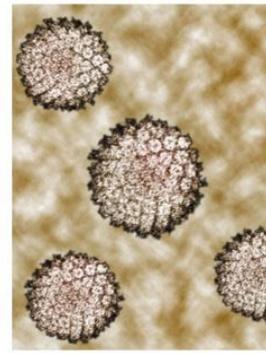# Radiation therapy
and
anti HPV treatments

Eric Deutsch
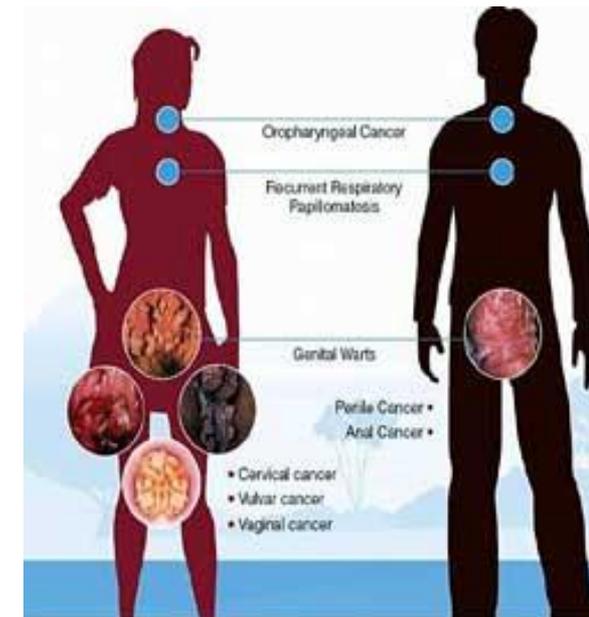
Gustave Roussy Cancer Campus

HPV

Le Papillomavirus humain (HPV)

- More than 98% <u>cervix cancer</u>, (IARC 2007).

- 85% of squamous cell <u>anal cancer</u>, (Daling JR, Cancer 2004).

- 50% of <u>penile cancer</u>, (Hernandez BY, Cancer. 2008).

- 33-72% of <u>oropharyngeal cancers</u> (Kreimer AR, Cancer Epid Biomarkers, 2005).

→26,000 cancers each year, 18,000 females

and 8,000 males (WU, JAMA 2012).
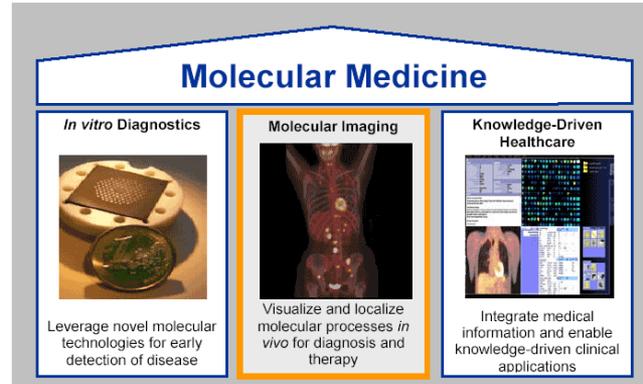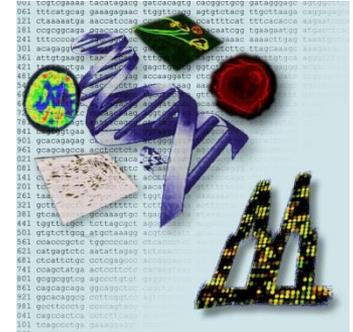
HPV & cancer : Clinical impact?

- Prevention

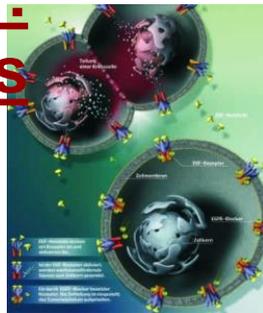(primary vaccination, secondary pap smear..)

HPV & cancer : Clinical impact?

- Prevention (primary vaccination, secondary pap smear..)

- Biomarker : predictive and prognostic

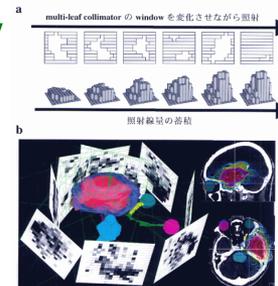# HPV as a biomarker in head and neck cancers :

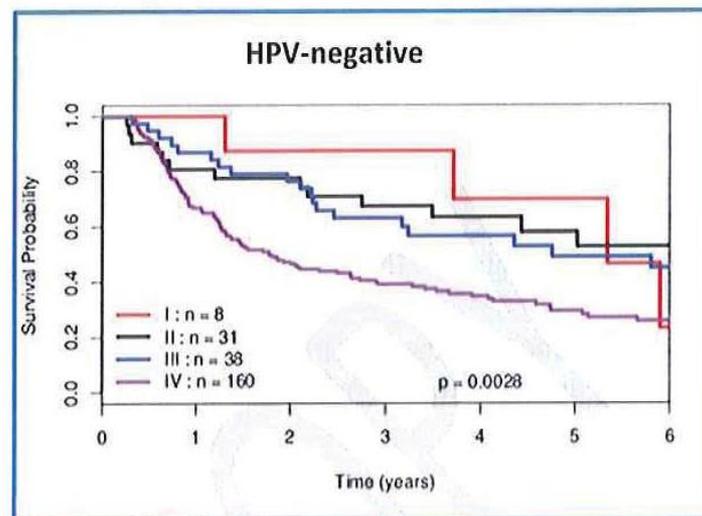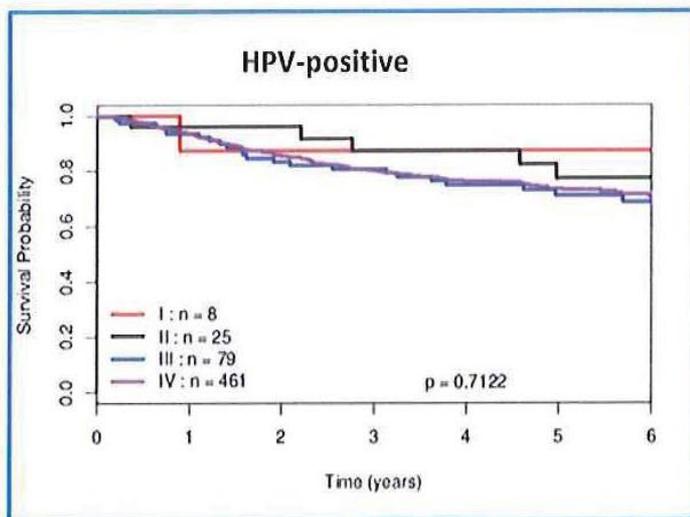**HPV negative :**
Response less
likely

Radiation sensitizer

HPV Positive :
Response likely
Optimise radiotherapy
Decrease late effects

OS by UICC/AJCC TNM Stage (7th edition)

HPV-positive	Events / Total	3 years	5 years	p value	HPV-negative	Events / Total	3 years	5 years	p value
Total	164 / 573	80% (77-84)	74% (70-78)		Total	161 / 237	49% (42-55)	38% (32-45)	
Stage I	1 / 8	88% (67-100)	88% (67-100)		Stage I	4 / 8	88% (67-100)	70% (42-100)	
Stage II	5 / 25	87% (75-100)	78% (62-97)		Stage II	16 / 31	67% (53-86)	58% (42-80)	
Stage III	27 / 79	81% (72-90)	71% (62-83)		Stage III	24 / 38	63% (49-80)	50% (36-70)	
Stage IV	131 / 461	80% (76-84)	74% (70-78)	0.560	Stage IV	117 / 160	39% (32-48)	30% (23-39)	0.004

Courtesy Brian O'Sullivan

Proposed Anatomic Stage Grouping

Recursive Partitioning Analysis (RPA) model:
- Based on an optimized binary partition of ordinal T- or N- categories
- Derived *stage* groups with minimal hazard difference within same stage
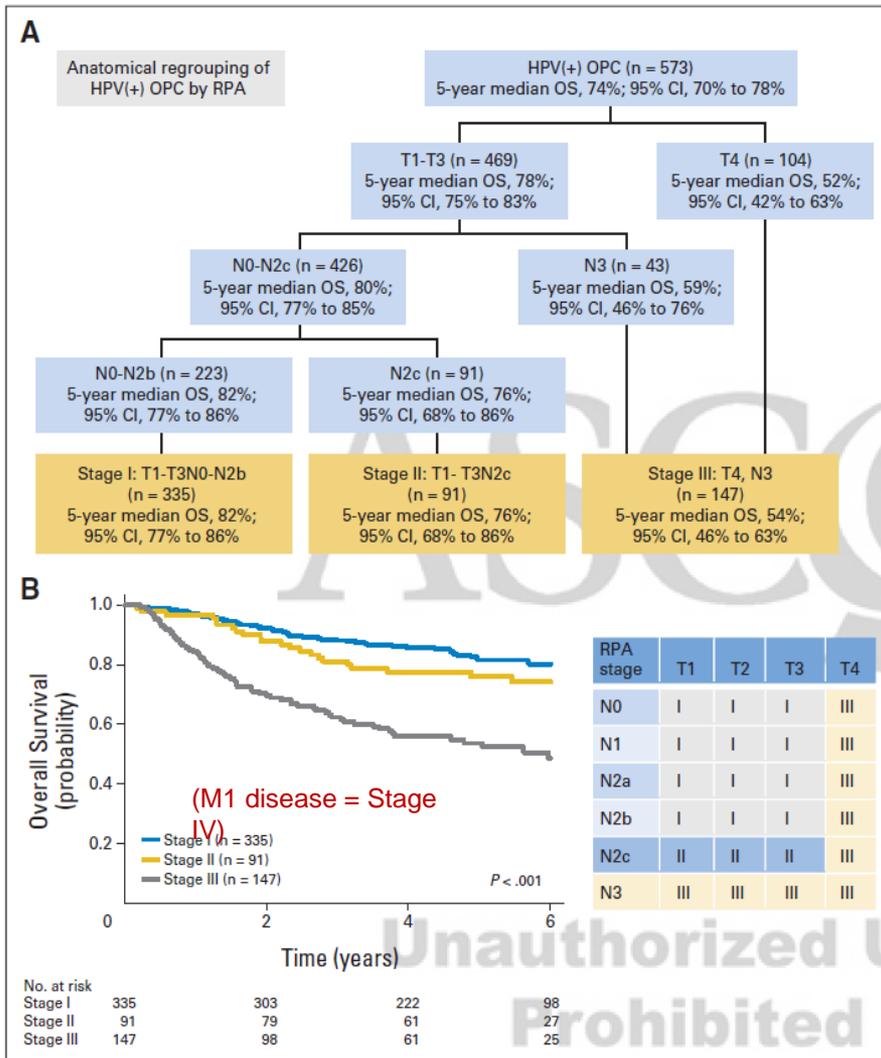
- Better performance than alternative AHR Model
- Consistent with current de-intensification trial criteria designed on the basis of the disease behaviour by T and N criteria (eg. NRG HN 02)
- Better "Grid" than AHR Model

Courtesy Brian O'Sullivan

HPV & cancer : Clinical impact?

- Prevention (primary vaccination, secondary pap smear..)

- Biomarker : predictive and prognostic

- Development of tailored therapies : pharmacological agents? therapeutic vaccines?

Cidofovir :
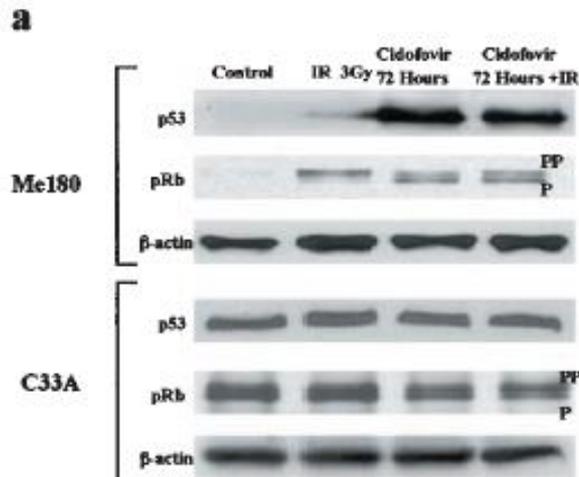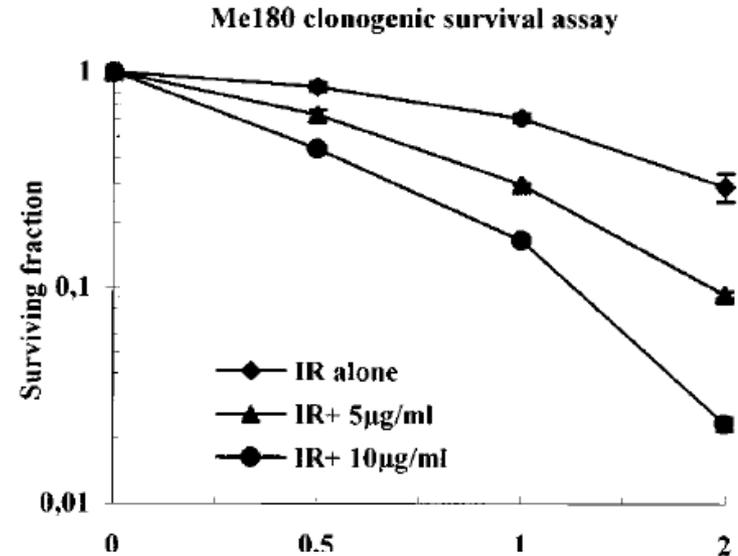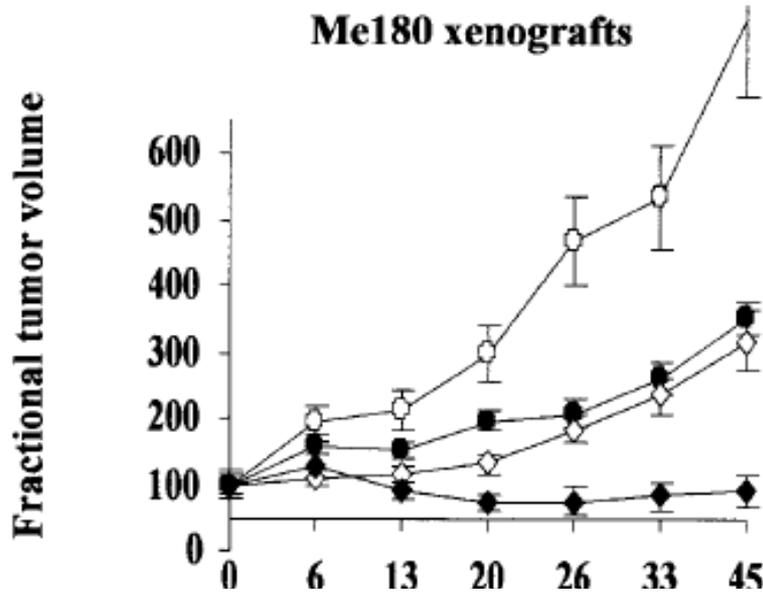## mechanism of action the antiviral agent
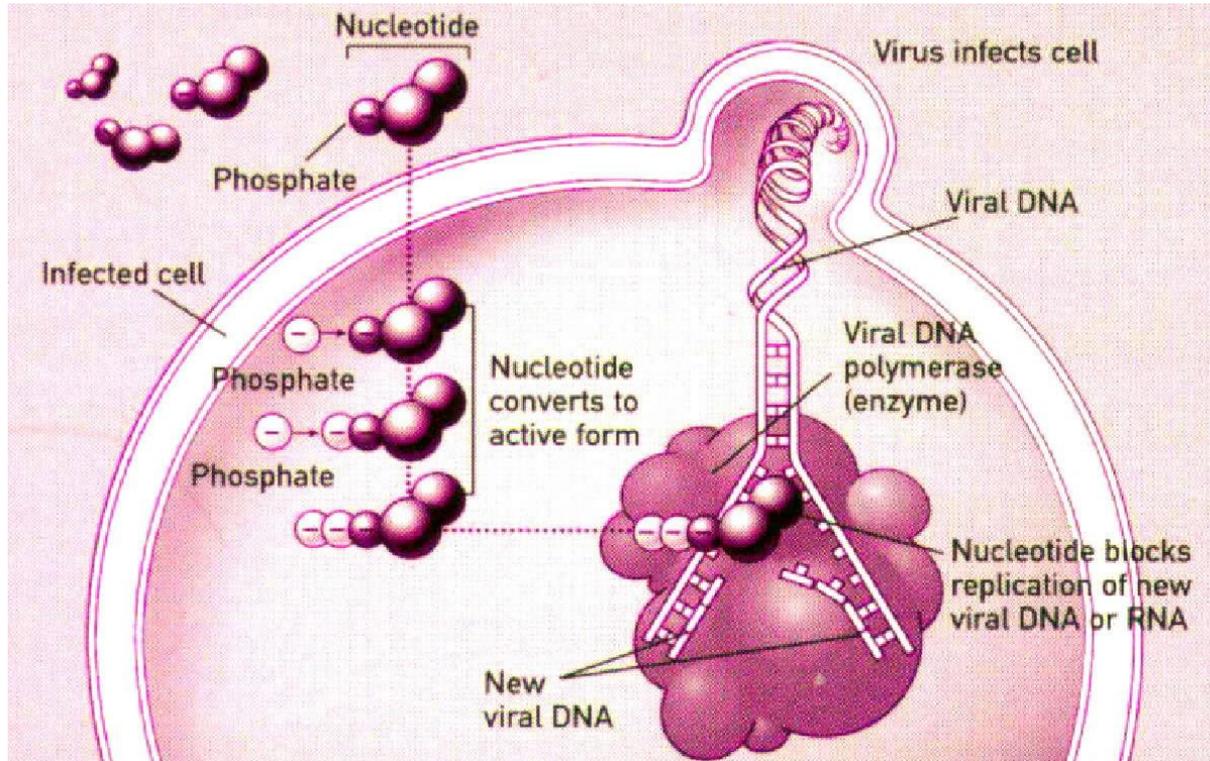
■ (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl) Cytosine: [(*S*)-HPMPC]

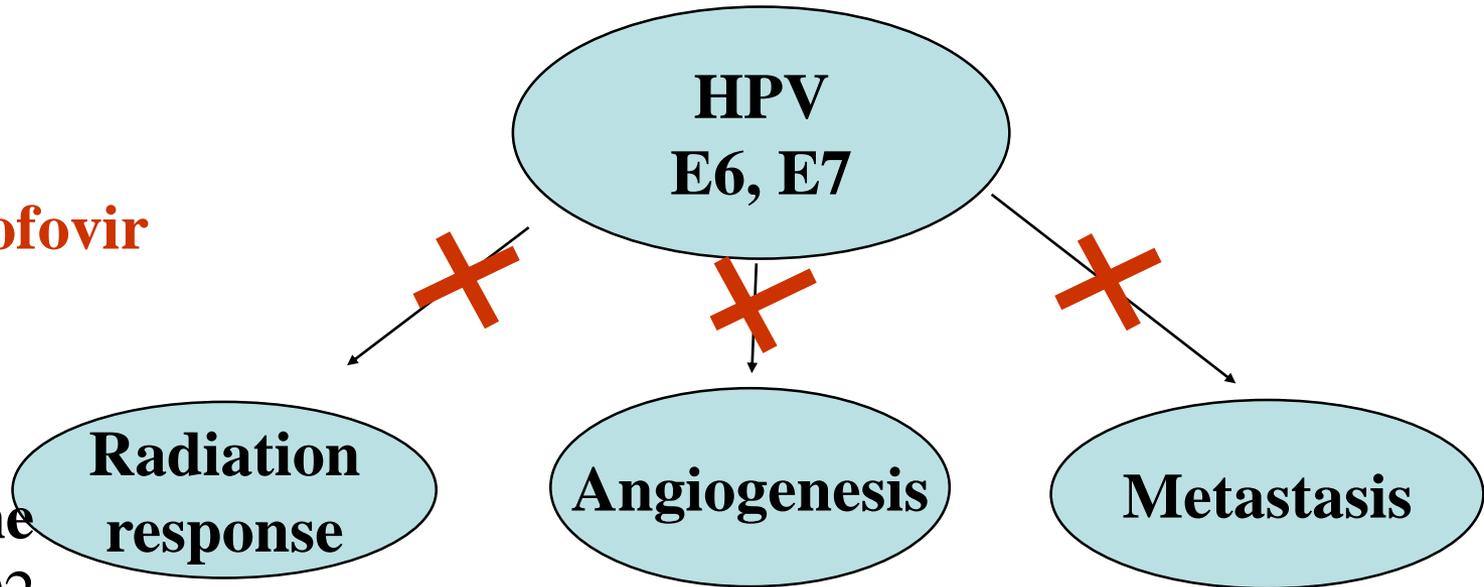■ Acyclic Phosphonate nucleosid

■ Half-life *in vivo* : 48 h

- **Johnson JA, Antimicrob Agents Chemother 1999;43(5):1198-205.**
- **Andrei G, Oncol Res 1998;10(10):523-31.**
- **Andrei G, Oncol Res 1998;10(10):533-9.**

Me180 cell line

Me180 xenografts

Me180 clonogenic survival assay

- ◆ IR alone
- ▲ IR+ 5µg/ml
- ● IR+ 10µg/ml

Abdulkarim et al. Oncogene, 2002
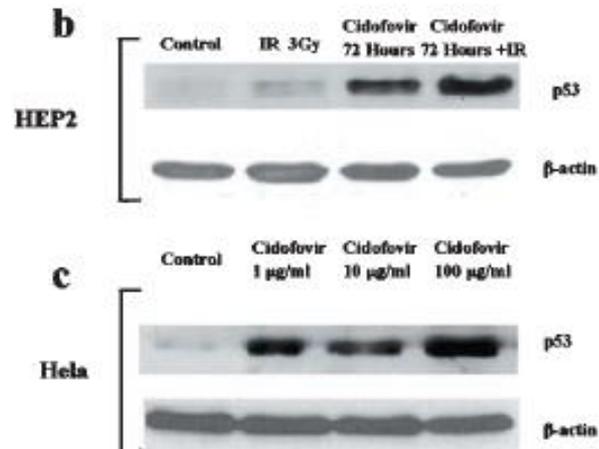
Cidofovir : translational approach

Cidofovir

Oncogene
2001,2002
Lancet Oncol
2003
Rad Res
2006
Plos One
2009

« HPV-RX » :
antiviral agent + chemoradiation phase I trial

J_0 ──────────────────────────────────────→ DLT

S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
CDV	CDV		CDV		CDV		CDV		CDV
			External beam 45 Grays (fraction hebdo : 1,8 Grays)						Brachy 15 Gy
			chemotherapy C Paraplatine® AUC=2.5						chemo C

Tumor biopsy ↑   ↑   ↑

C= Weekly Carboplatin, AUC=2,5

CDV=Weekly Cidofovir

HPV vaccines

Two HPV vaccines are currently on the market: Gardasil (Merck) and Cervarix (Glaxo).

Both vaccines are based on recombinant **L1 viral protein**, assembled in virus-like particles (VLPs) and protect **against high-risk HPV 16 and 18**, responsible of around 60-70% of cervical cancer.

Gardasil also protects **from low risk HPV 6 and 11,** responsible of the majority of genital warts.

HPV L1 VLP Vaccine Synthesis

L1 gene on HPV DNA
L1 gene inserted into genome of yeast cell
Yeast cell DNA
Transcription
mRNA
tRNA
rRNA
Translation
Capsid proteins
Empty viral capsids
Elicits immune response in host
Yeast Cell (or Baculovirus Expression System)
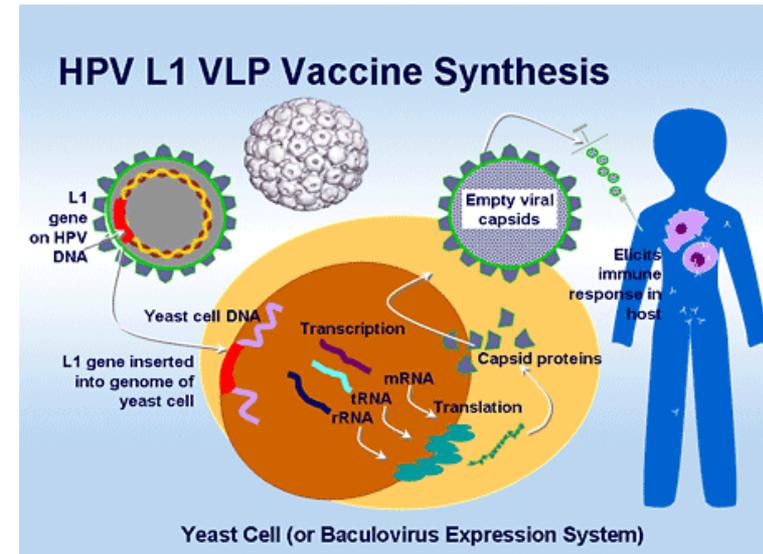
Partridge EE, Med Ed

BOTH ARE <u>PROPHYLACTIC</u> VACCINES ONLY!!

HPV-E7 vaccine

Targets antigen presenting cells.
Shigatoxine receptor
expressed on dendritic cells
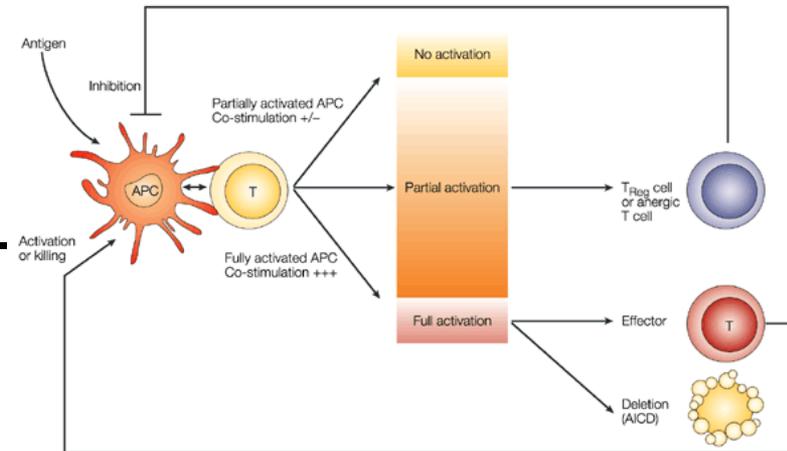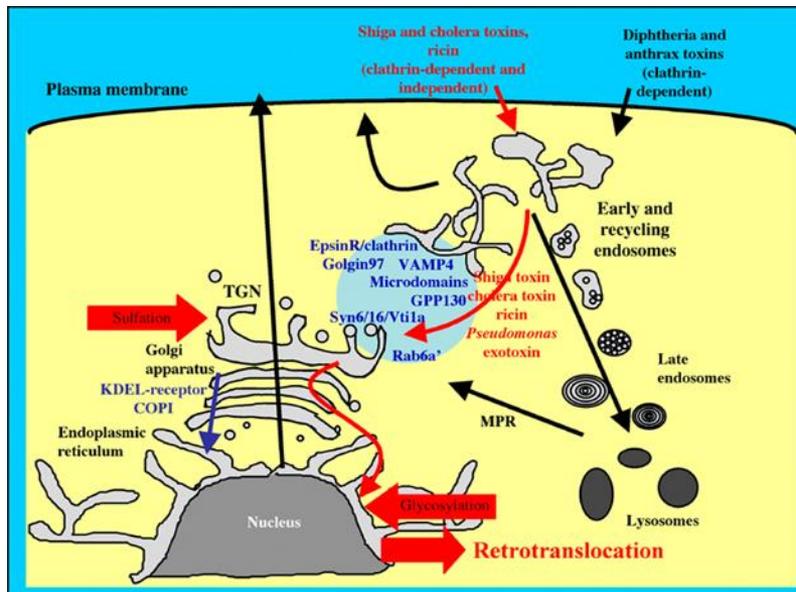
Johannes, Gene Ther 2005

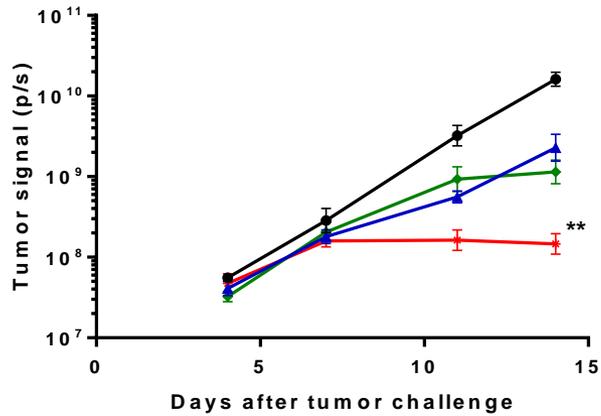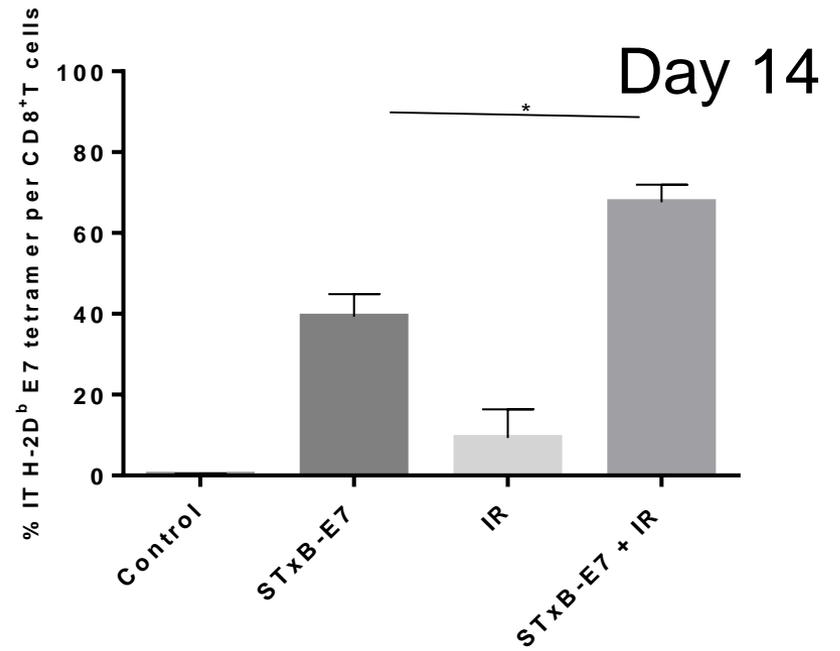# Combination treatment by local radiation and therapeutic STxB-E7 vaccine elicits an effective antitumor response.
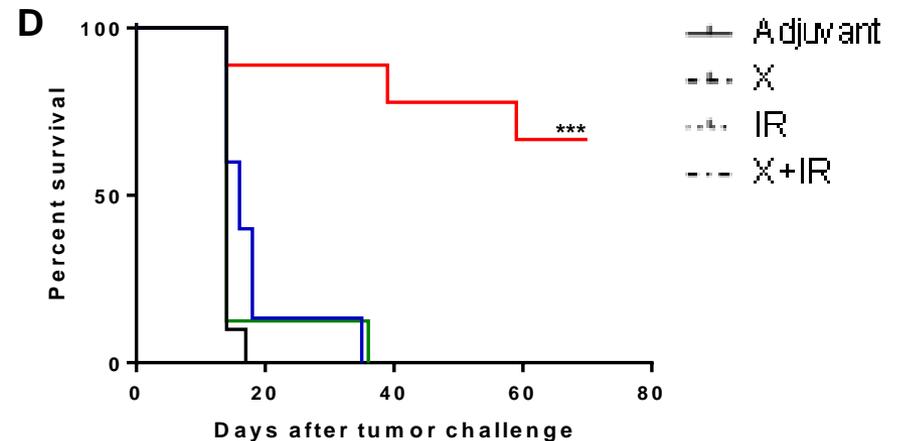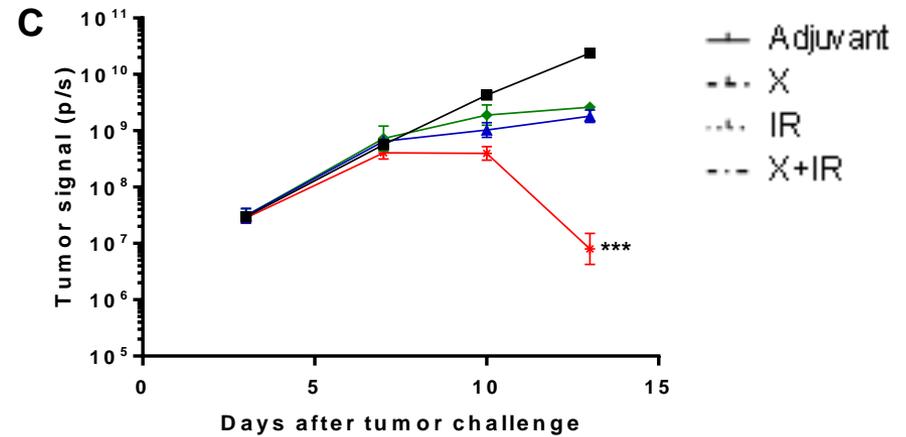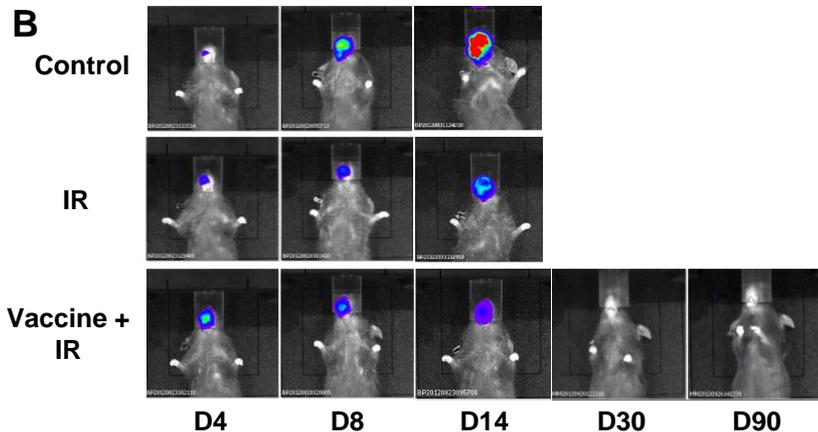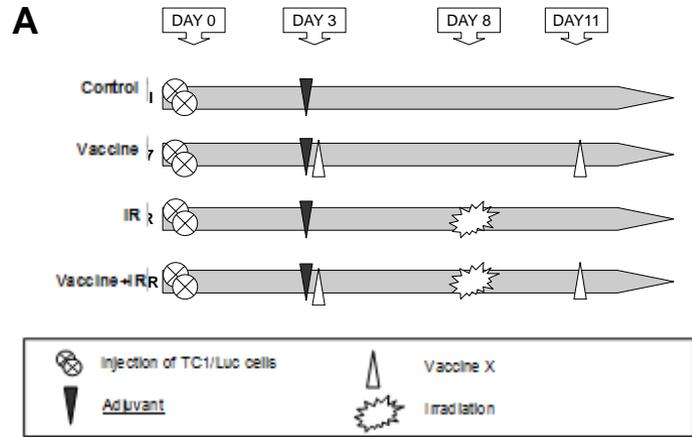
Adjuvant effect?
Threshold dose?
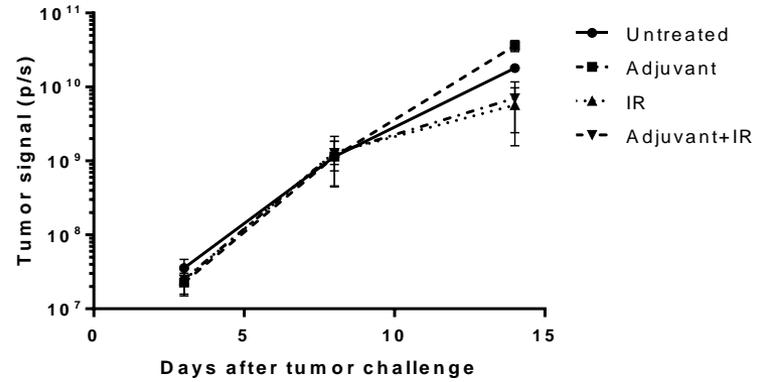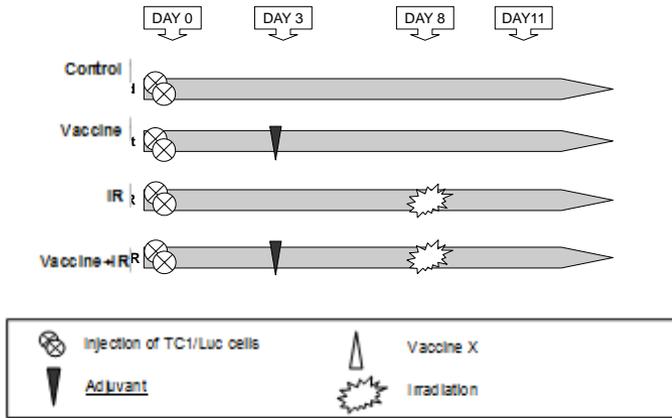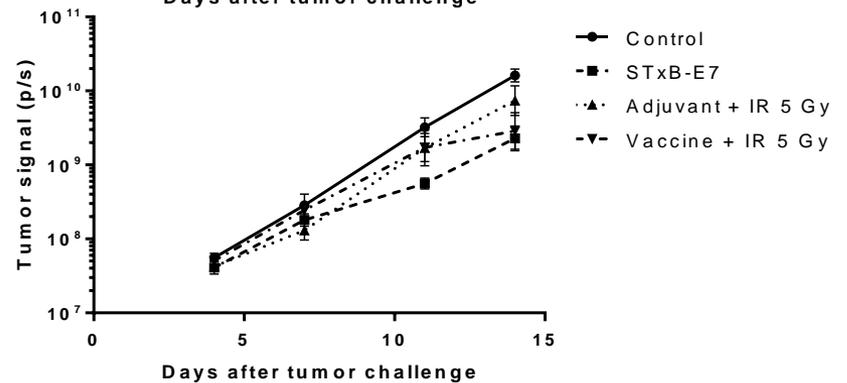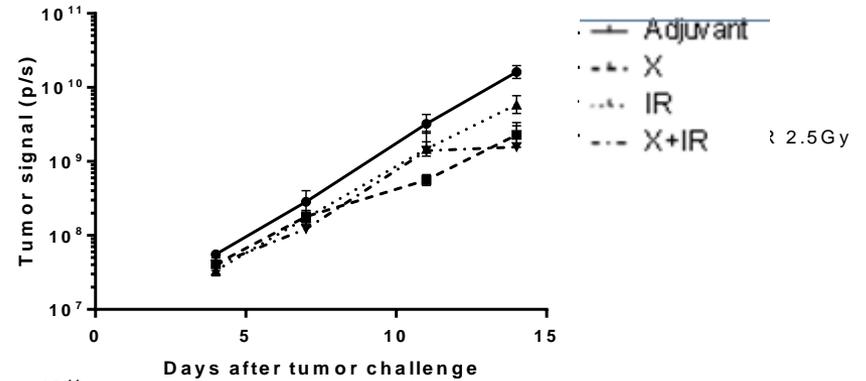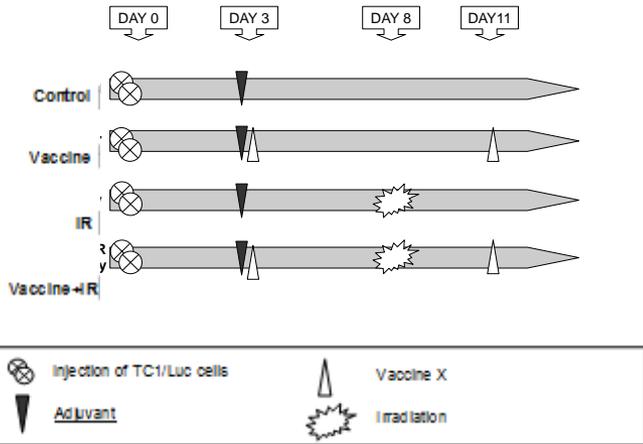
Fractionated irradiation?

E

| DAY 0 | DAY 3 | DAYS 7, 8, 9, 10 | DAY11 |

Control

-E7

IR FRAC

S   -E7+IR FRAC

Injection of TC1/Luc cells   -E7

KRN7000   Irradiation 2.6 Gy
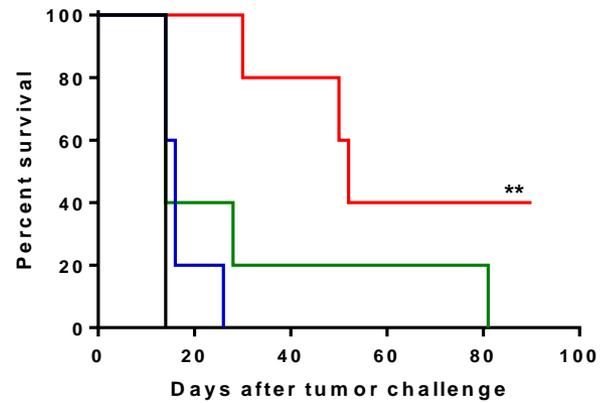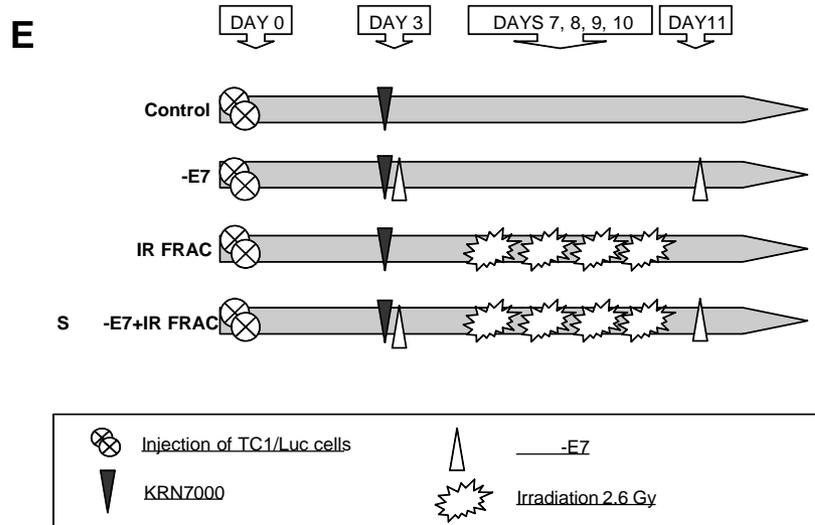
CD8+ cells into the tumor?
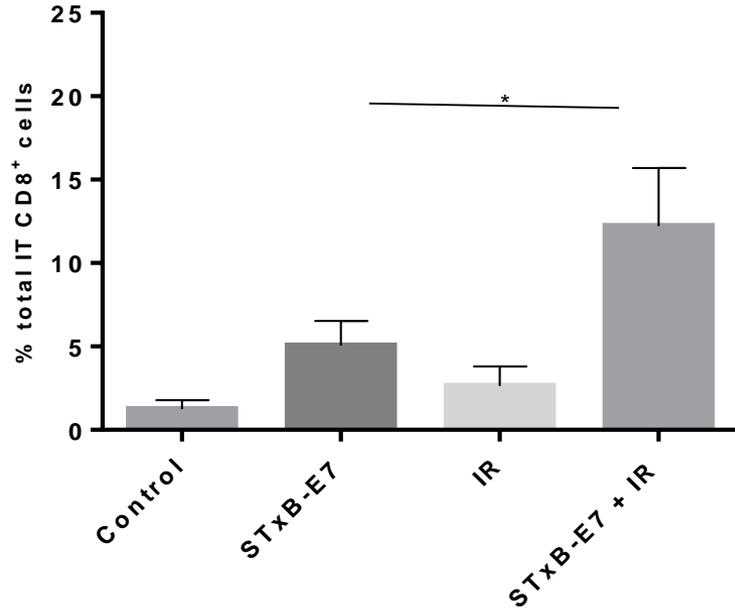
CD8+ lymphocytes linked with response?

CD8+
lymphocytes
inversely
correlate with
the tumor size

p<0.05, Pearson's correlation test
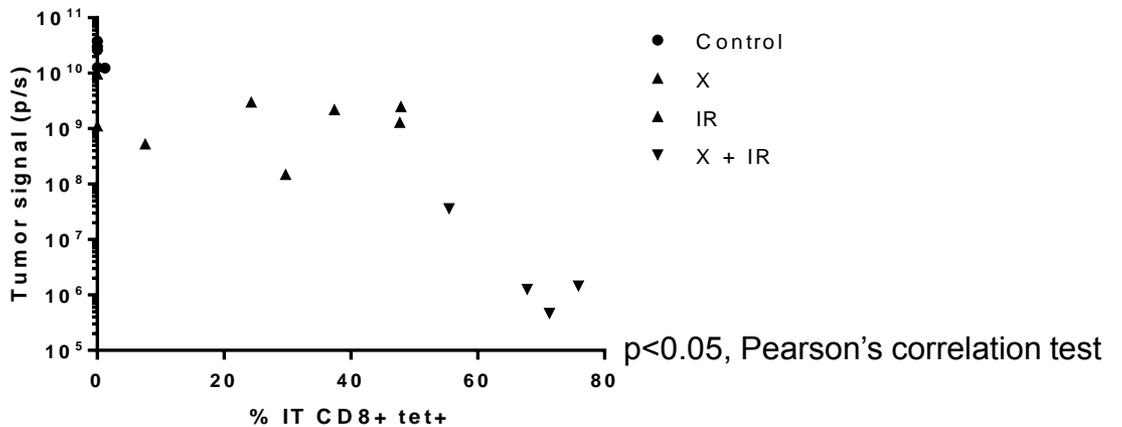
Do CD8+ cells play a role?
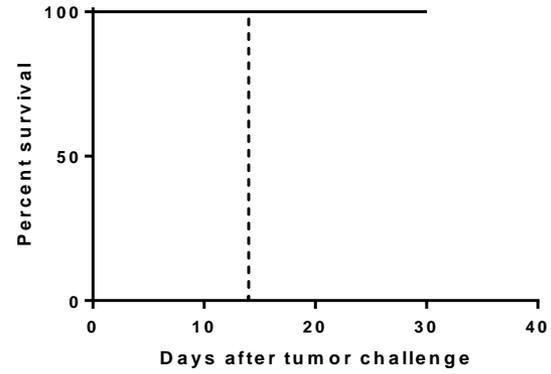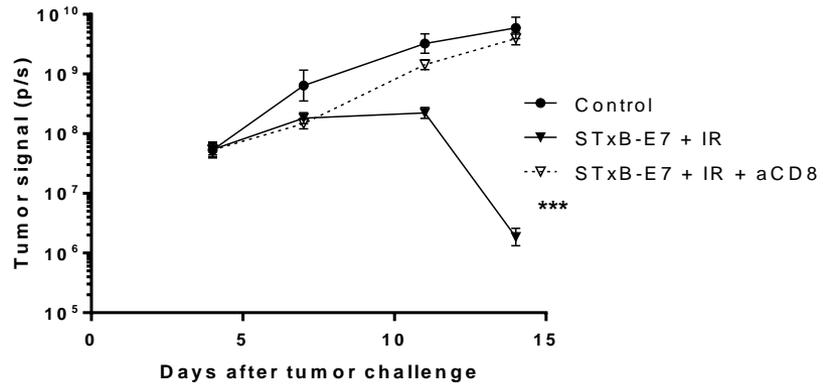
Mecanism of synergy ?

Any impact on immune check-points?
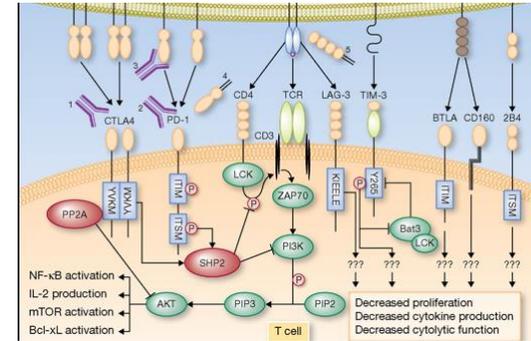
- Synergy between immune check-point blockers
and IR blocker reported to be fractionnation dependant
(Formenti, JNCI 2013).

- PD1+, TIM3 negative lymphocytes infiltrates « favorable » in HPV positive tumor
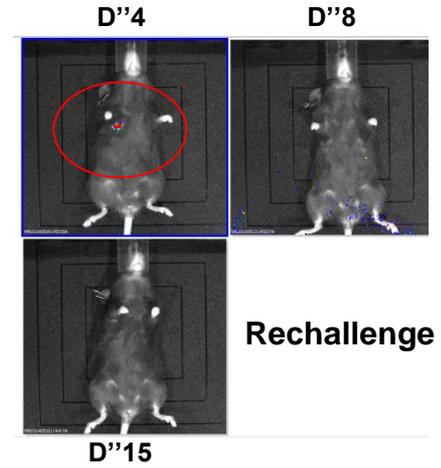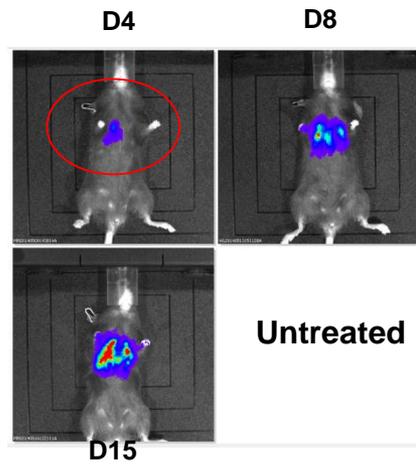context (Badoual Can Res 2013).

PD1, CTLA4 and Tim3 expression on CD8+ T cells not modulated by combination treatment.
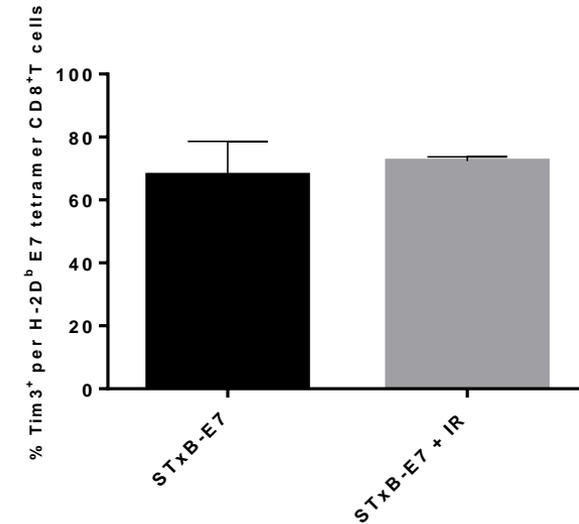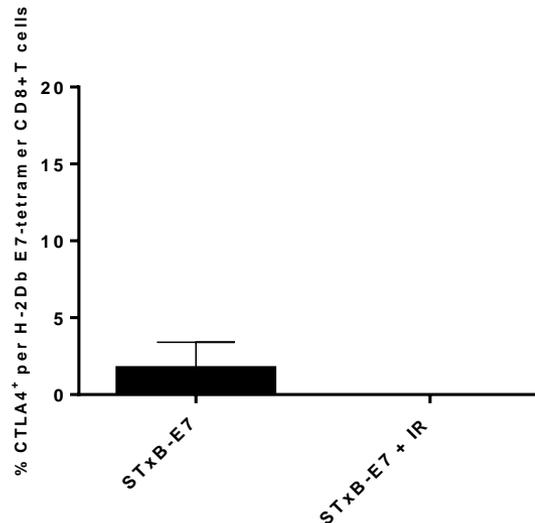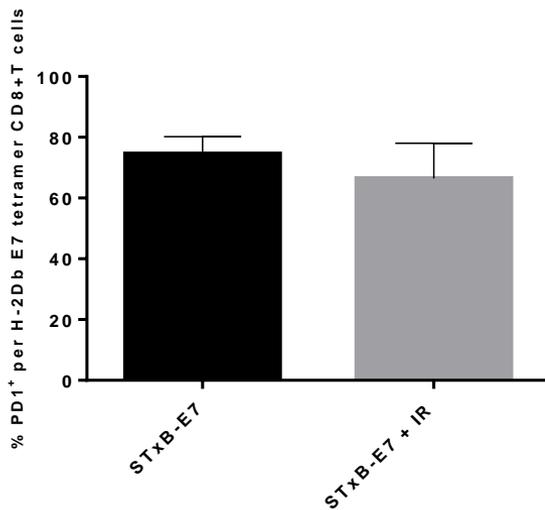
Duration of anti tumor response?
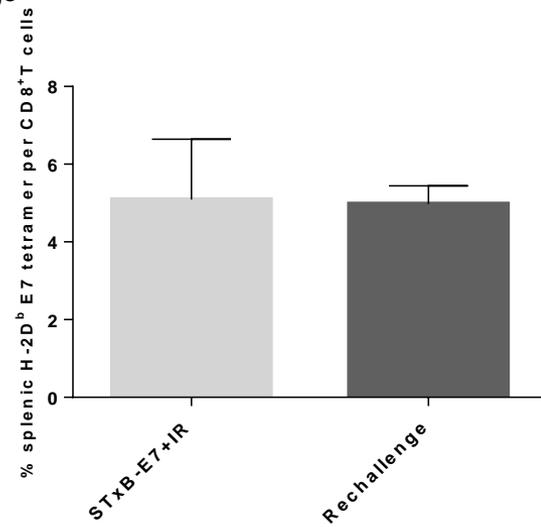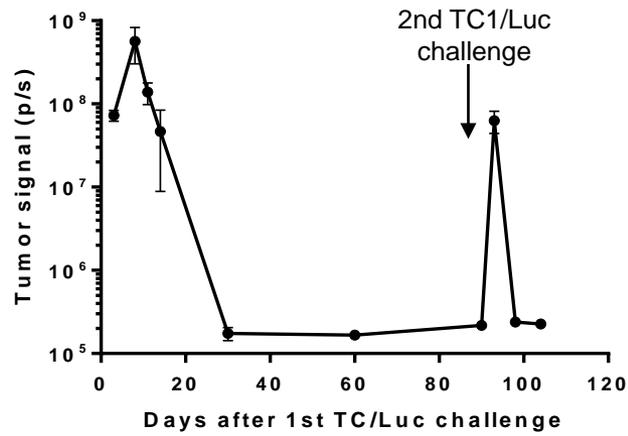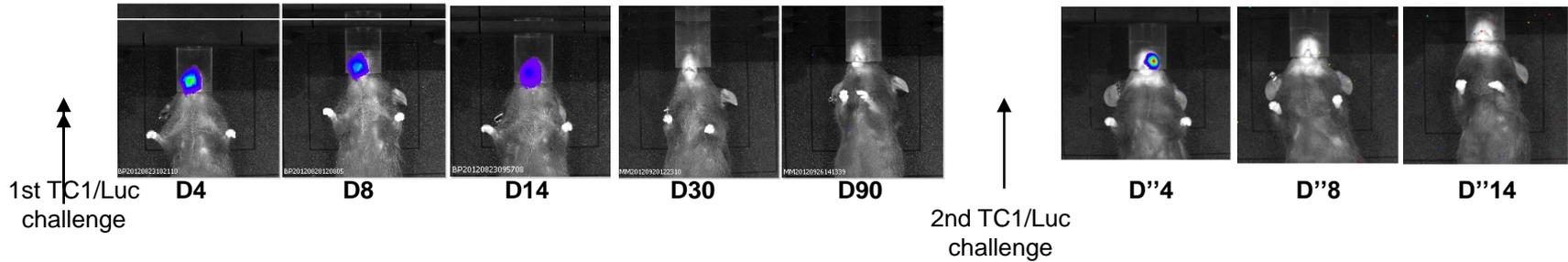
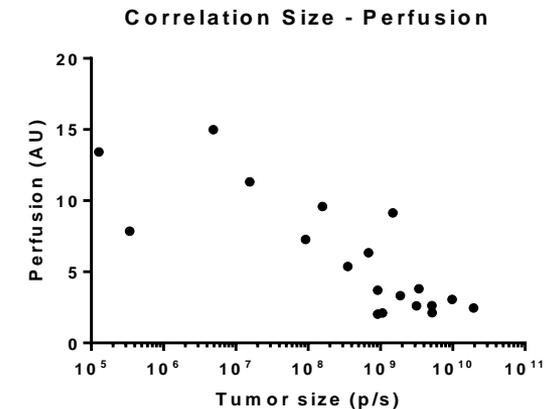# Long term local or systemic immune response?
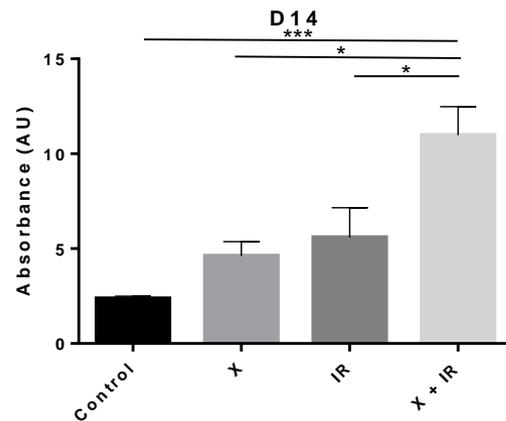

D4   D8

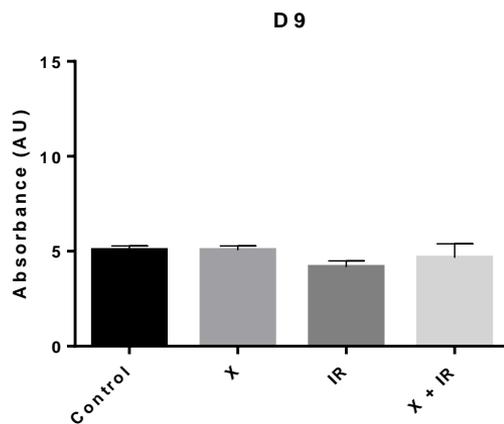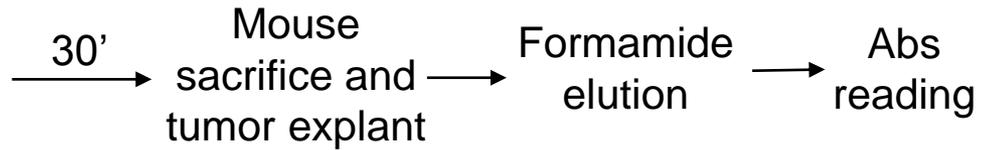Untreated

D15

D''4   D''8

Rechallenge

D''15

Increased vascular permeability upon combined treatment

Miles Assay
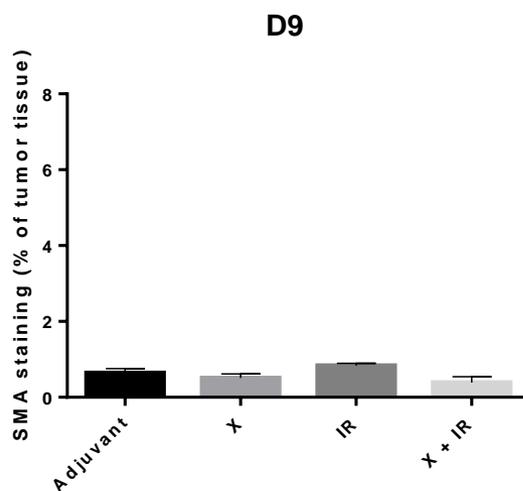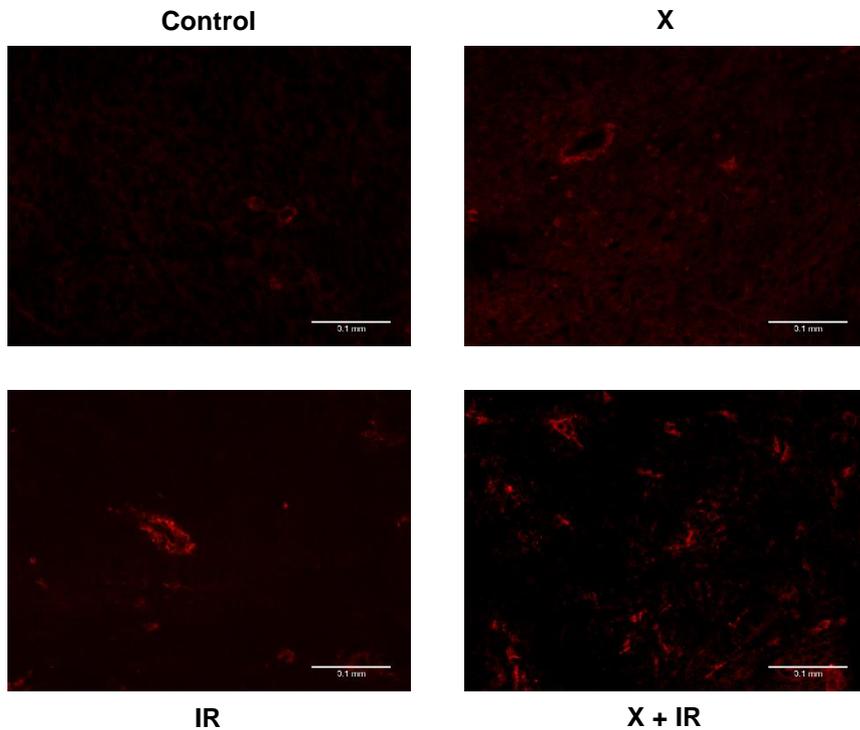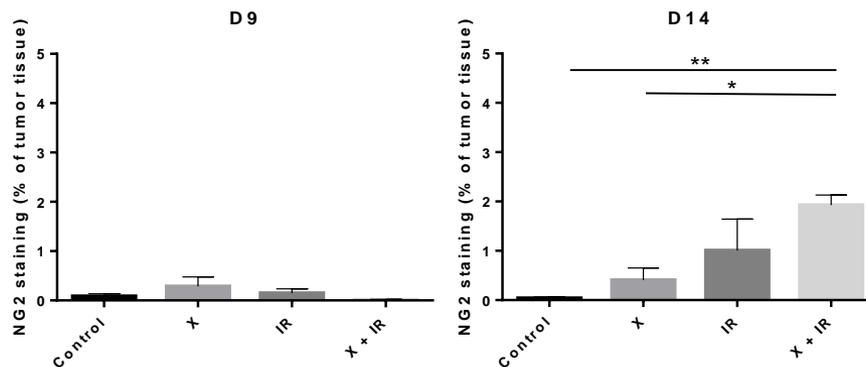
Effect of treatments on tumor vessels
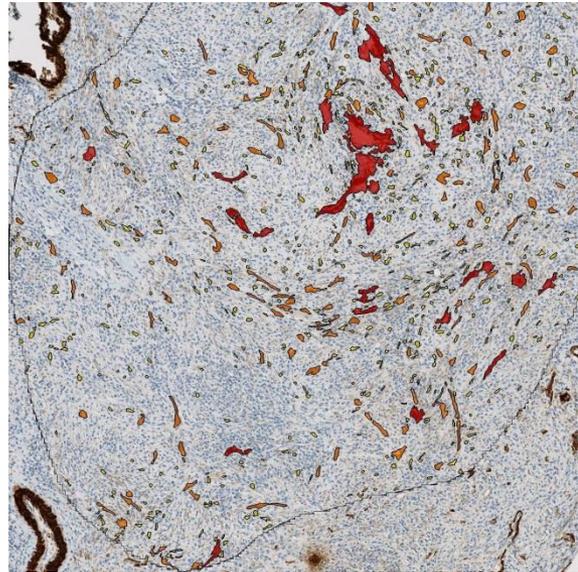
aSMA staining

(pericytes marker)
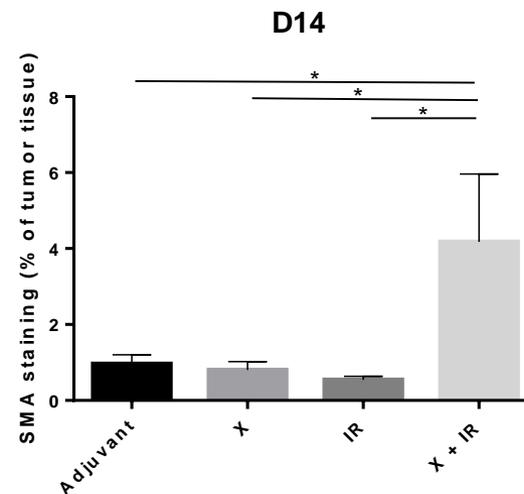
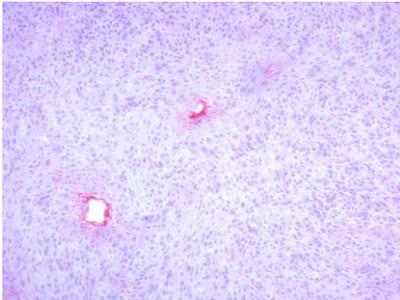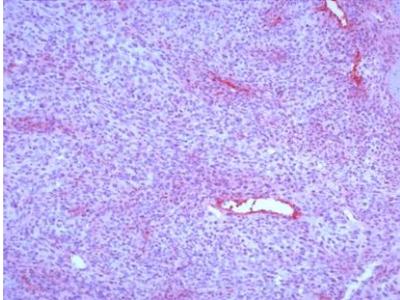# Effect of treatments on tumor vessels

NG2 staining

(pericytes marker)
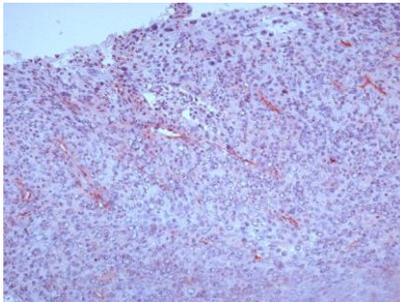
ICAM-1 staining increased by combined treatment.

Control

Vaccine

IR

Vaccine + IR
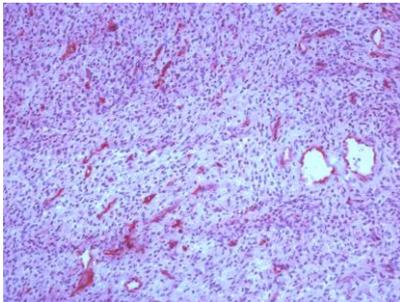
CD31 staining
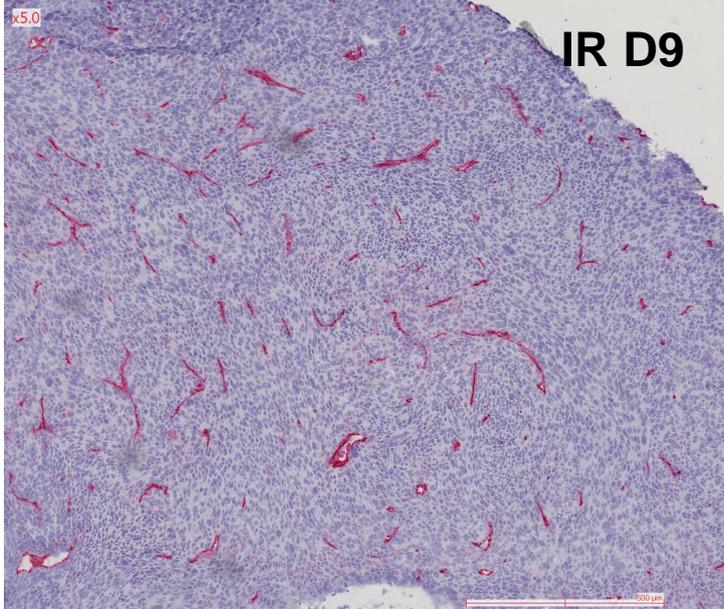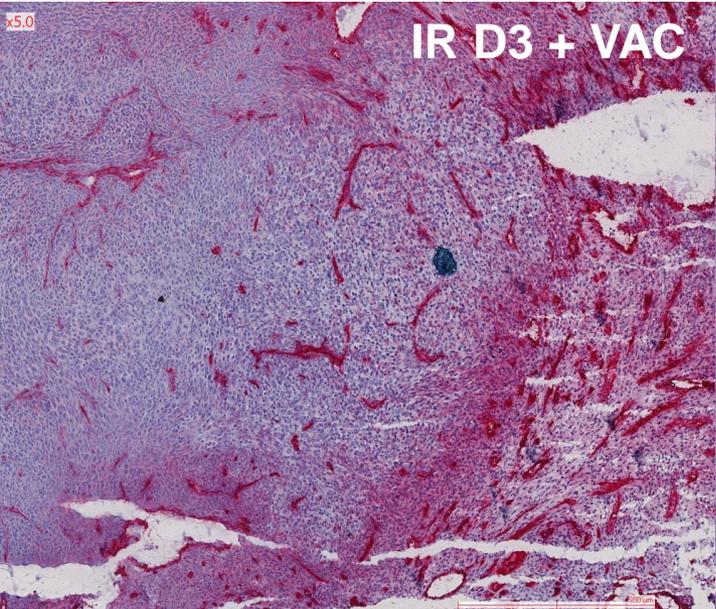
Synergy between anti-angiogenic and immunotherapy already suggested…

…similar case for radiotherapy??

From Bellone, Frontiers Oncol 2013

Conclusions

- Combined HPV vaccine/irradiation therapy promotes tumor regression and greatly improve survival.
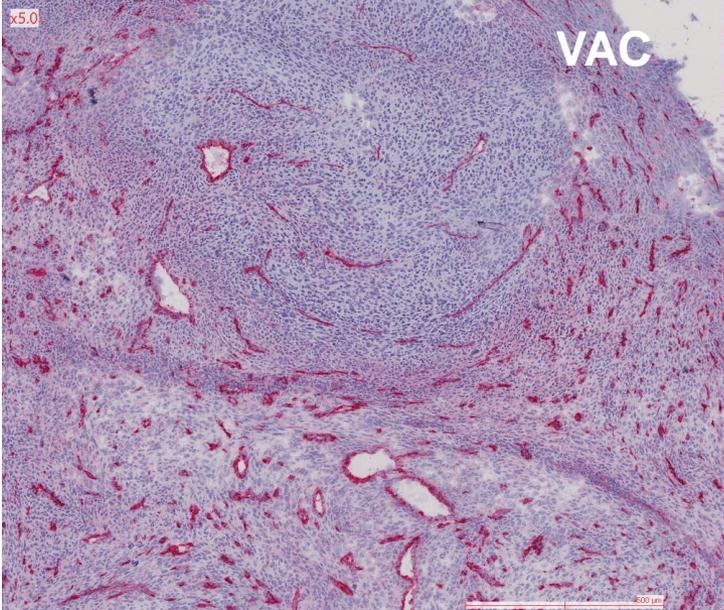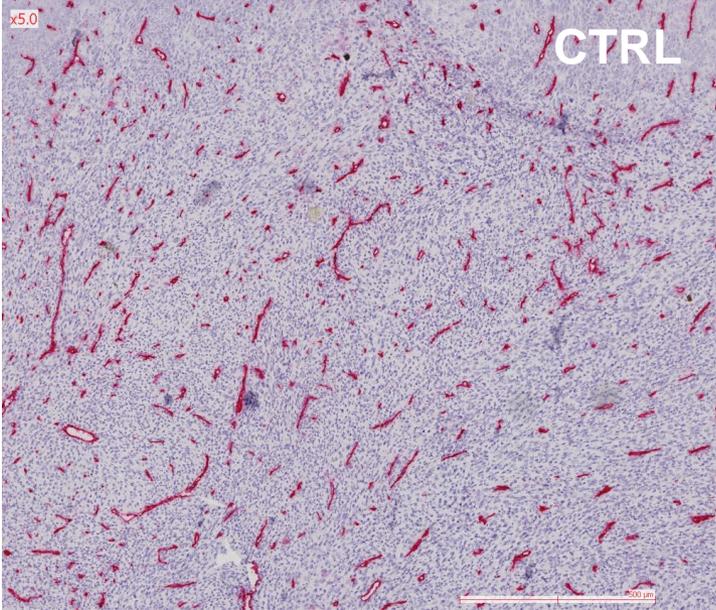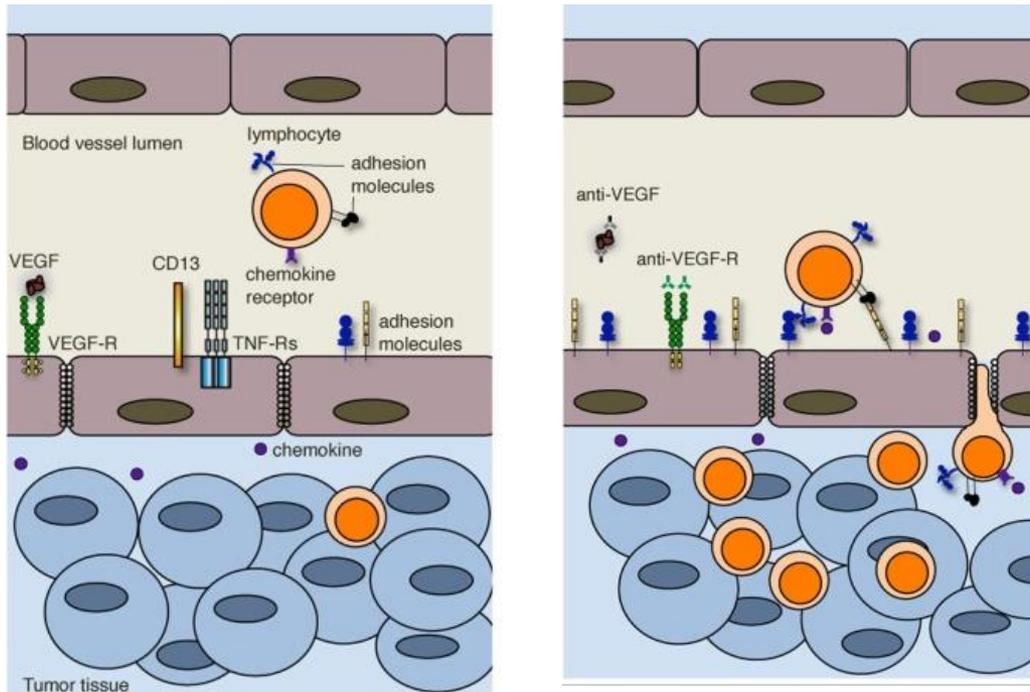
- Cytotoxic T-cell response against HPV antigen is required for anti-tumor efficacy and is greatly induced by combined therapy.

- Effective combined therapy protects from recurrences and metastases, through induction of T cell memory.

- Combined therapy promotes tumor vessel remodeling and increases perfusion

Are all vaccines even?

Recently, two vaccines targeting HPV antigens have been tested in association with radiotherapy in murine models (Wu, 2014,Draghiciu 2014). However, though HPV-associated cancers are located in mucosal sites, both studies were conducted using subcutaneous tumors.

Recent data indicate that the site of tumor implantation affects the response to cancer vaccine and the homing of induced CD8$^+$ cells (Sandoval, Sci Trans Med 2013).

No back to back comparison available.

Acknowledgments

C Haie
P Morice
C Lhomme
P Pautier