SPACE ENVIRONMENT AND KIBO UTILISATION WORKSHOP (SEKUW)


# Involvement of Malaysia in MARS-520

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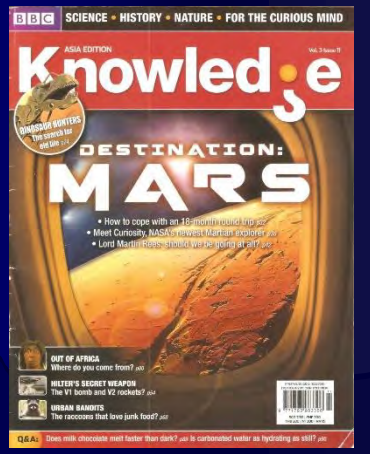
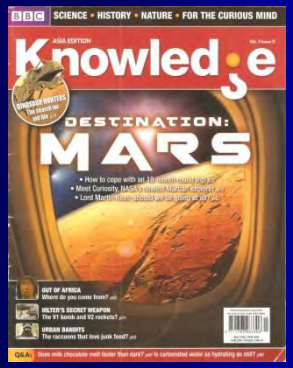


# Involvement of Malaysia in MARS-520


## Biomarkers of Inflammation, Endothelial Activation, Oxidation Stress and Prothrombogenesis with Long Term Confined Isolation: MARS 520 Program

Rahman T, Muid S, Ahmad R, Ismail TS, Froemming G, Burakova L, Andreeva E, Andrianova I and Nawawi H



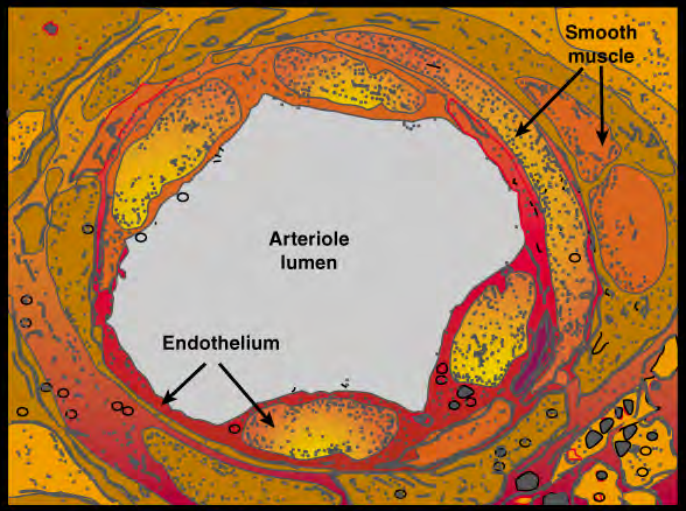



# INTRODUCTION


- Atherosclerosis is a chronic inflammatory disease leading to atheroma formation resulting in atherosclerosis-related complications such as CAD, stroke and PVD
- Inflammation, endothelial activation, oxidative stress and prothrombogenesis are important in the pathogenesis of atherosclerosis.
- If the status of these pro-atherosclerotic factors are enhanced during prolonged confinement and space travel, specific countermeasures may be instituted to ameliorate these factors to favour safe outcome for astronauts during space expeditions.
- Lack of studies on the effects of long term isolation under either 1g facility, simulated microgravity environment or actual space travel on *in vivo* lipid levels, inflammation, endothelial activation, oxidative stress and prothrombogenesis

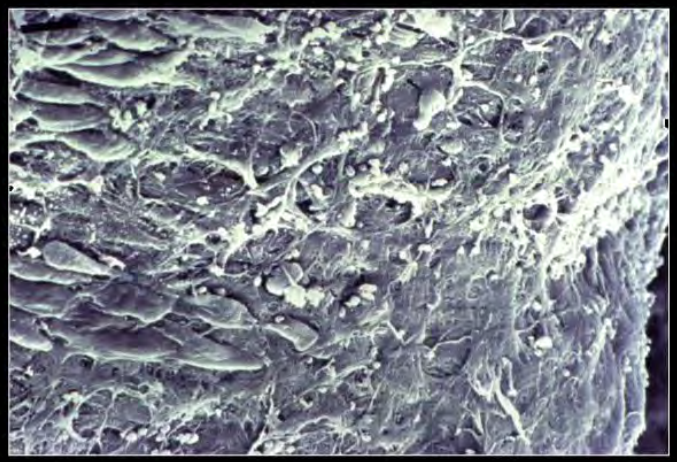
## The endothelium: A living organ

VBWG




## The endothelium

VBWG

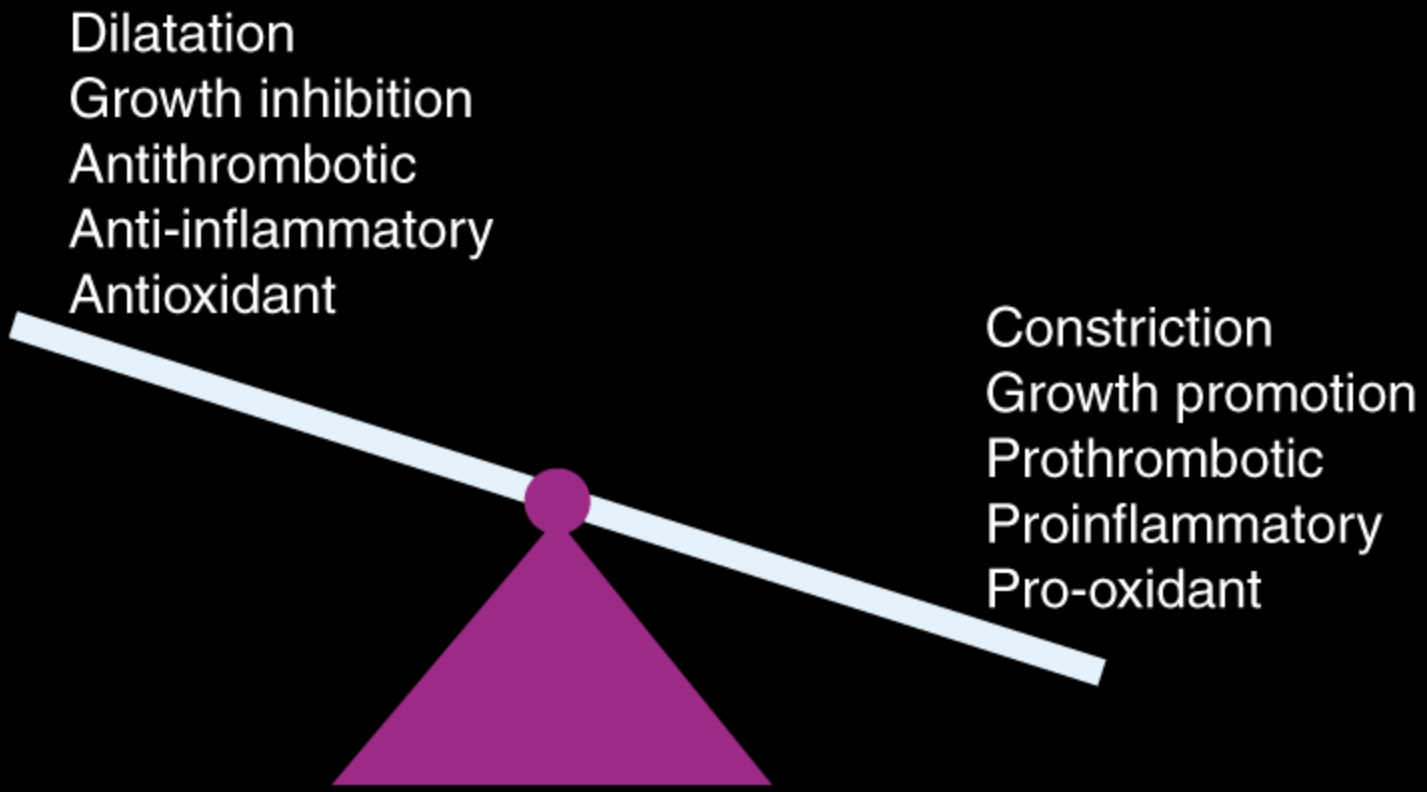


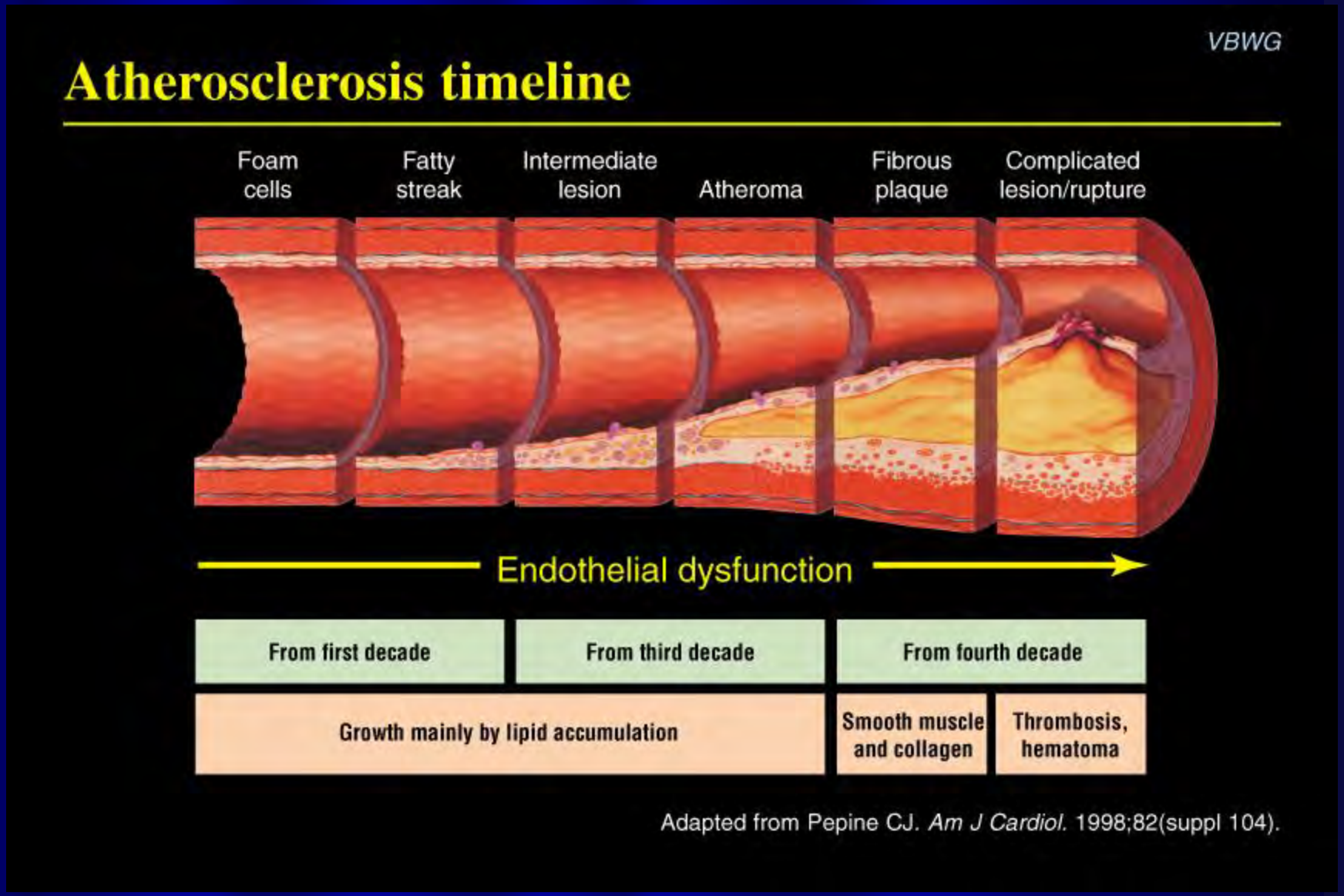
Photograph courtesy of Carl J. Pepine, MD.

- Endothelium - dynamic, heterogenous disseminated organ
- Secretory, synthetic, metabolic and immunologic functions
- Endothelial cells form the inner lining surface of blood vessels
- Play a crucial role in maintaining vascular functional integrity

VBWG

# The endothelium maintains vascular health






Atherosclerosis – progressive chronic inflammatory disorder, inflammation, oxidative stress & and endothelial dysfunction pivotal in pathogenesis of atherosclerosis


MARS-500
MARS 500
ИМБП

# OBJECTIVES

1. To investigate the effects of long term confinement in MARS500 ground isolation facility on biomarkers of inflammation, endothelial activation, oxidative stress and prothrombogenesis.

2. To study the effects of confined isolation on biomarkers of endothelial activation and endothelial function as assessed by FMD of the brachial artery.

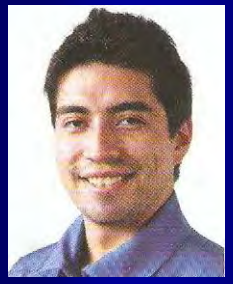
# MARS-520 CREWS

- Sitev Alexey Sergeevich
- 39 years
- Moscow, Russia
- Engineer-shipbuilder

- Kamalov Sukhrob Rustamovich
- 39 years
- Moscow, Russia
- Surgeon

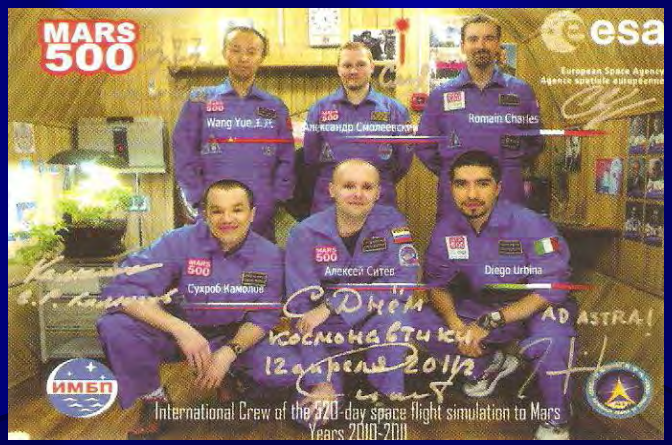
- Smoleevskiy Alexandr Egorovich
- 34 years
- Moscow, Russia
- Military physician, physiologist

- Charles Romain
- 32 years
- Saint Malo, France
- Engineer



- Urbina Diego
- 28 years
- Italy
- Engineer

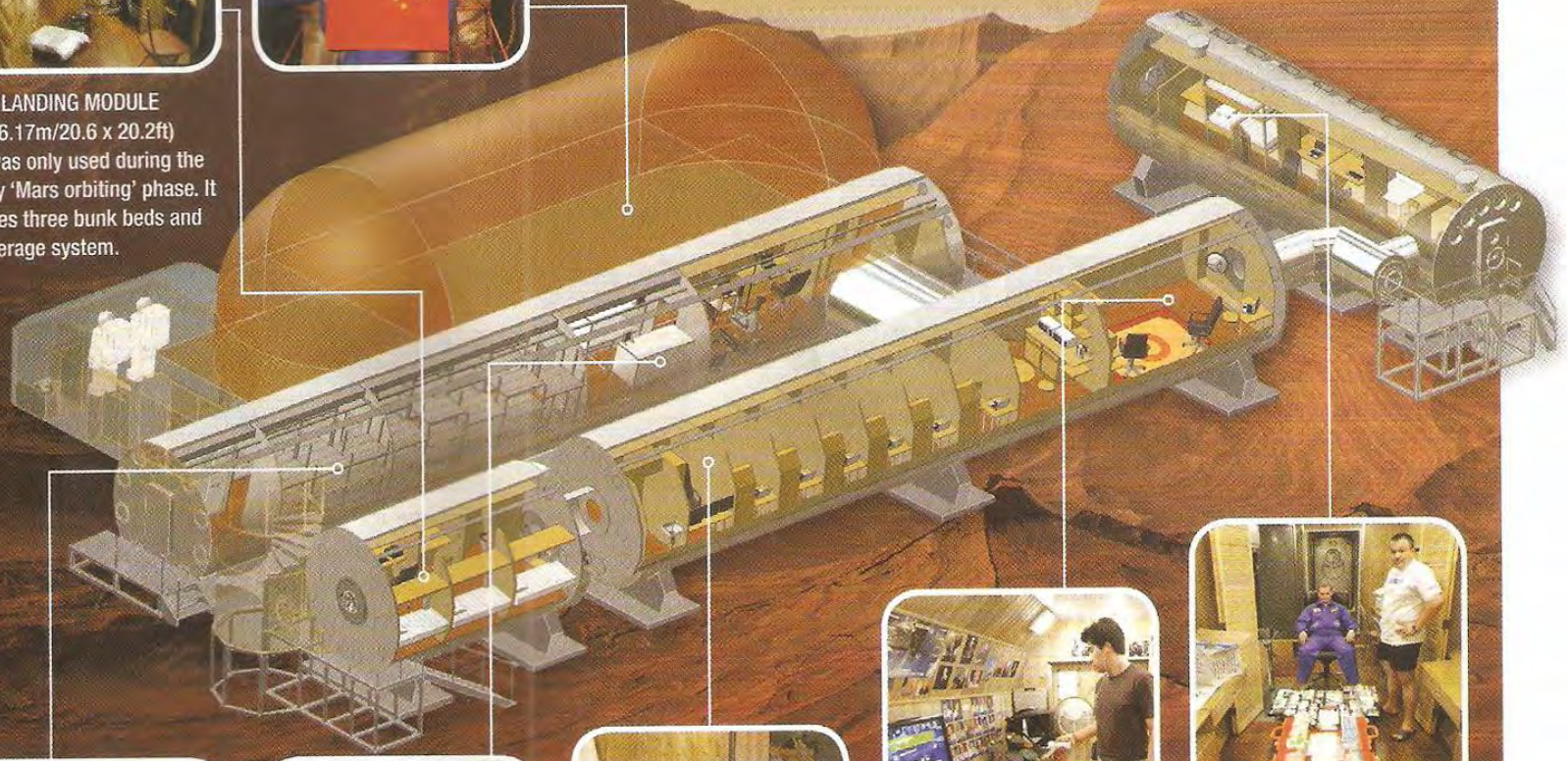
- Wang Yue
- 29 years
- Beijing, China
- Teacher's Assistant for cosmonauts, dealing with trainings on adaptation for the environment and selection



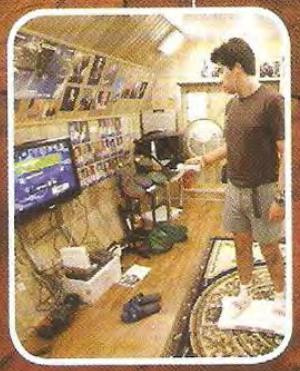
# INSIDE THE MARS500 MODULES

MARS LANDING MODULE
(6.3 x 6.17m/20.6 x 20.2ft)
This was only used during the 30-day 'Mars orbiting' phase. It includes three bunk beds and a sewerage system.


MARS SURFACE SIMULATOR
Between 14 and 22 February 2011, Russian Alexandr Smoleevskiy, Italian Diego Urbina and Chinese Wang Yue performed extra-vehicular activities on the surface of 'Mars'.



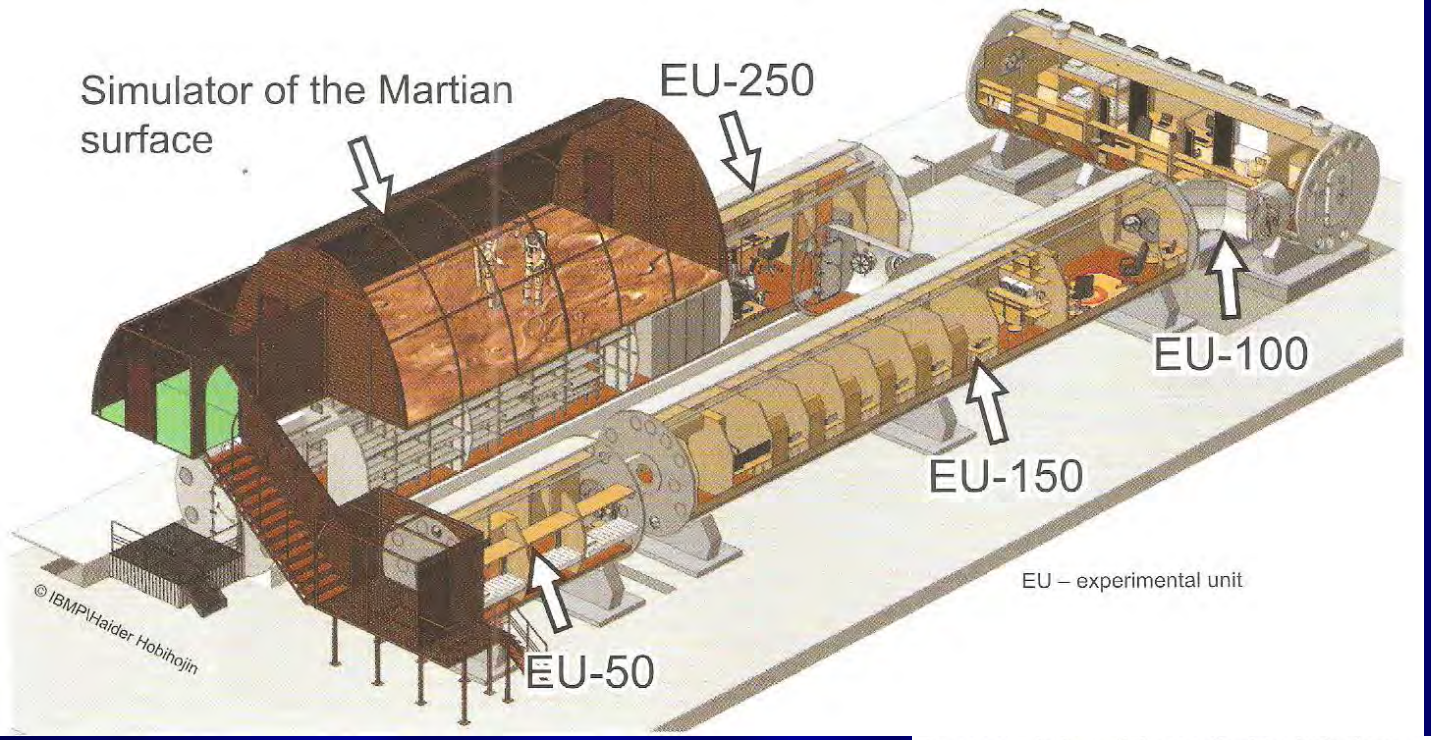
UTILITY MODULE (3.9 x 24m/12.8 x 78.7ft)
This houses the fridges and dry food storage, the gym, bathroom and sauna, and the experimental greenhouse – home to the only living organisms on board other than the men themselves.



HABITABLE MODULE (3.6 x 20m/11.8 x 65.6ft)
The six bedroom compartments each measure 2.8-3.2m² and have a bed, desk, chair and shelves. The module also contains the community kitchen/dining room, a living room, the main control room and a toilet.



MEDICAL MODULE
(3.2 x 11.9m/10.5 x 39ft)
Telemedical, laboratory and diagnostic medical investigations are carried out here, as well as routine medical examinations.




The six-man crew is all smiles at the start of the 'mission'. Once sealed, the door remains closed until 4 November 2011 – a total of 520 days

The general view of the medical-technical experimental facility

# Methodology

## Subjects

6 astronauts in Russia (confinement)

6 ground controls in Malaysia (free living)

7 ground controls in Russia (free living)

## Inclusion Criteria

Males

Normotensive (BP < 140/90 mm/Hg)

Normoglycaemic [Fasting plasma glucose < 6.1mmol/L]

Normolipaemic [LDL-c < 3.4mmol/L, TG < 2.3 mmol/L, HDL-c > 1.0 mmol/L]

Non-smoker

Not obese [BMI < 25]

FMD was performed following the standard protocols set by the International Brachial Artery Reactivity Task Force by trained personnel

## FMD reading & Fasting venous sampling

Astronauts: FMD reading on days -7, 30, 90, 150, 210, 270, 330, 390, 450, +7 of isolation (10)

Malaysian Ground controls: FMD reading on days -14, -7, 30, 150, 280, 390, 520 and +14 of isolation (8)

## SAMPLE COLLECTION

- Six Cosmonauts confined in an isolated environment for 520 days (pre, D30, D90, D150, D280, D390, D450, D520, post) and 12 age and gender matched healthy, 7 free living Russians and 6 Malaysian -based ground controls were included in this study.
- Fasting venous whole blood and urine specimens were collected serially for the duration of 520 days.
- Training programme for cosmonauts

Blood taking for experimental investigations

# Serum samples were analysed for:

- Fasting serum lipid profiles (FSL)
- High sensitive C-reactive protein (hsCRP)
- Interleukin 6 (IL-6) - ELISA

Biomarkers of inflammation

- Intercellular Adhesion Molecule 1 (ICAM-1)
- Vascular Cell Molecule 1 (VCAM-1)
- E-selectin

Biomarkers of endothelial activation

- Lipid peroxidation [Malondialdehyde (MDA) assay]
- Oxidized LDL (ox-LDL)
- Endothelial Nitric Oxide Synthase (eNOS)

Biomarkers of oxidative stress

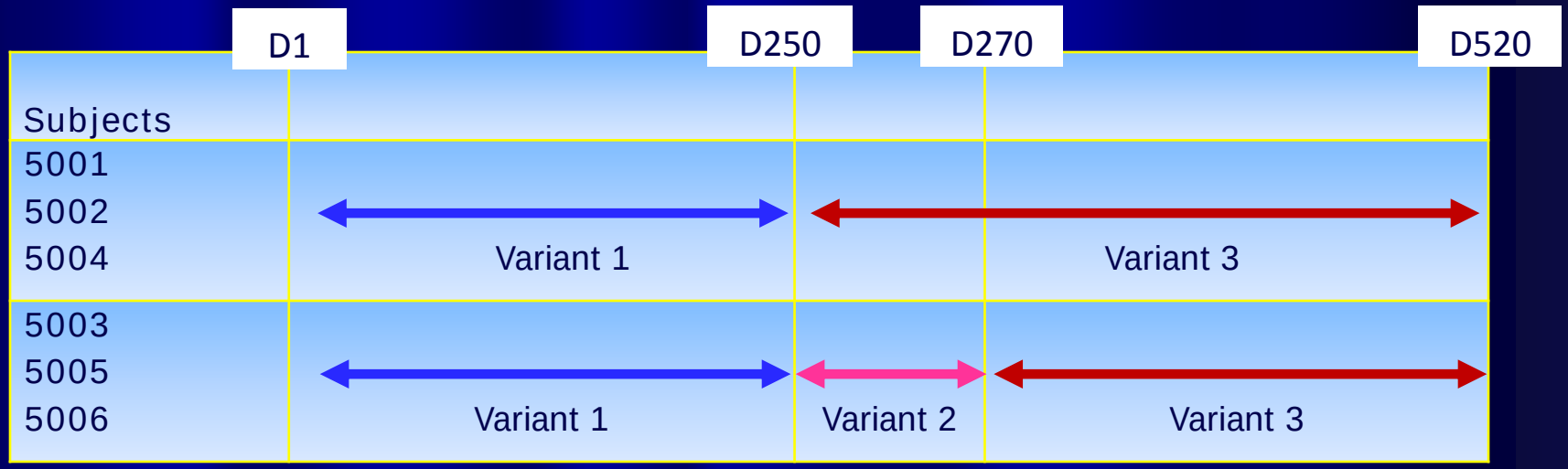
- Homocysteine (Hcys) levels
- Plasminogen Activator Inhibitor 1 (PAI-1)

Biomarkers of prothrombogenesis

# Exercise Programme

- The cosmonauts were divided into 3 gps (2 investigators per gp)
- Training regimes were alternated between gps
- Entire 520 D period experiment was divided into 3 stages of physical exercise regimes:
  - 1st stage: strength training device, expanders, vibro training devices
  - 2nd stage: treadmill (active and passive), cyclo-ergometer
  - 3rd stage: weaning off physical training

# Nutritional Intake

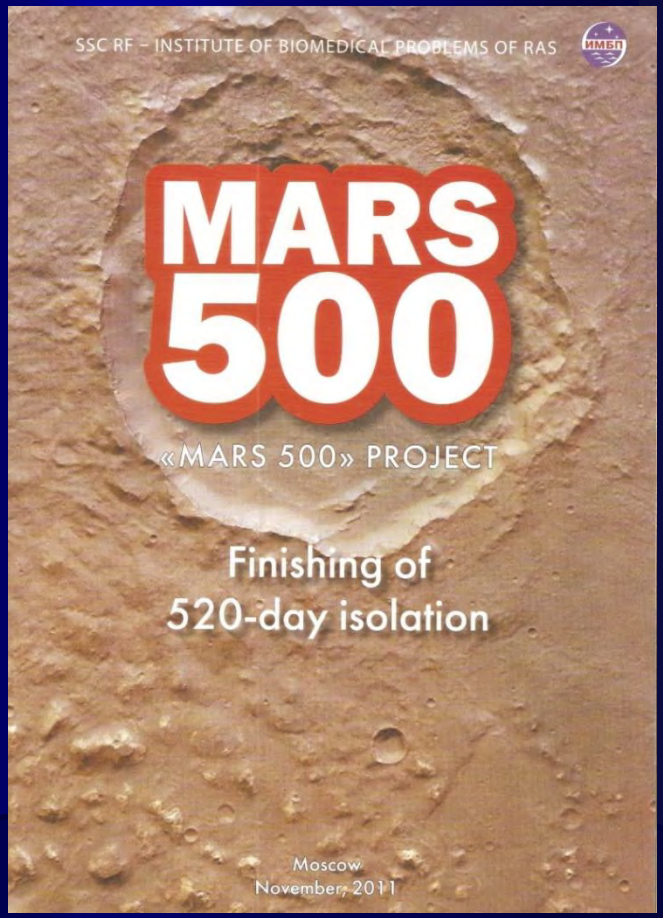



| | | Variant 1 Diet g (%) | Variant 2 Diet g (%) | Variant 3 Diet g (%) |
|---|---|---|---|---|
| 1. | Protein | 106.9 (14) | 138.2 (17) | 112.9 (14.3) |
| 2. | Fat | 115.8 (33.2) | 126.8 (35) | 110.9 (31.9) |
| 3. | Carbohydrate | 402.2 (52.8) | 370.8 (47) | 419.5 (53.7) |
| 4. | Average Calorie intake (kCal) | 3120 | 3170 | 3130 |

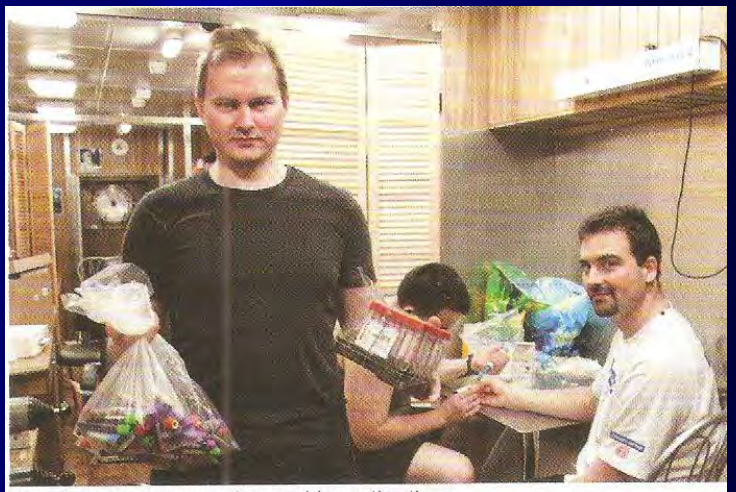
Omega 3 fatty acid supplementation first 250 days
3g/day EPA+ DHA supplementation compared to placebo groups, Double blind cross over study


The crew of the Mars landing.
*Left to right:* Diego Urbina, Alexandr Smoleevskiy, Wang Yue





Diego and Romain prepare an 'on-board' experiment (*top*), a welcome distraction from the crew's many hours of relaxation (*above*)



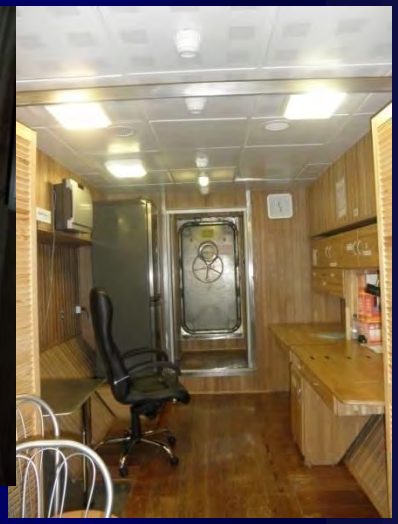
Blood taking for experimental investigations


MARS
500

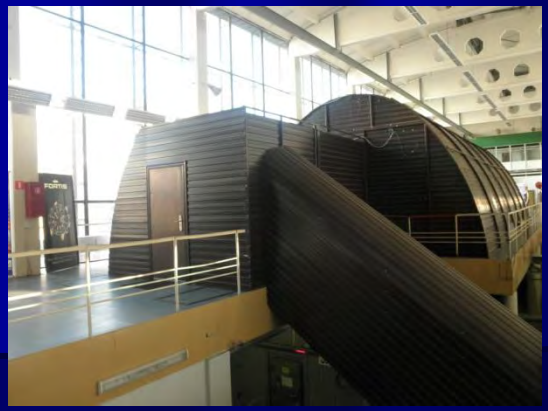

MARS
500


ОТКРЫВАТЬ






Nov 2011
Moscow


АВАРИЙНЫЙ
ВЫХОД


Отряд космонавтов ИМБП
IBMP Cosmonaut's Team


ТРАНСФОРМИРУЕМАЯ БАРОКАМЕРА
ЗАО «СКБ ЭО при ИМБП РАН»
ОСНОВНЫЕ НАПРАВЛЕНИЯ ДЕЯТЕЛЬНОСТИ


ИМБП


STEM CELL BIOLOGY
SANYO

# ACKNOWLEDGEMENT


PROJECT LEADERS: Profesor Dr Hapizah Mohd Nawawi

CO-RESEARCHERS:

UNIVERSITI TEKNOLOGI MARA

- Profesor Dr Hapizah Mohd Nawawi
- Assoc Prof Dr. Tengku Saifudin Tengku Ismail
- Dr. Thuhairah Hasrah Abd. Rahman
- Suhaila Muid
- Radzi Ehsan
- Fahmi Mokhtar
- Associate Profesor Dr Gabriele Anisah Ruth Froemming

- ANGKASA – MALAYSIAN SPACE AGENCY
- THE MALAYSIAN MINISTRY OF SCIENCE, TECHNOLOGY & INNOVATION (MOSTI)

GRANT CODE: Grant code: MARS-520 100/RMI/ANGKASA 16/6/2 (1/2010)

INSTITUTE FOR BIOMEDICAL PROBLEMS (IBMP), MOSCOW, RUSSIA

- Profesor Ludmila Buravkova
- E. Andreeva
- I. Andrianova





THANK YOU

# Research Output

## Publications:

1. Abstracts in Journals:
    1. Effects Of Long Term Confined Isolation On Inflammation And Endothelial Function In Human, *Mohtar F[1], Ahmad R[1], Rahman T[1], Froemming GRA[1], Ismail TS[1], Moreva T[2], Kholin S[2], Suvorov A[2], Muid S[1], & Nawawi H[1]. Malaysian J Pathol* (2012): 171-220
    2. Effects Of Prolonged, Confined Isolation On Serum Levels Of Intercellular Adhesion Molecule-1 And Interleukin-6. *Ahmad R., Mohtar F., Rahman T., Nawawi H., Froemming G.R.A., Ismail T.S., Muid S. Malaysian J Pathol* (2012): 171-220

1. Absracts in Proceedings:
    1. 2 abstracts presented at the MARS 500 Symposium, Russian Academy of Sciences, Moscow Russia, April 23rd - 25th, 2012
        1. Effects Of Isolated Confined Environment On Brachial Artery Flow Mediated Dilatation
        2. Effects Of Long Term Confined Isolation On The Lipid Profile And High Sensitive C-reactive Protein
    2. 2 abstracts presented at the 19th Asia Pacific Regional Space Agency Forum, Berjaya Times Square, Kuala Lumpur, 11-14th December 2012
        1. Biomarkers Of Inflammation, Endothelial Activation, Oxidation Stress And Prothrombogenesis With Long Term Confined Isolation: Mars 520 Program
        2. Association between Endothelial Function and Endothelial Activation in Long Term Confined Isolation

## Human Resource Development

- Research Assistants:
  - Ainul Hatem Hamzah
  - Mohamad Hafizal Mansor
- Postgraduate MSc students:
  - Radzi Ikhsan Ahmad (2011600398)
  - Muhammad Fahmi Mohtar (2011292342)

## Network and Linkages

- Institute of Biomedical Problem (IBMP), Moscow, Russia
- JAXA, Japan
- ANGKASA, Malaysia

## Others:

1. Invited speakers (Prof. Dr. Hapizah Mohd. Nawawi and Dr. Thuhairah Abdul Rahman) at the 19th Asia Pacific Regional Space Agency Forum, Berjaya Times Square, Kuala Lumpur, 11-14th December 2012

# Future Plans (Cadangan Masa Depan)

## A) In Vivo Human Studies:

- Done:
  - Prolonged confinement (18 months) 1g/ground isolation in vivo studies on inflammation, endothelial activation, oxidative stress, prothrombogenesis and endothelial function
- Future in vivo human studies:
  - Ground simulated ug – parabolic studies
  - Microgravity in space – short (2 weeks) and long term (3-6 months) studies in addition to FMD

## B) In Vitro Studies:

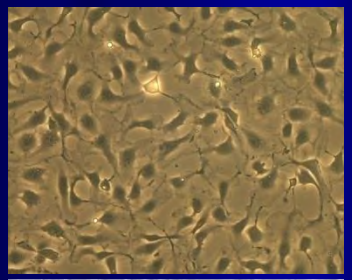
- Done in vitro HUVEC studies:
  - Short term space flight
  - Simulated ground ug
  - 1g ground studies
- Future studies:
  - HUVECS 1g in space studies (HUVECS)
  - HCAECs studies for following
    - 1g on ground
    - ug on ground
    - 1g in space
    - ug in space

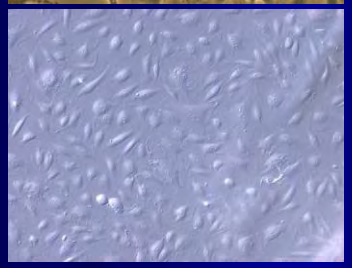
## C) Enhance collaboration and networking:

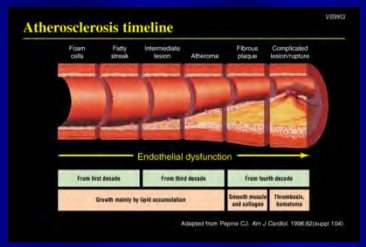
1. JAXA, Japan
2. Volgograd University and ROSCOSMOS, Russia
   - collaboration with ROSCOSMOS on in vivo human – cosmonauts in ISS
   - Prof. Marina Kapitanova (Professor from Volgograd)
3. ANGKASA, Malaysia

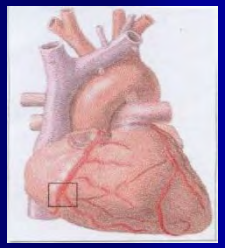
# ENHANCED INFLAMMATION AND ENDOTHELIAL CELL ACTIVATION IN BOTH IMMEDIATE POST FLIGHT AND REVIVED LIVE ENDOTHELIAL CELLS FOLLOWING SPACEFLIGHT MISSION

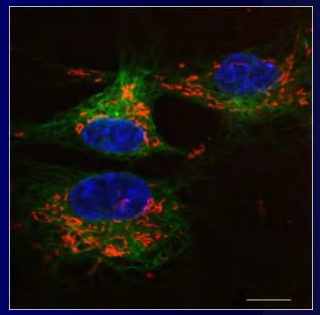
Grant Code: MOSTI 306000070005

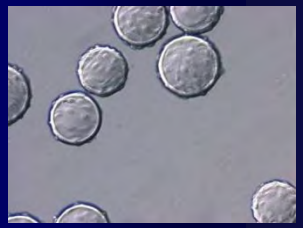










**Hapizah Mohd Nawawi**

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**University Teknologi MARA**

**Malaysia**

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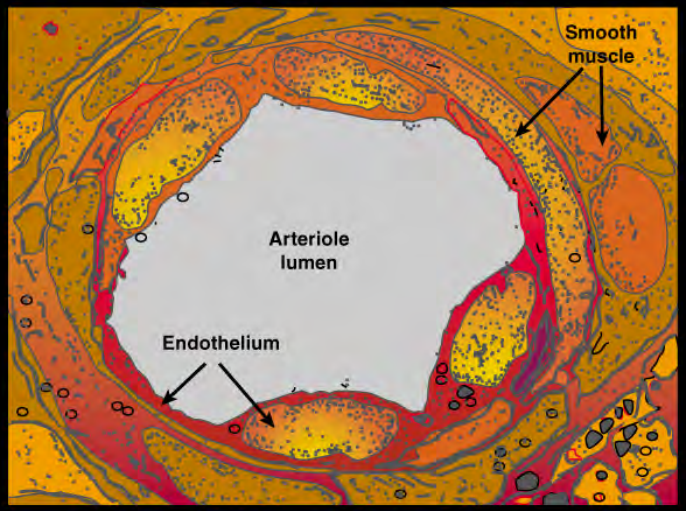


## The endothelium

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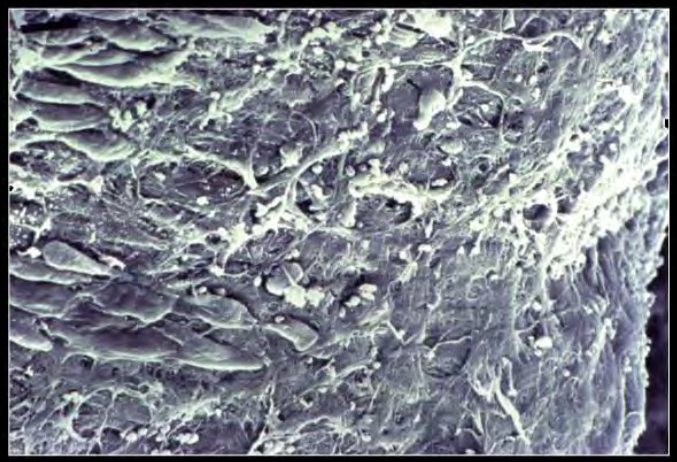

Photograph courtesy of Carl J. Pepine, MD.

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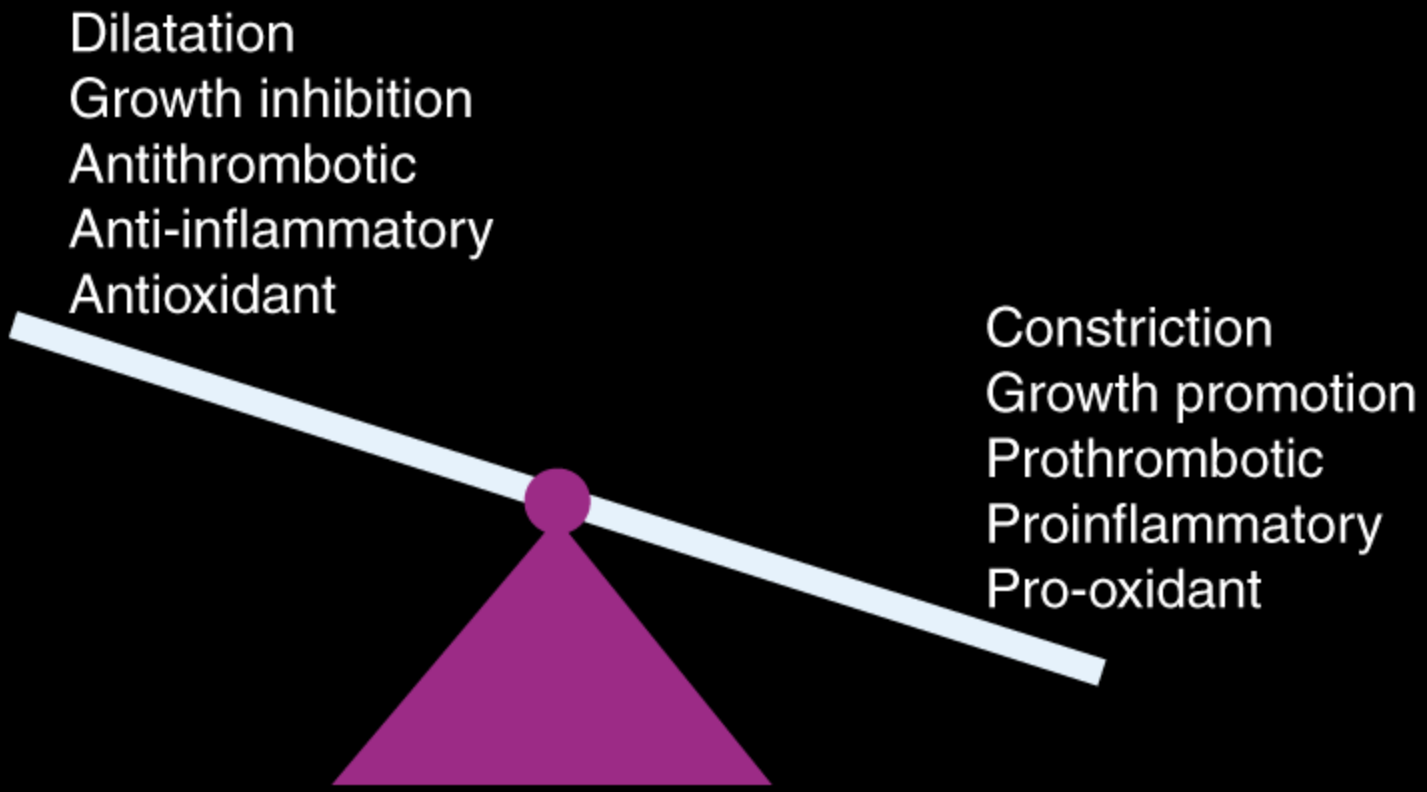
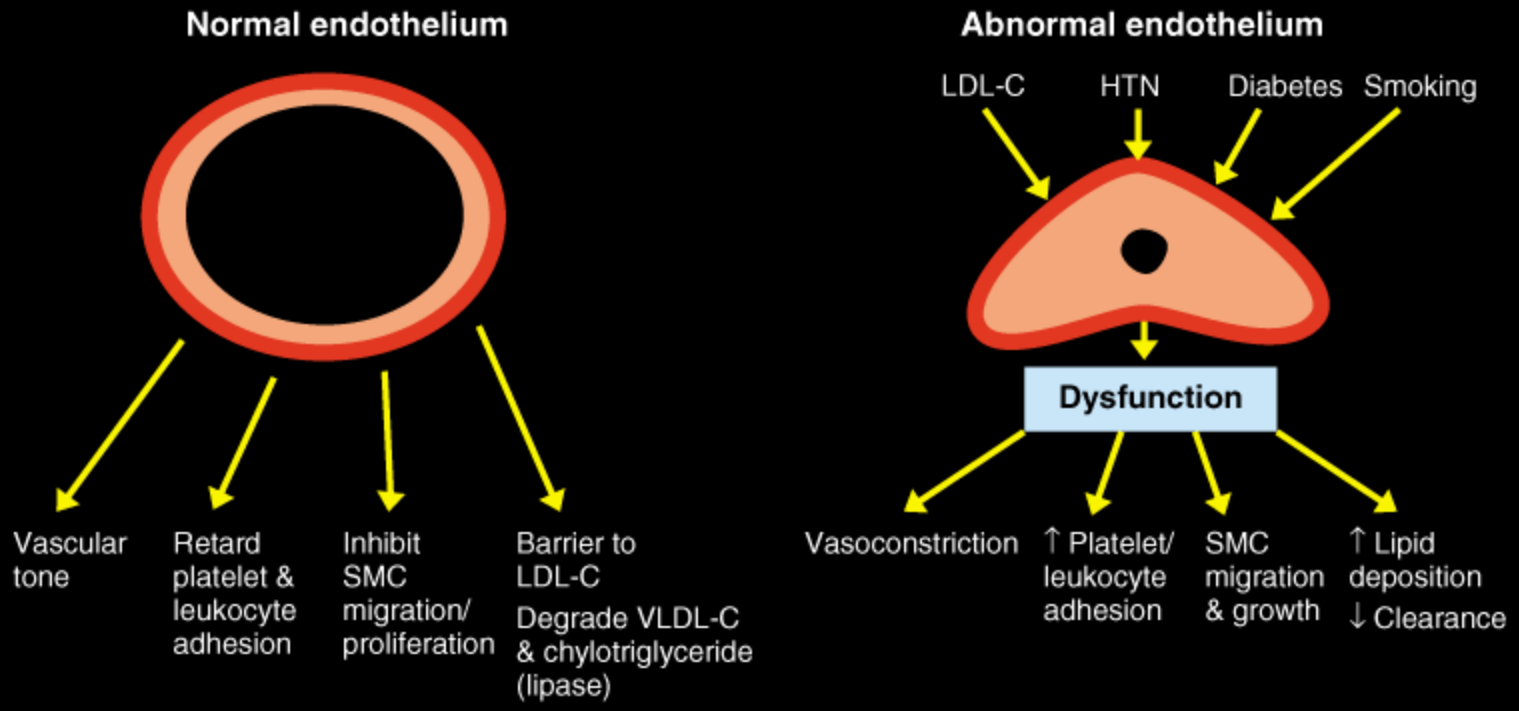


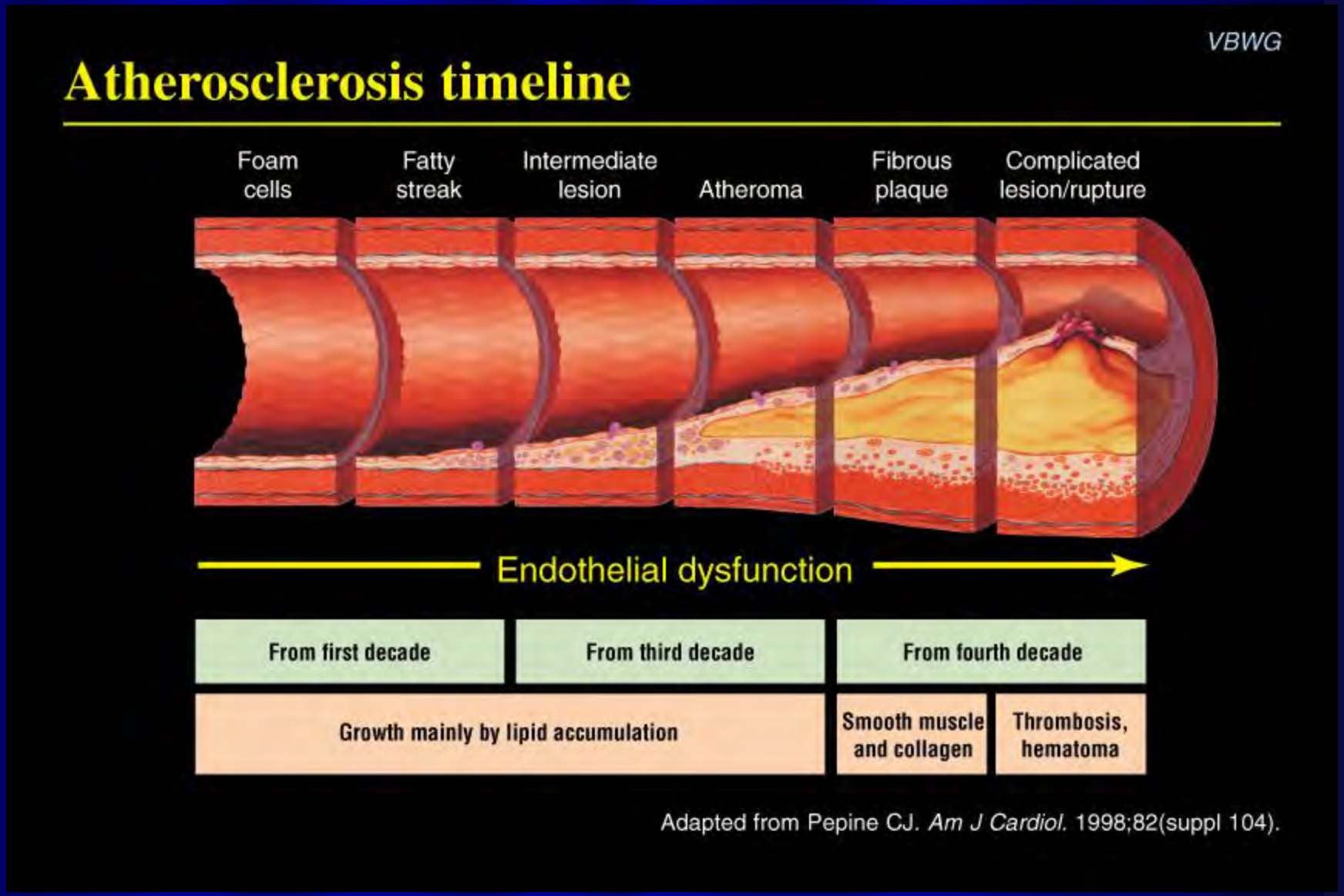
VBWG

# Endothelial dysfunction leads to imbalance of factors resulting in vascular disease



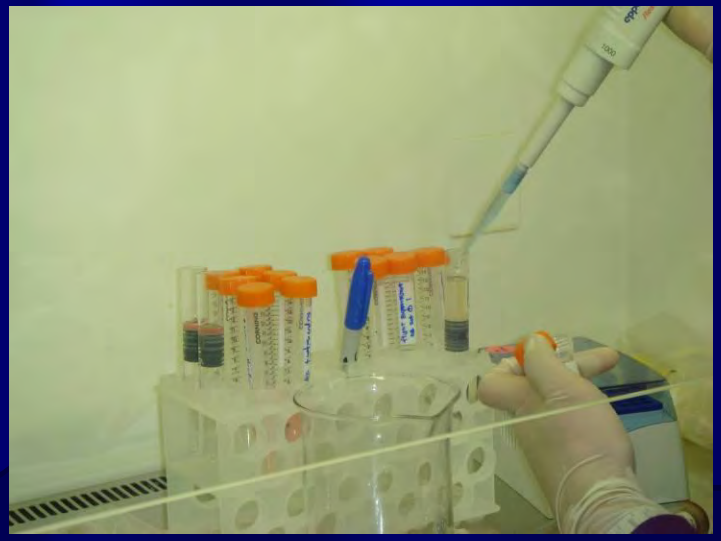

Adapted from Omoigui N, Dzau VJ. *J Vasc Med Biol.* 1991;3:382-391.

**Inflammation and endothelial activation leading to endothelial dysfunction are important factors in atherogenesis.**

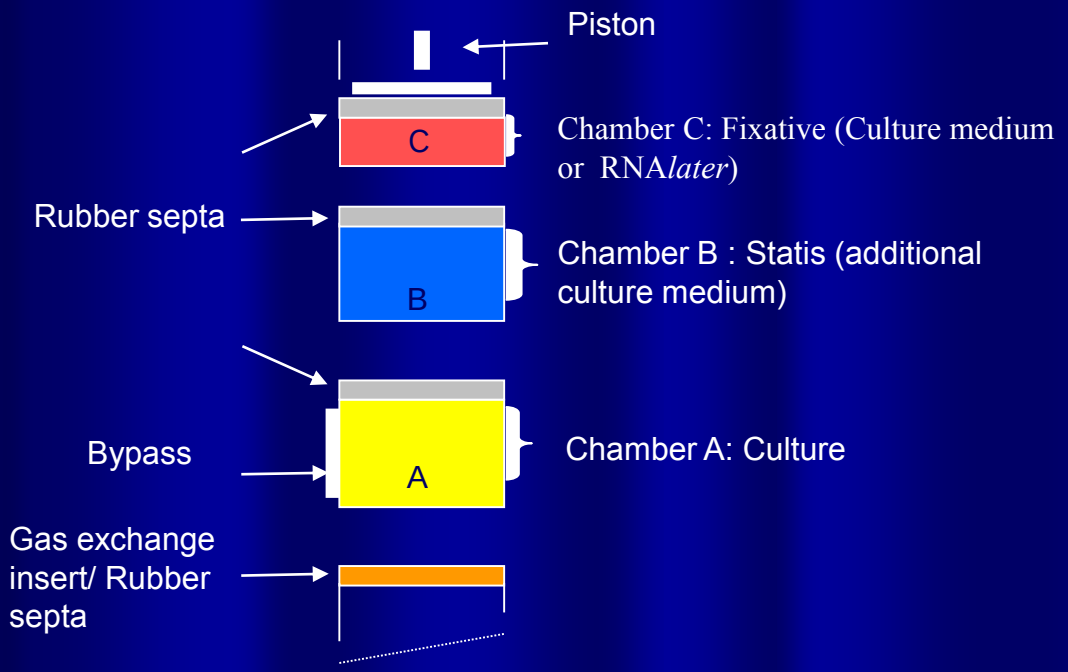



Atherosclerosis – progressive chronic inflammatory disorder, inflammation, oxidative stress & and endothelial dysfunction pivotal in pathogenesis of atherosclerosis

# METHODOLOGY



# FLUID PROCESSING APPARATUS (FPA)




FPA diagram showing the three chambers separated by septa. The fluid bypass enables fluid from the stasis chamber to be injected into the culture chamber during activation and enables the termination reagent to be injected into the growing culture for growth cessation during termination.

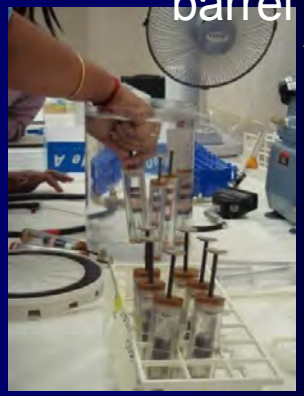
# PRE- FLIGHT EXPERIMENT

Cells in 15 ml centrifuge tubes

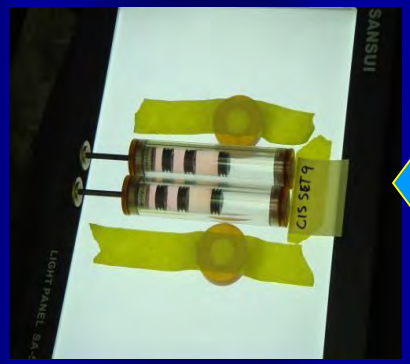
Loading of cells into glass barrel

Glass barrel on the labeling jig

Flight and back up glass barrel



Leakage test




Visible contamination test

Flight samples in Lexan sheath

Handed over to engineers

# ACKNOWLEDGEMENT

**PROJECT LEADERS: Profesor Dr Hapizah Mohd Nawawi**

**CO-RESEARCHERS:**

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***Centre for Pathology Diagnostic and Research Laboratories***

- **Profesor Dr Hapizah Mohd Nawawi**
- **Suhaila Muid**
- **Wan Norhasanah Wan Yusof**

***IMMB (Institute for Medical Molecular Biotechnology***

- **Associate Profesor Dr Gabriele Anisah Ruth Froemming**
- **Dr Nor Ashikin Mohd Noor Khan**
- **Associate Profesor Dr Flossie Jayakara**
- **Profesor Dr Marina Kapitanova**
- **Salina Othman**
- **Mohd Shahir Abd Rahman**

**UnisZA, DARUL IMAN, TRENGGANU**

- **Profesor Dr. Manaf Ali**

**ANGKASA**

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- MOSTI
- ANGKASA
- UiTM
- UnisZA
- IBMP, Russia
- ROSCOSMOS
- ESA
- BIOSERVE

# Atherosclerosis Research Group

# Angkasawan Science Programme – Baikonur, Oct 2007


## PROJECT LEADER :

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Shah Alam

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- ✓ Dr. Gabriele Anisah Froemming
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- ✓ Associate Prof. Dr. Flossie Jayakaran
- ✓ Prof Marina Kapitanova

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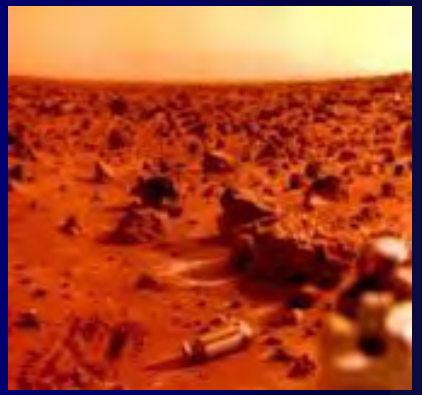
DINNER AND PRESENTATION
THE RUSSIAN EMBASSY
KUALA LUMPUR
30 NOV 2011


# MARS-520

(May 2010 – Nov 2011)



## EFFECTS OF PROLONGED LIVING IN A CONFINED ISOLATION FACILITY ON

## ENDOTHELIAL FUNCTION, INFLAMMATION, OXIDATIVE STRESS AND PROTHROMBOGENESIS

# MARS-520 PROJECT

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- ✓ Prof Marina Kapitanova

UiTM

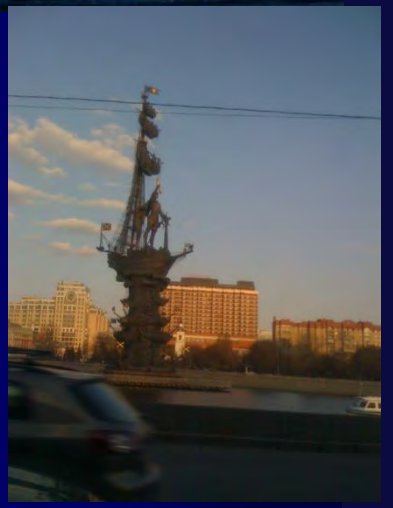
- ❖ Universiti Teknologi MARA
- ❖ ANGKASA
- ❖ MOSTI
- ❖ IBMP, Moscow

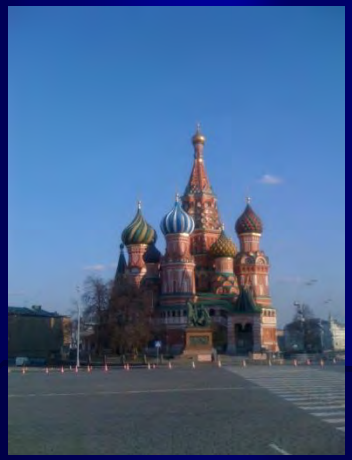
# Objectives

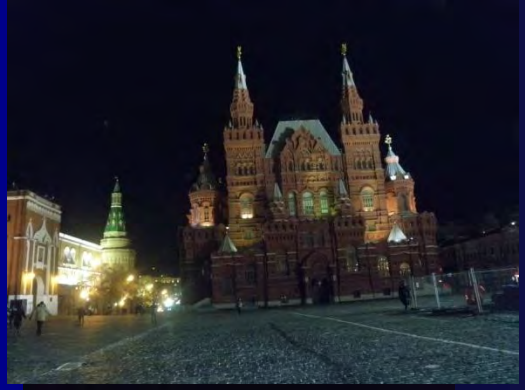
1. To investigate the effects of long term confinement in MARS500 ground isolation facility on biomarkers of inflammation, endothelial activation, oxidative stress and prothrombogenesis.
2. To study the effects of confined isolation on biomarkers of endothelial activation and endothelial function as assessed by FMD of the brachial artery.
3. To generate new understanding on the potential changes in the vascular system that occurs as a result of prolonged confinement which may have long term health consequences to the astronauts

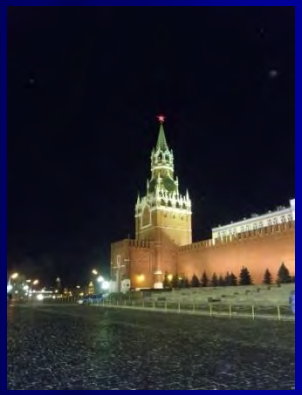


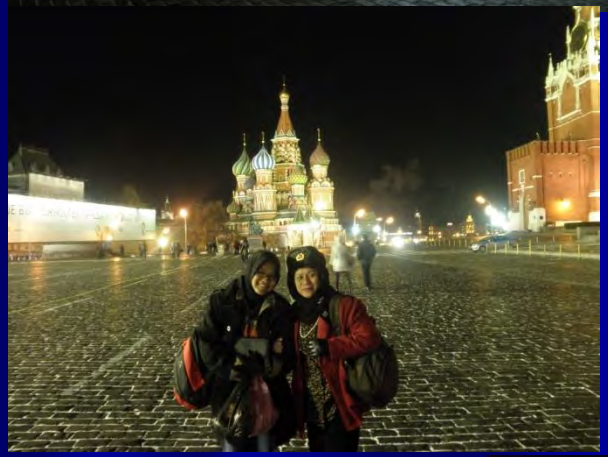
May 2010

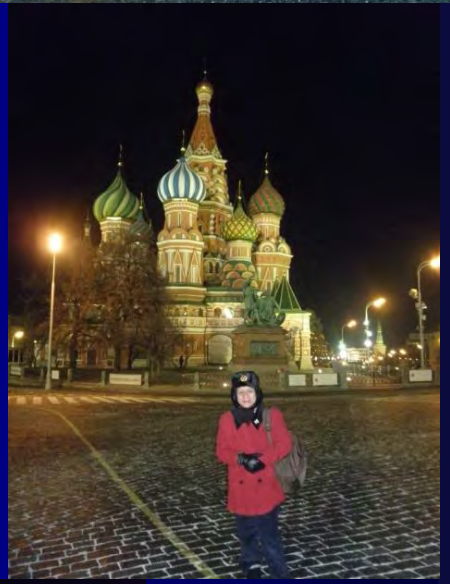










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