A múlt év legfontosabb közleményei az onkokardiológiában

Újdonságok az alapkutatásban

Dr. Czuriga Dániel PhD
Debreceni Egyetem Klinikai Központ,
Kardiológiai és Szívsebészeti Klinika

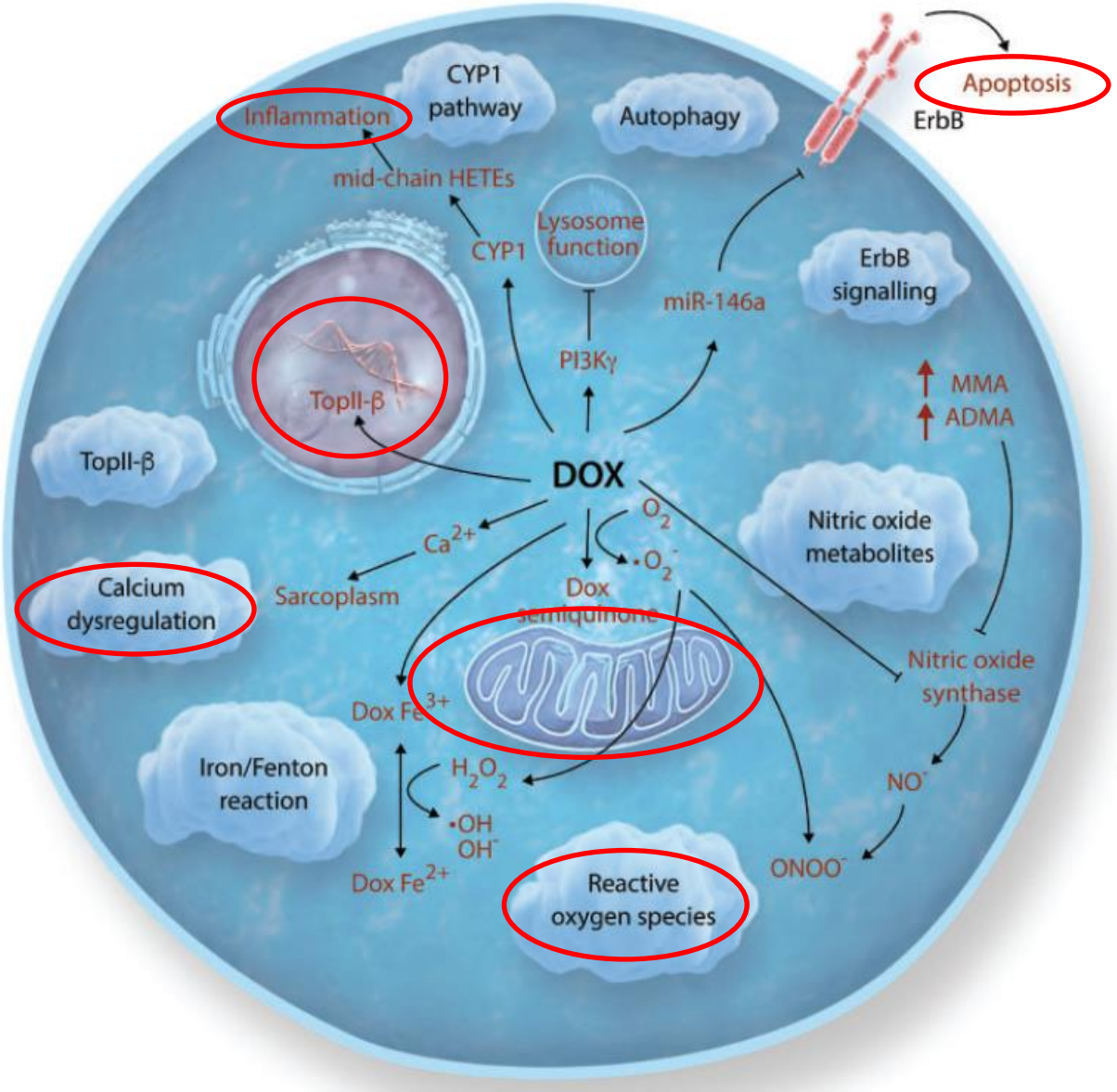
III. ONKO-KARDIOLÓGIAI NAPOK

2019. Szeptember 13.

Four Points by Sheraton Kecskemét Hotel & Konferenciaközpont****

DEBRECENI EGYETEM

A DOX kardiotoxicitás molekuláris mechanizmusai



Raber et al. Cardiovasc Res. 2019;115(5):915-921.

Az antraciklin kardiotoxicitás kivédésének újabb lehetőségei

ESC European Society of Cardiology
Cardiovascular Research (2019) **115**, 915–921
doi:10.1093/cvr/cvz023

SPOTLIGHT REVIEW

Cardioprotection in cancer therapy: novel insights with anthracyclines

Inbar Raber[1,2] and Aarti Asnani[2,3]*

Table 1 Summary of currently available and emerging cardioprotective therapies

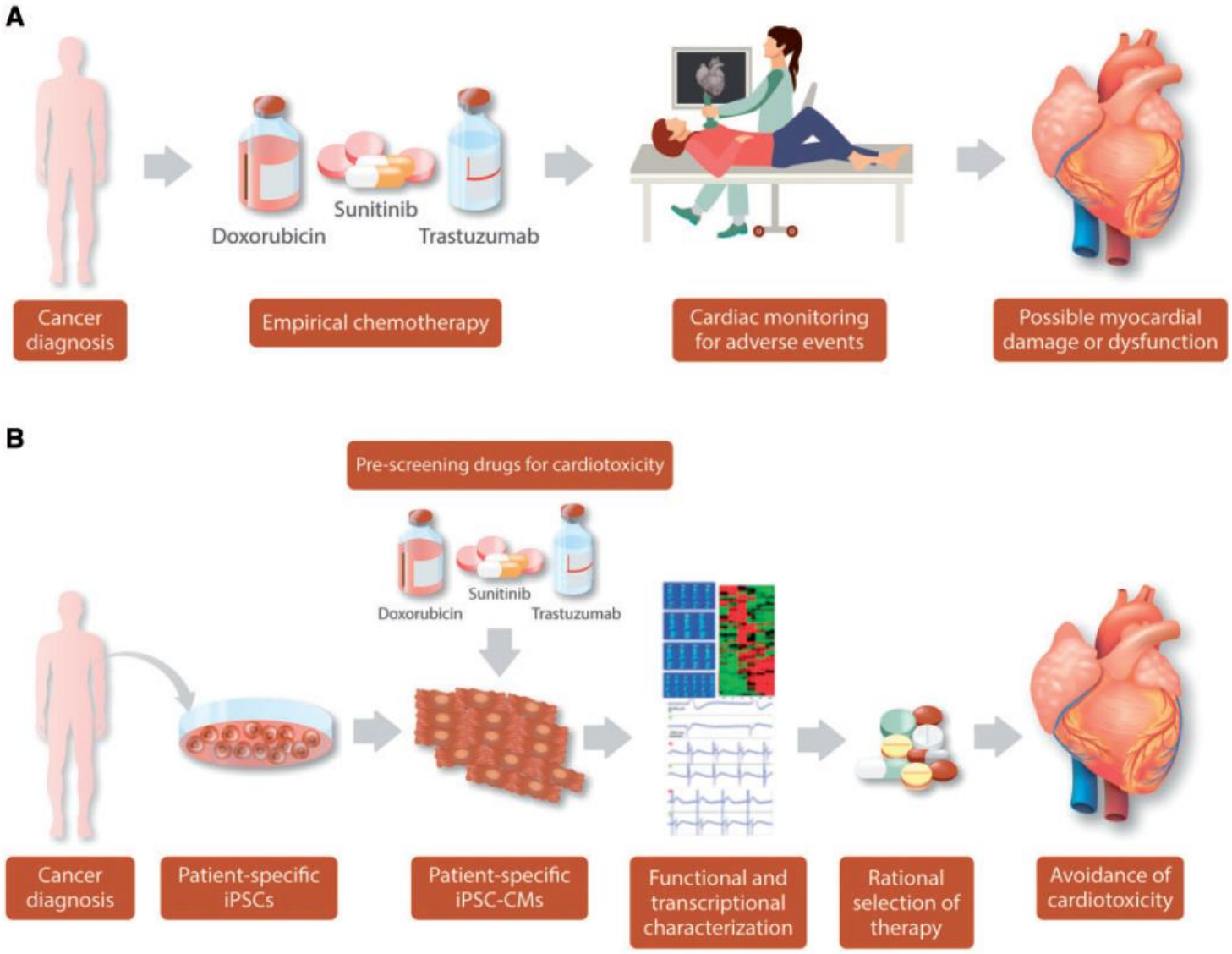
Therapy	Proposed mechanism(s)	Level of evidence	Limitations
Currently available cardioprotective therapies			
Dexrazoxane	Iron chelator, antioxidant, and Top2β inhibitor	Preclinical studies and large randomized controlled trials[13–19]	Concerns regarding cancer outcomes and secondary malignancies[16,17]
Beta-blockers	Reduce catecholamine-induced myocardial remodelling; may have antioxidant effects	Preclinical studies and small randomized controlled trials[20–23]	Conflicting data regarding efficacy and ideal patient population[24]
ACE inhibitors, ARBs	Inhibit renin–angiotensin–aldosterone system	Preclinical studies and small randomized controlled trials[25,27,28]	Conflicting data regarding efficacy and ideal patient population[29]
Statins	Anti-inflammatory and antioxidant effects	Observational cohort studies[30,31]	Unknown efficacy in patients
Emerging cardioprotective therapies			
MPO inhibitors	Antioxidant effects	Preclinical studies—*in vivo* animal models[34]	Unknown efficacy in patients
Arginase inhibitors	Increase arginine and nitric oxide	Preclinical studies—*in vivo* animal models[35]	Unknown efficacy in patients
P13K inhibitors	Stimulate autophagic flux	Preclinical studies—*in vivo* animal models[36]	Unknown efficacy in patients
Neuregulin	Activates ErbB signalling	Preclinical studies—*in vivo* animal models[37,38]	Potential for pro-neoplastic effects; unknown efficacy in patients
CYP1 inhibitors	Under investigation	Preclinical studies—*in vivo* animal models[39]	Unknown efficacy in patients

Jelen

Jövő

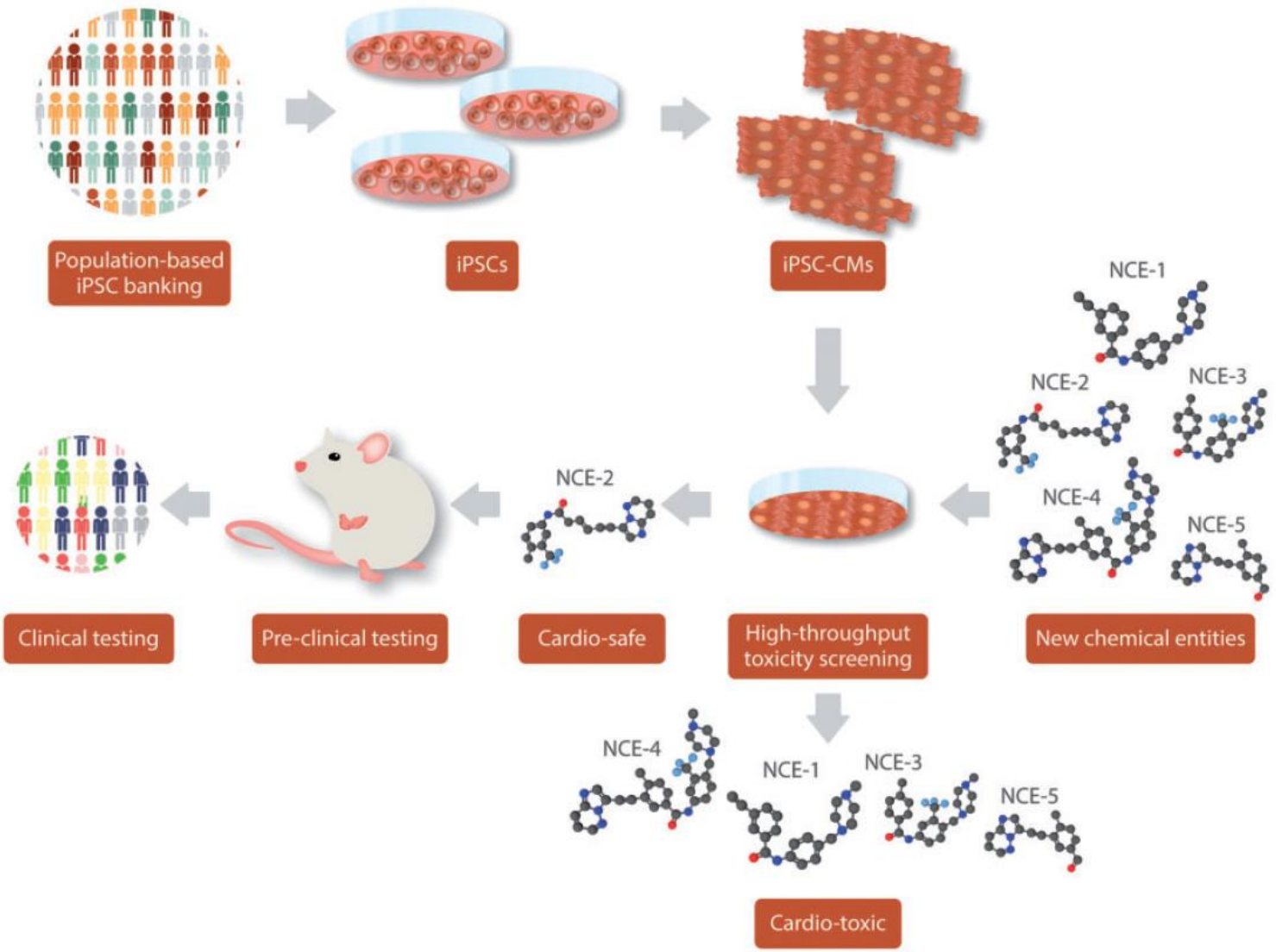
Raber et al. Cardiovasc Res. 2019;115(5):915-921.

Indukált pluripotens őssejt kutatások onkokardiológiai vonatkozásai



Sayed et al. Cardiovasc Res. 2019;115(5):949-959.

Indukált pluripotens őssejt kutatások onkokardiológiai vonatkozásai



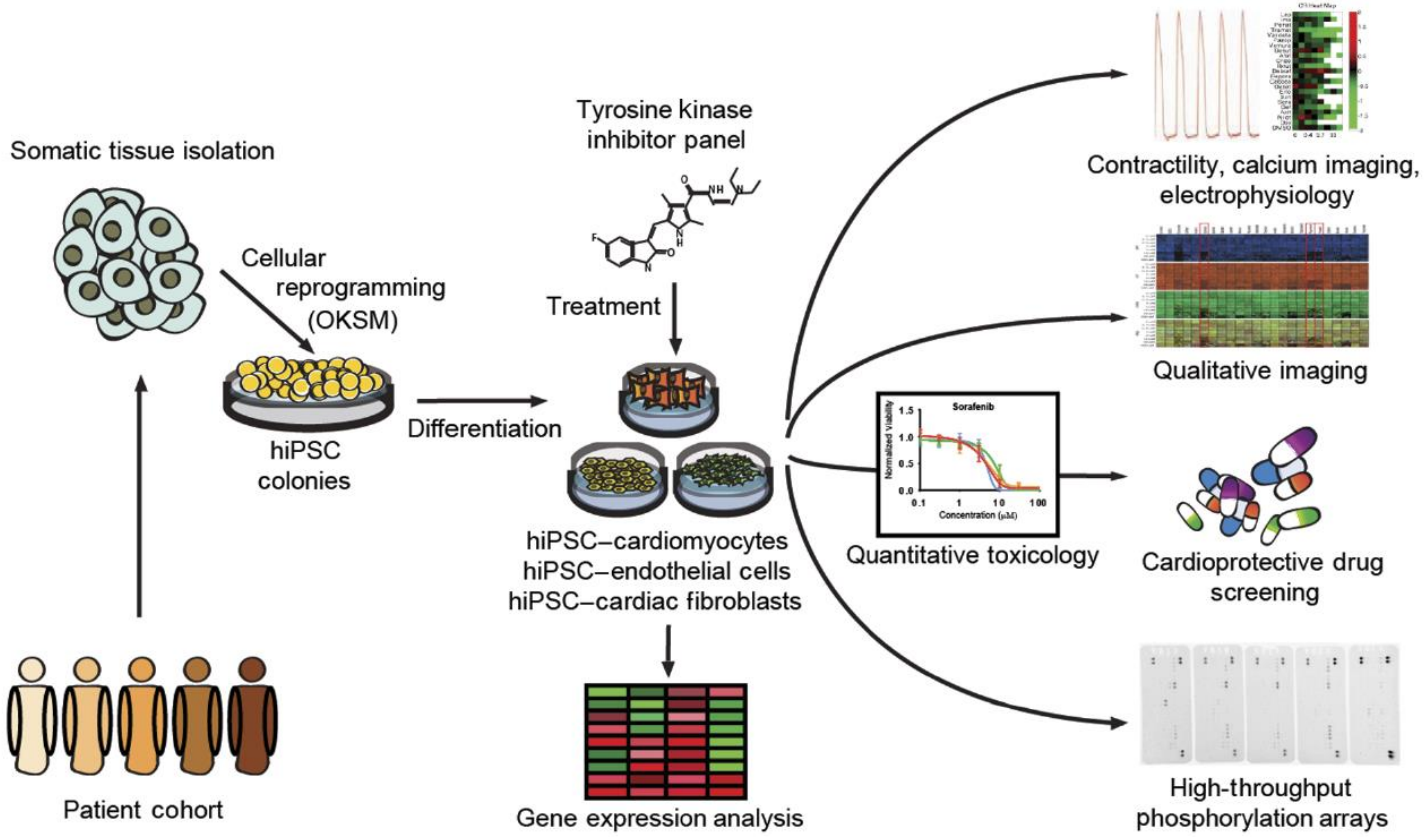
Sayed et al. Cardiovasc Res. 2019;115(5):949-959.

Indukált pluripotens őssejt kutatások onkokardiológiai vonatkozásai

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

TOXICITY SCREENING

High-throughput screening of tyrosine kinase inhibitor cardiotoxicity with human induced pluripotent stem cells



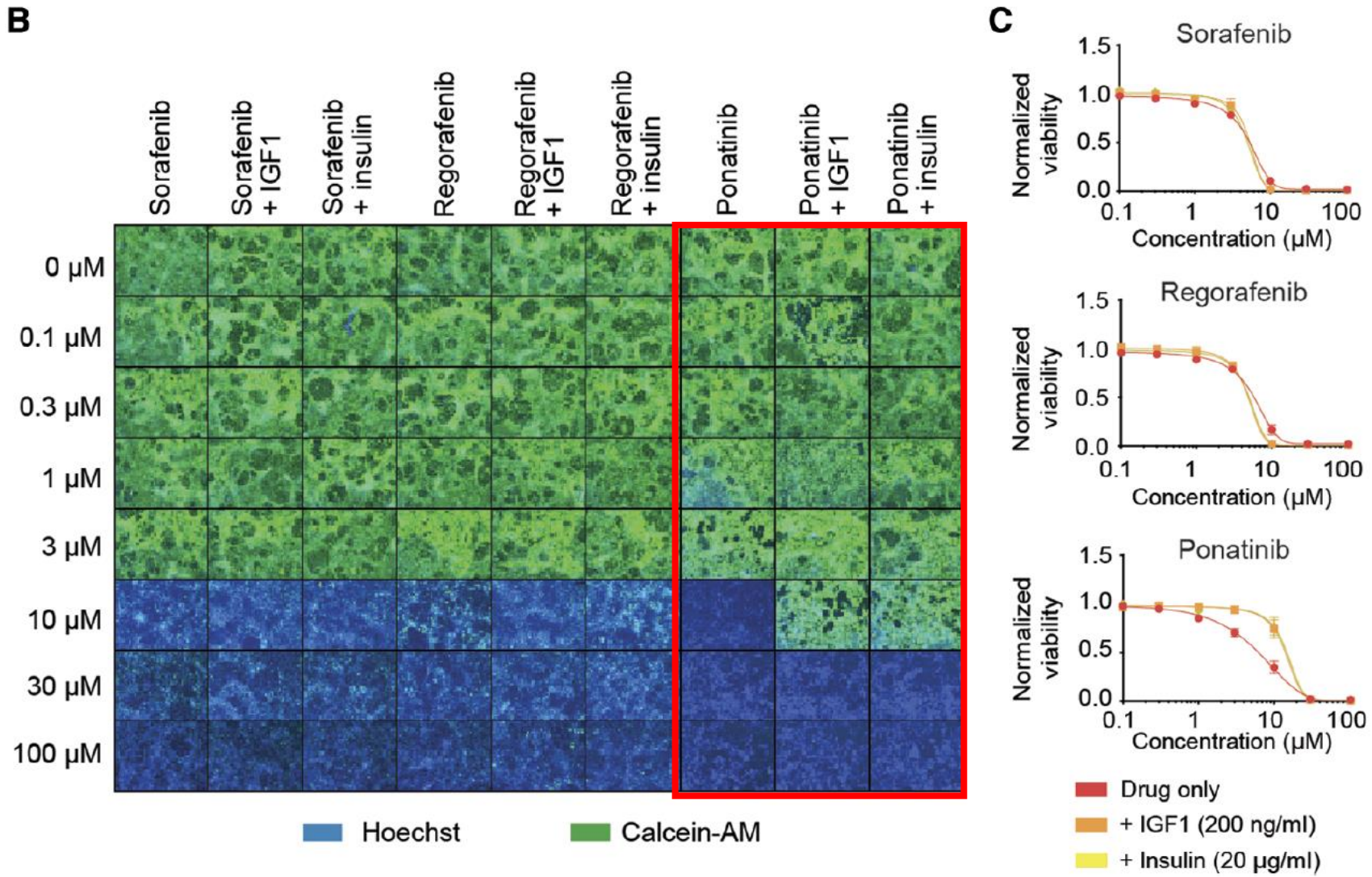
Sharma et al. Sci Transl Med. 2017 Feb 15;9(377)

Indukált pluripotens őssejt kutatások onkokardiológiai vonatkozásai

Drug	Cessation of beating (μM)	Effective concentration (μM)	Amplitude of effect	LD_{50} (μM)	C_{max} (μM)	Cardiac safety index	Clinically reported cardiotoxicity
Vemurafenib	33	11.00	0.34	32.10	126.04	0.003	QT
Sorafenib	3.7	2.51	1.03	3.40	8.43	0.004	QT, LV, HF, MI, Hy
Doxorubicin	3.7	1.20	0.60	0.78	2.93	0.010	****HF, LV**
Regorafenib	11	3.70	0.84	7.10	8.08	0.010	#MI, Hy
Vandetanib	33	5.68	2.47	20.60	4.26	0.041	****QT, TdP, SCD, HF, Hy**
Crizotinib	11	1.91	0.59	8.60	1.24	0.063	QT, Brady
Nilotinib	100	8.31	2.65	29.00	4.27	0.104	****QT, LV, Vas**
Imatinib	100	33.00	1.59	78.20	5.11	0.126	LV (rare)
Lapatinib	33	11.00	0.40	100.76	2.30	0.209	#LV, QT
Sunitinib	3.7	0.81	1.33	12.70	0.18	0.218	#HF, LV, MI, QT, Hy
Bosutinib	33	4.73	1.92	12.39	0.51	0.315	PE
Gefitinib	33	3.11	1.24	26.30	0.45	0.409	None
Afatinib	3.7	1.65	1.11	12.30	0.10	0.444	None
Dabrafenib	100	36.75	0.71	100.68	4.16	0.459	LV
Ponatinib	3.7	3.70	0.54	4.30	0.14	0.483	****Vas, HF, LV, Hy**
Ibrutinib	33	10.01	1.54	11.90	0.37	0.507	Afib
Dasatinib	3.7	1.20	0.31	42.00	0.21	0.524	QT, PE, Hy
Erlotinib	N/A	63.38	0.51	87.60	3.11	0.653	MI (rare)
Pazopanib	N/A	73.86	1.19	N/A	103.08	0.671	#QT, LV (rare)
Cabozantinib	N/A	91.14	1.37	N/A	4.43	0.769	#None
Trametinib	100	33.00	2.37	66.80	0.02	1.000	LV
Axitinib	N/A	71.79	0.44	N/A	0.07	1.000	HF (rare) Hy
DMSO	N/A	100.00	0.58	N/A	N/A	1.000	None

Sharma et al. Sci Transl Med. 2017 Feb 15;9(377)

Indukált pluripotens őssejt kutatások onkokardiológiai vonatkozásai



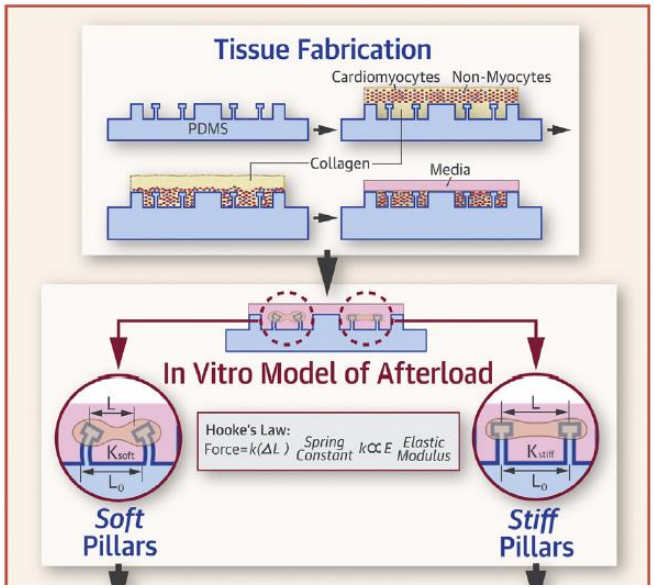
Sharma et al. Sci Transl Med. 2017 Feb 15;9(377)

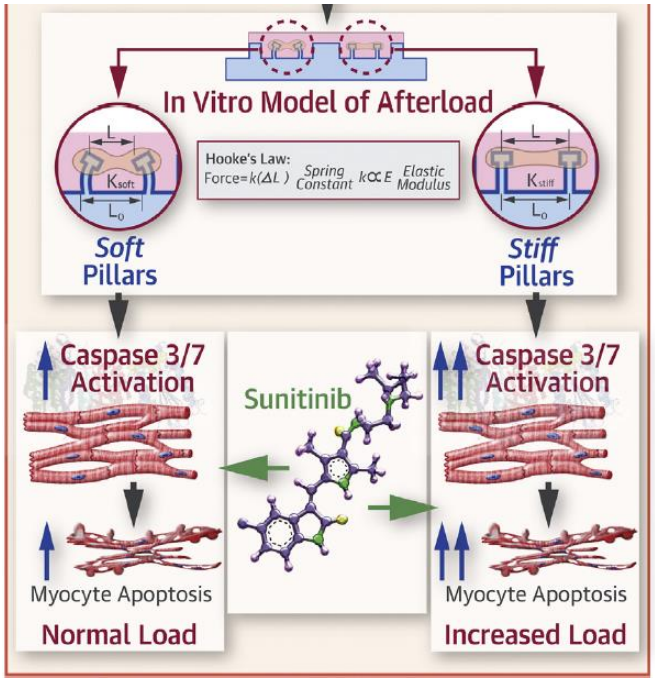
A „tissue engineering” onkokardiológiai vonatkozásai

JACC: BASIC TO TRANSLATIONAL SCIENCE

Increased Afterload Augments Sunitinib-Induced Cardiotoxicity in an Engineered Cardiac Microtissue Model

Rachel Truitt, PhD,[a,b] Anbin Mu,[b] Elise A. Corbin, PhD,[b,c] Alexia Vite, PhD,[b] Jeffrey Brandimarto, PhD,[b] Bonnie Ky, MD, MSCE,[b,d] Kenneth B. Margulies, MD[b]





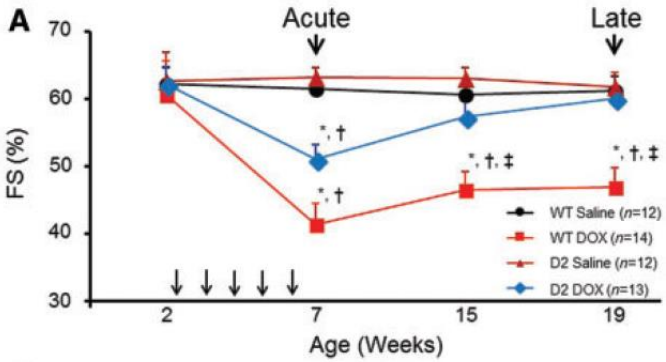
Truitt et al. JACC Basic Transl Sci. 2018;3(2):265-276.

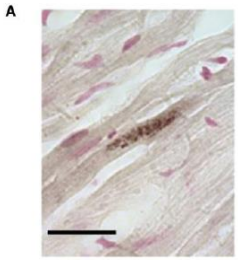
Az antraciklin kardiotoxicitás kivédésének újabb lehetőségei

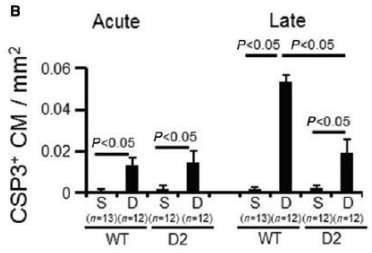
ESC European Society of Cardiology
Cardiovascular Research (2019) **115**, 960–965
doi:10.1093/cvr/cvy273

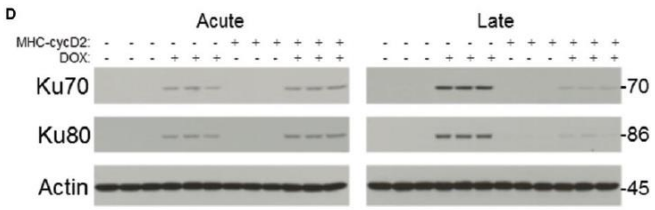
Targeted expression of cyclin D2 ameliorates late stage anthracycline cardiotoxicity

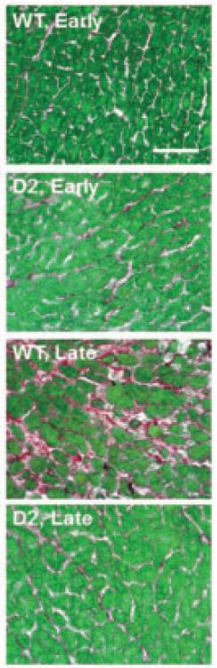
Wuqiang Zhu†, Sean Reuter, and Loren J. Field*









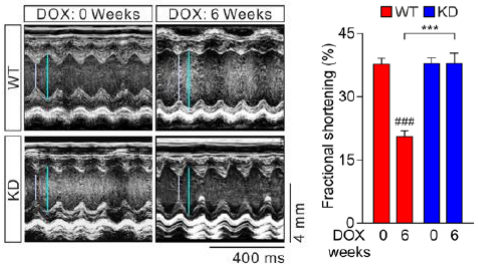


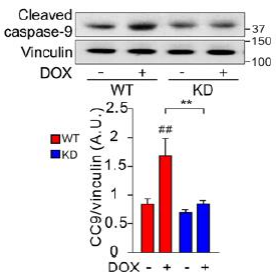
Zhu et al. Cardiovasc Res. 2019;115(5):960-965.

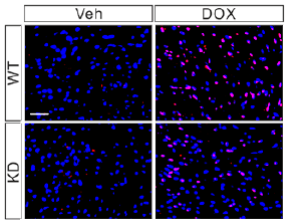
Az antraciklin kardiotoxicitás kivédésének újabb lehetőségei

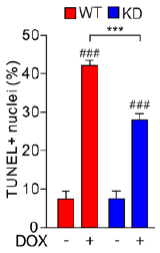
Circulation

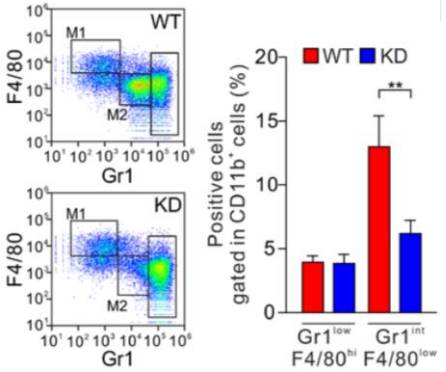
Phosphoinositide 3-Kinase Gamma Inhibition Protects From Anthracycline Cardiotoxicity and Reduces Tumor Growth

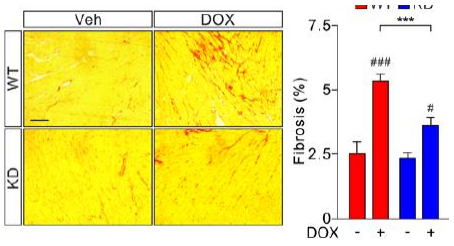


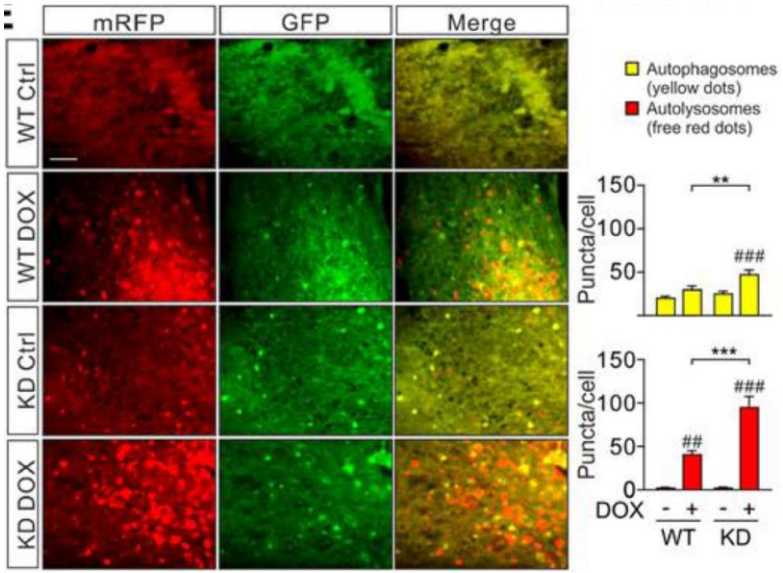


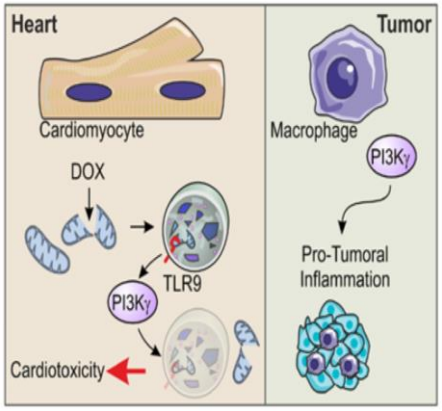


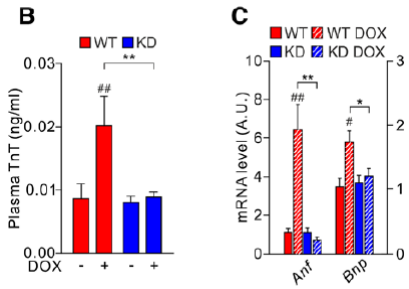












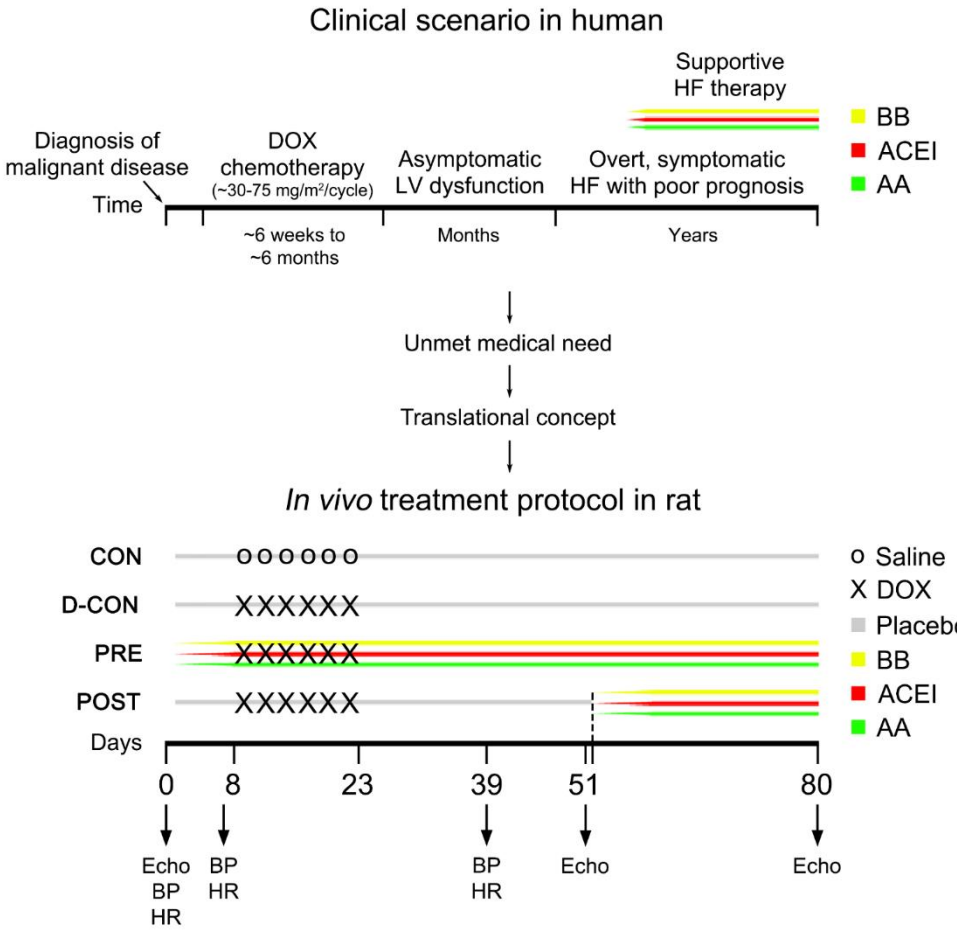
Li et al. Circulation. 2018;138(7):696-711.

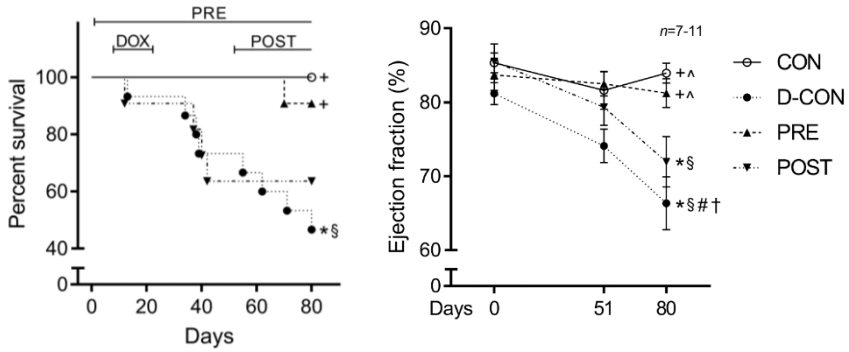
Az antraciklin kardiotoxicitás kivédésének újabb lehetőségei

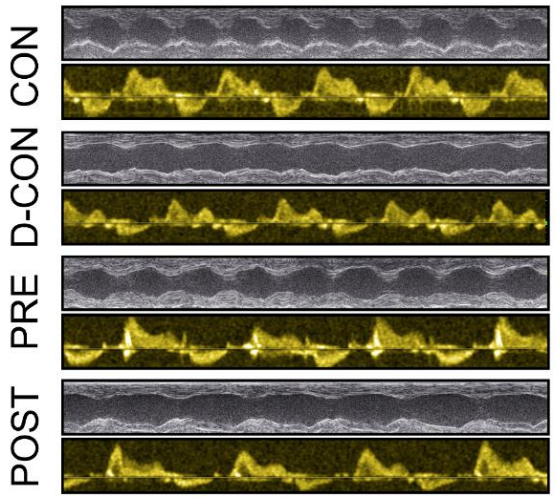
RESEARCH Open Access

Advantages of prophylactic versus conventionally scheduled heart failure therapy in an experimental model of doxorubicin-induced cardiomyopathy

Mária Lódi[1], Dániel Priksz[2], Gábor Áron Fülöp[1], Beáta Bódi[1], Alexandra Gyöngyösi[3], Lilla Nagy[8], Árpád Kovács[1], Attila Béla Kertész[6], Judit Kocsis[4,5], István Édes[6], Zoltán Csanádi[6], István Czuriga[6^], Zoltán Kisvárday[7], Béla Juhász[2], István Lekli[3], Péter Bai[8], Attila Tóth[1], Zoltán Papp[1] and Dániel Czuriga[6*]

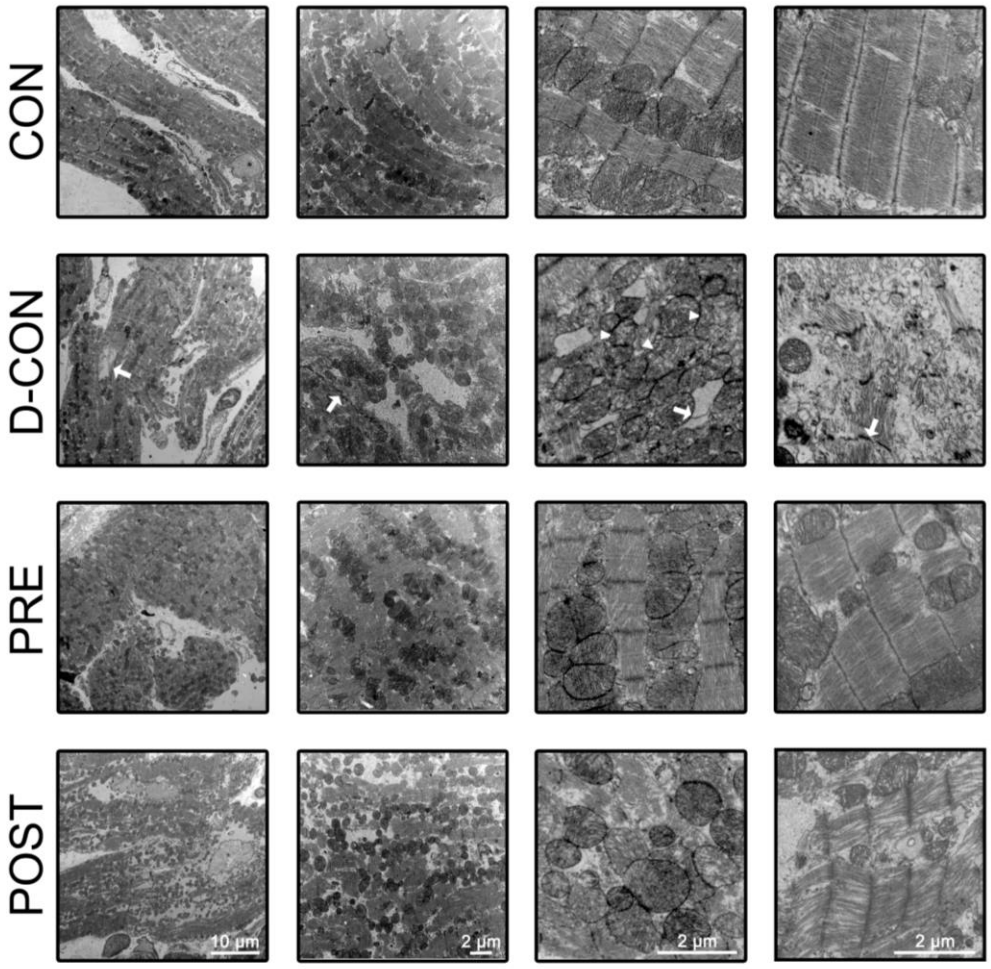


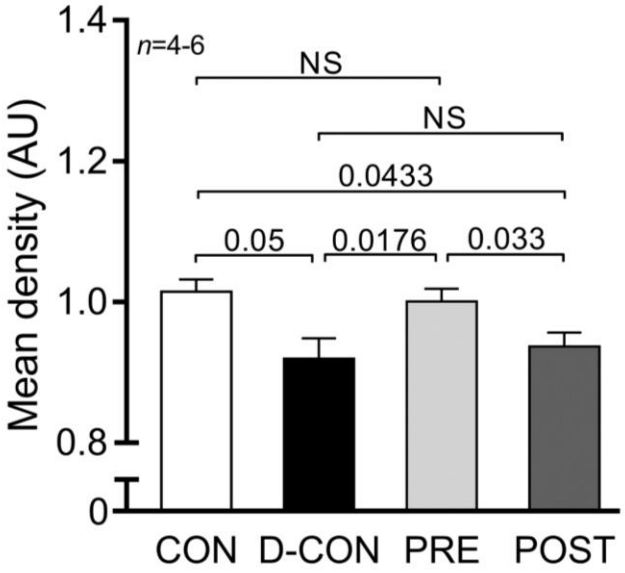




Lódi, … Czuriga et al. *J Transl Med* 2019;17(1):229.

Az antraciklin kardiotoxicitás kivédésének újabb lehetőségei





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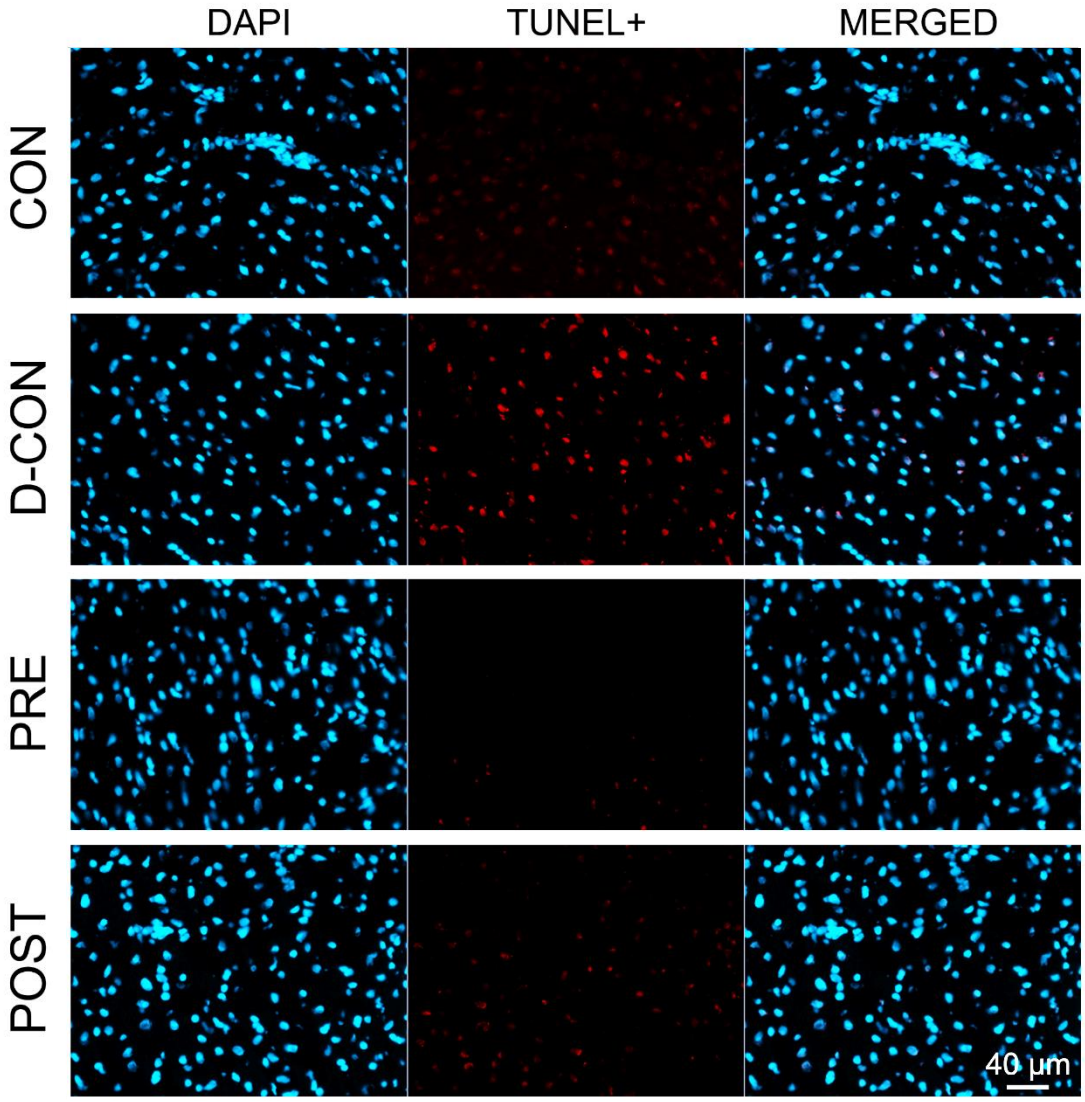

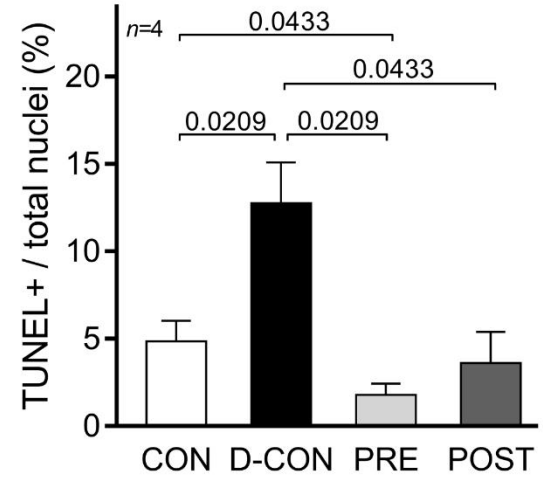

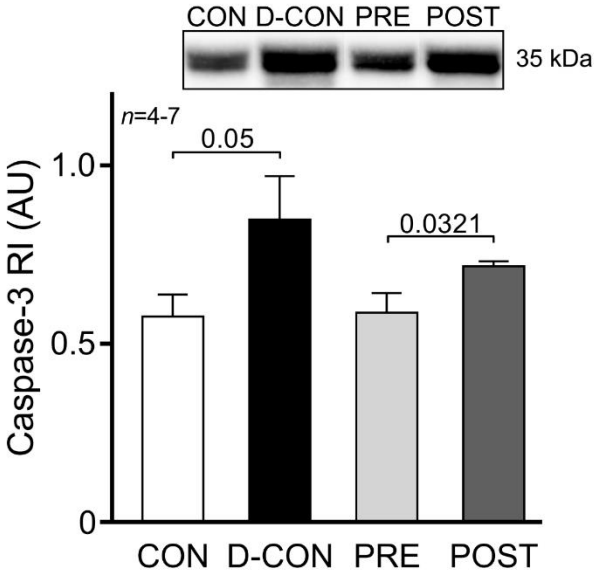

Lódi, … Czuriga et al. *J Transl Med* 2019;17(1):229.

Összefoglalás

- Az onkoterápia okozta kardiovaszkuláris mellékhatások megelőzésének, kivédésének tanulmányozása forrongó területet képez mind a klinikai, mind a preklinikai kutatások terén.
- A korábbi, feltáró jellegű kutatások helyét mindinkább átveszik a transzlációs, precíziós kutatások, azonban az új hatásmechanizmusokra irányuló eredmények továbbra is fontos információkat hordoznak.
- Valószínűsíthető, hogy a jövőben a kardiotoxikus mellékhatások kivédésére olyan komplex klinikai megközelítésre lesz szükség, mely ötvözni képes a beteg kardiovaszkuláris státuszát, komorbiditásait, életmódját, az alkalmazott daganatellenes szerre mutatott egyéni toleranciáját, valamint az elérhető legelőnyösebb preventív gyógyszeres kezelést.

Köszönöm a figyelmet!