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

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Faculty Disclosure

<table>
<thead>
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<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
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Pharmacological modulation of radiation-induced normal tissue damage – criteria to be considered....

- What is the best target? –

- What is a best druggable target? –

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

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

![Diagram showing the therapeutic window, tumor control, normal tissue damage, and protection.](image)
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)

5 µM lovatstatin

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<td>γH2AX foci, Annexin V/PI Western blotting etc.</td>
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**B**

Apoptosis (TUNEL assay)

- **Endothelial cells**: *p < 0.05 vs. Con

- **Fibroblasts**: ns vs. Con

- **Epithelial cells**: ns vs. Con

Legend:
- Viable
- Early apoptotic
- Late apoptotic
- Necrotic
Lovastatin promotes DSB repair following fractionated irradiation of primary human lung cells in vitro

A

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<tr>
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<td>1 h post IR</td>
<td>Con</td>
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<td>4 x 4 Gy</td>
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DNA damage

1 nuclear γH2AX focus = 1 DSB

B

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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

Right lung Left lung Heart Liver

γH2AX DAPI

B

Apoptosis (TUNEL assay)

Number of TUNEL-positive cells/ DAPI-positive area

Con Lova EHT

4 x 0 Gy

4 x 4 Gy

10 mg/kg bw lovastatin or 5 mg/kg bw EHT1864
Lovastatin and EHT1864 reduce fractionated IR-stimulated residual DNA damage (DSBs) in lung tissue

Subacute model

A

4 x 0 Gy

\[ \gamma H2AX \]

\[ \text{DAPI} \]

4 x 4 Gy

\[ \gamma H2AX \]

\[ \text{DAPI} \]

B

DNA damage

\[ \gamma H2AX \text{-positive cells [%]} \]

1 nuclear \( \gamma H2AX \) 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

10 mg/kg bw/d lovastatin (via food) or 5 mg/kg bw EHT1864 (i.p.) 3 x per week

week 1  week 2-3  week 4-20

Irradiation (4 x 5 Gy)

Final analyses

B

Inflammation (Anti-CD68 staining)

CD68-positive cells [%]

4 x 0 Gy  4 x 5 Gy

Con  Lova  EHT

4 x 0 Gy  4 x 5 Gy

Con  Lova  EHT
Lovastatin protects from fractionated IR-induced subchronic lung injury

**Subchronic model**

**DNA damage**

(γH2AX - DSB)

**Apoptosis**

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<tr>
<th>4 x 0 Gy</th>
<th>4 x 5 Gy</th>
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<td>TUNEL</td>
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- **Con**
- **Lova**
- **EHT**

**TUNEL-positive cells [%]**

- **4 x 0 Gy**
- **4 x 5 Gy**

- **ns**
- ***"**

**γH2AX-positive cells [%]**

- **Con**
- **IR**
Beneficial effects of pharmacological targeting of Rac/Rho signaling – Hypothetical model

Radiotherapy (of thoracic malignancies)

GFR
CR
Rac/Rho GTPase

Protein kinases
Transcription factors

DNA damage response (DDR)

DNA repair
Apoptosis
Inflammation
Fibrosis

Residual Lung injury

Lovastatin EHT1864

Lung cell
Further preclinical data using rodent model systems

Simvastatin Attenuates Radiation-Induced Murine Lung Injury and Dysregulated Lung Gene Expression
Biji Mathew1, Yong Huang2 ..........Ralph R. Weichselbaum4*, and Joe G. N. Garcia1*

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

Pravastatin Inhibits the Rho/CCN2/Extracellular Matrix Cascade in Human Fibrosis Explants and Improves Radiation-Induced Intestinal Fibrosis in Rats
Valene Haydont,1,2 Céline Bourgier,1,2 Marc Pocard,2,6 Antoine Lusinchi,3 Jocelyne Aigueperse,5 Denis Mathé,1 Jean Bourhis,1,3 and Marie-Catherine Vozenin-Brotos1,4
Clinical data

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
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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Thanks for your attention!