



## Immunothérapie anti-tumorale

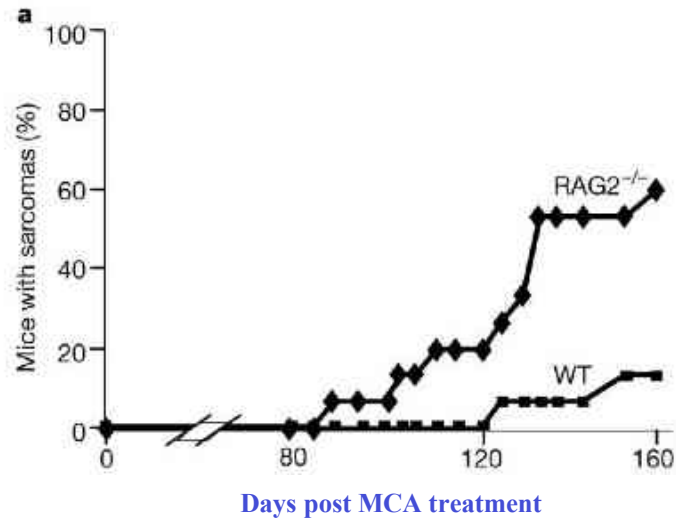
*Eric Tartour*

**1909** : **Paul Ehrlich** predicted that the immune system repressed the growth of carcinomas.

**1957-1970** : **MacFarlane Burnet and Lewis Thomas**

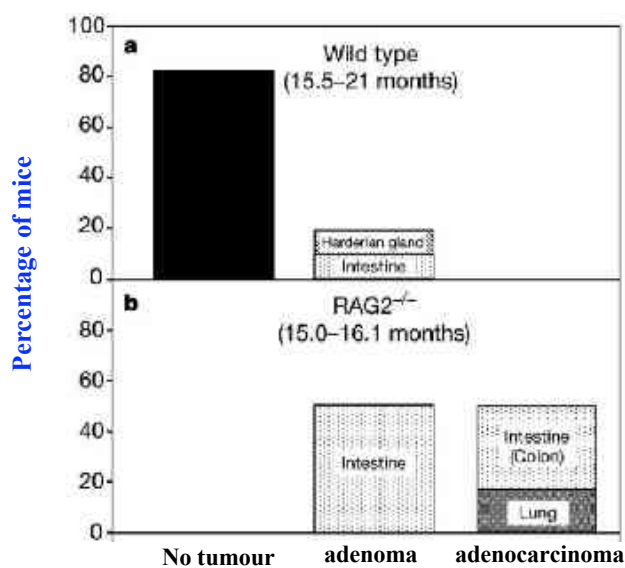
**Immunosurveillance theory** : « they proposed that tumor cell-specific neoantigens could provoke an effective immunologic reaction that would eliminate developing cancer »

**Lymphocyte-deficient mice are highly susceptible to MCA-induced tumour development**



Shankaran et al. Nature 2001

**Increased development of spontaneous neoplastic disease in immunodeficient mice.**



## IMMUNOSUPPRESSION ET CANCER

- Augmentation de la fréquence de certains cancers (Sarcome de Kaposi, Lymphome B-EBV, Cancers du col de l'utérus..) chez des patients immunodéprimés :

- . Déficits immunitaires congénitaux
- . Acquis (SIDA, Traitements immunosuppresseurs..)

- Après 20 ans de traitements immunosuppresseurs, 40% des transplantés développeront un cancer. Le risque est liée à la dose d'immunosuppresseur reçu et aux types de drogues. (Stallone N Eng J Med 2005)

## ANTIGENES DE TUMEURS

**A Peptides dérivés d'antigènes reconnus par des lymphocytes T-CD8**

### **1 Antigènes de différenciation**

mélanocytaire

- Mart-1 (Melan A), Gp100 (pmel-17), Tyrosinase, TRP1 (gp75)

-TRP2, MSH- R

Prostatique

PSA, PAP, PSMA, PSCA

### **2 Cancer-Testis antigen**

- Mage 1, Mage 2, Mage 3, Mage 12

- Bage, Gage, Rage

- NY-ESO-1

- N-acetylglucosaminyltransferase V (peptide intronique).

### 3 Antigènes mutés

- $\beta$  catenine
- CDK-4
- Caspase-8
- KIA0205
- HLA-A2
- Idiotype d'Ig

### 4 Antigènes surexprimés dans les tumeurs

- G-250
- Her-2/neu
- p53
- Telomerase catalytic protein
- ACE
- $\alpha$  foeto-proteine ( $\alpha$ FP)

## Lien entre la réponse anti-tumorale et la réponse auto-immune

Réponse anti-tumorale dans le mélanome -> vitiligo



➔ Association entre le bénéfice clinique d'une immunothérapie et l'apparition de signes cliniques d'auto-immunité induits par ces traitements.

VIRUS	TUMORS	Other symptoms associated with viral infections
EBV	- Burkitt Lymphomas - Cavum carcinomas - Hodgkin lymphomas	Infectious mononucleosis Hemophagocytosis syndrome. Immunodeficiency (Purtillo syndrome)
HTLV1	- T -Leukemias	Spasmodic paralysis syndrome
HPV16,18	- Cervix carcinomas	Cervical intraneoplasia laryngeal papillomatosis
HPV1-45	- Bowen disease (In situ carcinoma) - Squamous-cell carcinomas (immunodépressed patiens)	Dyskératosis , Wart
HBV / HCV	- Hépatocarcinoma	Hépatitis, Cirrhosis
KSHV (HHV8)	- Kaposi Sarcomas	Castleman disease

**TABLE 4. INCIDENCE OF LIVER CANCER PER 100,000 CHILDREN IN BIRTH COHORTS DETERMINED ACCORDING TO THE DATE OF IMPLEMENTATION OF THE HEPATITIS B VACCINATION PROGRAM.**

AGE AT DIAGNOSIS (YR)	BEFORE-PROGRAM COHORT (JULY 1974-JUNE 1984)		AFTER-PROGRAM COHORT (JULY 1984-JUNE 1986)	
	POPULATION	NO. OF CANCERS (INCIDENCE)	POPULATION	NO. OF CANCERS (INCIDENCE)
6	3,940,747	18 (0.46)	648,642	0 (0.00)
7	3,938,119	21 (0.53)	647,051	1 (0.15)
8	3,931,983	19 (0.48)	644,892	2 (0.31)
9	3,928,721	24 (0.61)	340,521*	0 (0.00)
Total	15,739,570	82 (0.52)	2,281,106	3 (0.13)†

\*This value is based on data for the cohort born from July 1984 to June 1985.

†P<0.001 for the comparisons between birth cohorts.

Chang MH N Engl J Med 1997

## **Existence d 'une réponse immunitaire naturelle dirigée contre les tumeurs**

### **1 Réponse humorale**

- Présence d 'anticorps dirigés contre de nombreux antigènes tumoraux (p53, HER2/neu, Muc 1, GD2, NY-ESO1, HU...) dans le sérum de patients atteints de cancers.

### **2 Présence de lymphocytes T-CD4 et CD8 dirigés contre des peptides tumoraux.**

Historique : **Antigène du groupe Cancer-testis** (Mage. (T Boon))

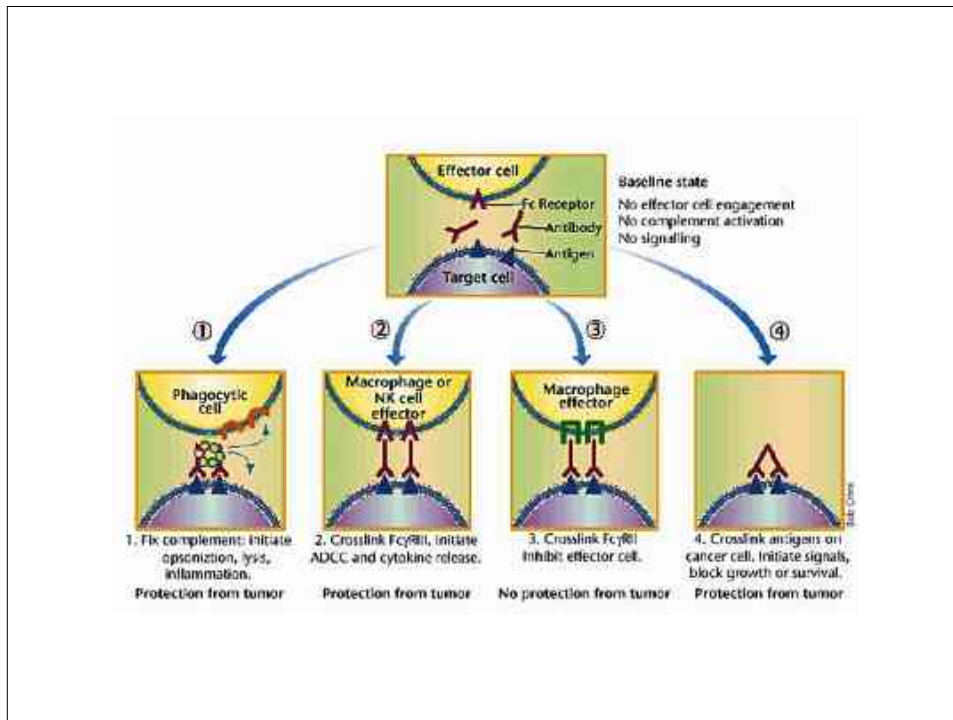
**Antigènes de différenciation** : Melan 1, tyrosinase, PMSA

**Protéines mutées** : ras, P53

**Protéines du soi** : Muc 1, Her2/neu, proteinase 3, survivine, telomerase

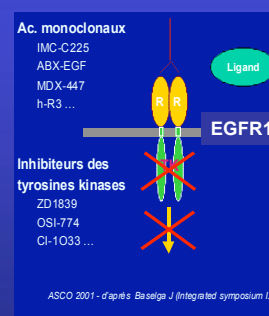
**Virus.**

## **EFFECTEURS IMMUNOLOGIQUES IMPLIQUES DANS LA REPOSE ANTI-TUMORALE**



## Les Ac en thérapeutique :

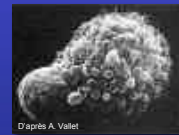
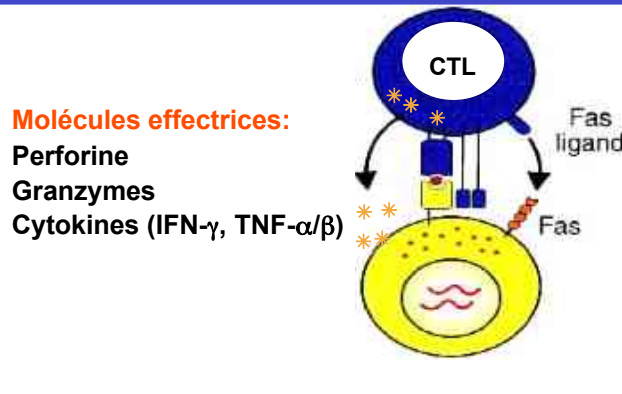
- Lymphomes folliculaires, LLC :  
anti-CD20 : Rituximab
- Cancer du colon :  
anti-EGFR1 : Cetuximab (Erbix®) étude BOND  
anti-angiogéniques : (bevacizumab, Avastin®);  
SU11248, ....)
- Cancer du sein :  
anti-Her2/neu : (Herceptin)



### Ciblage thérapeutique sur la cellule tumorale

➔ gain thérapeutique +++  
effet synergique avec la chimiothérapie / radiothérapie

## Lymphocytes T CD8 cytotoxiques



Lymphocyte T CD8 cytotoxique

### ROLE DES LYMPHOCYTES T CYTOTOXIQUES (CTL) DANS LE CONTRÔLE DE LA CROISSANCE DES TUMEURS

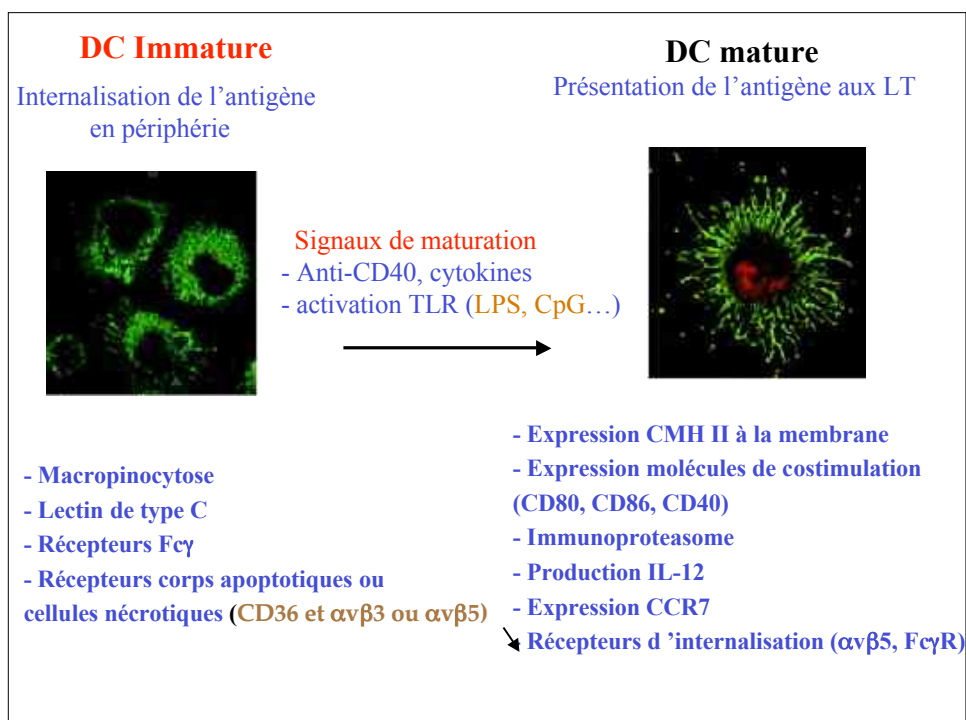
- **Efficacité anti-tumorale en immunothérapie adoptive**
- **Mise en évidence de CTL anti-tumoraux dans des modèles de tumeurs humaines spontanément régressives**
- **Corrélation dans des modèles murins entre la capacité d'induire des CTL in vivo et la réponse anti-tumorale.**
- **Infiltration des tumeurs par des LT-CD8 est associée à un bon pronostic clinique**



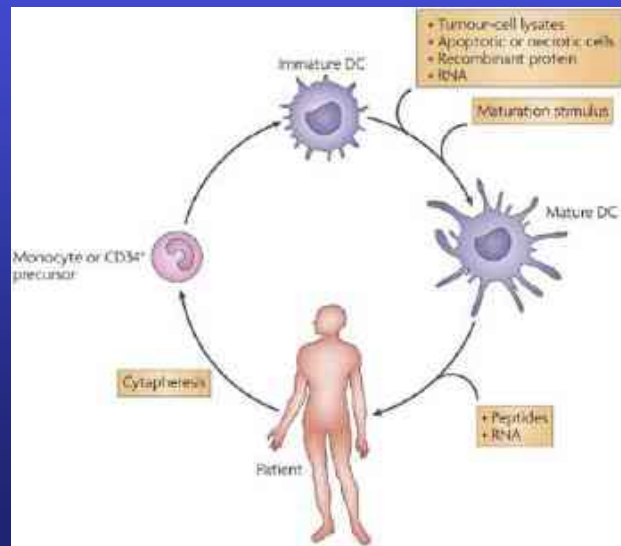
Patients	Sites of evaluable metastases	response (duration months)	Autoimmunity
1	Lymph nodes (axillary, mesenteric, pelvic)	PR (24+)	None
2	Cutaneous, subcutaneous	PR (8)	Vitiligo
3	Brain, cutaneous, liver, lung	NR	None
4	Cutaneous, subcutaneous	PR (2)	None
5	Brain, lung, lymph nodes	NR-mixed	None
6	Intraperitoneal, subcutaneous	PR (15+)	None
7	Lymph nodes, subcutaneous	NR-mixed	Vitiligo
8	Subcutaneous	NR	None
9	Cutaneous, subcutaneous	PR (10+)	Vitiligo
10	Lymph nodes, cutaneous, subcutaneous	PR (9+)	Uveitis
11	Liver, pericardial, subcutaneous	NR-mixed	Vitiligo
12	Liver, lung, gallbladder, lymph nodes	NR mixed	None
13	Subcutaneous	NR	None

Administration of TIL + IL-2 in patients pretreated with chemotherapy

Dudley Science 2002



## DC based vaccines using *ex vivo* loaded DCs to induce immunity



- Proof of concept of immunogenicity in human (Dhodapakar *et al*, *J Clin Invest*, 1999) and clinical responses observed in cancer patients (Thurner *et al*, *J Exp Med*, 1999; Palucka *et al*, *J Immunother*, 2006)...

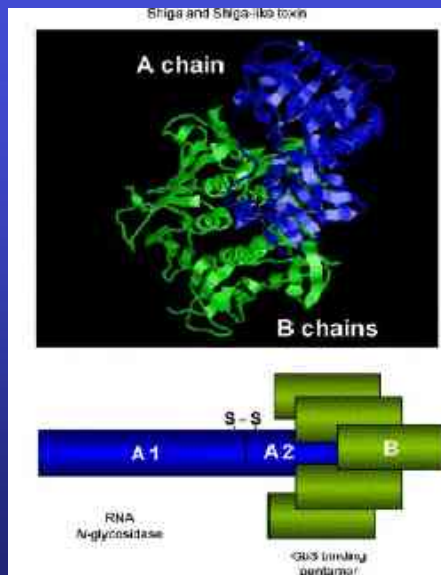
...but up until now in randomized phase III clinical trials, DC was not demonstrated to provide statistically significant benefit in term of overall clinical response than conventional chemotherapy alone (Schadendorf *et al*, *Ann Oncol*, 2006).

- The choice of DC lineage, the dosage, and the administration schedule still need to be optimized.

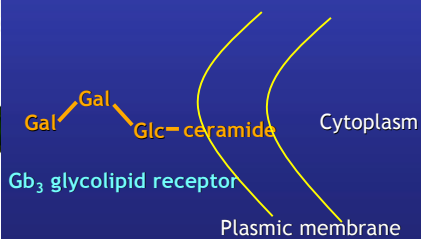
After injection of DCs, only 3-5% reach lymphoid organs and their migration is restricted to the regional lymph node (De Vries *et al*, *Cancer Res*, 2003).

**Direct antigen targeting to DCs *in vivo* will therefore offer several advantages.**

## B Subunit of Shiga toxin and its Gb<sub>3</sub> receptor



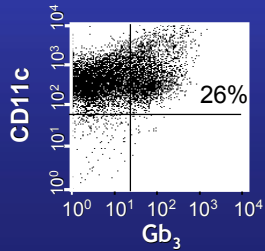
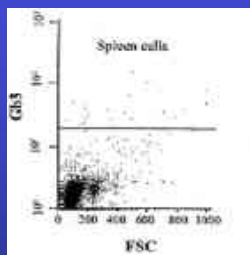
(toxin AB5)



Distribution and sequence of Gb<sub>3</sub> identical in various species

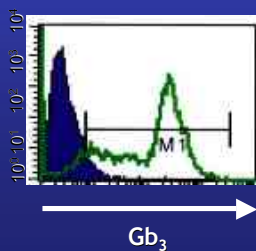
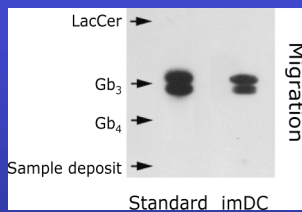
## Gb<sub>3</sub> is preferentially expressed on dendritic cells

• Mice



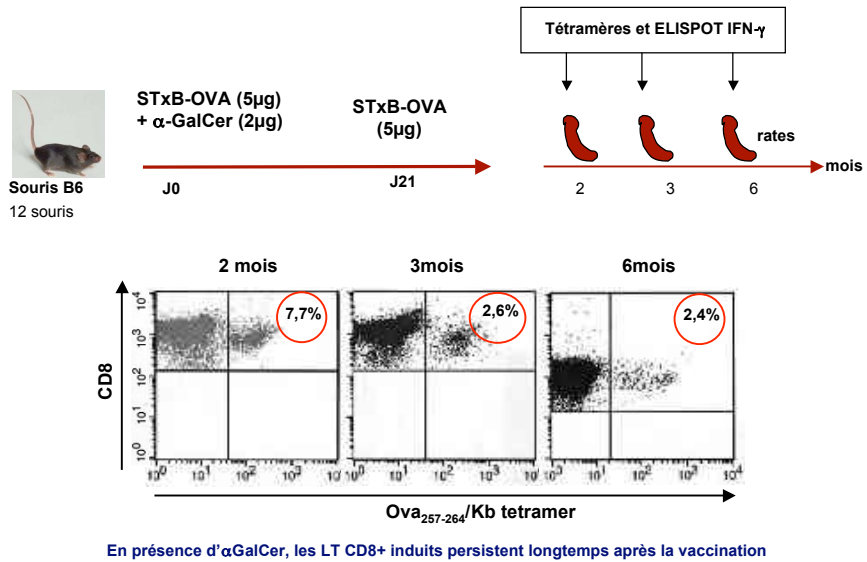
Murine DC

• Human



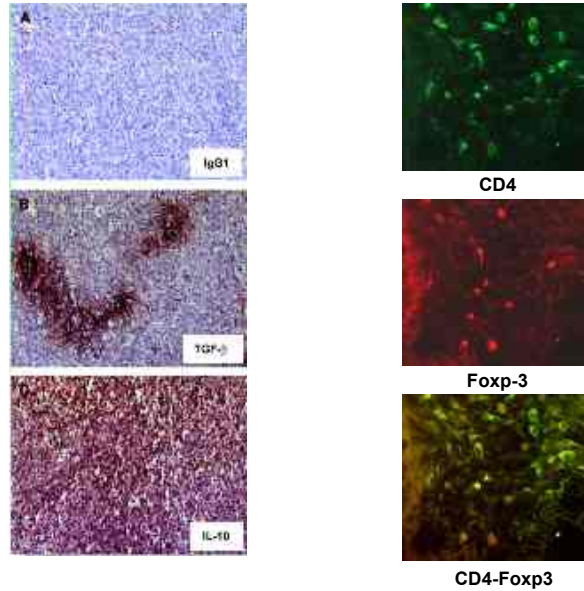
Human DC

## Etude de la persistance des réponses TCD8+ in vivo



**POTENTIAL MECHANISMS LEADING TO TUMOR  
ESCAPE FROM IMMUNE RECOGNITION.**

### Immunosuppressive factors within tumor microenvironment



Lizee et al CCR 2007  
Badoual et al CCR 2006

### LT-CD4-CD25 EN CANCEROLOGIE

**Phénotype** : CD4+, CD25+, GITR+, Foxp3+, CTLA4+, CD62L+ , CD44+, CD69-

**Rôle** : Action suppressive sur les lymphocytes T effecteurs.

-Augmentation des LT CD4+CD25+ chez des patients atteints de cancers.

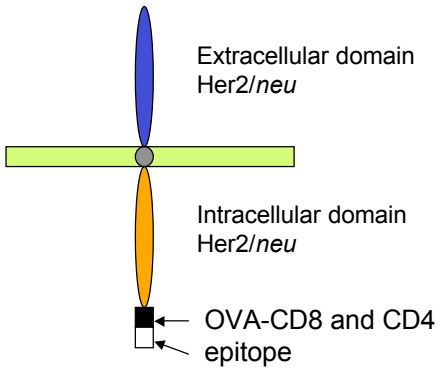
- Infiltration tumorale de ces cellules est corrélée à un mauvais pronostic dans les cancers de l'ovaire (Curjel Nature Med 2004).

- Chez la souris déplétion de populations CD4+CD25+ entraine une augmentation des réponses immunitaires anti-tumorales.

**Models of self tumor antigen : Her2/neu TG mice**  
 (Nelson BH . British Columbia Canada)

H&E

Anti-Neu

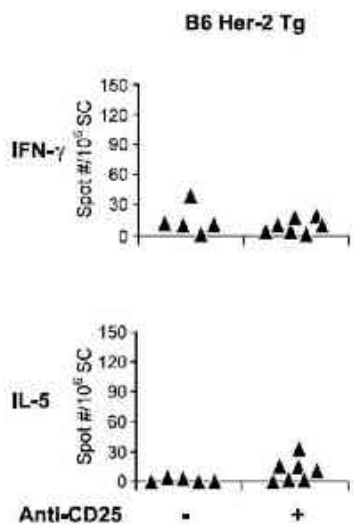


Extracellular domain  
Her2/neu

Intracellular domain  
Her2/neu

OVA-CD8 and CD4  
epitope

**Most anti-Her2/neu vaccines failed in Her2/neu TG mice in B6 genetic background**

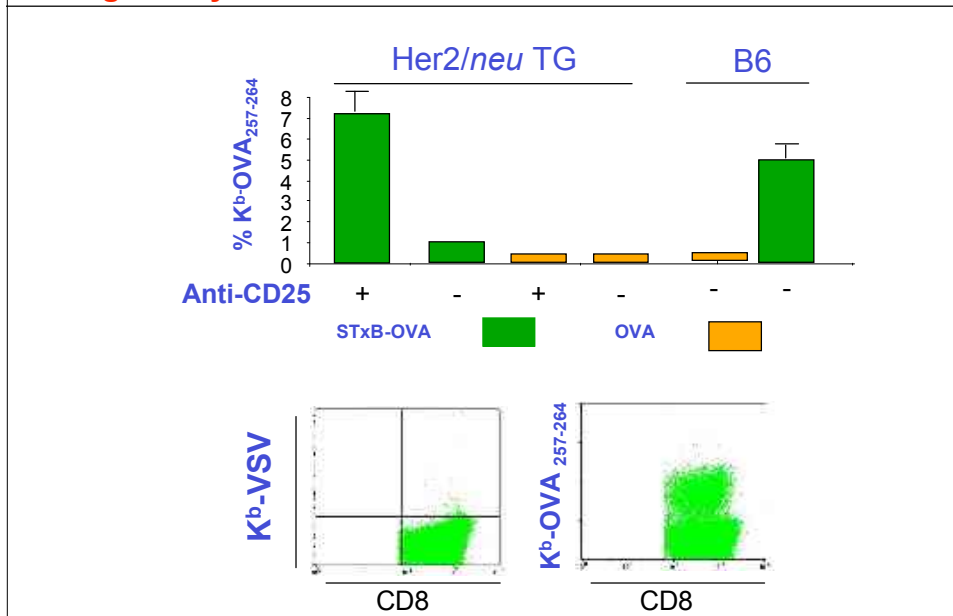


**Her2 DNA vaccine**

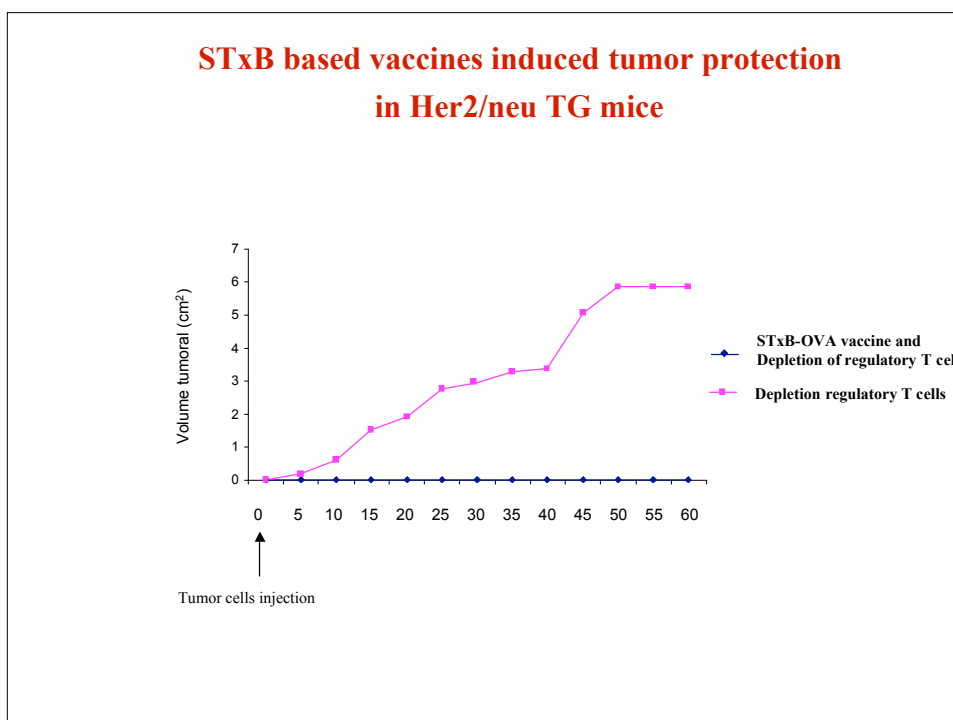
Radkevich O et al, *Cancer Res*, 2009

Anti-CD25 was used as it has been shown that breast cancer are heavily infiltrated by regulatory T cells which is associated with a poor prognosis (Bates, *JCO*, 2006) and Treg frequency is increased in Her2/neu<sup>+</sup> tumors (Perez SA, *Clin Cancer Res*, 2007)

**Combination of STxB based vaccines with depletion of regulatory T cells break tolerance in Her2/neu TG mice**



**STxB based vaccines induced tumor protection in Her2/neu TG mice**



## Conclusions

- Le système immunitaire reconnaît les cellules tumorales et peut exercer un contrôle sur le développement des cancers.
- Au cours de ces dernières années, les anticorps anti-tumoraux ont constitué une avancée thérapeutique majeure en cancérologie.
- Les travaux actuels cherchent à combiner ces anticorps à des approches permettant d'induire aussi des lymphocytes T anti-tumoraux. Des premiers résultats encourageants ont été obtenus avec des approches vaccinales associées à des molécules levant l'immunosuppression.