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Institute for Health and Bioeconomy

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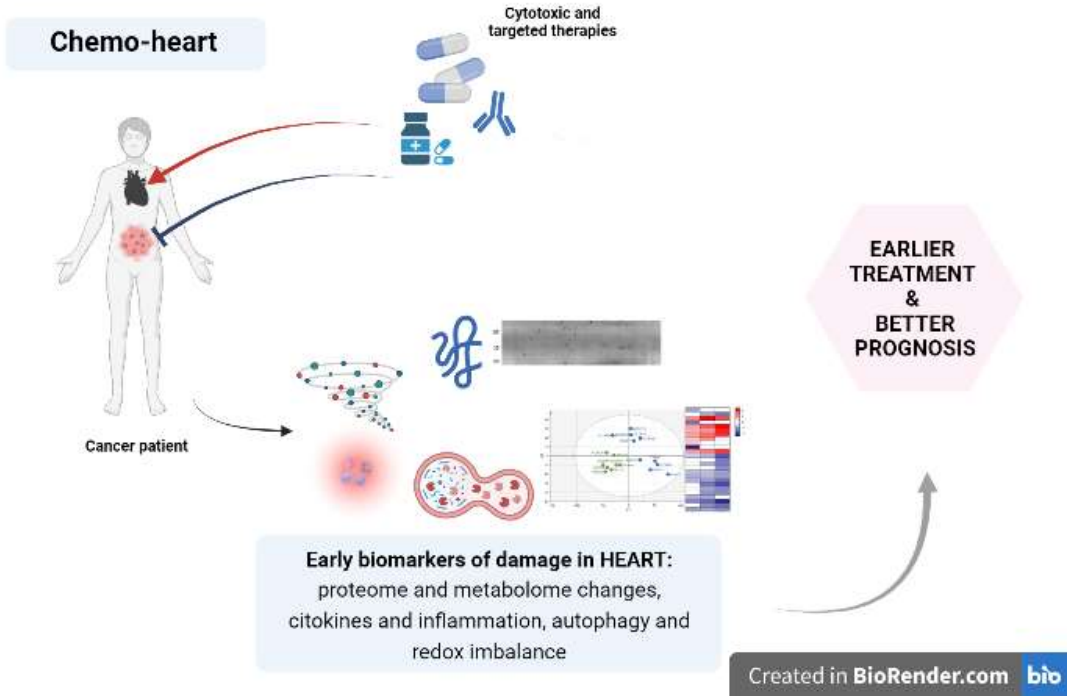
In the heart of cardio-oncology: the targets and biomarkers of anticancer drugs cardiotoxicity

Graphical Abstract



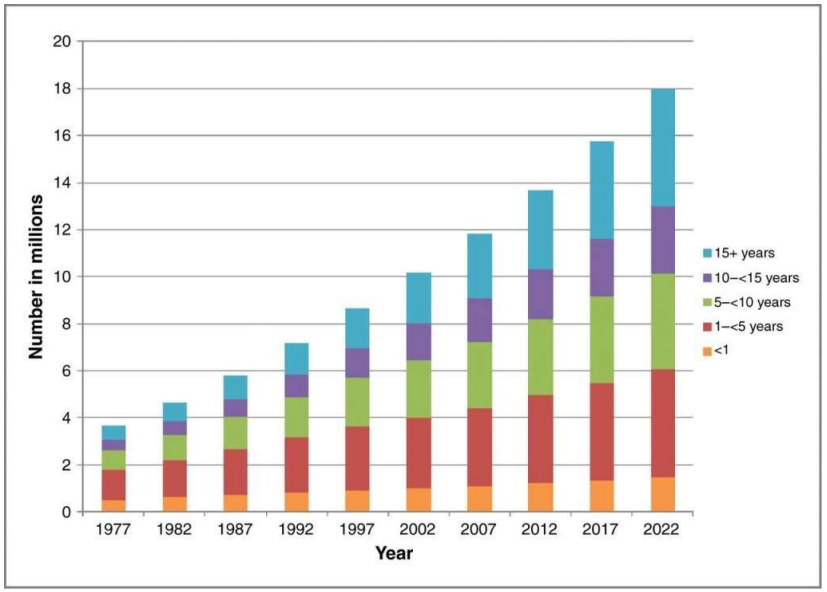
Abstract:
The cardiotoxicity of anticancer drugs is the second leading cause of death in cancer patients. Among other adverse effects, left ventricular ejection fraction decrease or heart failure emerge after anticancer treatments comprising old or new targeted therapies. In the last few years, our group has been trying to unveil the cardiac adverse outcome pathways of classic chemotherapeutic agents, mainly focusing on two topoisomerase inhibitors, mitoxantrone and doxorubicin.
Mitoxantrone and doxorubicin both cause cumulative dose cardiotoxicity and were tested in *in vitro* and in pre-clinical models. Results obtained in mice and rats, following a clinical relevant dosing scheme, were mimicked *in vitro* and demonstrated that those drugs change cellular redox homeostasis and promote inflammation, although in different biomarkers. Moreover, autophagy and energetic pathways were affected, the first mainly after mitoxantrone treatments and the latter when doxorubicin was used. Thus, distinct cardiac fingerprints for these two drugs exist.
In conclusion, although their clinical cardiac effects are similar in humans, mitoxantrone and doxorubicin have different initiating cardiotoxic events. These were revealed taking into account the use of proper experimental models, clinical relevant concentrations and Omics methods. These data are of the essence to promote drug specific cardioprotective measures in the future, for patients treated with these drugs.
Keywords: Cardio-oncology; cardiotoxicity; doxorubicin; mitoxantrone.

Introduction

- Cancer is the second leading cause of death worldwide, following cardiovascular diseases.

- Still, and even though cancer incidence is increasing, the rate of survival among most cancers is steadily increasing too.

- **CANCER TREATMENT IS IN FACT A SUCCESS STORY.**



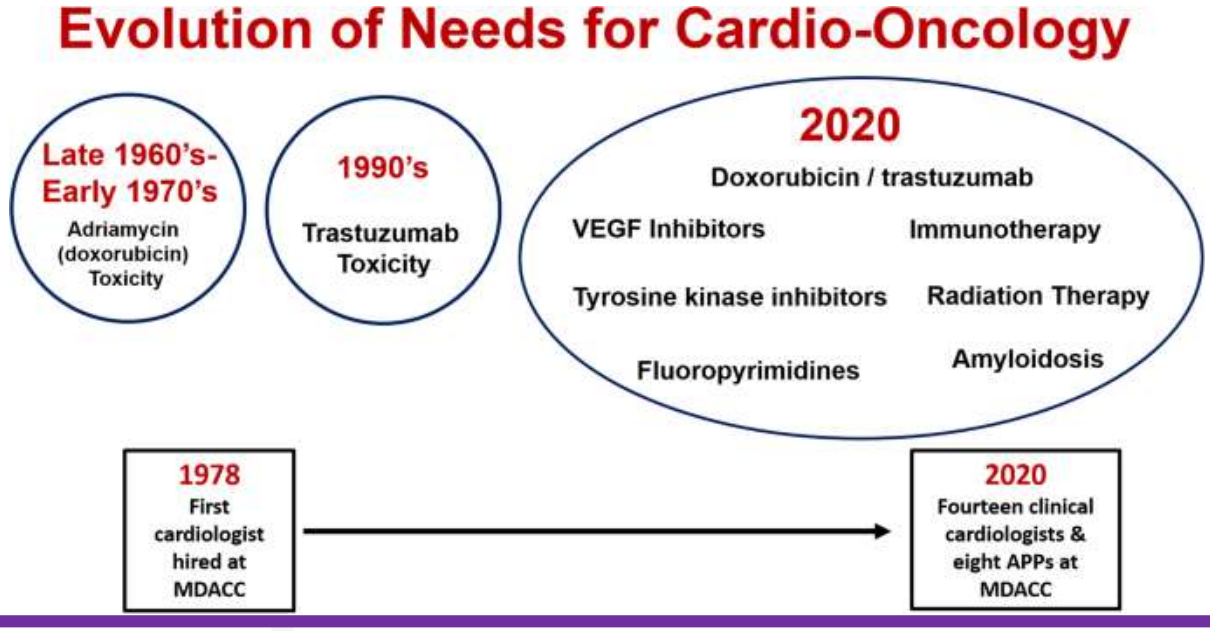
Introduction

- **NEW VISION TOWARDS CANCER**

Short term and long term side effects of cancer treatments: alopecia, myelosupression, **cardiotoxicity,** neurotoxicity**,** recurrent cancer, hepatoxicity and so on...

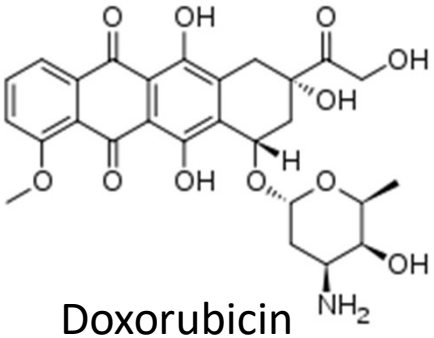
Introduction

- **CARDIO-ONCOLOGY**

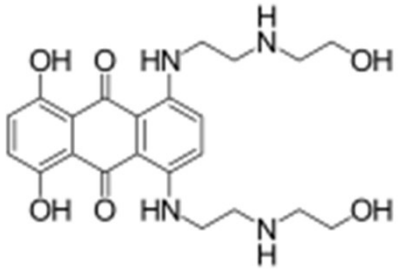


AIMS

- To unveil the **cardiotoxic adverse outcome pathways (AOPs)** and the **early biomarkers of cardiotoxicity** that enable treatment or triage of patients before end stage heart failure, using both *in vitro* and *in vivo* models regarding 2 topoisomerase II inhibitors used in cancer: mitoxantrone and doxorubicin



Doxorubicin



Mitoxantrone

- Mitoxantrone *versus* doxorubicin

Pubmed entries (7th September 2022)

((doxorubicin OR adriamycin) AND (heart OR cardiac): 9,013 results

mitoxantrone AND (heart or cardiac): 534 entries

Both have similar clinical cardiotoxicity related to total lifelong cumulative dose

BUT ARE THE MECHANISMS SIMILAR?

Results and discussion

Oxidative stress and Redox homeostasis

pharmaceuticals

MDPI

Article

Inflammation as a Possible Trigger for Mitoxantrone-Induced Cardiotoxicity: An In Vivo Study in Adult and Infant Mice

Ana Reis-Mendes [1,*], José Luís Dores-Sousa [1], Ana Isabel Padrão [2], Margarida Duarte-Araújo [3,4], José Alberto Duarte [2,5], Vítor Seabra [5], Salomé Gonçalves-Monteiro [6,7], Fernando Remião [1], Félix Carvalho [1], Emília Sousa [8,9], Maria Lourdes Bastos [1] and Vera Marisa Costa [1,*]

biomolecules

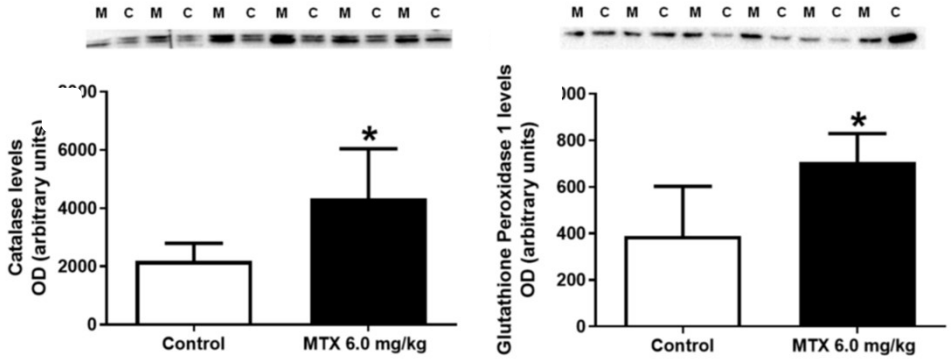
an Open Access Journal by MDPI

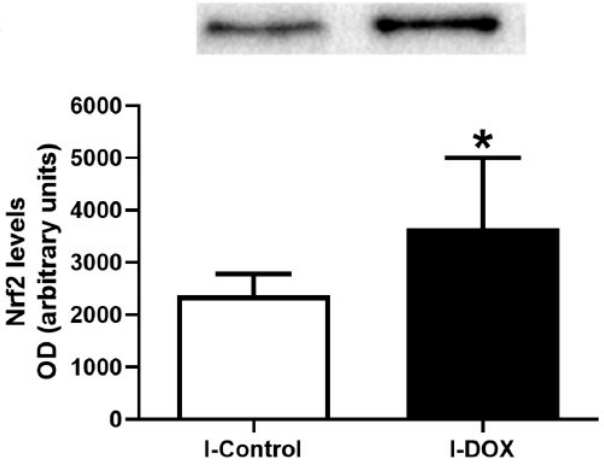
Role of Inflammation and Redox Status on Doxorubicin-Induced Cardiotoxicity in Infant and Adult CD-1 Male Mice

Ana Reis-Mendes; Ana Isabel Padrão; José Alberto Duarte; Salomé Gonçalves-Monteiro; Margarida Duarte-Araújo; Fernando Remião; Félix Carvalho; Emília Sousa; Maria Lourdes Bastos; Vera Marisa Costa

Biomolecules 2021, Volume 11, Issue 11, 1725

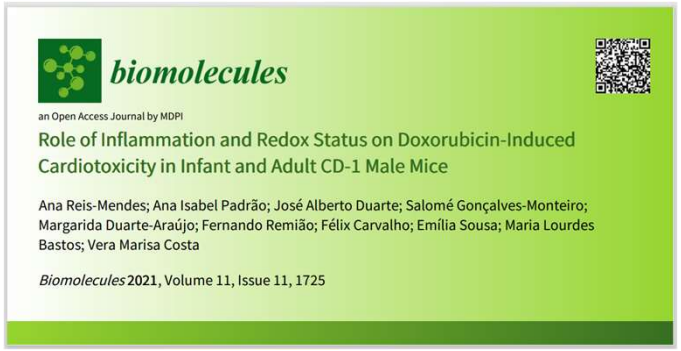
Infants

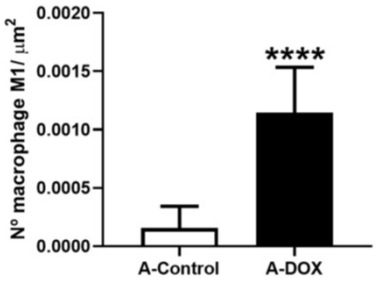


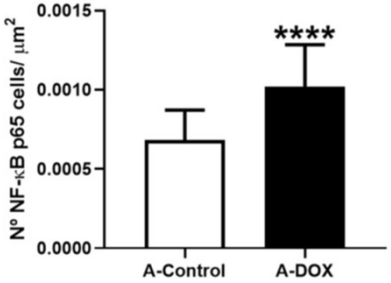


Results and discussion

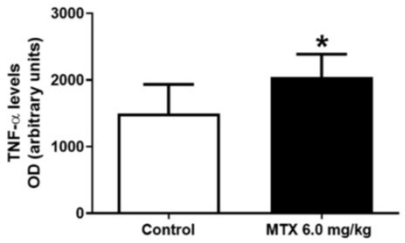
Inflammation



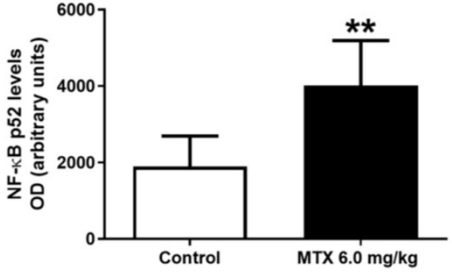




Infants



Adults



Results and discussion

Energetic pathways and mitochondrial homeostasis

H9c2 cells

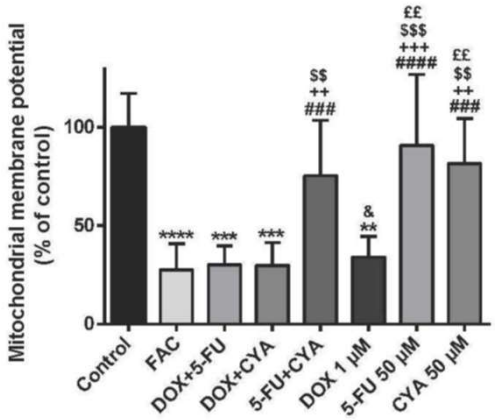
biomolecules

MDPI

Article

Doxorubicin Is Key for the Cardiotoxicity of FAC (5-Fluorouracil + Adriamycin + Cyclophosphamide) Combination in Differentiated H9c2 Cells

Maria Pereira-Oliveira, Ana Reis-Mendes, Félix Carvalho, Fernando Remião, Maria de Lourdes Bastos and Vera Marisa Costa *



HL-1 cardiomyocytes

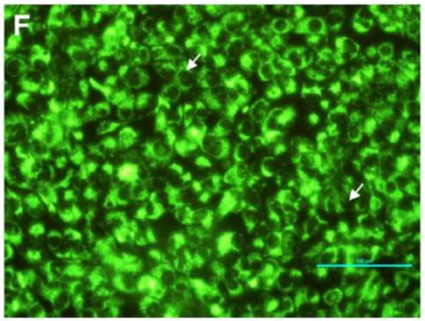
Archives of Toxicology
https://doi.org/10.1007/s00204-020-02874-4

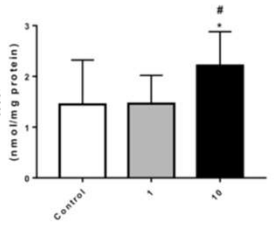
ORGAN TOXICITY AND MECHANISMS

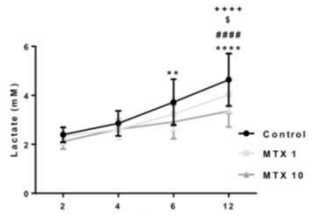
Check for updates

Mitoxantrone impairs proteasome activity and prompts early energetic and proteomic changes in HL-1 cardiomyocytes at clinically relevant concentrations

Vera Marisa Costa[1] · João Paulo Capela[1,2] · Joana R. Sousa[3] · Rute P. Eleutério[3] · Patrícia R. S. Rodrigues[3] · José Luís Dores-Sousa[1,4] · Rui A. Carvalho[5] · Maria Lourdes Bastos[1] · José Alberto Duarte[6] · Fernando Remião[1] · M. Gabriela Almeida[3,7] · Kurt J. Varner[8] · Félix Carvalho[1]





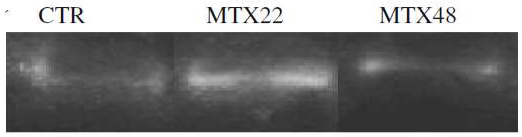


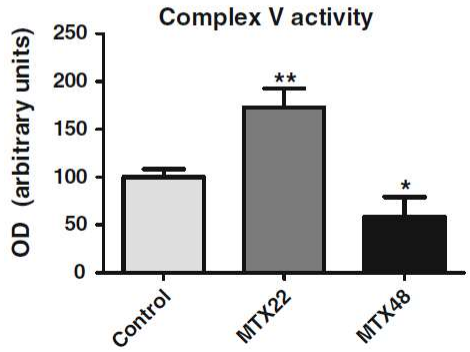
Results and discussion

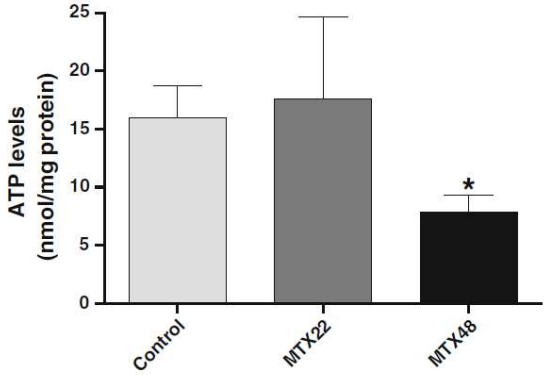
Energetic pathways and mitochondrial homeostasis

Rat with 7.5mg/kg cumulative dose MTX

Sacrificed at 2 time-points







Rossato *et al*. 2013 Cardiovascular Toxicology

Results and discussion

Energetic pathways and mitochondrial homeostasis

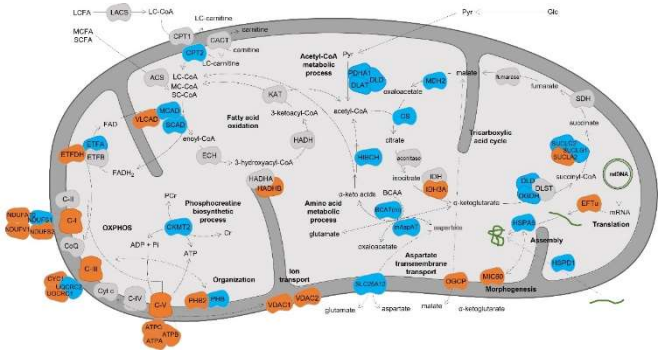
Contents lists available at ScienceDirect

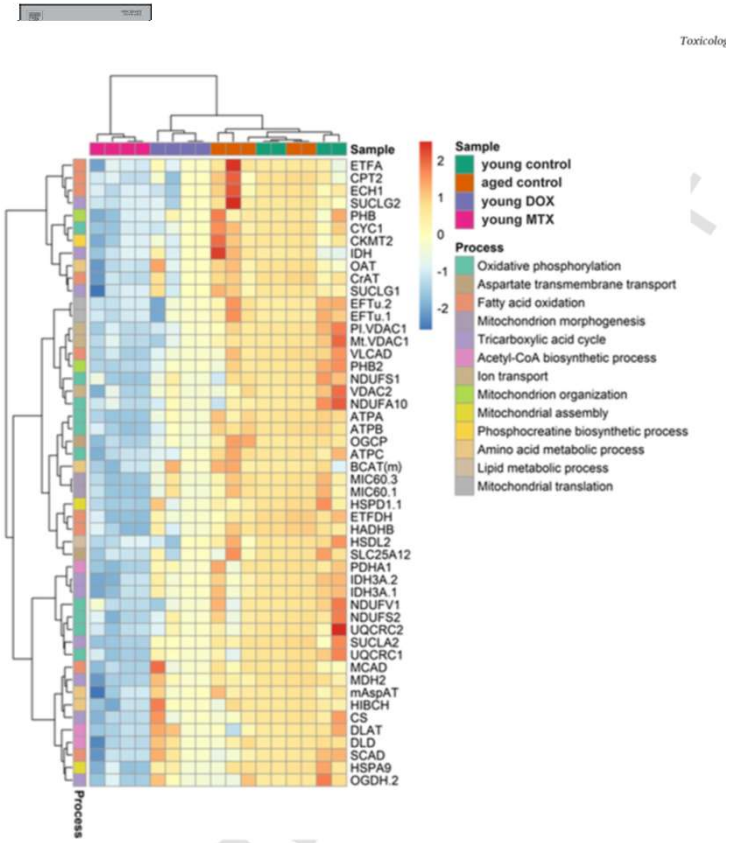
Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Exploring the aging effect of the anticancer drugs doxorubicin and mitoxantrone on cardiac mitochondrial proteome using a murine model

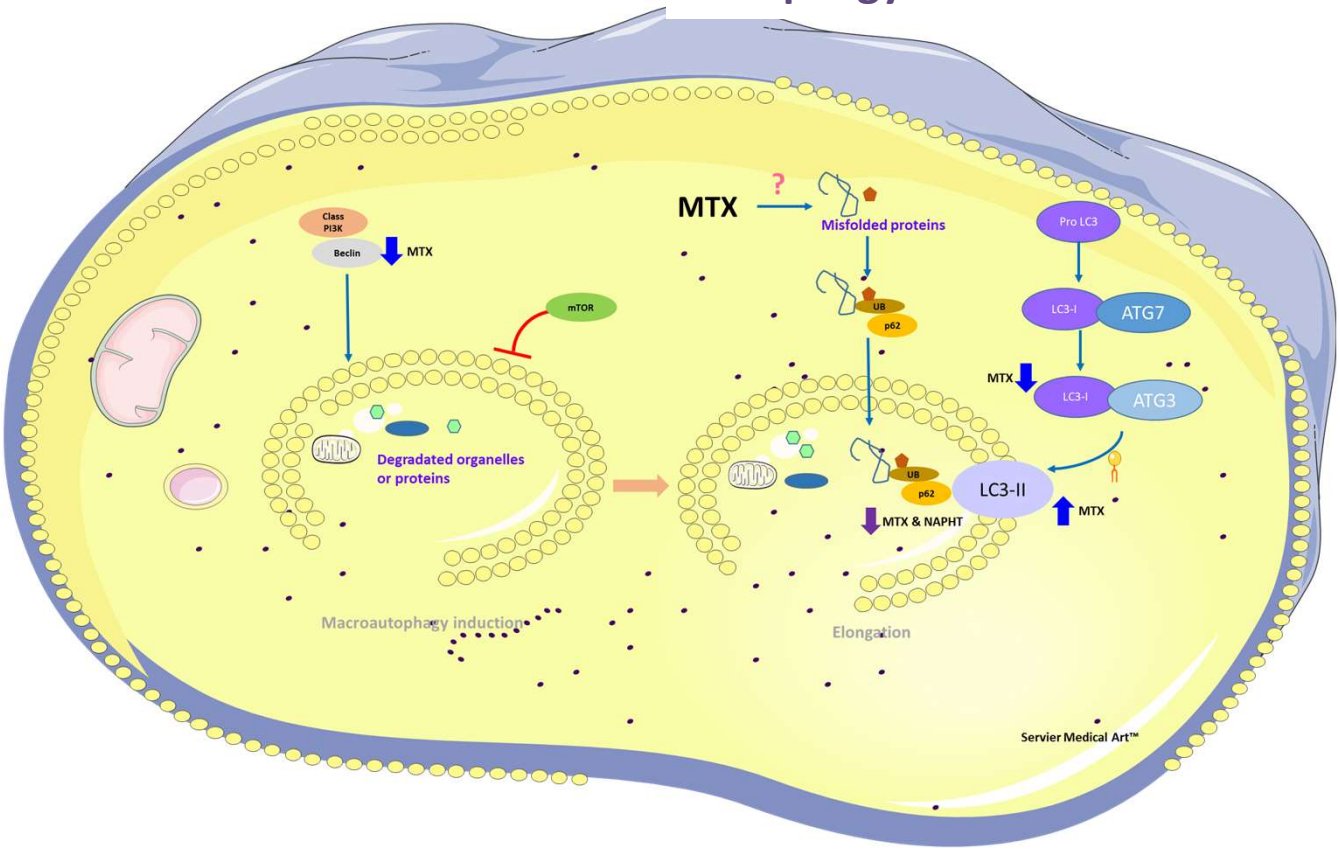
Sofia Reis Brandão [a,b,c], Ana Reis-Mendes [a,c], Pedro Domingues [b], José Alberto Duarte [d,e], Maria Lourdes Bastos [a,c], Félix Carvalho [a,c], Rita Ferreira [b], Vera Marisa Costa [a,c,*]





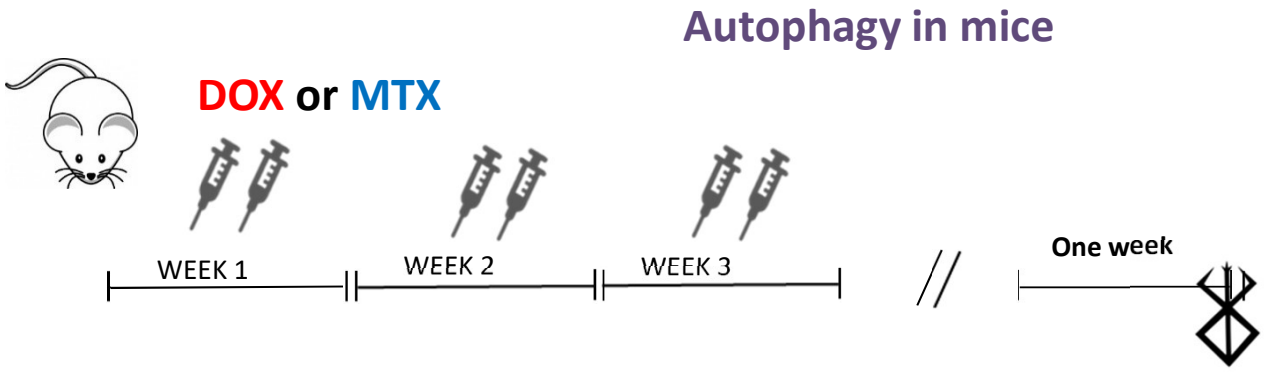
Results and discussion

Autophagy in AC16 cells



Reis-Mendes *et al*. Archives in Toxicology In press

Results and discussion



	DOX	MTX
Beclin 1	=	=
ATG5	↓	↓
LC3	↓	↓

Brandão *et al*. in preparation

Conclusions

Although both drugs have similar anti-cancer mechanisms and clinical signs of cardiotoxicity, they have different underlying adverse outcome cardiac pathways:

- **Redox homeostasis**
- **Energetic and mitochondrial homeostasis**
- **Inflammation**
- **Autophagy**

Thus, biomarkers of cardiotoxicity should be addressed in a DRUG by DRUG context using in vitro and in vivo models to identify susceptible patients and discover new pharmacological treatments

Acknowledgments

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QUADRO DE REFERÊNCIA ESTRATÉGICO NACIONAL
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