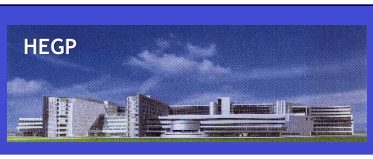
PARIS DESCARTES



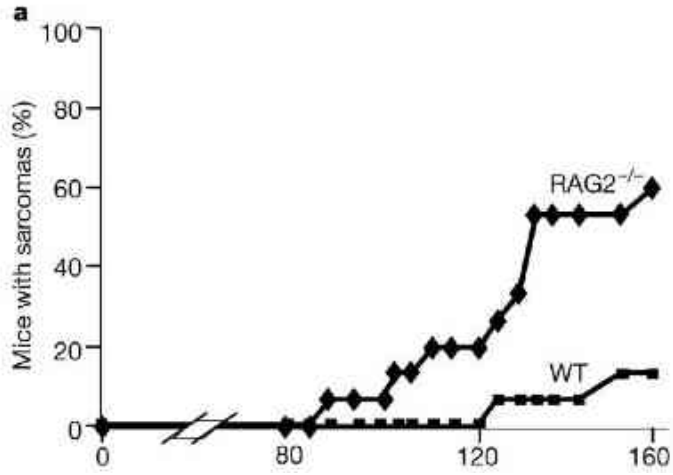
Immunothérapie anti-tumorale

Eric Tartour

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

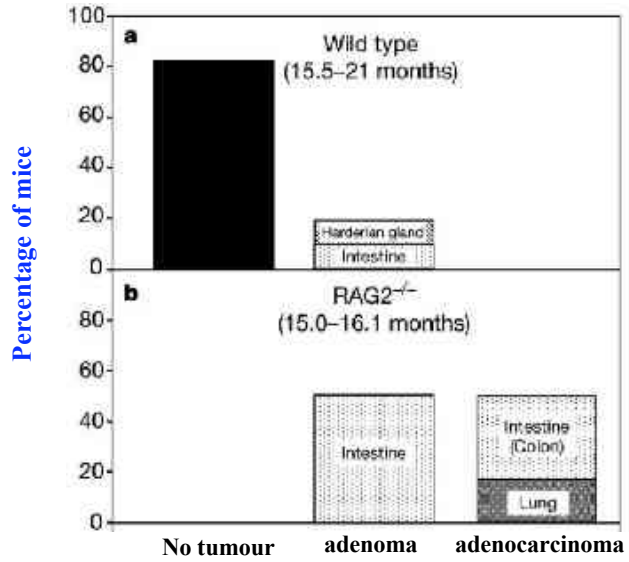
1957-1970 : MacFarlane Burnet and Lewis Thomas
Immunosurveillance theory : « they proposed that tumor cell-specific neoantigens could provoke an effective immunologic reaction that would eliminate developping cancer »

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

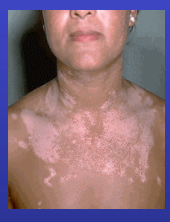
- Mage 1, Mage 2, Mage 3, Mage 12
- Bage, Gage, Rage
- NY-ESO-1
- N-acetylglucosaminyltransferase V (peptide intronique).

3 Antigènes mutés
- β 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
- α foeto-proteine (αFP)

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 symptomes associated with viral infections
EBV	- Burkitt Lymphomas	Infectious mononucleosis
	- Cavum carcinomas	Hemophagocytosis syndrome.
	- Hodgkin lymphomas	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

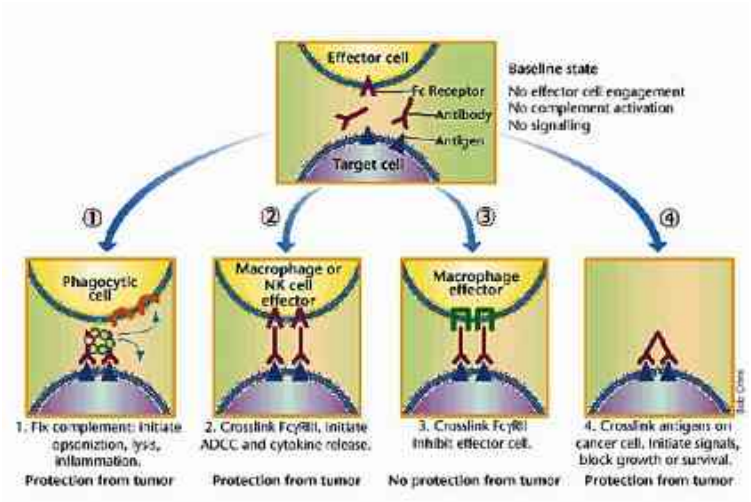
1 Réponse humorale

- 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.

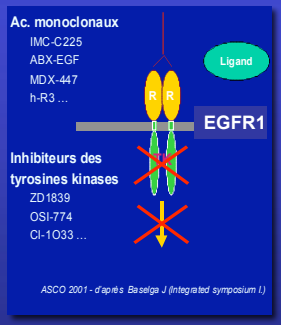
Historique : **Antigène du groupe Cancer-testis** (**Mage**. (T Boon))
Antigènes de différenciation : **Melan 1, tyrosinase, PMSA**
Protéines mutées : ras, P53
Protéines du soi : Muc 1, Her2/neu, proteinase 3, survivine, telomerase
Virus.

EFFECTEURS IMMUNOLOGIQUES IMPLIQUES DANS LA REPONSE ANTI-TUMORALE



Les Ac en thérapeutique :

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

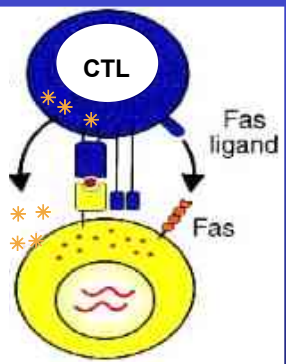


Ciblage thérapeutique sur la cellule tumorale

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

Lymphocytes T CD8 cytotoxiques

Molécules effectrices:
Perforine
Granzymes
Cytokines (IFN-γ, TNF-α/β)



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 Immature

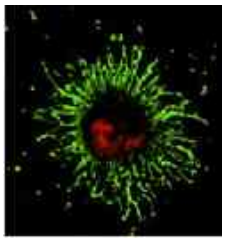
Internalisation de l'antigène en périphérie

Signaux de maturation
- Anti-CD40, cytokines
- activation TLR (LPS, CpG…)

→

DC mature

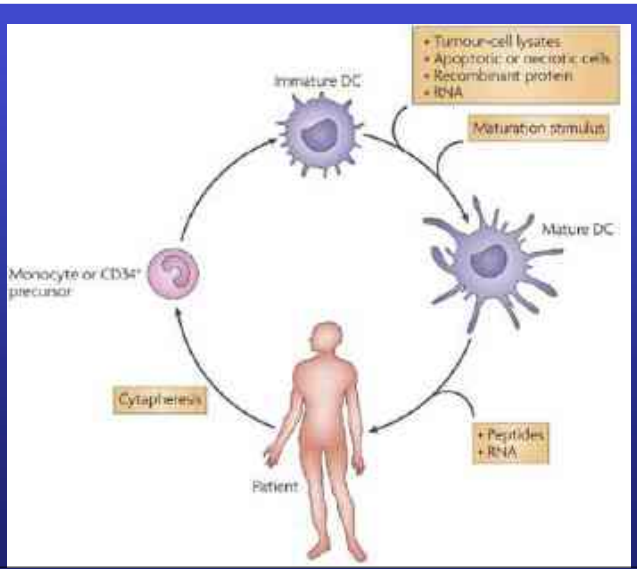
Présentation de l'antigène aux LT



- Macropinocytose
- Lectin de type C
- Récepteurs Fcγ
- Récepteurs corps apoptotiques ou cellules nécrotiques (CD36 et αvβ3 ou αvβ5)

- Expression CMH II à la membrane
- Expression molécules de costimulation (CD80, CD86, CD40)
- Immunoproteasome
- Production IL-12
- Expression CCR7
- Récepteurs d 'internalisation (αvβ5, FcγR)

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



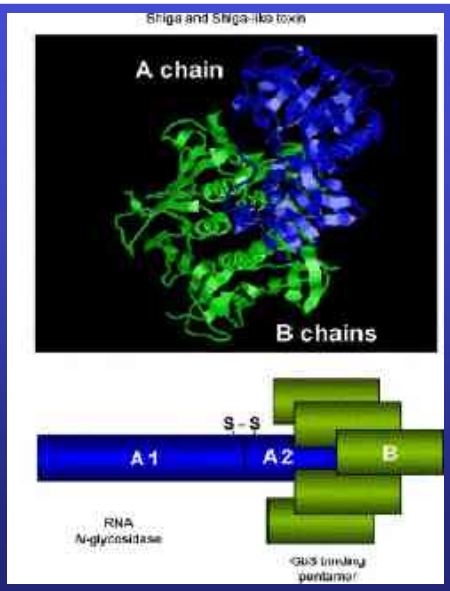
- Proof of concept of immunogenicity in human (Dhodapakar *et al, J Clin Invest*, 1999) and clinical responses observed in cancer patients (Thurner *et al, J Exp Med*, 1999; Palucka *et al, J Immunother*, 2006)…

…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).

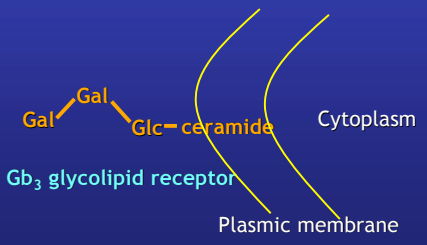
- The choice of DC lineage, the dosage, and the administration schedule still need to be optimized.
After injection of DCs, only 3-5% reach lymphoid organs and their migration is restricted to the regional lymph node (De Vries *et al, Cancer Res*, 2003).

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

B Subunit of Shiga toxin and its Gb_3 receptor



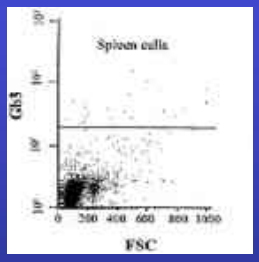
(toxin AB5)

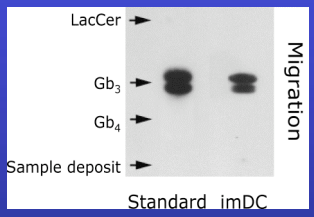


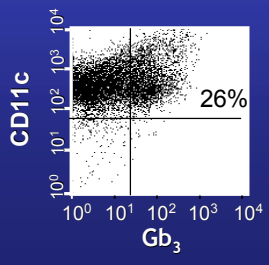
Distribution and sequence of Gb_3 identical in various species

Gb_3 is preferentially expressed on dendritic cells

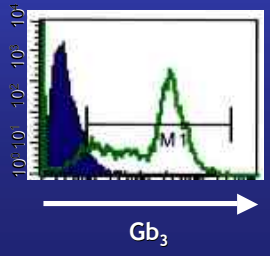
- Mice
- Human





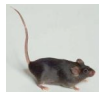


Murine DC



Human DC

Etude de la persistance des réponses TCD8+ in vivo



Souris B6
12 souris

STxB-OVA (5µg)
+ α-GalCer (2µg)

J0

STxB-OVA
(5µg)

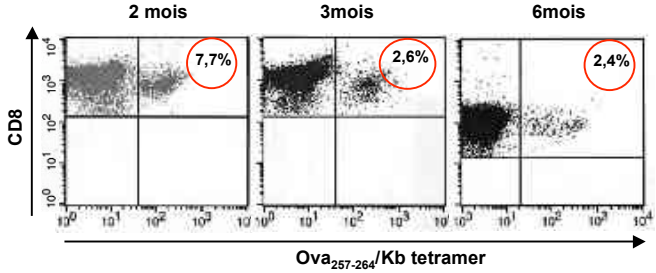
J21

Tétramères et ELISPOT IFN-γ

rates

mois

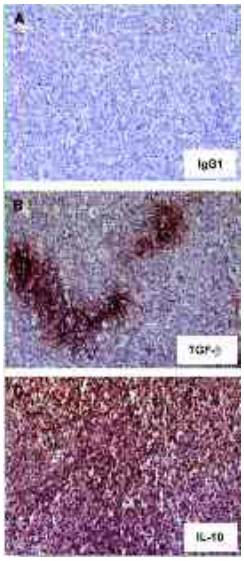
2 3 6

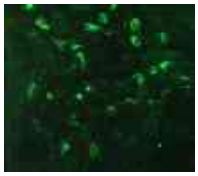


En présence d'αGalCer, les LT CD8+ induits persistent longtemps après la vaccination

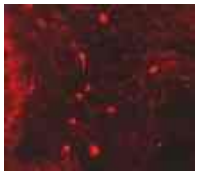
POTENTIAL MECHANISMS LEADING TO TUMOR ESCAPE FROM IMMUNE RECOGNITION.

Immunosuppressive factors within tumor microenvironment

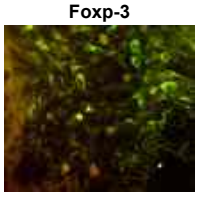




CD4



Foxp-3



CD4-Foxp3

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 (Curiel Nature Med 2004).

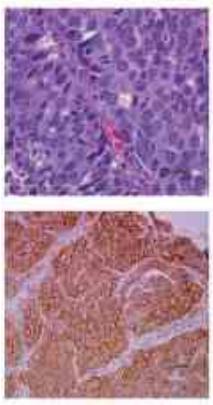
- Chez la souris déplétion de populations CD4+CD25+ entraine une augmentation des réponses immunitaires anti-tumorales.

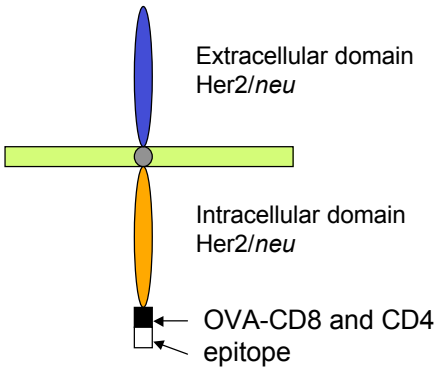
Models of self tumor antigen : Her2/neu TG mice

(Nelson BH . British Columbia Canada)

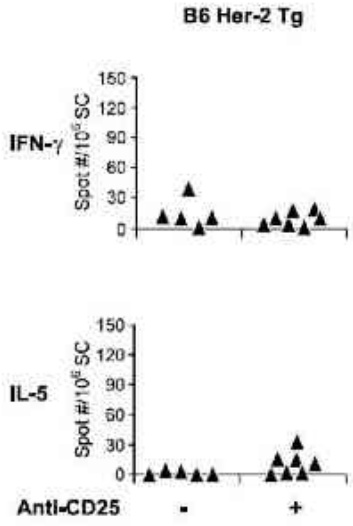
H&E

Anti-Neu





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

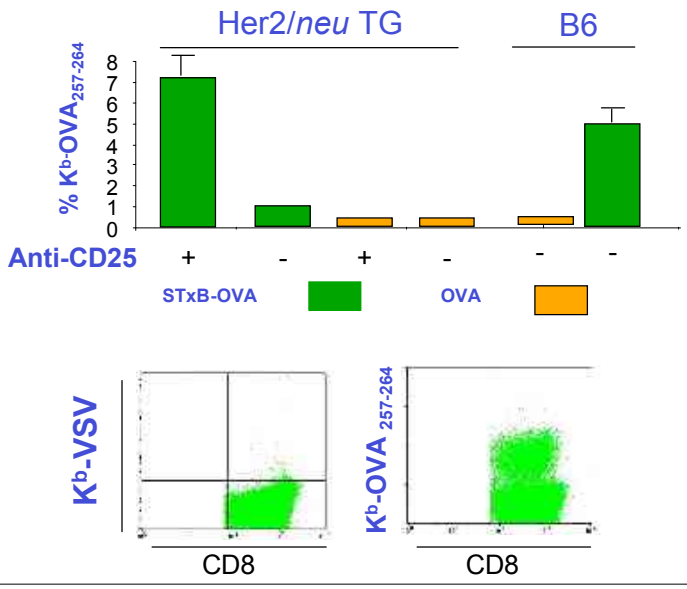


Her2 DNA vaccine

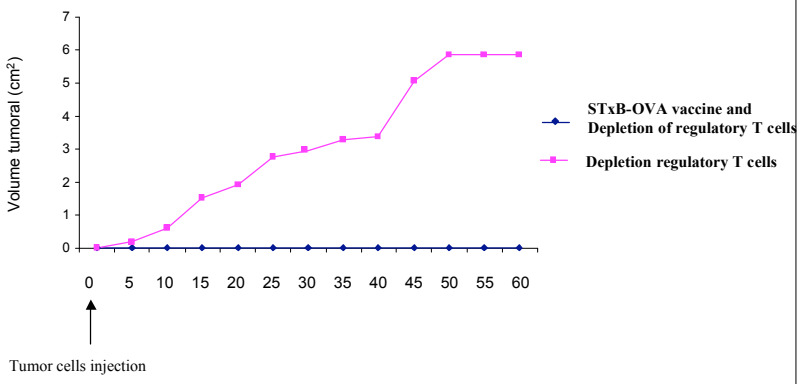
Radkevich O et al, *Cancer Res*, 2009

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^{+} tumors (Perez SA, *Clin Cancer Res*, 2007)

Combination of STxB based vaccines with dépletion 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 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.