UNIVERSITI SAINS MALAYSIA

ANIMAL ETHICS COMMITTEE UNIVERSITI SAINS MALAYSIA

Application for Approval of a Project Involving the Use of Animals, and Approval as an Investigator for the Project

NOTE:

1. Please complete the application form in accordance to the Animal Ethics Committee Guidelines. Incomplete application will result in the return of the application and delay in the granting of the approval.
2. Attach a copy of the proposal (research / elective / teaching / other).
3. Application must be word-processed or typewritten and forwarded to the Chairperson, Animal Ethics Committee (AEC), School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Penang.
4. Please submit the application and direct all enquiries to the following address:

   (a) Secretary I, Animal Ethics Committee, School of Pharmaceutical Sciences, USM Main Campus, Penang
   Attn to: Mrs Salida Ibrahim Tel: (6)04-653 2234; Fax(6)04-6570017 Email: salida@usm.my

   (b) Secretary II, Animal Ethics Committee, Office of Research Platform, USM Health Campus, Kubang Kerian, Kelantan
   Attn to: Mr Tengku Ahmad Damitri Al-Astani Tengku Din Tel: (6)09-767 2364;
   Fax: (6)09-7648064; Email: damitri@kb.usm.my

TYPE OF APPLICATION: [Please tick (/)]

RESEARCH (✓) / ELECTIVE ( ) / TEACHING ( ) / OTHER ( ) Please specify: _____

If teaching / elective project, state course name and code:

_____

NAME OF PRINCIPAL INVESTIGATOR / CO-ORDINATOR / CHAIRPERSON:

Dr Oon Chern Ein

SCHOOL / CENTRE:

Institute For Research in Molecular Medicine (INFORMM), USM

_____

PROJECT TITLE:

In vivo studies of BZD9L1: a novel sirtuin inhibitor as a potential therapeutic agent in colorectal cancer.

_____

Received by Secretary, Animal Ethics Committee

AEC File No: **Date:**

1. PROPOSAL

1.1 Project Title:

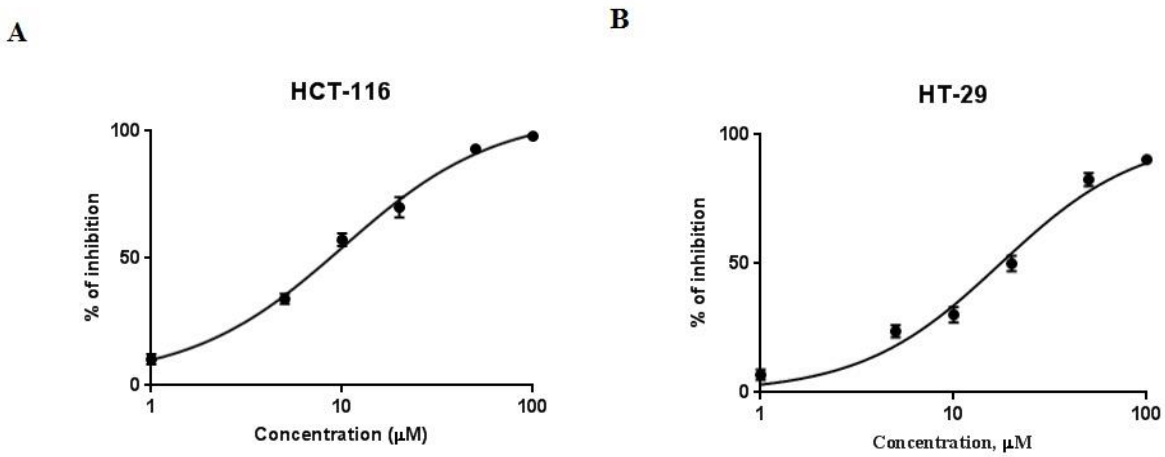
BZD9L1: Establishment of a novel sirtuin inhibitor as a potential therapeutic agent in colorectal cancer.

1.2 Project Objectives:

1. **To investigate the efficiency of single dose response treatment of BZD9L1 on human colorectal cancer tumours using subcutaneous model.**
2. **To determine the efficiency of BZD9L1 in combination with standard chemotherapy drug 5-fluorouracil (5FU) in human colorectal cancer tumours using orthotopic xenograft model.**

1.3 Summary of the Project (not more than 250 words):

The project aims to study the effect of BZD9L1 on human colorectal cancer tumours HCT116 and HT29, in sole BZD9L1 treatment or in combination with a standard colorectal cancer chemotherapy drug 5-fluorouracil (5FU). Human colorectal cancer tumours will be implanted into nude mice and allowed to grow to a certain volume before treatment are administered to the mice intraperitoneally [2-5]. Different concentrations of BZD9L1 will be used to determine the dose response relationship, efficiency as well as effectiveness towards the tumours. HCT116 cell line will then be used to study the combination effect of BZD9L1 and 5FU using the orthotopic xenograft model. This model resembles the entire spectrum of colorectal cancer ranging from *in situ* tumours to metastatic tumours, thus in the same time allow study of colorectal cancer inhibition *in situ* and metastasis [6]. *In vitro* data showed promising combination effect of BZD9L1 and 5FU as shown below (unpublished data):



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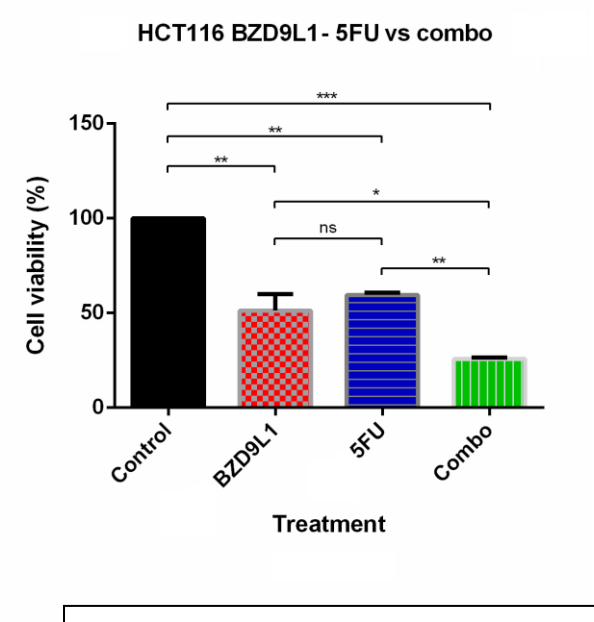


BZD9L1 as a potential compound for adjuvant chemotherapy. Data shown the inhibition of BZD9L1 on colorectal cancer cell line HCT116 **(A)** and HT29 **(B)**. Percentage inhibition of BZD9L1 toward both cell lines increase as dosage increases. A combination of BZD9L1 and 5FU showed higher effectiveness towards HCT116 cell line, as compared to stand-alone treatment **(C)**. Data are the mean ± SEM of triplicates (n=3) determination using GraphPad Prism 6 software. (*, $P<0.05$; ANOVA with Tukey's comparison test). Figures A & B were adapted from Yeong 2016, p. 140 [1] and Figure C unpublished data.

1.4 State the Ethical Implications of the Project:

Human colorectal cancer (HCT116 and HT29) tumours will be implanted into mice through subcutaneous injection for BZD9L1 single dose response treatment study, and through microinjection for study involving combination treatment of BZD9L1 and 5FU. Tumors will then allowed to grow and test compound will be administered parentally via intraperitoneal injection. Mice will subsequently euthanized using cervical dislocation and tumors will be harvested through dissection.

1.5 Explain why techniques, which do not use animals, have been rejected as unsuitable.

i. The *in vivo* models involve not only cells and organs but also the entire living system, which are needed to assess the comprehensive condition. The tumour microenvironment plays a complex role in determining the effectiveness of any therapy. In vivo model is important to recapitulate in vitro observations. Of many available models, the mice model has become the most widely accepted and used.

ii. This model system is considered by many to come closest to simulating the *in vivo* conditions in human.

iii. The *in vivo* animal models involve very important biological processes changes such as physical changes, blood biochemistry, body weight, etc., which are the very essential factors involved in the development and progression of the disease. These pathological processes are lacking in the *in vitro* models.

1.6 Duration (Please note that ethical clearance can only be given for a maximum period of 3 years starting from the commencement date. The AEC should be informed in writing the actual date of commencement of the project.)

Proposed commencement date : **01/04/2017**

Estimated duration from : **01/04/2017** to: **01/04/2020**

1.7 Investigators / Co-ordinators / Chairperson:

Please list the names of persons responsible in handling animals.

No.	Name	Dept/ School	Investigators / Co-ordinators / Chairperson	I/C / Passport No.	Contact No.	Signature & Date
1.	Tan Yi Jer	INFORMM	Investigator	920918055403	+60165437480	20/12/16
2.	Fong Kwong Soon	INFORMM	Investigator	920320135855	+60178833675	
3.	Dr Oon Chern Ein	INFORMM	Investigator	830722075366	+6046534879	20/12/16
4.	Dr Amin Malik Shah Abdul Majid	Pharmaceutical Sciences	Co-ordinator	730608075647	+60124230842	20/12/16
5.	Prof Tan Soo Choon	INFORMM / Biomics	Co-ordinator	5610008075489	+60124872142	29/12/16
6.						

2. CLASSIFICATION OF PROJECT (Please circle one or more)

(i.) Project requiring animals to be sacrificed for the preparation of the whole animals or tissue specimens.

(ii.) Procedure carried out under anaesthesia and the animals sacrificed without regaining consciousness.

iii. Survival after an intervention, which causes minimal stress of short duration (e.g. venepuncture, brief restraint, and blood vessel cannulation under anaesthesia).

iv. Survival after an intervention, which causes major or prolonged stress (e.g. major surgery, prolonged restraint, administration of toxic or painful substances and major behavioural modification).

v. Purely breeding projects.

vi. Production of antisera.

vii. Teaching purposes.

viii. Fieldwork.

ix. Other procedures – please specify:

_____

3. ANIMALS REQUIRED

3.1 TABLE OF PROPOSED ANIMAL USAGE:

(**NOTE**: Ethical Clearance can only be given for work involving **LIVE VERTEBRATES** for a maximum period of three calendar years only.)

No.	***Scientific* and Common Name**	**Male (No.)**	**Female (No.)**	**Total (No.)**
1.	***Scientific Name:* Mus Musculus NCR Nu/Nu** ***Common Name: NUDE Mice***			
2.	Subcutaneous model for BZD9L1 dose response study using HCT116 tumours: 10 male per group (5 male per group performed in duplicates) X 4 treatment groups + 4 drop out HT29 tumours: 10 male per group (5 male per group performed in duplicates) X 4 treatment groups + 4 drop out	88	-	88
3.	Orthotopic model for combination study of BZD9L1 and chemotherapy drug 5FU using HCT116 tumours: 10 male per group (5 male per group performed in duplicates) X 4 treatment groups + 4 drop out	44	-	44
	Grand Total	132	-	132

3.1 SOURCES OF ANIMALS:
(Address of Source / Supplier:)

EMAN Biodiscoveries Sdn Bhd, Eureka Complex, USM Main Campus

3.3 LOCATION OF ANIMALS:
(Please indicate where the animals will be housed during the experimental period)

The nude mice will be housed in specific pathogen free (SPF) individually ventilated cages (IVC) located at EMAN Research Laboratory, School of Pharmaceutical Sciences, USM

3.4 ENVIRONMENTAL ENRICHMENT:
(Please indicate type(s) of environmental enrichment (special / specific) to be used)

The animals will be housed in IVC with constant purification of air through high efficiency particulate air (HEPA) filters. Housing beddings, food and water will be autoclaved.

3.5 CARE OF ANIMALS:
(State the name and contact address of the persons responsible for the daily care of animals (including after office hours, weekends and public holidays))

1) **Name: Tan Yi Jer**
   H/p Number: +60165437480
2) **Name: Fong Kwong Soon**
   H/p Number: +60178833675

3.6 PERMITS REQUIRED:
(If protected native species, provide details of appropriate permits held)

Holder	: N/A
Issuing Agency	: N/A
Date of Issue	: N/A
Serial No.	: N/A
Period of Validity	: N/A

3.7 JUSTIFICATION:
(Please explain the basis for selection of the species and justification for the number of animals to be used.)

This project uses male nude mice as study subjects as previously established in the lab [7-9]. Nude mice were used due to the abnormal thymus present in the mice, which cause a deficiency in T cells. This allows the athymic nude mice to accept and grow xenografts of malignant tissues. The absence of T cells will also result in the absence of inflammation process which will be beneficial in reducing pain in the mice. Either male or female nude mice can be used, however male mice were more preferred due to the higher percentage uptake rate (approximately 80%) of human tumours compared to female mice (approximately 50%) uptake rate [10, 11]. A minimum number of animals is used for achieving statistical significance.

4. EXPERIMENTAL METHODS

4.1 Procedures to be carried out on the animals: (Please circle)

(a) Surgery: YES / (NO)
(If YES, answer 4.2 and 4.3)

(b) Anesthesia: (YES) / NO
(If YES, answer 4.4 and 4.5)

(c) Other: (YES) / NO

(If YES, answer 4.6 and 4.7)

4.2 State surgical procedures to be carried out on the animals: **Microinjection for orthotopic model**

4.3 Name the person(s) having experience in performing the procedures: **Dr Oon Chern Ein**

4.4 Anaesthetic to be used:

Name	: Ketamine and Xylazine
Dose	: 80 and 10 mg/kg, respectively.
Route of Administration	: Intraperitoneal (IP)
Duration	: 5 min (Onset), 90 min (Anaesthetic effect)

Clinical signs to ensure anaesthesia are adequate: Loss of consciousness, loss of eye lids blinking and finally loss of response when a strong pinch is applied on the paw.

4.5 Neuromuscular Blocking Agent to be used: YES / (NO)

If YES,

Agent:	Dose:
Route of Administration:	Duration:

Justification for use of neuromuscular blocking agent:

4.6 Outline the procedure:

Subcutaneous Tumour Xenograft Model for BZD9L1 dose response study

Briefly, 6-8 weeks old nude mice will be injected with human colorectal cancer tumours (HCT116 or HT29) through subcutaneous injection. Tumours will be formed with $5x10^6$ cells and injection cocktail (100µL) will be prepared using 1:1 ratio cell suspension (50µL) and Matrigel (50µL) (BD Biosciences). Tumour cells will be loaded into a one ml syringe attached to a 27 ½ gauge needle and administered through the subcutaneous injection. The growth of tumour will be monitored 2 to 3 times per week by measuring the length (L), width (W) and height (H) of each tumour with a calliper. Tumour volumes (V) will be calculated from the formula (V = 0.52 x L x W x H). Treatments with PBS (control), or BZD9L1 will be given intraperitoneally every three days when the tumours reach the size of $50mm^3$. Mice will be euthanized when three tumours from any group attain 1000 mm^3 tumor volume. Tumours will be harvested through dissection. In order to dissect the mechanisms contributing to tumor growth, histopathology studies will be carried out through immunostaining for proliferation (Ki67), EMT markers (Vimentin), apoptosis (Caspase 3), hypoxia (CAIX) and necrosis (hematoxylin and eosin).

Orthotopic Tumour Xenograft Model

Briefly, 6-8 weeks old nude mice will be used for surgical micro-injection in cecal wall with $5x10^6$ human tumour cells in 0.2 mL sterile PBS. The mice will be anesthetized with combination of 80mg/kg ketamine and 10 mg/kg xylazine. Anesthetized mice will be maintained between 37-40 °C on a heating pad. Using sterile surgical blades and forceps, the cells will be implanted in the respective organ (cecal wall) via micro-injection. The incision in the skin will be closed by a two or three sutures and the mice will be monitored for 2-3 hours during recovery from anesthesia. Once revived, mice will be placed into sterile cages containing food and water ad libitum. Mice will be weighed every 2-3 days and monitored using fluorescence tomography for tumour onset. Treatments with PBS (control), 5FU, BZD9L1, or combination of both BZD9L1 and 5FU will be given intraperitoneally every three days when the tumours reach the size of $50mm^3$. Mice will be euthanized when three tumours from any group attain 1000 mm^3 tumour volume. Tumours will be harvested through dissection. In order to dissect the mechanisms contributing to tumor growth, histopathology studies will be carried out through immunostaining for proliferation (Ki67), EMT markers (Vimentin), apoptosis (Caspase 3), hypoxia (CAIX) and necrosis (hematoxylin and eosin).

Dose response study

Three BZD9L1 doses and vehicle control per cell line will be used for this study. These 3 doses will be pre-determined using toxicology study based on LD (lethal dosage) 50 which will be determined through another project **(Ethics approval number: USM /Animal Ethics Approval/ 2016/ (99) (810))**. The targeted cell line of study consists of p53 wild-type (HCT-116) and p53 mutant (HT-29).

Combination treatment

The purpose of this study is to determine the potential of BZD9L1 as an adjuvant therapeutic agent. The study will be conducted via combination treatment of implanted tumour with 5FU (existing chemotherapy drug for colorectal cancer) and BZD9L1. Dosage of 5FU will be obtained via literature search. Dosage of BZD9L1 will be determined from Dose Response Study (experiment as above).

Statistical analysis

All values will be expressed as mean ± SEM. Comparisons between groups will be performed using ANOVA followed by Tukey's multiple comparison tests using Graph Pad Prism. $P<0.05$ will be considered to be a significant difference.

3.7 Name the person(s) having experience in performing the procedure:

Dr Oon Chern Ein

Dr Amin Malik Shah Abdul Majid

4.8 Supervision during experimentation:

(Detail the extent and method of supervision of animals during experimentation, including methods to be used for assessing and preventing pain and distress).

Health status of the animals will be monitored by food and water consumption, movement, activity and behavioural changes. Observation will also include changes in skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous system, and somatomotor activity. Attention will be directed to observations of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma. Animals found in moribund condition and animals showing severe pain or enduring signs of severe distress will be humanely killed.

4.9 Post-procedural care:

(Detailed arrangements made by the investigators for immediate and continuing post-operative and / or post-procedural care, including details of restraint, housing and analgesics to be used).

Physical restraint will be applied during injection and surgery, animals will be housed in IVC cages, and health status of the animals will be monitored daily for signs of distress and pain. The weight of the animals will be recorded at the beginning of the experiment and weekly thereafter, tumour size will be monitored 3 times per week. Animals found to be moribund will be euthanized.

4.10 Post-procedural survival time for the animals: (hours / days / months / years)

The survival time of the animals depend on the growth of tumour from any group to 1000mm^3 tumour volume, which then the mice will be euthanized.

5. COMPLETION OF PROJECT

5.1 Animals to be sacrificed: (YES) / NO

If YES,

(i) state the method to be used:

Animals will be euthanized through cervical dislocation. Removal of tumour will be carried out after euthanasia.

(ii) Name of the person performing euthanasia:

Tan Yi Jer and supervised by Dr Amin Malik Shah Abdul Majid

1. Method of disposal of euthanized animals:

   Sacrificed and dead animal will be wrapped in bio-safety envelops and kept in deep freezer before collection by laboratory staffs for disposal through incineration.

2. If animals are not sacrificed, state what happen to them:

   All animals will be sacrificed.

6. HAZARDOUS MATERIALS

Does the project involved exposure of live animals to any of the following:

6.1 Ionising Radiation: YES / (NO)

If YES, Agent:

6.2 Carcinogen / Teratogen: YES / (NO)

If YES, Agent:

6.3 Pathogenic Organisms: YES / (NO)

If YES, Agent:

6.4 Other: YES / (NO)

Please give details.

If YES to any above;

7. GENETIC MATERIALS

7.1 Will you be isolating the DNA? YES / (NO)

7.2 Will you be inserting DNA into live animals? YES / (NO)

8. ANY OTHER COMMENTS

Not applicable

9. DECLARATION BY PRINCIPAL INVESTIGATOR / COORDINATOR / CHAIRPERSON:

I hereby declare that I and / or co-investigators / co-coordinators / vice chairperson have the appropriate qualifications and experience to perform the procedures described in this project. I am familiar with the provisions of the USM rules and regulation in animals for the Care and Use of Animals for Scientific Purposes; and accept responsibility for the conduct of the experimental procedures detailed above; in accordance with the requirement of the rules and regulation laid down by Animal Ethics Committee USM.

I further declare that the procedures described in this project do not constitute unnecessary repetition of work previously carried out by other research workers or myself, and that each person engaged in this project has been adequately instructed in, and is competent to perform, procedures that they are to carry out. If they are not already skilled in the procedures, I will be responsible for seeing that they obtain the necessary training in advance, so that each procedure on an animal will be carried out in the most appropriate manner.

Signature: Principal Investigator

3/1/2017

Date

DR. OON CHERN EIN
Senior Lecturer
Institute for Research in Molecular Medicine (INFORMM)
Universiti Sains Malaysia
11800 Penang

10. CERTIFICATION OF THE AEC (Chairperson / Authorised Representative

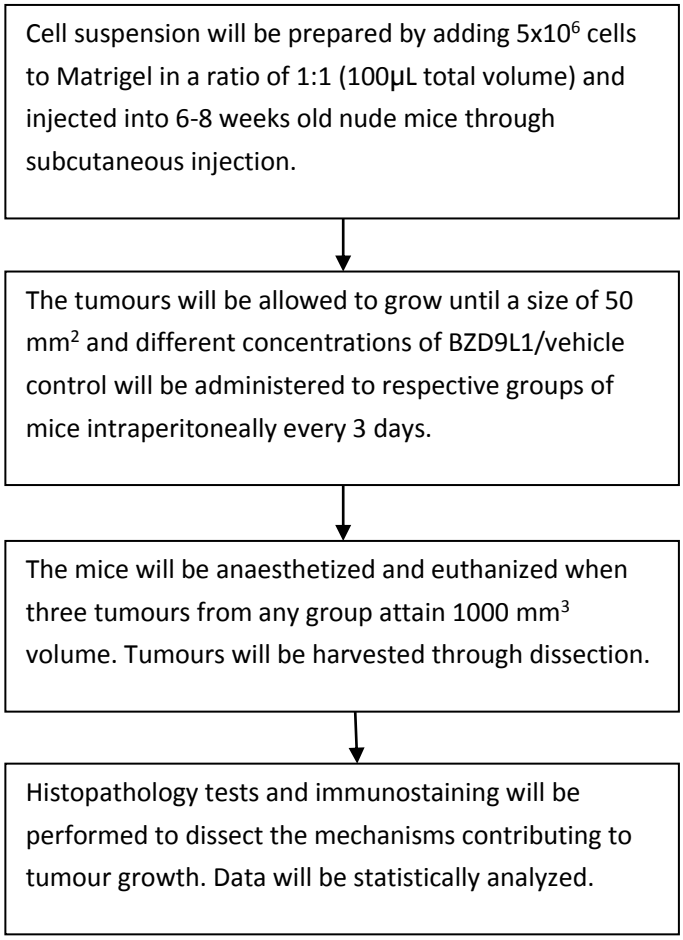
Name :

Signature : _____

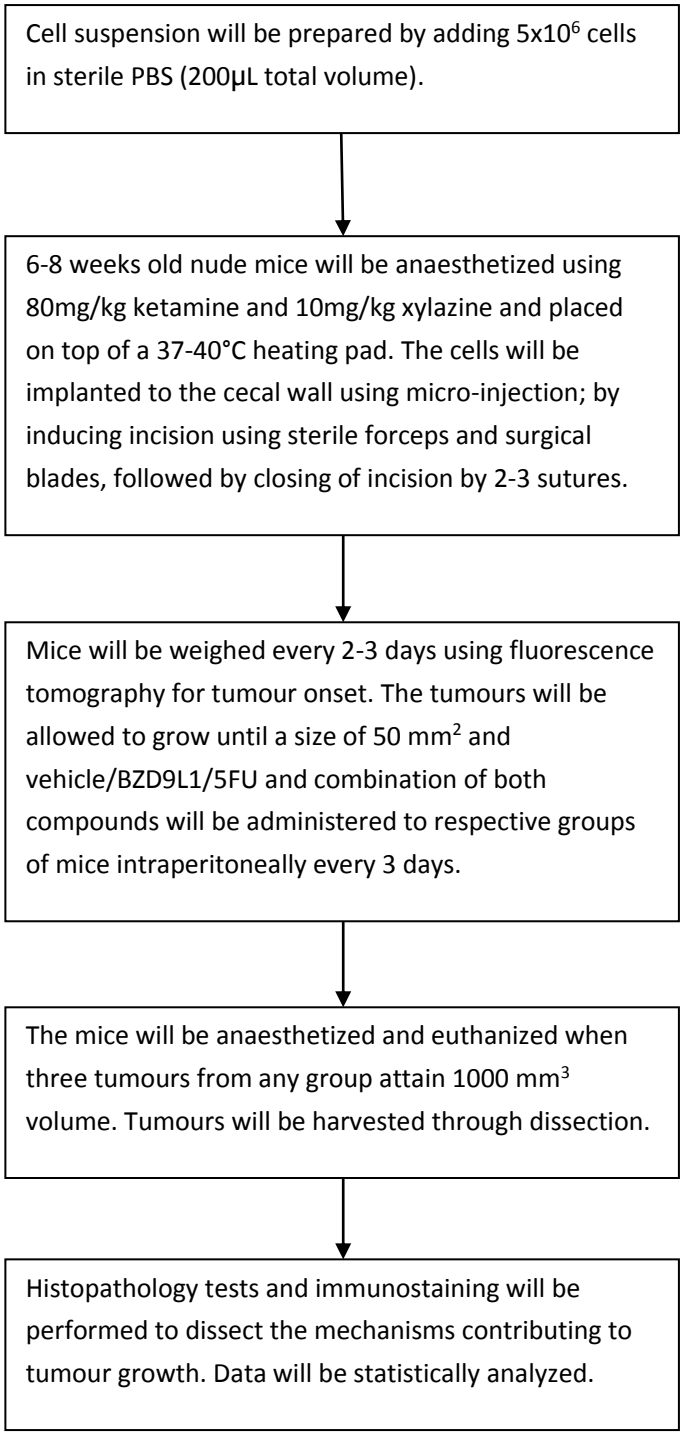
Date :

Methodology Flow Chart

Subcutaneous Tumour Xenograft Model for BZD9L1 dose response study



Orthotopic Tumour Xenograft Model for studying combined effect of BZD9L1 and 5FU



References:

1. Yeong, K.Y., *Synthesis and Biological Activity of Benzimidazole Analogs Targeted at Sirtuin Enzyme*. 2016, Universiti Sains Malaysia.
2. Chern Ein Oon , C.S., Keng Yoon Yeong, Arne Östman, Jai Prakash, *SIRT1 inhibition in pancreatic cancer models: contrasing effects in vitro and in vivo.* European journal of pharmacology, 2015. **757**: p. 59 - 67.
3. Islam, K., et al., *In vivo Anticancer Activities of Benzophenone Semicarbazone against Ehrlich Ascites Carcinoma Cells in Swiss Albino Mice.* Cancer Biol Med, 2012. **9**(4): p. 242-7.
4. Li, J.L., et al., *DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy in vivo.* Cancer Res, 2011. **71**(18): p. 6073-83.
5. Prasad, S., A.K. Tyagi, and B.B. Aggarwal, *Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice.* Cancer Res Treat, 2014. **46**(1): p. 2-18.
6. Mittal, V.K., J.S. Bhullar, and K. Jayant, *Animal models of human colorectal cancer: Current status, uses and limitations.* World J Gastroenterol, 2015. **21**(41): p. 11854-61.
7. Aisha, A.F., et al., *In vitro and in vivo anti-colon cancer effects of Garcinia mangostana xanthones extract.* BMC Complement Altern Med, 2012. **12**: p. 104.
8. Al-Salahi, O.S., et al., *Anti-tumor activity of Eurycoma longifolia root extracts against K-562 cell line: in vitro and in vivo study.* PLoS One, 2014. **9**(1): p. e83818.
9. Dahham, S.S., et al., *In vivo toxicity and antitumor activity of essential oils extract from agarwood (Aquilaria crassna).* BMC Complement Altern Med, 2016. **16**: p. 236.
10. Deng, Y.C., et al., *Activity of boanmycin against colorectal cancer.* World J Gastroenterol, 2001. **7**(1): p. 93-7.
11. Watson, S.A. and T.M. Morris, *Theoretical Considerations in Using Animal Models of Metastasis and Brief Methodology for In Vivo Colorectal Cancer Models in SCID and Nude Mice.* Methods Mol Med, 2001. **58**: p. 195-204.

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Jawatankuasa Etika Haiwan USM (JKEH-USM)
Animal Ethics Committee USM (AECUSM)

Kampus Induk:
Pusat Pengajian Sains Farmasi, 11800 USM
Pulau Pinang
Kampus Kesihatan:
Pusat Inisiatis Penyelidikan (Sains Klinikal & Kesihatan)
USM Kampus Kesihatan,
16150, Kubang Kerian, Kelantan
Tel: (6)04-653 2234/2229/4580/2412 & (6) 09-767 2364 / 2352
Faks: (6) 04-653 2555 & (6) 09-767 2351
W: www.research.usm.my

Date : 19 December 2016

Dr. Oon Chern Ein
Institute for Research in Molecular Medicine(INFORMM)
11800 USM
Penang

Dear Dr.,

Animal Ethics Approval

Project title (810): ***In vivo toxicology studies of BZD9L1 : a novel sirtuin inhibitor in BALB/c mice***

The Animal Ethics Committee USM held its 99th meeting on the 3 February 2016 and has approved the above research project.

No. of Animal Ethics Approval: USM / Animal Ethics Approval / 2016 / (99) (810)

Title	: *In vivo toxicology studies of BZD9L1 :a novel sirtuin inhibitor in BALB/c mice*
Research Centre	: Animal Research and Service Centre(ARASC)
Duration	: 19 December 2016 to 31 December 2019
Number of Samples	: 10 (1 Drop out) *Mus musculus* BALB/c (Albino Mice) [Male] 18 (2 Drop out) *Mus musculus* BALB/c (Albino Mice) [Female]
Name of Principal Investigator	: Dr. Oon Chern Ein
Co-Investigator	: Prof. Tan Soo Choon Assoc. Prof. Dr. Sasidharan Sreenivasan Tan Yi Jer Lee Yeuan Ting

The following items (X) were received and reviewed in connection with the above study to be conducted by the investigator.

() Copy of Proposal	(Date: January 2016)
(X) Animal Ethics Committee Approval Application Form	(Date: January 2016)
(X) Reviewer's Comment Form	(Date: February 2016)
(X) Reply for Clarification Letter	(Date : -)

Members of the Animal Ethics Committee USM who reviewed the documents during the meeting are as follows:

Member (Title and Name)		Occupation (Designation)
Chairperson: Prof.Dr.Hj Munavvar Zubaid Abd Sattar		Lecturer, School of Pharmaceutical Sciences (Physiology)
Secretary: Mrs. Salida Binti Ibrahim Ms Siti Fatihah Ariffin		Asst. Science Officer Research Officer
Members :		
1	Prof Dr. Siti Amrah Sulaiman	Lecturer, School Of Medical Sciences (Pharmacology)
2	Prof Dr. Nik Soriani Yaacob	Lecturer, School of Medical Sciences (Chemical Pathology)
3	Prof Sharif Mahsufi Mansor	Lecturer, Centre for Drug Research (Pharmacology)
4	Prof. Dr. Mohd Zaini Asmawi	Lecturer, School of Pharmaceutical Sciences (Pharmacology)
5	Assoc. Prof. Dr. Rapeah Suppian	Lecturer, School of Health Sciences (Immunology)
6	Assoc. Prof. Dr. Noor Hayati Abdul Razak	Lecturer, School of Dental Sciences (Maxillofacial Surgery)
7	Assoc. Prof. Dr. Vikneswaran Murugaiyah	Lecturer, School of Pharmaceutical Sciences (Pharmacology)
8	Assoc. Prof. Dr.Lim Boon Huat	Lecturer, School of Health Sciences (Medical Parasitology)
9	Dr Saidi Jaafar	Director, Animal Research and Service Centre, ARASC (Developmental Biology/Knock-out & Transgenic)
10	Dr. Nor Aini Saidin	Lecturer, Advance Medical & Dental Institute (Toxicology)
11	Dr.Hassaan A.Rathore	Lecturer, School of Pharmaceutical Sciences (Physiology)
12	Dr. Khoo Boon Yin	Lecturer, Institute for Research in Molecular Medicine (INFORMM)(Molecular Biology/ Medical Biotechnology)
13	Dr Isma Suzyta Ismail	Veterinary Officer (Animal Research and Service Centre, ARASC)
14	Mr Tg. Ahmad Damitri Al-Astani Tg Din	Science Officer, Center for Research Initiatives (CRI-CHS)

Thank you.

"Global competitiveness: Our commitment"

Yours sincerely,

(PROF.DR.HJ MUNAVVAR ZUBAID ABD SATTAR)
Chairman