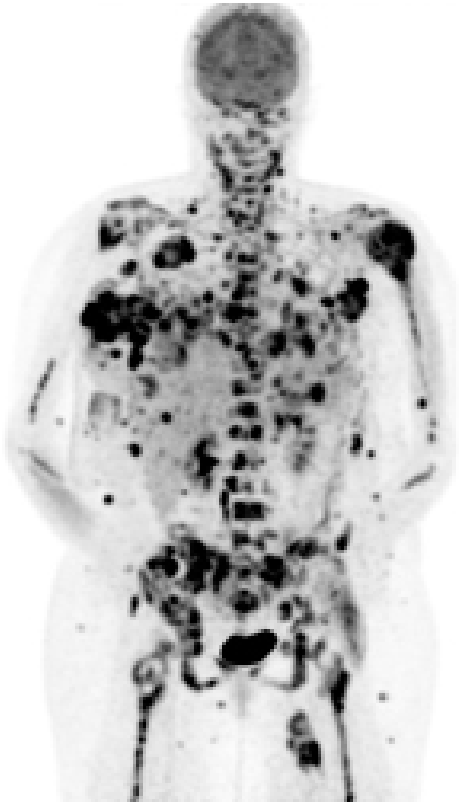
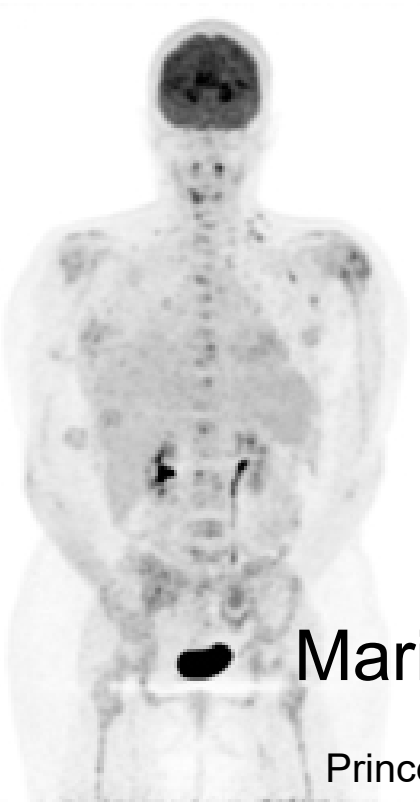
Biological response modifiers





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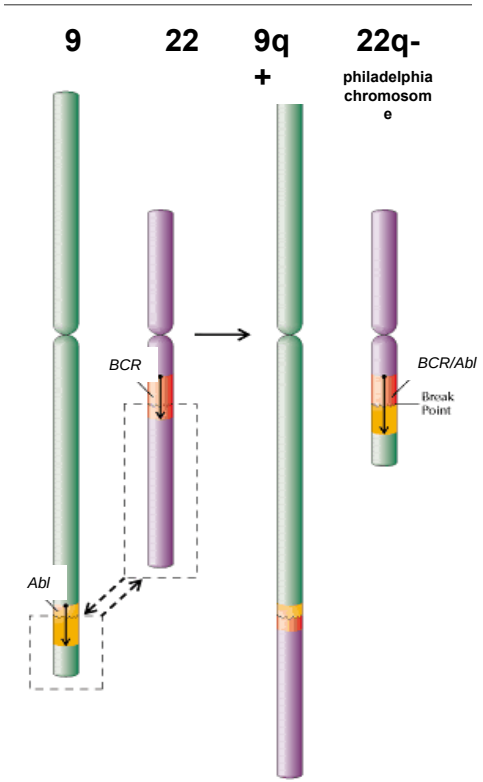
Learning objectives

- Identify different classes of biological response modifiers and how they work.
- Describe rationales to obtain a therapeutic index using biological response modifiers in cancer.
- Identify rationales to obtain a therapeutic index using biological response modifiers in radiotherapy.

Molecular targeting of cancer



Molecular targeting of cancer

original reports

Overall Survival, Progression-Free Survival, and Tumor Response Benefit Supporting Initial US Food and Drug Administration Approval and Indication Extension of New Cancer Drugs, 2003-2021

Daniel Tobias Michaeli, MS[1,2,3]; and Thomas Michaeli, MS[1,2,3,4]

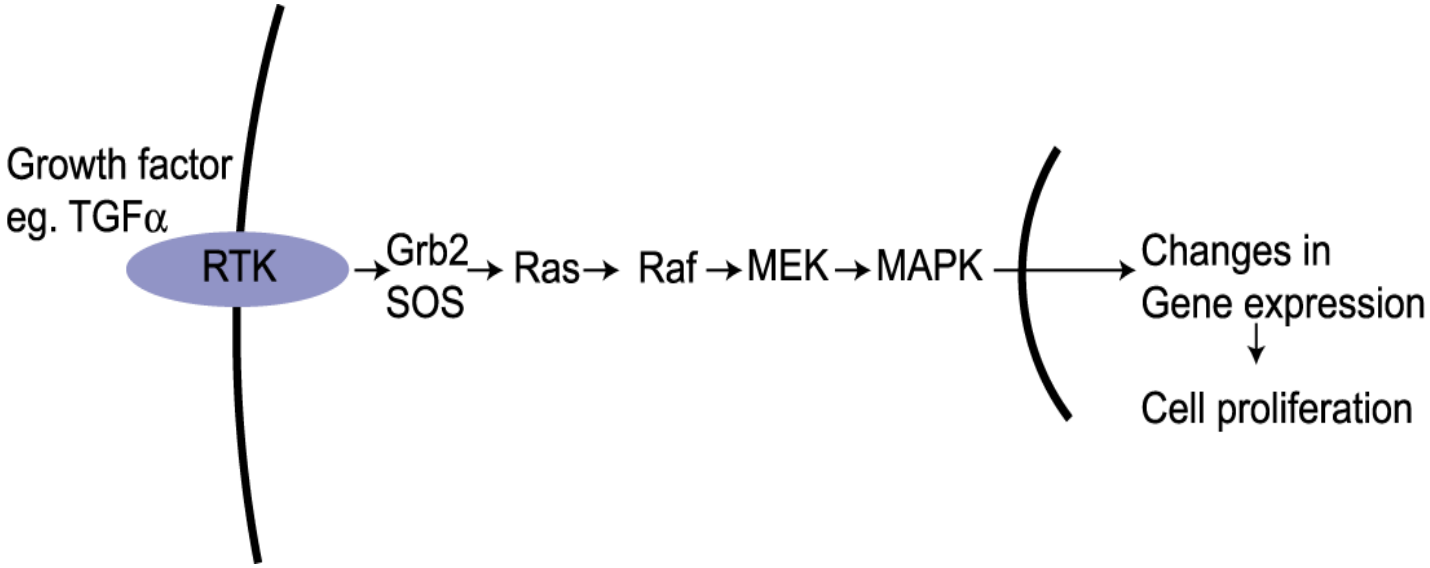
Journal of Clinical Oncology®
Volume 40, Issue 35 4095

- 124 new drugs for 374 cancer indications
- Overall survival increased by 2.8 months
- Progression free survival increased by 3.3 months

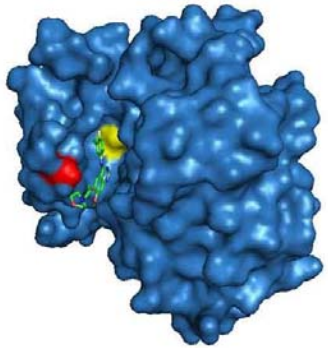
Biological response modifiers

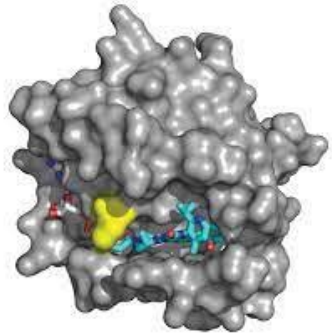
- New drugs designed to target the function of specific molecules
  - Small molecules
  - Biologics
- Can have low toxicity
- Can have extremely high specificity

Small molecules



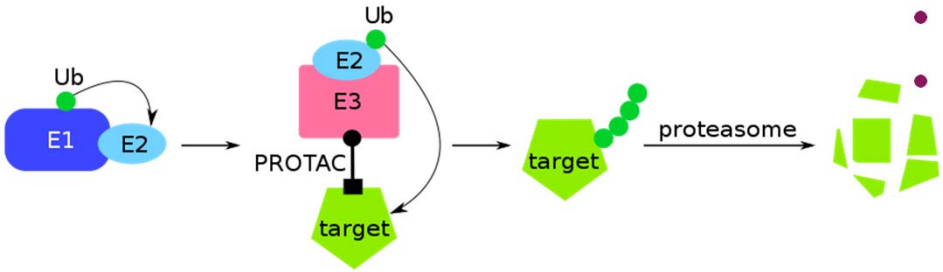
- Cell penetration
- Long development time

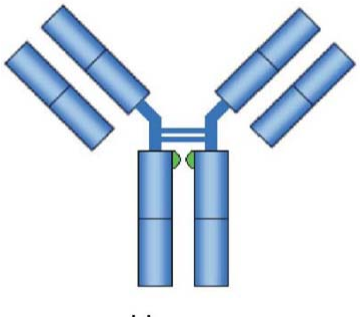


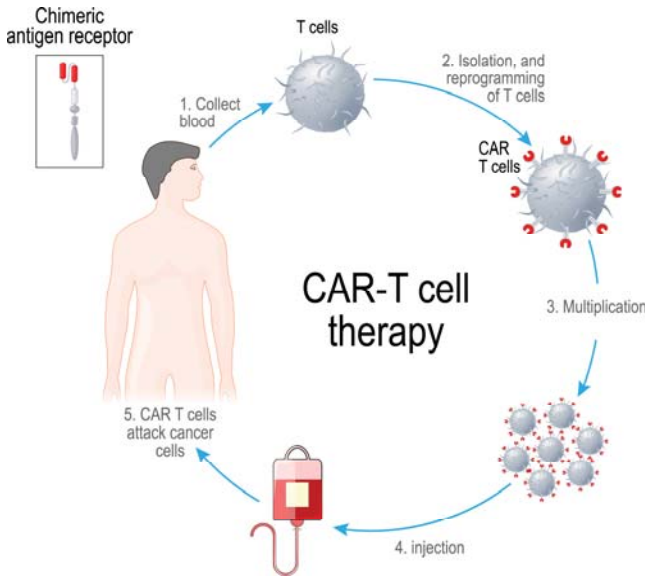


Small molecules

- Tyrosine Kinase Inhibitors
  - Bcr-Abl (Imatinib)
  - EGFR (Gefitinib)
- Other Function inhibitors
  - HIF2a (Belzutifan)
  - Braf-V600E (PLX3240)
  - Ras-G12C (AMG 510)
- Proteolysis Targeting Chimeras (PROTACS) and Molecular Glues
  - Bcl-XL (DT2216)
  - AR (ARV110)





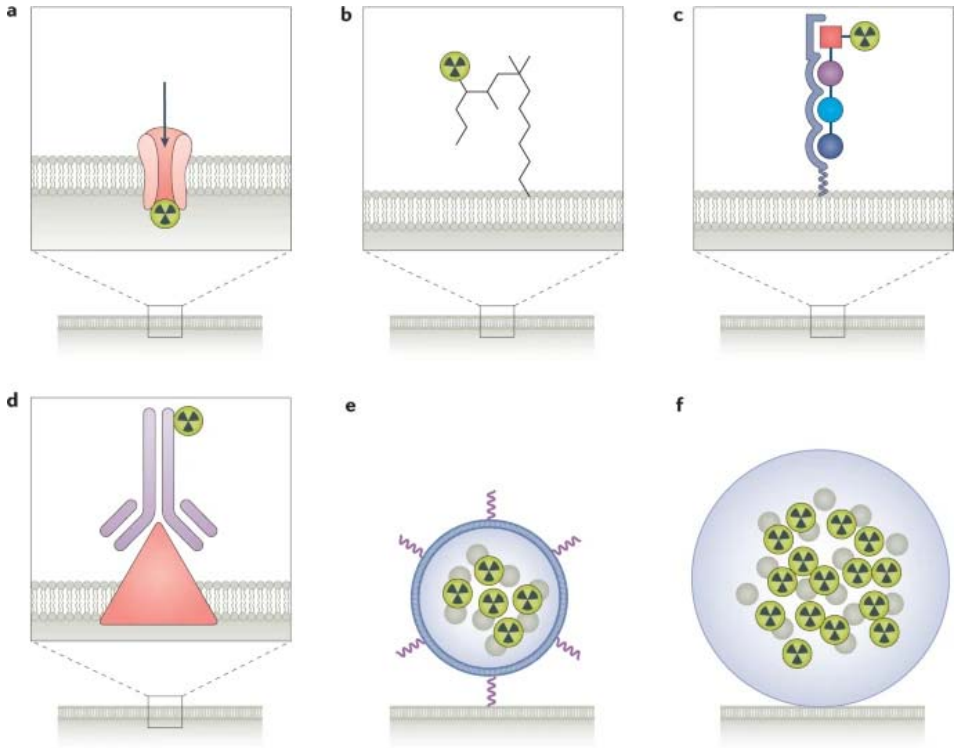


Biologics

- Antibodies
  - EGFR (Cetuximab)
  - VEGF (Bevacizumab)
  - PD-1 (Nivolumab)
  - CTLA-4 (Ipilumumab)
- Cells
  - CAR-T
- Peptides
- Nucleic acids

- Antibodies not cell permeable
- Faster development

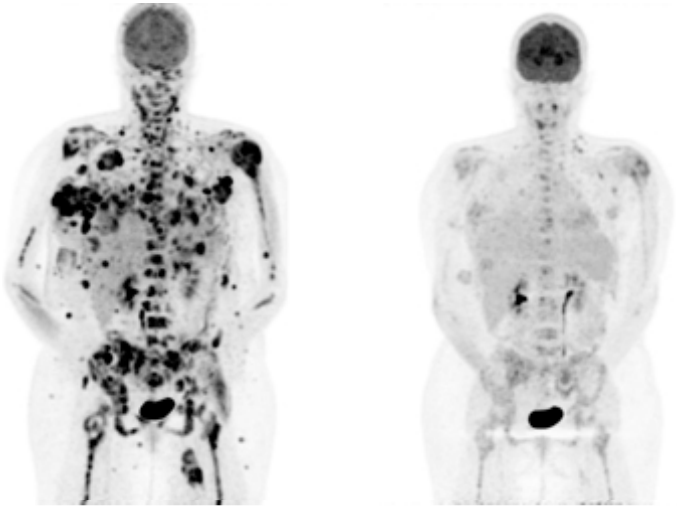
Radiopharmaceuticals



- Targeted radionuclides
- Primarily alpha particles and electrons
- Can be theranostic (photons, positrons)
- Complex (micro)dosimetry
- Very limited radiobiology

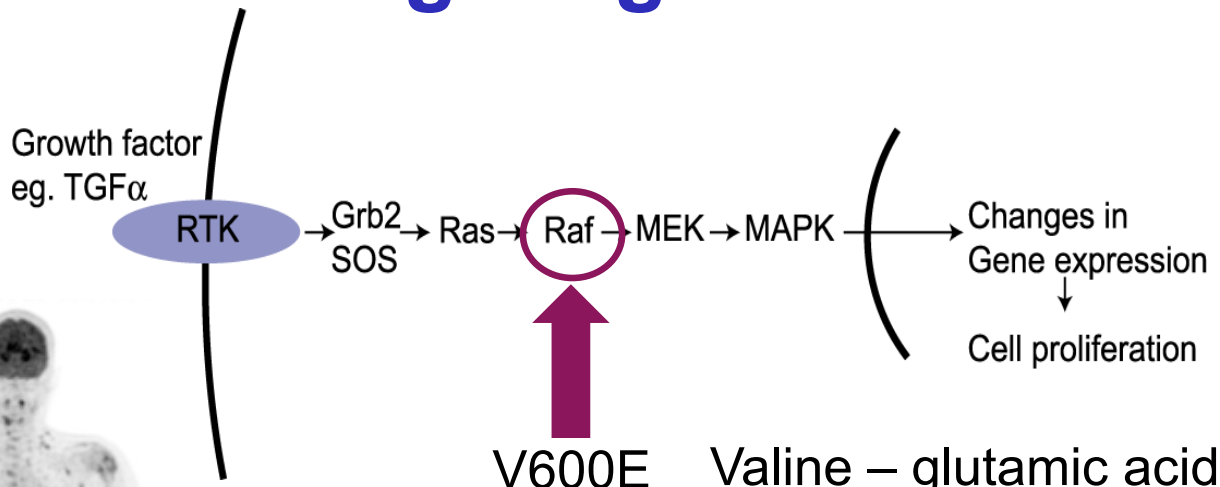
- I^{131}
- Ra^{223}
- Lu^{177}-PSMA-targeting
- Lu^{177}-Dotatate

Molecular targeting of cancer



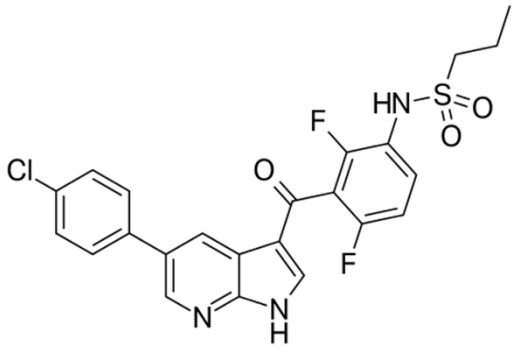
The New York Times

February 2010



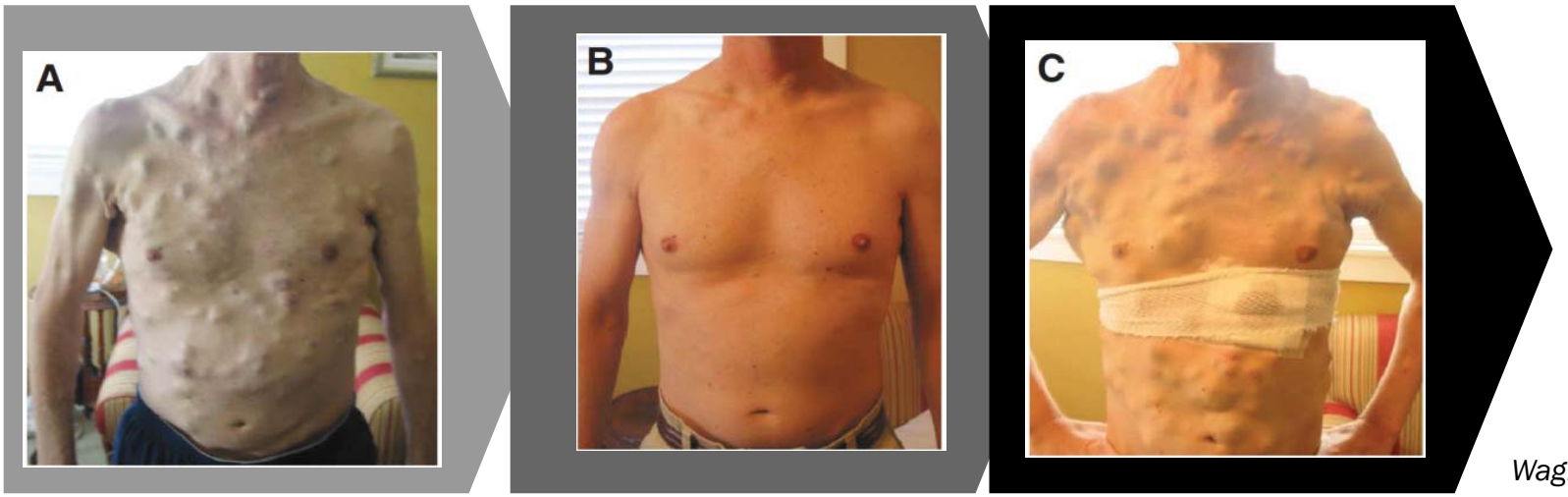
V600E Valine – glutamic acid

Vemurafenib



V600E mutated braf inhibitor

‘Perfect’ drugs but resistance develops

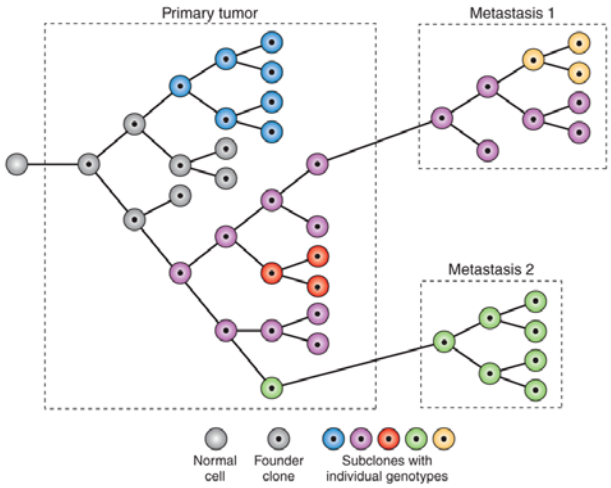


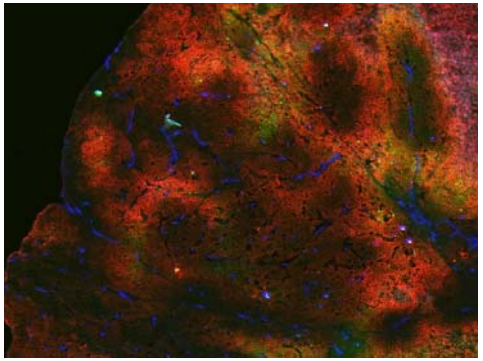
Wagle, JCO, 29, 3085

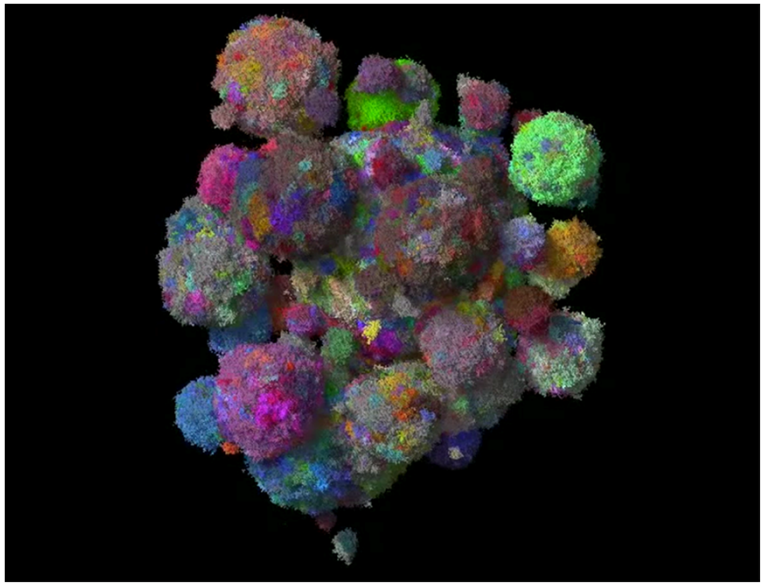
15 weeks 23 weeks

Tumors are heterogeneous within patients

- genetic
- epigenetic
- microenvironmental

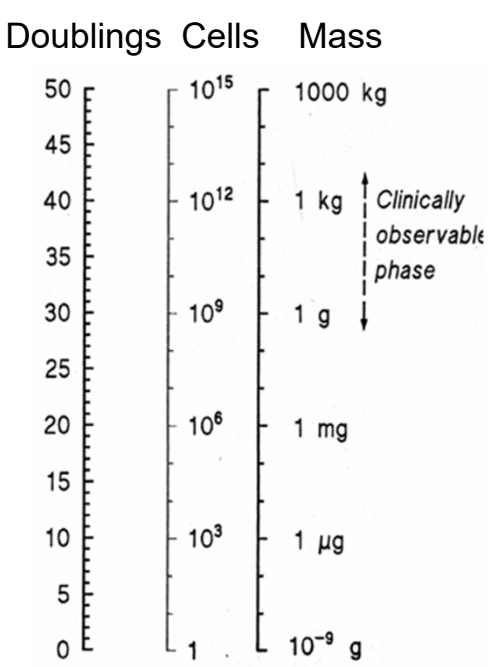


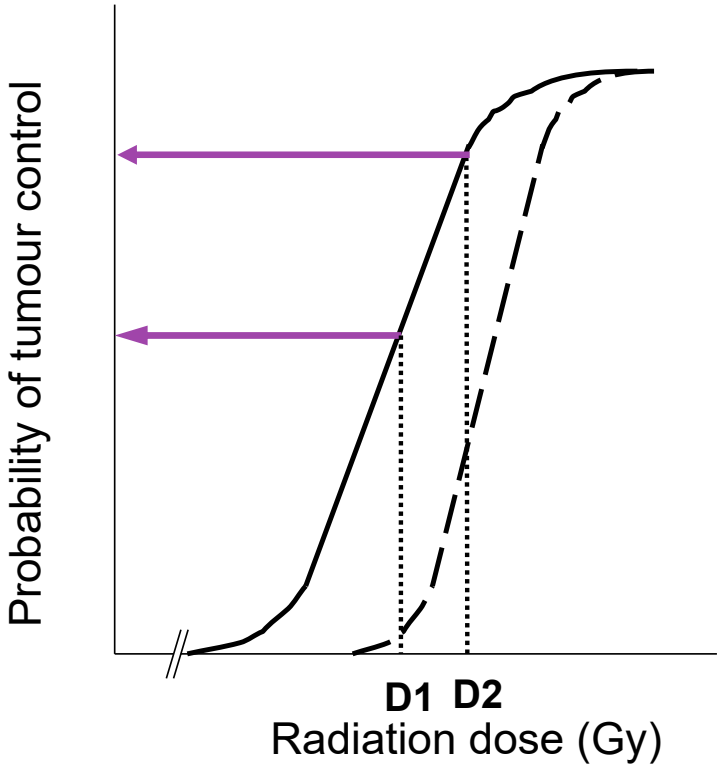




RT –ideal for combination therapy

Some patients fail RT even though we get very close to control!



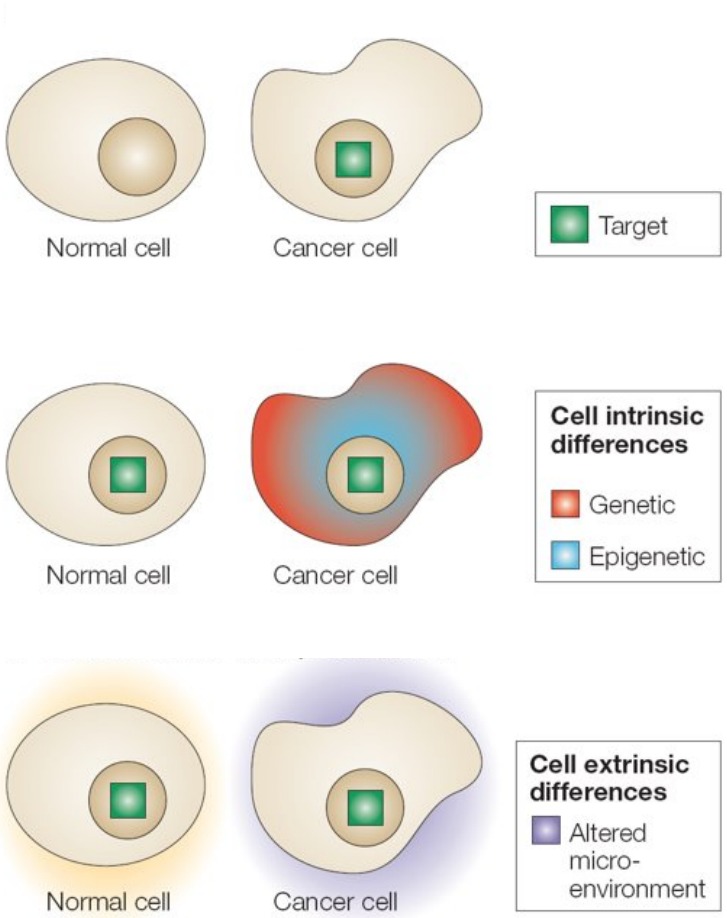


Making choices: Strategies to target cancer

- Oncogene addiction
  - Target the Driver
  - Target is overexpressed/mutated
  - Cancer cells are dependent on the target

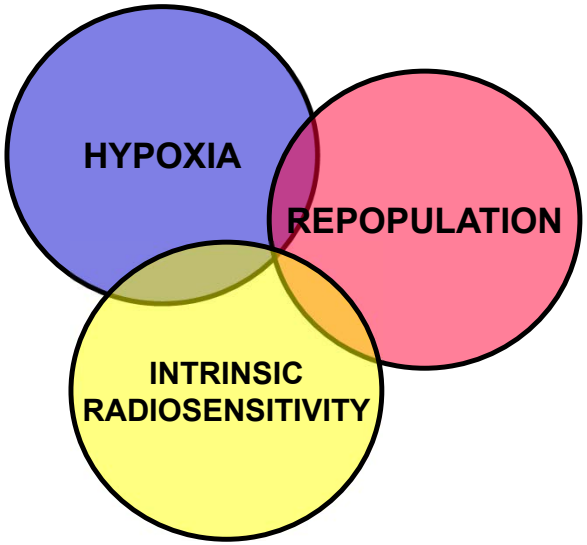
- Synthetic Lethality
  - Target is normal
  - Genetic alteration in cancer creates a novel dependency

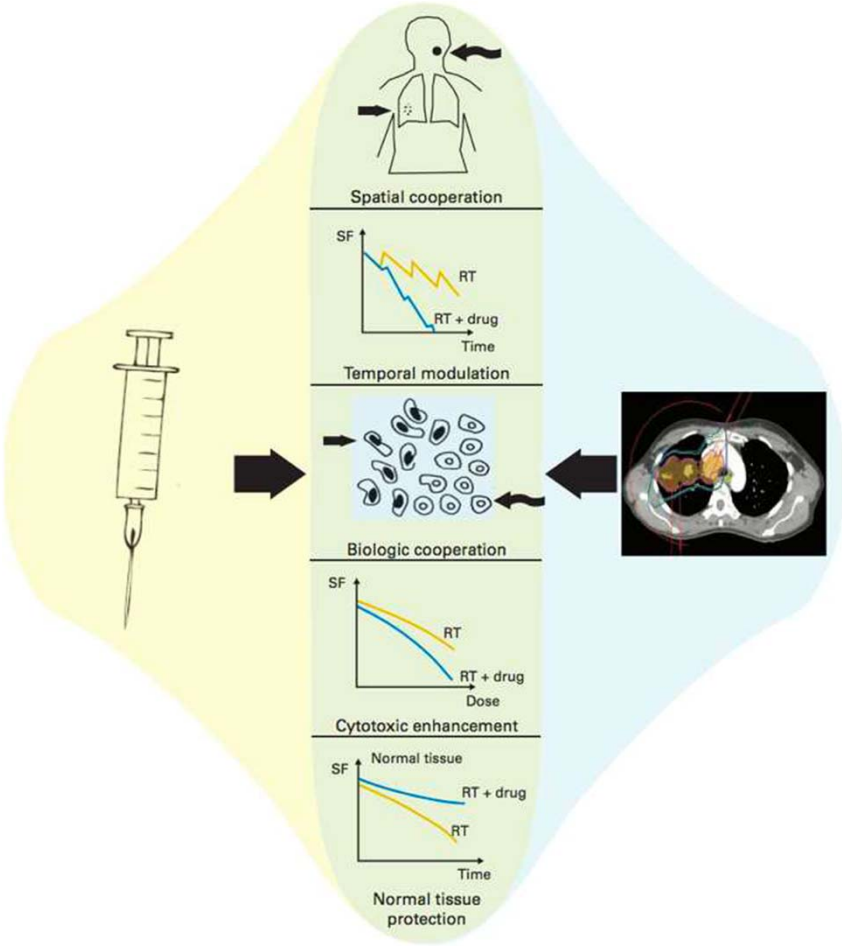
- Contextual synthetic lethality
  - Tumor microenvironment creates a novel dependency



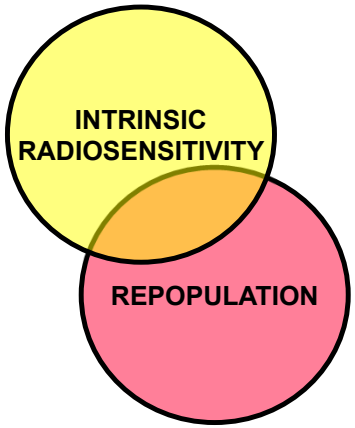
Adapted from Kaelin Nat Rev Cancer 2005

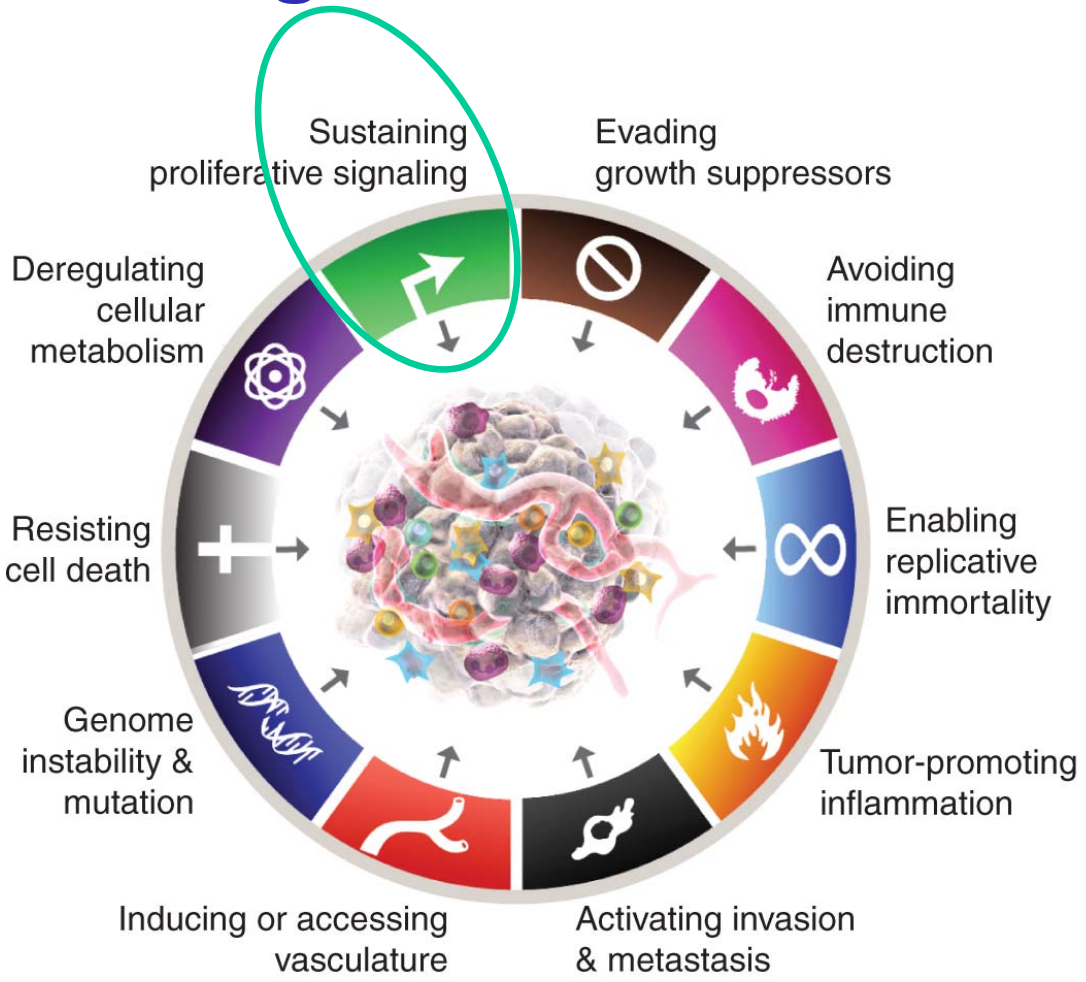
Making choices: Strategies to target with RT



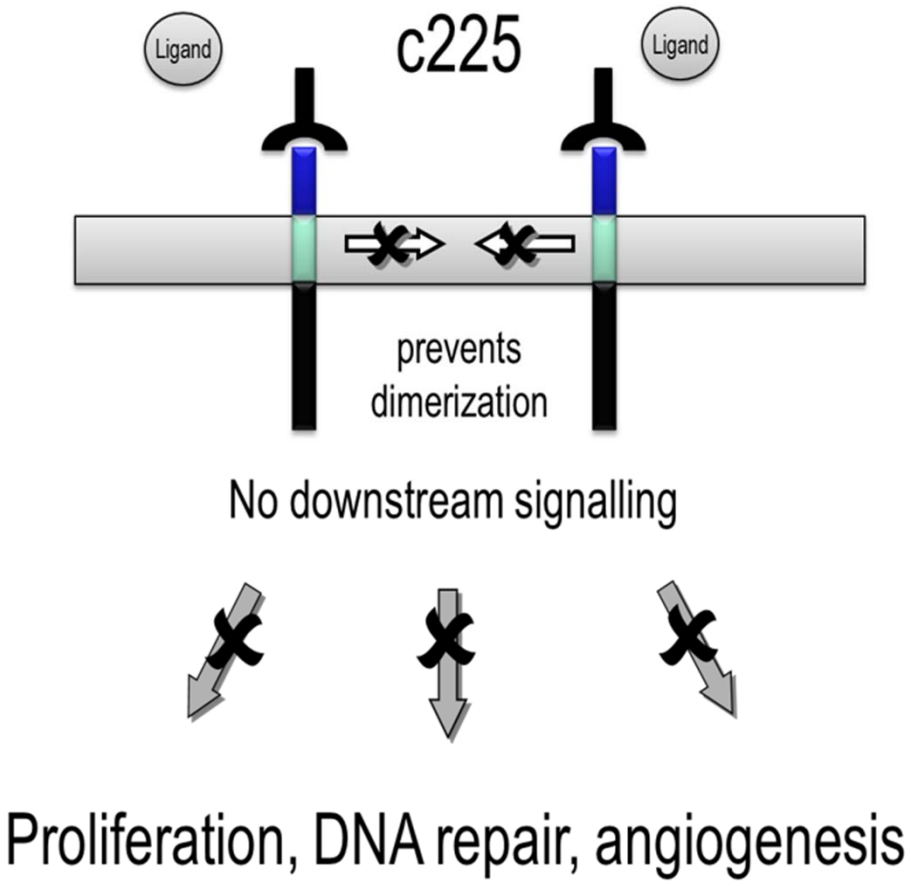


Example: Oncogene addiction - EGFR



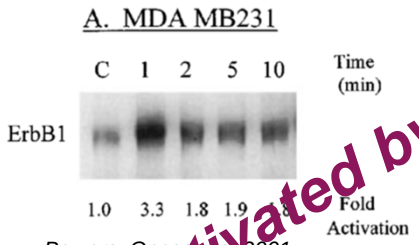


Example: Oncogene addiction - EGFR



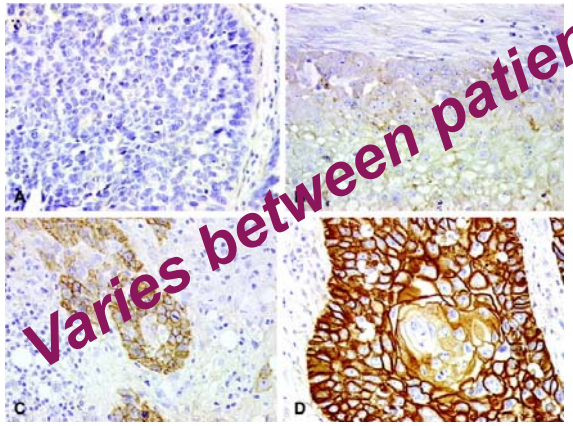
C22%: Cetuximab

Example: Oncogene addiction - EGFR

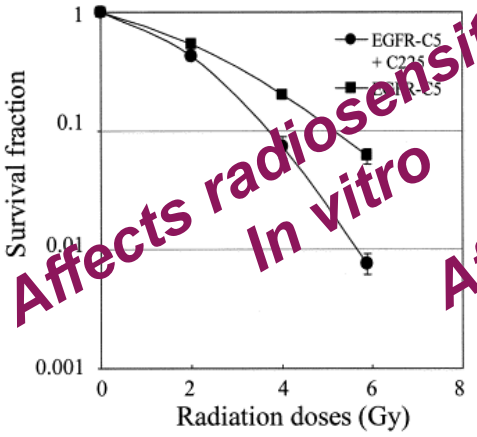


Bowers, Oncogene, 2001

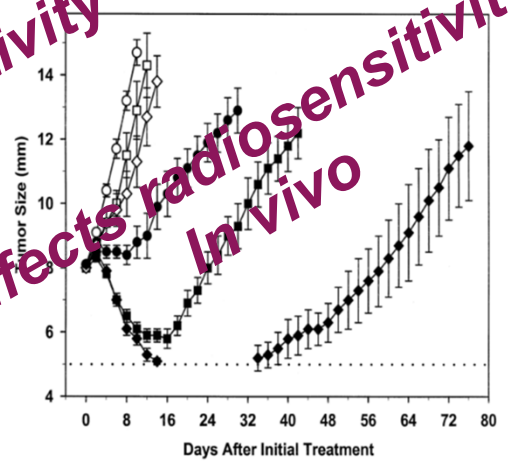
Activated by radiation



Varies between patients

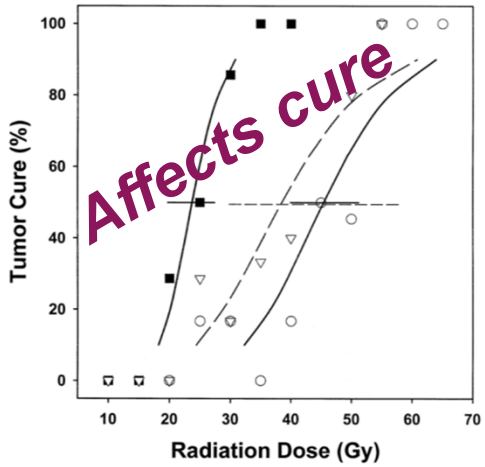


Affects radiosensitivity In vitro



Affects radiosensitivity In vivo

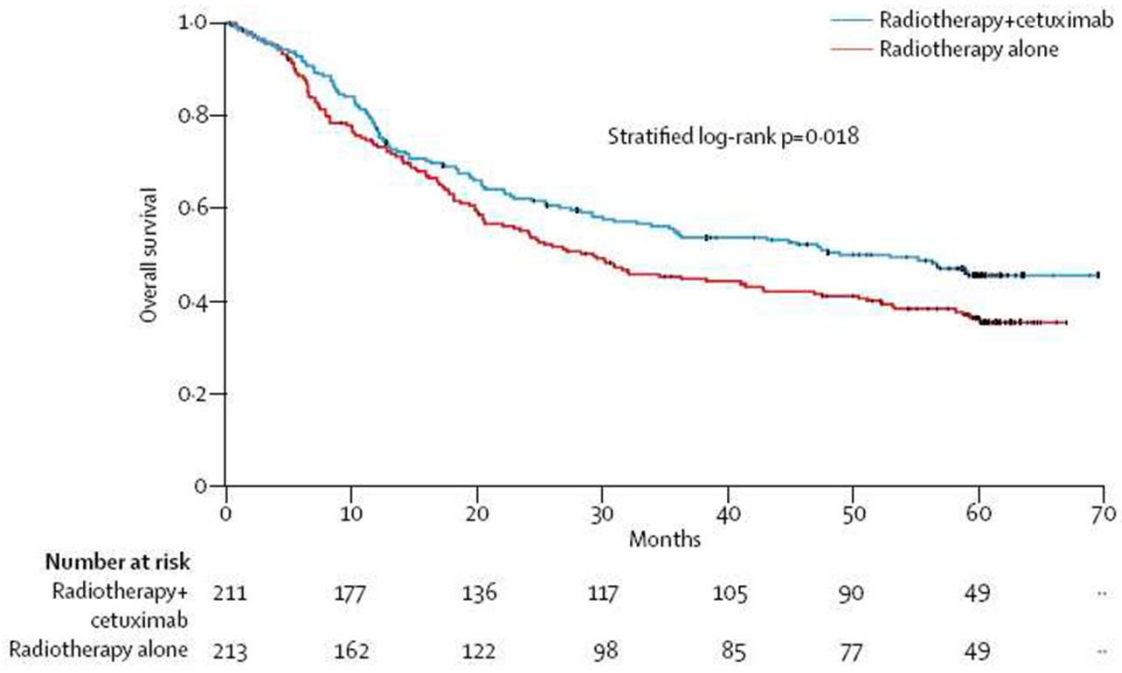
Liang, IJROBP, 2003



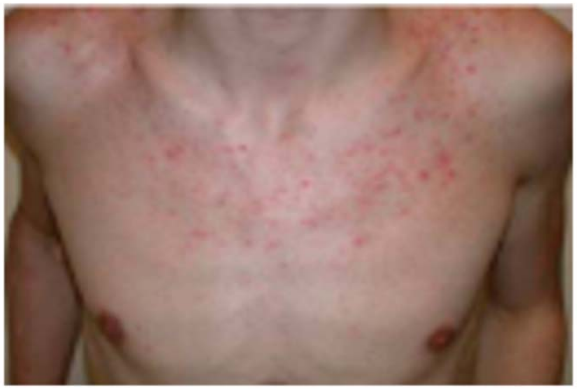
Affects cure

Milas, IJROBP, 2004

Example: Oncogene addiction - EGFR

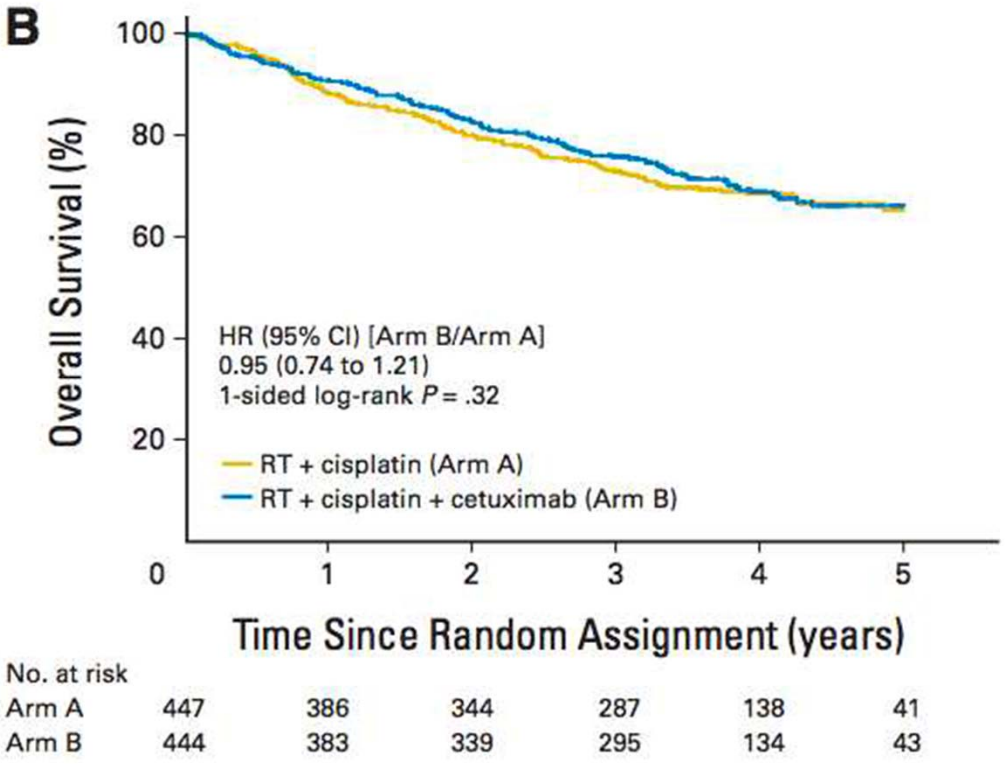


- Survival benefit
- Some toxicity
- Acneiform rash predictive

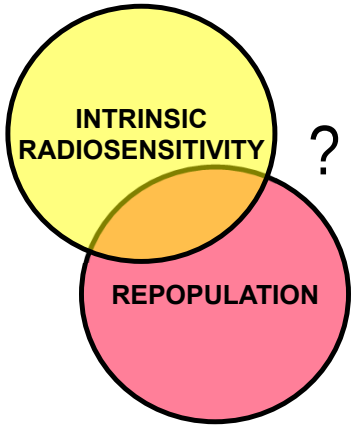


Bonner et al., NEJM 2006, LO 2010

Example: Oncogene addiction - EGFR

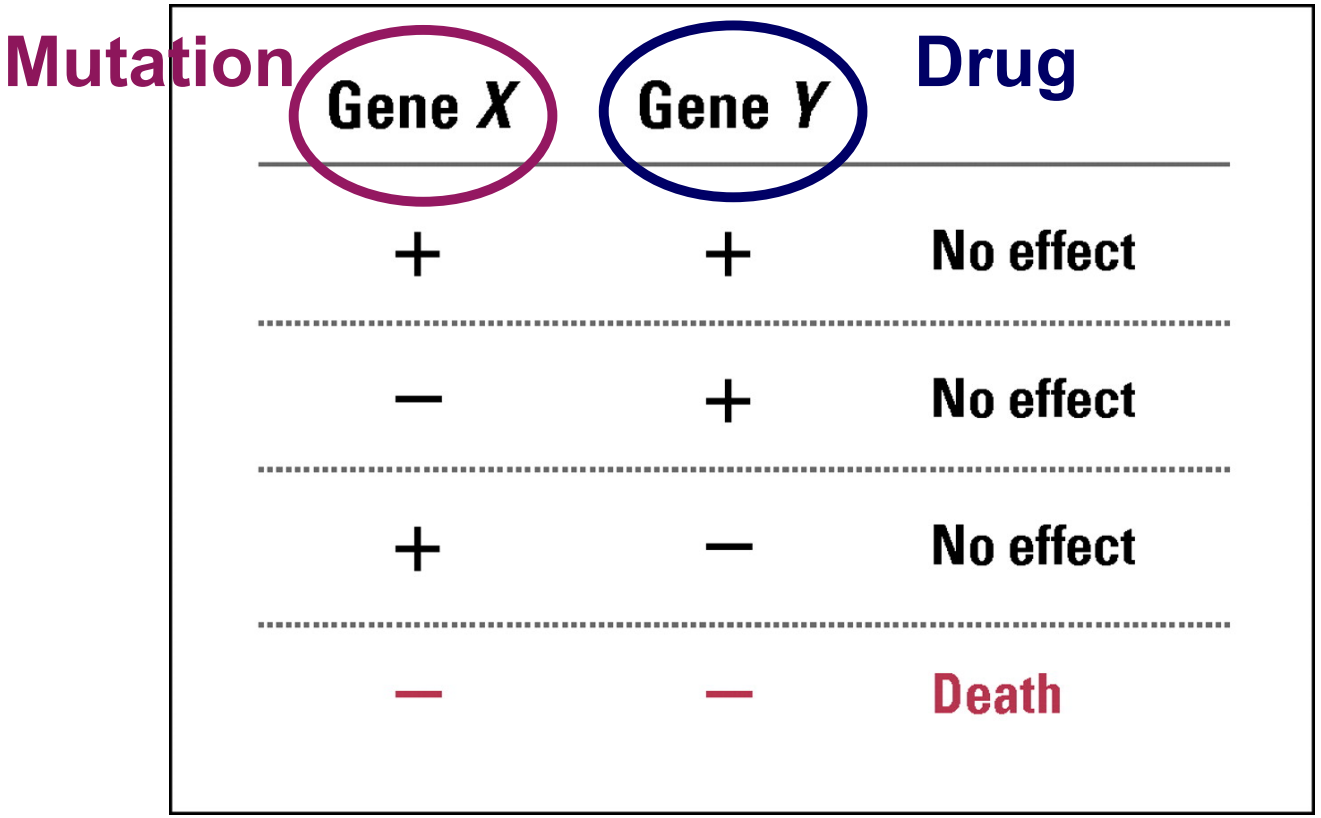


- No survival benefit
- Some toxicity



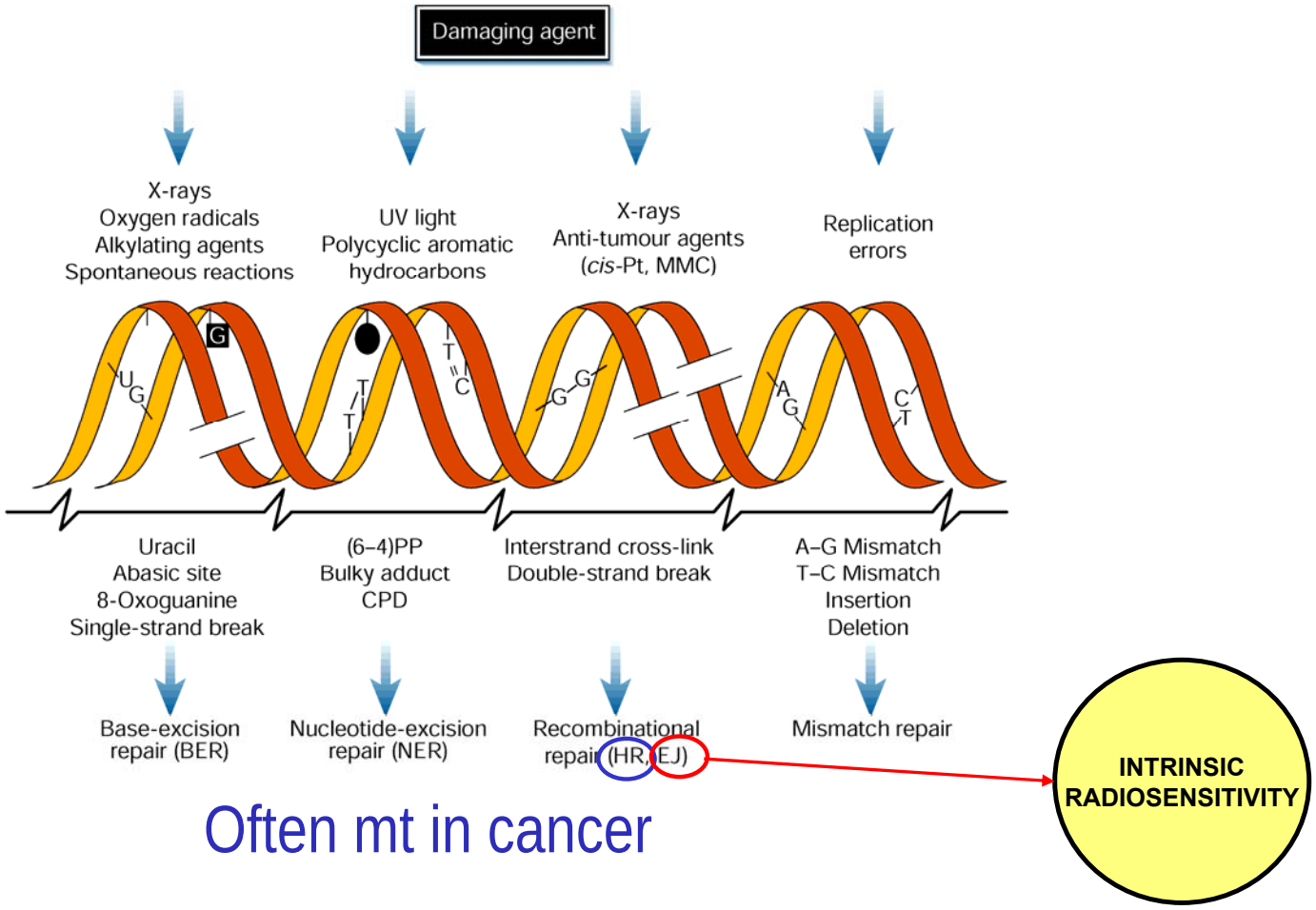
Ang et al., JCO 2014

Example: Synthetic lethality



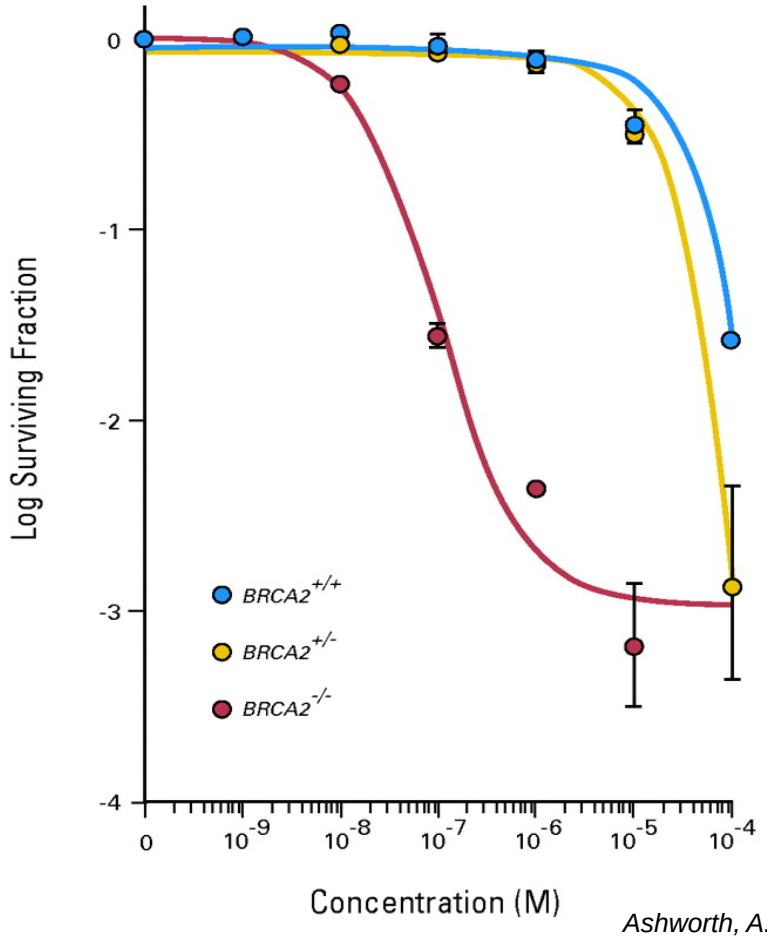
Ashworth, A. J Clin Oncol; 26:3785-3790 2008

Example: Synthetic lethality - DNA Repair



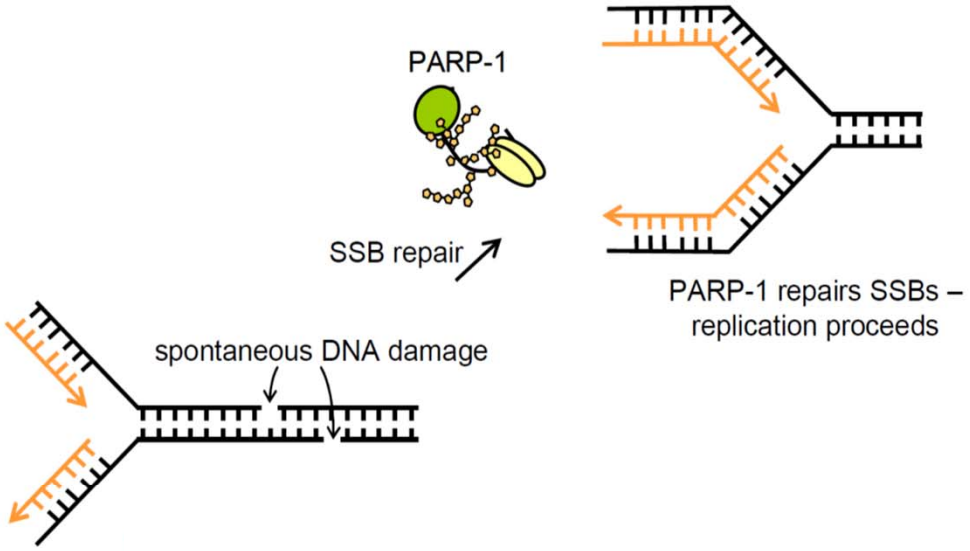
Often mt in cancer

Example: Synthetic lethality – PARP/BRCA

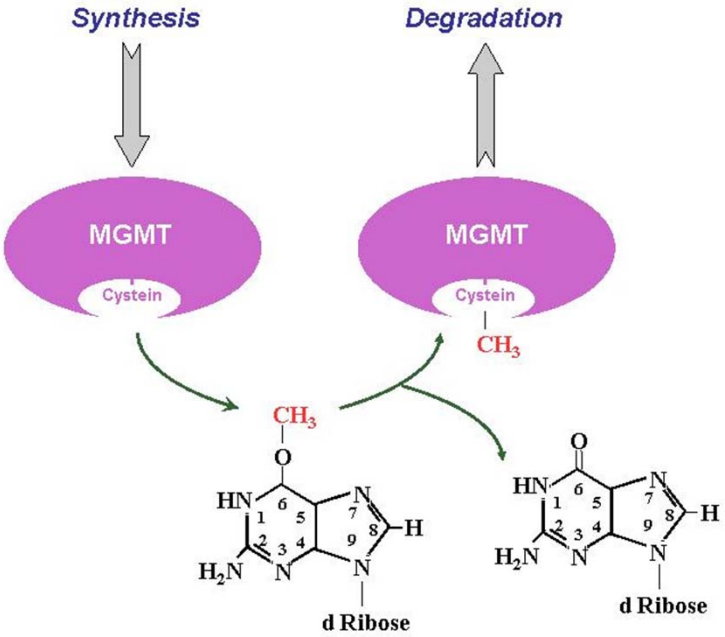


Ashworth, A. J Clin Oncol; 26:3785-3790 2008

Example: Synthetic lethality – PARP/BRCA2



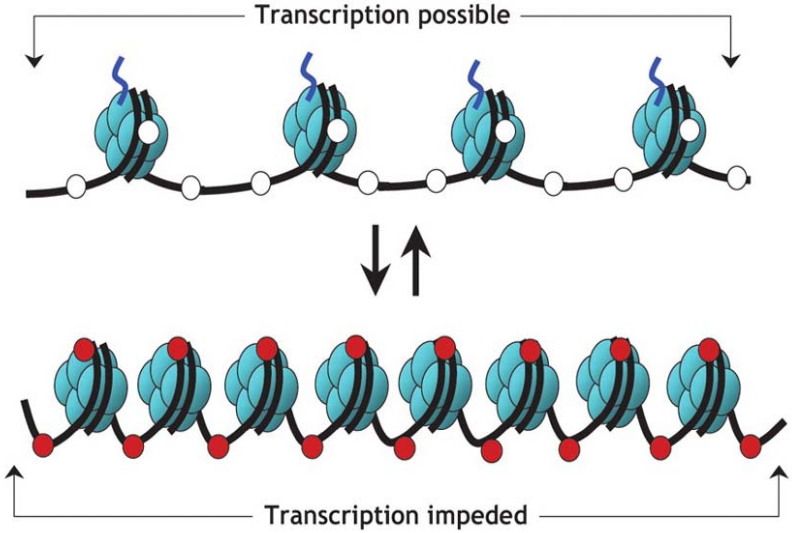
Example: Synthetic lethality – MGMT/TMZ



Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

Gene "switched off"
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

http://cnx.org/content/m26565/latest/graphics35.jpg



Example: Synthetic lethality – MGMT/TMZ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

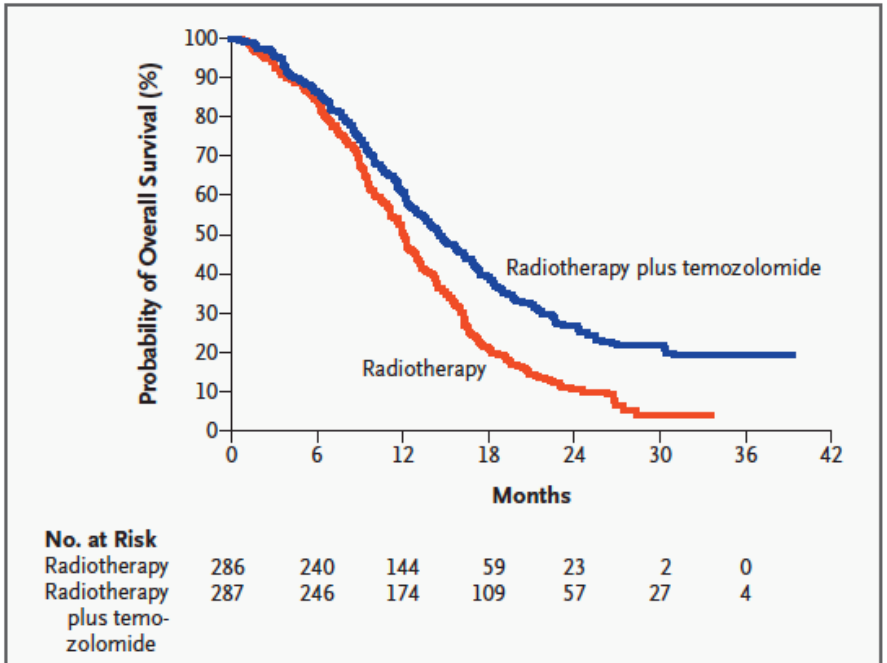
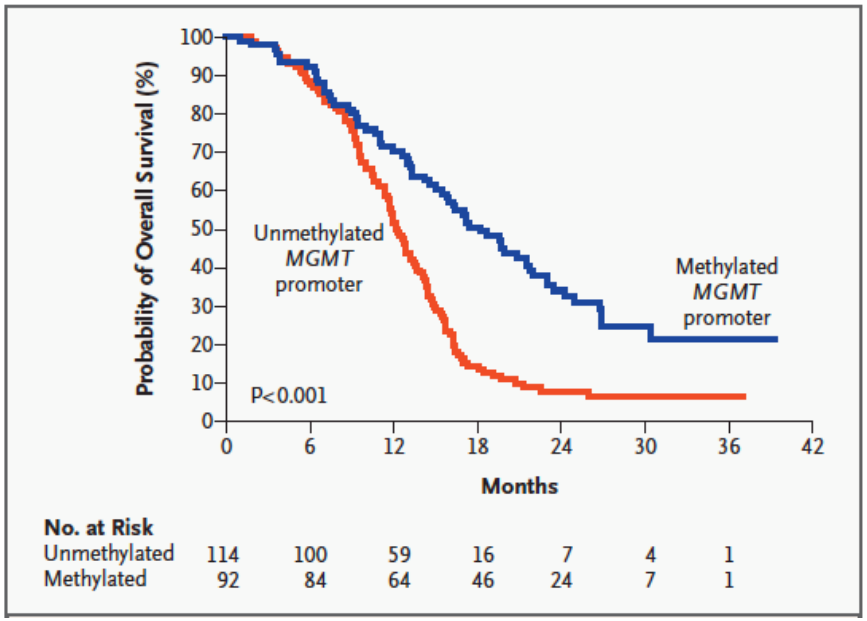
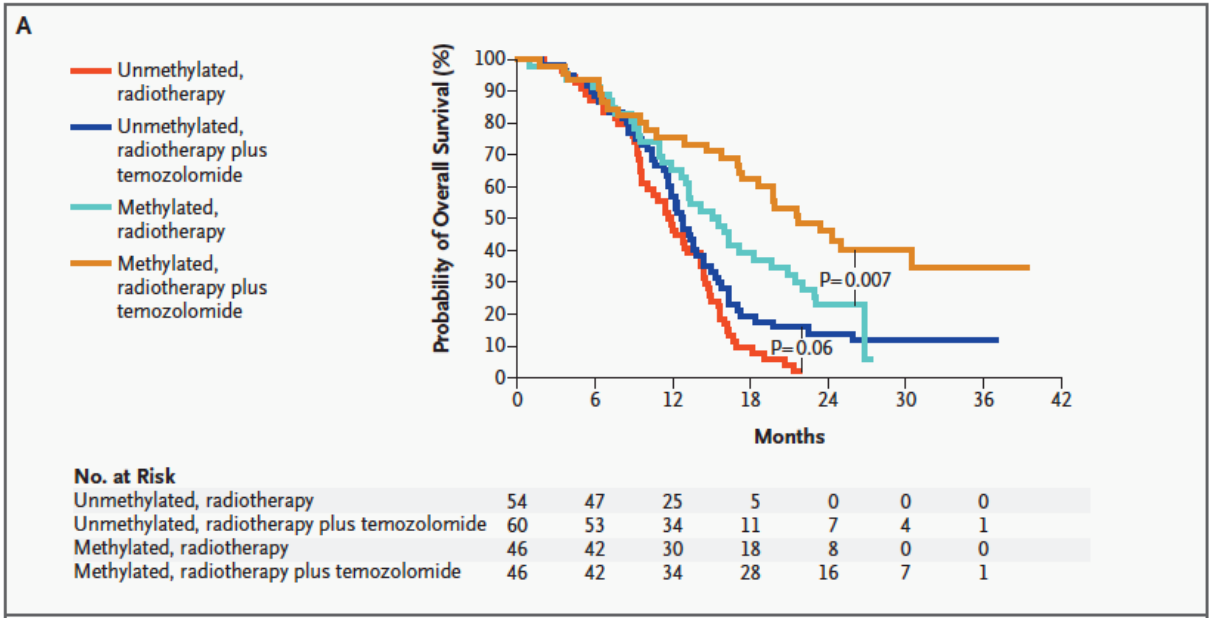


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

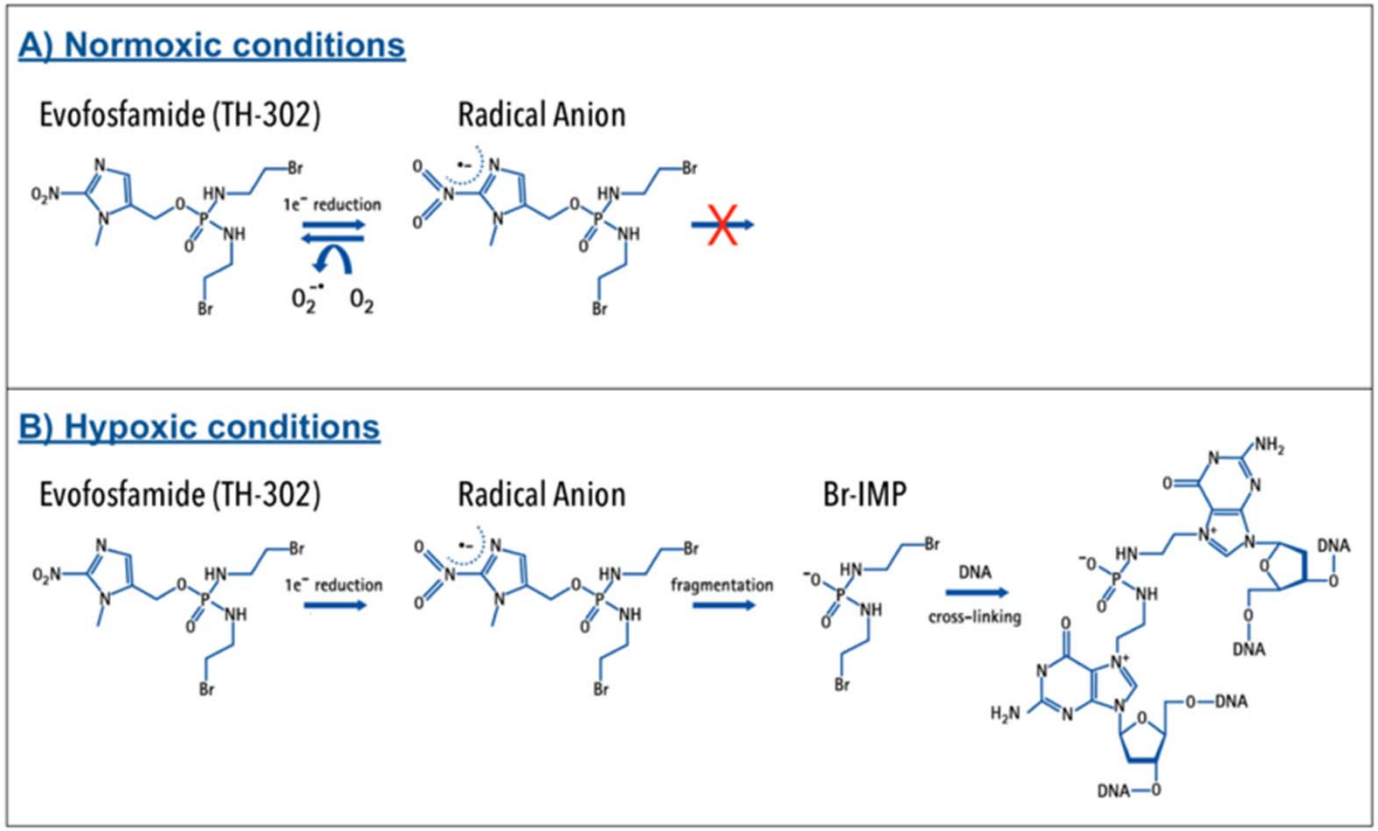
Example: Synthetic lethality – MGMT/TMZ



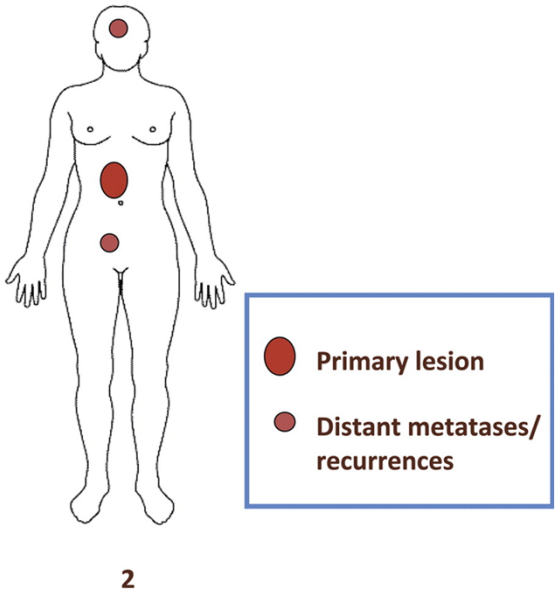


Benefit for patients with and without MGMT expression

Example: Contextual lethality - Hypoxia



Can radiation become a part of curative systemic therapies?



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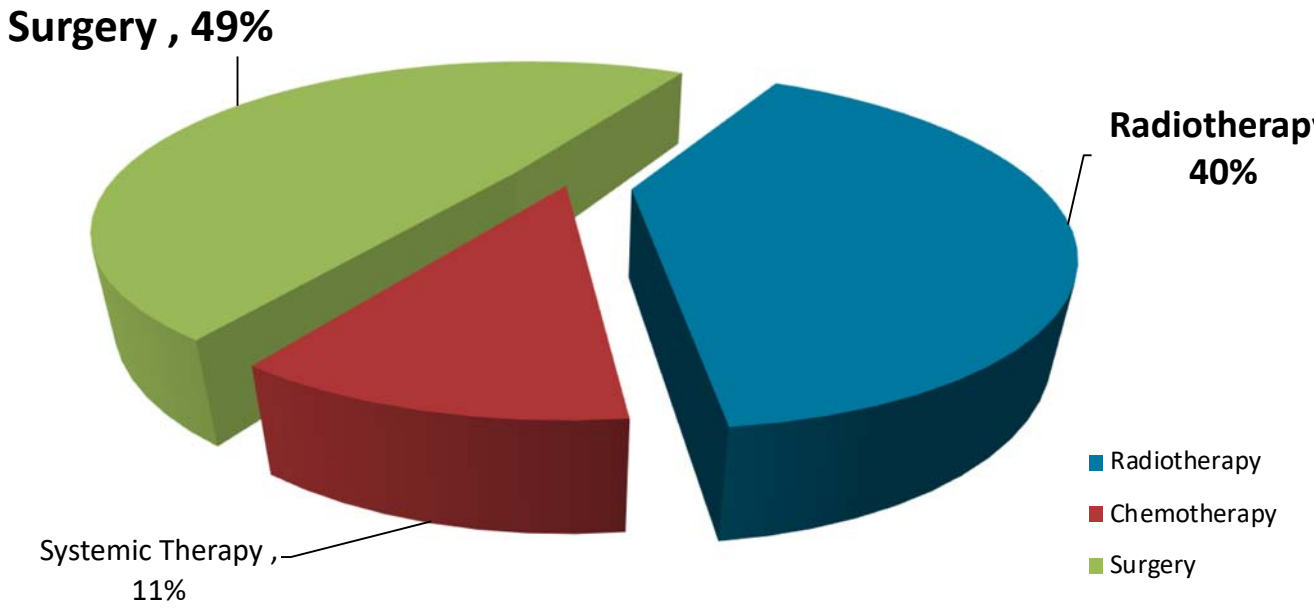
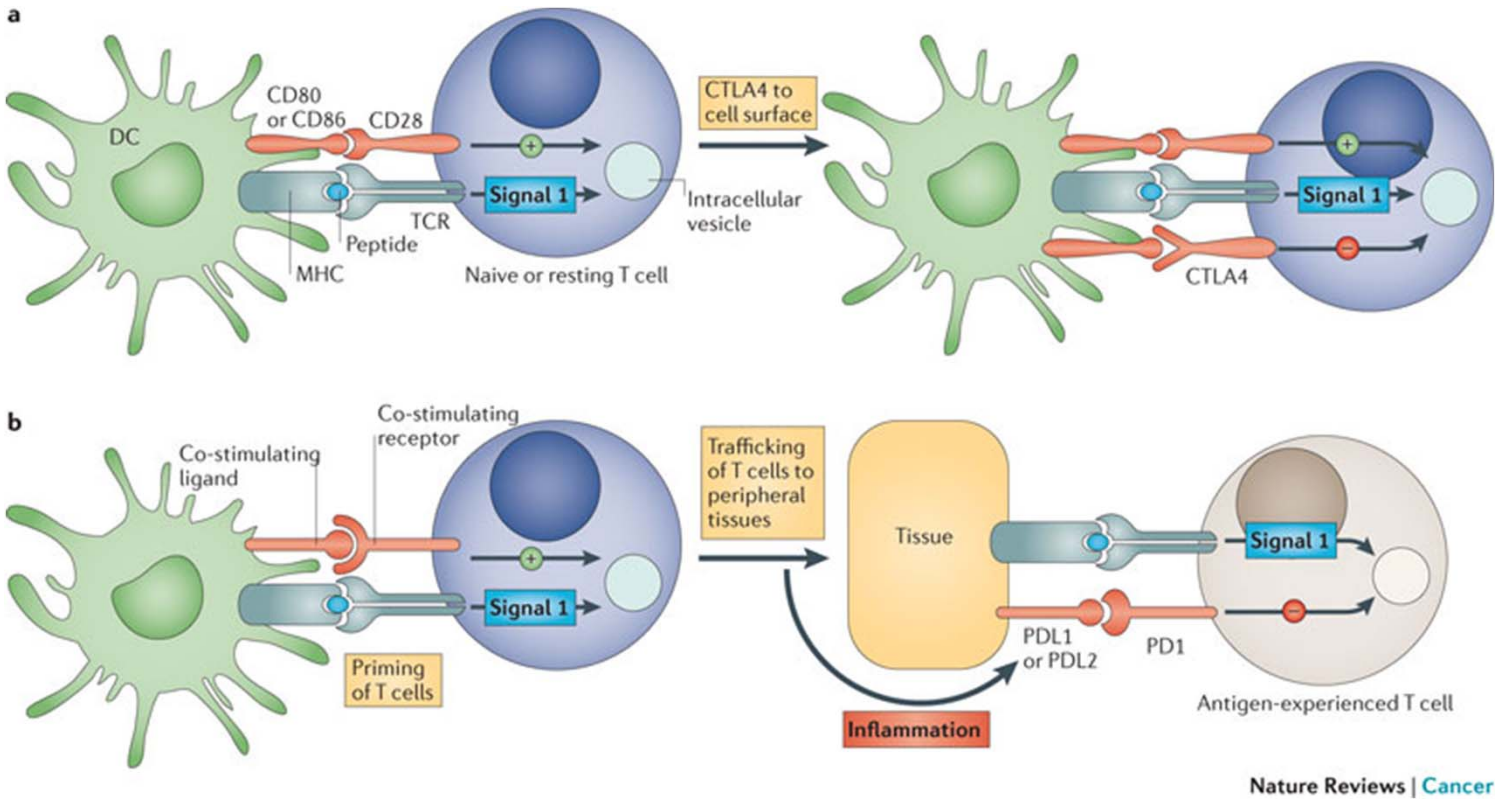
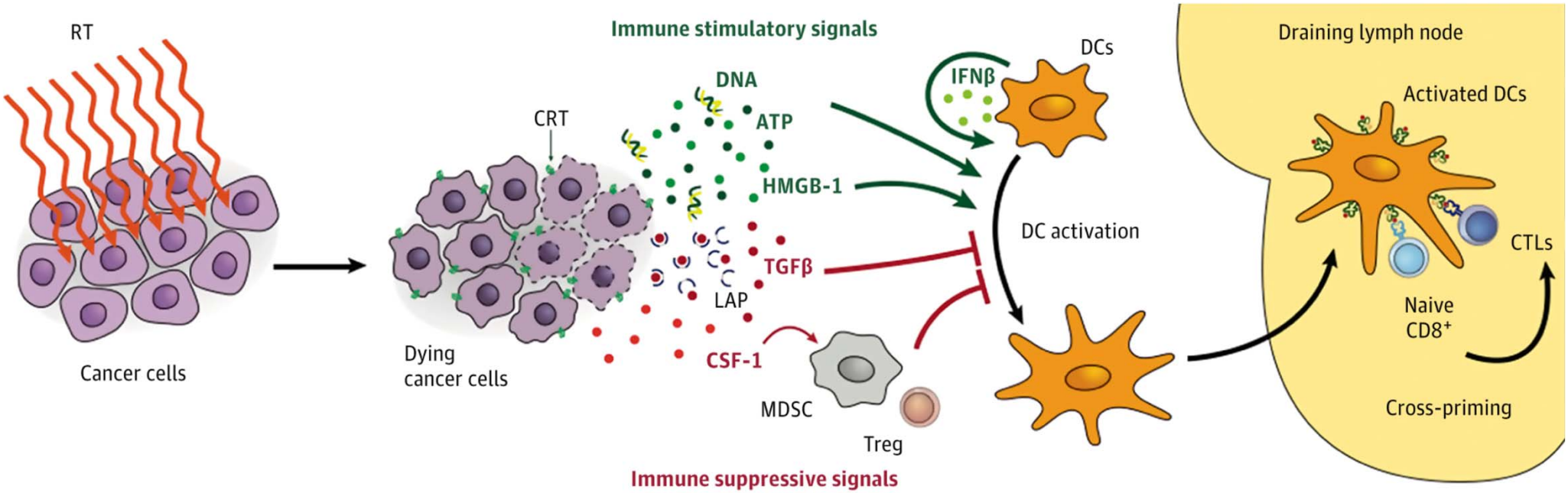


*from Gillies McKenna
Professor Sir Mike Richards, NCRI 2011

Immune therapy





The total dose and fractionation dose affect these processes in a way that may be distinct from effects on cell survival

JAMA Oncol. Published online August 13, 2015. doi:10.1001/jamaoncol.2015.2756

ARTICLE

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DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

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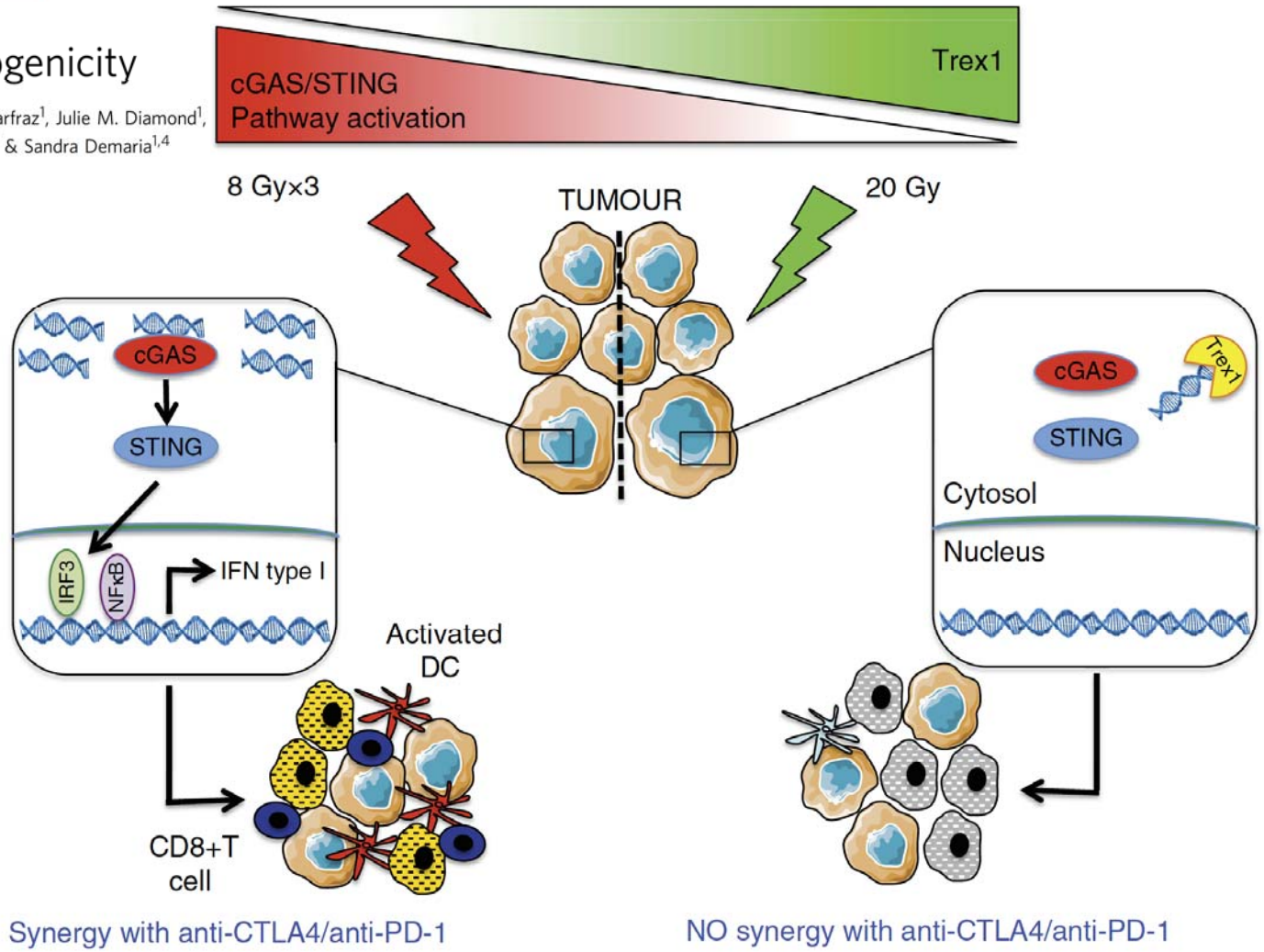

Summary

- Targeted therapies include small molecules and biologics

- Targeted therapies can be combined with radiation in a rational way to improve local control
  - Target pathways that provide therapeutic window in cancer
  - Target pathways that limit the response to radiotherapy
  - Identify patients who can benefit first - individualization

- Targeted therapies/immunotherapies may be combined with radiation to improve systemic control