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Non-selective beta-blockers as potential coadjutants for prostate cancer treatment

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Non-selective beta-blockers as potential coadjutants for prostate cancer treatment

Pharmaceutical Alone

Propranolol
Carvedilol
Atenolol
Metoprolol

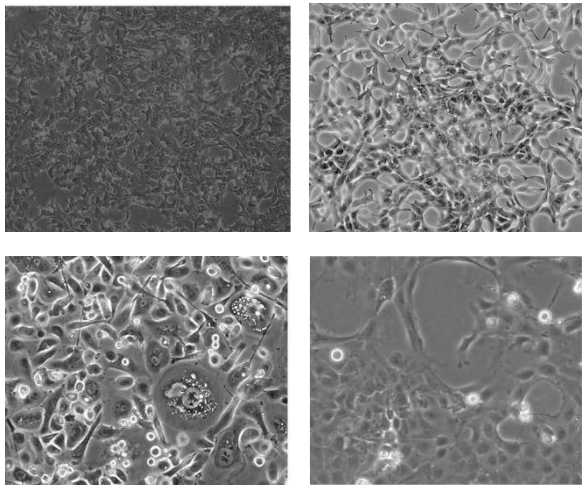
Cisplatin
Flutamide

Combined Exposure

Propranolol + Cisplatin
Propranolol + Flutamide

Different Cells Lines

22Rv1 LNCaP



PC3 PNT-2

Effects

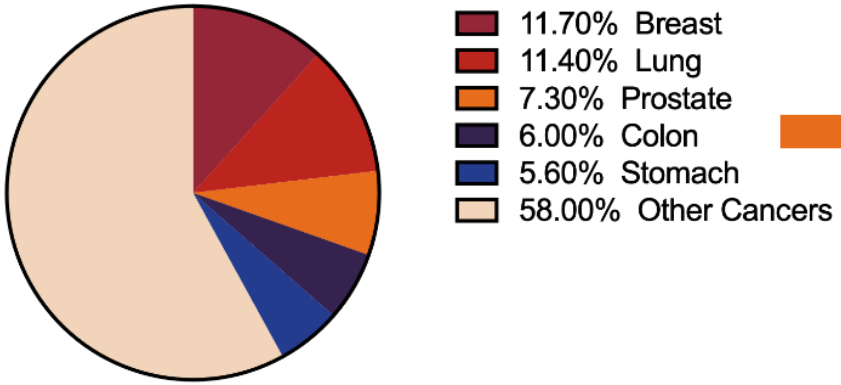
Cell Viability

Abstract: Prostate cancer is the third most diagnosed cancer worldwide, and the second cause of cancer death in men. The treatments currently available are not always effective. For that reason, new treatment options need to be explored, which can include the use of drugs, already clinically available, used for the treatment of other conditions, such as β-blockers. The present study aimed to explore the effects of several β-blockers and cytostatic drugs in prostate cancer cell lines (22Rv1, LNCaP and PC3) and a normal prostate cell line (PNT-2). Cells were exposed up to 72 h to increasing concentrations of propranolol, carvedilol (both non-selective β-blockers), atenolol, metoprolol (both β1-blockers), cisplatin (a cytostatic drug) and flutamide (an androgen receptor blocker) and cell viability was assessed. The non-selective β-blockers selected, propranolol and carvedilol and cytostatic drugs displayed cytotoxic effect on all cell lines, while the β1-blockers, metoprolol and atenolol did not alter significantly cells viability. Of the tested cell lines, 22Rv1 was the most sensitive to propranolol, carvedilol and cisplatin and PC3 was the most resistant. Therefore, sensitive line 22Rv1, resistant line PC3 and normal cell line PNT-2 were chosen for combined treatment between propranolol and cytostatic cisplatin and flutamide. Overall, the combined exposures revealed concentration dependent interactions between the cytostatic drugs and propranolol.

Keywords: beta-blockers, cancer cell lines, cell viability, combined treatments

Introduction

Percentage of new cases of cancer in 2020, both sexes, worldwide



Global Cancer Observatory of 2020

Available Treatments for Prostate Cancer:

Active Surveilence
Radical Prostatectomy
Radiation Therapy
Focal Therapy
Hormone Therapy
Chemotherapy
Immunotherapy
Nanotherapeutics

Limited Efficiency
Specially in advanced disease

New Approaches

β-Blockers

Introduction

β-Adrenergic Signalling

↓

"Fight-or-flight" stress response

↓

Catecholamines ↑

↓

Related to:
Angiogenesis
Migration
Metastasis

β-Adrenergic Receptors

- β1
  - Can be found in: Heart, Peripheral sympathetic nerves, Kidney, Vascular
  - → β1-Blockers (e.g., Atenolol, Metoprolol)
- β2
  - Can be found in: Heart, Lung, Perypheral sympathetic nerves, Vascular, Principal isoform in Prostate Cancer
- β3
  - Can be found in: Adipocytes, Heart, Colon, Perypheral sympathetic nerves, Vascular

→ Non selective β-Blockers (e.g., Carvedilol, Propranolol)

Introduction

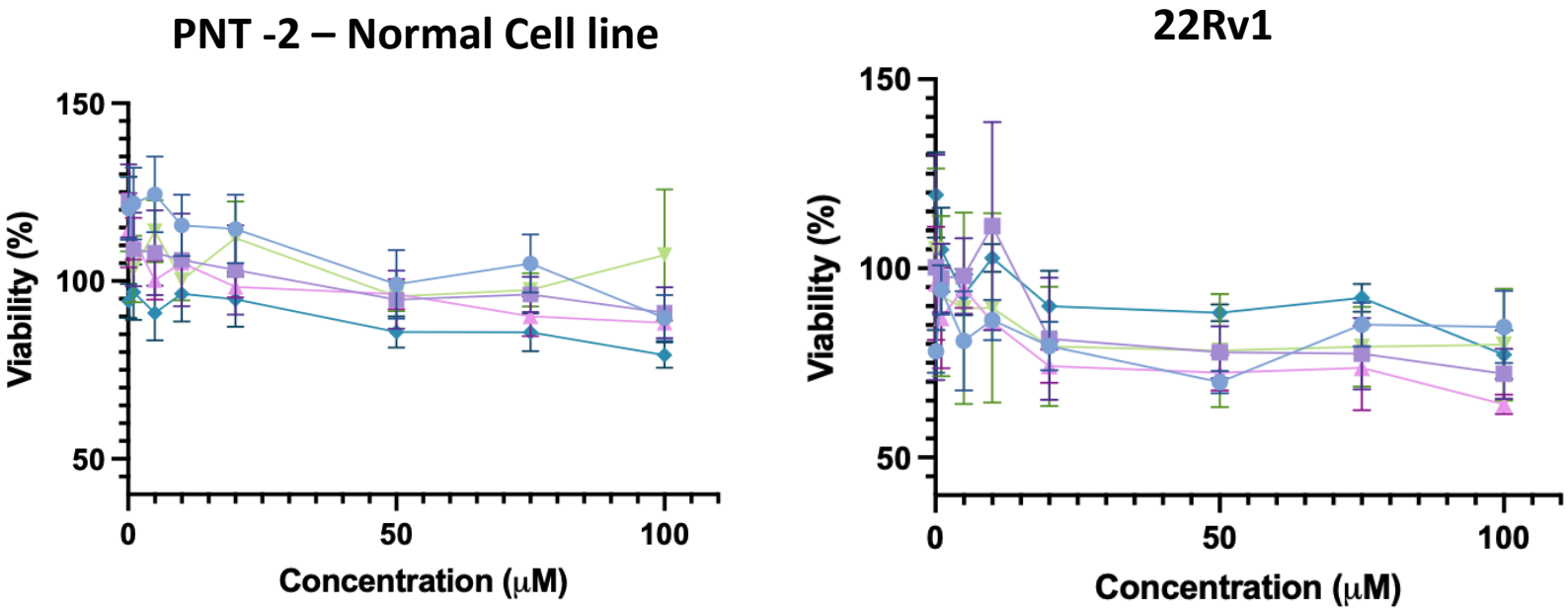
In this study:

The cytotoxicity of **β1-blockers** (atenolol and metoprolol), **non-selective β-blockers** (carvedilol and propranolol), and **cytostatic drugs** (cisplatin and flutamide), was assessed **on prostate cancer cell lines** (22Rv1, LNCaP and PC3) and on a **normal prostate cell line** (PNT-2).

Effects of **binary combinations** of propranolol with cisplatin and propranolol with flutamide, were assessed on PNT-2, 22Rv1 and PC3 cells.

Results and Discussion

Atenolol

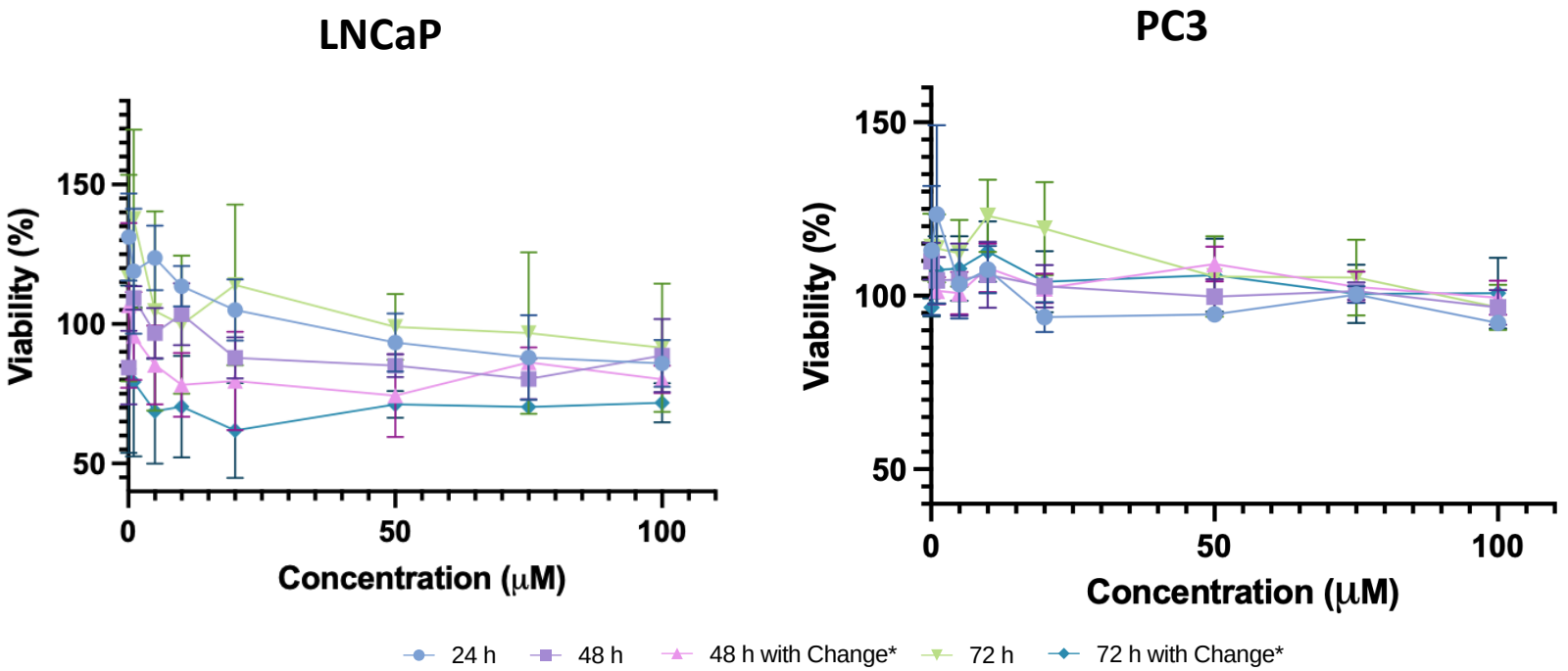


*test media renewal at every 24 h

Atenolol induced small reduction of cell viability in a time and concentration dependent manner

Results and Discussion

Atenolol

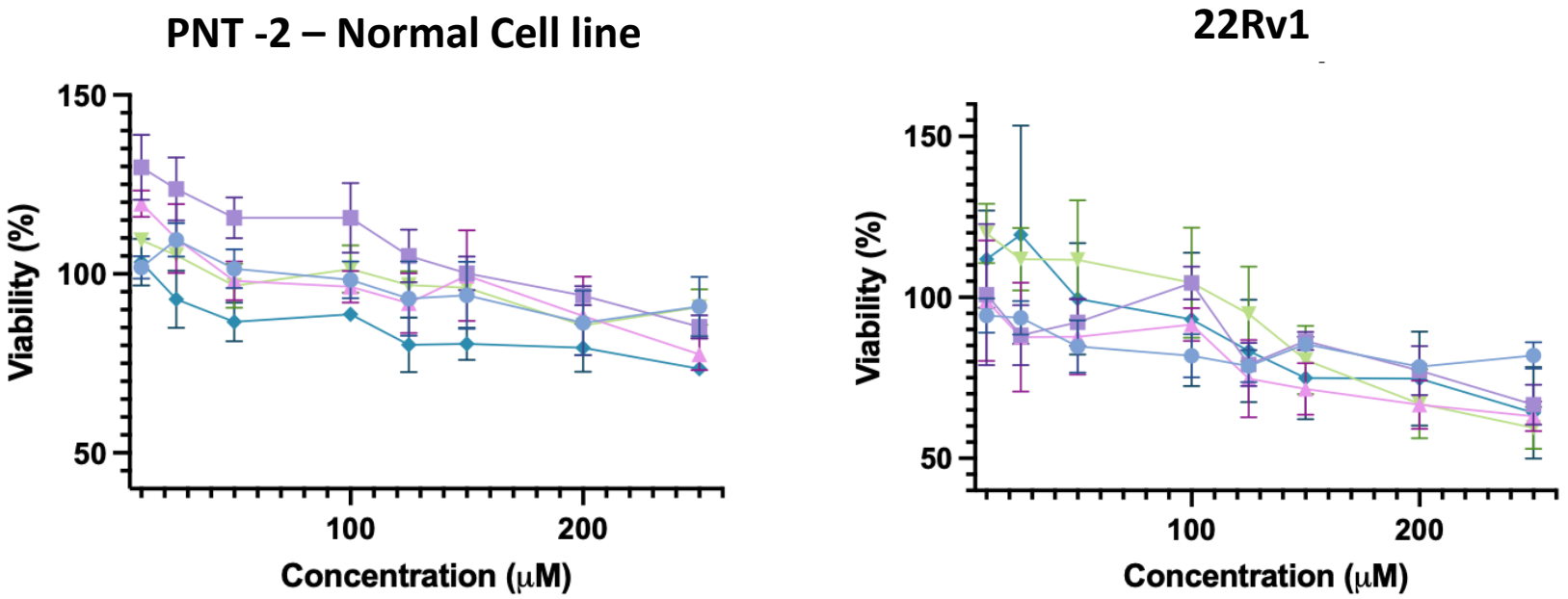


*test media renewal at every 24 h

Atenolol induced small reduction of cell viability in a time and concentration dependent manner

Results and Discussion

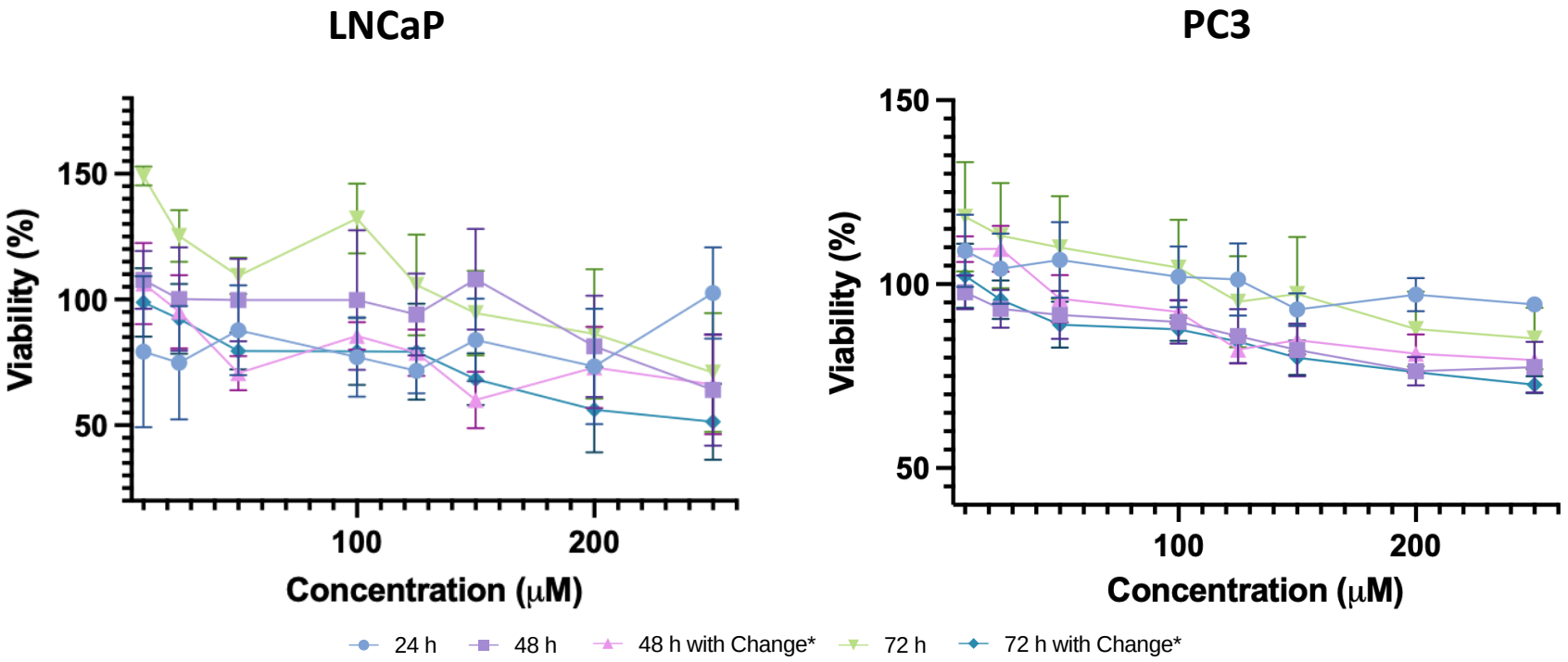
Metoprolol



Metoprolol induced small reduction of cell viability in a time and concentration dependent manner

Results and Discussion

Metoprolol



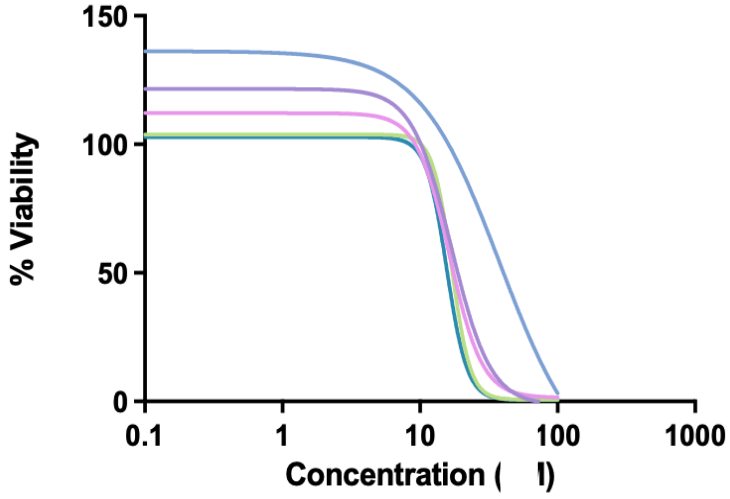
*test media renewal at every 24 h

Metoprolol induced small reduction of cell viability in a time and concentration dependent manner

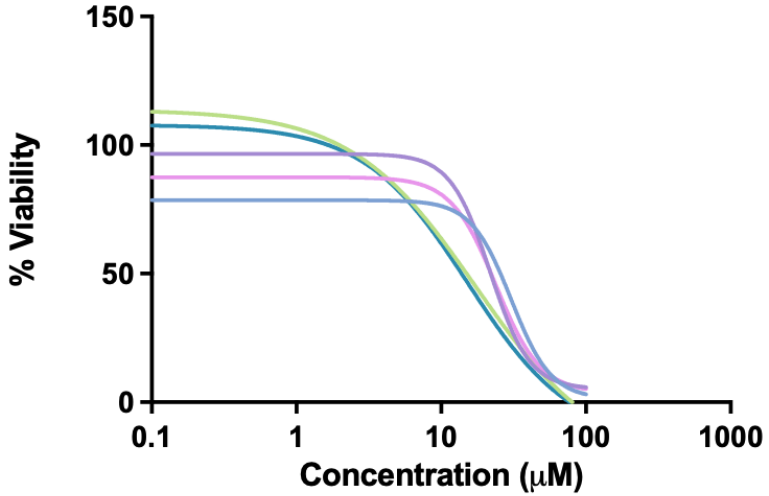
Results and Discussion

Carvedilol

PNT -2 – Normal Cell line



22Rv1



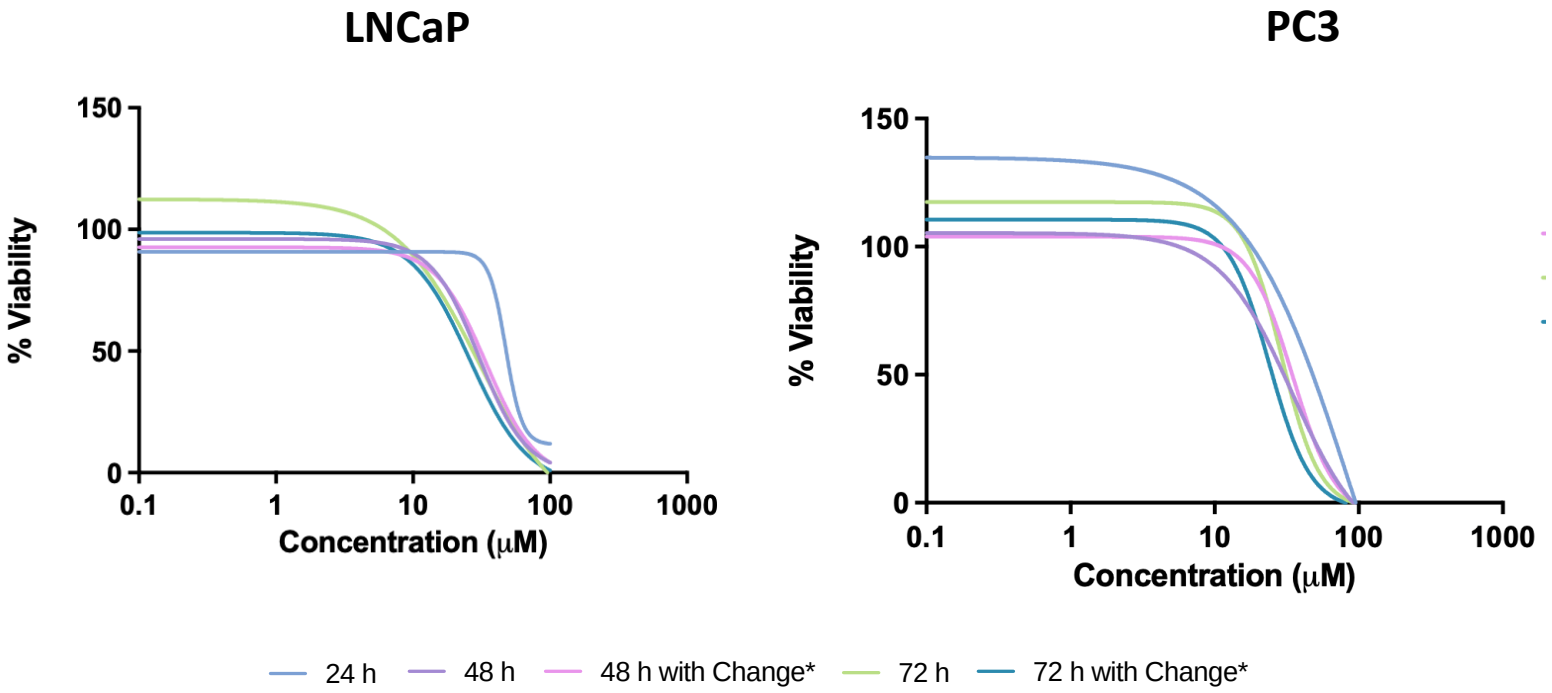
24 h 48 h 48 h with Change* 72 h 72 h with Change*

*test media renewal at every 24 h

Carvedilol showed time and concentration dependent cytotoxicity

Results and Discussion

Carvedilol

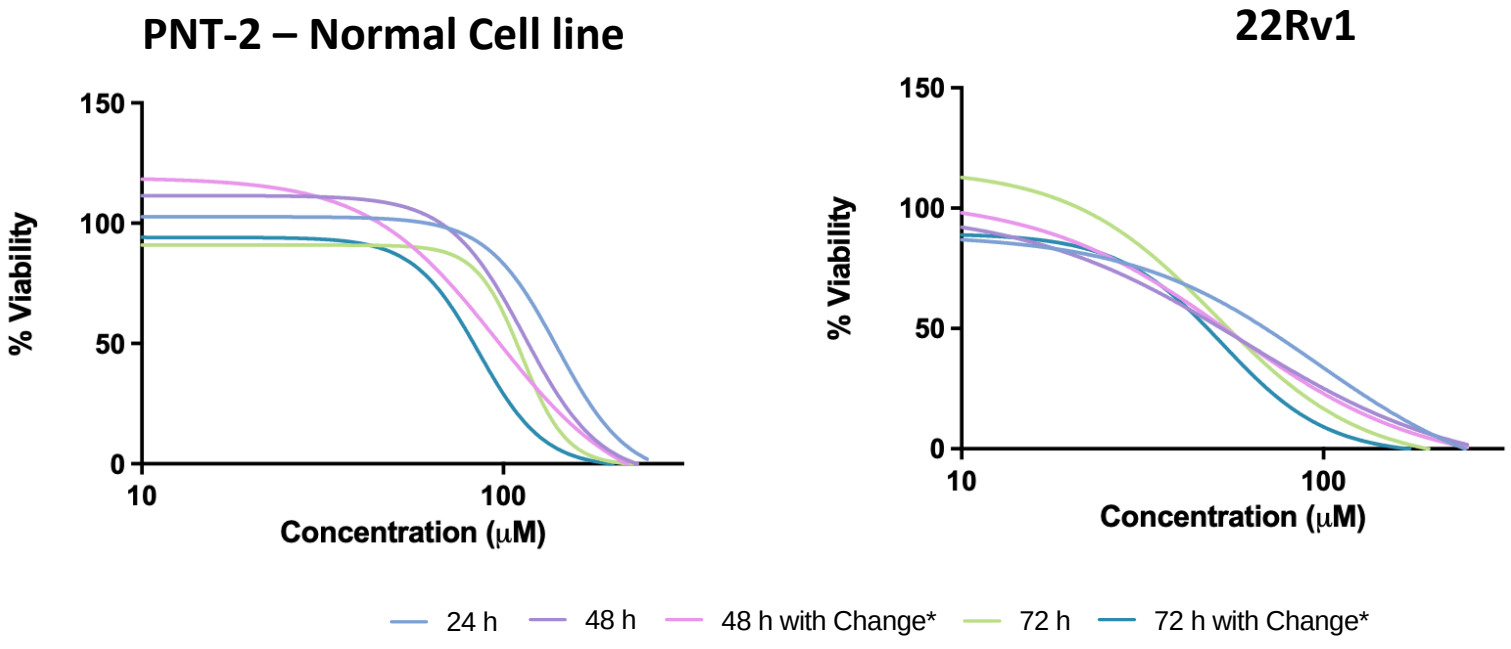


*test media renewal at every 24 h

Carvedilol showed time and concentration dependent cytotoxicity

Results and Discussion

Propranolol

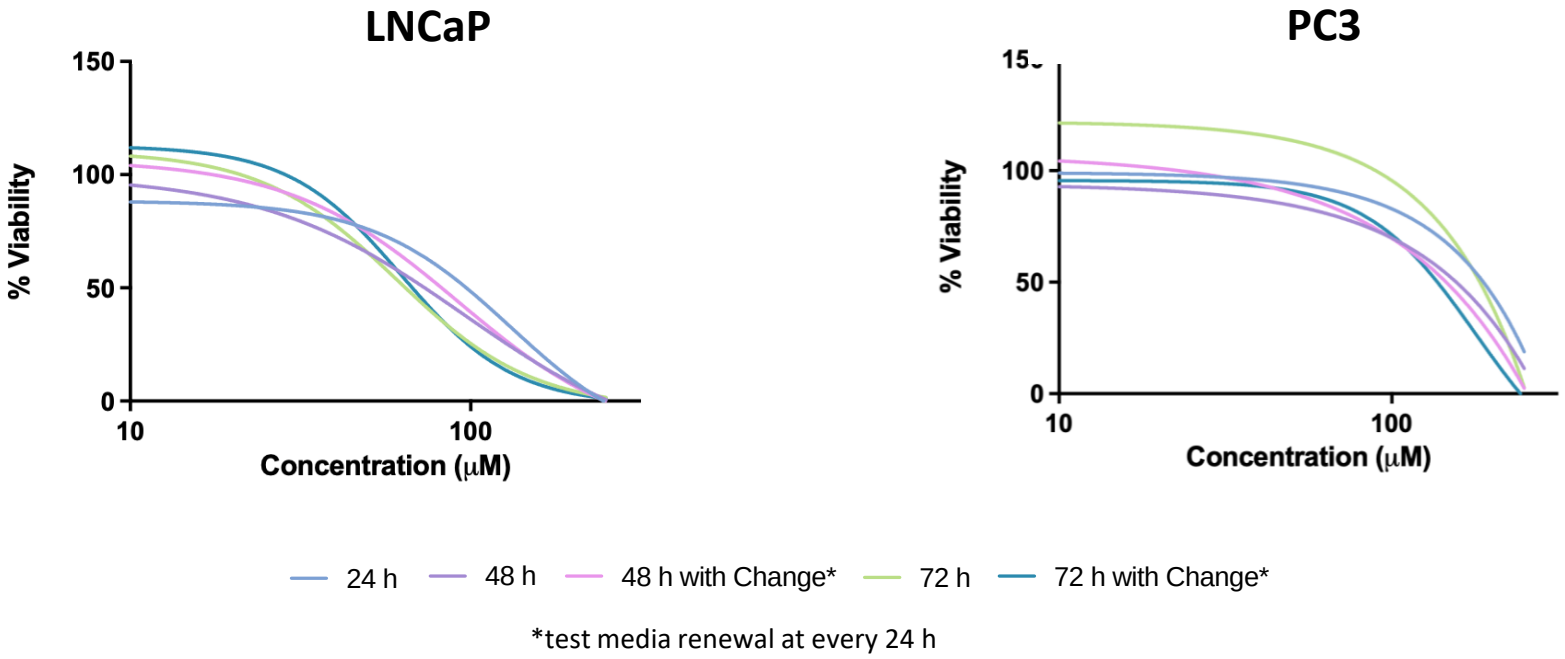


*test media renewal at every 24 h

Propranolol showed time and concentration dependent cytotoxicity

Results and Discussion

Propranolol



*test media renewal at every 24 h

Propranolol showed time and concentration dependent cytotoxicity

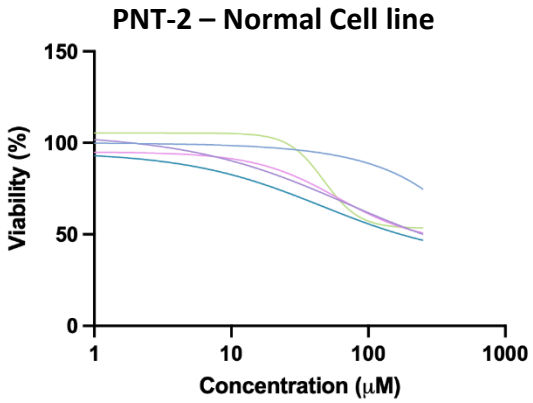
Results and Discussion

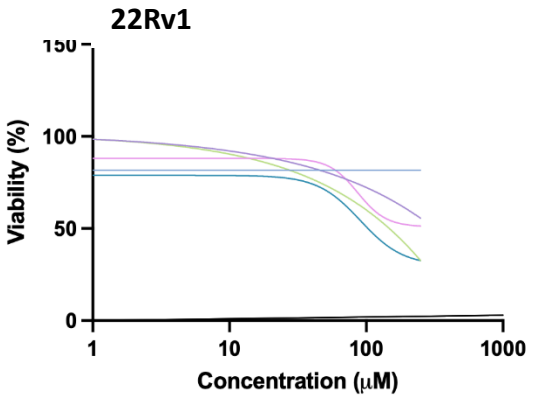
72 h LD_{50} (μM)	Carvedilol	Propranolol
PNT-2	17.211	108.953
22Rv1	**14.990**	**54.639**
LNCaP	27.328	64.366
PC3	**31.368**	**183.899**

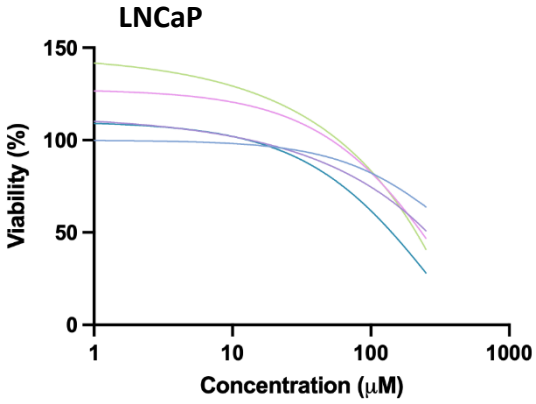
22Rv1 was the most sensitive cell line and PC3 was the most resistant

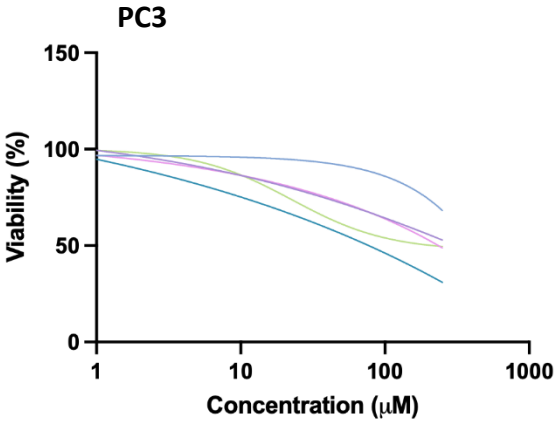
Results and Discussion

Cisplatin









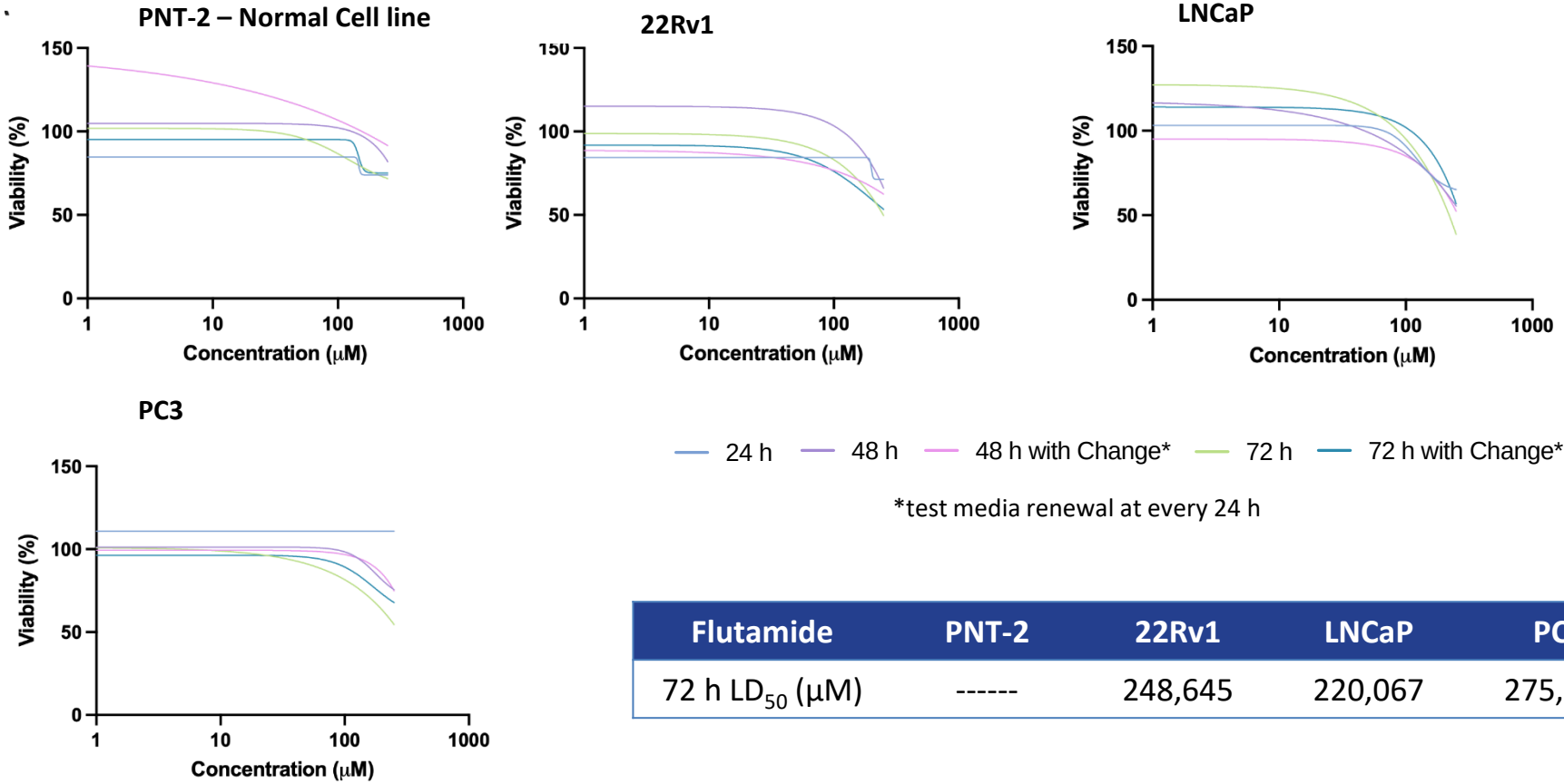
24 h 48 h 48 h with Change* 72 h 72 h with Change*

*test media renewal at every 24 h

Cisplatin	PNT-2	22Rv1	LNCaP	PC3
72 h LD_{50} (μM)	------	147.568	212.775	214.681

Results and Discussion

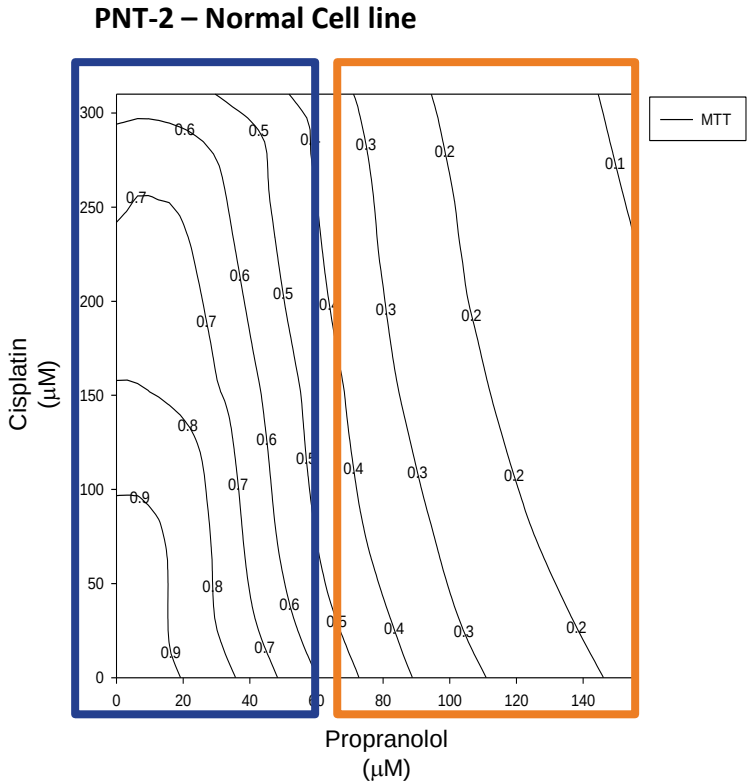
Flutamide



Flutamide	PNT-2	22Rv1	LNCaP	PC3
72 h LD_{50} (μM)	------	248,645	220,067	275,430

Results and Discussion

Combined Exposure – Propranolol and Cisplatin



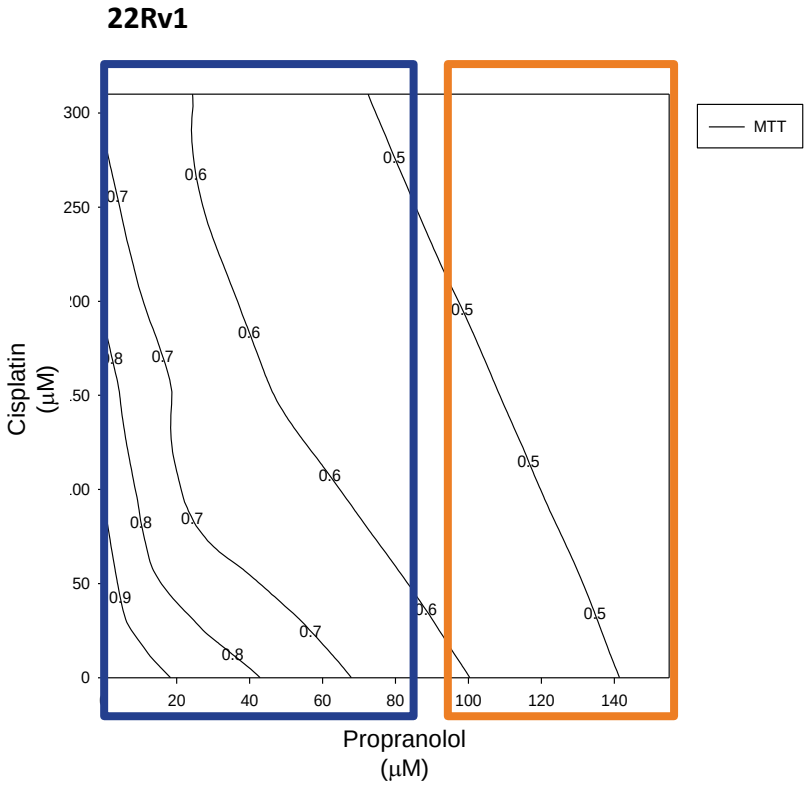
MixTox Model Dose ratio-dependent deviation	
a	2.149485
b	-3.829912

a > 0 → **Antagonism at lower concentrations of propranolol**

b < 0 → **Synergism at higher concentrations of propranolol**

Results and Discussion

Combined Exposure – Propranolol and Cisplatin



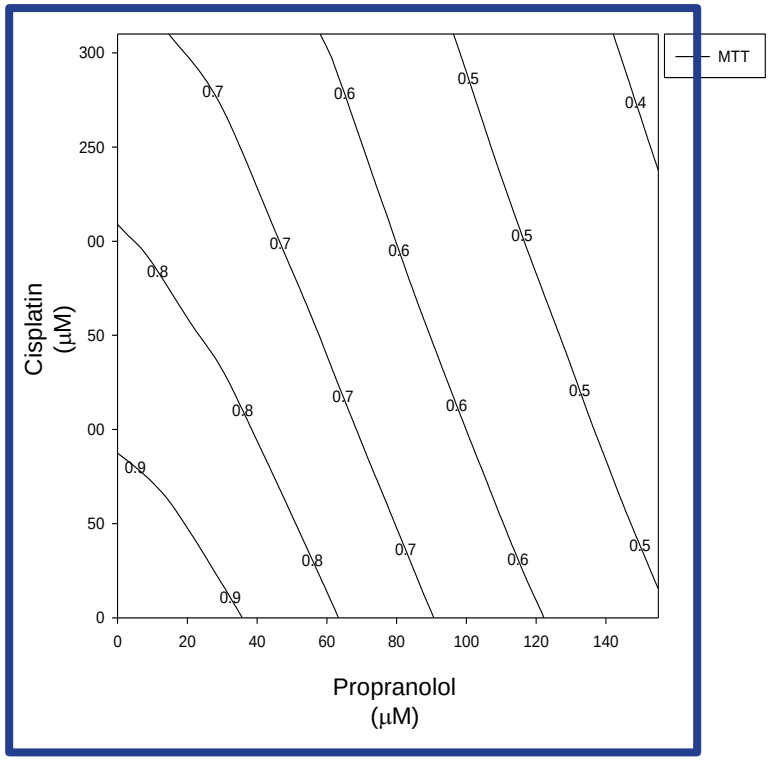
MixTox Model Dose level-dependent deviation	
a	-2.2778721
b	2.1004136

a < 0 → **Synergism at lower concentrations of propranolol**

b > 0 → **Antagonism at higher concentrations of propranolol**

Results and Discussion

PC3



MixTox Model
Independent Action

Antagonism

Conclusions

Non-selective β-Blockers (carvedilol and propranolol) showed higher cytotoxic effects than β1-Blockers (atenolol and metoprolol) in all cell lines.

Non-selective β-Blockers, β1-Blockers, Cisplatin and Flutamide cytotoxicity increased in a time-dependent manner.

22Rv1 was the most sensitive cell line to carvedilol, propranolol and cisplatin and PC3 the most resistant cell line.

The binary mixtures showed that at lower concentrations propranolol has a protective effect on PNT-2 (normal cell line), while for the same concentrations, the cytotoxic effects of cisplatin to the prostate cancer cell 22Rv1 was increased

Data suggest the potential role of propranolol on cancer treatment.

Acknowledgments

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