THE EFFECTS OF I-131 ON DIFFERENT TYPES OF CANCER CELL LINES

By

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CERTIFICATE

This is to certify that the dissertation entitled

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LIST OF ABBREVIATIONS AND SYMBOLS

NAME	DEFINITION
%	Percent
I-131	Iodine-131
ATCC	American Type Culture Collection
Bq	Becquerel
BSC	Biological Safety Cabinet
Ci	Curie
CO2	Carbon Dioxide
cpm	Count per Minute
DNA	Deoxyribonucleic Acid
FBS	Fetal Bovine Serum
IAEA	International Atomic Energy Agency
µCi	Micro Curie
mL	Milli Liter
PBS	Phosphate Buffer Saline
RPMI-1640	Roswell Park Memorial Institute-1640
Trypsin-EDTA	Trypsin-Ethylenediaminetetraacetic Acid
°c	Degree Celcius
µL	Micro Liter
DMEM	Dulbecco's Modified Eagle's Medium

LIST OF EQUATIONS

ABSTRACT

Aim: The aim of this study is to investigate the effect of I-131 on different type of cancer cell lines.

Method: HeLa, T24, and DBTRG-05 cells exposed to radioiodine-131 of activity 100, 200, 300, 400, and 500 μCi were incubated at 37°C temperature in 1 hour, 2 hours and 3 hours. The cells then washed with PBS and being trypsinized followed by performing measurement using well counter to acquire the cell counts. Percentage uptake was calculated, proceeded with the cells viability and clonogenic assay procedure.

Result: HeLa cells uptake was found to be inversely correlated to the radioactivity and uptake by DBTRG-05 cells was significantly high than compare to HeLa and T24 cells. T24 cells uptake was increased with activity in 3 hours incubation time. As for the cells viability, result obtained was increased by time in HeLa that reverse to T24 and DBTRG-05 cells which viability was reduced by time but the viability with respect to activity was not significantly obtained. Meanwhile, the use of high activity I-131 within few days was found suppressed the proliferation of cancer cells especially for DBTRG-05 cells followed by T24 and HeLa..

Conclusion: The findings of this study suggest that the cellular uptake of I-131, cells viability and proliferation were highly dependent on cells metabolism, mitotic rate, occurrence of apoptosis, doubling time, cells radiosensitivity, and so on with consideration of some limitations.

ABSTRAK

Tujuan: Kajian ini dijalankan bertujuan untuk menyiasat kesan I-131 terhadap jenis sel-sel kanser yang berbeza

Kaedah: Sel-sel HeLa, T24, dan DBTRG-05 telah didedahkan kepada I-131 dengan aktiviti 100, 200, 300, 400, dan 500 μCi yang telah dieramkan pada suhu 37°C selama 1 jam, 2 jam dan 3 jam. Sel-sel tersebut kemudiannya dibasuh dengan penampan larutan fosfat (PBS) dan tripsin diikuti dengan melakukan pengukuran menggunakan pembilang wel untuk mendapatkan bilangan sel. Peratusan pengambilan telah dikira, diikuti dengan mengukur daya maju sel dan kemudian membuat pengklonan semula.

Result: Peratusan pengambilan sel HeLa didapati berkait songsang terhadap aktiviti I-131 dan pengambilan oleh sel DBTRG-05 adalah jelah sangat tinggi berbanding sel HeLa and sel T24. Pengambilan oleh sel T24 telah meningkat dengan aktiviti dalam masa 3 jam pengeraman. Sementara bagi daya maju sel, keputusan yang diperoleh telah menunjukkan peningkatan terhadap masa pengeraman bagi HeLa dan sebaliknya bagi sel T24 dan DBTRG-05 yang mana daya maju sel ini berkurang dengan masa akan tetapi daya maju sel terhadap aktiviti adalah tidak jelas. Sementara, penggunaan aktiviti I-131 yang tinggi dalam masa beberapa hari telah didapati boleh menindas sel kanser dari membentuk semula koloni terutamanya sel DBTRG-05 diikuti dengan sel T24 dan sel HeLa.

Kesimpulan: Dapatan kajian ini mendapati pengambilan I-131 oleh sel, daya maju sel, dan pembahagian sel atau pembentukan koloni adalah sangat bergantung

kepada metabolism sel, kadar mitosis, kejadian apoptosis, masa penggandaan, radiosensitiviti dan sebagainya dengan pertimbangan beberapa keterbatasan.

CHAPTER 1

INTRODUCTION

1.1 Iodine-131

Iodine-131 (^{131}I) is a kind of radioisotope that is most widely used in nuclear medicine for therapeutic purpose and can also be used for diagnostic purpose. ^{131}I has a very short half-life of 8.02 days. In order for the atom to become stable, radioiodine-131 emits gamma (Y) and beta (β) radiations. The emission of these gamma (Y) and beta (β) radiations would result in tissues or cells damage as they are classified as ionizing radiation. This property makes radioiodine-131 become more needed in the nuclear medicine field. This ^{131}I was frequently used in medicine to diagnose and treat thyroid cancers. The example of its use in radiation therapy is to destruct the cancerous or abnormal tissues in thyroid gland after the radioiodine uptake by the tissue. The use of radiodine-131 giving only little effect on the rest of the body since the radiation would only destroy the thyroid gland and any other thyroid cells (including cancer cells) that take up iodine (American Cancer Society, 2014).

In nuclear medicine, the radioidine-131 is prescribed to the patient orally where the patient must drink the liquid radioidine-131 through the straw. The prescription of radioiodine-131 to the patient is based on the desired amount and activity (in mCi) that is calculated. A controlled dose of radioiodine-131 must be given to the patient in a way that the dose prescribed is enough to destroy all the cancer cells. This radioiodine-131 is kind of tracer that will directly go towards the thyroid gland

and accumulates inside this organ. The emission of the gamma rays by the thyroid tissues containing radioiodine-131 make it easier to be imaged or display in the gamma camera monitor. The accumulation of the radioidine-131 in the thyroid gland permits its use to study the radiation kinetics.

Radioidine-131 generally used for therapy and imaging purpose. The therapeutic radioiodine-131 is usually combined with surgical intervention and anti-thyroid medication in treating thyroid cancer and metastases. The prescribed dose to treat patient is depend on the type of disease. The therapeutic study concerns on treating cancers and hyperthyroidism patient. As for hyperthyroidism patient, the dose administered to the patient is usually in the range of 30 to 50 mCi that is considered as moderate activity of radioiodine-131. However the treatment of cancers and metastases diseases needs the use of high activity of radiodine-131 which is about 100 to 200 mCi. This is considered high enough to destroy (ablate) the cancer cells in thyroid tissue.

The survival rate of patients with papillary or follicular thyroid cancer (differentiated thyroid cancer) that has spread to the neck or other body parts is improved when the patients are treated using radioactive iodine, and this treatment is now standard practice in such cases. However, the advantage and the significant of radioactive iodine therapy for patients with small cancers of the thyroid gland that do not seem to have spread are less clear since it is often can be removed completely with surgery. The use of radioactive iodine to treat anaplastic (undifferentiated) and medullary thyroid carcinomas is not applicable because these types of cancer do not take up iodine (American Cancer Society, 2014).

The treatment of cancer using radioiodine not only involving the use of radiation to kill the cancerous and metastases tissue, however it also concerns on sparing the normal tissues since the distribution of the radiation is specifically in the organ that take up the radioiodine tracer only. A tremendous knowledge of the biological effect is thus become necessary since the consideration in the treatment should also involve the surrounding tissues instead of area to be treated.

1.2 Molecular imaging

The process of visualize, characterize, and measure of biological processes at the molecular and cellular levels in humans and other living systems is the basic approaches in molecular imaging that basically involving 2- or 3-dimensional imaging as well as quantification over time. The radiotracer imaging or nuclear medicine, MR imaging, MR spectroscopy, optical imaging, ultrasound, and others are most common well known techniques used in molecular imaging (David A. Mankoff, et al., 2007).

There are two main imaging strategies in molecular imaging which "direct" and "indirect," imaging. The imaging of the target directly is known as direct imaging, usually with a target-specific probe, and can be defined in terms of a probe–target interaction. The resultant image of probe localization and magnitude (image intensity) is directly related to its interaction with the target epitope or enzyme. The use of monoclonal antibody targeting to a cell membrane epitope, imaging the activity of specific enzyme such as hexokinase using an enzyme specific probe like deoxyglucose, and so on are common strategies done in nuclear medicine and is known as the direct imaging strategies (Blasberg, 2003).

Indirect molecular imaging is a little more complex in that it may involve multiple components. One example of indirect imaging that is now being widely used is reporter imaging, which usually includes a reporter gene and probe. The reporter gene product can be an enzyme that converts a reporter probe to a metabolite that is selectively trapped within transduced cells. Alternatively, the reporter gene

product can be a receptor or transporter that irreversibly traps the probe in transduced cells during the period of image acquisition (Blasberg, 2003).

The basic of molecular imaging include providing and visualizing the details of picture regarding the process inside the body at the molecular as well as cellular level. A small amount of radioactive materials or radiopharmaceuticals giving the details of the image that provide many information on how the body functioning which allows the doctor to diagnose the disease and at the same time giving some information to the researchers in order to understand as well as measure the chemical and biological processes (SNMMI, 2014).

1.3 Aims

The aim of this research is to investigate the effect of I-131 on different types of cancer cell lines.

1.4 Objectives

- To measure the uptake of I-131 by different types of cells using different incubation times and activities.
- To assess the cells viability and proliferation of different cells type using different incubation times and activities.
- To find the correlation between the I-131 uptake by the cells to viability of the cells.

CHAPTER 2

LITERATURE REVIEW

2.1 Incidence of Cancer

The case of cancer have been known rapidly increase from year to year and cancer was a major cause of worldwide mortality. According to Wan Aslizan (as cited in World Health Organization 2013), the rate of cancer in the year 2020 could increase by 50% to reach 15 million new cases. About 14.1 million new cases of cancer and 8.2 million cancer-related deaths occurrence was estimated in 2012 (World Health Organization, 2013).Instead known as an uncommon cancer, thyroid cancer was considered as the most common malignancy of the endocrine system.

The thyroid cancer was rarely occurred in youngsters, but most commonly in adults with rate of incidence steadily rise with age (Wan Aslizan, as cited in Hayley 2012). The thyroid gland may once be the site of other primary tumours which include sarcomas, lymphomas, epidermoid carcinomas, and so on. The metastases from other cancers such as lung, kidney, and breast may also occur in the thyroid gland. Over the past 30 years, the mortality from thyroid cancer had declined despite increasing incidence (Cancer Research UK, 2014)

The most common primary treatment for thyroid cancer is surgery of total thyroidectomy (Paek SH, 2013). The thyroidectomy is involving the removal of entire thyroid gland and was an accepted approach recently (American Thyroid Association, 2012). The radioactive iodine was the radionuclide used in destroying the remaining thyroid tissue after the removal of thyroid gland through

thyroidectomy if there was possibility spread of cancer cells or patient is at risk for recurrent cancer (Hayley, 2013).

2.2 Iodine-131 in the Treatment of Cancer

I-131 was frequently used in the thyroid cancer management (Richard and Martin, 2005). The radioiodine-131 was a beta-particle emitter that can ionize at least one electron in an atom with the maximal energy of 606 keV. I-131 can generate free radicals, break the chemical bonds, produce new chemical bonds or cross-link macromolecules that involved in cells regulation processes. These effects can harmful and damage the living cells as the energy from the ionizing radiation was loosed by disrupting the chemical bond, provide a damage disturbance on the DNA molecule, triggering cellular dysfunction and ultimately cell death. The death in cells usually resulted from mutation which caused by I-131 that also affecting other cells up to millimeters away (IAEA, 2009).

The emission of short-range beta radiation makes the I-131 effective in killing the remaining cancer cells and normal thyroid tissue that readily absorb I-131 (Frigren, 1998). The energy of I-131 was high enough to remove electron from atoms that make up the cell molecules (American Cancer Society, 2013). The ionizing radiation was generally harmful that potentially mortal to tissue of cells (Rebecca and Rhona, 2011). The study by Norden (2008) found that high concentrations I-131 would cause the DNA damage in thyroid cells and eventually result in apoptois.

2.3 The Metabolism of Tumour

The metabolism of tumor is dissimilar from the normal tissues which depend on the cancer origin (Cairns RA, 2011). The alteration in tumor metabolism now becomes an interesting topic for intense study. The tumor metabolism was always be related to the Warburg effect which also known as aerobic glycolysis. Most cancer cells were believed to have increased glucose uptake. The glucose is not just oxidized in order to produce adenosine triphosphate (ATP) by oxidative phosphorylation, but the excess glucose will be fermented into lactate (Ward PS, 2012).

Previous finding had suggested that the occurrence of aerobic glycolysis was due to the effect of damaged mitochondria (O, 1956) or due to cancer cells response to tumor hypoxia (Gatenby RA, 2004). The aerobic glycolysis in cancer cells was observed in such a way that independent of oxygen level. Most tumor having mitochondria with no defect and well functioned (Vander Heiden MG, 2009). There was various studies had been done in order to describe a key role of mitochondrial function in cancer and it was believed that for many tumor cells, the main source of ATP was through oxidative phosphorylation (Zu XL, 2004).

Many cancer cells have characteristic of high rate aerobic glycolysis. An individual cancer cell that undergoes aerobic glycolysis would experience an increase macromolecules production which will result in a rapid production or construction of new cells. In support of this idea, many rapidly proliferating normal

tissues and microorganisms undergo aerobic glycolysis (Vander Heiden MG, 2009).

The ATP was very important in supporting the macromolecular synthesis. The cells proliferation can be initiated by acquiring ATP since small amount of ATP would allow the occurrence of cells proliferation (Lunt SY, 2011). However, there must be sufficient ATP generated to confirm the survival of all cells and the relative contribution of different pathways to ATP production likely varies across cancer types and tumor **contexts.** Most of normal mammalian tissues were nutrient consuming rather than glucose and some cancer cells were observed in relative to its alternative fuel source consumption.

The most abundant amino acid in cell culture medium was Glutamine which served as an important source of nitrogen for cells (Lunt SY, 2011). The generation of ATP was through the oxidation of carbon skeleton of glutamine. The carbon skeleton of glutamine was significantly important in replenish TCA cycle which to facilitate biosynthesis. Glutamine was an alternative choice of nutrients after glucose in which the cancer cells most highly consumed in tissue culture (Lunt SY, 2011).

CHAPTER 3

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Cell Lines

3.1.1.1 HeLa Cell

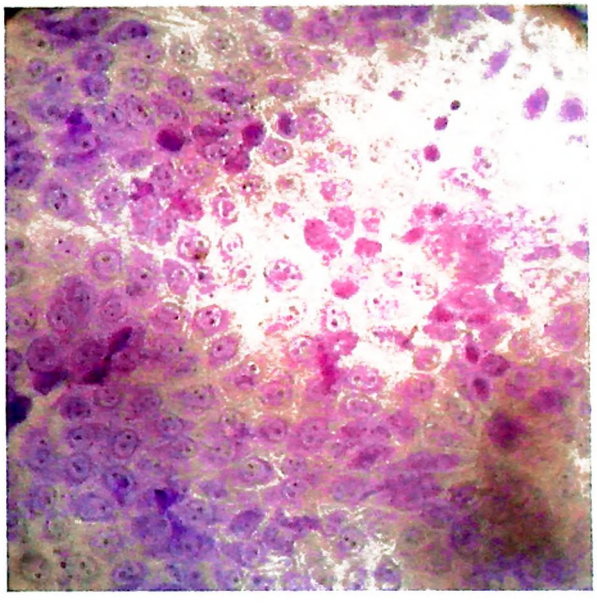

Plate 1: HeLa cells imaged under microscope

The first human cell line established in culture (Gey et al, 1952). The cell line originates from a cervical cancer tumor pt. named Henrietta Lacks, who died of her cancer in 1951. This cell line is derived from epithelial lining cell of the cervix cancer patient.

3.1.1.2 T24 Cell

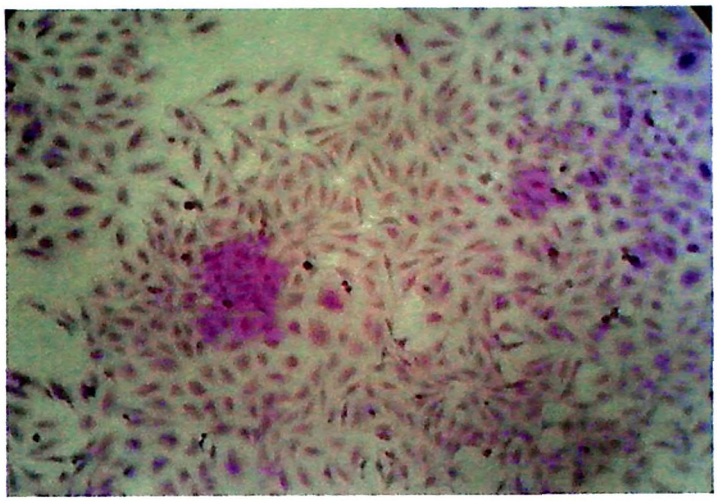

Plate 2: T24 cells imaged under microscope

T24 is the bladder cancer cells which are derived from transitional cancers of human urine bladder, grown in cell culture. The donor of T24 cell was a Swedish female patient, C.M., aged 82, with long diagnosed urinary bladder papillomatosis treated by electro-coagulation. The growth of T24 in tissue culture was characterized by a disorderly pattern of growth in one or more layers and by mixed epithelioid-fibroblastoid morphology.

3.1.1.3 DBTRG-05 Cell

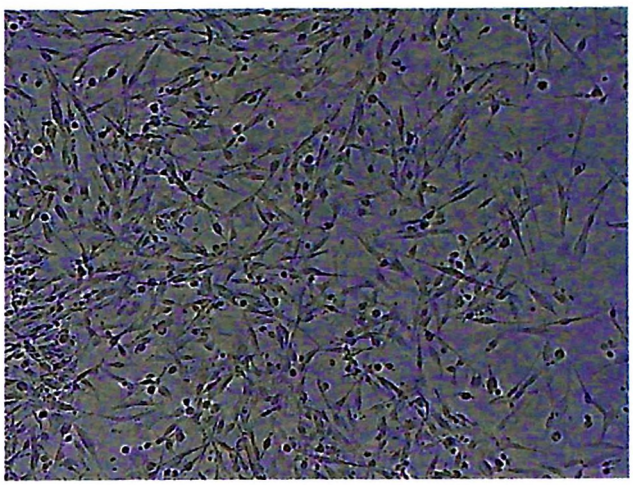

Plate 3: The image of DBTRG-05 cells

The DBTRG-O5MG (Denver Brain Tumor Research Group 05) cell line was established from tissue from a patient with glioblastoma multiformed who had been treated with local brain irradiation and multidrug chemotherapy. Glioblastomas (GBM) are tumors made up of astrocytes which are the star-shaped cells that make up the "glue-like," or supportive tissue of the brain. Since the cells are reproduced so fast and they are supported by large network of blood vessels, they are considered as highly malignant (cancerous) and the dead cells can be seen especially at the center of the tumors. Glioblastomas are usually found in the cerebral hemispheres of the brain, but can be found anywhere in the brain or spinal cord. Since these tumors come from normal brain cells, it is easy for them to invade and live within normal brain tissue. However, glioblastoma rarely spreads elsewhere in the body (American Brain Tumour Association, 2014). Glioblastoma multiforme (GBM) is an extremely invasive, well-vascularized tumor believed to be

of astroglial origin (Wilkins, 2001). It is the most prevalent and lethal of all primary malignant brain tumors, with a median survival rate of 12 months. Despite the standard treatment of surgical resection of the tumor followed by radiation and/or chemotherapy, the survival rate has increased only slightly over the past three decades (Jill Wykosky, 2005).

3.1.2 Six-Well Plate

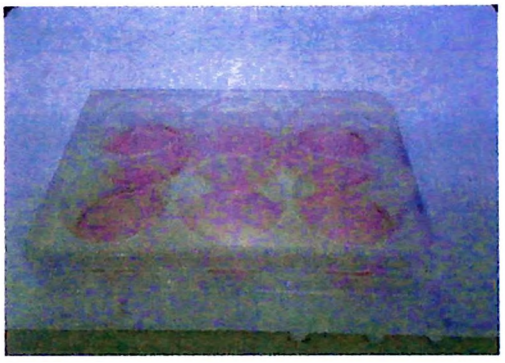

Plate 4: Six-well plate for cells seeding

Six-well plate is a container with six circular wells which is used to place the cells to be plated. The six-well plate has high standard condition as to make sure the cells grow well. The advantages of this well plate include giving a homogenous cells growth, improve cells adherence, providing consistent cells attachment, providing high sterility, must be non-pyrogenic, non-cytotoxic, and others.

3.1.3 3 mL Syringe and 23 G Needle

Syringe and needle is used in injecting the radioiodine-131 into the six-well plate. Small volume syringe is preferred because small syringe needs less pressure that the work becomes easier and the most important is less time consumed in handling radioactive material.

3.1.4 Pipette and Tips

Plate 5: Pipette 1000 µL used to transfer cells

The 1000 µL pipette is an adjustable pipette which is basically used to draw the solution with volume about 100 µL to 1000 µL. This type of pipette is used together with the blue tip to draw the solution and transfer it to another container. This pipette also can be used to measure the volume of the cells and solution. A desired volume of solution needed can be drawn easily and accurately by simply adjusting the pipette.

3.1.5 Centrifuge Tubes and Parafilm

Centrifuge tube is used to place the washed media and the trypsinized cells before being centrifuged to separate the cells and media so that we can take the cell's pellet. Parafilm is used as a stopper which is wrapped on the top of the test tube to prevent spillage.

3.1.6 Hettich Micro 22R Microcentrifuge

Plate 6: Microcentrifuge used to separate cells and media

Microcentrifuge is used to concentrate the cells at the bottom of the test tube. The washed media and the trypsinized cells inside the test tube were centrifuged about 5 minutes at 1500 rpm until a suspension is created at the bottom of the tube which is known as cell's pellet.

3.1.7 Dulbecco's Modified Eagle's Medium (DMEM) Complete Media

The media used is produced by Gibco which was purchased from Life Technologies. The DMEM is ready-made to use and it is a modification of Basal Medium Eagle (BME). This media originally formulated to culture the embryonic mouse cells since it contains 1000mg/L of glucose which is important in culturing process to maintain cell lives. However, it has been modified to be used in several ways which to support primary cultures of mouse and chicken cells, variety of normal cells, and transformed human cells. In this study, DMEM is used to culture HeLa cells, T24 cells, and DBTRG-05 cells.

3.1.8 Roswell Park Memorial Institute Medium-1640 (RPMI-1640)

A complete growth medium must be prepared in order to maintain the cell growth. The base medium for this cell line is 1:1 mixture of Ham's F12 medium. Roswell Park Memorial Institute Medium-1640 (RPMI-1640) is supplied by Gibco, Life Technologies. There are few components were added to the base medium in order to produce a complete growth medium. One of the components is an antibiotic penicillin-streptomycin which is added to prevent the cells culture from getting contaminated (Invitrogen, 2012). Another component is fetal bovine serum (FBS) of 10% final concentration.

3.1.9 Fetal Bovine Serum

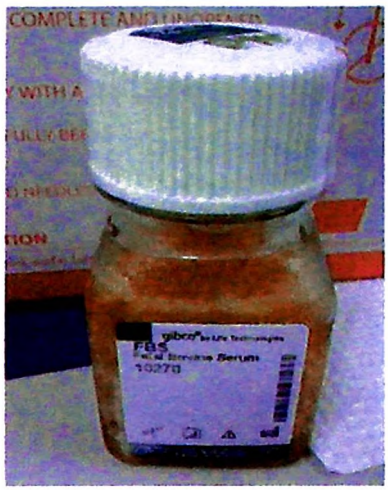

Plate 7: Fetal Bovine Serum (FBS) as nutrients to cells

Fetal Bovine Serum (FBS) originates from the blood of the bovine fetus from South America. This serum contains albumin and other globular protein known as growth factors. These growth factors are important in providing nutrition for cell growth. The FBS from Gibco, Invitrogen, is primarily used in supporting the cloning and growth of cell culture.

3.1.10 Penicillin-Streptomycin Antibiotic

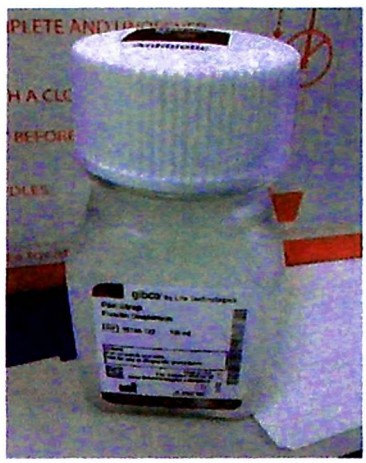

Plate 8: Penicillin-Streptomycin as cell's antibiotics

Penicillin-Streptomycin (Pen-Strep) from Gibco, Life Technologies is a type of antibiotic that is usually added into the media. This antibiotic is an important substance which is needed in the cell culture media to prevent the cells from contaminate. Once the cultured cells contaminated by bacteria or fungi, this can affect the cell growth which therefore effect the result of this experiment.

3.1.11 Phosphate Buffer Saline

Plate 9: PBS used in washing the cells

Phosphate Buffer Saline (PBS) by Gibco, Life Technologies, is a buffer solution or balanced salt formulation which has various uses in cell culture application. It is commonly use to wash the cells, transporting the cells or tissues, diluting the cells for counting, and others. The PBS also acts to control any changes in pH level.

3.1.12 Trypsin-EDTA

Plate 10: Trypsin-EDTA as cell's antibiotics

The trypsin-EDTA (Ethylenetriaminetetraacetic Acid) by Gibco, Life Technologies, is used to detach any adherent cells. In order to transfer the cell from one container to another, we must detach it from the bottom of the flask or container by adding desired amount of trypsin-EDTA into the container using pipette. After about 15 minutes, all the cells can be pipetted and transferred as they are now fully detached since trypsin-EDTA works in cutting the adhesion protein in cell-cell and cell-matrix interaction by enzymatic action.

3.1.13 Trypan Blue 0.4%

Plate 11: Trypan blue used in colouring the cells

The trypan blue from Gibco, Life Technologies was a cell stain that act as a colouring to the cells so that they can be easily assess in cells viability procedure using the dye exclusion test. Before performing the cell counting using hemacytometer, a small amount of cell suspension is mixed with the trypan blue. Under the microscope, we could see different colours of cells which represent different uptake by the cells. The viable cells were seen colourless than compare to the dead cells which is seen darker. This is because the viable cells not take up impermeable dyes since the cell membrane is selective permeable.

3.1.14 Countess™ Automated Cell Counter (Invitrogen)

Plate 12: Automated Cell Counter used for cells counting

Instead of using hemacytometer, this cell counter is also used in order to measure the cell count and viability. This is one step easier in counting the cells since it is automatically count the cells in just about one minute or less. Firstly, put the cells and mix with the trypan blue, and put it on the disposable cell counting chamber slide which then placed inside the slide port. Next, count the cells then the cell count and cell viability are measured and displayed. This way of counting cells gives an accurate and precise reading than compare to manual counting.

3.1.15 Radioiodine-131

Plate 13: Iodine-131 source in shielded container

The Iodine-131 is taken from Nuclear Medicine Department under supervision of staff. Using a proper knowledge of radiation safety, the Iodine-131 is brought to the Medical Radiation Laboratory and I-131 is prepared based on the desired amount to be used on that day which is about 1.5 mCi per six-well plate. Each well must contain 100 µCi, 200 µCi, 300 µCi, 400 µCi, and 500 µCi. The radioiodine-131 is prepared in the syringe before being injected into the well containing cells.