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Tamoxifen bisphenol: a modulator of ERβ in estrogen receptor-positive breast cancer

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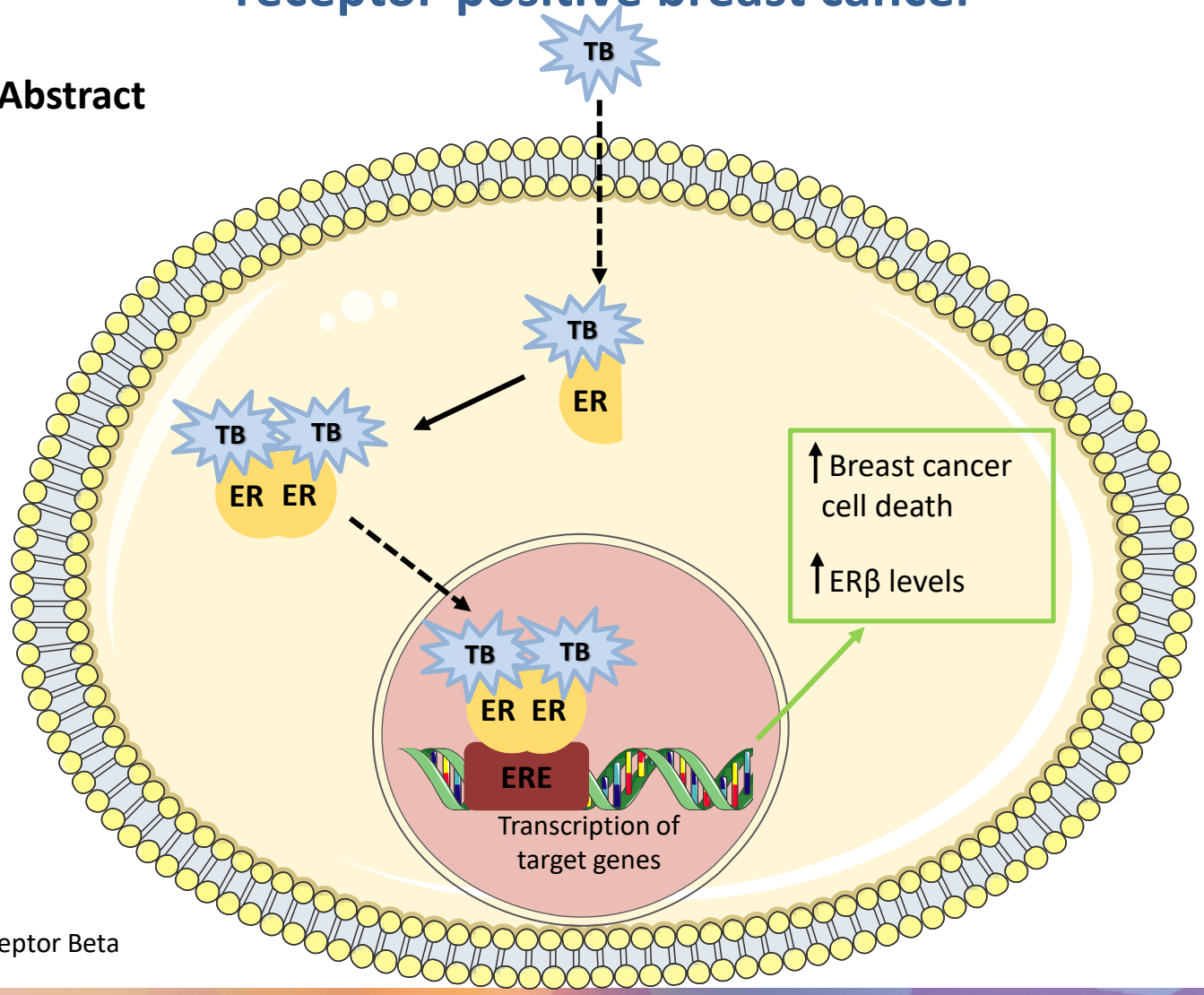
Tamoxifen bisphenol: a modulator of ERβ in estrogen receptor-positive breast cancer

Graphical Abstract



Abstract

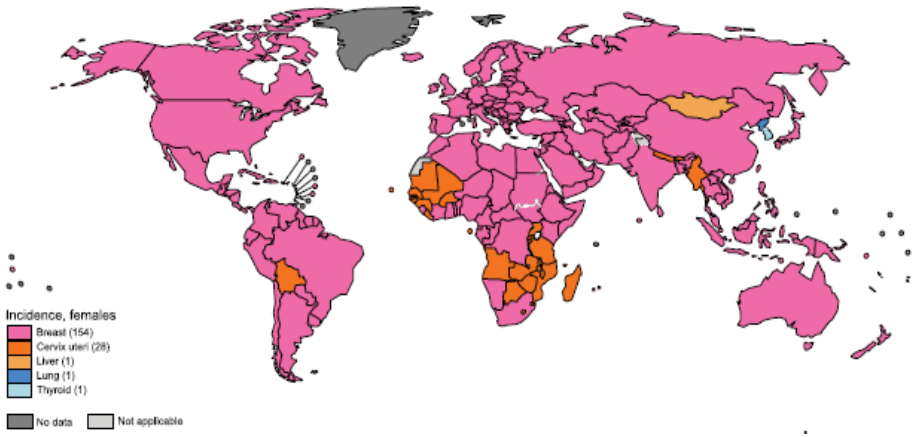
Breast cancer is the main cause of cancer-related death in women worldwide, being estrogen receptor-positive (ER^+) the most common subtype. In this type of cancer, while ERα has pro-survival effects, ERβ displays anti-proliferative actions, counteracting ERα effects. Thus, ERβ modulators may represent a great advantage for breast cancer treatment. Considering that Tamoxifen Bisphenol (TAM-Bis), a tamoxifen metabolite, can act as an ERα antagonist, our goal is to investigate whether this compound can also modulate ERβ. Through molecular docking analysis**,** it was addressed the ability of TAM-Bis to bind to ERβ. HFF-1 and MCF-7aro cells were used to evaluate the effects of TAM-Bis. To confirm the involvement of ERβ, the down-regulator PHTPP was used. The effects of TAM-Bis on ERβ protein levels were also investigated. Molecular docking results pointed that TAM-Bis can bind to ERβ. Moreover, this compound only decreased the viability of breast cancer cells, MCF-7aro, being this behavior reverted by PHTPP. In addition, TAM-Bis induced an up-regulation of ERβ. Our results clearly demonstrated that, besides being an ERα antagonist, TAM-Bis is an ERβ up-regulator. This is very favorable for better prognosis, since ERβ inhibits the transcriptional activity of ERα and decreases the sensitivity of breast cancer cells to estrogens, impairing tumor growth.

Keywords: Estrogen receptor-positive breast cancer; Estrogen receptor beta; Molecular docking

Introduction

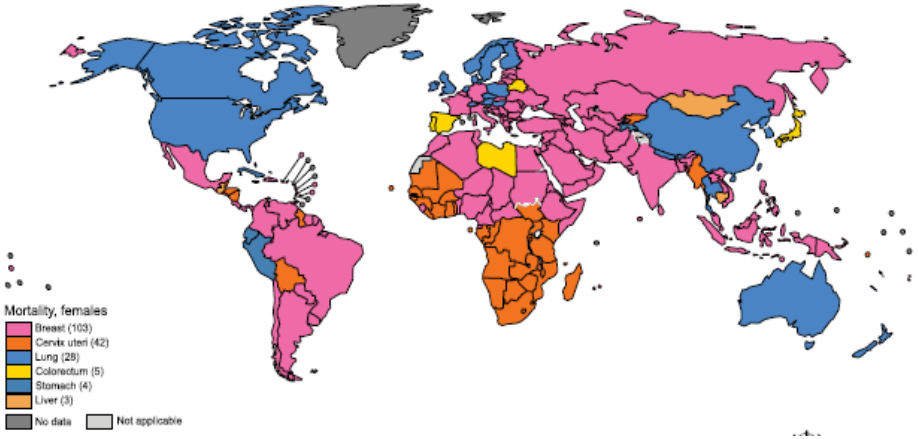
Breast cancer
2018

Incidence



New cases/2018: 2 088 849

Mortality

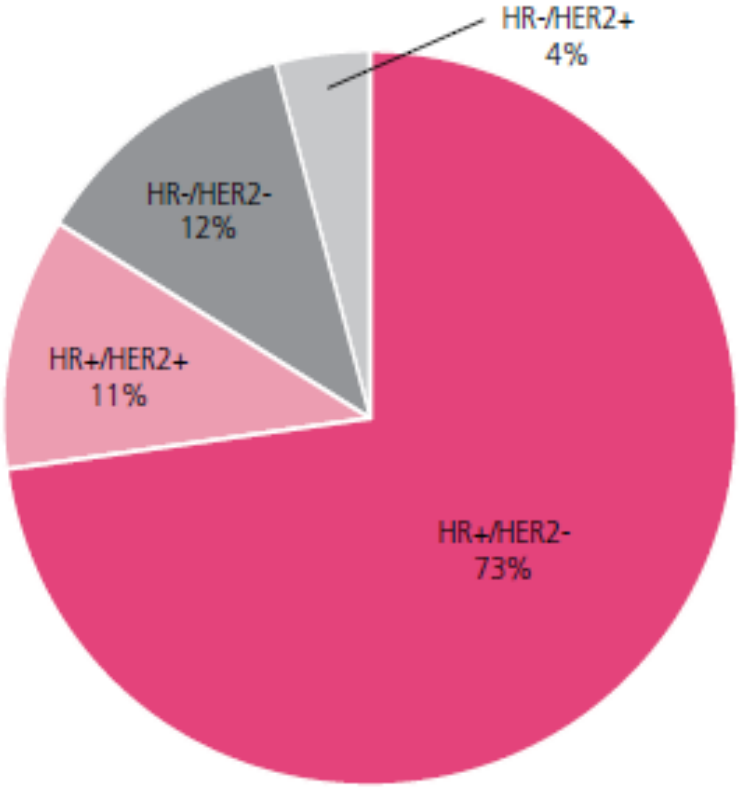


Deaths/2018: 626 679

Bray F. *et al* (2018) CA CANCER J CLIN, 68:394–424
The Global Cancer Observatory, March 2019

Introduction

Breast cancer



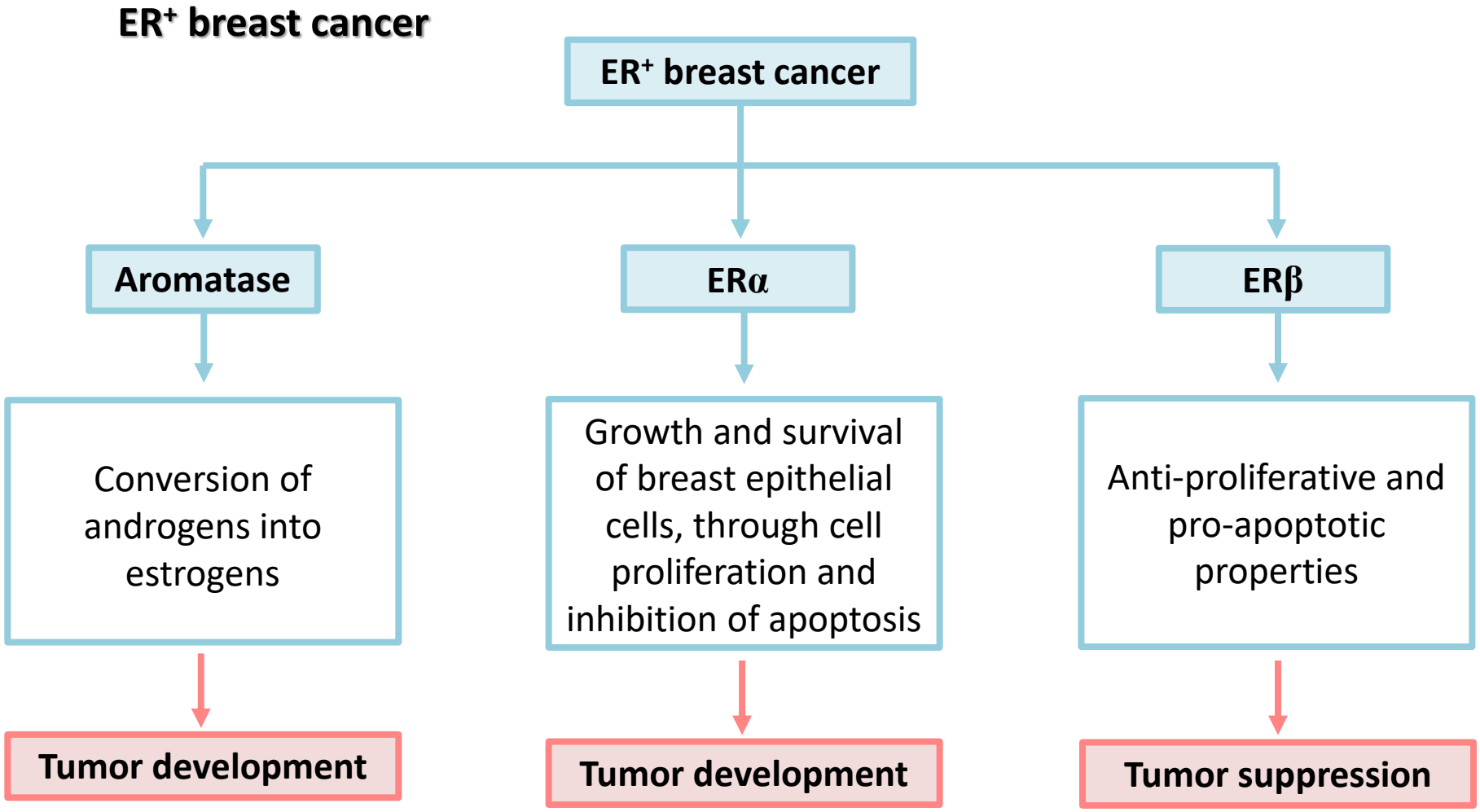
70-80% ER$^+$

60% pre-menopausal women

75% post-menopausal women

Amaral C et al. (2017) J Steroid Biochem Mol Biol;171:218-28
Breast Cancer Facts & Figures 2019-2020, American Cancer Society

Introduction

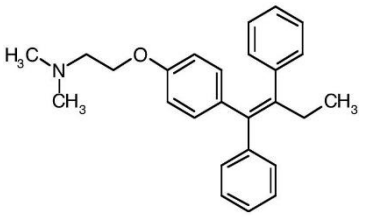


Almeida CF et al. (2020) Biochemical Pharmacology; 177: p. 113989
Augusto TV et al. (2018) Endocr Relat Cancer;25(5):R283-R301

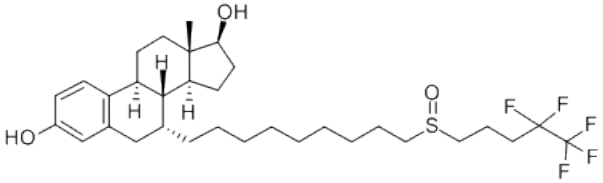
Introduction

Endocrine Therapy

ER Modulators



Tamoxifen



Fulvestrant

Pre-menopausal women

Pre- and post-menopausal women

Augusto TV et al. (2018) Endocr Relat Cancer;25(5):R283-R301

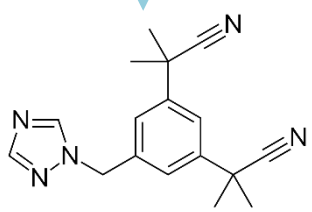
Introduction

Endocrine Therapy

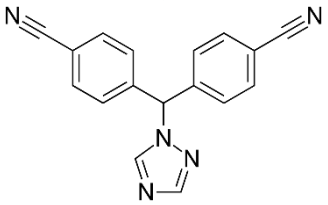
Aromatase Inhibitors (AIs)

Non-Steroidal

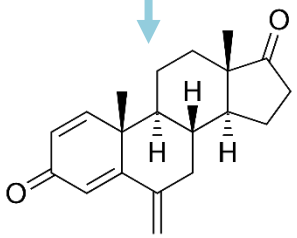
Steroidal



Anastrozole



Letrozole



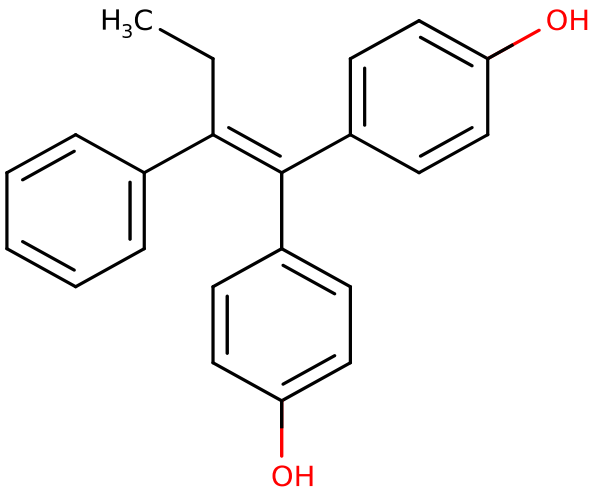
Exemestane

Post-menopausal women and pre-menopausal women after ovaries ablation

Augusto TV et al. (2018) Endocr Relat Cancer;25(5):R283-R301

Introduction

Tamoxifen Bisphenol (TAM-Bis)



- **ERα antagonist**
  - IC_{50} = 15 nM
  - MCF-7-2a
- **Aromatase inhibitor**
  - IC_{50} = 24880 nM
  - Recombinant enzymes

Lubczyk V. et al. (2002) Journal of Medicinal Chemistry; 45(24): p. 5358-5364
Zhao LM. et al. (2016) Bioorg Med Chem; 24(21): p. 5400-5409

Aim

TAM-Bis is already known to act as an AI and an ERα antagonist

Evaluate the ability of TAM-Bis to modulate ERβ

- HFF-1 cells
- MCF-7aro cells

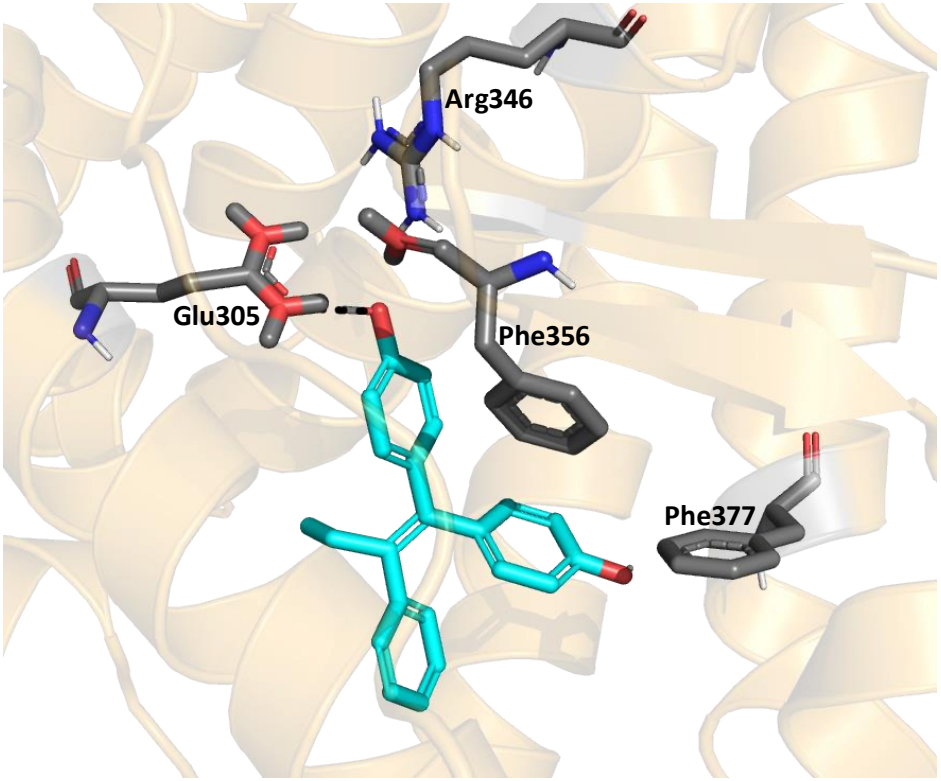
Viability

ERβ protein levels

Improvement of ER$^+$ breast cancer treatment

Results and discussion

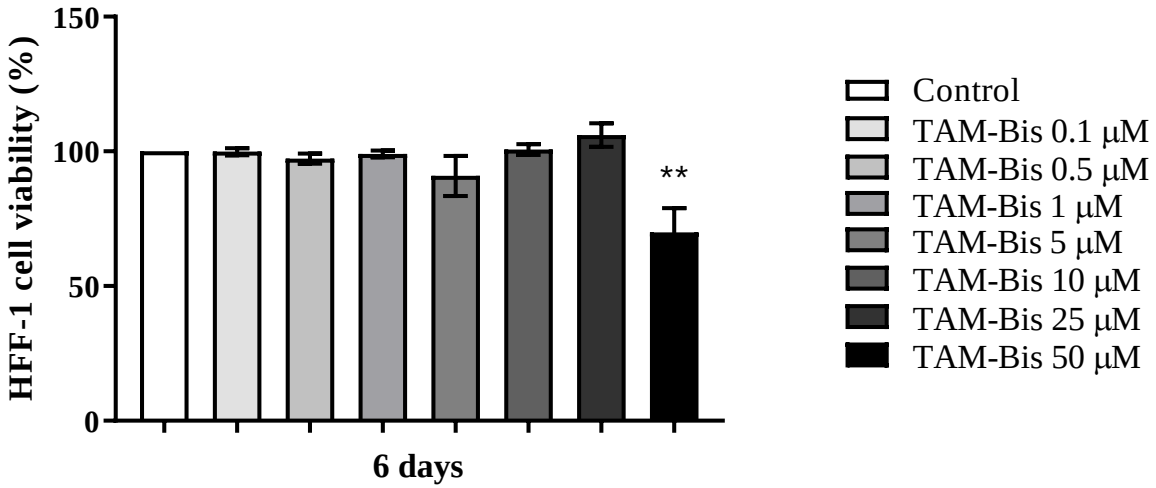
Molecular docking study of TAM-Bis complexed with ERβ



TAM-Bis interacted with important residues for ERβ modulation

Results and discussion

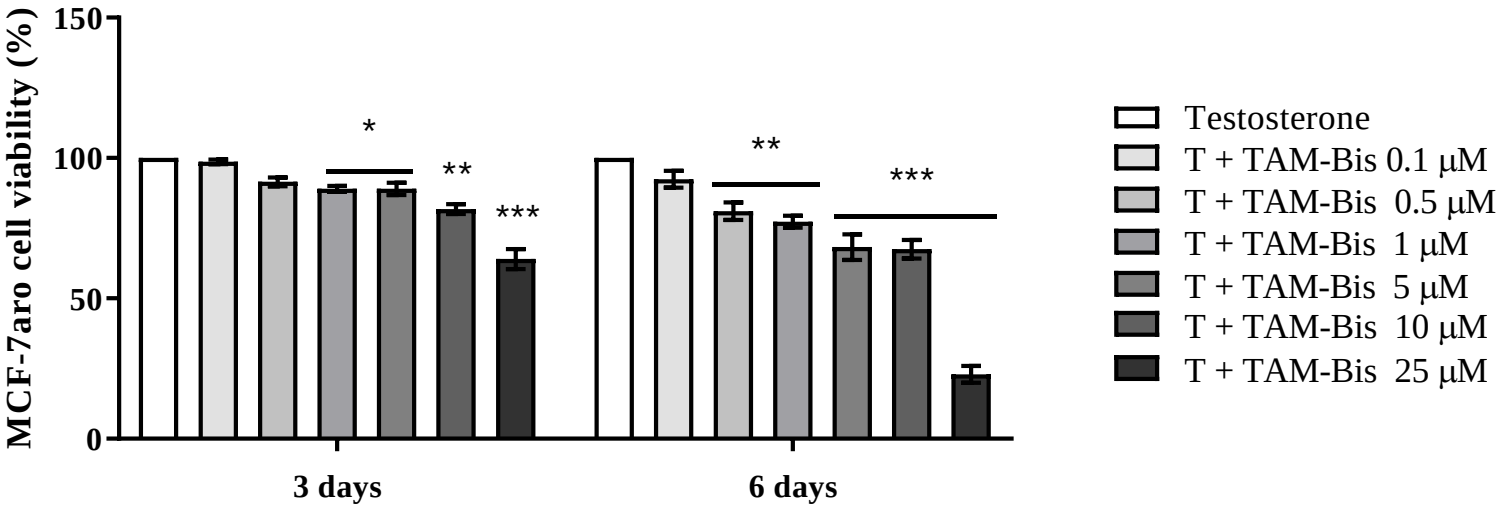
Effects of TAM-Bis on non-cancerous cells (HFF-1)



TAM-Bis only induced a decrease in HFF-1 cell viability at 50 μM

Results and discussion

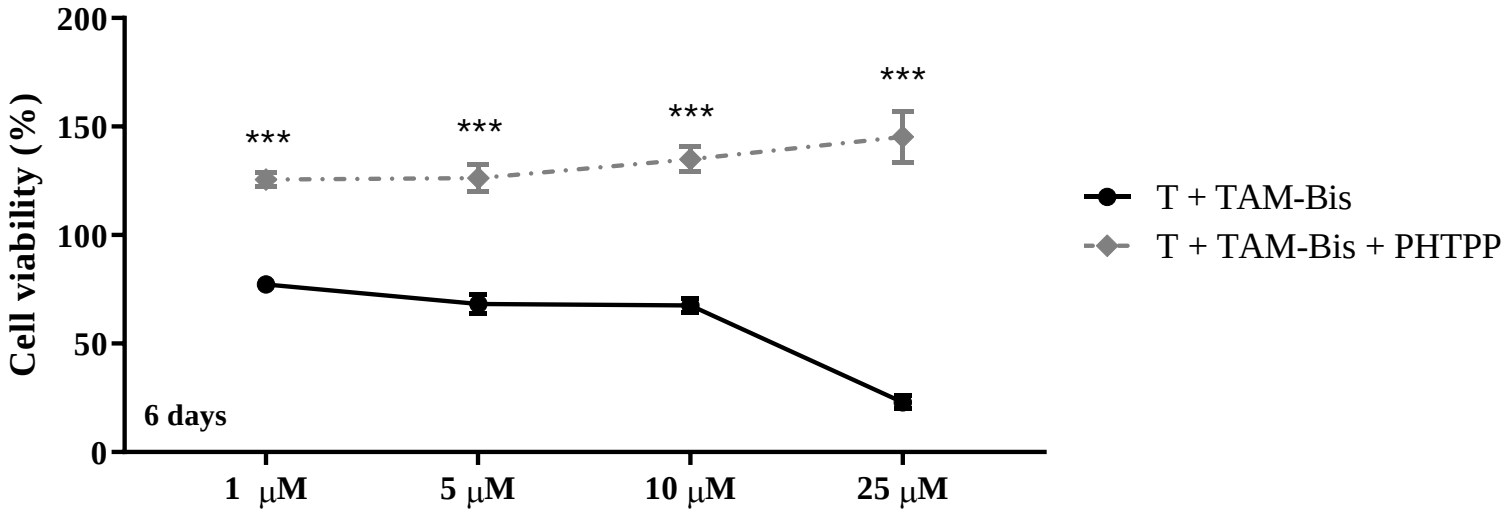
Effects of TAM-Bis on ER+ breast cancer cells (MCF-7aro)



TAM-Bis induced a decrease in MCF-7aro cell viability in a dose and time-dependent manner

Results and discussion

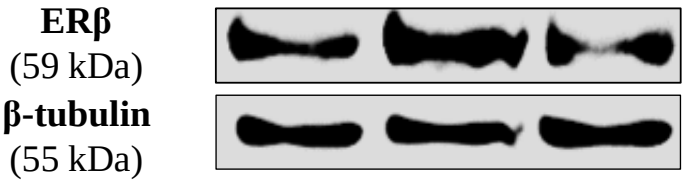
Dependence of ERβ on the effects induced by TAM-Bis

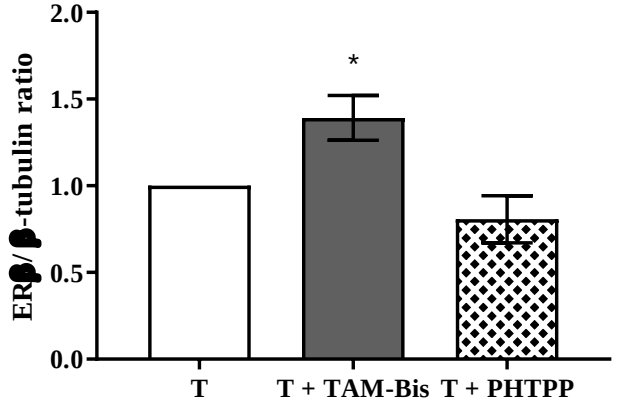


PHTPP reverted the anti-proliferative effects induced by TAM-Bis

Results and discussion

Effects of TAM-Bis on ERβ protein levels





TAM-Bis induced an up-regulation of ERβ

Conclusions

- TAM-Bis interacted with key residues of ERβ
- TAM-Bis did not affect the viability of the non-tumoral HFF-1 cells
- TAM-Bis induced a decrease in MCF-7aro cell viability in a dose and time-dependent manner
- PHTPP reverted the anti-proliferative effects of TAM-Bis, which reinforces the dependence of TAM-Bis on ERβ modulation
- TAM-Bis induced an up-regulation of the ERβ protein levels

TAM-Bis may act as an ERβ agonist

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SFRH/BPD/98304/2013attributed to Cristina Amaral

BD/128333/2017 attributed to Tiago Augusto

UIDB/04378/2020