranan faktor transkripsi, *hypoxia inducible factor-1 $\alpha$*  (HIF-1 $\alpha$ ) dalam meningkatkan penghasilan molekul Nav1.5 dan nNav1.5 dalam kanser payudara yang mengubahnya menjadi agresif. siRNA telah dijalankan untuk *knock-down* pengekspresan HIF-1 $\alpha$  dalam sel kanser payudara agresif MDA-MB-231 manakala ejen hipoksia, *cobalt chloride* (CoCl<sub>2</sub>) telah digunakan untuk menstabilkan HIF-1 $\alpha$  dalam sel kanser payudara kurang agresif MCF-7. Jumlah RNA dan protein dinilai menggunakan *real-time PCR* dan *Western blot*. Cerakin migrasi dan motiliti telah dijalankan untuk mengkaji kesan rawatan (siRNA dan CoCl<sub>2</sub>) ke atas kelakuan metastatik sel. Penghasilan mRNA Nav1.5, nNav1.5, HIF-1 $\alpha$  dan CA9 semuanya meningkat dalam MDA-MB-231 sel. siRNA menyebabkan penurunan ketara penghasilan protein HIF-1 $\alpha$  (mRNA dan protein) dan gen sasaran-HIF-1 $\alpha$  umum, CA9. Penghasilan mRNA Nav1.5 tetapi tidak nNav1.5 telah menurun dengan ketara oleh siRNA-HIF-1 $\alpha$  diikuti oleh pengurangan migrasi. Melalui rawatan CoCl<sub>2</sub> pula, penghasilan protein HIF-1 $\alpha$ , CA9 dan mRNA Nav1.5 telah meningkat dengan ketara tetapi tidak nNav1.5 diikuti oleh peningkatan motiliti dan migrasi. Kesimpulannya, faktor transkripsi, HIF-1 $\alpha$  dapat mengawal Nav1.5 (tetapi tidak nNav1.5) dalam kanser payudara untuk menggalakkan kelakuan agresif.

**C BUDGET & EXPENDITURE**

**i**

**Total Approved Budget : RM 203,800.00**

**Yearly Budget Distributed**

Year 1 : RM 108,500

Year 2 : RM 53,100

Year 3 : RM 42,200

**Total Expenditure : RM 203,800.00**

**Balance : RM 473.14**

**Percentage of Amount Spent (%) : 99.8**

**# 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
1	Liquid Nitrogen Storage Tank Model : BIO10 Brand : Statebourne, UK	4,400.00	INFORMM KK	DIGUNAKAN

**# 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)**