

# 방사선 기술의 의학적 이용



한국원자력연구원  
Korea Atomic Energy Research Institute



한국원자력의학원  
Korea Research Institute of Human Sciences

From bench to bed to community and beyond



## 방사선의학기술기반 국외 중개연구 동향

2018.10.24  
포항공과대학교  
안지완

# Radiation Research Meeting 2018



Bringing Science to The City That Works

Historic Hilton Chicago | September 23-26, 2018

Held in conjunction with the Conference on Radiation and Health

Registration Desk Open 7:30am - 8:30am
<b>OPTIONAL CAREER DEVELOPMENT WORKSHOP OPENS</b> 4
<b>Part 1: One-On-One Networking Appointments (3:15pm-5:15pm)</b> Sign up for 10-minute meetings and visit your mentors in the following areas: <ul style="list-style-type: none"> <li>Meet the Councilors - members of the Governing Councilors on hand to address your questions and provide insight to the Society</li> <li>Meet the MD - our ECI members will have an opportunity to meet our MD/PhD leaders and help those of you seeking a home base to find resources within RRS community</li> <li>Meet the Scientist (by discipline) - leaders from Chemistry, Biology and Physics will provide insight into key sessions to attend at the annual meeting as well as discuss your career needs</li> <li>Meet the Funding Agencies - we have up to five agencies that will each be represented and available to address your individual questions</li> <li>Meet the Employers - corporate sponsors and university representatives offer advice and opportunity</li> <li>Women in Science - at long last, this amazing group of leaders will offer women insight and advice of how to succeed in the field</li> </ul>
<b>Part 2: The Successful Grant (4:15pm-5:15pm)</b> Tips, tricks and tools on how grants are evaluated and scored will be presented during this one-hour mock study session. Join our leaders as they share lessons learned from their failures and successes into the "science" of acquiring funds. Instructors will accept up to 6 one-page grant submissions and will review them with attendees. Take advantage of this unique chance to improve your grant-writing abilities!
<b>New Member Orientation</b> (by invite) - PDR 4   5:30pm - 6:30pm
<b>SIT Social</b> (RSVP required) - 720 South Bar   7:30pm - 9:30pm
<b>ECI Reception</b> (by invite) - PDR 4   7:30pm - 9:30pm

RRS CME

RRS  
Non-CME

CRH

Networking

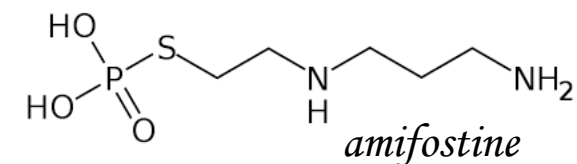
Featured

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Exhibitor Hall	Grand Ballroom	Waldorf Room	Astoria Room	Marquette Room	Joliet Room	Boulevard C	Williford Room	Boulevard A,B

7am	Registration Desk Open 7:30am - 5:00pm					
8am	Coffee Break with Exhibitors					
8:30am	CRH Welcome	RRS Welcome and Opening Remarks				
8:45am	Selected Abstracts	Plenary 1: Modeling cancer in the mouse: Tyler Jacks				
9am						
10am	9	Coffee Break with Exhibitors				
10:15am	EPI-CT: Design, dosimetry, and latest results	S1 Radiation-induced GI Syndrome	S2 Radiation dosimetry: in patients and phantoms	S3 Mechanisms of cell death after radiation	S4 Hypo-fractionation: from pre-clinical models to clinical trials	S5 Genomics of normal tissue toxicity and tumor response to radiation
12:15pm	9	3	4	5	6	7
1:45pm	Lunch	SIT Mentor Lunch (SITs only, RSVP Required)				
2:30pm	Controversial issues in radiation protection	PS1- Epidemiology, epigenetics, omics & mouse models				
3:15pm		9	PS2- DNA- oxidative damage responses & physico-chemistry			
3:15pm	S10: Joint CRH/RRS Session: Space radiation and cancer risk	S6 Hypoxia and ER Stress	S7 Imaging and circulating biomarkers of radiation response	S8 Radio-nuclides for imaging, therapy, and dosimetry	S9 Chromatin biology and radiation response	
5:15pm	7	2	4	5	6	
5:30pm	Coffee Break with Exhibitors					
6:30pm	Failla Lecture- Adaciu Adaciu si fa Gran Viaggio: With a heavy ion accelerator you can travel to Mars: Francis A. Cucinotta					
8:30pm	Welcome Reception (RSVP Required) 6:30 - 8:45pm   Normandie Lounge					
11:30pm	Karaoke 8:30 - 11:30pm   Waldorf Room					

S1. Cullen Taniguchi (MD Anderson)

- FG-4592,  $\alpha$  PHD2 (prolyl hydroxylase-2) inhibitor (hence HIF- $\alpha$  stabilizer) & oral WR2721 (amifostine) protects GI from high dose RT (12.5 Gy  $\times$  5).
- Mice survived longer than 30 days while control died less than 10 days



S6. 2 key speakers (Koumenis @ Upenn, Koritzinsky @ Toronto) could not come.

- Cameron Koch –  $\gamma$ H2AX in aerobic regions providing pO2 reading wrt EF5.



RRS CME	RRS Non-CME	CRH	Networking	Featured
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**S11.**

- Andy Minn – stromal exosomes containing RNA transferring to cancer and other cells triggering IFN signaling pathway.
- Ravi Patel – Y<sup>90</sup>-NM600 (100  $\mu$ Ci, 50  $\mu$ Ci) + CTLA-4 results in antitumor immune response in B78 melanoma model.

**S17.**

- Fen Xia – IR initiates BRCA1 translocation to cytoplasm suppressing DNA repair and induces synthetic PARPi lethality and these effects were dependent on functional p53.

7am	Registration Desk Open 7:00am - 5:00pm				
7:30am	Coffee Break with Exhibitors				
8am	TR1 Radiation-induced carcinogenesis through alterations in adaptive landscapes <i>James DeGregori</i> 3	TR2 Exploring radiation chemistry in DNA damage using various model systems <i>Amitava Adhikary</i> 4	TR3 Information-driven radiotherapy: integrating a data-driven approach with radiobiological principles to understand outcomes <i>Joseph Deasy</i> 5	TR4 Recent clinical and experimental insight into radiation-induced heart disease <i>Marjan Boerma</i> 6	TR5 Chromatin dynamics: the landscape for response to DNA damage <i>Scott Floyd</i> 7
9am	Plenary 2: Cancer etiology and mutational signatures: Cristian Tomasetti				
10am	Coffee Break with Exhibitors				
10:15am	A review of the recent low-dose/ low dose-rate epidemiology: can biases explain the results? 9	S11 Pre-clinical mechanisms of radiation and immuno-therapy 2	S12 Dose rate and radiation toxicity 4	S13 A tribute and celebration: the contributions and impact of Michael Fry to radiation research 5	S14 Reactive oxygen species, redox and metabolism 6
12:15pm	Lunch	Business Forum (Members Only, RSVP Required)			
1:45pm	What is the current state of knowledge in low-dose radiobiology?	PS3- Basic science - space/physics/biology			
2:30pm		PS4- (Stem) cell and tissue- kinetics, signaling, microenvironment, mutations			
3:15pm	Discussion on the responses to low-dose exposures	Presidential Symposium 1: Future radiobiology for advanced radiotherapies <i>Michael Baumann   Dorthe Schaeue   Marco Durante   Soren Bentzen</i>			
4:15pm	ESRI Workshop Part 1	Marie Curie Award Lecture- EZH2 mediates cisplatin resistance in small cell lung cancer through nucleotide excision repair: <i>Allyson Koyen</i>			
5:15pm	Coffee Break				
6pm	ESRI Workshop Part 2	Michael Fry Award- Modeling effects of radiation using multi-scale Monte Carlo Simulations: <i>Jan Schuemann</i>			
6:45pm					
7:00pm					
7:30pm	CRH Banquet (RSVP Required)				
9:00pm	<i>Alina Brenner</i>				

7am	Registration Desk Open 7:00am - 12:00pm				
7:30am	Coffee Break with Exhibitors				
8am	TR6 Computational biophysics: a new tool for radiation research? <i>Gianluca Lattanzi</i>  3	TR7 Hibernation: impact on radio-protection <i>Walter Tinganelli</i>  4	TR8 What we know (and what we don't know) about radiation risks associated with contemporary medical imaging <i>David Brenner</i>  5	TR9 Biology didactics for radiation oncology residents: the past, present <i>Elaine Zeman</i>  6	TR10 Nano-particles: applications for imaging and therapy <i>Gayle Woloschak</i>  7
9am	CRH Poster Session 9	Plenary 3: A new role for radiation therapy in the era of cancer immunotherapy: Sandra Demaria			2
10am	Coffee Break with Exhibitors				
10:15am	International and domestic health studies among radiation exposed  9	S16 Radiation biology of model organisms: flies, worms and fish  3	S17 DNA damage response and DNA repair  4	S18 (Co-Sponsored by ASTRO) Clinical trials of radiation therapy and immuno-therapy  5	S19 Radiomics, radio-genomics and artificial intelligence  6
12:15pm	S20 Medical counter-measures of radiation (mitigators)  7				
Afternoon On Own					
Visit the concierge for assistance in booking activities.					

RRS CME	RRS Non-CME	CRH	Networking	Featured
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S18.

Ann Klopp – Gut microbiome from 30 cervical cancer patients w CRT. Greater microbiome diversity was associated with exceptional response and clonal T cell expansion. Immunosuppressive *Lactobacillus* species in the cervix was associated with failure of clonal T cell expansion. In orthotopic HPV cancer model, depletion of gut microbiome diversity and presence of vicinal *Lactobacillus* lead to decreased CD8 T cell and poorer IR response.

7am	Registration Desk Open 7:00am - 2:00pm								
7:30am	Coffee Break with Exhibitors								1
8am	TR11 DNA damage signaling to immune checkpoints <i>Christopher Bakkenist</i>	TR12 The rationale, physics and radiobiology of carbon ion radiative therapy <i>Piero Fossati</i>	TR13 Transitioning to scientific independence <i>Claudia Wiese, David Yu</i>	TR14 Non-carcinogenic effects of space radiation <i>Polly Chang</i>	TR15 Radiation injuries to the immune system <i>James Lederer</i>				
9am	Plenary 4: Biologically motivated treatment planning in proton therapy: Harald Paganetti								2
10am	Coffee Break with Exhibitors								1
10:15am	S21 Stem cells and radiation toxicity	S22 Radiation chemistry	S23 Radiation modifiers (protectors & sensitizers)	S24 Proton and carbon ion radiotherapy	S25 Small animal irradiation				
12:15pm	Painter Debate: This house believes that the biological mechanisms that underlie cancer development are sufficient to dismiss linear-no-threshold (LNT) modeling of cancer risk (Box Lunch Provided, RSVP Required) For: Mary Helen Barcellos-Hoff   Against: Francis Cucinotta								2
1pm	Osborne Award: Metabolomics as a pre-emptive tool for discerning radiation induced antecedent normal tissue injury: <i>Amrita Cheema</i>								2
1:45pm	PS5: Radiation protection - biodosimetry/mitigators/treatment								8
2:30pm	PS6: Experimental therapeutics/radiotherapy/translational research								8
3:15pm	Presidential Symposium 2: p53 in radiation response and tumor suppression <i>Michael Kastan   Laura Attardi   Andrei Gudkov   Allan Balmain</i>								2
5:15pm	PS7 & PS8: Poster Reception (RSVP Required) PS7: CNS and normal tissue response PS8: Late-Breaking								8
6:30pm	Final Night Event (RSVP Required) 6:30pm - 11:00pm   Aboard the Odyssey   Meet in main lobby for shuttle								
11:00pm									

## S23.

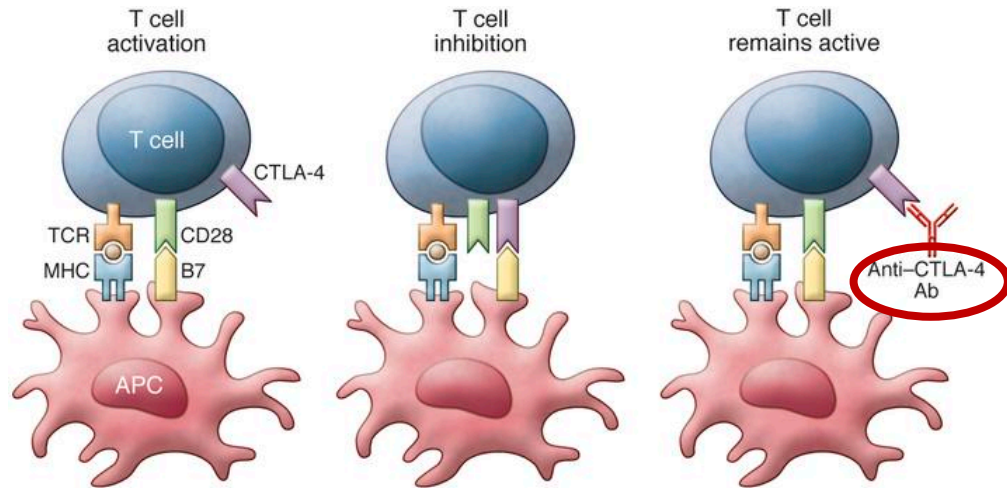
- Meredith Morgan – discussion of this presentation.
- Sunil Advani – Delivering cell penetrating peptide conjugated to CHK1/2 inhibitor, AZD7762. Peptide linker cleavable by MMP2/9. When combined with IR, it prolonged tumor xenograft (HCT116, PANC1, CAL27, A549) regression.

RRS CME	RRS Non-CME	CRH	Networking	Featured
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# 1. 방사선 병용 항암 면역치료 (1) Sandra Demaria Group at NYU



## Fractionated but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti-CTLA-4 Antibody

M. Zahidunnabi Dewan,<sup>1</sup> Ashley E. Galloway,<sup>1</sup> Noriko Kawashima,<sup>1</sup> J. Keith Dewyngaert,<sup>3</sup> James S. Babb,<sup>2</sup> Silvia C. Formenti,<sup>3</sup> and Sandra Demaria<sup>1</sup>

Clin Cancer Res 2009;15(17) September 1, 2009

### ARTICLE

Received 27 Mar 2017 | Accepted 12 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15618

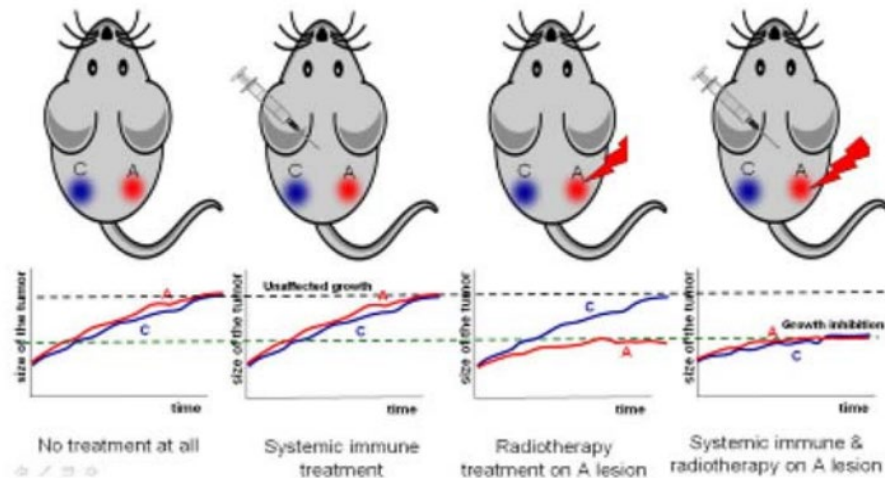
OPEN

## DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

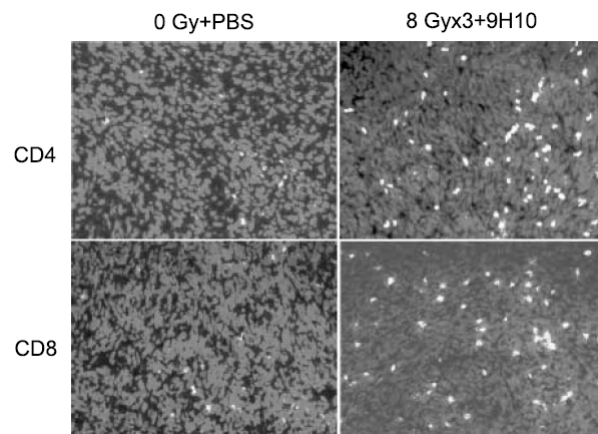
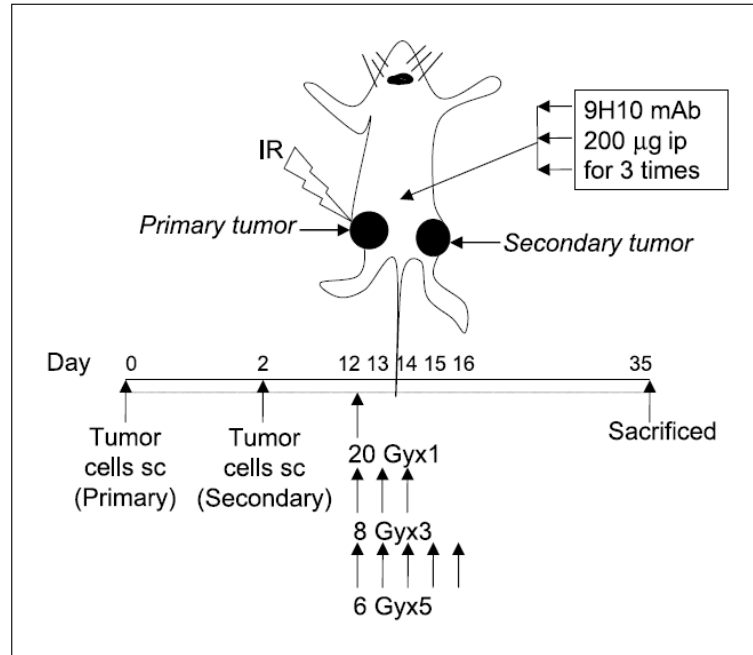
Claire Vanpouille-Box<sup>1</sup>, Amandine Alard<sup>2,†</sup>, Molykutty J. Aryankalayil<sup>3</sup>, Yasmeen Sarfraz<sup>1</sup>, Julie M. Diamond<sup>1</sup>, Robert J. Schneider<sup>2</sup>, Giorgio Inghirami<sup>4</sup>, C. Norman Coleman<sup>3</sup>, Silvia C. Formenti<sup>1</sup> & Sandra Demaria<sup>1,4</sup>

NATURE COMMUNICATIONS | 8:15618 | DOI: 10.1038/ncomms15618 | www.nature.com/naturecommunications

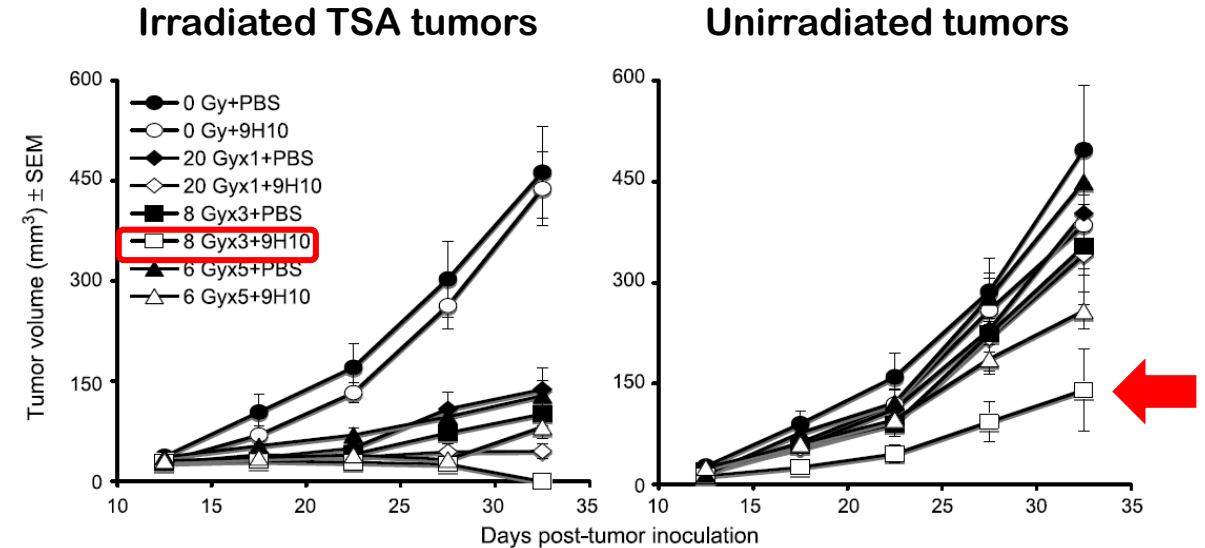
### Abscopal (bystander) effect with local radiotherapy



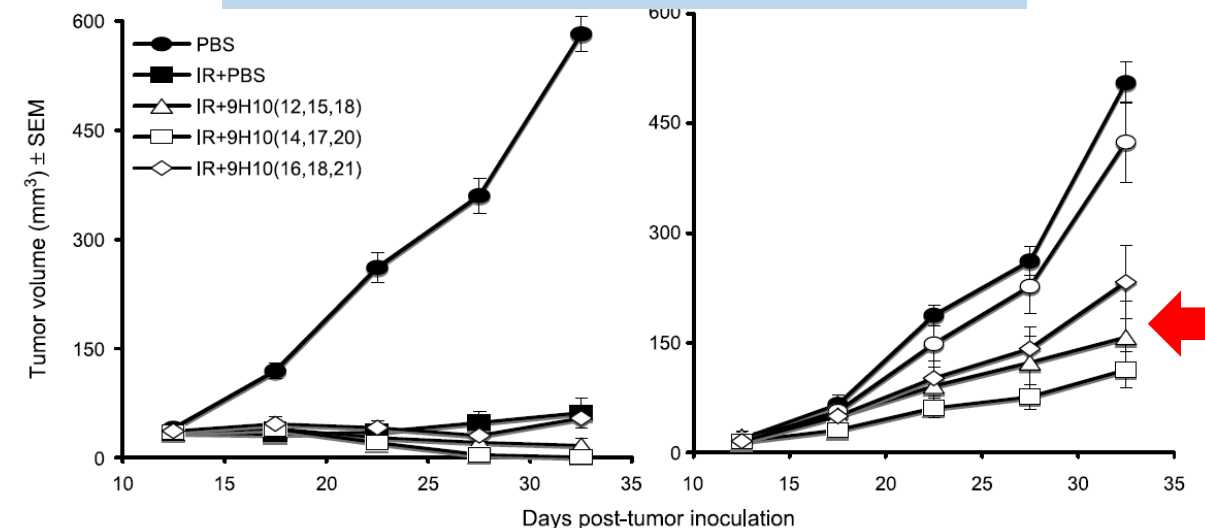
# 8Gy x 3 fractionations are the most effective for inducing abscopal effect



## Dose fractionation optimization

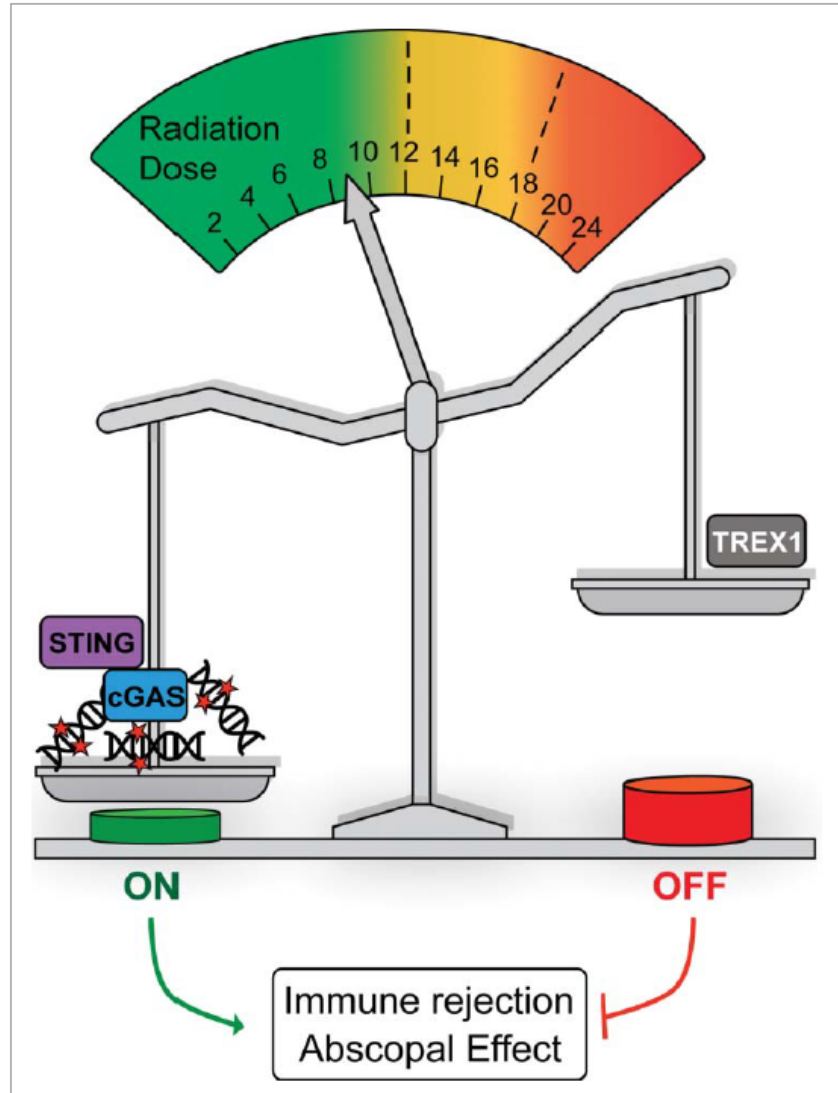


## Treatment schedule optimization





# 1. 방사선 병용 항암 면역치료 (1) Sandra Demaria Group at NYU



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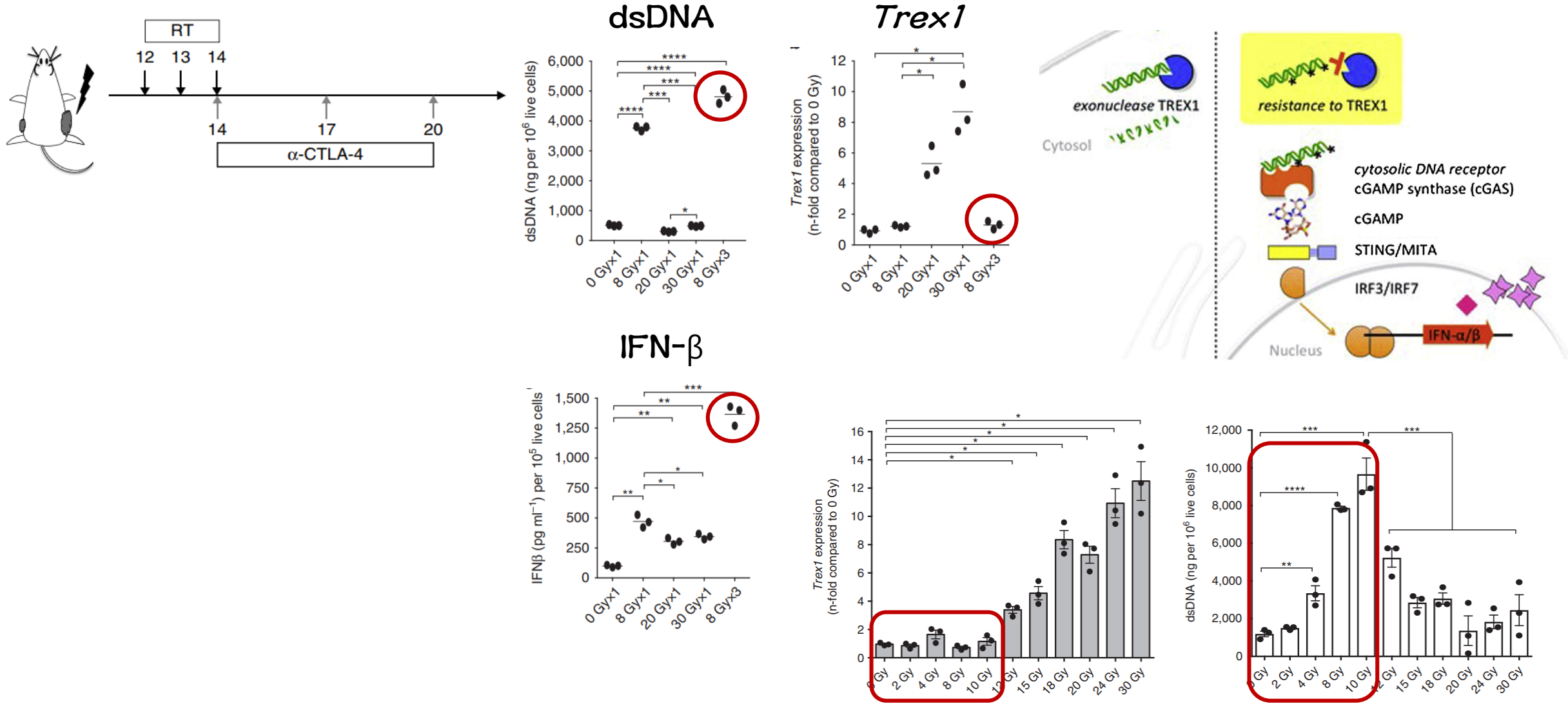
OPEN

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NATURE COMMUNICATIONS | 8:15618 | DOI: 10.1038/ncomms15618 | www.nature.com/naturecommunications

# 8Gy x 3 fractionations produce highest dsDNA and lowest *Trex1* expression



# 1. 방사선 병용 항암 면역치료 (2) Andy Minn at UPenn

## LETTER

doi:10.1038/nature14292

### Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor<sup>1,2\*</sup>, Andrew J. Rech<sup>2\*</sup>, Amit Maity<sup>3,4</sup>, Ramesh Rengan<sup>3,4†</sup>, Kristen E. Pauken<sup>5,6</sup>, Erietta Stelekati<sup>5,6</sup>, Joseph L. Benci<sup>2,3</sup>, Bihui Xu<sup>2,3</sup>, Hannah Dada<sup>2,3</sup>, Pamela M. Odorizzi<sup>5,6</sup>, Ramin S. Herati<sup>1,6</sup>, Kathleen D. Mansfield<sup>5,6</sup>, Dana Patsch<sup>3</sup>, Ravi K. Amaravadi<sup>1,4</sup>, Lynn M. Schuchter<sup>1,4</sup>, Hemant Ishwaran<sup>7</sup>, Rosemarie Mick<sup>4,8</sup>, Daniel A. Pryma<sup>4,9</sup>, Xiaowei Xu<sup>4,10</sup>, Michael D. Feldman<sup>4,10</sup>, Tara C. Gangadhar<sup>1,4</sup>, Stephen M. Hahn<sup>3,4†</sup>, E. John Wherry<sup>4,5,6§</sup>, Robert H. Vonderheide<sup>1,2,4,6§</sup> & Andy J. Minn<sup>2,3,4,6§</sup>

16 APRIL 2015 | VOL 520 | NATURE | 373

Cell

Article

### Tumor Interferon Signaling Regulates a Multigenic Resistance Program to Immune Checkpoint Blockade

Joseph L. Benci<sup>1,7</sup>, Bihui Xu<sup>1,7</sup>, Yu Qiu<sup>1,7</sup>, Tony J. Wu<sup>1,7</sup>, Hannah Dada<sup>1,7</sup>, Christina Twyman-Saint Victor<sup>2,7</sup>, Lisa Cucolo<sup>1,7</sup>, David S.M. Lee<sup>1,7</sup>, Kristen E. Pauken<sup>3,5</sup>, Alexander C. Huang<sup>2,5</sup>, Tara C. Gangadhar<sup>2</sup>, Ravi K. Amaravadi<sup>2</sup>, Lynn M. Schuchter<sup>2</sup>, Michael D. Feldman<sup>4</sup>, Hemant Ishwaran<sup>8</sup>, Robert H. Vonderheide<sup>2,5,6,7</sup>, Amit Maity<sup>1</sup>, E. John Wherry<sup>3,5,6</sup> and Andy J. Minn<sup>1,5,6,7,9,\*</sup>

<sup>1</sup>Department of Radiation Oncology

<sup>2</sup>Department of Medicine

<sup>3</sup>Department of Microbiology

<sup>4</sup>Department of Pathology and Laboratory Medicine

<sup>5</sup>Institute for Immunology

<sup>6</sup>Parker Institute for Cancer Immunotherapy

<sup>7</sup>Abramson Family Cancer Research Institute

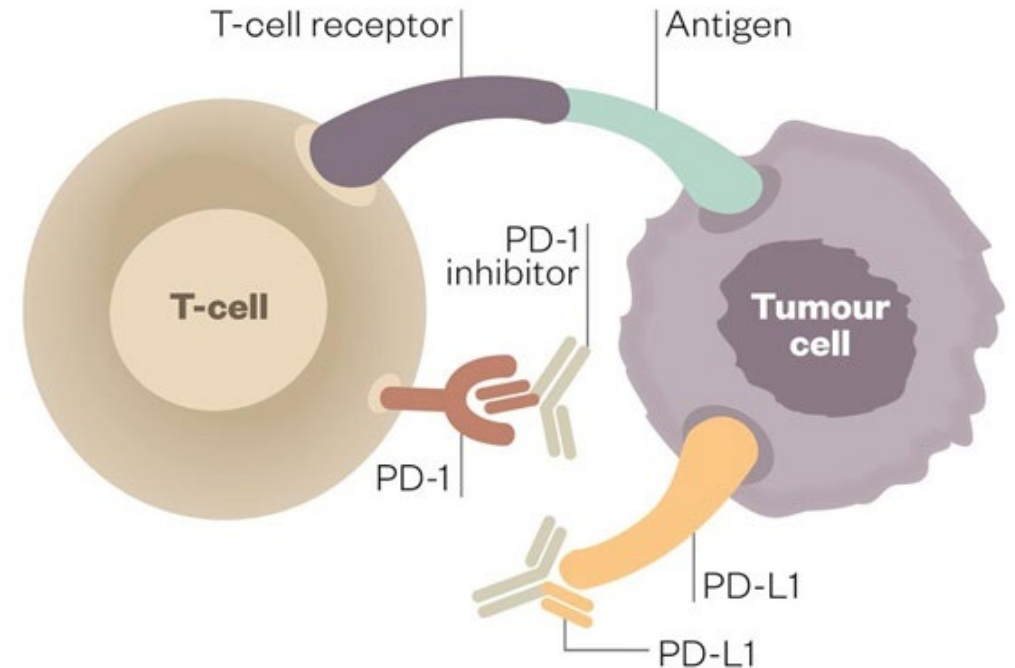
Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>8</sup>Division of Biostatistics, Department of Epidemiology and Public Health, University of Miami, Miami, FL 33136, USA

<sup>9</sup>Lead Contact

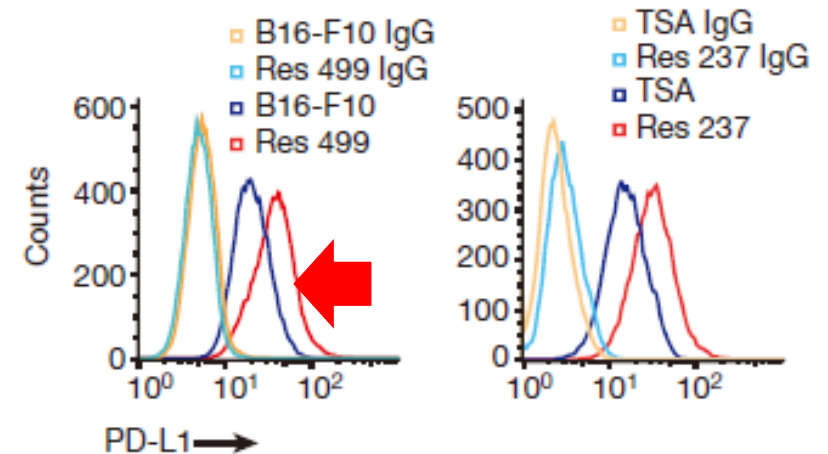
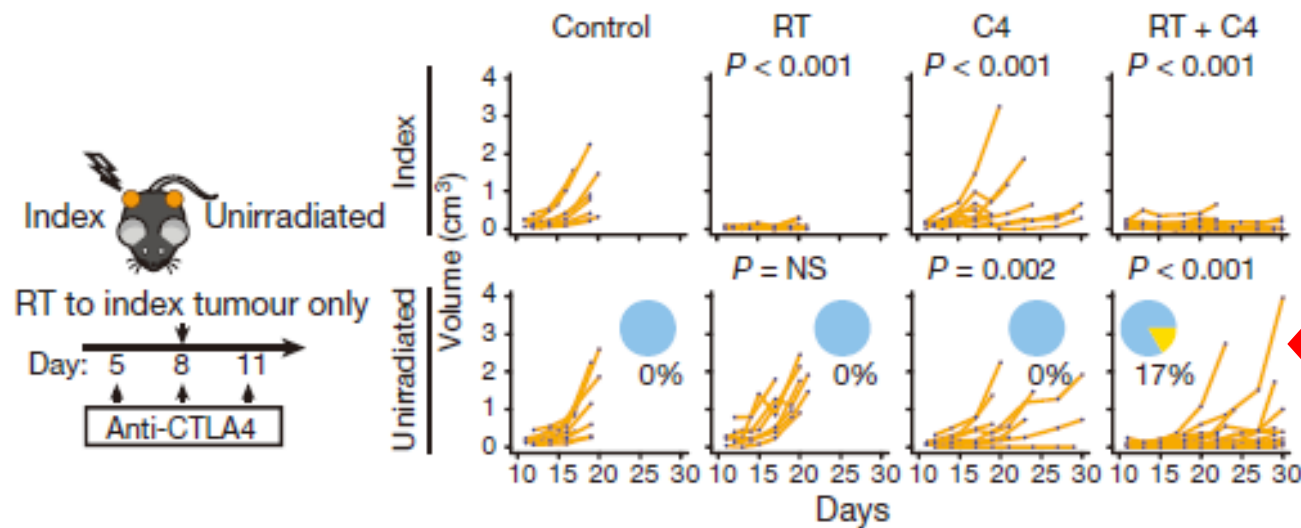
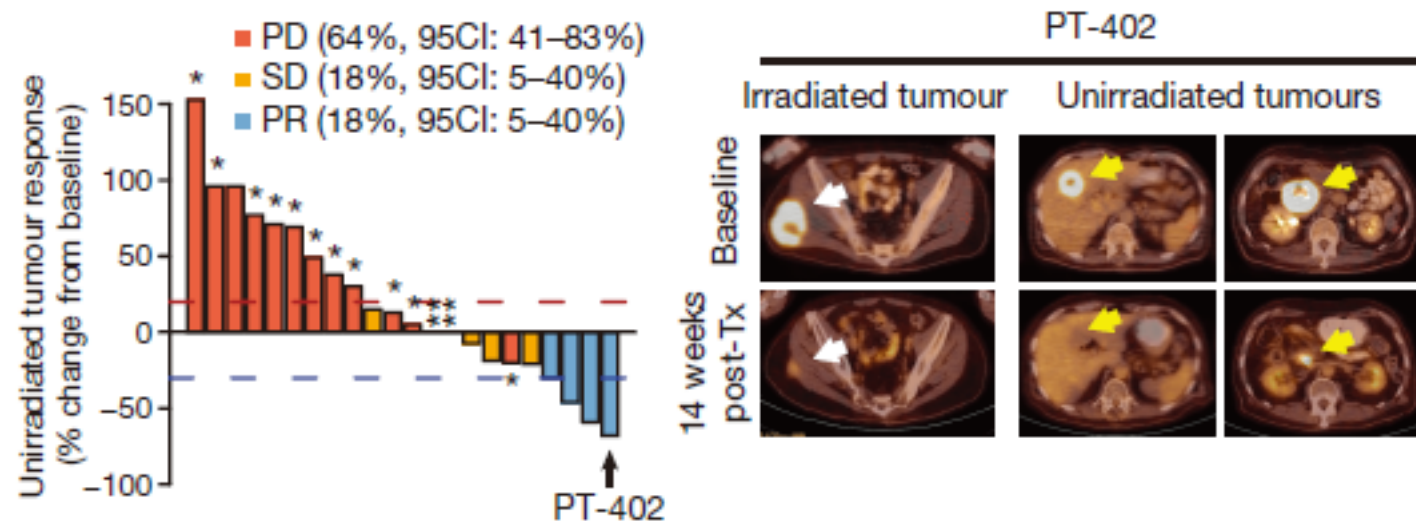
\*Correspondence: [andyminn@mail.med.upenn.edu](mailto:andyminn@mail.med.upenn.edu)

<http://dx.doi.org/10.1016/j.cell.2016.11.022>

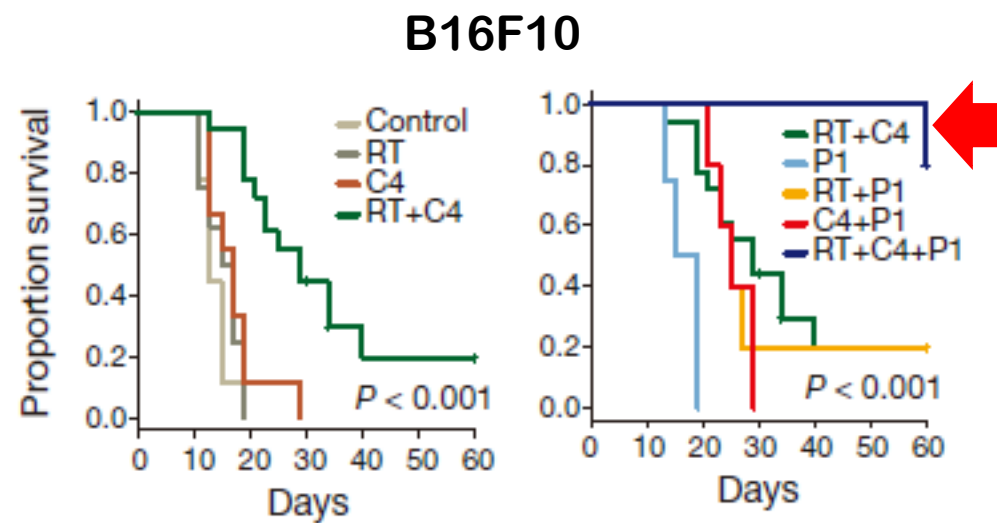
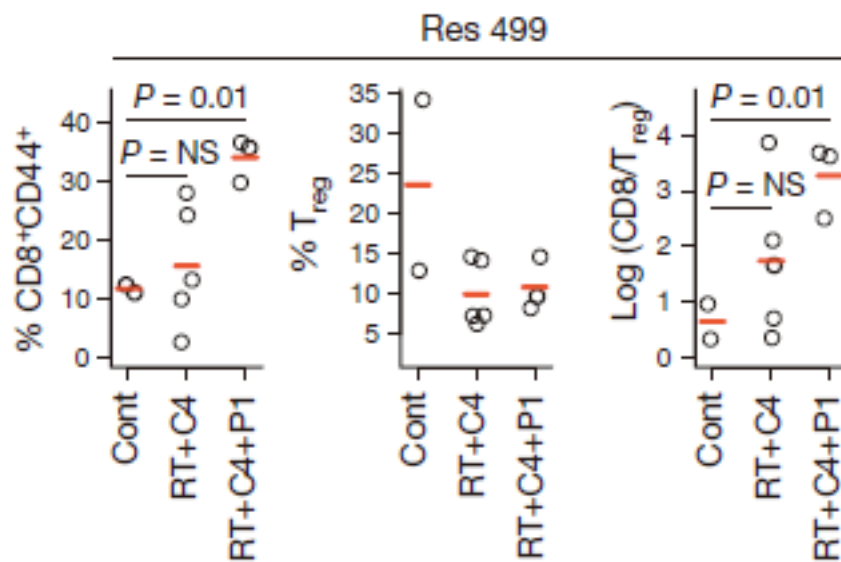
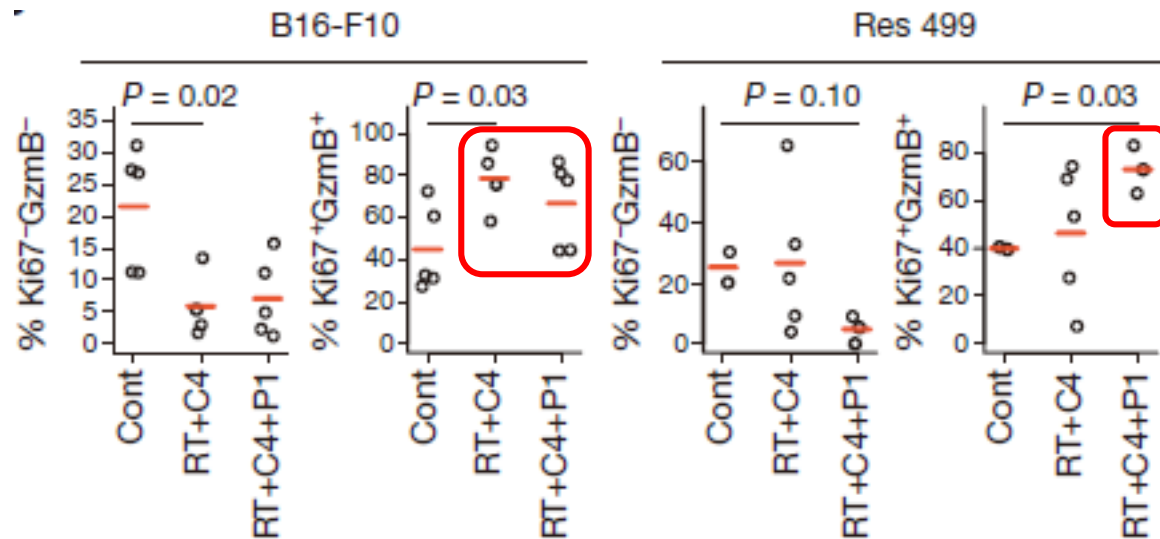
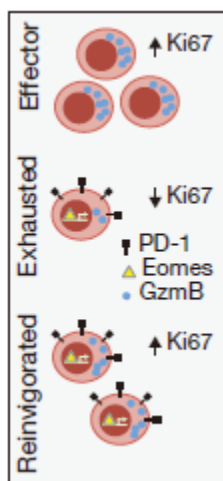




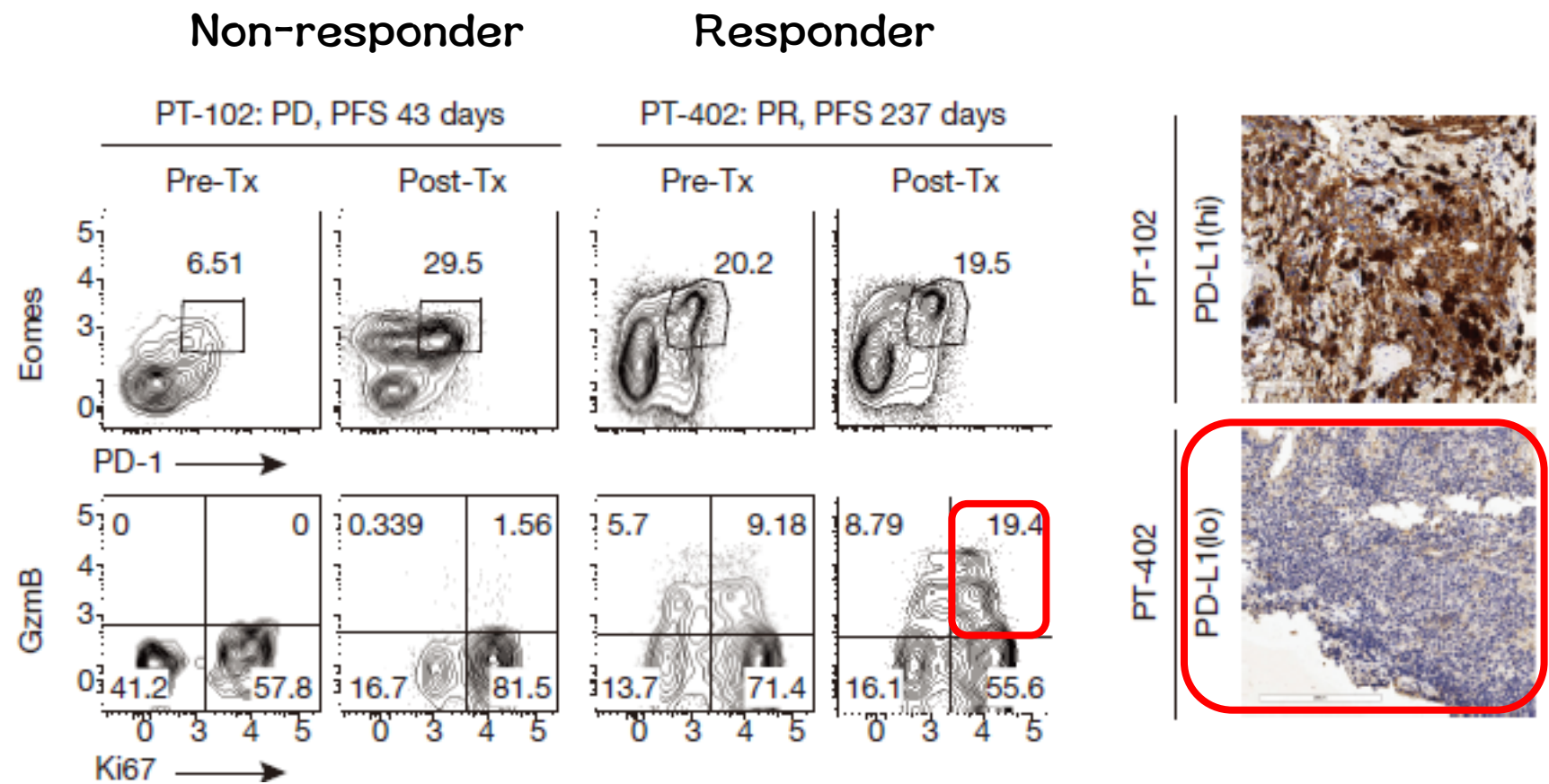
# Abscopal resistance to CTLA4 - induction of tumor PD-L1 expression



# Reinvigorated T cells by PD-L1 Ab



# Responder exhibits increased reinvigorated T cells and reduced PD-L1





# 1. 방사선 병용 항암 면역치료 (2) Andy Minn at UPenn

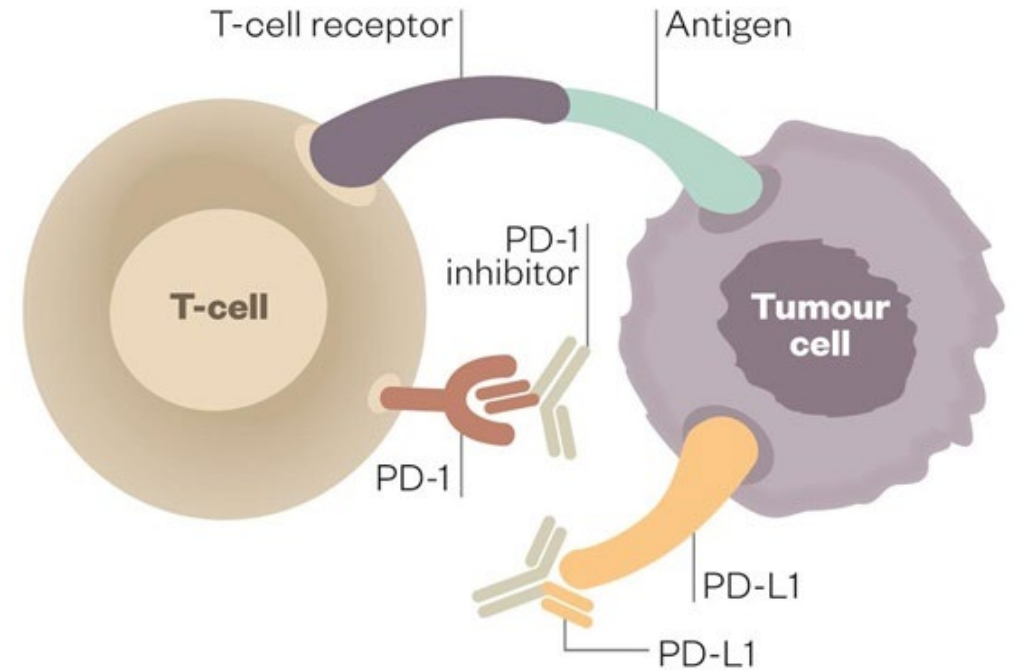
## LETTER

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<sup>1</sup>Department of Radiation Oncology

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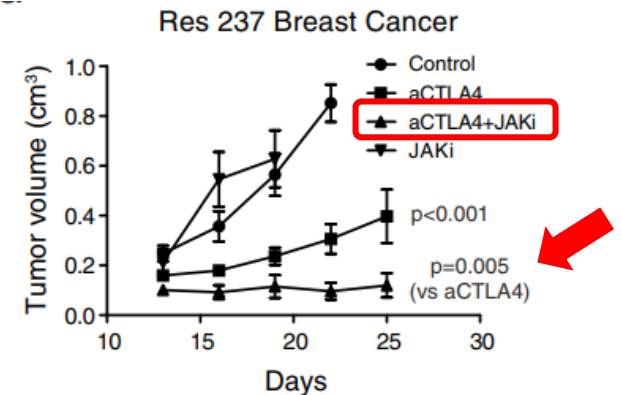
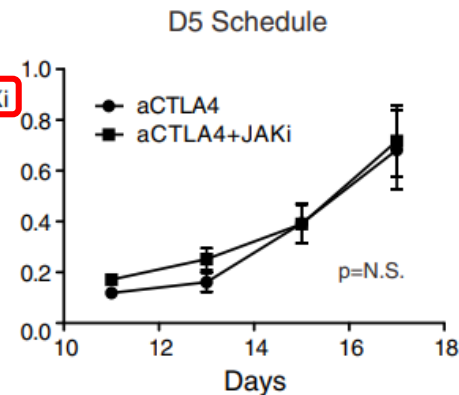
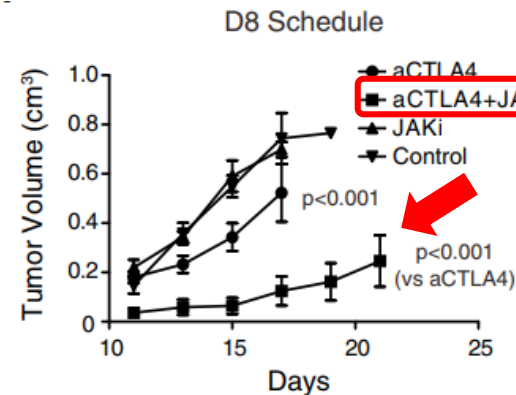
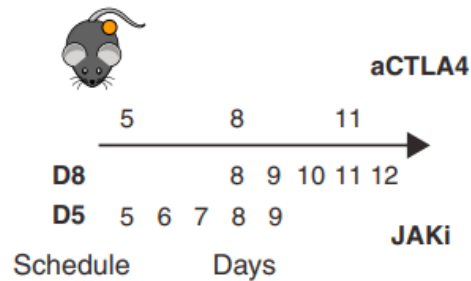
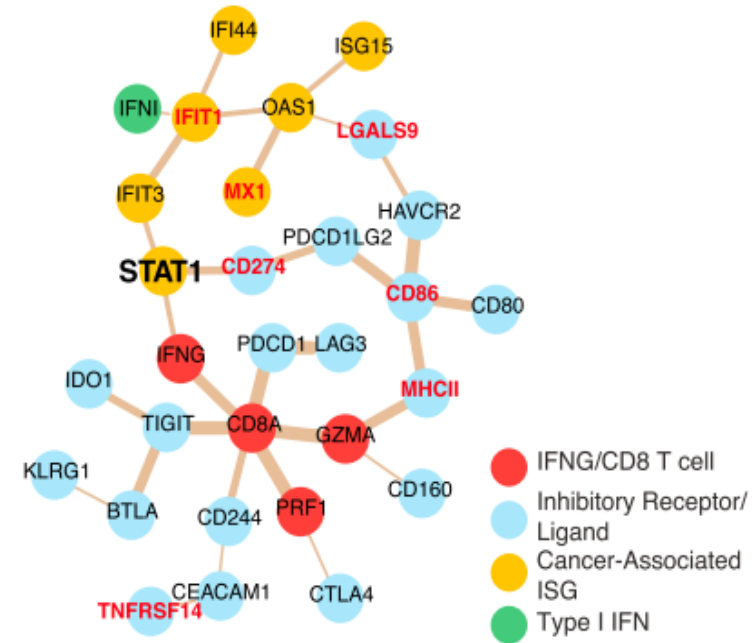
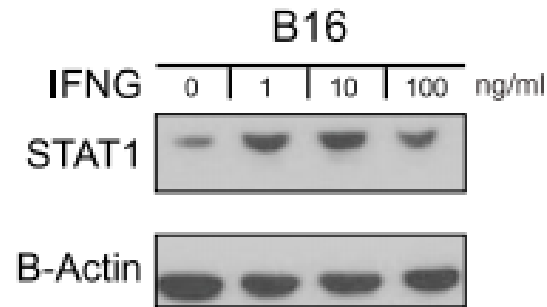
<sup>8</sup>Division of Biostatistics, Department of Epidemiology and Public Health, University of Miami, Miami, FL 33136, USA

<sup>9</sup>Lead Contact

\*Correspondence: andyminn@mail.med.upenn.edu

<http://dx.doi.org/10.1016/j.cell.2016.11.022>

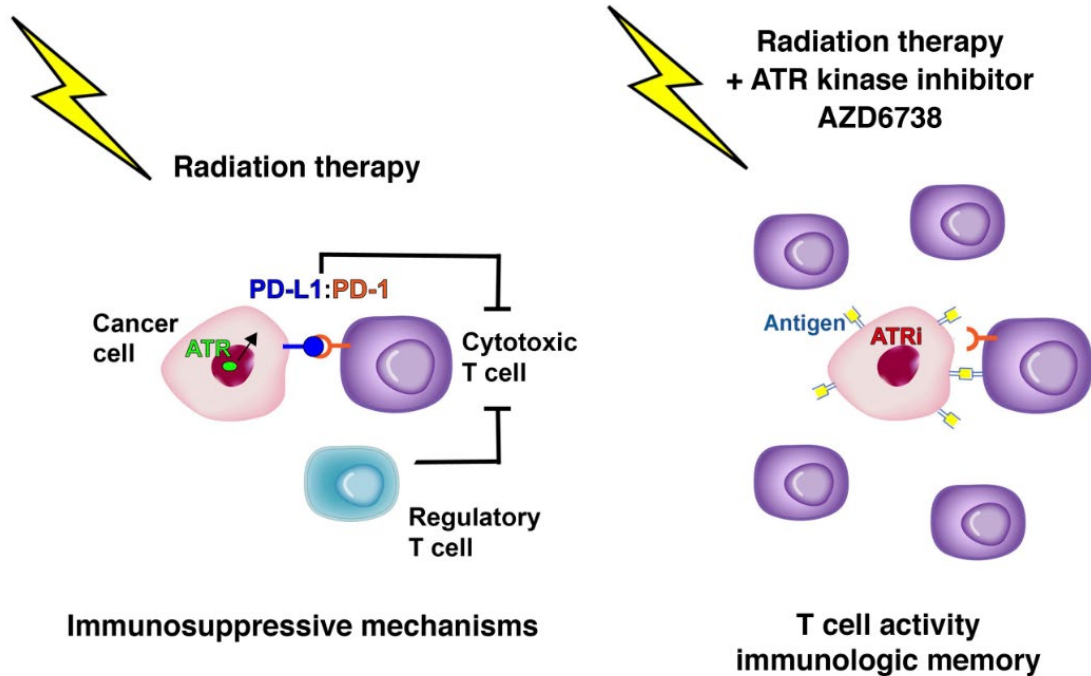
# Persistent IFN signaling leads to PD-L1-independent resistance



JAKi = JAK1/JAK2 inhibitor, Ruxolitinib

Starting at D10

## 2. 방사선 유도 DNA 손상 및 복구



RESEARCH ARTICLE

The Journal of Clinical Investigation

### ATR kinase inhibitor AZD6738 potentiates CD8<sup>+</sup> T cell-dependent antitumor activity following radiation

Frank P. Vendetti,<sup>1</sup> Pooja Karukonda,<sup>1</sup> David A. Clump,<sup>1</sup> Troy Teo,<sup>1</sup> Ronald Lalonde,<sup>1</sup> Katriana Nugent,<sup>2</sup> Matthew Ballew,<sup>2</sup> Brian F. Kiesel,<sup>3</sup> Jan H. Beumer,<sup>3</sup> Saumendra N. Sarkar,<sup>4,5</sup> Thomas P. Conrads,<sup>6</sup> Mark J. O'Connor,<sup>7</sup> Robert L. Ferris,<sup>5,8</sup> Phuoc T. Tran,<sup>2</sup> Greg M. Delgoffe,<sup>4</sup> and Christopher J. Bakkenist<sup>1,9</sup>

JCI

3926

jci.org

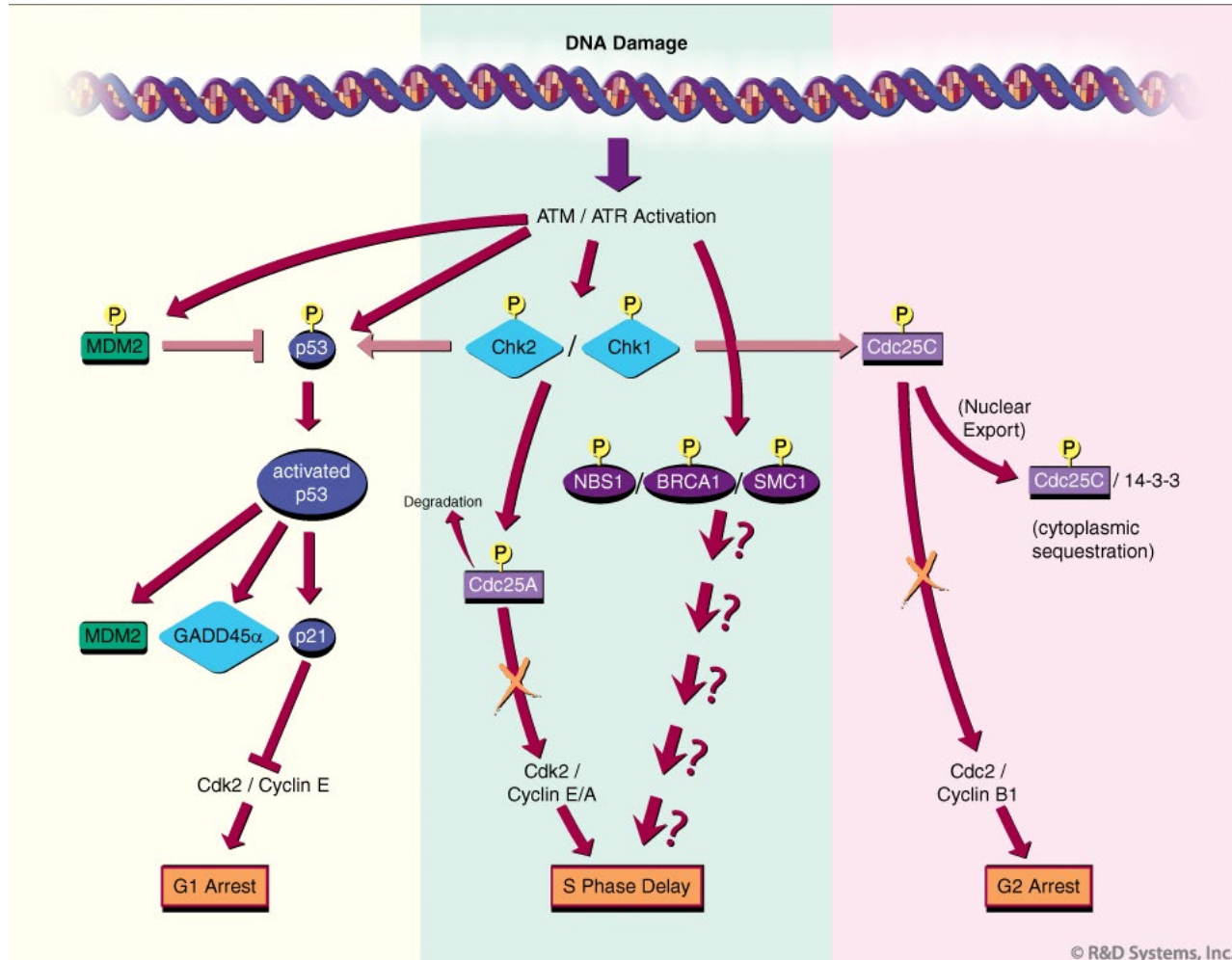
Volume 128

Number 9

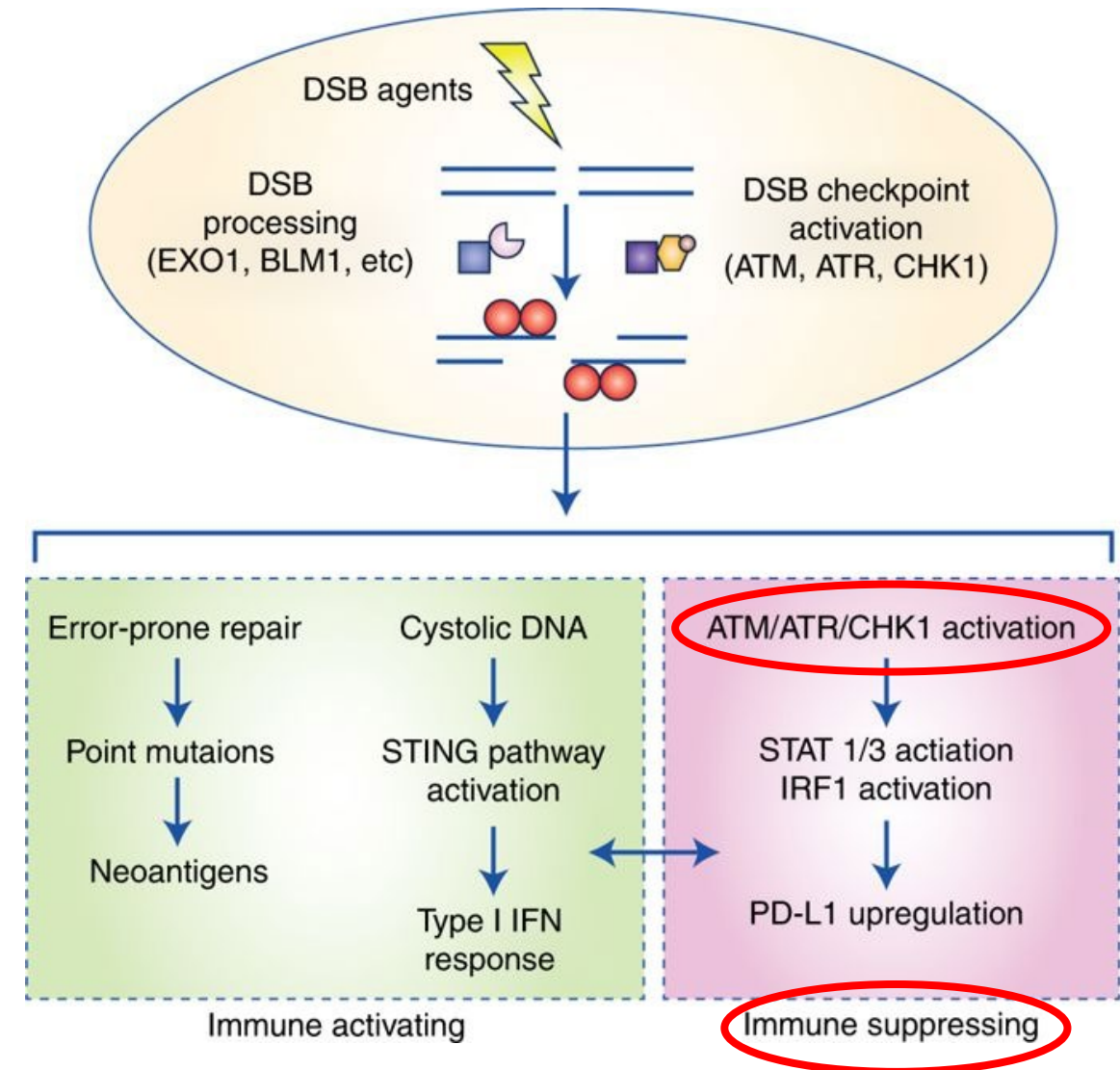
September 2018



## What is known

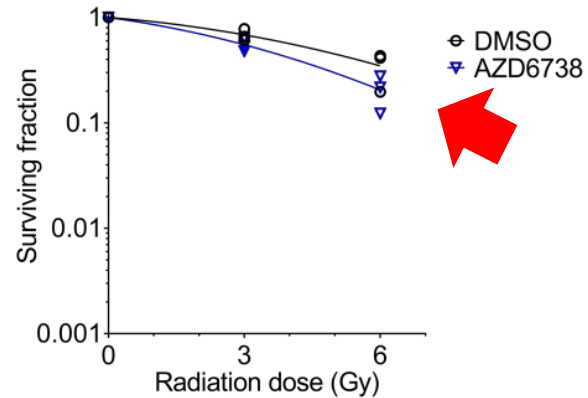


## What is new



# ATR inhibitor sensitizes tumors to IR through T cell-mediated immunity

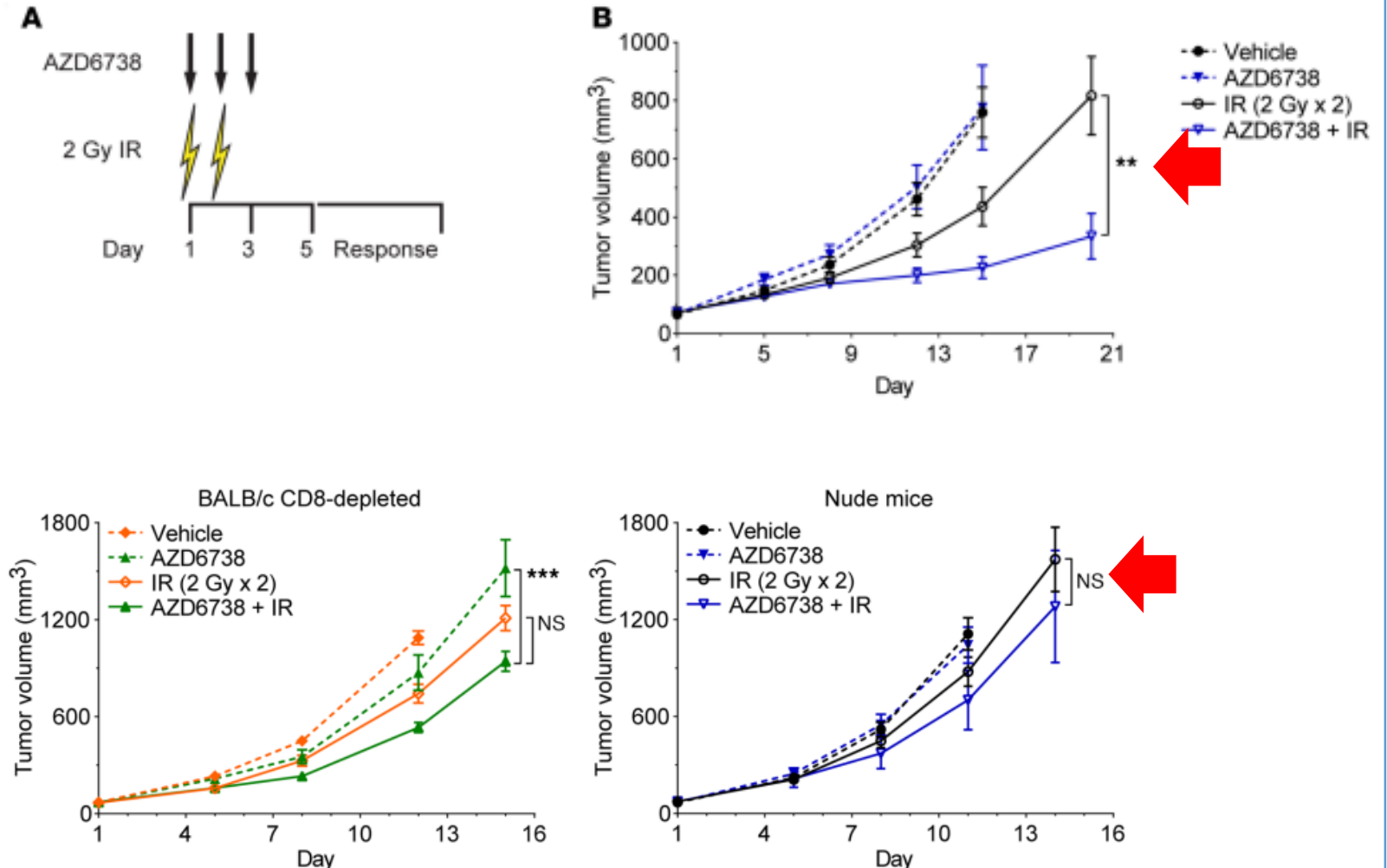
## CT26 cells *in vitro* IR



## AZD6738

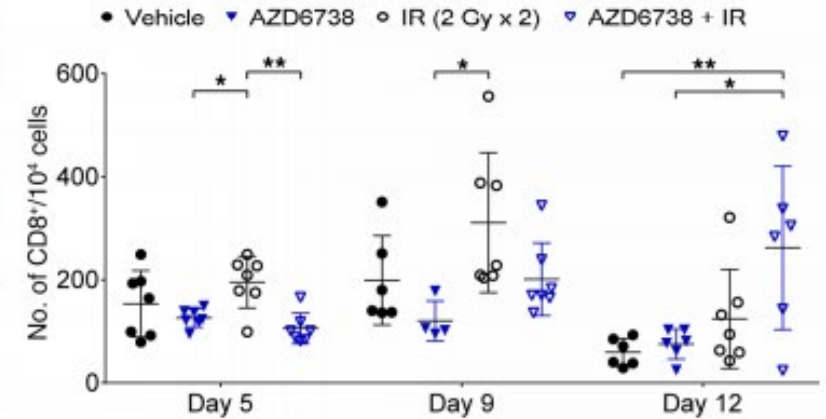
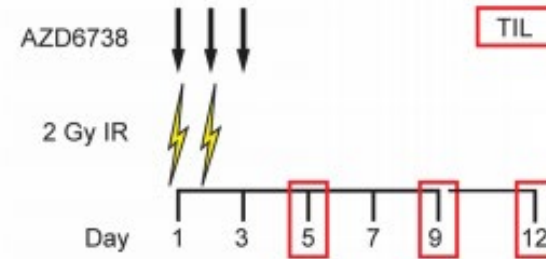
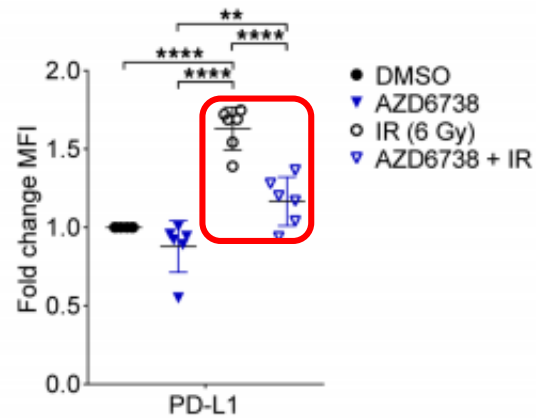
- Currently in clinical trials
- ATP-competitive ATR kinase inhibitor
- Inhibits CHK1 phosphorylation at  $IC_{50} = 0.074 \mu M$
- Does not inhibit other kinases (ATM, DNA-PK, mTOR) at this concentration

## CT26 cells *in vivo* IR

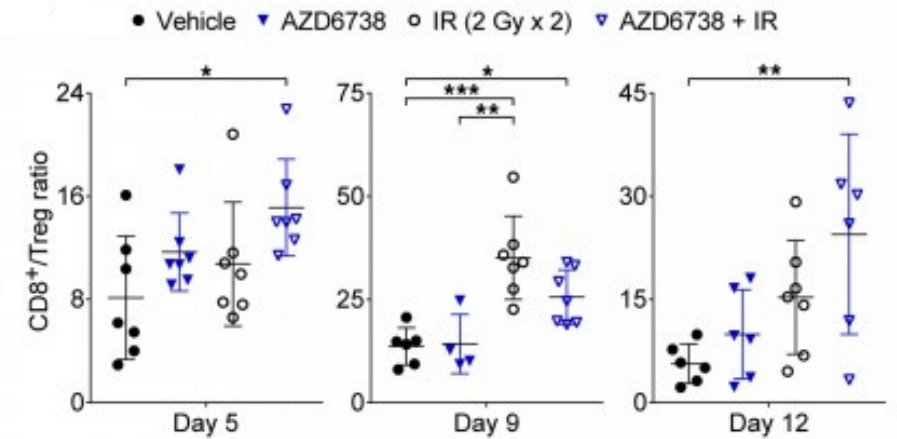
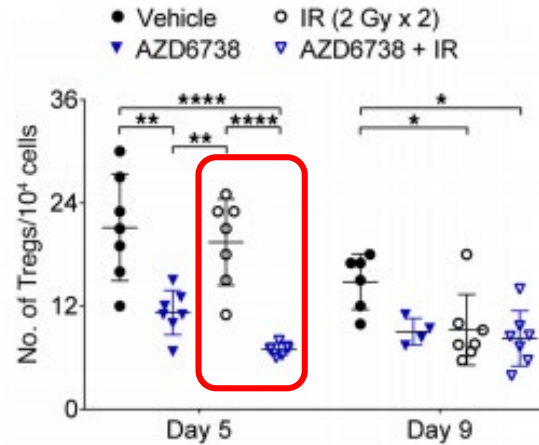
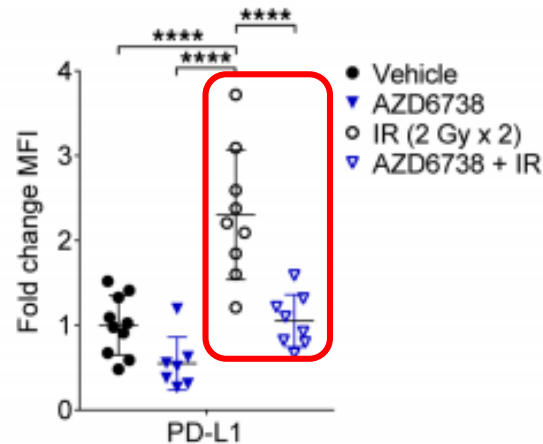
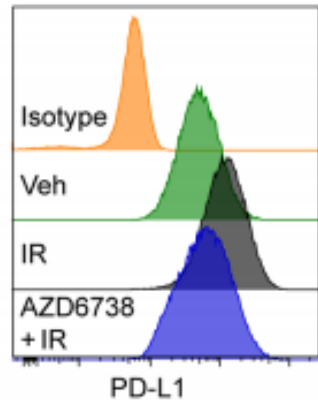


# ATR inhibitor dampens IR-induced PD-L1 expression

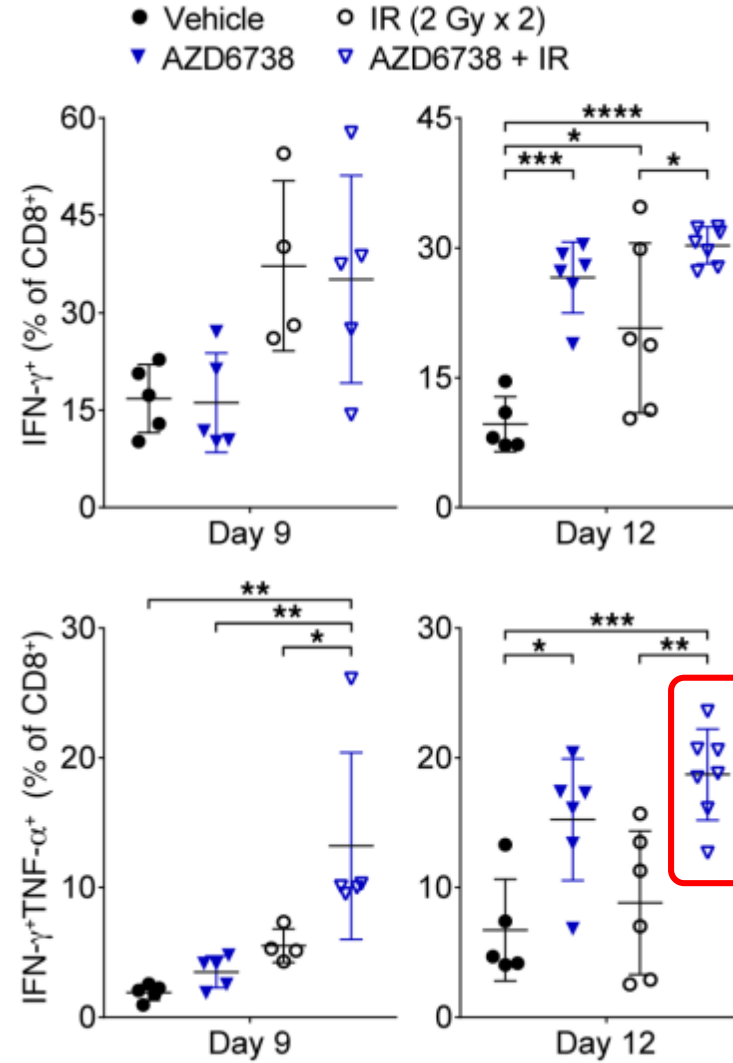
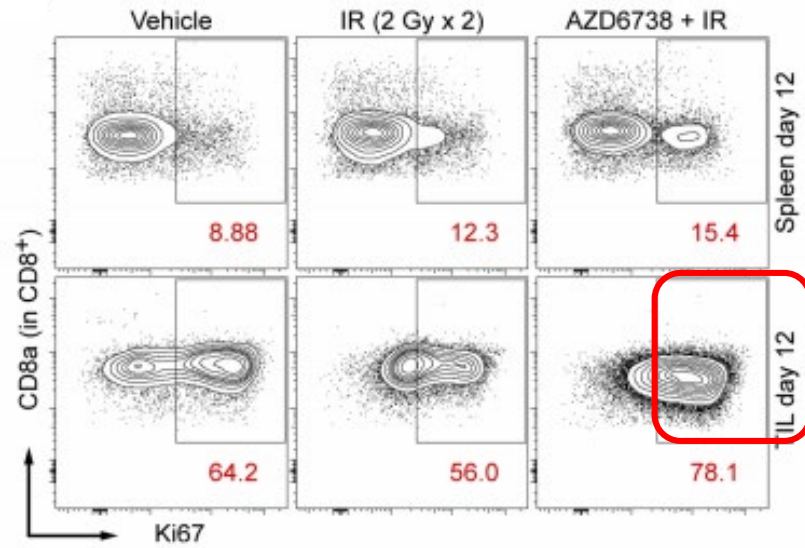
In vitro PD-L1



In vivo PD-L1 day 5



# ATR inhibitor enhances CD8 T effector functions





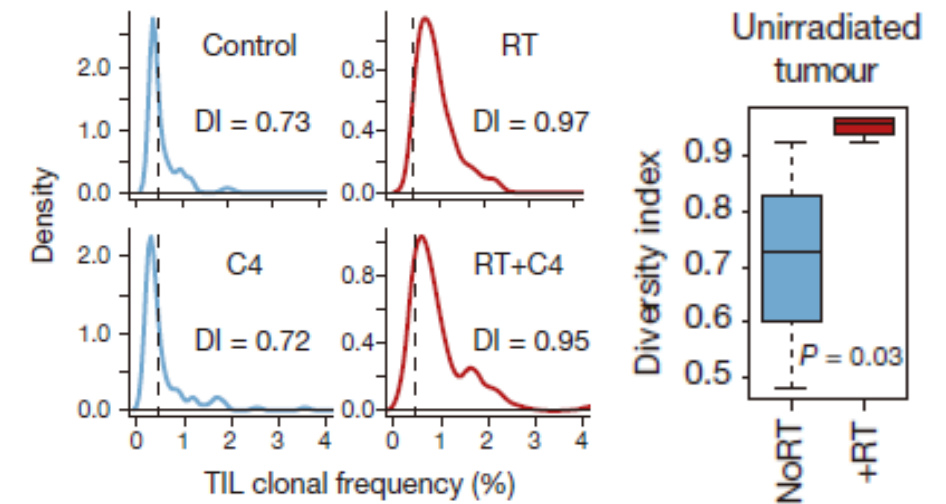
# Points for discussion and some unanswered questions

## 1. Other DNA damage repair inhibitors?

- ATMi
  - by Meredith Morgan (U Michigan).
  - AZD0156 + IR (3 days post 8 Gy IR) – IFN- $\beta$  response.
  - ATM loss promotes PD-L1 expression 2 days post 8 Gy.
  - Sensitizes RT + PD-L1 Ab
  - Cf. Chris Bakkenist – no CD8 increase/enhancement by ATMi (personal communications. Perhaps due to differences in radiation doses?)
- PARPi – induces T-cell mediated antitumor immune response
  - Meng et al., Mol Ther (2012) 20, 1046-1056

## 2. IR does increase clonal diversity of T cells (Nature paper by Andy Minn).

- Rationale for combining with immunotherapy is proven.
- Why is it difficult to achieve good response with just one immune checkpoint blockade?



## 3. How does hypoxia interfere antitumor immunity? By Silvia Formenti

- HIF-1 $\alpha$  drives PD-L1 expression (limits T cell activities)
- HIF-1 $\alpha$  increases NKG2D ligand MICA shedding (limits NK cell activities)