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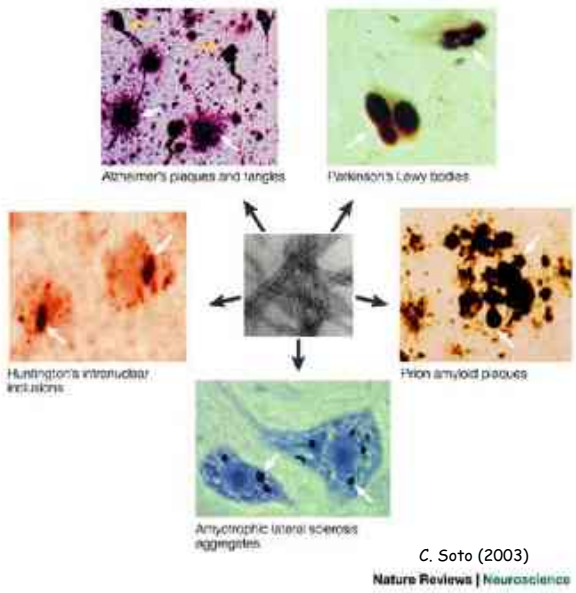
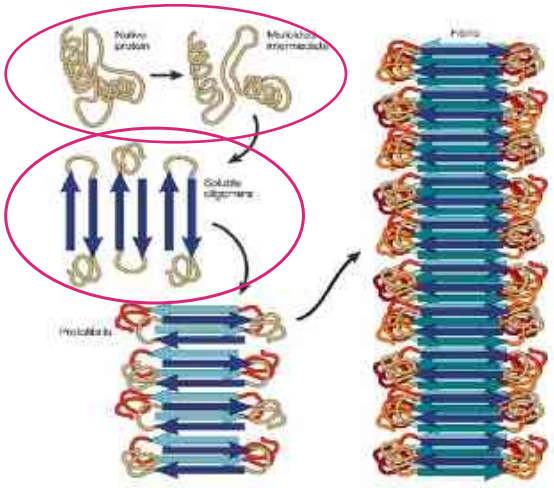
Le point sur l’immunothérapie des maladies neurodégénératives: faut-il changer de paradigme thérapeutique?

Communication à l’Académie Vétérinaire du 9 juin 2011

Les maladies neurodégénératives amyloïdes

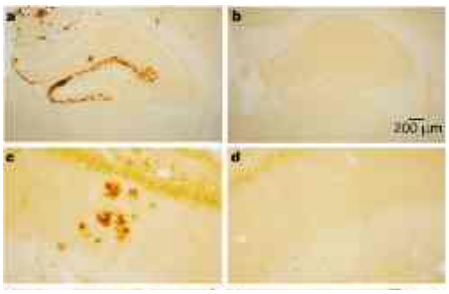


C. Soto (2003)
Nature Reviews | Neuroscience



C. Soto (2003) Nature Reviews | Neuroscience

L'immunothérapie appliquée aux pathologies neurodégénératives



Schenk D, et al. Nature. 1999 400:173-7.

Morgan D, et al. **A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease.** Nature. 2000 Dec 21-28;408(6815):982-5.

Janus C, et al., **A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease.** Nature. 2000 Dec 21-28;408(6815):979-82.

Immunothérapie des ESST

The history of TSE immunotherapy follows closely that of AD
(focus has been on Abs)

1] Abs were first shown to block PrPSc formation in vitro in cell lines (**Peretz et al. *Nature 2001***, **Enari et al. *PNAS 2001***)

2] Shortly later, Abs were shown to delay or prevent disease in scrapie infected mice (**Heppner *et al. Science 2001***, **White *et al. Nature 2003***)

White *et al. Nature 2003*

Les essais cliniques en cours contre la MA

Company	Approach	Abeta Epitope	Biological	Stage
Janssen/Wyeth (Elan)	Passive	N-terminus	Bapineuzumab	Phase III
Eli Lilly	Passive	Central domain	Solanezumab	Phase III
Baxter	Passive	IVIg – mix	Gammaguard	Phase III
Janssen/Wyeth (Elan)	Active	N-terminus	ACC-001	Phase II
Novartis	Active	N-terminus	CAD106	Phase II
Pfizer	Passive	C-terminus	Ponezumab	Phase II
GSK/Affiris	Active	Abeta mimetic	Affitope AD1 and AD2	Phase II
Roche	Passive	N-terminus + central domain	Gantunerumab R1450	Phase I
Merck	Active	Conformational	V950	Phase I
GlaxoSmithKline	Passive		GSK933776A	Phase I
Janssen/Wyeth (Elan)	Passive	N-terminus	Bapineuzumab s.c.	Phase I
Eisai/BioArctic	Passive	Protofibrils	BAN2401	Phase I
Abbott	Passive	Conformational		Preclinical
Elan/Wyeth	Passive	Conformational	AAB-002	Preclinical
Genentech/ ACImmune	Passive	Conformational		Preclinical
BiogenIdec/ Neurimmune	Passive			Preclinical
Boehringer/Ablynx	Nanobodies	Abeta		Preclinical

Salloway S et al.; Neurology. 2009 Dec 15;73(24):2061-70. Epub 2009 Nov 18.

A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease.

Abstract

BACKGROUND:
Bapineuzumab, a humanized anti-amyloid-beta (Abeta) monoclonal antibody for the potential treatment of Alzheimer disease (AD), was evaluated in a multiple ascending dose, safety, and efficacy study in mild to moderate AD.

METHODS:
The study enrolled 234 patients, randomly assigned to IV bapineuzumab or placebo in 4 dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Patients received 6 infusions, 13 weeks apart, with final assessments at week 78. The prespecified primary efficacy analysis in the modified intent-to-treat population assumed linear decline and compared treatment differences within dose cohorts on the Alzheimer's Disease Assessment Scale-Cognitive and Disability Assessment for Dementia. Exploratory analyses combined dose cohorts and did not assume a specific pattern of decline.

RESULTS:
No significant differences were found in the primary efficacy analysis. Exploratory analyses showed potential treatment differences ($p < 0.05$, unadjusted for multiple comparisons) on cognitive and functional endpoints in study "completers" and APOE epsilon4 noncarriers. Reversible vasogenic edema, detected on brain MRI in 12/124 (9.7%) bapineuzumab-treated patients, was more frequent in higher dose groups and APOE epsilon4 carriers. Six vasogenic edema patients were asymptomatic; 6 experienced transient symptoms.

CONCLUSIONS:
Primary efficacy outcomes in this phase 2 trial were not significant. Potential treatment differences in the exploratory analyses support further investigation of bapineuzumab in phase 3 with special attention to APOE epsilon4 carrier status. Classification of evidence: Due to varying doses and a lack of statistical precision, this Class II ascending dose trial provides insufficient evidence to support or refute a benefit of bapineuzumab.

Les limites de la thérapie anti-prion par Ac

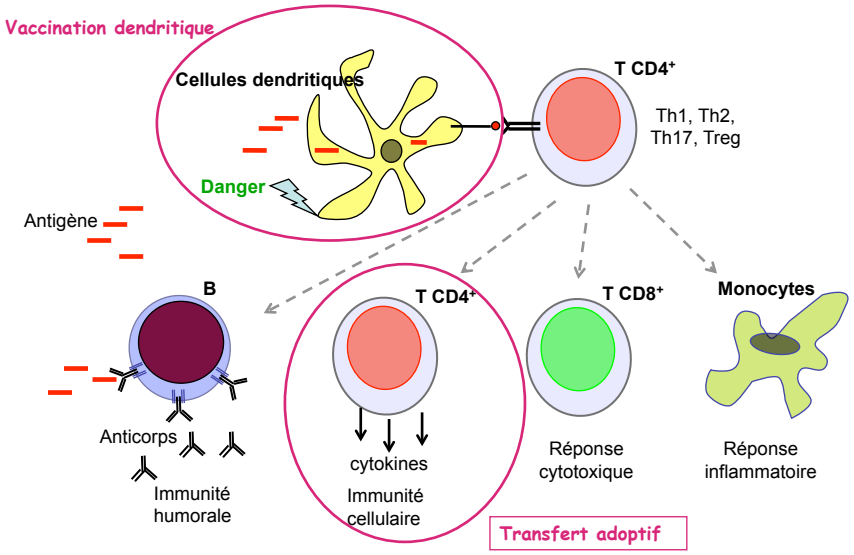
1) Les Ac doivent être injectés massivement, régulièrement et, surtout, peu de temps après le départ de l'infection

2) Les Ac retardent la survenue des signes cliniques chez la souris. Ils ne donnent pas de rémission définitive.

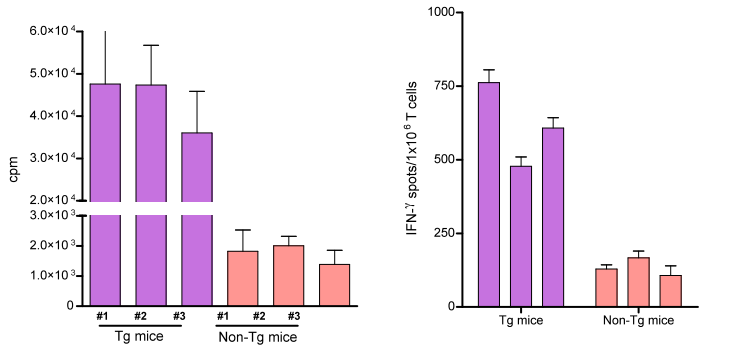
3) Les Ac ne sont opérationnels qu'à la phase extraneurale de la tremblante. Ils perdent tout pouvoir thérapeutique lorsque les prions ont déjà envahi le cerveau ou qu'ils ont été directement inoculés dans le parenchyme cérébral (inutilisables donc en clinique)

4) Certains Ac sont neurotoxiques

Quelles sont les alternatives ?

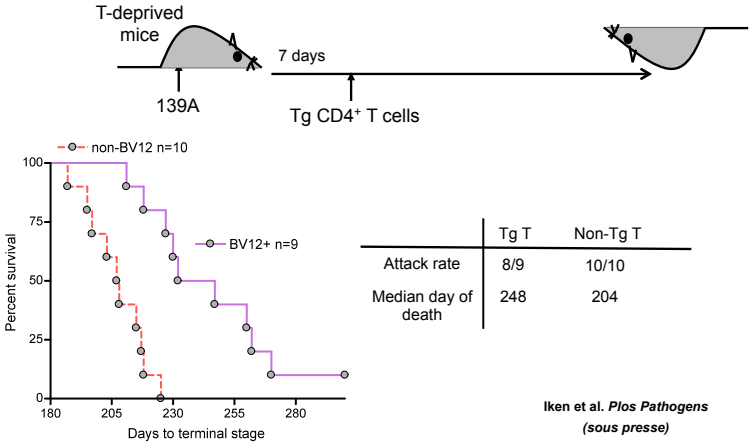


Réponse à la protéine prion de souris TCR Tg



Iken et al. *Plos Pathogens*
(sous presse)

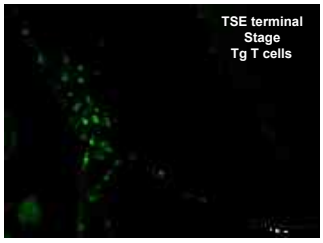
Le transfert adoptif de lymphocytes T prolonge la survie de souris infectées

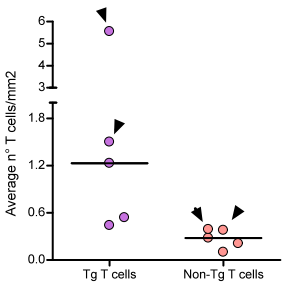


	Tg T	Non-Tg T
Attack rate	8/9	10/10
Median day of death	248	204

Iken et al. *Plos Pathogens* *(sous presse)*

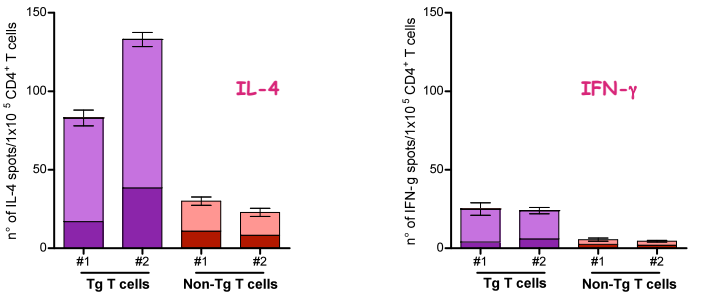
Les lymphocytes T infiltrent le cerveau





Iken et al. *Plos Pathogens* *(sous presse)*

Ils produisent des cytokines de type Th2



Iken et al. *Plos Pathogens*
(sous presse)

Conclusions/Questions ouvertes

1) La mise en jeu des lymphocytes T et de l'immunité cellulaire ouvre de nouvelles perspectives thérapeutiques plus efficaces que les Ac, en agissant in situ dans le cerveau via la production de cytokines de type Th2

2) Les lymphocytes T peuvent-ils enrayer la propagation des prions lorsque ces derniers sont directement inoculés dans le cerveau?

3) Est-ce que le pouvoir prionostatique des lymphocytes T implique l'enrôlement de la microglie?

4) Est-ce que ces conclusions obtenues à partir d'expériences sur la tremblante murine peuvent être étendues aux autres maladies neurodégénératives, et en tout premier lieu à la maladie d'Alzheimer?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