Immune response to low dose radiation

Silvia Formenti, M.D.
Weill Cornell Medical College
New York Presbyterian Hospital
New York, NY
Disclosures

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I will discuss the following off label use and/or investigational use in my presentation:

*Ipilimumab (BMS)*
Radiotherapy and immune rejection

Abscopal effects are rare
Tumor irradiation + CTLA-4 blockade

4T1 mouse model of metastatic breast cancer

Lung metastases

Primary tumor

 Experimental Endpoints:
- Primary tumor growth
- Lung metastases
- Immune response evaluation

AH1

IFN-γ

α-CTLA4

RT

Clinical Cancer Res 2005
Abscopal response to RT+Ipilimumab

Response: 18% (RECIST v1.1)

CR = 2
PR = 5
SD = 5
PD = 28
Total pts = 39

Nature Medicine, Nov 2018
• Dose and fractionation dependence of the abscopal effects of radiotherapy

• Low dose RT: application to benign diseases

• Scattered dose /low dose RT impact on the abscopal effect of RT+ICB?

• “Lower dose TBI” to enhance CAR-T
Radiation-induces viral mimicry

Claire Vanpouille-Box

Vanpouille-Box et al., Nature Communications, 2017

Fuertes et al., J Exp Med 2011
Diamond et al., J Exp Med 2011
Cytoplasmic dsDNA sensed by cGAS activates IFN-I pathway via STING

Radiation Fraction Size, IFN-I and TREX1

Are there similar thresholds for lower dose ionizing radiation?

Vanpouille-Box et al., Nature Communications, 2017
• Dose and fractionation dependence of the abscopal effects of radiotherapy

• **Low dose RT: application to benign diseases**

• Scattered dose /low dose RT impact on the abscopal effect of RT+ICB?

• “Lower dose TBI” to enhance CAR-T
Effects of Low-Dose Radiation on the Immune System of Mice after Total-Body Irradiation

Enikő Noemi Bogdándi, Andrea Balogh, Nikolaett Felgyinszki, Tünde Szatmári, Eszter Perss, Guðlaug Hildebrandt, Geza Saffany and Katalin Lumnitszky

* Department of Molecular and Tissue Radiobiology, Ferenc József-Curie National Research Institute for Radiobiology and Radiogenetics, Budapest, Hungary; \(^{a}\) Department of Cellular and Immune Radiobiology, Ferenc József-Curie National Research Institute for Radiobiology and Radiogenetics, Budapest, Hungary; \(^{b}\) Department of Radiotherapy, University of Rostock, Medical Faculty, Rostock, Germany

### TABLE 4
Percentages of T-Cell Subpopulations 3 Days after Irradiation

<table>
<thead>
<tr>
<th>Investigated cellular subtypes</th>
<th>Dose (Gy)</th>
<th>CD4 + CD25\textsuperscript{bright}</th>
<th>CD4\textsuperscript{+}CD25\textsuperscript{−} Foxp3\textsuperscript{+}</th>
<th>CD8\textsuperscript{+}CD44\textsuperscript{+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Gy</td>
<td>9.82 (± 1.17)</td>
<td>9.98 (± 2.84)</td>
<td>0.63 (± 0.08)</td>
<td></td>
</tr>
<tr>
<td>0.01 Gy</td>
<td>10.53 (± 1.71)</td>
<td>10.05 (± 2.69)</td>
<td>1.46 (± 0.35)</td>
<td></td>
</tr>
<tr>
<td>0.05 Gy</td>
<td>10.26 (± 0.87)</td>
<td>10.46 (± 1.97)</td>
<td>1.92 (± 0.57)</td>
<td></td>
</tr>
<tr>
<td>0.1 Gy</td>
<td>11.25 (± 1.86)</td>
<td>10.43 (± 2.04)</td>
<td>1.70 (± 0.38)</td>
<td></td>
</tr>
<tr>
<td>0.5 Gy</td>
<td>11.54 (± 1.88)</td>
<td>10.03 (± 1.54)</td>
<td>2.78 (± 0.74)</td>
<td></td>
</tr>
<tr>
<td>2 Gy</td>
<td>13.63 (± 2.06)</td>
<td>13.36 (± 2.07)</td>
<td>2.87 (± 0.87)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes.** Data represent the average of three independent experiments, where the pooled data for the splenocytes of two mice per dose per experiment were evaluated. Standard deviations are shown in parentheses. Significance of difference from the nonirradiated, control value of the corresponding column is indicated by * (\(P < 0.05\)) or ** (\(P < 0.005\)).
Low-Dose Radiotherapy Ameliorates Advanced Arthritis in hTNF-α tg Mice by Particularly Positively Impacting on Bone Metabolism

Lisa Deloch, Anja Derer, Axel J. Hueber, Martin Herrmann, Georg Andreas Schett, Jens Wolffschneider, Jonas Hahn, Paul-Friedrich Rühle, Will Stilkrieg, Jana Fuchs, Rainer Fietkau, Benjamin Frey and Udo S. Gaipl*

Erlangen, Germany, 2 Department of Internal Medicine 3 and Institute for Clinical Immunology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU) and Universitätsklinikum, Erlangen, Germany

Decrease of Markers related to Bone erosion in serum of Patients with Musculoskeletal Disorders after serial low-Dose radon spa Therapy Aljona Cucu†, Kateryna Shreder†, Daniela Kraft, Paul Friedrich Rühle, Gerhart Klein, Gerhard Thiel, Benjamin Frey, Udo S. Gaipl and Claudia Fournier.*
• Dose and fractionation dependence of the abscopal effects of radiotherapy

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• “Lower dose TBI” to enhance CAR-T
“Low dose” is not so low...

Basket trial concept – Radscopal™ Trial

Based on the scientific rationale that ablative RT could enhance antigen presentation and low dose RT (~7 Gy/5 fx) could “draw in the T cells” by modulating the TME, the combination could help enhance immunotherapy effects (Welsh)

Potential: Applying SABR with low dose RT in multiple disease sites progressing on immune checkpoint blockade potentially could prolong the use and response of immunotherapies

- Work with relevant site committees for one master protocol

Primary endpoint: ORR, DFS

Translational biomarkers

James Welsh et al
ViewRay,
7.25 Gy X 5

Yellow line: 3625 (5x725) cGy  Pink line: 10 cGy
LD = 75mGy x 4
HD = 1Gy x 4
The NK cells were irradiated with 25, 75, 150, and 500 mGy X-rays (X-ray generator operated at 6 MV, at 60 cm SSD, and at a dose rate of 12.5 mGy/min)
Low-Dose Radiation Conditioning Enables CAR T Cells to Mitigate Antigen Escape

Carl DeSelm,1,2 M. Lia Palomba,3 Joachim Yahalom,3 Mohamed Hamieh,4 Justin Eryquem,1 Vinagolu K. Rajasekhar,4 and Michel Sadelain1,2

1Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5Immunology Program, Sloan Kettering Institute, New York, NY, USA

Figure 2. TRAIL Expressed by Activated CAR T Cells Is Active against Antigen-Negative Tumor Cells in a Heterogeneous Tumor Population Exposed to Low-Dose Radiation

(A) CAR-activated T cells produce TRAIL, which acts upon radiation-sensitized antigen-positive and antigen-negative tumor cells. B and C Ag1 cells were mixed with luciferase-expressing Ag2 cells at a ratio of 75:25, exposed to low-dose RT, and cocultured with LBBz (B) or Ldub (C). CAR T cells for 4 days, followed by luciferase-based quantification of cell killing. **p < 0.01.
In vivo samples, FDXR expression 24 hr after the first RT fraction dose where cancer patients were irradiated with blood doses of 150 mGy for patient I, 140 mGy for patient II and 80 mGy for patient III.
Conclusions

• Low dose radiation (<10 cGy) has significant effects on immune cells

• Scattered radiation from classical RT may contribute to the response to ICB

• Preliminary data suggest a role for doses of TBI in the range of 1-2 Gy to enhance CAR-T therapy

• Studies to test hormesis are warranted
RADIATION & IMMUNITY PROGRAM

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