University at Buffalo The State University of New York | REACHING OTHERS

ROSWELL PARK CANCER INSTITUTE

Emerging Techniques in Cancer Therapy

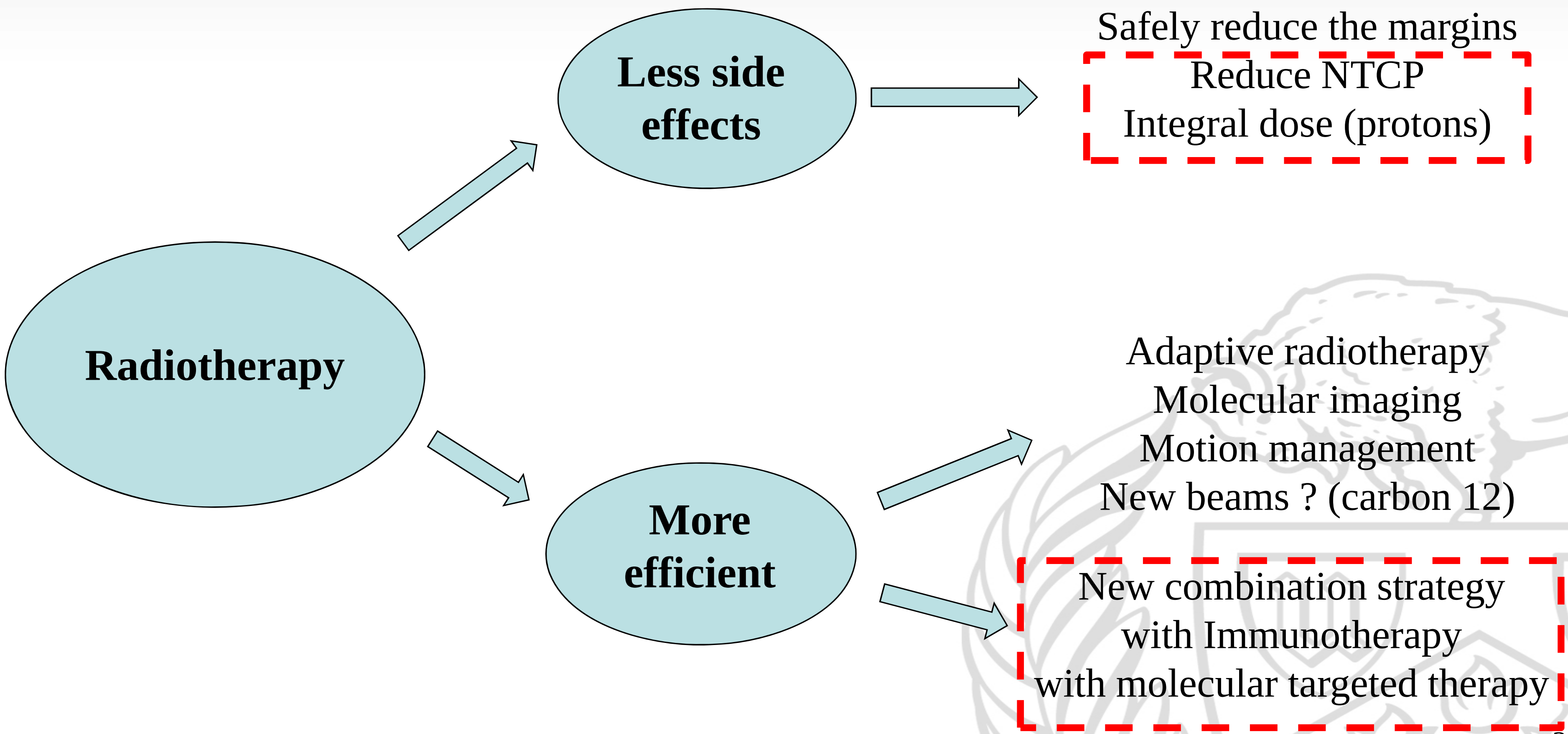
Lalith K. Kumaraswamy, Ph.D
Roswell Park Comprehensive Cancer Center

Outline

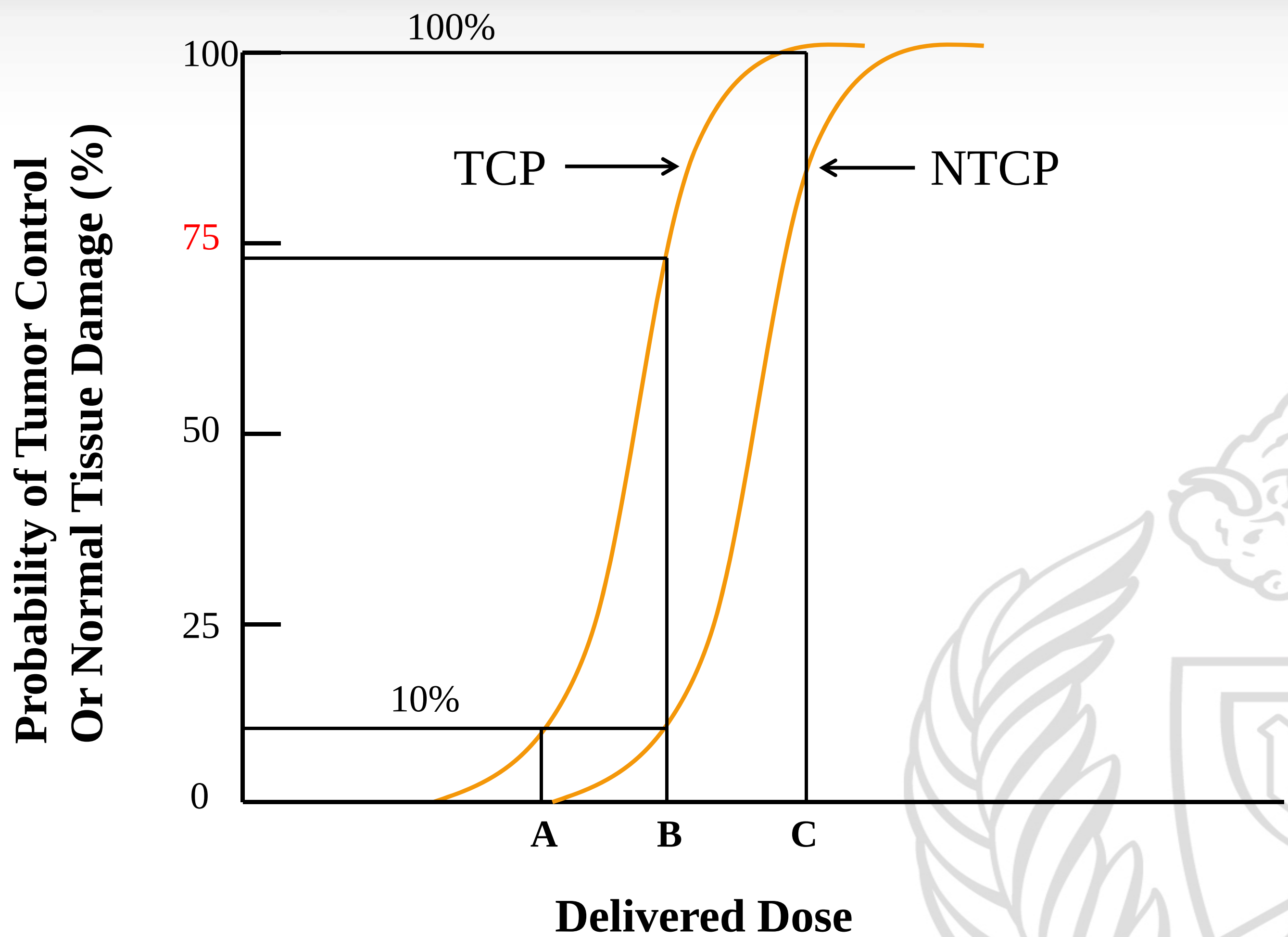
Emerging Technologies in Cancer Therapy

1. FLASH
2. Minibeam Radiotherapy
3. Nanoparticles
4. Immunotherapy with RT

How to improve radiotherapy ? ...



Slide curtsey of J Bourhis


100%
100
75
50
25
0
TCP
NTCP
10%
A
B
C
Probability of Tumor Control
Or Normal Tissue Damage (%)
Delivered Dose

FLASH Radiation Therapy

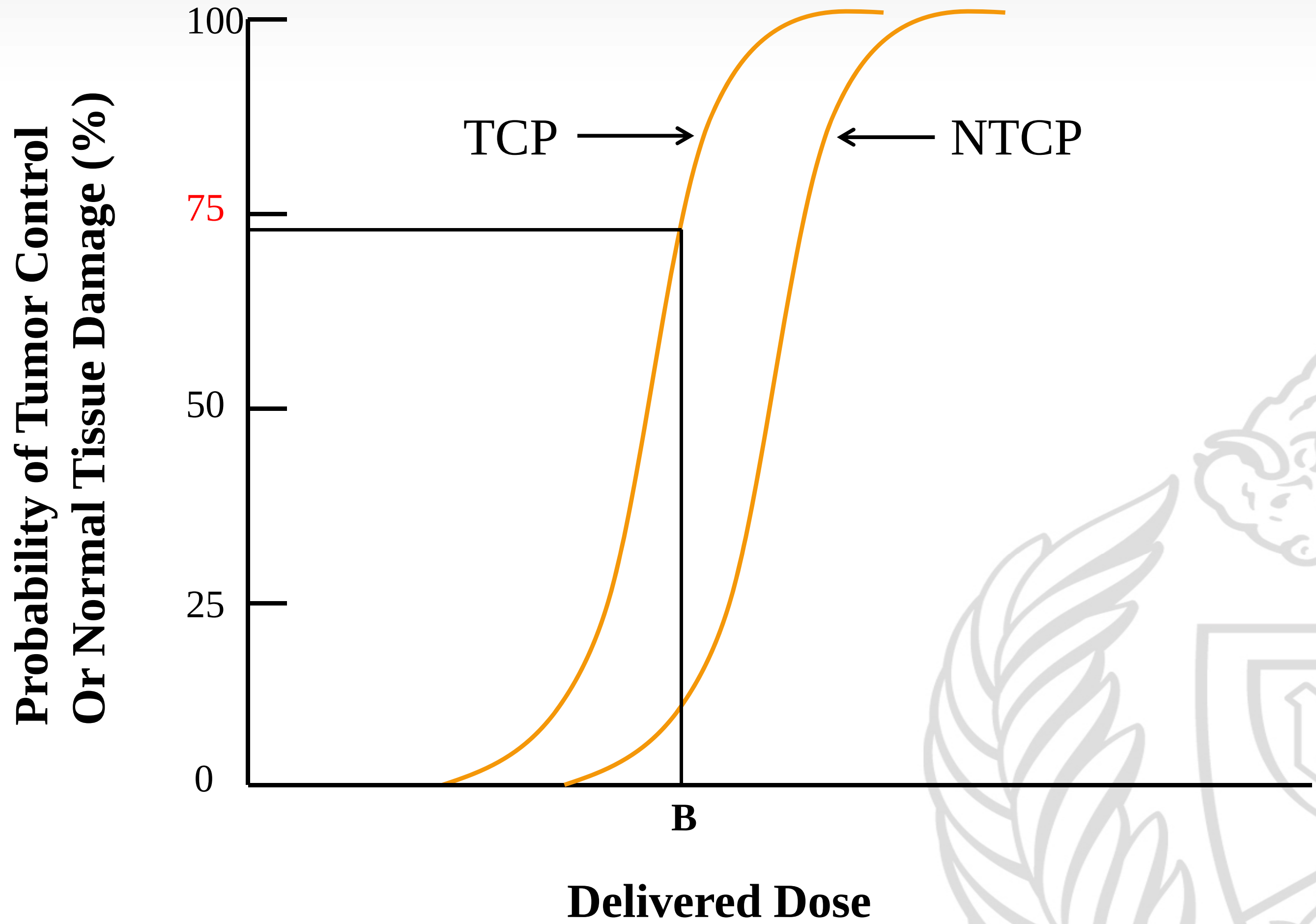
FLASH! – Ultra-high dose rate in radiotherapy

1. Technique developed at Institute Curie (France) by Vincent Favaudon

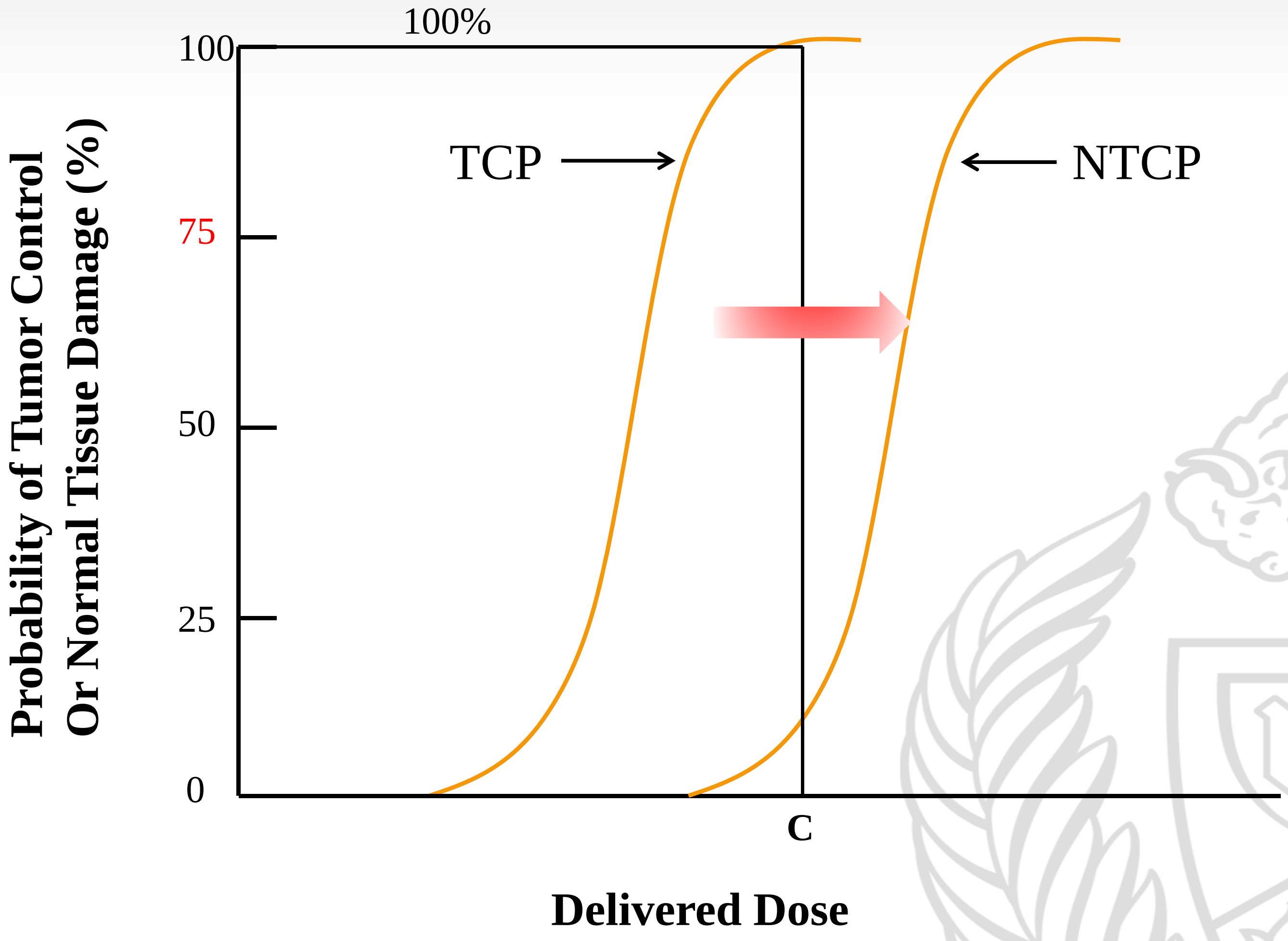
2. Delivering a dose of radiation in a short period of time (~ 200 ms)

	Conventional	**FLASH**
Dose Rate	4 – 7 cGy / sec	5000 cGy / sec (50 Gy/s)
Time for 20 Gy	500 sec (≈ 8 min)	400 ms

Conventional RT



Flash RT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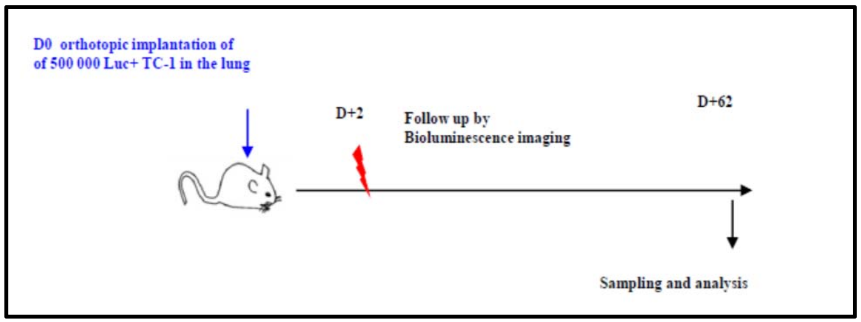
25
0
TCP
NTCP
C
Probability of Tumor Control
Or Normal Tissue Damage (%)
Delivered Dose

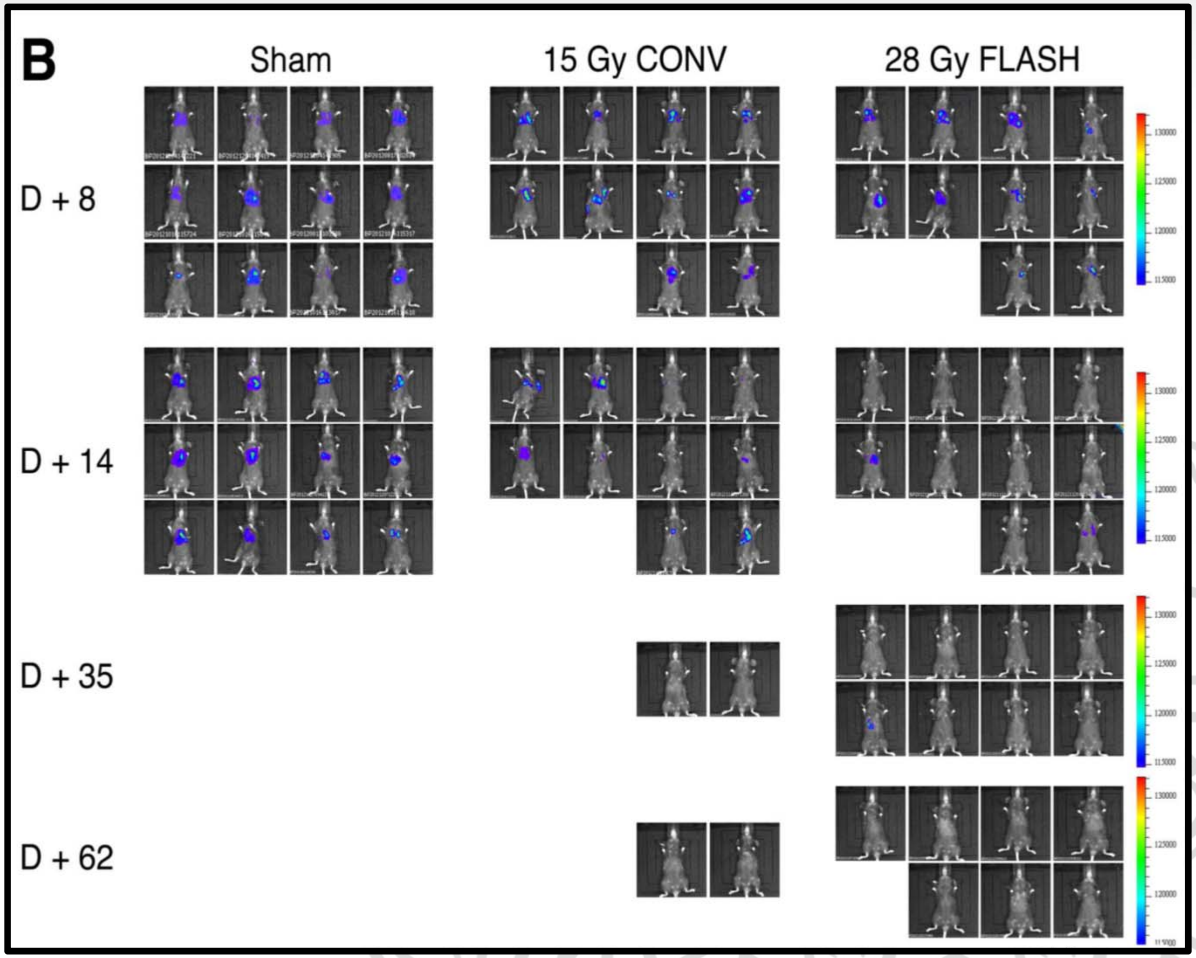
RESEARCH ARTICLE

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

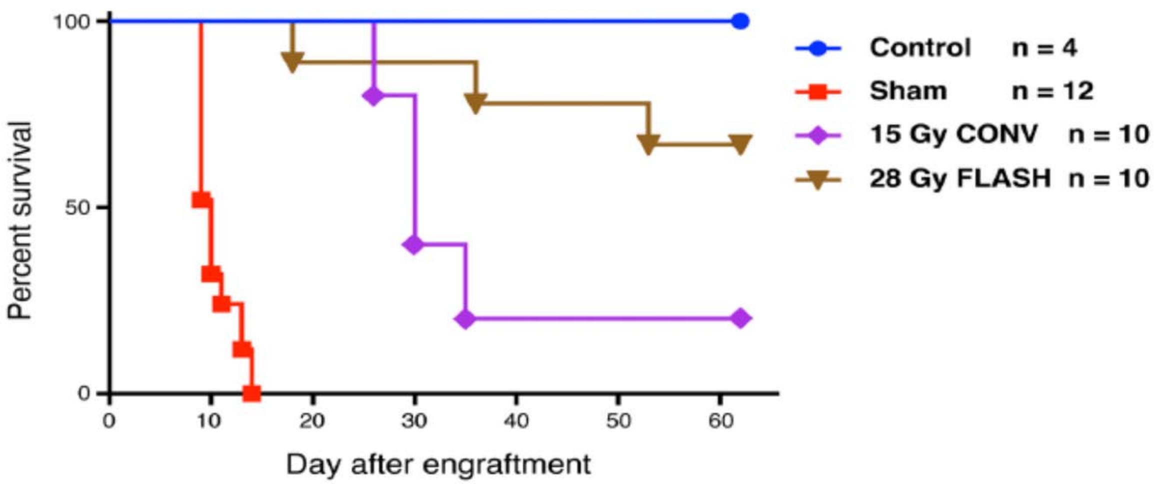

D0 orthotopic implantation of
of 500 000 Luc+ TC-1 in the lung
D+2
Follow up by
Bioluminescence imaging
D+62
Sampling and analysis


B
Sham
15 Gy CONV
28 Gy FLASH
D + 8
D + 14
D + 35
D + 62

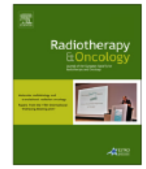
Science Translational Medicine AAAS

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon *et al.*
Sci Transl Med **6**, 245ra93 (2014);
DOI: 10.1126/scitranslmed.3008973



Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com



Flash irradiation

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

Pierre Montay-Gruel [a,b,1], Kristoffer Petersson [c,1], Maud Jaccard [c], Gaël Boivin [a], Jean-François Germond [c], Benoit Petit [a], Raphaël Doenlen [d], Vincent Favaudon [b], François Bochud [c], Claude Bailat [c], Jean Bourhis [a,1], Marie-Catherine Vozenin [a,*,1]

[a] Department of Radiation Oncology/DO/CHUV, Lausanne University Hospital, Switzerland; [b] Institut Curie, INSERM U1021/CNRS UMR3347, Université Paris-Saclay, Orsay, France; [c] Institute of Radiation Physics (IRA), Lausanne University Hospital; and [d] Faculty of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Switzerland

Asses whether FLASH RT altered the neurocognitive function as compared to conventional RT.

Brain model – Flash-RT with a dose of 10 Gy delivered at 100 Gy/s did not alter neurocognitive function as compared to conventional RT.

Published OnlineFirst June 6, 2018; DOI: 10.1158/1078-0432.CCR-17-3375
Clinical Trial Brief Report
Clinical Cancer Research

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

Contents lists available at ScienceDirect
Radiotherapy and Oncology
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Flash irradiation

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

Pie... Ben...

RESEARCH ARTICLE

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

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journal homepage: www.thegreenjournal.com

Original Article

An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and ...nal tissue responses

...as R. Spitz [a,*], Garry R. Buettner [a], Michael S. Petronek [a], Joël J. St-Aubin [a], Ryan T. Flynn [a], ...hy J. Waldron [a], Charles L. Limoli [b]
...dical and Radiation Biology Program, Department of Radiation Oncology, Free Radical Metabolism and Imaging Program, Holden Comprehensive Cance... ...rsity of Iowa, United States; and [b] Department of Radiation Oncology, University of California, Irvine, United States

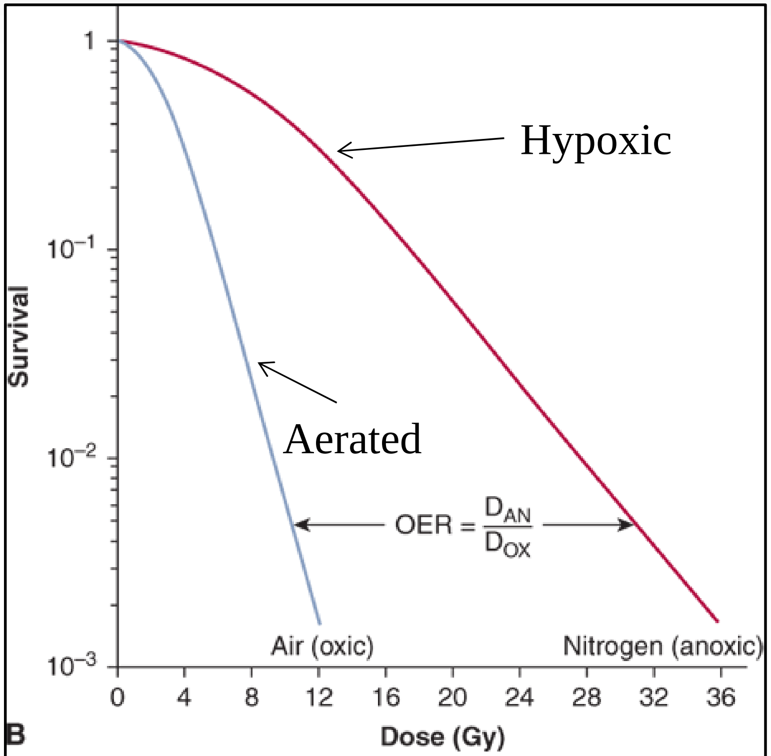
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Orignal Article

Biological effects in normal cells exposed to FLASH dose rate protons

Manuela Buonanno *, Veljko Grilj, David J. Brenner
Radiological Research Accelerator Facility (RARAF), New York, United States

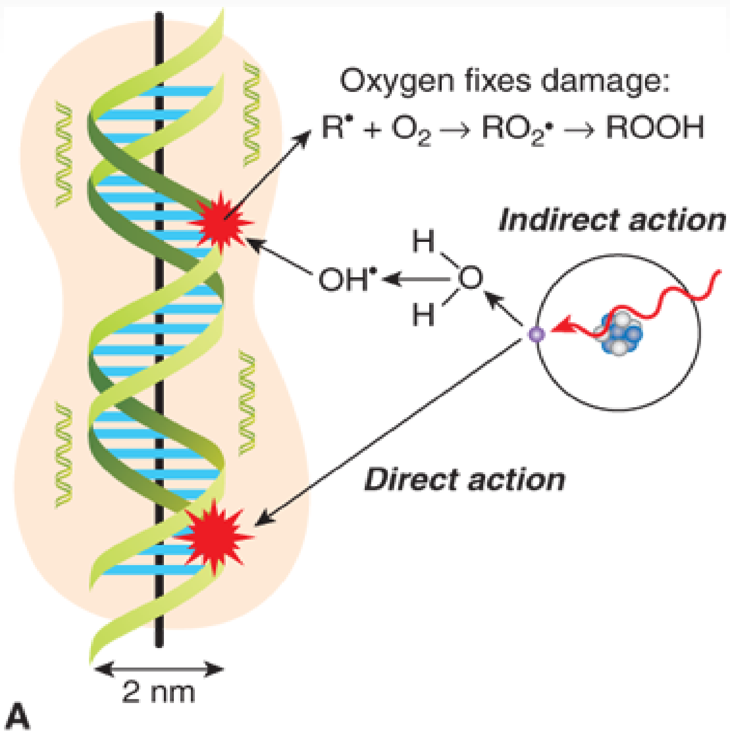
Oxygen Effect



Source: Ian F. Tannock, Richard P. Hill, Robert G. Bristow, Lea Harrington: The Basic Science of Oncology, 5th Edition www.hemonc.mhmedical.com

- In the presence of oxygen, cells become radiosensitive.
- **Oxygen enhancement ratio (OER)**
  - Ratio of dose administered under hypoxic to aerated conditions needed to achieve the same biological effect.
- OER for x-rays is about 2.5 to 3.5

Mechanism of the oxygen effect



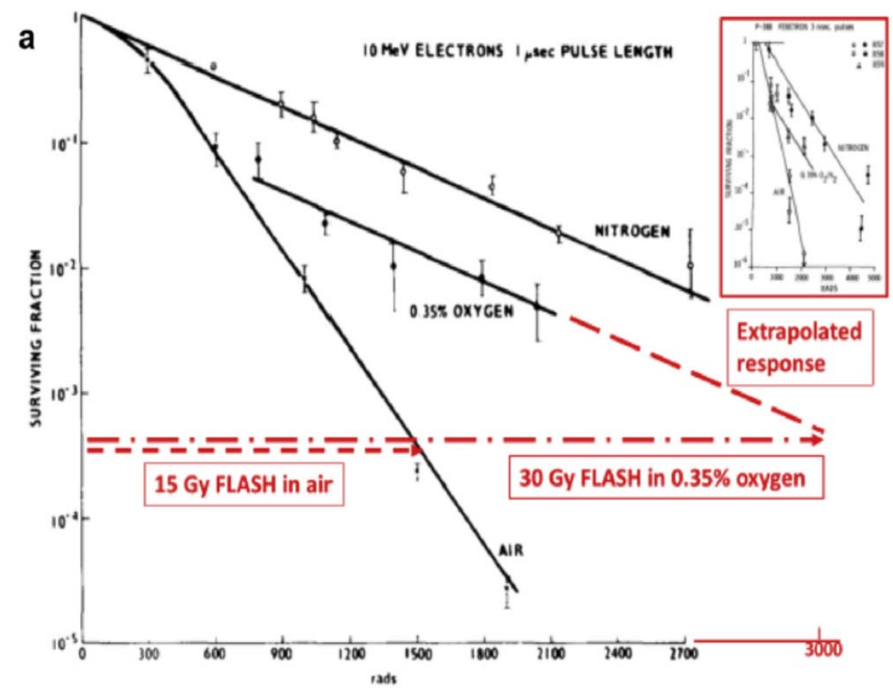
Source: Ian F. Tannock, Richard P. Hill, Robert G. Bristow, Lea Harrington: The Basic Science of Oncology, 5th Edition
www.hemonc.mhmedical.com

- Absorption of radiation leads to fast charged particles.
- Charged particles helps to produce **free radicles**.(highly reactive)
- Free radicles react with DNA and causes damage.
- But DNA damage can be repaired through reaction with a SH group
- Oxygen “fix” or make permeant the DNA damage – SH group cannot repair the damage.

Why FLASH is effective ?

- FLASH is effective for treating hypoxic tumors surrounded by aerated normal cells
- FLASH RT causes a rapid decrease in O_2 levels in the aerated normal cells
- Normal aerobic cells becomes hypoxic
- Normal cells become radioresistant

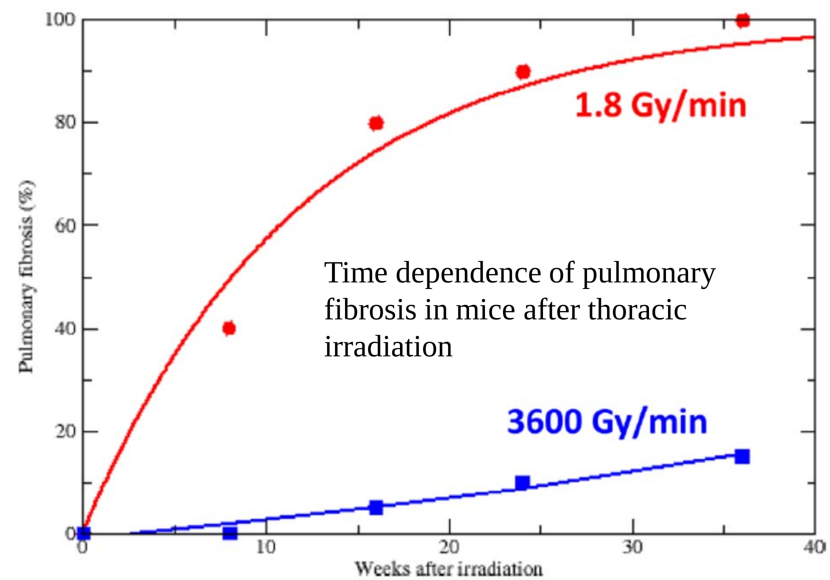
M.-C. Vozenin et al. / Clinical Oncology 31 (2019) 407–415



FLASH effect is possible with sufficiently high dose and exposure duration must be sufficiently low

1. FLASH RT Reduced normal tissue toxicity
   - Dose escalation is possible

2. Ultra fast delivery
   - No intra-fraction motion management
   - Potential for markedly reducing radiotherapy workload



Faster and safer? FLASH ultra-high dose rate in radiotherapy

[1]MARCO DURANTE, PhD, [2]ELKE BRÄUER-KRISCH, PhD and [3]MARK HILL, PhD
[1]National laboratories, Trento Institute for Fundamental Physics and Applications (TIFPA), National Institute of Nuclear Physics (INFN), University of Trento, Trento, Italy
[2]National laboratories, ESRF-The European Synchrotron, Grenoble, France
[3]Department of Oncology, CRUK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, UK

High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use

Maud Jaccard, Maria Teresa Durán, Kristoffer Petersson, and Jean-François Germond
Institute of Radiation Physics, Lausanne University Hospital, Lausanne, Switzerland

- Prototype linac producing an electron beam between 5 and 6 MeV
- Designed to produce a maximum peak current of 300 mA as compared to 1 mA in a standard linac.
- Deliver dose rates up to 200 Gy/s.
- No standard monitor chamber due to saturation effects

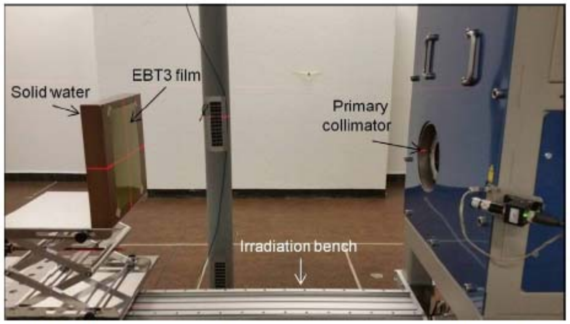
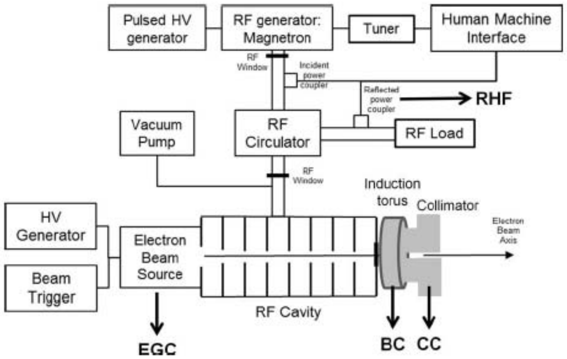
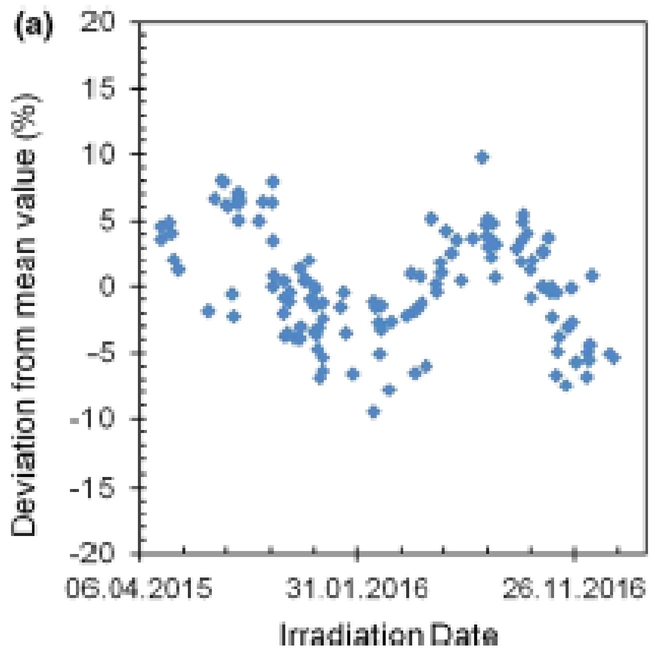


FIG. 2. Oriatron eRT6 linac and irradiation bench: set-up for film dosimetry at the surface of the solid water phantom at an SSD of 1 m. [Color figure can be viewed at wileyonlinelibrary.com]

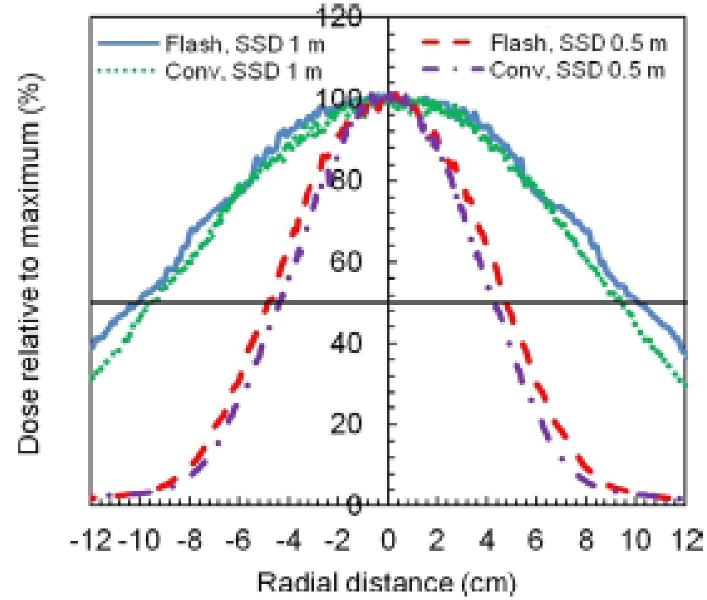


Output stability



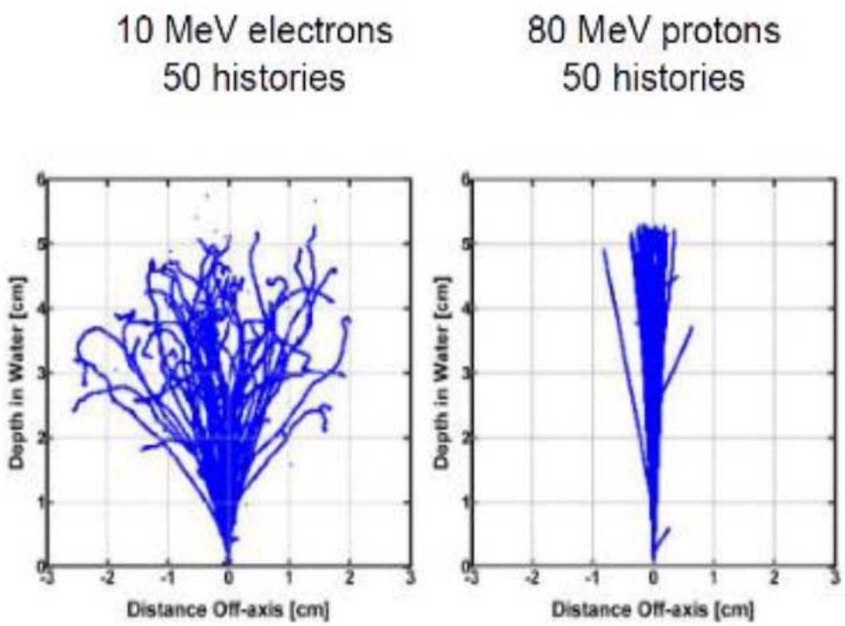
20 Month period → ± 10%

Beam Profiles



Specially designed scattering foil

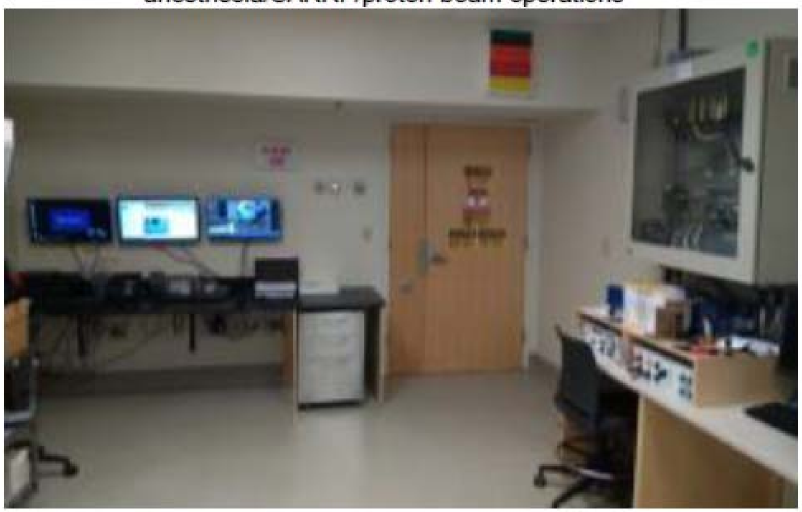
FLASH Protons



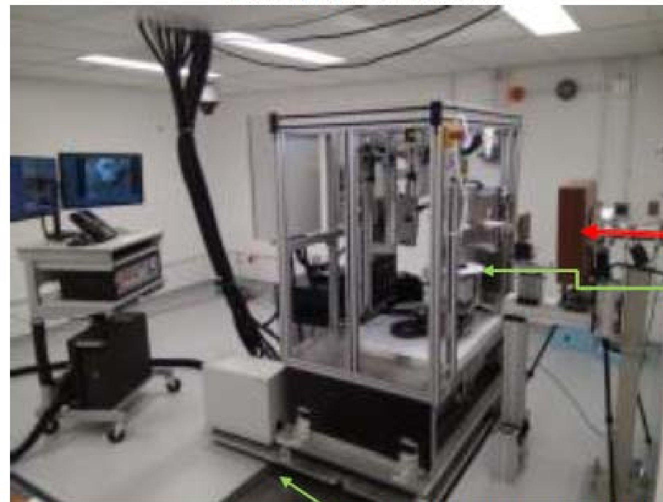
Slide courtesy of Lei Dong, Ph.D

Small Animal Radiation Facility-SARRP with proton beams - UPENN

Prep/Control room with remote anesthesia/SARRP/proton beam operations



Vault with Image-Guided Proton/Photon irradiators



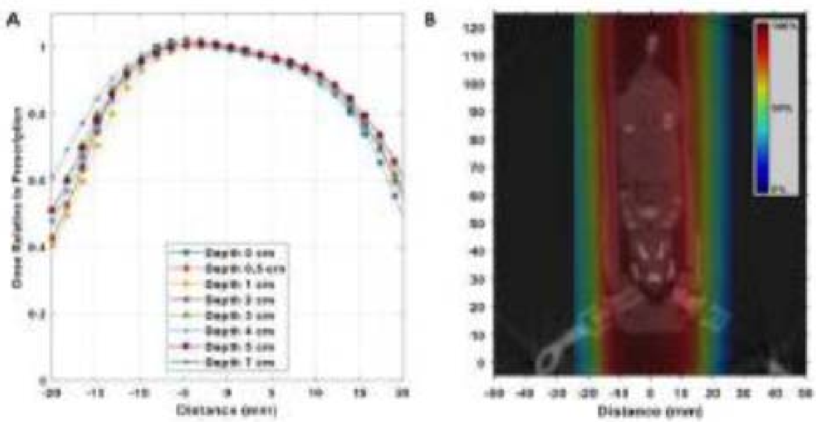
M. Kim *et al. Phys. Med. Biol.* **64** (2019) 135013 (12pp)

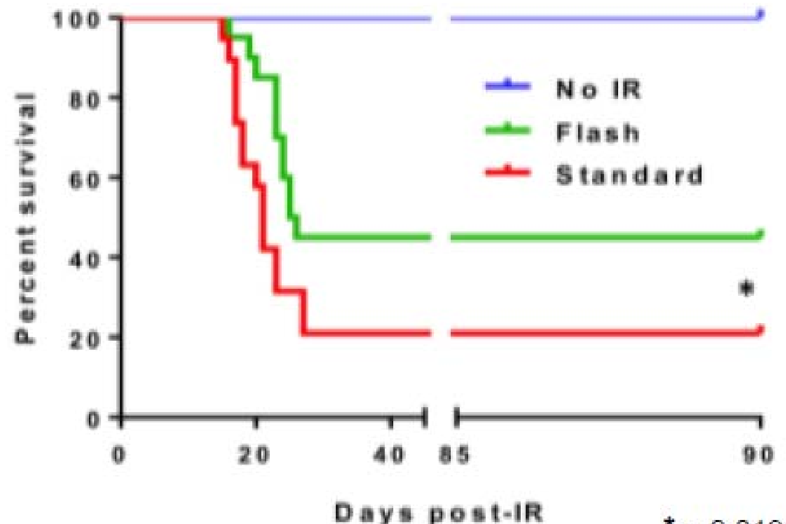
Facility supports:

- 23 Penn investigators for animal RT
- Core Facility for P01 "Immune Checkpoints and Radiation in Cancer" (Vonderheide)
- Current FLASH RT efforts

Increased survival of C57BL/6 mice treated with FLASH vs conventional WBRT

Mice were whole body-irradiated either with 1 Gy/s or 75 Gy/s irradiation at a **single dose of 7.5Gy**.





Diffenderfer *et al., in revision*

Slide courtesy of Lei Dong, Ph.D

FLASH RT

1. Can deliver dose rate up to 100 Gy/s.
2. Hypoxic cells are more radiosensitive than aerated cells.
3. Electrons are more suitable for FLASH since they are more forward peaked than protons.
4. Animal studies show survival rate with FLASH RT is lower compared with conventional RT.

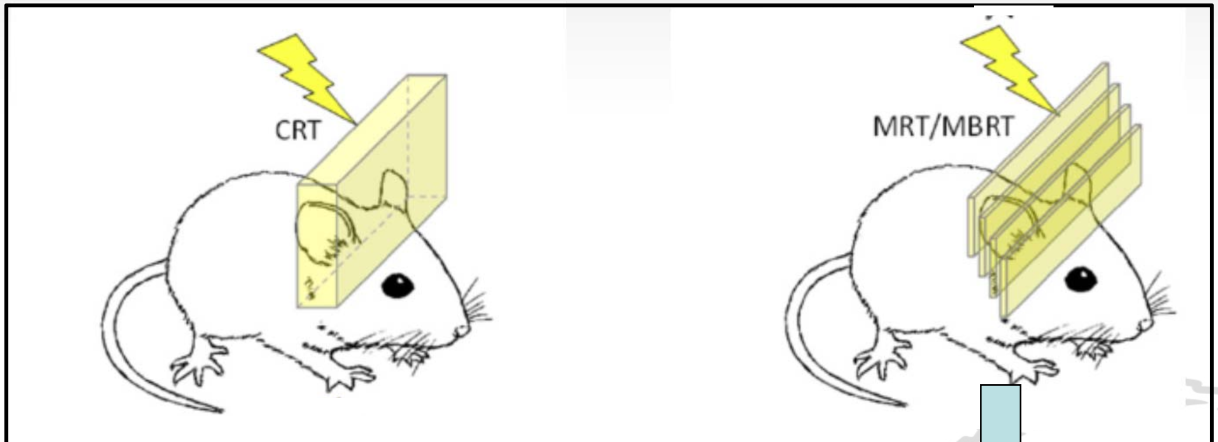
Summary of FLASH RT

- FLASH RT demonstrate significant normal tissue sparing in animal studies.
- Biological effects and rationales of FLASH are unclear.
- More research needs to be performed to improve deliverability and safety before starting human trials.

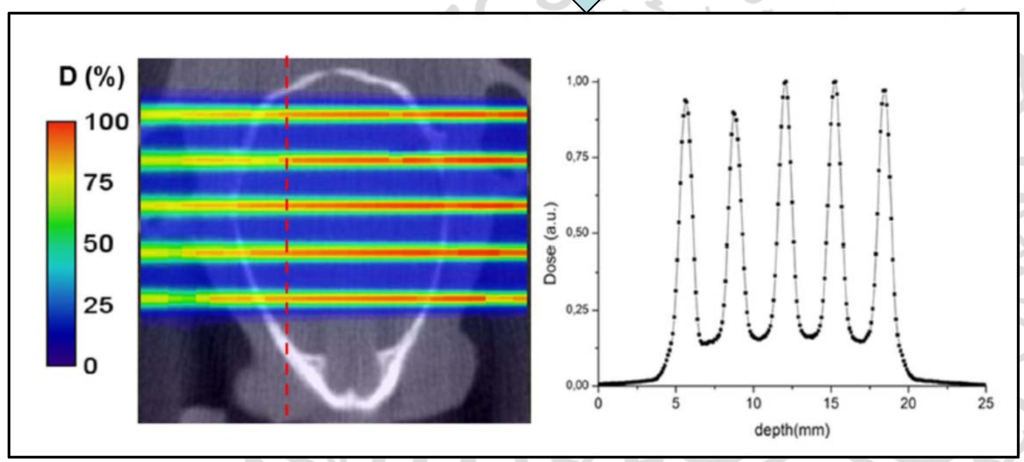
MicroBeam Radiation Therapy

Microbeam Radiation Therapy (MRT)

- Delivers ultrahigh dose (50 – 100 Gy)
- 200 – 1000 µm beam (peaks), separated by wider non-irradiated regions (valleys)
- Reduced normal tissue toxicities – NTCP ↓
- Most research are focused on Brain lesions.



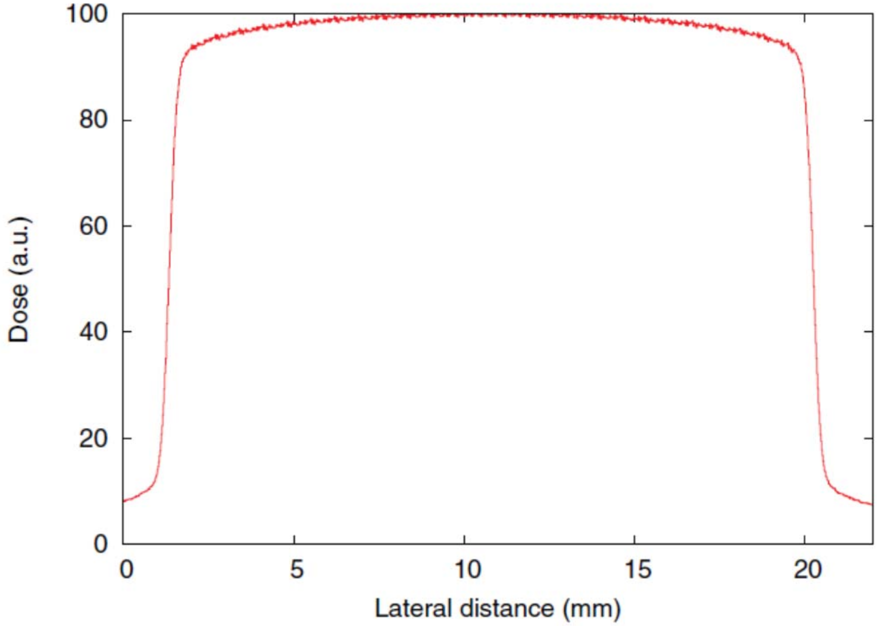
S Bazyar et al. Phys. Med. Biol. 62 (2017)



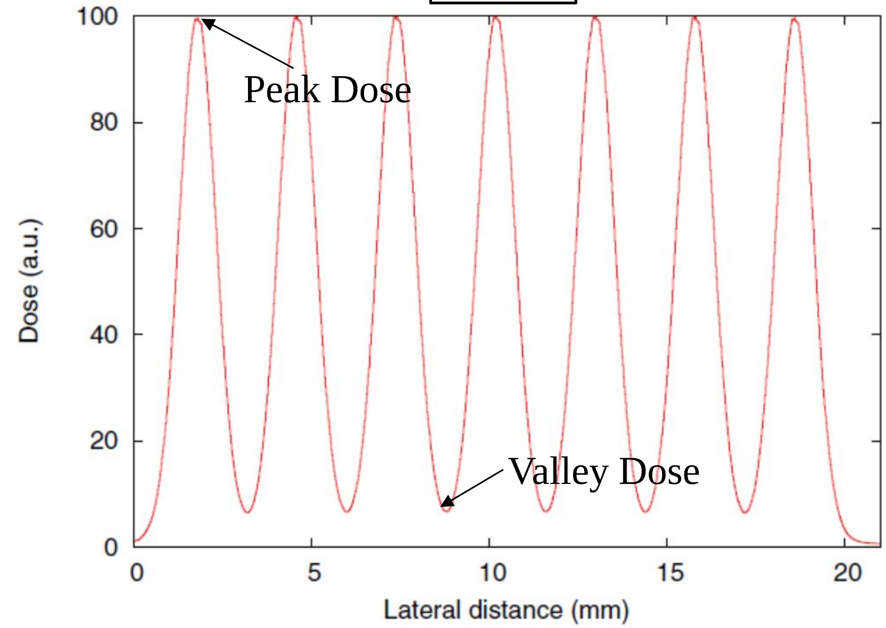
Prezado et. al. Scientific Reports (2018) 8: 16479

Convention Vs MRT beam

Conventional RT

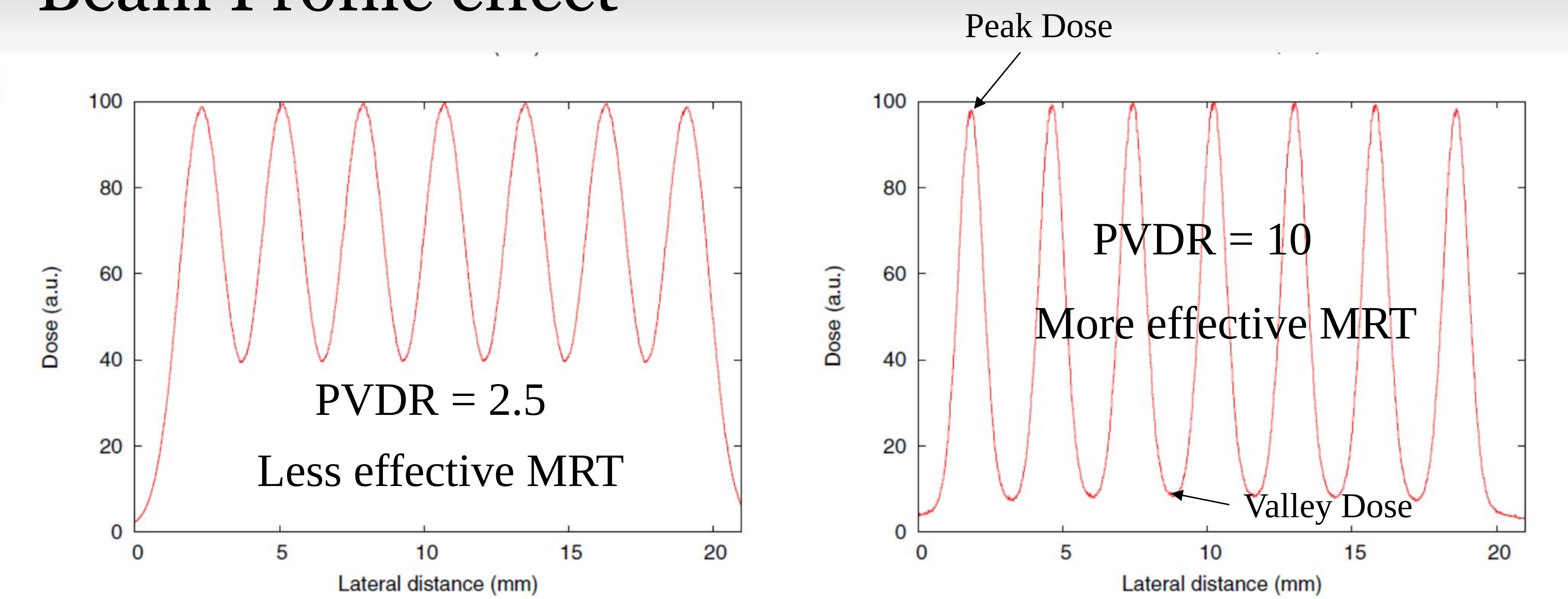


MRT



- MRT dose profiles consist of patterns of peaks and valleys
- Ratio between peak and valley doses is called **peak-to-valley dose ratio (PVDR)**
- The higher the PVDR the better the biological response

Beam Profile effect



- MRT spares normal tissue when beam spacing is less than twice that of beam width
- Sparing effect of MRT depends mostly on valley dose and little on peak dose
- Normal tissue sparing effect vanishes when valley dose approaches tissue tolerance of to broad beam

Preservation of normal cell function with MRT

RADIATION RESEARCH 15, 496–514 (1961)

Histopathologic Effect of High-Energy-Particle Microbeams on the Visual Cortex of the Mouse Brain[1]

W. ZEMAN, H. J. CURTIS, AND C. P. BAKER

Departments of Physics and Biology, Brookhaven National Laboratory, Upton, New York, and the Department of Pathology, Indiana University, Medical Center, Indianapolis, Indiana

- 140 Gy was delivered to side of the visual cortex of female mice
- 3 groups **1)** 1 mm wide beam **2)** 75 µm **3)** 25 µm

- 1 mm wide beam resulted in complete tissue destruction and cavity formation
- 25 µm caused no damage with a 240 days observation period
- Only after 4000 Gy, nerve and glial cells died in the path of the 25 µm beam

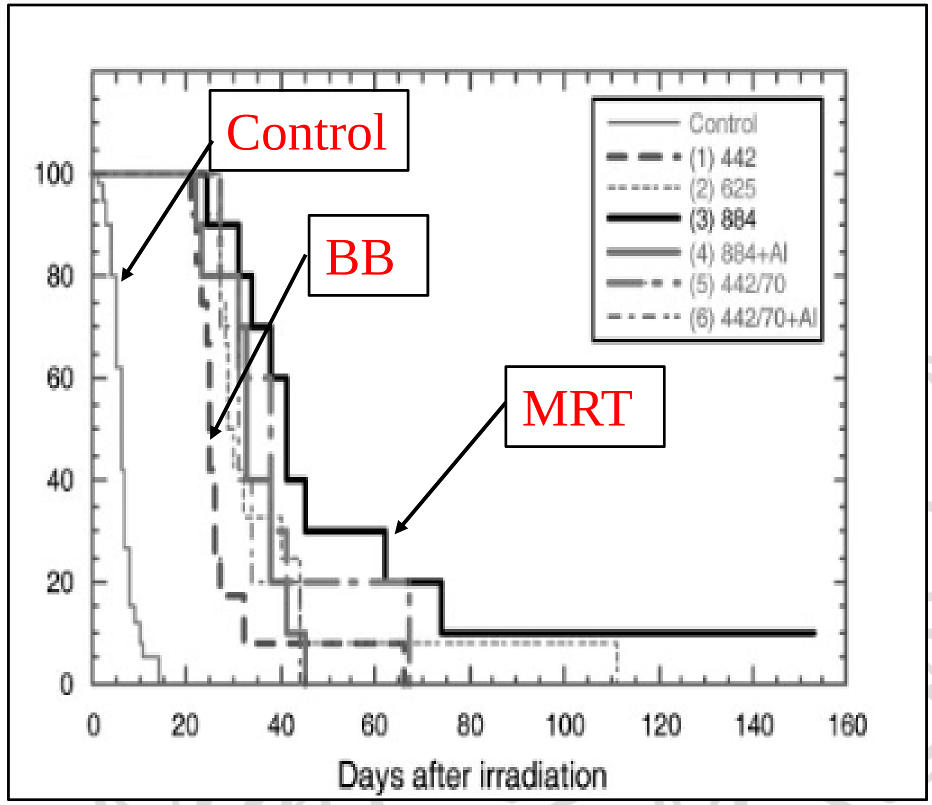
MRT Vs Broad Beam – Aggressive tumor type

The British Journal of Radiology, 79 (2006), 71–75 © 2006 The British Institute of Radiology
DOI: 10.1259/bjr/50464795

Short communication

Radiosurgical palliation of aggressive murine SCCVII squamous cell carcinomas using synchrotron-generated X-ray microbeams

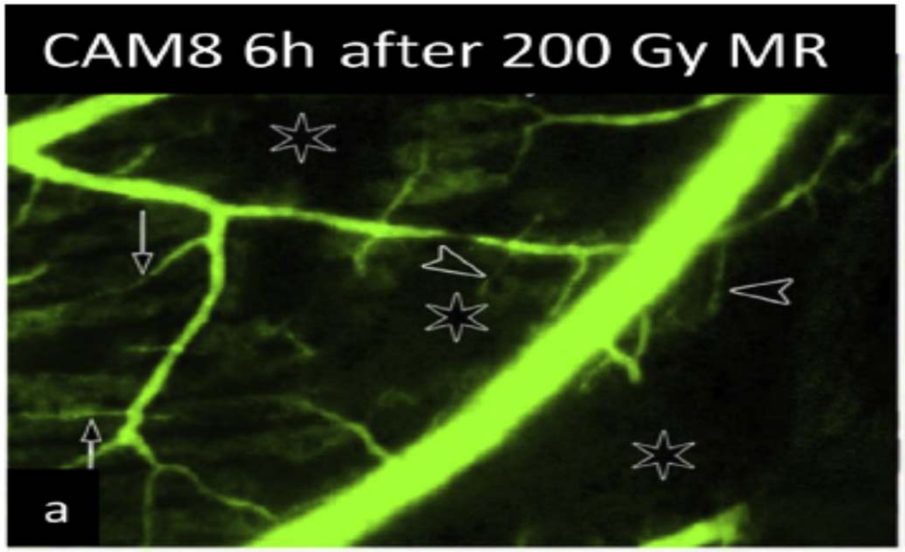
[1]M MIURA, PhD, [2]H BLATTMANN, PhD, [3]E BRÄUER-KRISCH, BEng, [3]A BRAVIN, PhD, [1]A L HANSON, PhD, [1]M M NAWROCKY, BA, [1]P L MICCA, BS, [1,4]D N SLATKIN, MD and [4]J A LAISSUE, MD



- Medial survival time (MST) :
  - for BB ~ 20 days
  - for MRT ~ 41 days

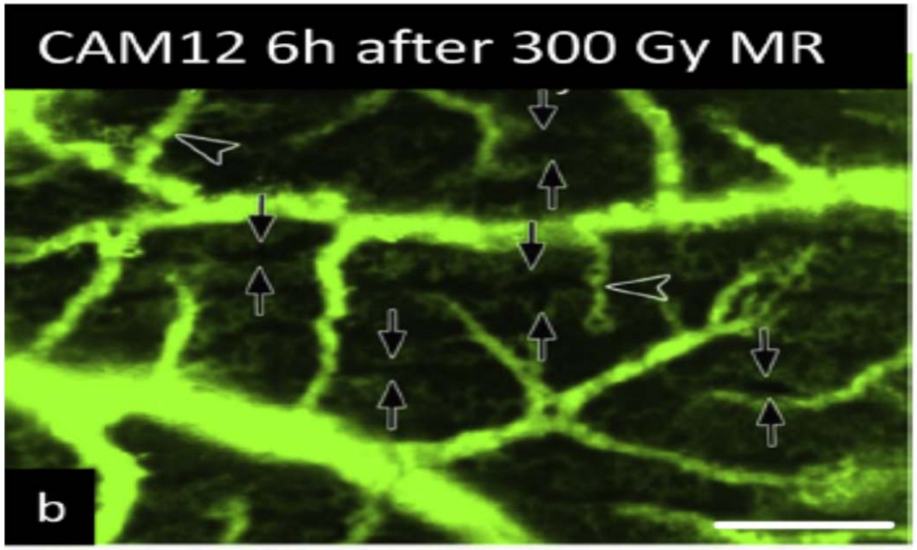
Tumor Vs Normal cell – Microbeam radiation

CAM8 – Cells representing **tumor vasculature**



- Total destruction of capillaries
- Large areas were no longer perfused after 6 hrs (asterisks)
- Destroyed supplying vessels (arrows)

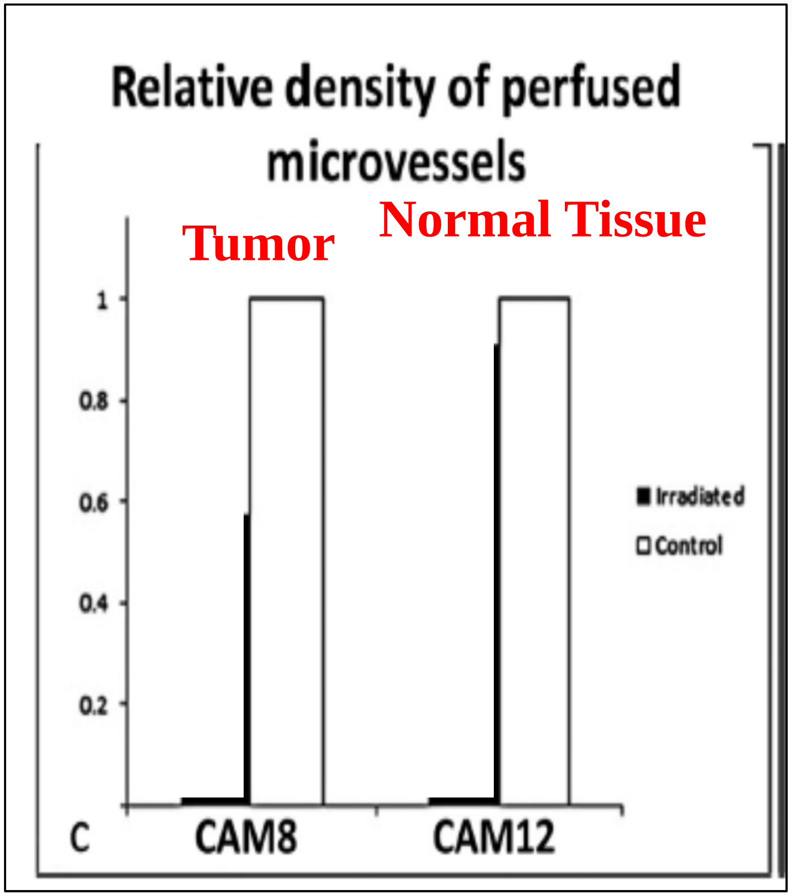
CAM12 – Cells representing **normal tissue vasculature**



- Negligible effects on vasculature
- Large density of preserved micro vessels
- Few small suppling vessels were mildly affected

Sabatasso et al – Int J Radia Oncol Biol Phys 2011;80:1522-32

Perfusion Rate – Tumor Vs Normal tissue after radiation



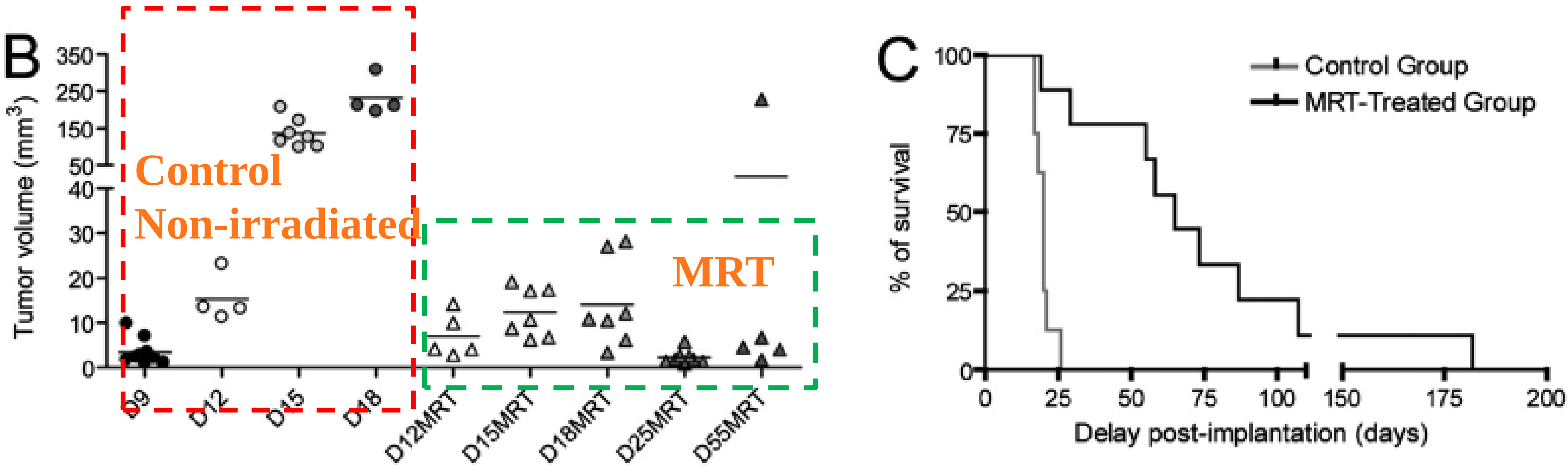
- Immature tumor vessels cannot repair damage induced by MRT
- Mature vessels in the normal tissue are able to repair themselves

Sabatasso et al – Int J Radia Oncol Biol Phys 2011;80:1522-32

BIOLOGY CONTRIBUTION

PREFERENTIAL EFFECT OF SYNCHROTRON MICROBEAM RADIATION THERAPY ON INTRACEREBRAL 9L GLIOSARCOMA VASCULAR NETWORKS

Audrey Bouchet, M.S.,* Benjamin Lemasson, M.S.,†‡§ Géraldine Le Duc, Ph.D.,* Cécile Maisin, M.S.,†‡ Elke Bräuer-Krisch, M.S.,* Erik Albert Siegbahn, Ph.D.,¶ Luc Renaud,‖** Enam Khalil, Ph.D.,†† Chantal Rémy, Ph.D.,†§ Cathy Poillot, M.S.,†§ Alberto Bravin, Ph.D.,* Jean A. Laissue, M.D.,‡‡ Emmanuel L. Barbier, Ph.D.,†§ and Raphaël Serduc, Ph.D.*



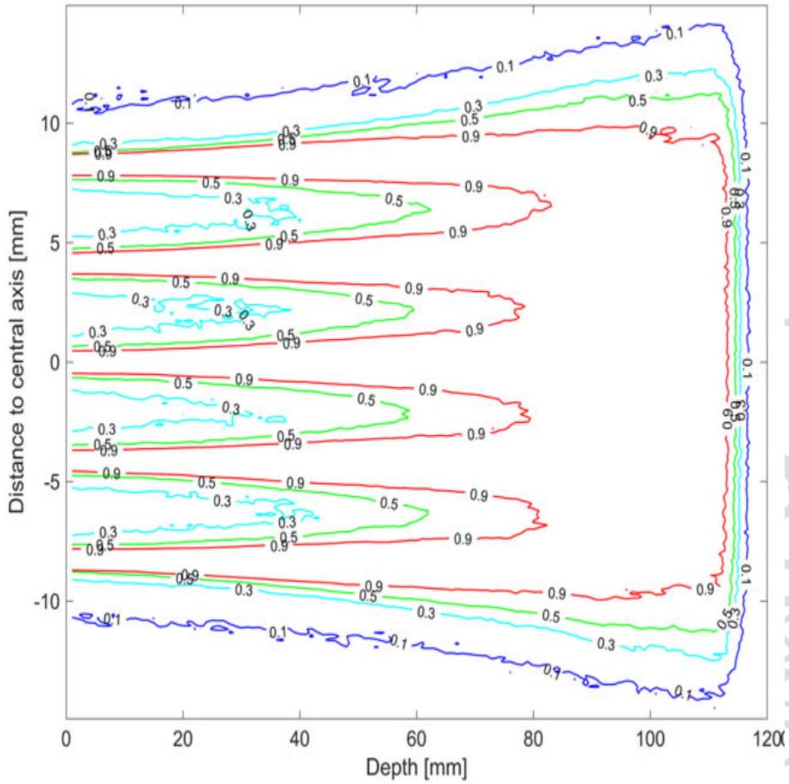
MRT efficiently slows down the intracranial 9L gliosarcoma growth in rats

Requirement of MRT

- Very high dose rate ~ 100 Gy/s
  - Avoid dose smearing due to movement
- High peak to valley dose ratio
  - Maintain high dose to target while avoiding reaching dose limit to OAR

Proton minibeam radiation therapy (pMBRT)

- Reduced lateral scatter – more distinctive peak to valley doses.
- Sparing of proximal tissue (Bragg Peak)
- Can produce very high dose rates with protons.



Microbeam radiation preferentially affects tumor

- Sparing of normal tissue:
  - Resistance of MATURE normal blood vessels to microbeam irradiation

- Damage to tumor:
  - IMMATURE tumor vessels cannot repair damage
  - Decrease in number of vessels
  - Decrease in perfusion
  - Increase in tumor hypoxia
  - Death

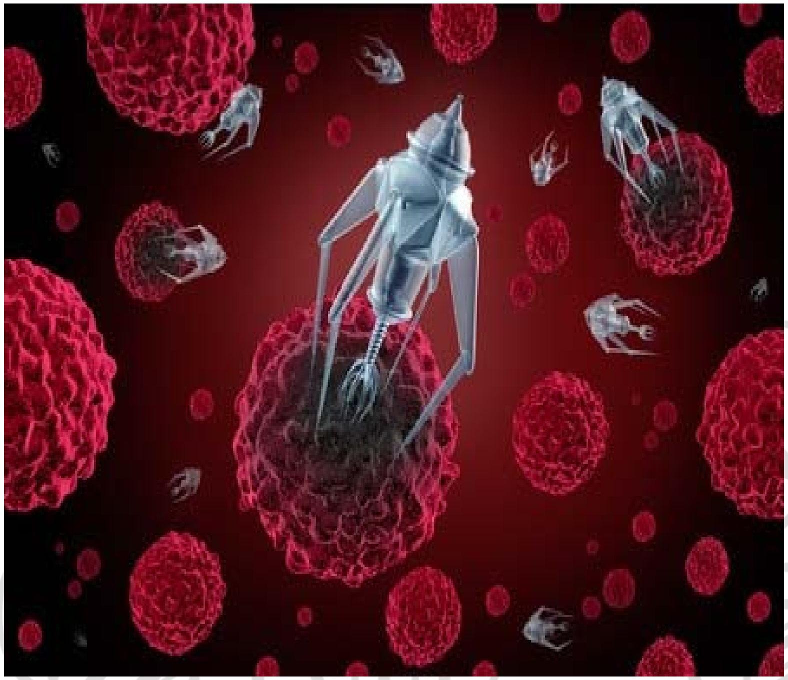
Nanorobot

What is Nanotechnology?

- Nanometer is 10^{-9} meters (one billionth of a meter)
- The thickness of one human hair is 100,000 nanometers
- Nanotech is the design of technology on the very small (nano) scale
- Made possible with advances in microscopy, chemistry, physics and computer science

Nanotechnology and Cancer

- Currently cancer is treated by surgery, chemotherapy, or radiation therapy
- These treatments have side effects
- What if we specifically target cancer using nanotechnology (Nano robots)
- Nano robots have potential as intelligent drug delivery that respond only to tumor cells

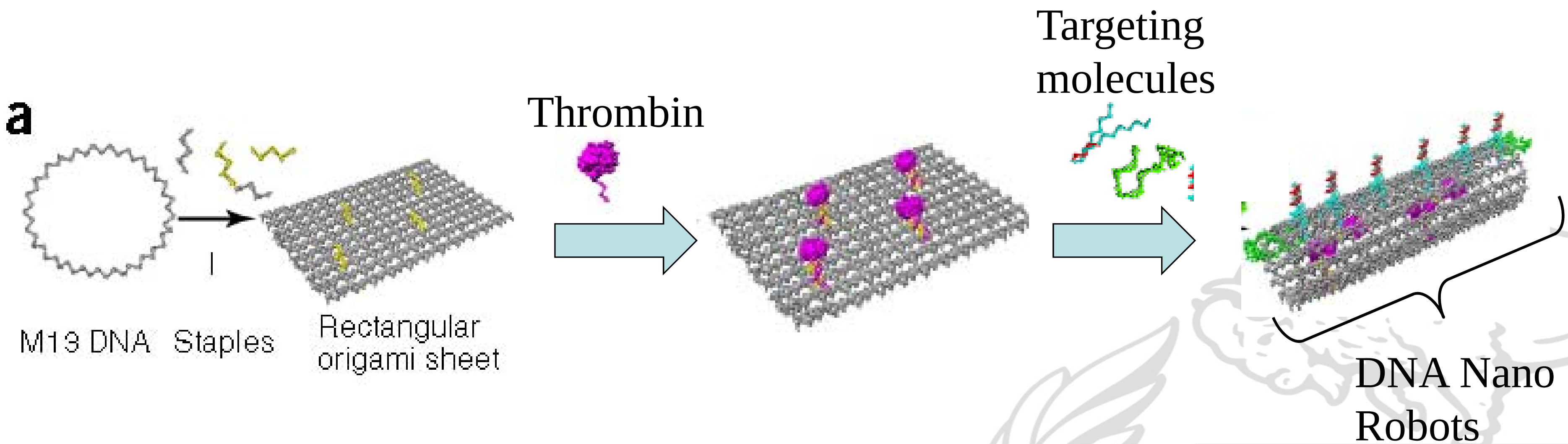


Nanobots

- Selective occlusion of tumor blood vessels, to deprive tumors of nutrients and oxygen and start an avalanche of tumor cell depth
- This strategy can be used on all solid tumors
- Coagulation protease **thrombin** regulates obstructive thrombosis

- Nanobots - Little devices the size of red blood cells
- Nanobots protects the thrombin until exposure is triggered by interaction with tumor marker

Creation of DNA Nano robots



A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger *in vivo*

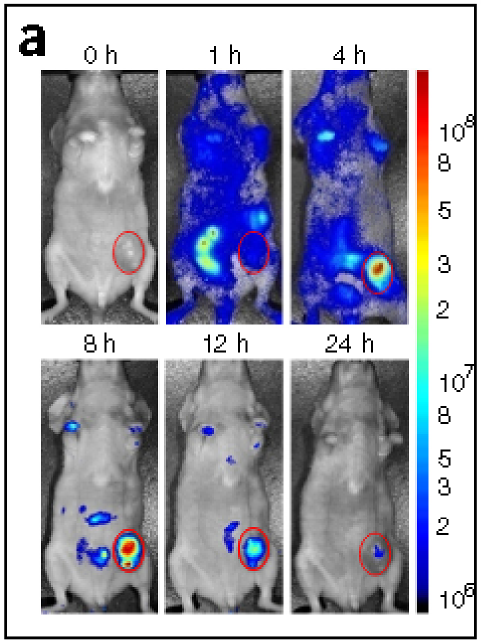
Suping Li[1,2,10], Qiao Jiang[1,10], Shaoli Liu[1,2,10], Yinlong Zhang[1,3,10], Yanhua Tian[1,4], Chen Song[1], Jing Wang[1], Yiguo Zou[1], Gregory J Anderson[5], Jing-Yan Han[6], Yung Chang[7], Yan Liu[7], Chen Zhang[8], Liang Chen[9], Guangbiao Zhou[8], Guangjun Nie[1,2], Hao Yan[7], Baoquan Ding[1,2] & Yuliang Zhao[1,2]

Cancer treatment with Nano Robots

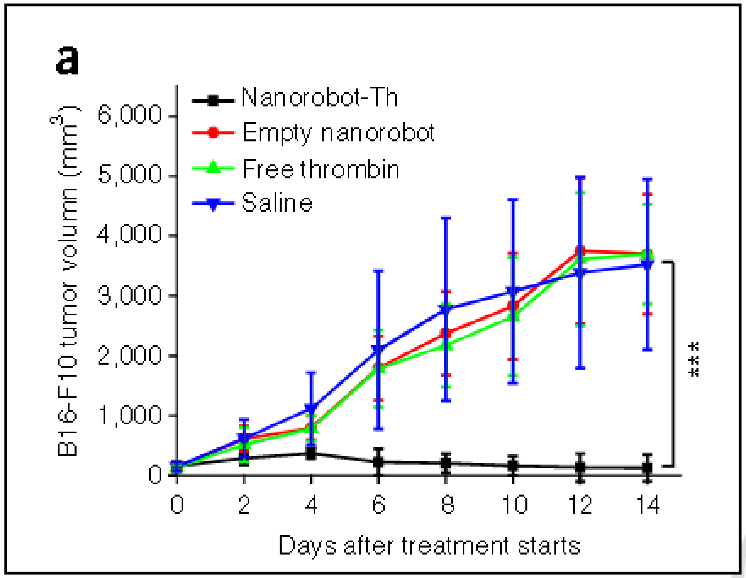
https://www.youtube.com/watch?v=H4ALjfzDSpI

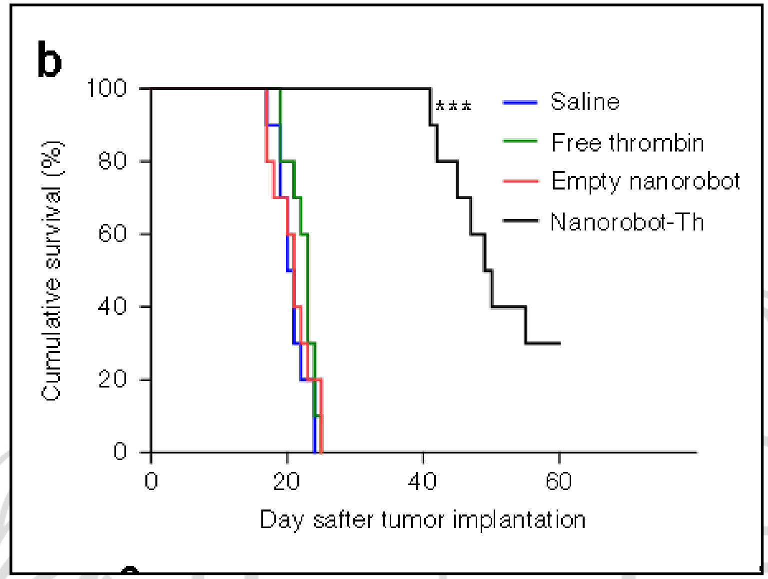
A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger *in vivo*

Suping Li[1,2,10], Qiao Jiang[1,10], Shaoli Liu[1,2,10], Yinlong Zhang[1,3,10], Yanhua Tian[1,4], Chen Song[1], Jing Wang[1], Yiguo Zou[1], Gregory J Anderson[5], Jing-Yan Han[6], Yung Chang[7], Yan Liu[7], Chen Zhang[8], Liang Chen[9], Guangbiao Zhou[8], Guangjun Nie[1,2], Hao Yan[7], Baoquan Ding[1,2] & Yuliang Zhao[1,2]



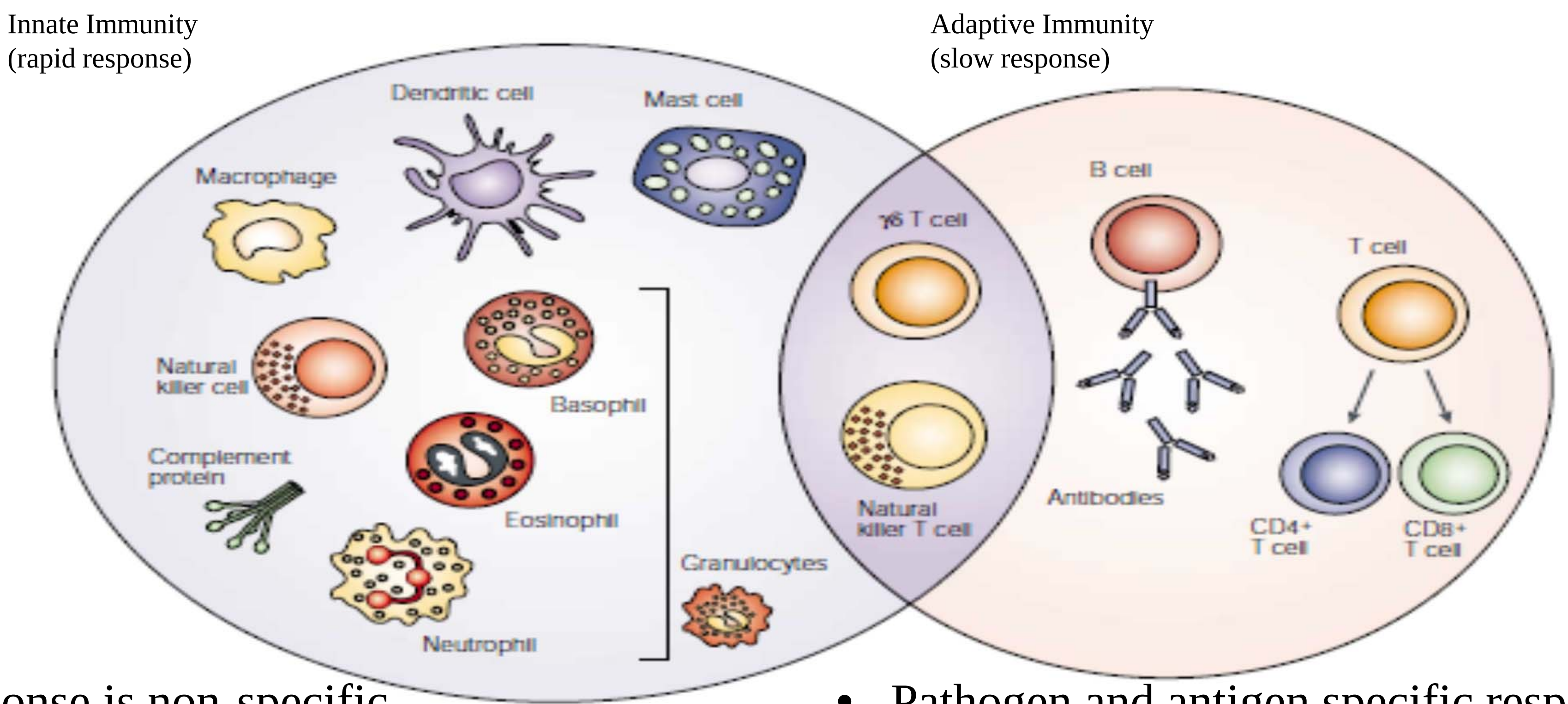
Mouse implanted with human breast tumor





Immuno-Radiotherapy

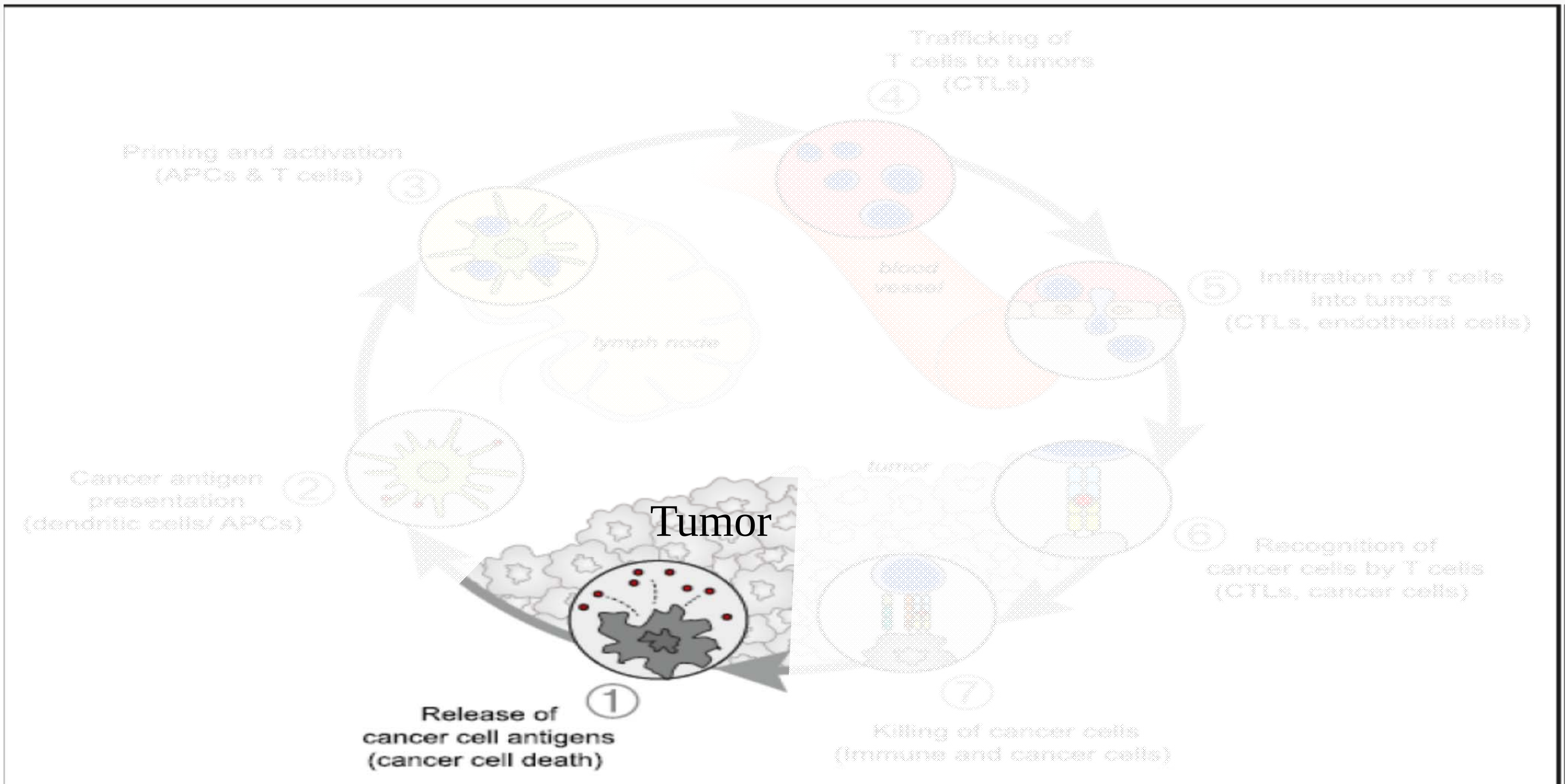
Immune Sub-Systems



- Response is non-specific
- Exposure leads to immediate response
- No immunological memory

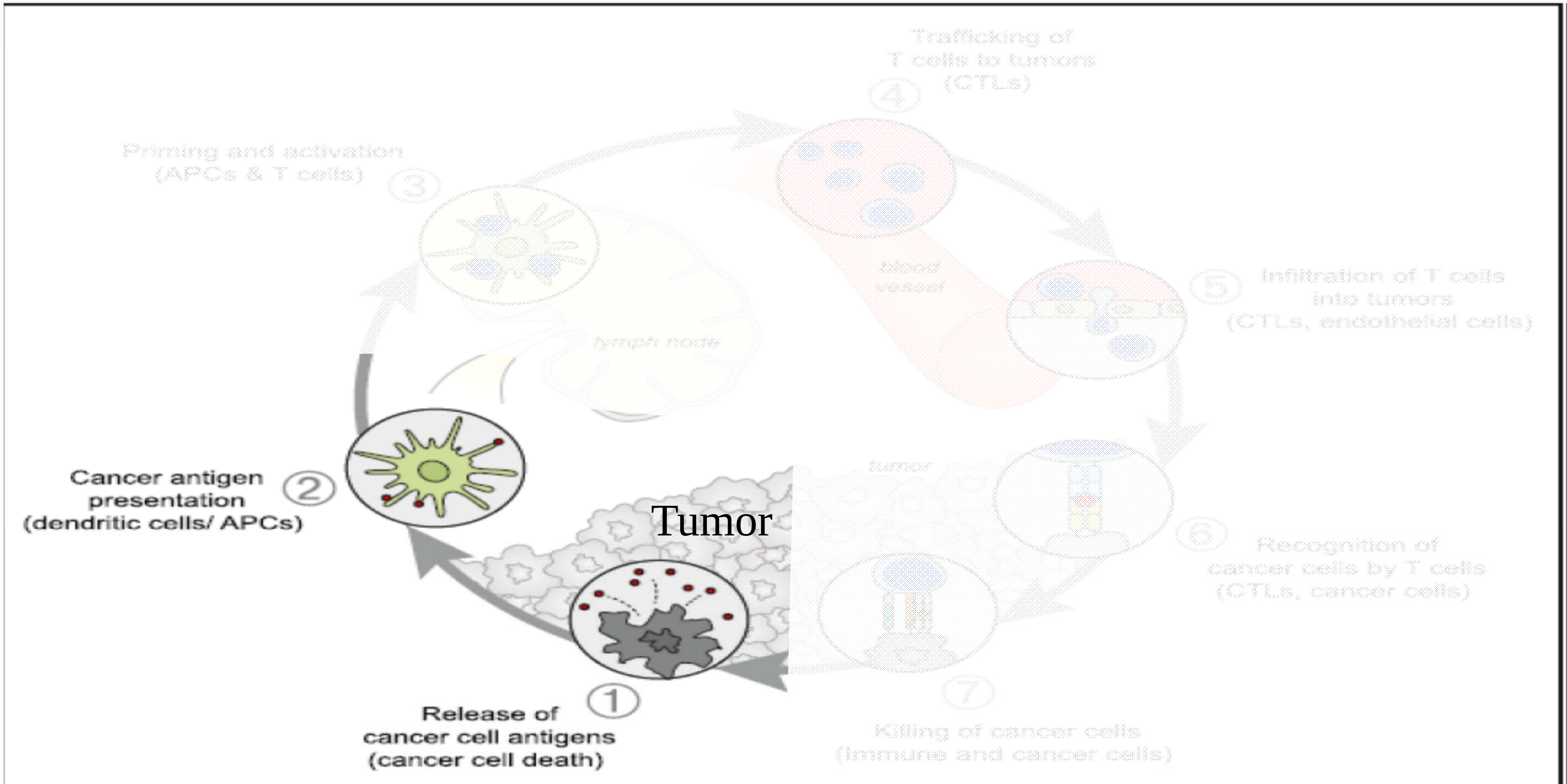
- Pathogen and antigen specific response
- Lag time between exposure and response
- Exposure leads to immunological memory

The Cancer detection by Immune system



Chen and Mellman Immunity 39; 2013

The Cancer detection by Immune system



Chen and Mellman Immunity 39; 2013

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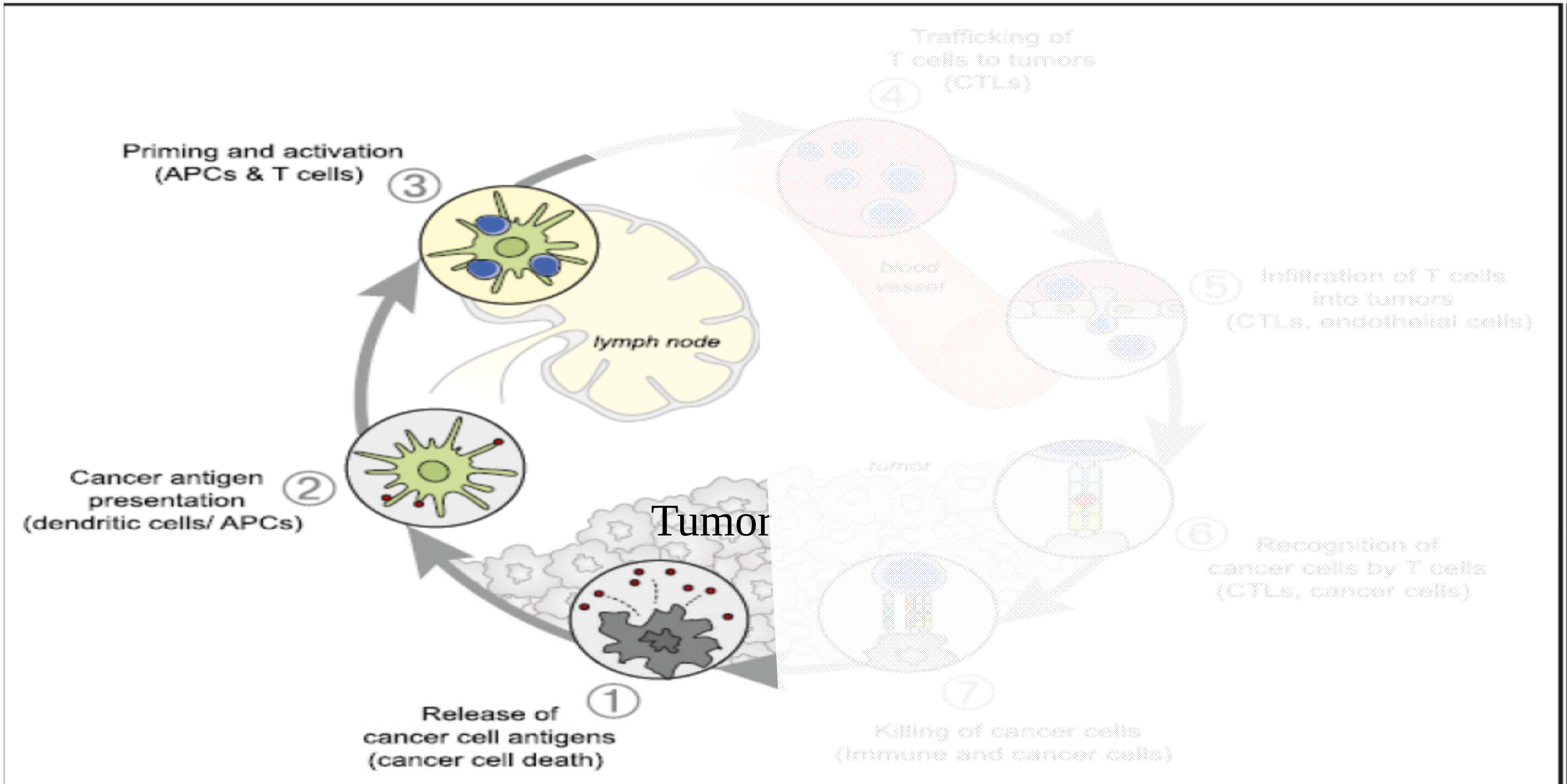

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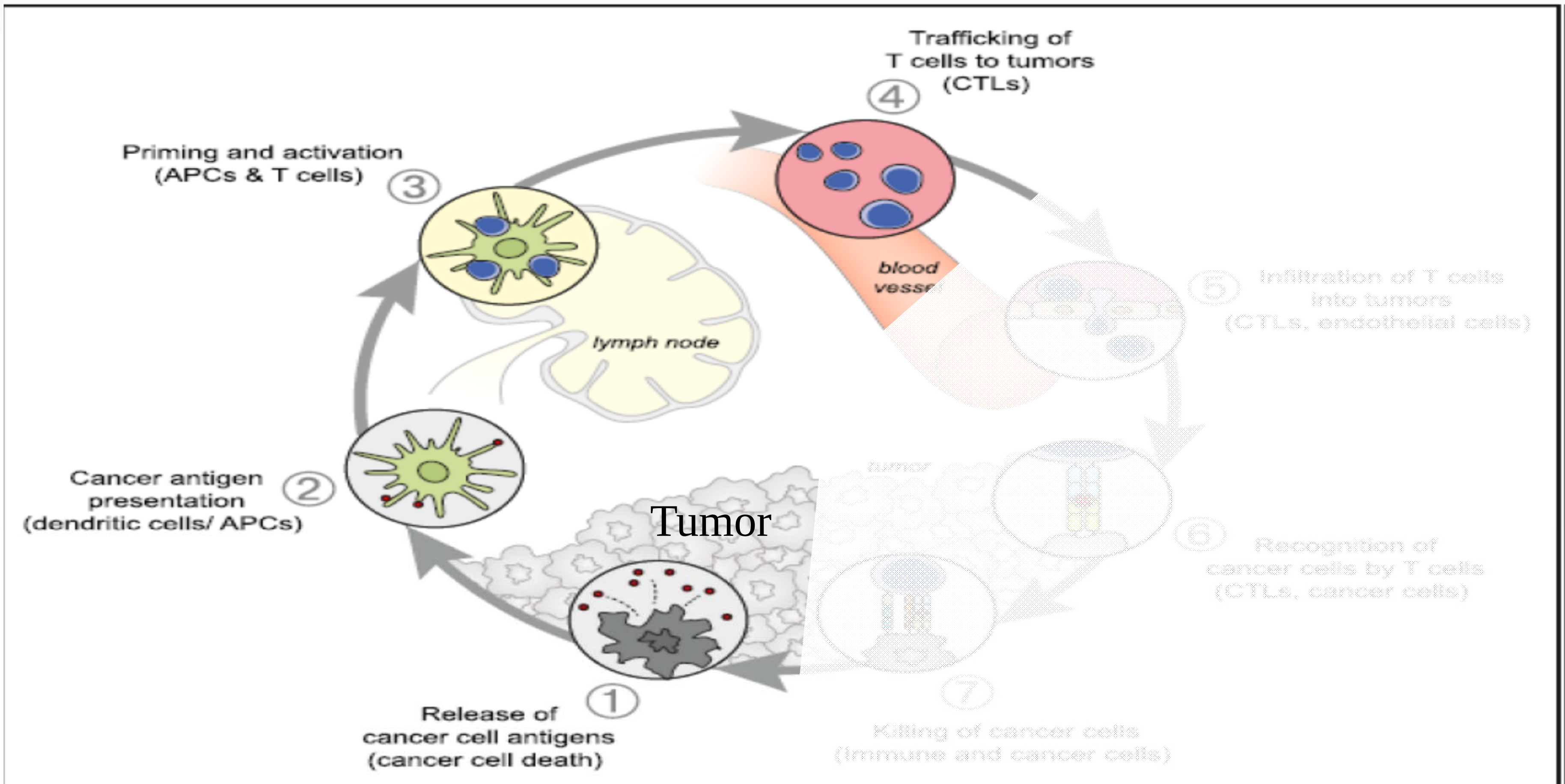

Chen and Mellman Immunity 39; 2013

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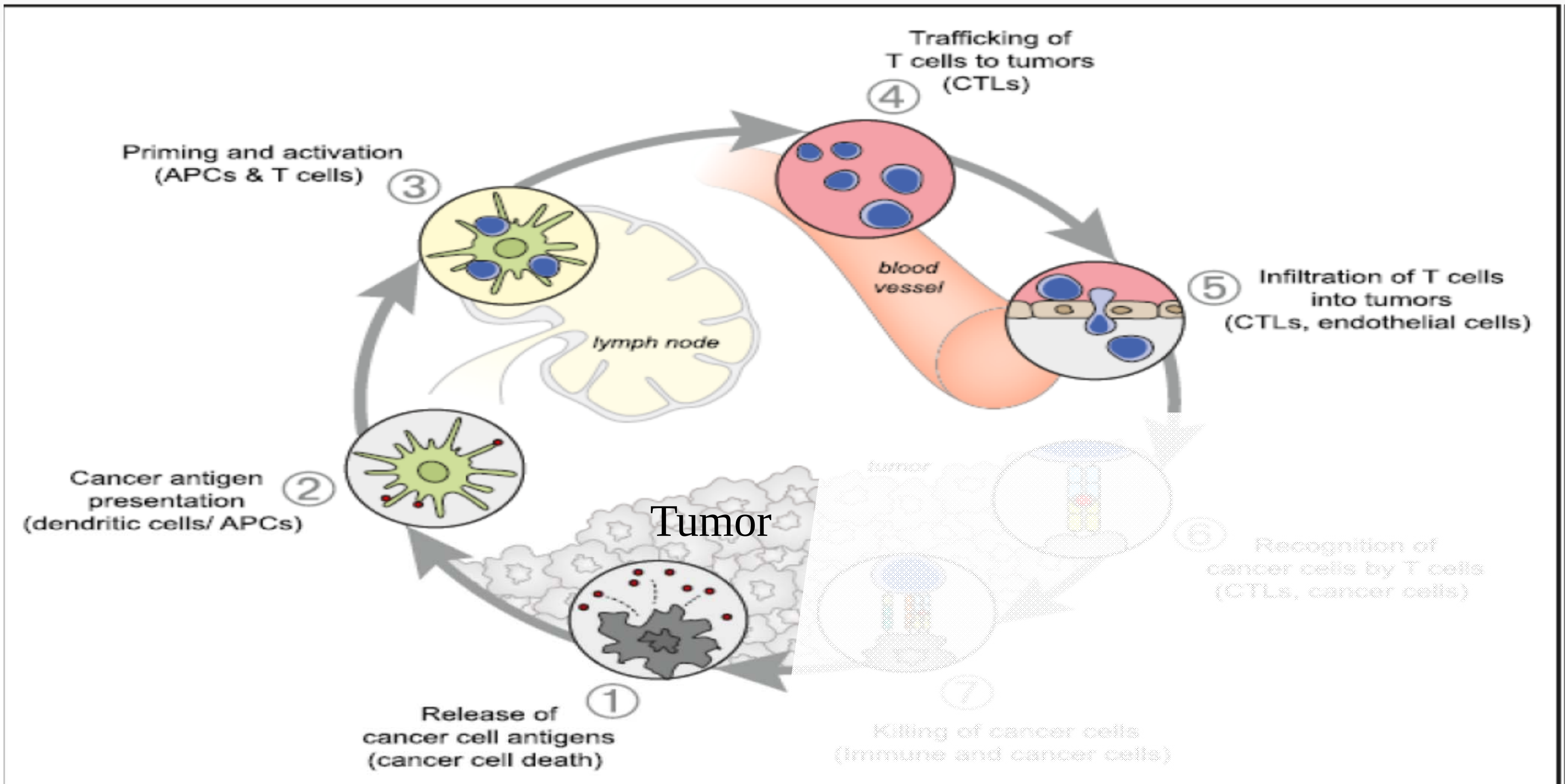

Chen and Mellman Immunity 39; 2013

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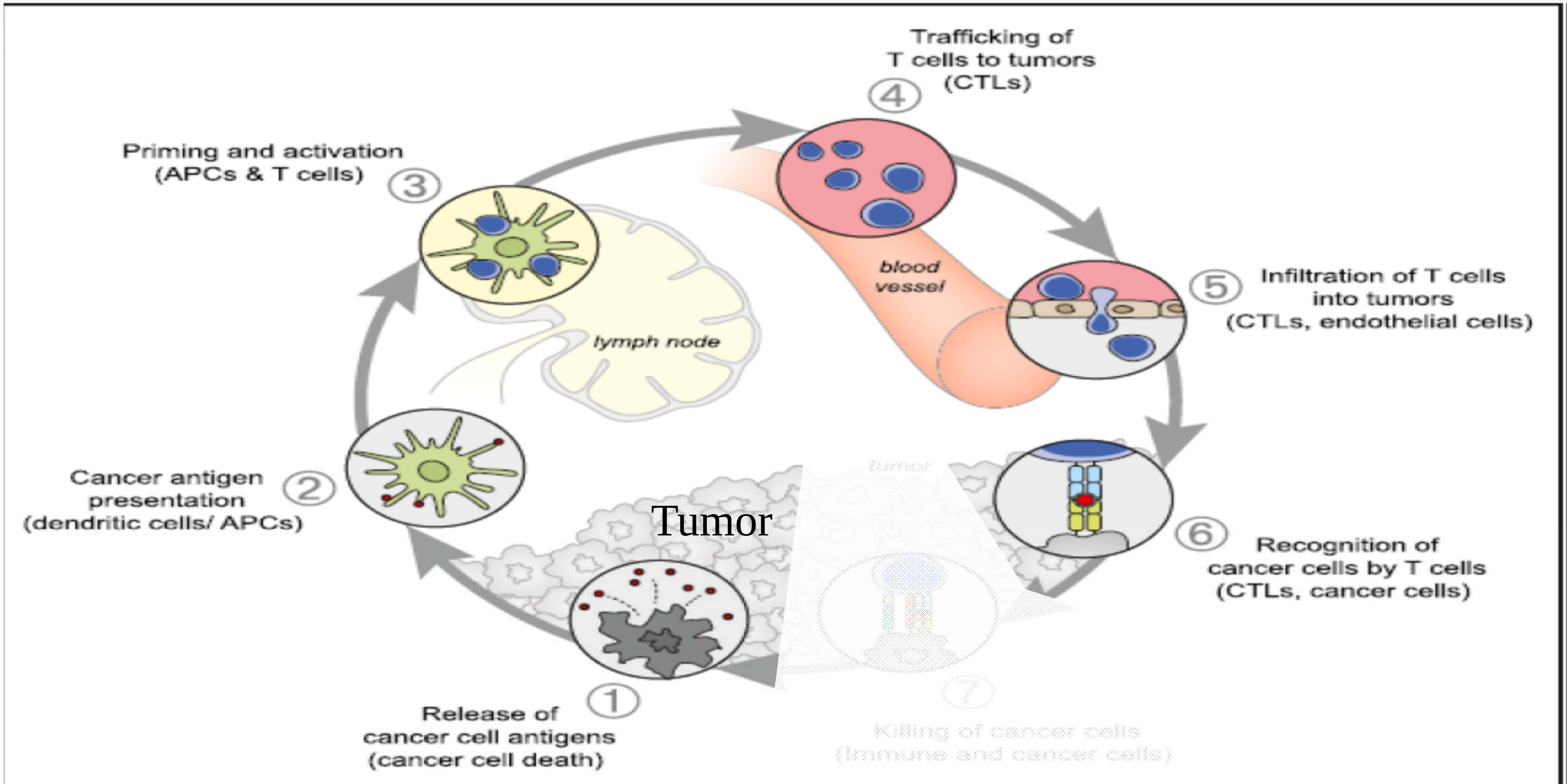

Chen and Mellman Immunity 39; 2013

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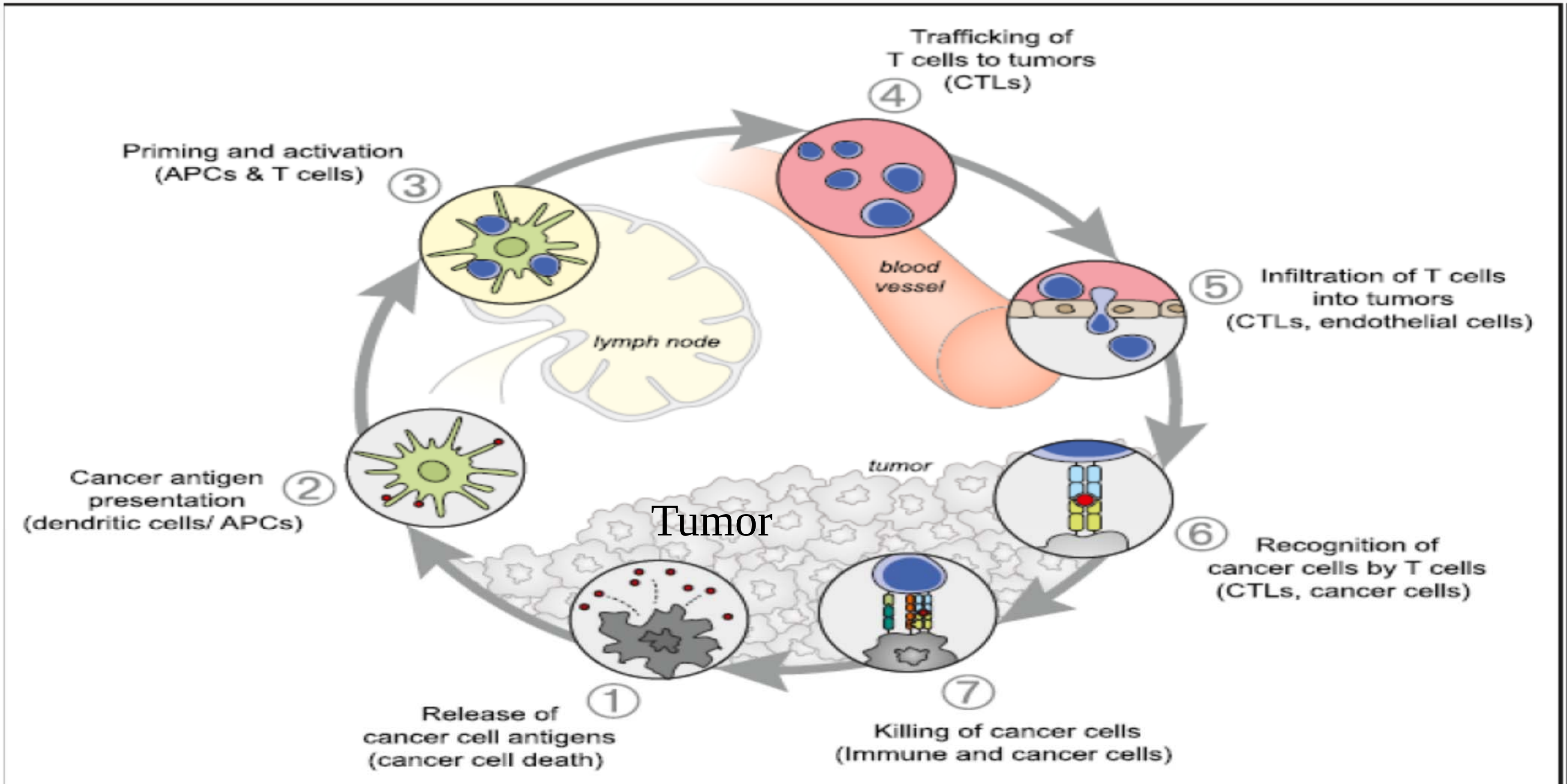
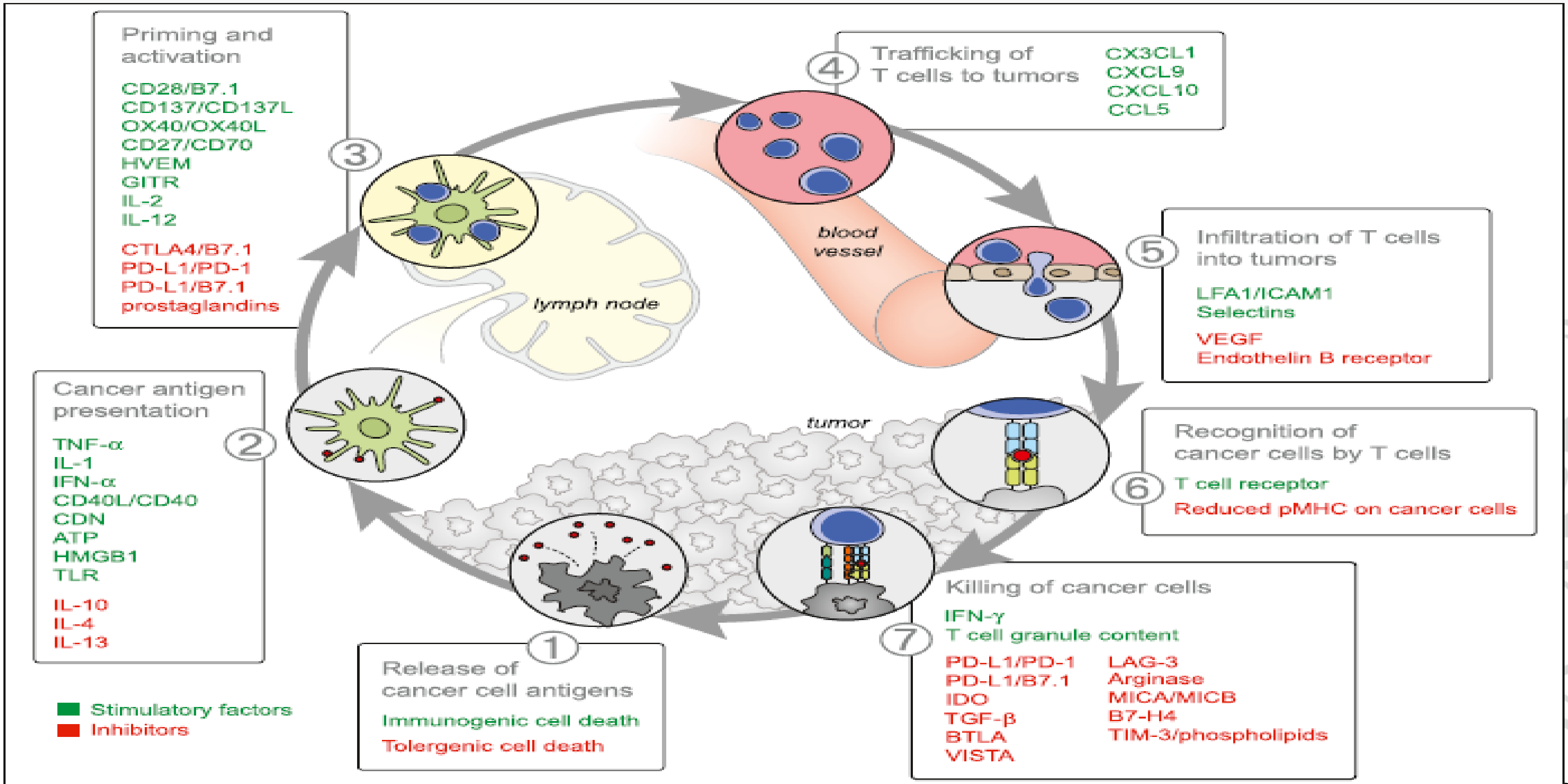


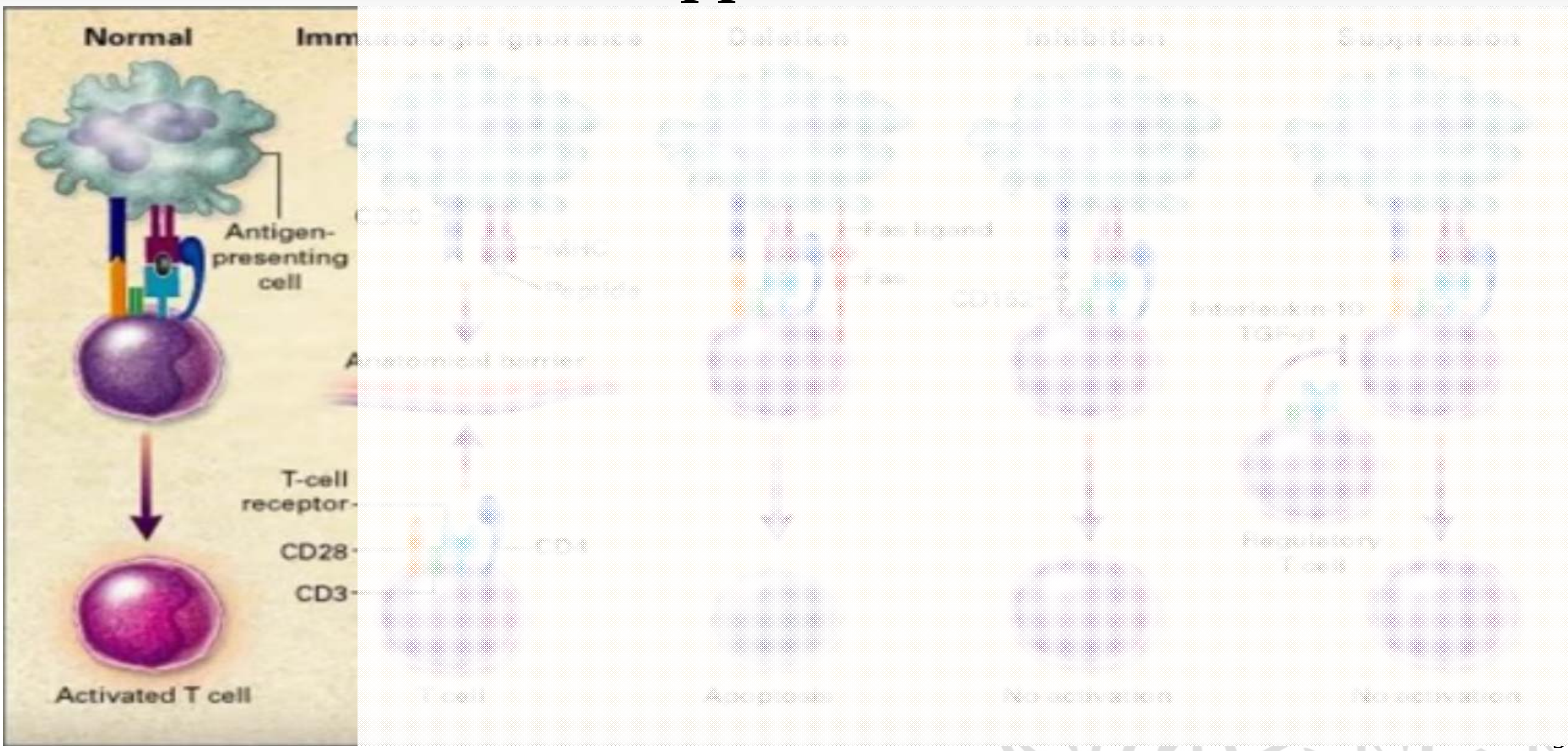
Chen and Mellman Immunity 39; 2013

The Cancer Immunity Cycle



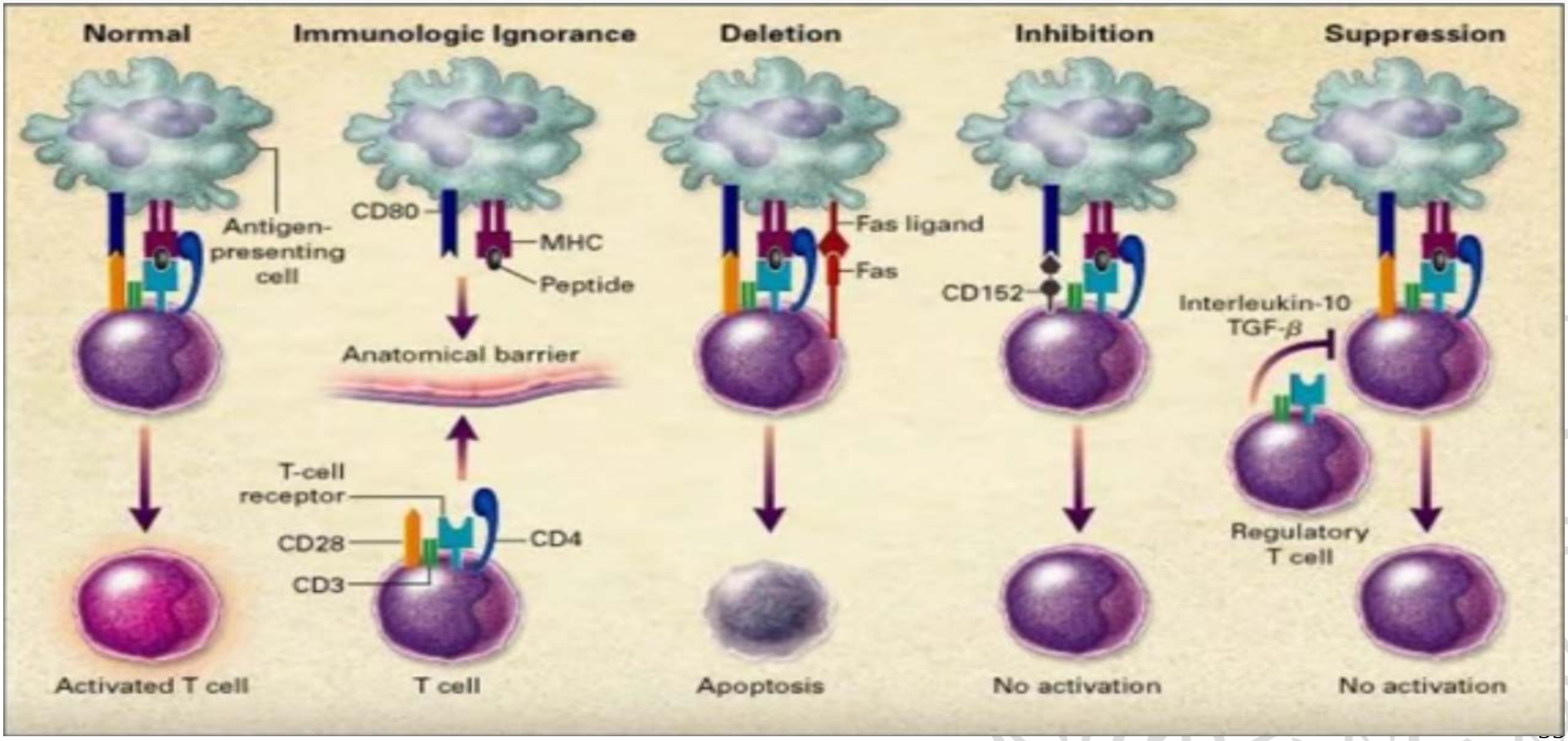
Chen and Mellman Immunity 39, 2013

Cancer - Immunosuppression



https://www.youtube.com/watch?v=3hlGq-3F1uQ

Cancer - Immunosuppression



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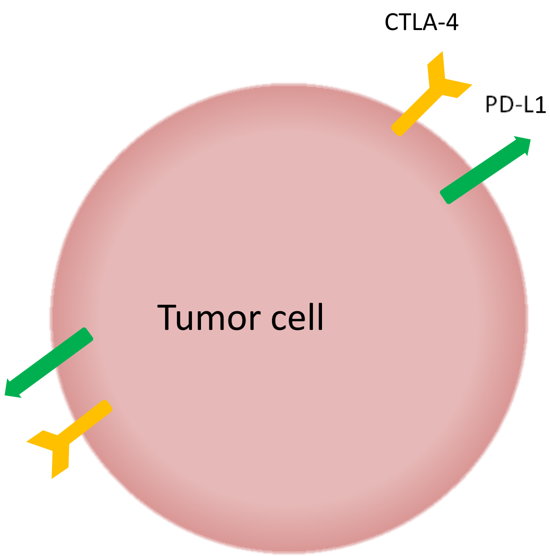
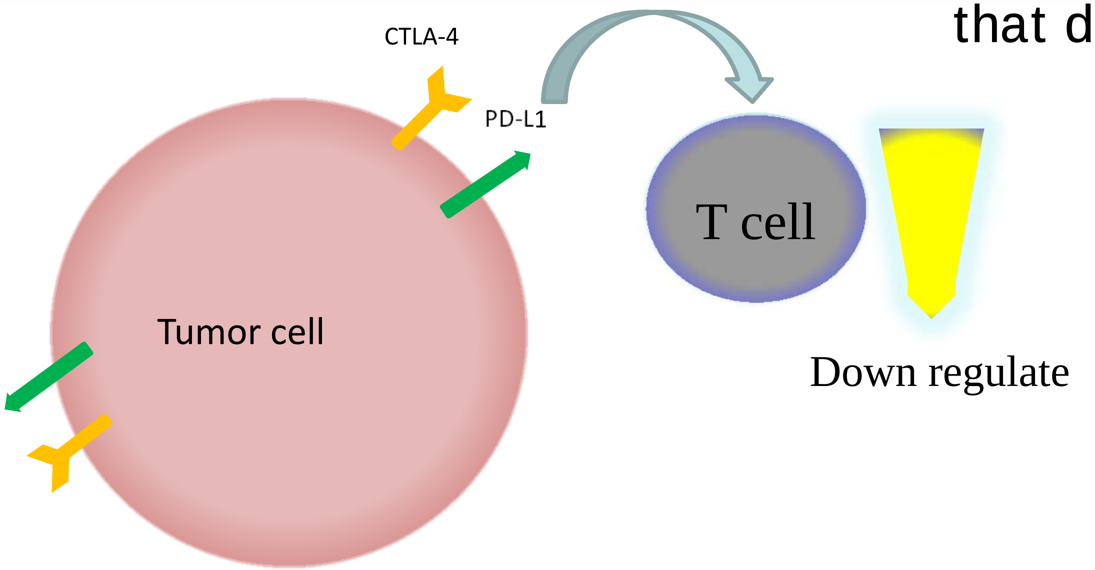
Radiation and Immunotherapy



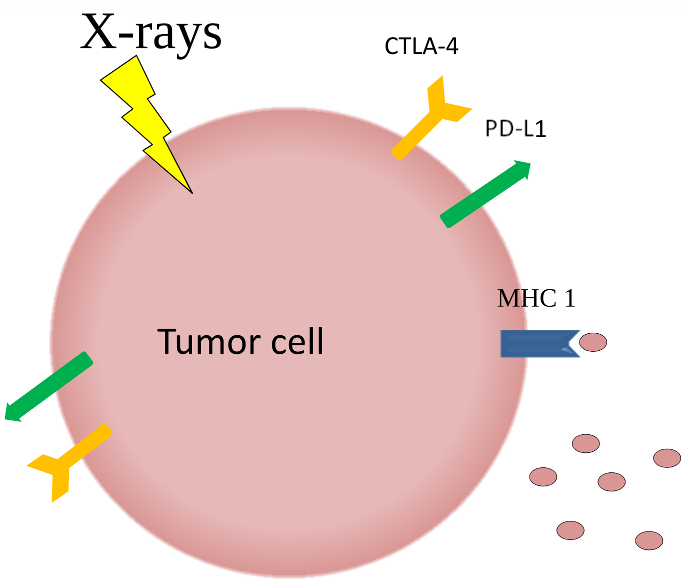
- To kill tumor cells by the immune system
  1. Induce tumor cells to release tumor specific antigens.
  2. Suppress inhibitory molecules/receptors.

Radiation and Immunotherapy



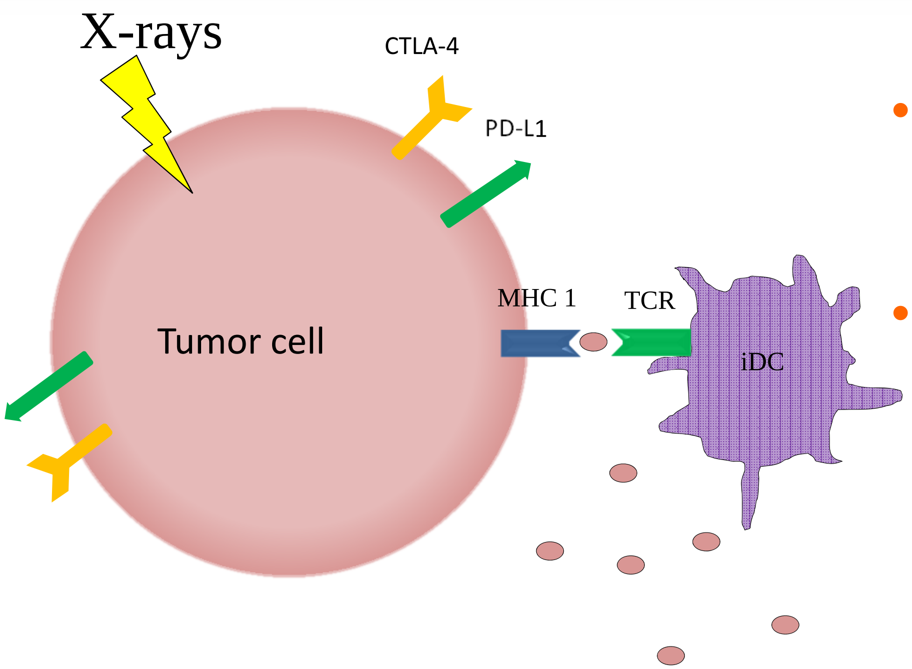
- CTLA-4 and PD-L1 are inhibitory receptors that down regulate T cell function.

Radiation and Immunotherapy



- CTLA-4 and PD-L1 are inhibitory receptors that down regulate T cell function.
- Radiation increases the expression of death receptors called MHC 1 and promotes the release of tumor antigens.

Radiation and Immunotherapy



- CTLA-4 and PD-L1 are inhibitory receptors that down regulate T cell function.
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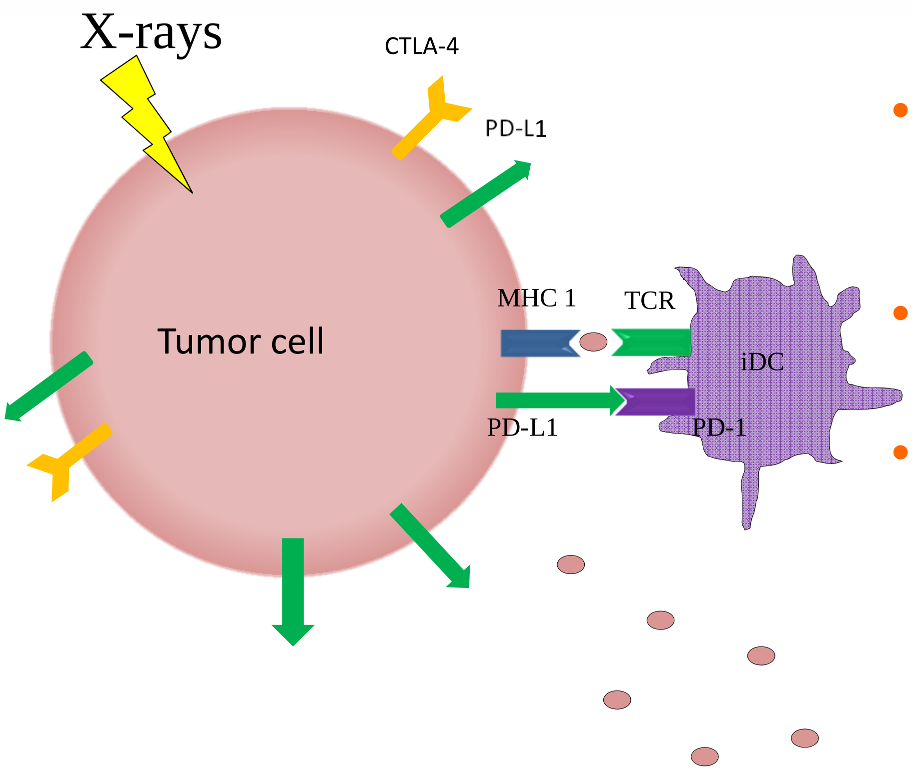
- Macrophages and dendritic phagocytes picks up the tumor antigens.

Radiation and Immunotherapy



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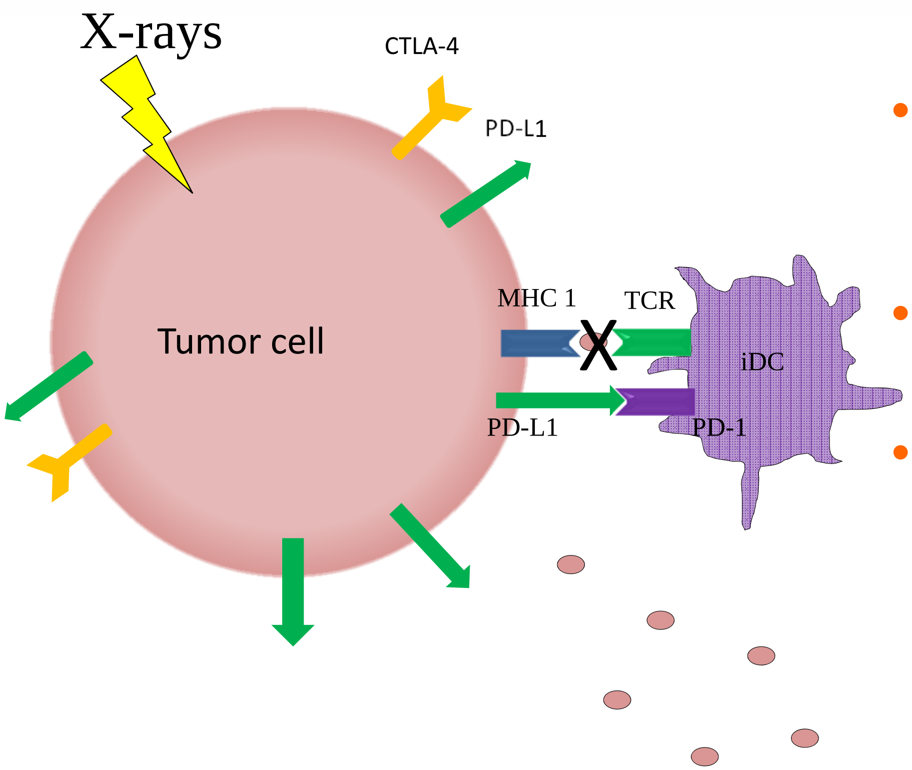
Radiation and Immunotherapy



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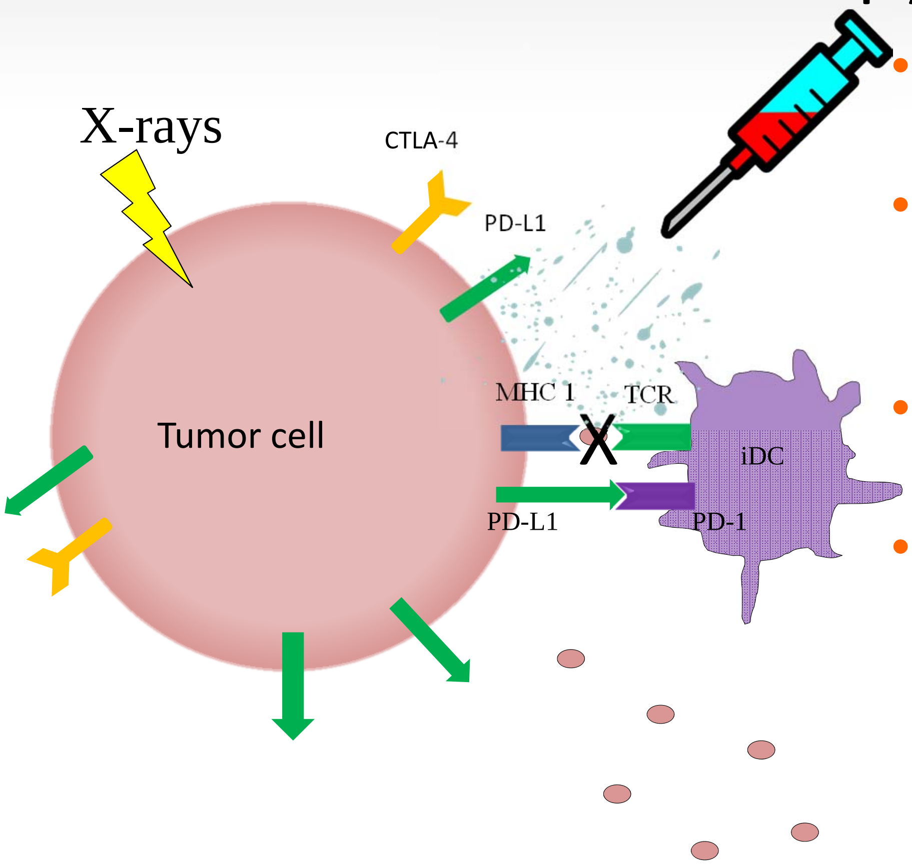
Radiation and Immunotherapy



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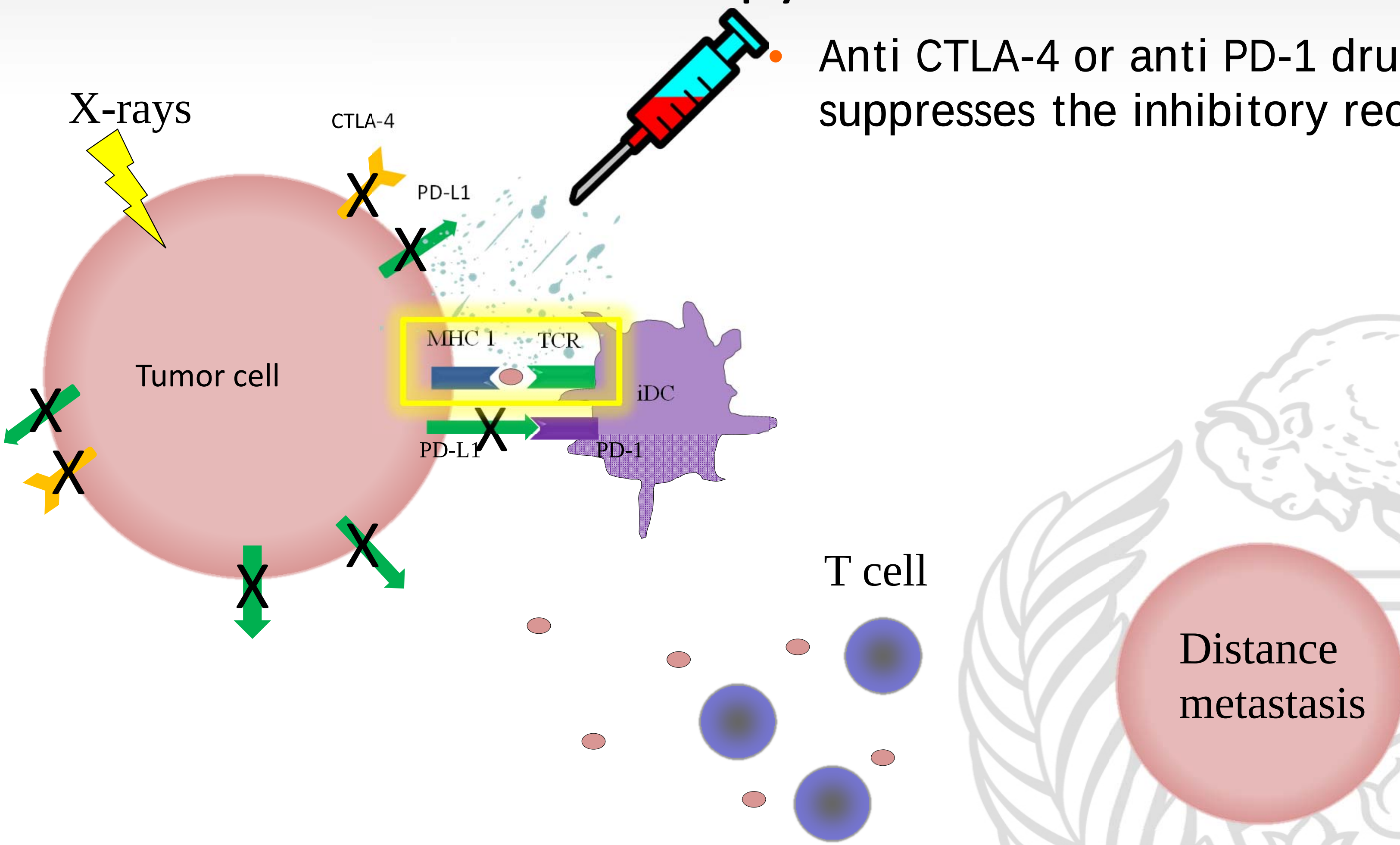
Radiation and Immunotherapy

- Anti CTLA-4 or anti PD-1 drugs/antibodies suppresses the inhibitory receptors.



Radiation and Immunotherapy

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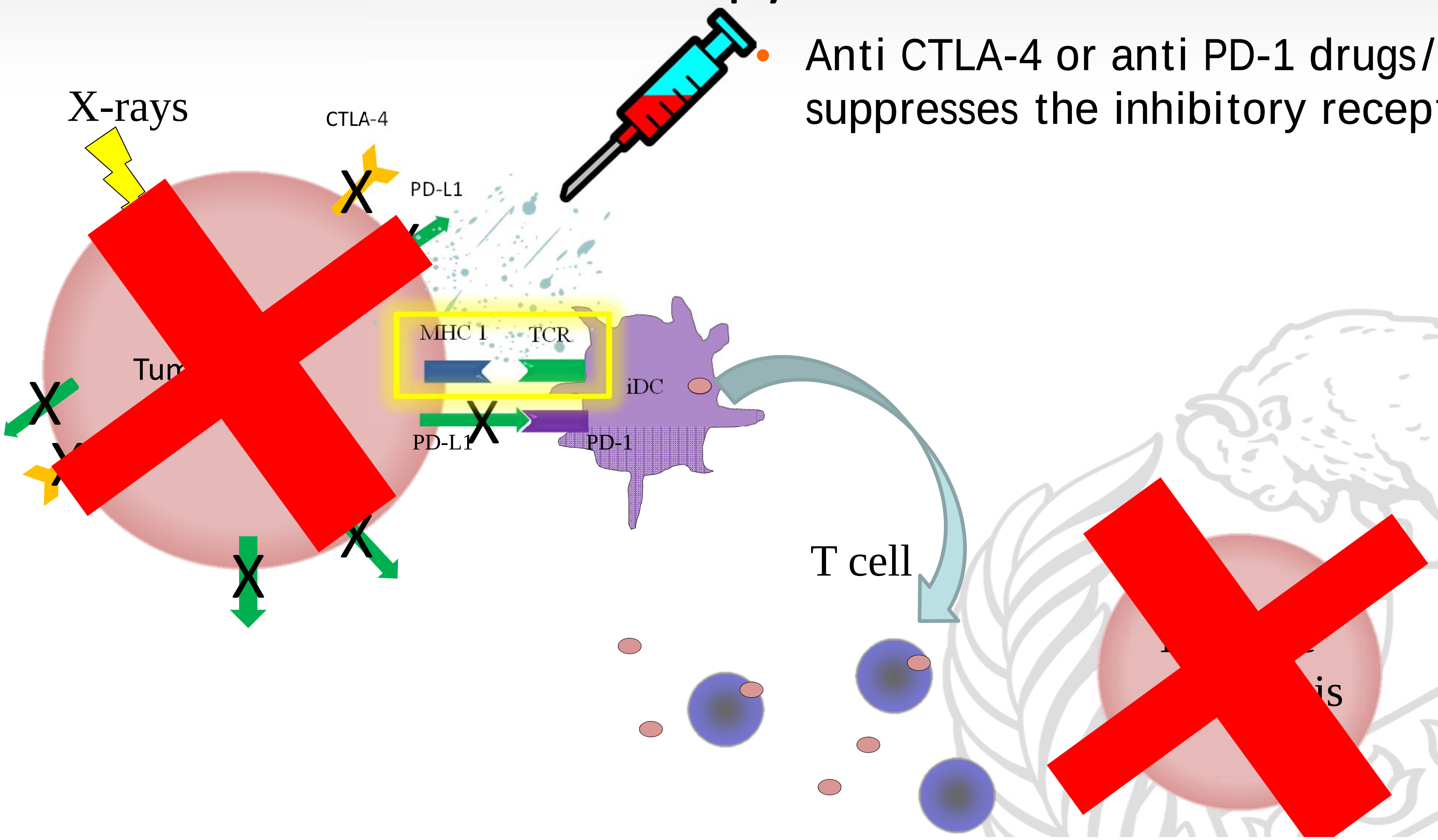

Radiation and Immunotherapy

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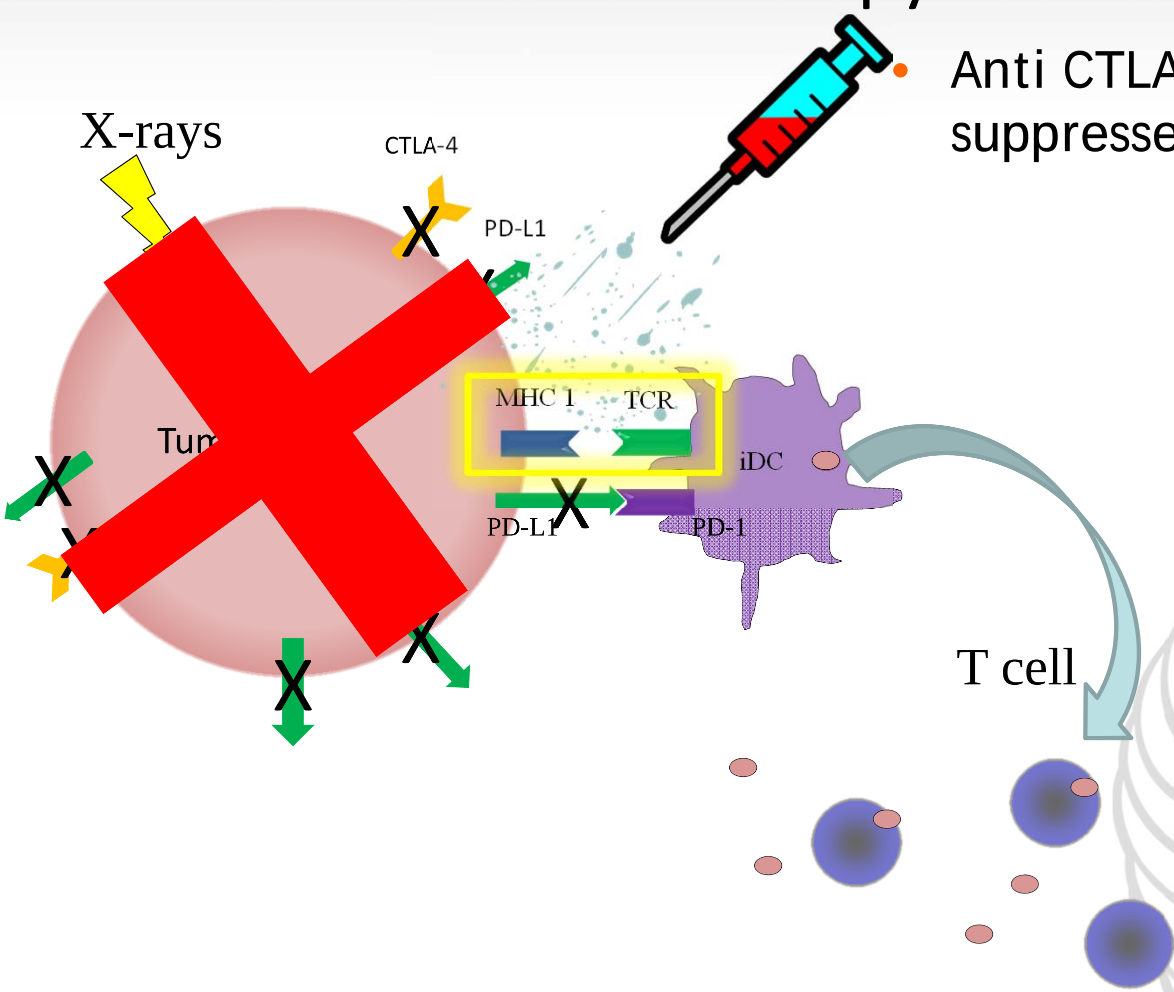
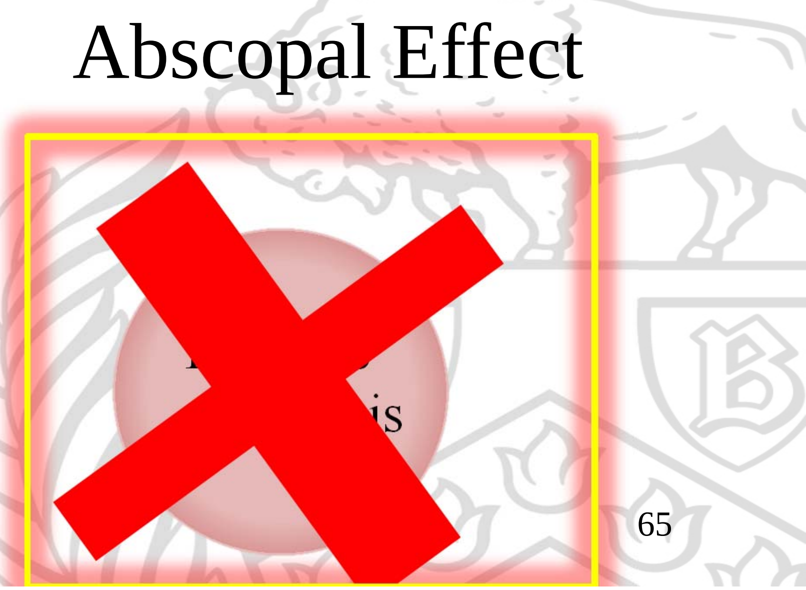




Abscopal Effect

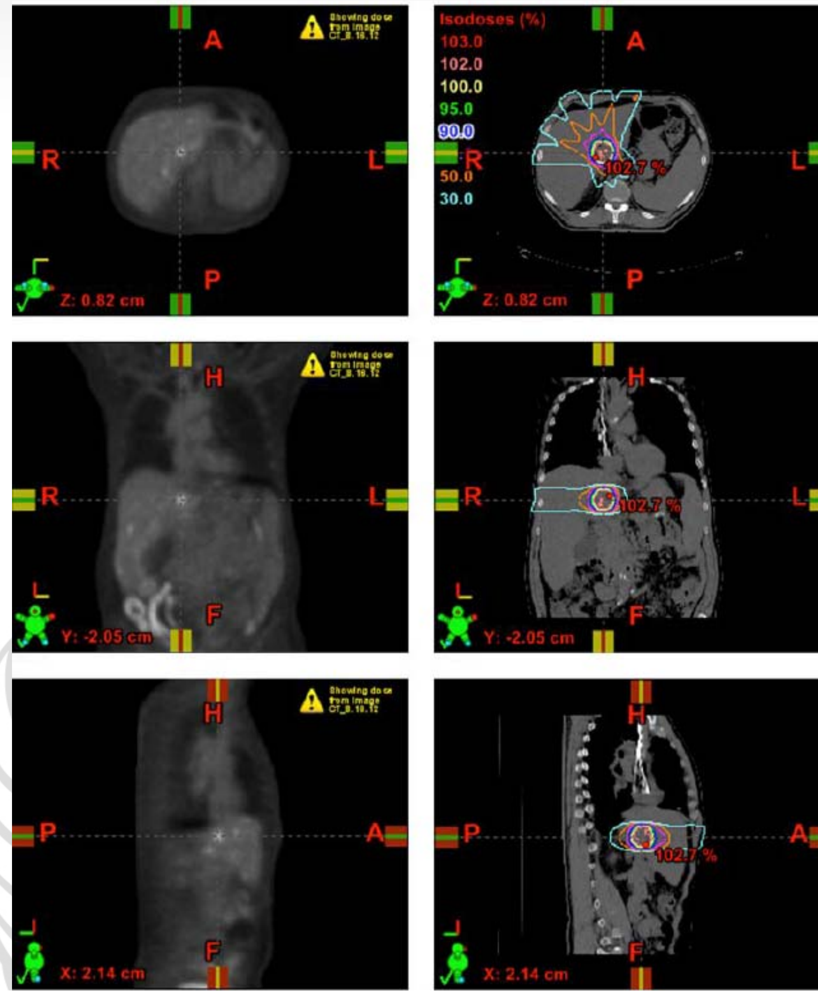
- Is a phenomenon in the treatment of metastatic cancer where localized radiation treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the scope of the localized treatment.

- Combination of RT and immunotherapy are resulted in successful treatment of:
  - Metastatic breast cancer
  - Colorectal cancer
  - Lung cancer
  - Melanoma

Patient with Metastatic NSCLC

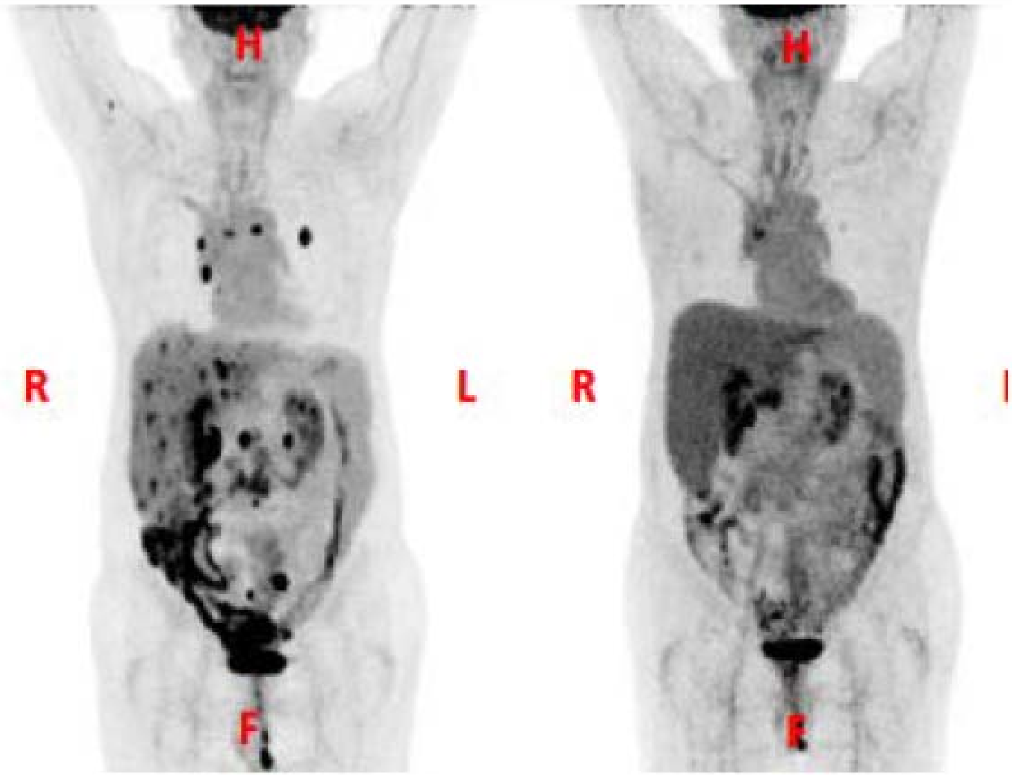
Progression after 3 lines of chemo: Multiple lung, bone and liver metastasis

Slide courtesy of Silvia C Formenti

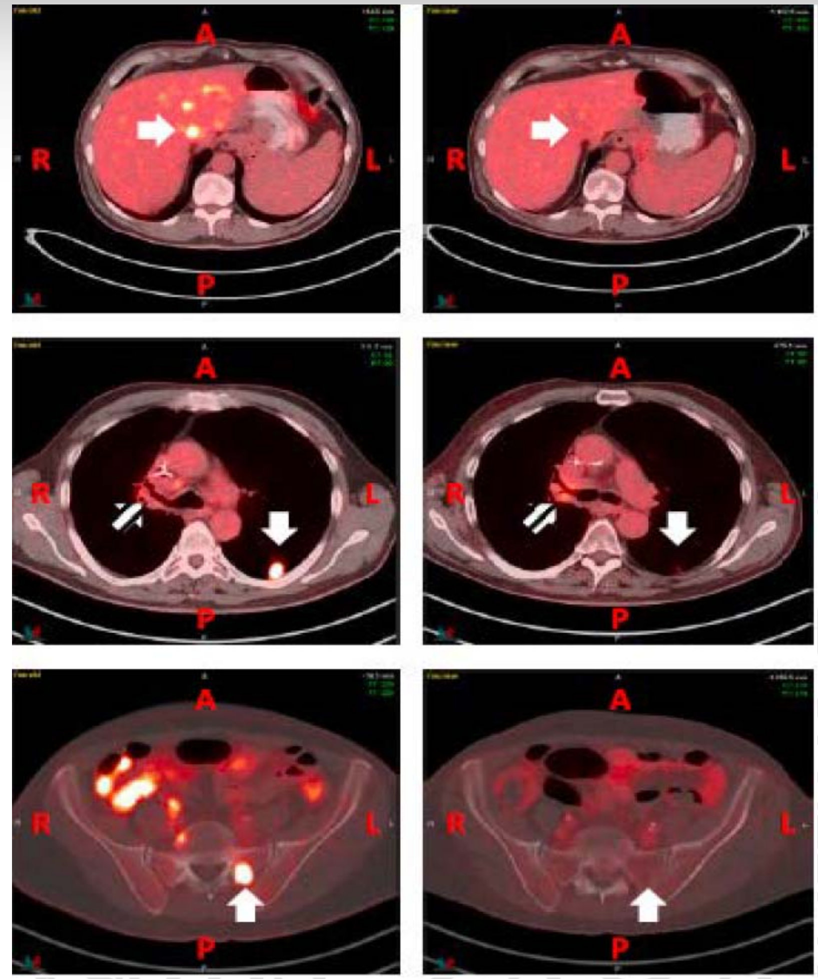


RT to one liver met 6 Gy x 5 (TD 30 Gy) + lpilimumab

Metastatic NSCLC: Response to RT + ipilimumab



August 2012 January 2013

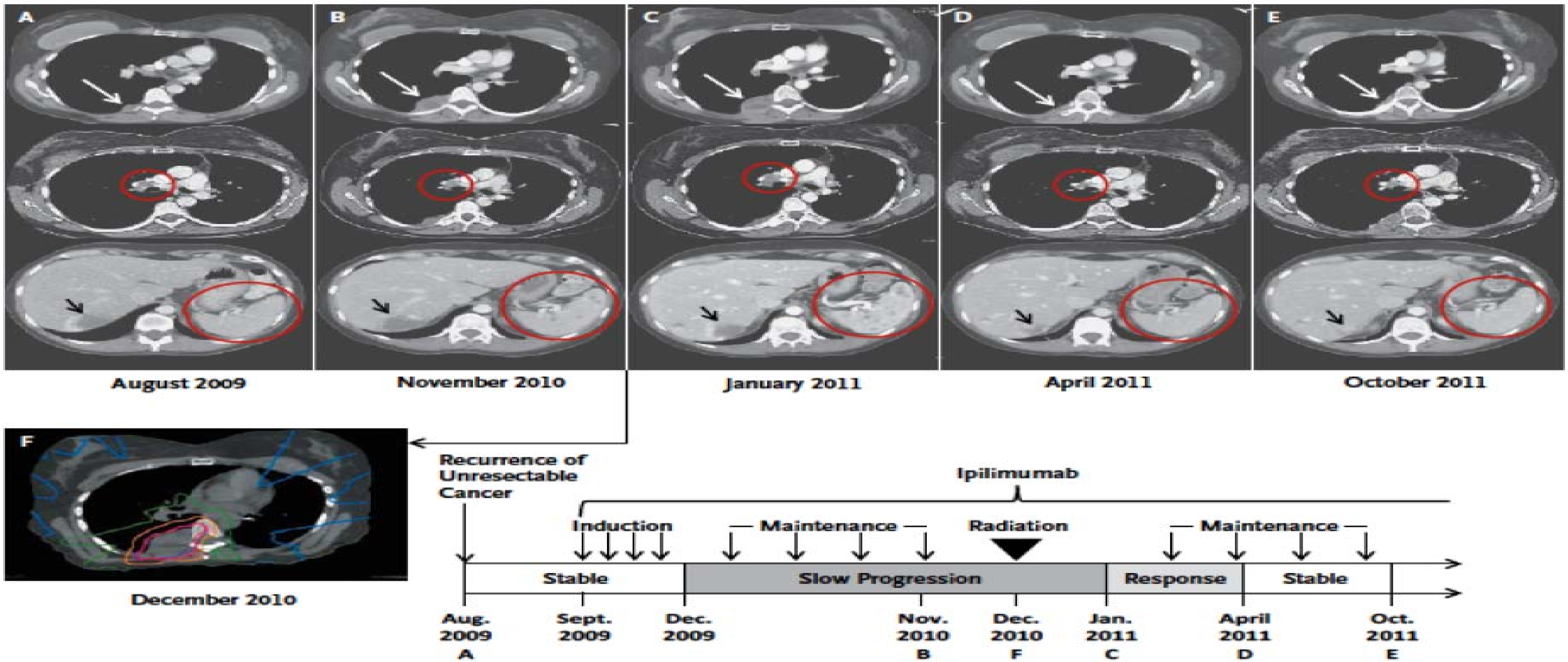


August 2012 January 2013

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma



Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice

JCI, 2014

Liufu Deng,[1] Hua Liang,[1] Byron Burnette,[1] Michael Beckett,[1] Thomas Darga,[1] Ralph R. Weichselbaum,[1] and Yang-Xin Fu[2]

[1]Department of Radiation and Cellular Oncology, The Ludwig Center for Metastasis Research, and [2]Department of Pathology, University of Chicago, Chicago, Illinois, USA.

Am J Clin Oncol. 2015 Feb;38(1):90-7. doi: 10.1097/COC.0b013e3182868ec8.

Immune-priming of the Tumor Microenvironment by Radiotherapy: Rationale for Combination With Immunotherapy to Improve Anticancer Efficacy.

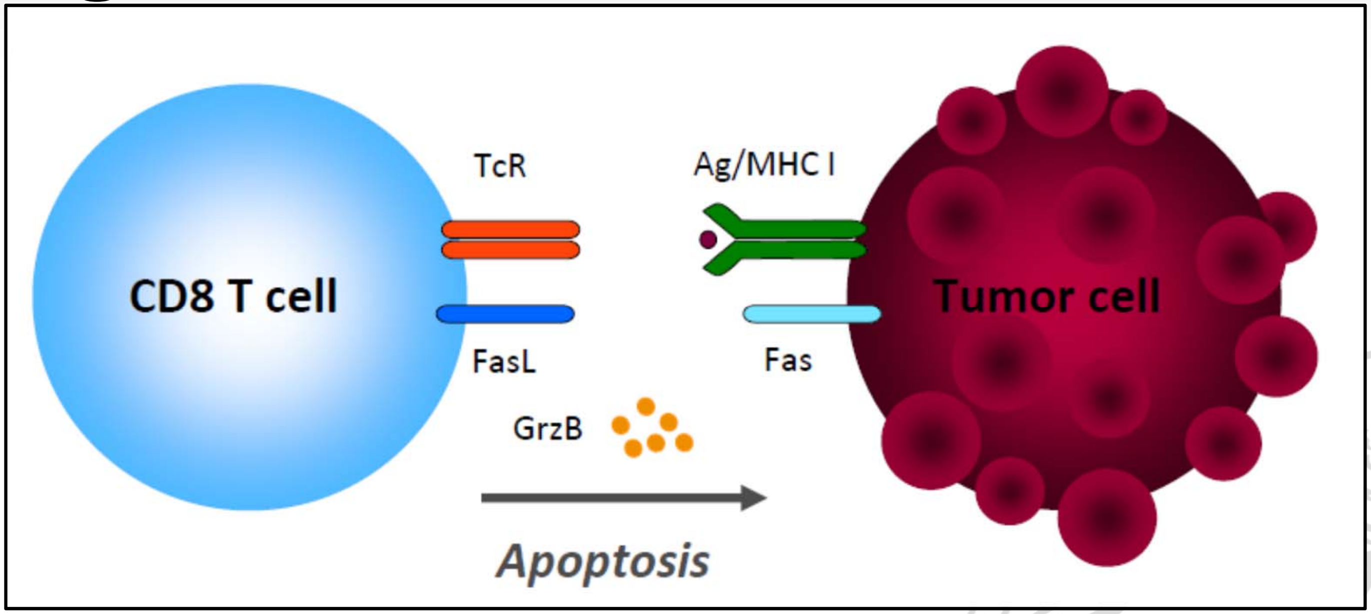
Shahabi V[1], Postow MA, Tuck D, Wolchok JD.

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Anti-PD-1 Blockade and Stereotactic Radiation Produce Long-Term Survival in Mice With Intracranial Gliomas

Zeng et al, 2013

Advantages of RT Based Cancer Immunotherapy



1. Exquisite specificity for target; limit collateral damage.
2. Target non-resectable tumors.
3. T cells can target tumors at sites throughout the body.
4. Long-lasting protection.

Slide courtesy of Elizabeth Rapasky

Many questions remain:

- Optimal site to irradiate in metastatic disease.
- Patient selection
- Sequencing of radiotherapy/immunotherapy
- RT dose and fractionation
- Best combinations

Summary

- Preclinical and clinical evidence suggest that local radiotherapy can contribute to the efficacy of cancer immunotherapy, by rendering the irradiated tumor more immunogenic.
- Radiotherapy can be harnessed as an adjuvant to immunotherapy as it may convert non-responding patients to responders to same immunotherapy.
- Dose/fractionation and sequencing of radiotherapy need to be explored in combination with immunotherapy strategies.

What are the mechanisms of Tumor Escape from Immune Response ?

1. Target cells down regulate the proteins responsible for presenting the tumor antigens to the immune system.
2. There is a anatomical barrier preventing the T cells from reaching the target cell
3. Target cell can use a FAS ligand to promote T cell apoptosis
4. Regulatory T cells could send false messages (TGF–β and IL-10) to the killer T cells preventing the T cells from killing the target cells
5. All of the above

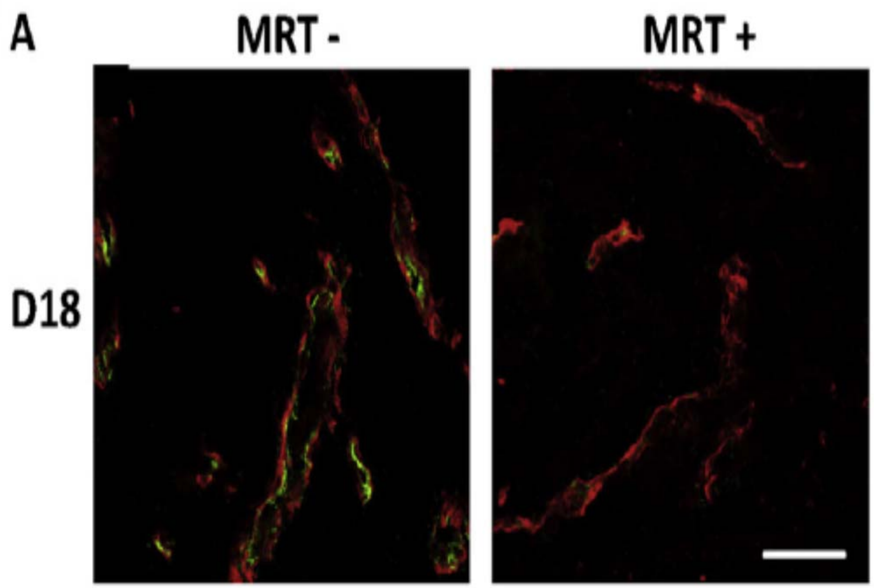
Thank You

Mechanisms of Tumor Escape from Immune Response

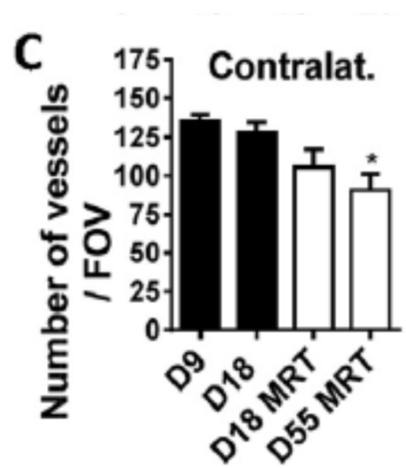
- Loss of MHC or TAP – proteins responsible for transporting and presenting foreign substances to the immune system.
- Secretion of immunosuppressive factors
  - e.g. TGF-b, IL-10
- T cells don’t penetrate solid tumors
- Exhaustion of T cells

Decrease in tumor blood volume, and vessel density

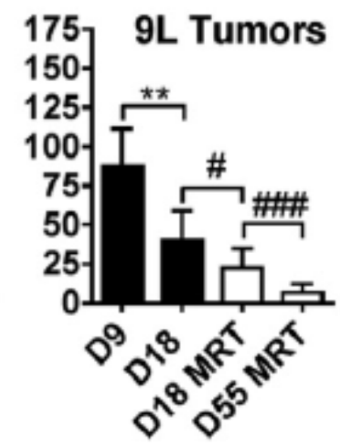
Control | MRT



Normal Cells

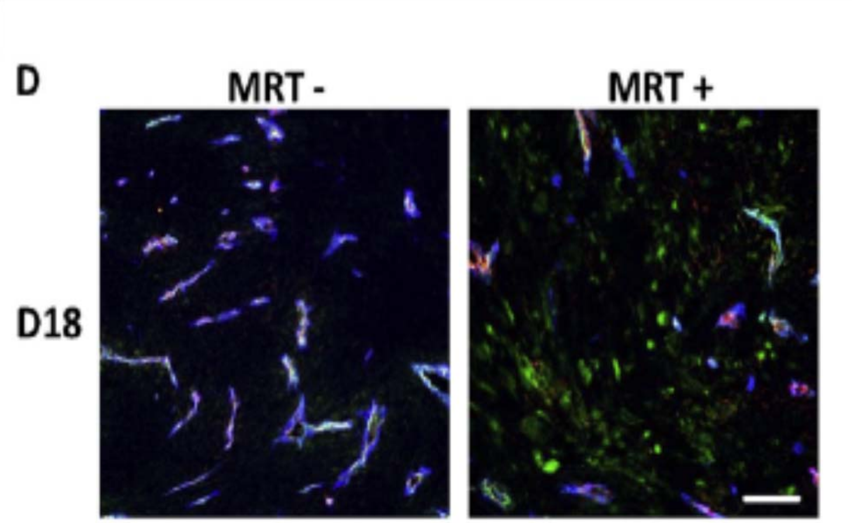


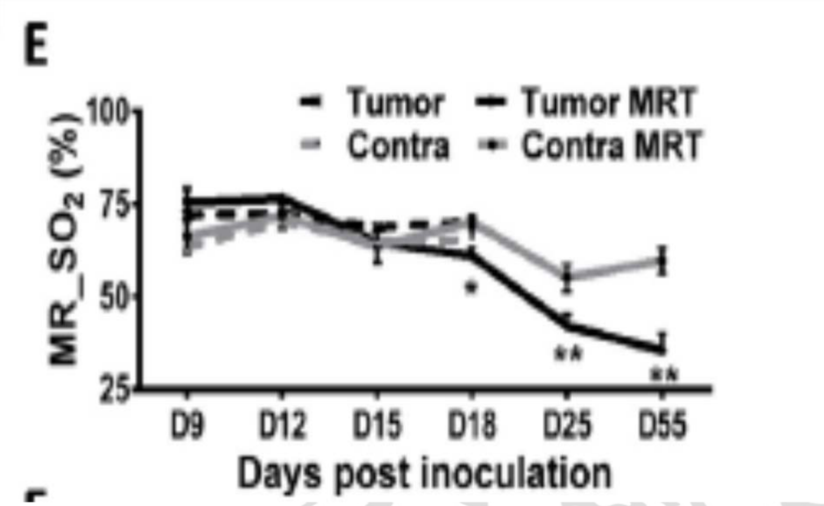
Tumor Cells



- RECA-1 (green labelling) is absent in MRT irradiated tumor cells
  - RECA-1 is a protein essential for DNA repair.
- Significant decrease in the fractional blood volume and in diameter of tumor vessel.

Decrease in tumor oxygenation





- Significant changes in blood volume causes hypoxia in tumors
  - Over-expression of GLUT1 (marker for hypoxia)
- MRT preferentially induces vessel damage in tumor cells which led to reduction of tumor oxygenation