PARP INHIBITOR COMBINATIONS WITH OLAPARIB FOR SYNERGISTIC EFFICACY IN OLAPARIB-RESISTANT TRIPLE-NEGATIVE BREAST CANCER CELLS

By

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Chair : Haslina Ahmad, PhD
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Triple-negative breast cancer (TNBC) is associated with aggressive and heterogenous tumour phenotype, early tumour relapse and poor prognosis than other types of invasive breast cancer. TNBC does not respond to endocrine therapy due to the lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2) expression. Although poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have been successfully developed to treat breast cancer; however, these PARPi as monotherapies are limited to TNBC patients with defective gene where BRCA-deficient TNBC accounts for a small subset (< 30%) of TNBC patients. With few exceptions, monotherapy remains ineffective due to insufficient tumour suppression, requires high dose of drug, dose-limiting toxicity and acquired drug resistance is common. Thus, combining PARPi with other therapeutics to increase efficacy, reduce drug dosage, and overcome drug resistance is a promising strategy to treat TNBC. Moreover, drug combination screening of a PARPi is a relatively new concept and having a compound library with diverse chemical space to be screened alongside PARPi holds potential to new drug combination discovery. Therefore, this study aims to discover new combinations of Olaparib, the most successful PARPi to date, alongside other therapeutic in MDA-MB-231 TNBC cells without BRCA mutation. The library used in this screen comprises of a total of > 100 molecules including DNA-binding ruthenium compounds and commercially-available drugs. In this study, Olaparib-resistant (OlaR) MDA-MB-231R cells were developed from the parental MDA-MB-231 cells after prolonged treatment (~8 months) with Olaparib. Olaparib resistance was assessed by clonogenic survival assay in which 28-fold level of Olaparib resistance was observed in MDA-MB-231R cells in comparison to the parental cells. The acquisition of Olaparib resistance is associated with upregulation of drug efflux pumps of P-glycoprotein (P-gp), loss of poly(ADP-ribose) glycohydrolase (PARG) and the activation of ATR/Chk1 signalling pathway. Synergistic drug combinations were identified using Chou and Talalay

combination index (CI) method in which CI < 0.9 demonstrated synergy. This study identified four hits including a natural compound, curcumin; two ruthenium(II)-rhenium(I) metallomacrocyles, Ru(bpy)Re and Ru(dppz)Re; and FDA-approved Exemestane (CI < 0.9 across the tested concentrations). Synergy was confirmed using long-term clonogenic survival assay in which single agents showed survival fractions (S.F.) of > 45%, and upon co-treatments, significant (P < 0.01) loss in clonogenic potential of cells was observed. Moreover, synergy was retained in the acquired OlaR MDA-MB-231R cells. Mechanistic studies indicated synergy was achieved via significant (P < 0.05) enhancement of DNA damage and the resultant apoptosis. Most importantly, all identified combinations showed low cytotoxicity in MCF10A normal breast cells with substantial cancer versus normal cell selectivity (selectivity index (SI) > 50). These identified combinations were also able to inhibit the growth of 3D breast cancer spheroids. Thus, this study supports the concept that PARPi Olaparib combination strategy represents a promising approach towards aggressive strains of BRCA-proficient TNBC and can overcome acquired PARPi resistance. Additionally, co-treatment with the synergistic pairing of Olaparib and Ru-PIP, a ruthenium compound, in non-small cell lung cancer (NSCLC) cells showed enhanced (P < 0.05) DNA damages and reactive oxygen species (ROS) levels, and was able to inhibit the lung cancer spheroids growth, providing further affirmation of expanding the benefits of these identified combinations to other cancer types beyond TNBC. Moreover, exposure of zebrafish embryos to these identified synergistic pairings over 96 h did not lead to any noticeable signs of toxicity, making these newly identified combinations as suitable candidates for future *in vivo* investigations.

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

RAWATAN GABUNGAN PERENCAT PARP OLAPARIB YANG MEMBERI KESAN SINERGI TERHADAP SEL KANSER PAYUDARA *TRIPLE-NEGATIF* YANG MEMPUNYAI RINTANGAN TERHADAP OLAPARIB

Oleh

NUR AININIE BINTI YUSOH

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Kanser payudara *triple-negatif* (TNBC) telah dikaitkan dengan fenotip tumor yang agresif, kepelbagaian tumor, kanser kambuh semula dan mempunyai prognosis yang buruk berbanding kanser payudara bersifat invasif yang lain. TNBC tidak memberi tindak balas terhadap terapi endokrin kerana kanser ini tidak mempunyai ekspresi reseptor progesterone, reseptor estrogen dan reseptor faktor pertumbuhan epidermis manusia jenis 2 (HER2). Walaupun perencat polimerase poli(ADP-ribosa) (PARP) telah berjaya dibangunkan untuk merawat kanser payudara, tetapi keberkesanan aktiviti PARPi sebagai agen tunggal adalah terhad kepada pesakit kanser yang mempunyai mutasi pada gen BRCA dimana bilangan pesakit yang mempunyai mutasi pada gen BRCA adalah sangat kecil (< 30% daripada pesakit TNBC). Tambahan pula, rawatan agen tunggal masih tidak berkesan untuk merawat kanser disebabkan tidak dapat membunuh sel-sel kanser dengan sepenuhnya, memerlukan dos ubat yang tinggi, ketoksikan ubat, dan terdapat risiko berlakunya rintangan terhadap agen tunggal. Oleh itu, strategi menggunakan rawatan gabungan PARPi yang dapat memperluas kesan keberkesanan, mengurangkan dos ubat dan dapat mengatasi masalah rintangan ubat merupakan strategi yang berpotensi untuk merawat TNBC. Di samping itu, rawatan gabungan PARPi adalah satu konsep baharu dan dengan penggunaan agen yang pelbagai menjadikan strategi ini berpotensi tinggi untuk menemukan rawatan gabungan yang baharu. Oleh itu, kajian ini bertujuan untuk menemukan rawatan gabungan Olaparib, salah satu PARPi yang paling berpotensi buat masa sekarang, bersama agen yang lain terhadap sel kanser MDA-MB-231 yang tidak mempunyai mutasi pada gen BRCA. Agen yang digunakan dalam kajian ini berjumlah sebanyak > 100 agen, yang terdiri daripada agen antikanser yang telah berada di pasaran, dan kompleks rutenium yang mengikat dengan DNA. Dalam kajian ini, sel MDA-MB-231 yang menunjukkan rintangan terhadap Olaparib telah berjaya dibangunkan daripada sel MDA-MB-231 di mana sel tersebut telah dirawat secara berpanjangan dengan ubat Olaparib (~8 bulan). Berbanding sel MDA-MB-231,

sel MDA-MB-231R menunjukkan tahap rintangan sebanyak 28 kali ganda terhadap agen Olaparib apabila menggunakan ujian klonogenik. Rintangan terhadap agen Olaparib juga dikaitkan dengan peningkatan jumlah pam efluks P-glikoprotein (P-gp), pengurangan aktiviti *glycohydrolase* poli(ADP-ribosa) (PARG) dan peningkatan aktiviti ATR/Chk1. Gabungan ubat-ubatan yang menghasilkan kesan sinergistik dinilai dengan menggunakan kaedah Chou dan Talalay kombinasi indeks (CI) di mana CI < 0.9 menunjukkan kesan sinergistik. Hasil dapatan kajian ini telah dapat mengenal pasti empat *hits* yang terdiri daripada bahan aktif daripada kunyit yang dikenali sebagai kurkumin; dua *macrocyles* yang berasaskan logam rutenium(II)-renium(I), Ru(bpy)Re dan Ru(dppz)Re; dan ubat yang telah mendapat kelulusan FDA iaitu Exemestane. Seterusnya, kesan sinergistik rawatan gabungan baharu ini juga dikaji dengan menggunakan ujian klonogenik. Agen tunggal menunjukkan kelangsungan hidup sel (S.F.) > 45%, dan rawatan gabungan menunjukkan pengurangan kelangsungan hidup sel yang ketara (P < 0.01). Di samping itu, rawatan gabungan ini juga menunjukkan kesan sinergistik terhadap sel MDA-MB-231R. Kajian mekanistik menunjukkan kesan sinergistik telah diperoleh melalui peningkatan kerosakan DNA yang ketara (P < 0.05) yang menyebabkan kematian sel melalui mekanisme *apoptosis*. Pertama sekali, semua rawatan gabungan baharu yang dikenal pasti menunjukkan kesan sitotoksik yang rendah terhapat sel payudara normal MCF10A dimana rawatan ini menunjukkan tahap selektif yang tinggi terhadap sel kanser berbanding sel normal (nilai indeks selektif (SI) > 50). Rawatan gabungan baharu yang dikenal pasti ini juga turut berjaya menghalang pertumbuhan sferoid 3D kanser payudara. Oleh itu, kajian ini menyokong konsep dimana rawatan gabungan PARPi Olaparib berpotensi untuk merawat kanser TNBC yang agresif termasuklah kanser yang tidak mempunyai mutasi pada gen BRCA, dan rawatan ini dapat mengatasi masalah rintangan ubat PARPi. Tambahan lagi, rawatan gabungan Olaparib dan kompleks rutenium Ru-PIP yang menunjukkan kesan sinergistik terhadap sel kanser paru-paru (NSCLC) menunjukkan peningkatan kerosakan DNA yang ketara (P < 0.05) dan peningkatan spesies oksigen reaktif (ROS), dan juga dapat menghalang pertumbuhan sferoid 3D kanser paru-paru. Ini memberi justifikasi yang kukuh untuk memperluas manfaat rawatan gabungan yang telah dikenal pasti ini untuk digunakan terhadap jenis kanser yang lain selain TNBC. Selain itu, melalui ujian ketoksikan embrio ikan Zebra dimana walaupun rawatan gabungan baharu ini telah diberikan kepada embrio ikan Zebra selama 96 jam, tiada tanda kesan ketoksikan yang ketara yang ditunjukkan oleh rawatan tersebut. Ini menjadikan rawatan gabungan baharu ini sebagai rawatan yang sesuai untuk dikaji dalam kajian lanjutan secara *in vivo*.

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°C	degree celsius
3-AB	3-aminobenzamide
ABCB1	ATP-binding cassette sub-family B member 1
AI	Aromatase inhibitor
ALC1	Amplified in Liver Cancer 1
ANOVA	One-way analysis of variance
ATCC	American Type Culture Collection
ATM	Ataxia-telangiectasia mutated
ATR	Ataxia-telangiectasia-mutated-and-Rad3-related kinase
ATRi	ATR inhibitor
BCA	Bicinchoninic acid
BER	Base excision repair
bpy	2,2'-bipyrine
BRCA	Breast cancer susceptibility genes
BSA	Bovine serum albumin
Chk1	Checkpoint kinase 1
CI	Combination index
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CUR	Curcumin
DCF	2'7'-dichlorofluorescein
DCFDA	2',7'-dichlorofluorescein diacetate
DDB2	DNA damage-binding protein 2
DDR	DNA damage response

dmb	4,4'-dimethyl-2,2'-bipyridine
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dppz	dipyrido[3,2-a:2′,3′-c]phenazine
DSB	Double-strand breaks
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERβ	Oestrogen receptor beta
EXE	Exemestane
FBS	Fetal bovine serum
FDA	U.S. Food and Drug Administration
HDACi	Histone deacetylase inhibitors
hEGF	Recombinant human EGF
HER2	Human epidermal growth factor receptor type 2
hpf	Hours of post-fertilisation
HR	Homologous recombination
HRP	Horseradish peroxidase
IACUC	Institutional Animal Care and Use Committee
IC_{50}	Half maximal inhibitory concentration
Im	Imidazole
Kb	Binding constant
KP1019	indazolium trans-tetrachlorobis(1H-indazole)ruthenate(III)
LC_{50}	Half maximal lethal concentration
LIG3	DNA ligase III

LL’	2-((2’,2’’:5’’,2’’’-terthiophene)-imidazo[4,5-*f*][1,10]phenanthroline)
log P	Octanol/water partition coefficient
MCE	MedChemExpress
MDA-MB-231R	Olaparib-resistant MDA-MB-231 cells
MDR1	Multi drug resistance protein 1
mTOR	Mammalian target of rapamycin
MTT	Thiazolyl blue tetrazolium bromide
NAMI-A	ImH][trans-RuCl4(DMSO)(Im)
NCI	National Cancer Institute
NER	Nucleotide excision repair
NHEJ	Non-homologous end joining
NSCLC	Non-small cell lung cancer cells
OLAP	Olaparib
OlaR	Olaparib-resistant
ORR	Objective response rates
P/S	Penicillin/streptomycin
PAIN	Pan-assay interference
PARG	Poly(ADP-ribose) glycohydrolase
PARP	Poly(ADP-ribose) polymerase
PARPi	PARP inhibitor
p-ATM	ATM phosphorylated at Ser1981
p-ATR	ATR phosphorylated at Thr1989
PBS	Phosphate buffered saline
p-Chk1	Chk1 phosphorylated at Ser345
PDT	Photodynamic therapy

PDX	Patient-derived tumour xenograft
PFA	Paraformaldehyde
PFS	Progression-free survival
P-gp	p-glycoprotein
phen	1,10-phenanthroline
p-HPIP	2-(4-hydroxyphenyl)imidazo[4,5-*f*][1,10]phenanthroline
PI	Propidium iodide
PIP	2-(phenyl)imidazo[4,5-*f*][1,10]phenanthroline
Polβ	DNA polymerase β
PR	Progesterone receptor
qtpy	2,2':4,4"4',4"' quaterpyridyl
RI	Resistance index
RIPA	Radioimmunoprecipitation assay
ROS	Reactive oxygen species
RPC	Ruthenium polypyridyl complex
RT	Room temperature
BR	Ru(bpy)Re
DR	Ru(dppz)Re
Ru-PIP	$[Ru(dppz)_2(PIP)]^{2+}$
S.F.	Survival fraction
SCLC	Small cell lung cancer
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel
SERM	Selective ER modulator
SI	Selectivity Index

siRNA	Small-interfering RNA
SSB	Single-strand breaks
T2	Cell doubling time
TBS	Tris buffered saline
TBS-T	0.1% Tween 20 in 1X TBS
TI	Therapeutic index
TLD1433	$[Ru(dmb)_2(LL')]^{2+}$
TNBC	Triple-negative breast cancer
UPM	Universiti Putra Malaysia
UV	Ultraviolet light
VEGF	Vascular endothelial growth factor
vs.	versus
XRCC1	X-ray repair cross complementing protein 1
γH2AX	H2AX phosphorylated at Ser139

CHAPTER 1

INTRODUCTION

1.1 Research background

Triple-negative breast cancer (TNBC) is a subtype of breast cancer which is characterised by the lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2) expression (Almansour, 2022; Zagami & Carey, 2022). TNBC accounts for approximately 15-20% of all breast cancer cases and nearly 12-18% of Malaysian breast cancer patients are TNBC (Abdul Aziz et al., 2020; Almansour, 2022). Due to the heterogenous nature of TNBC together with high metastatic potential and high invasiveness, TNBC is associated with early tumour relapse leading to poor prognosis compared to non-TNBC subtypes (Bianchini et al., 2022). Despite successful development of advanced therapies for breast cancers, limited treatment options are available for TNBC patients. In contrast to non-TNBC patients with ER, PR and/or HER2 expression that are more susceptible to therapies targeting these receptors (endocrine therapies), these therapies are not effective for TNBC patients which lack these ER, PR and HER2 receptors (Yin et al., 2020).

Nowadays, with greater understanding and insights on the hallmarks of cancer including genomic instability have led to some important advances and breakthroughs in treating TNBC (Huang & Zhou, 2021; Groelly et al., 2023). Cellular DNA is continuously being subjected to various endogenous damage such as reactive oxygen species (ROS) generated from cellular metabolism, and exogenous damages such as ultraviolet light (UV), ionising radiation or DNA damaging chemicals, that can be detrimental to cells. Thus, in response to the accumulation of DNA lesion, cancer cells have evolved numerous complicated and entangled network of DNA damage response (DDR) signalling pathways to repair DNA lesion to ensure cell survival (Alhmoud et al., 2020; Huang & Zhou, 2021; Nikfarjam & Singh, 2023). Based on this understanding, the development of targeted therapeutics in particular, the inhibitors to DDR, have resulted in a paradigm shift in small molecule-based cancer therapy (Huang & Zhou, 2021; Huang et al., 2022a). This is perhaps best exemplified by the development of poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) which have high selectivity towards cancers harbouring mutations in breast cancer susceptibility (BRCA) genes, achieved by the concept of synthetic lethality (Mateo et al., 2019; Curtin & Szabo, 2020). This cancer selectivity is achieved through the exploitation of cancer cells with impaired DNA repair characteristics together with targeting the compensatory DNA repair pathways (Bryant et al., 2005; Lord & Ashworth, 2017). Briefly, PARP enzyme is crucial for DNA single-strand breaks (SSBs) repair; meanwhile, BRCA1/2 genes are required for DNA double-strand breaks (DSBs) repair by homologous recombination (HR), and the simultaneous impairment of both repair mechanisms leads to cancer selective cell death

through synthetic lethality. Several PARPi have gained U.S. Food and Drug Administration (FDA) approval for treating BRCA-deficient cancers, with prominent examples include Olaparib, niraparib, rucaparib and talazoparib (Curtin & Szabo, 2020). However, BRCA-deficient cancers account for a relatively small subset (< 30%) of TNBC patients which substantially limits the population of TNBC patients that could benefit from PARPi-based therapy (Chen et al., 2018). Besides, PARPi monotherapies may not be effective for BRCA-proficient TNBC.

Moreover, with very few exceptions, anticancer monotherapies including PARPi single agents are clinically limited due to insufficient tumour suppression, intolerable side effects and the prevalence of acquired PARPi resistance, in which any of these occurrences will result in treatment failure (Mokhtari et al., 2017; Toss et al., 2022). Nowadays, drug resistance remains a major therapeutic challenge to successful cancer therapy. Besides, TNBC is heterogenous in nature and exhibits inherently aggressive clinical behaviour with significantly higher risk of relapse compared to non-TNBC subtypes. Based on this background, adopting the therapeutic approach to combine PARPi with other therapeutics for synergy to enhance drug efficacy and overcome acquired PARPi resistance is a promising approach in treating the aggressive and heterogenous cancer BRCA-proficient TNBC (Wang et al., 2022). Moreover, reduced drug dosage as a result of synergistic response is predicted to represent a lower risk in a clinical setting by minimising adverse effects (Mokhtari et al., 2017). Newly identified combinations also need to have a high cancer selectivity, as an indication of margin of safety for future clinical investigations. Accordingly, drug combination will result in manageable toxicity profile, higher survival rate and improve the cost-effectiveness of the treatment over monotherapies.

Typically, a rational combination strategy is the most common method to establish new effective drug combination in which complimentary small molecules were selected based on their mechanisms of action (Falchi et al., 2017; Kim et al., 2020a). However, unbiased (hypothesis-free) drug combination screen may allow for serendipity in drug discovery (Kummar et al., 2010; Al-Lazikani et al., 2012). Moreover, screening a compound library with diverse chemical space aided by the inclusion of the DNA-binding ruthenium compounds holds the potential to new drug combination discovery with different chemical reactivities. The interest in metal-based anticancer drug is based on the discovery of cis-diamminedichloroplatinum (II), or cisplatin, by the Rosenberg group in 1960 (Rosenberg et al., 1969), where cisplatin becomes the first FDA-approved metallodrug in 1978 (Kelland, 2007). Since then, extensive efforts were made in designing complexes based on other alternative transition metal centres including ruthenium to replace or as an alternative to cisplatin (Zeng et al., 2017; Lee et al., 2020). Several ruthenium compounds have successfully entered clinical trials including NAMI-A, KP1019, NKP1339 and until now, the most successful clinical ruthenium compound is TLD1433 which has entered phase II trial to treat bladder cancer patients (Trondl et al., 2014; Monro et al., 2019). Interestingly, some ruthenium compounds target DNA through intercalation (reversible), a unique and different binding mode compared to the covalent binding showed by cisplatin (Zeng et al., 2017; Rilak Simović et al.,

2019). Briefly, these ruthenium compounds intercalate DNA inducing structural changes to the DNA strand by lengthening of the DNA strand or twisting of the base pairs resulting to its functional arrest. For example, our group have developed the ruthenium(II) polypyridyl complex (RPC) of $[Ru(dppz)_2(PIP)]^{2+}$ (dppz = dipyrido[3,2-a:2′,3′-c]phenazine and PIP = 2-(phenyl)imidazo[4,5-*f*][1,10]phenanthroline) (or Ru-PIP) which intercalates DNA with high affinity (Gill et al., 2016). The addition of Ru-PIP led to the stalling of DNA replication fork progression resulting in the activation of DDR and G1 cell cycle arrest (Gill et al., 2016).

Previously, our group described the potential of combining Ru-PIP with PARPi Olaparib in breast cancer cells where strong synergy was observed as a result of complementary mechanisms of action, with low cytotoxicity in normal healthy cells (Yusoh et al., 2020b). For this reason, ruthenium compounds have appeared as suitable and attractive candidates for exploration in combination therapy for cancer. Moreover, the combination of ruthenium compounds with DDR-targeting agents for cancer is still relatively a new concept. Therefore, having these emerging DNA-binding ruthenium compounds in the library provides chemical novelty to this drug combination screen as this library uses much diverse chemical space than the small molecules that are typically used in PARPi combination strategy. In this study, the most successful PARPi to date, Olaparib, will be screened alongside a compound library comprising of commercially available drugs and ruthenium compounds in BRCA-proficient TNBC. This approach may expand the applications of PARPi in BRCA-proficient cancers or other cancers with different sources of genomic instability and overcome acquired drug resistance.

1.2 Problem statement

Although PARPi have successfully been developed for BRCA-deficient TNBC cancers based on synthetic lethality concept; however, BRCA-deficient cancers accounts for a small subset (< 30%) of TNBC patients (Chen et al., 2018). Besides, PARPi monotherapies may not be effective for BRCA-proficient TNBC. Moreover, with very few exceptions, monotherapy was not able to prolong patient survival as single drug therapies may lead to insufficient tumour suppression and high dose of drug required for single therapeutic may cause intolerable side effects (Mokhtari et al., 2017). Furthermore, constant or prolonged exposure to single drug may lead to rapid emergence of acquired resistance which continues to be a challenge. For example, upon prolonged oral administration of PARPi single agents, more than 40% BRCA1/2-deficient patients did not respond to PARPi treatment indicating that they have acquired PARPi resistance (Li et al., 2020). Relapse is also frequent in a significant number of TNBC patients (occurs mostly in the first 5 years following diagnosis) which resulted in failure of the currently available treatments (Toss et al., 2022). Stewart et al. (2019) described that 40% of patients with stage I to III TNBC will suffer cancer recurrence after standard neoadjuvant chemotherapy and surgery (Stewart et al., 2019). Although PARPi combinations have been examined, these strategies are mainly effective in BRCA-deficient cancers (Lee et al., 2016; Fasching et al., 2021;

Drewett et al., 2022). This justifies the needs to find other effective PARPi combinations for BRCA-proficient cancers including for the aggressive cancer of TNBC and in the acquired PARPi-resistant tumours.

1.3 Aims and research objectives

This study aims to discover new synergistic combinations of PARPi Olaparib alongside other therapeutics from a compound library comprising of commercially available anticancer agents and ruthenium anticancer compounds in BRCA-proficient MDA-MB-231 TNBC cells including in Olaparib-resistant cells, and expand this approach to other cancer cell line beyond TNBC such as non-small cell lung cancer (NSCLC) cells.

1) To establish Olaparib-resistant (OlaR) MDA-MB-231R TNBC cells and determine the Olaparib resistance mechanisms.
2) To evaluate new synergistic combinations of Olaparib with a mixed organic/ruthenium compounds library in MDA-MB-231 cells, determine the mechanisms of synergy, evaluate their cytotoxic effects in OlaR MDA-MB-231R cells and in breast cancer spheroids and assess their acute toxicity in zebrafish embryos.
3) To evaluate new synergistic combinations of Olaparib with FDA-approved anticancer drugs library in MDA-MB-231 cells, determine the mechanisms of synergy and evaluate their cytotoxic effects in OlaR MDA-MB-231R cells.
4) To evaluate the previously identified synergistic combination of Olaparib with Ru-PIP, a ruthenium metallocompound, in lung cancer cells, determine the mechanisms of synergy, evaluate their cytotoxic effects in lung cancer spheroids and assess their acute toxicity in zebrafish embryos.

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