

Emerging Role of Senescence in Cardiotoxicity

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Cancer and Cardiovascular Disease

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HARVARD MEDICAL SCHOOL
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Disclosures

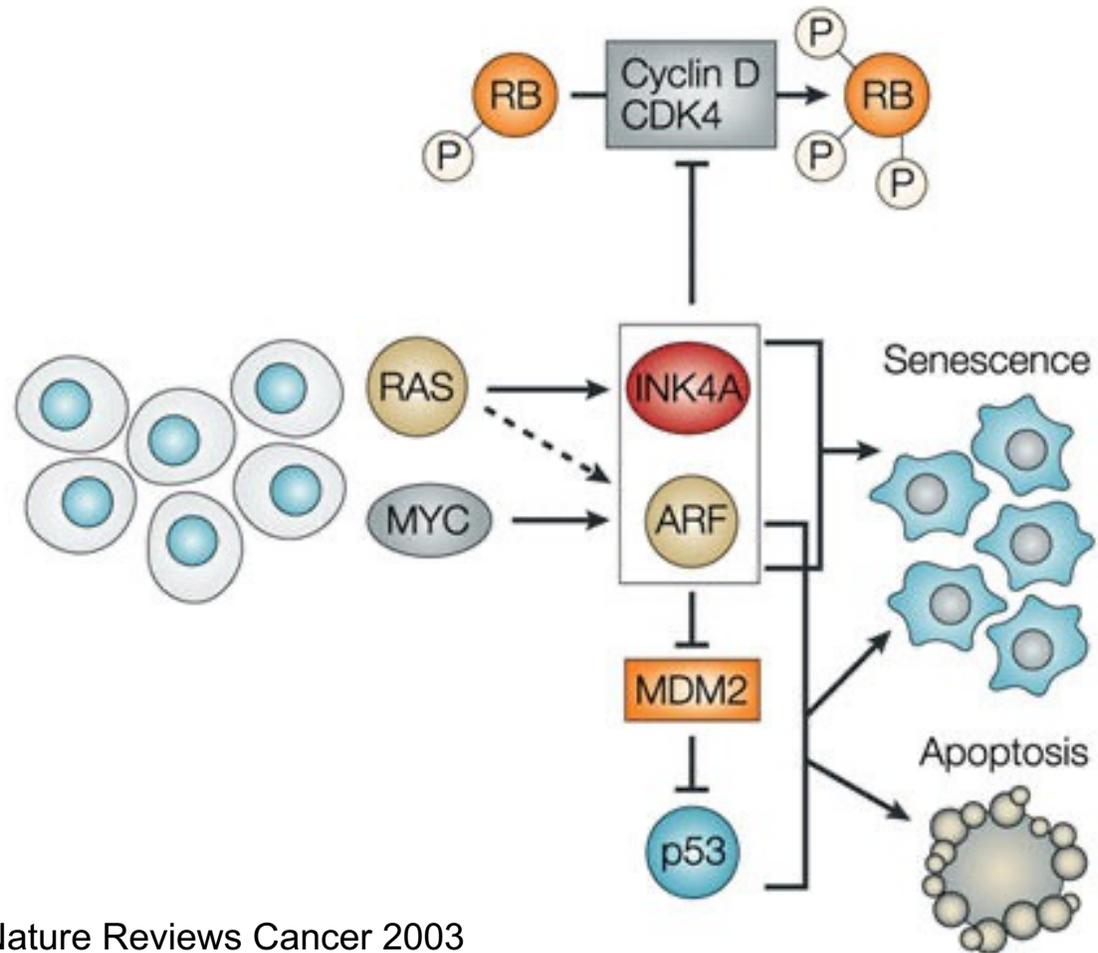
Consulting fees/honoraria: Cytokinetics, Sanofi-Aventis, AstraZeneca, UpToDate

Sponsored research agreement: Genentech

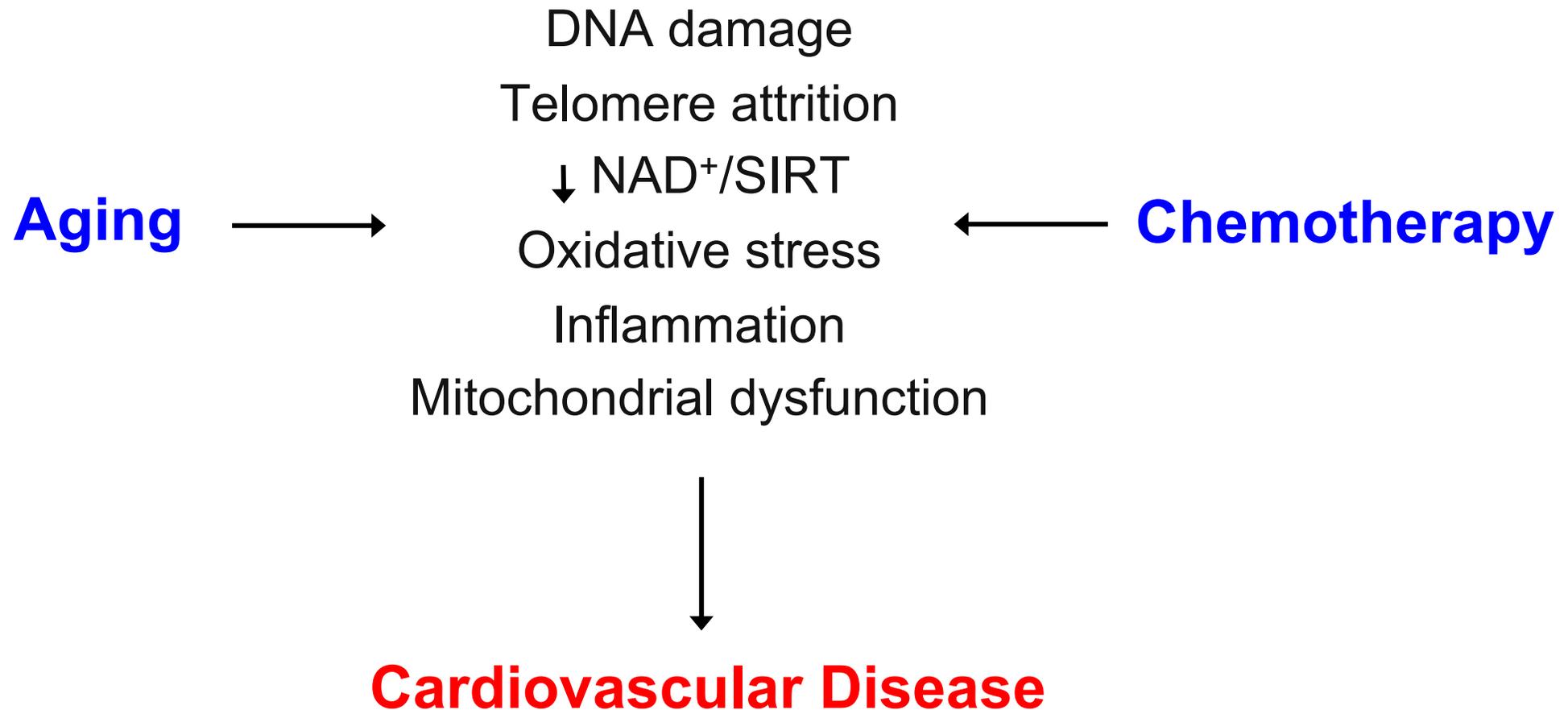
None relevant to this presentation

What is cellular senescence?

The process by which damaged cells permanently exit the cell cycle

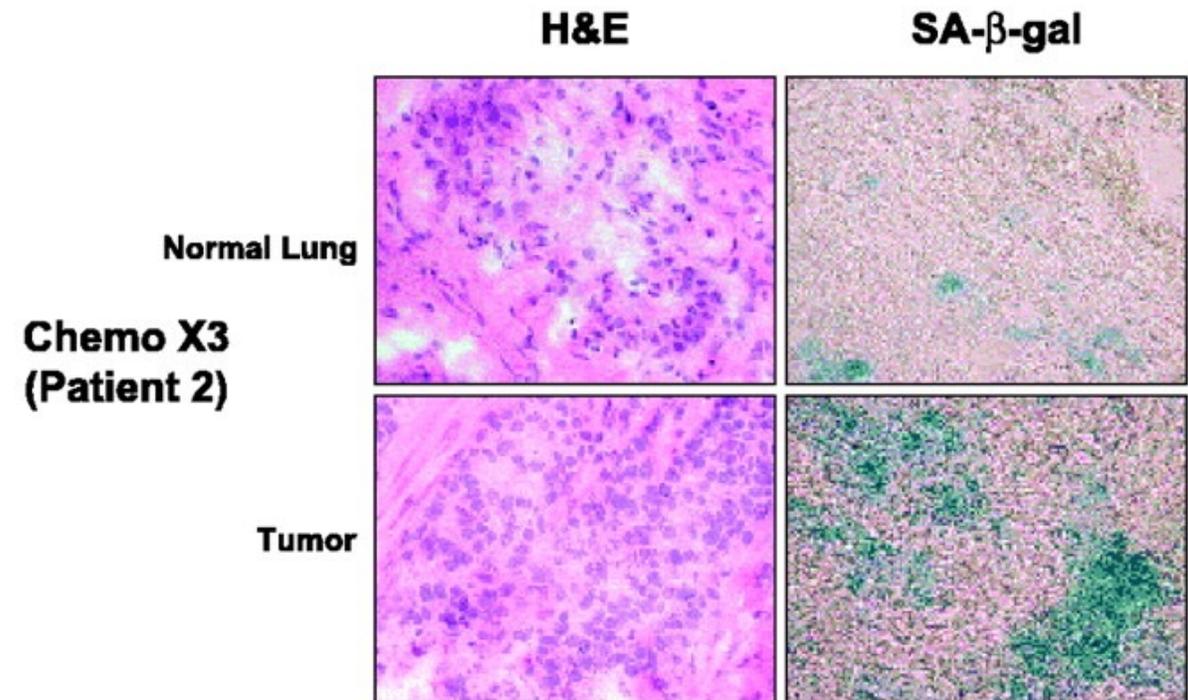


Shared pathways leading to senescence

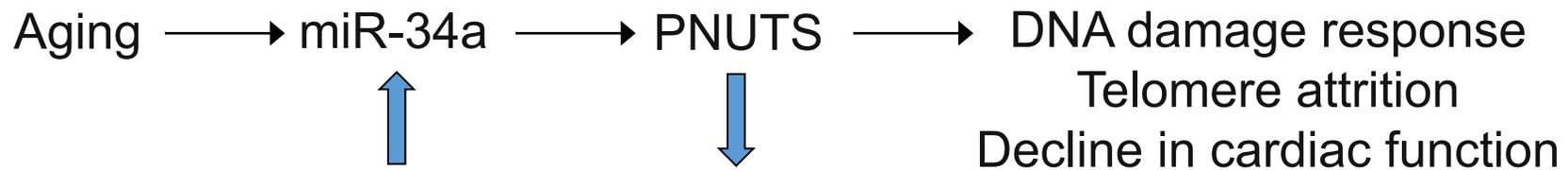
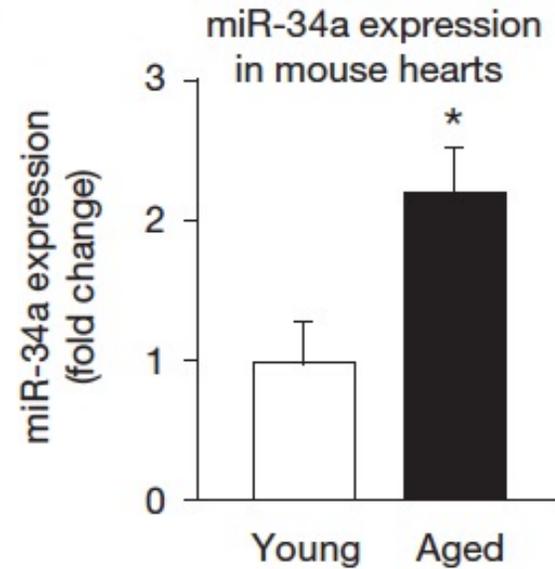
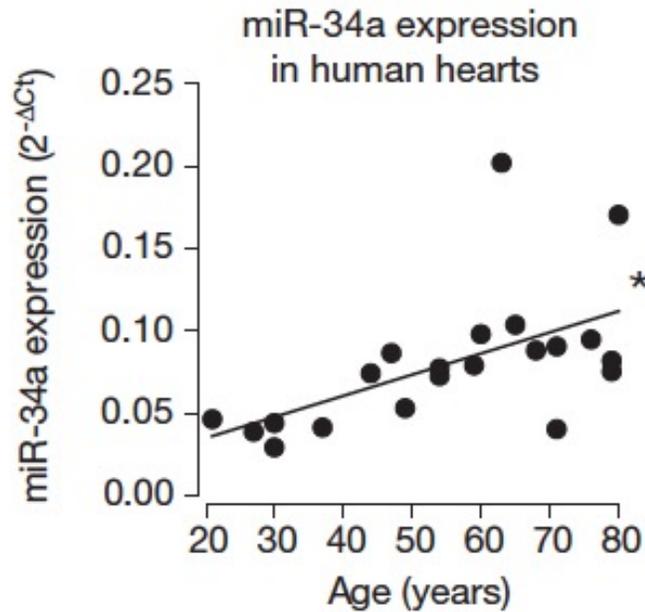


Chemotherapy induces senescence in tumor cells

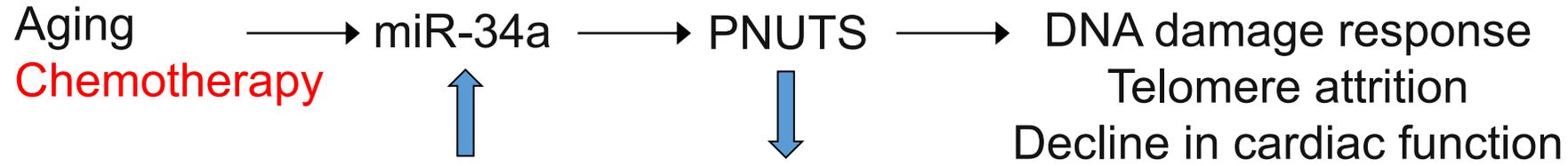
Agent	Mechanism
Aphidocolin	DNA polymerase inhibitor
Bleomycin	DNA damage
Camptothecin	DNA damage
Carboplatin + docetaxel	DNA damage
Cisplatin	DNA damage
Cyclophosphamide + doxorubicin	DNA damage
5-Fluorouracil	DNA damage
Diaziquone/AZQ	DNA damage
Doxorubicin	DNA damage
Epigallocatechin gallate	Telomerase inhibition
Etoposide	DNA damage
Gamma irradiation	DNA damage
Hydroxyurea	ROS
K858	KIF11
Lovastatin	HMG-CoA-reductase inhibitor
Mitoxantrone	DNA damage
MLN4924	Cul1 SCF subunit inhibitor
MLN8054	Aurora kinase A inhibitor
Pyrithione	Zinc/calcium regulation, ROS
Resveratrol	ROS



Does senescence occur in the heart?

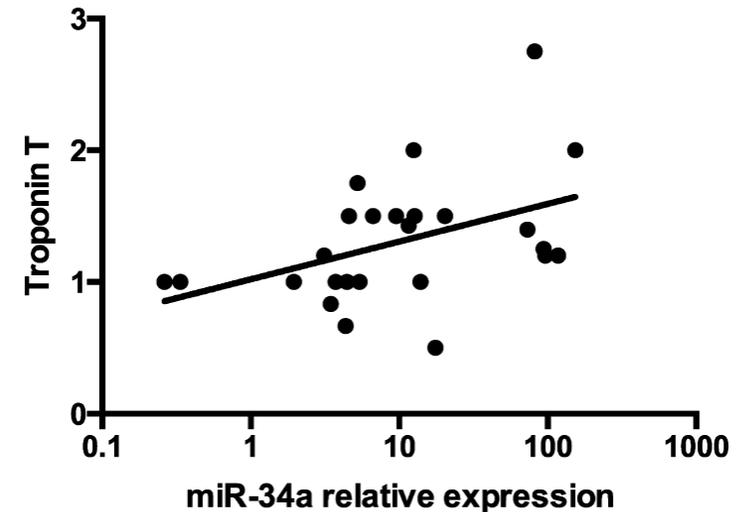


Does senescence occur in the heart of patients with cancer?



- Anthracyclines
- Alkylating agents
- Taxanes
- Cisplatin

Correlation between upregulation of plasma miR-34a and troponin T



$p < 0.05$, $r = 0.47$, $n = 25$

Senolysis protects the heart against doxorubicin

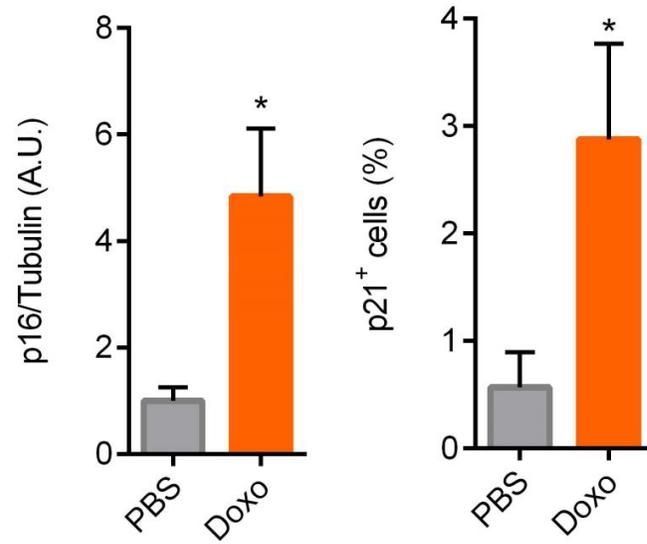
Doxorubicin
10 mg/kg IP



5 days

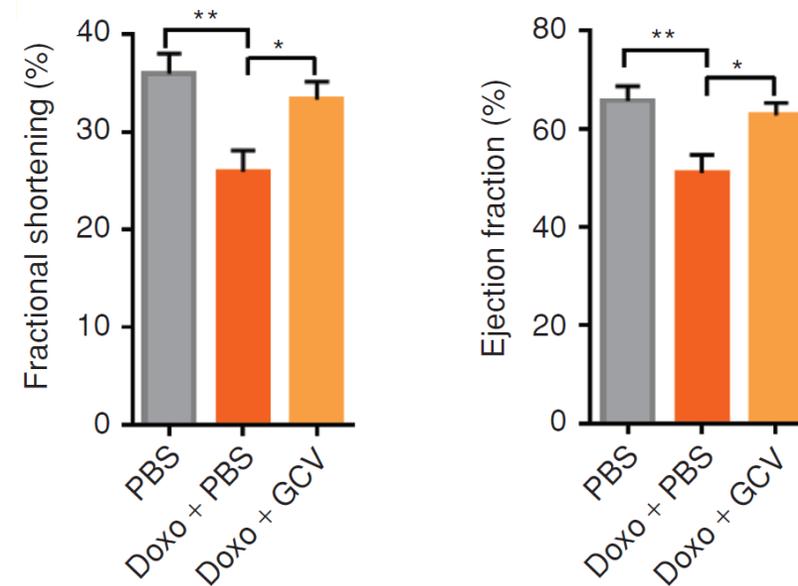
Ganciclovir
25 mg/kg IP

Induction of $p16^{INK4a}$ and $p21$ in the heart*



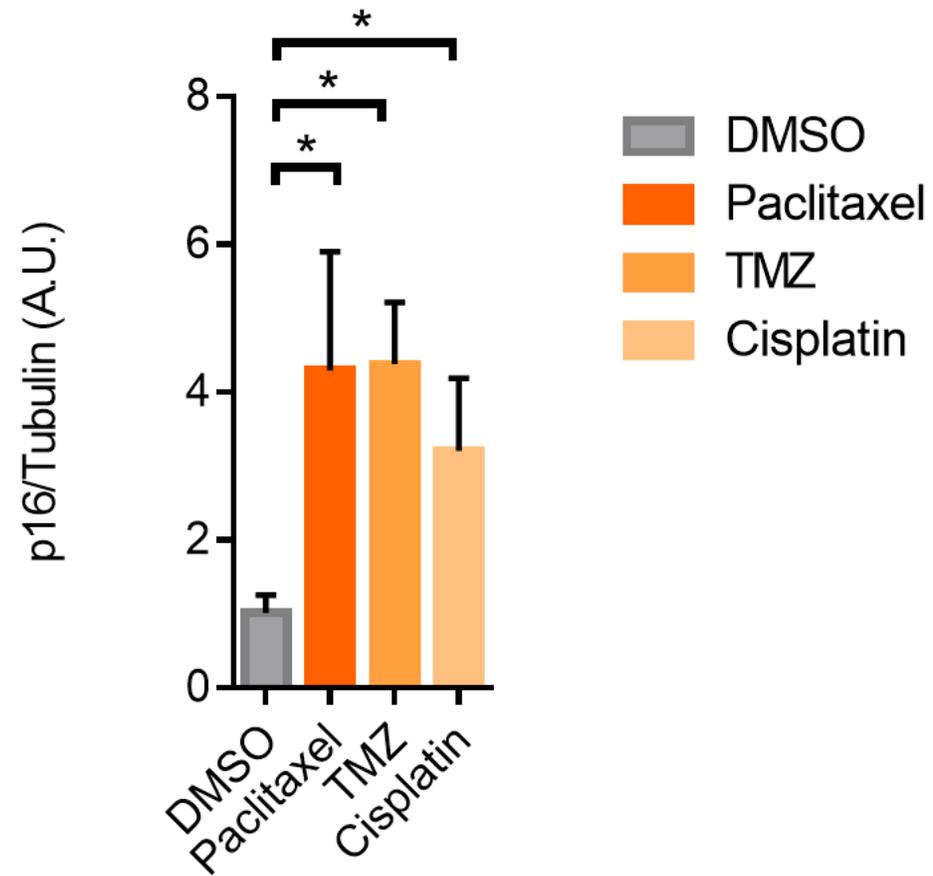
*Endothelial cells and fibroblasts

Rescue of cardiac function with ganciclovir

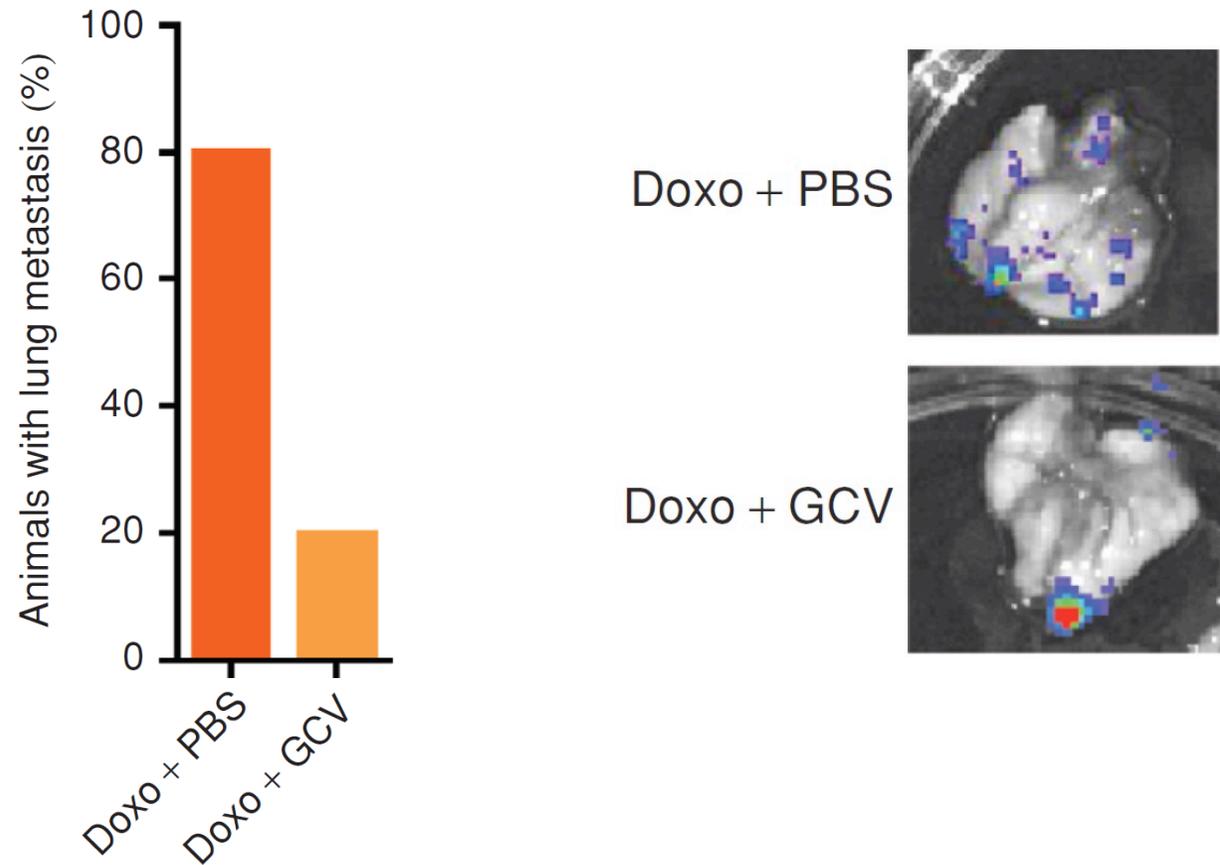


Demaria M, Cancer Discovery 2017

Other chemotherapies induce senescence in non-cancerous tissues



What is the effect of senolysis on cancer outcomes?



Summary and future directions

Therapies targeting senescence could be beneficial in patients at risk for cancer treatment-associated heart toxicity.

Unmet needs for future research include:

- Molecular markers that are more specific for cellular senescence
- Clarification of the cardiovascular cell type(s) most affected by cancer therapy-induced senescence
- Preclinical platforms that enable evaluation of the effects of senolytic therapies on the cardiovascular system and tumor within the same model