UNIVERSITI PUTRA MALAYSIA

GENOTYPIC AND METABOLIC PHENOTYPE CHANGES IN BREAST CELLS USING GOLD-BASED COMPOUND CANCER TREATMENT

RICHARD YU MING CHUAN

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By

RICHARD YU MING CHUAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August 2018

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DEDICATION

With my deepest gratitude and most humble efforts, I would like to dedicate this thesis:

To Professor Dr. Cheah Yoke Kqueen, my supervisor, who supported and encouraged me throughout this PhD program.

To my dear wife, daughter and son who sacrificed and helped solve whatever matters arose while I was away from home for study.

To my beloved parents and siblings who empathized, encouraged and assisted me throughout this journey.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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Chairman : Professor Cheah Yoke Kqueen, PhD
Faculty : Medicine and Health Sciences

Breast cancer incidence rate remains very high, being one of the top deadly diseases in women around the world. Survival rate has increased in recent years due to modern advanced technologies capable of detecting this disease earlier. However, in the treatment area, researchers are still trying to get new effective chemotherapeutic compounds for breast cancers. Existing popular anticancer platinum-based compounds cause resistance and a decreased response rate. In addition, they are less effective in advanced breast cancers. Recent findings highlighted that cancer stem cells are the root of cancer that causes cancers, and its recurrence after remission to certain years (5 years in average) followed by treatments. This re-emerging of cancer stem cell theory also triggered researchers to find new effective metal-based compounds for cancer stem cells and advanced breast cancers. The aim of this research is to measure genotype and metabolic phenotype changes of breast cancer cells upon treated with novel gold-based 3F series compounds in order to prove the hypothesis that these novel gold-based compounds are less toxic and have better inhibition against the growth of breast cancer cells compared to platinum-based compounds. Thus, in this research, the novel gold-based 3F series compounds such as 3F1: Triphenylphosphanegold (I) O-methyl-N- (3-fluorophenyl) thiocarbamate, 3F2: Tricyclohexylphosphanegold (I) O-methyl-N-

(3-flurophenyl) thiocarbamate, 3F3: Bis (diphenylphosphinoferrocene) di gold (I) O-methyl-N- (3-fluorophenyl) thiocarbamate and 3FL: O-methyl-N- (3-fluorophenyl) thiocarbamate were used *in vitro* experiments with human breast cancer cell lines (MDA-MB-231 & MCF-7), human primary breast cancer cells (in-house cultured) and human breast cancer stem cells (parental breast cancer stem cell & breast cancer stem cell). Canine mammary tumor cell (CMT-stylo) was also used in the assessment of the selected gold compound. Cytotoxicity assay, real-time cell analysis (RTCA), apoptosis, caspase 3/7 activity assays and cell cycle assays were done followed by phenotypic microarrays and microRNA expression profile experiments. The novel compound 3F1 was found to be less toxic and effective against breast cancer cells such as MDA-MB-231, MCF-7 cells, primary breast cancer cells (BCA) and breast cancer stem cells (BCSC-P & BCSC). The IC50 dose of the novel 3F1 compound against those breast cancer cells was approximately 6 times lower than that of cisplatin (CDDP). This meant the novel gold-based 3F1 compound is 6 times stronger anticancer properties than cisplatin. The compound 3F1 induced caspase 3/7 dependent apoptosis and affected cell cycle arrest at both "S"and "G2/M"phases. Furthermore, significant downregulation of commonly upregulated miR-155 of breast cancers was observed in all the tested breast cancer cells: MDA-MB-231, MCF-7, BCA (primary breast cancer cells), BCSC-P (parental breast cancer stem cells) and BCSC (breast cancer stem cells) which were treated with respective IC50 dose of the novel gold compound 3F1 except in the canine mammary tumor cells (CMT-stylo). Last but not the least, the high-throughput modern technology, Phenotypic Microarrays for mammalian cells system (PM-M) was used for identifying reproducible metabolic phenotypic profile of the breast cancer cells, MDA-MB-231 cells. Overall PM-M results indicated that the novel gold-based compound 3F1 caused significant metabolic shifts in the treated MDA-MB-231 cell in terms of markedly reduction of utilizing energy substrates compared to the non-treated MDA-MB-231, control samples. Arginine and arginine containing dipeptides were found to be prominent energy sources in the treated breast cancer cells. All in all, findings from this research are beneficial not only in breast cancer therapeutic drug development but they can also be applied to translational medicines in the field of diagnosis, prognosis, prediction and ultimately towards targeted curative rather than palliative treatments for breast cancers.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERUBAHAN GENOTIP DAN METABOLIK PHENOTIP SEL PAYUDARA DENGAN RAWATAN KANSER BERASASKAN KOMPAUN EMAS

Oleh

RICHARD YU MING CHUAN

Ogos 2018

Pengerusi : Profesor Cheah Yoke Kqueen, PhD
Fakulti : Perubatan dan Sains Kesihatan

Penyakit kanser payudara kekal sebagai punca utama pembawa maut di kalangan wanita di seluruh dunia. Perkembangan teknologi canggih yang mampu mengesan penyakit tersebut pada peringkat awal telah memanjangkan hayat pesakit dalam tahun-tahun kebelakangan ini. Walau bagaimanapun, dari segi rawatan, penyelidik masih berusaha mendapatkan ubat rawatan yang lebih berkesan seperti kompaun logam untuk kanser payudara. Kompaun platinum anti kanser yang sedia ada menyebabkan rintangan dan penurunan kadar tindak balas. Di samping itu, ia juga kurang berkesan dalam kanser payudara yang mara. Penemuan terkini menegaskan bahawa sel stem kanser adalah punca kejadian kanser dan kemunculan semula kanser selepas rawatan. Teori kemunculan semula kanser telah mencetuskan penyelidik untuk mencari kompaun baru berasaskan logam yang berkesan untuk sel stem kanser dan kanser payudara yang mara. Ujuan penyelidikan ini adalah untuk mengukur dan menentukan perubahan genotip dan fenotip metabolik sel kanser payudara terhadap kompound baru berasaskan emas. Hal ini demikian supaya dapat membuktikan hipotesis bahawa kompound emas mempunyai sifat yang kurang toxic dan kebolehan untuk menghalang sel kanser payudara yang lebih kuat daripada kompound platinum. Oleh yang demikian, dalam kajian ini, silikon logam berasaskan emas

siri kompaun 3F1: Triphenylphosphanegold (I) O-methyl-N- (3-fluorophenyl) thiocarbamate, 3F2: Tricyclohexylphosphanegold (I) O-methyl-N- (3-flurophenyl) thiocarba-mate, 3F3 : Bis (diphenylphosphino-ferrocene) di emas (I) O-methyl-N- (3-fluorophenyl) thiocarbamate dan 3FL: O-methyl-N- (3-fluorophenyl) thiocarbamate digunakan untuk eksperimen *in vitro* dengan sel kanser payudara manusia (MDA-MB-231 & MCF-7), sel-sel kanser payudara primer manusia (kultura dalam makmal) dan sel stem kanser payudara manusia (sel stem kanser payudara primer dan sel stem kanser payudara). Sel-sel mammary tumor anjing (CMT-stylo) juga digunakan dalam penilaian kompaun emas terpilih. Ujian cytotoxicity, analisis "real-time" sel (RTCA), apoptosis dan caspase 3/7 assay telah diuji dan diikuti oleh fenotip microarrays dan kajian profil ekspresi microRNA. Kompaun novel 3F1 didapati kurang toxic dan berkesan terhadap sel-sel kanser payudara seperti MDA-MB-231, sel-sel MCF-7, sel kanser payudara primer dan sel stem kanser payudara. Dos IC50 kompaun 3F1 adalah kira-kira 6 kali lebih rendah daripada cisplatin (CDDP) terhadap sel-sel kanser payudara. Ini bererti kompaun 3F1 baru berasaskan emas mempunyai ciri-ciri antikanser 6 kali lebih berkesan berbanding daripada cisplatin. Kompaun 3F1 mengarah apoptosis caspase 3/7 dan menjejas kitaran sel pada fasa "S" dan "G2/M". Tambahan pula, penurunan signifikan yang biasanya meningkat miR-155 kanser payudara diperhatikan di semua sel kanser payudara yang diuji: MDA-MB-231, MCF-7, BCA (sel kanser payudara primer), BCSC-P (sel stem kanser payudara induk) dan BCSC (sel stem kanser payudara) yang telah dirawat dengan dos IC50 3F1 kompaun emas kecuali dalam sel-sel tumor mammary anjing (CMT-stylo). Selain itu, eksperimen berasaskan teknologi tinggi seperti Phenotypic Microarrays (PM-M) digunakan untuk mengenal pasti profil fenotipik metabolik yang boleh dihasilkan daripada sel-sel kanser payudara, sel MDA-MB-231. Keputusan PM-M secara keseluruhan menunjukkan bahawa 3F1 kompaun berasaskan emas yang baru merangsang pergerakan metabolik yang lebih ketara dalam sel MDA-MB-231 iaitu pengurangan ketara pengunaan substrat tenaga berbanding dengan sample kawalan yang tidak dirawati sel MDA-MB-231. Selain itu, arginine dan arginine yang mengandungi dipeptida didapati merupakan sumber tenaga yang berkesan dalam sel-sel kanser payudara yang dirawati. Kesimpulannya, hasil kajian ini bermanfaat bukan sahaja dalam pembangunan ubat terapeutik kanser payudara tetapi juga boleh digunakan untuk ubat-ubatan translasi dalam bidang diagnosis, prognosis, ramalan dan akhirnya ke arah rawatan yang bersifat kuratif berbanding dengan rawatan paliatif dalam kanser payudara.

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Finally, I would like to extend my gratitude to my parents and siblings who always give their moral support and being on standby to assist in every matter.

I certify that a Thesis Examination Committee has met on 7 August 2018 to conduct the final examination of Richard Yu Ming Chuan on his thesis entitled "Genotypic and Metabolic Phenotype Changes in Breast Cells Using Gold-Based Compound Cancer Treatment" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by graduate student

I hereby confirm that:

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- this thesis has not been submitted previously or concurrently for any other degree at any institutions;
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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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Signature: _____
Name of Chairman of Supervisory Committee: Professor Dr. Cheah Yoke Kqueen

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Name of Member of Supervisory Committee: Associate Professor Dr. Gayathri Thevi Selvarajah

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Tan Geok Chin

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LIST OF ABBREVIATIONS

AGO2	Argonaute protein 2
ANOVA	Analysis of variance
AO/PI	Acridine orange (AO) and propidium iodide (PI)
BAK	Pro-apoptotic protein encoded by BAK gene
BAX	Pro-apoptotic protein encoded by gene BAX
BC	Before Christ
BCA	Primary breast cancer cell
Bcl-2	B-cell lymphoma 2 protein which regulates mitochondrial pathway apoptosis
BCSC	Breast cancer stem cell
BCSC-P	Parental breast cancer stem cell
BRCA	Breast cancer susceptibility gene
CCD digital camera	Charge-coupled device digital camera
CDDP/cis-DDP	Cisplatin/ Cis- Dichlorodiammine Platinum (II)
CDKs	Cyclin-dependent kinases
CMT	Canine mammary tumor
CO_2	Carbon dioxide gas
DGCR8	DiGeorge Critical Region 8 (double-stranded RNA-binding protein)
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid

dNTP	Deoxyribonucleotide triphosphate
DR3	Death receptor 3
ECIS	Electrical cell-substrate impedance sensing system
ECM	Extra cellular matrix
EDTA	Ethylenediamine tetra acetic acid
ER	Estrogen receptor
Fas	First apoptosis signal receptor
FBS	Fetal bovine serum
G0/G1	G0/G1 phase of the cell cycle
G2/M	G2/M phase of the cell cycle
H9c2	Myoblast cell
HBSS	Hank's Balanced Salt Solution
HER2	Human epidermal growth factor receptor 2
IC50	Half maximal inhibitory concentration
Ki-67	Nuclear protein cellular marker for proliferation
MCF-7	Estrogen receptor positive breast cancer cell
MDA-MB-231	Triple negative breast cancer cell
miR/miRNA	Micro-RNA
mL	Millilitre
mRNA	Messenger RNA
MTT	Methylthiazol terazolium
MUSE	The name of flow cytometer from Merck
N_2	Nitrogen gas

Neu+	Neural tumor positive
nt	Nucleotide
O_2	Oxygen gas
PAZ	PIWI, AGO, and Zwille
PBS	Phosphate buffered saline
PHDGH	Phosphoglycerate dehydrogenase
PIWI	P-element-induced wimpy testis
PM-M	Phenotype microarray- for mammalian cells
PR	Progesterone receptor
Pre-miRNA	Premature microRNA
Pri-MiRNA	Primary microRNA
qPCR	Real-time PCR
RISC	RNA-induced silencing complex
RNase	Ribonuclease
RTCA	Real-time cell analysis
RT-PCR	Reverse transcription polymerase chain reaction
S.D.	Standard deviation
S and G2/M	Both S phase and G_2/M phase of the cell cycle
TNFαR	Tumor necrosis factor alpha receptor
TRBP	Transactivating response RNA binding protein
tRNA	Transfer RNA
uL	Microlitre
uM	Micro-molar

WHO	World Health Organization
x g	Times gravity
°C	Degree Centigrade/Celsius
3F1	Triphenylphosphanegold(I)O-methyl-N-(3-fluorophenyl) thiocarbamate
3F2	Tricyclohexylphosphanegold (I) O-methyl-N-(3-fluorophenyl) thiocarbamate
3F3	Bis(diphenylphosphinoferrocene) di gold(I) O-methyl-N-(3-fluorophenyl) thiocarbamate
3FL	O-methyl-N-(3-fluorophenyl) thiocarbamate

CHAPTER 1

INTRODUCTION

Breast cancer remains one of the highest leading causes of death in women aged 35 to 49. In 2012, nearly 1.7 million new breast cancer cases were diagnosed globally. More than 411,000 death among women worldwide were caused by breast cancer (Anderson & Tsu, 2008) and this death figure went up to over 508,000 in 2011 ("WHO | Breast cancer: prevention and control," 2016). Although breast cancer has been identified as early as in BC 1500, scientists today are still working hard on findings of effective treatments (Sudhakar, 2010). It has also noted that breast cancer incidence rates have increased globally since 1990. In Asia, breast cancer rate has noticeably increased up to double or triple in the past four decades. It was reported that the average age of breast cancer patients is in their 40's in Asia while in North America and Europe is 60's (Trieu, Mello-Thoms, & Brennan, 2015; Youlden, Cramb, Yip, & Baade, 2014). Breast cancer can be found in female patients as young as 16 and as old as 92. The incidence rate of breast cancer among women in western countries is about 12.5%. There are also cases of breast cancers in male, but the incidence rate is low. Asia and Africa are recognized as low-risk while South America and South Europe are middle risk and North America and North Europe are high-risk regions of breast cancer. However, mortality rate is higher in those low-risk countries due to lower health care standard and socio-economic status. It is also reported that the life time probability of developing breast cancer in women is one in eight ("Risk of Developing Breast Cancer | Breastcancer.org," n.d.). Although breast cancer incidence rate is increasing globally, overall mortality rate is decreasing due to new findings for early diagnostics and prognostics, new strategies of treatments as well as new compounds. Due to research and developments, healthcare providers nowadays are more aware of existing sub-types of breast cancers that need to be treated differently in order to have better outcomes. This is much improvement compared to 1980's when all breast cancers were assumed to be the same single type of disease.

Up to now, the exact cause of breast cancer is still unknown. However, risks factors that could potentially cause breast cancers were documented. The two main risk factors are known to be of female gender over 50. Estrogen and progesterone play a crucial role such as initiation, promotion and progression of breast cancers (Jerry, 2007; Russo & Russo, 2006; Wang & Di, 2014). Life time exposure of breast to estrogen and progesterone in women is accounted for major

risk factor of breast cancers (Barber, Thomas, & Dixon, 2012). Other risks factors are accounted for only a small percentage (Saunders & Jassal, 2009). Breast cancers are most commonly treated through surgery followed by a combination of chemotherapy, radiation therapy, hormonal therapy and monoclonal antibody therapy. It has been over four decades since estrogen receptors were found on breast cancer cells (Breast, Clarke, & Potten, 1997; Fallis, 2013; Love & Philips, 2002). Anti-estrogen therapy such as tamoxifen showed effectiveness of controlling the growth of breast cancer tumors (Jordan, 1993, 2008; Sunderland & Osborne, 1991). *In vitro* studies proved that estrogen is the main factor that causes uncontrolled growth in hormone-dependent breast cancer cell lines (Lippman, Bolan, & Huff, 1976). It is fortunate that estrogen positive (ER+) breast cancer is about 70% to 80% of all breast cancers and most of them respond to antiestrogenic treatment (Perou et al., 2000). It was noted that about 60% of these ER positive breast cancers are also PR+ (progesterone receptor +). About 20 percent of all breast cancers are HER2-positive while about 10~15 percent of all breast cancers are triple negative (Arnedos, Bihan, Delaloge, & Andre, 2012; Lachapelle & Foulkes, 2011). These Triple negatives breast cancers are aggressive and difficult to treat as they do not respond to hormonal therapy such as Tamoxifen or aromatase inhibitors, or other therapies that target HER-2, such as Herceptin or Tykerb. Those patients may also be unable to fight against breast cancer recurrence with the existing metal-based compounds. Cisplatin also known as cis-DDP is commercially available well known first anticancer metal compound. Other platinum associated compounds such as carboplatin (global), oxaliplatin (global), nedaplatin (Japan), lobaplatin (China) and heptaplatin (South Korea) were also introduced later for the treatment of breast cancers today (Galanski, Jakupec, & Keppler, 2005). Although Carboplatin was later introduced as lower toxicity compound, cisplatin still showed better response rate in previously untreated metastatic breast cancer (Decatris, Sundar, & O'Byrne, 2004). Breast cancer treatment response rate decreased by about 10% in patients who received cisplatin or carboplatin in the past (O 'brien, Talbot, Smith, & Smith, 1993).

Nowadays, drawing attractions towards research on gold-based anticancer compounds has increased due to their capability of killing cancer cells that are resistant to platinum-based compounds (Nardon et al., 2015). Gold I and gold III-based complexes showed satisfactory anticancer activities. However, it was reported that gold-based compounds previously tested were unstable and subjected to synthesize another appropriate gold-based compounds in terms of improvements in anticancer properties. (Zou, Lum, Lok, Zhang, & Che, 2015).

Problem statement

Overall, cisplatin associated compounds showed limitations in the treatment of cancers due to their toxicity to neurons and kidneys (Florea & Büsselberg, 2011). Furthermore, only less effectiveness was observed in cancers resistant to cisplatin naturally. Development of acquired resistance in patients who were treated with cisplatin previously remains as one of the main challenges as well. Therefore, it is evidently a need to explore more on metal-based anticancer compounds and its related research that lead to discovery of new treatment drugs in breast cancers.

Current problems as described above, existing metal-based compounds caused resistance and recurrence of tumors, decreased response rate once they have been exposed to tumor cells. Recently, these existing compounds were reported targeting to fast growing tumor cells but not to the root of a tumor, cancer stem cells (Radpour, 2017; Zhao, 2016). Therefore, existing metal-based anticancer compounds including platinum-based compound are less effective for the treatment of triple negative breast cancers, metastatic breast cancers, cisplatin resistant breast cancers and breast cancer stem cells. Literature research revealed that gold-based compounds are alternative promising agents that work on cisplatin resistant breast cancer cells.

In this research, novel structure of gold-based metal compounds series: 3F1: Triphenylphosphanegold (I) O-methyl-N-(3-fluorophenyl) thiocarbamate, 3F2: Tricyclohexylphosphanegold (I) O-methyl-N-(3-fluorophenyl) thiocarbamate, 3F3: Bis(diphenylphosphinoferrocene) di gold(I) O-methyl-N-(3 fluorophenyl) thiocarbamate and 3FL: O-methyl-N-(3-fluorophenyl) thiocarbamate were investigated anticancer properties against commercial cancer cell lines such as MDA-MB-231 (triple negative), MCF-7 (ER positive), in-house cultured primary breast cancer cell (BCA), two commercial breast cancer stem cells (BCSC-P: parental breast cancer stem cells and BCSC: breast cancer stem cells) and eventually we also tested on canine primary tumor cells (CMT-stylo). Findings in this research may contribute to further development in discovery of a new effective gold-based compound to treat different type of breast cancers including breast cancer stem cells effectively. Furthermore, investigations towards miRNA expression profiles and the metabolic fingerprints of invasive type of breast cancer cell, MDA-MB-231 might help assist further in early diagnostic, prognostic and therapeutic of breast cancers.

Hypothesis

Novel gold-based compound 3F series (3F1, 3F2, 3F3, 3FL) are less toxic and have better inhibition of the growth of breast cancer cells compared to platinum-based compound (cisplatin). Therefore, *in vitro* mode of actions of the best novel gold-based compound among above 4 compounds against breast cancer cells: MDA-MB-231, MCF-7, BCA (primary breast cancer cell), and breast cancer stem cells: BCSC-P (parental breast cancer cell), BCSC (breast cancer stem cell) can be determined.

General Objective

To measure the genotype and phenotype changes of the breast cancer cell lines, primary breast cancer cell and breast cancer stem cells including one canine mammary tumor cell line treated with IC50 dose of one of the best novel gold compounds among 3F1, 3F2, 3F3 and 3FL.

To achieve the general objective stated above, the following specific objectives were set.

Specific Objectives

1. To measure *in vitro* cytotoxicity of 2 human breast cancer cell line, 2 commercial breast cancer stem cells, and one canine mammary tumor cell treated with the novel gold-based compound series (3F1, 3F2, 3F3 and 3FL) in order to select the best compound which demonstrated the most effective and less toxic IC50 dosage.
2. To establish primary breast cancer cell line from histopathologically confirmed biopsy sample for cytotoxicity study of the selected gold compound.
3. To determine *in vitro* cytotoxicity of the selected gold compound in inducing apoptosis, cell cycle arrest and caspase dependent apoptosis on breast cancer cells: MDA-MB-231 and MCF-7.
4. To quantify selected miRNA (miR-10b, miR-21, miR-155, miR-92a and miR-181a) expression profiles of the breast cancer cell lines, breast cancer stem cells and one canine mammary tumor cell line treated with the selected novel gold compound.
5. To identify phenotypic profile of a representative breast cancer cell, MDA-MB-231 treated with the selected novel gold compound.

Overall workflow (**Figure 1.1)** of this research is shown at the next following page**.**

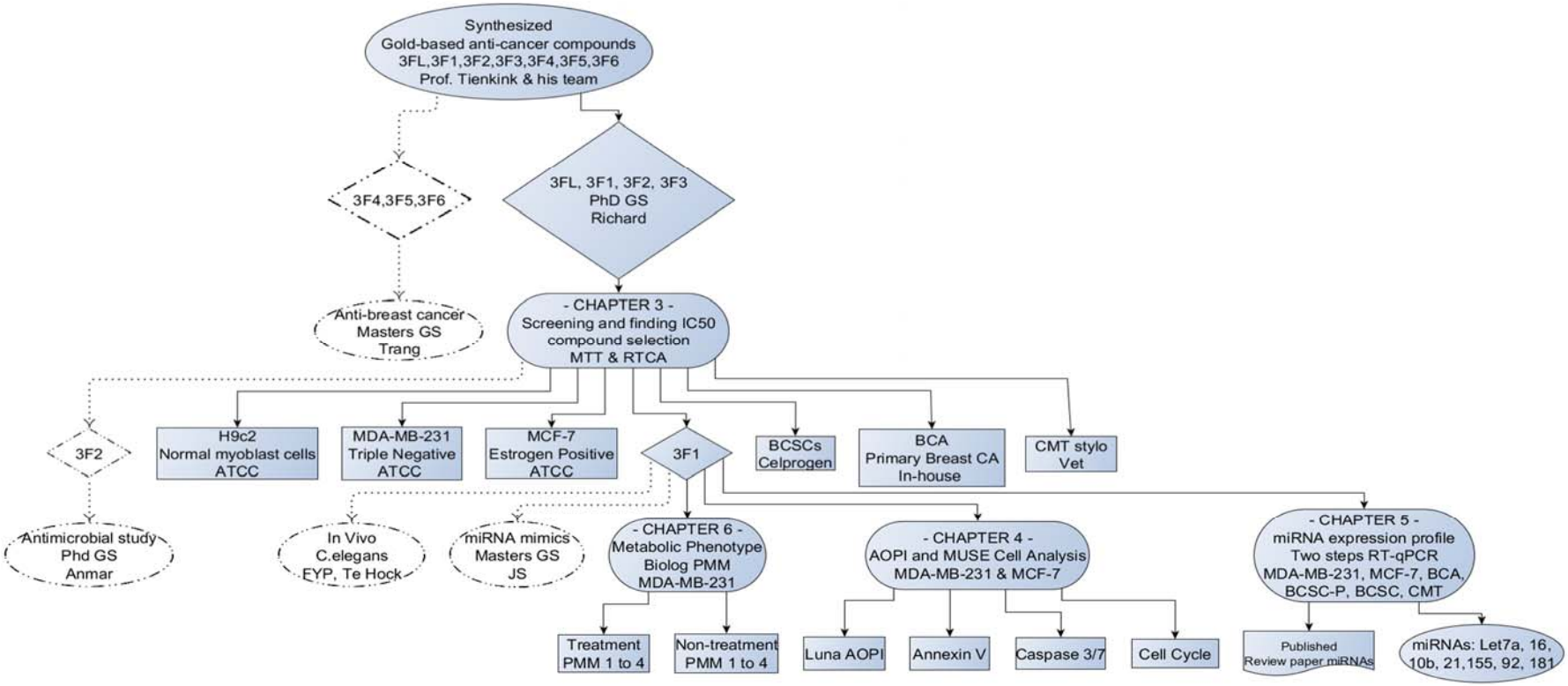

Figure 1.1 : Conceptual Framework of This Research

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