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Potential Role of β-blockers and lipid regulators in lung cancer treatment: an *in vitro* approach

Chaired by **Dr. Alfredo Berzal-Herranz** and **Prof. Dr. Maria Emília Sousa**

pharmaceuticals MDPI

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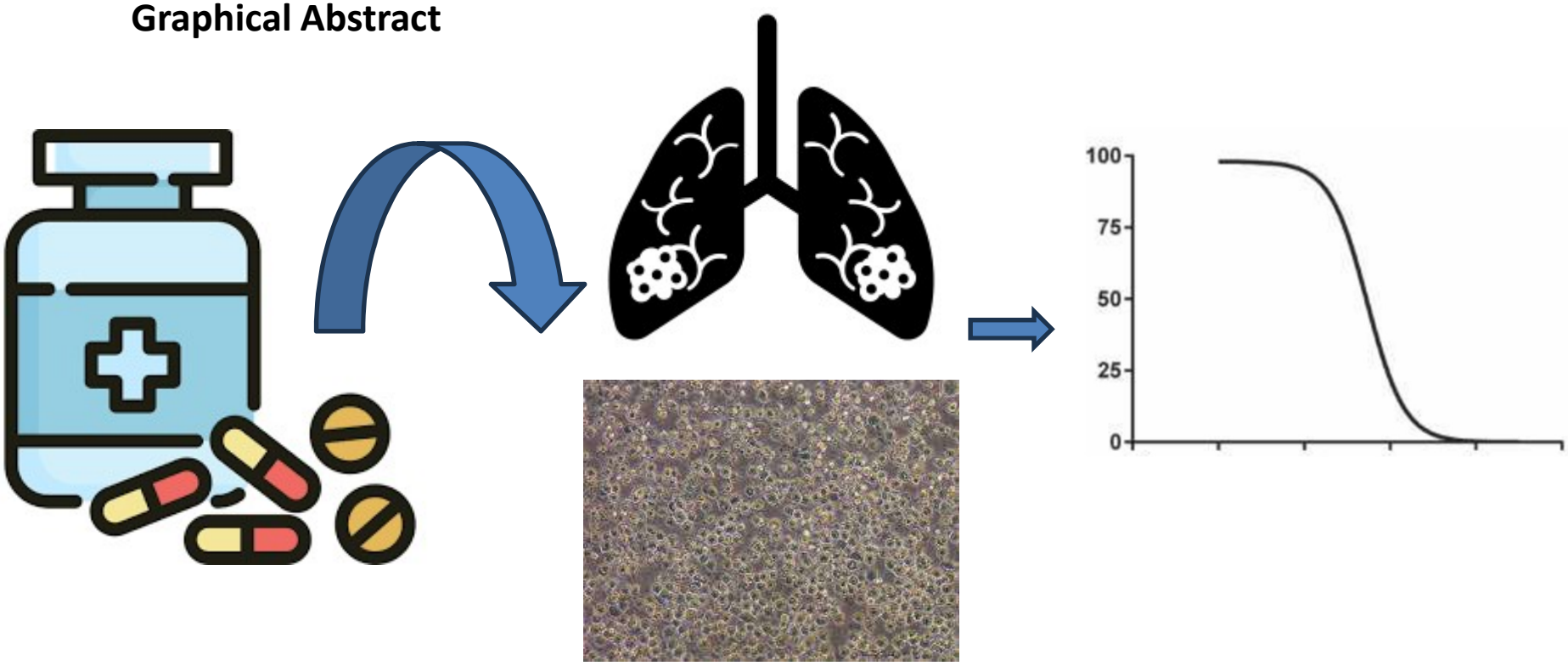
Potential Role of β-blockers and lipid regulators in lung cancer treatment: an in vitro approach

Graphical Abstract

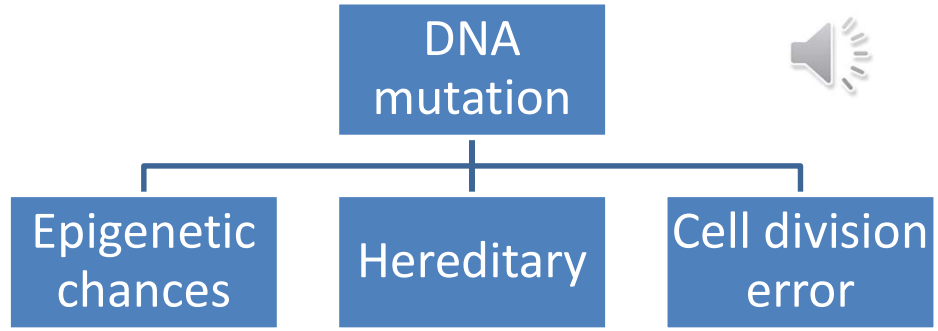


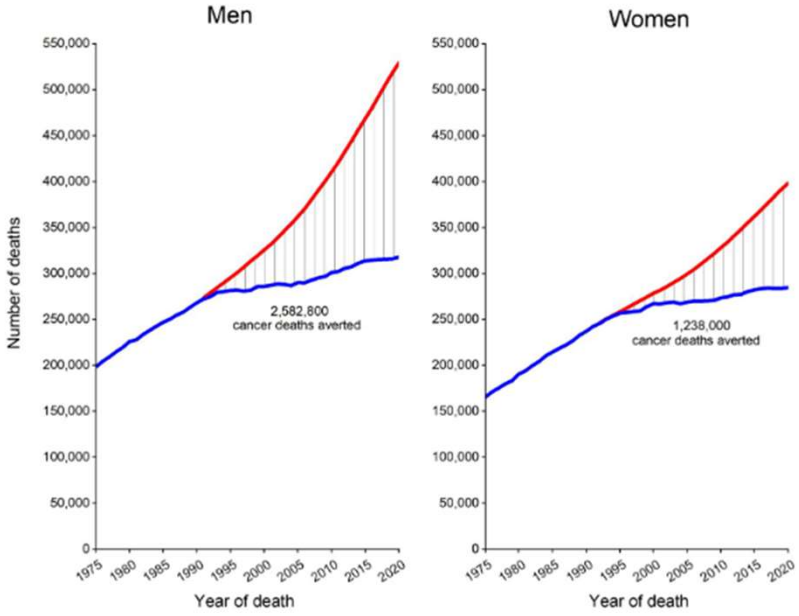
Abstract:
Lung cancer is the second most common type of cancer, affecting more than two million people. The available treatments show limited effectiveness and undesirable side effects, thus, there is a huge demand for more effective treatments. The use of drugs already on the market has been proposed as a potential valuable approach. The aim of this study was to test the potential use of β-blockers, atenolol and metoprolol, and the peroxisome proliferator-activated receptor alpha (PPAR-α) receptor agonists, fenofibrate and gemfibrozil as coadjuvant in the treatment of this pathology. Thus, non-small cell lung cancer cell lines, A549 and H460, were exposed to different concentrations of β-blockers (500, 250, 125, 62.5, 31.25, 15.625 and 7.8125 µM) and PPAR-α receptor agonists (25, 12.5, 6.25, 3.125, 1.563, 0.781 and 0.391 µM). Metabolic viability was assessed by Resazurin and MTT viability assay at three different time points, 24, 48 and 72 hours. Atenolol and metoprolol did not demonstrate toxicity towards both cell lines in the tested concentrations and time-points. Gemfibrozil demonstrated limited toxicity towards both cell lines, with decreases of 20% of cellular viability at the maximum concentration tested at 24 hours and Fenofibrate showed toxicity only towards H460 with a calculated LC50 of 20.6 µM. Therefore, Fenofibrate is a strong candidate to act as coadjuvant in the treatment of non-small cell lung cancer. Further studies are necessary to understand the impact of lipid regulators in the treatment of lung cancer.

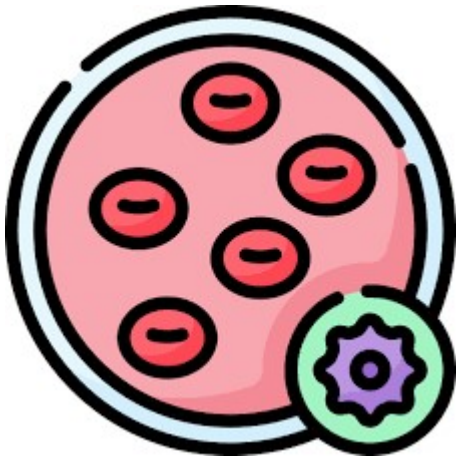
Keywords: 3 to 5 keywords in alphabetical order and separated by semi colons

Introduction

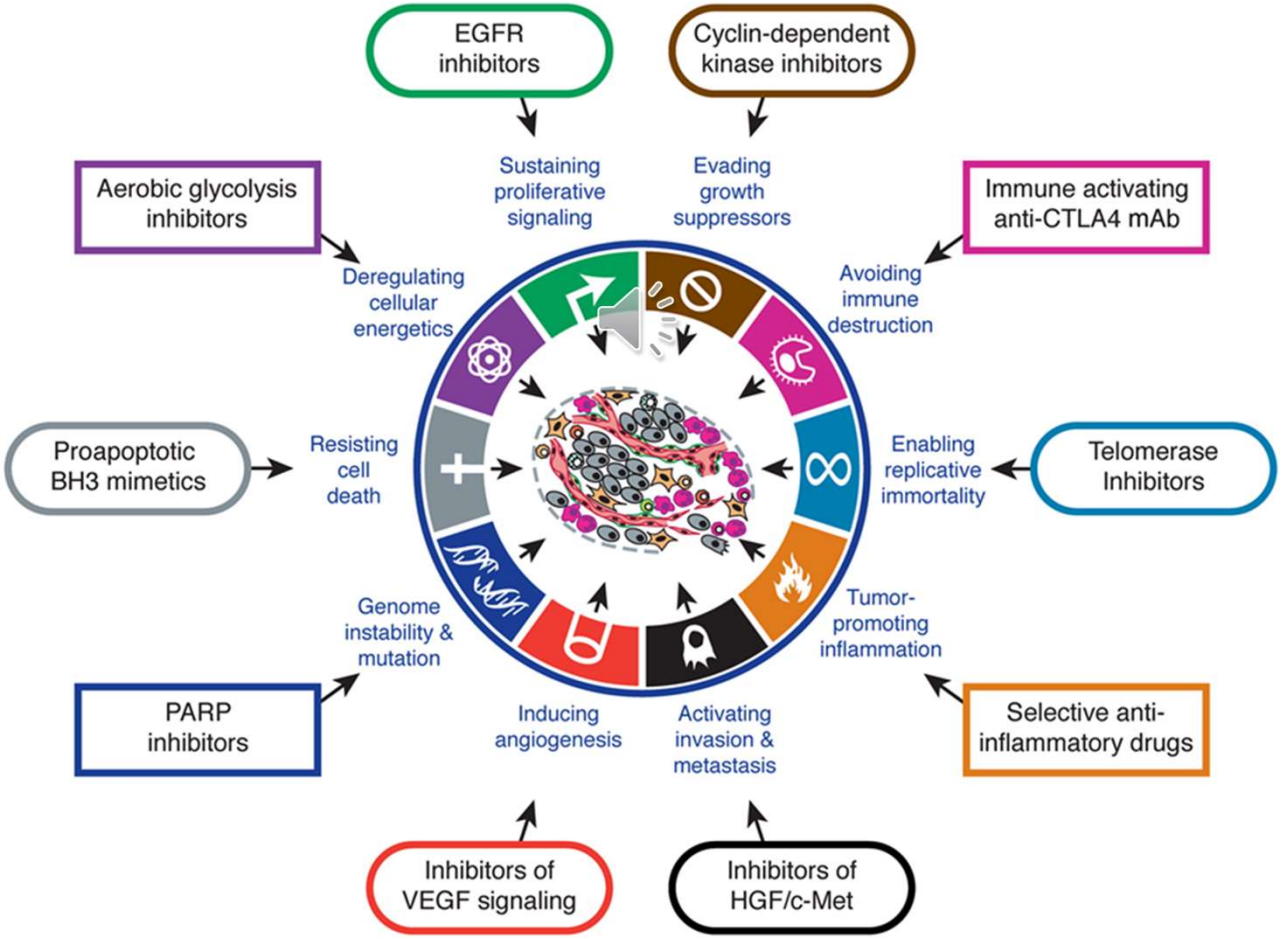
Cancer



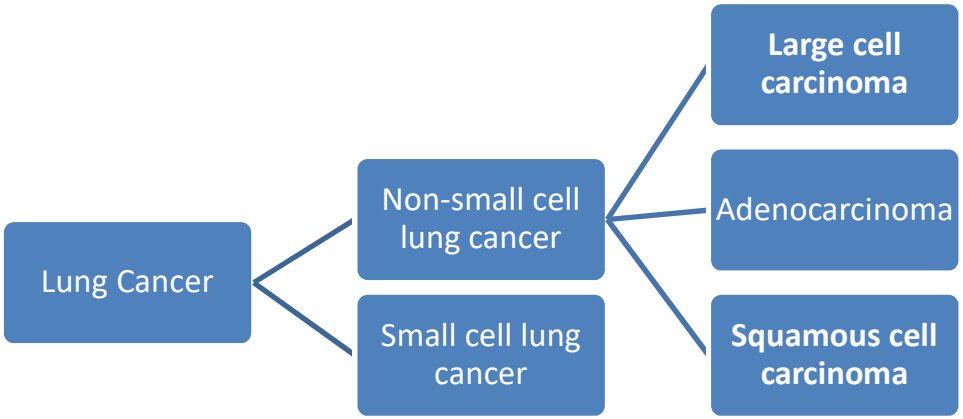




Hallmarks of cancer



Lung Cancer

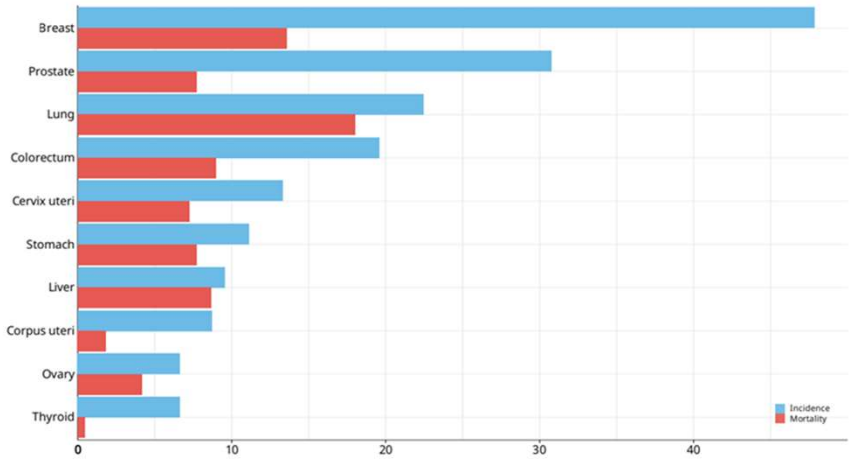


TREATMENT

Surgery

Chemotherapy, radiation therapy

Targeted therapy



Beta-adrenergic system

α

1
- Muscles contraction

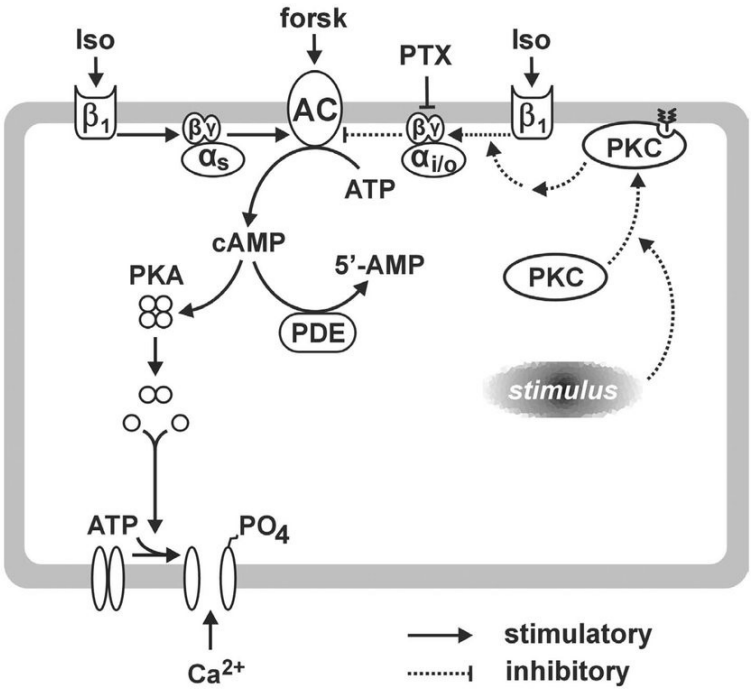
2
- Pre-synaptic

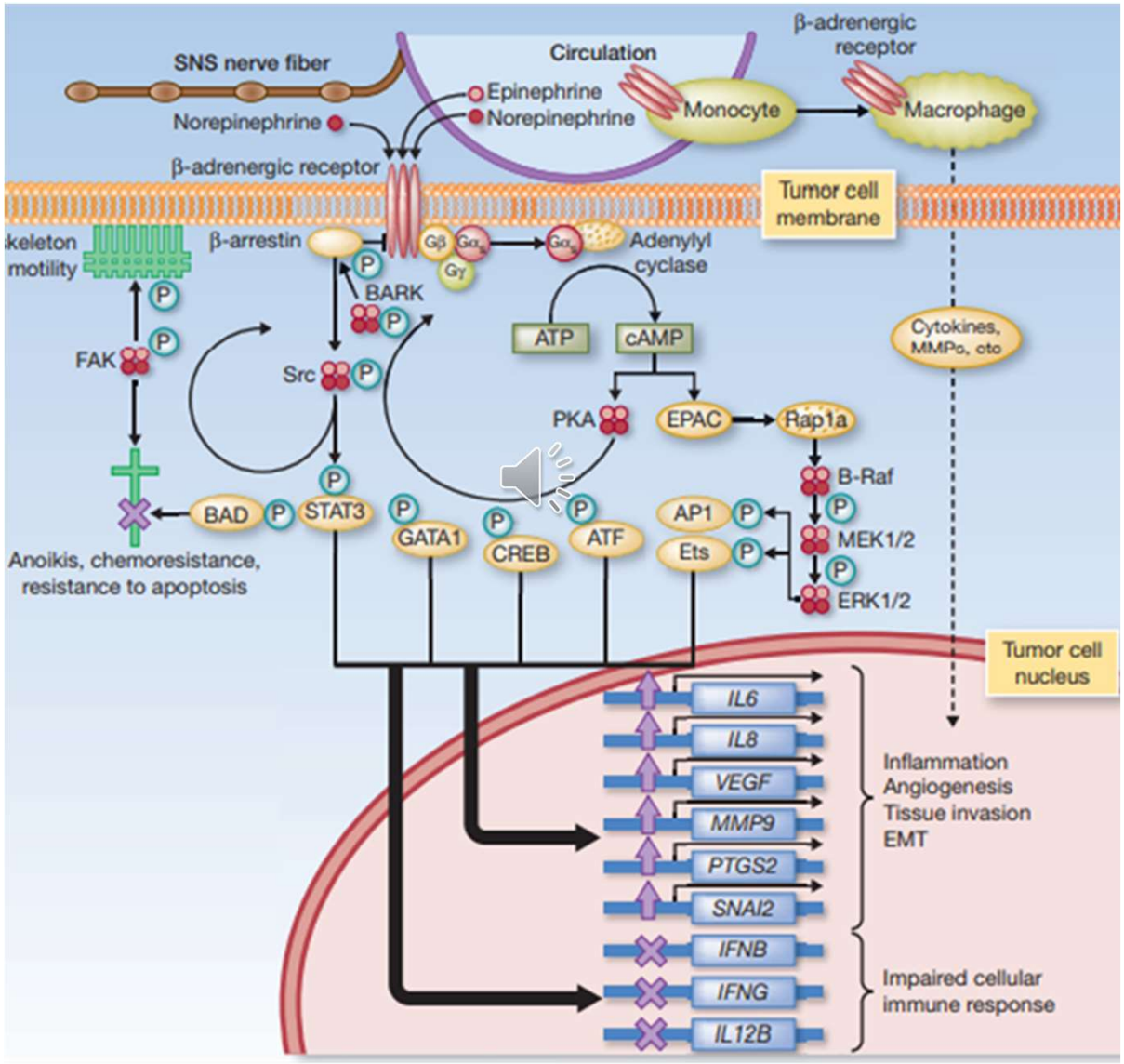
β

1
- Stimulates heart rate

2
- muscle relaxation

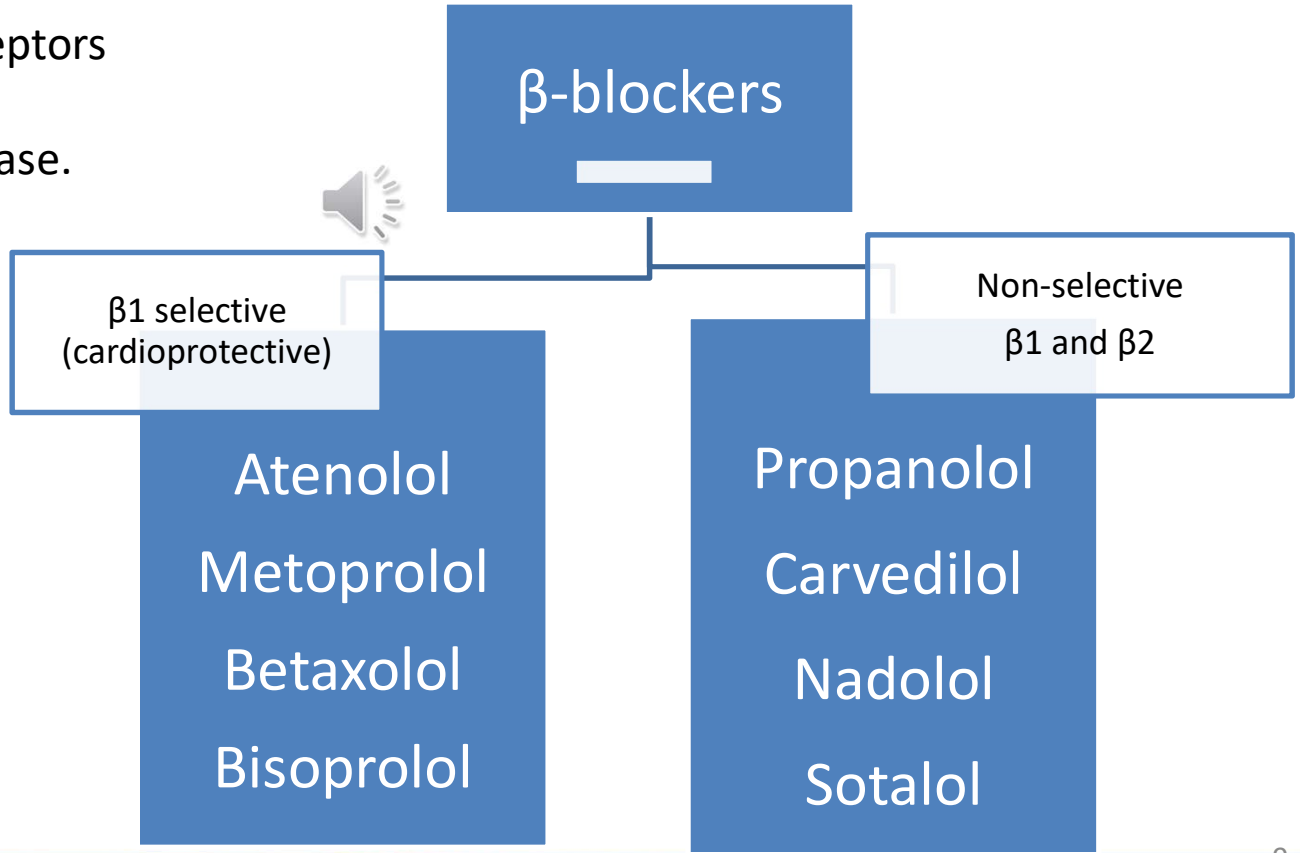
3
- lipolysis




β-adrenergic receptor
SNS nerve fiber
Circulation
Epinephrine
Norepinephrine
Monocyte
Macrophage
Norepinephrine
β-adrenergic receptor
Tumor cell membrane
β-arrestin
Adenylyl cyclase
BARK
ATP
cAMP
Cytokines, MMPs, etc
FAK
Src
PKA
EPAC
Rap1a
B-Raf
BAD
STAT3
GATA1
CREB
ATF
AP1
Ets
MEK1/2
ERK1/2
Anoikis, chemoresistance, resistance to apoptosis
Tumor cell nucleus
IL6
IL8
VEGF
MMP9
PTGS2
SNAI2
IFNB
IFNG
IL12B
Inflammation
Angiogenesis
Tissue invasion
EMT
Impaired cellular immune response

Beta-blockers

- Antagonists of the β-receptors
- Selectivity
- Prescribed for heart disease.



Beta-Blockers and cancer

Table1 -Clinical evidence of beta-blockers and cancer treatment

Lung cancer	Reduces risk of mortality, less distant metastases, late onset of the disease
Prostate cancer	Prolonged survival and reduction of distant metastases
Breast cancer	Reduces the rate of metastasis development

(H.H. et al., 2014), (H. M. Wang et al., 2013), (Powe et al., 2010)

PPAR Receptors

PPAR-α

Main tissue expression:
Tissues exhibiting high carbolic rates of fatty acids (mainly liver and skeletal muscle)

Lipid catabolism and homeostasis
Control of inflammatory processes and vascular integrity

PPAR-β

Tissue expression:
Ubiquitous, but the biggest expression is in the gastrointestinal tract (esophagus, liver, intestines) kidneys, and skeletal muscle

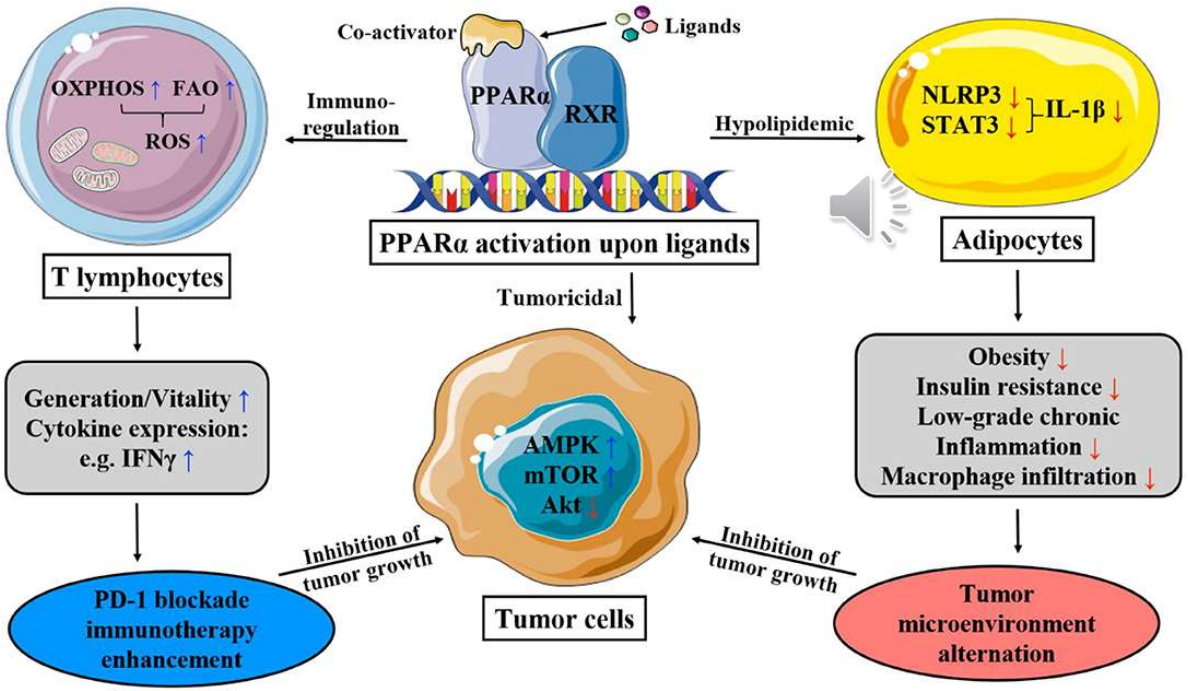
Responsible for insulin sensitivity and glucose homeostasis

PPAR-γ

Main tissue expression:
Adipose tissue (white and brown)
Other tissues:
Intestines, liver, kidneys, retina, immunologic system (bone marrow, lymphocytes, monocytes, and macrophages), trace amounts in muscles

Glucose homeostasis and lipid storage

PPAR-α and cancer



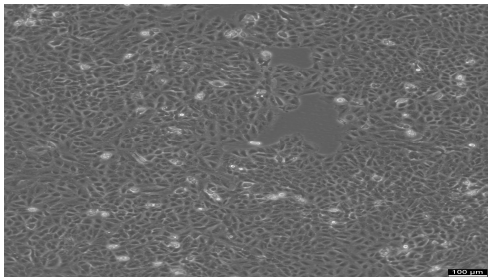
- Inhibition of angiogenesis
- Prioritization of FAO to glycolysis and disruption of the balance of glucose and lipid metabolism to inhibit ATP production
- Accumulation of ROS and mitochondrial damage

Table 2- Clinical evidence of PPAR-α agonist and cancer

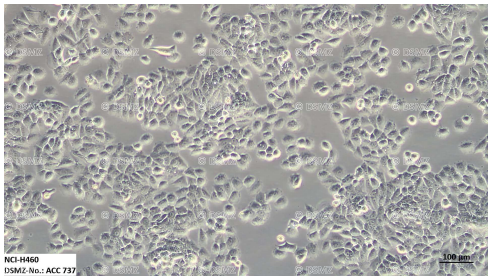
Oral cancer	Agonist	Fenofibrate	Regulating the gene expression of mitochondrial energy metabolism
			Restraining the process of preneoplastic lesion to oral squamous cell carcinoma
Brest cancer	Agonist	Fenofibrate	Reducing the phosphorylation levels of Akt/NF-κB and augmenting chemosensitivity when combined with paclitaxel
		Clofibrate	Regulating inflammatory, lipogenic pathways, and expression of genes involving FAO
Lung cancer	Agonist	Ave8134	Reducing the production of AA-derived EETs and promoting the levels of 11-HETE
		Fenofibrate	Arresting G1 cell cycle, restraining NF-κB activity and ERK signaling pathway

(Tan et al., 2021)

Material and methods



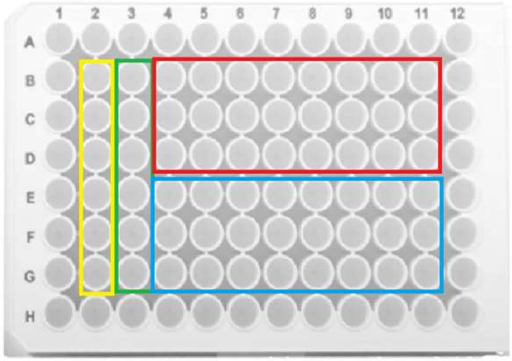
A549



H460

Atenolol and Metoprolol: 500; 250; 125; 62.5; 31.25; 15.625 e 7.8125 µM

Gemfibrozil and Fenofibrate: 25; 12.5; 6.25; 3.125; 1.563; 0.781; 0.391 µM

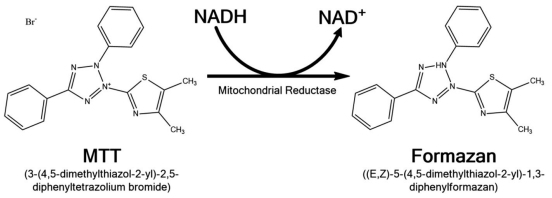


Control

Control with cell

Atenolol/Gemfibrozil

Metoprolol/Fenofibrate



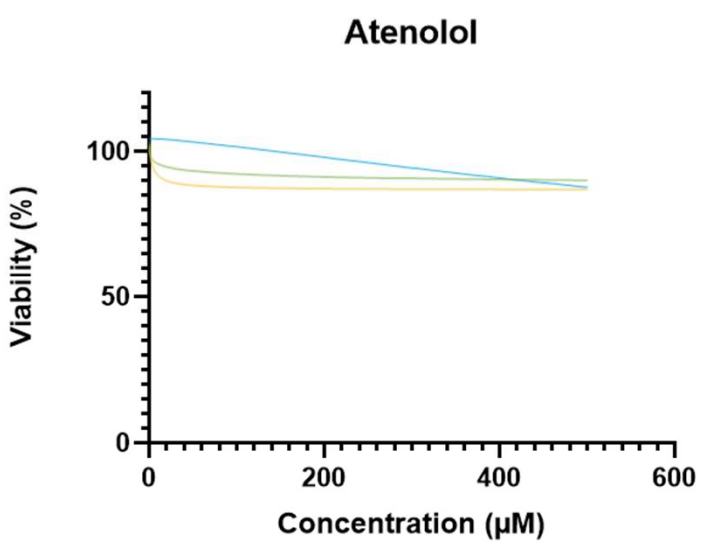
Prism

Results and discussion

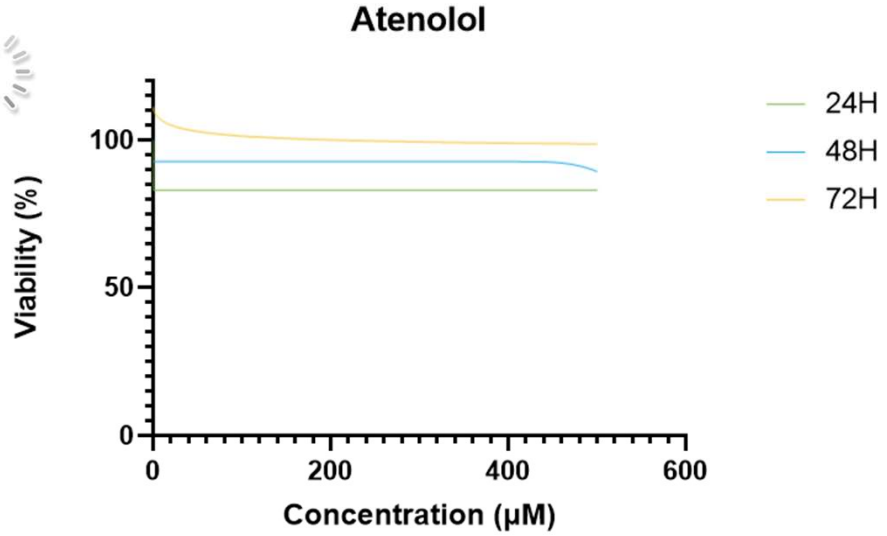
No cytotoxicity

Atenolol

A549



H460



Metoprolol

No cytotoxicity

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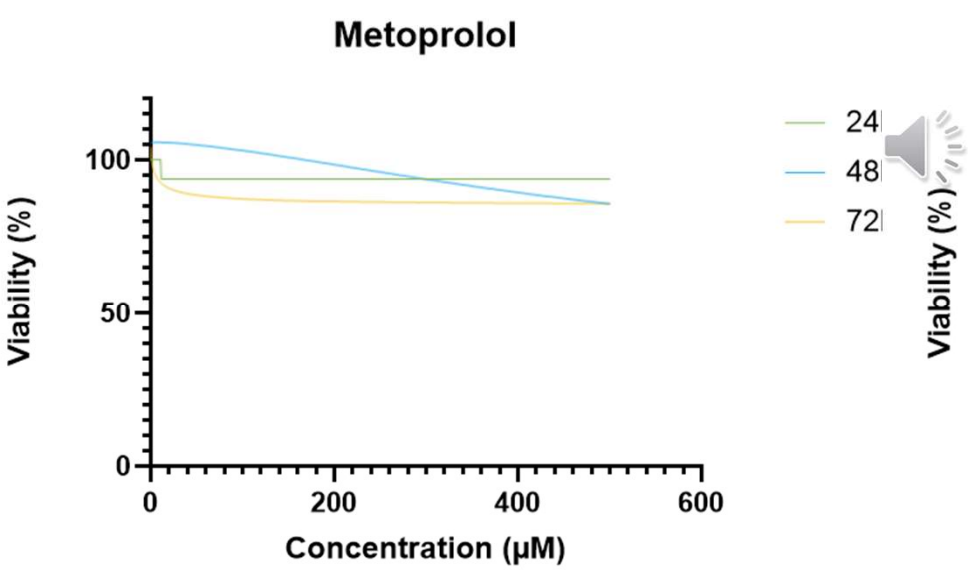
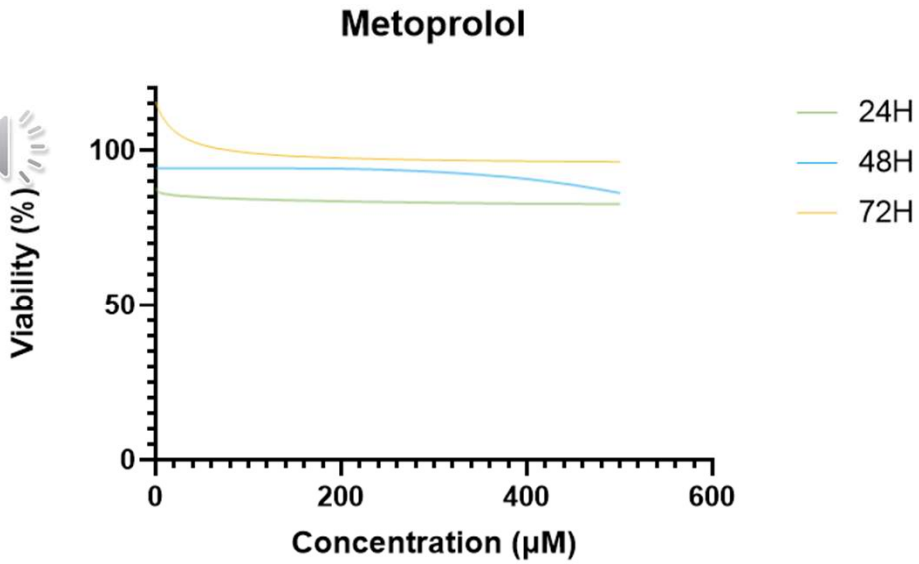


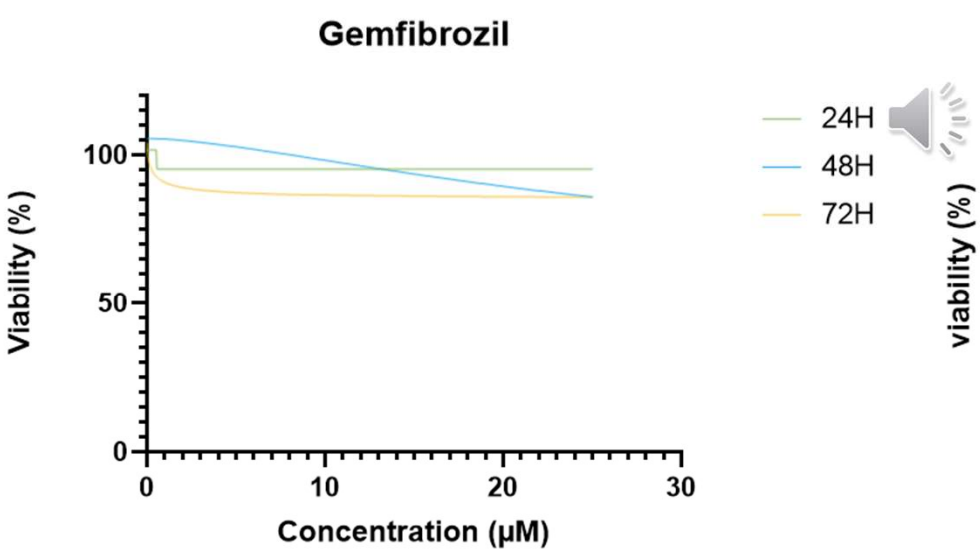
H460



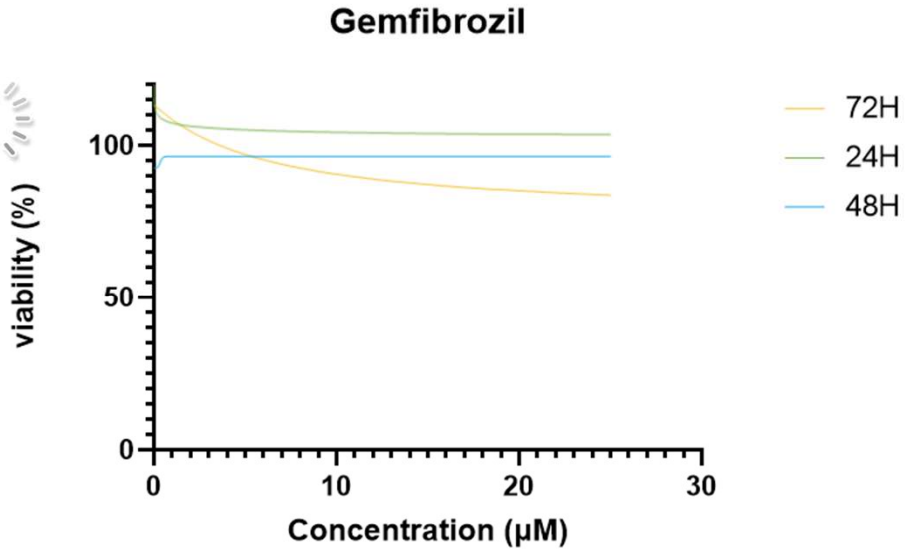
Gemfibrozil

Low cytotoxicity, no significant effect

A549

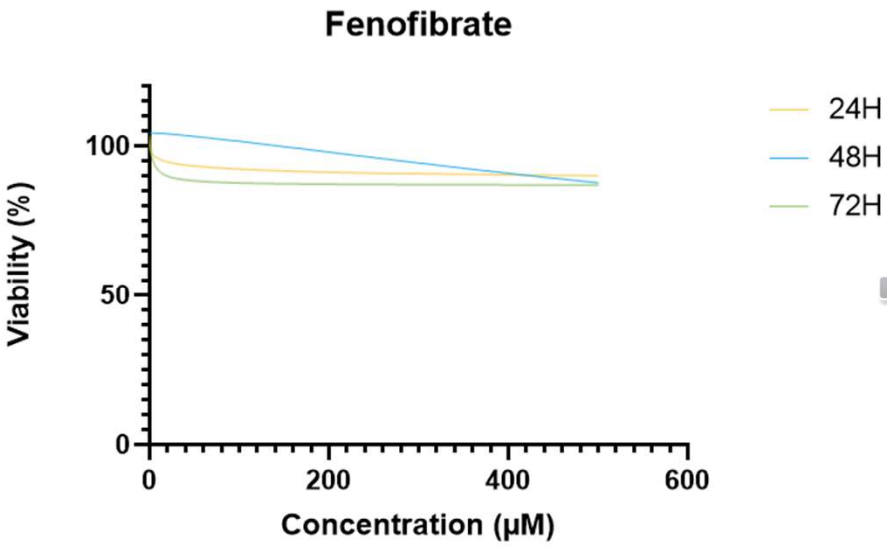


H460

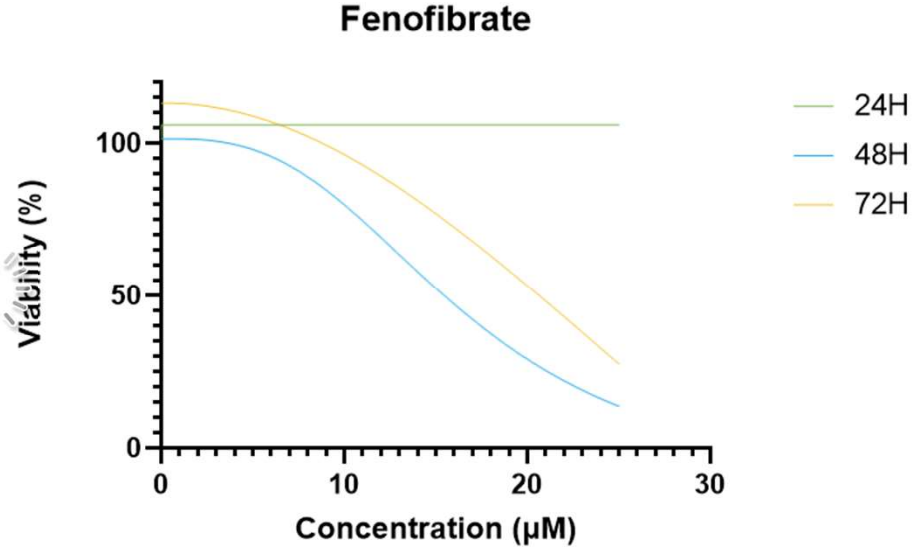


Fenofibrate

A549



H460



A549			
	24H	48H	72H
EC50 (μM)	_	_	_
EC10 (μM)	_	19.31	1.361

	24H	48H	72H
EC50 (μM)	_	15.464	20.651
EC10 (μM)	_	7.747	11.801

Conclusions

- The viability of A549 cells was not affected by any of the studied compounds
- Fenofibrate shows cytotoxicity towards H460 cells at low concentrations
- Future studies using combinations should be performed

Acknowledgments:

Thank you for your attention!

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fct Fundação para a Ciência e a Tecnologia