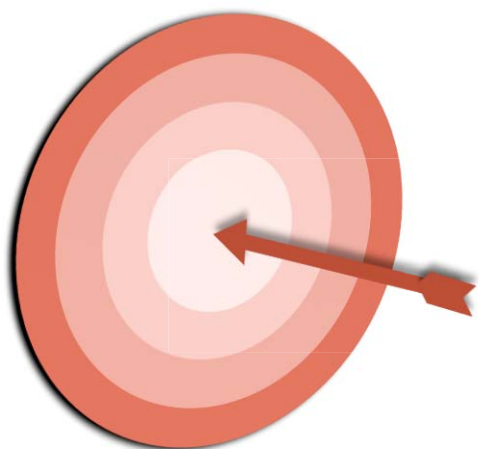


# Delivered targeted cancer therapy



Georgia Biniari

**Georgia Biniari**

Chemist

MSc, PhD Candidate



Ευρωπαϊκή Ένωση  
Ευρωπαϊκό Ταμείο  
Περιφερειακής Ανάπτυξης

**ΕΠΑνεΚ** 2014-2020  
ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ  
ΑΝΤΑΓΩΝΙΣΤΙΚΟΤΗΤΑ  
ΕΠΙΧΕΙΡΗΜΑΤΙΚΟΤΗΤΑ  
ΚΑΙΝΟΤΟΜΙΑ



**19<sup>th</sup> Hellenic Symposium on Medicinal Chemistry**  
**9-11 March 2023, Patras**

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Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης



01

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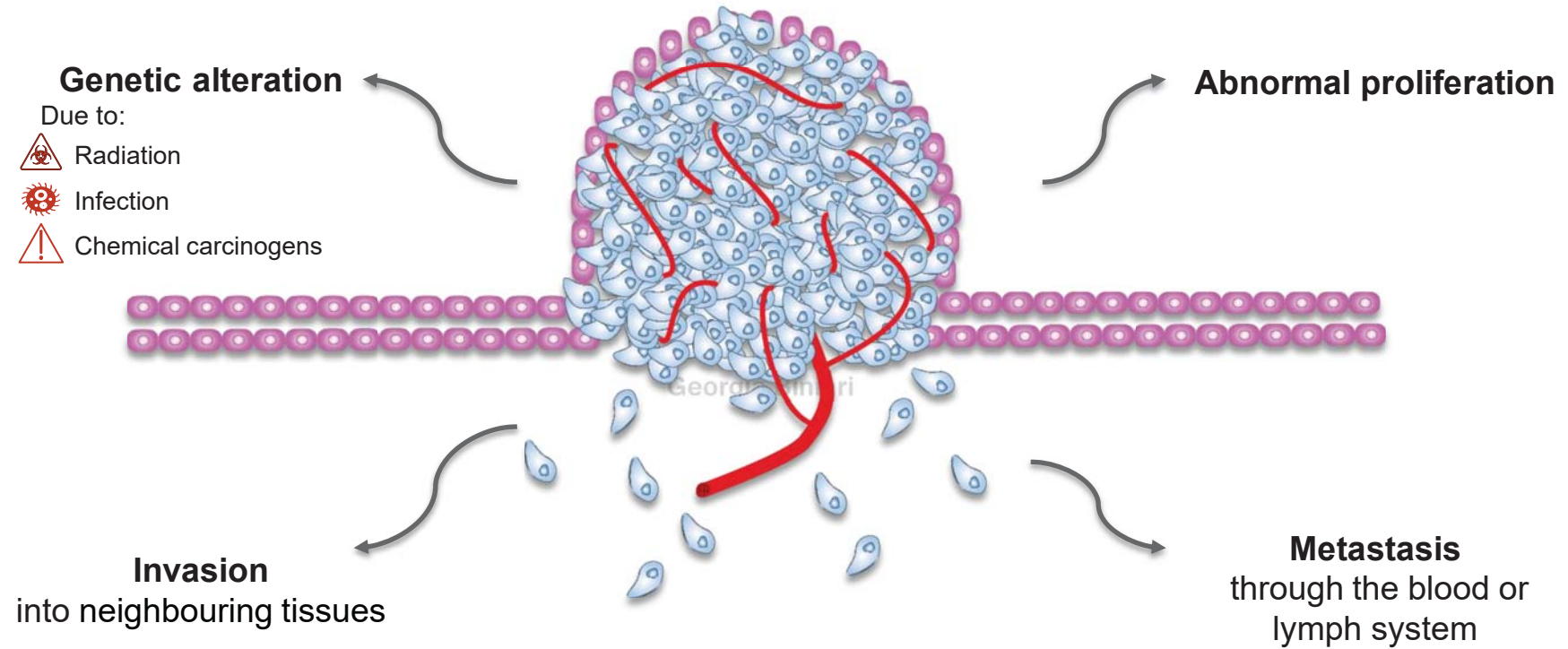
# Cancer

Hormone - Dependent Cancer

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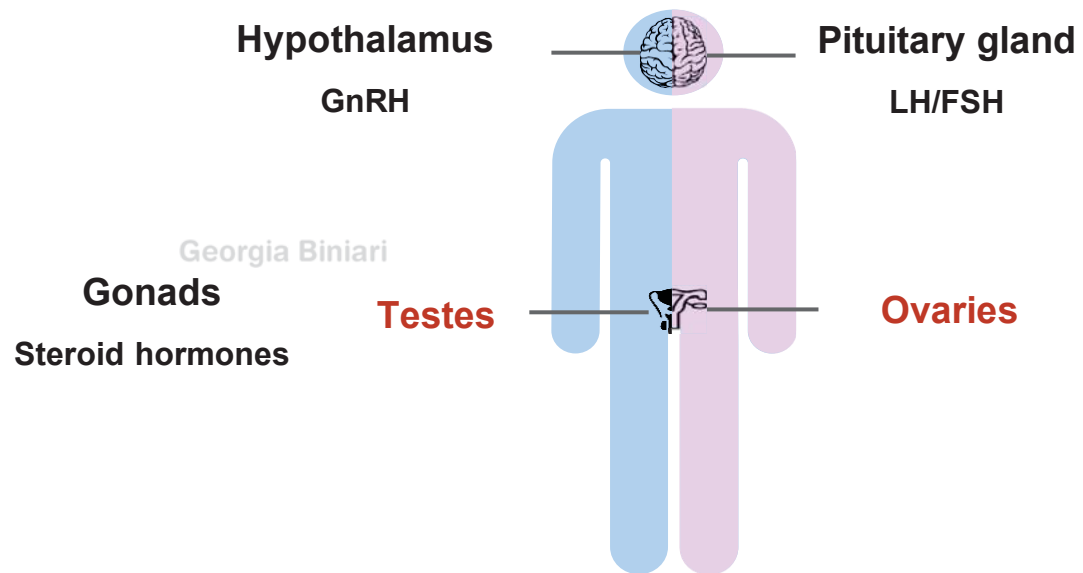
# Cancer



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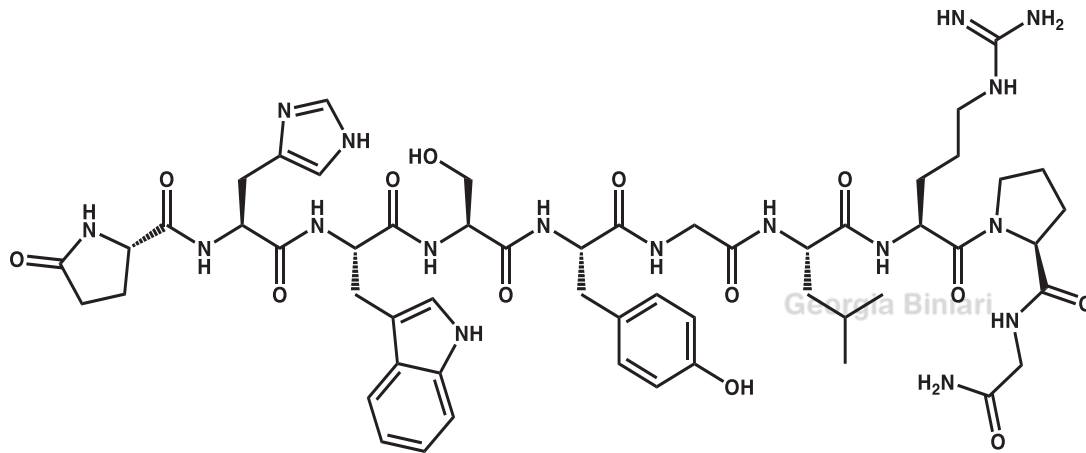
# Hormone - Dependent Cancer

- Endocrine system
- Hormone's function
- HPG Axis



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# GnRH



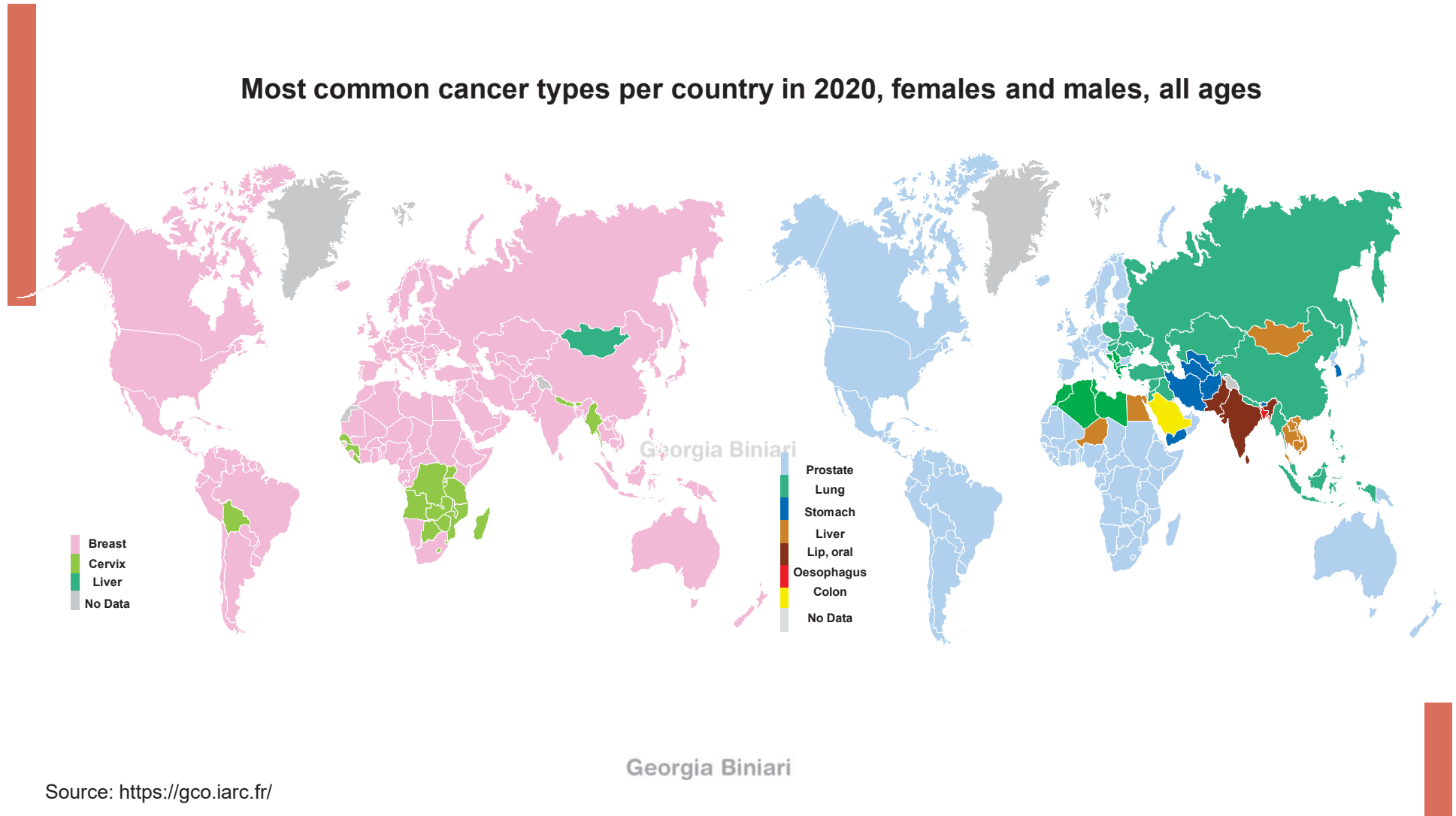
- Hypothalamic Hormone
- HPG Axis
- Releasing of Gonadotropins (LH/FSH)
- Infertility problems, Cancer (breast, prostate, bladder, endometrium etc)

↓  
numerous GnRH receptors

pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub>

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## Most common cancer types per country in 2020, females and males, all ages





# 02

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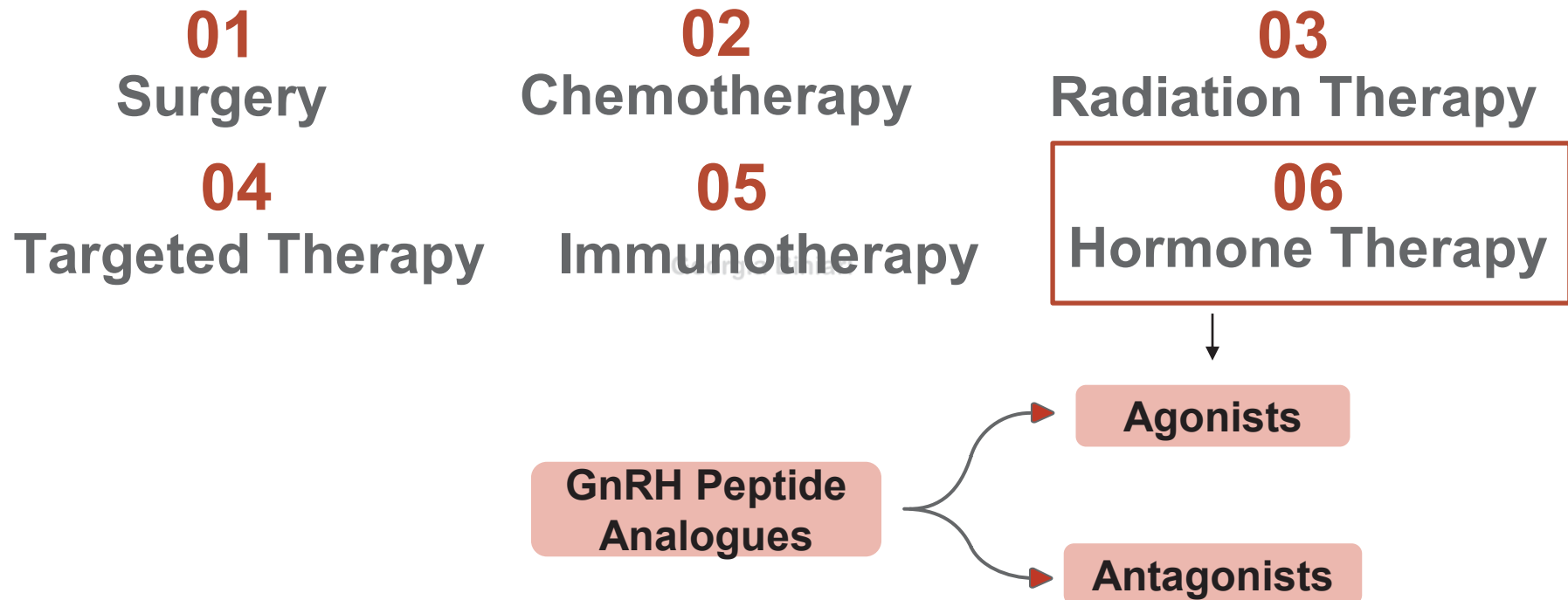
## Treatment

Peptides, Cytotoxic Compounds and Conjugates

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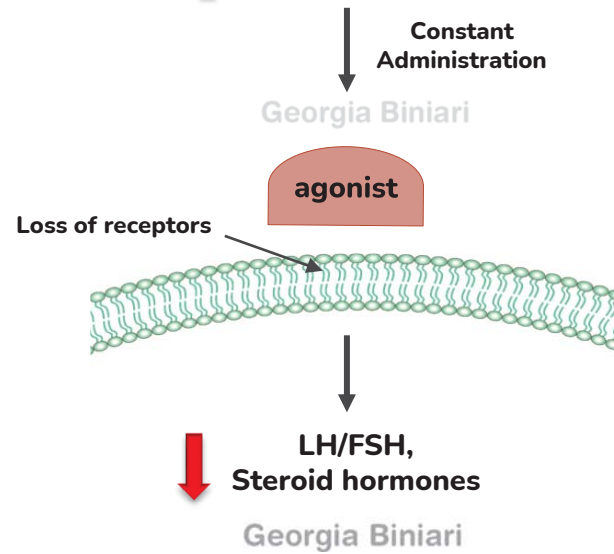
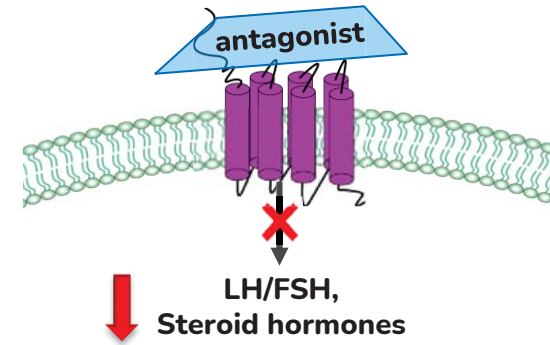
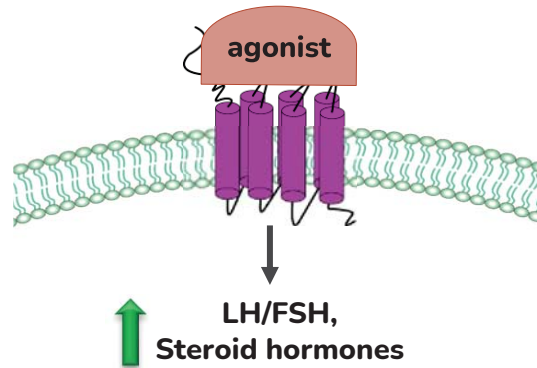
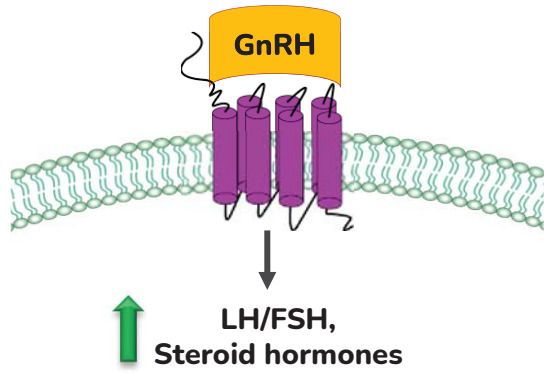


# Treatment Types



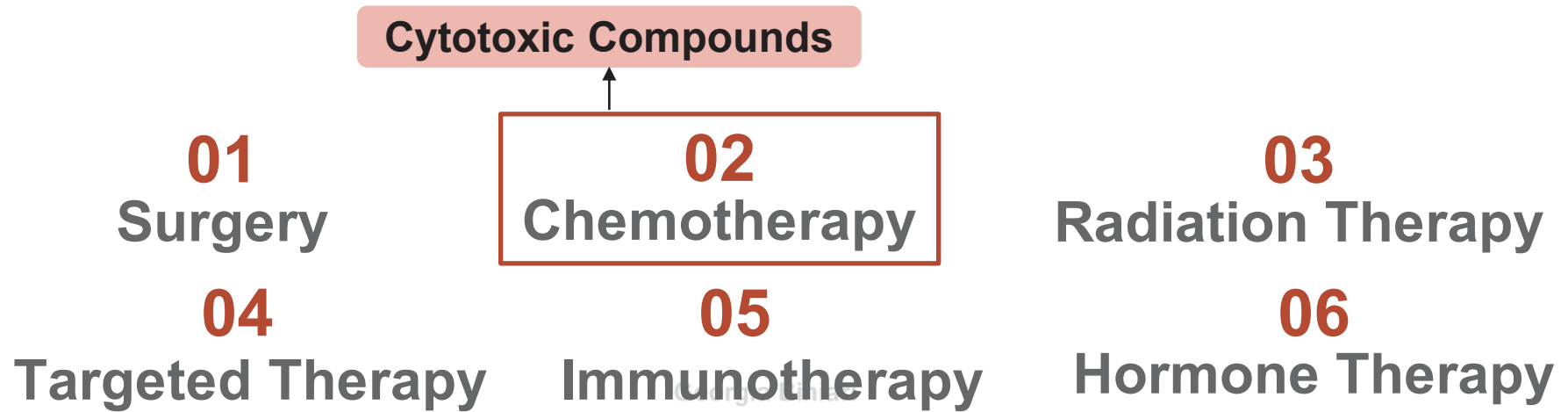
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**Disadvantage:**  
Proteolytic degradation  
↓  
Elimination half-time  
↓  
Decrease of activity

# Treatment Types



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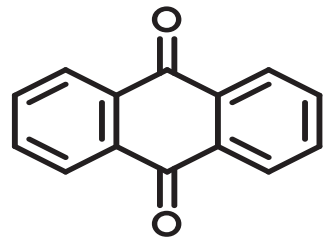
<https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types.html>

# Chemotherapy

Cytotoxic compounds

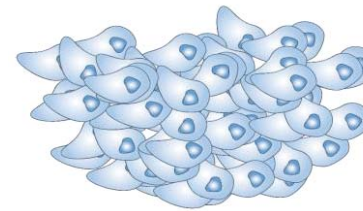


Anthraquinones

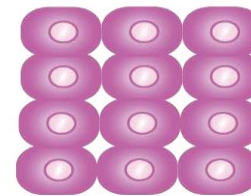


Anthraquinone structure

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Cancer cells

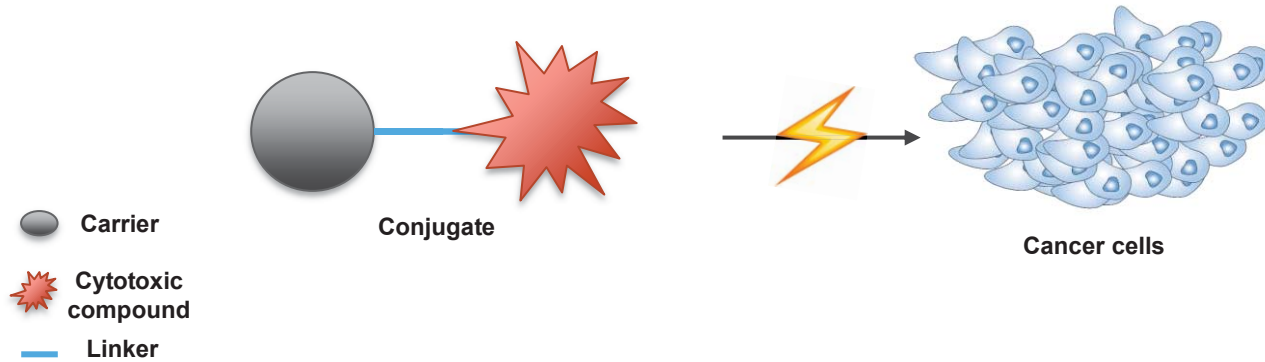


Normal cells

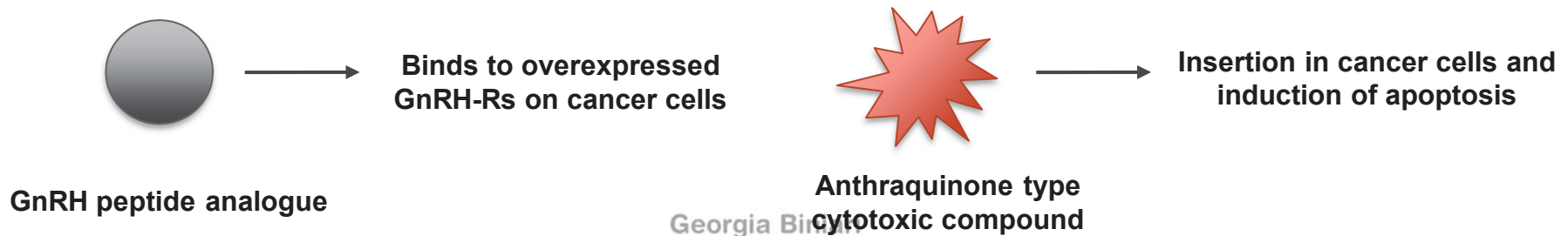
Disadvantage

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# Targeted Therapy (Conjugates)



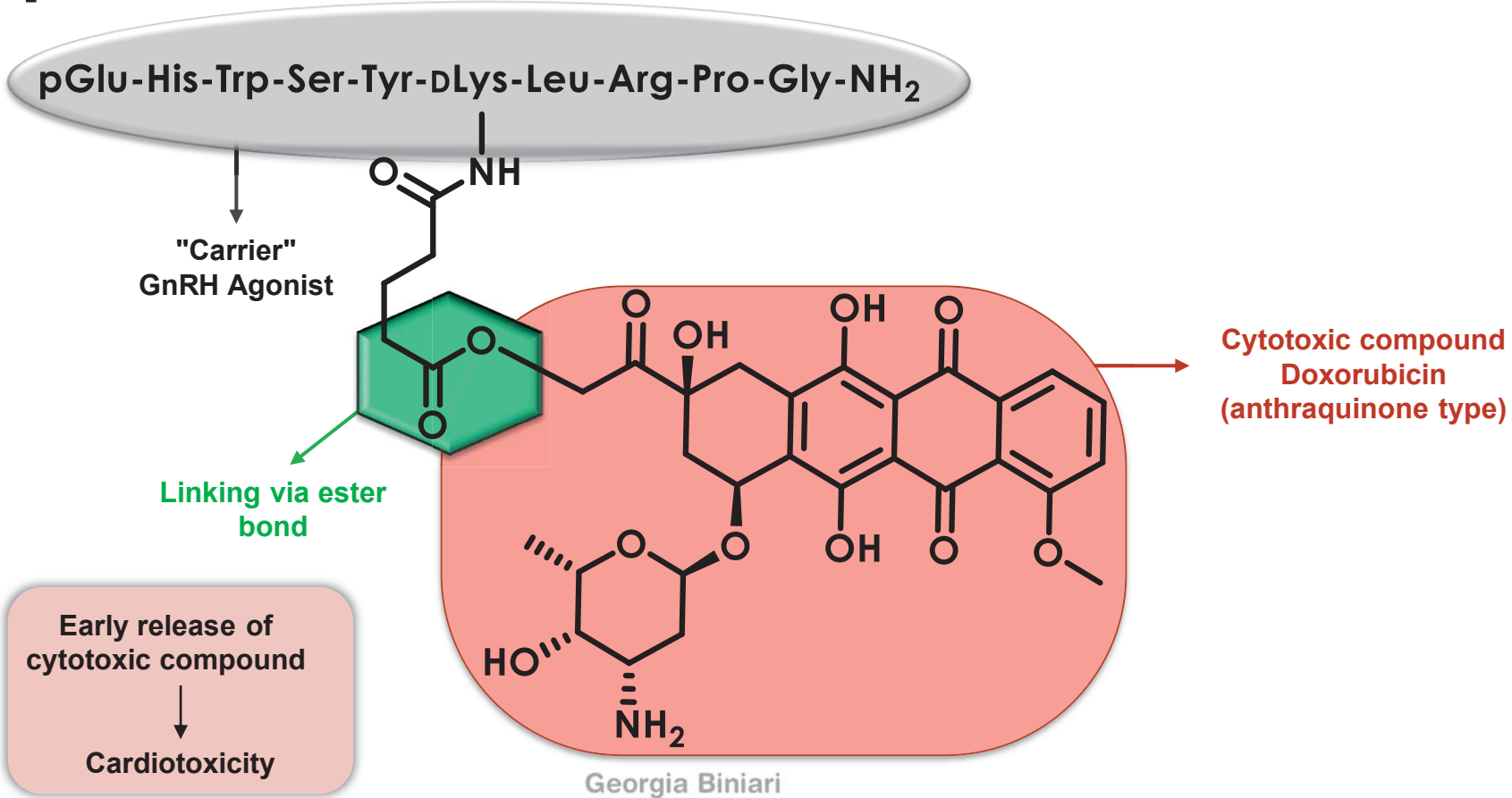
## GnRH - Dependent Cancer



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# Zoptrex





# 03

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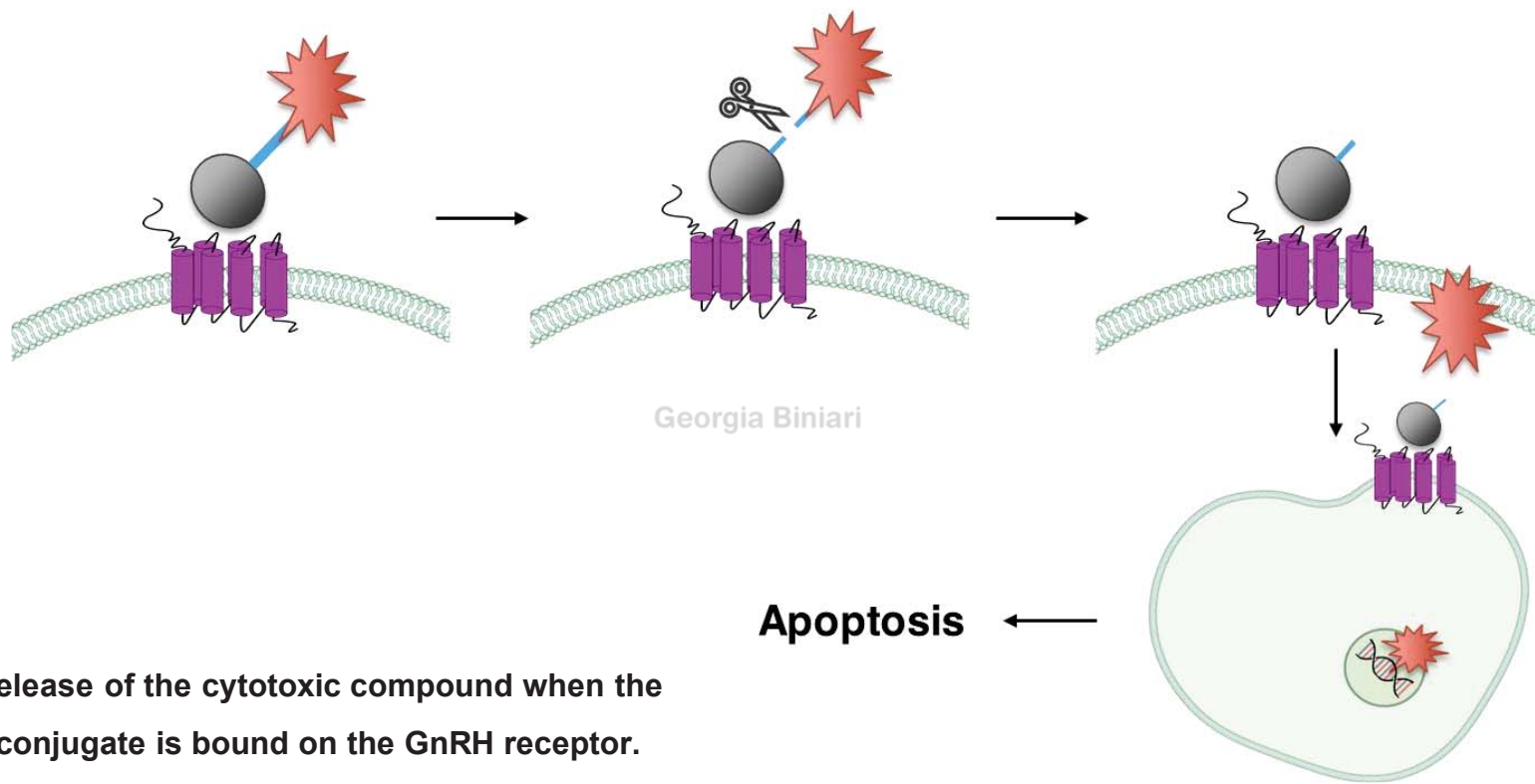
## Our Research

Design, Synthesis and Evaluation of Conjugates

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# Our Research



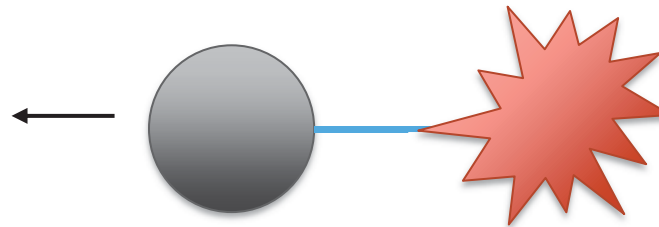
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**Apoptosis**

Release of the cytotoxic compound when the conjugate is bound on the GnRH receptor.

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GnRH Peptide Analogue  
Agonist



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pGlu-His-Trp-Ser-Tyr-**DLeu**-Leu-Arg-**Pro-NHEt**

Leuprolide

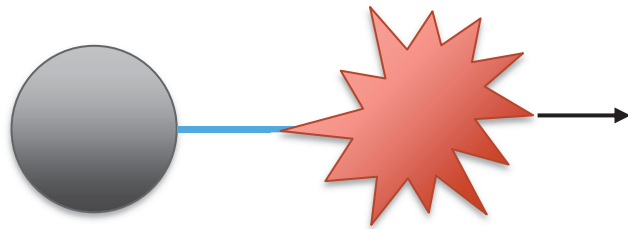
pGlu-His-Trp-Ser-Tyr-**DXaa**-Leu-Arg-**Pro-NHEt**

Con-peptide

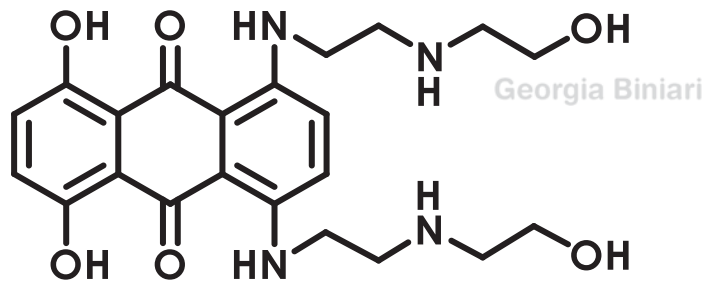
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A red horizontal bar is located at the bottom of the slide.





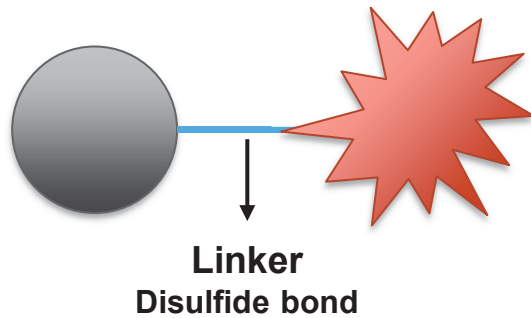
**Cytotoxic compound**  
**Mitoxantrone analogue**



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- **Anthraquinone analogue**
- **Anti-cancer chemotherapy drug**
- **Type II topoisomerase inhibitor**
- **Less cardiotoxicity than doxorubicin**

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- Disulfide Bond
- Reduction by the thioredoxin system
- Controlled release of cytotoxic compound in cancer cells

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#### Thioredoxin system:

- Overexpressed in cancer cells

No early release of the cytotoxic compound in the bloodstream, so **less toxicity!!!**

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# Lab Synthesis

## GnRH peptide analogue

- Solid phase peptide synthesis
- Fmoc/tBu methodology
- CLTR-Cl and Ethyl Indole AM Resin

↓  
Modification of  
C-terminal

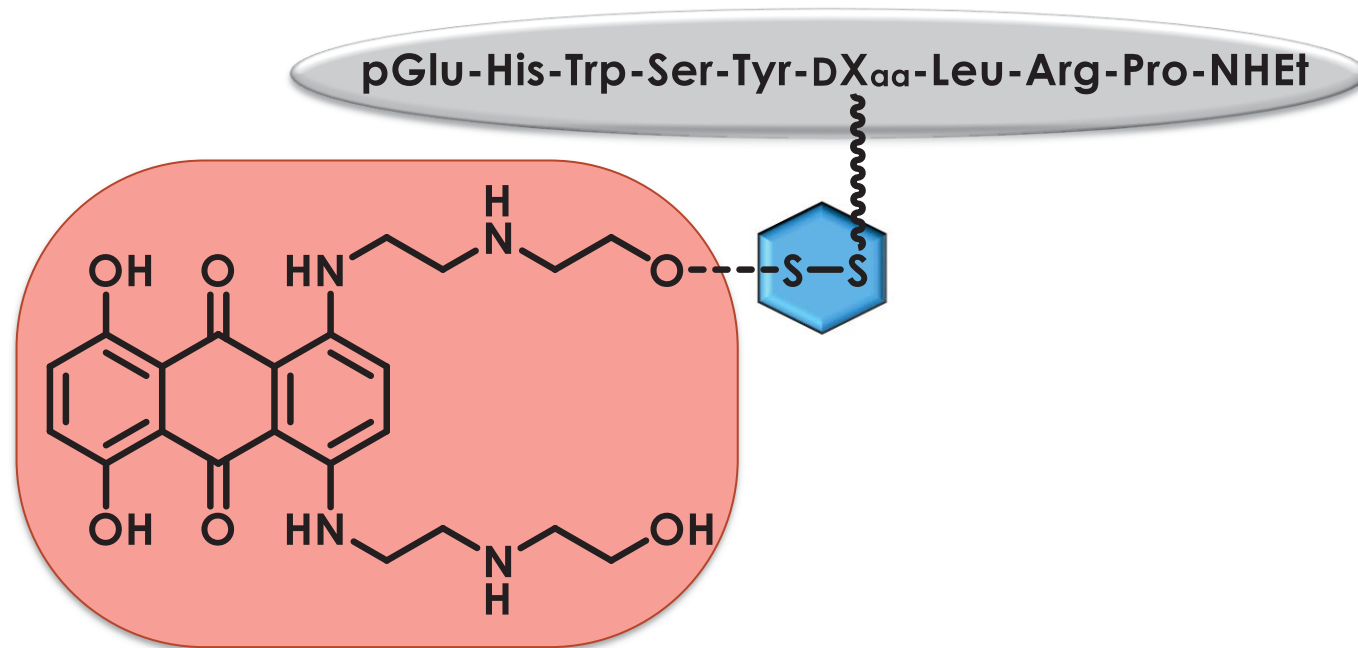
↓  
Modified  
C-terminal

## Mitoxantrone analogue

- Insertion of a thiol group
- Formation of an ester bond in the one side chain of mitoxantrone
- Modified Steglich Esterification

## Synthesis of conjugates

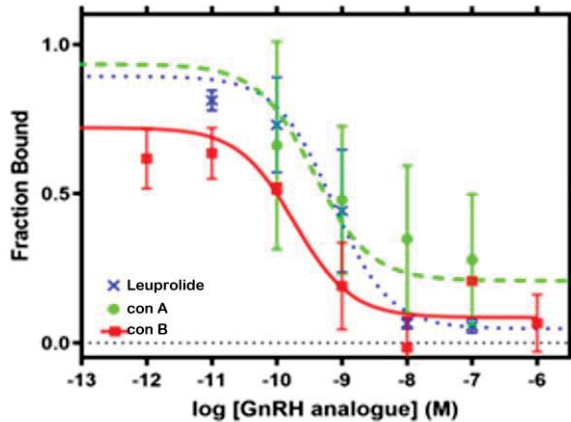
- Thiol-Disulfide Exchange
- High Dilution of MeOH



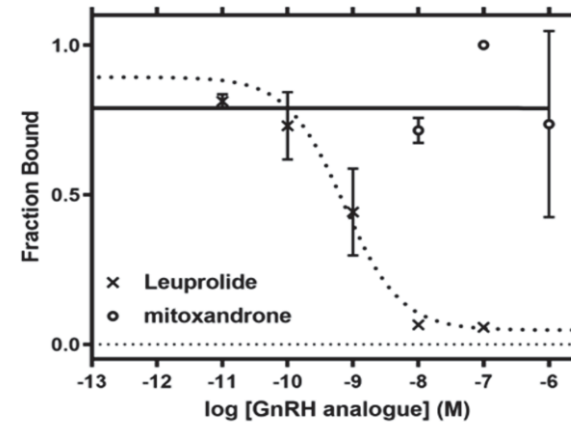
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# Binding affinity assays

- Inhibition of the specific binding of [<sup>125</sup>I]-DTyr<sup>6</sup>-His<sup>5</sup>-GnRH
- HEK 293 cells
- Overexpressing GnRH receptor



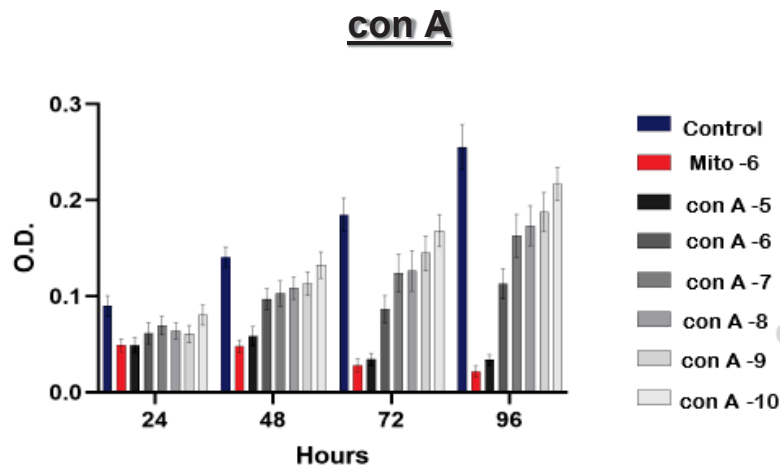
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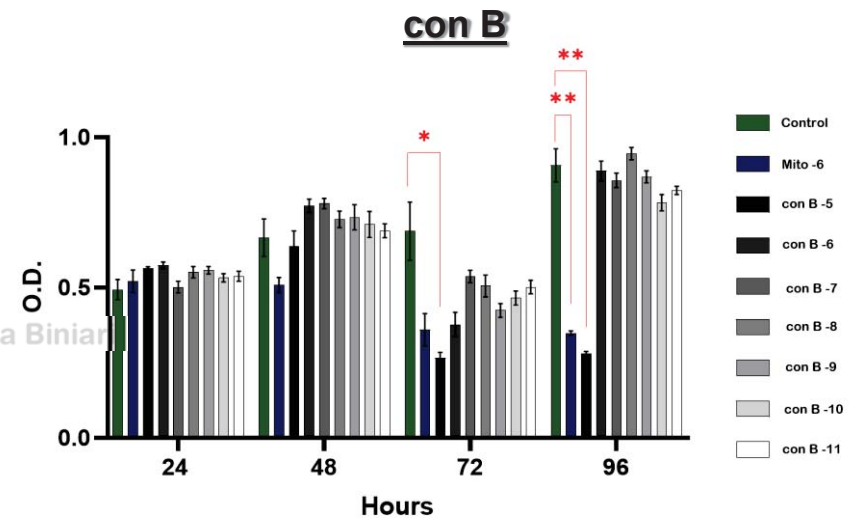
- con A and con B: **Higher affinities** than Leuprolide (control)
- Mitoxantrone: **Did not bind** to GnRH-R

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# Antiproliferative effect of con A and con B



- Incubation of Ovarian cancer cell line SK-OV-3
- MTT assay
- Inhibition in a **dose-dependent** manner

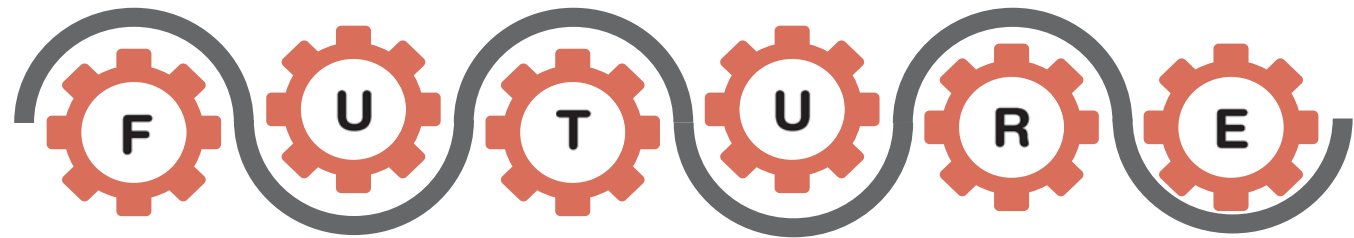


- Incubation of Breast cancer cell line MDA-MB-231
- MTT assay
- Inhibition in a **time-dependent** manner

# Perspectives

- Further in vivo & in vitro evaluation
- Stability evaluation
- NMR studies
- Molecular modeling

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## Team Members



UNIVERSITY OF  
**PATRAS**  
ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ

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# THANK YOU



UNIVERSITY  
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- Michalis Deiktakis, PhD Candidate
- Ekaterini Kalantidou, PhD Candidate



Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης