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Off-label use of statins for the prevention of radiation-induced normal tissue damage

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Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

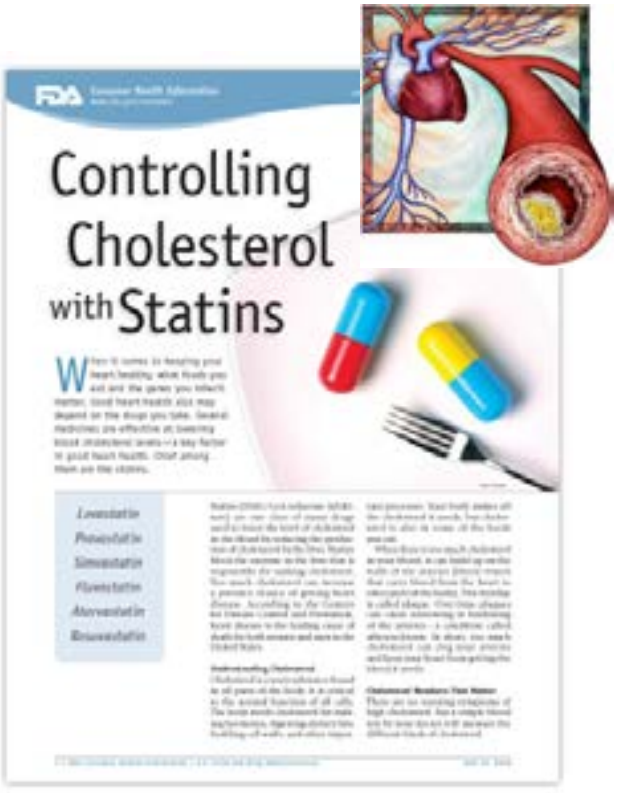
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

Pharmacological modulation of radiation-induced normal tissue damage – criteria to be considered....

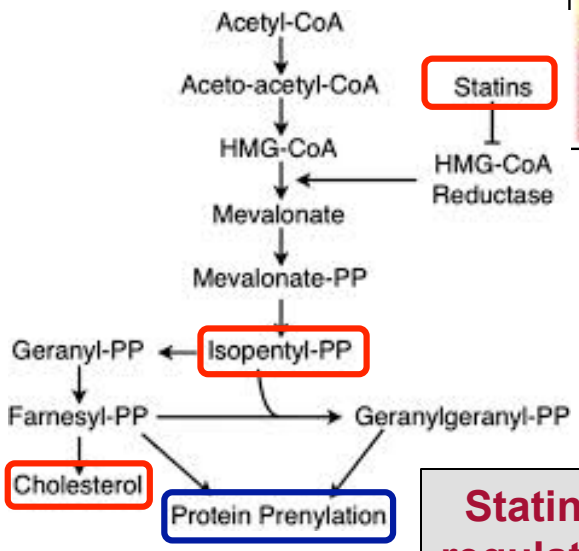
- *What is the best target ? –*

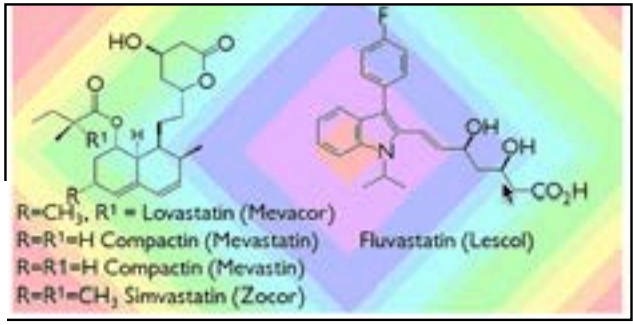
- *What is a best druggable target ? –*

- Are clincally approved drugs (with good safety profile) available for targeting? -



Statins and Cholesterol





Statins inhibit the prenylation of regulatory GTPases (i.e. Rac1/Rho)

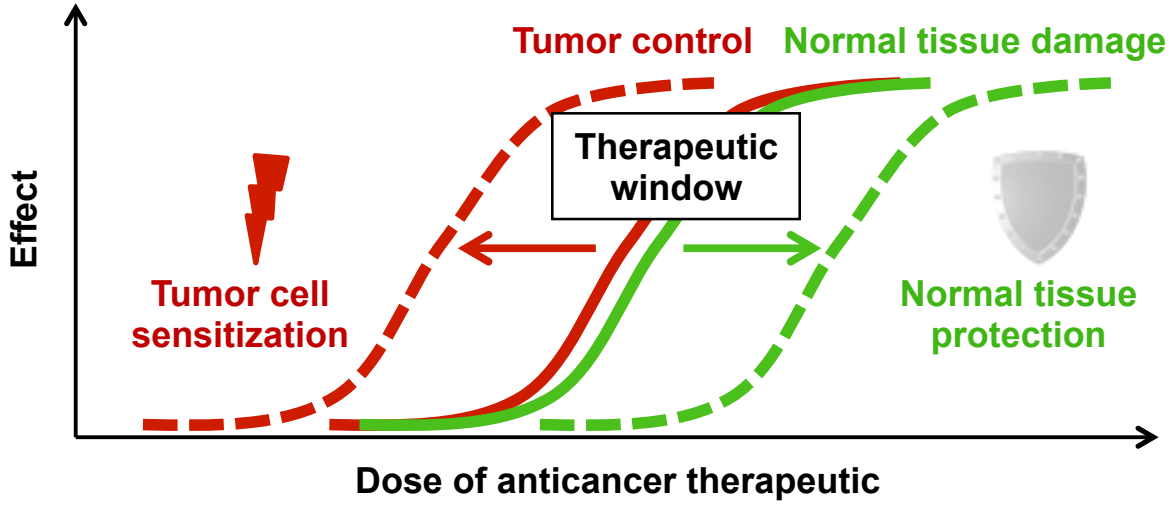
Working hypothesis

Off-label use of statins reduces the incidence and severeness of radiotherapy-induced

LUNG TOXICITY

- Widening of the therapeutic window of IR

- Improving the quality of life of cancer patients



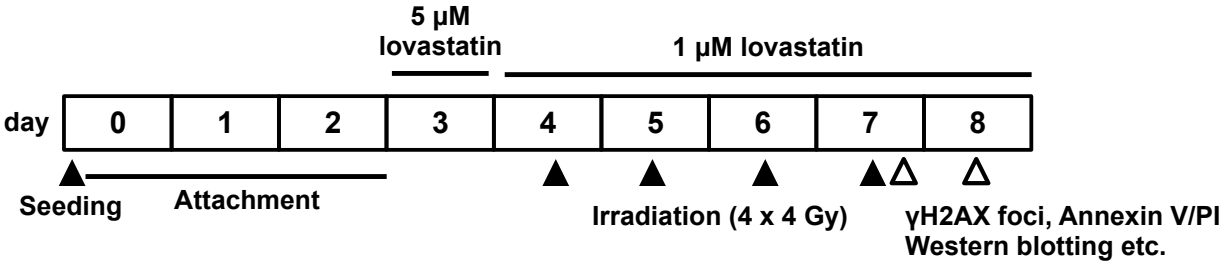
In vitro model system – non-proliferating primary human lung cells

A

HMVEC-L (Human microvascular **endothelial** cells of the lung)

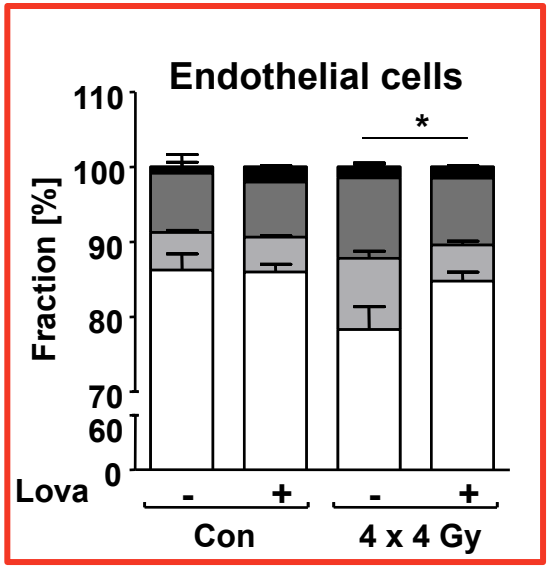
HPF (Human pulmonary **fibroblasts**)

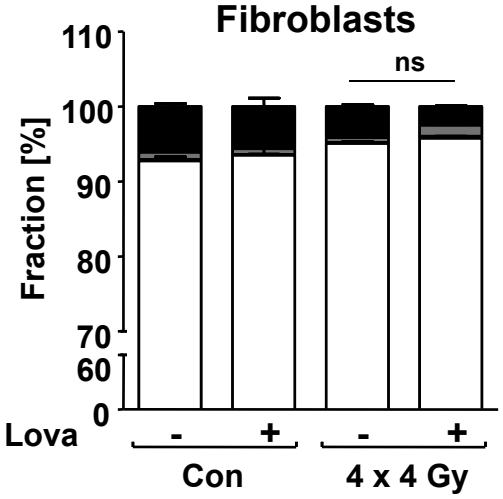
HSAEpC (Human small airway **epithelial** cells)

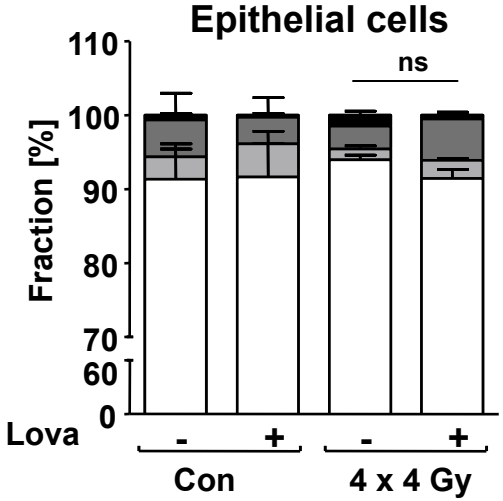


B

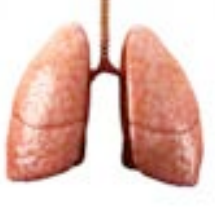
Apoptosis (TUNEL assay)







Lovastatin promotes DSB repair following fractionated irradiation of primary human lung cells *in vitro*



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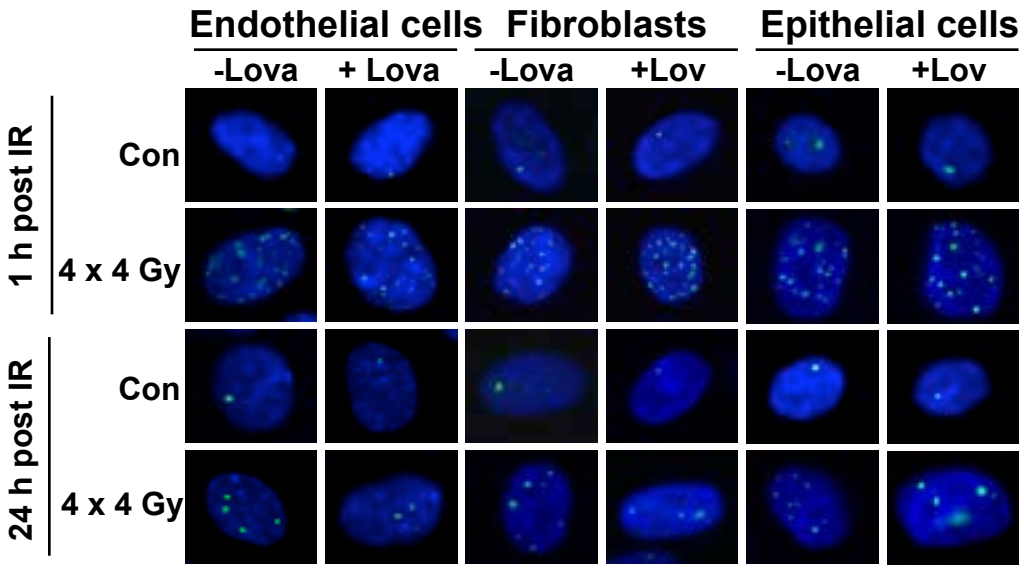
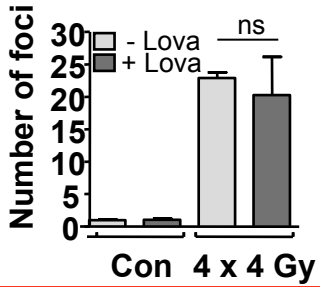


DNA damage

1 nuclear γH2AX focus
=
1 DSB

B



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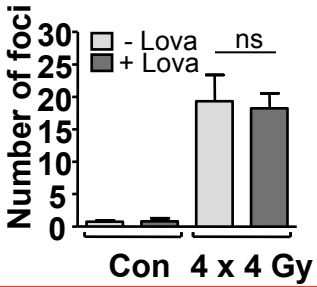

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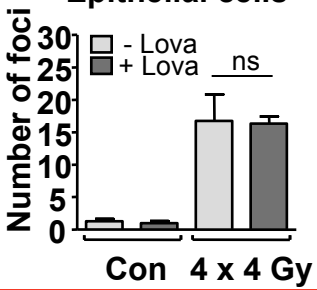
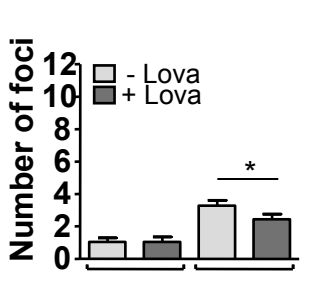


1 h post IR

C



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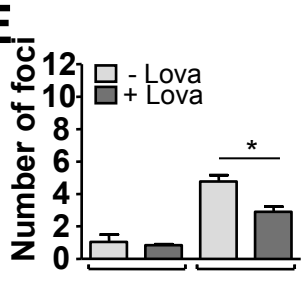

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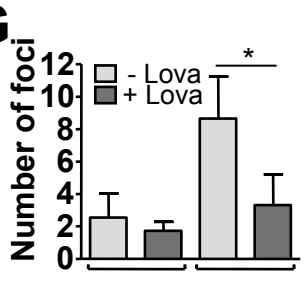
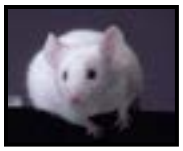
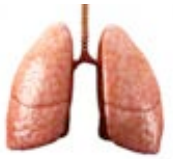


24 h post IR

Residual DSBs
=
Indicative of DSB repair

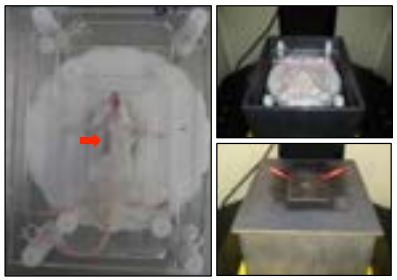


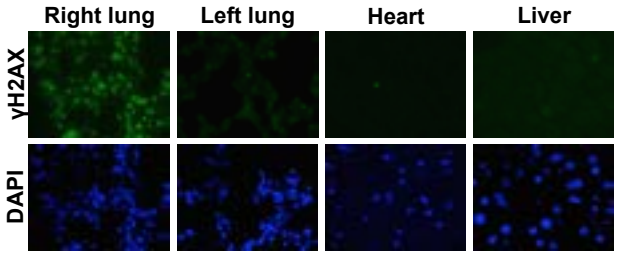
Lovastatin and the Rac1 inhibitor EHT1864 protect from fractionated IR-induced lung cell apoptosis

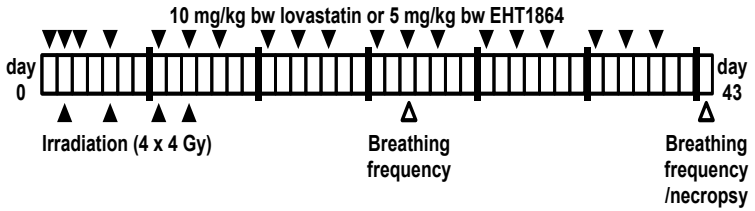


Model: Hypofractionated irradiation of the right lung (4 x 4 Gy)
- Analysis after 4 weeks (subacute model) -

A

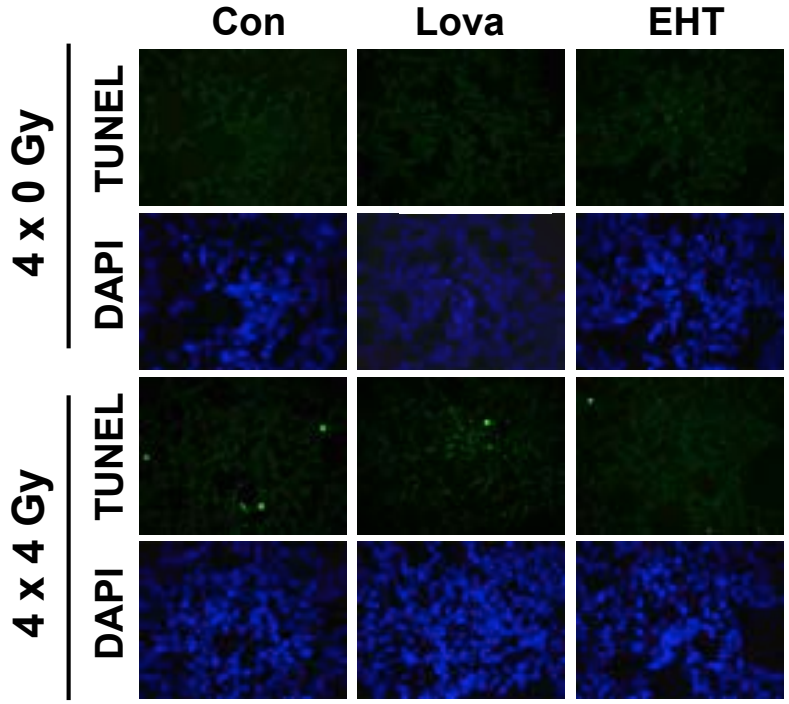


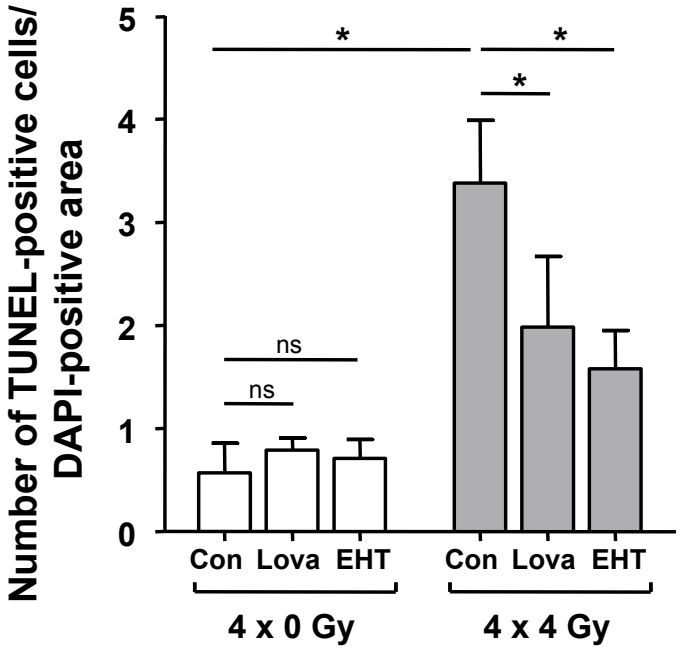




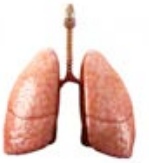
B

Apoptosis (TUNEL assay)



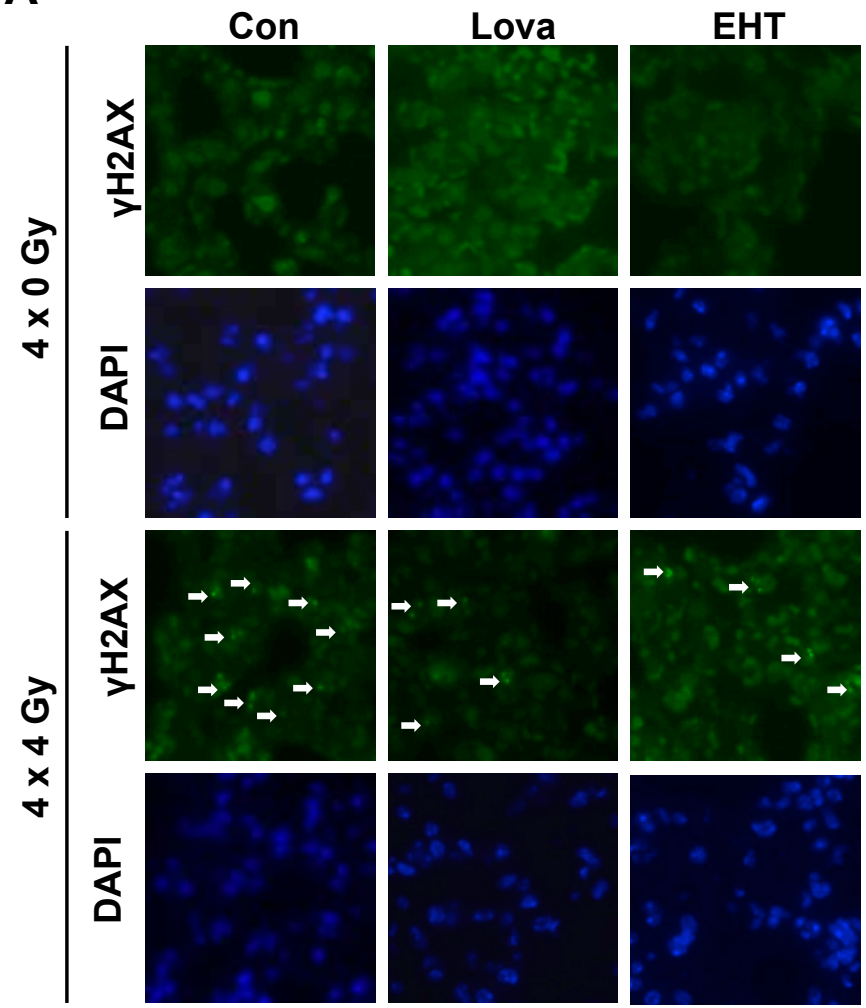


Lovastatin and EHT1864 reduce fractionated IR-stimulated residual DNA damage (DSBs) in lung tissue

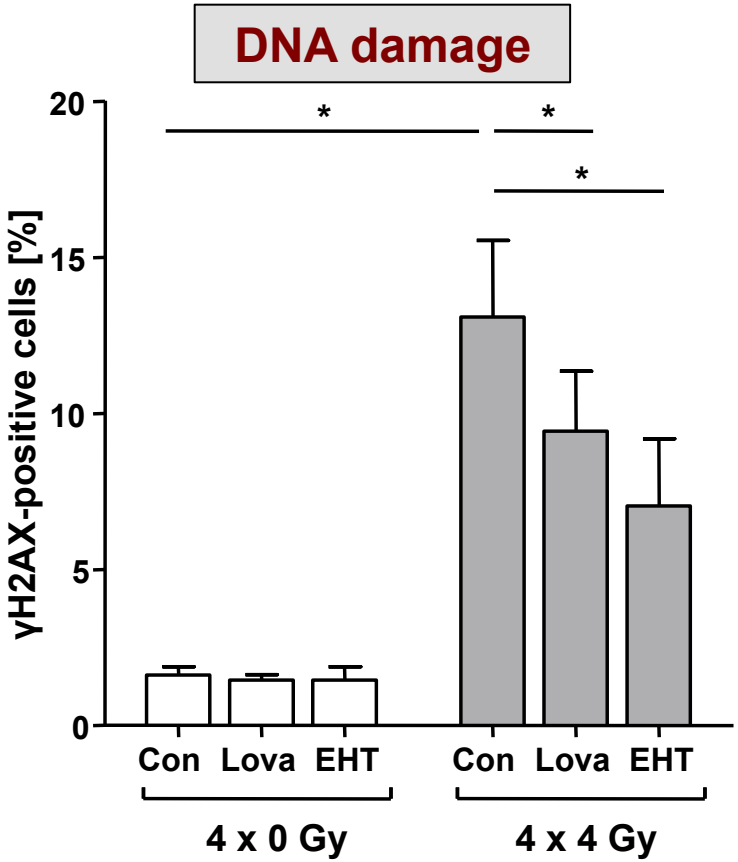


Subacute model

A

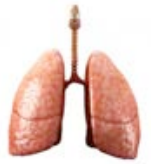


B



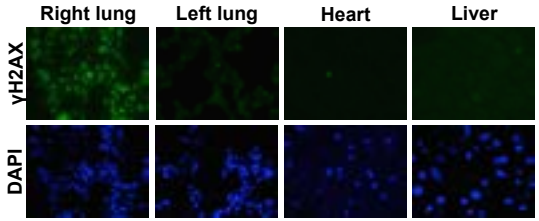
1 nuclear γH2AX focus
=
1 DSB

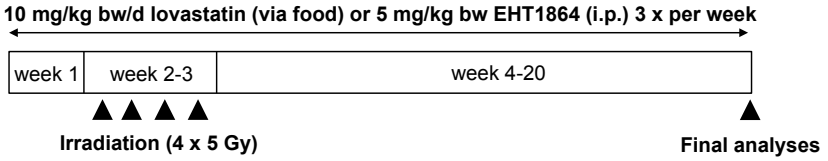
Lovastatin and EHT1864 mitigate sustained inflammatory responses resulting from fractionated lung irradiation



Model: Hypofractionated irradiation of the right lung (4 x 4 Gy)
- Analysis after 20 weeks (subchronic model) -

A





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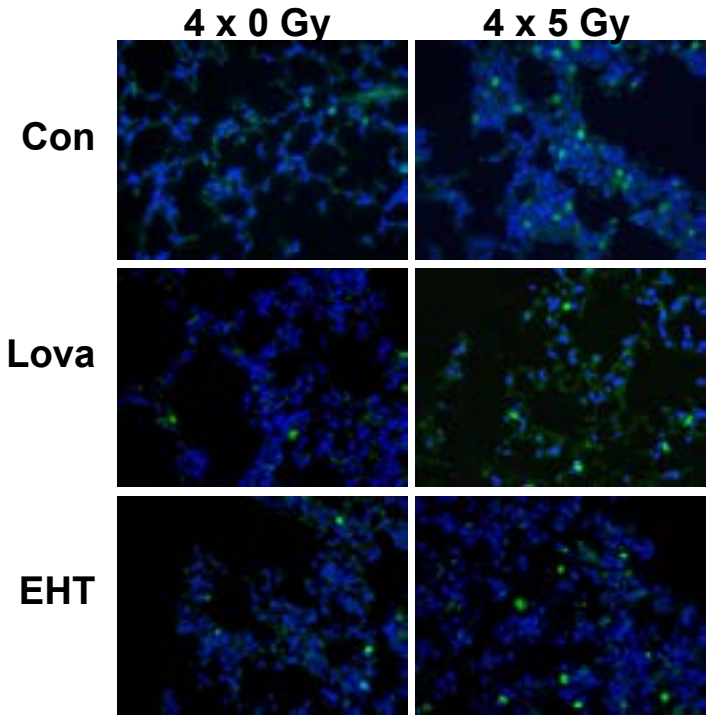
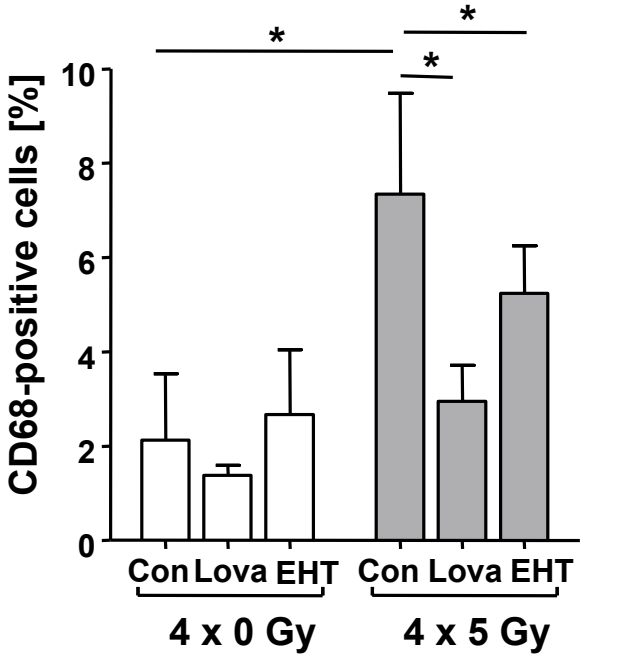
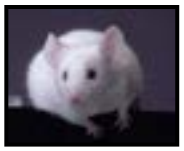
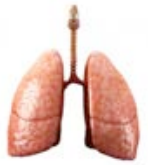


Inflammation (Anti-CD68 staining)





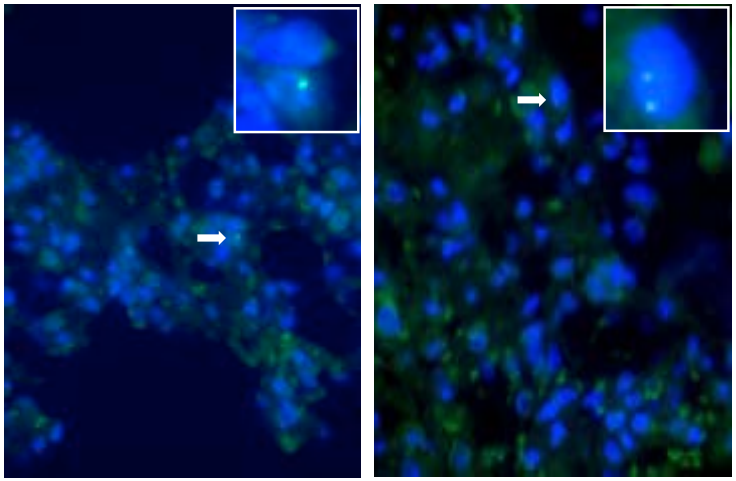
Lovastatin protects from fractionated IR-induced subchronic lung injury

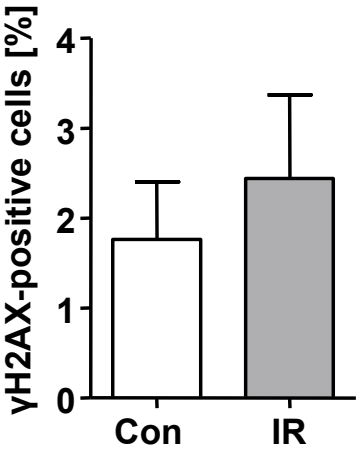


Subchronic model

DNA damage (γH2AX - DSB)

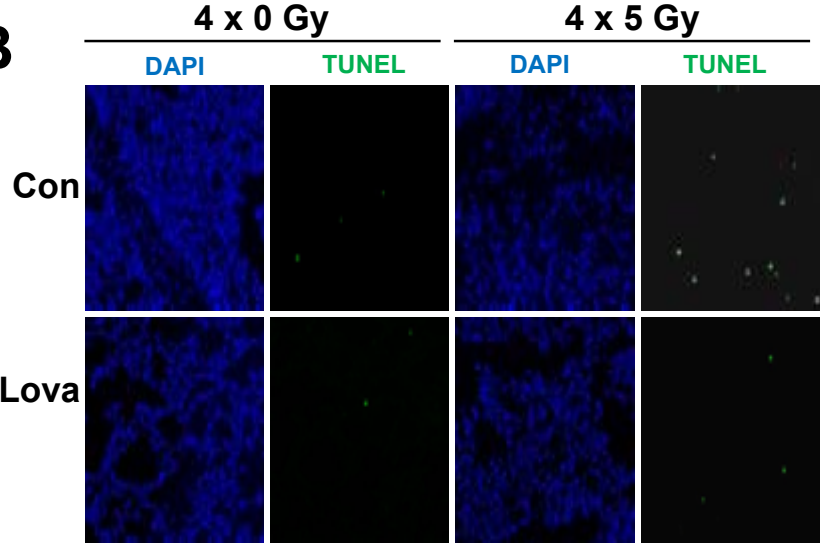
A

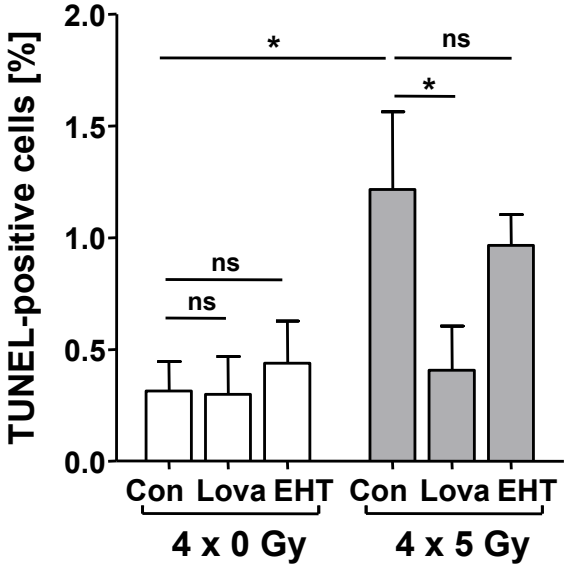




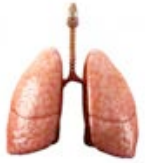
Apoptosis

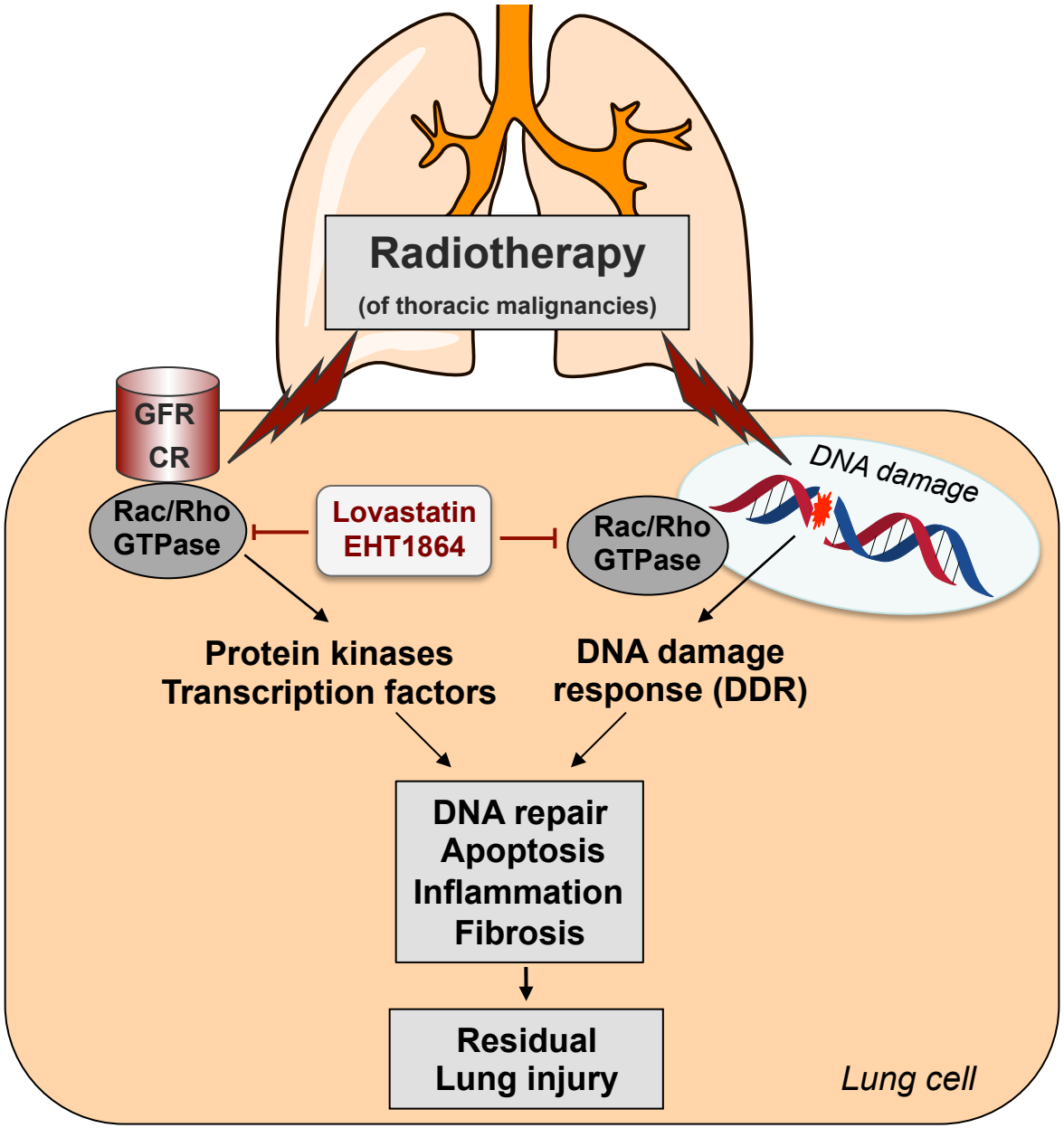
B





Beneficial effects of pharmacological targeting of Rac/Rho signaling – Hypothetical model





Further preclinical data using rodent model systems

Am J Respir Cell Mol Biol Vol 44. pp 415–422, 2011

Simvastatin Attenuates Radiation-Induced Murine Lung Injury and Dysregulated Lung Gene Expression

Biji Mathew1, Yong Huang2 .....Ralph R. Weichselbaum4*, and Joe G. N. Garcia1*

DOI:10.1158/1078-0432.CCR-07-0625

Clin Cancer Res. 2007 Sep 15;13(18 Pt 1):5331-40.

Human Cancer Biology

Pravastatin Inhibits the Rho/CCN2/Extracellular Matrix Cascade in Human Fibrosis Explants and Improves Radiation-Induced Intestinal Fibrosis in Rats

Valérie Haydont,[1,4] Céline Bourgier,[1,4] Marc Pocard,[2,6] Antoine Lusinchi,[3] Jocelyne Aigueperse,[5] Denis Mathé,[1] Jean Bourhis,[1,3] and Marie-Catherine Vozenin-Brotons[1,4]

Clincial data

European Journal of Cancer (2012) 48, 2117–2124

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Evaluating the efficacy of statins and ACE-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies

Linda J. Wedlake [a], Foteini Silia [b], Barbara Benton [b], Amyn Lalji [b], Karen Thomas [c], David P. Dearnaley [d,e], Peter Blake [f], Diana Tait [b], Vincent S. Khoo [d], H. Jervoise N. Andreyev [b,*]

ANTICANCER RESEARCH *37*: 1453-1458 (2017)
doi:10.21873/anticanres.11469

Statins Protect Against Acute RT-related Rectal Toxicity in Patients with Prostate Cancer: An Observational Prospective Study

ISABELLA PALUMBO[1,2], FABIO MATRONE[1], GIAMPAOLO MONTESI[1], RITA BELLAVITA[2], MARCO LUPATTELLI[2], SIMONETTA SALDI[1], ALESSANDRO FRATTEGIANI[2], ELEONORA ARENA[1], CRISTINA MARIUCCI[1], LORENZO FALCINELLI[2], VITTORIO BINI[3] and CYNTHIA ARISTEI[1,2]

SUMMARY AND CONCLUSIONS

Off-label use of lipid lowering statins might attenuate multiple acute and chronic adverse effects of radiotherapy, thereby

(i) widening the therapeutic window of radio-chemotherapy and

(ii) favouring aspects of supportive care in cancer

without impairing the anticancer efficacy of radiotherapy

Further retrospective and prospective clinical trials reassessing the radioprotective potency of statins in humans are preferable!

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-Stefanie Hülsenbeck
-Friedrich Wartlick
-Anita Bopp
-Lena Schumacher
- and many more....

V. Ziegler
PhD student

Kooperation partners

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-A. Schad, K. Lackner (Mainz)
-P. Wenzel, M. Brand (Mainz)
-M. Merx, M. Kelm, J. Ohlig (Düsseldorf)
-G. Kögler, S. Liedtke (Düsseldorf)
-K. Gottmann (Düsseldorf)
-J. Adjaye (Düsseldorf)

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- **Deutsche Krebshilfe**
- **Inneruniversitäre Forschungsförderung**

Thanks for your attention!