Induction of donor-specific hyporesponsiveness after renal transplantation. Long term follow-up

Marc Lúcia, Oriol Bestard, Marcel·la Franquesa, Josep M Cruzado,
Montse Gomà, Núria Bolaños, Gema Cerezo, Joan Torras, Josep M. Grinyó
Experimental Nephrology Lab.
Hospital Universitari de Bellvitge
Feixa Llarga, s/n.
Hospitalet de Ll. (Barcelona)

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

INTRODUCTION

DS Hyporesponsiveness in Transplantation

- **Non circulating Donor Specific Alloantibodies (DSA)**

- **Non donor specific T-cell Alloreactivity**

- **Stable Graft function**

- **No histologic signs of Rejection**

BACKGROUND

Immune-monitoring the donor-specific alloimmune response in strategies promoting donor-specific hyporesponsiveness

- Pilot, non-randomized study

- 20 renal transplant patients

→"low immunological risk":

-First Transplant, 0% PRA, negative pre-transplant crossmatching

→ Thymoglobulin (low doses), SRL, MMF (CNI and steroid-free regimen)

- Functional Immune-monitoring: **cellular, humoral and regulatory responses**

  → T-cell alloresponse: IFN-γ Elispot (pre-TX, 1, 3, 6, 12, 24 months)

  → donor-specific anti-HLA Antibodies (6 and 24 months)

  → Regulatory response (FoxP3+Tregs)

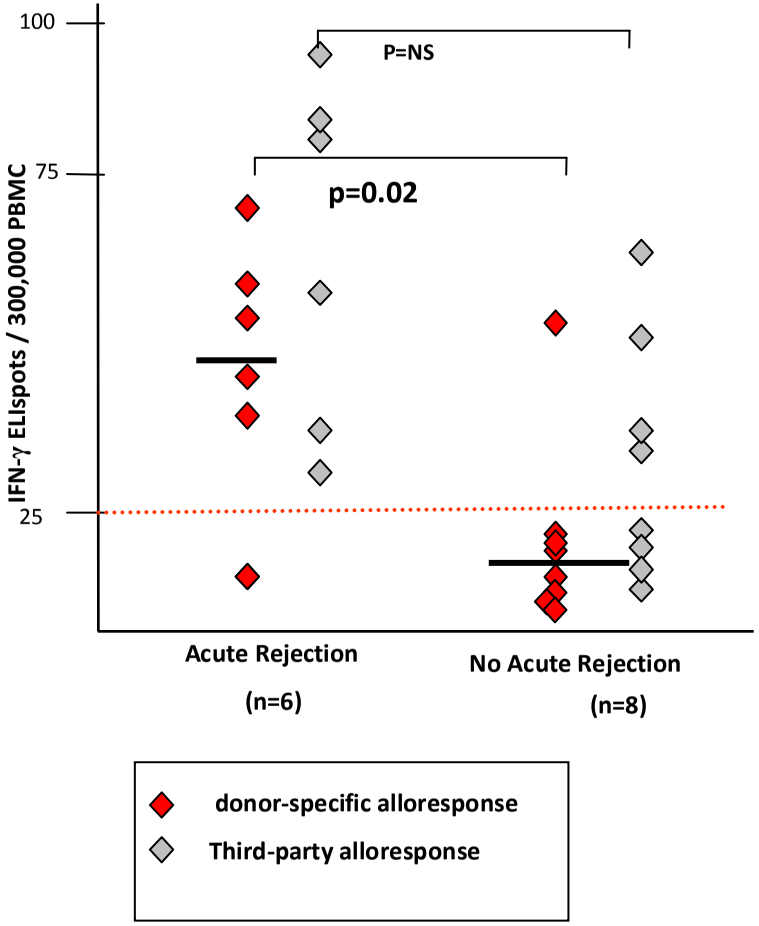
  → Histology assessment (6-month protocol biopsies)

Bestard O et al.. J Immunol 2007

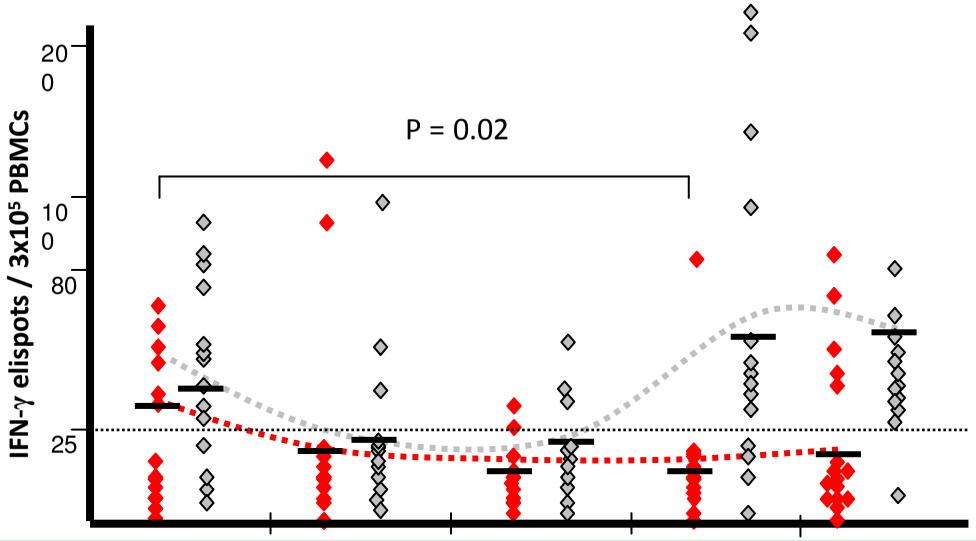
BACKGROUND

(T CELL IMMUNEMONITORING)

Pre elispot and risk of AR



T cell alloresponse evolution

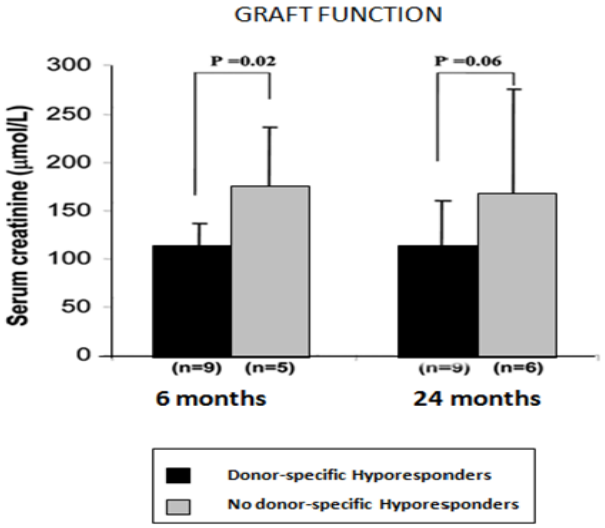


IFN-γ	Baseline (%)	1 month (%)	3 month (%)	6 month (%)	24 month (%)
+ anti-donor	6 (42.8)	2 (15)	1 (9.1)	1 (7)	5 (33)
- anti-donor - anti-Third party	4 (28.5)	10 (77)	8 (72.7)	4 (28,5)	1 (7)
d-s HypoResp	**4 (28.5)**	**1 (7.6)**	**2 (18.2)**	**9 (64.2)**	**9 (60)**
n	14	13	11	14	15

Bestard O et al. J Immunol 2007

BACKGROUND

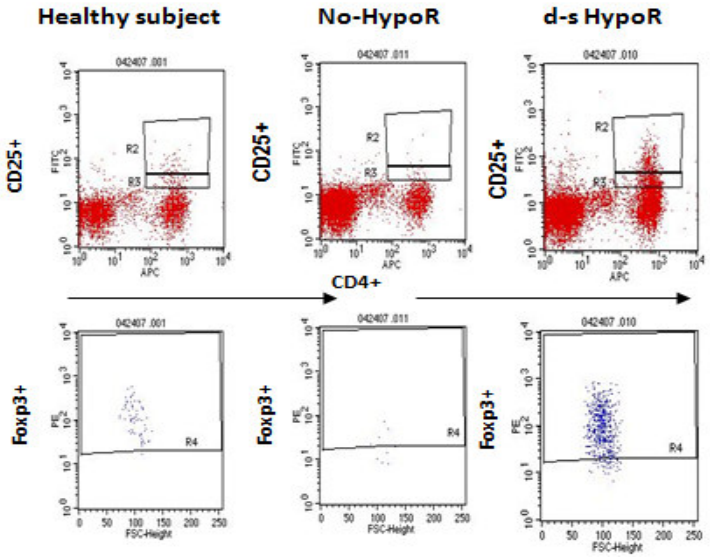
DONOR HYPORESPONSIVENESS ,GRAFT FUNCTION,GRAFT DAMAGE AND Tregs



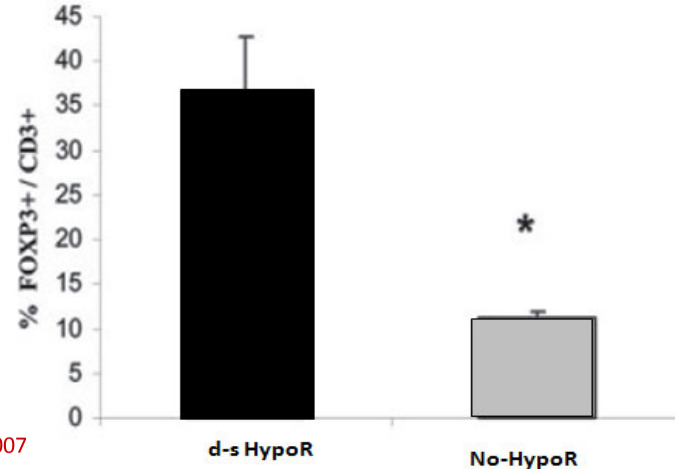
GRAFT DAMMAGE

Allostatus	Banff score
d-s HypoR	Normal
d-s HypoR	Normal
d-s HypoR	Normal
d-s HypoR	Normal
d-s HypoR	Normal
d-s HypoR	IF/TA Ia
d-s HypoR	IF/TA Ia
d-s HypoR	IF/TA Ia
No-HypoR	IF/TA IIa
No-HypoR	IF/TA IIa
No-HypoR	IF/TA IIb

Treg Facs determination



Infiltrate analisis Treg and dsh



Bestard O et al. J Immunol 2007

OBJECTIVES :ASSESSMENT OF CLINICAL AND IMMUNOLOGICAL EVOLUTION AT 5 YEARS FOLLOW UP

METHODS:

- GRAFT FUNCTION EVOLUTION
- 5-YEAR PROTOCOL BIOPSIES
  - BANFF SCORE
  - FoxP3 TREG GRAFT INFILTRATES
- FLOW CITOMETRY ANALISIS OF DIFFERENT PBMC's
  - CD3
  - CD4
  - CD8
  - NK
  - B cell
  - FoxP3 Treg
  - EFFECTOR MEMORY
  - CENTRAL MEMORY
  - Naïve

5 YEAR CLINICAL EVOLUTION

15 Patients: (3 exitus; 2 HD)

Patient survival: 17/20 (85%)
Graft survival: 15/20 (75%)

Maintenance Immunosuppression

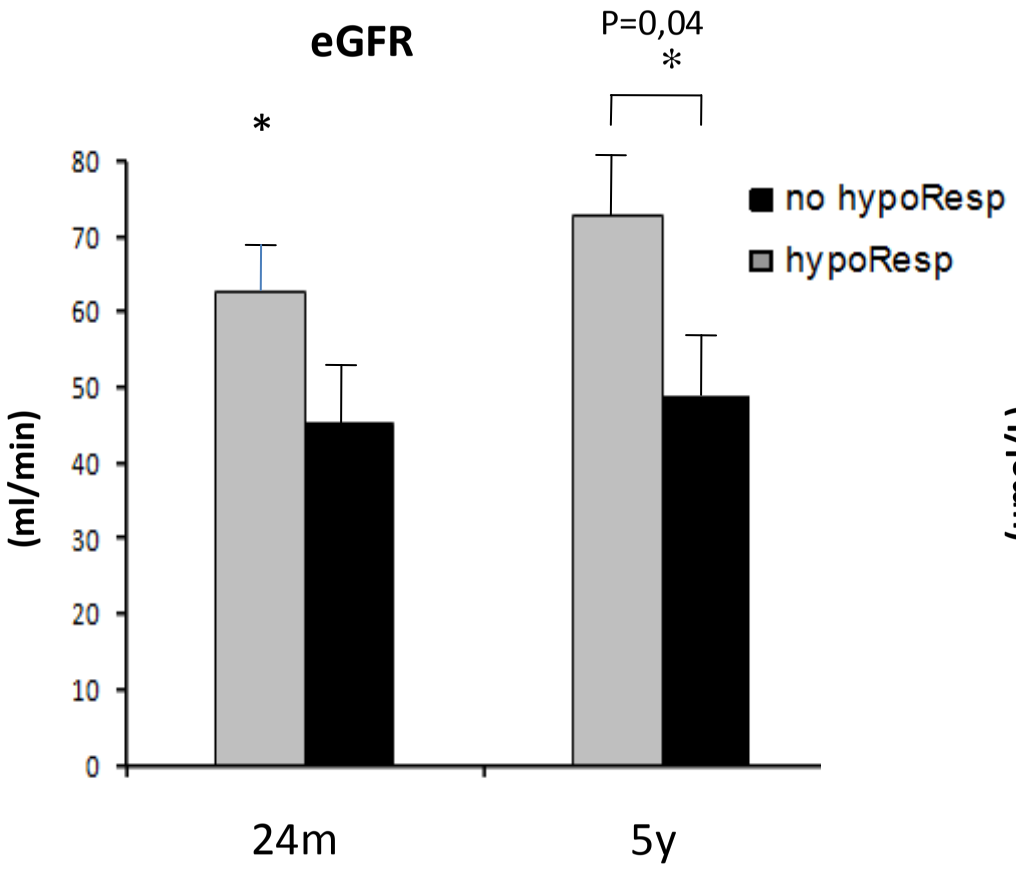
→ (**73**%) are **CNI-free**

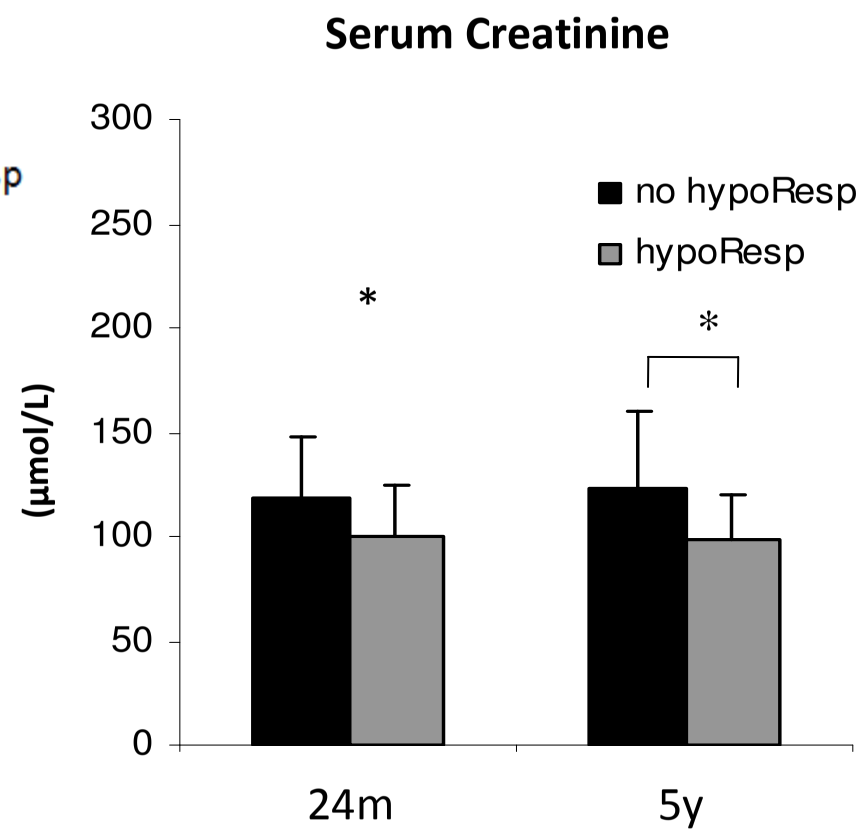
→ (**53%**) are **steroid-free**

→ (**53**%) remain on **protocol**

→ 3 patients on SRL monotherapy

24M Donor hyporesponsiveness and 5-Year Graft function

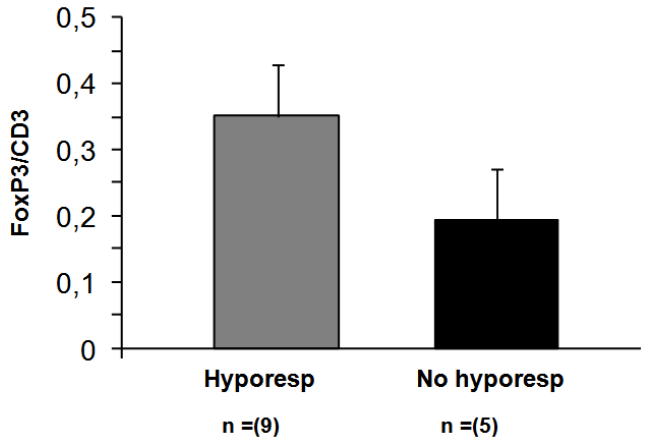


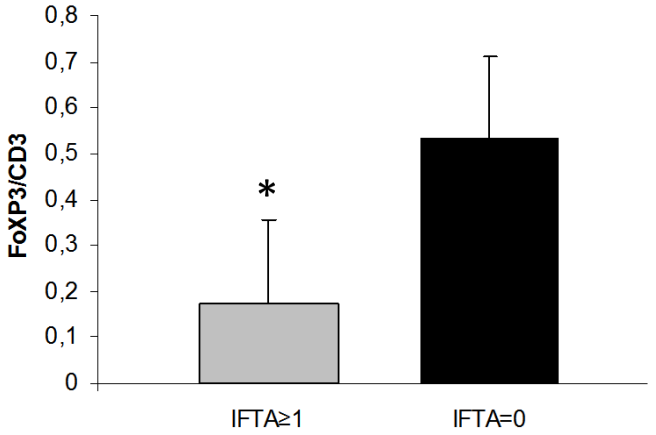


Dsh show significantly better graft function than T-cell responder patients at 5 years

T-cell alloresponse and Graft dammage

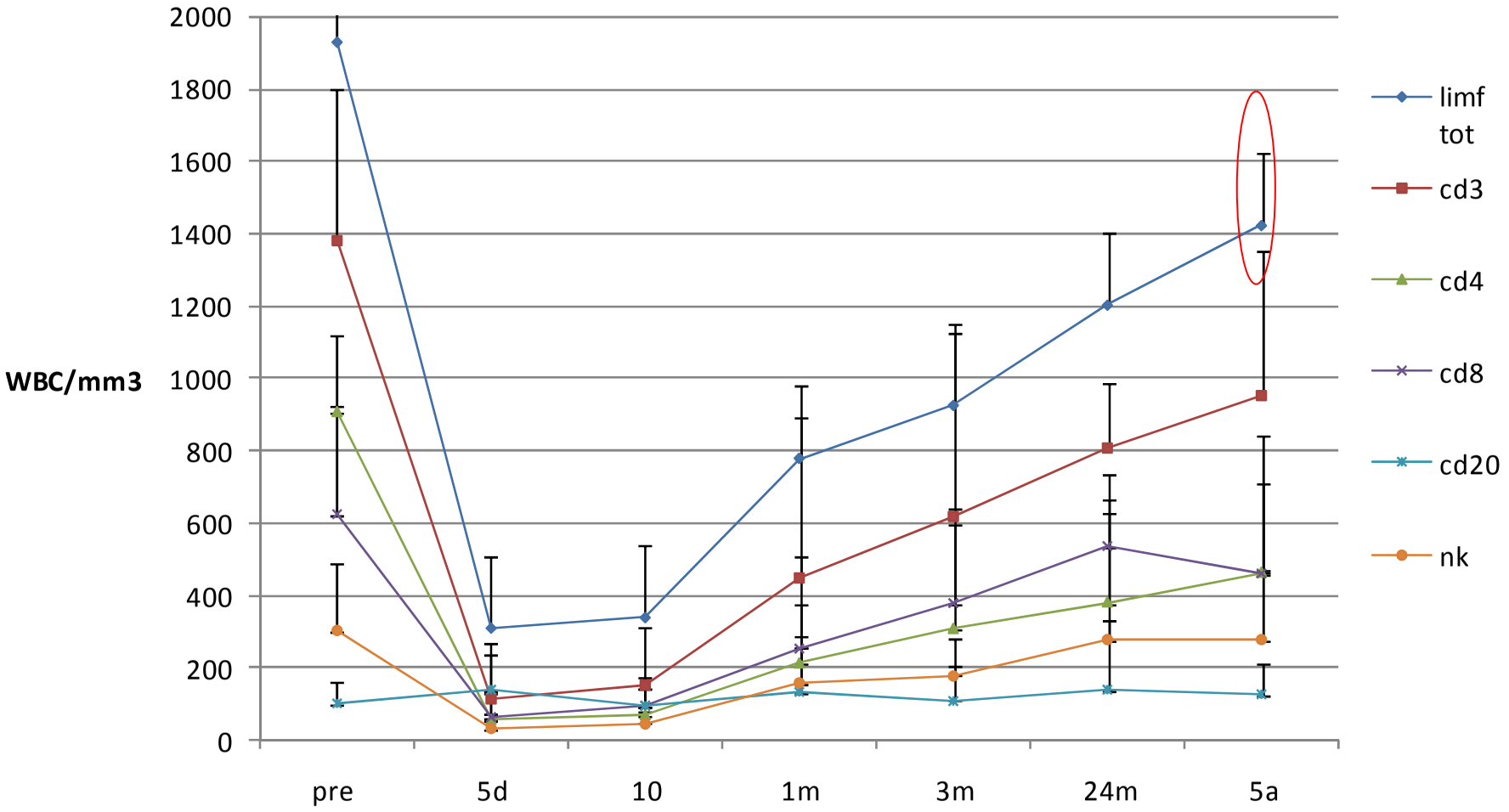
Banff score 6m	Allostatus	Banff score 5 Years
Normal	d-s HypoR	Normal
Normal	d-s HypoR	Normal
Normal	d-s HypoR	Normal
Normal	d-s HypoR	Normal
Not available	d-s HypoR	IF/TA Ia
Normal	d-s HypoR	IF/TA Ia
IF/TA Ia	d-s HypoR	IF/TA Ia
IF/TA Ia	No-HypoR	IF/TA Ia
IF/TA Ib	No-HypoR	IF/TA IIa
IF/TA IIb	No-HypoR	IF/TA IIb



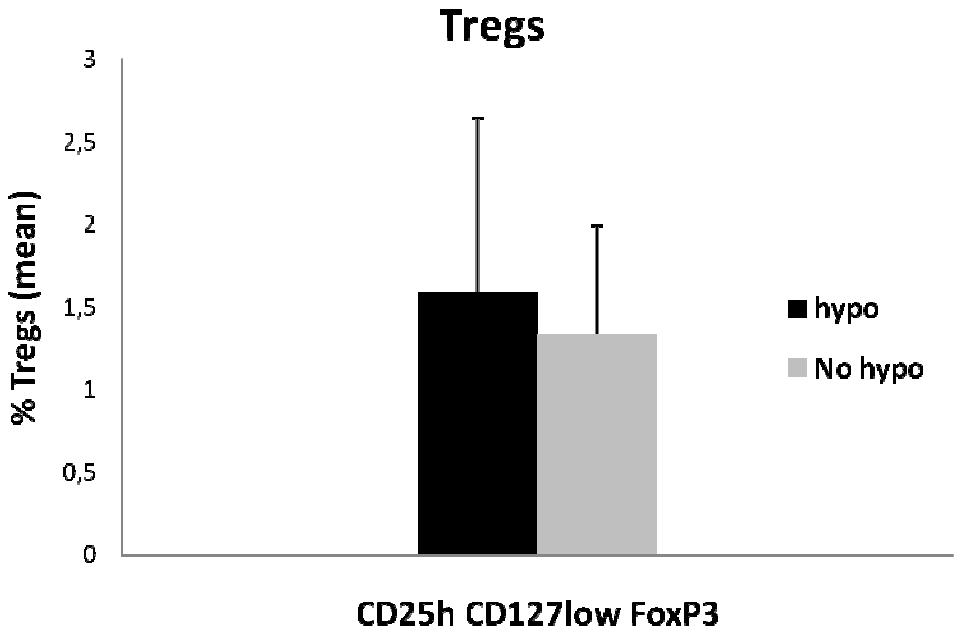


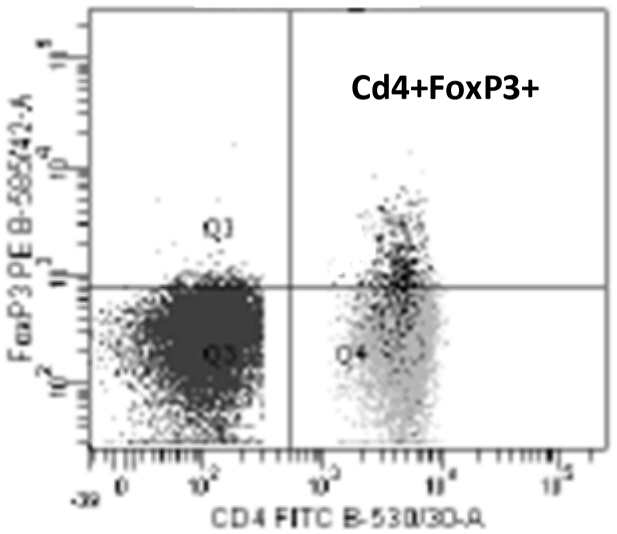
DSH present less chronic allograft dammage and higher Treg number

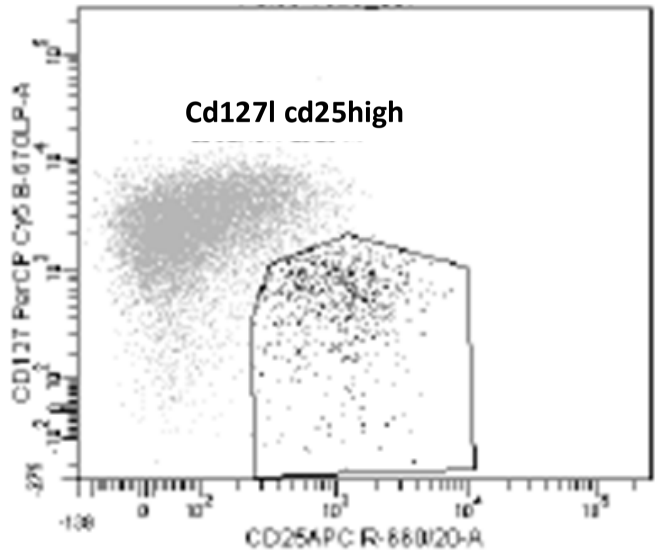
Evolution of different Lymphocyte subsets after transplantation

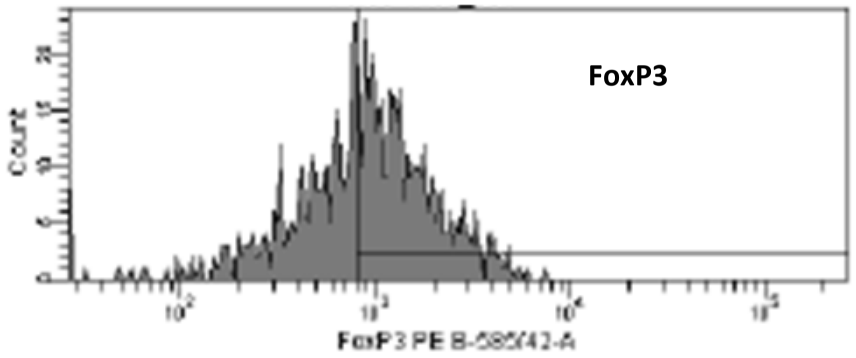


FACS subpopulation determination

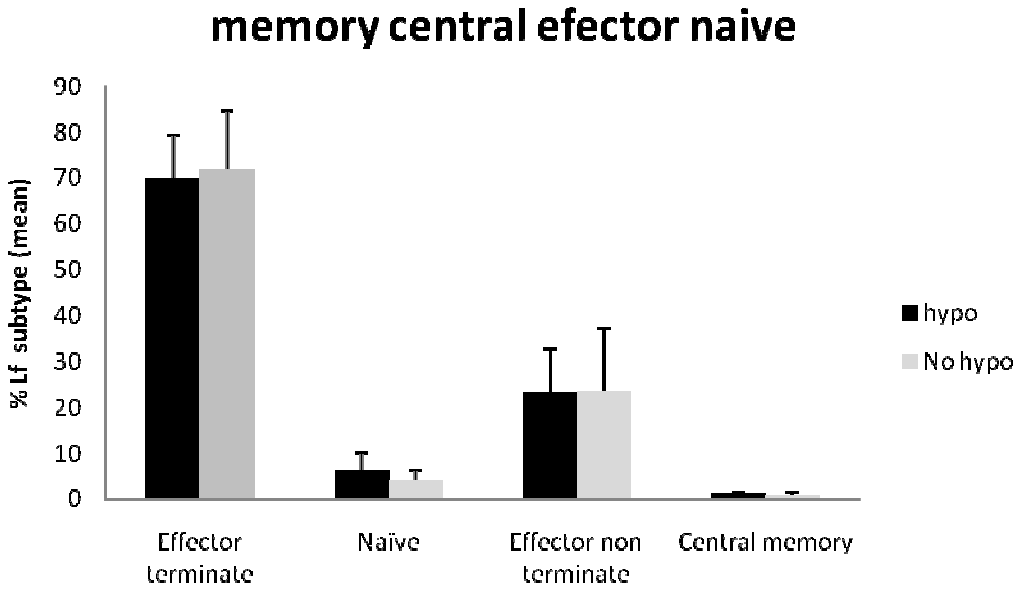


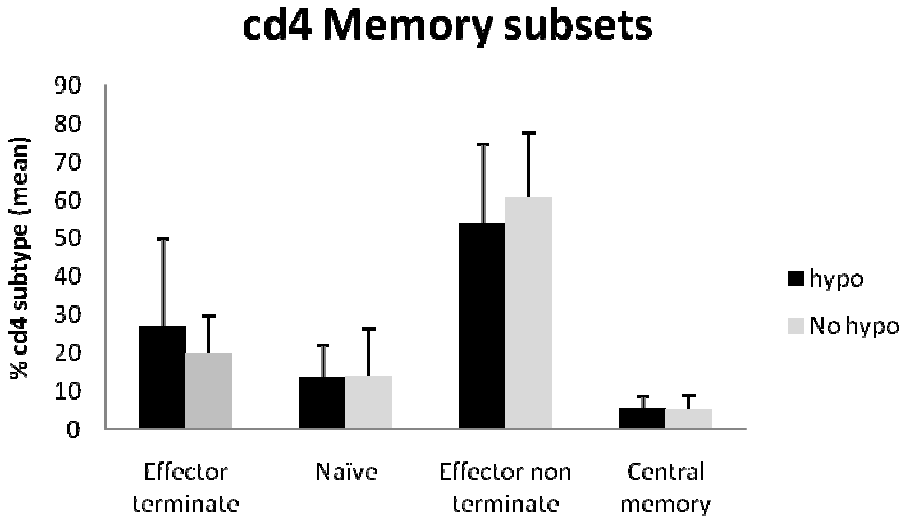


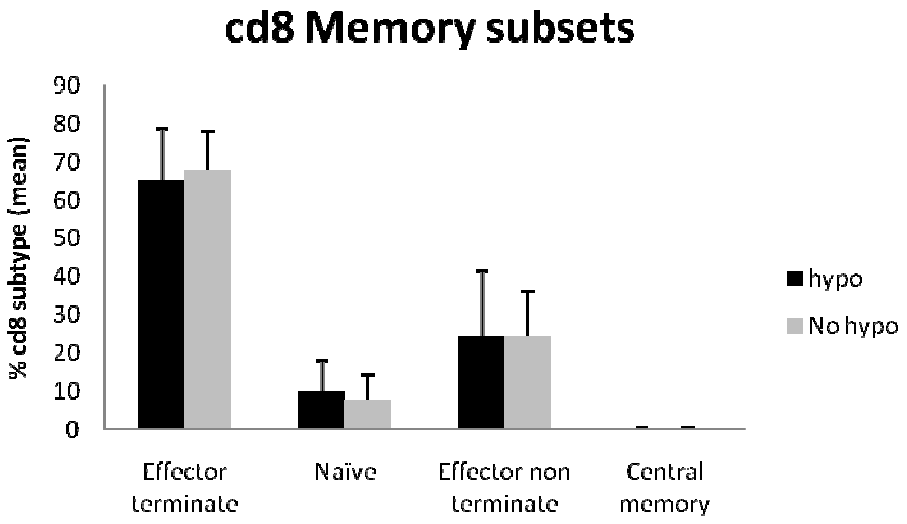




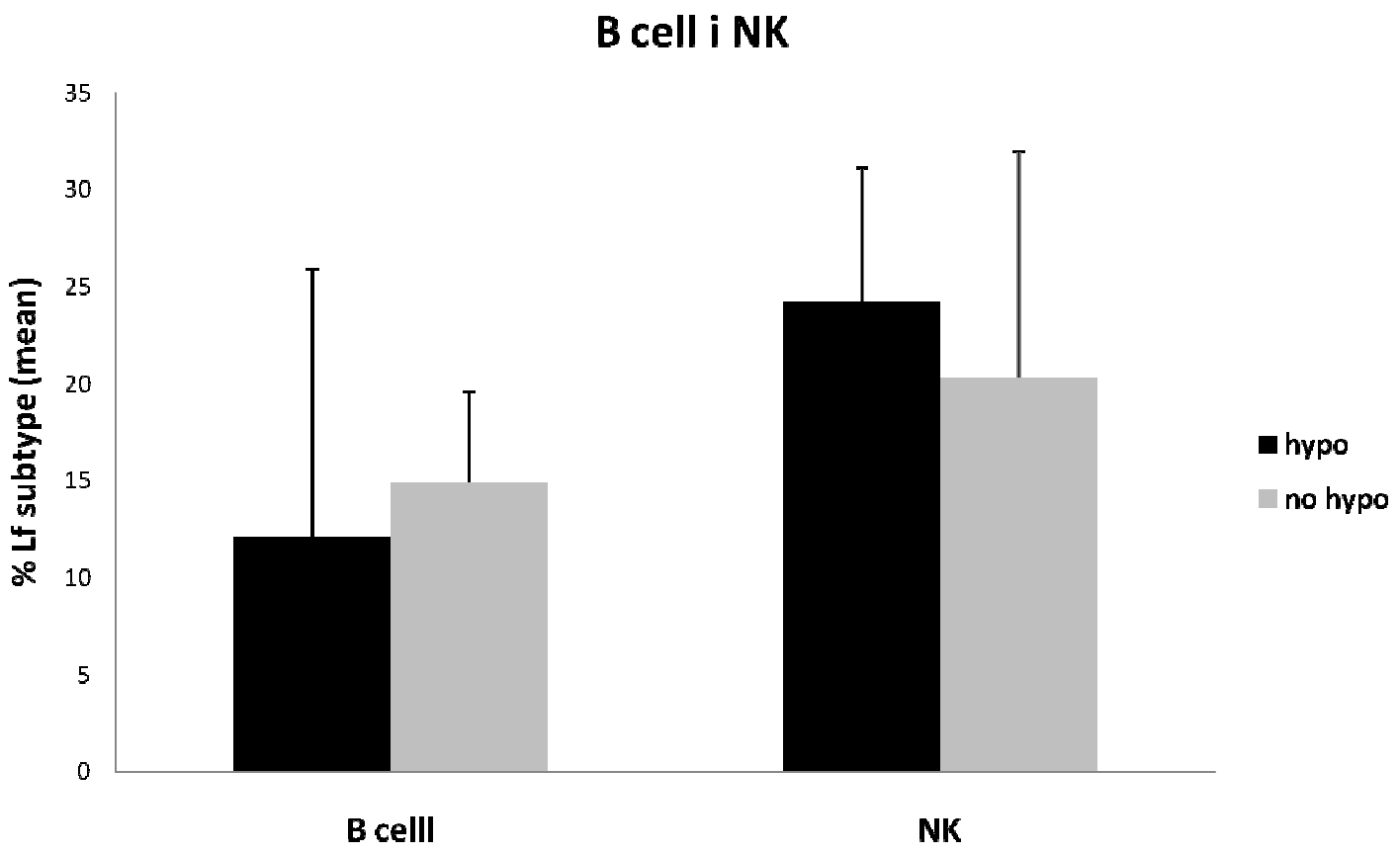
FACS subpopulation determination







FACS subpopulation determination



SUMMARY

❖Immune-monitoring the anti-donor T-cell alloimmune response seems to be feaseble with an IFN-γ Elispot assay

❖The achievement of donor-specific T-cell hyporesponsiveness is associated with a better graft function evolution as compared to T-cell responder patients and is associated with a better preserved allograft parenchyma

❖In this group of patients, regulatory T cells seem to play a relevant role for the achievement and maintenance of such immune privilege state

❖Prospectively immune-monitoring the humoral and cellular anti-donor alloimmune responses may allow drug minimization and early intervention in low and high-risk patients, respectively

❖These results needs to be further confirmed in larger and prospective studies

MOLTES GRÀCIES