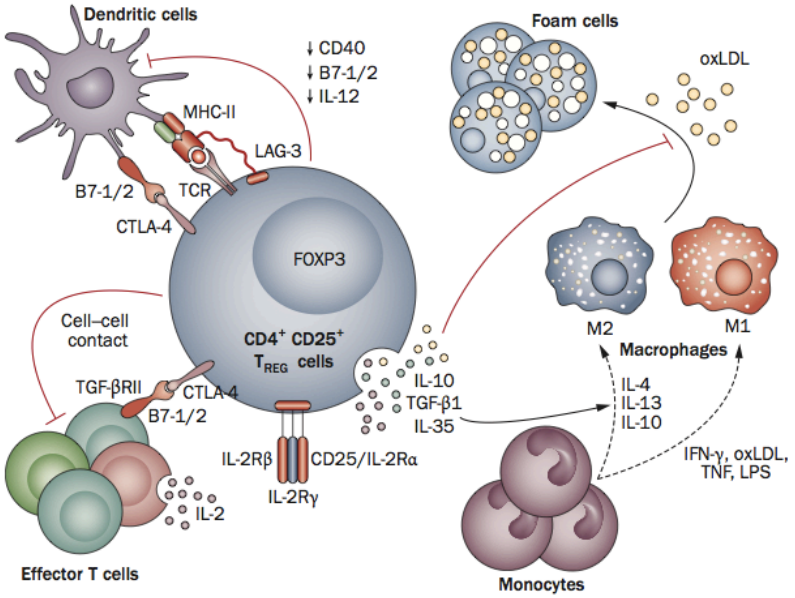
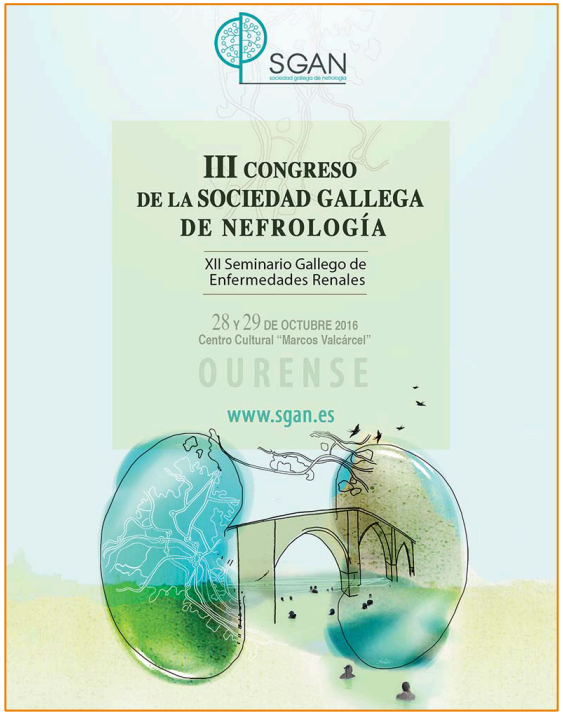
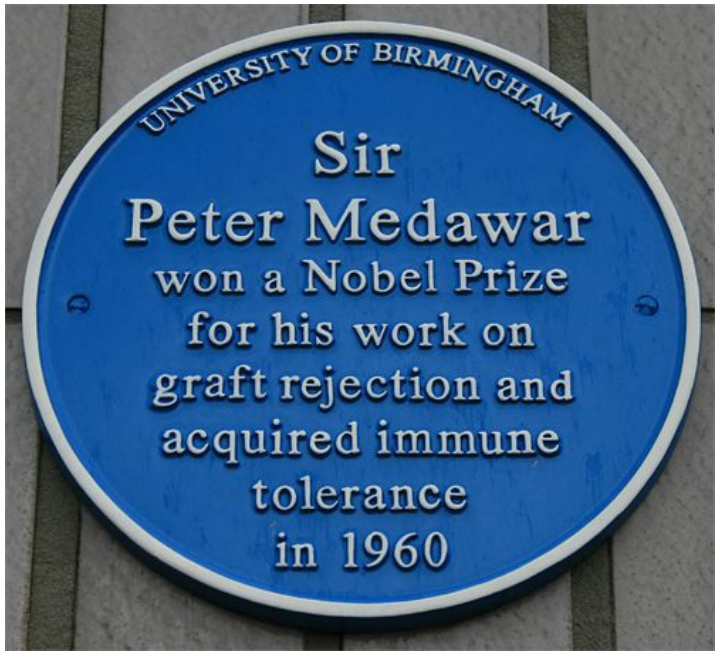
# LINFOCITOS T
## EN LA TOLERANCIA A LARGO PLAZO DEL INJERTO RENAL



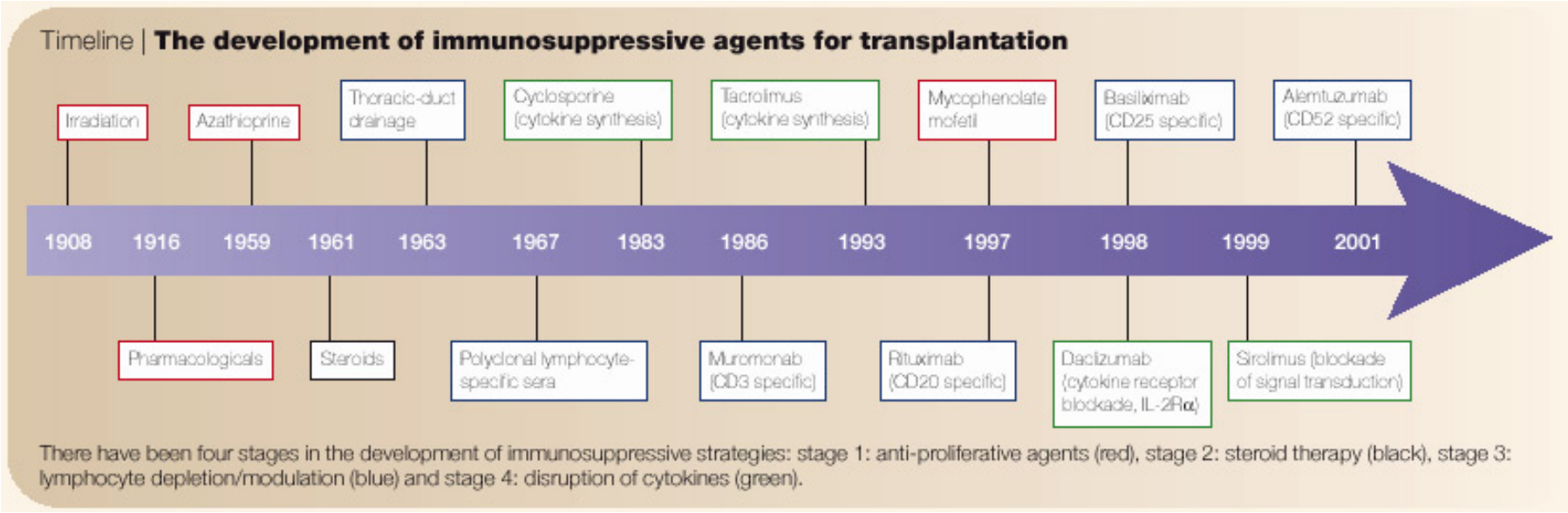




Jose Gómez Rial
F.E.A. Inmunología
Hospital Clínico Universitario de Santiago


UNIVERSITY OF BIRMINGHAM
Sir
Peter Medawar
won a Nobel Prize
for his work on
graft rejection and
acquired immune
tolerance
in 1960

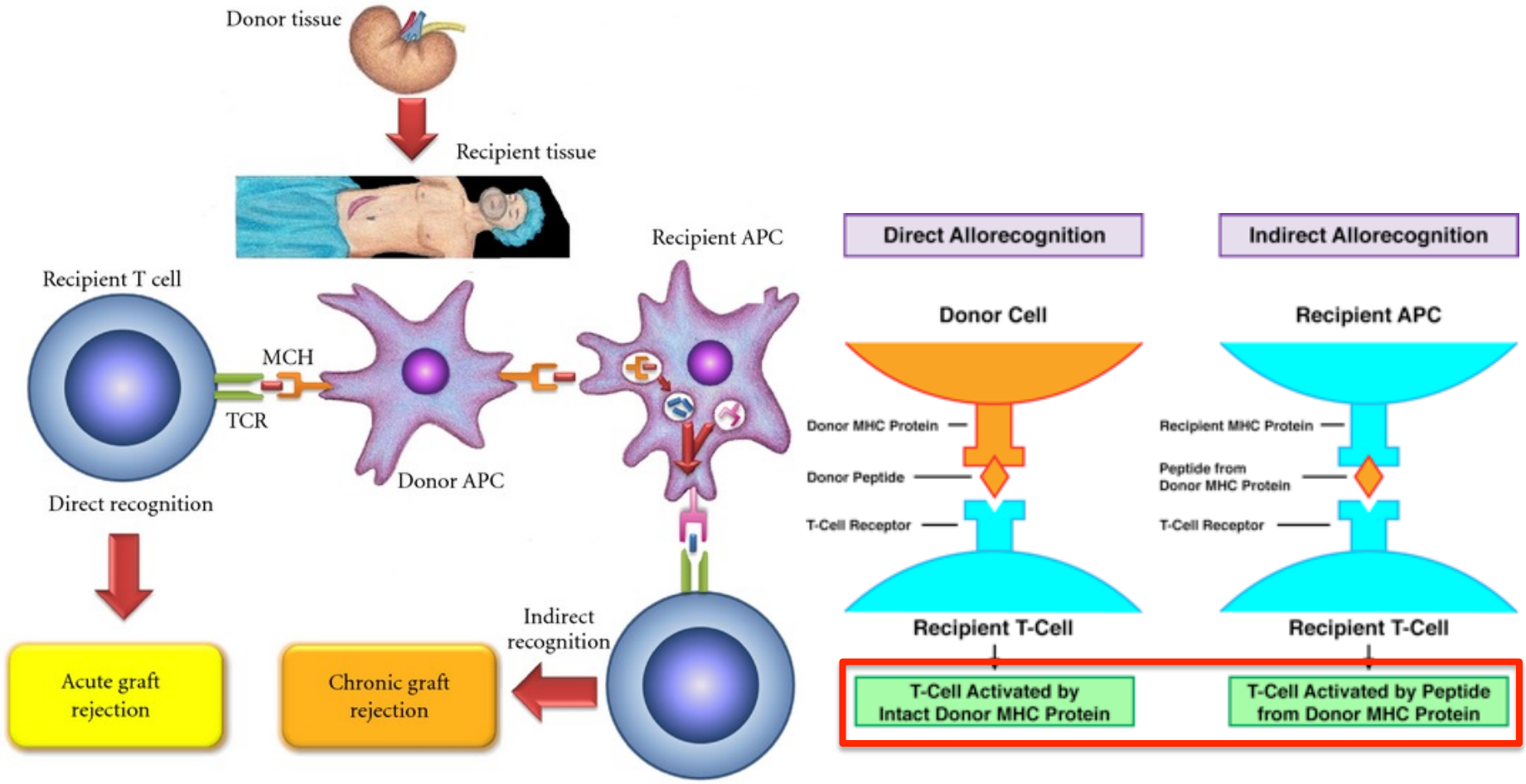
Joseph E. Murray (Boston, 24-Ene-1959)  Primer Alo-trasplante Riñón

La evolución en la terapia inmunosupresora ha permitido el desarrollo de los trasplantes de órganos.

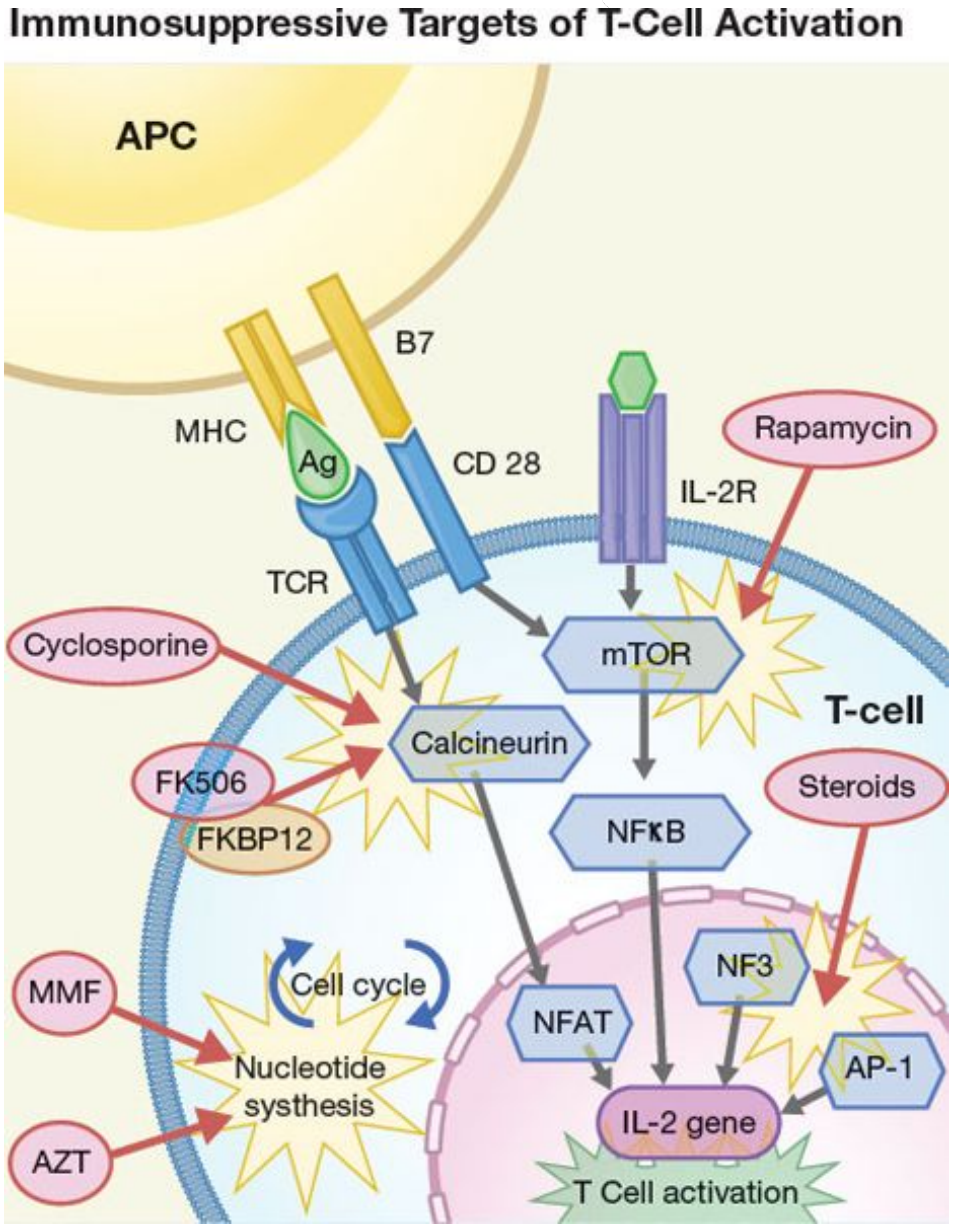



There have been four stages in the development of immunosuppressive strategies: stage 1: anti-proliferative agents (red), stage 2: steroid therapy (black), stage 3: lymphocyte depletion/modulation (blue) and stage 4: disruption of cytokines (green).

# EL MECANISMO DEL RECHAZO INMUNOLÓGICO



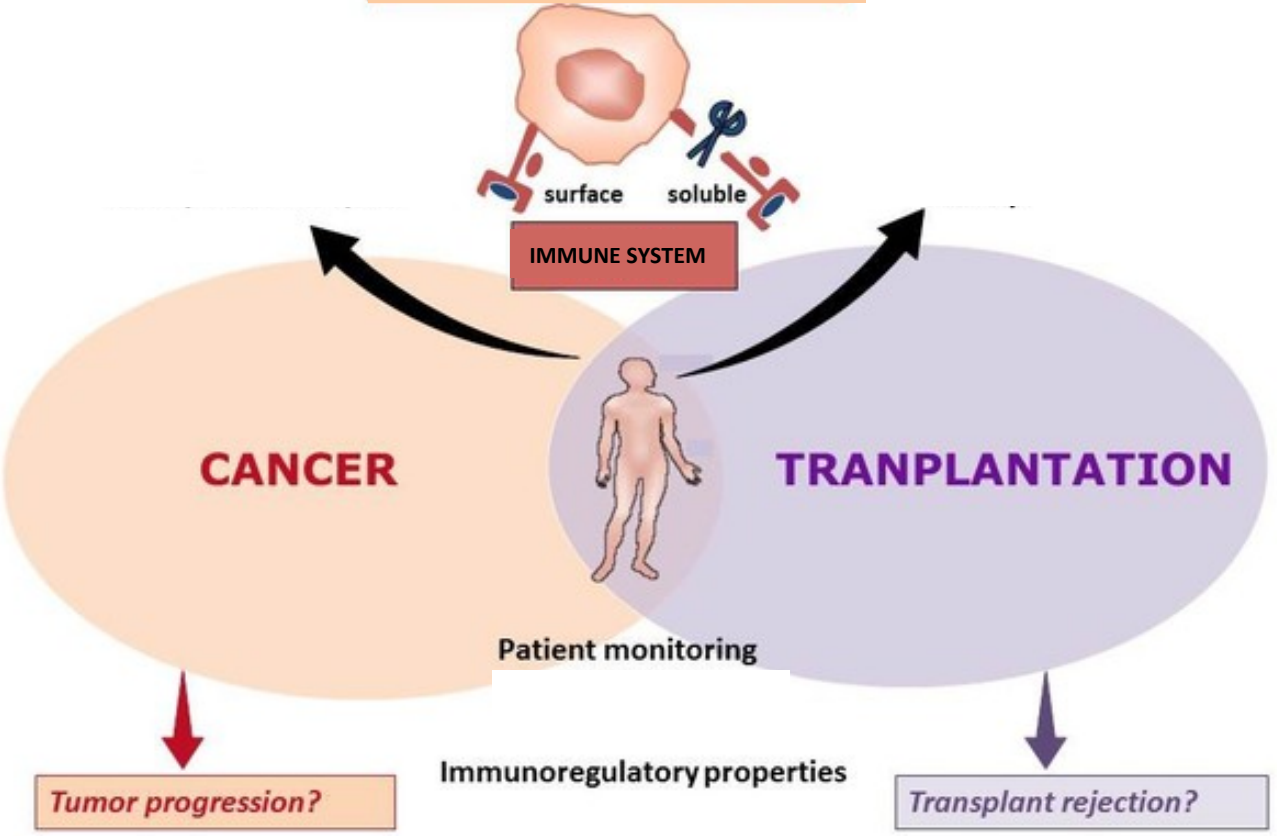
La terapia inmunosupresora previene la activación de la células T del huésped y el inicio del mecanismo inmunológico de rechazo del órgano.



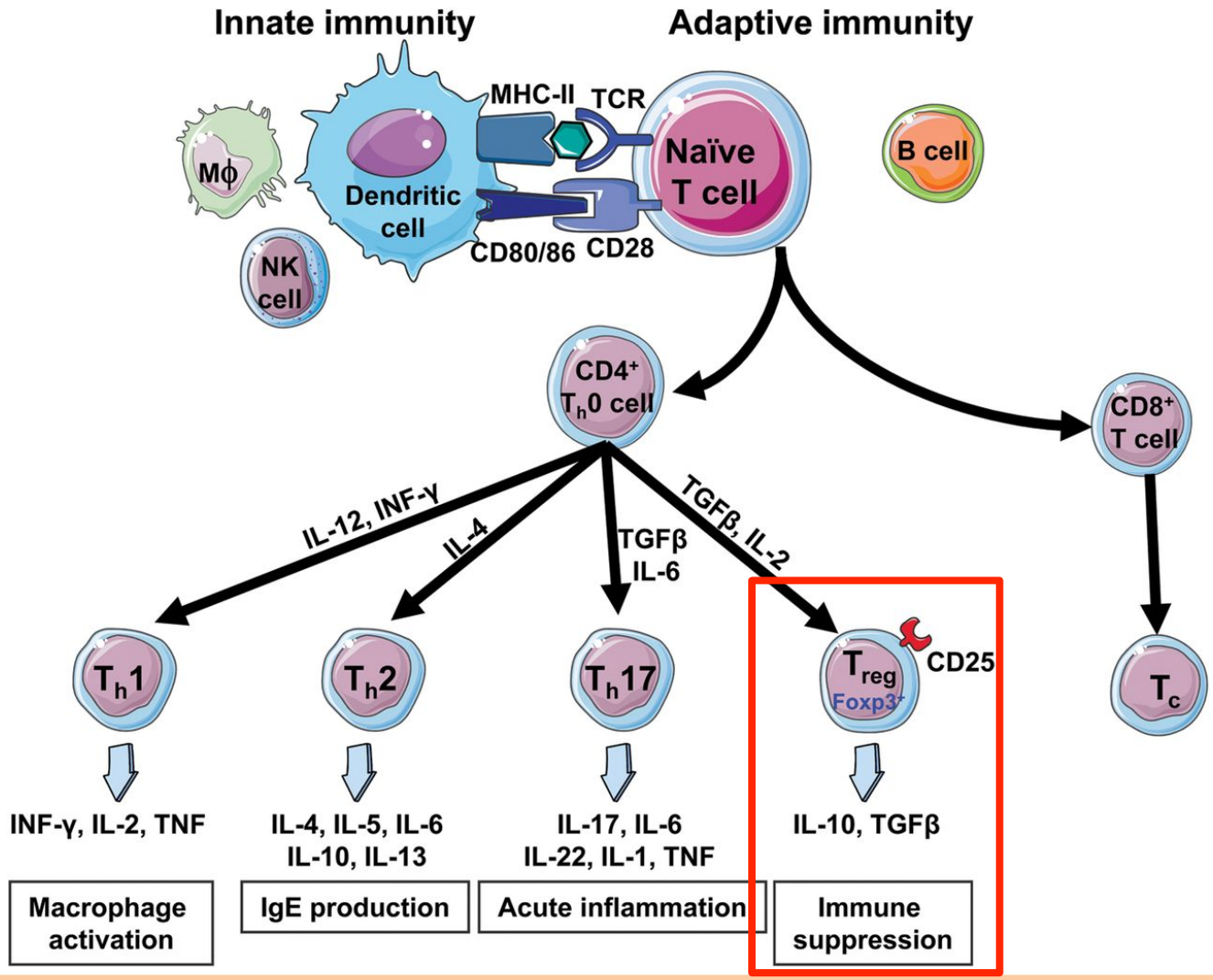
# TODAY'S IMMUNOSUPPRESSION

| The Good | The Bad | The Ugly |
|---|---|---|
| Overall outcomes | Side effects | Death with Function |

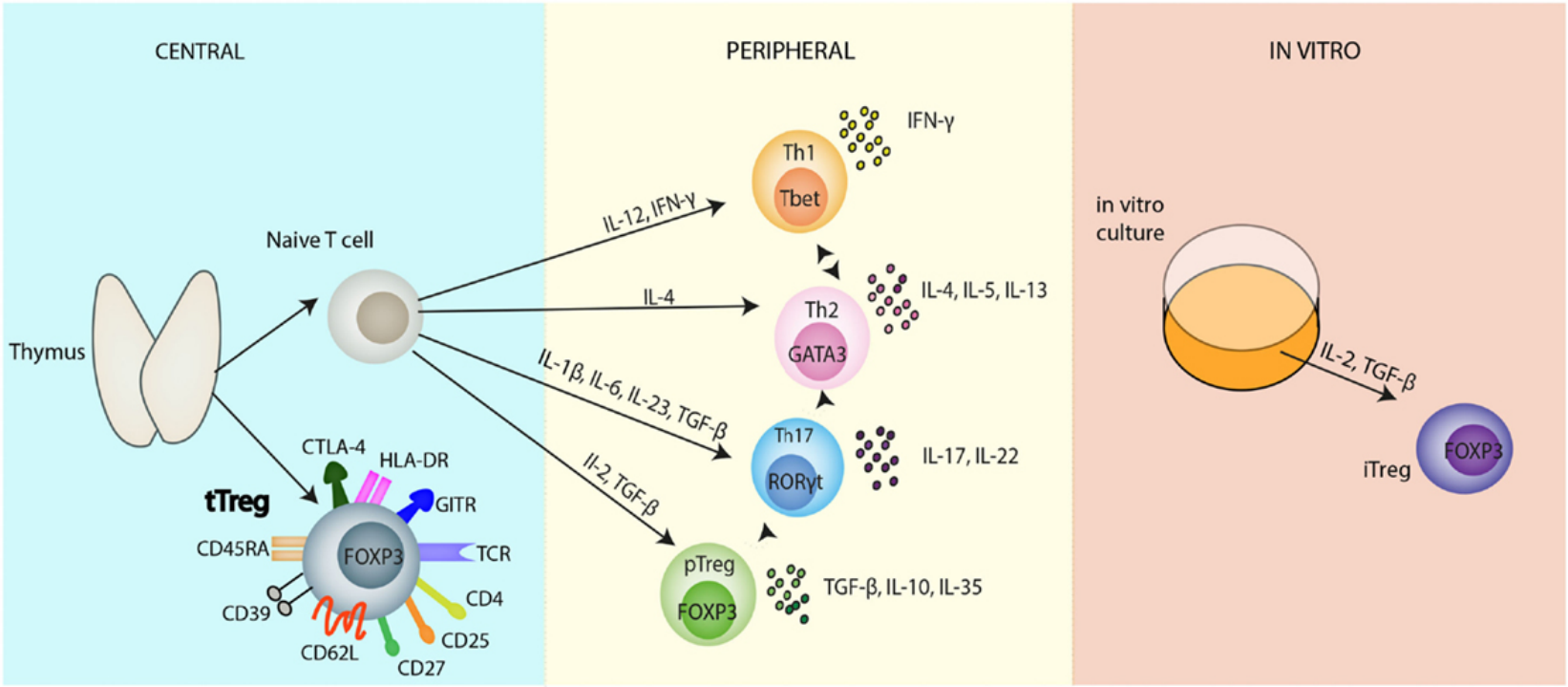
**¿Tumor cell or Allograft?**



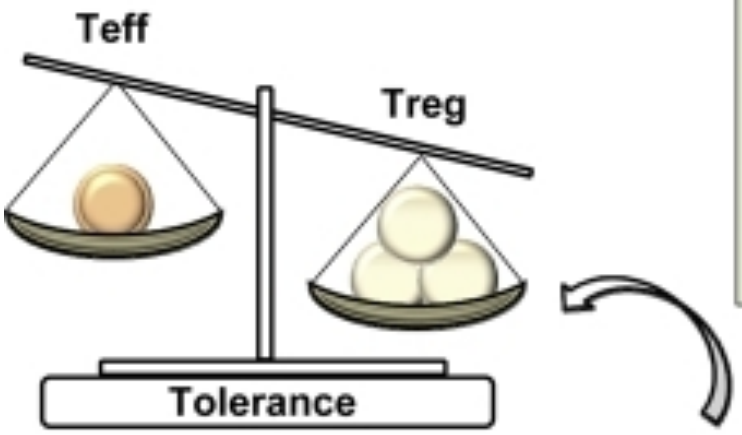
Toda respuesta inmunitaria presenta un componente de AUTOLIMITACIÓN de la propia respuesta: CÉLULAS T REGULADORAS



Las células T reguladoras son las encargadas de mantener la TOLERANCIA hacia los componentes propios y de SUPRIMIR la respuesta inmunológica una vez esta se ha iniciado.

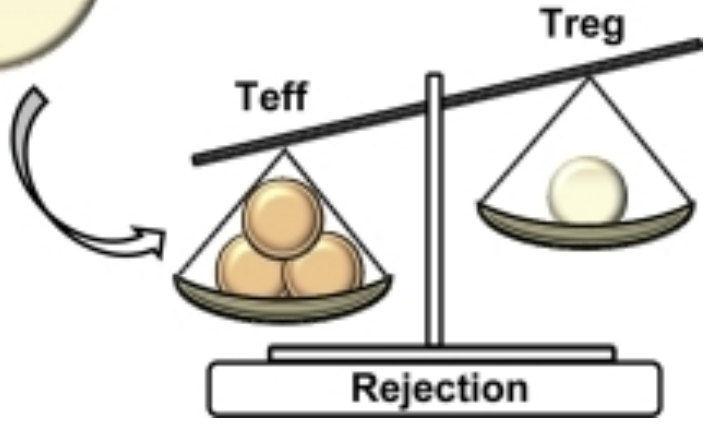



¿Se podría emplear como TERAPIA CELULAR en el trasplante de órganos?

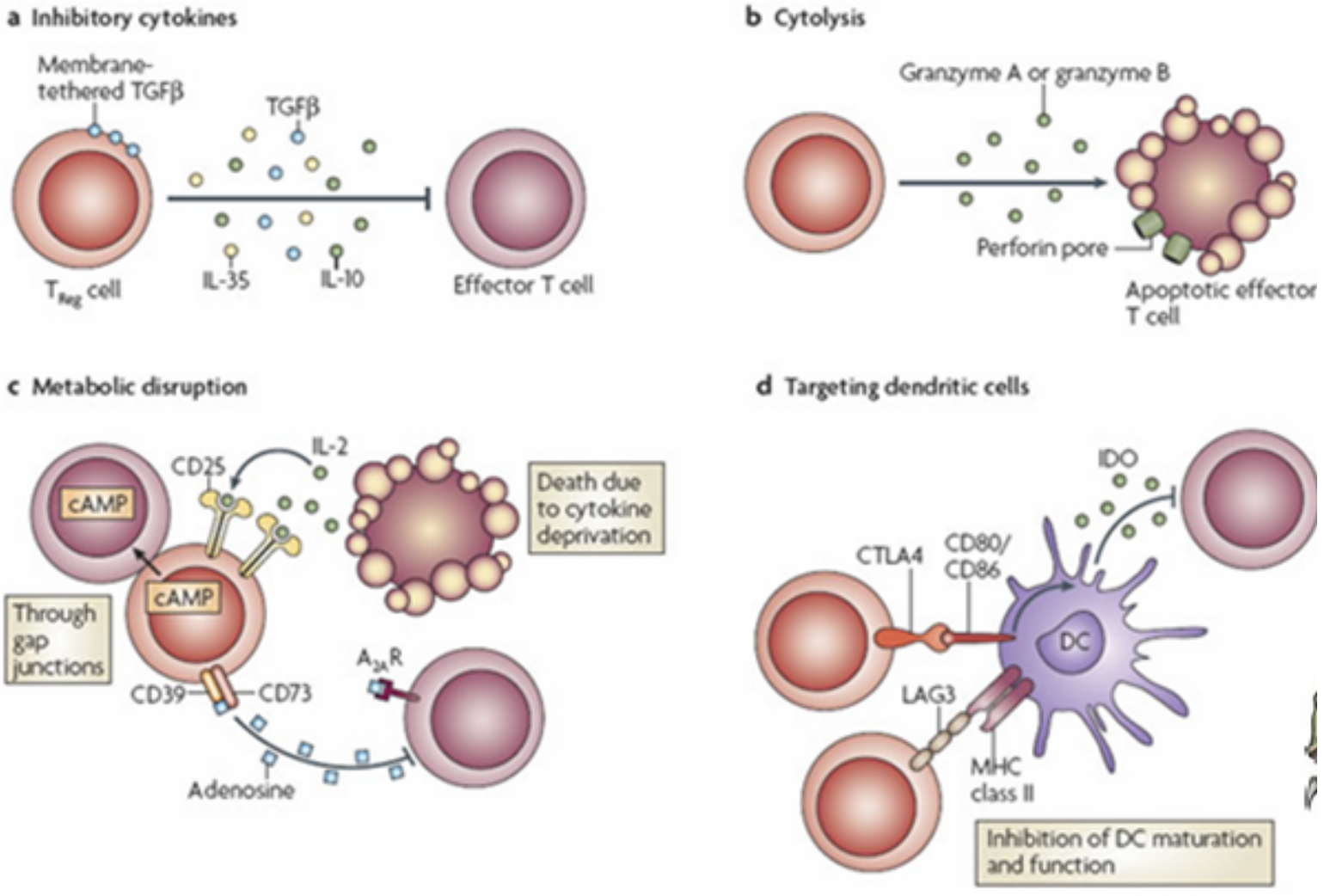



**Tolerance-promoting milieu**
- $TGF\beta_1$
- IL-2, IL-2.Ig, IL-2/anti-IL-2 complex
- retinoic acid
- IL-10
- anti-inflammatory agents (AAT, anti-IL-6, anti-TNFα)


**Rejection-promoting milieu**
- ischemia-reperfusion
- infection
- proinflammatory cytokines (IL-6, TNFα, IL-1β, IL-12)



# MECANISMO DE ACCIÓN DE LA CELULA T REGULADORA



# CÉLULAS T REGULADORAS EN EL TRASPLANTE: DATOS PRE-CLINICOS

nature REVIEWS IMMUNOLOGY

## Review

*Nature Reviews Immunology* **3**, 199-210 (March 2003) | doi:10.1038/nri1027

## Regulatory T cells in transplantation tolerance

**Kathryn J. Wood & Shimon Sakaguchi**

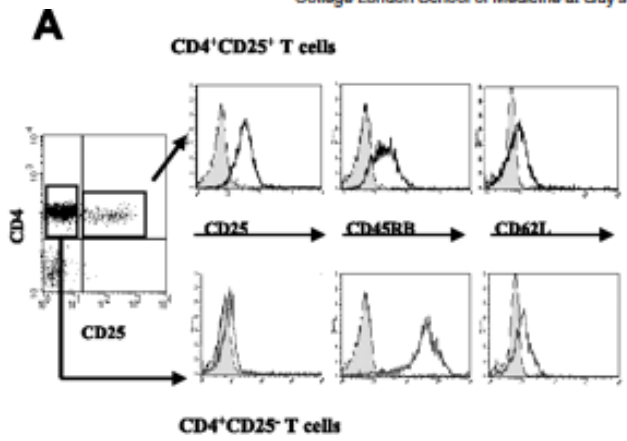
**The identification and characterization of regulatory T ($T_{Reg}$) cells that can control immune responsiveness to alloantigens have opened up exciting opportunities for new therapies in transplantation. After exposure to alloantigens *in vivo*, alloantigen-specific immunoregulatory activity is enriched in a population of $CD4^+$ T cells that express high levels of CD25. *In vivo*, common mechanisms seem to underpin the activity of $CD4^+CD25^+$ $T_{Reg}$ cells in both naive and manipulated hosts. However, the origin, allorecognition properties and molecular basis for the suppressive activity of $CD4^+CD25^+$ $T_{Reg}$ cells, as well as their relationship to other populations of regulatory cells that exist after transplantation, remain a matter of debate.**

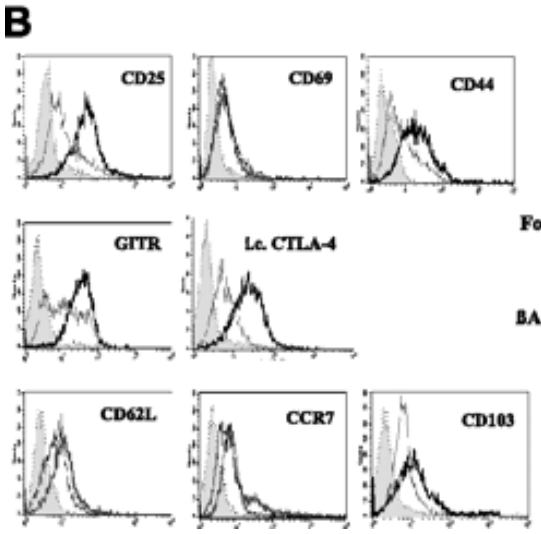
# In vitro–expanded donor alloantigen–specific CD4+CD25+ regulatory T cells promote experimental transplantation tolerance

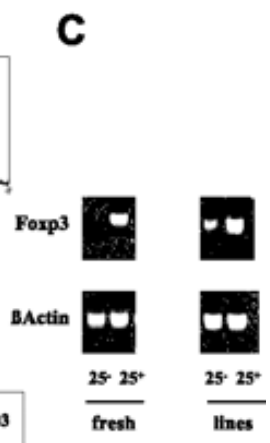
Dela Golshayan,[1] Shuiping Jiang,[1,2] Julia Tsang,[1,2] Marina I. Garin,[1,2] Christian Mottet,[3] and Robert I. Lechler[1,2]

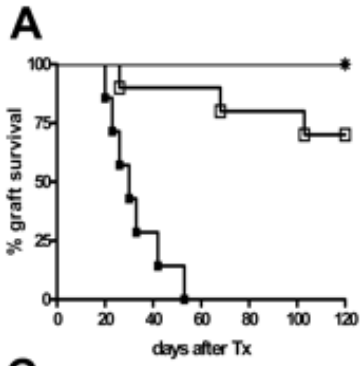
[1]Department of Immunology, Imperial College, Hammersmith Hospital, London, United Kingdom; [2]Department of Nephrology and Transplantation, King's College London School of Medicine at Guy's King's College and St Thomas' Hospitals, London, United Kingdom; [3]Sir William Dunn School of Pathology,

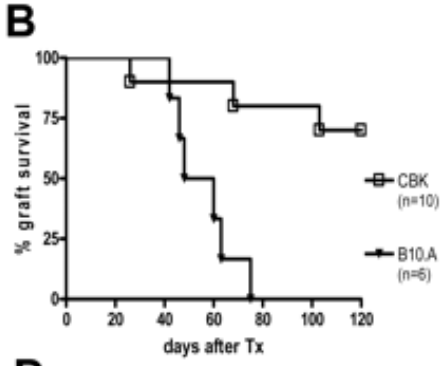
blood

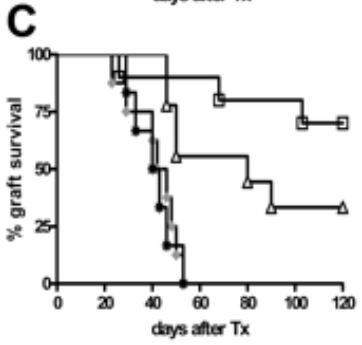


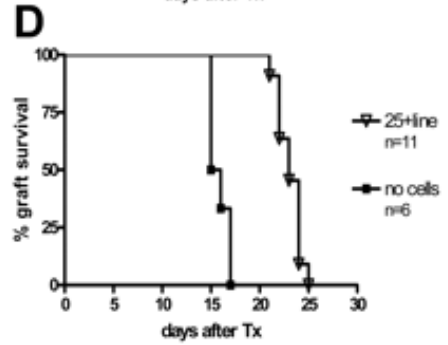



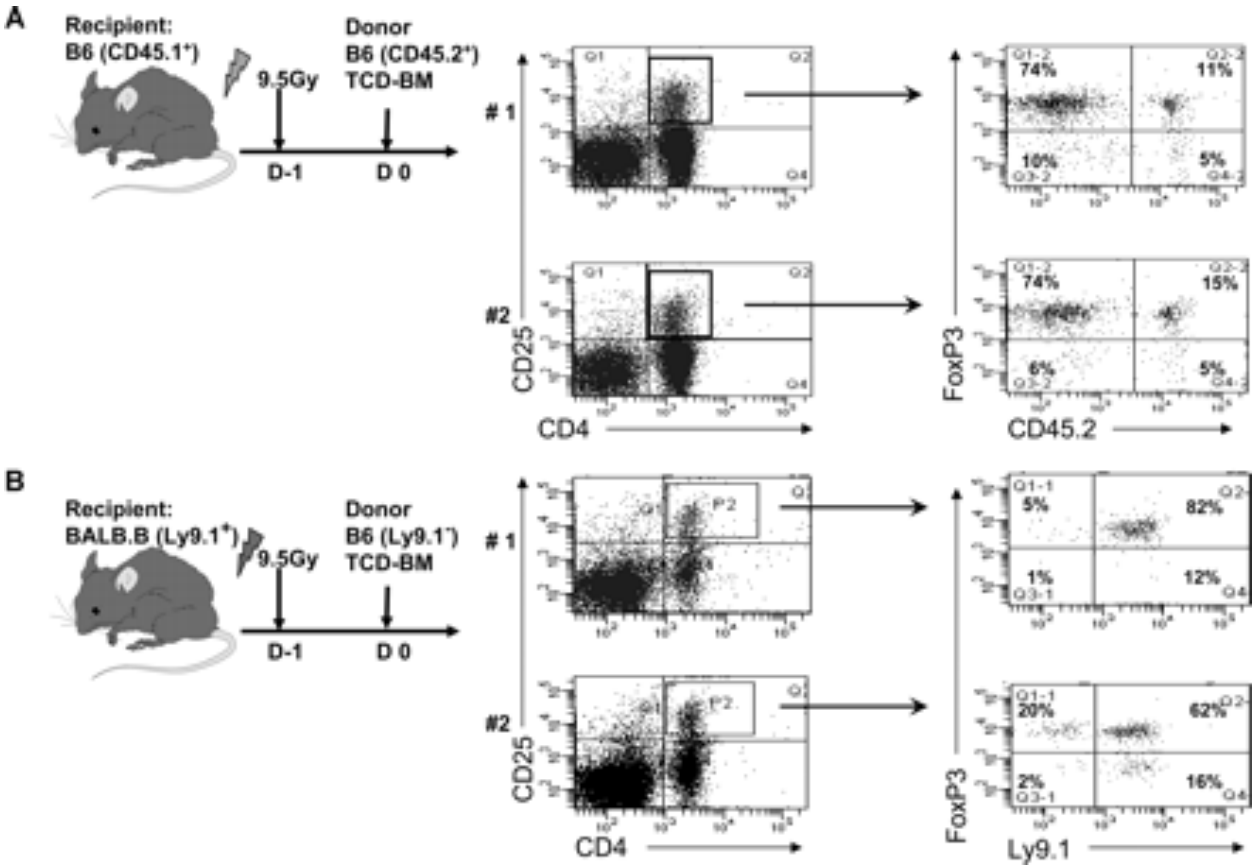
TRANSPLANTATION

# Host CD4+CD25+ T cells can expand and comprise a major component of the Treg compartment after experimental HCT

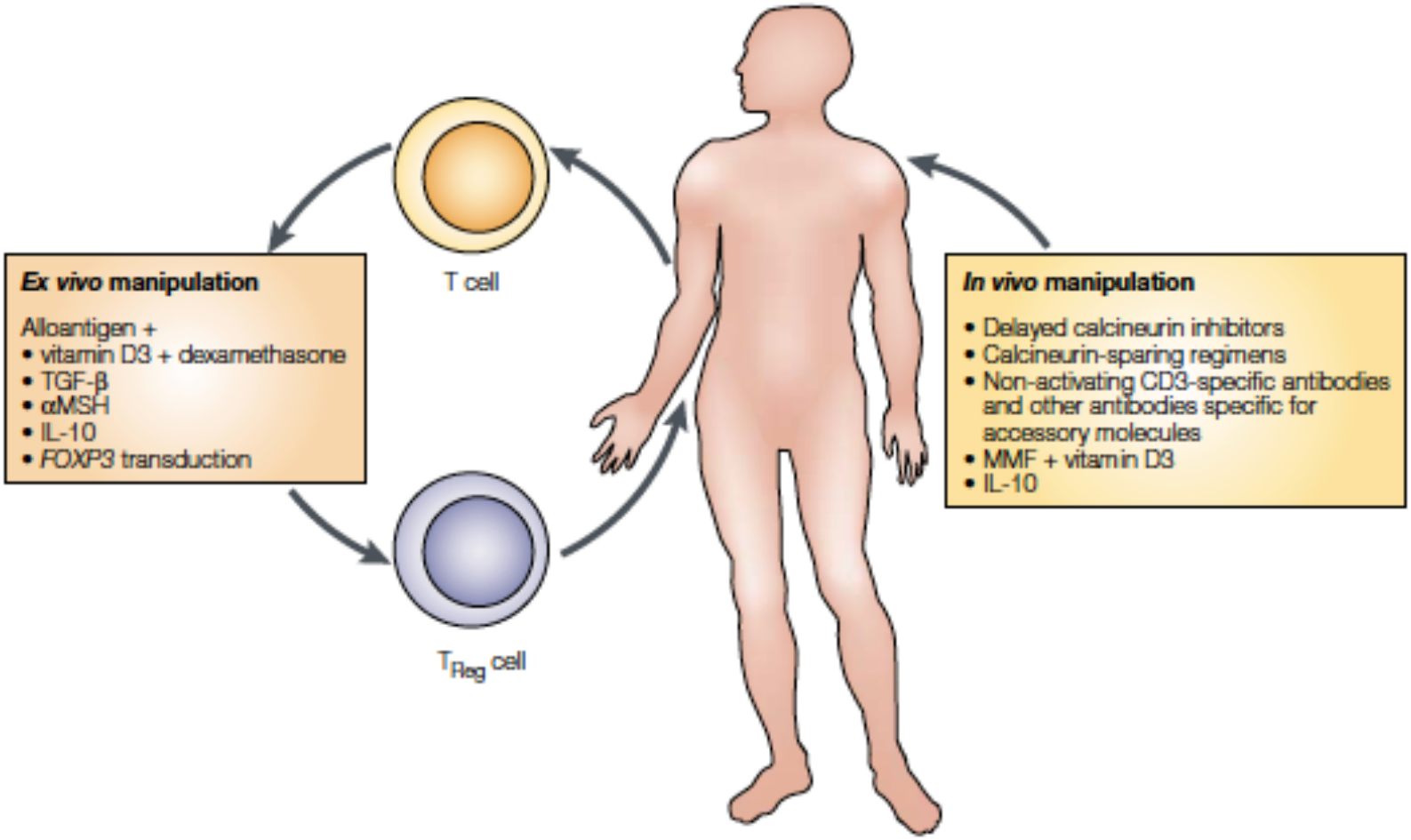
Allison L. Bayer,[1,2] Monica Jones,[1] Jackeline Chirinos,[1] Lesley de Armas,[1] Taylor H. Schreiber,[1] Thomas R. Malek,[1,2] and Robert B. Levy[1]

[1]Department of Microbiology/Immunology and [2]Diabetes Research Institute, Miller School of Medicine, University of Miami, FL

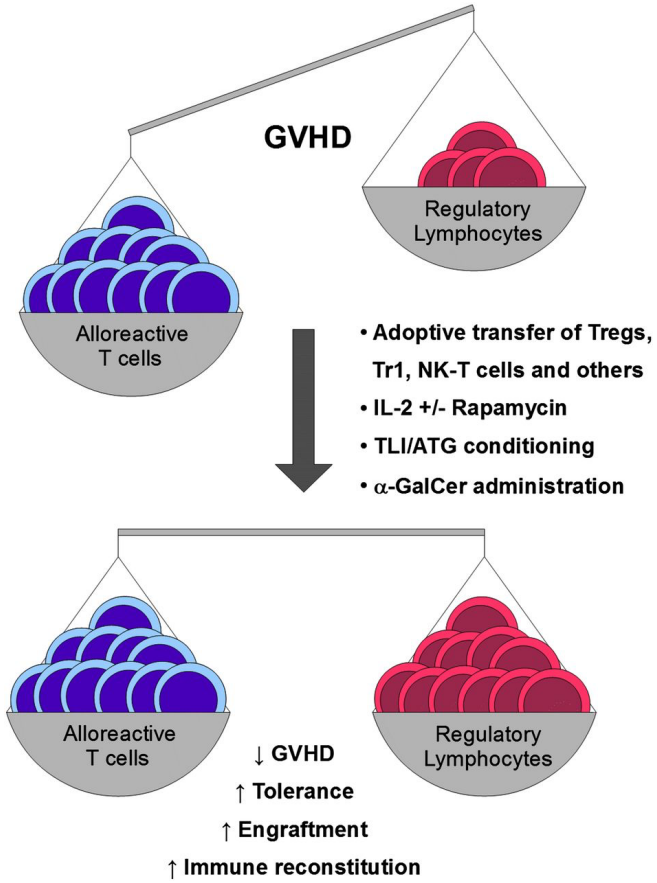
blood



# TRANSFERENCIA ADOPTIVA DE CÉLULAS $T_{REG}$ EN EL TRASPLANTE



# TRANSFERENCIA ADOPTIVA DE CÉLULAS $T_{REG}$ EN EL TRASPLANTE



nature REVIEWS IMMUNOLOGY



# Regulatory T-cell immunotherapy for tolerance to self antigens and alloantigens in humans

*Maria-Grazia Roncarolo* [*‡] and Manuela Battaglia* [*§]

Abstract | Substantial progress in understanding the biology of regulatory T cells and their roles in health and disease has been achieved in the past 10 years. This has led to an increasing interest in the possibility of using regulatory T cells as a biological therapy to preserve and restore tolerance to self antigens and alloantigens. Immunotherapy by the adoptive transfer of regulatory T cells may have several advantages over conventional treatments. However, several hurdles have to be overcome before such a therapy can enter clinical practice. This Review summarizes our current knowledge of regulatory T cells, illustrates the ongoing regulatory T-cell-based clinical trials, analyses the strengths and pitfalls of this new therapeutic approach, and highlights the future perspectives.

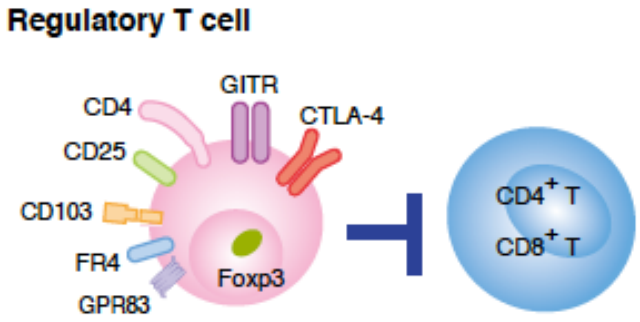
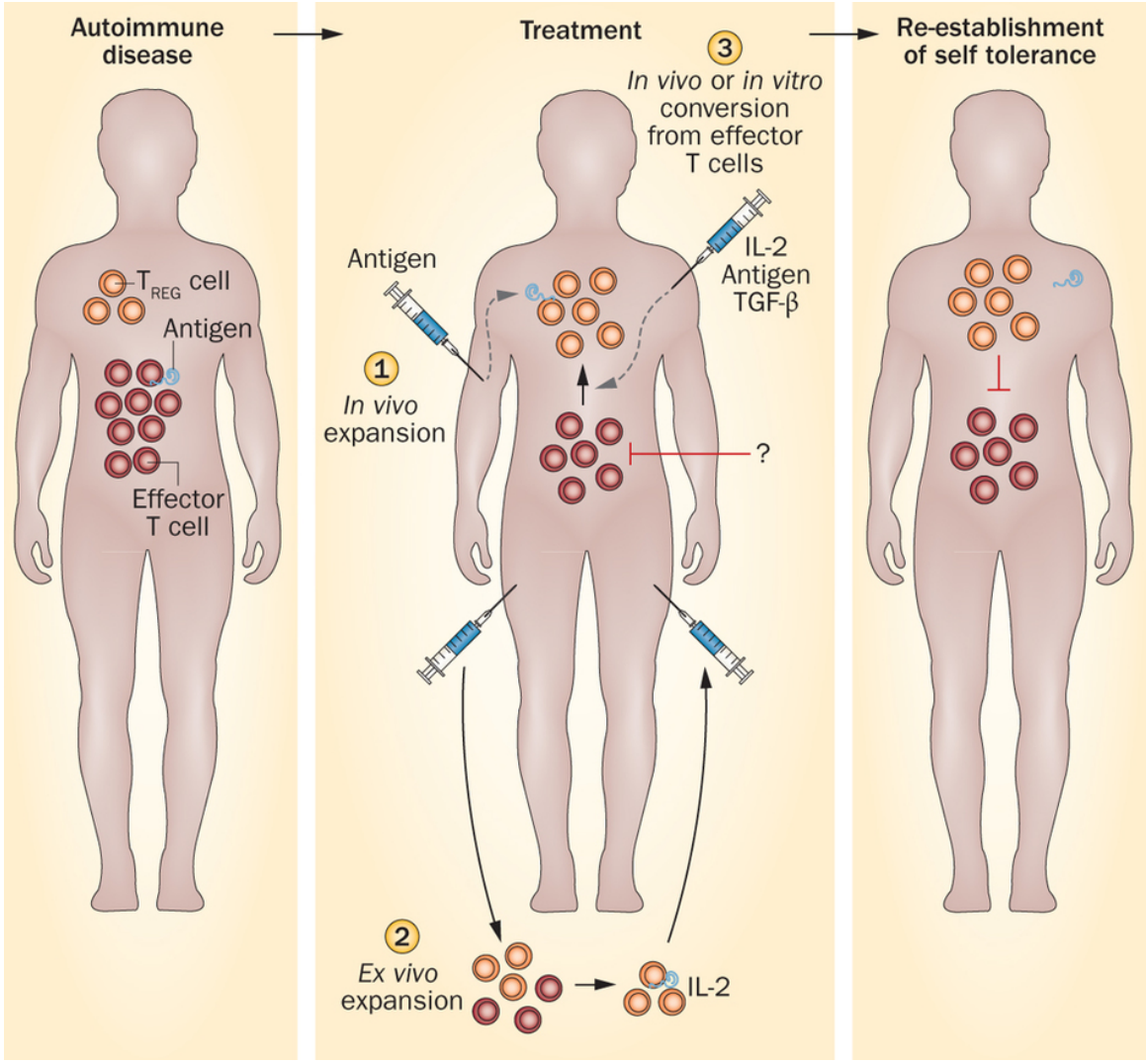



Table 2 | **Adoptive transfer of regulatory T cells in experimental mouse models**

| Disease | Regulatory T cells | Mouse model | Effect on disease | Refs |
|---|---|---|---|---|
| *Autoimmune disease* | | | | |
| Type 1 diabetes | BDC2.5 TCR-transgenic $T_{Reg}$ cells (from NOD mice) | NOD.*Rag*$^{-/-}$ mice reconstituted with diabetogenic T cells | Prevention | 30 |
| | | NOD.*Cd28*$^{-/-}$ mice (which lack $T_{Reg}$ cells) | Prevention | 30 |
| | | Diabetic NOD mice receiving syngeneic islets | Prevention | 30 |
| | | NOD mice with new onset diabetes | Remission (60%) | 30 |
| | BDC2.5 TCR-transgenic $T_{Reg}$ cells expanded by DCs *in vitro* | BDC2.5 TCR-transgenic mice treated with high doses of cyclophosphamide | Prevention | 86 |
| | | NOD.SCID mice reconstituted with diabetogenic T cells | Prevention | 86 |
| | | Pre-diabetic NOD mice | Prevention | 86 |
| | | NOD mice with new onset diabetes | Remission (50%) | 81 |
| | Antigen-specific NOD $T_{Reg}$ cells expanded *in vitro* | NOD.*Cd28*$^{-/-}$ mice | Prevention | 87 |
| | GAD65-specific $T_R1$ cells | NOD.SCID mice reconstituted with diabetogenic T cells | Prevention | 88,89 |
| Multiple sclerosis (EAE) | TCR-transgenic MBP-specific $T_{Reg}$ cells | *Rag*$^{-/-}$ TCR-transgenic (MBP-specific) mice | Prevention of spontaneous disease | 90 |
| | $T_{Reg}$ cells from naive C57BL/6 mice | C57BL/6 mice immunized with $MOG_{35-55}$ peptide | Prevention of induced disease | 91 |
| | OVA-specific $T_R1$ cells | BALB/c mice immunized with mouse spinal-cord homogenate and with heat-killed *Mycobacterium tuberculosis* | Prevention of induced disease | 44 |
| | $T_R1$ cells induced by B7H1–immunoglobulin fusion protein plus immobilized CD3-specific antibody | C57BL/6 mice immunized with $MOG_{35-55}$ peptide | Prevention of induced disease | 85 |
| Rheumatoid arthritis | $T_{Reg}$ cells | Collagen-induced arthritis | Inhibited progression of early stage disease | 92 |
| Inflammatory bowel disease | $T_{Reg}$ cells | SCID mice reconstituted with CD45RB$^{hi}$ cells | Reversal of established disease | 29 |
| | OVA-specific $T_R1$ cells | SCID mice reconstituted with CD45RB$^{hi}$ cells | Prevention | 2 |
| | Caecal-bacteria-specific $T_R1$ cells from C3H/HeJBir mice | SCID mice reconstituted with pathogenic $T_H1$ cells from C3H/HeJBir mice | Prevention | 93 |
| Systemic lupus erythematosus | Thymus-derived $T_{Reg}$ cells | NZB× NZW mice | Control of autoimmunity | 94 |
| Scurfy disease | $T_{Reg}$ cells | FOXP3-deficient mice | Rescue of the lymphoproliferative syndrome in neonatal mice | 95 |
| *Transplantation* | | | | |
| GVHD | $T_{Reg}$ cells | Mice having received an allogeneic BMT | Inhibition of GVH lethality | 96 |
| | $T_{Reg}$ cells | Mice having received an allogeneic BMT | Delay and prevention | 35 |
| | Donor $T_{Reg}$ cells | Mice having received an allogeneic BMT | Inhibition of GVH lethality | 36 |
| | Alloantigen-specific $T_R1$ cells | Mice having received an allogeneic BMT | Inhibition of GVH lethality | 38 |
| Graft rejection | $T_{Reg}$ cells expanded *in vivo* | Mice having received an allogeneic islet-cell transplant | Prevention of allograft rejection | 39 |
| | $T_{Reg}$ cells expanded *ex vivo* with rapamycin | Mice having received an allogeneic islet-cell transplant | Prevention of allograft rejection | 41 |
| | $T_R1$ cells induced *in vivo* | Mice having received an allogeneic islet-cell transplant | Prevention of allograft rejection | 42 |
| | TCR-transgenic HA-specific $T_{Reg}$ cells | Mice having received an allogeneic skin transplant (HA expressing) | Prolonged survival of established graft | 40 |

# TERAPIA CELULAR EN ENFERMEDADES AUTOINMUNITARIAS

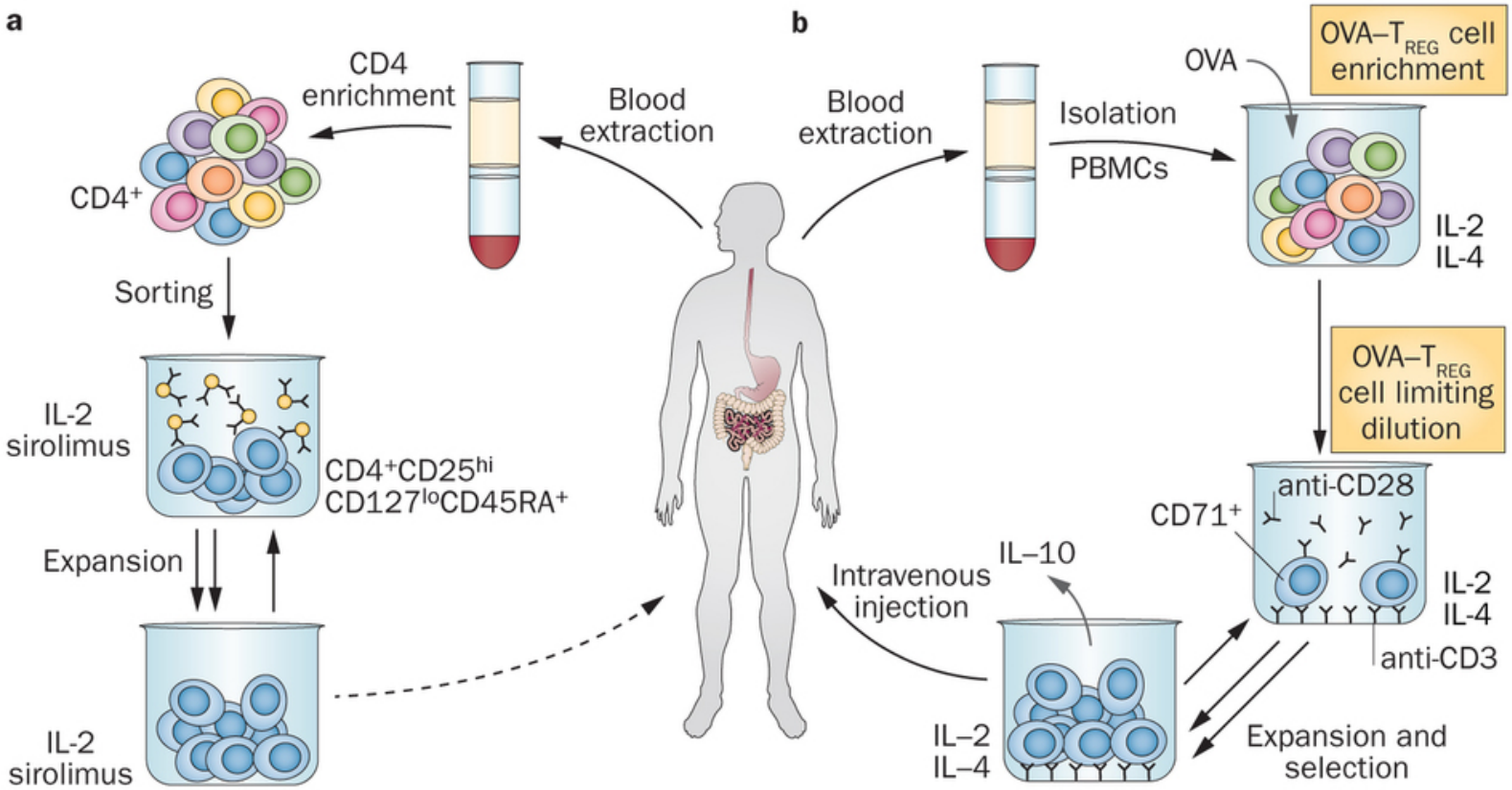


# ThRIL;A 'first-in-human' study, evaluating the safety, tolerability with an investigation into the efficacy of Tregs in liver transplant recipients

2014

Lead Research Organisation: King's College London

Department Name: Transplantation Immunology & Mucosal Bio



# ENSAYOS CLINICOS EN MARCHA

| Clinical trial number | Investigators | Setting | Patients recruited | Isolation | Treg doses | Study overview and results | Reference |
|---|---|---|---|---|---|---|---|
| N/A | Trzonkowski et al. | GVHD adult | 2 | FACS: $CD4^+CD25^+CD127^-$ | $1 \times 10^5$ to $3 \times 10^6$/kg | The first patient had chronic GvHD 2 years post BMT. After receiving $0.1 \times 10^6$/kg FACS purified *ex vivo* expanded Tregs from the donor, the patient was successfully withdrawn from immunosuppression without evidence of recurrence. The second patient had acute GvHD at 1-month post transplantation, treated with several infusions of expanded donor Tregs. Despite the initial and transitory improvement, the disease progressed and ultimately resulted in the patient's death | (58) |
| NCT00602693 | Brunstein, McMillan, Blazar (2010) | GvHD adult | 23 | CliniMACS: $CD25^+$ | 0.1, 0.3, 1, and $3 \times 10^6$/kg | Tregs were isolated from a third party UCB graft and expanded polyclonally with anti-CD3/CD28 coated beads and recombinant IL-2 over a period of 18 days. Patients received expanded Tregs at doses ranging from $1 \times 10^5$/kg to $30 \times 10^5$/kg. Targeted Treg dose was only achieved in 74% of cases. Compared with the 108 historical controls, there was a reduced incidence of grades II–IV acute GvHD (from 61–43%; $p = 0.05$), although the overall incidence of GvHD was not significantly different. | (56) |
| N/A | Di Ianni et al. | GvHD adult | 28 | CliniMACS: $CD4^+CD25^+$ | $2–4 \times 10^6$/kg | Patients received donor Tregs without *ex vivo* expansion and donor effector T cells (Teff) without any other adjuvant immunosuppression. Different dose regimens were used, ranging from $5 \times 10^5$/kg Teffs with $2 \times 10^6$/kg Tregs to $2 \times 10^6$/kg Teffs with $4 \times 10^6$/kg Tregs. As two patients receiving the latter regimen developed acute GvHD, compared with none of the other patients, the dose of $1 \times 10^6$/kg Teffs with $2 \times 10^6$/kg Tregs was reported to be safe. Patients receiving Tregs demonstrated accelerated immune reconstitution, reduced CMV reactivation, and a lower incidence of tumor relapse and GvHD when compared to historical controls. Disappointing patient survival was reported with only 13 out of the 26 patients surviving | (57) |
| N/A | Marek-Trzonkowska et al. | Type-I diabetes children | 12 | FACS: $CD4^+CD25^+CD127^-$ | $10–20 \times 10^6$/kg | One year follow-up of 12 children with Type-I diabetes, treated with autologous-expanded *ex vivo* Tregs. Patients received either a single or double Treg infusion up to a total dose of $30 \times 10^6$/kg. The data supported the safety of the infused Tregs, with 8/12 treated patients requiring lower requirements of insulin, with two children completely insulin independent at 1 year | (118) |
| NCT01210664 | Bluestone et al. | Type-I diabetes adult | 14 | FACS: $CD4^+CD25^+CD127^-$ | $5 \times 10^6–2.6 \times 10^9$/kg | Infusion of 14 type-I diabetic patients with *ex vivo*-expanded Tregs (FACS purified and two rounds of anti-CD3/anti-CD28 stimulation). The first cohort of patients received $0.05 \times 10^8$ cells, the second: $0.4 \times 10^8$ cells, the third: $3.2 \times 10^8$ cells, and the fourth: $2.6 \times 10^9$ cells. Enrolment and infusion is complete | Bluestone, in preparation |

*UCB, umbilical cord blood; GVHD, graft versus host disease; BMT, bone marrow transplantation.*

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Santiago de Compostela

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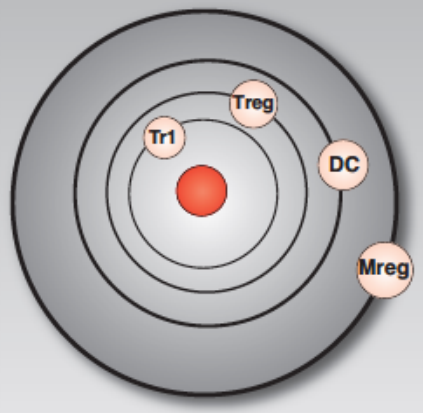
# ONE STUDY


## A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation




ONE FOCUS OUTCOME DESIGN ALLIANCE

**ACADEMIC INSTITUTES:**

University of Regensburg
University Hospital Regensburg, Germany
www.uniklinikum-regensburg.de

King's College London, UK
www.kcl.ac.uk

University of Oxford, UK
ww.ox.ac.uk

Charité, Germany
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Fondazione Centro San Raffaele, Italy
www.sanraffaele.org

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**MANAGEMENT**

ALTA Srlu, Italy
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The central focus of the ONE Study cooperative work programme is to:

- produce and manufacture distinct populations of haematopoietic immunoregulatory cells
- comparatively study the immunosuppressive characteristics of these regulatory cell types
- test these cell therapy products side-by-side in a clinical trial in living donor renal transplant recipients

WWW.ONESTUDY.ORG

SEVENTH FRAMEWORK PROGRAMME

EU contribution:
10,836,201Euro
Total Costs:
14,833,854 Euro

EUROPEAN COMMISSION

SERVIZO GALEGO de SAÚDE | Xerencia de Xestión Integrada de Santiago de Compostela Santiago de Compostela

Science

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IMMUNOLOGY

# Regulatory T Cells Get Their Chance to Shine

ONE STUDY


## Regulatory T Cells Enter the Clinic

| Target | Source of T regs | Type of trial | Status |
|---|---|---|---|
| Graft-versus-host disease (GVHD) | Cord blood | Phase I | Completed |
| GVHD | Peripheral blood | Phase I | Completed |
| Type 1 diabetes | Autologous | Phase I | Recruiting patients |
| Kidney transplant rejection | Autologous | Phase I | Received funding |
| GVHD | Induced in patient by interleukin-2 | Phase II | Recruiting patients |

ONE STUDY

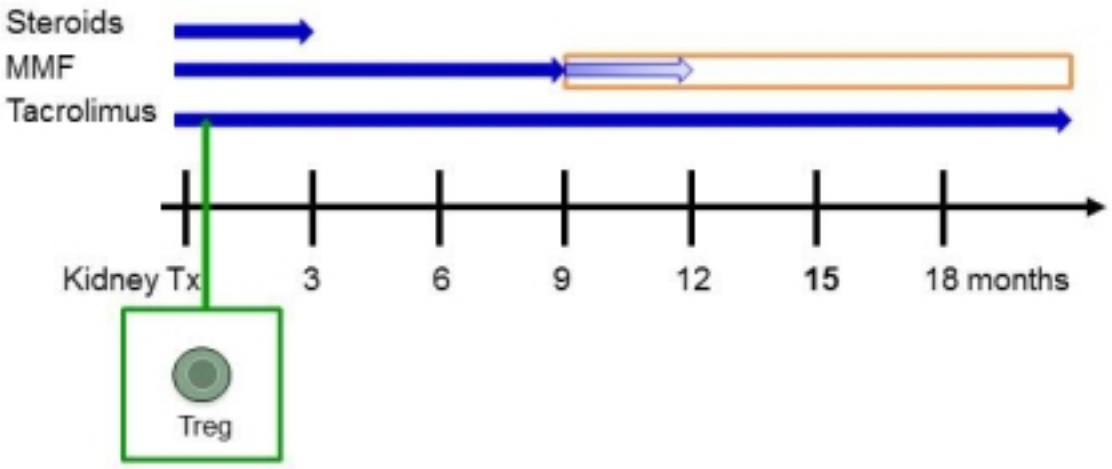
*"It's a terrific, exciting time in the field."*

—ALEXANDER RUDENSKY, MEMORIAL SLOAN-KETTERING CANCER CENTER

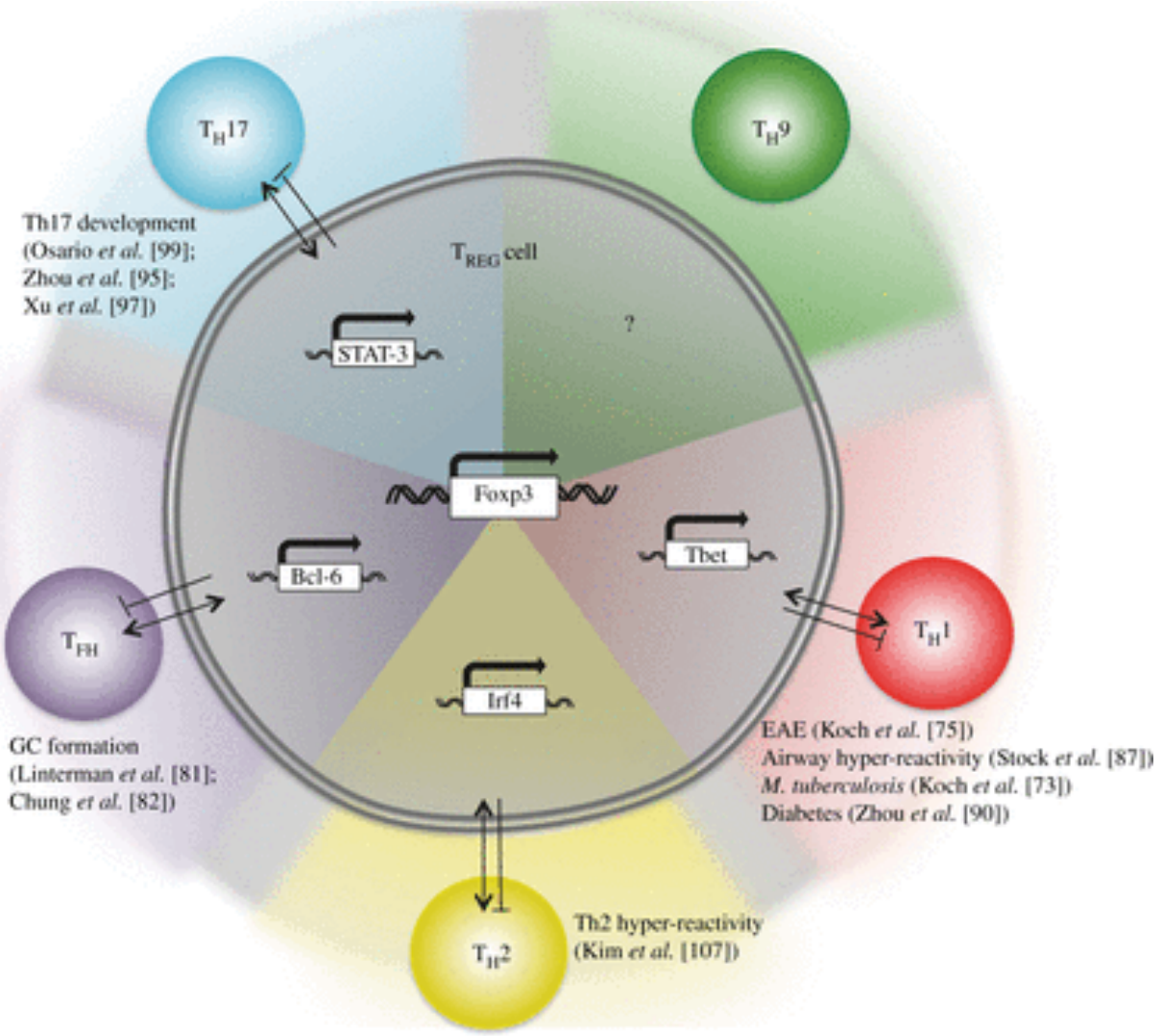
*"Yes, we are going to see these cells in the clinic."*

—ANDREW BUSHELL, UNIVERSITY OF OXFORD

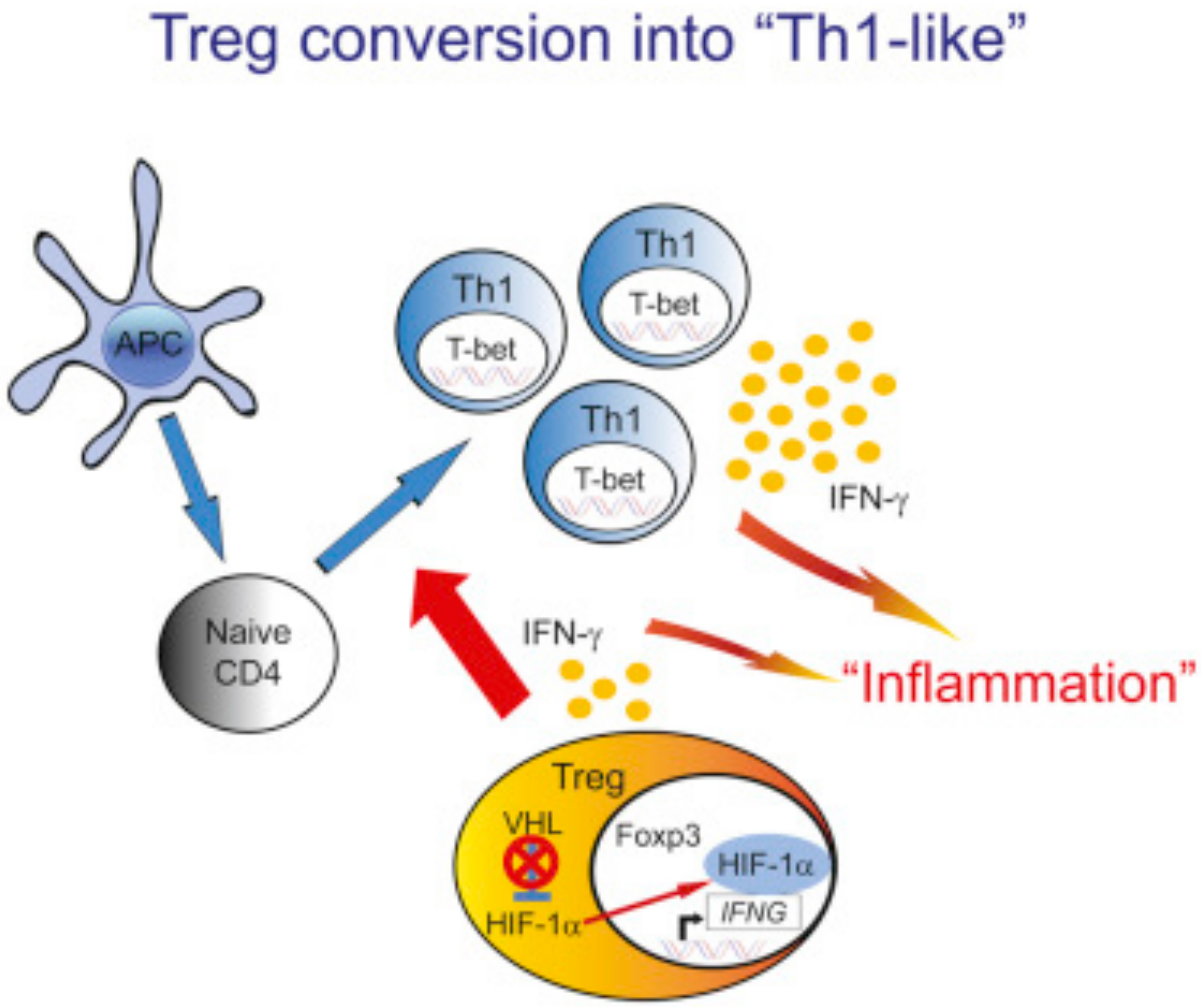
## Figure 1. Immunosuppression in Treg cell therapy trial



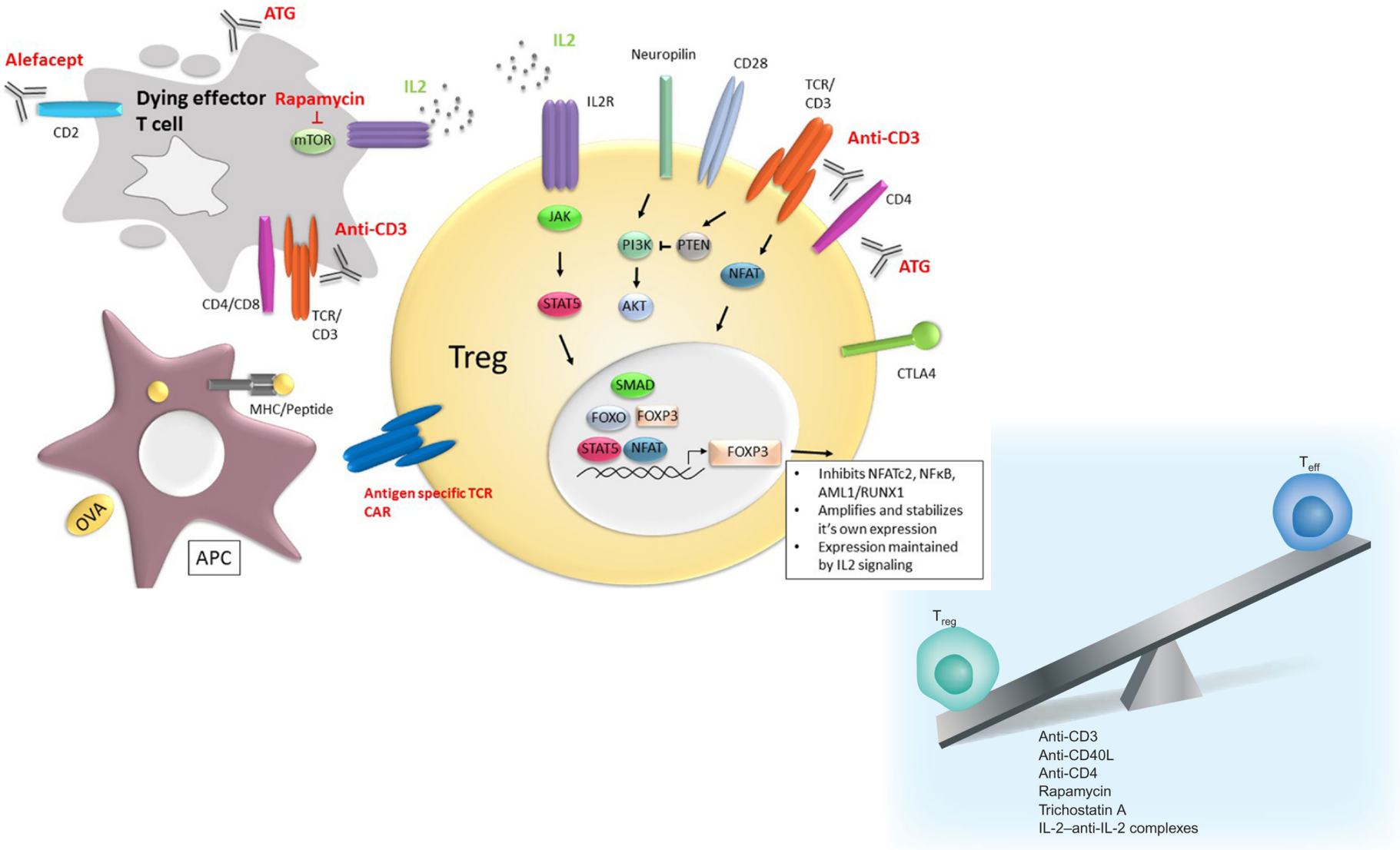
# PLASTICIDAD DE LAS $T_{REG}$ : PRINCIPAL INCOVENIENTE



En determinadas condiciones de inflamación las células $T_{REG}$ *pueden convertirse en células Th efectoras*



# Las TERAPIAS INMUNOSUPRESORAS influencian el desarrollo de las células $T_{REG}$



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Trends in Immunology

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Review

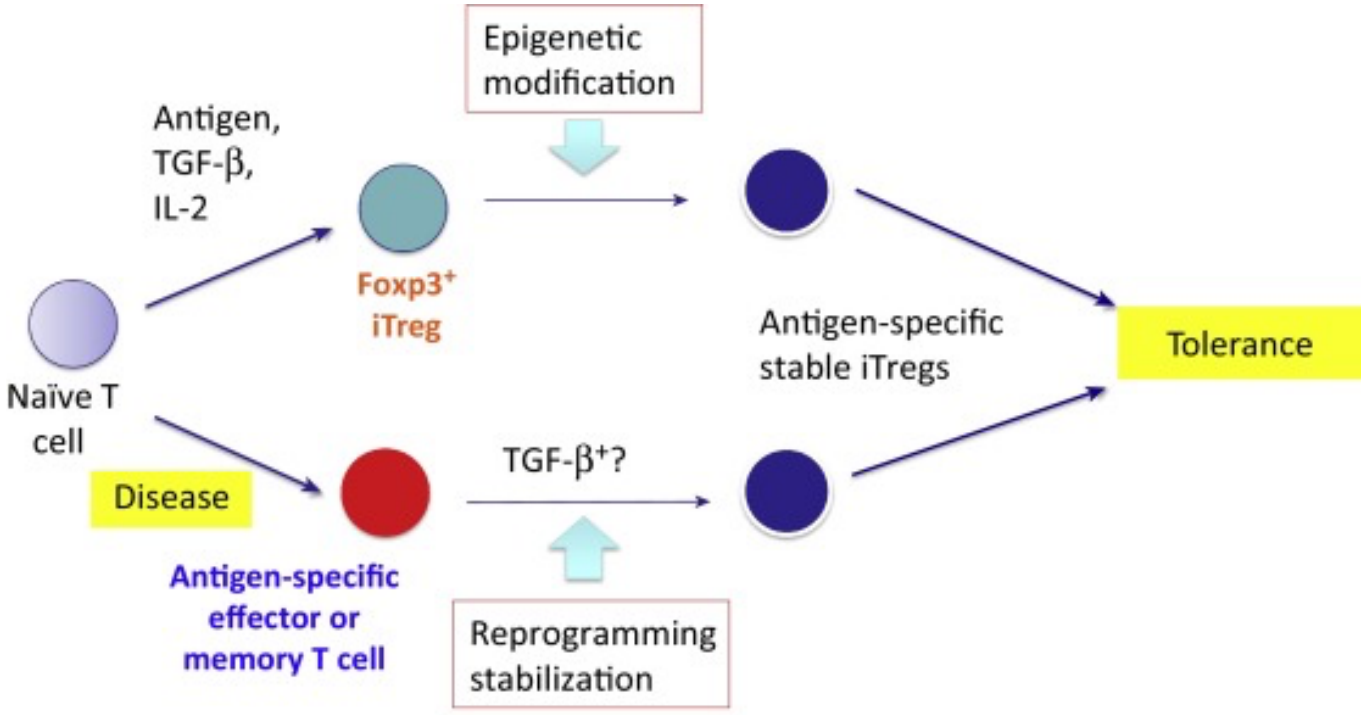
Switch to Standard View

# Induced Regulatory T Cells: Their Development, Stability, and Applications

Mitsuhiro Kanamori, Hiroko Nakatsukasa, Masahiro Okada, Qianjin Lu, Akihiko Yoshimura

DOI: http://dx.doi.org/10.1016/j.it.2016.08.012 | CrossMark

Actualmente se trabaja en la REPROGRAMACION EPIGENETICA de las células $T_{REG}$ para conseguir su ESTABILIZACION



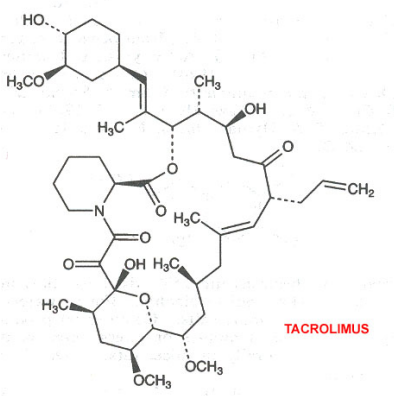
## CONCLUSIONES:

- TOLERANCIA INMUNOLOGICA: el comienzo de una nueva época

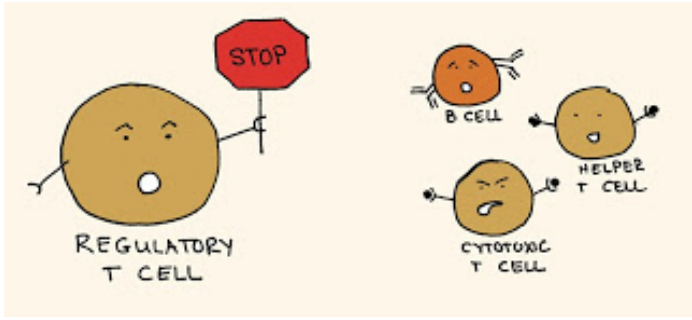
- Los ensayos clínicos ahora en marcha permitirán conocer si esta Terapia Adoptiva de células $T_{REG}$ es realidad o solo promesa

- Búsqueda de nuevos biomarcadores que permitan predecir el éxito en la inducción de la tolerancia inmunológica

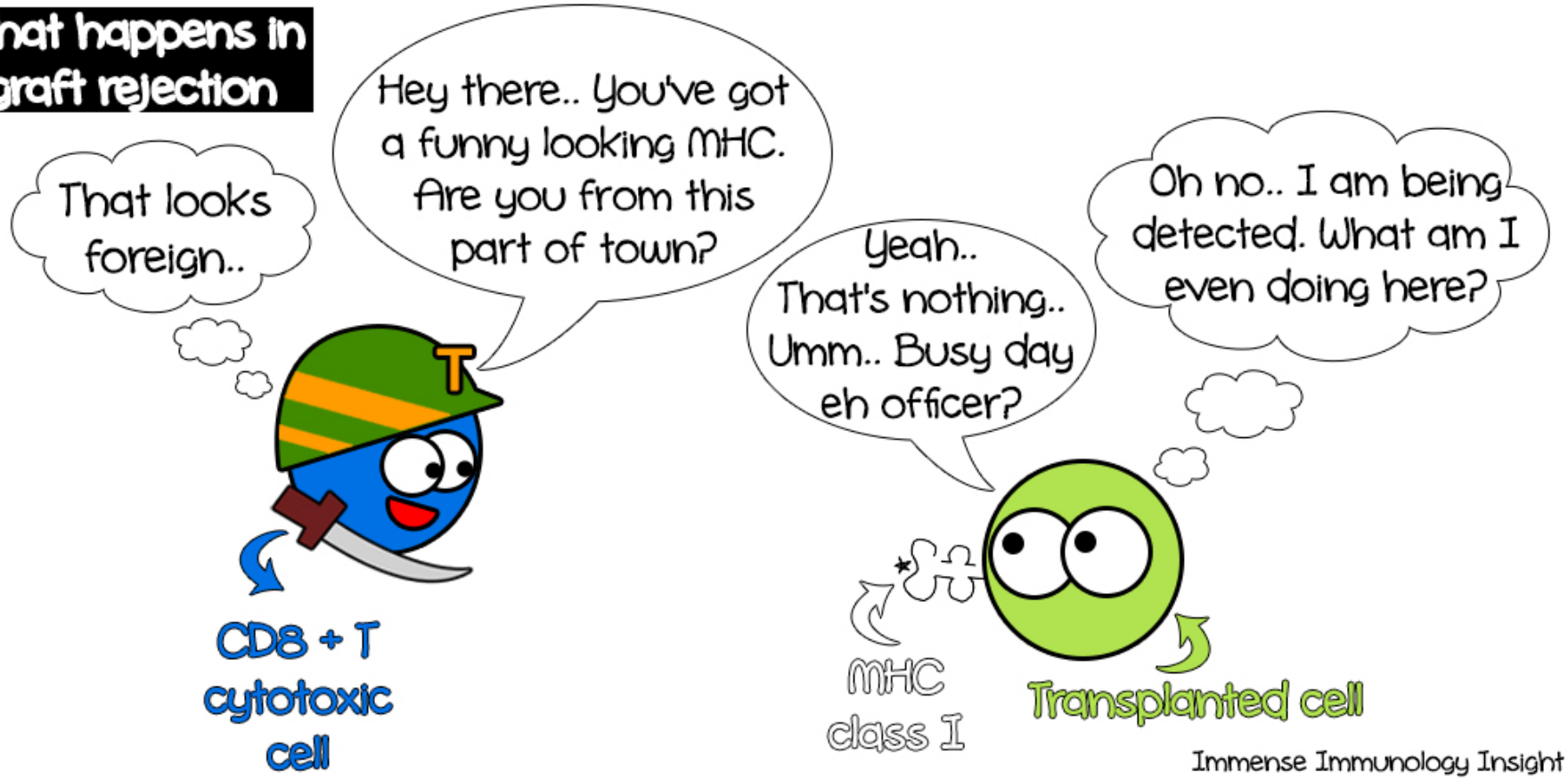
- Objetivo: Minimización de la terapia inmunosupresora farmacológica actual







# What happens in graft rejection




Immense Immunology Insight

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