UNIVERSITI PUTRA MALAYSIA

BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

CHEN BAO JING

FPSK(p) 2018 6

BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

By

CHEN BAO JING

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

December 2017

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

BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

By

CHEN BAO JING

December 2017

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

The notable achievement of medicinal inorganic chemistry in particular transition metal and the development of medicinal metal complexes is extended beyond platinum class. Gold complexes aims to solve chemoresistance and toxic side effects of platinum have inspired the idea of synthesizing mononuclear phosphanegold(I) dithiocarbamate complexes series, $R_3PAu[S_2CN(CH_2CH_2OH)_2]$, R = phenyl (Ph) (1a), cyclohexyl (Cy) (1b) and ethyl (Et) groups (2a and 3a). Antibacterial screening of the four complexes by antimicrobial susceptibility tests encompasses disc diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determination and time kills assay allowed the identification of antibacterial properties against 24 Gram-positive and Gram-negative pathogens. The antibacterial activity of the complexes was found to differ among each other, either broad range or specific and bacteriostatic or bactericidal. Anticancer properties of the complexes was demonstrated in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and flow-cytometry, showed to be effective against breast, lung and colorectal cancer cell lines with identified IC_{50} in µM over 24 hours interaction. The anticancer activity also found to be associated with the ability to inhibit breast cancer invasion and migration through BioCoat™ Matrigel™ Invasion Chamber and scratch assay. Investigation of the cell death mode induced by the four complexes through acridine orange (A0)/ propidium iodide (PI) double staining and DNA fragmentation, indicated the apoptosis event was occurring with the observation of apoptotic morphological features and fragmented DNA. Complexes 1a, 1b, 2a, and 3a resulted apoptosis were further assessed with fluorescent detection. Translocation of phosphatidylserine (PS), cell cycle arrest, and increase caspases expressions provided the hint of increase mitochondrial membrane potential related to intrinsic and extrinsic pathways. Data was then supported by RT^2 Profiler ™ PCR array which involve the study of 84 apoptotic genes, exhibited the upregulation of p53/p73 and higher expression of pro-apoptotic genes over anti-apoptotic genes. Toxicity of the complexes were determined through *in vivo* survival assay on *Caenorhabditis elegans* and *in vitro* MTT assay on human embryonic kidney cell (HEK293) and rat myocardium cell (H9C2). Result showed the complexes at low dosage showed generally not effect on lifespan but high dosage cause lifespan reduction. However, all four complexes displayed

low toxicity on HEK293 and H9C2 with higher IC_{50} than cancer cells. Apart from that, mutagenicity of the complexes were evaluated through Ames test and showed lack of mutagenic potential. Based on *in vitro* antibacterial and anticancer potency, all four complexes were arranged in the descending order 2a > 3a > 1a > 1b. However, the four complexes exhibited toxicity in the descending order 1b > 1a > 2a > 3a. Complex 2a represented the complex with greatest antibacterial and anticancer activities and lower toxic than complex 3a. As a conclusion, mononuclear phosphanegold(I) dithiocarbamates have excellent antibacterial and anticancer activities which induce both mitochondria and death receptors apoptotic pathways with generally low toxicity and not mutagenic.

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

PEMERIKSAAN SIFAT BIOPERUBATAN MONONUKLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

Oleh

CHEN BAO JING

Disember 2017

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

Pencapaian yang penting dari perubatan mengenai kimia tidak organik, terutamanya logam peralihan, pembangunan kompleks logam perubatan telah dilanjutkan kepada kelas selain daripada platinum. Kompleks emas yang bertujuan untuk menyelesaikan masalah rintangan kemoterapi dan kesan sampingan platinum telah menginspirasikan idea untuk menghasilkan siri komplexes mononuklear phosphanegold(I) dithiocarbamates, R3PAu[S2CN(CH2CH2OH)2], R = phenyl (Ph) (1a), cyclohexyl (Cy) (1b) dan ethyl (Et) (2a dan 3a). Pemeriksaan anti-bakteria keempat-empat kompleks dengan ujian antimikrob kecenderungan merangkumi disc diffusion, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determination dan time kills assay membenarkan untuk mengenal pastikan aktiviti anti-bakteria terhadap 24 Gram-positive dan Gram-negative patogens. Sifat anti-bakteria keempat-empat komplexes itu didapati berbeza antara sama satu lain, sama ada kesan yang luas atau tertentu dan bakteriostatik atau bactericidal. Sifat anti-kanser keempat-empat komplexes telah didemotrasi melalui 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay dan sitometri aliran, menunjukkan keberkesanan terhadap kanser payudara, paru-paru dan kolorektal dengan IC50 dalam unit µM selepas 24 jams interaksi. Aktiviti anti-kanser tersebut juga didapati berkaitan dengan keupayaan untuk meghalang kanser payudara pencerobohan dan penghijrahan melalui BioCoat™ Matrigel™ Invasion Chamber dan eksperimen pemulihan luka. Penyiasatan mod kematian sel yang disebabkan oleh empat kompleks melalui pewarnaan Akridina Jingga (A0)/ Propidium iodida (PI) dan ujian fragmentasi DNA, menunjukkan aktiviti apoptosis telah berlaku dengan pemerhatian morfologi apoptotik dan pembentukan fragmentasi DNA. Kompleks 1a, 1b, 2a, dan 3a yang menyebabkan apoptosis telah lanjut dinilai dengan pengesanan pendarfluor. Translokasi Phosphatidylserine (PS), perencatan kitaran sel, dan peningkatan caspases ungkapan memberikan tanda-tanda bahawa peningkatan mitokondria membran berpotensi yang berkaitan dengan jalur intrinsik dan ekstrinsik. Data adalah seterusnya disokong oleh RT^2 Profiler ^{TM} PCR yang melibatkan kajian 84 gen apoptotic, mempamerkan peningkatan p53/ p73 dan ungkapan yang lebih tinggi oleh gen pro-apoptotic daripada gen anti-apoptotic. Kesan toksik daripada keempat-empat kompleks yang diuji telah ditentukan melalui ujian jangka hayat pada *Caenorhabditis elegans in vivo* dan MTT assay pada sel manusia embrio

buah pinggang (HEK293) dan sel tikus miokardium (H9C2) *in vitro*. Keputusan menunjukkan kompleks pada sukatan yang rendah menunjukkan secara amnya tidak kesan ke atas jangka hayat tetapi dos tinggi mengurangan jangka hayat. Walau bagaimanapun, keempat-empat kompleks yang diuji telah mempaparkan toksik rendah pada HEK293 dan H9C2 dengan nilai IC_{50} lebih tinggi daripada sel-sel kanser. Selain itu, mutagen kompleks telah dinilai melalui ujian Ames dan menunjukkan kekurangan potensi mutagen. Berdasarkan potensi aktiviti-aktiviti antibackteria and anticancer, keempat-empat komplek adalah disusun mengikut giliran menurun 2a > 3a > 1a > 1b. Sebaliknya, kesan toksik keempat-empat komplex adalah disusun mengikut giliran menurun 1b > 1a > 2a > 3a. Komplex 2a mewakili sebagai komplex yang mempunyai aktiviti antibakteria dan antikanser yang terkuat dan tosiksiti yang rendah daripada komplex 3a. Kesimpulannya, kompleks mononuklear phosphanegold(I) dithiocarbamates mempunyai aktiviti anti-bakteria dan anti-kanser yang sangat baik dengan kedua-dua mitokondria dan reseptor kematian jalur apoptotik dan keracunan seluruhannya rendah dan tidak mutagen.

ACKNOWLEDGEMENTS

Hereby I would like to express my appreciation to all that had help me and gave me advices throughout the course of this project.

First and foremost, I especially would like to thank my supervisor, Associate Professor Dr. Cheah Yoke Kqueen throughout my experiments. Many thanks go into my co-supervisors, Associate Professor Roslida Abdul Hamid @ Abdul Razak, Dr Tham Chau Ling and Professor Edward Richard Tom Tiekink for their guidance. Their advice and encouragement has given me motivation during the course of my project and the completion of this thesis. They have always been accessible and patiently willing to help all his students in their research.

Besides that, I would like to express my gratitude to my project postdoctoral researcher, Dr. Khoo Chai Hoon for her supervision and guidance as well. She always shares her valuable opinions and provides spiritual support. With her help, I successfully complete my research project and thesis.

I would like to express my sincere appreciation to the help from laboratory staff members, Madam Martini Katimin, my lab colleagues, See Tian Hong, Samuel Ooi Kah Kooi, Elaine Chin Jin Feng, Jerry Chu Pek Lim, Chu Wern Cui, Gwee Chin Piaw, Alvirous Lim Wei Meng, Le Tran khanh trang, Tan Poh Keong, Shirley Lee Sze Li, Catherine Yeoh, Eunice Chan Pit Foong, Dylan Lim, Richard, Anmar and Ubaidah Naim. They had sharing knowledge, experiences, time and most importantly, nourished up my life during my postgraduate studies.

Furthermore, a special tribute to the Molecular Biology Laboratory, Biochemistry Laboratory, Physiology Laboratory, Signaling Laboratory and Institute Bioscience for kindly provide technical supports, services and facilities required. My appreciation also goes to inorganic chemistry group, Faculty of Science and Technology, Sunway University under guidance of Professor Edward Richard Tom Tiekink for synthesizing compounds used to be studied in this project.

Last but not least, I would like to thank my family, especially my parents who have always lent a listening ear, as well as providing me with financial support and transportation. Their help has empowered me to complete this project. I would like to apologize for any inconvenience that I arised throughout this period of time.

Thank you.

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

Cheah Yoke Kqueen, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Roslida Abdul Hamid @ Abdul Razak, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Tham Chau Ling, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Edward Richard Tom Tiekink, PhD
Professor
University of Malaya
Malaysia
(Member)

_____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: _____

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

Signature: _____
Name of Member of Supervisory Committee: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABC	Adenosine triphosphate-binding cassette
AJ	Adherens junctions
ARID1A	AT-rich interactive domain 1A
ASK1	Apoptosis signal-regulating kinase 1
ATM	Ataxia telangiectasia-mutated
ATP	Adenosine triphosphate
Au	Gold
BER	Base excision repair
BL1 and BL2	Basal-like 1 and 2
CARD	Caspase recruitment domain
CDC	Centers for Disease Control and Prevention
C elegans	Caenorhabditis elegans
CIN	Chromosomal instability
Cy	Cyclohexyl
DCIS	Ductal carcinoma in situ
DHPS	Dihydropteroate synthetase
DHFR	Dihydropteroate reductase
DISC	Death-inducing signaling complex
DNA	Deoxyribonucleic acid
DSBR	DNA double strand break repair
EGF	Epidermal growth factor
ER	Estrogen receptor
ERK	Extracellular signal-regulated protein kinase
Et	Ethyl
FADH2	Flavin adenine dinucleotide
FGF-2	Fibroblast growth factor-2
GDF15	Growth differentiation factor 15
GJ	Gap junctions
HER2	Human epidermal receptor 2
IGF	Insulin-like growth factor
IDC	Infiltrating ductal carcinomas
IL	Interleukin
ILC	Invasive lobular carcinoma
IM	Immunomodulatory
JNK	C-Jun N-terminal kinase
KLF5	Krüppel-like factor 5
LAR	Luminal androgen receptor
LCIS	Lobular carcinoma in situ
M	Mesenchymal
MAPK	Mitogen-activated protein kinase
MATE	Multidrug and toxic compound extrusion
MBC	Minimum bactericidal concentration
MFS	Major facilitator superfamily
MIC	Minimum inhibition concentration
MMR	Mismatch repair
MOMP	Membrane outer membrane permeability
MSI or MIN	Microsatellite instability

MSL	Mesenchymal stem–like
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NADH	Nicotinamide adenine dinucleotide
NHC	N-heterocyclic carbine
NER	Nucleotide excision repair
NF-kB	Nuclear factor-kappab
NK	Natural killer
NST	Invasive carcinoma of no special type
OECD	Organisation for Economic Cooperation and Development
PBP	Penicillin binding protein
PDGF	Platelet derived growth factor
PEt3	Triethylphosphine
Ph	Phenyl
PIGF	Placental growth factor
PPh3	Triphenyphosphine
PR	Progesterone receptor
PS	Phosphatidylserine
PTEN	Phosphatase and tensin homolog
rRNA	Ribosomal ribonucleic acid
RND	Resistance-nodulation-division
ROS	Reactive oxygen species
SMR	Mall multidrug resistance
Stat3	Signal transducer activator of transcription-3
TAM	Tumor-associated macrophages
tBid	Truncated Bid
TGF-β	Transforming growth factor-beta
TJ	Tight junctions
TMP	Trimethoprim
TNBC	Triple negative breast cancer
TNF	Tumour necrosis factor
TP53	Tumor protein 53
TRAIL	TNF-related apoptosis-inducing ligand
Trx	Thioredoxin
VEGF	Vascular endothelial growth factor
WHO	World health organisation
Wnt	Wingless and Integrase-1
XIAP	X-linked inhibitor of apoptosis protein

CHAPTER 1

INTRODUCTION

Urbanization, modernization and industrialization that occurred rapidly since 1950, leads to increase health burden not only in low income countries, but also in developing and developed countries. The epidemiological transition fuelled by growing aging population and shifting towards chronic diseases and injuries has impacted on worldwide mortality by changing the lifestyle and socioeconomic. Communicable and non-communicable diseases are two major etiologies contribute to most of mortality cases and global burden. Communicable diseases refer to those contagious illness transmitted from animal or human. On the other hands, non-communicable diseases are those non-infectious or non-transmissible resulted from chronic exposure to environmental factors or those carry with inherited genes. Bacterial infections are example of communicable diseases, while cancers are under non-communicable diseases. Bacterial infection and cancer are interconnected where bacterial infections can cause cancer, while cancer patients who are immunocompromised have greater risk of bacterial infections (Samaras et al., 2010; Steele, 2012). Hence, antibacterial and anticancer are two important aspects in pharmaceutical research and development.

Metallopharmaceutical involves the application of metal in the treatment of various illnesses and highlights the importance of metal coordination geometry in medicinal inorganic chemistry field (Gielen and Tiekink, 2005). Metal was widely utilized as treatment regime in many diseases since thousand years ago. For example, gold complex was used in the treatment of rheumatoid arthritis, bismuth was applied in the gastric lymphoma and arsenic trioxide for acute promyelocytic leukemia. The importance of the metals with interesting medical values in various clinical diseases is undisputed, as can be determined as treatment of various diseases (Desoize, 2004). Albeit metal was first reported as chemotherapy for cancer and leukemia started from sixteenth century, the research into metal-based drugs was began in the early 1900s. In mid-1870, first metal compound synthesizing work was started by Sophus Jorgensen and followed by Alfred Werner who was awarded the Nobel Prize in 1913 for his work on synthesizing of a series of metal based compounds (Rafique et al., 2010).

Besides as coinage metal, gold metal is also found to have great medicinal potential. Gold has been well-documented with anti-arthritic (Youn et al., 2006; Shoeib et al., 2010), anti-inflammatory (Trávníček et al., 2012; Hošek et al., 2013), anticancer (Iii, 1999; Che and Sun, 2011), antimicrobial (Novelli et al., 1999) including antibacterial (Fernández et al., 2014; Glišić and Djuran, 2014), antiviral (Fonteh et al., 2010), and anti-parasitic activities (Navarro et al., 2001; Navarro et al., 2004; Navarro, 2009). Auranofin, an orally administered gold based disease modifying anti-rheumatic drug (DMARD), is a relatively late comer in the treatment of rheumatoid arthritis (Kean and Kean, 2008; Corti and Holliday, 2009) and is recently listed as "drug repurposing/repositioning" attribute to its applications against other diseases (Pessetto et al., 2013). Indeed, auranofin® displays anticancer potential (Roder and Thomson, 2015)

and antimicrobial applications (Cassetta et al., 2014). Following that, a numbers of gold (I) complexes are coupled with phosphine-type and dithiocarbamate ligands were extensively studied their biological activities including the determination of biological targets and mechanisms of cell death (Jamaludin et al., 2013; Keter et al., 2014; Altaf et al., 2015).

Given the emerging interest in the metallopharmaceutical and the ideas of phosphane, dithiocarbamates and auranofin, two series of phosphanegold(I) dithiocarbamates, namely $R_3PAu[S_2CN(iPr)CH_2CH_2OH]$ for R= ethyl (Et), cyclohexyl (Cy) and phenyl (Ph), were investigated for antibacterial and anticancer activities, as well as determine their toxicities.

1.1 Problem statement and justification

Raising cost in research and development and declining productivity are challenges in pharmaceutical industry (Khanna, 2012). From 2013 to 2015, 218 clinical trial failures were reported. Oncology and infectious diseases are two therapeutic areas in which the failure was commonly detected. The failure was due to lack of therapeutic index owing to reduced drug efficacy and safety (Harrison, 2016). Multidrug resistance greatly reduces drug efficacy in current treatments of communicable and non-communicable diseases (Tanwar et al., 2014). In addition, there is lack of biological characteristics assessment of novel mononuclear phosphanegold(I) dithiocarbamate complexes. Therefore, it is necessary to determine effectiveness and toxicity of mononuclear phosphanegold(I) dithiocarbamate complexes.

1.2 Hypothesis

Mononuclear phosphanegold(I) dithiocarbamates is expected to exhibit antibacterial and apoptosis related antiproliferative activities with low toxicity and less mutagenic than cisplatin.

1.3 Objectives

1.3.1 General Objectives

The general objective for this study is to investigate the *in vitro* antibacterial, anticancer properties, mutagenicity and toxicity of four mononuclear phosphanegold(I) dithiocarbamates and *in vivo* toxicity assessment in *Caenorhabditis elegans*.

1.3.2 Specific Objectives

a) To determine the antibacterial activity of four mononuclear phosphanegold(I) dithiocarbamates (Chapter 3)
b) To evaluate *in vitro* anticancer properties of four mononuclear phosphanegold(I) dithiocarbamates on breast, colon and lung cancer cell lines. (Chapter 4)

c) To determine the apoptosis pathway induced by the four mononuclear phosphanegold(I) dithiocarbamates (Chapter 5)
d) To profile *in vivo*, *in vitro* toxicity and mutagenic characteristics of the four mononuclear phosphanegold(I) dithiocarbamates. (Chapter 6)

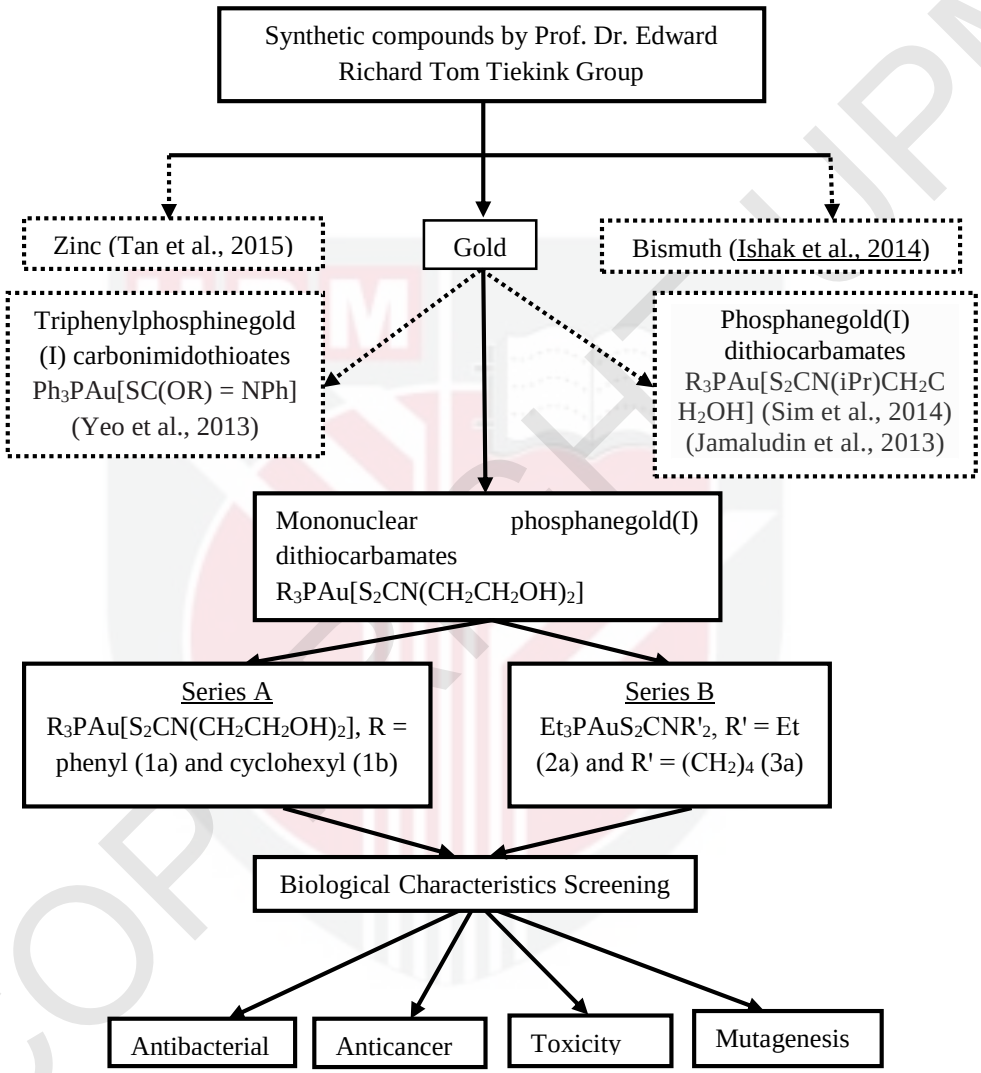

Figure 1.1: Conceptual framework illustrates the workflow of antibacterial, anticancer, toxicity and mutagenicity determination of mononuclear phosphanegold(I) dithiocarbamates. Bold line indicates for relevant part to be discussed in this study. Dotted line indicates for irrelevant parts which conducted by others, but under same project.

REFERENCES

Abbas, T., Keaton, M. A., and Dutta, A. (2013). Genomic instability in cancer. *Cold Spring Harbor Perspectives in Biology, 5*(3), a012914.

Aboud, O. A., Wettersten, H. I., and Weiss, R. H. (2013). Inhibition of PPARα induces cell cycle arrest and apoptosis, and synergizes with glycolysis inhibition in kidney cancer cells. *PloS ONE, 8*(8), e71115.

Abu, N., Akhtar, M. N., Yeap, S. K., Lim, K. L., Ho, W. Y., Zulfadli, A. J., Omar, A. R., Sulaiman, M. R., Abdullah, M. P., and Alitheen, N. B. (2014). Flavokawain A induces apoptosis in MCF-7 and MDA-MB231 and inhibits the metastatic process *in vitro*. *PloS ONE, 9*(10), e105244.

Acerbi, I., Cassereau, L., Dean, I., Shi, Q., Au, A., Park, C., Chen, Y., Liphardt, J., Hwang, E., and Weaver, V. (2015). Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. *Integrative Biology, 7*(10), 1120-1134.

Aguinagalde, L., Díez-Martínez, R., Yuste, J., Royo, I., Gil, C., Lasa, Í., Martín-Fontecha, M., Marín-Ramos, N. I., Ardanuy, C., and Liñares, J. (2015). Auranofin efficacy against MDR *Streptococcus pneumoniae* and *Staphylococcus aureus* infections. *Journal of Antimicrobial Chemotherapy*, dkv163.

Ahmad, S. (2010). Platinum–DNA interactions and subsequent cellular processes controlling sensitivity to anticancer platinum complexes. *Chemistry and Biodiversity, 7*(3), 543-566.

Alanis, A. J. (2005). Resistance to antibiotics: are we in the post-antibiotic era? *Archives of Medical Research, 36*(6), 697-705.

Aldred, K. J., Kerns, R. J., and Osheroff, N. (2014). Mechanism of quinolone action and resistance. *Biochemistry, 53*(10), 1565-1574.

Alderden, R. A., Hall, M. D., and Hambley, T. W. (2006). The discovery and development of cisplatin. *Journal of Chemical Education, 83*(5), 728.

Alekshun, M. N., and Levy, S. B. (2007). Molecular mechanisms of antibacterial multidrug resistance. *Cell, 128*(6), 1037-1050.

Altaf, M., Monim-ul-Mehboob, M., Seliman, A. A., Sohail, M., Wazeer, M. I., Isab, A. A., Li, L., Dhuna, V., Bhatia, G., and Dhuna, K. (2015). Synthesis, characterization and anticancer activity of gold (I) complexes that contain tri-tert-butylphosphine and dialkyl dithiocarbamate ligands. *European Journal of Medicinal Chemistry, 95*, 464-472.

Alvan, G., Edlund, C., and Heddini, A. (2011). The global need for effective antibiotics - a summary of plenary presentations. *Drug Resistance Updates, 14*(2), 70-76.

Amaral, J. D., Xavier, J. M., Steer, C. J., and Rodrigues, C. M. (2010). The role of p53 in apoptosis. *Discovery medicine*, *9*(45), 145-152.

Amin, A. R., Karpowicz, P. A., Carey, T. E., Arbiser, J., Nahta, R., Chen, Z. G., Dong, J.-T., Kucuk, O., Khan, G. N., Huang, G. S, Mi, S. and Lee, H. Y (2015). Evasion of anti-growth signaling: a key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds. *Seminars in Cancer Biology*, *35*, S55-S77.

Amrit, F. R. G., Ratnappan, R., Keith, S. A., and Ghazi, A. (2014). The *Caenorhabditis elegans* lifespan assay toolkit. *Methods*, *68*(3), 465-475.

Anido, J., Matar, P., Albanell, J., Guzmán, M., Rojo, F., Arribas, J., Averbuch, S., and Baselga, J. (2003). ZD1839, a specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, induces the formation of inactive EGFR/HER2 and EGFR/HER3 heterodimers and prevents heregulin signaling in HER2-overexpressing breast cancer cells. *Clinical Cancer Research*, *9*(4), 1274-1283.

Ardiel, E. L., and Rankin, C. H. (2010). An elegant mind: learning and memory in *Caenorhabditis elegans*. *Learning and Memory*, *17*(4), 191-201.

Artandi, S. E., and DePinho, R. A. (2010). Telomeres and telomerase in cancer. *Carcinogenesis*, *31*(1), 9-18.

Ashby, J., and Styles, J. (1978). Does carcinogenic potency correlate with mutagenic potency in the Ames assay? *Nature*. 271, 452 - 455

Astashkina, A., Mann, B., and Grainger, D. W. (2012). A critical evaluation of *in vitro* cell culture models for high-throughput drug screening and toxicity. *Pharmacology and Therapeutics*, *134*(1), 82-106.

Bai, L., and Wang, S. (2014). Targeting apoptosis pathways for new cancer therapeutics. *Annual Review of Medicine*, *65*, 139-155.

Baig, S., Seevasant, I., Mohamad, J., Mukheem, A., Huri, H., and Kamarul, T. (2016). Potential of apoptotic pathway-targeted cancer therapeutic research: Where do we stand and quest. *Cell Death and Disease*, *7*(1), e2058.

Balcázar, J. L., Subirats, J., and Borrego, C. M. (2015). The role of biofilms as environmental reservoirs of antibiotic resistance. *Frontiers in Microbiology*, *6*, 1216.

Barré-Sinoussi, F., and Montagutelli, X. (2015). Animal models are essential to biological research: issues and perspectives. *Future Science OA*, *1*(4), FSO63.

Barnard, P. J., and Berners-Price, S. J. (2007). Targeting the mitochondrial cell death pathway with gold compounds. *Coordination Chemistry Reviews*, *251*(13), 1889-1902.

Basu, A., and Krishnamurthy, S. (2010). Cellular responses to cisplatin-induced DNA damage. *Journal of Nucleic Acids, 2010,* 1-16.

Baylin, S. B., and Ohm, J. E. (2006). Epigenetic gene silencing in cancer–a mechanism for early oncogenic pathway addiction? *Nature Reviews Cancer, 6*(2), 107-116.

Beckman, R. A., and Loeb, L. A. (2005). Genetic instability in cancer: theory and experiment. *Seminars in Cancer Biology*, *15*(6), 423-435.

Benjamin Garbutcheon-Singh, K., P Grant, M., W Harper, B., M Krause-Heuer, A., Manohar, M., Orkey, N., and R Aldrich-Wright, J. (2011). Transition metal based anticancer drugs. *Current Topics in Medicinal Chemistry, 11*(5), 521-542.

Bertrand, B., Citta, A., Franken, I. L., Picquet, M., Folda, A., Scalcon, V., Rigobello, M. P., Le Gendre, P., Casini, A., and Bodio, E. (2015). Gold (I) NHC-based homo- and heterobimetallic complexes: synthesis, characterization and evaluation as potential anticancer agents. *Journal of Biological Inorganic Chemistry, 20*(6), 1005-1020.

Bhattacharya, B., and Mukherjee, S. (2015). Cancer therapy using antibiotics. *Journal of Cancer Therapy*, *6*(10), 849.

Bischof, L. J., Huffman, D. L., and Aroian, R. V. (2006). Assays for toxicity studies in *Caenorhabditis elegans* with Bt crystal proteins. *Caenorhabditis elegans*. *Methods and Applications*, 139-154.

Bindoli, A., Rigobello, M. P., Scutari, G., Gabbiani, C., Casini, A., and Messori, L. (2009). Thioredoxin reductase: a target for gold compounds acting as potential anticancer drugs. *Coordination Chemistry Reviews, 253*(11), 1692-1707.

Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., and Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology, 13*(1), 42-51.

Bogen, K. T. (1995). Improved prediction of carcinogenic potencies from mutagenic potencies for chemicals positive in rodents and the Ames test. *Environmental and Molecular Mutagenesis, 25*(1), 37-49.

Boone, D. R., Micci, M.-A., Taglialatela, I. G., Hellmich, J. L., Weisz, H. A., Bi, M., Prough, D. S., DeWitt, D. S., and Hellmich, H. L. (2015). Pathway-focused PCR array profiling of enriched populations of laser capture microdissected hippocampal cells after traumatic brain injury. *PloS ONE, 10*(5), e0127287.

Boucher, H. W., Talbot, G. H., Bradley, J. S., Edwards, J. E., Gilbert, D., Rice, L. B., Scheld, M., Spellberg, B., and Bartlett, J. (2009). Bad bugs, no drugs: no ESKAPE! An update from the infectious diseases society of America. *Clinical Infectious Diseases, 48*(1), 1-12.

Brenner, D. R., Scherer, D., Muir, K., Schildkraut, J., Boffetta, P., Spitz, M. R., Le Marchand, L., Chan, A. T., Goode, E. L., and Ulrich, C. M. (2014). A review of the application of inflammatory biomarkers in epidemiologic cancer research. *Cancer Epidemiology Biomarkers and Prevention*, *23*(9), 1729-1751.

Brenner, S. (1974). The genetics of *Caenorhabditis elegans*. *Genetics*, *77*(1), 71-94.

Brewster, A. M., Chavez-MacGregor, M., and Brown, P. (2014). Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. *The Lancet Oncology*, *15*(13), e625-e634.

Buac, D., Schmitt, S., Ventro, G., Rani Kona, F., and Ping Dou, Q. (2012). Dithiocarbamate-based coordination compounds as potent proteasome inhibitors in human cancer cells. *Mini Reviews in Medicinal Chemistry*, *12*(12), 1193-1201.

C Tella, A., and A Obaleye, J. (2009). Copper (II) complexes of 4, 4-diaminodiphenylsulphone: synthesis, characterization and biological studies. *Journal of Chemistry*, *6*(S1), S311-S323.

Cancer, I. A. f. R. o. (2013). Latest world cancer statistics Global cancer burden rises to 14.1 million new cases in 2012: Marked increase in breast cancers must be addressed. *World Health Organization*, *12*, 1-3.

Candido, J., and Hagemann, T. (2013). Cancer-related inflammation. *Journal of Clinical Immunology*, *33*(1), 79-84.

Capozza, F., Trimmer, C., Castello-Cros, R., Katiyar, S., Whitaker-Menezes, D., Follenzi, A., Crosariol, M., Llaverias, G., Sotgia, F., and Pestell, R. G. (2012). Genetic ablation of Cav1 differentially affects melanoma tumor growth and metastasis in mice: role of Cav1 in Shh heterotypic signaling and transendothelial migration. *Cancer Research*, *72*(9), 2262-2274.

Cars, O., Hedin, A., and Heddini, A. (2011). The global need for effective antibiotics—moving towards concerted action. *Drug Resistance Updates*, *14*(2), 68-69.

Caselli, D., and Paolicchi, O. (2012). Empiric antibiotic therapy in a child with cancer and suspected septicemia. *Pediatric Reports*, *4*(e2), 5-9.

Casini, A., Hartinger, C., Gabbiani, C., Mini, E., Dyson, P. J., Keppler, B. K., and Messori, L. (2008). Gold (III) compounds as anticancer agents: relevance of gold–protein interactions for their mechanism of action. *Journal of Inorganic Biochemistry*, *102*(3), 564-575.

Cassetta, M. I., Marzo, T., Fallani, S., Novelli, A., and Messori, L. (2014). Drug repositioning: auranofin as a prospective antimicrobial agent for the treatment of severe staphylococcal infections. *Biometals*, *27*(4), 787-791.

Castillo-Salgado, C. (2010). Trends and directions of global public health surveillance. *Epidemiologic Reviews*, *32* (1), 93-109.

Che, C.-M., and Sun, R. W.-Y. (2011). Therapeutic applications of gold complexes: lipophilic gold (III) cations and gold (I) complexes for anti-cancer treatment. *Chemical Communications, 47*(34), 9554-9560.

Chiang, S. P., Cabrera, R. M., and Segall, J. E. (2016). Tumor cell intravasation. *American Journal of Physiology, 311*(1), C1-C14

Chipuk, J., Bouchier-Hayes, L., and Green, D. (2006). Mitochondrial outer membrane permeabilization during apoptosis: the innocent bystander scenario. *Cell Death and Differentiation, 13*(8), 1396-1402.

Chow, K. H.-M., Sun, R. W.-Y., Lam, J. B., Li, C. K.-L., Xu, A., Ma, D.-L., Abagyan, R., Wang, Y., and Che, C.-M. (2010). A gold (III) porphyrin complex with antitumor properties targets the Wnt/β-catenin pathway. *Cancer Research, 70*(1), 329-337.

Choudhury, R., Panda, S., and Singh, D. (2012). Emergence and dissemination of antibiotic resistance: A global problem. *Indian Journal of Medical Microbiology, 30*(4), 384-390.

Clancy, S. (2008). DNA damage and repair: mechanisms for maintaining DNA integrity. *Nature Education, 1*(1), 103.

CLSI (1999). Methods for determining bactericidal activity of antimicrobial agents. *In Approved Guideline M26-A* (Vol. 19, No. 18). Wayne, PA: Clinical and Laboratory Standards Institute.

CLSI. (2012). Performance standards for antimicrobial susceptibility testing; 22nd informational supplement. In *CLSI M100-S22* (Vol. 32, pp. 1-184). Wayne, PA: Clinical and Laboratory Standards Institute.

Colotta, F., Allavena, P., Sica, A., Garlanda, C., and Mantovani, A. (2009). Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis, 30*(7), 1073-1081.

Colvin, M. (2003). Alkylating Agents. In R Kufe, D. W., Pollock, R. E., Weichselbaum, R. R., Bast Jr, R. C., Gansler, T. S., Holland, J. F., and Frei III, E. *Holland-Frei Cancer Medicine* (6th. edt ed.). Hamilton (ON): BC Decker. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12772/.

Corsi, A. K. (2006). A biochemist's guide to *Caenorhabditis elegans*. *Analytical Biochemistry, 359*(1), 1-17.

Corsi, A. K., Wightman, B., and Chalfie, M. (2015). A transparent window into biology: A primer on *Caenorhabditis elegans*. *Genetics, 200*(2), 387-407.

Corti, C., and Holliday, R. (2009). *Gold: science and applications*. New York: CRC Press.

Council, N. R. (2000). Scientific frontiers in developmental toxicology and risk assessment. Washington: National Academies Press.

Cree, I. A., and Charlton, P. (2017). Molecular chess? Hallmarks of anti-cancer drug resistance. *BMC Cancer, 17*(1), 10.

Cree, I. A., Kurbacher, C. M., Untch, M., Sutherland, L. A., Hunter, E. M., Subedi, A. M., James, E. A., Dewar, J. A., Preece, P. E., and Andreotti, P. E. (1996). Correlation of the clinical response to chemotherapy in breast cancer with ex *vivo* chemosensitivity. *Anti-Cancer Drugs, 7*(6), 630-635.

Culetto, E., and Sattelle, D. B. (2000). A role for *Caenorhabditis elegans* in understanding the function and interactions of human disease genes. *Human Molecular Genetics, 9*(6), 869-877.

Czabotar, P. E., Lessene, G., Strasser, A., and Adams, J. M. (2014). Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nature Reviews Molecular cell biology, 15*(1), 49-63.

Dahlui, M., Ramli, S., and Bulgiba, A. M. (2011). Breast cancer prevention and control programs in Malaysia. *Asian Pacific Journal of Cancer Prevention, 12*(6), 1631-1634.

Dai, X., Li, T., Bai, Z., Yang, Y., Liu, X., Zhan, J., and Shi, B. (2015). Breast cancer intrinsic subtype classification, clinical use and future trends. *American Journal of Cancer Research, 5*(10), 2929.

Dang, C. V. (2010). Glutaminolysis: supplying carbon or nitrogen or both for cancer cells? *Cell cycle, 9*(19), 3884-3886.

Dasari, S., and Tchounwou, P. B. (2014). Cisplatin in cancer therapy: molecular mechanisms of action. *European Journal of Pharmacology, 740*, 364-378.

Daughaday, W., and Deuel, T. (1991). Tumor secretion of growth factors. *Endocrinology and Metabolism Clinics of North America, 20*(3), 539-563.

Delcour, A. H. (2009). Outer membrane permeability and antibiotic resistance. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics, 1794*(5), 808-816.

de Bono, M. (2003). Molecular approaches to aggregation behavior and social attachment. *Journal of Neurobiology, 54*(1), 78-92.

Desalermos, A., Muhammed, M., Glavis-Bloom, J., and Mylonakis, E. (2011). Using *Caenorhabditis elegans* for antimicrobial drug discovery. *Expert Opinion On Drug Discovery, 6*(6), 645-652.

Desoize, B. (2004). Metals and metal compounds in cancer treatment. *Anticancer Research, 24*(3A), 1529-1544.

DeVita, V. T., and Chu, E. (2008). A history of cancer chemotherapy. *Cancer Research, 68*(21), 8643-8653.

Dhillon, K. K., Swisher, E. M., and Taniguchi, T. (2011). Secondary mutations of BRCA1/2 and drug resistance. *Cancer Science, 102*(4), 663-669.

Ding, D. l., Shinichi, S., Hai–yan, J., Wei–dong, Q., Dong–zhen, Y., Tanokura, M., and Salvi, R. (2011). Detection of apoptosis by RT–PCR array in mefloquine–induced cochlear damage. *Journal of Otology, 6*(1), 1-9.

Doyle, L. A., and Ross, D. D. (2003). Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). *Oncogene, 22*(47), 7340-7358.

Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J., and Schreiber, R. D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nature Immunology, 3*(11), 991-998.

Dunn, G. P., Old, L. J., and Schreiber, R. D. (2004). The three Es of cancer immunoediting. *Annual Review of Immunology, 22*, 329-360.

Dvorak, H. F. (2002). Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. *Journal of Clinical Oncology, 20*(21), 4368-4380.

Dziedzic, A., Kubina, R., Kabała-Dzik, A., and Tanasiewicz, M. (2017). Induction of cell cycle arrest and apoptotic response of head and neck squamous carcinoma cells (detroit 562) by caffeic acid and caffeic acid phenethyl derivative. *Evidence-Based Complementary and Alternative Medicine, 2017*, 1-10.

El-Tabl, A. S., Mohamed Abd El-Waheed, M., Wahba, M. A., and Abd El-Halim Abou El-Fadl, N. (2015). Synthesis, characterization, and anticancer activity of new metal complexes derived from 2-hydroxy-3-(hydroxyimino)-4-oxopentan-2-ylidene) benzohydrazide. *Bioinorganic Chemistry and Applications, 2015*, 1-14.

Elenbaas, B., and Weinberg, R. A. (2001). Heterotypic signaling between epithelial tumor cells and fibroblasts in carcinoma formation. *Experimental cell Research, 264*(1), 169-184.

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicologic Pathology, 35*(4), 495-516.

Emam, S. M., Abdou, S., Ahmed, H. M., and Emad, E. A. (2014). Synthesis, structural characterization, electrochemical and biological studies on divalent metal chelates of a new ligand derived from pharmaceutical preservative, dehydroacetic acid, with 1, 4-diaminobenzene. *Arabian Journal of Chemistry, 2014*, 1-10.

Farber, E. (1979). Reversible and irreversible lesions in processes of cancer development. *IARC Scientific Publications*, (27), 143-151.

Fei, P., Wang, W., Kim, S.-h., Wang, S., Burns, T. F., Sax, J. K., Buzzai, M., Dicker, D. T., McKenna, W. G., and Bernhard, E. J. (2004). Bnip3L is induced by p53 under hypoxia, and its knockdown promotes tumor growth. *Cancer Cell, 6*(6), 597-609.

Feng, X., Liu, X., Zhang, W., and Xiao, W. (2011). p53 directly suppresses BNIP3 expression to protect against hypoxia-induced cell death. *The EMBO Journal, 30*(16), 3397-3415.

Ferguson, L. R., Chen, H., Collins, A. R., Connell, M., Damia, G., Dasgupta, S., Malhotra, M., Meeker, A. K., Amedei, A., and Amin, A. and Ashraf, S. S. (2015). Genomic instability in human cancer: Molecular insights and opportunities for therapeutic attack and prevention through diet and nutrition. *Seminars in Cancer Biology, 35,* S5-S24.

Fernald, K., and Kurokawa, M. (2013). Evading apoptosis in cancer. *Trends in Cell Biology, 23*(12), 620-633.

Fernández, G. A., Vela Gurovic, M. S., Olivera, N. L., Chopa, A. B., and Silbestri, G. F. (2014). Antibacterial properties of water-soluble gold (I) N-heterocyclic carbene complexes. *Journal of Inorganic Biochemistry, 135*, 54-57.

Finberg, R. W., Moellering, R. C., Tally, F. P., Craig, W. A., Pankey, G. A., Dellinger, E. P., West, M. A., Joshi, M., Linden, P. K., and Rolston, K. V. (2004). The importance of bactericidal drugs: future directions in infectious disease. *Clinical Infectious Diseases, 39*(9), 1314-1320.

Finn, O. (2012). Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. *Annals of Oncology, 23* (suppl 8), viii6-viii9.

Florea, A.-M., and Büsselberg, D. (2011). Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers, 3*(1), 1351-1371.

Fonteh, P. N., Keter, F. K., and Meyer, D. (2010). HIV therapeutic possibilities of gold compounds. *Biometals, 23*(2), 185-196.

Franke, S., Ckless, K., Silveira, J., Rubensam, G., Brendel, M., Erdtmann, B., and Henriques, J. (2004). Study of antioxidant and mutagenic activity of different orange juices. *Food Chemistry, 88*(1), 45-55.

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., Mullen, C. A., Raad, I. I., Rolston, K. V., Young, J.-A. H., and Wingard, J. R. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases, 52*(4), e56-e93.

Freire-Moran, L., Aronsson, B., Manz, C., Gyssens, I. C., So, A. D., Monnet, D. L., and Cars, O. (2011). Critical shortage of new antibiotics in development against

multidrug-resistant bacteria-Time to react is now. *Drug Resistance Updates, 14*(2), 118-124.

Fridman, J. S., and Lowe, S. W. (2003). Control of apoptosis by p53. *Oncogene, 22*(56), 9030-9040.

Fulda, S. (2010). Evasion of apoptosis as a cellular stress response in cancer. *International Journal of Cell Biology, 2010,* 1-6.

Fulda, S. (2011). Targeting apoptosis signaling pathways for anticancer therapy. *Frontiers in Oncology, 1*(23), 1-7.

Fulda, S., and Debatin, K. (2006). Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene, 25*(34), 4798-4811.

Furge, L. L., and Guengerich, F. P. (2006). Cytochrome P450 enzymes in drug metabolism and chemical toxicology: An introduction. *Biochemistry and Molecular Biology Education, 34*(2), 66-74.

Gabbiani, C. (2009). Proteins as possible targets for antitumor metal complexes. In *Biophysical Studies of Their Interactions* (Vol. 9). Firenze University Press.

Gabbiani, C., Guerri, A., Cinellu, M. A., and Messori, L. (2010). Dinuclear gold (III) complexes as potential anticancer agents: structure, reactivity and biological profile of a series of gold (III) oxo-bridged derivatives. *The Open Crystallography Journal, 3*, 29-40.

Gabbiani, C., Mastrobuoni, G., Sorrentino, F., Dani, B., Rigobello, M. P., Bindoli, A., Cinellu, M. A., Pieraccini, G., Messori, L., and Casini, A. (2011). Thioredoxin reductase, an emerging target for anticancer metallodrugs. Enzyme inhibition by cytotoxic gold (III) compounds studied with combined mass spectrometry and biochemical assays. *Medicinal Chemistry Communications, 2*(1), 50-54.

Ganapathi, R., and Ganapathi, M. K. (2013). Mechanisms regulating resistance to inhibitors of topoisomerase II. *Frontiers in Pharmacology, 4*(89), 1-7.

Gandin, V., Fernandes, A. P., Rigobello, M. P., Dani, B., Sorrentino, F., Tisato, F., Björnstedt, M., Bindoli, A., Sturaro, A., and Rella, R. (2010). Cancer cell death induced by phosphine gold (I) compounds targeting thioredoxin reductase. *Biochemical Pharmacology, 79*(2), 90-101.

Gebaeck. (2009). TScratch: a novel and simple software tool for automated analysis of monolayer wound healing assays (2009). *BioTechniques, 46*(6), 265-274.

Ghobrial, I. M., Witzig, T. E., and Adjei, A. A. (2005). Targeting apoptosis pathways in cancer therapy. *CA: A Cancer Journal For Clinicians, 55*(3), 178-194.

Gibson, D. (2009). The mechanism of action of platinum anticancer agents—what do we really know about it? *Dalton Transactions,* (48), 10681-10689.

Giedraitienė, A., Vitkauskienė, A., Naginienė, R., and Pavilonis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina, 47*(3), 137-146.

Gielen, M., and Tiekink, E. R. (2005). *Metallotherapeutic drugs and metal-based diagnostic agents: the use of metals in medicine*. John Wiley and Sons.

Gilbert, S. F. (2000). Early Development of the Nematode *Caenorhabditis elegans*. In Gilbert, S. F. *Developmental Biology* (6th eds). Sunderland (MA): Sinauer Associates.

Giurumescu, C. A., and Chisholm, A. D. (2011). Cell identification and cell lineage analysis. *Methods in Cell Biology, 106*, 325.

Glišić, B. Đ., and Djuran, M. I. (2014). Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of the gold ion and the ligand structure. *Dalton Transactions, 43*(16), 5950-5969.

Gordon, L. A., Mulligan, K. T., Maxwell-Jones, H., Adams, M., Walker, R. A., and Jones, J. L. (2003). Breast cell invasive potential relates to the myoepithelial phenotype. *International Journal of Cancer, 106*(1), 8-16.

Gottesman, M. M. (2002). Mechanisms of cancer drug resistance. *Annual Review of Medicine, 53*(1), 615-627.

Gottesman, M. M., Fojo, T., and Bates, S. E. (2002). Multidrug resistance in cancer: role of ATP–dependent transporters. *Nature Reviews Cancer, 2*(1), 48-58.

Gross, A., McDonnell, J. M., and Korsmeyer, S. J. (1999). BCL-2 family members and the mitochondria in apoptosis. *Genes and development, 13*(15), 1899-1911.

Grunnet, L. G., Aikin, R., Tonnesen, M. F., Paraskevas, S., Blaabjerg, L., Størling, J., Rosenberg, L., Billestrup, N., Maysinger, D., and Mandrup-Poulsen, T. (2009). Proinflammatory cytokines activate the intrinsic apoptotic pathway in β-cells. *Diabetes, 58*(8), 1807-1815.

Guarente, L., and Kenyon, C. (2000). Genetic pathways that regulate ageing in model organisms. *Nature, 408*(6809), 255-262.

Guicciardi, M. E., and Gores, G. J. (2003). The death receptor family and the extrinsic pathway. In *Essentials of Apoptosis* (pp. 67-84). Springer.

Guideline, H. T. (2008). S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. In *The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* (pp. 1-26).

Guillemin, R., Brazeau, P., Bohlen, P., Esch, F., Ling, N., and Wehrenberg, W. B. (1982). Growth hormone-releasing factor from a human pancreatic tumor that caused acromegaly. *Science, 218*(4572), 585-587.

Haiduc, I., and Silvestru, C. (1990). Metal compounds in cancer chemotherapy. *Coordination Chemistry Reviews, 99*, 253-296.

Hanahan, D., and Weinberg, R. A. (2000). The hallmarks of cancer. *Cell, 100*(1), 57-70.

Hanahan, D., and Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell, 144*(5), 646-674.

Harbut, M. B., Vilchèze, C., Luo, X., Hensler, M. E., Guo, H., Yang, B., Chatterjee, A. K., Nizet, V., Jacobs, W. R., and Schultz, P. G. (2015). Auranofin exerts broad-spectrum bactericidal activities by targeting thiol-redox homeostasis. *Proceedings of the National Academy of Sciences, 112*(14), 4453-4458.

Harris, S. L., and Levine, A. J. (2005). The p53 pathway: positive and negative feedback loops. *Oncogene, 24*(17), 2899-2908.

Harrison, R. K. (2016). Phase II and phase III failures: 2013-2015. *Nature Reviews Drug Discovery, 15*(12), 817-818.

Hartmann, J. T., and Lipp, H.-P. (2003). Toxicity of platinum compounds. *Expert Opinion on Pharmacotherapy, 4*(6), 889-901.

Hartung, T. (2007). Food for thought... on cell culture. *Altex, 24*(3), 143.

Hassan, M., Watari, H., AbuAlmaaty, A., Ohba, Y., and Sakuragi, N. (2014). Apoptosis and molecular targeting therapy in cancer. *BioMed Research International, 2014*, 1-23.

Herr, I., and Debatin, K.-M. (2001). Cellular stress response and apoptosis in cancer therapy. *Blood, 98*(9), 2603-2614.

Hikisz, P., Szczupak, Ł., Koceva-Chyła, A., Oehninger, L., Ott, I., Therrien, B., Solecka, J., and Kowalski, K. (2015). Anticancer and antibacterial activity studies of gold (i)-alkynyl chromones. *Molecules, 20*(11), 19699-19718.

Hoelder, S., Clarke, P. A., and Workman, P. (2012). Discovery of small molecule cancer drugs: Successes, challenges and opportunities. *Molecular Oncology, 6*(2), 155-176.

Høiby, N., Bjarnsholt, T., Givskov, M., Molin, S., and Ciofu, O. (2010). Antibiotic resistance of bacterial biofilms. *International Journal of Antimicrobial Agents, 35*(4), 322-332.

Holenya, P., Can, S., Rubbiani, R., Alborzinia, H., Jünger, A., Cheng, X., Ott, I., and Wölfl, S. (2014). Detailed analysis of pro-apoptotic signaling and metabolic adaptation triggered by a N-heterocyclic carbene–gold (i) complex. *Metallomics, 6*(9), 1591-1601.

Holliday, D. L., and Speirs, V. (2011). Choosing the right cell line for breast cancer research. *Breast Cancer Research, 13*(4), 1-7.

Hon, J. D. C., Singh, B., Sahin, A., Du, G., Wang, J., Wang, V. Y., Deng, F.-M., Zhang, D. Y., Monaco, M. E., and Lee, P. (2016). Breast cancer molecular subtypes: from TNBC to QNBC. *American Journal of Cancer Research, 6*(9), 1864–1872.

Hošek, J., Vančo, J., Štarha, P., Paráková, L., and Trávníček, Z. (2013). Effect of 2-chloro-substitution of adenine moiety in mixed-ligand gold (I) triphenylphosphine complexes on anti-inflammatory activity: the discrepancy between the *in vivo* and *in vitro* models. *PloS ONE, 8*(11), e82441.

Housman, G., Byler, S., Heerboth, S., Lapinska, K., Longacre, M., Snyder, N., and Sarkar, S. (2014). Drug resistance in cancer: an overview. *Cancers, 6*(3), 1769-1792.

Howell, S. B., Safaei, R., Larson, C. A., and Sailor, M. J. (2010). Copper transporters and the cellular pharmacology of the platinum-containing cancer drugs. *Molecular Pharmacology, 77*(6), 887-894.

Huai, J., Jöckel, L., Schrader, K., and Borner, C. (2010). Role of caspases and non-caspase proteases in cell death. *F1000 Biology Reports, 2*(1), 1-6.

Hughes, J., Rees, S., Kalindjian, S., and Philpott, K. (2011). Principles of early drug discovery. *British Journal of Pharmacology, 162*(6), 1239-1249.

Humphreys, B. D., Soiffer, R. J., and Magee, C. C. (2005). Renal failure associated with cancer and its treatment: an update. *Journal of the American Society of Nephrology, 16*(1), 151-161.

Hunt, P. R., Olejnik, N., and Sprando, R. L. (2012). Toxicity ranking of heavy metals with screening method using adult *Caenorhabditis elegans* and propidium iodide replicates toxicity ranking in rat. *Food and Chemical Toxicology, 50*(9), 3280-3290.

Hynes, N. E., and Lane, H. A. (2005). ERBB receptors and cancer: the complexity of targeted inhibitors. *Nature Reviews Cancer, 5*(5), 341-354.

Iii, C. F. S. (1999). Gold complexes with anti-arthritic, anti-tumour and anti-HIV activity. In *Uses of Inorganic Chemistry in Medicine* (pp. 26-57). Cambridge: The Royal Society of Chemistry.

Iordanov, M., Kirsch, J., Ryabinina, O., Wong, J., Spitz, P., Korcheva, V., Thorburn, A., and Magun, B. (2005). Recruitment of TRADD, FADD, and caspase 8 to double-stranded RNA-triggered death inducing signaling complexes (dsRNA-DISCs). *Apoptosis, 10*(1), 167-176.

Ishak, D. H. A., Ooi, K. K., Ang, K.-P., Akim, A. M., Cheah, Y.-K., Nordin, N., Halim, S. N. B. A., Seng, H.-L., and Tiekink, E. R. (2014). A bismuth diethyldithiocarbamate compound promotes apoptosis in HepG2 carcinoma, cell cycle arrest and inhibits cell invasion through modulation of the NF-κB activation pathway. *Journal of Inorganic Biochemistry, 130*, 38-51.

Jafri, M. A., Ansari, S. A., Alqahtani, M. H., and Shay, J. W. (2016). Roles of telomeres and telomerase in cancer, and advances in telomerase-targeted therapies. *Genome Medicine, 8*(1), 69.

Jamaludin, N. S., Goh, Z.-J., Cheah, Y. K., Ang, K.-P., Sim, J. H., Khoo, C. H., Fairuz, Z. A., Halim, S. N. B. A., Ng, S. W., and Seng, H.-L. (2013). Phosphanegold (I) dithiocarbamates, R_3PAu [SC(S)N(i Pr)CH_2CH_2OH] for R= Ph, Cy and Et: Role of phosphane-bound R substituents upon *in vitro* cytotoxicity against MCF-7R breast cancer cells and cell death pathways. *European Journal of Medicinal Chemistry, 67*, 127-141.

Johnstone, R. W., Ruefli, A. A., and Lowe, S. W. (2002). Apoptosis: a link between cancer genetics and chemotherapy. *Cell, 108*(2), 153-164.

Kaletta, T., and Hengartner, M. O. (2006). Finding function in novel targets: *Caenorhabditis elegans* as a model organism. *Nature Reviews Drug Discovery, 5*(5), 387-399.

Kamber, M., Flückiger-Isler, S., Engelhardt, G., Jaeckh, R., and Zeiger, E. (2009). Comparison of the Ames II and traditional Ames test responses with respect to mutagenicity, strain specificities, need for metabolism and correlation with rodent carcinogenicity. *Mutagenesis, 24*(4):359-66.

Karin, M., Cao, Y., Greten, F. R., and Li, Z.-W. (2002). NF-κB in cancer: from innocent bystander to major culprit. *Nature Reviews Cancer, 2*(4), 301-310.

Kaur, G. J., and Arora, D. S. (2009). Antibacterial and phytochemical screening of *Anethum graveolens*, *Foeniculum vulgare* and *Trachyspermum ammi*. *BMC Complementary and Alternative Medicine, 9*(30), 1-10.

Kean, W., Hart, L., and Buchanan, W. (1997). Auranofin. *Rheumatology, 36*(5), 560-572.

Kean, W., and Kean, I. R. (2008). Clinical pharmacology of gold. *Inflammopharmacology, 16*(3), 112-125.

Kelland, L. (2007a). The resurgence of platinum-based cancer chemotherapy. *Nature Reviews Cancer, 7*(8), 573-584.

Kelland, L. (2007b). Targeting the limitless replicative potential of cancer: the telomerase/telomere pathway. *Clinical Cancer Research, 13*(17), 4960-4963.

Keter, F. K., Guzei, I. A., Nell, M., Zyl, W. E. v., and Darkwa, J. (2014). Phosphinogold (I) dithiocarbamate complexes: Effect of the nature of phosphine ligand on anticancer properties. *Inorganic Chemistry, 53*(4), 2058-2067.

Khanna, I. (2012). Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discovery Today, 17*(19), 1088-1102.

Kim, S., Kim, T. M., Kim, D.-W., Go, H., Keam, B., Lee, S.-H., Ku, J.-L., Chung, D. H., and Heo, D. S. (2013). Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. *Journal of Thoracic Oncology, 8*(4), 415-422.

Kirkland, D., Aardema, M., Henderson, L., and Müller, L. (2005). Evaluation of the ability of a battery of three *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens: I. Sensitivity, specificity and relative predictivity. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 584*(1), 1-256.

Kirkland, D., Reeve, L., Gatehouse, D., and Vanparys, P. (2011). A core *in vitro* genotoxicity battery comprising the Ames test plus the *in vitro* micronucleus test is sufficient to detect rodent carcinogens and *in vivo* genotoxins. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 721*(1), 27-73.

Kirkland, D., Zeiger, E., Madia, F., Gooderham, N., Kasper, P., Lynch, A., Morita, T., Ouedraogo, G., Morte, J. M. P., and Pfuhler, S. (2014). Can *in vitro* mammalian cell genotoxicity test results be used to complement positive results in the Ames test and help predict carcinogenic or *in vivo* genotoxic activity? I. Reports of individual databases presented at an EURL ECVAM Workshop. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 775*, 55-68.

Koff, J. L., Ramachandiran, S., and Bernal-Mizrachi, L. (2015). A time to kill: targeting apoptosis in cancer. *International Journal of Molecular Sciences, 16*(2), 2942-2955.

Kohanski, M. A., Dwyer, D. J., and Collins, J. J. (2010). How antibiotics kill bacteria: from targets to networks. *Nature Reviews Microbiology, 8*(6), 423-435.

Kostova, I. (2006). Gold coordination complexes as anticancer agents. *Anti-Cancer Agents in Medicinal Chemistry, 6*(1), 19-32.

Krakhmal, N., Zavyalova, M., Denisov, E., Vtorushin, S., and Perelmuter, V. (2015). Cancer invasion: patterns and mechanisms. *Acta Naturae, 7*(2), 17-28.

Kutuk, O., and Letai, A. (2008). Alteration of the mitochondrial apoptotic pathway is key to acquired paclitaxel resistance and can be reversed by ABT-737. *Cancer research, 68*(19), 7985-7994.

Kuwabara, P., and O'Neil, N. (2001). The use of functional genomics in *Caenorhabditis elegans* for studying human development and disease. *Journal of Inherited Metabolic Disease, 24*(2), 127-138.

Kyriakakis, E., Markaki, M., and Tavernarakis, N. (2015). *Caenorhabditis elegans* as a model for cancer research. *Molecular and Cellular Oncology, 2*(2), e975027.

Lai, C.-C., Lee, K., Xiao, Y., Ahmad, N., Veeraraghavan, B., Thamlikitkul, V., Tambyah, P. A., Nelwan, R., Shibl, A. M., and Wu, J.-J. (2014). High burden

of antimicrobial drug resistance in Asia. *Journal of Global Antimicrobial Resistance, 2*(3), 141-147.

Lai, C.-H., Chou, C.-Y., Ch'ang, L.-Y., Liu, C.-S., and Lin, W.-C. (2000). Identification of novel human genes evolutionarily conserved in *Caenorhabditis elegans* by comparative proteomics. *Genome Research, 10*(5), 703-713.

Lamb, R., Ozsvari, B., Lisanti, C. L., Tanowitz, H. B., Howell, A., Martinez-Outschoorn, U. E., Sotgia, F., and Lisanti, M. P. (2015). Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: treating cancer like an infectious disease. *Oncotarget, 6*(7), 4569-4584.

Lemon, S. M., Hamburg, M. A., Sparling, P. F., Choffnes, E. R., and Mack, A. L. I. S. O. N. (2007). Global infectious disease surveillance and detection: assessing the challenges. Workshop summary. In *Global infectious disease surveillance and detection: assessing the challenges. Workshop summary*. Washington: National Academies Press.

Lettre, G., and Hengartner, M. O. (2006). Developmental apoptosis in *Caenorhabditis. elegans*: a complex CEDnario. *Nature Reviews Molecular Cell Biology, 7*(2), 97-108.

Leung, M. C., Williams, P. L., Benedetto, A., Au, C., Helmcke, K. J., Aschner, M., and Meyer, J. N. (2008). *Caenorhabditis elegans*: an emerging model in biomedical and environmental toxicology. *Toxicological Sciences, 106*(1), 5-28.

Levison, M. E. (2004). Pharmacodynamics of antimicrobial drugs. *Infectious Disease Clinics of North America, 18*(3), 451-465.

Lewis, K. (2010). Persister cells. *Annual Review of Microbiology, 64*, 357-372.

Lewis, R. (1999). From basic research to cancer drug: The story of cisplatin. *The Scientist, 13*(14),11.

Li, S., Huang, S., and Peng, S.-B. (2005). Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. *International Journal of Oncology, 27*, 1329-1339.

Li, Y., Gao, S., Jing, H., Qi, L., Ning, J., Tan, Z., Yang, K., Zhao, C., Ma, L., and Li, G. (2013). Correlation of chemical acute toxicity between the nematode and the rodent. *Toxicology Research, 2*(6), 403-412.

Liberti, M. V., and Locasale, J. W. (2016). The Warburg effect: how does it benefit cancer cells? *Trends in Biochemical Sciences, 41*(3), 211-218.

Liu, C., Liu, Z., Li, M., Li, X., Wong, Y.-S., Ngai, S.-M., Zheng, W., Zhang, Y., and Chen, T. (2013). Enhancement of auranofin-induced apoptosis in MCF-7 human breast cells by selenocystine, a synergistic inhibitor of thioredoxin reductase. *PloS ONE, 8*(1), e53945.

Liu, Y., Yin, T., Feng, Y., Cona, M. M., Huang, G., Liu, J., Song, S., Jiang, Y., Xia, Q., and Swinnen, J. V. (2015). Mammalian models of chemically induced primary malignancies exploitable for imaging-based preclinical theragnostic research. *Quantitative Imaging in Medicine and Surgery*, *5*(5), 708 –729.

Livak, K. J., and Schmittgen, T. D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the 2− ΔΔCT method. *Methods*, *25*(4), 402-408.

Longley, D., and Johnston, P. (2005). Molecular mechanisms of drug resistance. *The Journal of Pathology*, *205*(2), 275-292.

Longley, D. B., Harkin, D. P., and Johnston, P. G. (2003). 5-fluorouracil: mechanisms of action and clinical strategies. *Nature Reviews Cancer*, *3*(5), 330-338.

Louro, H., Silva, M. J., and Boavida, M. G. (2002). Mutagenic activity of cisplatin in the lacZ plasmid-based transgenic mouse model. *Environmental and Molecular Mutagenesis*, *40*(4), 283-291.

Lu, H., Ouyang, W., and Huang, C. (2006). Inflammation, a key event in cancer development. *Molecular Cancer Research*, *4*(4), 221-233.

Lu, L., Liu, L.-J., Chao, W.-c., Zhong, H.-J., Wang, M., Chen, X.-P., Lu, J.-J., Li, R.-n., Ma, D.-L., and Leung, C.-H. (2015). Identification of an iridium (III) complex with anti-bacterial and anti-cancer activity. *Scientific Reports*, *5*, 1-9.

Mah, T.-F. C., and O'Toole, G. A. (2001). Mechanisms of biofilm resistance to antimicrobial agents. *Trends in Microbiology*, *9*(1), 34-39.

Mak, I., Evaniew, N., and Ghert, M. (2014). Lost in translation: animal models and clinical trials in cancer treatment. *American Journal of Translational Research*, *6*(2), 114-118.

Malhotra, G. K., Zhao, X., Band, H., and Band, V. (2010). Histological, molecular and functional subtypes of breast cancers. *Cancer Biology and Therapy*, *10*(10), 955-960.

Mantovani, A. (2010). Molecular pathways linking inflammation and cancer. *Current Molecular Medicine*, *10*(4), 369-373.

Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008). Cancer-related inflammation. *Nature*, *454*(7203), 436-444.

Marcon, G., Carotti, S., Coronnello, M., Messori, L., Mini, E., Orioli, P., Mazzei, T., Cinellu, M. A., and Minghetti, G. (2002). Gold (III) complexes with bipyridyl ligands: solution chemistry, cytotoxicity, and DNA binding properties. *Journal of Medicinal Chemistry*, *45*(8), 1672-1677.

Marques, L. L., de Oliveira, G. M., Lang, E. S., de Campos, M. M. A., and Gris, L. R. S. (2007). New gold (I) and silver (I) complexes of sulfamethoxazole: Synthesis,

X-ray structural characterization and microbiological activities of triphenylphosphine (sulfamethoxazolato-N2) gold (I) and (sulfamethoxazolato) silver (I). *Inorganic Chemistry Communications, 10*(9), 1083-1087.

Martin, S., Reutelingsperger, C., McGahon, A. J., Rader, J. A., Van Schie, R., LaFace, D. M., and Green, D. R. (1995). Early redistribution of plasma membrane phosphatidylserine is a general feature of apoptosis regardless of the initiating stimulus: inhibition by overexpression of Bcl-2 and Abl. *The Journal of Experimental Medicine, 182*(5), 1545-1556.

Martin, T. A., Ye, L., Sanders, A. J., Lane, J., and Jiang, W. G. (2000). Cancer invasion and metastasis: molecular and cellular perspective. In *Madame Curie Bioscience Database [Internet]*. Austin (TX): Landes Bioscience. Available from: https://www.ncbi.nlm.nih.gov/books/NBK164700/.

Marusyk, A., and Polyak, K. (2010). Tumor heterogeneity: causes and consequences. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1805*(1), 105-117.

McIlwain, D. R., Berger, T., and Mak, T. W. (2013). Caspase functions in cell death and disease. *Cold Spring Harbor Perspectives in Biology, 5*(4), a008656.

McKeage, M. J., Maharaj, L., and Berners-Price, S. J. (2002). Mechanisms of cytotoxicity and antitumor activity of gold (I) phosphine complexes: the possible role of mitochondria. *Coordination Chemistry Reviews, 232*(1), 127-135.

McKim, J., and James, M. (2010). Building a tiered approach to *in vitro* predictive toxicity screening: a focus on assays with *in vivo* relevance. *Combinatorial Chemistry and High Throughput Screening, 13*(2), 188-206.

Mehta, K., and Fok, J. Y. (2009). Targeting transglutaminase-2 to overcome chemoresistance in cancer cells. In *Drug Resistance in Cancer Cells* (pp. 95-114): Springer.

Meng, Q., Shi, Y., Wang, C., Jia, H., Gao, X., Zhang, R., Wang, Y., and Zhang, Z. (2015). NBD-based fluorescent chemosensor for the selective quantification of copper and sulfide in an aqueous solution and living cells. *Organic and Biomolecular Chemistry, 13*(10), 2918-2926.

Meyerson, M. (2000). Role of telomerase in normal and cancer cells. *Journal of Clinical Oncology, 18*(13), 2626-2634.

Milacic, V., and Dou, Q. P. (2009). The tumor proteasome as a novel target for gold (III) complexes: implications for breast cancer therapy. *Coordination Chemistry Reviews, 253*(11), 1649-1660.

Milacic, V., Fregona, D., and Dou, Q. P. (2008). Gold complexes as prospective metal-based anticancer drugs. *Histology and Histopathology, 23*(1), 101-108.

Morrison, W. (2010). Cancer chemotherapy: an annotated history. *Journal of Veterinary Internal Medicine, 24*(6), 1249-1262.

Mortelmans, K., and Zeiger, E. (2000). The Ames Salmonella/microsome mutagenicity assay. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 455*(1), 29-60.

Mueller, M., de la Pena, A., and Derendorf, H. (2004). Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. *Antimicrobial Agents and Chemotherapy, 48*(2), 369-377.

Muskawar, P. N., Karthikeyan, P., Aswar, S. A., Bhagat, P. R., and Kumar, S. S. (2012). NHC–metal complexes based on benzimidazolium moiety for chemical transformation. *Arabian Journal of Chemistry, 9*(2), S1765–S1778.

Navarro, M. (2009). Gold complexes as potential anti-parasitic agents. *Coordination Chemistry Reviews, 253*(11), 1619-1626.

Navarro, M., Cisneros-Fajardo, E. J., Lehmann, T., Sánchez-Delgado, R. A., Atencio, R., Silva, P., Lira, R., and Urbina, J. A. (2001). Toward a novel metal-based chemotherapy against tropical diseases. 6. Synthesis and characterization of new copper (II) and gold (I) clotrimazole and ketoconazole complexes and evaluation of their activity against *Trypanosoma Cruzi. Inorganic Chemistry, 40*(27), 6879-6884.

Navarro, M., Vasquez, F., Sánchez-Delgado, R. A., Pérez, H., Sinou, V., and Schrével, J. (2004). Toward a novel metal-based chemotherapy against tropical diseases. 7. Synthesis and *in vitro* antimalarial activity of new gold-chloroquine complexes. *Journal of Medicinal Chemistry, 47*(21), 5204-5209.

Neelakantan, M., Esakkiammal, M., Mariappan, S., Dharmaraja, J., and Jeyakumar, T. (2010). Synthesis, characterization and biocidal activities of some schiff base metal complexes. *Indian Journal of Pharmaceutical Sciences, 72*(2), 216-222.

Negrini, S., Gorgoulis, V. G., and Halazonetis, T. D. (2010). Genomic instability—an evolving hallmark of cancer. *Nature Reviews Molecular Cell Biology, 11*(3), 220-228.

Nemeth, J., Oesch, G., and Kuster, S. P. (2015). Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy, 70*(2), 382-395.

Neumann, A. A., and Reddel, R. R. (2002). Telomere maintenance and cancer? Look, no telomerase. *Nature Reviews Cancer, 2*(11), 879-884.

Neve, R. M., Chin, K., Fridlyand, J., Yeh, J., Baehner, F. L., Fevr, T., Clark, L., Bayani, N., Coppe, J.-P., and Tong, F. (2006). A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. *Cancer Cell, 10*(6), 515-527.

Nikaido, H. (2001). Preventing drug access to targets: cell surface permeability barriers and active efflux in bacteria. *Seminars in Cell and Developmental Biology*, *12*(3), 215-223.

Niles, A. L., Moravec, R. A., and Riss, T. L. (2009). *In vitro* viability and cytotoxicity testing and same-well multi-parametric combinations for high throughput screening. *Current Chemical Genomics, 3*, 33-41.

Nishida, N., Yano, H., Nishida, T., Kamura, T., and Kojiro, M. (2006). Angiogenesis in cancer. *Vascular Health and Risk Management, 2*(3), 213-219.

Nishimura, R., Osako, T., Okumura, Y., Hayashi, M., Toyozumi, Y., and Arima, N. (2010). Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. *Experimental and Therapeutic Medicine, 1*(5), 747-754.

Ng, A. K., Kenney, L. B., Gilbert, E. S., and Travis, L. B. (2010). Secondary malignancies across the age spectrum. *Seminars in Radiation Oncology*, *20*(1), 67-78.

Noguchi, R., Hara, A., Sugie, A., and Nomiya, K. (2006). Synthesis of novel gold (I) complexes derived by AgCl-elimination between [AuCl (PPh_3)] and silver (I) heterocyclic carboxylates, and their antimicrobial activities. Molecular structure of [Au (R, S-Hpyrrld)(PPh_3)](H 2 pyrrld= 2-pyrrolidone-5-carboxylic acid). *Inorganic Chemistry Communications, 9*(4), 355-359.

Nomiya, K., Noguchi, R., Ohsawa, K., Tsuda, K., & Oda, M. (2000). Synthesis, crystal structure and antimicrobial activities of two isomeric gold (I) complexes with nitrogen-containing heterocycle and triphenylphosphine ligands,[Au (L)(PPh 3)](HL= pyrazole and imidazole). *Journal of Inorganic Biochemistry*, *78*(4), 363-370.

Novelli, F., Recine, M., Sparatore, F., and Juliano, C. (1999). Gold(I) complexes as antimicrobial agents. *Il Farmaco, 54*(4), 232-236.

OECD (1997). *Test No. 471: Bacterial Reverse Mutation Test*. Paris: OECD Publishing.

Okeke, I. N., Laxminarayan, R., Bhutta, Z. A., Duse, A. G., Jenkins, P., O'Brien, T. F., Pablos-Mendez, A., and Klugman, K. P. (2005). Antimicrobial resistance in developing countries. Part I: recent trends and current status. *The Lancet Infectious Diseases, 5*(8), 481-493.

O'Reilly, L. P., Luke, C. J., Perlmutter, D. H., Silverman, G. A., and Pak, S. C. (2014). *Caenorhabditis elegans* in high-throughput drug discovery. *Advanced Drug Delivery Reviews, 69*, 247-253.

Ozben, T. (2006). Mechanisms and strategies to overcome multiple drug resistance in cancer. *FEBS Letters, 580*(12), 2903-2909.

Özdemir, İ., Denizci, A., Öztürk, H. T., and Cetinkaya, B. (2004). Synthetic and antimicrobial studies on new gold (I) complexes of imidazolidin-2-ylidenes. *Applied Organometallic Chemistry, 18*(7), 318-322.

Parrish, A. B., Freel, C. D., and Kornbluth, S. (2013). Cellular mechanisms controlling caspase activation and function. *Cold Spring Harbor Perspectives in Biology, 5*(6), a008672.

Park, H.-E. H., Jung, Y., and Lee, S.-J. V. (2017). Survival assays using *Caenorhabditis elegans*. *Molecules and Cells, 40*(2), 90-99.

Pankey, G., and Sabath, L. (2004). Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clinical Infectious Diseases, 38*(6), 864-870.

Patel, R., Rawat, S., and Choudhary, M. (2013). Synthesis, electrochemical, spectroscopic, antimicrobial, and superoxide dismutase activity of nickel (II) complexes with bidentate schiff bases. *International Journal of Inorganic Chemistry, 2013*, 1-8.

Pereira, S., and Tettamanii, M. (2005). Ahimsa and Alternatives-the Concept of the 4th R. The CPCSEAin India. *Altex, 22*(1/05), 3-6.

Pessetto, Z. Y., Weir, S. J., Sethi, G., Broward, M. A., and Godwin, A. K. (2013). Drug repurposing for gastrointestinal stromal tumor. *Molecular Cancer Therapeutics, 12*(7), 1299-1309.

Petersen, P. J., Jones, C. H., and Bradford, P. A. (2007). *In vitro* antibacterial activities of tigecycline and comparative agents by time-kill kinetic studies in fresh Mueller-Hinton broth. *Diagnostic Microbiology and Infectious Disease, 59*(3), 347-349.

Phan, L. M., Yeung, S.-C. J., and Lee, M.-H. (2014). Cancer metabolic reprogramming: importance, main features, and potentials for precise targeted anti-cancer therapies. *Cancer Biology and Medicine, 11*(1), 1-19.

Pietras, R. J., Arboleda, J., Reese, D. M., Wongvipat, N., Pegram, M. D., Ramos, L., Gorman, C. M., Parker, M. G., Sliwkowski, M. X., and Slamon, D. J. (1995). HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene, 10*(12), 2435-2446.

Pistritto, G., Trisciuoglio, D., Ceci, C., Garufi, A., and D'Orazi, G. (2016). Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. *Aging, 8*(4), 603-619.

Polyak, K. (2011). Heterogeneity in breast cancer. *The Journal of Clinical Investigation, 121*(10), 3786-3788.

Pommier, Y., Sordet, O., Antony, S., Hayward, R. L., and Kohn, K. W. (2004). Apoptosis defects and chemotherapy resistance: molecular interaction maps and networks. *Oncogene, 23*(16), 2934-2949.

Porter, P. (2008). "Westernizing" women's risks? Breast cancer in lower-income countries. *New England Journal of Medicine, 358*(3), 213-216.

Policy, I. P. (2010). The 10 '20 initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clinical Infectious Diseases, 50*, 1081-1083.

Porter, A. G., and Jänicke, R. U. (1999). Emerging roles of caspase-3 in apoptosis. *Cell Death and Differentiation, 6*(2), 99-104.

Portt, L., Norman, G., Clapp, C., Greenwood, M., and Greenwood, M. T. (2011). Anti-apoptosis and cell survival: a review. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1813*(1), 238-259.

Price, P. S., Keenan, R. E., and Swartout, J. C. (2008). Characterizing interspecies uncertainty using data from studies of anti-neoplastic agents in animals and humans. *Toxicology and Applied Pharmacology, 233*(1), 64-70.

Pugsley, M. K., Authier, S., and Curtis, M. (2008). Principles of safety pharmacology. *British Journal of Pharmacology, 154*(7), 1382-1399.

Rackham, O., Nichols, S. J., Leedman, P. J., Berners-Price, S. J., and Filipovska, A. (2007). A gold (I) phosphine complex selectively induces apoptosis in breast cancer cells: implications for anticancer therapeutics targeted to mitochondria. *Biochemical Pharmacology, 74*(7), 992-1002.

Rafique, S., Idrees, M., Nasim, A., Akbar, H., and Athar, A. (2010). Transition metal complexes as potential therapeutic agents. *Biotechnology and Molecular Biology Reviews, 5*(2), 38-45.

Ray, S., Mohan, R., Singh, J. K., Samantaray, M. K., Shaikh, M. M., Panda, D., and Ghosh, P. (2007). Anticancer and antimicrobial metallopharmaceutical agents based on palladium, gold, and silver N-heterocyclic carbene complexes. *Journal of the American Chemical Society, 129*(48), 15042-15053.

Rakoff-Nahoum, S. (2006). Why cancer and inflammation. *Yale Journal of Biology and Medicine, 79*(3-4), 123-130.

Reed, A. E. M., Kutasovic, J. R., Lakhani, S. R., and Simpson, P. T. (2015). Invasive lobular carcinoma of the breast: morphology, biomarkers and'omics. *Breast Cancer Research, 17*(1), 1-11.

Reymond, N., d'Água, B. B., and Ridley, A. J. (2013). Crossing the endothelial barrier during metastasis. *Nature Reviews Cancer, 13*(12), 858-870.

Rigobello, M. P., Messori, L., Marcon, G., Cinellu, M. A., Bragadin, M., Folda, A., Scutari, G., and Bindoli, A. (2004). Gold complexes inhibit mitochondrial

thioredoxin reductase: consequences on mitochondrial functions. *Journal of Inorganic Biochemistry, 98*(10), 1634-1641.

Rigobello, M. P., Scutari, G., Folda, A., and Bindoli, A. (2004). Mitochondrial thioredoxin reductase inhibition by gold (I) compounds and concurrent stimulation of permeability transition and release of cytochrome c. *Biochemical Pharmacology, 67*(4), 689-696.

Robillard, M. S., and Reedijk, J. (2005). Platinum-based anticancer drugs. *Encyclopedia of Inorganic and Bioinorganic Chemistry*, 1-11.

Roder, C., and Thomson, M. J. (2015). Auranofin: repurposing an old drug for a golden new age. *Drugs in Research and Development, 15*(1), 13-20.

Romero, L., and Vela, J. M. (2014a). Alternative models in drug discovery and development part I: in silico and *in vitro* models. *In Vivo Models for Drug Discovery*, 27-58.

Romero, L., and Vela, J. M. (2014b). Alternative models in drug discovery and development part II: *in vivo* nonmammalian and exploratory/experimental human models. *In Vivo Models for Drug Discovery*, 59-90.

Ronconi, L., Giovagnini, L., Marzano, C., Bettìo, F., Graziani, R., Pilloni, G., and Fregona, D. (2005). Gold dithiocarbamate derivatives as potential antineoplastic agents: design, spectroscopic properties, and *in vitro* antitumor activity. *Inorganic Chemistry, 44*(6), 1867-1881.

Rosenberg, B., Van Camp, L., and Krigas, T. (1965). Inhibition of cell division in Escherichia coli by electrolysis products from a platinum electrode. *Nature, 205*(4972), 698-699.

Rosenberg, B., and Vancamp, L. (1969). Platinum compounds: a new class of potent antitumour agents. *Nature, 222*, 385-386.

Roymahapatra, G., M Mandal, S., F Porto, W., Samanta, T., Giri, S., Dinda, J., L Franco, O., and K Chattaraj, P. (2012). Pyrazine functionalized Ag (I) and Au (I)-NHC complexes are potential antibacterial agents. *Current Medicinal Chemistry, 19*(24), 4184-4193.

Sabaté, D. (2015). Ethical Issues and regulations and guidelines concerning animal research. *In Vivo Models for Drug Discovery*, 91-106.

Sabounchei, S. J., Shahriary, P., Salehzadeh, S., Gholiee, Y., Nematollahi, D., Chehregani, A., and Amani, A. (2014). Gold (III) complexes of 5-methyl-5-(pyridyl)-2, 4-imidazolidenedione: synthesis, physicochemical, theoretical, antibacterial, and cytotoxicity investigation. *New Journal of Chemistry, 38*(3), 1199-1210.

Saeidnia, S., Manayi, A., and Abdollahi, M. (2015). From *in vitro* experiments to *in vivo* and clinical studies; pros and cons. *Current Drug Discovery Technologies, 12*(4), 218-224.

Saggioro, D., Rigobello, M. P., Paloschi, L., Folda, A., Moggach, S. A., Parsons, S., Ronconi, L., Fregona, D., and Bindoli, A. (2007). Gold (III)-dithiocarbamato complexes induce cancer cell death triggered by thioredoxin redox system inhibition and activation of ERK pathway. *Chemistry and Biology, 14*(10), 1128-1139.

Saletta, F., Dalla Pozza, L., and Byrne, J. A. (2015). Genetic causes of cancer predisposition in children and adolescents. *Translational Pediatrics, 4*(2), 67.

Samaras, V., Rafailidis, P. I., Mourtzoukou, E. G., Peppas, G., and Falagas, M. E. (2010). Chronic bacterial and parasitic infections and cancer: a review. *The Journal of Infection in Developing Countries, 4*(05), 267-281.

Sandalova, T., Zhong, L., Lindqvist, Y., Holmgren, A., and Schneider, G. (2001). Three-dimensional structure of a mammalian thioredoxin reductase: implications for mechanism and evolution of a selenocysteine-dependent enzyme. *Proceedings of the National Academy of Sciences, 98*(17), 9533-9538.

Santajit, S., and Indrawattana, N. (2016). Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed Research International, 2016*.

Sasakura, H., and Mori, I. (2013). Behavioral plasticity, learning, and memory in *Caenorhabditis elegans*. *Current Opinion in Neurobiology, 23*(1), 92-99.

Sauvage, E., Kerff, F., Terrak, M., Ayala, J. A., and Charlier, P. (2008). The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. *FEMS Microbiology Reviews, 32*(2), 234-258.

Sayers, T. J. (2011). Targeting the extrinsic apoptosis signaling pathway for cancer therapy. *Cancer Immunology, Immunotherapy, 60*(8), 1173-1180.

Schlegel, R., and Williamson, P. (2001). Phosphatidylserine, a death knell. *Cell death and Differentiation, 8*(6), 551.

Schnitt, S. J. (2010). Classification and prognosis of invasive breast cancer: from morphology to molecular taxonomy. *Modern Pathology, 23*, S60-S64.

Schug, Z. T., Gonzalvez, F., Houtkooper, R., Vaz, F. M., and Gottlieb, E. (2011). BID is cleaved by caspase-8 within a native complex on the mitochondrial membrane. *Cell Death and Differentiation, 18*(3), 538-548.

Schuler, M., and Green, D. (2001). Mechanisms of p53-dependent apoptosis. *Biochemical Society Transactions, 29*(6), 684-688.

Sengupta, P., and Samuel, A. D. (2009). *Caenorhabditis elegans*: a model system for systems neuroscience. *Current Opinion in Neurobiology, 19*(6), 637-643.

Setlow, P. (2014). Spore resistance properties. *Microbiology Spectrum*, *2*(5), 1-14.

Shalapour, S., and Karin, M. (2015). Immunity, inflammation, and cancer: an eternal fight between good and evil. *The Journal of Clinical Investigation, 125*(9), 3347-3355.

Shay, J. W., and Wright, W. E. (2011). Role of telomeres and telomerase in cancer. *Seminars in Cancer Biology, 21(6)*, 349-353.

Shay, J. W., Zou, Y., Hiyama, E., and Wright, W. E. (2001). Telomerase and cancer. *Human Molecular Genetics, 10*(7), 677-685.

Shaye, D. D., and Greenwald, I. (2011). OrthoList: a compendium of *Caenorhabditis elegans* genes with human orthologs. *PloS ONE, 6*(5), e20085.

Shen, Z. (2011). Genomic instability and cancer: an introduction. *Journal of Molecular Cell Biology, 3*(1), 1-3.

Shoeib, T., Atkinson, D. W., and Sharp, B. L. (2010). Structural analysis of the anti-arthritic drug Auranofin: Its complexes with cysteine, selenocysteine and their fragmentation products. *Inorganica Chimica Acta, 363*(1), 184-192.

Shulman, L. N., Willett, W., Sievers, A., and Knaul, F. M. (2010). Breast cancer in developing countries: opportunities for improved survival. *Journal of Oncology, 2010*, 1-6.

Siddik, Z. H. (2003). Cisplatin: mode of cytotoxic action and molecular basis of resistance. *Oncogene, 22*(47), 7265-7279.

Siegel, R. L., Miller, K. D., and Jemal, A. (2016). Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians, 66*(1), 7-30.

Silver, L. L. (2011). Challenges of antibacterial discovery. *Clinical Microbiology Reviews, 24*(1), 71-109.

Sim, J.-H., Jamaludin, N. S., Khoo, C.-H., Cheah, Y.-K., Halim, S. N. B. A., Seng, H.-L., and Tiekink, E. R. (2014). *In vitro* antibacterial and time-kill evaluation of phosphanegold (I) dithiocarbamates, $R_3PAu[S_2CN(iPr)CH_2CH_2OH]$ for R= Ph, Cy and Et, against a broad range of Gram-positive and Gram-negative bacteria. *Gold Bulletin, 47*(4), 225-236.

Sinn, H.-P., and Kreipe, H. (2013). A brief overview of the WHO classification of breast tumors. *Breast Care, 8*(2), 149-154.

Solis, G. M., and Petrascheck, M. (2011). Measuring *Caenorhabditis elegans* life span in 96 well microtiter plates. *Journal of Visualized Experiments*, (49), e2496-e2496.

Stanton, R. A., Gernert, K. M., Nettles, J. H., and Aneja, R. (2011). Drugs that target dynamic microtubules: a new molecular perspective. *Medicinal Research Reviews, 31*(3), 443-481.

Stein, G. M., and Murphy, C. (2013). The intersection of aging, longevity pathways, and learning and memory in *Caenorhabditis elegans*. *Neuronal Inputs and Outputs of Aging and Longevity*, 104, 1-13.

Steele, R. W. (2012). Managing infection in cancer patients and other immunocompromised children. *The Ochsner Journal, 12*(3), 202-210.

Stergiou, L., and Hengartner, M. (2004). Death and more: DNA damage response pathways in the nematode *Caenorhabditis elegans. Cell Death and Differentiation, 11*(1), 21-28.

Stewart, P. S. (2002). Mechanisms of antibiotic resistance in bacterial biofilms. *International Journal of Medical Microbiology, 292*(2), 107-113.

Stiernagle, T. (1999). Maintenance of *Caenorhabditis elegans*. *Caenorhabditis elegans, 2*, 51-67.

Stoletov, K., Kato, H., Zardouzian, E., Kelber, J., Yang, J., Shattil, S., and Klemke, R. (2010). Visualizing extravasation dynamics of metastatic tumor cells. *Journal of Cell Science, 123*(13), 2332-2341.

Sulston, J. E., Schierenberg, E., White, J. G., and Thomson, J. (1983). The embryonic cell lineage of the nematode *Caenorhabditis elegans*. *Developmental Biology, 100*(1), 64-119.

Sun, J., Deng, Z., and Yan, A. (2014). Bacterial multidrug efflux pumps: mechanisms, physiology and pharmacological exploitations. *Biochemical and Biophysical Research Communications, 453*(2), 254-267.

Sun, R. W.-Y. (2013). Strategies to improve the anti-cancer properties of gold (III) complexes. *Modern Chemistry and Applications, 1*(3), 1-3.

Szikriszt, B., Póti, Á., Pipek, O., Krzystanek, M., Kanu, N., Molnár, J., Ribli, D., Szeltner, Z., Tusnády, G. E., and Csabai, I. (2016). A comprehensive survey of the mutagenic impact of common cancer cytotoxics. *Genome Biology, 17*(1), 1-16.

Tait, S. W., and Green, D. R. (2010). Mitochondria and cell death: outer membrane permeabilization and beyond. *Nature Reviews Molecular Cell Biology, 11*(9), 621-632.

Tam, V. H., Schilling, A. N., and Nikolaou, M. (2005). Modelling time–kill studies to discern the pharmacodynamics of meropenem. *Journal of Antimicrobial Chemotherapy, 55*(5), 699-706.

Tan, Y. S., Ooi, K. K., Ang, K. P., Akim, A. M., Cheah, Y.-K., Halim, S. N. A., Seng, H.-L., and Tiekink, E. R. (2015). Molecular mechanisms of apoptosis and cell selectivity of zinc dithiocarbamates functionalized with hydroxyethyl substituents. *Journal of Inorganic Biochemistry, 150*, 48-62.

Tanida, S., Mizoshita, T., Ozeki, K., Tsukamoto, H., Kamiya, T., Kataoka, H., Sakamuro, D., and Joh, T. (2012). Mechanisms of cisplatin-induced apoptosis and of cisplatin sensitivity: potential of BIN1 to act as a potent predictor of cisplatin sensitivity in gastric cancer treatment. *International Journal Of Surgical Oncology, 2012*.

Tanwar, J., Das, S., Fatima, Z., and Hameed, S. (2014). Multidrug resistance: an emerging crisis. *Interdisciplinary Perspectives on Infectious Diseases, 2014*, 1-7.

Tenover, F. C. (2006). Mechanisms of antimicrobial resistance in bacteria. *The American Journal of Medicine, 119*(6), S3-S10.

Thangamani, S., Mohammad, H., Abushahba, M. F., Sobreira, T. J., Hedrick, V. E., Paul, L. N., and Seleem, M. N. (2016). Antibacterial activity and mechanism of action of auranofin against multi-drug resistant bacterial pathogens. *Scientific Reports, 6*, 1-13.

Thangamani, S., Mohammad, H., Younis, W., and N Seleem, M. (2015). Drug repurposing for the treatment of staphylococcal infections. *Current Pharmaceutical Design, 21*(16), 2089-2100.

Tiekink, E. R. (2002). Gold derivatives for the treatment of cancer. *Critical Reviews In Oncology/Hematology, 42*(3), 225-248.

Tivnan, A., Zakaria, Z., O'Leary, C., Kögel, D., Pokorny, J. L., Sarkaria, J. N., and Prehn, J. H. (2015). Inhibition of multidrug resistance protein 1 (MRP1) improves chemotherapy drug response in primary and recurrent glioblastoma multiforme. *Frontiers In Neuroscience, 9*, 1-10.

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A. (2015). Global cancer statistics, 2012. *CA: A Cancer Journal For Clinicians, 65*(2), 87-108.

Trávníček, Z. k., Štarha, P., Vančo, J. n., Šilha, T. s., Hošek, J., Suchý Jr, P., and Pražanová, G. (2012). Anti-inflammatory active gold (I) complexes involving 6-substituted-purine derivatives. *Journal of Medicinal Chemistry, 55*(10), 4568-4579.

Trinchieri, G. (2012). Cancer and inflammation: an old intuition with rapidly evolving new concepts. *Annual Review of Immunology, 30*, 677-706.

Tweedy, B. (1964). Plant extracts with metal ions as potential antimicrobial agents. *Phytopathology, 55*, 910-914.

Valachis, A., and Nilsson, C. (2014). Cardiac risk in the treatment of breast cancer: assessment and management. *Breast Cancer (Dove Medical Press), 7*, 21-35.

Van Hoek, A., Mevius, D., Guerra, B., Mullany, P., and Robberts, A. (2011). Acquired antibiotic resistance genes: an overview. *Frontiers In Microbiology, 2*, 1-27.

Van Rijt, S. H., and Sadler, P. J. (2009). Current applications and future potential for bioinorganic chemistry in the development of anticancer drugs. *Drug Discovery Today, 14*(23), 1089-1097.

Van Zijl, F., Krupitza, G., and Mikulits, W. (2011). Initial steps of metastasis: cell invasion and endothelial transmigration. *Mutation Research/Reviews in Mutation Research, 728*(1), 23-34.

Vander Heiden, M. G., Cantley, L. C., and Thompson, C. B. (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science, 324*(5930), 1029-1033.

Varghese, E., and Büsselberg, D. (2014). Auranofin, an anti-rheumatic gold compound, modulates apoptosis by elevating the intracellular calcium concentration ([Ca2+] i) in MCF-7 breast cancer cells. *Cancers, 6*(4), 2243-2258.

Vela, J. M., Maldonado, R., and Hamon, M. (2014). The 3Ns of preclinical animal models in biomedical research. *In Vivo Models for Drug Discovery*, 1-26.

Vergara, E., Cerrada, E., Casini, A., Zava, O., Laguna, M., and Dyson, P. J. (2010). Antiproliferative activity of gold (I) alkyne complexes containing water-soluble phosphane ligands. *Organometallics, 29*(11), 2596-2603.

Viale, G. (2012). The current state of breast cancer classification. *Annals of Oncology, 23*(suppl 10), x207-x210.

Vinay, D. S., Ryan, E. P., Pawelec, G., Talib, W. H., Stagg, J., Elkord, E., Lichtor, T., Decker, W. K., Whelan, R. L., and Kumara, H. S and Signori, E. (2015). Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Seminars in Cancer Biology, 35*, S185-S198.

Walmsley, R. M., and Billinton, N. (2011). How accurate is *in vitro* prediction of carcinogenicity? *British Journal of Pharmacology*, 162(6), 1250-1258.

Walsh, C. (2000). Molecular mechanisms that confer antibacterial drug resistance. *Nature, 406*(6797), 775-781.

Wang, D., and Lippard, S. J. (2005). Cellular processing of platinum anticancer drugs. *Nature Reviews Drug discovery, 4*(4), 307-320.

Wang, S., and El-Deiry, W. S. (2003). TRAIL and apoptosis induction by TNF-family death receptors. *Oncogene, 22*(53), 8628-8633.

Wang, X., Wang, X., Li, L., and Wang, D. (2010). Lifespan extension in *Caenorhabditis elegans* by DMSO is dependent on sir-2.1 and daf-16. *Biochemical and Biophysical Research Communications, 400*(4), 613-618.

Wang, Z., Dabrosin, C., Yin, X., Fuster, M. M., Arreola, A., Rathmell, W. K., Generali, D., Nagaraju, G. P., El-Rayes, B., and Ribatti, D.and Chen, Y. C. (2015). Broad targeting of angiogenesis for cancer prevention and therapy. *Seminars in Cancer Biology*, *35*, S224-S243.

Ward, P. S., and Thompson, C. B. (2012). Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer Cell, 21*(3), 297-308.

Waring, M. J., Arrowsmith, J., Leach, A. R., Leeson, P. D., Mandrell, S., Owen, R. M., Pairaudeau, G., Pennie, W. D., Pickett, S. D., and Wang, J. (2015). An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nature Reviews Drug Discovery, 14*(7), 475-486.

Waris, G., and Ahsan, H. (2006). Reactive oxygen species: role in the development of cancer and various chronic conditions. *Journal of Carcinogenesis, 5*(1), 1-8.

Warra, A. A. (2011). Transition metal complexes and their application in drugs and cosmetics – A Review. *Journal of Chemical and Pharmaceutical Research 3*(4), 951-958.

Waterston, R. (1998). Genome sequence of the nematode *Caenorhabditis elegans:* a platform for investigating biology. *The Caenorhabditis elegans Sequencing Consortium. Science*, 282(5396), 2012-2018.

Wawruszak, A., Luszczki, J. J., Grabarska, A., Gumbarewicz, E., Dmoszynska-Graniczka, M., Polberg, K., and Stepulak, A. (2015). Assessment of interactions between cisplatin and two histone deacetylase inhibitors in MCF7, T47D and MDA-MB-231 human breast cancer cell lines–an isobolographic analysis. *PloS ONE, 10*(11), 1-19.

Weinberg, R. A. (1995). The retinoblastoma protein and cell cycle control. *Cell, 81*(3), 323-330.

West, A. K. V., Wullkopf, L., Christensen, A., Leijnse, N., Tarp, J. M., Mathiesen, J., Mathiesen, J., Erler, J.T. and Oddershede, L. B. (2017). Dynamics of cancerous tissue correlates with invasiveness. *Scientific Reports,* 7, 1-11.

Weston, A., and Harris, C. C. (2000). Chemical carcinogenesis. In Kufe, D. W., Pollock, R. E., Weichselbaum, R. R., Bast Jr, R. C., Gansler, T. S., Holland, J. F., and Frei III, E. *Holland-Frei cancer medicine* (6th eds). Hamilton (ON): BC Decker. Available from: https://www.ncbi.nlm.nih.gov/books/NBK13982/.

Wetzel, C., Kunz, P. C., Kassack, M. U., Hamacher, A., Böhler, P., Watjen, W., Ott, I., Rubbiani, R., and Spingler, B. (2011). Gold (I) complexes of water-soluble diphos-type ligands: synthesis, anticancer activity, apoptosis and thioredoxin reductase inhibition. *Dalton Transactions, 40*(36), 9212-9220.

WHO. (2014). *Antimicrobial resistance: global report on surveillance*. Switzerland: World Health Organization Press.

Wilson, D. N. (2014). Ribosome-targeting antibiotics and mechanisms of bacterial resistance. *Nature Reviews Microbiology, 12*(1), 35-48.

Wise, R., Blaser, M., Carrs, O., Cassell, G., Fishman, N., Guidos, R., Levy, S., Powers, J., Norrby, R., and Tillotson, G. (2011). The urgent need for new antibacterial agents. *Journal of Antimicrobial Chemotherapy, 66*(9), 1939-1940.

Wong, R. S. (2011). Apoptosis in cancer: from pathogenesis to treatment. *Journal of Experimental and Clinical Cancer Research, 30*(87), 1-14.

Woodford, N., and Ellington, M. (2007). The emergence of antibiotic resistance by mutation. *Clinical Microbiology and Infection, 13*(1), 5-18.

WoŸniak, K., and Błasiak, J. (2002). Recognition and repair of DNA-cisplatin adducts. *Acta Biochimica Polonica, 49*, 583-596.

Wright, G. D. (2005). Bacterial resistance to antibiotics: enzymatic degradation and modification. *Advanced Drug Delivery Reviews, 57*(10), 1451-1470.

Wyatt, M. D., and Wilson III, D. M. (2009). Participation of DNA repair in the response to 5-fluorouracil. *Cellular and Molecular Life Sciences, 66*(5), 788-799.

Xu, Y., and Villalona-Calero, M. (2002). Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. *Annals of Oncology, 13*(12), 1841-1851.

Yao, Y., and Dai, W. (2014). Genomic instability and cancer. *Journal of Carcinogenesis and Mutagenesis, 5*, 1-17.

Ye, L., Yan, C., and Schor, N. F. (2001). Apoptosis in the absence of caspase 3. *Oncogene, 20*(45), 6570-6578.

Yeo, C. I., Ooi, K. K., Akim, A. M., Ang, K. P., Fairuz, Z. A., Halim, S. N. B. A., Ng, S. W., Seng, H.-L., and Tiekink, E. R. (2013). The influence of R substituents in triphenylphosphinegold (I) carbonimidothioates, Ph3PAu [SC (OR)= NPh](R= Me, Et and iPr), upon *in vitro* cytotoxicity against the HT-29 colon cancer cell line and upon apoptotic pathways. *Journal of Inorganic Biochemistry, 127*, 24-38.

Yeung, S., Pan, J., and Lee, M.-H. (2008). Roles of p53, MYC and HIF-1 in regulating glycolysis—the seventh hallmark of cancer. *Cellular and Molecular Life Sciences, 65*(24), 3981-3999.

Yoon, M.-K., Ha, J.-H., Lee, M.-S., and Chi, S.-W. (2015). Structure and apoptotic function of p73. *BMB Reports, 48*(2), 81-90.

Youlden, D. R., Cramb, S. M., Yip, C. H., and Baade, P. D. (2014). Incidence and mortality of female breast cancer in the Asia-Pacific region. *Cancer Biology and Medicine, 11*(2), 101-115.

Youle, R. J., and Strasser, A. (2008). The BCL-2 protein family: opposing activities that mediate cell death. *Nature Reviews Molecular Cell Biology, 9*(1), 47-59.

Youn, H. S., Lee, J. Y., Saitoh, S. I., Miyake, K., and Hwang, D. H. (2006). Auranofin, as an anti-rheumatic gold compound, suppresses LPS-induced homodimerization of TLR4. *Biochemical and Biophysical Research Communications, 350*(4), 866-871.

Yu Meng, Z., Chun-bao, Z., Dai-jie, C., and Ji-an, L. (2012). Preliminary acute toxicity assessment of pharmaceutical compounds by *Caenorhabditis elegans*. *Chinese Journal of Pharmacology and Toxicology, 26*(1), 99-104.

Zahreddine, H., and Borden, K. (2013). Mechanisms and insights into drug resistance in cancer. *Frontiers in Pharmacology, 4*(28), 1-8.

Zankari, E., Hasman, H., Cosentino, S., Vestergaard, M., Rasmussen, S., Lund, O., Aarestrup, F. M., and Larsen, M. V. (2012). Identification of acquired antimicrobial resistance genes. *Journal of Antimicrobial Chemotherapy, 67*(11), 2640-2644.

Zeiger, E. (2001). Mutagens that are not carcinogens: faulty theory or faulty tests? *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 492*(1), 29-38.

Zhang, R., Al-Lamki, R., Bai, L., Streb, J. W., Miano, J. M., Bradley, J., and Min, W. (2004). Thioredoxin-2 inhibits mitochondria-located ASK1-mediated apoptosis in a JNK-independent manner. *Circulation Research, 94*(11), 1483-1491.

Zou, T., Lum, C. T., Lok, C.-N., Zhang, J.-J., and Che, C.-M. (2015). Chemical biology of anticancer gold (III) and gold (I) complexes. *Chemical Society Reviews, 44*(24), 8786-8801.

Zou, Y., Ling, Y.-H., Sironi, J., Schwartz, E. L., Perez-Soler, R., and Piperdi, B. (2013). The autophagy inhibitor chloroquine overcomes the innate resistance of wild-type EGFR non-small-cell lung cancer cells to erlotinib. *Journal of Thoracic Oncology, 8*(6), 693-702.

LIST OF PUBLICATIONS

Journals

Bao Jing Chen and Yoke Kqueen Cheah. (2017). Platinum- and gold-based drugs on cancer. *Journal of Transdisciplinary Biomedicine, 1*(1), 1-9.

Bao-Jing Chen, Nazzatush Shimar Jamaludin, Chai-Hoon Khoo, Tian-Hong See, Jiun-Horng Sim, Yoke-Kqueen Cheah, Siti Nadiah Abdul Halim, Hoi-Ling Seng, Edward R.T. Tiekink. (2016). *In vitro* antibacterial and time kill evaluation of mononuclear phosphanegold(I) dithiocarbamates. *Journal of Inorganic Biochemistry, 163*, 68–80.

N. S. Jamaludin, S. N. A. Halim, C.-H. Khoo, **B.-J. Chen**, T.-H. See, J.-H. Sim, Y.-K. Cheah, H.-L. Seng and E. R. T. Tiekink. (2016). Bis(phosphane) copper(I) and silver(I) dithiocarbamates: crystallography and antimicrobial assay. *Zeitschrift für Kristallographie, 231* (2016), 341 – 349.

Yeo, C. I., Khoo, C.-H., Chu, W.-C., **Chen, B.-J.,** Chu, P.-L., Sim, J.-H., Cheah, Y.-K., Ahmad, J., Halim, S.N.A., Seng, H.-L., Ng, S., Otero-de-laRoza, A. and Tiekink, E.R.T. (2015). The importance of Au K (aryl) interactions in the formation of spherical aggregates in binuclear phosphanegold(I) complexes of a bipodal thiocarbamate dianion: A combined crystallographic and computational study, and anti-microbial activity. *RSC Advances, 5*:41401-41411.

Aznan, A., Mardia, A., Abdullah, Z., Khoo, C. H., **Chen, B. J.,** See, T. H., Sim, J. H., Cheah, Y. K., Seng, H. L and Tiekink, E. R. (2015). Three ammonium salts of sulfathiazole: crystallography and anti-microbial assay. *Zeitschrift für Kristallographie-Crystalline Materials, 230*(6), 385-396.

Proceedings and presentations

Bao Jing Chen, Yoke Kqueen Cheah, Nazzatush Shimar Jamaludin, Edward R.T. Tiekink. 2016. *In vitro* induction of apoptosis and inhibition of cell migration and invasion by synthetic gold complexes on breast cancer. Oral presented at International Translational Molecular Medicine Conference and Aero-Space Medicine and Physiology showcase, Sepang, Malaysia.

B. J. Chen, C. H. Khoo, T. H. See, J. H. Sim, Y. K. Cheah, N. S. Jamaludin, H. L. Seng and E. R. T. Tiekink. 2014. *In vitro* evaluation of the antibacterial activity of gold complex of [N,N-bis(hydroxyethyl)dithiocarbamate]. Poster presented at Joint Malaysia-UK Symposium on Natural Product Chemistry and Drug Discovery, International Medical University, Malaysia.

Chen Bao Jing, Shahrus Shakila Abdul Munir, See Tian Hong, Khoo Chai Hoon, Sim Jiun Horng and Cheah Yoke Kqueen. 2013. Isolation and Toxin Gene Detection of *Pseudomonas* spp. and *Vibrio* spp. in Acute Hepatopancreatic Necrosis Syndrome. Poster presented at International Congress of Malaysian Society for Microbiology, Langkawi, Malaysia.

UNIVERSITI PUTRA MALAYSIA

STATUS CONFIRMATION FOR THESIS / PROJECT REPORT AND COPYRIGHT

ACADEMIC SESSION : _____

TITLE OF THESIS / PROJECT REPORT :

BIOMEDICAL PROPERTIES OF NOVEL MONONUCLEAR PHOSPHANEGOLD(I) DITHIOCARBAMATES

NAME OF STUDENT: CHEN BAO JING

I acknowledge that the copyright and other intellectual property in the thesis/project report belonged to Universiti Putra Malaysia and I agree to allow this thesis/project report to be placed at the library under the following terms:

1. This thesis/project report is the property of Universiti Putra Malaysia.
2. The library of Universiti Putra Malaysia has the right to make copies for educational purposes only.
3. The library of Universiti Putra Malaysia is allowed to make copies of this thesis for academic exchange.

I declare that this thesis is classified as :

*Please tick (√)

☐	**CONFIDENTIAL**	(Contain confidential information under Official Secret Act 1972).
☐	**RESTRICTED**	(Contains restricted information as specified by the organization/institution where research was done).
☐	**OPEN ACCESS**	I agree that my thesis/project report to be published as hard copy or online open access.

This thesis is submitted for :

☐	**PATENT**	Embargo from_____ until _____ (date) (date)

Approved by:

_____	_____
(Signature of Student)	(Signature of Chairman of Supervisory Committee)
New IC No/ Passport No.:	Name:
Date :	Date :

[Note : If the thesis is CONFIDENTIAL or RESTRICTED, please attach with the letter from the organization/institution with period and reasons for confidentially or restricted.]