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Drug repurposing as an alternative in prostate cancer treatment

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

Leandro Cunha [1], Mónica Almeida [2], and Miguel Oliveira [2,*]

[1] Department of Biology, University of Aveiro, Campus Universitário de Santiago, 3810-193, Aveiro, Portugal
[2]Department of Biology & CESAM, University of Aveiro, Campus Universitário de Santiago, 3810-193, Aveiro, Portugal

* Corresponding author: migueloliveira@ua.pt

CESAM CENTRO DE ESTUDOS DO AMBIENTE E DO MAR
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Drug repurposing as an alternative in prostate cancer treatment

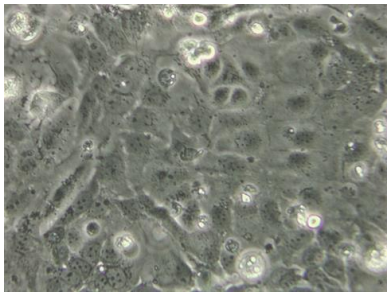
Pharmaceuticals

Sertraline
Carvedilol
5-Fluorouracil

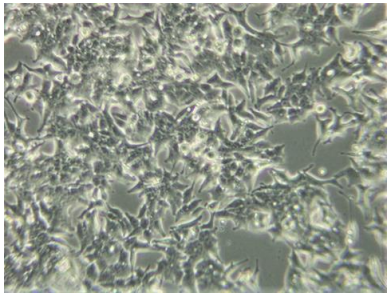
Combined Exposure

Carvedilol + 5-Fluorouracil
5-Fluorouracil + Sertraline

Cell lines



PNT-2
(Normal cell line)



22Rv1
(Cancer cell line)

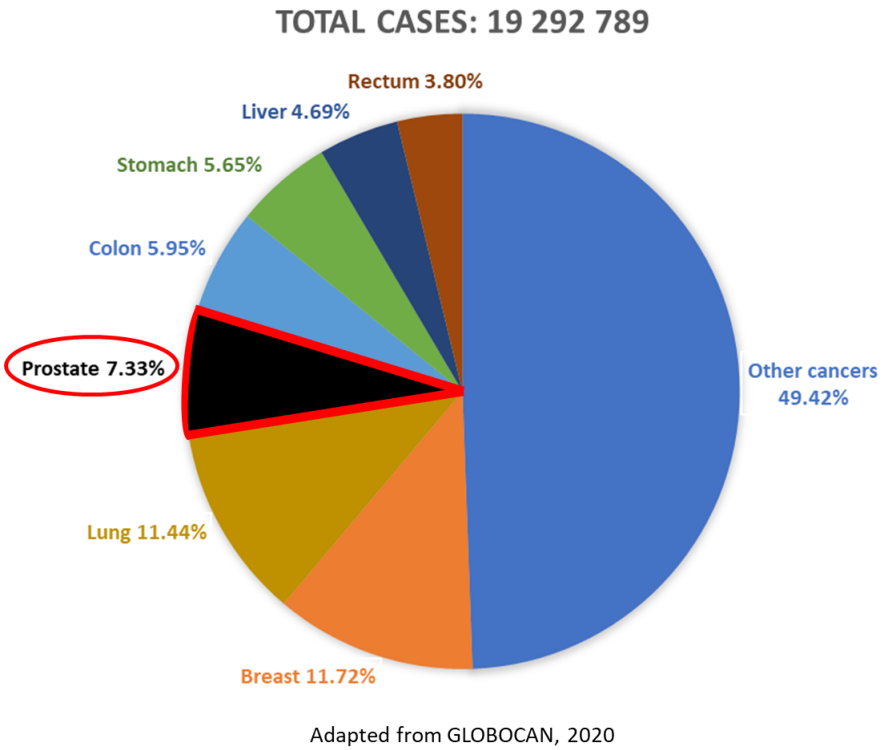
Effect

Cell viability

Abstract: Prostate cancer is the third most diagnosed cancer worldwide, and the second cause of cancer deaths in men. The currently available treatments are not always effective and may be associated with unwanted side effects. The process of developing new drugs is expensive and can take several years. Thus, drug repurposing emerges as an interesting alternative since it uses clinically studied and available drugs for a new clinical use. The present study aimed to explore the effects of a β-blocker (carvedilol), a selective serotonin reuptake inhibitor (sertraline) and an antimetabolite drug (5-fluorouracil), alone or in binary mixtures, on the cancer cell line (22Rv1) as well as on the normal prostate cell line (PNT-2) cell viability. Overall, the tested conditions demonstrated the ability of the drugs to induce toxic effects and allowed the estimation of median lethal concentrations. The cell line 22Rv1, compared to the normal cell line, was more sensitive to sertraline and 5-fluorouracil but more resistant to carvedilol. Data from combined exposures conditions demonstrated the potential value of these substances.

Keywords: cell viability, combined treatments, drug repurposing, prostate cancer

Introduction



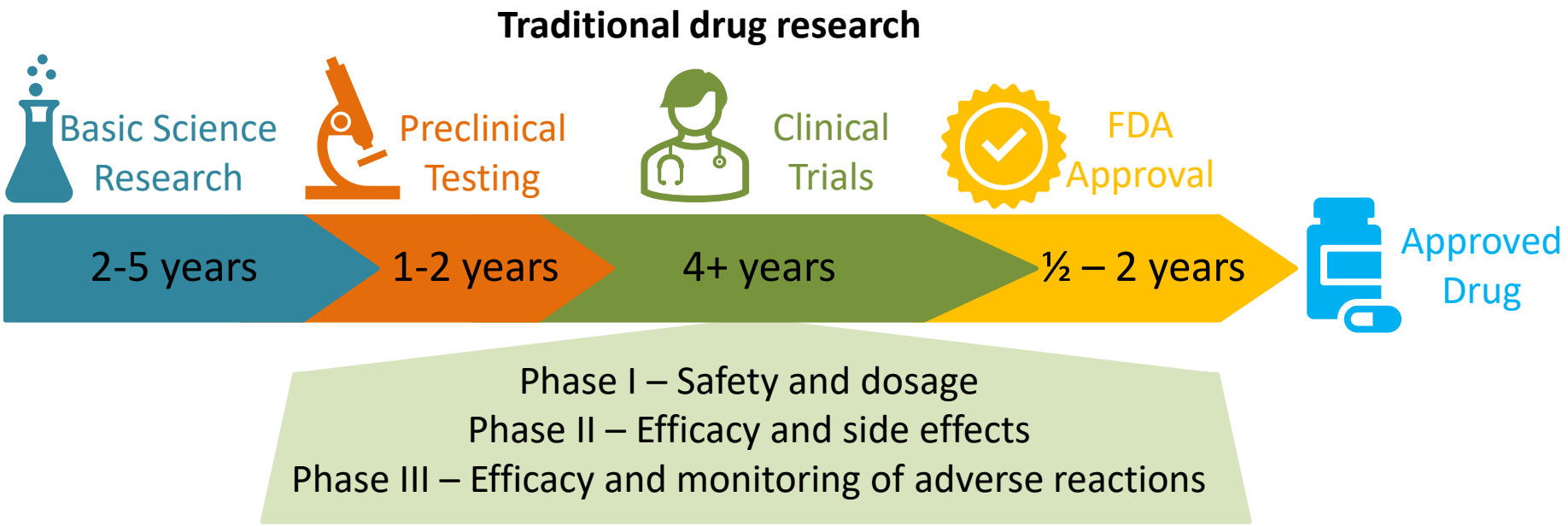
Adapted from GLOBOCAN, 2020

Available treatments for prostate cancer

- Active Surveillance
- Chemotherapy
- Focal Therapy
- Hormone Therapy
- Immunotherapy
- Nanotherapeutics
- Radiation Therapy
- Radical Prostatectomy

Available treatments — Limited efficiency → Requires → New approaches → Drug Repurposing

Introduction



Introduction

Non-cancer related drugs such as antidepressants (e.g., selective serotonin reuptake inhibitors (SSRI's)) and cardiovascular drugs have shown potential to fight cancer.

Antimetabolite

↓

Anticancer agent

↓

Possible interactions with

Antidepressants

↓

SSRI

↓

serotonin reuptake

↓

Associated with stimulatory effect on cancer cell proliferation, invasion, dissemination, and tumor angiogenesis

Cardiovascular drugs

↓

β-blocker

↓

β-adrenergic receptors

↓

Associated with mechanisms that trigger tumorigenesis, angiogenesis and tumor metastasis

Introduction

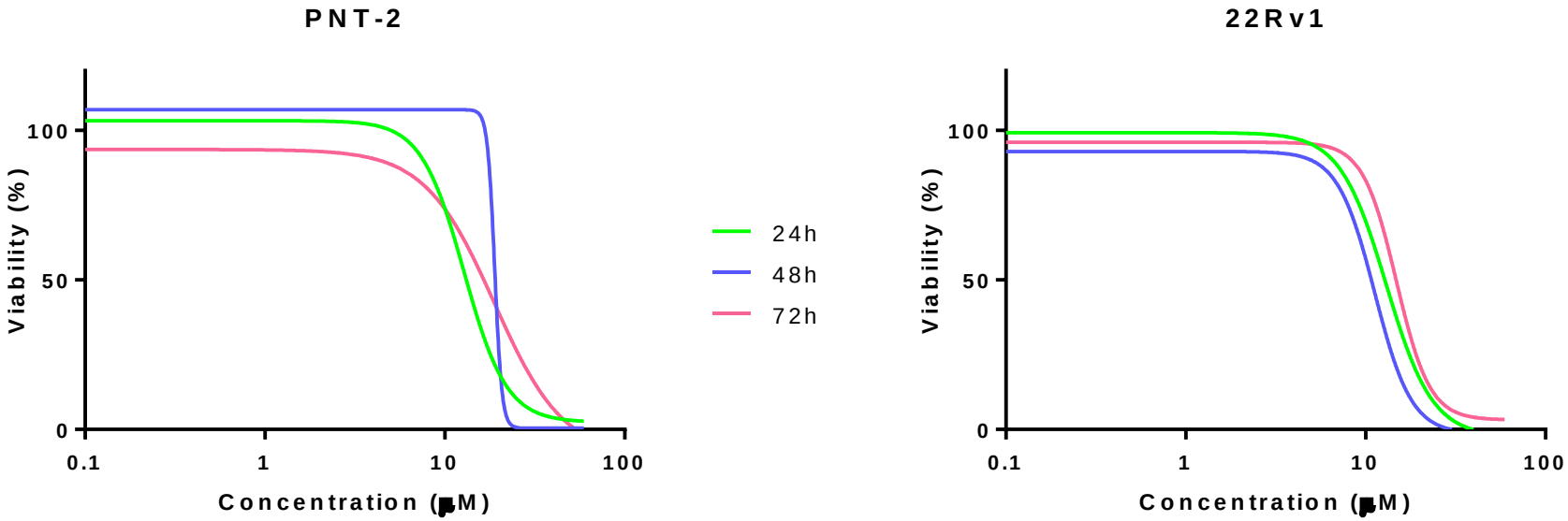
In this study:

The cytotoxicity of **carvedilol** (non-selective β-blocker), **sertraline** (selective serotonin reuptake inhibitor) and **5-fluorouracil** (antimetabolite) was assessed on **PNT-2** (normal prostate cell line) and on **22Rv1** (prostate cancer cell line).

Effects of **binary combinations** of carvedilol with 5-fluorouracil and sertraline with 5-fluorouracil were assessed on PNT-2 and 22Rv1.

Results and discussion

Sertraline

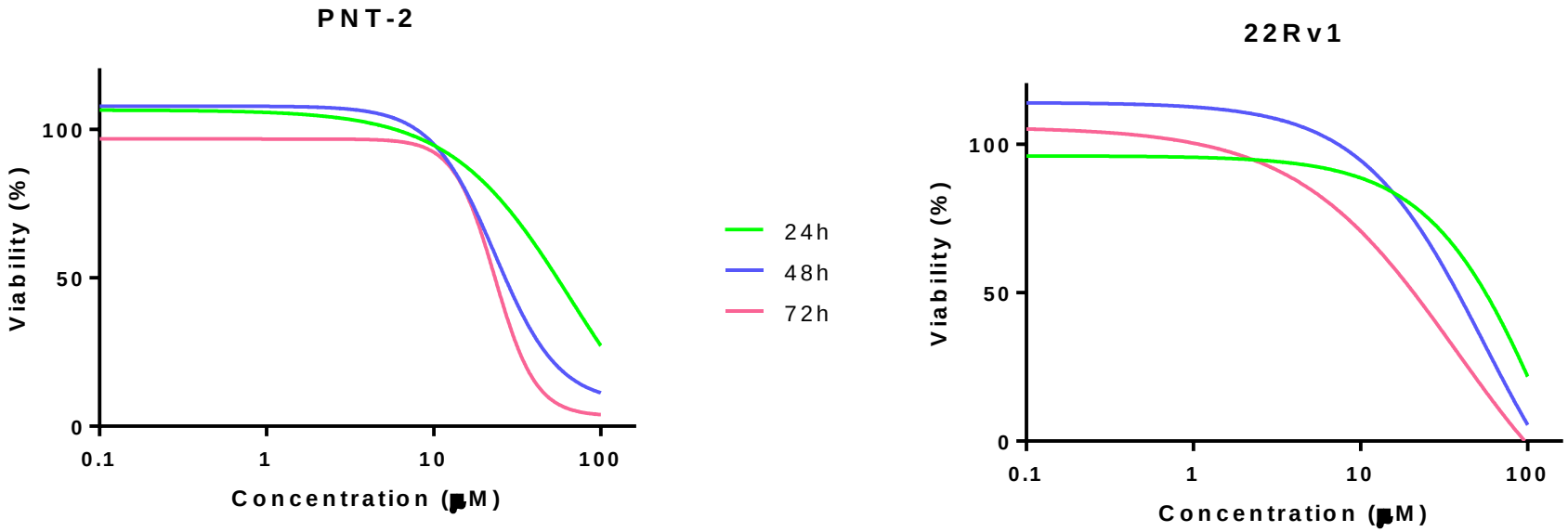


LC_{50}		LC_{50}	Time point
19.065	>	10.75878	48h

22Rv1 showed higher sensitivity toward sertraline

Results and discussion

Carvedilol

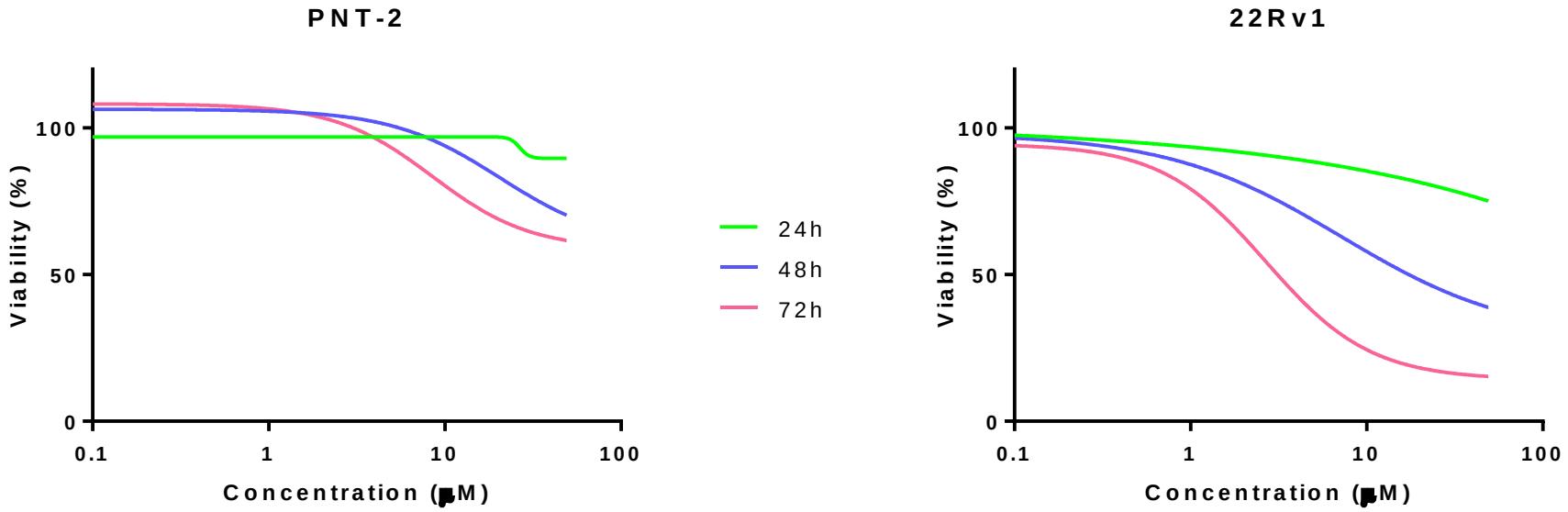


LC_{50}		LC_{50}	Time point
26.764	<	38.09203	48h

PNT-2 showed higher sensitivity toward carvedilol

Results and discussion

5-fluorouracil



LC_{50}		LC_{50}	Time point
-----	-----	17.345	48h

5-fluorouracil showed time and concentration dependent cytotoxicity

Tested concentrations did not allow estimation of LC_{50} for PNT-2

Results and discussion

Viability (%) of cells exposed to sertraline (0-19.07 µM) and 5-fluorouracil (0-50 µM)

PNT-2

5-fluorouracil µM \ Sertraline	0	4.77	9.53	14.3	19.07
0	100	135.03	88.41	11.55	1.20
12.5	74.58	103.42	78.29	15.84	1.65
25	65.92	84.83	69.94	16.17	1.42
37.5	63.74	83.44	65.58	21.06	2.40
50	72.01	78.32	66.33	23.40	3.39

22Rv1

5-fluorouracil µM \ Sertraline	0	4.77	9.53	14.3	19.07
0	100	105.75	71.16	25.94	3.25
12.5	61.71	67.83	60.71	17.76	1.41
25	55.18	47.49	29.67	4.75	1.86
37.5	53.99	49.09	21.31	3.36	0.74
50	50.74	35.21	9.21	2.94	0.16

<20 | >20 <40 | >40 <60 | >60 <80 | >80 <100 | >100

Results and discussion

Viability (%) of cells exposed to sertraline (0-10.76 µM) and 5-fluorouracil (0-17.345 µM)

PNT-2

5-fluorouracil µM	Sertraline 0	2.69	5.38	8.07	10.76
0	100	126.11	126.44	122.22	99.90
4.33625	106.77	131.53	131.05	120.44	107.27
8.6725	97.62	138.92	148.52	112.12	95.95
13.00875	91.89	119.80	101.63	104.88	83.09
17.345	78.57	105.10	93.97	91.70	91.87

22Rv1

5-fluorouracil µM	Sertraline 0	2.69	5.38	8.07	10.76
0	100	119.01	112.01	99.06	79.18
4.33625	96.86	100.45	104.89	88.66	63.96
8.6725	71.26	68.21	80.37	68.72	62.91
13.00875	71.71	72.00	69.45	63.68	57.17
17.345	64.99	66.15	73.56	66.45	57.13

<20 | >20 <40 | >40 <60 | >60 <80 | >80 <100 | >100

Results and discussion

Viability (%) of cells exposed to carvedilol (0-26.76 µM) and 5-fluorouracil (0-50 µM)

PNT-2

5-fluorouracil µM	Carvedilol 0	6.69	13.38	20.07	26.76
0	100	96.96	95.32	67.60	33.82
12.5	79.66	72.78	68.92	58.66	33.91
25	60.86	57.89	58.89	53.70	34.61
37.5	53.19	55.88	49.84	42.19	30.81
50	43.82	44.10	46.88	46.00	29.22

22Rv1

5-fluorouracil µM	Carvedilol 0	6.69	13.38	20.07	26.76
0	100	79.84	76.95	61.17	37.60
12.5	67.52	54.29	50.32	43.33	29.63
25	57.59	52.60	49.25	41.28	25.29
37.5	56.53	48.34	39.53	31.49	18.04
50	50.64	51.33	44.61	36.47	21.60

<20 | >20 <40 | >40 <60 | >60 <80 | >80 <100 | >100

Results and discussion

Viability (%) of cells exposed to carvedilol (0-38.09 µM) and 5-fluorouracil (0-17.345 µM)

PNT-2

5-fluorouracil µM	Carvedilol 0	9.52	19.05	28.57	38.09
0	100	110.25	89.71	53.37	32.49
4.33625	97.90	108.90	94.10	47.68	30.88
8.6725	87.53	97.14	75.98	54.19	31.33
13.00875	78.97	78.84	74.11	50.88	33.68
17.345	83.52	78.57	69.19	48.58	33.79

22Rv1

5-fluorouracil µM	Carvedilol 0	9.52	19.05	28.57	38.09
0	100	79.33	70.27	48.65	20.07
4.33625	80.90	69.17	61.08	50.52	21.83
8.6725	71.68	67.22	50.48	38.95	17.80
13.00875	62.77	61.68	59.72	42.84	19.83
17.345	69.12	59.56	59.17	40.27	18.33

<20	>20 <40	>40 <60	>60 <80	>80 <100	>100

Conclusions

Prostate cancer cell line 22Rv1 is more sensitive to sertraline and 5-fluorouracil than the normal cell line PNT-2.

However, 22Rv1 is more resistant to carvedilol than PNT-2 cell line.

Binary mixtures indicate that PNT-2 cell line is more resistant to the combined treatments of the tested drugs than 22Rv1 cell line.

The lower concentration mixture of sertraline with 5-fluorouracil showed promising results, maintaining high viability for PNT-2 normal cell line while having a respectable decrease in 22Rv1 cancer cell line.

Acknowledgments

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