

La tolérance opérationnelle en transplantation rénale

Richard Danger INSERM U1064-ITUN, Nantes

richard.danger@univ-nantes.fr

itun
institut
transplantation
urologie
néphrologie
INSERM - UMR 643

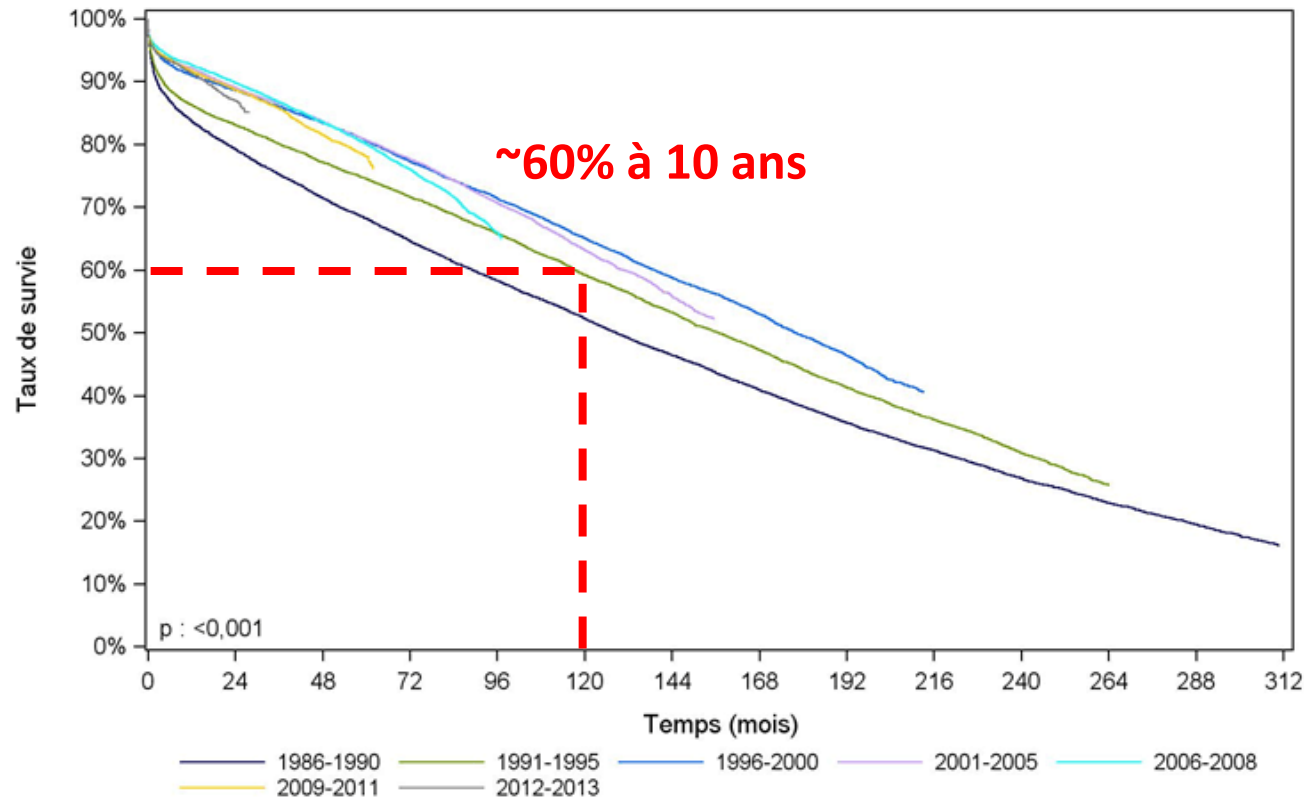
**CRTI**
UMR 1064
Centre de Recherche en
Transplantation et Immunologie

 **Inserm**
U1064



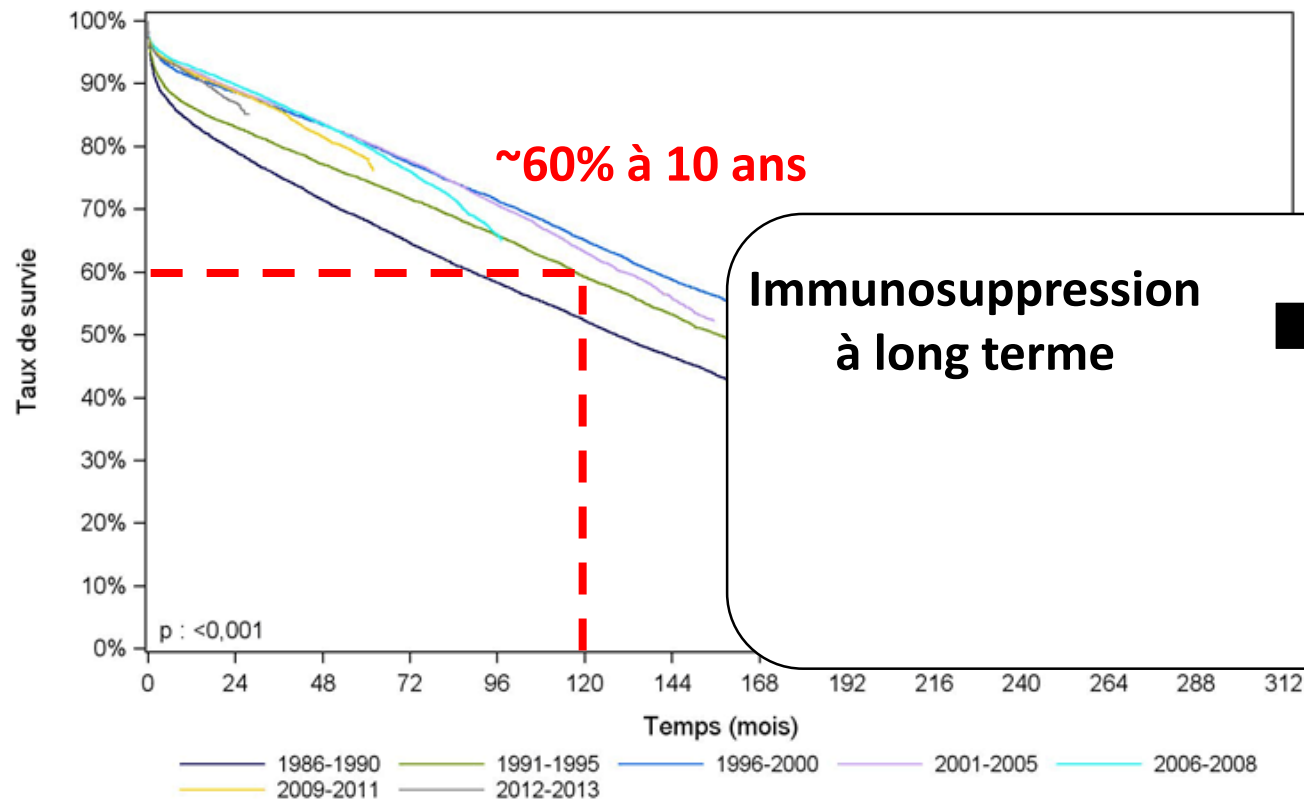
La transplantation rénale

- Traitement de choix de l'insuffisance rénale chronique terminale
- Ciclosporine (1981): survie greffon à 1 an 30% → 90-95%



La transplantation rénale

- Traitement de choix de l'insuffisance rénale chronique terminale
- Ciclosporine (1981): survie greffon à 1 an 30% → 90-95%



Infections opportunistes

Singh 2005

Cancers

Stallone, et al. 2005; Dantal, et al. 1998

Néphrotoxicité

Nankivell, et al. 2003; Bennett, et al. 1996

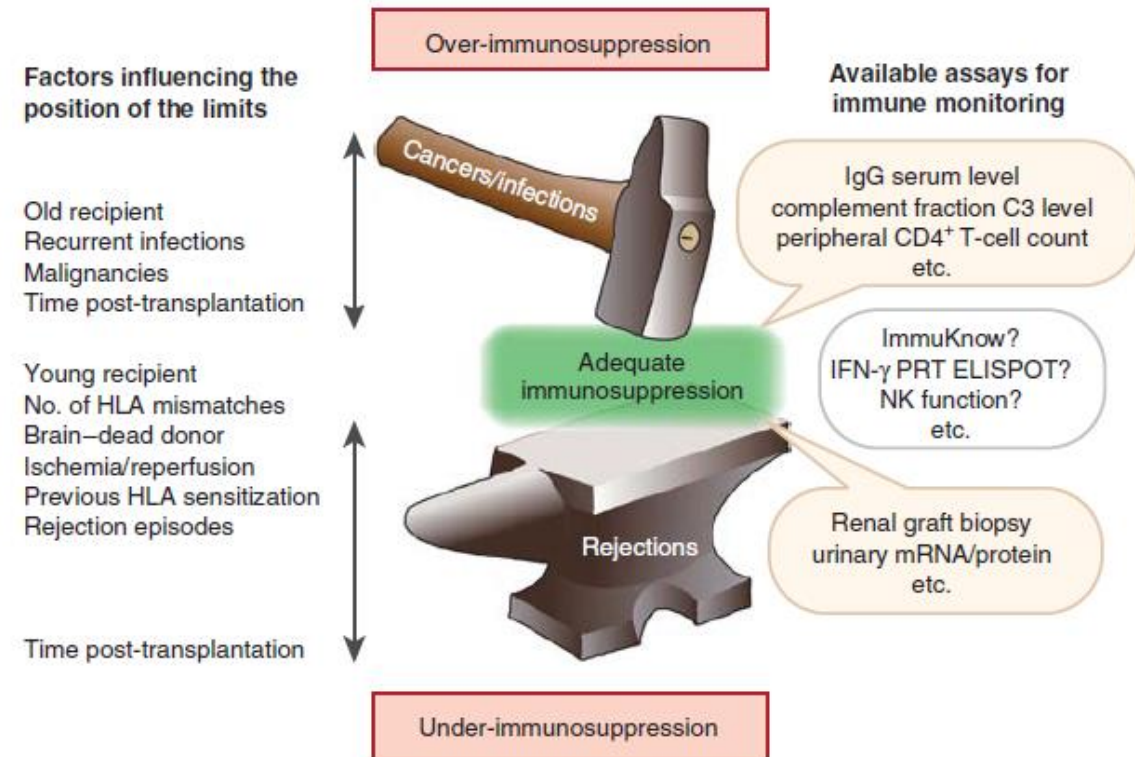
Réduire l'exposition aux CNI

1) Individualiser les doses de CNI

Finding the safe place between the hammer and the anvil: sounding the depth of therapeutic immunosuppression

Olivier Thaunat^{1,2,3}

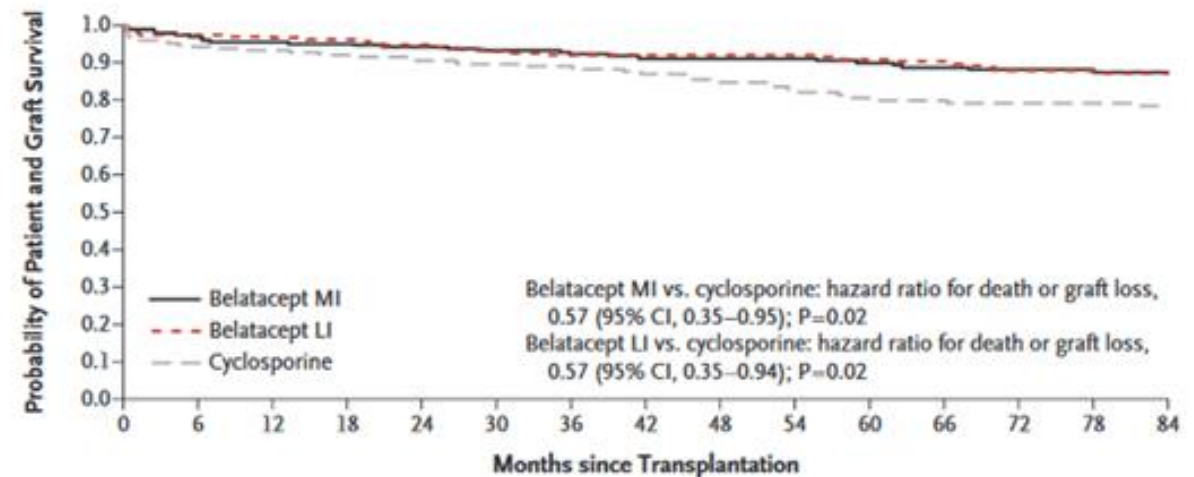
➔ Besoin de biomarqueurs



Réduire l'exposition aux CNI

- 1) Individualiser les doses de CNI
- 2) Nouveaux traitements

→ Compréhension des mécanismes immunologiques post-greffe



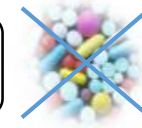
No. at Risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128	
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137	
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92	

Vincenti, N Engl J Med, 2016

Réduire l'exposition aux CNI

- 1) Individualiser les doses de CNI
- 2) Nouveaux traitements
- 3) La tolérance

Maintien d'une transplantation rénale sans immunosuppression



- Protocoles d'induction de tolérance: par chimérisme ou thérapie cellulaire
→ Compréhension des mécanismes immunologiques post-greffe
- Cas de tolérance spontanée = « **tolérance opérationnelle** »

La tolérance opérationnelle en transplantation rénale

<u>Tolérance « vraie » modèles animaux</u>	<u>Tolérance opérationnelle chez l'Homme</u>
Pas de signe histologique de rejet	
Absence d'immunosuppression	Arrêt de l'IS depuis ≥ 1 an
Acceptation d'une 2 ^e greffe du même donneur	
Rejet de greffe d'un tiers	

Billingham, *et al.* Nature; 1953

- Tolérance opérationnelle : critères fonctionnels exclusivement :
 - absence d'IS depuis plus d'un an
 - avec une créatininémie inférieure à $150\mu\text{mol/L}$
 - une protéinurie inférieure à $1\text{g}/24\text{h}$

Roussey-Kessler *et al.*, A.J.T., 2006

La tolérance opérationnelle en transplantation rénale

- Rare avec une centaine de cas décrits – principalement par non-observance
- Fonction greffon stable sans IS (> 20 ans)
- Pas d'infections opportunistes, réponse immune post-vaccinale normale
- Pas de différences cliniques et démographiques vs patients sous IS
- Immunisation post-greffe par anticorps spécifiques du donneur (DSA) moindre

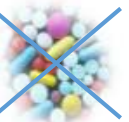
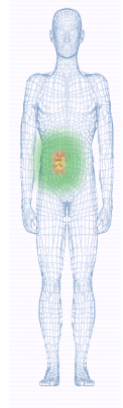
Roussey, Am J Transplant, 2006

Ballet, Am J Transplant, 2008

Sagoo, J Clin Invest, 2010

Brouard, Am J Transplant, 2012

Massart, Nephrol Dial Transplant, 2016



La tolérance opérationnelle en transplantation rénale

Roussey-Kessler *et al.*, Am J Transplant., 2006

= description : 10 patients TOL

Brouard *et al.*, Am J Transplant. 2012

= mise à jour : 10 + 17 patients TOL

Massart A *et al.*, NDT, 2016

= mise à jour européenne : 61 patients TOL

n	27 patients
Temps post-transplantation (période avec et sans IS)	10 ±7 ans (max. = 32ans)
Durée sans IS	9 ±6 ans
Transfusions sanguines >10	5
Incompatibilités HLA	3 ±2.25
Première greffe	22
PRA class I	7
Episode de rejet aigu	10
Non-observance	19/27
Perte de greffon	8/27

With 218 913 kidney recipients surveyed, cumulative incidences of operational tolerance estimated at 3 per 10 000 kidney recipients.

Massart A *et al.*, NDT, 2016

Pas de caractéristique clinique particulière

état « métastable »

Brouard *et al.*, Am J Transplant. 2012

Arrêter les CNI chez des patients à faible risque de rejet ?

Failure of Calcineurin Inhibitor (Tacrolimus) Weaning Randomized Trial in Long-Term Stable Kidney Transplant Recipients

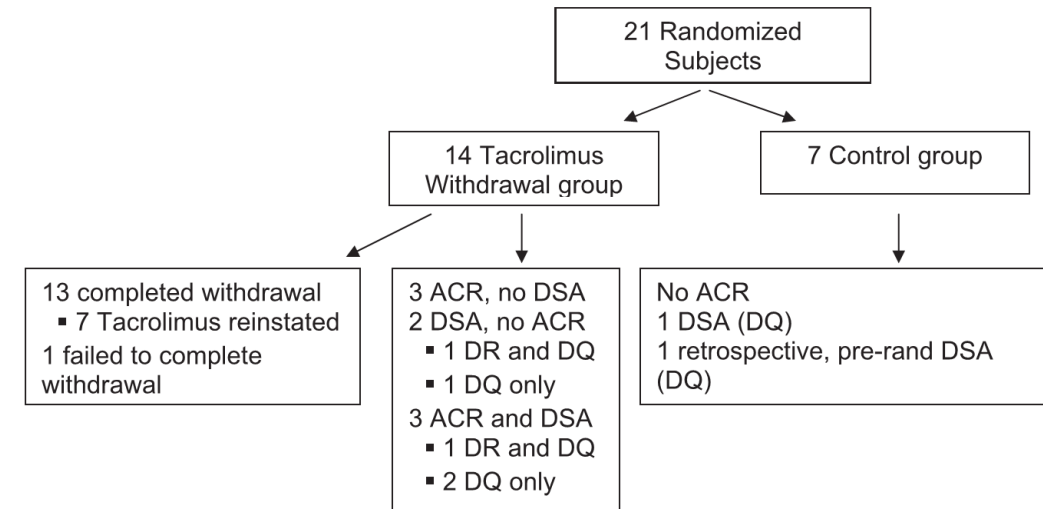
E. Dugast^{1,2}, J.-P. Souillou^{1,2}, Y. Foucher³, E. Papuchon^{1,4}, P. Guerif^{1,4}, C. Paul¹, D. Riochet^{5,6}, M. Chesneau¹, A. Cesbron^{7,8}, K. Renaudin^{1,2}, J. Dantal¹, M. Giral^{1,2,7,9,*,†} and S. Brouard^{1,7,9,10,†}

Contrastingly, in the placebo arm, all five patients had to reintroduce a full dose of tacrolimus since three of them presented an acute rejection episode (one humoral, one mixed, and one borderline) and two displayed anti-HLA antibodies without histological lesion (one donor-specific antibodies [DSA] and one non-DSA). Clearly, tacrolimus withdrawal must

Dugast, Am J Transplant, 2016

1500 prescreened patients

Hricik DE. et al., J Am Soc Nephrol 2015



« The study was terminated prematurely because of unacceptable rates of AR (4 of 14) and/or de novoDSAs (5 of 14) in the tacrolimus withdrawal arm »

Pas possible sur des patients sélectionnés sur critères cliniques uniquement

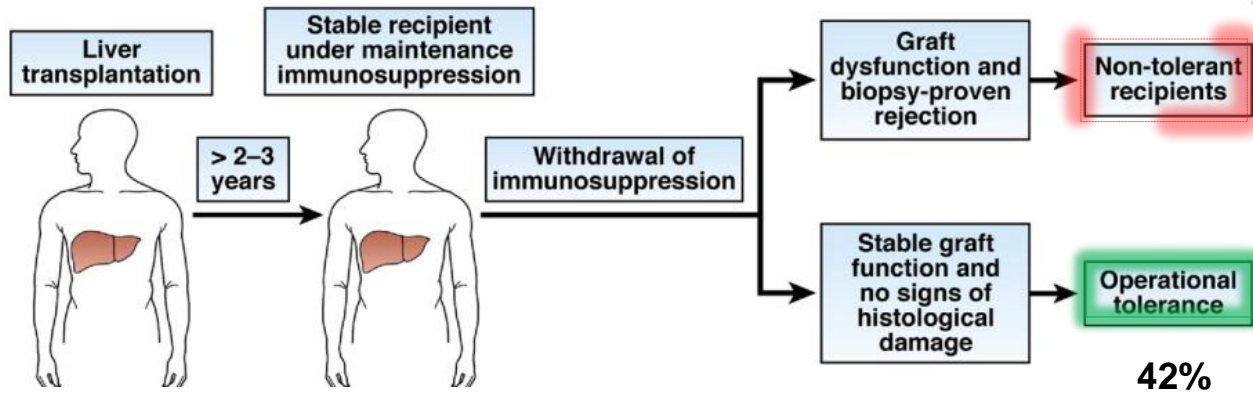
➔ Besoin de biomarqueurs

Tolérance opérationnelle en transplantation hépatique

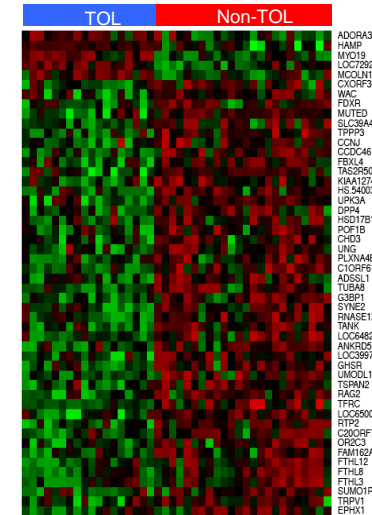
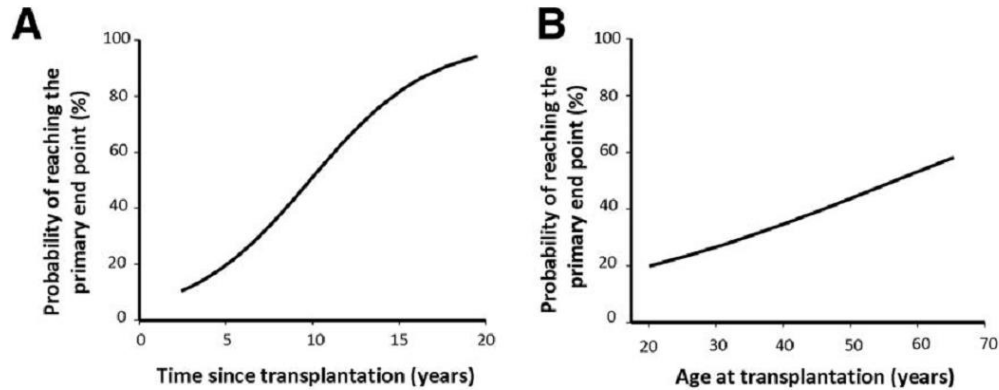
Year	Author	Number Patients	Drug withdrawal	Rejection Acute / Chronic	Graft loss
1997	Mazariegos	95	19%	26% / 0%	0
1998 2005	Devlin Girlanda	18	16.7%	28% / 5.6%	5.6%
2001	Takatsuki	26	23.8%	12% / 0%	0
2003 2008	Pons	21	38%	22% / 0%	0
2005	Eason	18	5.6%	61% / 0%	0
2005	Tryphonopoulos	104	19%	67% / 1.9%	0.96%
2006	Tisone	34	23.4%	76.4% / 0%	0
2007	Assy	26	8%	58% / 0%	0
2012	Feng	20	60%	35% / 0%	0
2013	Benitez	102	42%	58% / 0%	0
2012	Shacked (unpublished)	275	8%	90%	0

from A. Sanchez-Fueyo (KCL)

Paramètres associés à la tolérance opérationnelle en transplantation hépatique



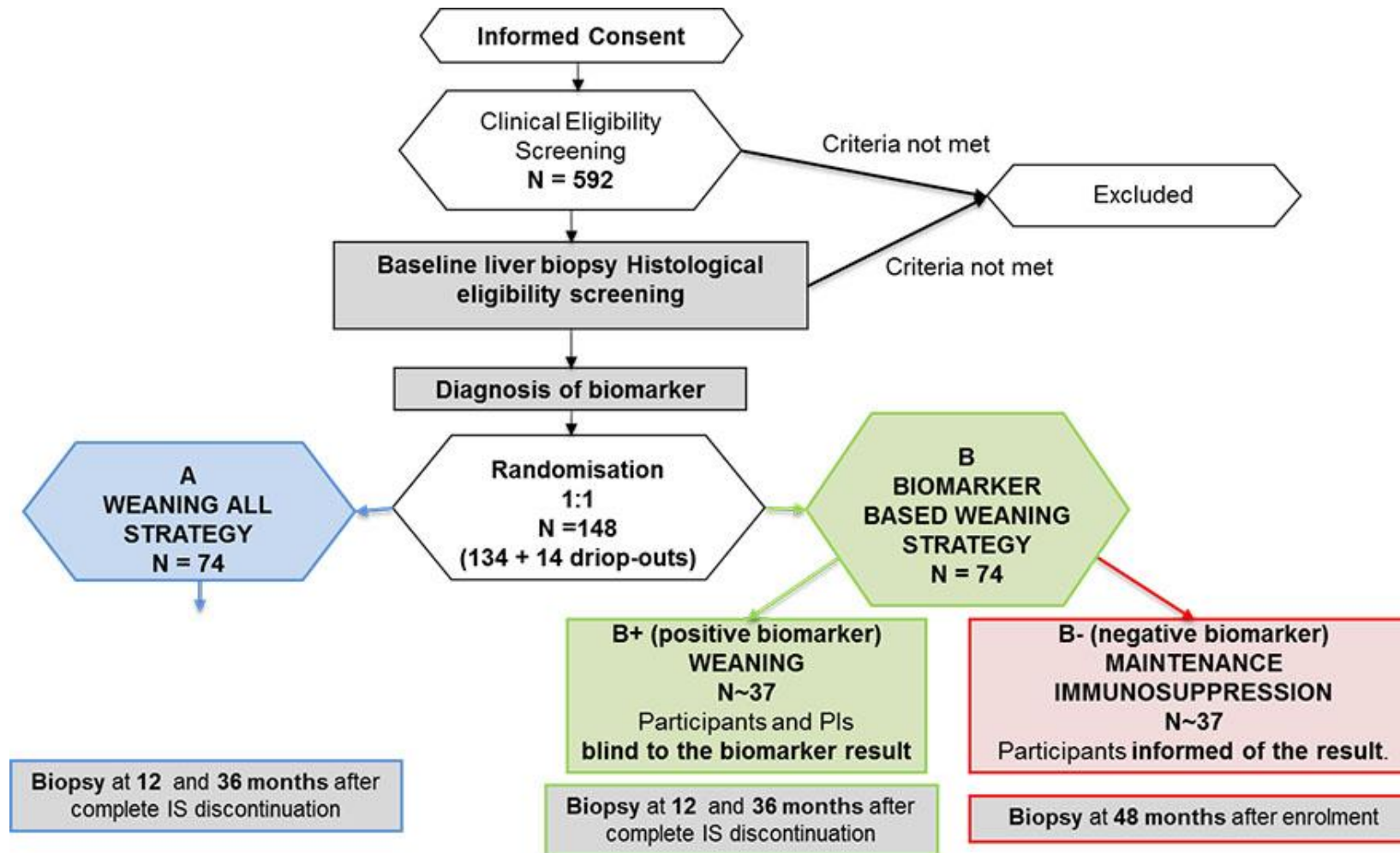
Benitez C. *et al.* Hepatology, 2013



Bohne F. *et al.* J Clin Invest, 2012

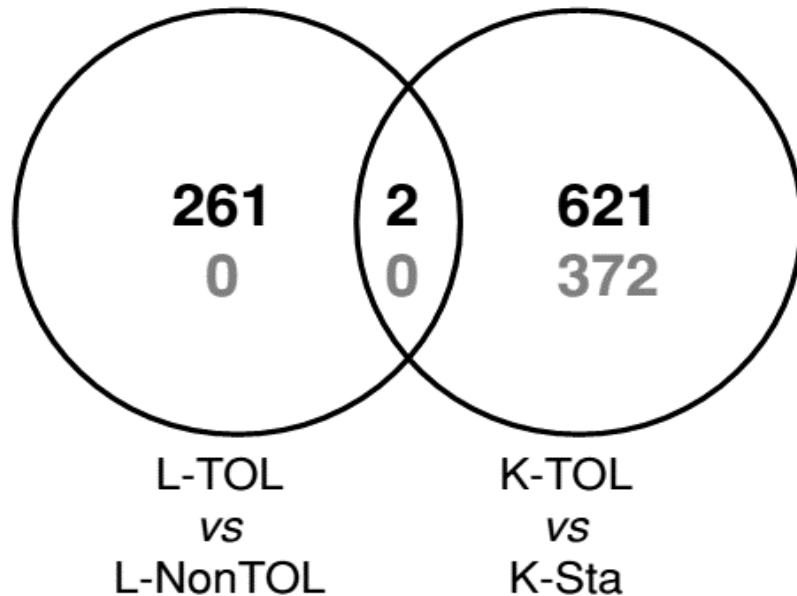
Validation de la signature prédictive du retrait d'IS

- Liver Immunosuppression Free Trial (LIFT)



Comparaison des signatures transcriptionnelles rénales et hépatiques

- Etude transcriptionnelle sur la même plateforme



American Journal of Transplantation 2011; 11: 1916–1926
Wiley Periodicals Inc.

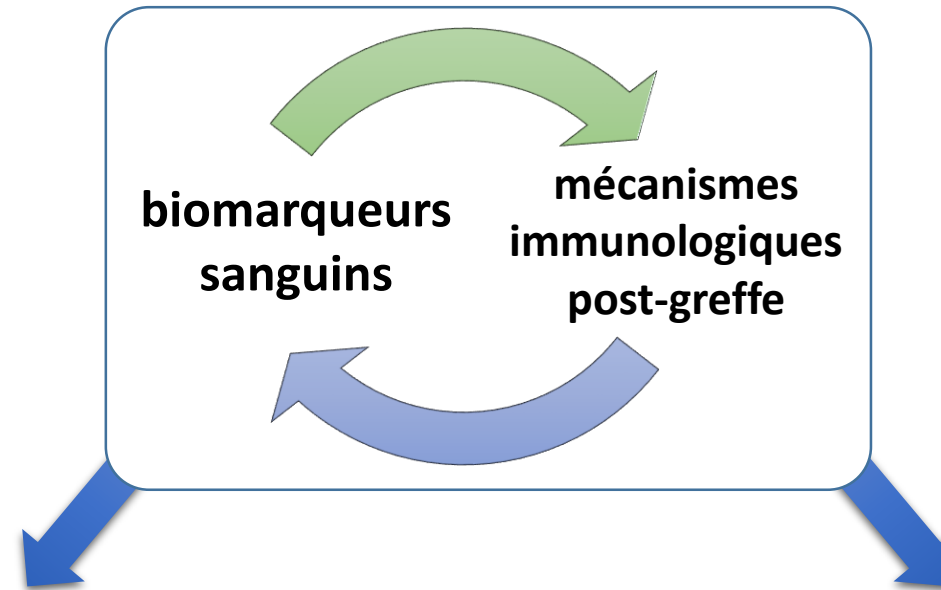
Comparison of Transcriptional and Blood Cell-Phenotypic Markers Between Operationally Tolerant Liver and Kidney Recipients

J. J. Lozano^a, A. Pallier^b, M. Martinez-Llordella^c,
R. Danger^b, M. López^c, M. Giral^{b,d},
M. C. Londoño^c, A. Rimola^c, J. P. Soulillou^{b,d,e},
S. Brouard^{b,†}, and A. Sánchez-Fueyo^{c,*,†}

 Signatures/ mécanismes organes-spécifiques

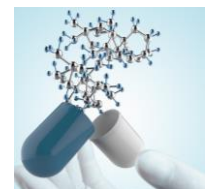
Etude de la tolérance opérationnelle rénale: **objectifs**

- Compréhension des mécanismes immunologiques post-greffe
- Recherche de marqueurs biologiques attestant du statut immunologique
 - identifier des patients à faible et fort risque de rejet
 - minimiser leur traitement immunosuppresseurs?



**Amélioration du diagnostic
/pronostic de perte de greffon**

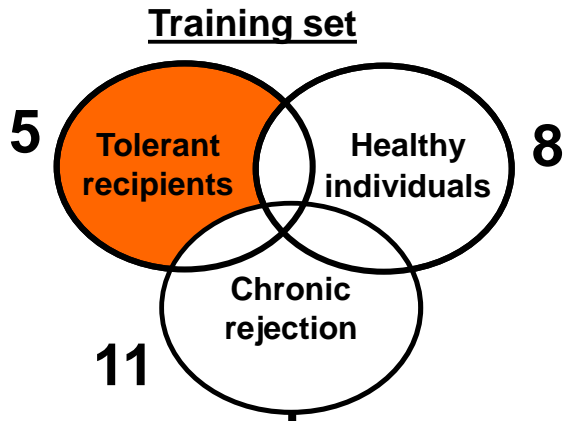
**Identification de nouvelles
cibles moléculaires**



Profil d'expression de patients transplantés rénaux

- Identification d'une signature de 49 gènes associée à la tolérance:

[Brouard S. et al., PNAS, 2007](#)



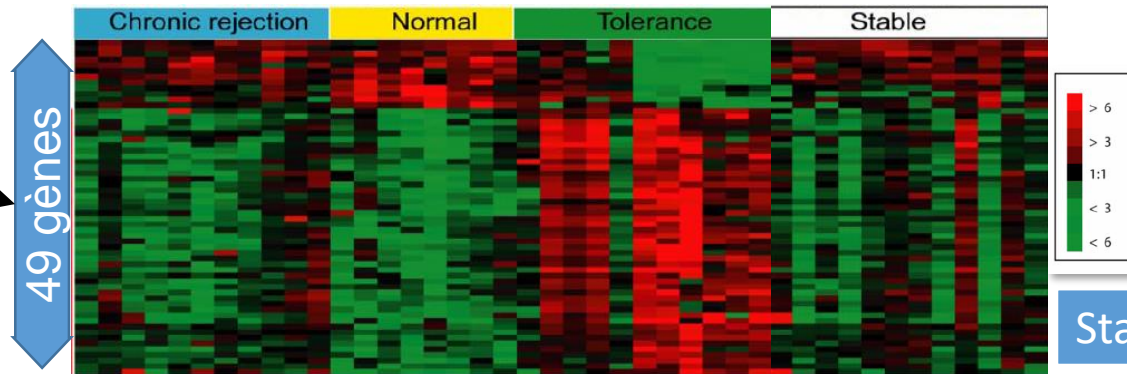
- 17 tolerant recipients
- 8 healthy individuals
- 22 chronic rejection
- 10 minimally immunosuppressed
- 12 immunosuppressed stable recipients
- 14 acute rejection

49-gene predictive signature

Testing set

- 12 Tolerant
- 11 Chronic rejection

Correct classification in 22/23



Stanford's Lymphochips

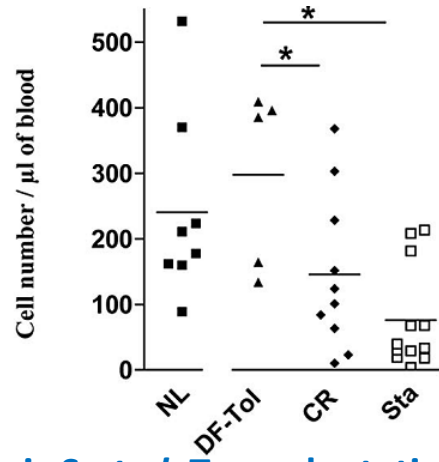
Mise en évidence de voies de signalisation:

Gènes impliqués dans le fonctionnement des lymphocytes B
27% des gènes associés au TGF β

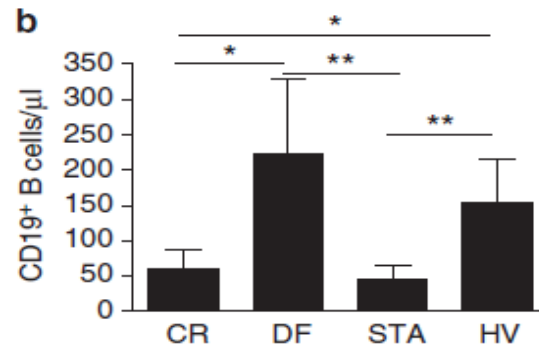
Lymphocytes B en tolérance rénale

Sagoo *et al.* J. Clinical. Invest. 2010

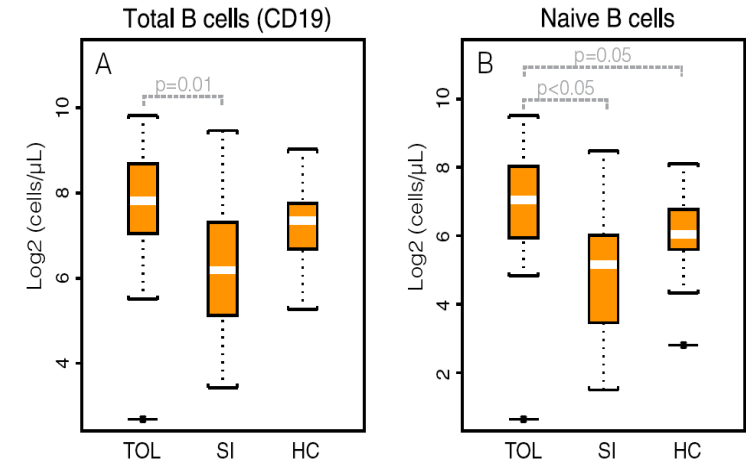
- Plus de lymphocytes B chez les patients tolérants



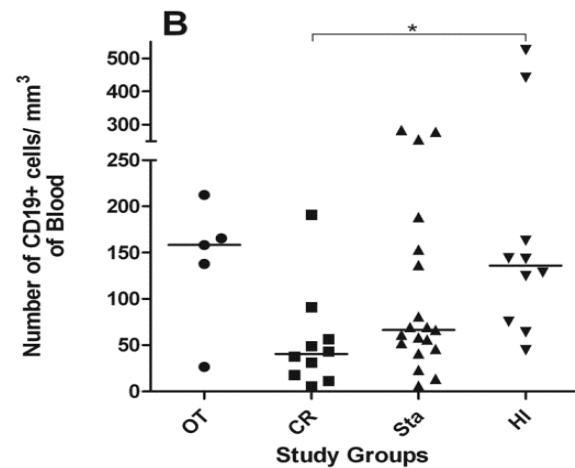
Louis S *et al.* Transplantation, 2006



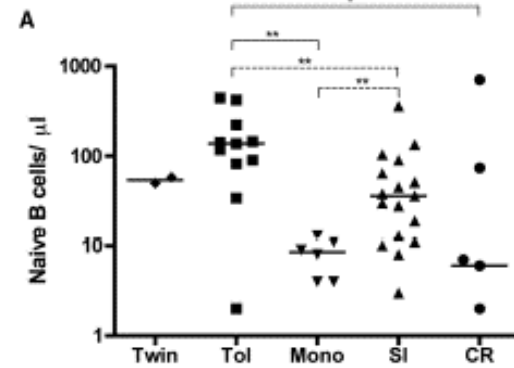
Pallier A *et al.* Kid. Int., 2010



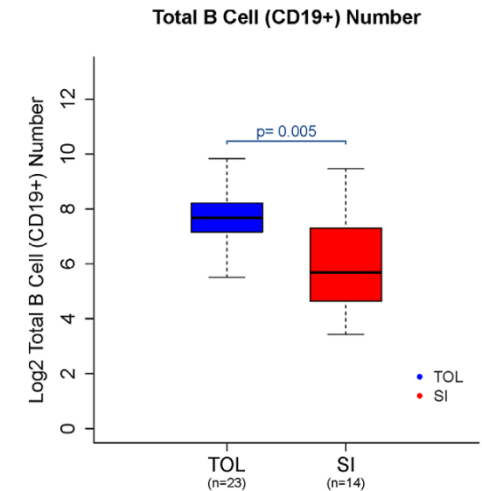
Newell *et al.* J. Clinical. Invest. 2010



Silva *et al.* Mol Med 2012

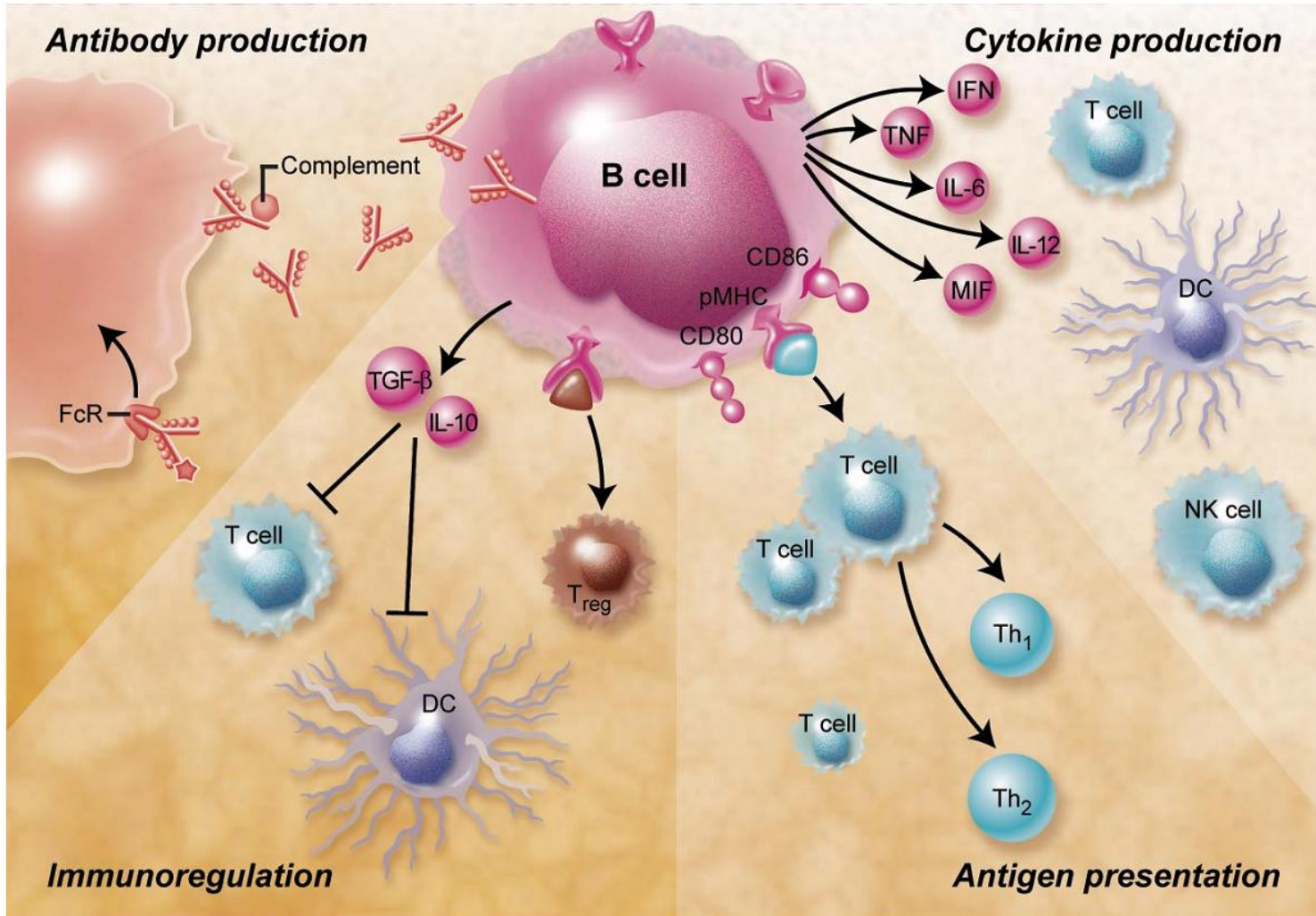


Haynes *et al.* Am. J. transplant. 2011



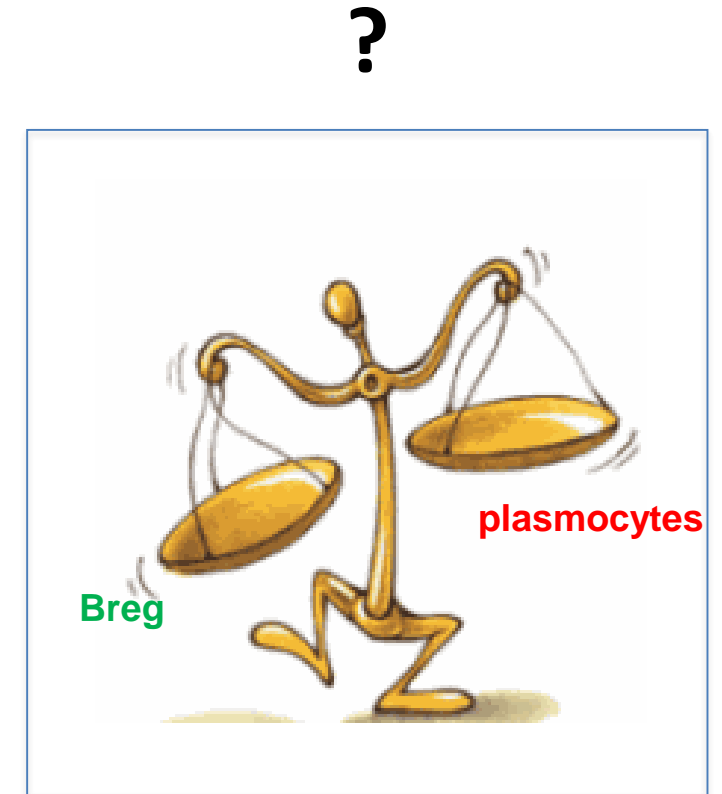
Newell *et al.* Am. J. transplant. 2015

Fonctions des lymphocytes B



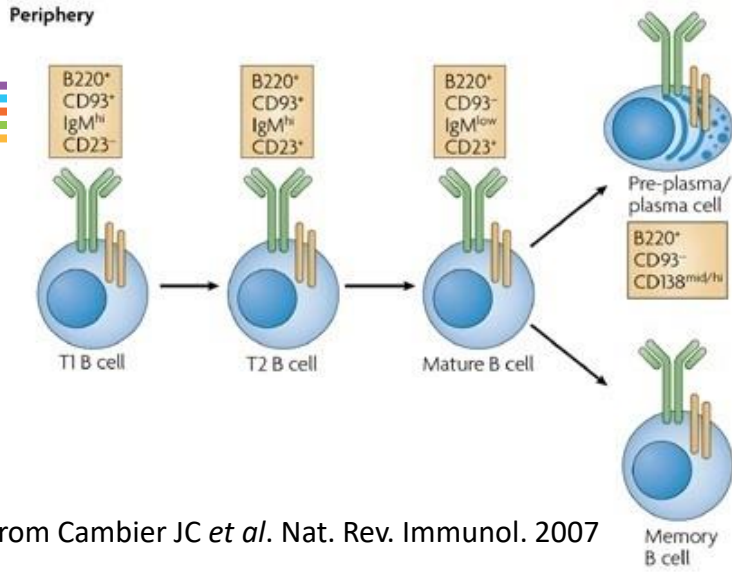
Shimabukuro-Vornhagen A. *et al.*, Blood, 2009

•Rarely develop antibodies ([Roussey et al. AJT 2006](#); [Brouard et al. AJT 2012](#))

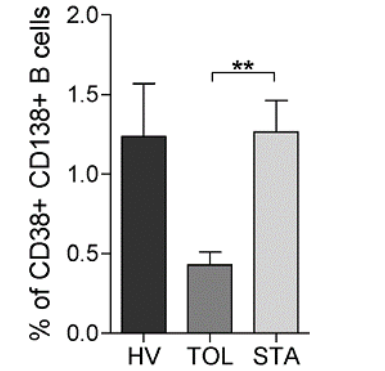
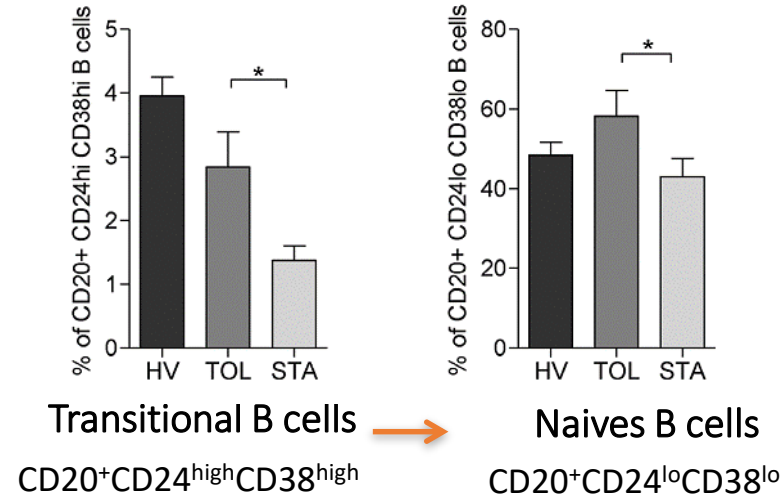


Lymphocytes B en tolérance rénale

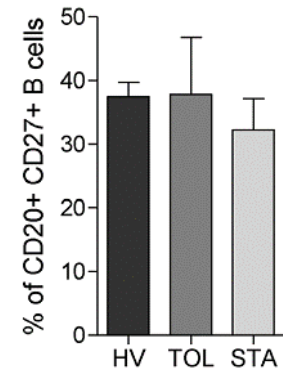
- Un défaut de différenciation des lymphocytes B chez les tolérants ?



from Cambier JC *et al.* Nat. Rev. Immunol. 2007



Plasma cells
CD38⁺CD138⁺CD20⁺

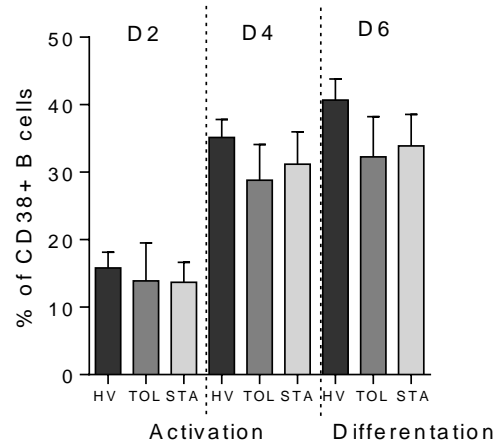


Memory B cells
CD20⁺CD27⁺

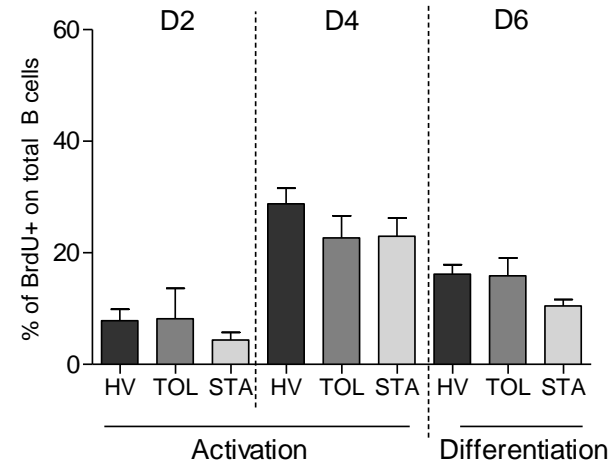
Chesneau M. *et al.* AJT 2013

Les lymphocytes B des patients tolérants...

- ...s'activent normalement

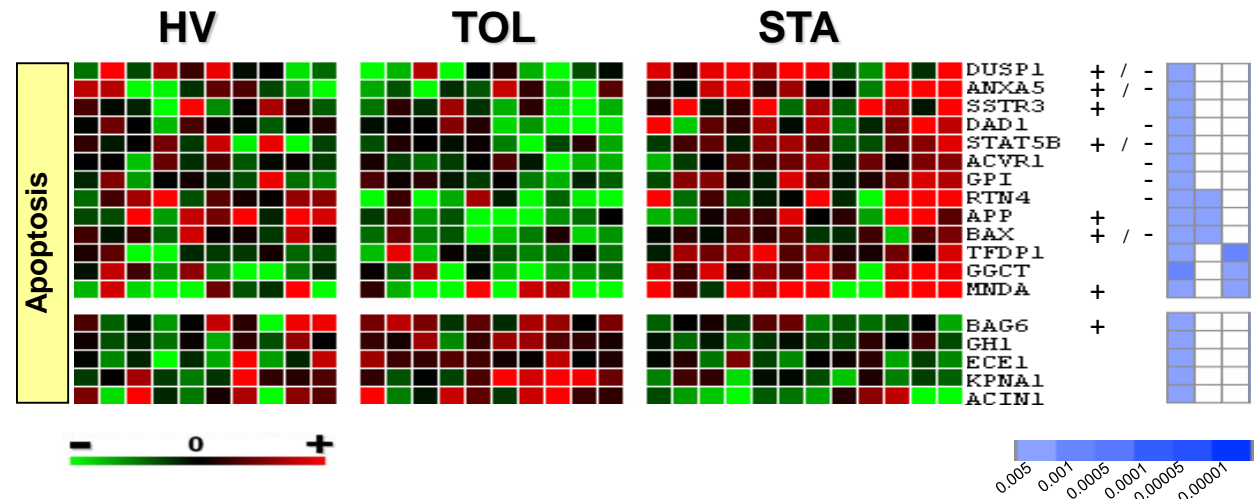
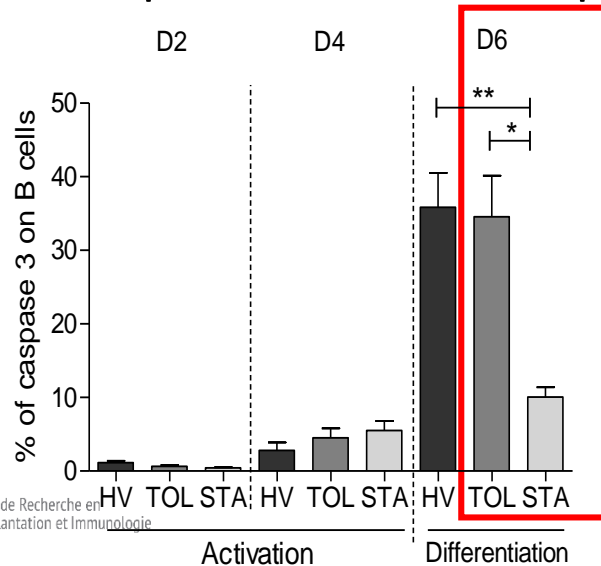


- ... prolifèrent normalement



Chesneau M. *et al.* AJT 2013

- ... sont plus sensibles à l'apoptose



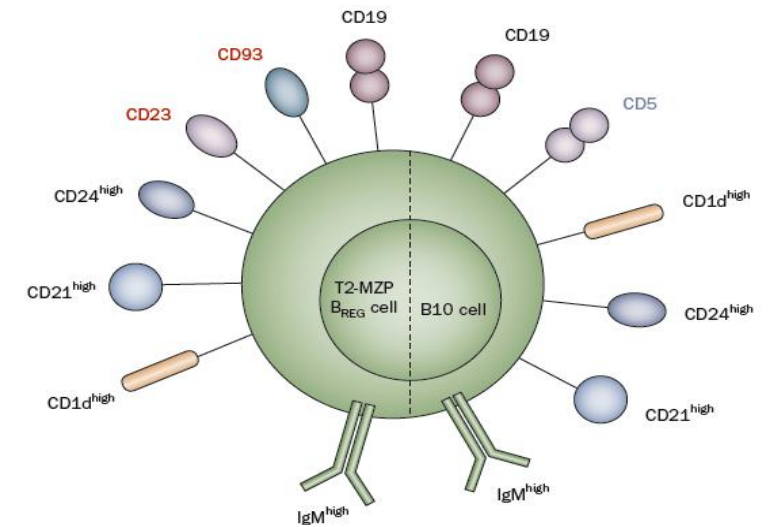
Lymphocytes B regulateurs?

Pas de phénotype commun décrit

- *Environnement*
- *Pathologie*
- *Rôle*

Type of Breg Cell	Mouse	Human	Key Features	Reference
T2-MZP cells	CD19 ⁺ CD21 ^{hi} CD23 ^{hi} CD24 ^{hi}	–	found in spleen, produce IL-10, induce Treg cells, and suppress effector CD4 ⁺ and CD8 ⁺ T cells	Blair et al., 2009; Carter et al., 2011; Evans et al., 2007; Schioppa et al., 2011
MZ cells	CD19 ⁺ CD21 ^{hi} CD23 [–]	–	found in spleen, produce IL-10, induce Treg cells, and suppress effector CD4 ⁺ and CD8 ⁺ T cells	Bankoti et al., 2012; Gray et al., 2007; Miles et al., 2012
B10 cells	CD5 ⁺ CD1d ^{hi}	CD24 ^{hi} CD27 ⁺	found in spleen (mice) and blood (humans), produce IL-10, and suppress effector CD4 ⁺ T cells, monocytes, and DCs	Horikawa et al., 2013; Iwata et al., 2011; Matsushita et al., 2010; Yanaba et al., 2008
Plasma cells	CD138 ⁺ MHC-11 ^{lo} B220 ⁺	–	found in spleen, produce IL-10 and IL-35, and suppress NK cells, neutrophils, and effector CD4 ⁺ T cells	Neves et al., 2010; Shen et al., 2014
Tim-1 ⁺ B cells	Tim-1 ⁺ CD19 ⁺	–	found in spleen (mice), produce IL-10, and suppress effector CD4 ⁺ T cells	Ding et al., 2011; Xiao et al., 2012
Plasmablasts	CD138 ⁺ CD44 ^{hi}	CD19 ⁺ CD24 ^{hi} CD27 ^{int}	found in dLNs (mice) and blood (humans), produce IL-10, and suppress DCs and effector CD4 ⁺ T cells	Matsumoto et al., 2014
Immature cells	–	CD19 ⁺ CD24 ^{hi} CD38 ^{hi}	found in blood and at site of inflammation, produce IL-10, induce Treg cells, suppress Th1 and Th17 cells, suppress virus-specific CD8 ⁺ T cell responses, are defective in patients with SLE and RA, and support iNKT cell homeostasis	Blair et al., 2010; Bosma et al., 2012; Das et al., 2012; Flores-Borja et al., 2013
Br1 cells	–	CD19 ⁺ CD25 ^{hi} CD71 ^{hi}	found in blood and produce IL-10 and IgG4	van de Veen et al., 2013

This table shows currently described subsets of Breg cells in mice and humans. Abbreviations are as follows: Br1, B regulatory 1; DC, dendritic cell; dLN, draining lymph node; IgG4, immunoglobulin G4; MHC, major histocompatibility complex; MZ, marginal zone; NK, natural killer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T2-MZP, transitional 2 marginal-zone precursor.

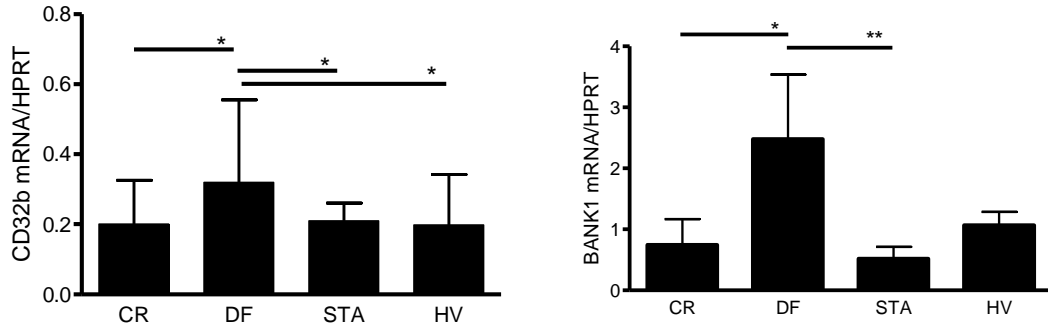


Mauri et al. Nat. Rev. 2012

Rosser et al. Immunity 2015

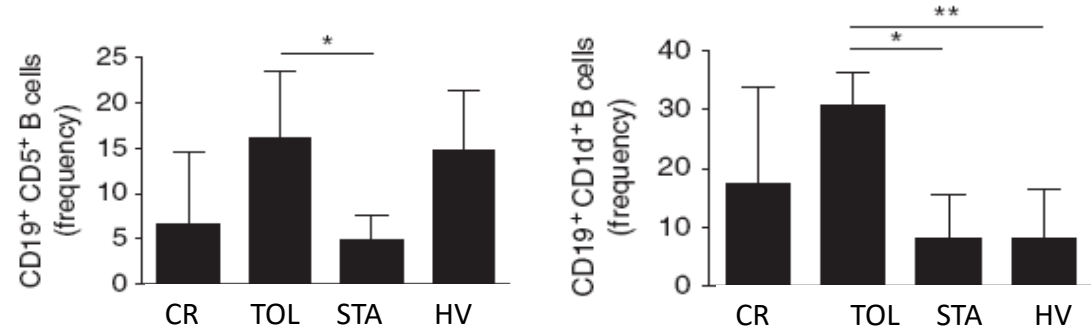
Lymphocytes B en tolérance rénale

- avec un profil inhibiteur?



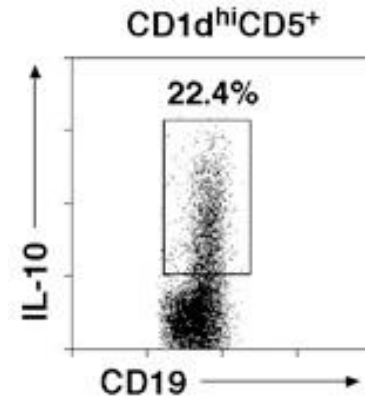
Pallier A. *et al. Kid. Int.*, 2010

- Augmentation des CD19⁺CD1d^{hi} et CD19⁺CD5⁺



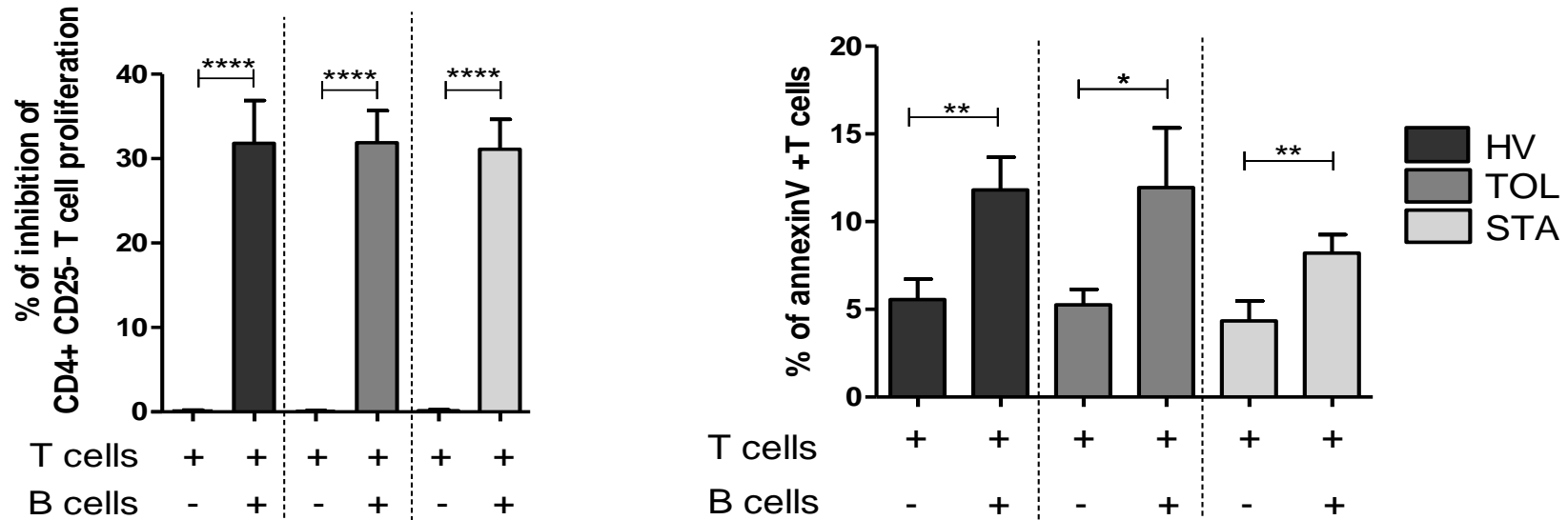
Le FcγRIIB (CD32b) induit un signal inhibiteur (motif ITIM)

BANK1 : un modulateur de l'activation des lymphocytes B en inhibant l'activation de la voie AKT induite par le CD40 (Aiba *et al. Immunity*, 2006)



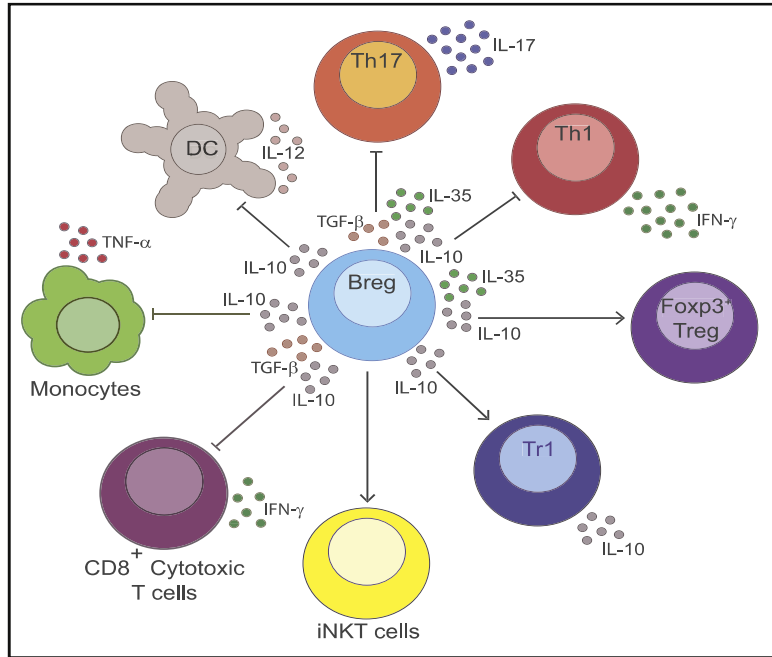
Bouaziz *et al.*, *Imm. Rev.* 2008

- inhibent la prolifération des lymphocytes T activés et induit leur apoptose

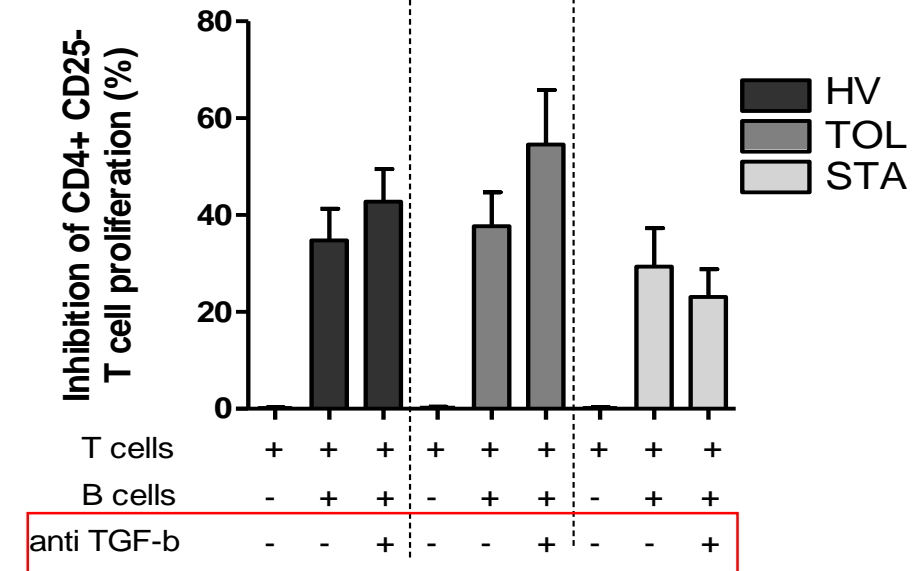
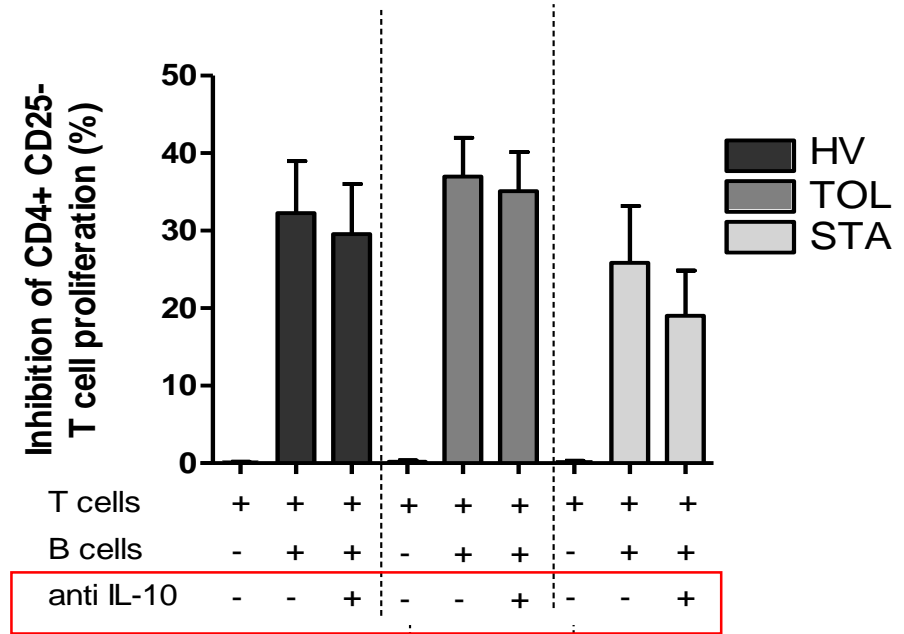


L'effet inhibiteur des B n'est pas dépendant de l'Il10 ni du TGFβ

Chesneau et al. JASN 2015



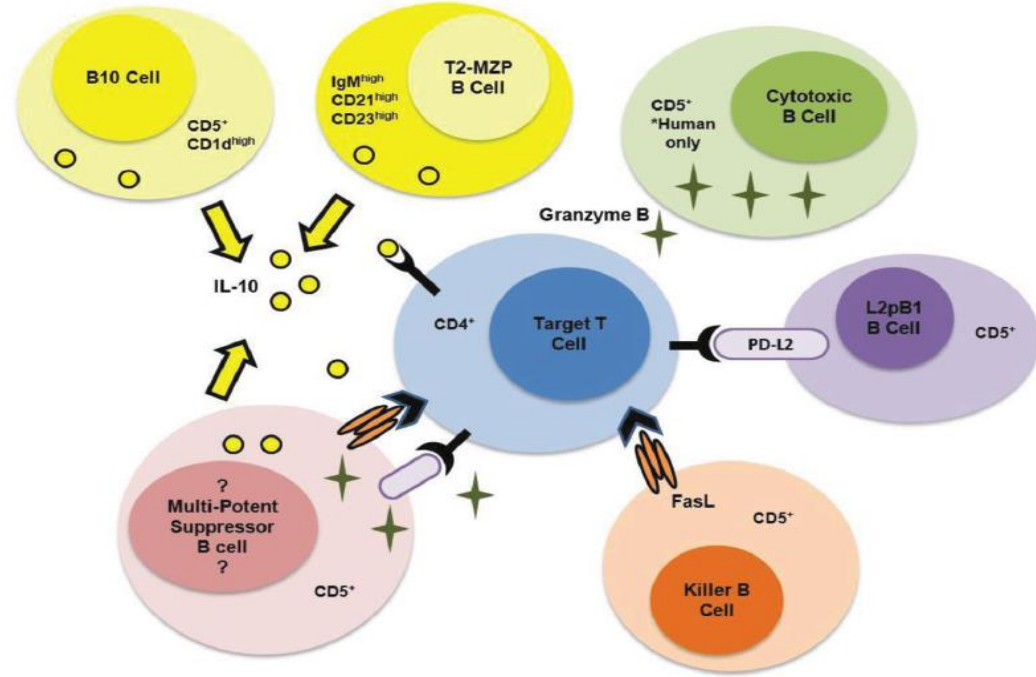
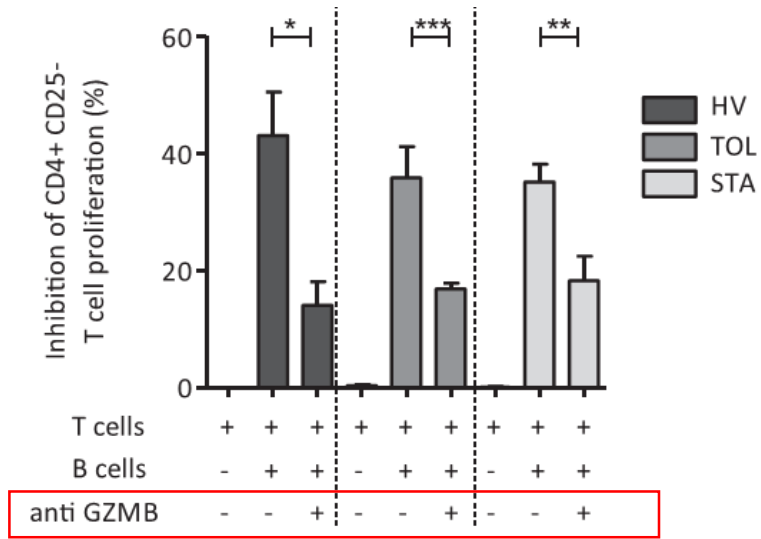
Rosser et al. Immunity 2015



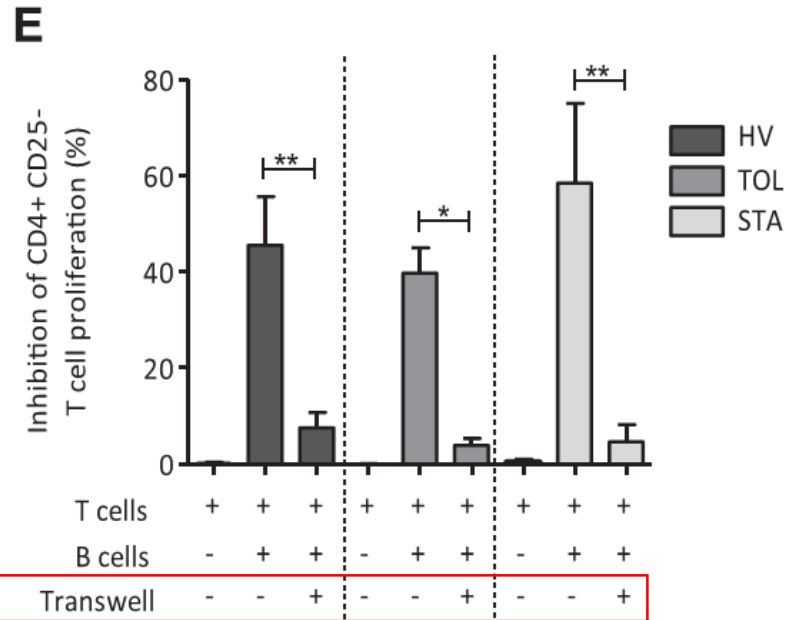
Chesneau et al. JASN 2015

L'effet inhibiteur des B est dépendant du Granzyme B et requiert un contact cellulaire

Chesneau et al. JASN 2015

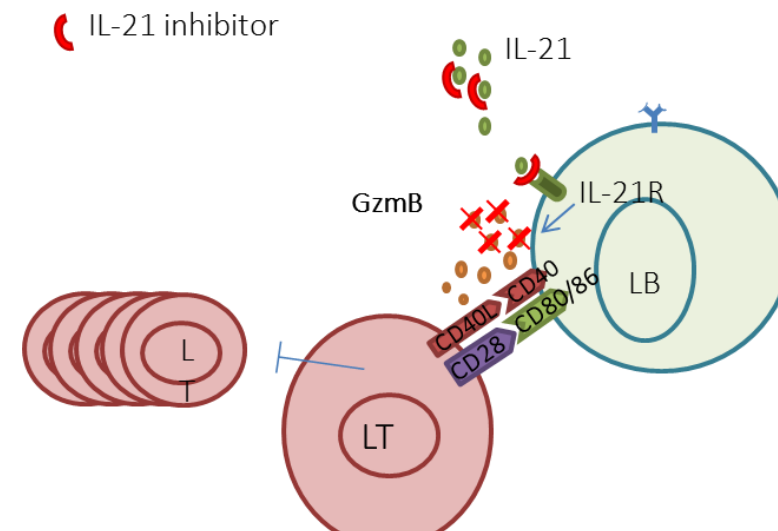
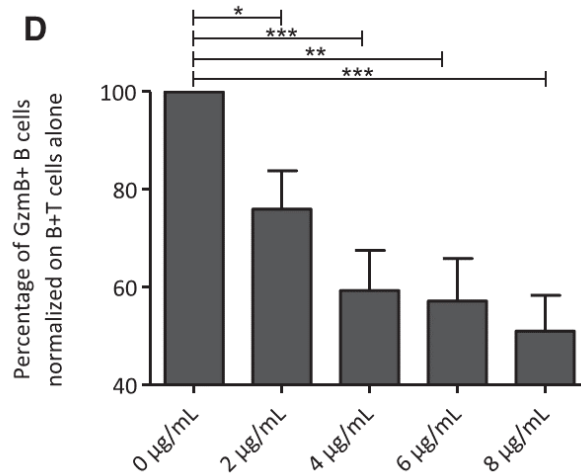
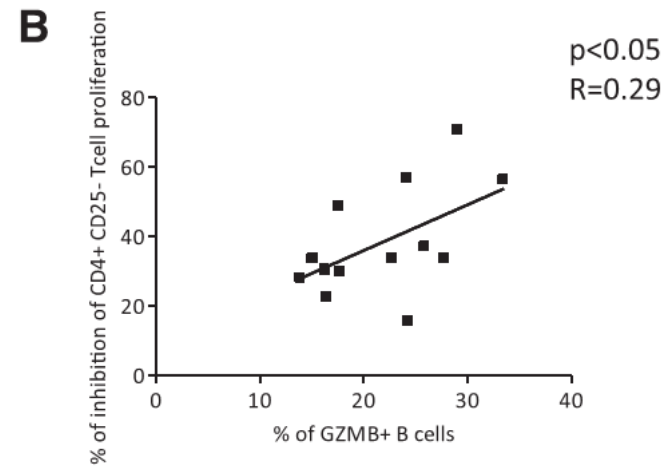
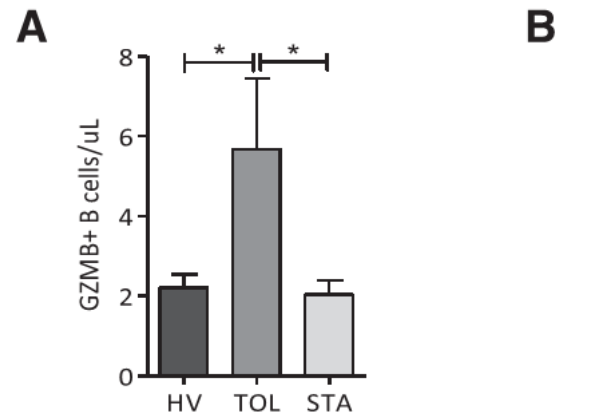


Klinker and Lundy, 2012, Mol Med 18: 123-137



Les lymphocytes B des patients tolérants ont des niveaux de Granzyme B plus élevé, inhibent la prolifération des lymphocytes T de façon dose-dépendante et dépendante de l'IL21

Chesneau et al. JASN 2015



Caractérisation des lymphocytes B GzmB+ travail en cours

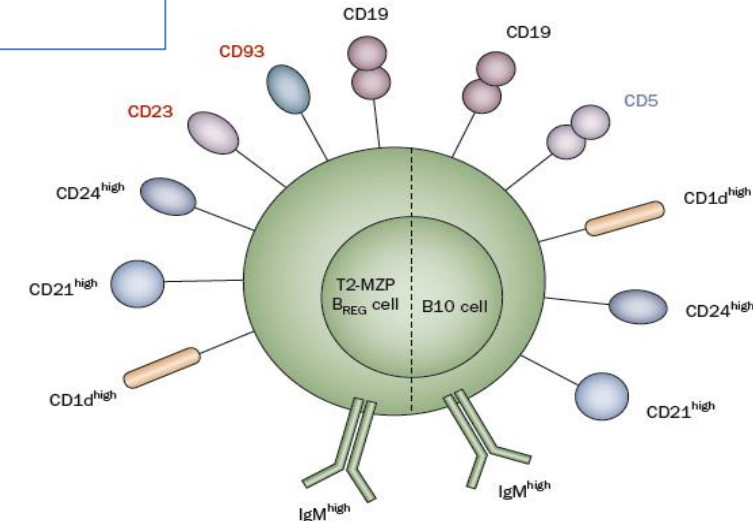
Table 1. Different Breg Cell Subsets

Type of Breg Cell	Mouse	Human	Key Features	Reference
T2-MZP cells	CD19 ⁺ CD21 ^{hi} CD23 ^{hi} CD24 ^{hi}	-	found in spleen, produce IL-10, induce Treg cells, and suppress effector CD4 ⁺ and CD8 ⁺ T cells	Blair et al., 2009; Carter et al., 2011; Evans et al., 2007; Schioppa et al., 2011
MZ cells	CD19 ⁺ CD21 ^{hi} CD23 ⁻	-	found in spleen, produce IL-10, induce Treg cells, and suppress effector CD4 ⁺ and CD8 ⁺ T cells	Bankoti et al., 2012; Gray et al., 2007; Miles et al., 2012
B10 cells	CD5 ⁺ CD1d ^{hi}	CD24 ^{hi} CD27 ⁺	found in spleen (mice) and blood (humans), produce IL-10, and suppress effector CD4 ⁺ T cells, monocytes, and DCs	Horikawa et al., 2013; Iwata et al., 2011; Matsushita et al., 2010; Yanaba et al., 2008
Plasma cells	CD138 ⁺ MHC-11 ^{lo} B220 ⁺	-	found in spleen, produce IL-10 and IL-35, and suppress NK cells, neutrophils, and effector CD4 ⁺ T cells	Neves et al., 2010; Shen et al., 2014
Tim-1 ⁺ B cells	Tim-1 ⁺ CD19 ⁺	-	found in spleen (mice), produce IL-10, and suppress effector CD4 ⁺ T cells	Ding et al., 2011; Xiao et al., 2012
Plasmablasts	CD138 ⁺ CD44 ^{hi}	CD19 ⁺ CD24 ^{hi} CD27 ^{int}	found in dLNs (mice) and blood (humans), produce IL-10, and suppress DCs and effector CD4 ⁺ T cells	Matsumoto et al., 2014
Immature cells	-	CD19 ⁺ CD24 ^{hi} CD38 ^{hi}	found in blood and at site of inflammation, produce IL-10, induce Treg cells, suppress Th1 and Th17 cells, suppress virus-specific CD8 ⁺ T cell responses, are defective in patients with SLE and RA, and support iNKT cell homeostasis	Blair et al., 2010; Bosma et al., 2012; Das et al., 2012; Flores-Borja et al., 2013
Br1 cells	-	CD19 ⁺ CD25 ^{hi} CD71 ^{hi}	found in blood and produce IL-10 and IgG4	van de Veen et al., 2013

This table shows currently described subsets of Breg cells in mice and humans. Abbreviations are as follows: Br1, B regulatory 1; DC, dendritic cell; dLN, draining lymph node; IgG4, immunoglobulin G4; MHC, major histocompatibility complex; MZ, marginal zone; NK, natural killer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T2-MZP, transitional 2 marginal-zone precursor.

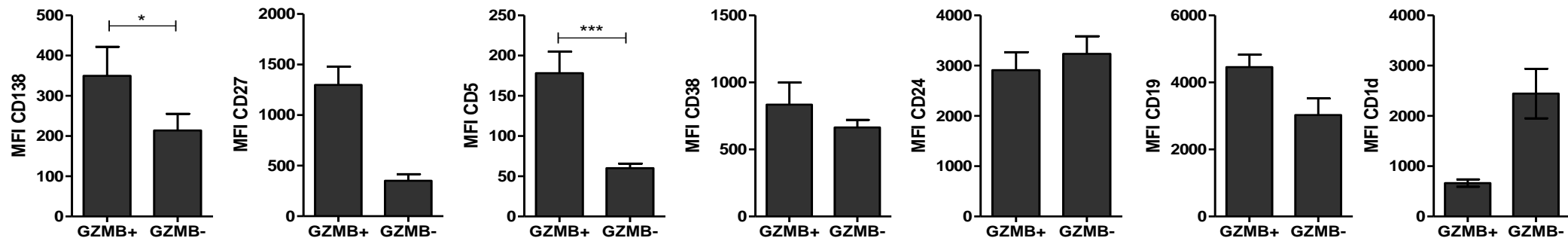
Pas de phénotype commun décrit

- *Environnement*
- *Pathologie*
- *Rôle*



Mauri et al. Nat. Rev. 2012

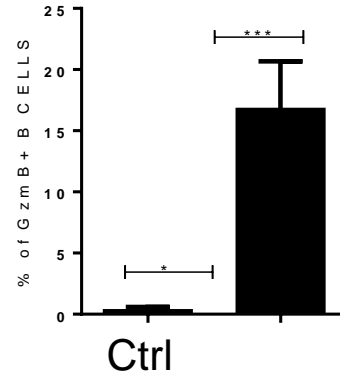
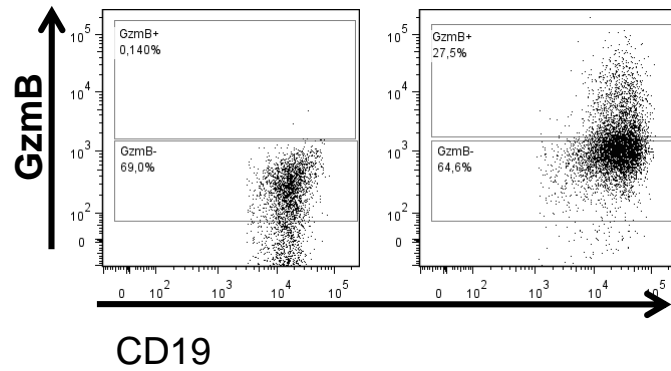
Rosser et al. Immunity 2015



Chesneau et al. JASN 2015

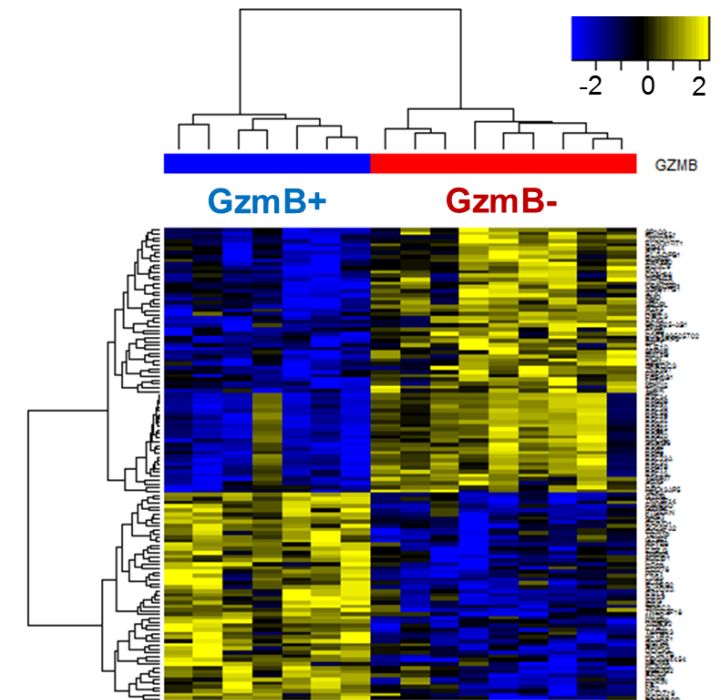
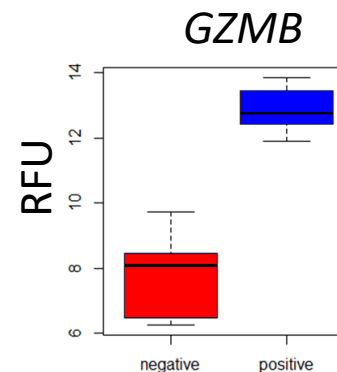
Expansion *in vitro* de lymphocytes B GzmB⁺

- Mise au point d'un protocole d'expansion *in vitro*: enrichissement de lymphocytes B GzmB⁺ après 3 jours de culture



unpublished data from M. Chesneau et al.

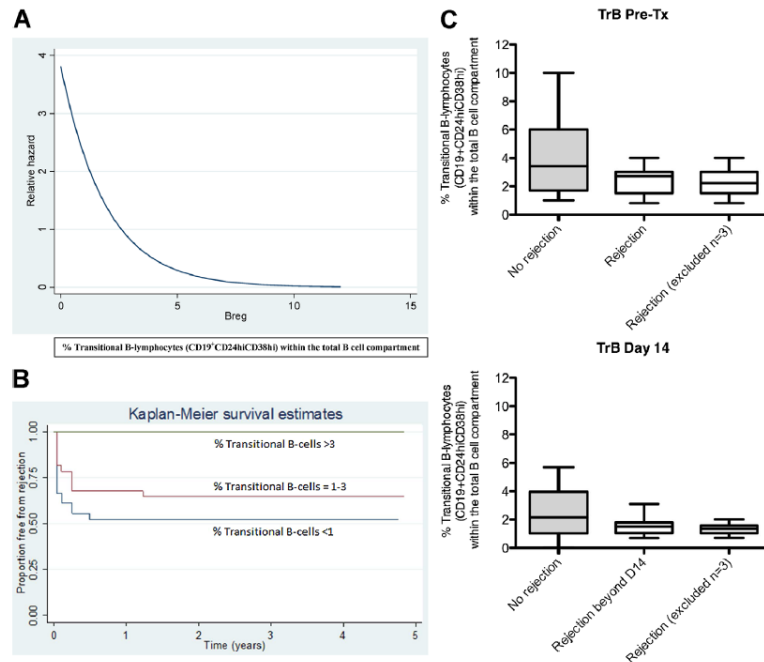
- Analyse du transcriptome des LyB GzmB⁺ expandus



Utilité clinique?

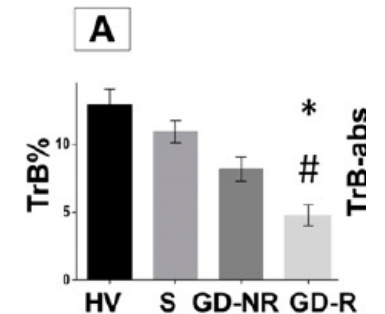
➔ Association de lymphocytes B régulateurs au devenir des patients transplantés rénaux

Transitional B Lymphocytes Are Associated With Protection From Kidney Allograft Rejection: A Prospective Study



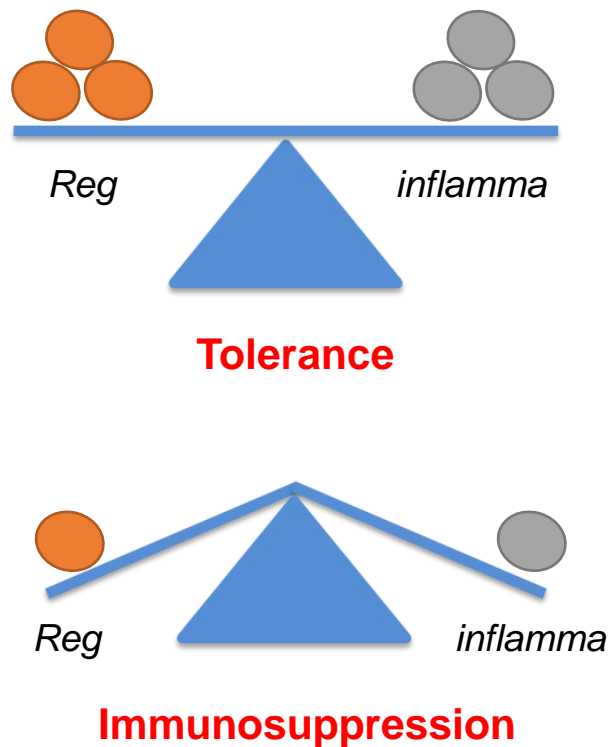
Immunologic Human Renal Allograft Injury Associates with an Altered IL-10/TNF- α Expression Ratio in Regulatory B Cells

Aravind Cherukuri,^{*†} David M. Rothstein,[‡] Brendan Clark,[†] Clive R. Carter,[†] Adam Davison,[§] Maria Hernandez-Fuentes,^{||} Eric Hewitt,[¶] Alan D. Salama,^{**} and Richard J. Baker^{*}

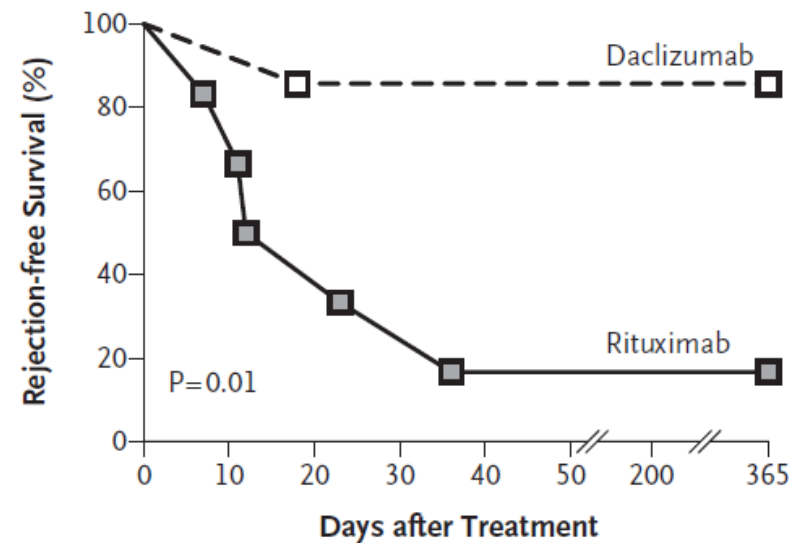


Shabir S et al. AJT 2015

Des stratégies pour diriger le compartiment B vers un profil immunorégulateur en transplantation d'organe?

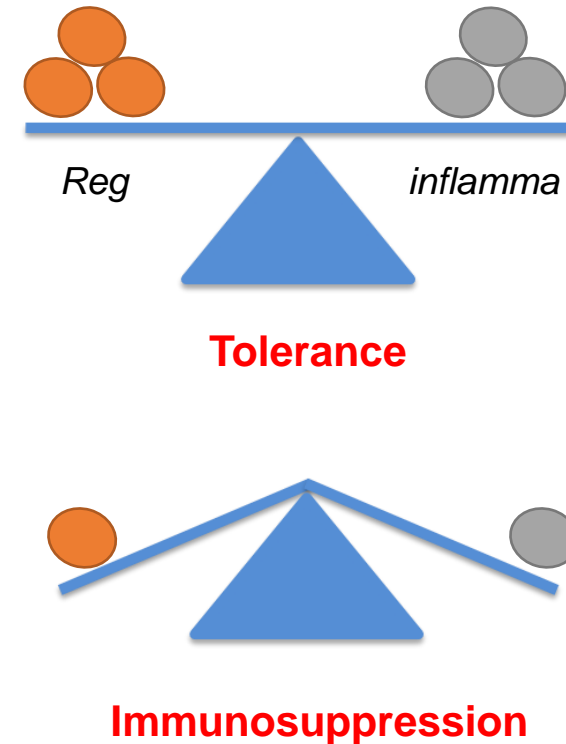
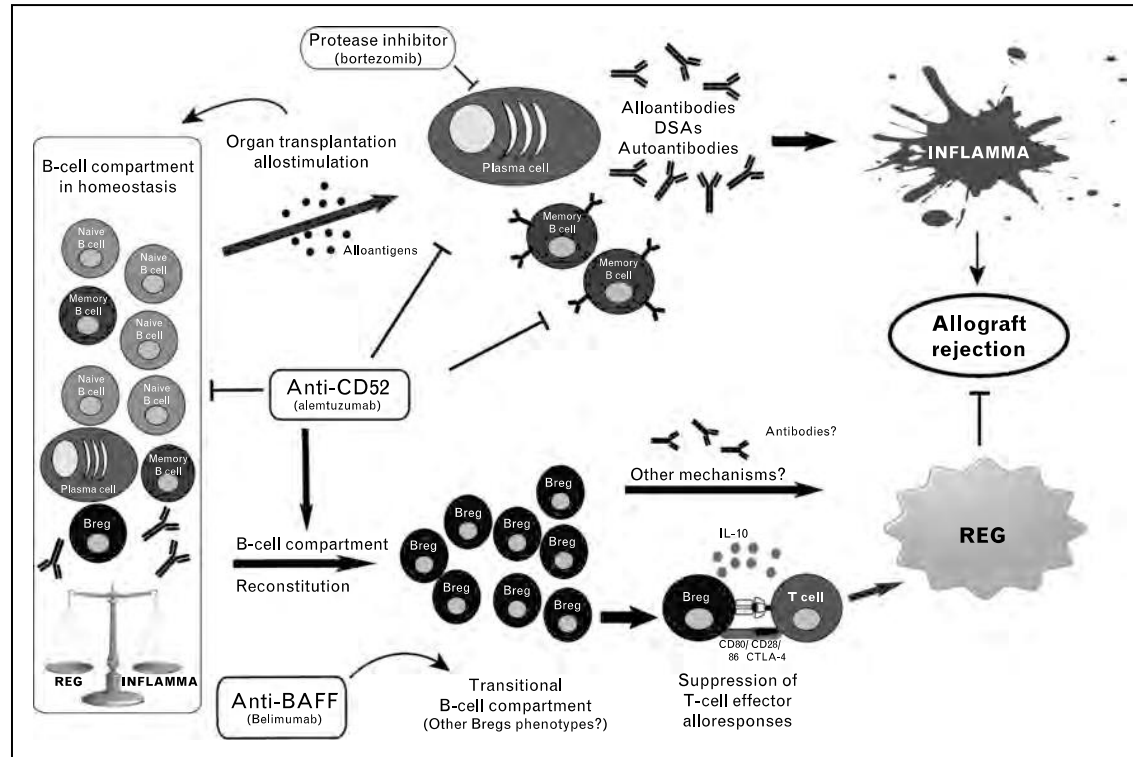


Rituximab induction et rejet aigu cellulaire



Clatworthy MR *et al.* NEJM 2009

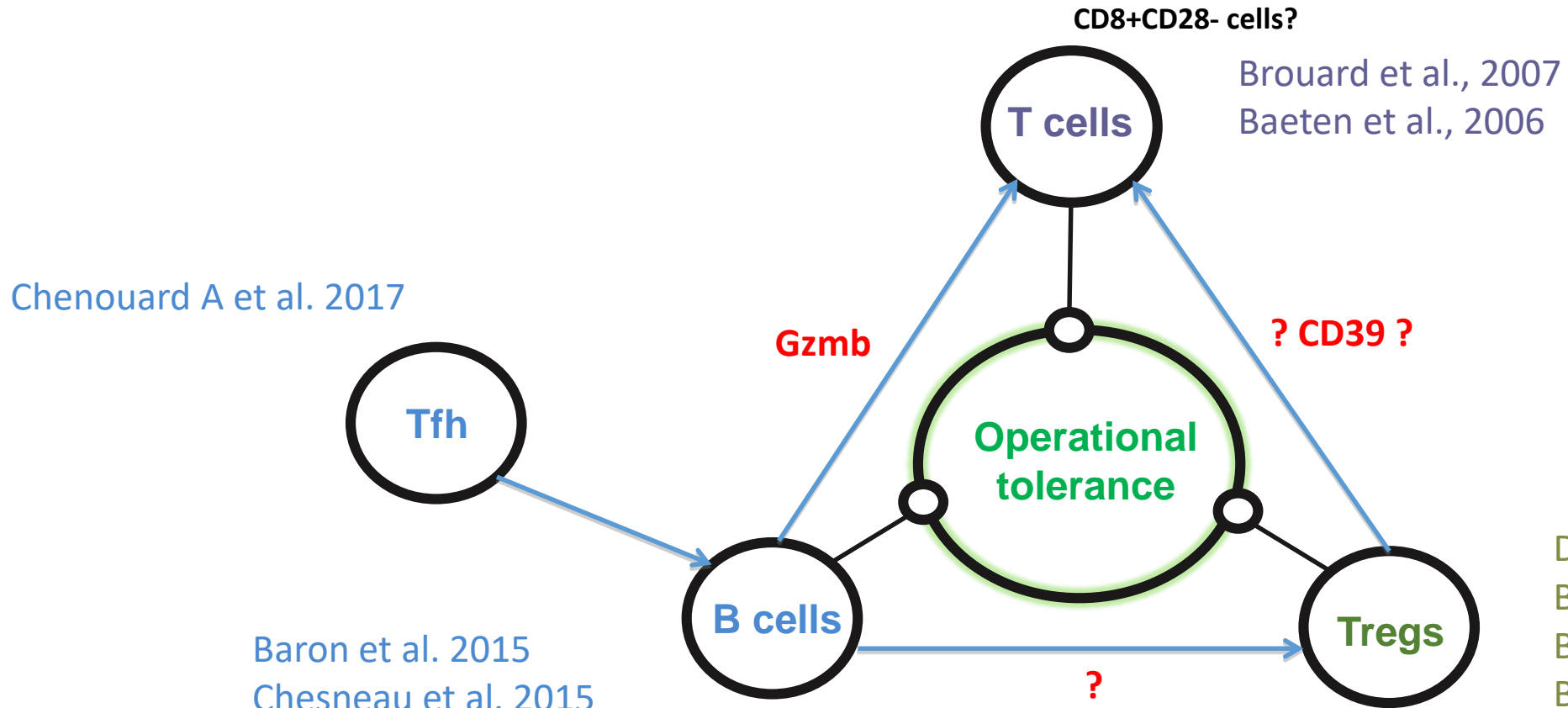
Des stratégies pour diriger le compartiment B vers un profil immunorégulateur en transplantation d'organe?



Coelho et al. Cur. op. 2013

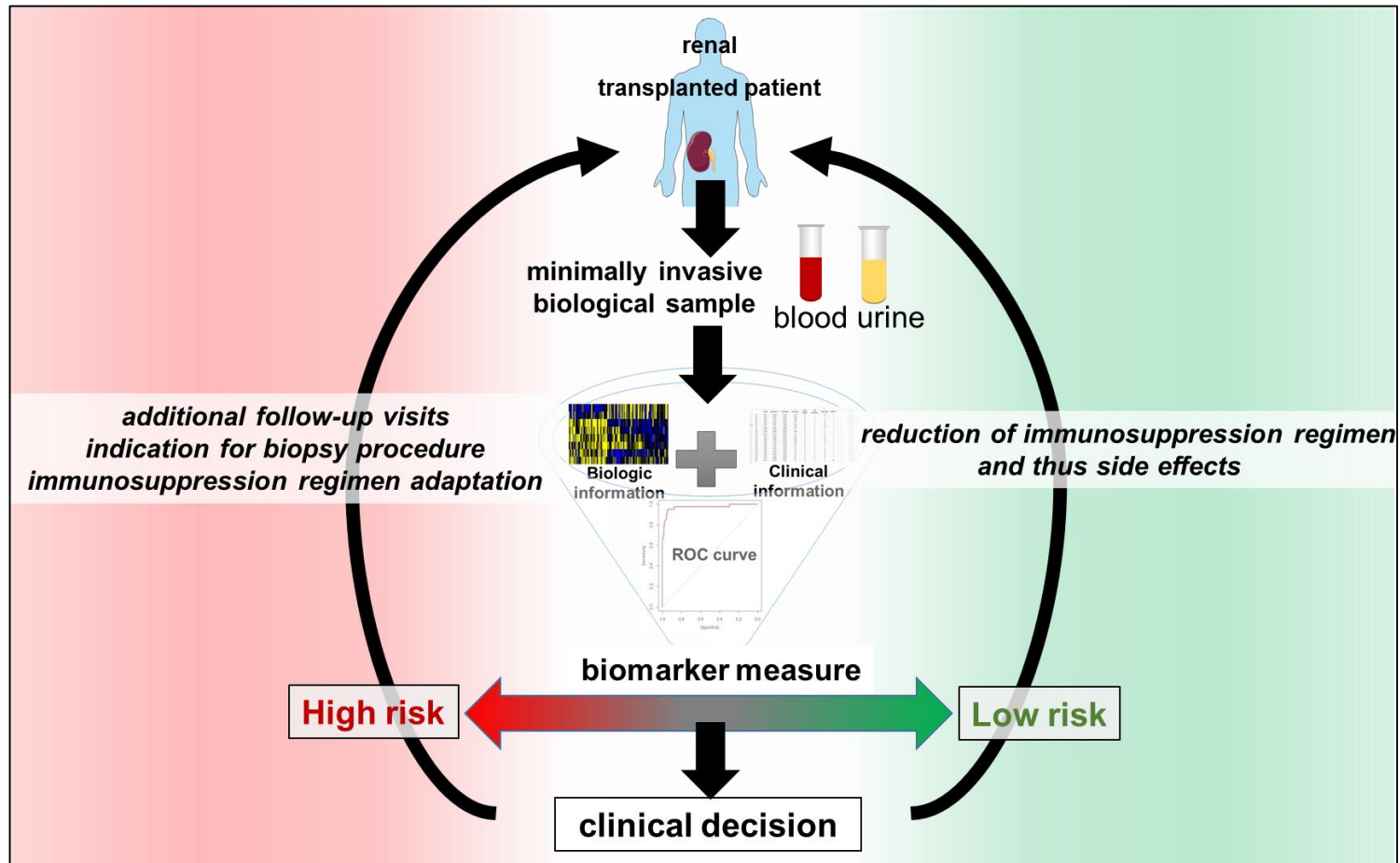
➔ Expansion de Breg pour une utilisation en thérapie cellulaire?

Immune cells in operational tolerance



Etude de la tolérance opérationnelle rénale: **objectifs**

- Compréhension des mécanismes immunologiques post-greffe
- Recherche de marqueurs biologiques attestant du statut immunologique
 - identifier des patients à faible et fort risque de rejet
 - minimiser leur traitement immunosuppresseurs?

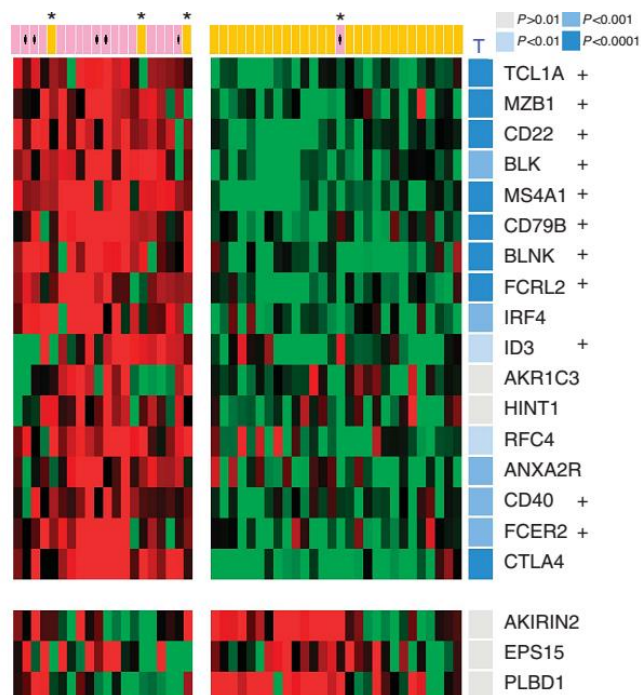


Profil d'expression de patients transplantés rénaux

Baron D. et al., Kid. Int., 2015

- 5 études de puces à ADN: nombre limité de patients par étude → méta-analyse

Study	PMID	GEO no.	GPL ID	Description	Total	HV	TOL	MIS	STA	CR	AR
Braud	17910029	GSE47755	GPL8798	Cancerchip (~ 7000 genes) _{a,c}	250 (528)	8 (16)	21 (54)	0	190 (380)	31 (78)	0
Brouard	17873064	GSE47683	GPL6271	Lymphochip (~ 18,000 genes) _{a,c}	67	8	12	10	12	11	14
Lozano	21827613	GSE22707	GPL570	Affymetrix HG-U133_Plus_2 (~ 33,000 genes) _{b,d}	42	6	12	0	12	12	0
Newell	20501946	GSE22229	GPL570	Affymetrix HG-U133_Plus_2 (~ 33000 genes) _{b,d}	58	12	19	0	27	0	0
Sagoo IOT	20501943	GSE14655	GPL8136	RISSET 2.0 Agilent custom (~ 5000 genes) _{b,c}	74 (95)	8	10 (13)	11 (16)	36 (48)	9 (10)	0
Sagoo ITN	20501943	GSE14655	GPL8136	RISSET 2.0 Agilent custom (~ 5000 genes) _{b,c}	105 (142)	20	22 (31)	11 (14)	34 (52)	18 (25)	0
					596 (932)	62 (70)	96 (141)	32 (40)	311 (531)	81 (136)	14

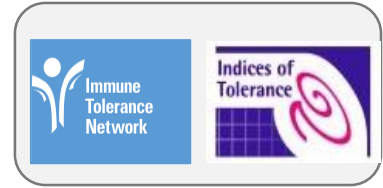


Signature lymphocytaire B associée à la tolérance?
Autre cellules (LyT) impliquées?

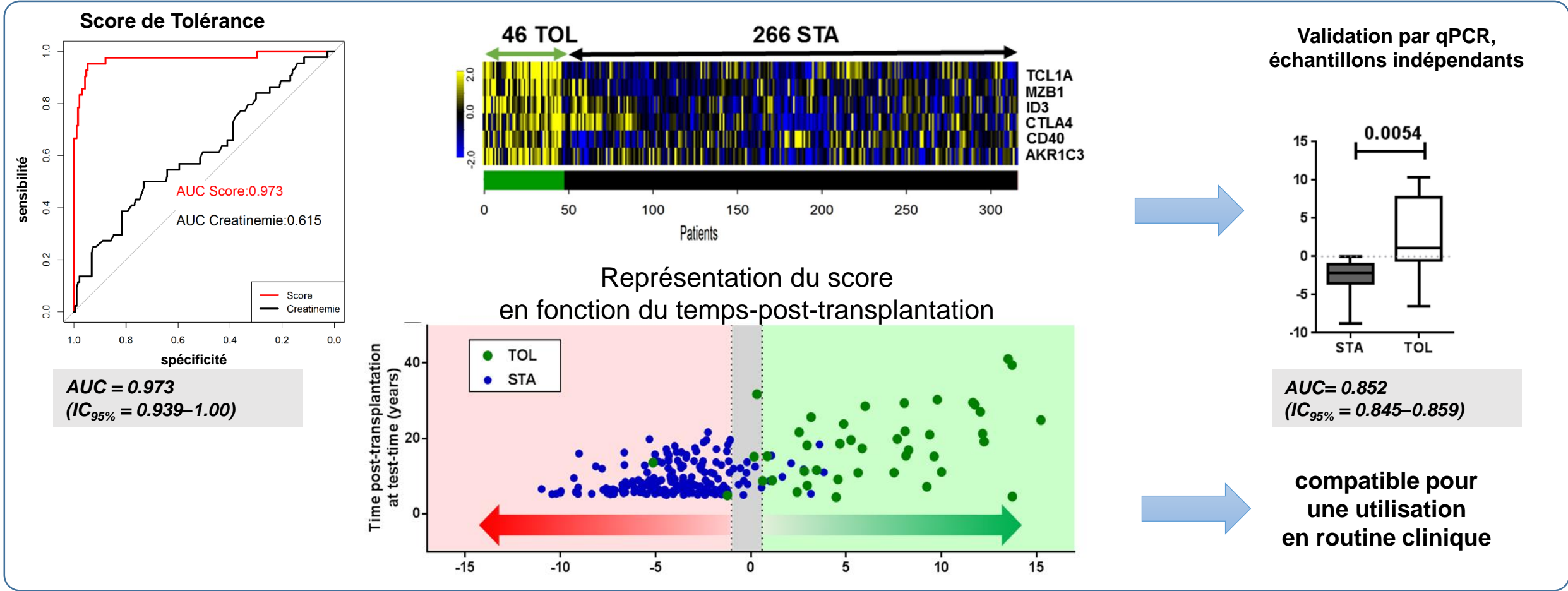


Utilisable pour diagnostiquer des patients potentiellement TOL sous IS?

Création d'un score composite associé à la tolérance opérationnelle en transplantation rénale



- Méta-analyse: 312 patients (42 TOL et 189 STA) avec des données démographiques
- Sélection des variables par la méthode Bolasso (*bootstrapped least-square linear regression*)



Utilité clinique?

→ évaluer le statut alloimmun du patient transplanté rénal

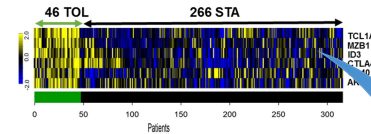
- Risque immunologique de perte de fonction du greffon (apparition d'Ac anti-donneur)
- Associé à une sur- ou sous-immunosuppression (fort ou faible risque de rejet)



- à 1 an post-transplantation → encore temps d'ajuster la prise en charge du patient
- biocollektion multicentrique → 901 patients



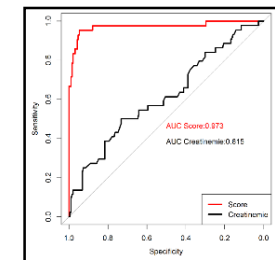
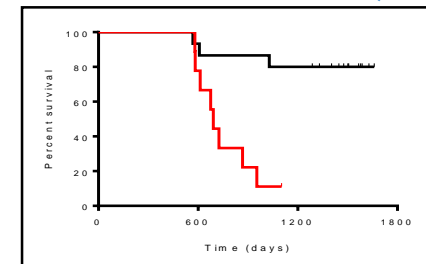
- ✓ Nantes (285)
- ✓ Lyon (258)
- ✓ Paris (358)



Mesure des gènes



Données cliniques



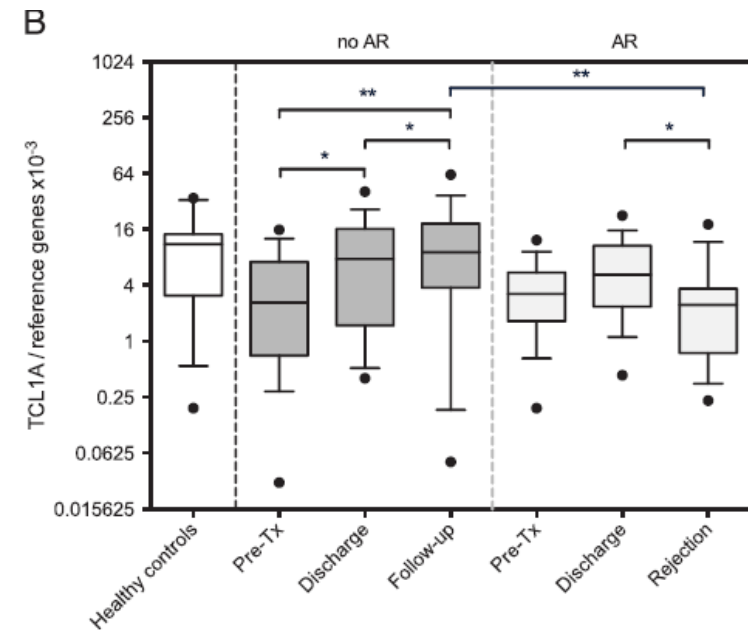
Stratification des patients

Utilité clinique?

→ évaluer le statut alloimmun du patient transplanté rénal

B Cell Markers of Operational Tolerance Can Discriminate Acute Kidney Allograft Rejection From Stable Graft Function

Sebastiaan Heidt,¹ Manon Vergunst,¹ Jacqueline D.H. Anholts,¹ Marlies E.J. Reinders,² Johan W. de Fijter,² Michael Eikmans,¹ and Frans H.J. Claas¹



B-Cell-Related Biomarkers of Tolerance are Up-Regulated in Rejection-Free Kidney Transplant Recipients

Ondrej Viklicky,^{1,2,7} Eva Krystufkova,¹ Irena Brabcova,¹ Alena Sekerkova,³ Peter Wohlfahrt,⁴ Petra Hribova,¹ Mariana Wohlfahrtova,^{1,2} Birgit Sawitzki,⁵ Janka Slatinska,² Ilja Striz,³ Hans-Dieter Volk,⁵ and Petra Reinke⁶

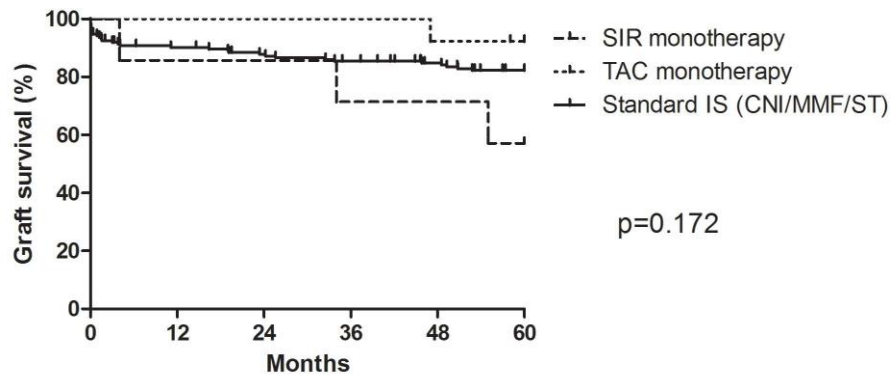
Heidt S. *et al.* Transplantation 2015

Viklicky O. *et al.* Transplantation 2013

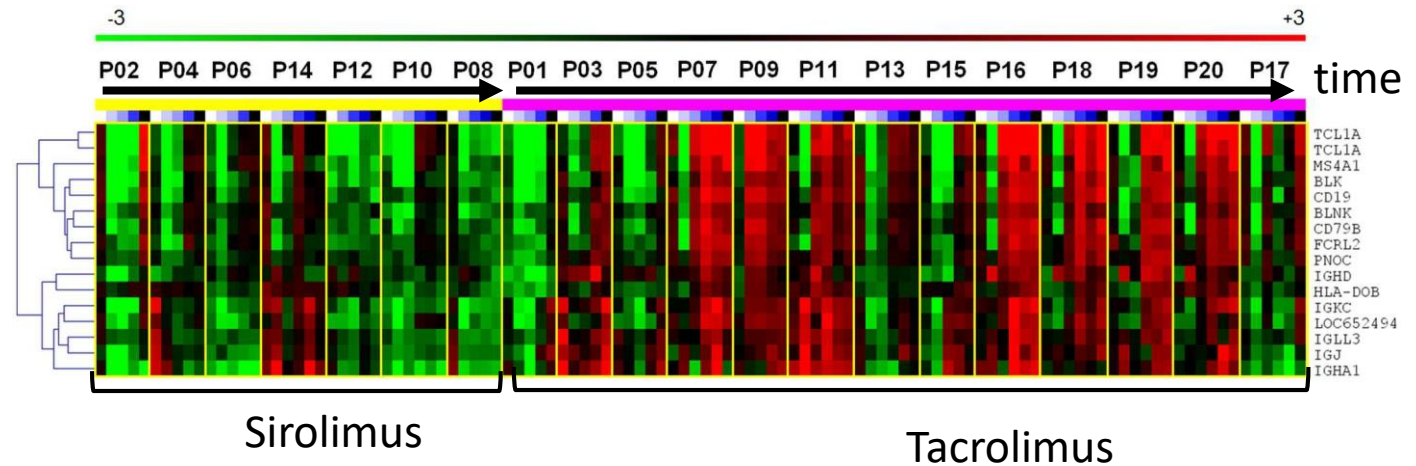
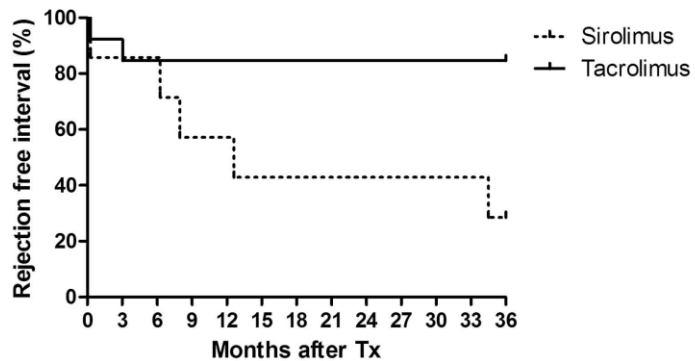
Utilité clinique?

→ évaluer le statut alloimmun du patient transplanté rénal

Augmentation d'expression de gènes liés aux lymphocytes B associée à une meilleur survie du greffon



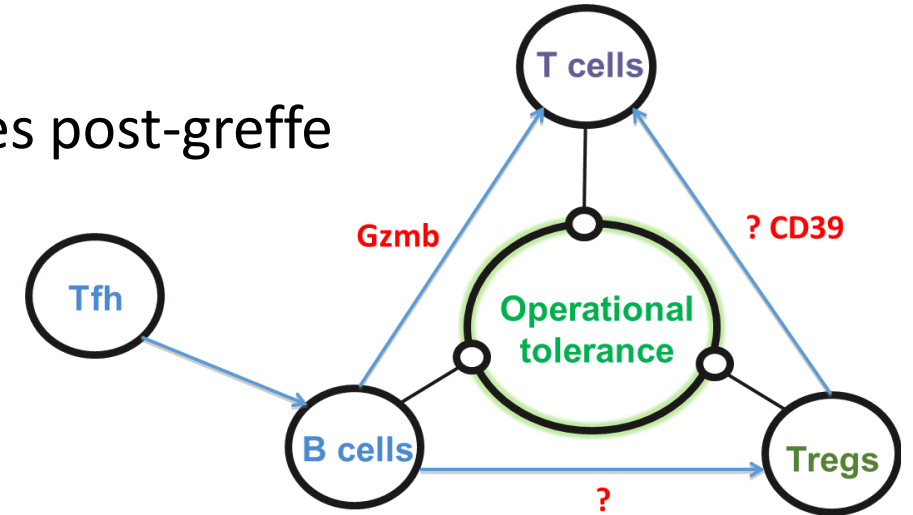
	0	12	24	36	48	60
SIR monotherapy	7	6	6	5	5	4
TAC monotherapy	13	13	13	13	12	12
Standar IS	174	155	148	144	134	125



sequential induction therapy with alemtuzumab and infliximab followed either by **tacrolimus or sirolimus monotherapy**

Etude de la tolérance opérationnelle rénale: **objectifs**

- Compréhension des mécanismes immunologiques post-greffe



- Recherche de marqueurs biologiques attestant du statut immunologique



INSERM, UMR 1064, Nantes, F-44093, France
CHU de Nantes, ITUN, Nantes, F-44093, France
Université de Nantes, Faculté de Médecine, Nantes, France

Mélanie Chesneau
Alexis Chenouard
Faouzi Braza
Emilie Dugast
Annaick Pallier
Chloé Paul
Pierrick Guérif
Maxim Durand
Sophie Conchon
Daniel Baron
Nicolas Degauque
Magali Giral
Jean-Paul Soulliou
Sophie Brouard



MRC Centre for Transplantation, King's College London, London, UK

Institute of Liver Studies
Maria P. Hernandez-Fuentes
Alberto Sanchez-Fueyo

INSERM UMR 917 (Rennes, France)

Karin Tarte
Gersende Lacombe
Simon Le Galou

INSERM, U954, Nancy, F-54511, France

Rémi Houlgatte

LINA COD, UMR 6241, Université de Nantes, Ecole des Mines de Nantes & CNRS, Nantes, F-44322, France

Gérard Ramstein

Department of Surgery, Emory University, Atlanta, Georgia, USA

Kenneth A. Newell

Immune Tolerance Network, Bethesda, Maryland, USA

Sai Kanaparthi
Laurence A Turka

Institute of Medical Immunology & Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité

University Berlin, Germany

Birgit Sawitzki