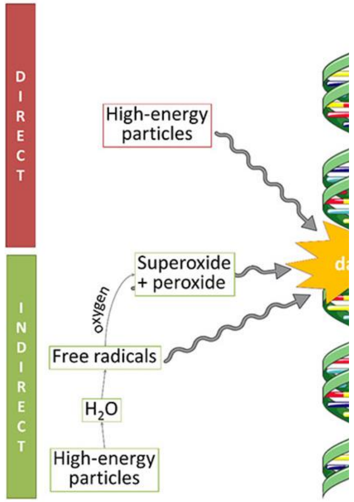
Heavy Ion Therapy Research Integration

Immunological Effects

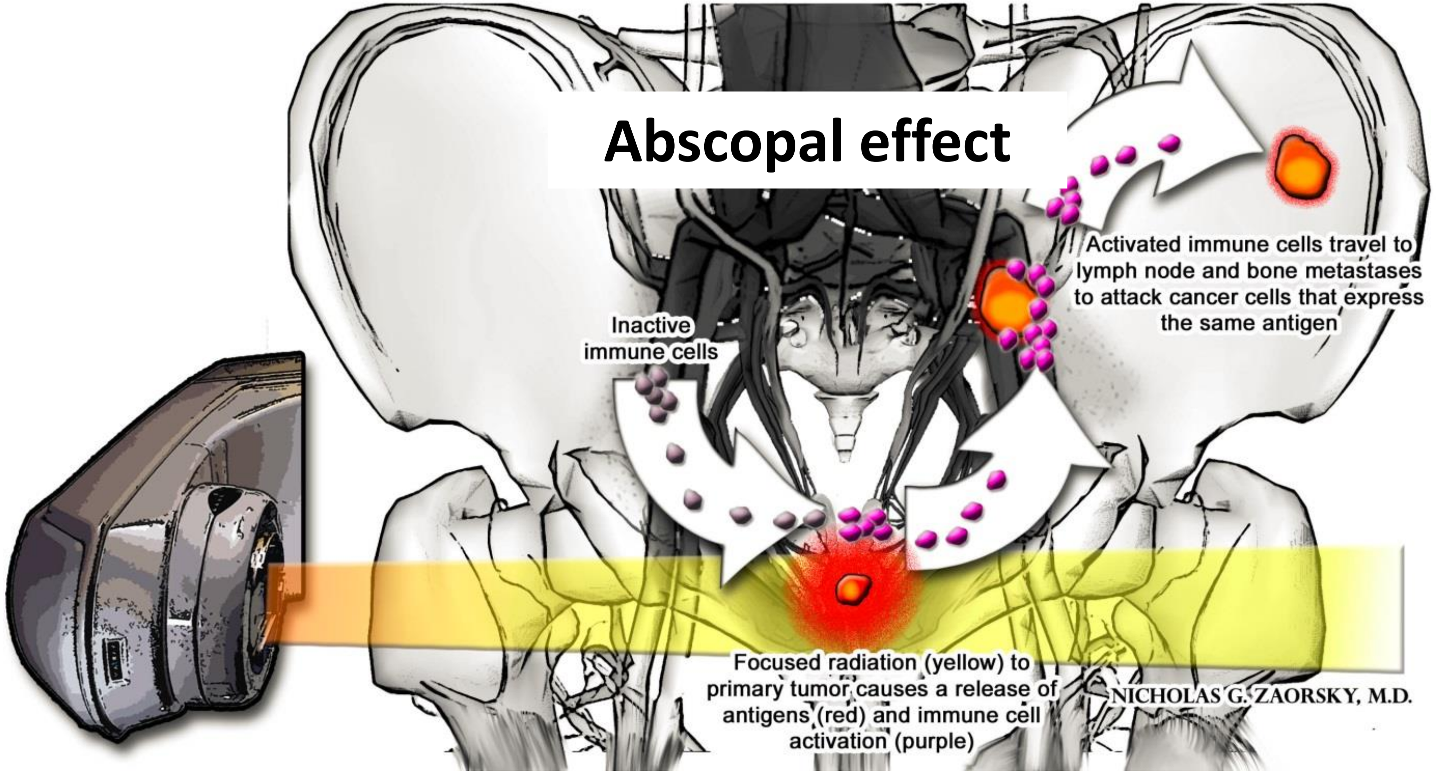
ALEXANDER HELM, GSI

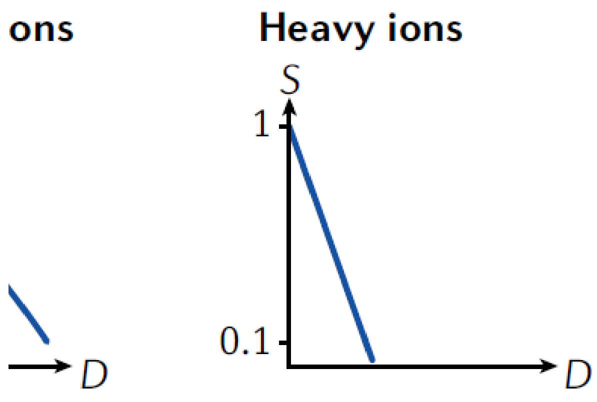
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

There is more in radiotherapy than „simple“ cell inactivation



Przystupski, Front Pharm





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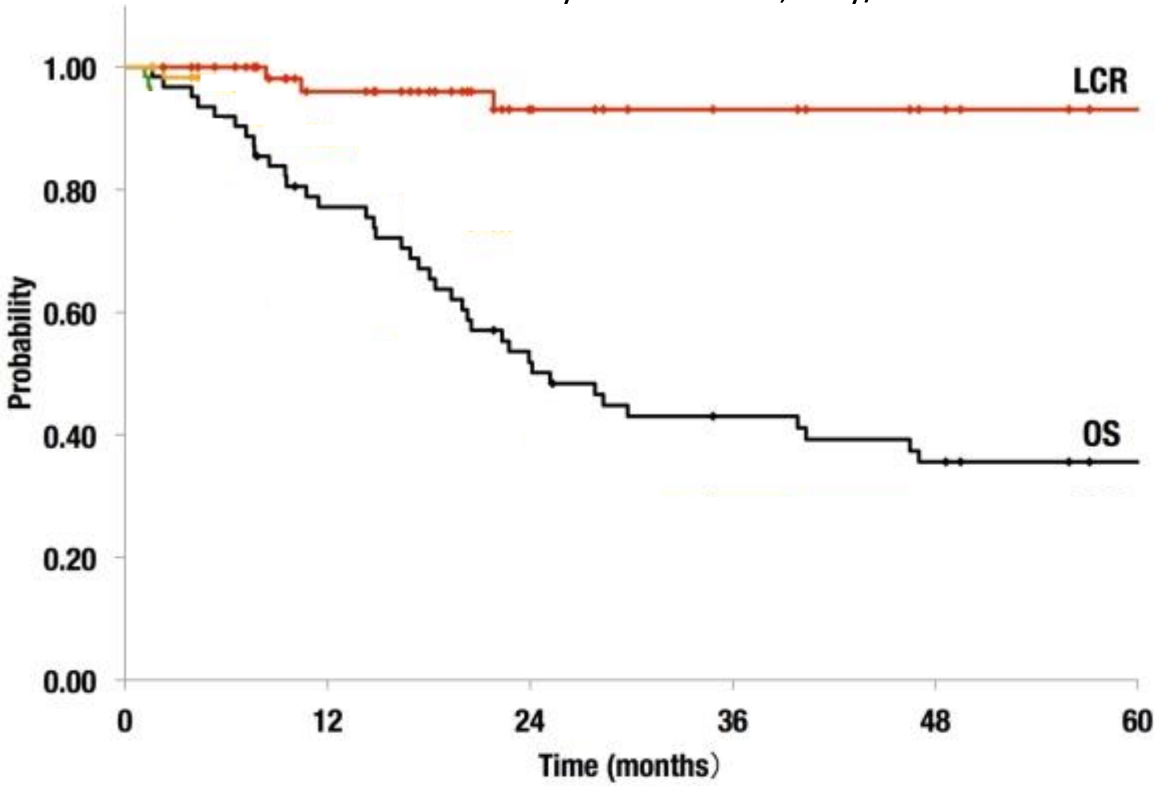
Improved local control rate after CIRT

Non-small cell lung cancer (NSCLC) stage IIA/IIIA, therapy regimen:
68-72 GyE carbon ions, 4 Gy/fraction



Local control rate, 93.1%

Overall survival

Takahashi et al., *Cancer* 2015

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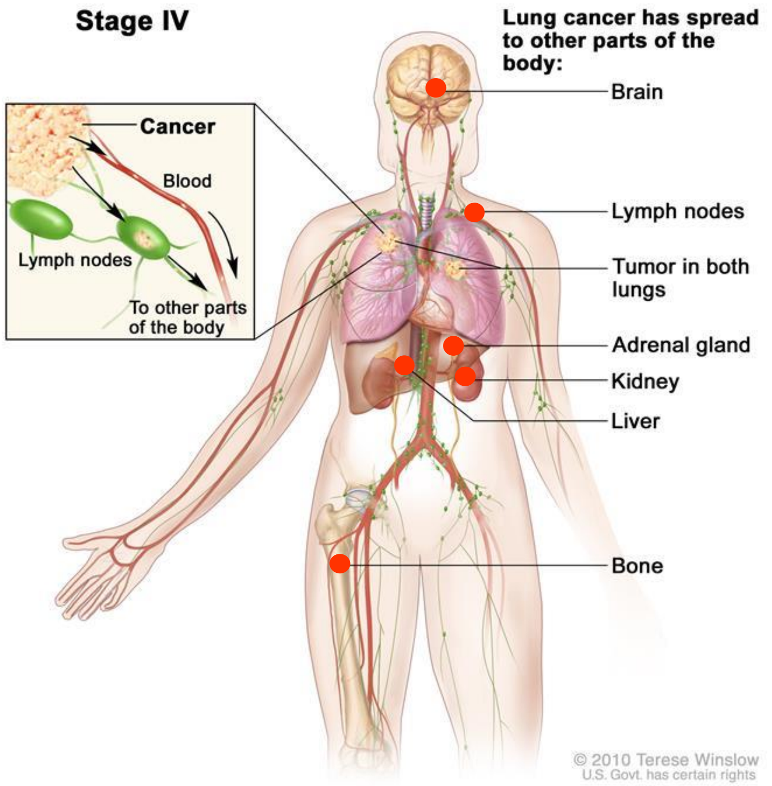
Metastatic cancer disease

- Therapy of metastastic cancer disease is normally palliative, with the clinical goal of improving quality of life
- Primary cause of cancer morbidity and mortality, responsible for about 90% of cancer deaths
- Rather low 5-year survival rates



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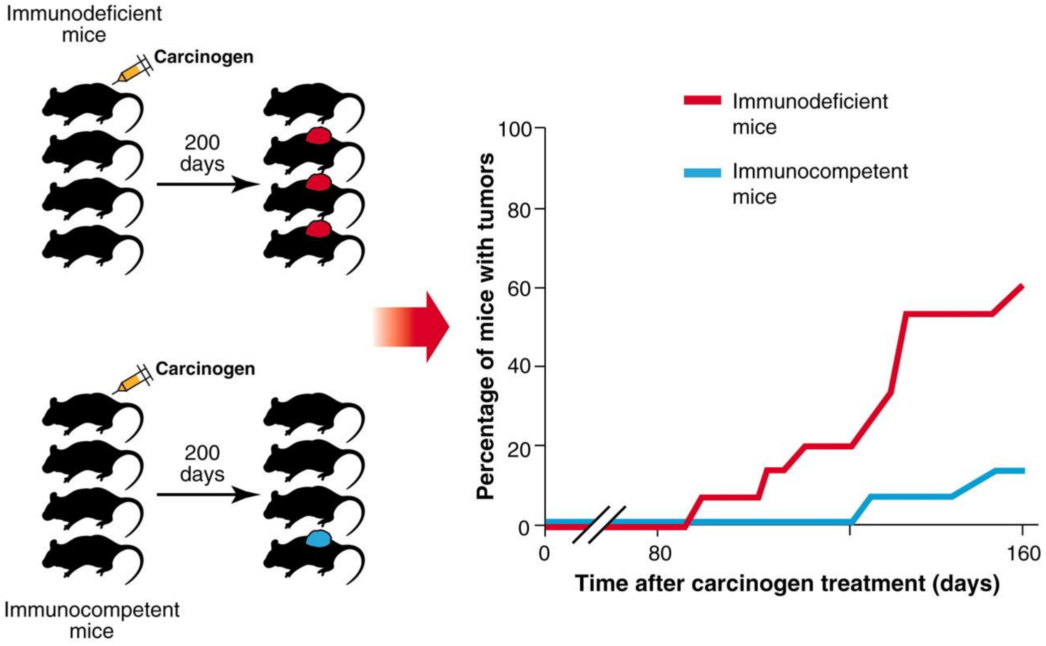
The immune system protects from cancer

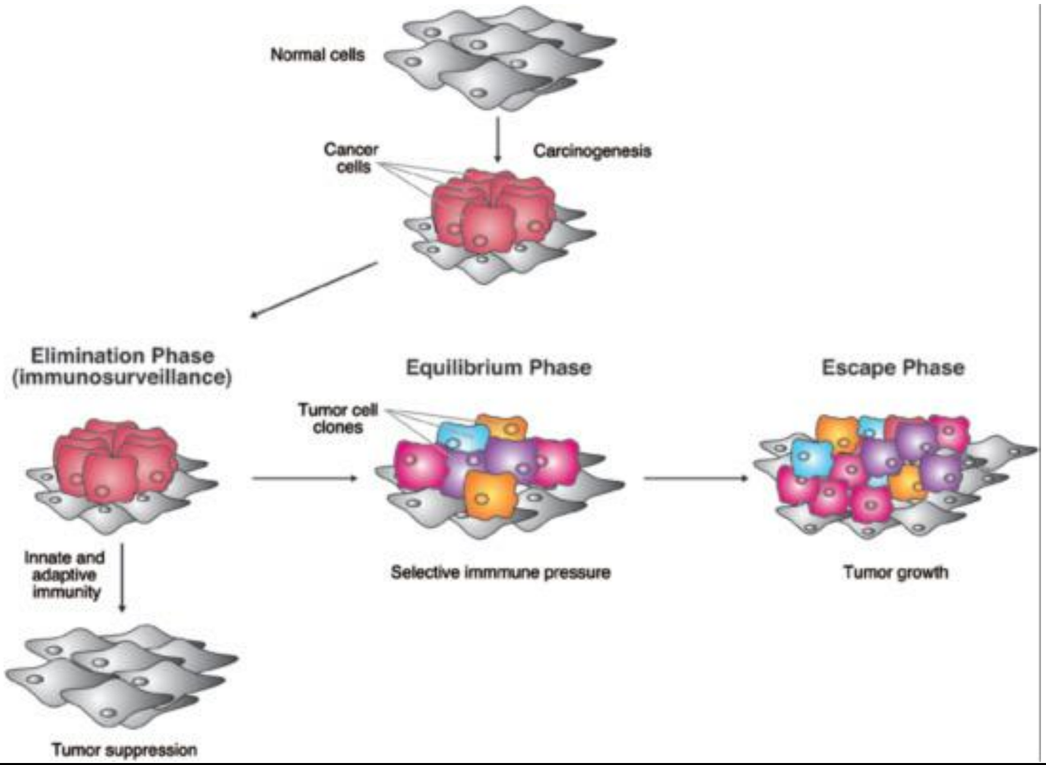


Schreiber et al., Science, 2011

Increased risk of cancers in immunocompromised populations:

- HIV/AIDS (standardized incidence ratio=4, IC95% 3.78-4.24)
- transplant recipients (standardized incidence ratio=3.28, IC95% 3.06-3.52)

Oliveira Cobucci et al., Cancer Epidemiol., 2012



Carbone et al., J Thorac Oncol., 2015

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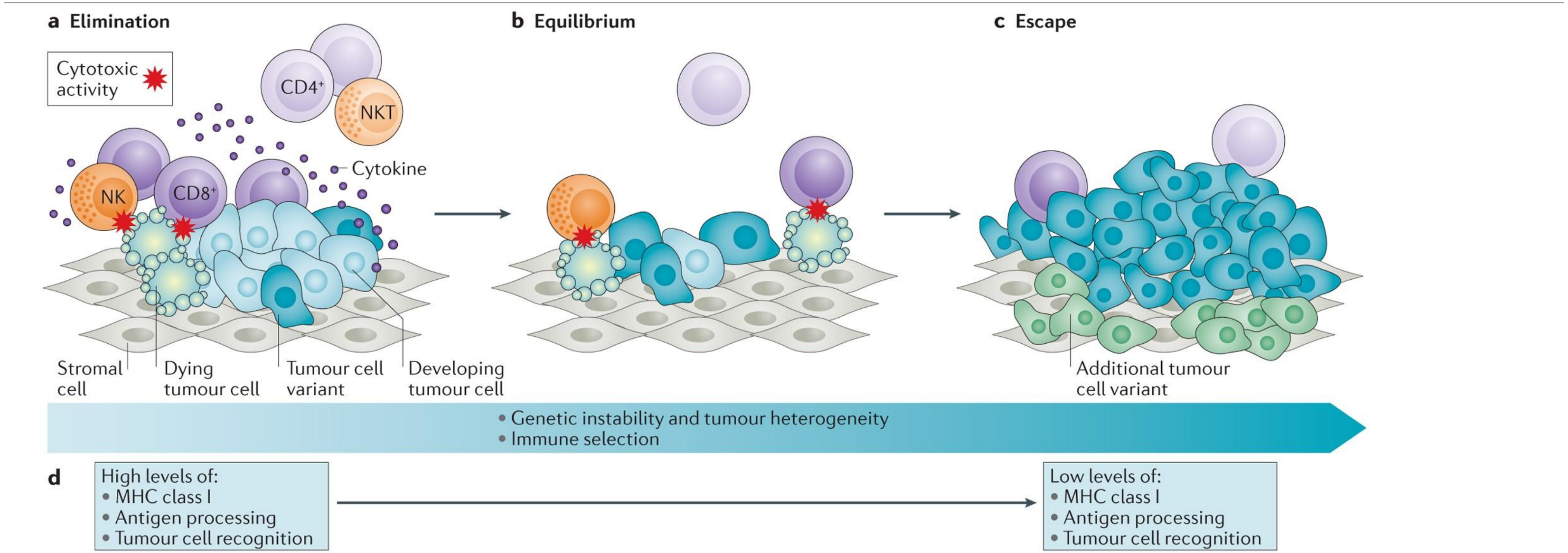
Cancer immunoediting



Van der Burg, Nat Rev Cancer, 2016

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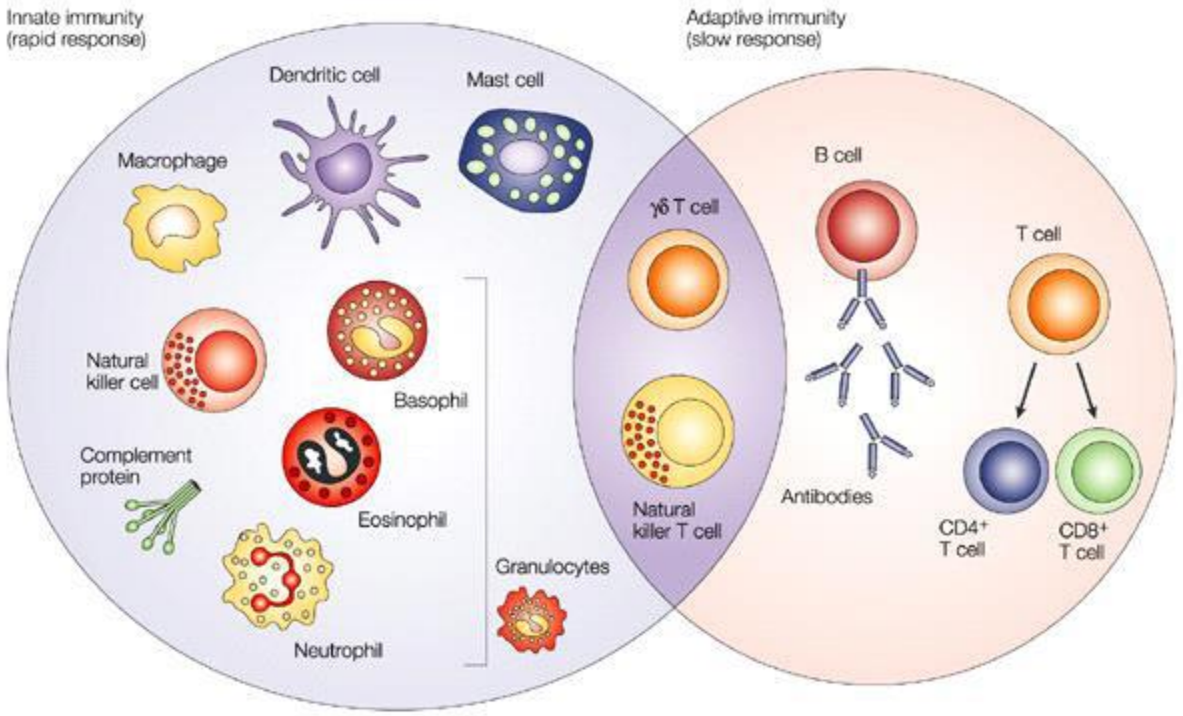
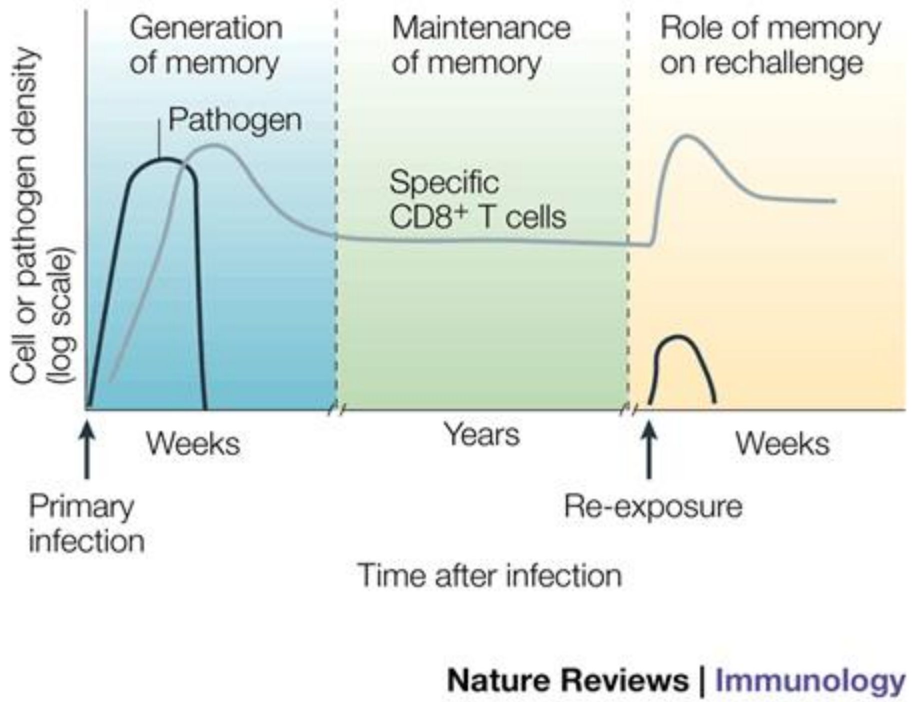
Immune system



Dranoff, Nat Rev Cancer, 2004



Antia et al., Nat Rev Immunol, 2005

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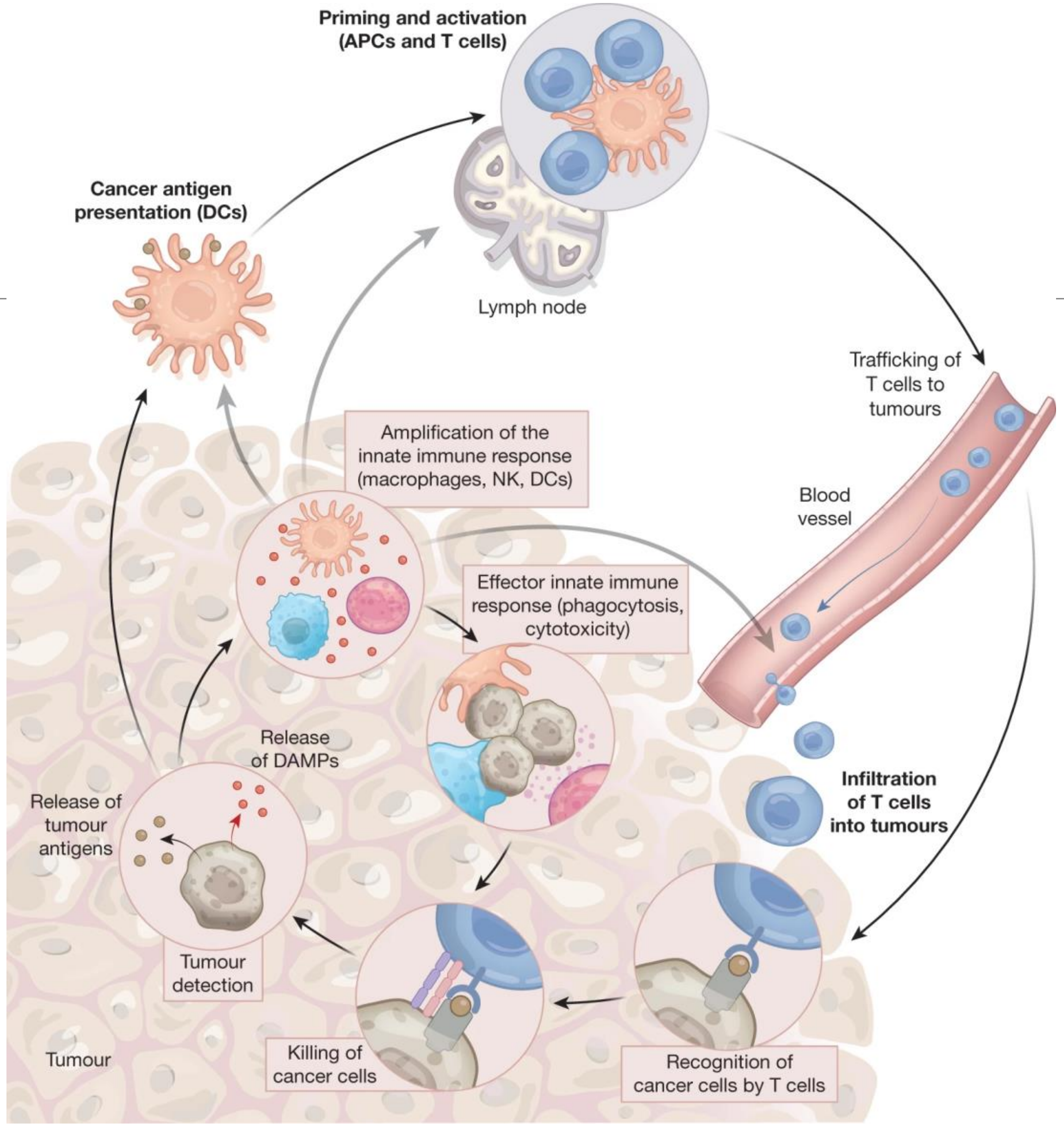
Cancer immune cycle



Demaria et al., Nature, 2019

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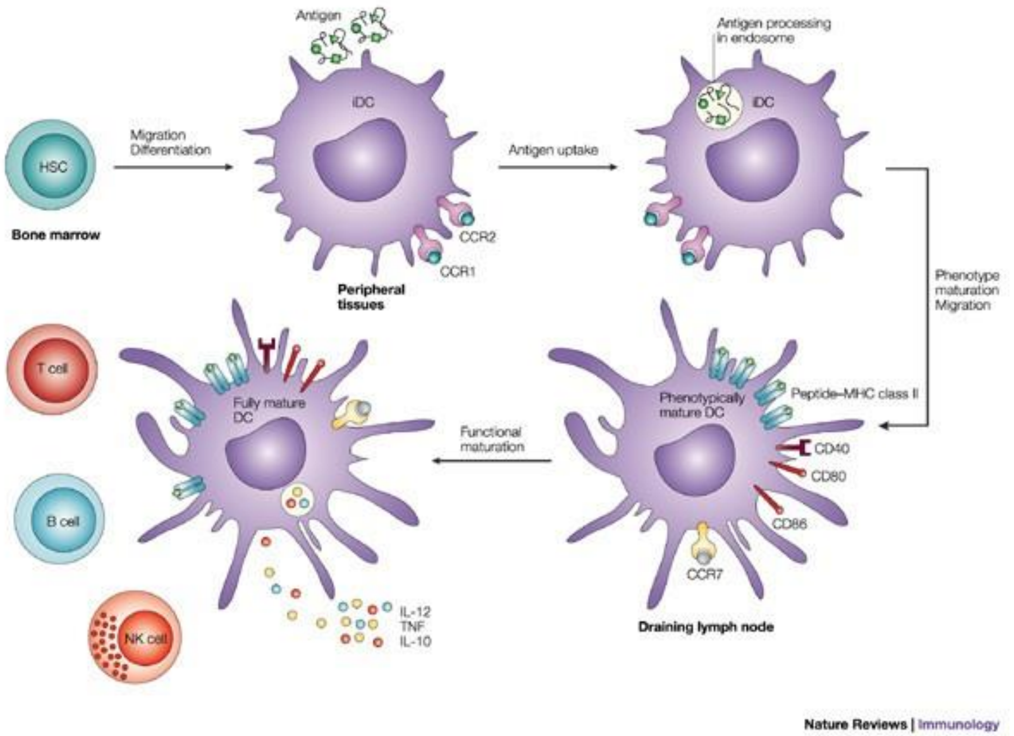
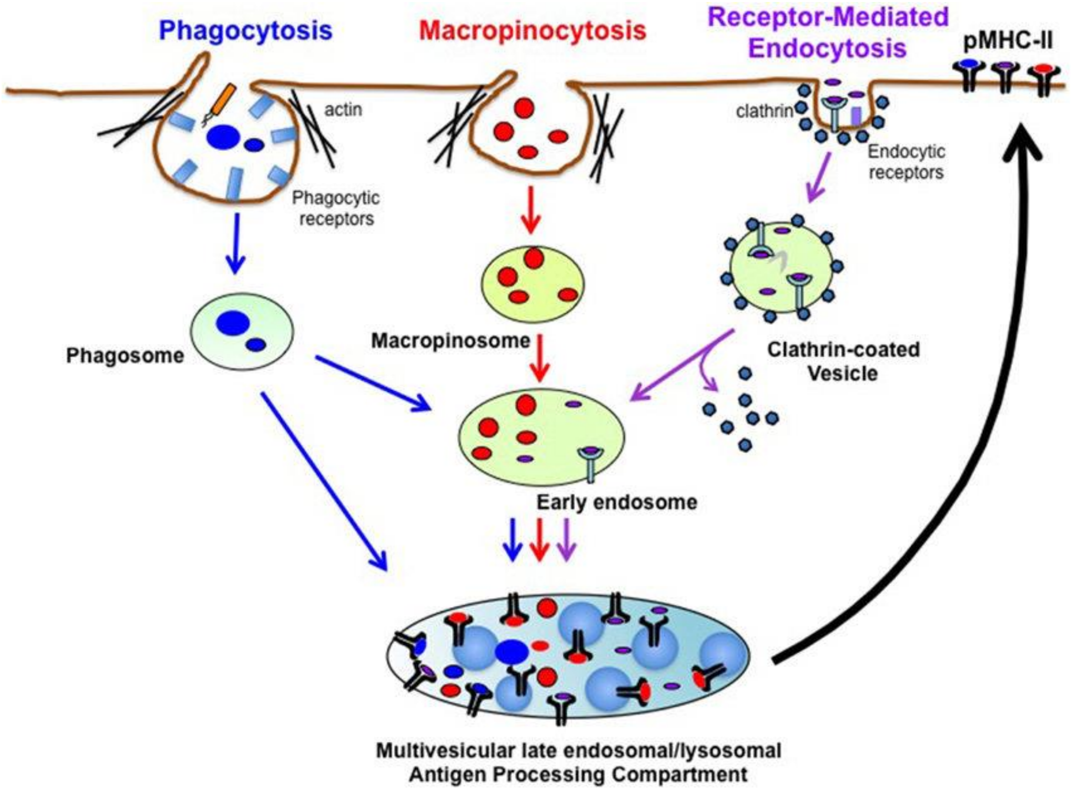
Antigen presenting cells



Hackstein and Thomson, Nat Rev Immunol, 2004



Liu and Roche, Front. Physiol., 2015

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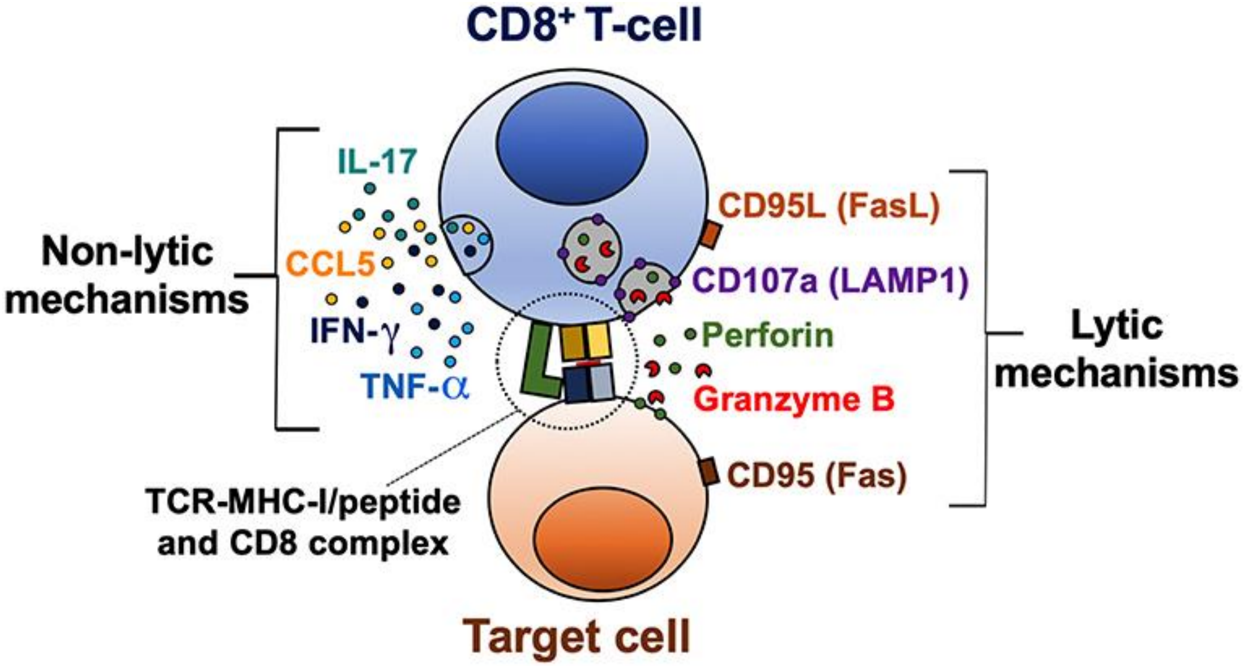
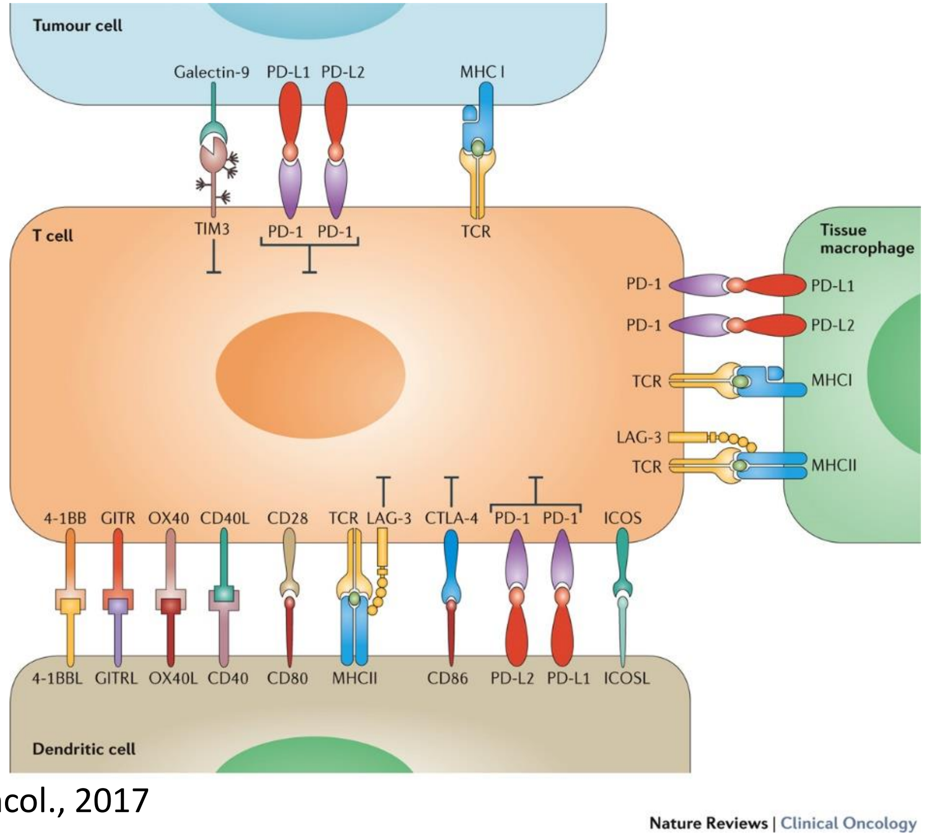
Cytotoxic T-cells and checkpoints



Perdomo-Celis et al., Front. Immunol., 2019



Nishino et al., Nat Rev Clin Oncol., 2017

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Checkpoint inhibition

AWARDS

Cancer immunologists scoop medicine Nobel prize

One of the hottest areas in cancer research, immunotherapy can dramatically extend lives.

BY HEIDI LEDFORD, HOLLY ELSE AND MATTHEW WARREN

Two scientists who pioneered a new way to treat cancer have won the 2018 Nobel Prize in Physiology or Medicine. James Allison at the University of Texas MD Anderson Cancer Center in Houston and Tasuku Honjo at Kyoto University in Japan showed how proteins on immune cells can be used to manipulate the immune system so that it attacks cancer cells. The approach has led to therapies that have extended lives, and even wiped out all signs of disease in some people with advanced cancers.

"To have my work really impact people is one of the best things I could think about," said Allison at a press conference on 1 October, the day the 9-million-Swedish-krona (US$1-million) prize was announced. "It's everybody's dream."

In the 1990s, Allison, then at the University of California, Berkeley, studied a protein,

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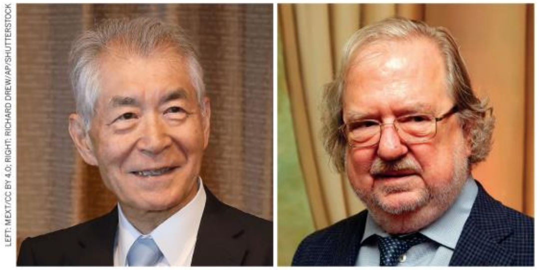
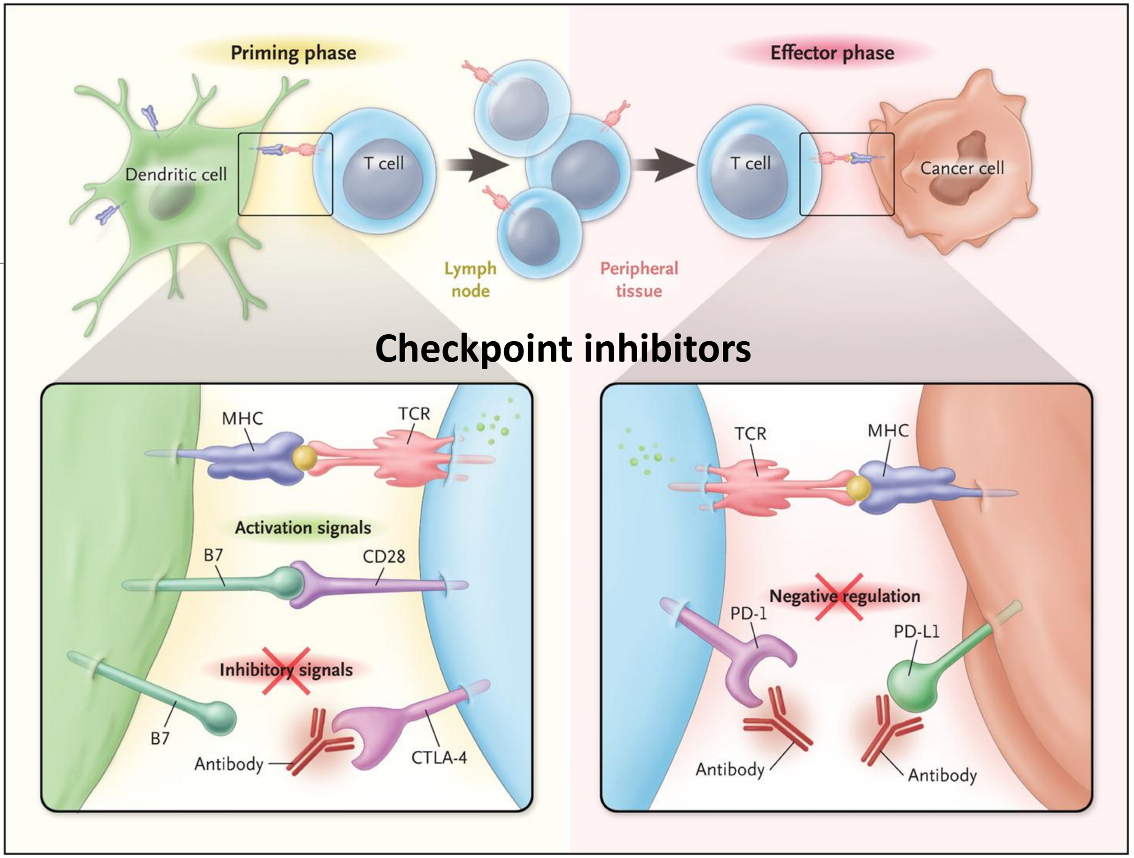


Tasuku Honjo (left) and James Allison share the 2018 Nobel Prize in Physiology or Medicine.



Ipilimumab
anti-CTLA-4

Nivolumab
anti-PD-1

Ribas et al., N Engl J Med., 2012

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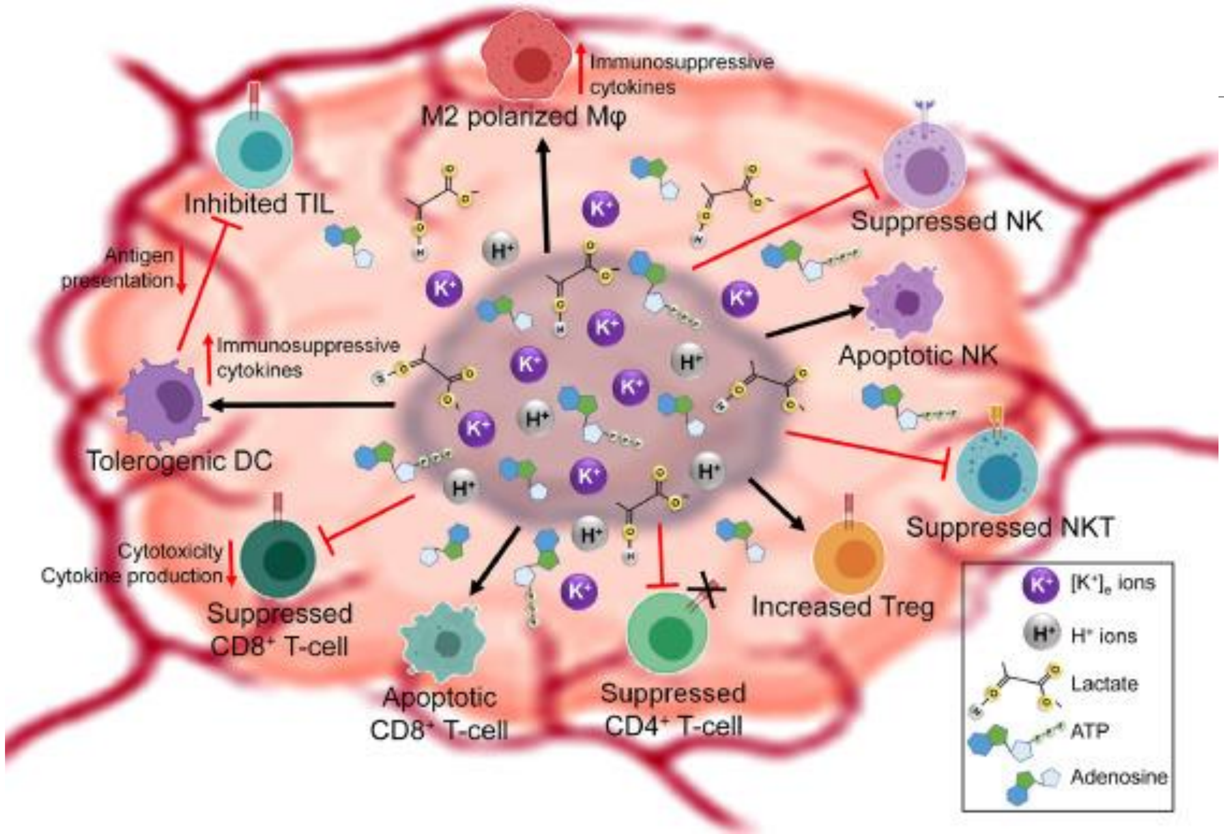
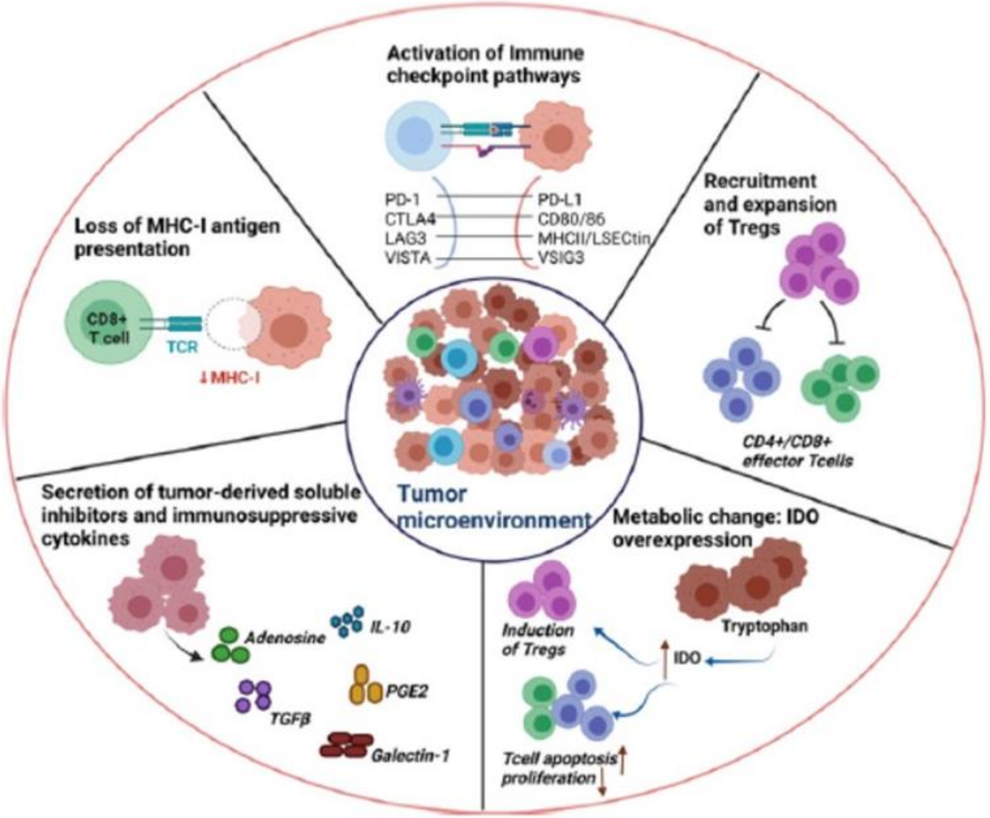
Tumor microenvironment alters the immune function



Verma et al., EBioMedicine, 2022



Wei and Tasken, Biochemical Journal, 2022

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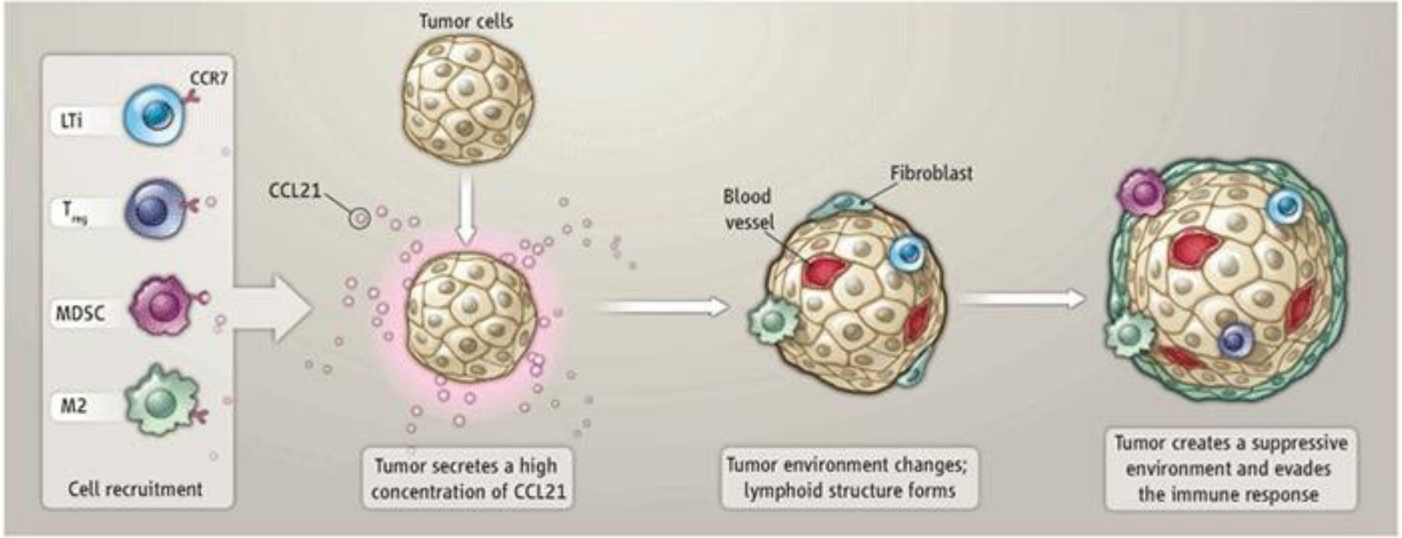
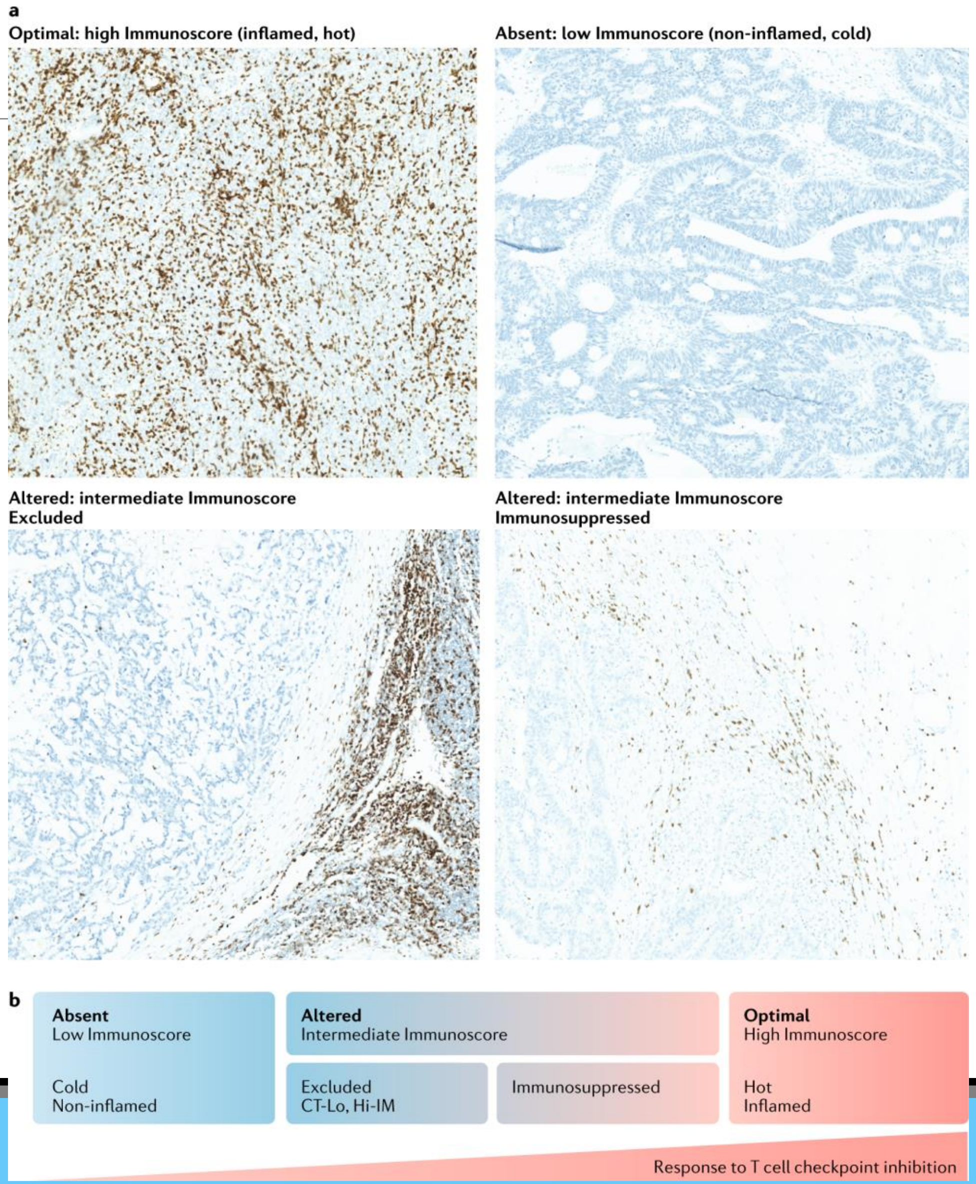
Tumors create immune suppressive environments



Zindl and Chaplin, Science, 2010



Galon and Bruni, Nat Rev Drug Discov., 2019

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Cancers exploit many immune evasion strategies

Table 2 | **Evasion of danger signalling by pathogens and cancer cells***

Danger signal	Strategy‡	Setting‡	Notes	Refs
Cancer cells				
UPR and ER chaperone signalling	Improved ER homeostasis	Patients affected by multiple tumours	High levels of GRP78 correlated with worsened disease outcome	123
	CALR loss	Patients with NSCLC	CALR levels of expression in malignant cells correlated with the phosphorylation of eIF2A and influenced disease outcome	93
	Limited HSP exposure	Patients with NHL	Limited HSP90 exposure was associated with no clinical responses to autologous cancer cell-based vaccination	123
	CD47 upregulation	Patients affected by multiple tumours	Low CD47 levels on neoplastic cells correlated with improved disease outcome	90–92
	LRP1 downregulation	Patients with melanoma	High LRP1 levels on monocytes were associated with slow progression	94
Autophagy and ATP signalling	Overexpression of BCL-2-like proteins	Patients affected by multiple tumours	Several cancers are characterized by the overexpression of BCL-2-like proteins, which potently inhibit autophagy	125
	BECN1 downregulation	Breast cancer patients	Decreased *BECN1* mRNA levels were associated with poor prognosis	25
	CD39 and/or CD73 overexpression	Patients affected by multiple tumours	High CD39 and/or CD73 levels on malignant or immune cells correlated with worsened disease outcome	123
	P2RX7 SNPs	Patients with breast cancer	Loss-of-function *P2RX7* mutation was associated with shortened time-to-metastasis	95
RNA signalling	*TLR3* SNPs	Patients affected by multiple tumours	*TLR3* mutational status influenced disease outcome	123
	TLR3 downregulation	Patients affected by multiple tumours	High TLR3 mRNA or protein levels were associated with improved disease outcome	123
	TRIF downregulation	Patients with hepatocellular carcinoma	Robust TRIF expression correlated with increased overall survival	123
Cancer cells (cont.)				
Type I IFN signalling	*IFNAR1* SNPs	Patients with glioma	Loss-of-function *IFNAR1* mutation was associated with worsened disease outcome	123
	IRF7 downregulation	Patients with breast cancer	Low IRF7 levels have been linked to decreased metastasis-free survival	110
	STAT1 deficiency	Patients with breast cancer	Approximately 33% of breast cancer biopsies displayed undetectable or extremely reduced STAT1 levels	111
ANXA1 signalling	*FRP1* SNPs	Patients with breast cancer	Loss-of-function *FPR1* mutation was associated with shortened time-to-metastasis and decreased overall survival	39
HMGB1 signalling	HMGB1 loss	Patients with breast cancer	Loss of nuclear HMGB1 positively correlated with tumour size	104
	TLR4 SNPs	Patients with breast cancer	Loss-of-function *TLR4* mutation was associated with shortened time-to-metastasis	38
Cell death	*TP53* mutations	Patients affected by multiple tumours	Mutations in *TP53* are found in >50% of all human cancers, and are associated with increased resistance to cell death	125
	Altered expression of BCL-2 family members	Patients affected by multiple tumours	Many cancers overexpress anti-apoptotic BCL-2-like proteins or inactivate their pro-apoptotic counterparts	125

Galluzzi et al., Nat Rev Immunol., 2017

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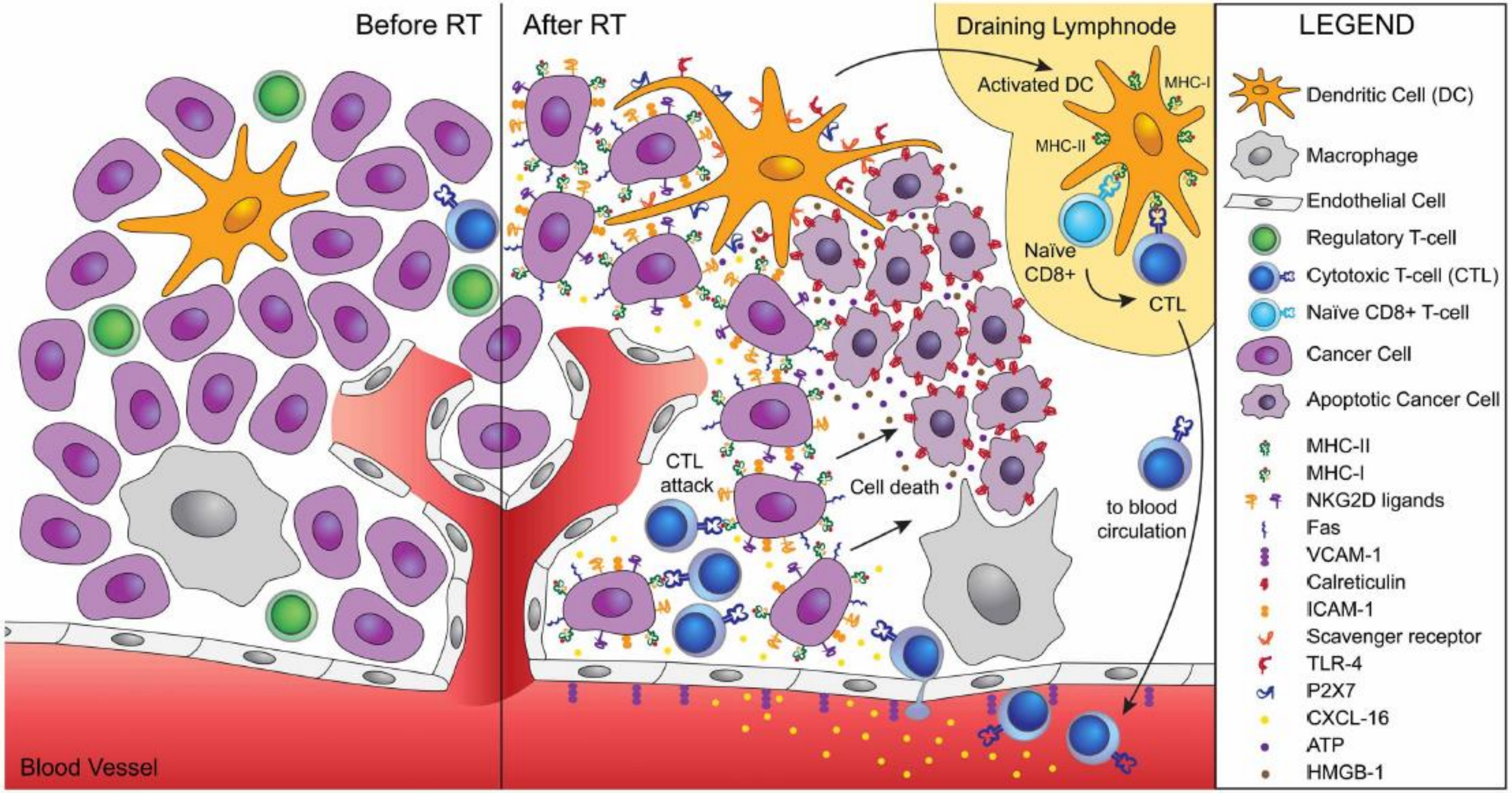
Radiotherapy can convert the tumor microenvironment



Demaria and Formenti, Front Oncol., 2012

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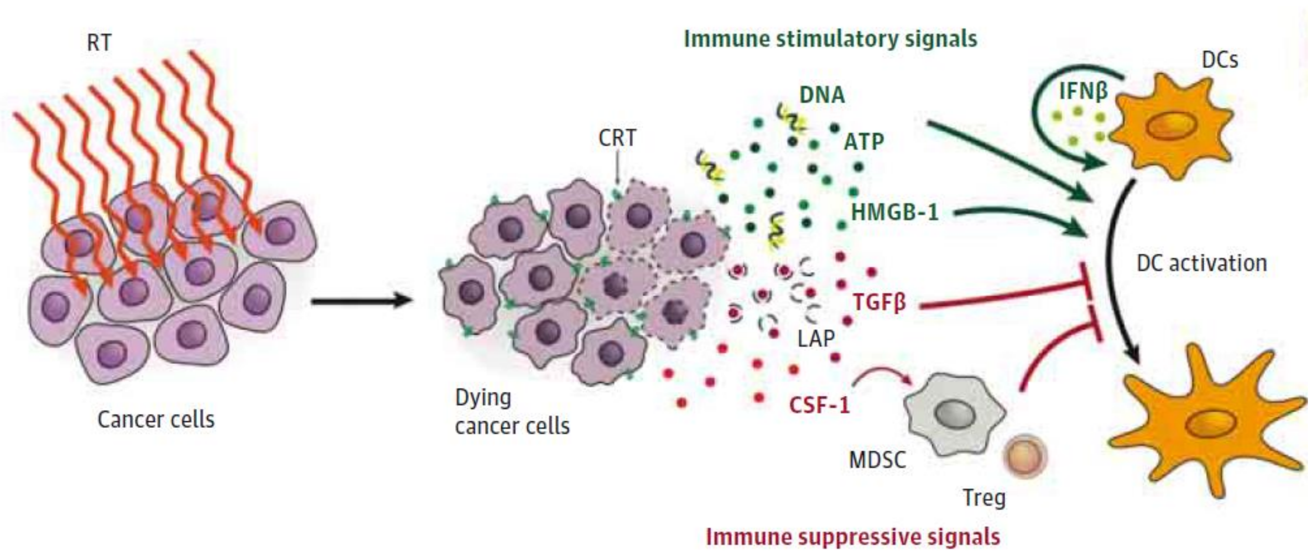
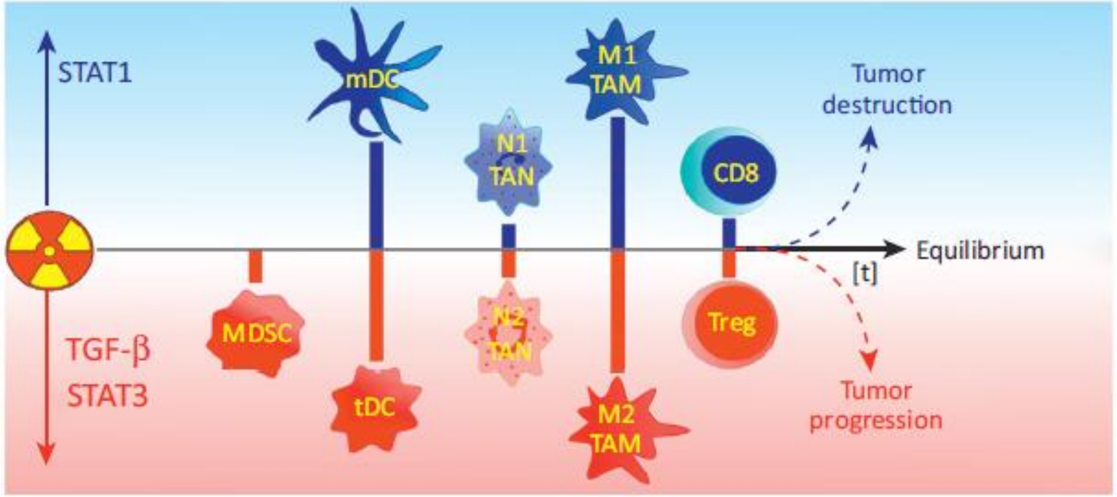
Radiotherapy can also be immunosuppressive





Durante et al., Trends Mol Med., 2013

Demaria et al., JAMA Oncol., 2015

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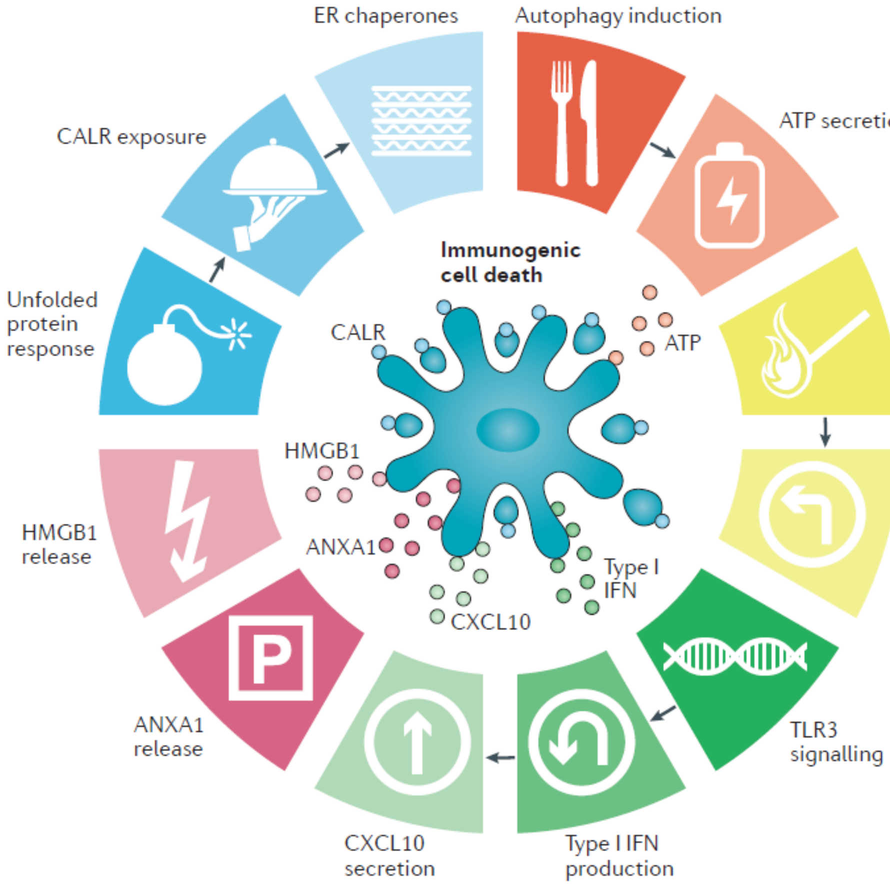
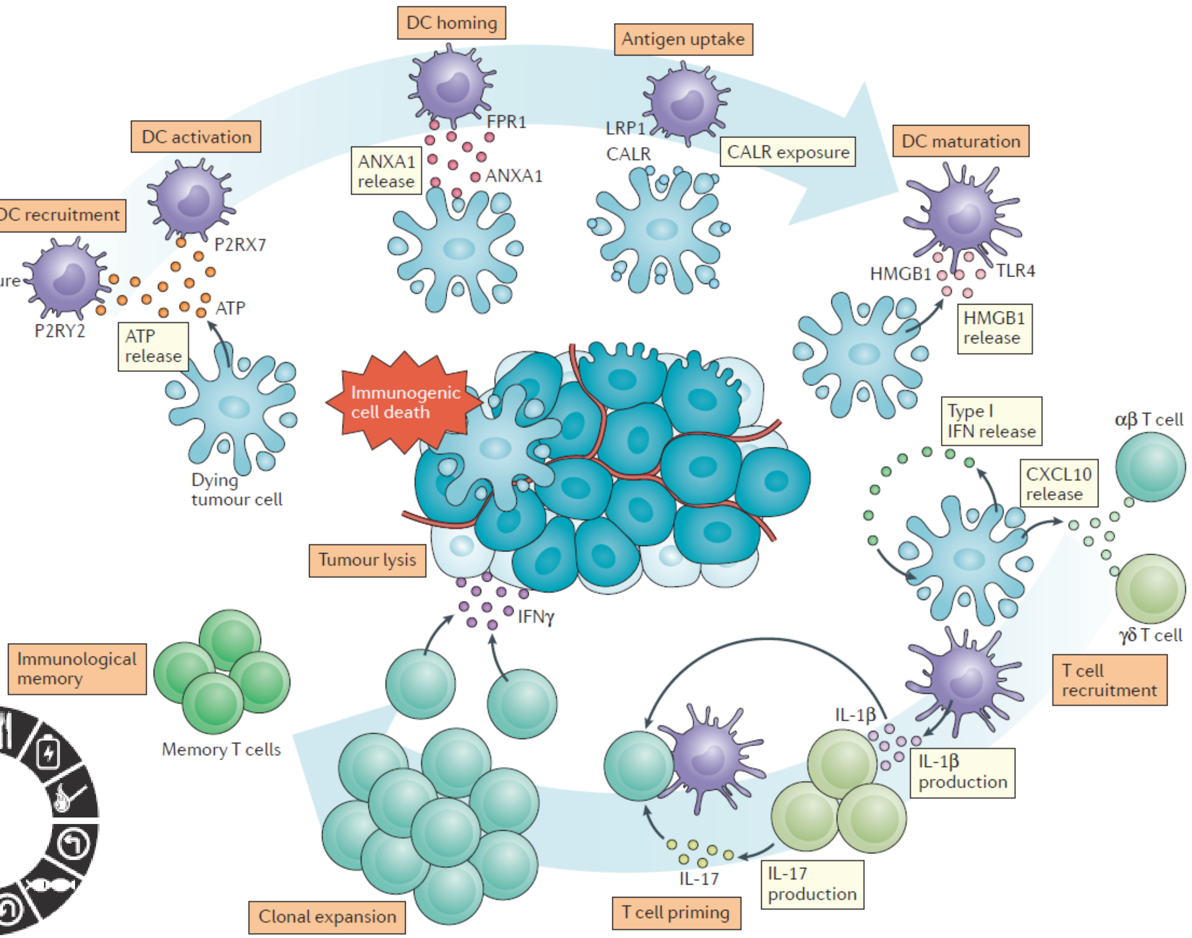
The way the cell dies matters – immunogenicity of the cell death



Radiation therapy



Galluzzi et al., Nat Rev Immunol., 2017

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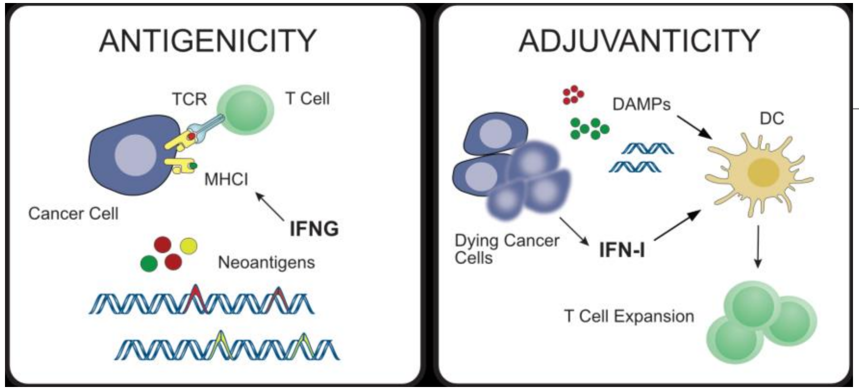
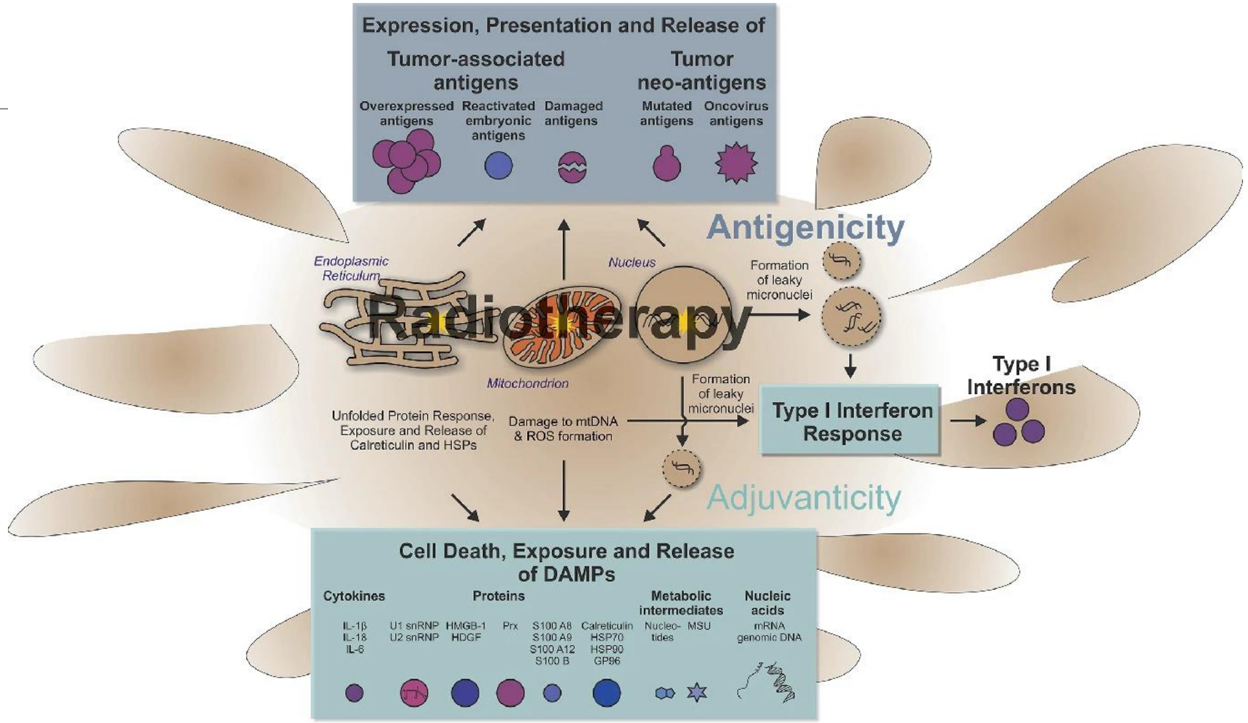
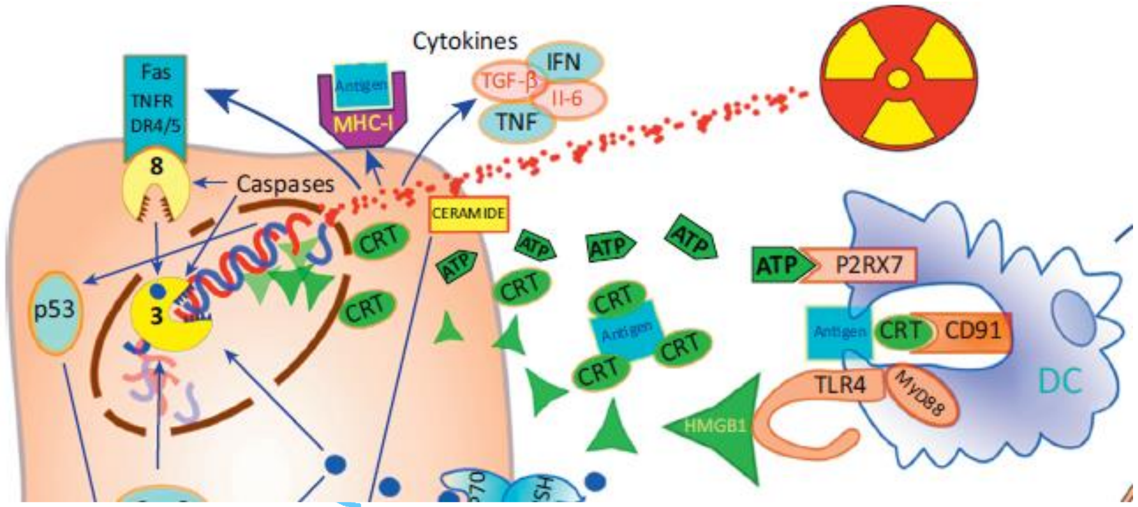
Immunogenicity of RT: antigenicity and adjuvanticity



Minn Lab, University of Pennsylvania



Brixx and Lauber, Springer, 2023



Durante et al., Trends Mol Med., 2013

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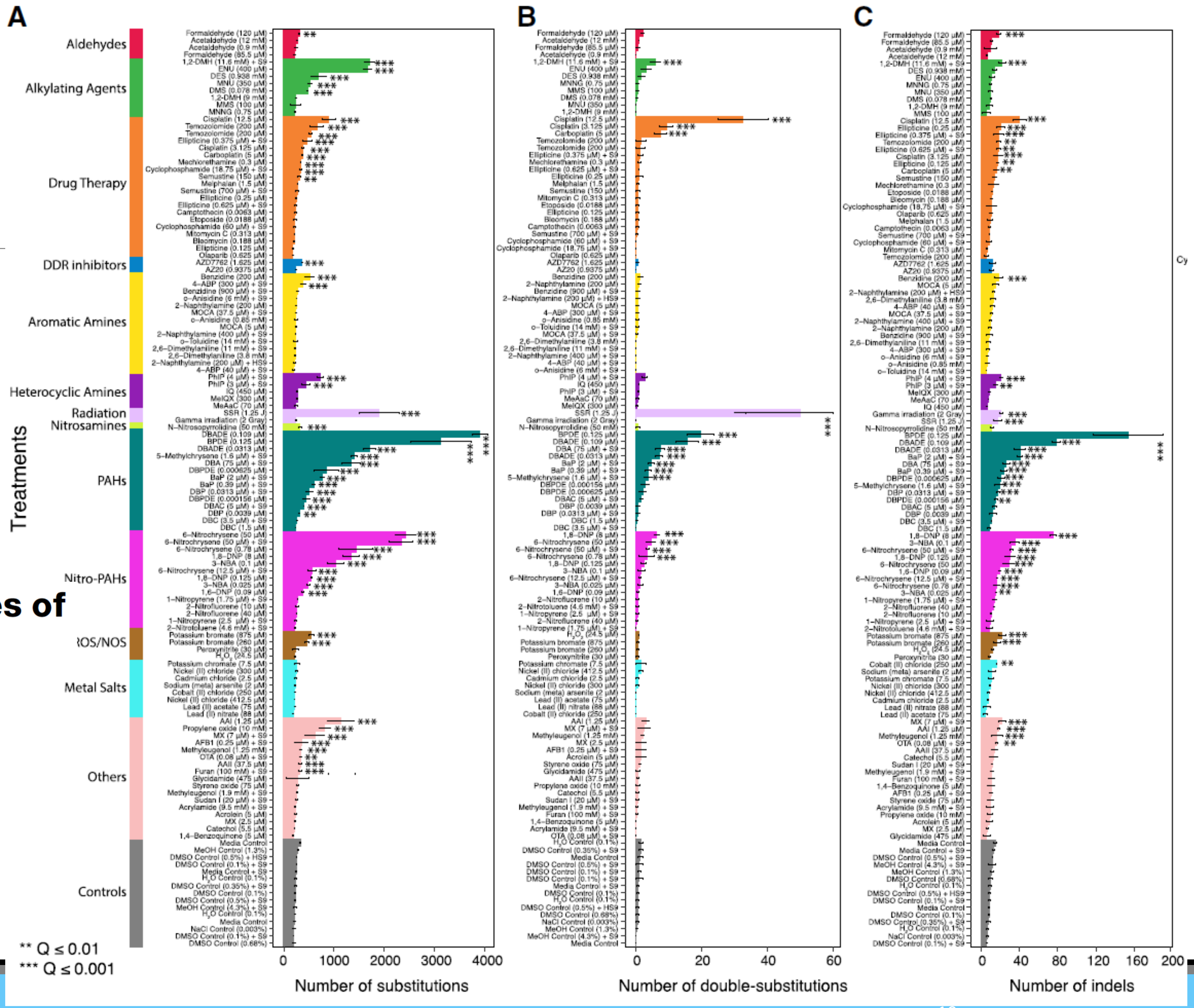
Antigenicity of RT



A Compendium of Mutational Signatures of Environmental Agents

Kucab et al., Cell, 2019

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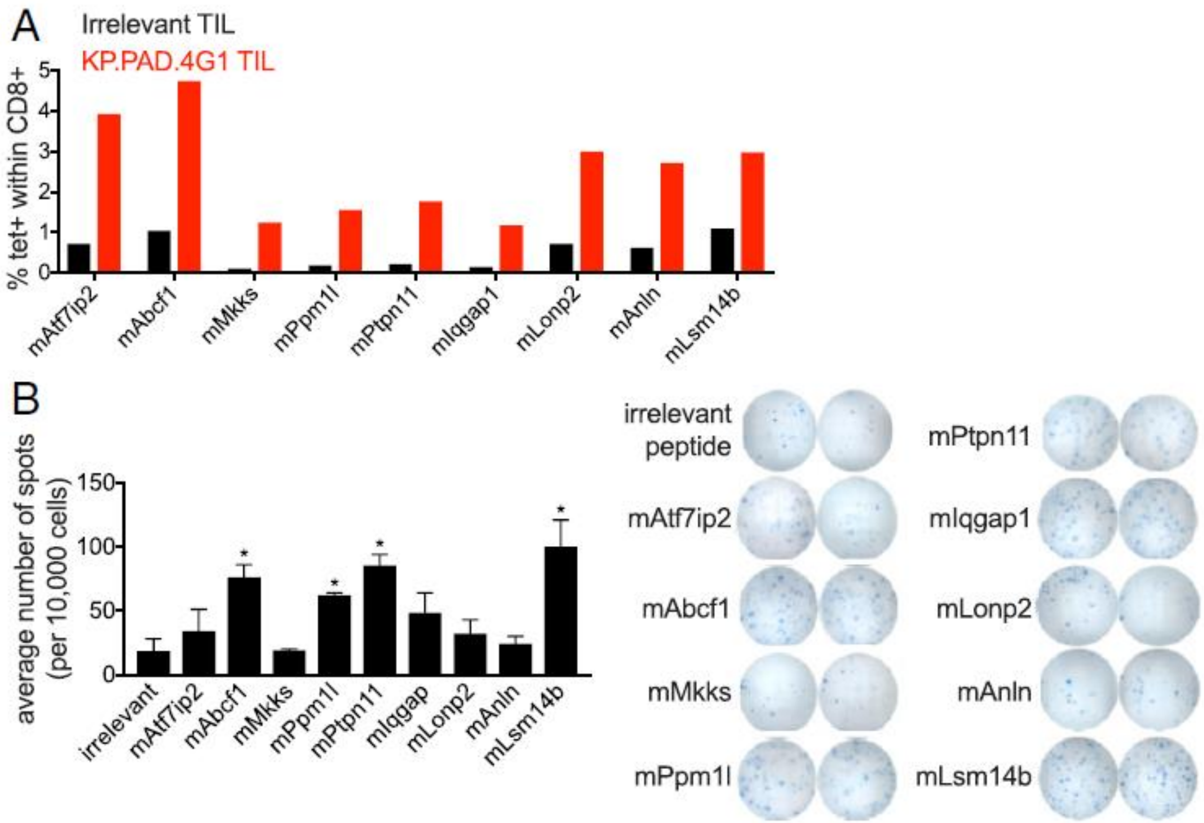
Antigenicity of RT

Radiation-induced neoantigens broaden the immunotherapeutic window of cancers with low mutational loads



Lussier et al., PNAS, 2021

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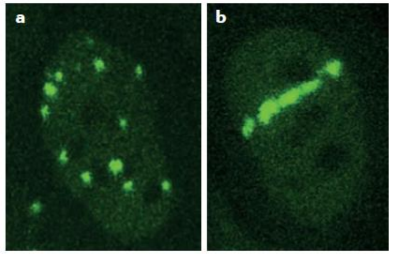
Antigenicity – improved for hadron therapy?

Clustered DNA lesions lead to a higher yield of unrepaired damage



Durante et al., *Nature Reviews* 2017

Differential gene expression after high LET radiation with respect to DDR

A Meta-Analysis of the Effects of High-LET Ionizing Radiations in Human Gene Expression

Theodora-Dafni Michalettou [1,2], Ioannis Michalopoulos [2], Sylvain V. Costes [3], Christine E. Hellweg [4], Megumi Hada [5,*] and Alexandros G. Georgakilas [1,*]

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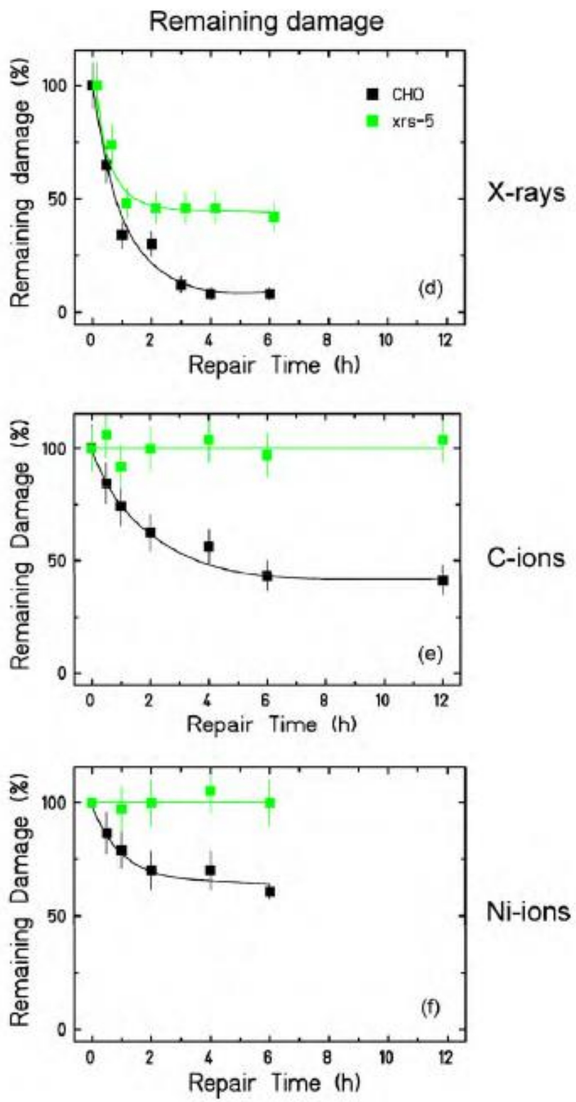
Antigenicity – improved for hadron therapy?

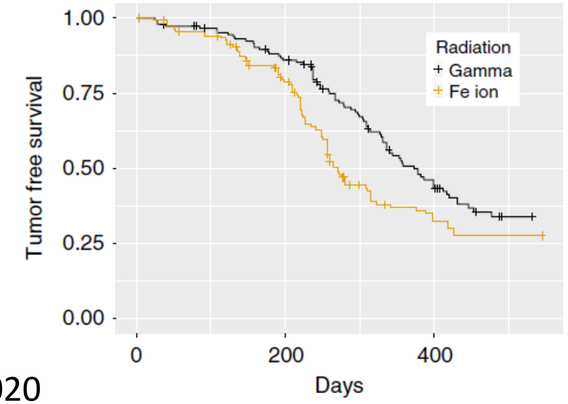


Hadron therapy might further improve the mutagenic landscape of tumors with low mutational burden

High LET particles feature different mutation signature as compared to photons

Mutational signatures in tumours induced by high and low energy radiation in *Trp53* deficient mice

Yun Rose Li[1,2,10], Kyle D. Halliwill[1,3,10], Cassandra J. Adams[1,4,10], Vivek Iyer[5], Laura Riva[5], Rashid Mamunur[5], Kuang-Yu Jen[1,6], Reyno del Rosario[1], Erik Fredlund[1,7], Gillian Hirst[1], Ludmil B. Alexandrov[8], David Adams[5*] & Allan Balmain[1,9*]



Rose Li et al., Nat Commun., 2020

Durante and Ritter, Mut Res., 2010

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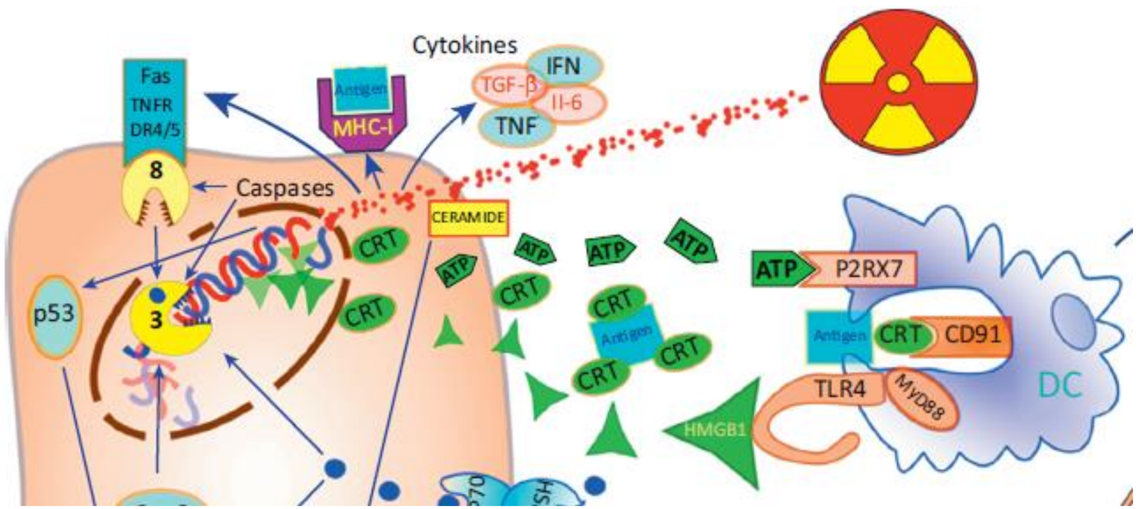
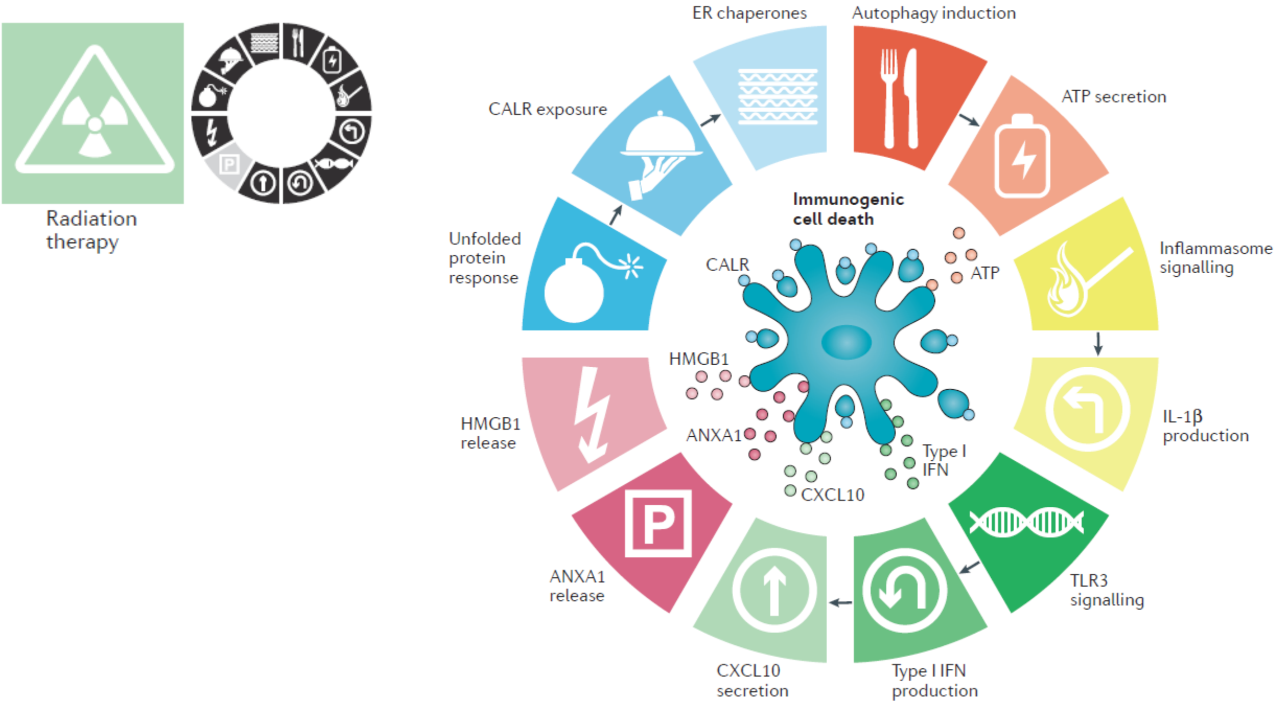
Adjuvanticity – danger signals



Durante et al., Trends Mol Med., 2013



Galluzzi et al., Nat Rev Immunol., 2017

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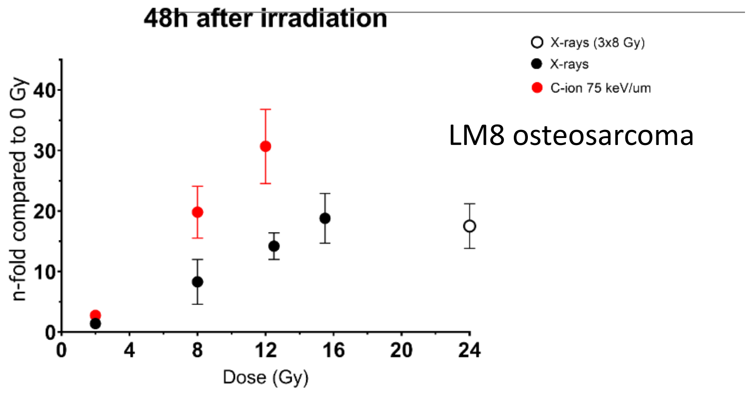
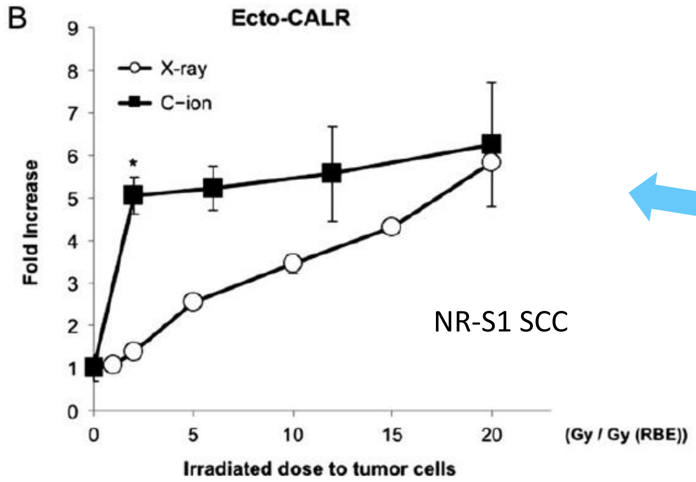
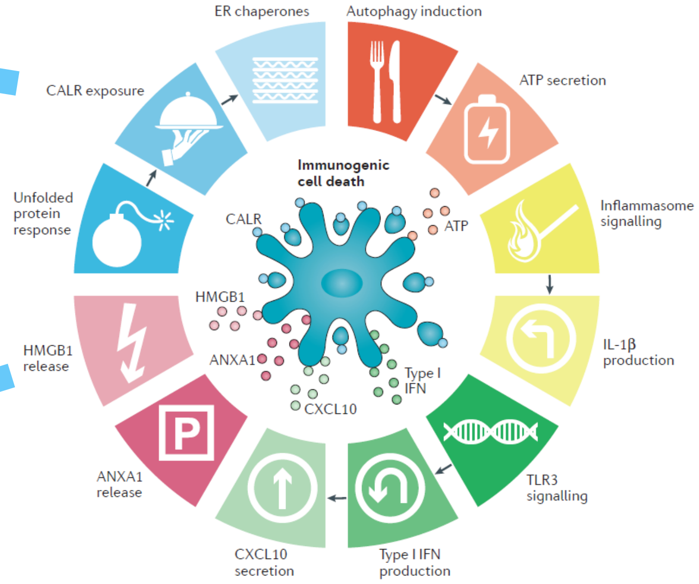
Adjuvanticity – increased danger signals after CIRT exposure

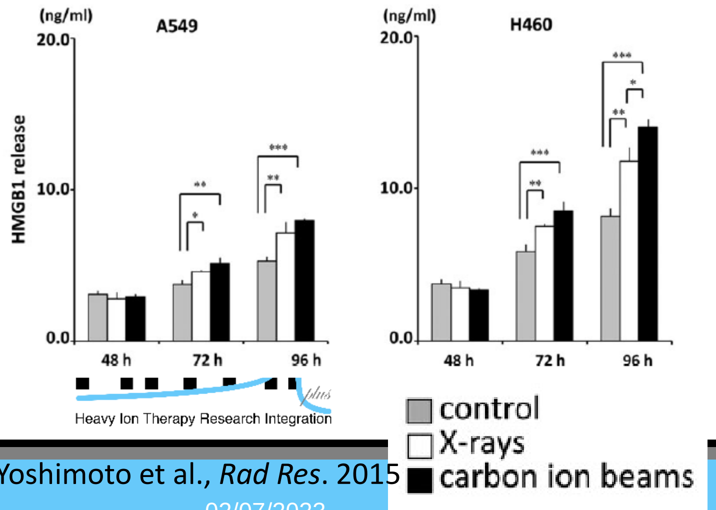


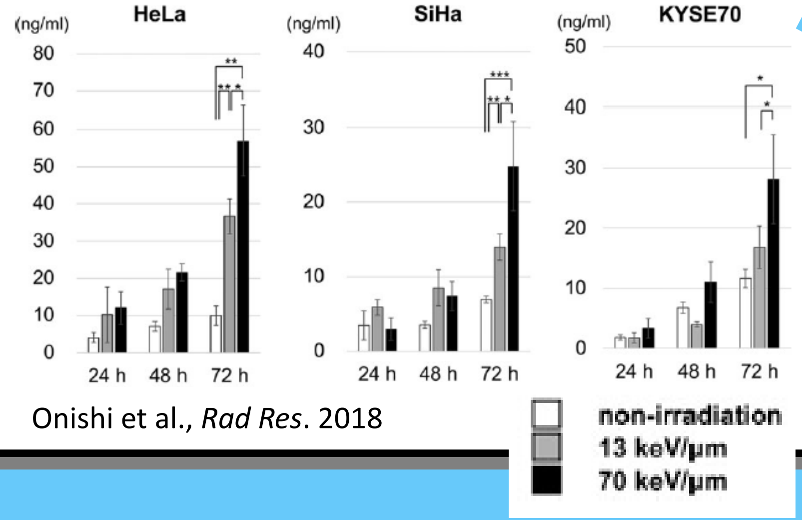




Galluzzi et al., Nat Rev Immunol., 2017

Iso-effective doses with respect to clonogenic cell survival





Onishi et al., *Rad Res*. 2018

Yoshimoto et al., *Rad Res*. 2015

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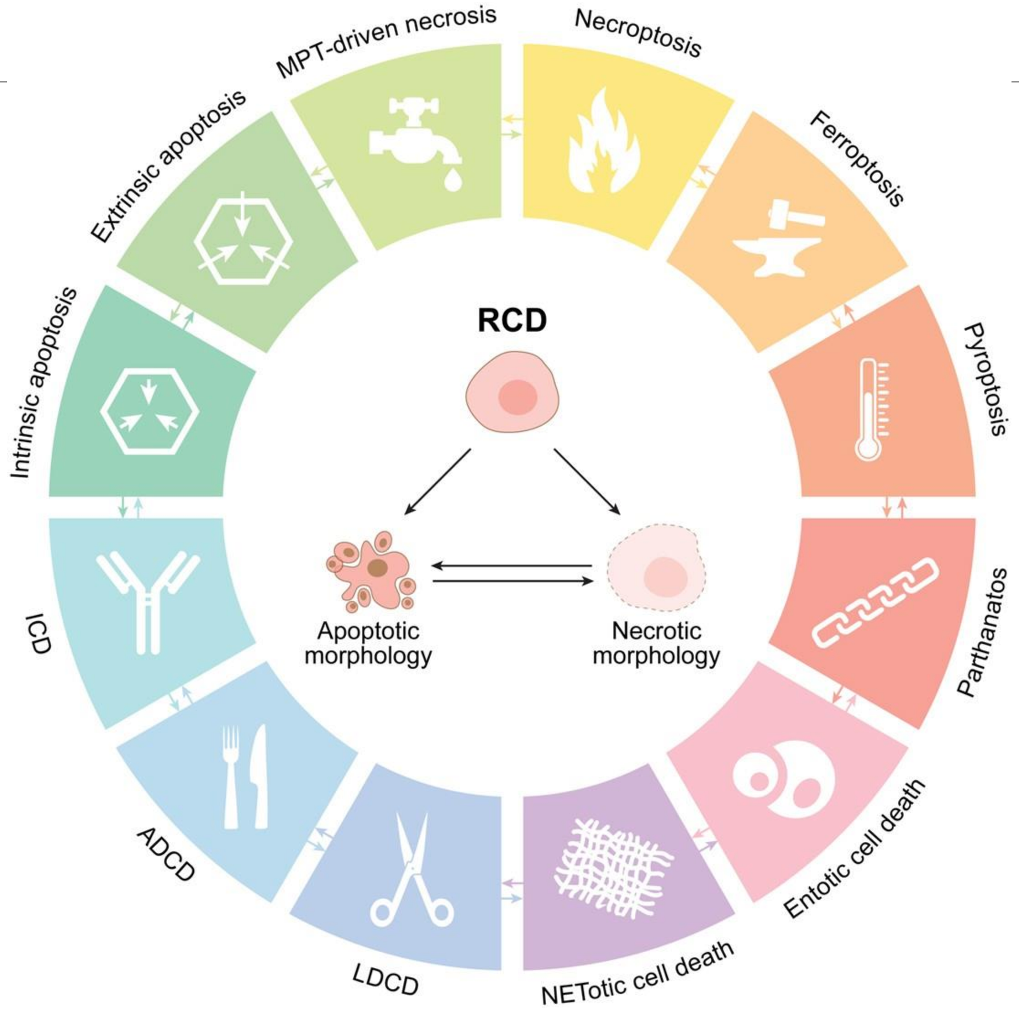
Different types of cell death – different immunogenicity



Galluzzi et al., Cell Death Differ., 2018

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Different (more immunogenic) types of cell death for hadron RT?

CIRT can induce p53-independent apoptosis

DIFFERENT MECHANISMS OF CELL DEATH IN RADIOSENSITIVE AND RADIORESISTANT P53 MUTATED HEAD AND NECK SQUAMOUS CELL CARCINOMA CELL LINES EXPOSED TO CARBON IONS AND X-RAYS

Mira Maalouf, M.S.,*† Gersende Alphonse, Ph.D.,†‡ Anthony Colliaux, M.S.,*†§ Michaël Beuve, Ph.D.,*§ Selena Trajkovic-Bodennec, Ph.D.,* Priscillia Battiston-Montagne, B.Sc.,*† Isabelle Testard, Ph.D.,¶ Olivier Chapet, M.D., Ph.D.,‡ Marcel Bajard, Ph.D.,*§ Gisela Taucher-Scholz, Ph.D.,‖ Claudia Fournier, Ph.D.,‖ and Claire Rodriguez-Lafrasse, Ph.D.*†‡

High LET Heavy Ion Radiation Induces p53-Independent Apoptosis

Eiichiro MORI[1], Akihisa TAKAHASHI[1], Nobuhiro YAMAKAWA[2], Tadaaki KIRITA[2] and Takeo OHNISHI[1]*

Indications for efficient induction of necroptosis

Carbon ion triggered immunogenic necroptosis of nasopharyngeal carcinoma cells involving necroptotic inhibitor BCL-x

Cihang Bao[1,3#], Yun Sun[2,3#], Bilikere Dwarakanath[2,3], Yuanli Dong[1,3,4], Yangle Huang[1,3,4], Xiaodong Wu[2,3], Chandan Guha[5], Lin Kong[1,3✉], Jiade J. Lu[1,3✉]

CIRT was found to trigger ceramide pathway

p53-independent early and late apoptosis is mediated by ceramide after exposure of tumor cells to photon or carbon ion irradiation

Gersende Alphonse[1,2,3,4], Mira Maalouf[1,2,3], Priscillia Battiston-Montagne[1,2,3], Dominique Ardail[1,2,3,5], Michaël Beuve[1,2,6], Robert Rousson[5], Gisela Taucher-Scholz[7], Claudia Fournier[7] and Claire Rodriguez-Lafrasse[1,2,3,4*]

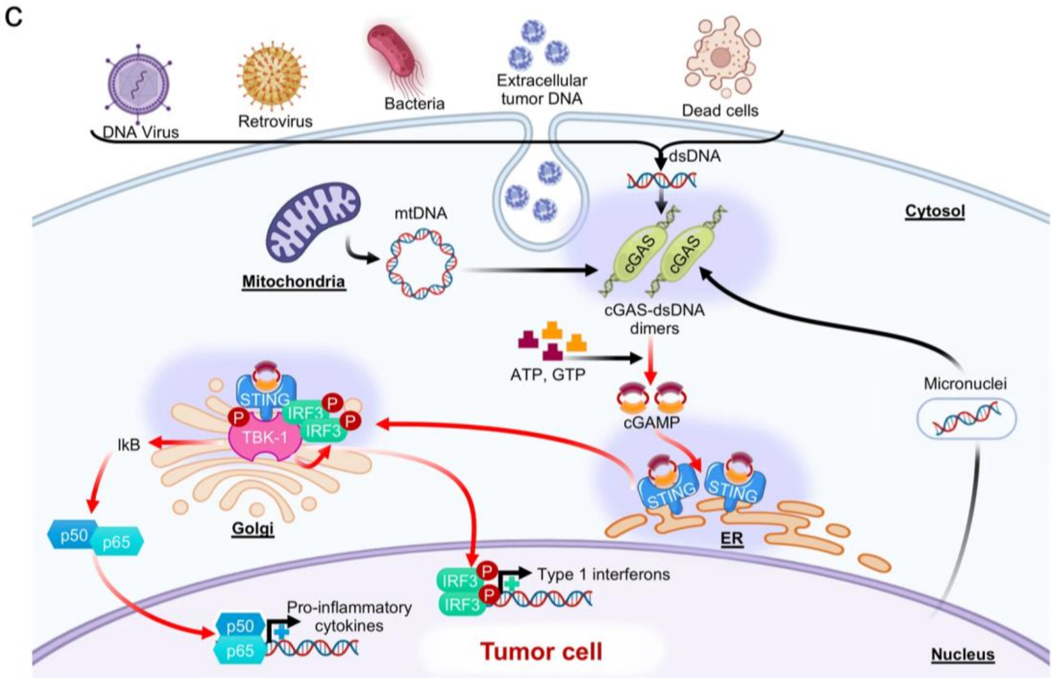
› J Pharmacol Exp Ther. 2021 Jun 22;JPET-AR-2021-000629. doi: 10.1124/jpet.121.000629. Online ahead of print.

Sphingosine kinase inhibition enhances dimerization of calreticulin at the cell surface in mitoxantrone-induced immunogenic cell death

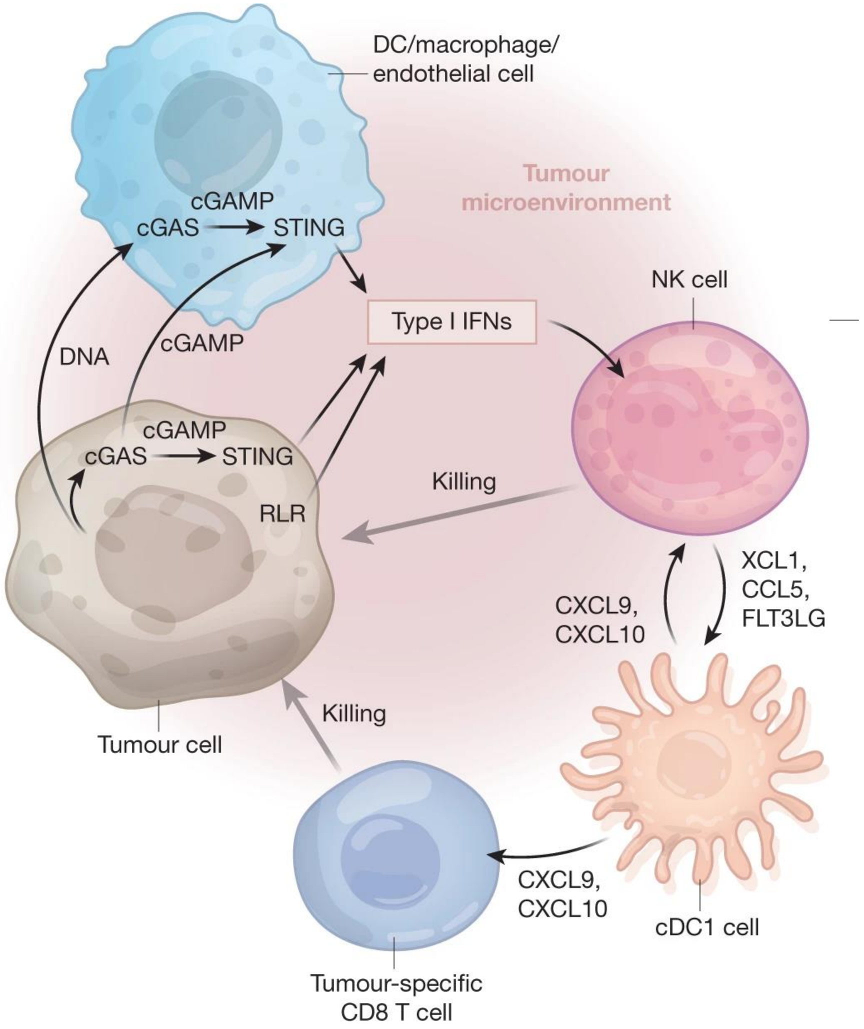
Asvelt J Nduwumwami [1], Jeremy A Hengst [1], Jong K Yun [2]

as received funding from the European Union's Horizon 2020 innovation programme under grant agreement No 101008548

Type-I interferons



Berglund et al., Exp Mol Med., 2021

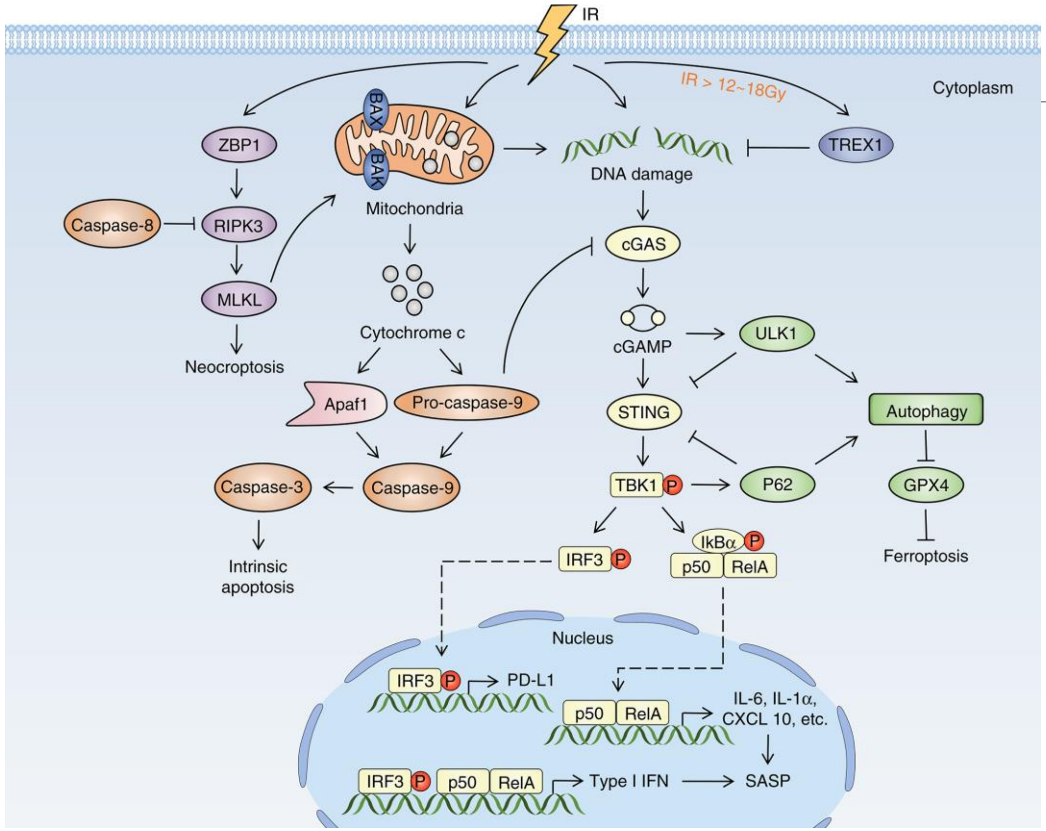


Demaria et al., Nature, 2019

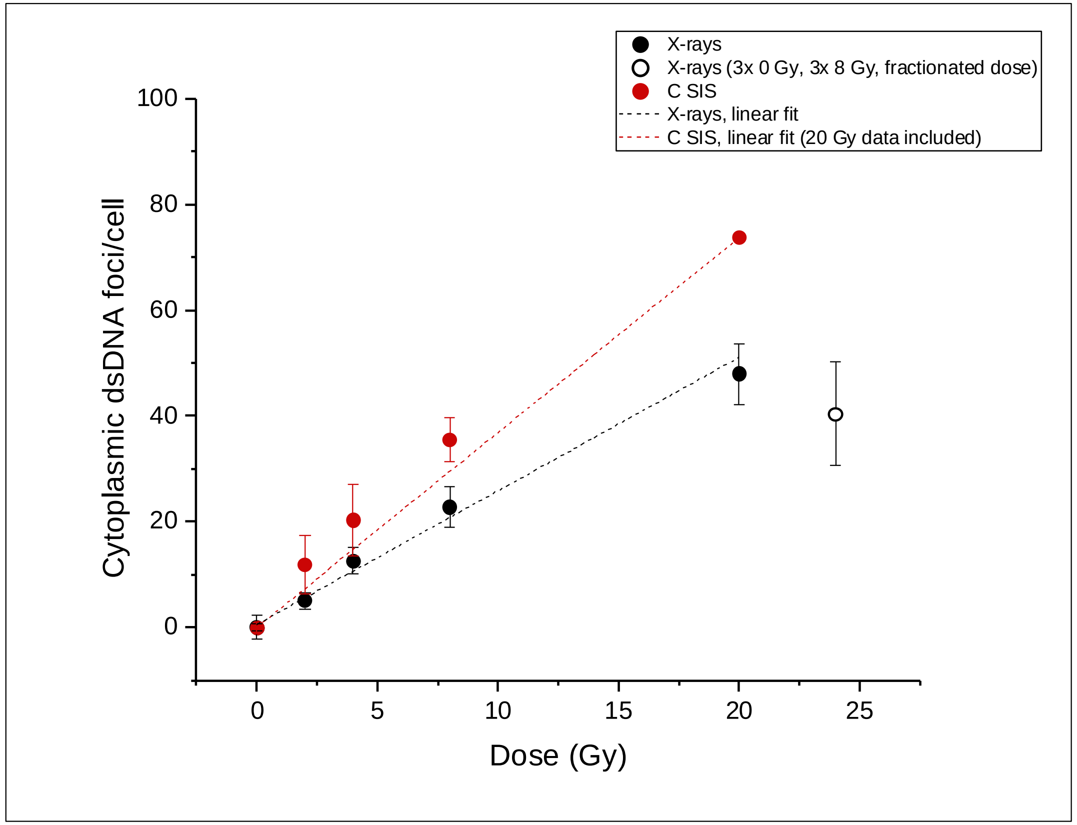
HITRIplus
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Type-I interferon signaling upon irradiation



Zhang et al., Immunology, 2023



N. Averbeck, GSI, unpublished data

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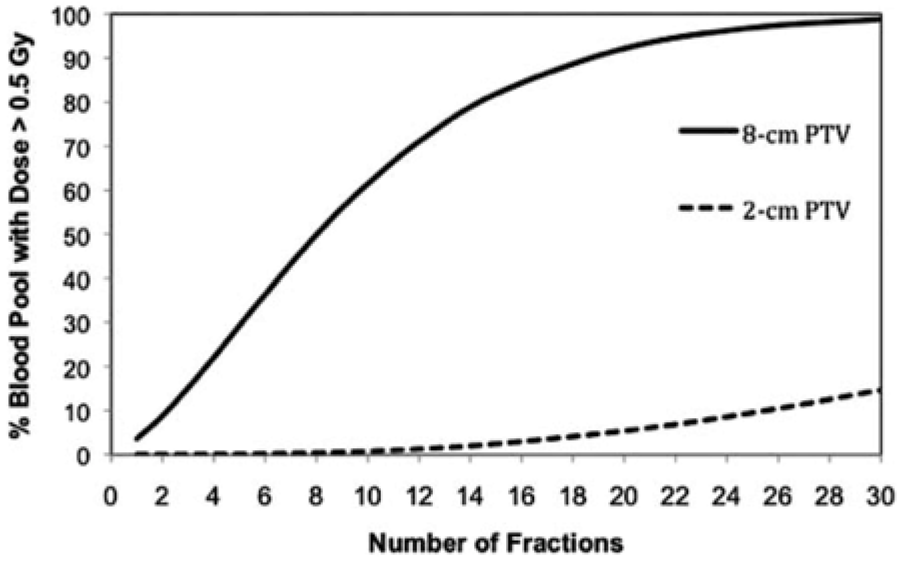
Sparing circulating blood/immune cells is important



Yovino et al., Cancer Invest, 2013

A single radiation fraction delivered 0.5 Gy to 5% of circulating cells,

after 30 fractions 99% of circulating blood had received ≥0.5 Gy

Need:

- Reduced integral dose
- High dose-rate
- Hypofractionation

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

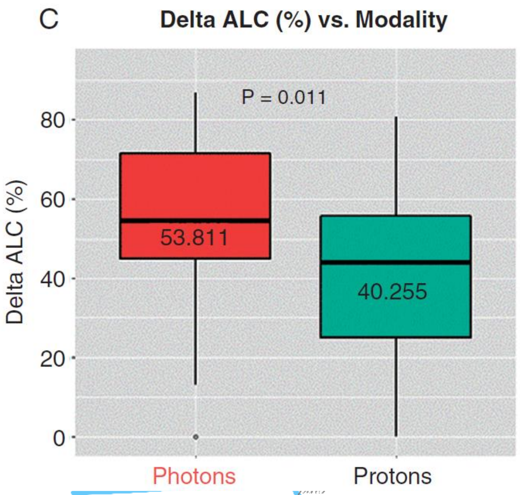
Particle therapy can better spare circulating immune cells

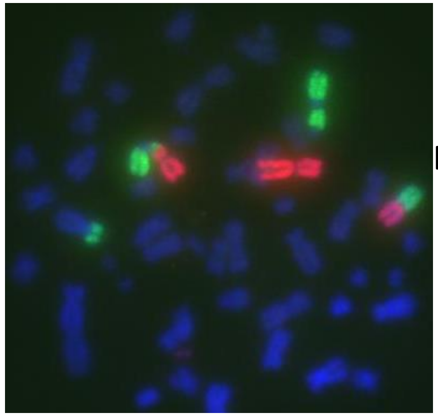
Neuro-Oncology

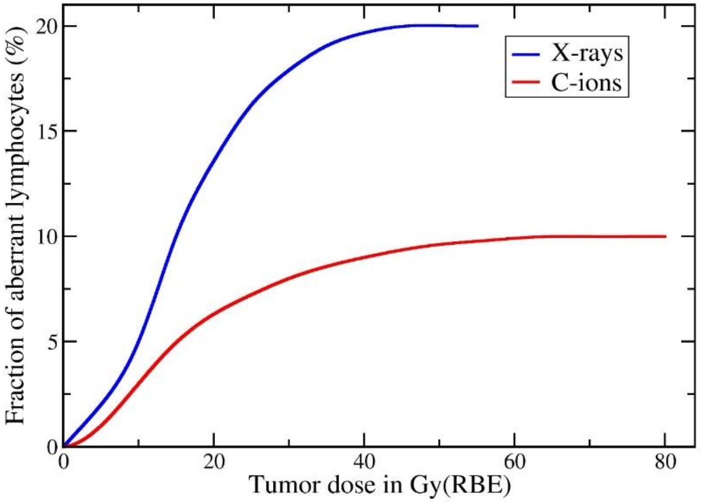
23(2), 284–294, 2021 | doi:10.1093/neuonc/noaa182 | Advance Access date 5 August 2020

Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: phase II randomized study of protons vs photons

Radhe Mohan, Amy Y. Liu, Paul D. Brown, Anita Mahajan, Jeffrey Dinh, Caroline Chung, Sarah McAvoy, Mary Frances McAleer, Steven H. Lin, Jing Li, Amol J. Ghia, Cong Zhu, Erik P. Sulman, John F. de Groot, Amy B. Heimberger, Susan L. McGovern, Clemens Grassberger, Helen Shih, Susannah Ellsworth, and David R. Grosshans







Durante et al., Int. J. Radiat. Oncol. Biol. Phys., 2000

Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Importance of (sparing) the draining lymph node

Translational Cancer Mechanisms and Therapy

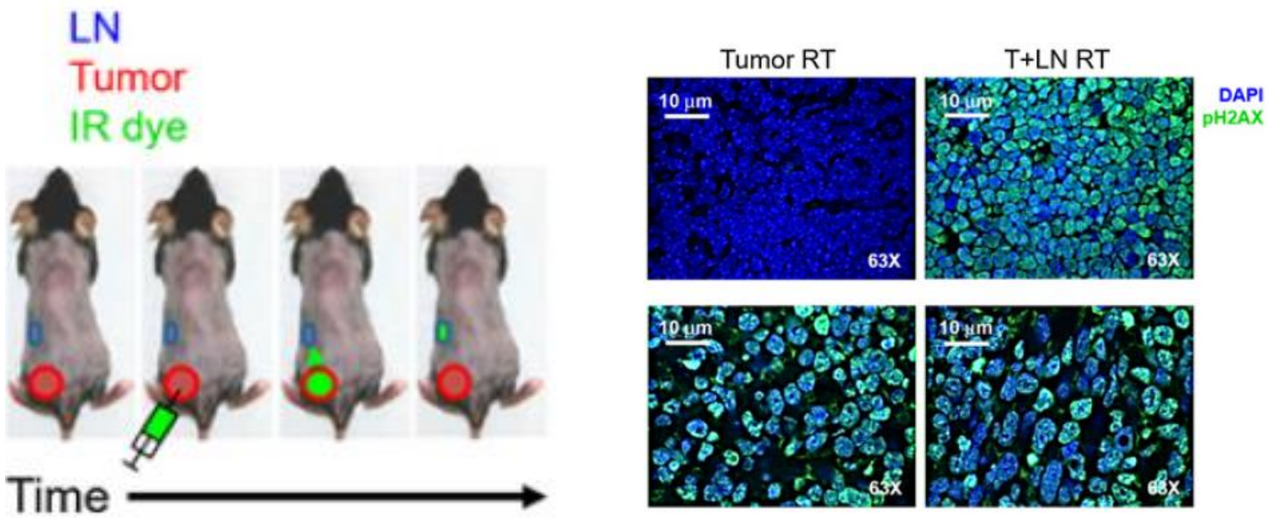
Clinical Cancer Research

Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy

Check for updates

Ariel E. Marciscano[1], Ali Ghasemzadeh[2], Thomas R. Nirschl[2], Debebe Theodros[2], Christina M. Kochel[2], Brian J. Francica[2], Yuki Muroyama[2], Robert A. Anders[2,3], Andrew B. Sharabi[4], Esteban Velarde[1], Wendy Mao[2], Kunal R. Chaudhary[5], Matthew G. Chaimowitz[6], John Wong[1], Mark J. Selby[7], Kent B. Thudium[7], Alan J. Korman[7], David Ulmert[8], Daniel L.J. Thorek[2,9], Theodore L. DeWeese[1,2], and Charles G. Drake[2,6]

Marciscano et al., Clin Cancer Res., 2018



Heavy Ion Therapy Research Integration

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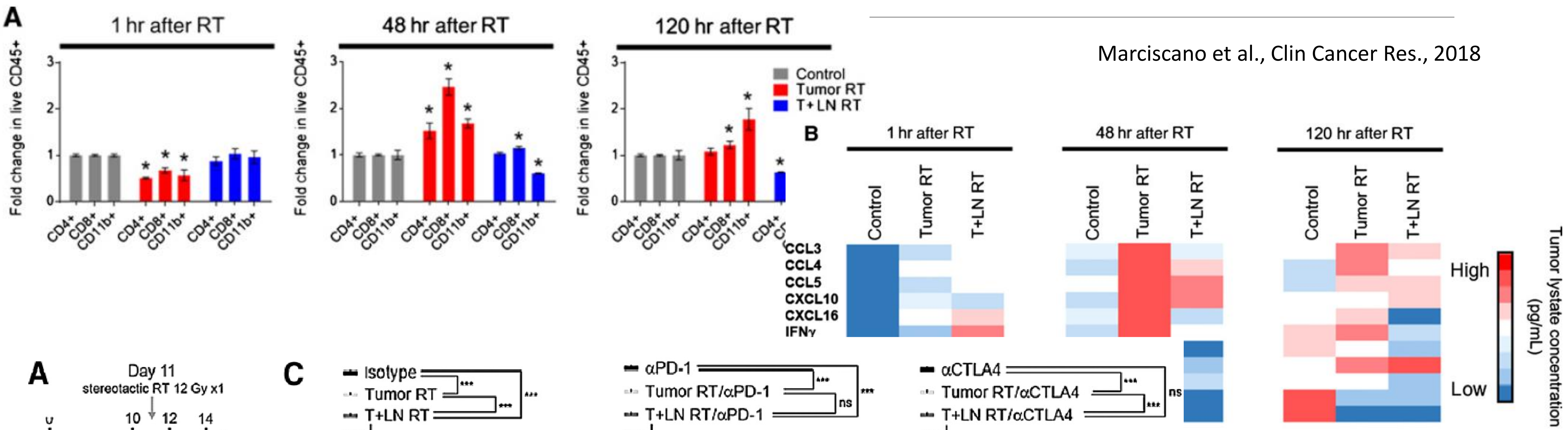
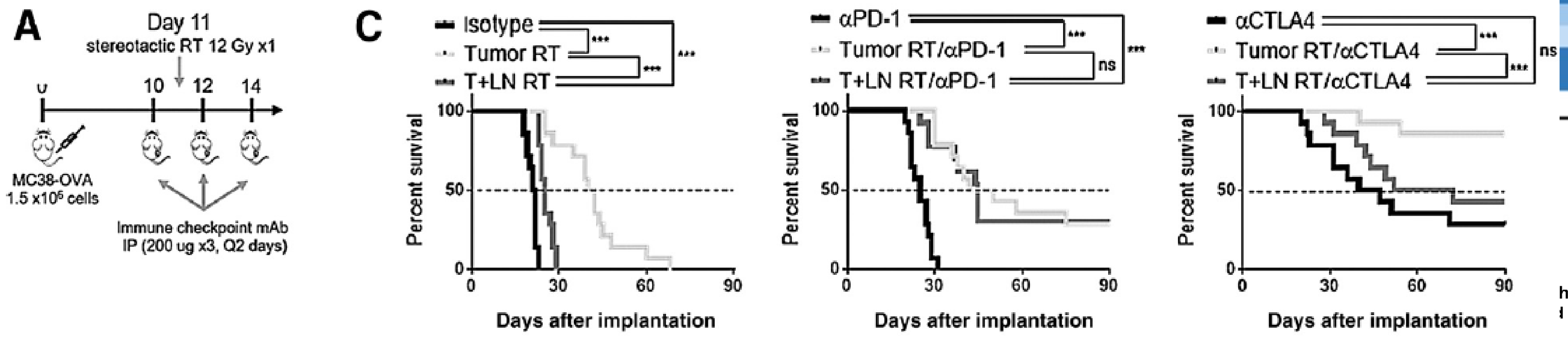
Importance of (sparing) the draining lymph node



Marciscano et al., Clin Cancer Res., 2018



has received funding from the European Union's Horizon 2020
innovation programme under grant agreement No 101008548

Combination of RT with immunotherapy

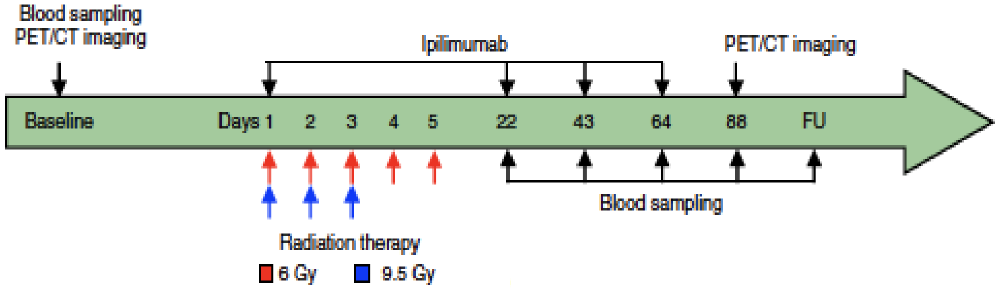
nature medicine

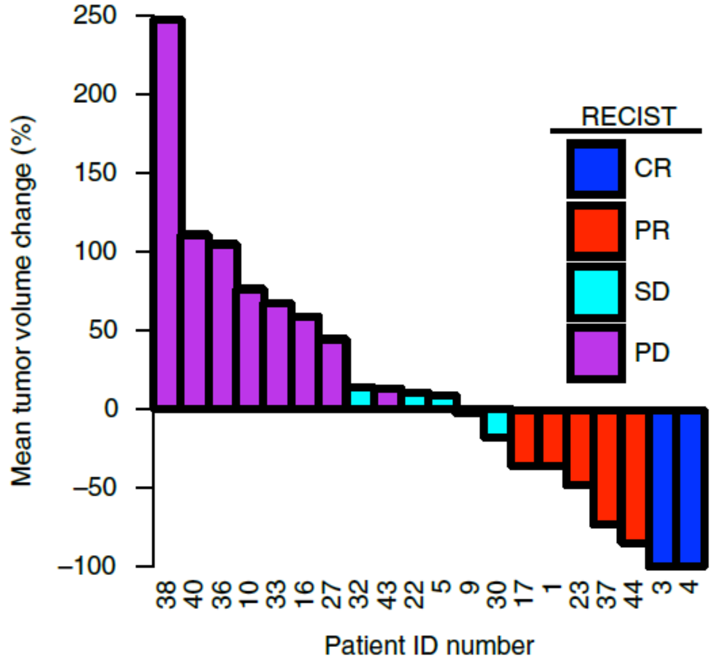
LETTERS

https://doi.org/10.1038/s41591-018-0232-2

Radiotherapy induces responses of lung cancer to CTLA-4 blockade

Silvia C. Formenti[1*], Nils-Petter Rudqvist[1,15], Encouse Golden[1,14,15], Benjamin Cooper[2], Erik Wennerberg[1], Claire Lhuillier[1], Claire Vanpouille-Box[1], Kent Friedman[3], Lucas Ferrari de Andrade[4,5], Kai W. Wucherpfennig[4,5], Adriana Heguy[6,7], Naoko Imai[8], Sacha Gnjatic[8], Ryan O. Emerson[9], Xi Kathy Zhou[10], Tuo Zhang[11], Abraham Chachoua[12] and Sandra Demaria[1,13*]





CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

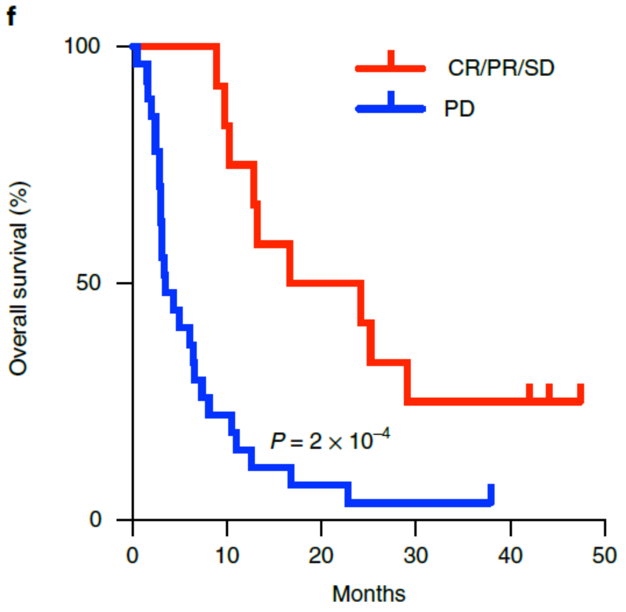
RECIST = Response Criteria In Solid Tumors

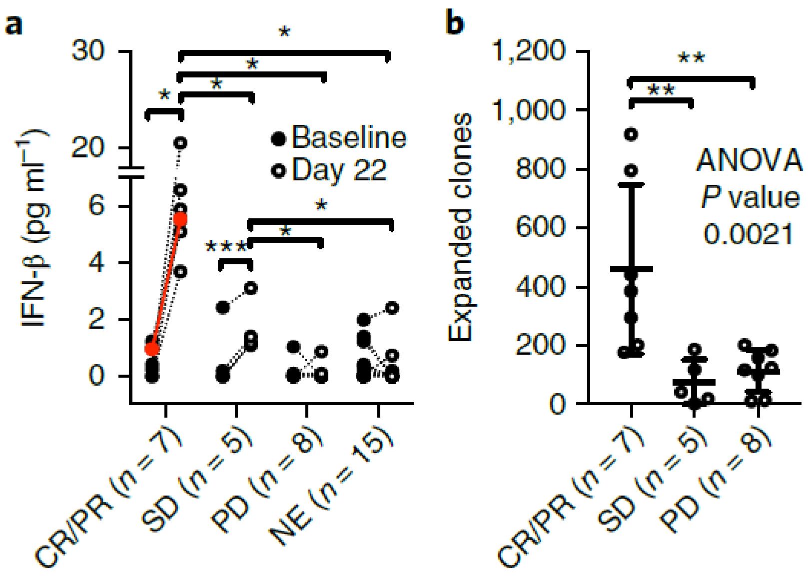
Disease control (CR+PR+SD) in ~31%

Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Combination of RT with immunotherapy





CR+PR+SD = disease control

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

RECIST = Response Criteria In Solid Tumors

Formenti et al., Nat Med., 2018

HITRI plus
Heavy Ion Therapy Research Integration

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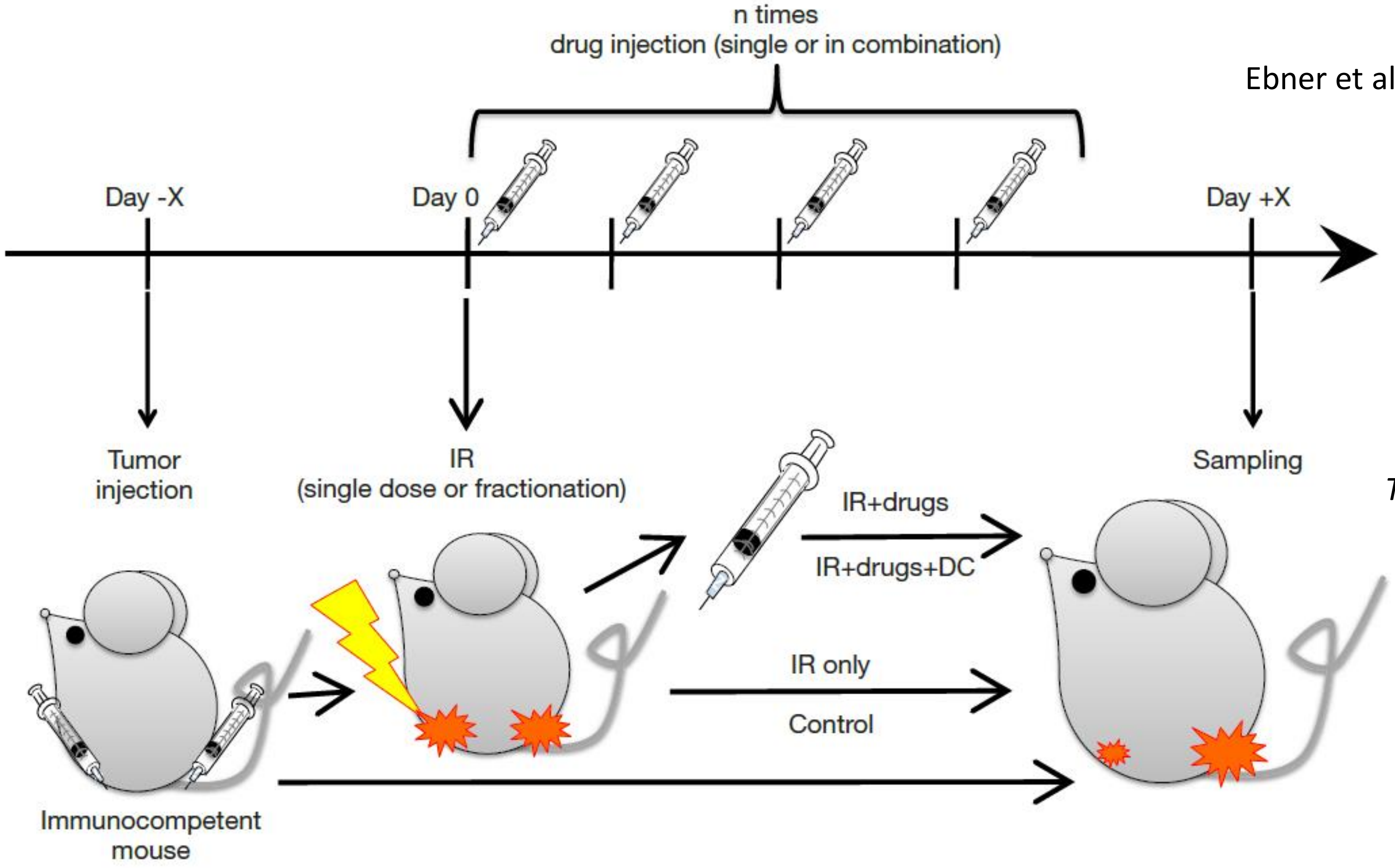
Abscopal tumor models

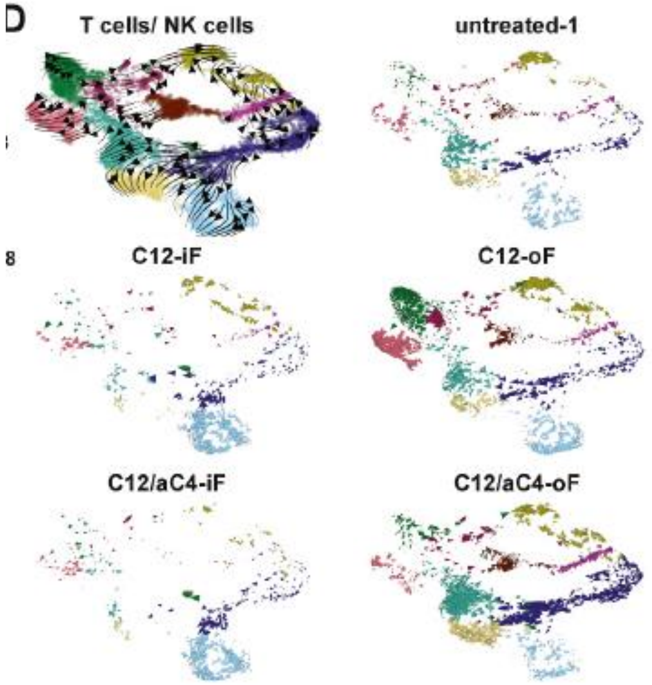


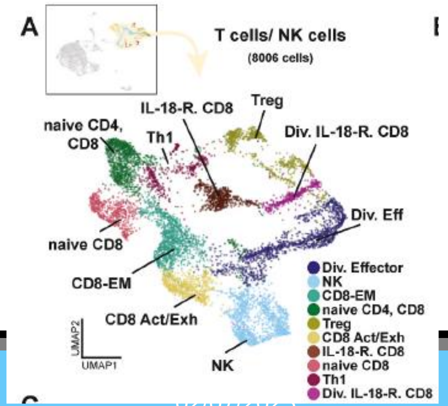
Ebner et al., Trans Cancer Res., 2017

These models often develop metastases

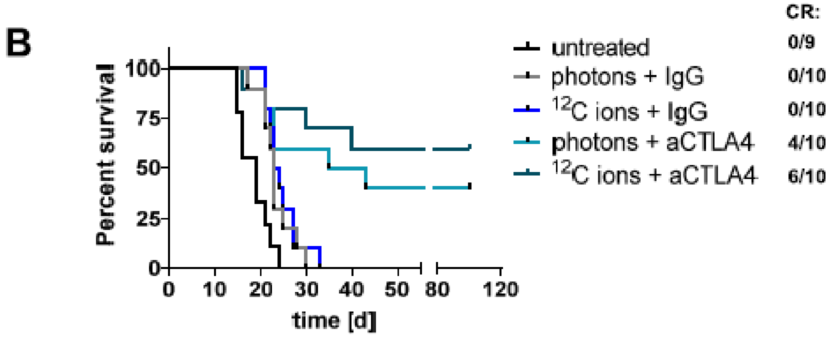
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Combination of CIRT with immunotherapy

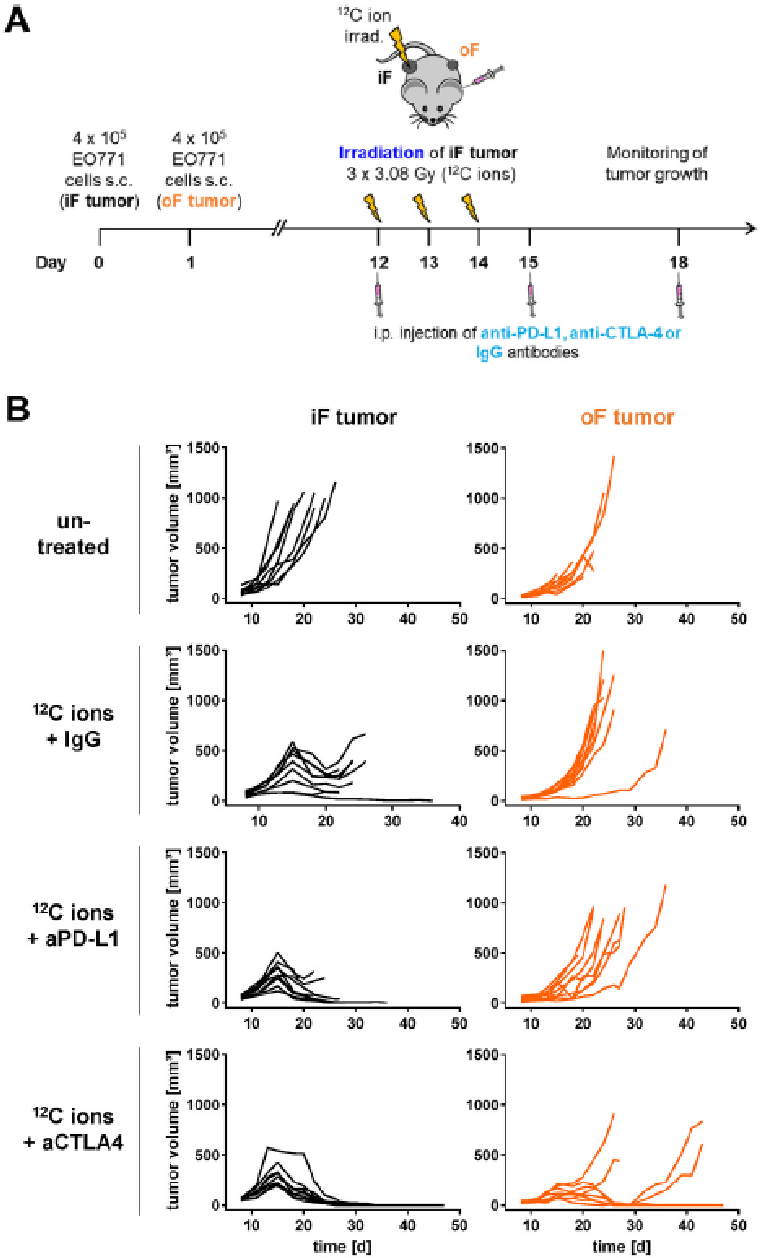




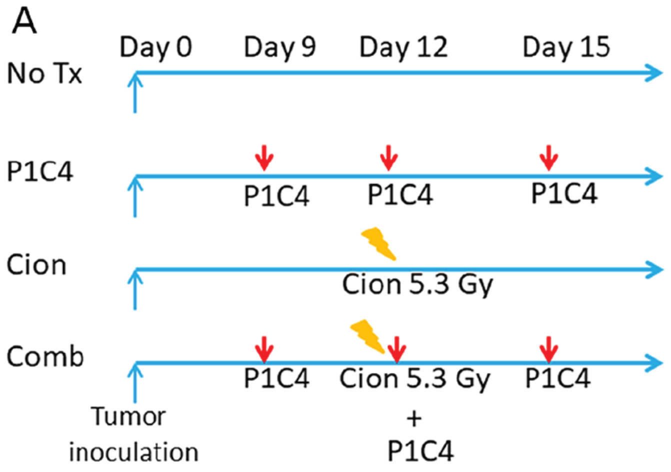
Iso-effective doses: 3.08 Gy CIRT vs. 5 Gy XRT



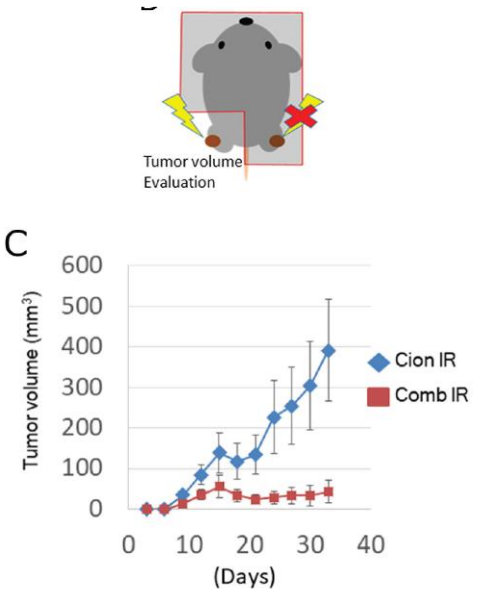
Hartmann et al., Cancer Lett., 2022

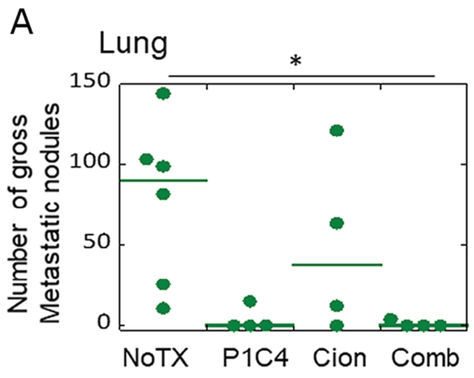


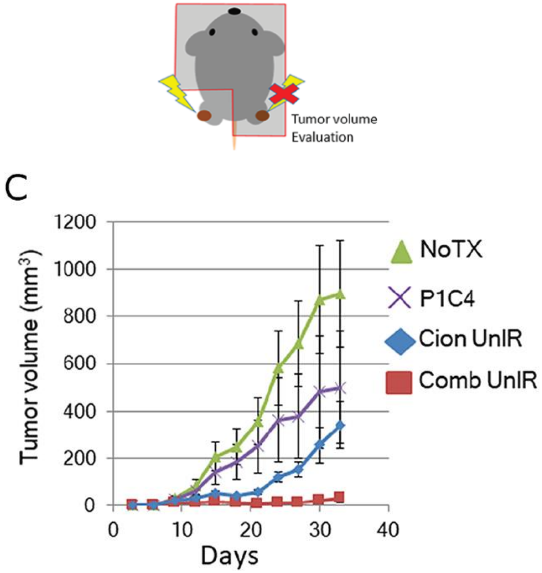
Combination of CIRT with immunotherapy



Takahashi et al., Oncotarget, 2019



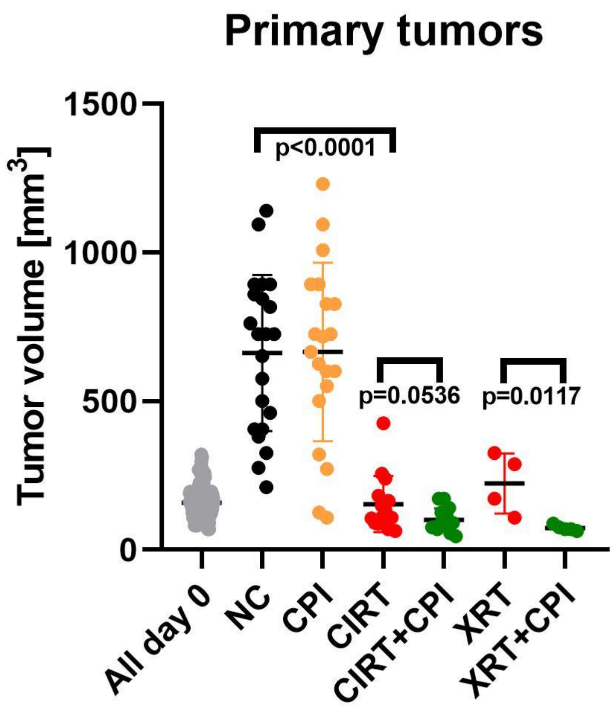


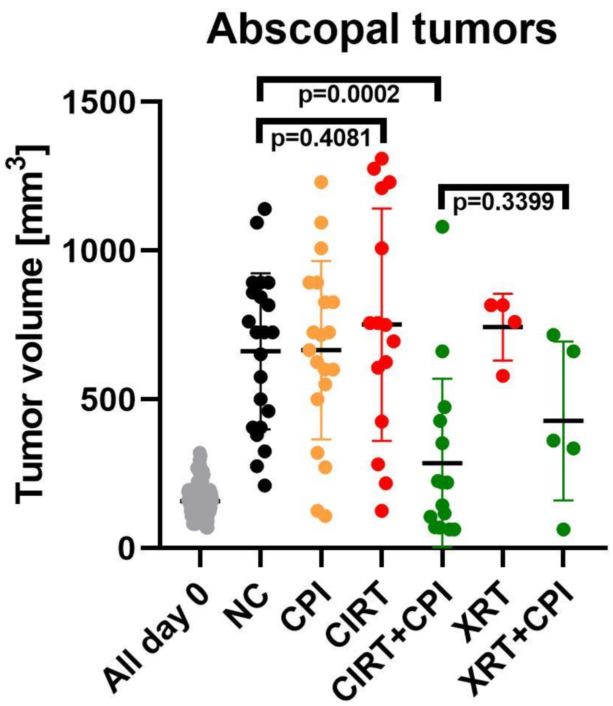


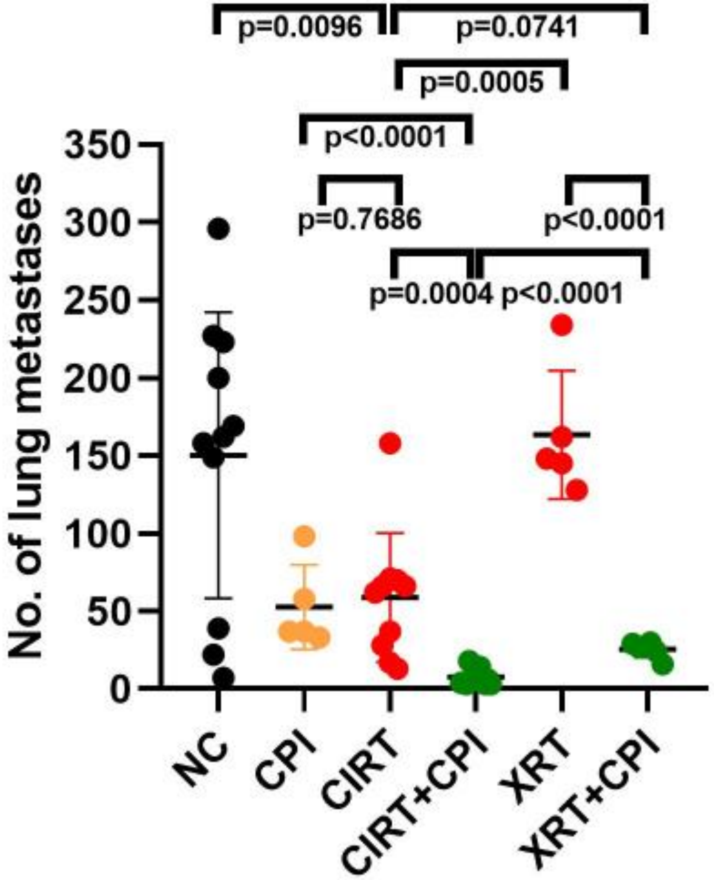
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Combination of CIRT with immunotherapy







NC = negative control
CPI = check point inhibitors only
CIRT = C-ions only, 10 Gy
XRT = photons, 10 Gy

Helm et al., Int J Radiat Oncol Biol Phys., 2021

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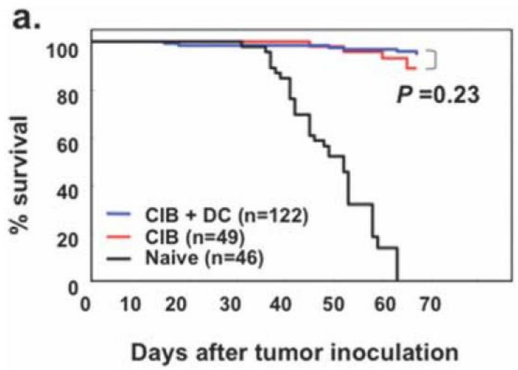
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Combination with dendritic cell injection

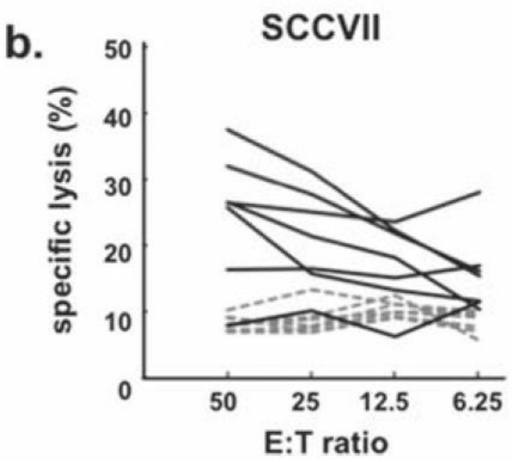
CIRT („clinically available dose“) +/- intratumoral DC injection in SCCVII (poorly immunogenic squamous cell carcinoma) in C3H/He mice

CIRT: efficient elimination of primary tumor, significant reduction of tumor formation after secondary challenge (contralateral site)

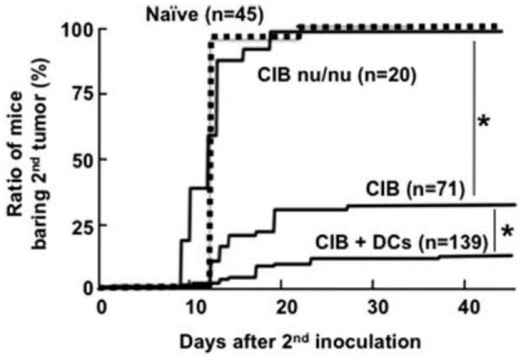
CIRT + DC: antitumor effects significantly increased (e.g. cytolytic activity)



	%survival (C.I.)
CIB+DC	94.4% (90.4-98.4)
CIB	88.9% (78.0-99.8)
Naïve	0.0% (0.0- 0.0)



Solid line: CIB+DC
Dashed line: CIB alone



*P<0.01

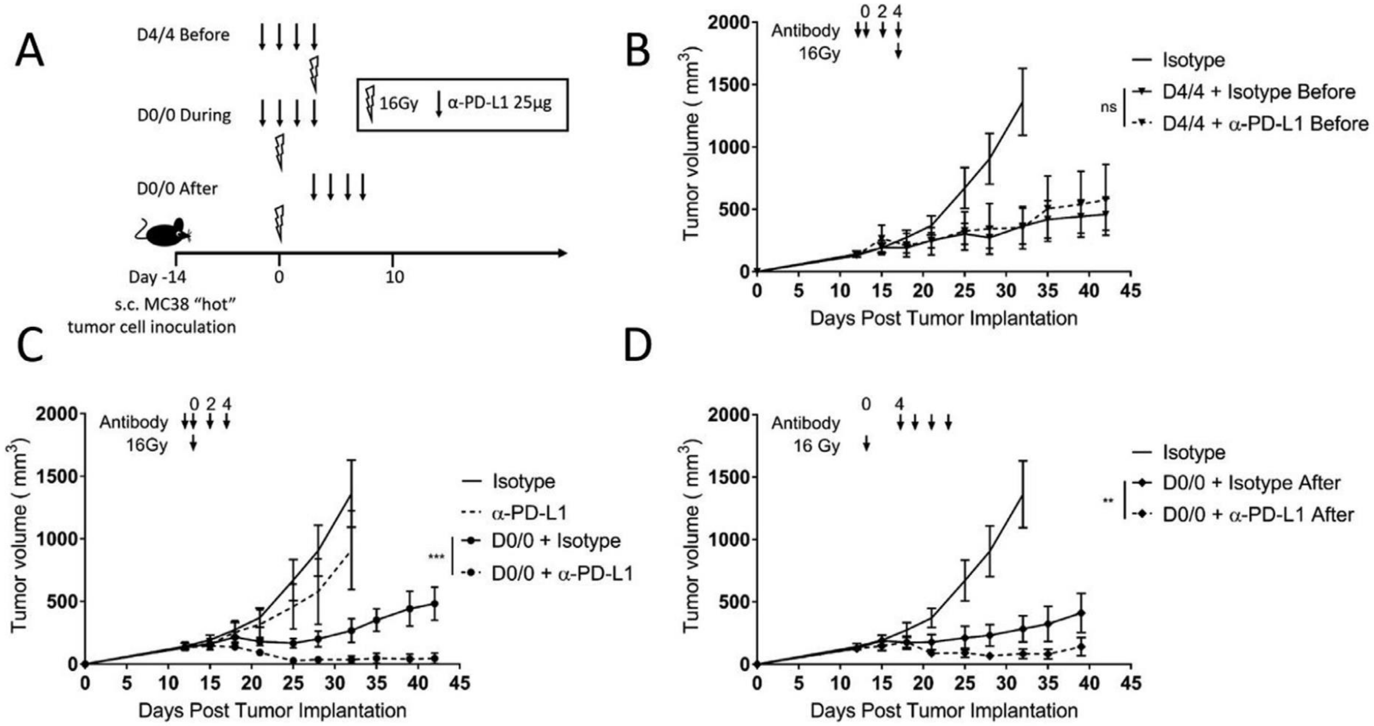
	rejection rate
CIB+DC	88.5%
CIB	70.4%
Naïve	2.2%
CIB (nu/nu)	0.0%

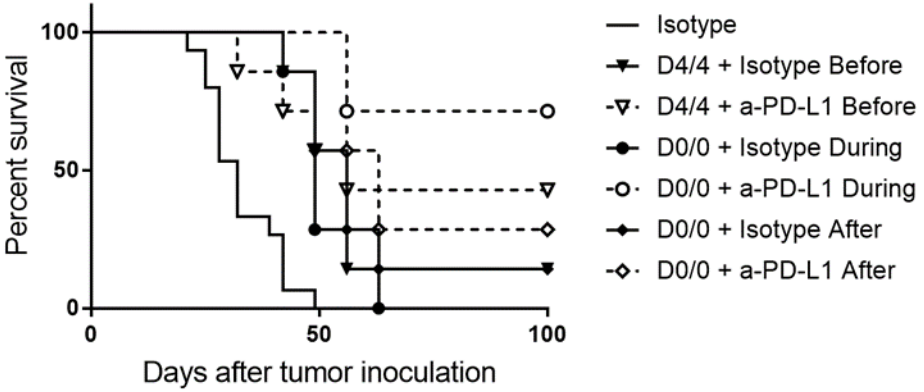
Matsunaga et al., Cancer, 2010

HITRIplus
Heavy Ion Therapy Research Integration

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

Importance of sequence in combination therapy





Moore et al., Int J Radiat Oncol Biol Phys., 2021

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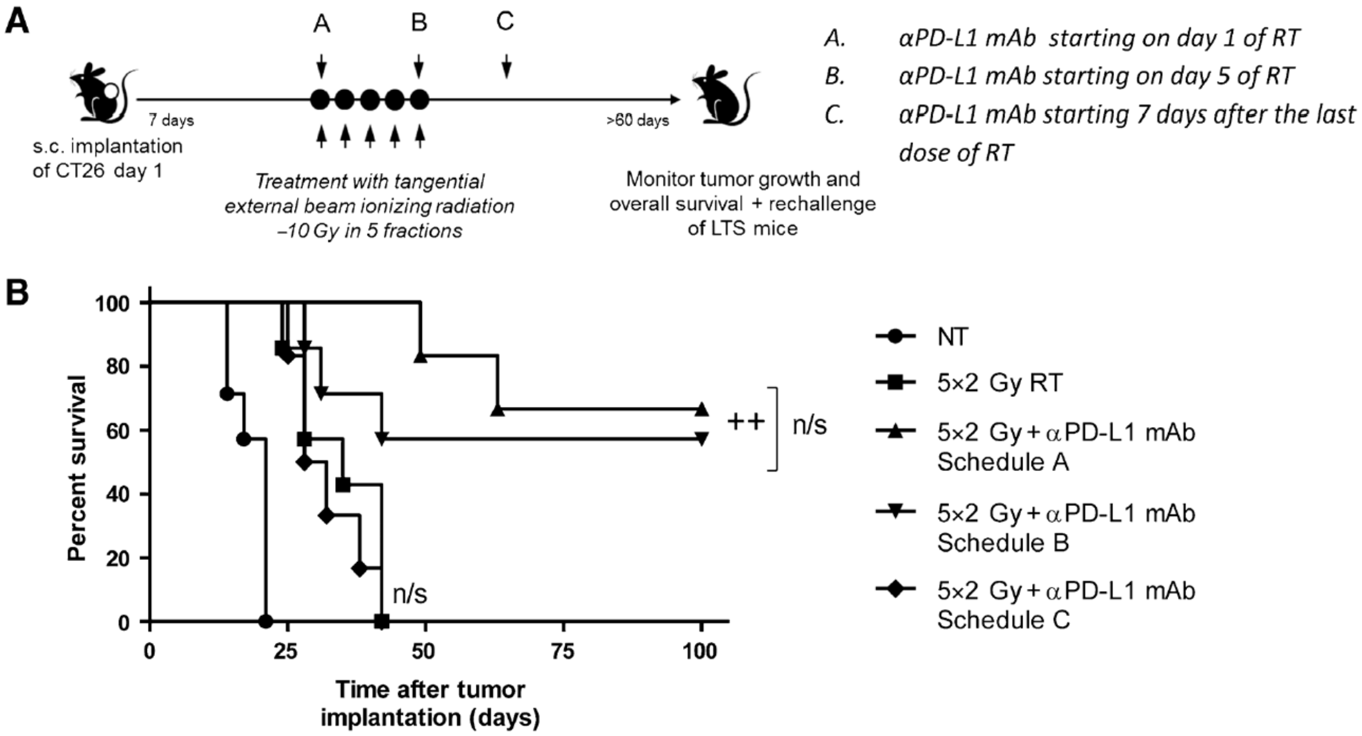
Importance of sequence in combination therapy



Dovedi et al., Clin Cancer Res., 2014

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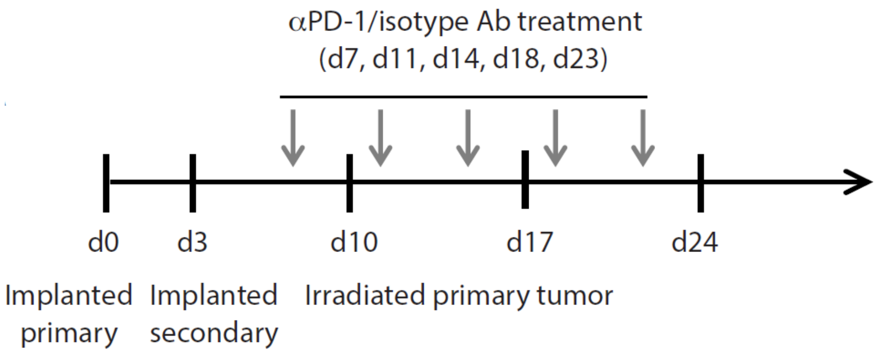
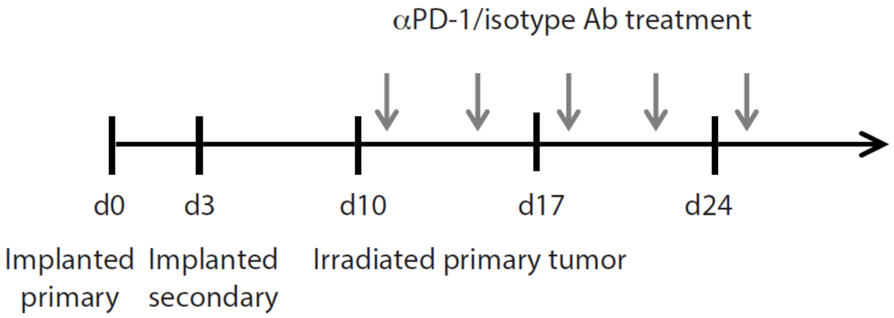
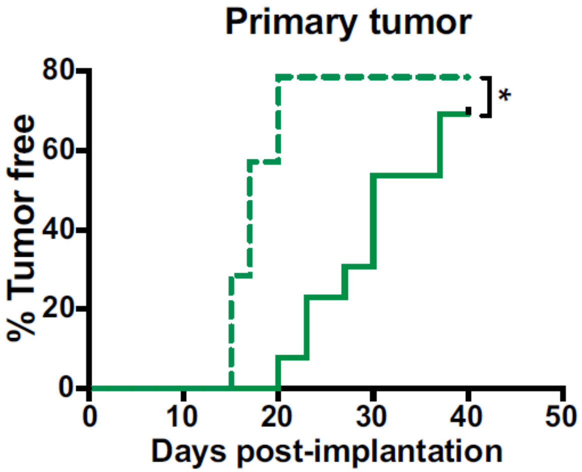
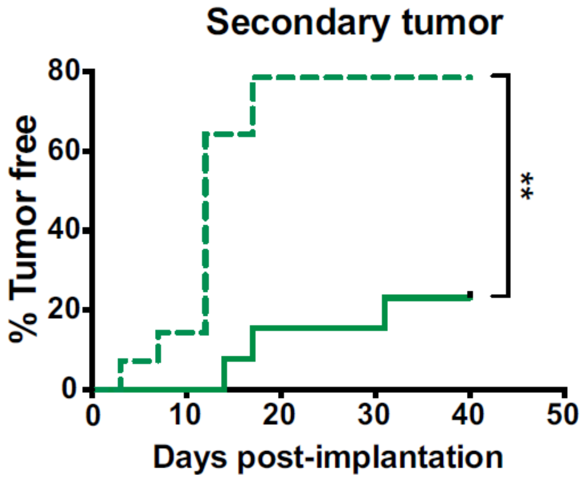
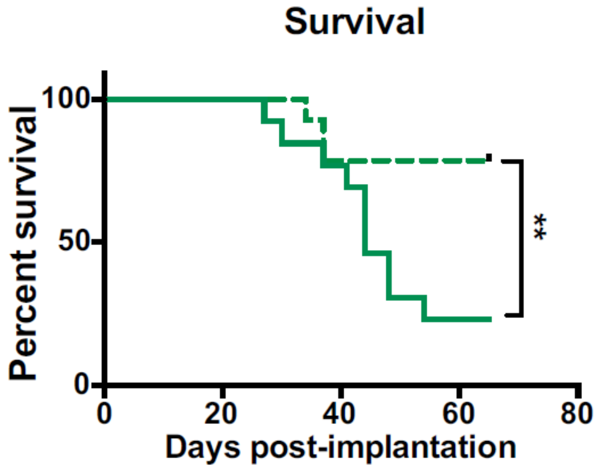
Importance of sequence in combination therapy







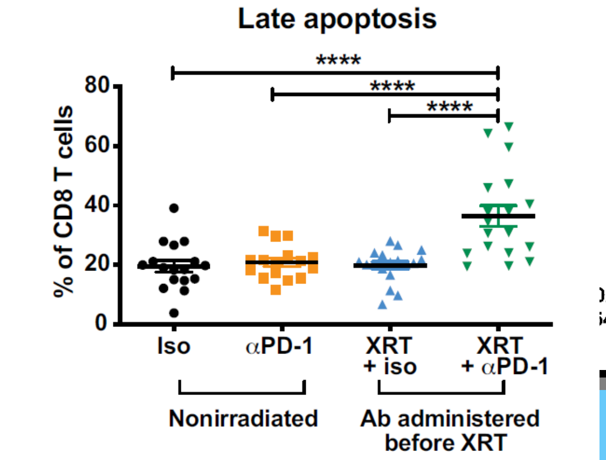




MC38 model

solid line: anti-PD-1 before RT

dashed line: anti-PD-1 after RT



Wei et al., Sci Immunol., 2021

Heavy Ion Therapy Research Integration

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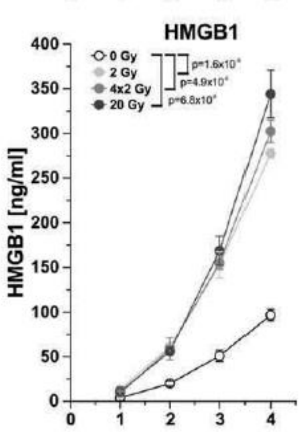
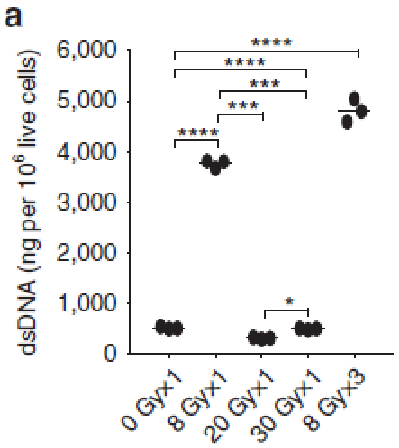
Dose and fractionation scheme

Hadron therapy allows for a more precise delivery of higher doses, which is of advantage if higher doses or hypofractionation are to be delivered (more immunogenic?)

Priming anti-tumor immunity by radiotherapy: Dying tumor cell-derived DAMPs trigger endothelial cell activation and recruitment of myeloid cells

Julia Krombach[a*], Roman Hennel [a*], Nikko Brix[a], Michael Orth[a,b,c], Ulrike Schoetz[a,d], Anne Ernst[a,e], Jessica Schuster[a], Gabriele Zuchtriegel[f,g,h], Christoph A. Reichel[f,g], Susanne Bierschenk[g], Markus Sperandio [g], Thomas Vogl[i], Steffen Unkel [j], Claus Belka[a,b,k], and Kirsten Lauber[a,b,k]





DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

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

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

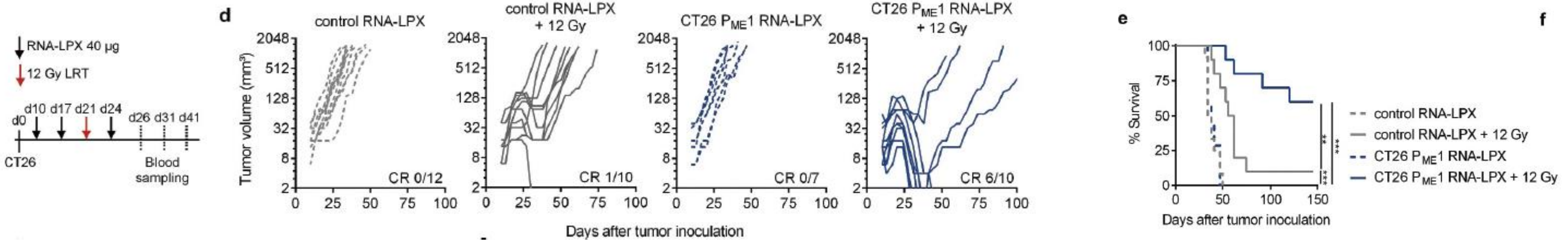
mRNA vaccines in combination with RT

ONCOIMMUNOLOGY
2020, VOL. 9, NO. 1, 1–13
https://doi.org/10.1080/2162402X.2020.1771925

A liposomal RNA vaccine inducing neoantigen-specific CD4$^+$ T cells augments the antitumor activity of local radiotherapy in mice

Nadja Salomon[a], Fulvia Vascotto[a], Abderaouf Selmi[a], Mathias Vormehr[b], Juliane Quinkhardt[b], Thomas Bukur[a], Barbara Schrörs[a], Martin Löewer[a], Mustafa Diken[a], Özlem Türeci[b], Ugur Sahin[b,c], and Sebastian Kreiter[a]

CT26 $P_{ME}1$ = RNA vaccine (pentatope, engineered from 5 highly expressed CT26-specific mutations)



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Clinical trials combining particle therapy and immunotherapy

Table 1. Currently ongoing or initiated clinical trials regarding proton RT (PrRT) and carbon ion RT (CIRT) in combination with immunotherapy (IO).

	Identifier	Pathology	RT Dose	IO	Dose	Status	Study Type
PrRT	NCT02648997	Meningiomas	Unknown	Nivolumab * Ipilimumab *	N: 1 mg/kg for 3 weeks I: 3 mg/kg for 3 weeks	Recruiting	Open-label Phase-II
	NCT03267836	Meningiomas	fRT; 5 × 0.04 Gy Total 0.2 Gy	Avelumab *	Concurrent RT, 10 mg/kg, every 2 weeks for 3 months	Recruiting	Phase I
	NCT03539198	Head and neck cancer	fRT; 5× Total 35–45 Gy	Nivolumab *	Before and after RT, Q2/week for 2 weeks	Recruiting	Observational
	NCT03764787	Unknown	Unknown	a-PD-1	Unknown, for 1 year	Not yet recruiting	Phase I/II
	NCT03765190	Neoplasm metastasis	Unknown	a-PD-1	Unknown	Not yet recruiting	Phase I/II
	NCT03818776	Non-small cell lung cancer	fRT; 20–23× Total 60–69 Gy (cardiac sparing)	Durvalumab	1500 mg Q4W, max. 12 months (to 13 doses/cycles)	Recruiting	Early Phase I
	NCT03087760	Non-small cell lung cancer	Reirradiation, unknown	Pembroluzimab	Unknown	Recruiting	Phase II
	NCT02444741	Non-small cell lung cancer	fRT, 15× low dose, Total unkown	Pembroluzimab	Unknown dose for 21 days, up to 16 cycles	Recruiting	Phase I/II

	Identifier	Pathology	RT Dose	IO	Dose	Status	Study Type
CIRT	NCT04143984	Locally recurrent nasopharyngeal carcinoma	fRT; 21 × 3 Gy Total 63 Gy	Camrelizumab *	C: 200 mg i.v. every 2 weeks for a year maximum	Not yet recruiting	Phase II/III
CIRT	NCT03705403 **, [102]	Non-small cell lung cancer	SABR	Darleukin	C: 15 Mio IU, 6 cycles, 3 infusions within one cycle, every 3 weeks	Not yet recruiting	Phase II

* Nivolumab and durvalumab are PD-L1 antibodies, ipilimumab is a CTLA-4 antibody, pembroluzimab, avelumab and camrelizumab are PD-1 antibodies, darleukin is the immunocytokine L19-IL2. ** CIRT treatment arm is currently being under consideration by BfS (Federal Office for Radiation Protection, Germany). fRT: fractionated RT, Q: dose per week (Q4 is 4 doses a week), i.v.: intravenous administration.

CIRT	NCT05229614	Non Small Cell Lung Cancer Head and Neck Squamous Cell Carcinoma Melanoma Urothelial Carcinoma	fRT; 3 x 8 Gy[RBE] Total 24 Gy [RBE]	Pembrolizumab (unknown dose)	Not yet recruiting	Phase II

HITRI plus
Heavy Ion Therapy Research Integration

Adapted from Marcus et al., Cancers, 2021

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Take Home Messages

The immune system plays a pivotal role in (metastatic) cancer treatment; immunotherapy is established as additonal pillar in cancer therapy

The mechanisms by which the immune system is triggered and interacts with radiotherapy are not well enough understood to reliably exploit it in a combined treatment strategy

Hadrontherapy has the potential to improve the outcome of a combined therapy

HITRI plus
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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Thank you for your kind attention

Heavy Ion Therapy Research Integration

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