

# L'EXPRESSION PRÉ-GREFFE DE CD45RC SUR LES LYMPHOCYTES T CD8+ EST PRÉDICTIF DU RA CELLULAIRE :

## ÉTUDE DE 128 TRANSPLANTÉS RÉNAUX.



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# CD45RC

- Isoform of CD45 expressed on T, B, NK cells and monocytes
- Bimodal expression on CD4 T cells: High/low expression
- Trimodal expression on CD8 T cells: high/intermediary/low expression

## In vitro polyclonal activation:

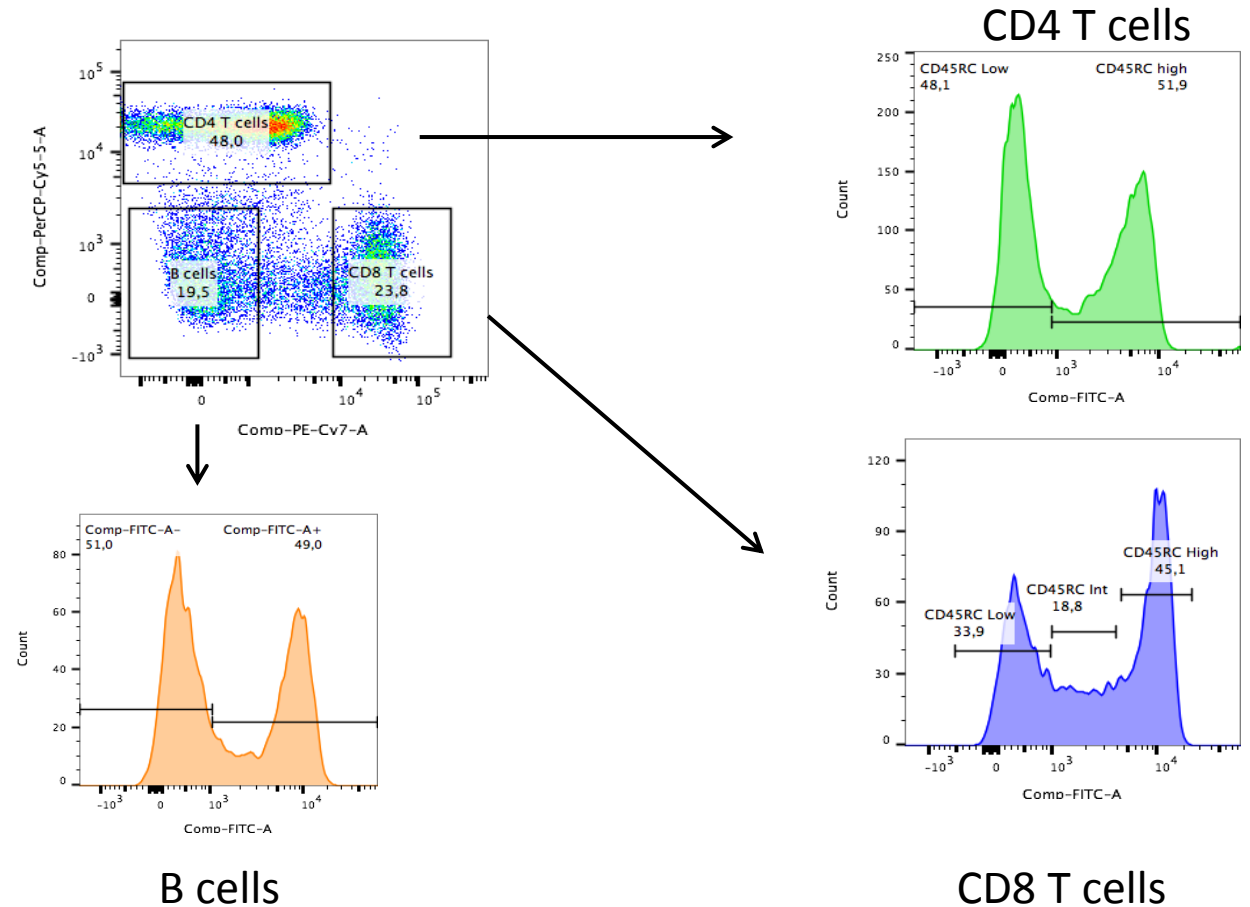
CD45RC high subsets: Th1 cytokines (IL-2, TNF)

CD45RC low subsets: Th2 cytokines (IL4, IL10)

## In vivo Murine models:

CD45RC<sup>high</sup> T cells mediate alloreactivity (GvHD/heart)

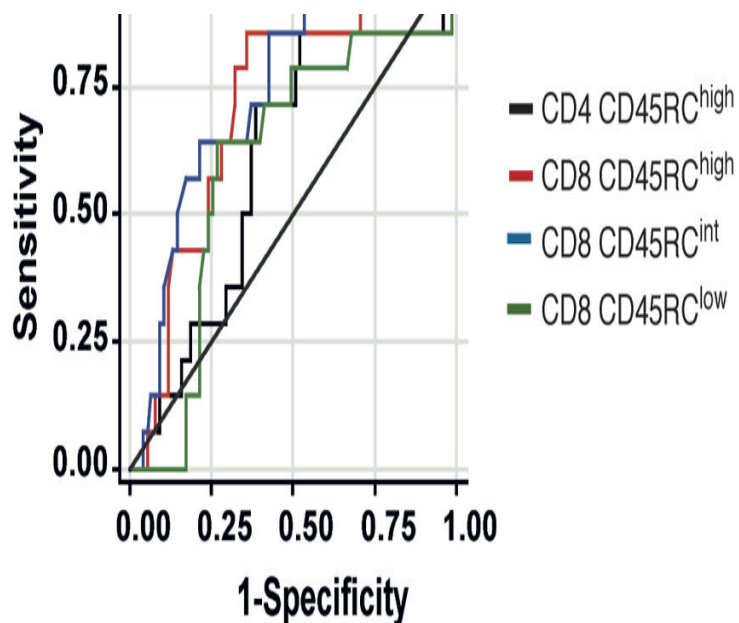
CD45RC<sup>high</sup> T cells depletion before transplantation induces tolerance



Is pre-transplant CD45RC expression on T cells associated with allograft rejection?

# Résultats préliminaires

- ❑ Etude de cohorte, 89 patients
- ❑ Transplantés rénaux entre 1999 et 2004 (**n=89 patients**)
- ❑ Echantillons prélevés à la consultation pré-greffe
- ❑ Faible risque immunologique (1<sup>ière</sup> TR, PRA <20%)



**Table 3.** Crude hazard ratio (HR), 95% confidence interval (CI) and p-value (p) of different human T-cell subsets according on transplant rejection.

### CD8 T cells

% CD45RC <sup>high</sup> < 54.7 <sup>a</sup>	54	3	1	
≥ 54.7	35	11	<b>5.99 (1.67–21.51)</b>	<b>0.006</b>
% CD45RC <sup>int</sup> ≥ 24.0 <sup>a</sup>	64	5	1	
< 24.0	25	9	<b>4.75 (1.59–14.23)</b>	<b>0.005</b>
% CD45RC <sup>low</sup> ≤ 16.9	45	10	1	
> 16.9	44	4	0.41 (0.13–1.31)	0.134

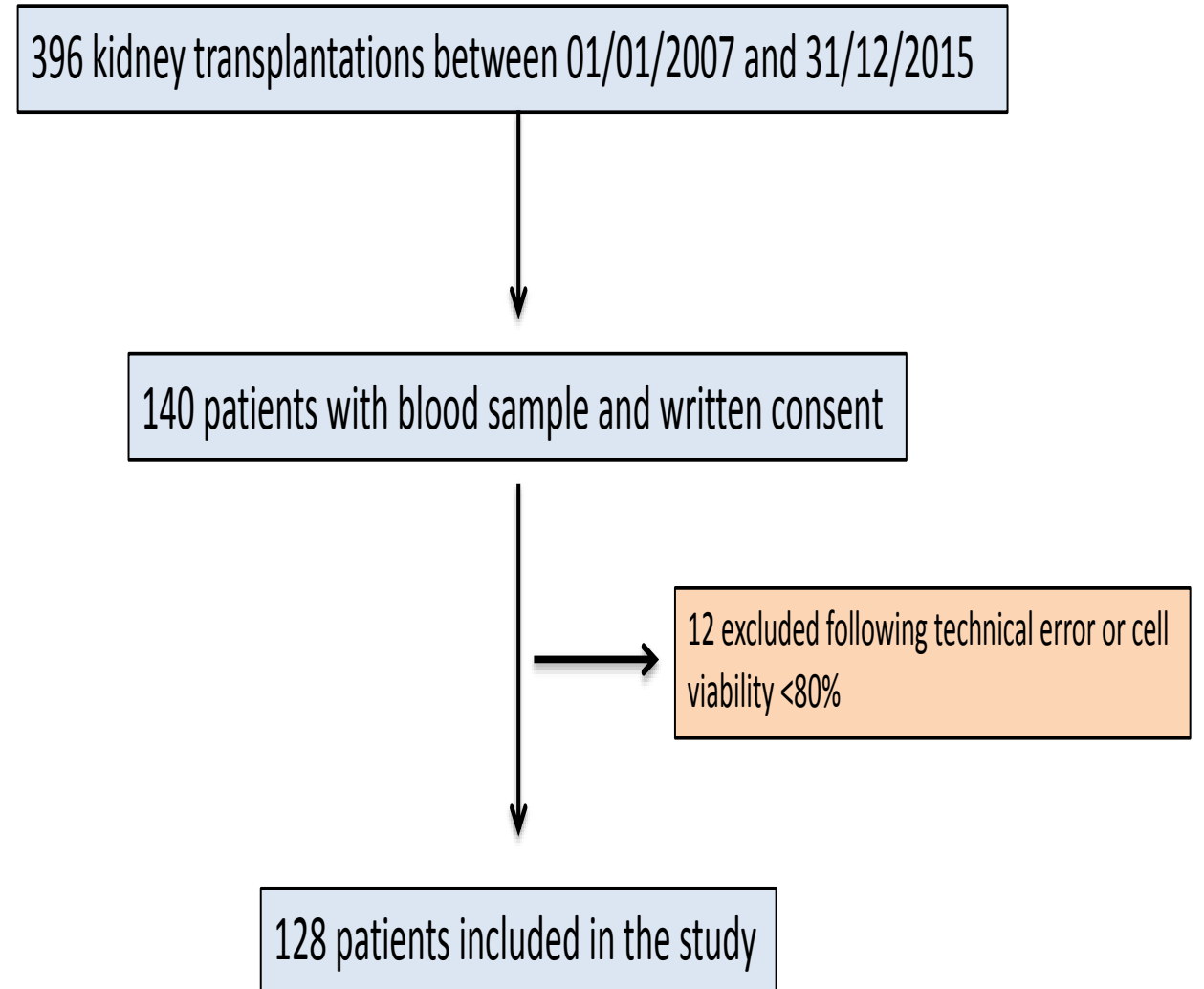
# Objectifs de l'étude et critères inclusion

## ❑ Valider la valeur prédictive de CD45RC dans une seconde cohorte

- Transplantés exposés à une IS «moderne »
- A faible et plus haut risque immunologique

## ❑ Préciser l'association de CD45RC avec RAC / RAH

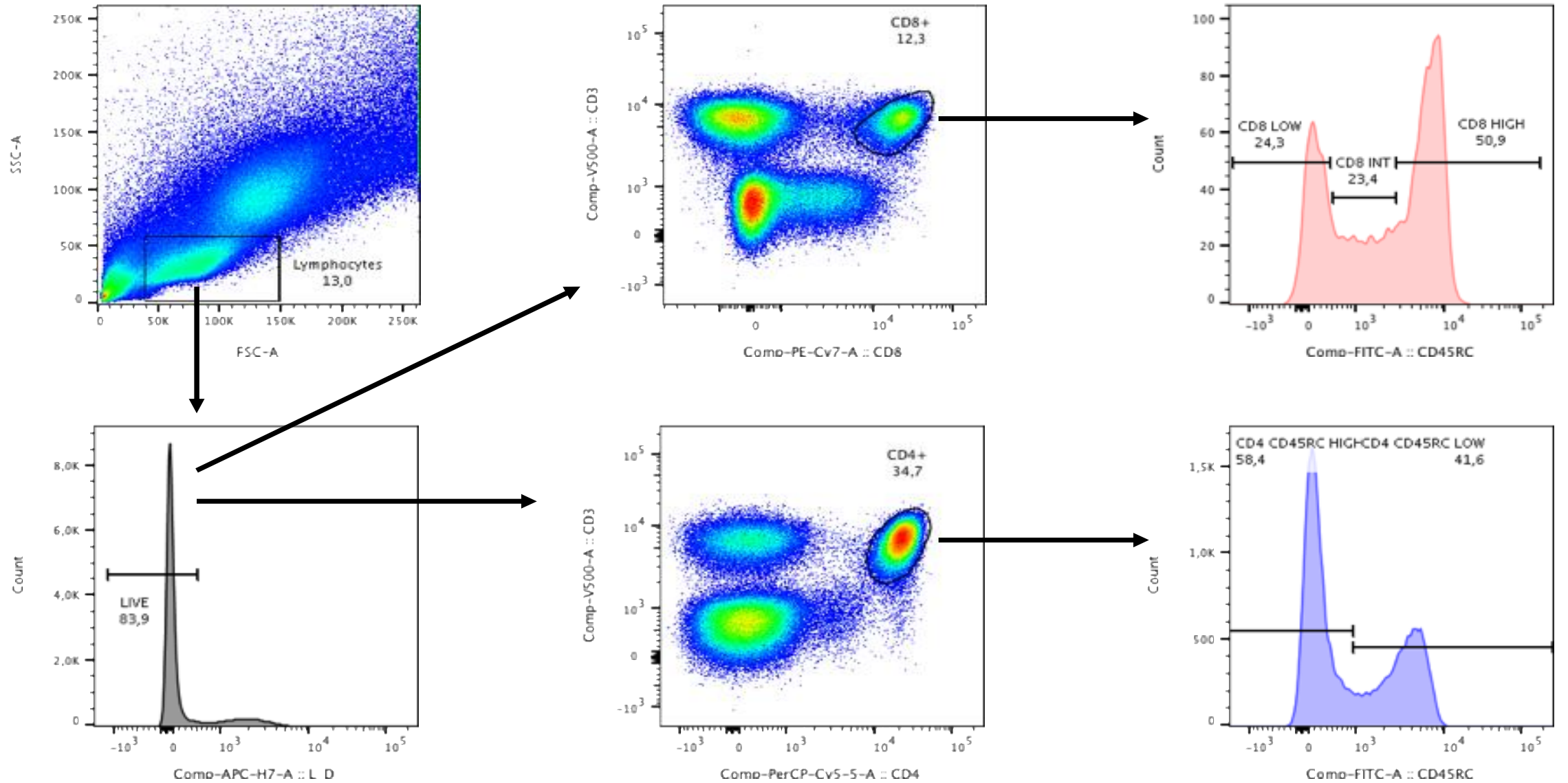
- TR entre 2007 et 2015
- Collection biologique pré-greffe



# Caractéristiques de la population

	All patients (n=128)
<b>Baseline characteristics</b>	
Sex (M/F)	80/48
Age (years)	50.1 ± 12.9
Weight (kg)	72.0 ± 15.4
BMI (Kg/m <sup>2</sup> )	25.3 ± 4.7
<b>History of transplantation</b>	
Pre-transplant dialysis, n (%)	92 (71.9)
Previous kidney transplantation	13 (10.2)
Donor age, years	50.9 ± 15.2
Cold ischemia time (hours)	16.8 ± 6.9
HLA A&B&DR mismatch, n	3.8 ± 1.3
<b>Sensitization, n (%)</b>	
Nonsensitized at transplantation	89 (69.5)
PRA ≥ 10%	9 (7.0)
<b>Immunosuppressive regimens</b>	
<b>Induction therapy</b>	
None, n (%)	6 (4.7)
Basiliximab, n (%)	72 (56.3)
Antithymocyte globulins, n (%)	50 (39.1)
<b>Maintenance regimen</b>	
Tac-based, n (%)	102 (79.6)
Cyclosporin-based, n (%)	26 (20.3)
MMF or MPA	127 (99.2)

# Stratégie de gating en cytométrie en flux



# Episodes de rejets

<b>Mean follow-up, years</b>	<b>3.82 ± 2.22 [0.02-8.53]</b>
<b>Acute rejection</b>	
Number of patients, n (%)	31 (24.2)
Mean delay to first AR (years)	0.73 ± 1.24 [0.02-4.83]
Histologically proven, n (%)	28 (90.3)
TCMR	24 (85.7)
Borderline	6 (25.0)
Grade IA	9 (37.5)
Grade IB	8 (33.3)
Grade IIA	1(4.2)
AMR	1 (3.6)
Mixed AR	3 (10.7)
Non histologically proved AR, n	3 (9.7)
DSA, n (%)	15 (11.7)
Class I	4 (26.7)
Class II	11 (73.3)
<b>Year 1 post-transplant biological results</b>	
Serum creatinine, (µmol/L)*	141.4 ± 75.2 [60.0-716]
GFR, (mL/min/1.73m2)*	53.2 ± 21.8 [7.3-123]
Proteinuria/creatininuria, (g/g)*	0.25 ± 0.69 [0-5.78]

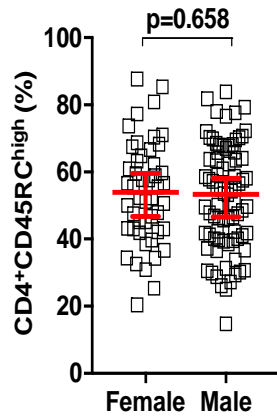
# Facteurs associés au risque de rejet

	No AR (n = 97)	AR (n = 31)	p	BPAR (n = 28)	p	Excluding Bor AR (n = 22)	p
<b>Baseline characteristics</b>							
Sex (M/F)	62/35	18/13	0.558	16/12	0.514	12/10	0.413
Age (years)	50.3 [18.0–79.2]	48.2 [23.3–66.5]	0.301	48.8 [23.3–66.5]	0.368	45.5 [23.3–66.5]	0.206
No pretransplant immunization, n (%)	64 (66.0)	25 (80.6)	0.123	23 (82.1)	0.160	18 (81.8)	0.203
PRA > 20%, n (%)	7 (7.2)	1 (3.2)	0.679	1 (3.6)	0.682	1 (4.5)	1.000
<b>History of transplantation</b>							
Previous kidney transplantation, n (%)	11 (11.3)	2 (6.5)	0.733	2 (7.1)	0.731	2 (9.1)	1.000
Pre-transplant dialysis, n (%)	77 (72.2)	22 (71.0)	0.897	20 (71.4)	0.939	15 (68.2)	0.709
Donor age, years	51.0 [3.0–87.0]	47.0 [36.0–80.0]	0.799	48. [36.0–80.0]	0.769	43 [37.0–68.0]	0.494
Cold ischemia time (hours)	17.0 [2.0–35.4]	15.6 [2.0–32.2]	0.434	15.5 [2.0–32.2]	0.299	15.5 [2.0–32.2]	0.359
HLA mismatch (ABDR), n	4.0 [0–6]	4.0 [0–6]	0.733	4.0 [0–6]	0.495	4.0 [0–6]	0.750
Delayed graft function, n (%)	22 (22.7)	6 (19.4)	0.658	5 (17.9)	0.551	4 (18.2)	0.779
De novo DSA, n (%)	12 (12.4)	3 (9.7)	1.000	3 (10.7)	1.000	3 (13.6)	1.000
<b>Immunosuppressive regimens</b>							
Induction (none/basiliximab/ATG), n (%)	4 (4.1)/49 (50.5)/44 (45.4)	2 (6.5)/23 (74.2)/6 (19.3)	<b>0.035</b>	2(7.1)/21(75.0)/5(17.9)	<b>0.031</b>	1(4.6)/16(72.7) /5(22.7)	0.145
Tacrolimus-based regimen, n (%)	78 (80.4)	23 (74.2)	0.393	22 (78.6)	0.752	16 (72.7)	0.370

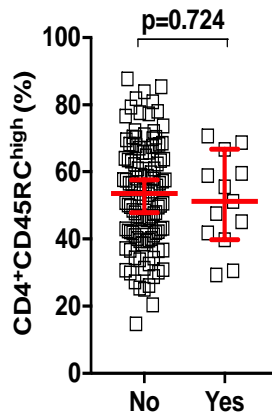


# Association entre expression CD45RC sur les LT CD4<sup>+</sup> et CD8<sup>+</sup> T et caractéristiques des patients

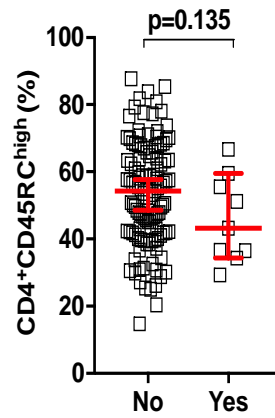
**A Gender**



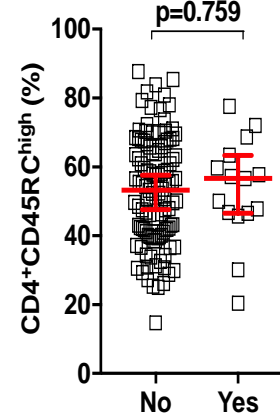
**B Previous transplant**



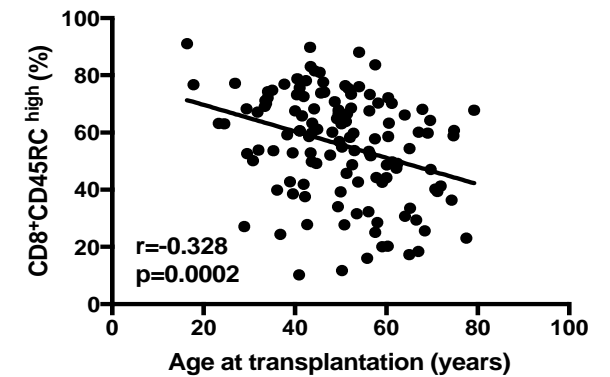
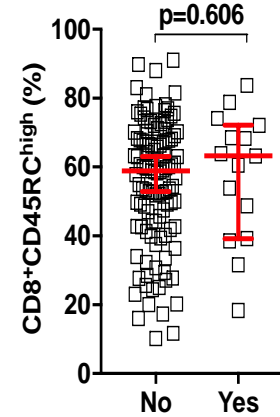
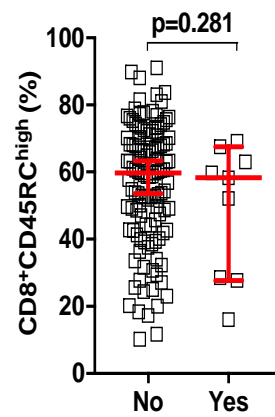
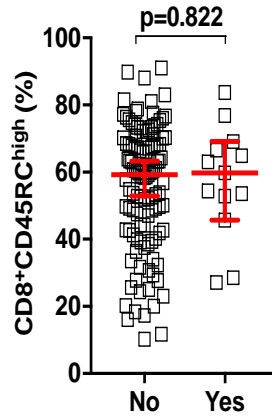
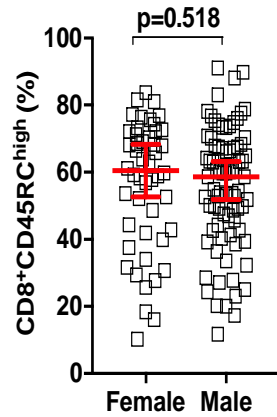
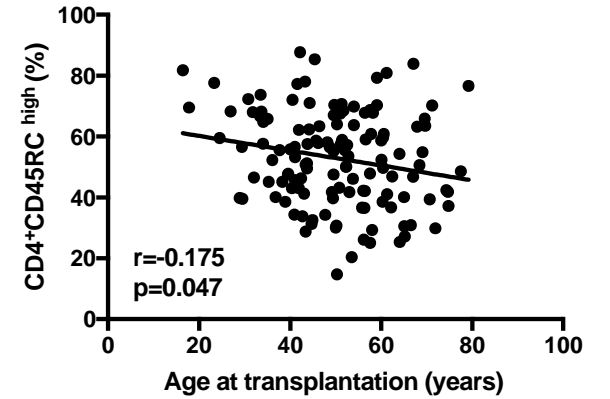
**C PRA > 10%**



**D DSA**



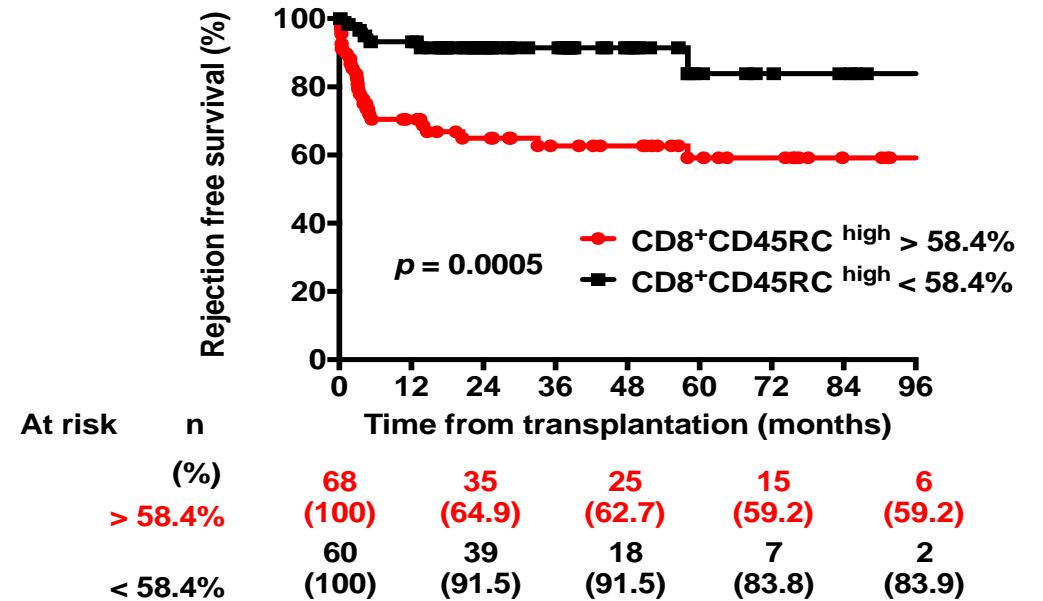
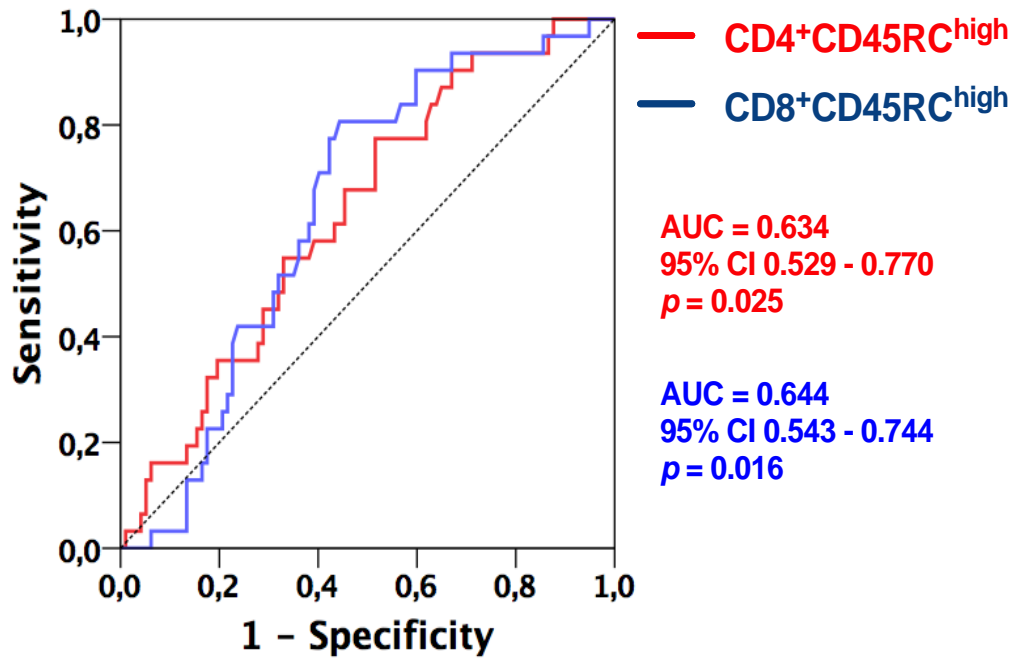
**E Age**



# Proportion des sous-populations de CD45RC selon la survenue d'un RA

Acute rejection (all)	Yes N=31	No N=97	P
CD4 CD45RC <sup>high</sup>	58.4 ± 13.7	51.2 ± 15.7	<b>0.023</b>
CD8 CD45RC <sup>high</sup>	62.5 ± 13.3	53.6 ± 19.3	<b>0.019</b>
CD8 CD45RC <sup>int</sup>	20.1 ± 7.7	23.2 ± 9.3	0.096
CD8 CD45RC <sup>low</sup>	17.9 ± 9.8	23.7 ± 14.2	<b>0.035</b>
<b>Biopsy proven AR</b>			
	Yes N=28	No N=97	P
CD4 CD45RC <sup>high</sup>	59.2 ± 13.3	51.2 ± 15.7	<b>0.016</b>
CD8 CD45RC <sup>high</sup>	62.3 ± 13.0	53.6 ± 18.0	<b>0.010</b>
CD8 CD45RC <sup>int</sup>	20.1 ± 7.9	23.2 ± 9.3	0.117
CD8 CD45RC <sup>low</sup>	18.0 ± 10.3	23.7 ± 14.2	<b>0.049</b>
<b>Acute rejection (excluding borderline AR)</b>			
	Yes N=25	No N=97	P
CD4 CD45RC <sup>high</sup>	60.0 ± 13.4	51.2 ± 15.7	<b>0.016</b>
CD8 CD45RC <sup>high</sup>	64.4 ± 12.2	53.6 ± 19.3	<b>0.014</b>
CD8 CD45RC <sup>int</sup>	19.7 ± 8.1	23.2 ± 9.3	0.110
CD8 CD45RC <sup>low</sup>	16.4 ± 7.9	23.7 ± 14.2	<b>0.020</b>

# Valeur prédictive de l'expression de CD45RC sur les LT CD8<sup>+</sup>



# Valeur prédictive de l'expression de CD45RC sur les LT CD8<sup>+</sup>

	Multivariate Cox models	HR	95% CI	P
<b>All AR</b>	CD8 CD45RC <sup>high</sup> (>58.4%)	3.96	1.58-9.96	<b>0.003</b>
	Age at transplantation	1.00	0.97-1.03	0.995
	Induction (ATG)	0.52	0.28-0.97	<b>0.040</b>
<b>AR excluding borderlines</b>	CD8 CD45RC <sup>high</sup> (>58.4%)	4.14	1.36-12.7	<b>0.013</b>
	Age at transplantation	0.99	0.96-1.03	0.730
	Induction (ATG)	0.57	0.27-1.21	0.146
<b>Biopsy-proven AR</b>	CD8 CD45RC <sup>high</sup> (>58.4%)	3.47	1.36-8.87	<b>0.009</b>
	Age at transplantation	0.99	0.97-1.03	0.941
	Induction (ATG)	0.48	0.25-0.93	<b>0.030</b>

# Conclusions et perspectives

- Expression de CD45RC sur les LT CD8+ associe au risque de RA cellulaire en post-greffe
- Marqueur simple et reproductible
- Intérêt pour définir l'intensité du traitement immunosuppresseur en pré-greffe ?
- Etude prospective « ECLAT »: Dr Anne-Sophie Garnier (AOI CHU Angers 2017)