NATIONAL CANCER INSTITUTE

NCI Center for Cancer Research
Reducing the Burden of Cancer Through Exploration, Discovery and Translation

LABORATORY OF TUMOR IMMUNOLOGY AND BIOLOGY CENTER FOR CANCER RESEARCH
LTIB CCR
NCI, NIH

The New Frontier: Immunotherapy of Cancer

Combination Immunotherapies: Engage, Expand, Enable

Demystifying Medicine
February 6th, 2018

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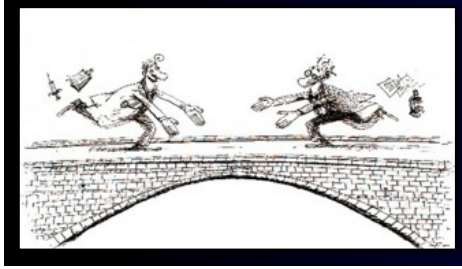

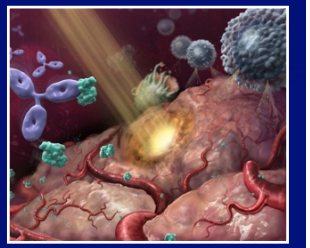

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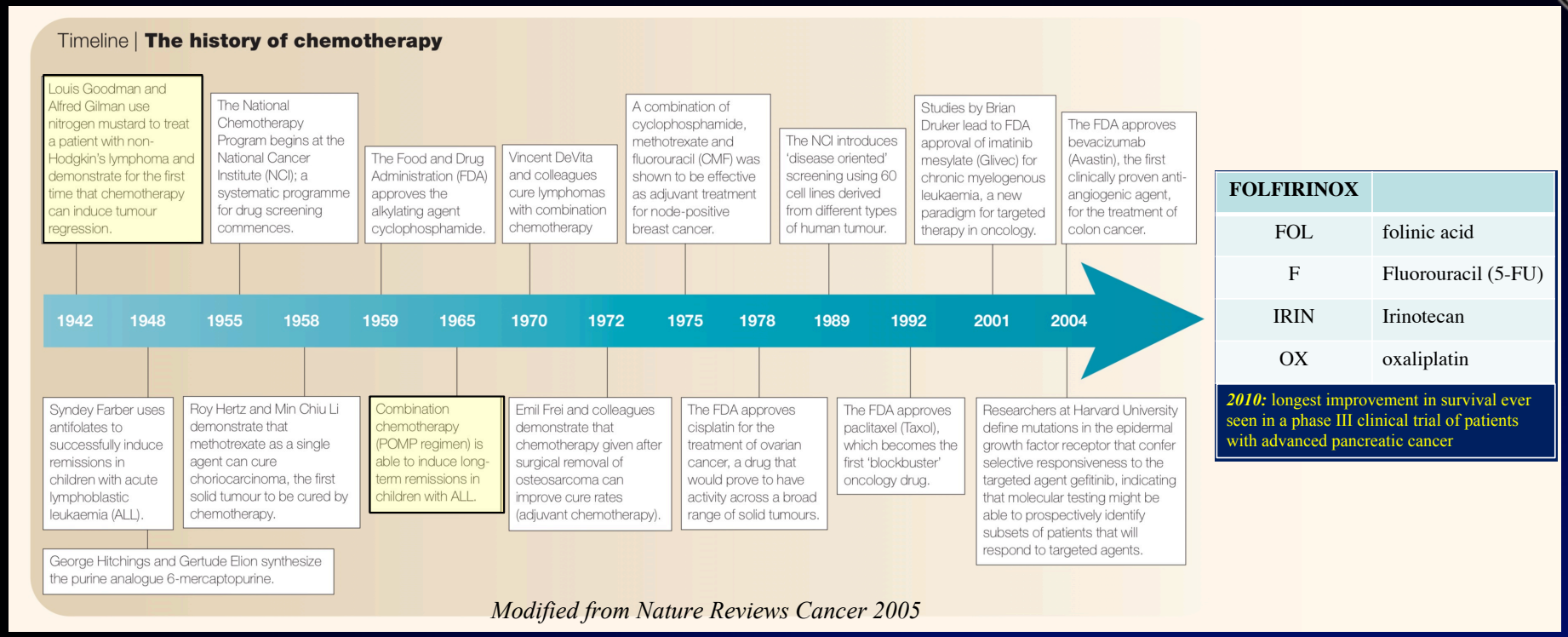
Dr. Gulley
Dr. Madan
Dr. Julius Strauss

Why is Combination Therapy Needed?



Modified from Nature Reviews Cancer 2005

FOLFIRINOX	
FOL	folinic acid
F	Fluorouracil (5-FU)
IRIN	Irinotecan
OX	oxaliplatin

2010: longest improvement in survival ever seen in a phase III clinical trial of patients with advanced pancreatic cancer

- Monotherapy: Some activity in select tumor types
- Combination Therapy: Improved ORR, DUR, and OS

Are we already seeing the same trend with immunotherapy?

- Monotherapy: Some activity in select tumor types
- Limited Data with Combination IO Therapy: (Improved ORR, DUR, and OS)
  - *How to rationally choose IO Agents?*

Next Generation Therapy: SOC Agents Plus IO Combinations

Standard-of-Care Therapy (Radiation/Chemotherapy, others): Combination with Immunotherapy

Hypotheses:

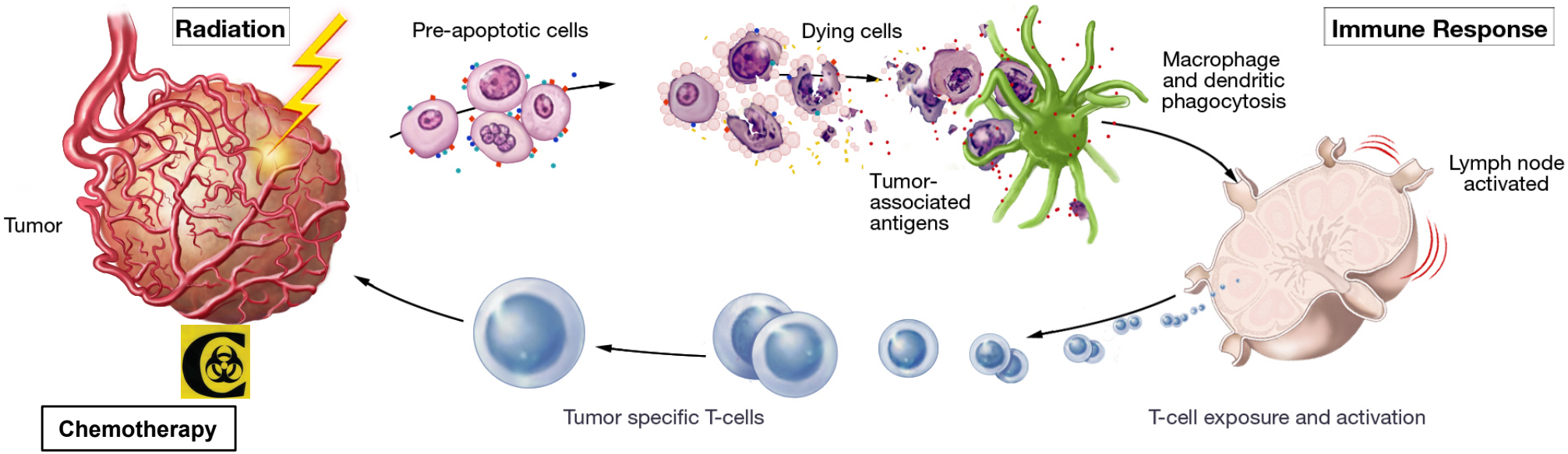
- Cancer Patients Harbor Tumor Antigen Specific T-cells
  - These T-cells can have activity increased by manipulation of the peripheral and tumor environment*

- Standard-of-Care Therapy** Can Induce and/or Enable Additional Antigen Specific T-cells
  - These T-cells can have activity increased by manipulation of the peripheral and tumor environment*

- *anti-CTLA-4, anti-PD1/PD-L1, Cytokines (IL-12, IL-15), anti-Vegf, anti-TGF-beta, JAK/STAT inhibitors, Inflammatory Agonists (CD137, TLR3/7/8), Vaccines

Not For Posting

Can Radiation or Chemotherapy Alone Induce Immune Responses?



Immunogenic Cell Death

Not Sufficient

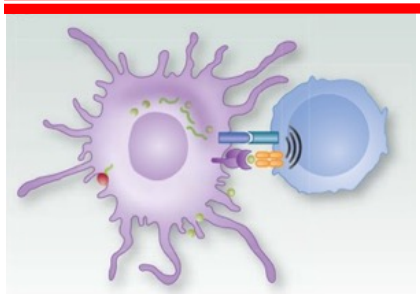
Nesslinger et al, *Clin Ca Res* 2007
Schaue et al,, Int. Clin. Can. Res. 2008
Kachikwu et al, Int. J. of Rad Onc Biol. Phys., 2011

Galluzzi et al., Cancer Cell, Dec 14, 2015

20 trials
2 radiation types
7 chemotherapy types

- Weak efficiency
- Potential to be augmented with active immunotherapy

Vaccines: Initiating an Antitumor Immune Response



Vector	Target	Phase I	II	III
Pox	PSA	✓	✓	✓
	CEA/MUC-1	✓	✓	
	Brachyury	✓	✓	
Yeast	CEA	✓	✓	
	Brachyury	✓	✓	
Adeno	CEA		✓	
	CEA-Triad	In review		
	PSA-Triad	In Review		
	TSNA	Planned		

TSNA: Tumor-specific neo-antigen

rec Pox viruses: Bavarian Nordic (BN)
rec Saccharomyces: NantCell
rec Adeno: Etubics

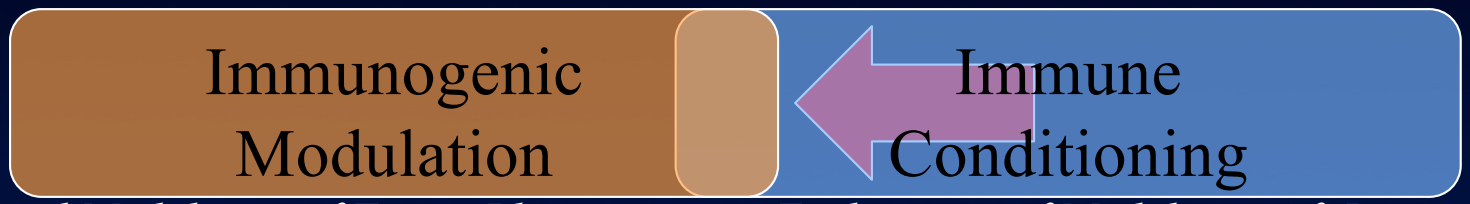
Combination of Standard-of-Care or Emerging Therapies with Immune Oncology Reagents

Immunogenic Modulation

Modulation of Tumor Phenotype to Render Cells More Sensitive to Immune Mediated Killing

Immune Conditioning

Modulation of Immune Cell Subsets to Enable Productive Immune Interactions

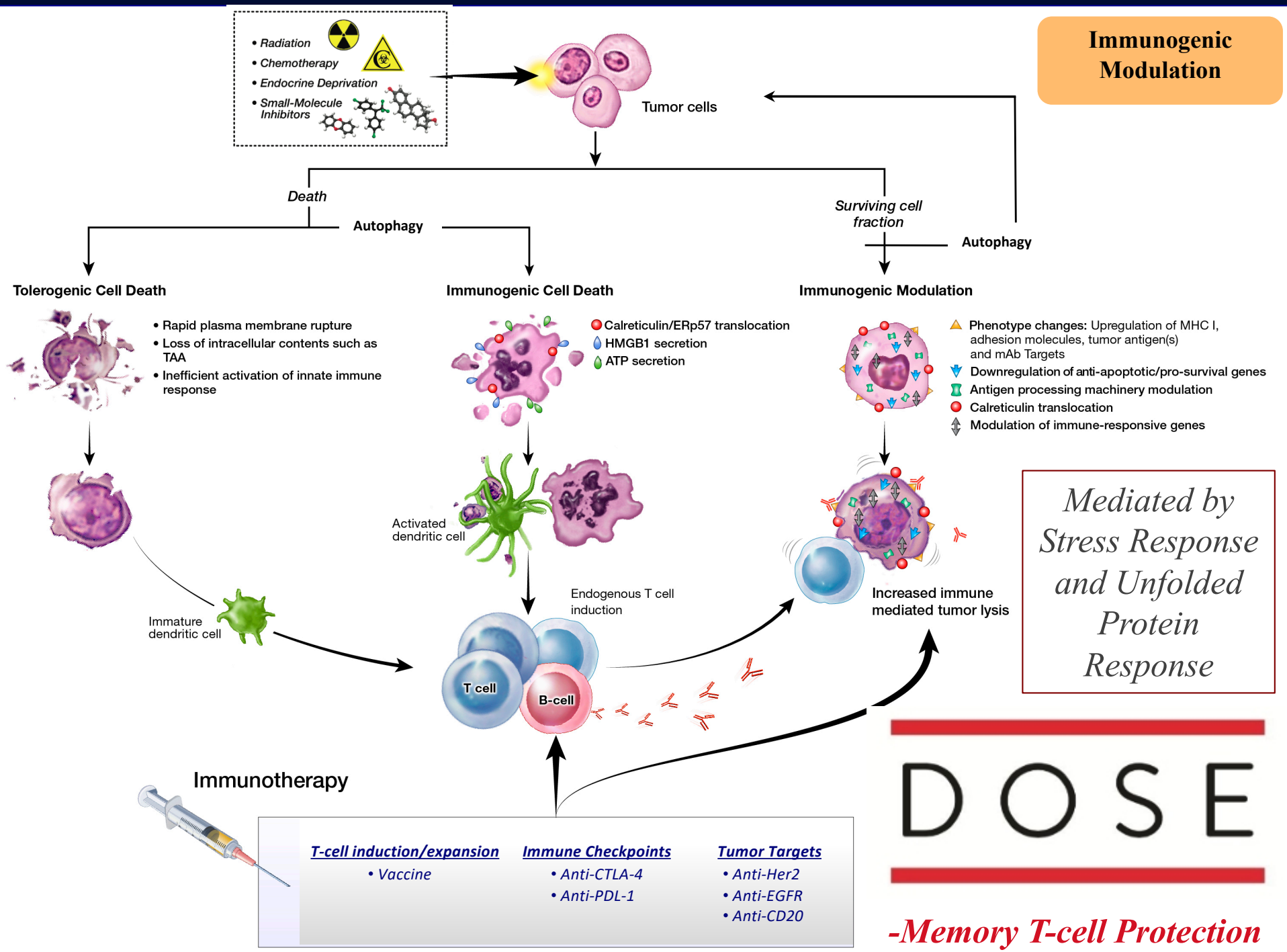


Therapy Induced Modulation of Tumor Phenotype *Exploitation of Modulation of Immune Cell Subsets*

Why Study Immunogenic Modulation and Immune Conditioning in the Context of Immunotherapy?

- The optimal use of immunotherapy may be in combination with standard of care or emerging experimental therapies
- Allows immunotherapy use earlier in the disease process
- Certain modalities may act synergistically with immunotherapy by:
  - enhancing immune responses
  - inhibiting immune suppressive functions
  - altering the phenotype of tumor cells to render them more susceptible to immune-mediated killing
- Radiation, chemotherapy, small-molecule inhibitors, or biologic therapy could serve as a boost to immunotherapy (vaccine)
- Can combination therapy convert increased overall survival to PFS or CR?

Attacking Tumor Cells That Survive Therapy: Exploiting Immunogenic Modulation



Immunogenic Modulation

Immune Conditioning

External-Beam Radiation

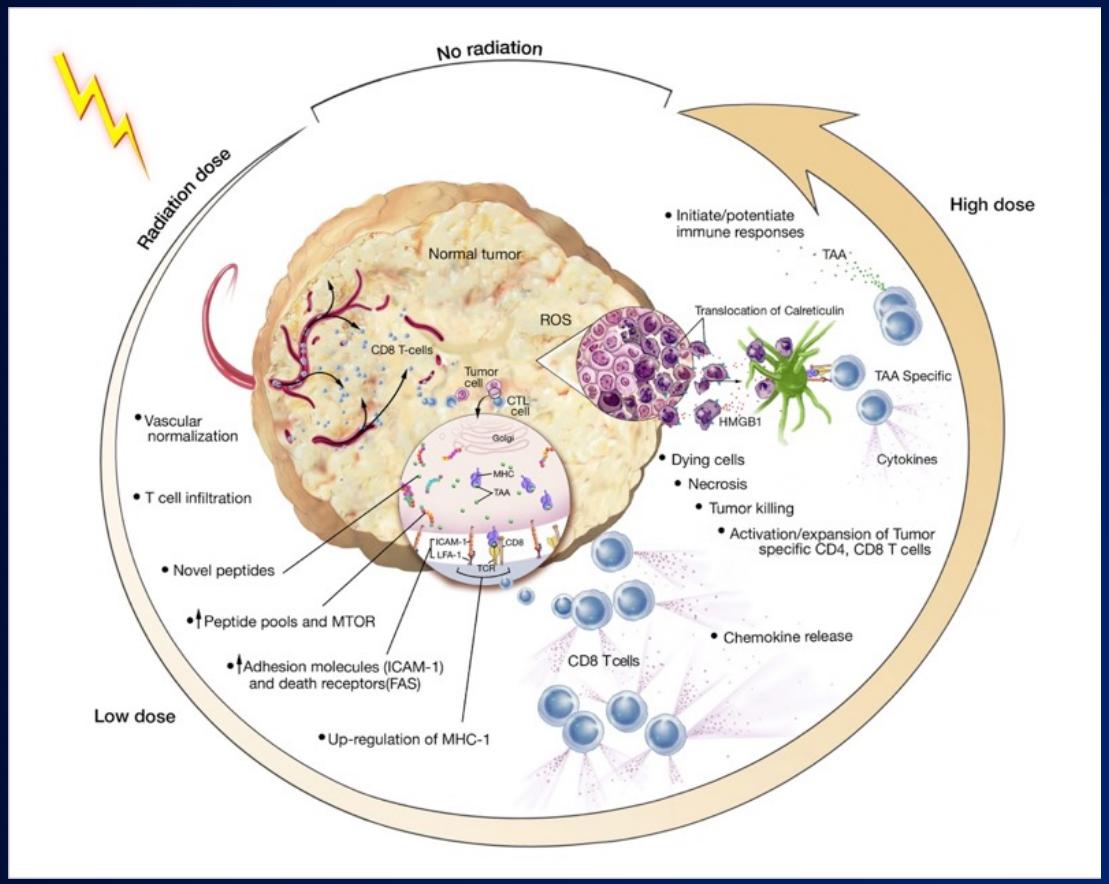
Multiple IO Combinations

Taxanes

Radiation Therapy: Immunogenic Modulation

Radiation Dose

No direct tumor killing Phenotypic Changes	Indirect Tumor Killing (Architecture Changes Vasculature Damage Apoptosis)	Direct Tumor Killing (Lysis, reactive oxygen species)



E. Reits, J.W. Hodge,…M. Chakraborty, E. Wansley, K. Camphausen, J. Schlom, J. Neefjes. Journal of Experimental Medicine, 203:1259-1271, 2006.

A. Gelbard, C. Garnett, S. Abrams, V. Patel, S. Gutkind, C. Palena, K. Tsang, J. Schlom, J.W. Hodge. Clinical Cancer Research. 12:1897-1905, 2006.

E. Wansley, M. Chakraborty, J. Carrasquillo, S. Yu, C. Paik, K. Camphausen, M. Becker, W. Goeckeler, J. Schlom, J.W. Hodge. Clinical Cancer Research. 14:4316-4325, 2008

J.W. Hodge, C. Guha, J. Neefjes, J. Gulley. Oncology. 9:1064-1070, 2008.

J.W. Hodge, S. Gameiro. Cancer Biotherapy an Radiopharmaceuticles. Jan 2012.

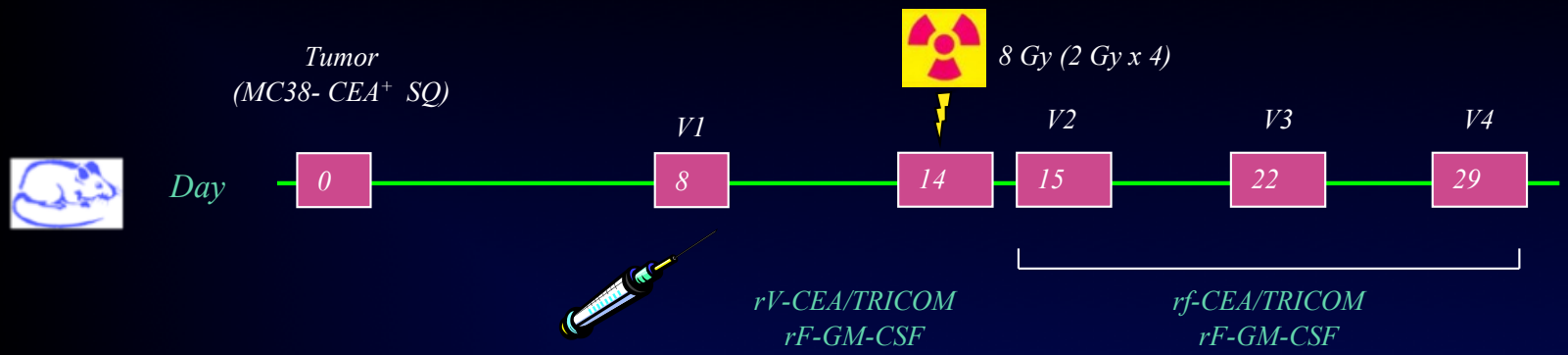
+ 5 Review Articles

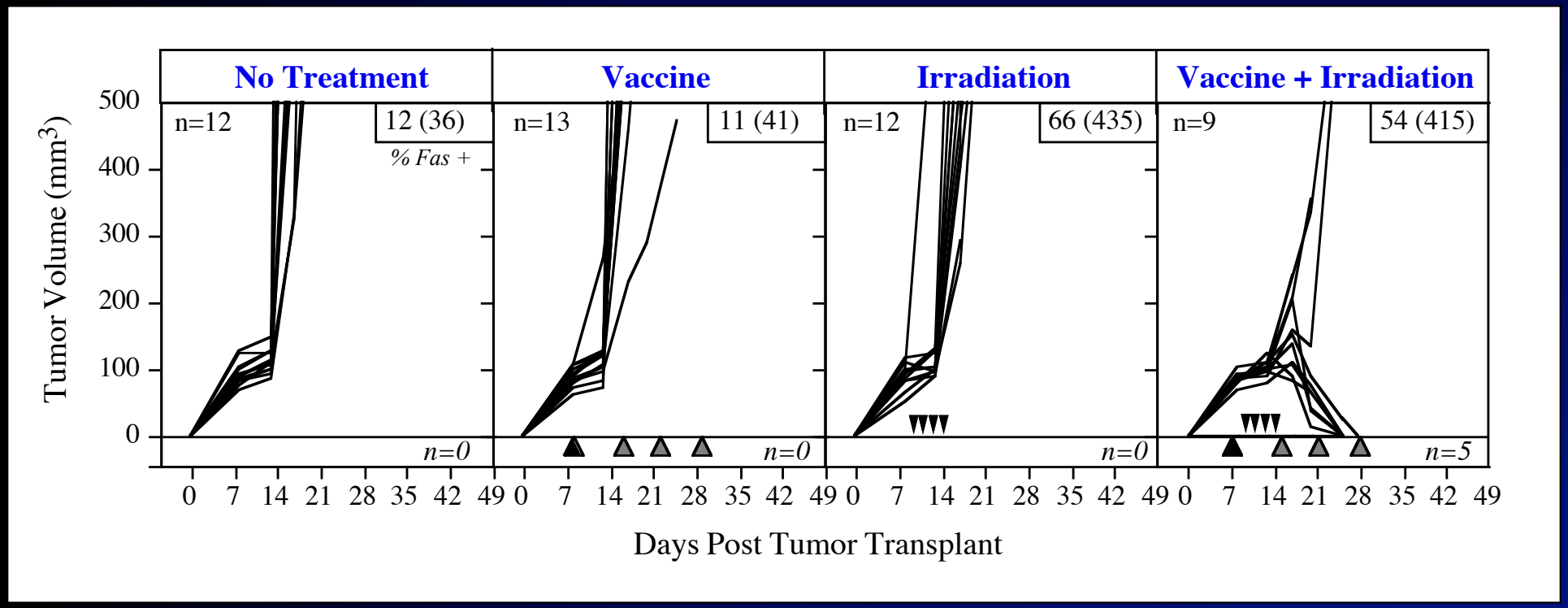
+ 3 Clinical Trials

Hodge, Guha, *Oncology* 2008

Treatment of tumor cells with sublethal therapy modulates tumor phenotype to render them more sensitive to immune mediated destruction

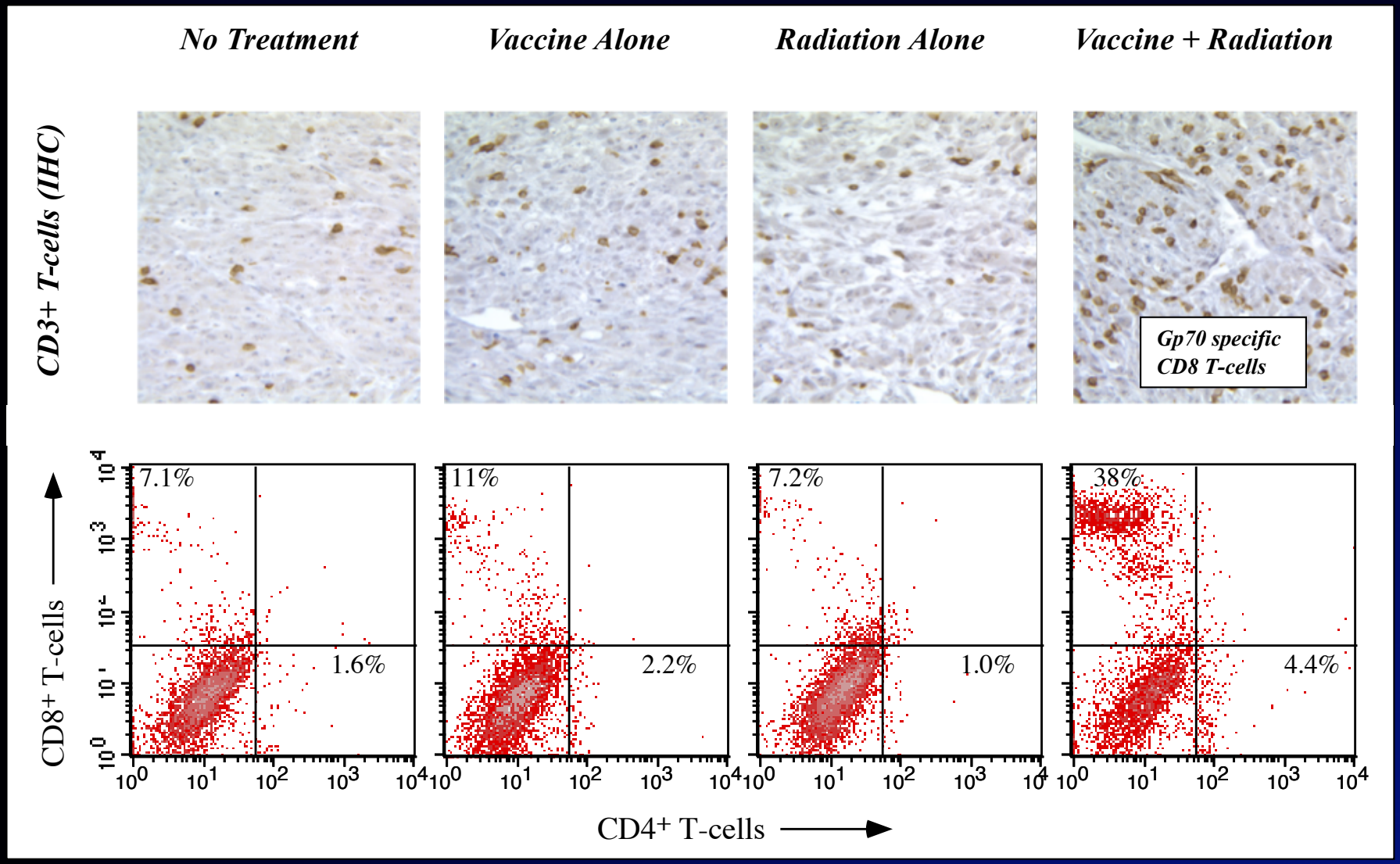
Combination Therapy : Vaccine + External Beam Radiation





J.W. Hodge, S. Gameiro. Cancer Biotherapy and Radiopharmaceuticals, January 2012.
M. Chakraborty, S.I. Abrams, C.N. Coleman, K. Camphausen, J. Schlom, J.W Hodge. Cancer Research, 15:4328-4337, 2004

Vaccine + Radiation: Tumor Infiltrating Cells and Antigen Cascade



J.W. Hodge, S. Gameiro. Cancer Biotherapy and Radiopharmaceuticals, January 2012.
M. Chakraborty, S.I. Abrams, C.N. Coleman, K. Camphausen, J. Schlom, J.W Hodge. Cancer Research, 15:4328-4337, 2004

Vaccine + Radiation: Induction of Antigen Cascade

CD4$^+$ T-cell Responses (stimulation index)

	CEA	p53
Vaccine + Radiation	3.9	3.8
Control	1.1	0.8

CD8$^+$ T-cell Responses (IFN-γ, pg/ml)

	CEA	p53	GP70
Vaccine + Radiation	2,000	320	28,940
Control	< 2.5	< 2.5	< 2.5

15X

Antigen Cascade Observed in a Phase II clinical trial of Metastatic Prostate Cancer Patients Treated with PSA/TRICOM Vaccine and Standard of Care Fractionated Radiation (PSA, PSMA, PAP, MUC-1)
Gulley, J., et al. Clinical Cancer Research, 14:5284-5291, 2008

M. Chakraborty, S.I. Abrams, C.N. Coleman, K. Camphausen, J. Schlom, J.W Hodge. Cancer Research, 15:4328-4337, 2004

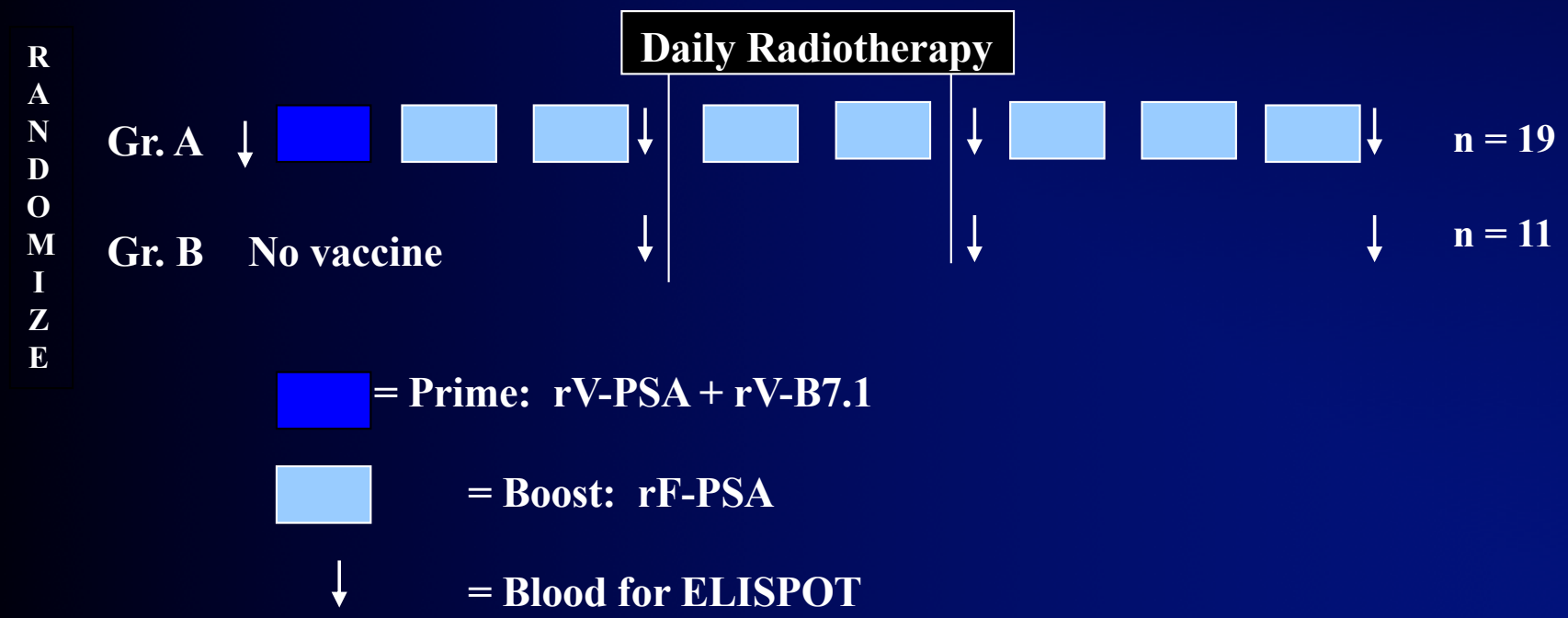
Antigen Cascade

- Cryptic determinants, epitope spreading, determinant spreading, cryptic epitopes, antigen spreading.
- Defined as an immunological response demonstrating epitopes distinct from and non-cross-reactive with the inducing epitope **(Including Neoepitopes)**
- Antigen cascade could be a possible mechanism for the regression of:
  - antigen variant tumors
  - tumors at distal sites
  - micrometastatic deposits

Randomized Phase II Trial: Radiotherapy ± Vaccine

Background: ~1/3 have PD after radiation therapy, often 2º to occult metastasis
Perhaps this could be improved with a well tolerated systemic therapy (vaccine)
The addition of vaccines to radiation → minimal risk of toxicity, potential synergy
Hypothesis: Immune responses can be raised to TAA despite local RT

30 patients with localized / locally advanced prostate cancer (most were high risk)



Gulley, Arlen, …Tsang, Camphausen, Coleman, Schlom, Dahut Clin Ca Res, 11(9):3353-3362 (2005)

Prostate Cancer Patients Receiving a PSA-based Poxviral Vaccine Generate Immune Responses to Multiple Tumor Antigens Not in the Vaccine (Antigen Cascade)

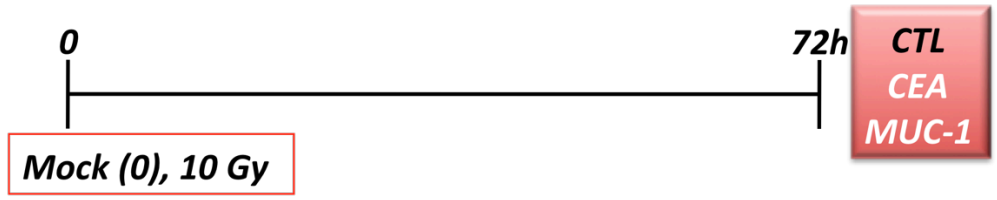
Patient	Sample	FMP	PSA3	PSMA	PAP	PSCA	MUC-1	HIV
3	pre	1/75,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000
	post 3	1/100,000	1/85,714	<1/200,000	1/85,714	1/85,714	1/23,077	<1/200,000
6	pre	1/20,690	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000
	post 3	1/22,222	1/66,667	1/85,714	<1/200,000	<1/200,000	1/60,000	<1/200,000
7	pre	1/21,429	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000
	post 3	1/21,429	1/60,000	1/200,000	1/85,714	<1/200,000	<1/200,000	1/200,000
8	pre	1/50,000	1/200,000	<1/200,000	<1/200,000	1/200,000	1/200,000	<1/200,000
	post 3	1/37,500	1/42,857	1/62,500	<1/200,000	<1/200,000	1/46,154	<1/200,000
11	pre	1/85,714	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000	<1/200,000
	post 3	1/54,545	1/75,000	<1/200,000	<1/200,000	<1/200,000	1/40,000	<1/200,000
12	pre	1/66,667	1/120,000	<1/200,000	1/200,000	1/200,000	<1/200,000	<1/200,000
	post 3	1/42,857	1/120,000	<1/200,000	<1/200,000	<1/200,000	1/35,294	<1/200,000

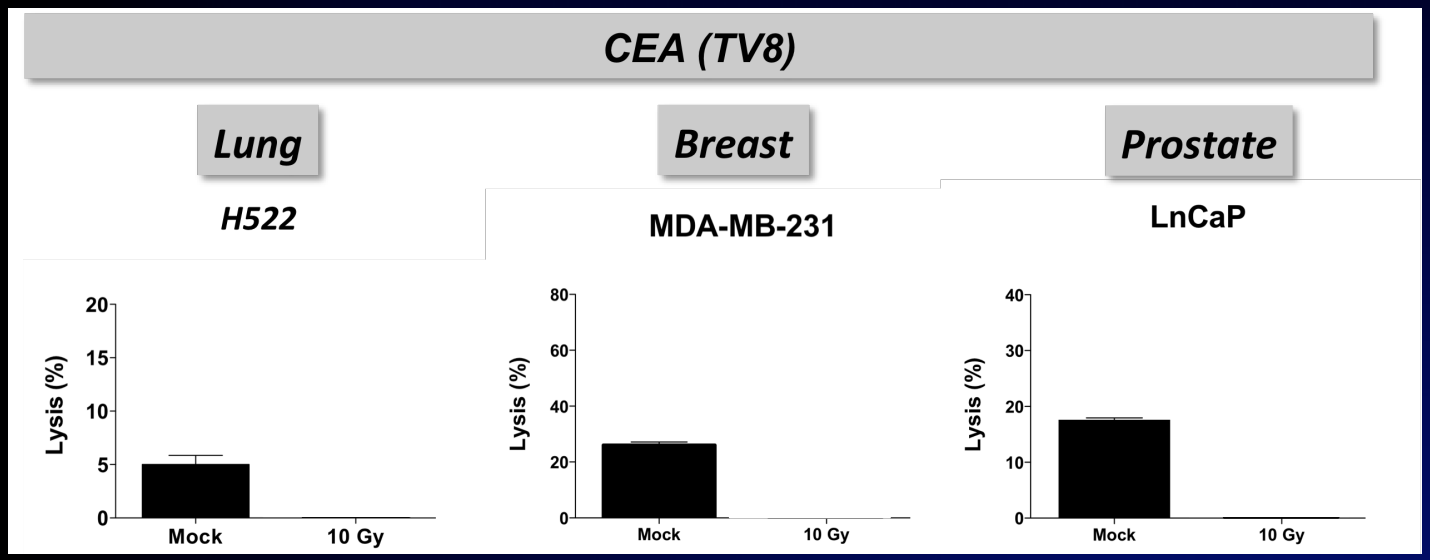
Results are expressed in precursor frequencies of specific T cells. ELISPOT assay for IFN-γ.

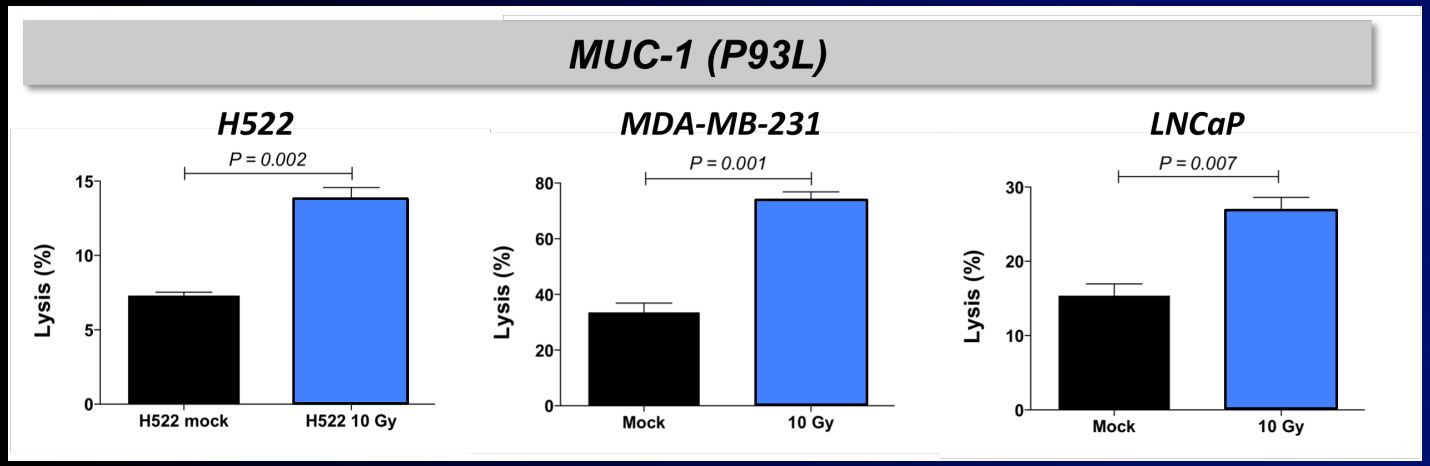
Gulley JL, Arlen PM, …Tsang K-Y, Yokokawa J, Hodge JW, Coleman CN, Camphausen K, Steinberg SM, Schlom J, and Dahut W. Clin. Cancer Res. 11:3353-3362, 2005

Effect of Radiation on Sensitivity to CTL Killing: Human Tumor Cells

Lung H522
Breast MDA-MB-231
Prostate LNCaP





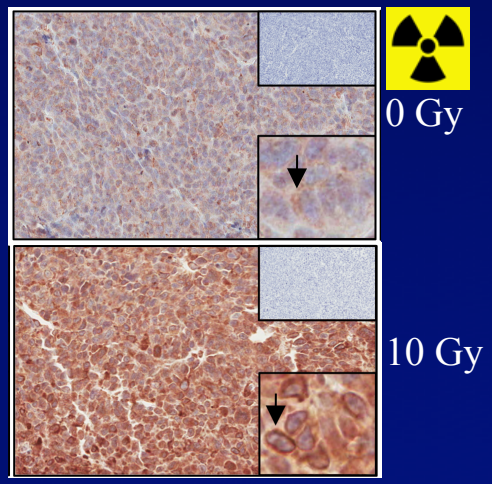


Mechanism:

-Modulation of Antigen Processing Machinery (APM)

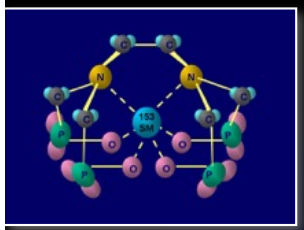
-Upregulation/ Translocation of Calreticulin

LnCaP



Gameiro, Jammeh, Wattenberg, Ferrone, Hodge. Oncotarget 5(2):403-416, 2014.

blood Calreticulin exposure by malignant blasts correlates with robust anticancer immunity and improved clinical outcome in AML patients
BLOOD, 29 DECEMBER 2016 • VOLUME 128, NUMBER 26



Translation: Use of Radionuclide Sm-153 with Vaccine

QUADRAMET is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenediaminetetramethylenephosphonic acid (EDTMP). It preferentially binds to osteoblastic metastatic tumor deposits in bone

^{153}Sm is currently FDA approved and clinically utilized for palliation of bone metastasis in multiple tumor histologies

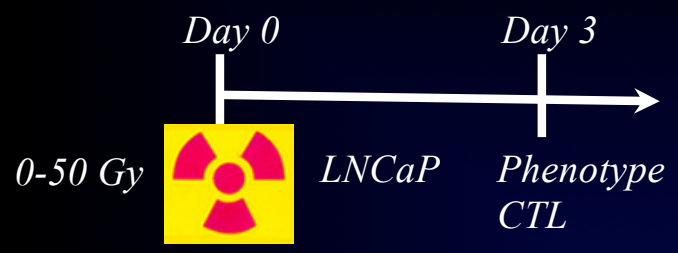
	Gamma	^{90}Y	^{153}Sm
Half-Life	0	64.1 hr	46.3 hr
Radiation Type	Pure γ	Pure β	Mixed β, γ
Dose to Tumor	10-20 Gy	18-25 Gy	17.5-80 Gy

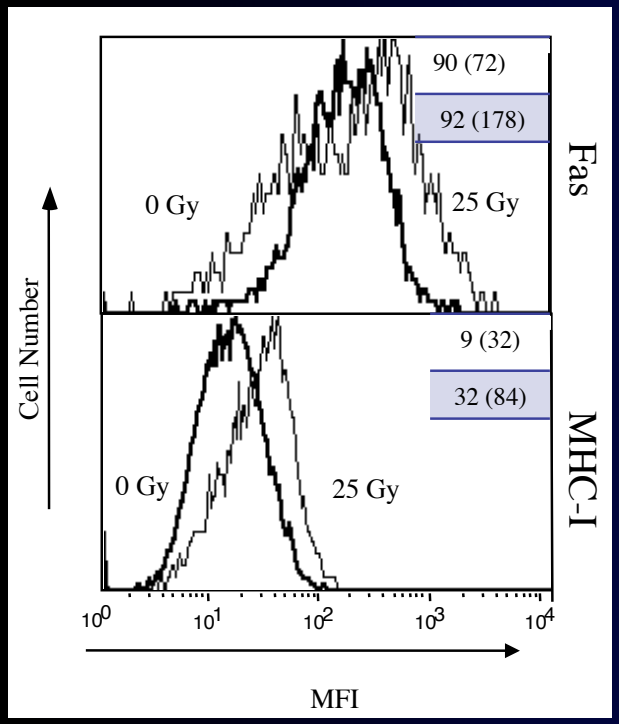
In-vitro Studies (human)

Do palliative levels of Sm-153 modulate metastatic human tumor phenotype? (0-50 Gy)?

Collaboration with NIH Nuclear Medicine

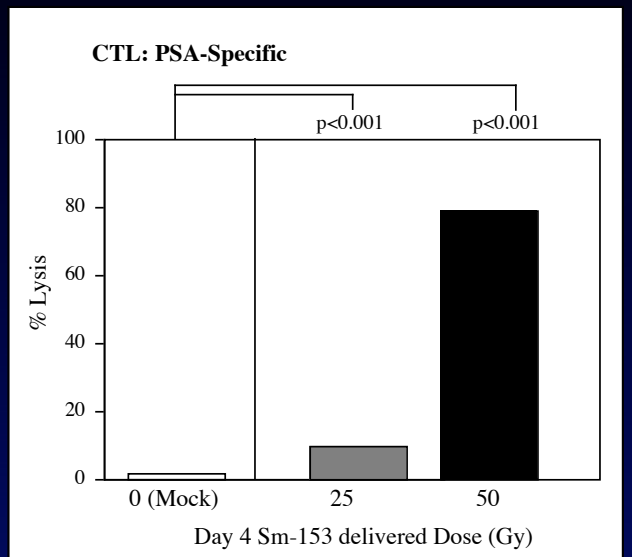
Treatment of LnCaP Prostate Cells with Palliative Levels of ^{153}Sm Modulates Phenotype, Upregulates TAA, and Increases Sensitivity to Antigen Specific CTL Killing

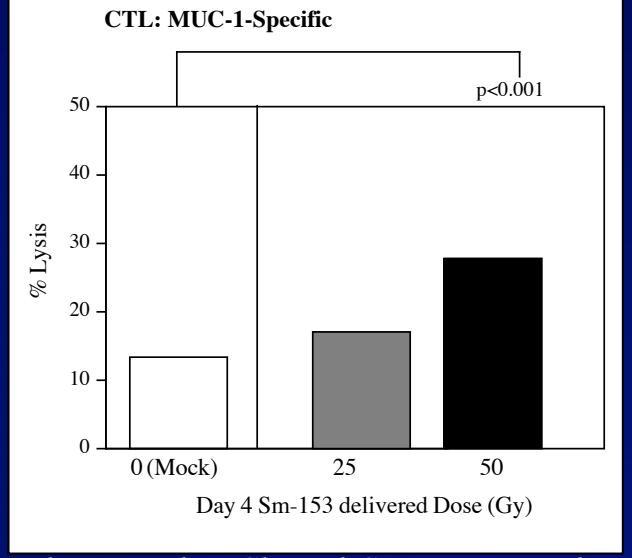




Tumor antigen genes

	0 Gy	25 Gy
PSA	1	2.79
PSMA	1	4.14
PAP	1	29.0
CEA	1	10.3
MUC-1	1	3.67



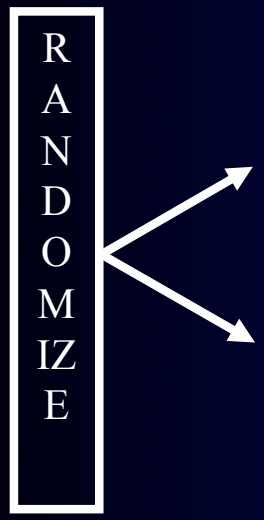


Phase II Clinical Trial

E. Wansley, M. Chakraborty, J. Carrasquillo, K. Camphausen, M. Becker, W. Goeckeler, J. Schlom, and J.W. Hodge, Clinical Cancer Research. 14:4316-4325, 2008

^{153}Sm +/- PSA-TRICOM

Patient Population: CRPC Metastatic to bone



Arm A: PSA-TRICOM + ^{153}Sm (n=34)

Arm B: ^{153}Sm (n=34)

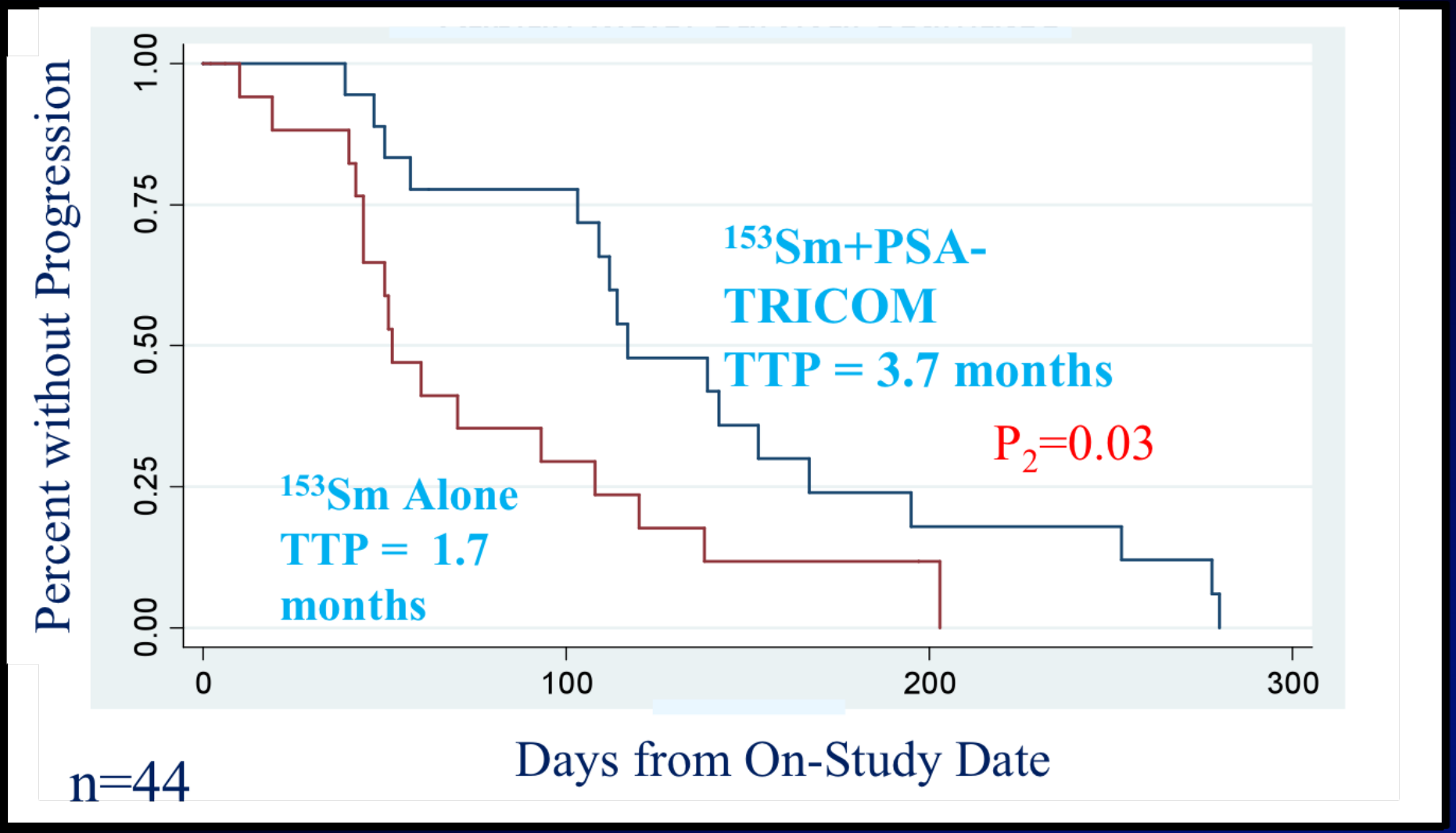
Vaccine: rV-PSA/TRICOM s.c. d 1
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

^{153}Sm: 1 mCi/kg **d8**, may be repeated
q 12 wks upon hematologic recovery.

NCI# 7678 PI Gulley
CINJ (DiPaola) and UC (Stadler)

^{153}Sm +/- PSA-TRICOM

- Final data of n = 44 patients with mCRPC
- 1º endpoint: PFS
- Progression defined by utilizing PCWG, but not PSA criteria



Heery…Gulley ASCO GU 2013

PCWG = Prostate Cancer Working Group response criteria

Foundation for Planned Phase II Trial (PROSTVAC + ^{223}Ra (Xofigo)

Combinatorial Therapies: Vaccine and Radiation

Immunogenic Modulation

Clinical Trial

1) External-Beam Radiation (Photon and Proton)

Local Therapy
Dosage Rates
Fractionation Schedules

J.W. Hodge, S. Gameiro. Cancer Biotherapy and Radiopharmaceuticals, January 2012.
S. Gameiro, J.W. Hodge, Int J. Rad Oncol Biol Phys, 2016

√

2) Radiofrequency Ablation

Local Therapy
Thermal Damage

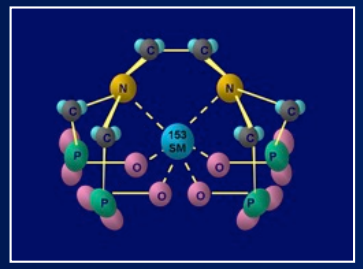
S. Gameiro, .J. Hodge, PLOS One, Sept 2013.

3) Brachytherapy

Local Therapy
Gamma Emission
^{125}I
Chronic exposure

J.W. Hodge, S. Gameiro. Cancer Biotherapy an Radiopharmaceuticals. Jan 2012.

4) Radionuclide Chelate for bone metastases

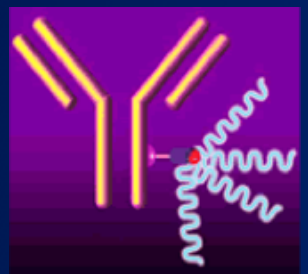


Systemic Therapy
^{153}Sm, ^{223}Ra

E. Wansley, M. Chakraborty, J. Carrasquillo, S. Yu, C. Paik, K. Camphausen, M. Becker, W. Goeckeler, J. Schlom, J.W. Hodge. Clinical Cancer Research. 14:4316-4325, 2008
A. Malamas, J.W. Hodge, Ocotarget, 2016

√

5) Radiolabeled anti-tumor antigen monoclonal antibody



Systemic Therapy
Antibody specificity
^{90}Y-Col-1 (anti-CEA)

A. Gelbard, C. Garnett, S. Abrams, V. Patel, S. Gutkind, C. Palena, K. Tsang, J. Schlom, J.W. Hodge. Clinical Cancer Research. 12:1897-1905.

Immunogenic Modulation

Immune Conditioning

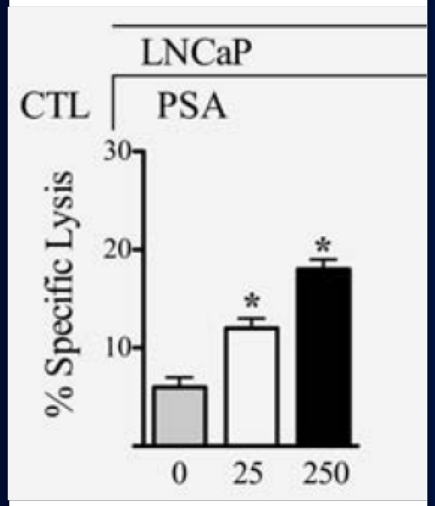
External-Beam Radiation

Multiple IO Combinations

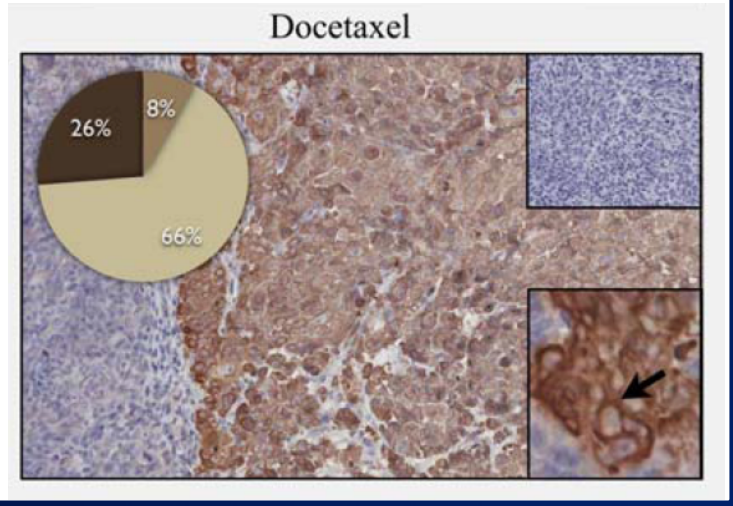
Taxanes

Can We Define Mechanism of Immunogenic Modulation With Chemotherapy (Docetaxel)?

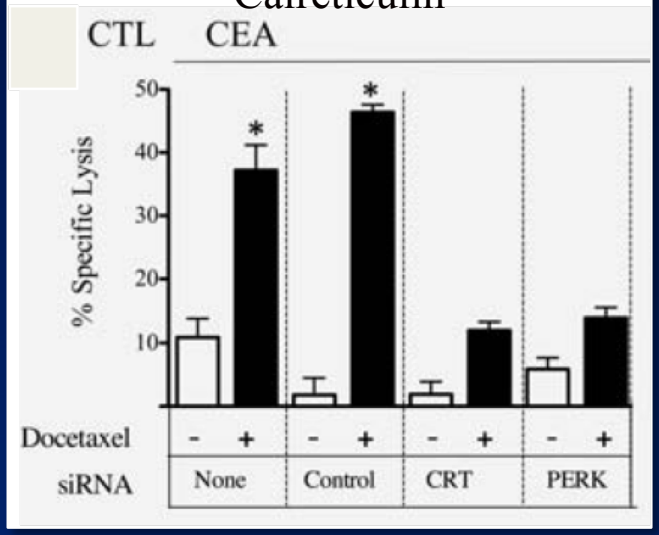
Increased CTL Sensitivity



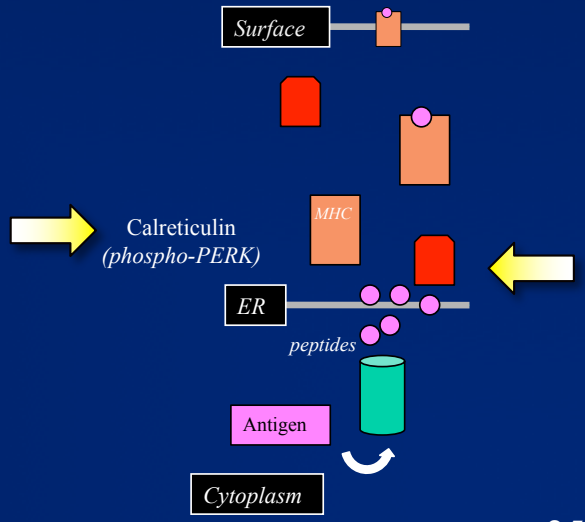
APM Modulation and Calreticulin Translocation



Dependence on Calreticulin



Chemotherapy Resistant Cells Treated with Docetaxel Still Undergo Immunogenic Modulation

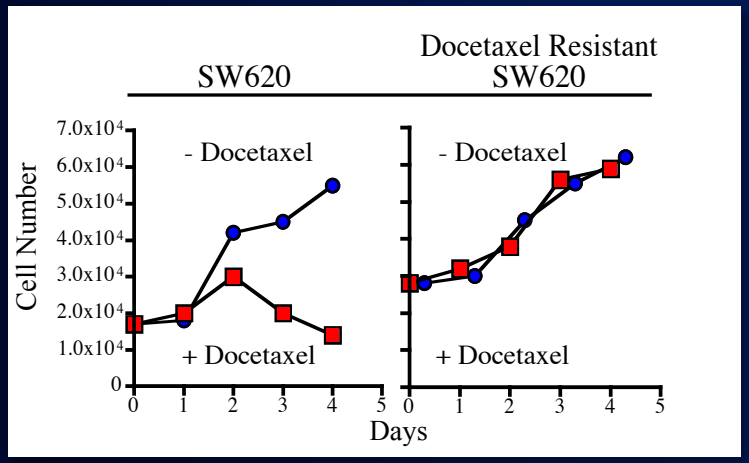


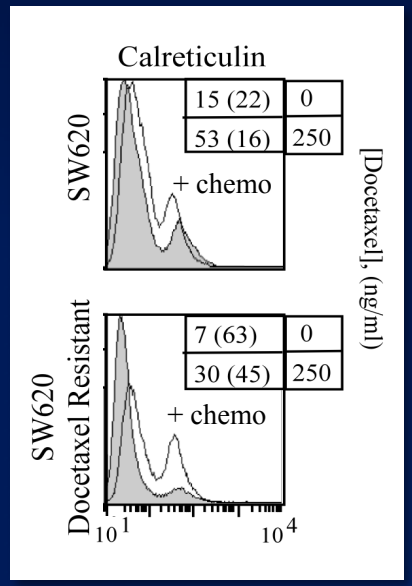
Hodge, Garnett, Farsaci, Ferrone, Gameiro. Int J. Cancer 133(3):624-636, 2013.

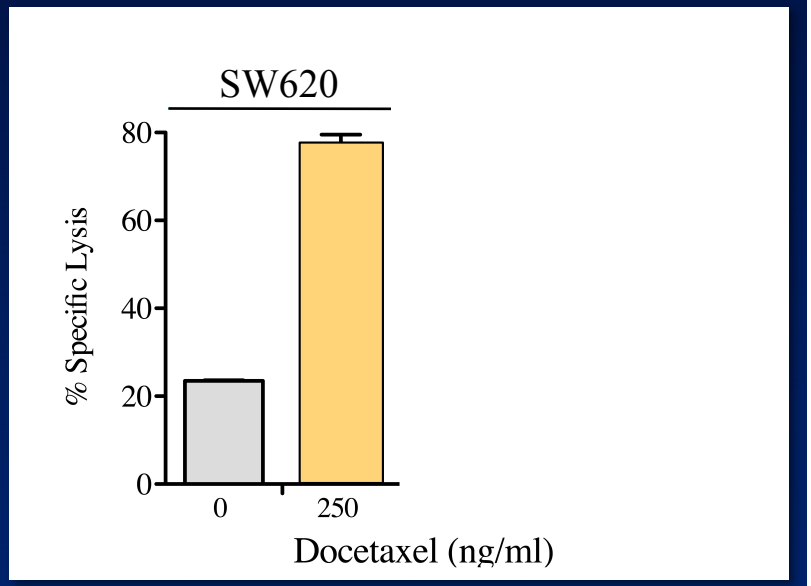
Do Cells Resistant to Docetaxel Increase Sensitivity to CTL Following Docetaxel Treatment?

SW620 Parental → SW620-Docetaxel Resistant

Docetaxel
(increased 3-fold every 3 weeks (2 passages) until MTD
(Final cell line=3000 ng/ml)







- immunogenic modulation was distinct from immunogenic cell death
- chemotherapy induced modulation of antigen-processing machinery and calreticulin
- chemotherapy resistant cells increased CTL sensitivity after chemotherapy exposure

- Also seen with Paclitaxel

→ Foundation for Phase II Clinical Trial:
Docetaxel + PANVAC in Breast Carcinoma

Hodge, Palena, Gameiro. Int J. Cancer 133(3):624-636, 2013.

Combination Therapy Vaccine Plus Chemotherapy

Original Investigation

Docetaxel Alone or in Combination With a Therapeutic Cancer Vaccine (PANVAC) in Patients With Metastatic Breast Cancer

A Randomized Clinical Trial

Christopher R. Heery, MD; Nuhad K. Ibrahim, MD; Philip M. Arlen, MD; Mahsa Mohebtash, MD; James L. Murray, MD; Kimberly Koenig, MD; Ravi A. Madan, MD; Sheri McMahon, RN; Jennifer L. Marté, M
Seth M. Steinberg, PhD; Renee N. Donahue, PhD; Italia Grenga, MD; Caroline Jochems, MD, PhD; Benedetto Farsaci, MD; Les Folio, MD; Jeffrey Schlom, PhD; James L. Gulley, MD, PhD

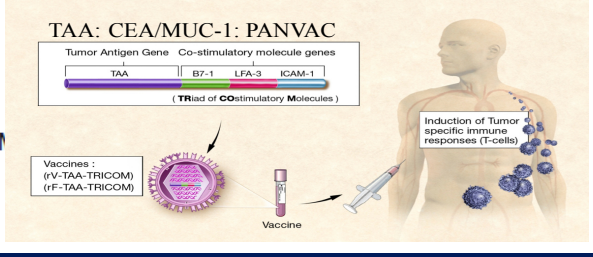
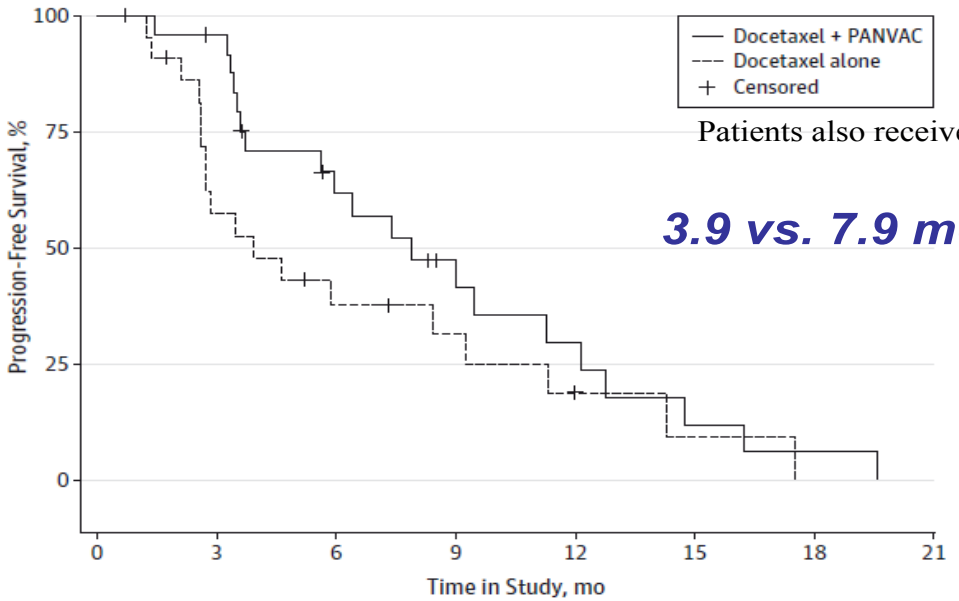


Figure 2. Progression-Free Survival in the 2 Treatment Arms

JAMA Onc, Aug 20, 2015



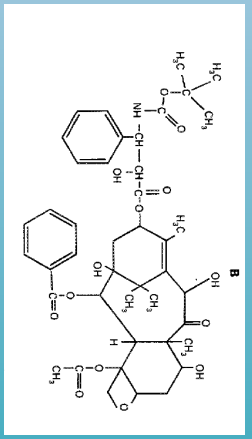
Docetaxel alone	23	12	7	5	2	1	0
Combination therapy	25	23	13	8	5	2	1

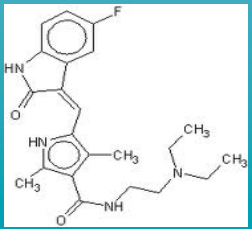
Patients also received steroid prior to docetaxel)

3.9 vs. 7.9 months

The combination treatment group underwent a median of 5 treatment cycles over 7.9 months; the docetaxel group, 3 cycles over 3.9 months (1-sided $P = .09$, which met the predefined statistical definition of $P \leq .10$); hazard ratio, 0.65 (95% CI, 0.34-1.14). Median potential follow-up was 42.8 months.

Immunotherapy Combinations: Chemotherapy, Radiation, Targeted Small Molecules





- Immunogenic Modulation Can be Exploited for Combination of Standard-of-Care and Emerging Experimental Therapeutics with Immunotherapy
  - Taxanes (Docetaxel, Paclitaxel, nab-Paclitaxel)
  - Cisplatin/5-FU, Cisplatin/Vinorelbine
  - Radiation (EBRT, Proton, Brachy, RAIT, Chelate, RFA)
  - PARPi (Olaparib)
  - TKIs (Sunitinib/Sorafanib/Cabozantinib)
  - HDAC Inhibition (Vorinostat, Entinostat)
  - Endocrine Deprivation

    (Enzalutamide, Abiraterone, Tamoxifen, Aromatase inhibitors); independent of ER or AR Expression (TNBC)

Immunogenic Modulation

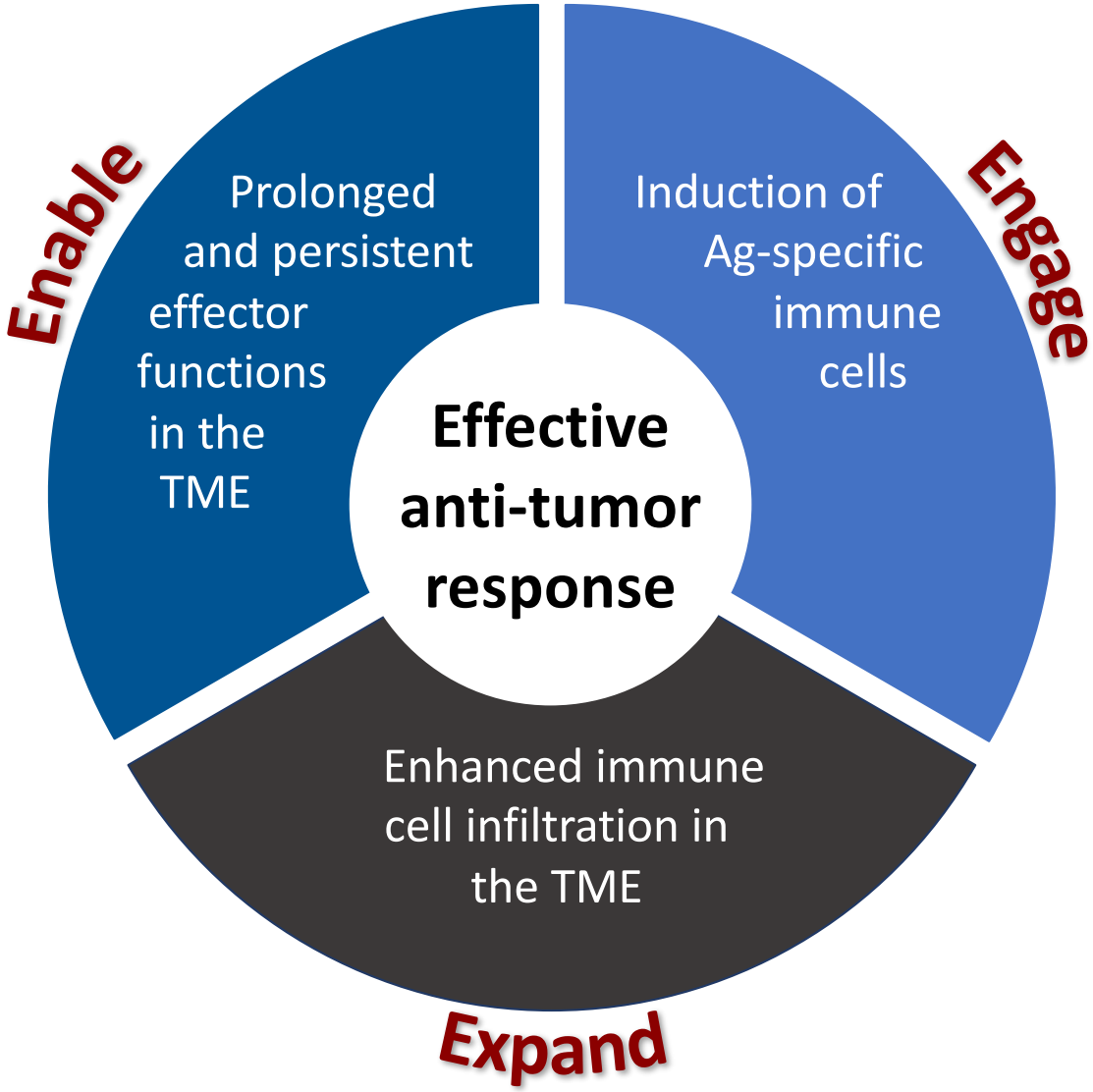
Immune Conditioning

External-Beam Radiation

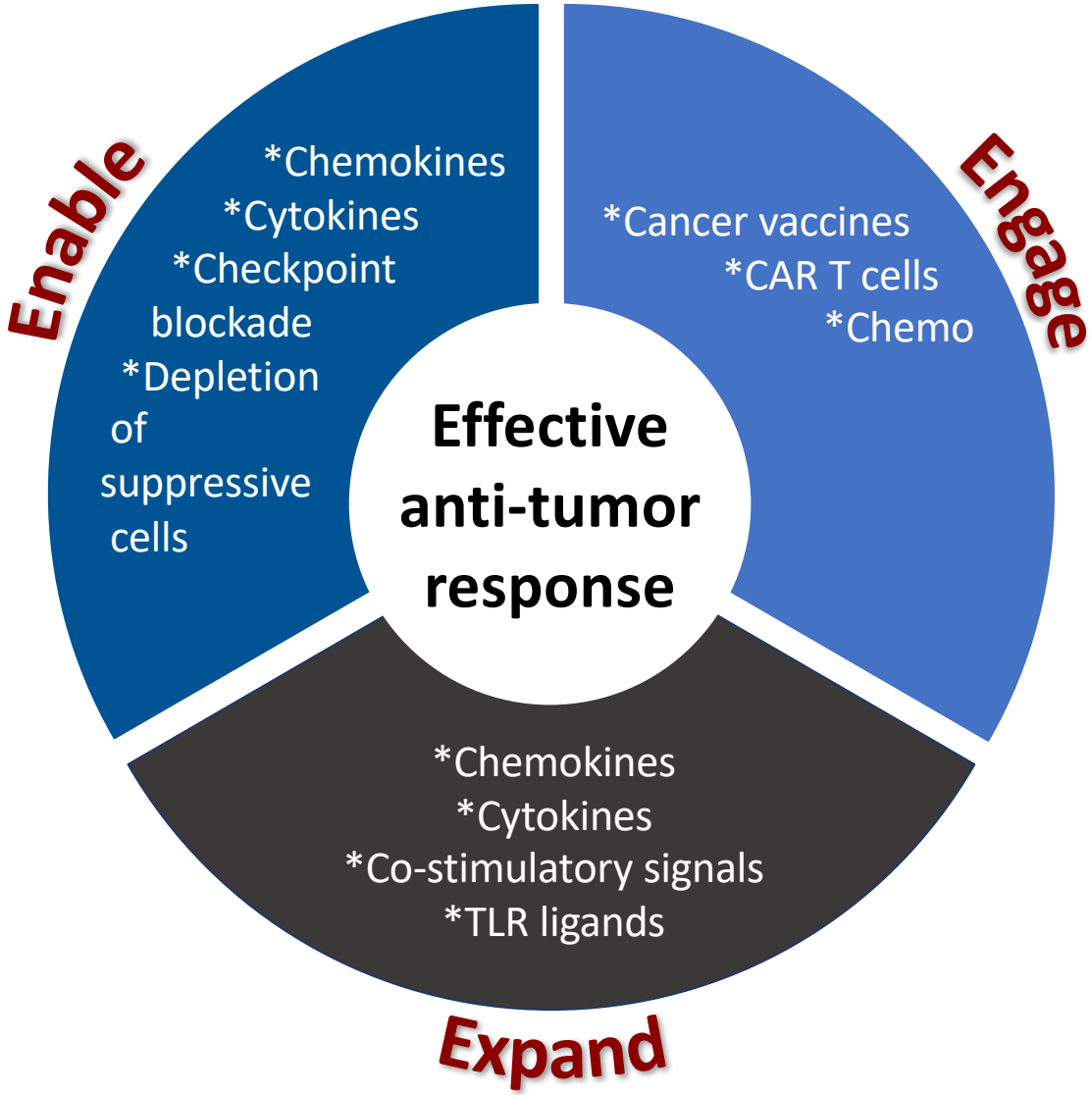
Multiple IO Combinations

Taxanes

Hypothesis: Effective Therapy of Established Tumors Requires Multiple Agents Targeting Diverse Immune-Tumor Interactions



Hypothesis: Effective Therapy of Established Tumors Requires Multiple Agents Targeting Diverse Immune-Tumor Interactions



Multifactoral Approach to Cancer Immunotherapy

I. ***Engage*: Generation of an Effective Immune Response**

- Vaccine: TAA, neoantigens
- Immunocytokine: IL-15 superagonist (ALT-803)
- IDOi: enhance DC function

II. ***Expand:* Maintenance of an Effective Immune Response at the Tumor Site/ Reduction of Immunosuppressive Entities**

- anti-PD-L1 (avelumab)
- anti-PD-L1/TGFβR2 (M7824)
- Immunocytokine: NHS-IL12
- Agonist MAbs to GITR, OX40, 41BB
- IDOi
- anti-PD-L1/IL15-FP (FP-809)

III. ***Enable:* Modification of the Tumor/Tumor Microenvironment to Enhance Immune-mediated Effectiveness**

- Immunogenic tumor cell death
- Immunogenic modulation of tumor phenotype
- anti-PD-L1/TGFβR2 (M7824)
- IL-8R antagonist

IV. **Adaptive Clinical Trial Designs Encompassing I, II, and III**

Questions?

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National Institutes of Health