

Modulación de la respuesta inmune

Nuevos abordajes

Jordi Cano Ochando

30 Septiembre, 2018

THE LANCET 1961 **IMMUNOLOGICAL FUNCTION** J. F. A. P. Miller
OF THE THYMUS



Three-month-old mouse thymectomized at birth and grafted
at 5 weeks with skin from C3H (dark hair) and Wistar rat (white hair)

Absence of Thymus in a Mouse Mutant

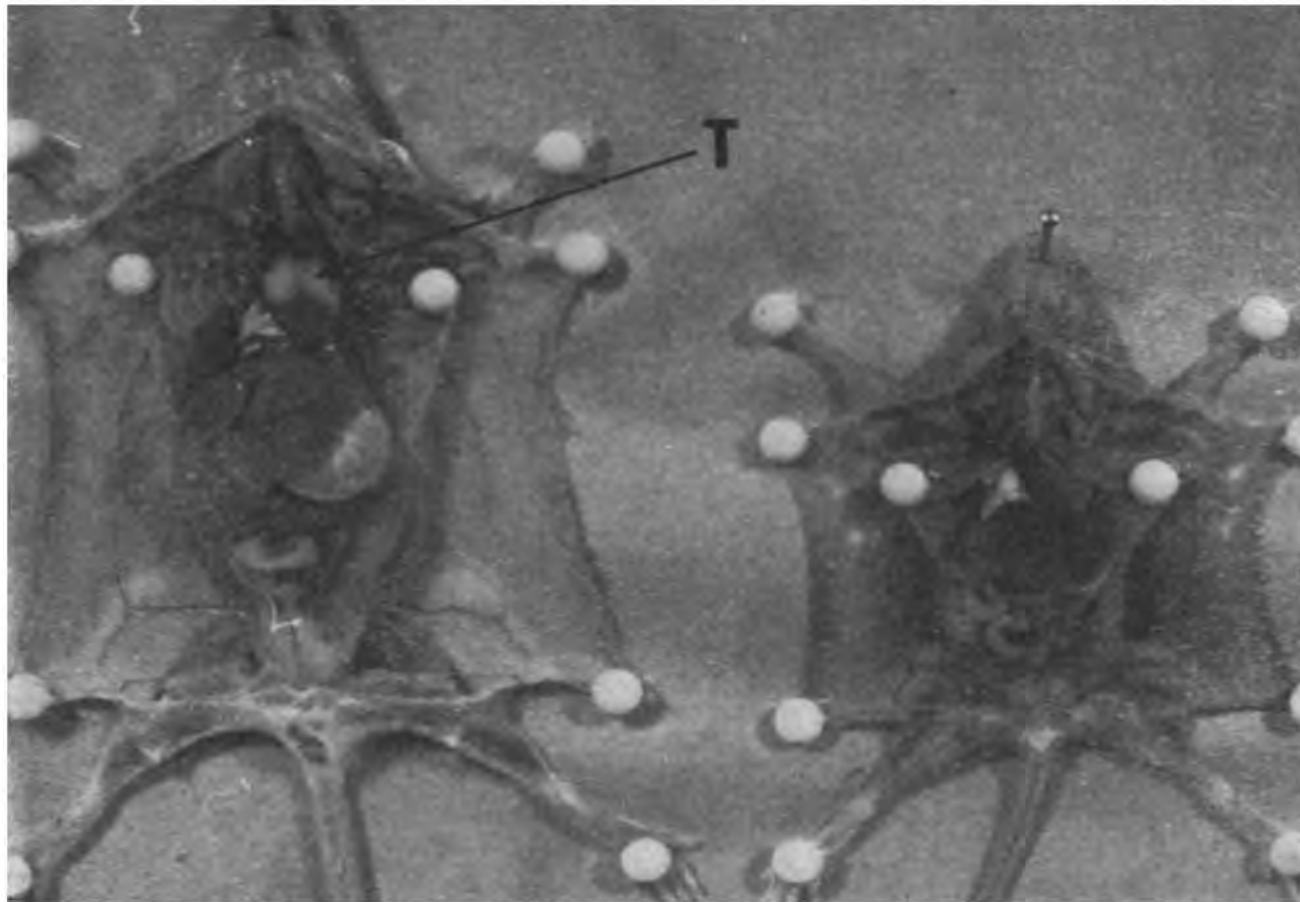


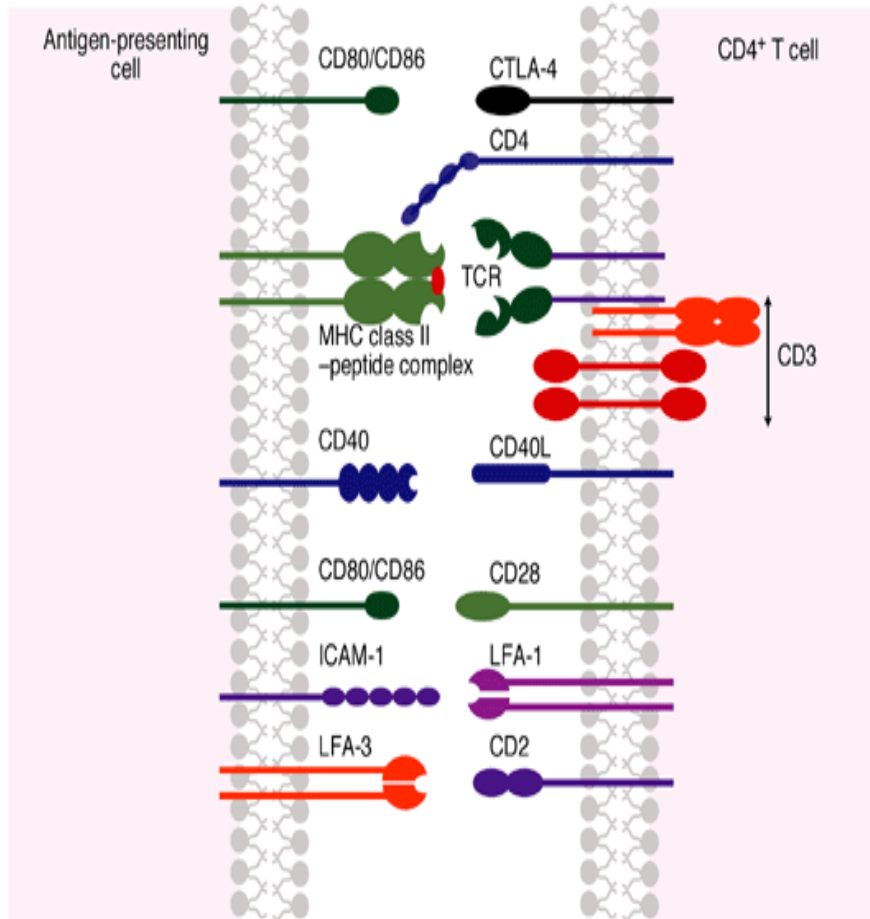
Fig. 1. Dissected normal (left) and homozygote nude (right) sibs. Note the absence of the thymus (T) from the latter.

Observations on the Immunobiology of 'Nude' Mice



FIG. 1. Two *nu nu* mice of the same age (6 weeks), 7 days after the grafting of a piece of skin from a donor of the inbred line, A. Left: 'Nude' mouse that had not been pretreated in any way retains the graft. Right: 'Nude' mouse that had received, when 1 day old, a thymus implant from a $+/?$ littermate, rejected the graft, wound is healing.

Preventing 1, 2, and 3 prolongs transplant survival



Some of the cell-surface molecules involved in T-cell activation that are potential targets for immunotherapy

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press

1. CD4, Cobbold Nature 1984
2. CD3, Hirsch J Immunol 1989
3. LFA-1 + ICAM-1, Isobe Science 1992
4. CD2, Chavin Transplantation 1992
5. CD2 + CD3, Chavin J Immunol 1993
6. CTLA4-Ig, Lin J Exp Med 1993
7. CD4 + DST, Scully Eur J Immunol 1994
8. Non-depleting CD3 Alegre J Immunol 1995
9. CD40L, Parker PNAS 1995
10. CD80, Hancock PNAS 1996
11. CD86, Hancock PNAS 1996
12. CD40L + CD28, Larsen Nature 1996
13. CD40, Fishbein Transplantation 20002
14. LFA3-Ig Weaver Nat. Medicine 2009

Monocytes Initiate Organ Rejection

The Journal of Immunology, 2009.

An Innate Response to Allogeneic Nonself Mediated by Monocytes¹

Daniel Zecher,* Nico van Rooijen,[†] David M. Rothstein,*[‡] Warren D. Shlomchik,[‡] and Fadi G. Lakkis^{2*}

J Clin Invest. 2014

Non-self recognition by monocytes initiates allograft rejection

Martin H. Oberbarnscheidt,^{1,2} Qiang Zeng,^{1,2} Qi Li,^{1,2} Hehua Dai,^{1,2} Amanda L. Williams,^{1,2} Warren D. Shlomchik,³ David M. Rothstein,^{1,2,4,5} and Fadi G. Lakkis^{1,2,4,5}

Macrophages accumulate in the rejected allograft

0041-1337/83/3505-0458\$02.00/0

TRANSPLANTATION

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Vol. 35, No. 5

Printed in U.S.A

COMPOSITION OF INTERSTITIAL CELLULAR INFILTRATE IDENTIFIED BY MONOCLONAL ANTIBODIES IN RENAL BIOPSIES OF REJECTING HUMAN RENAL ALLOGRAFTS

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Department of Nephrology, Prince Henry's Hospital, Melbourne, Australia

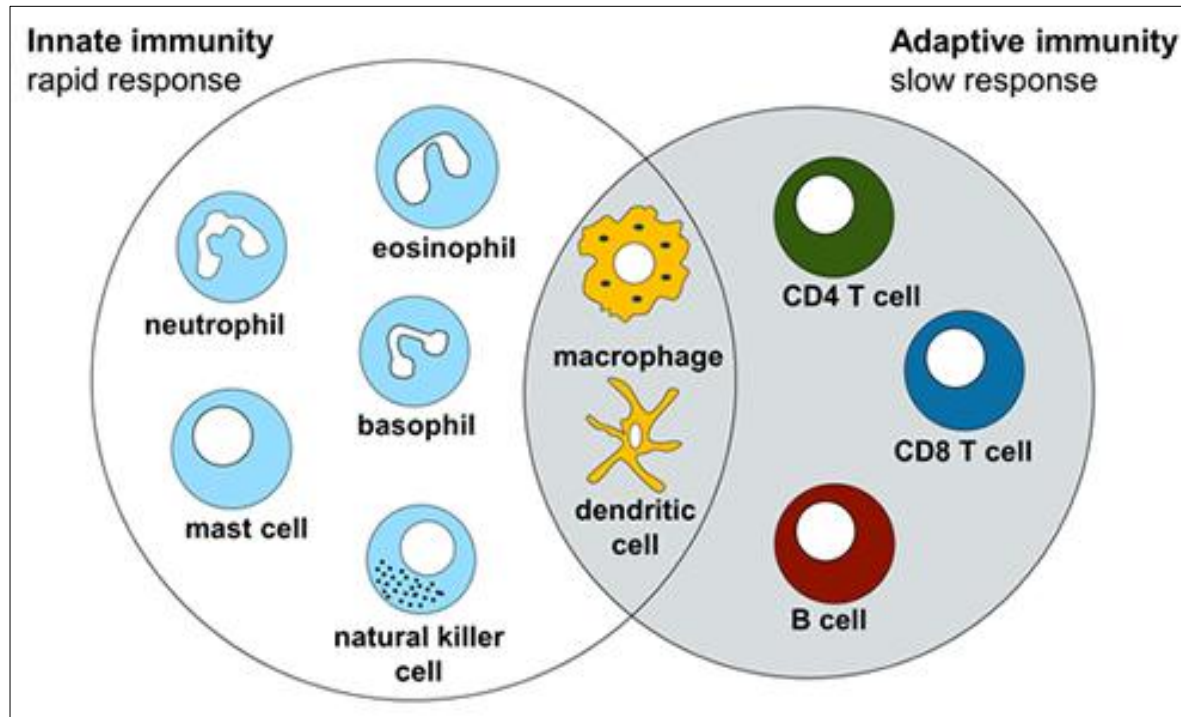
Group	Percentage of T cells			Percentage of macrophages
	Total	Percentage of OKT 4 ^b	Percentage of OKT 8 ^b	
Mild (n = 11)	34 ± 4 ^c	7 ± 3	90 ± 21	52 ± 6
Moderate (n = 7)	42 ± 7	27 ± 12	67 ± 14	38 ± 11
Severe (n = 7)	15 ± 3	14 ± 3	78 ± 12	60 ± 13

SUMARIO

1. Introducción “Inmunidad Entrenada” como mecanismo de rechazo
2. Nanoterapia de inhibición Inmunidad Entrenada en Trasplante

1. Introducción “Inmunidad Entrenada”: Un Nuevo Mecanismo de Rechazo

Sistema Innato vs Sistema Adaptativo



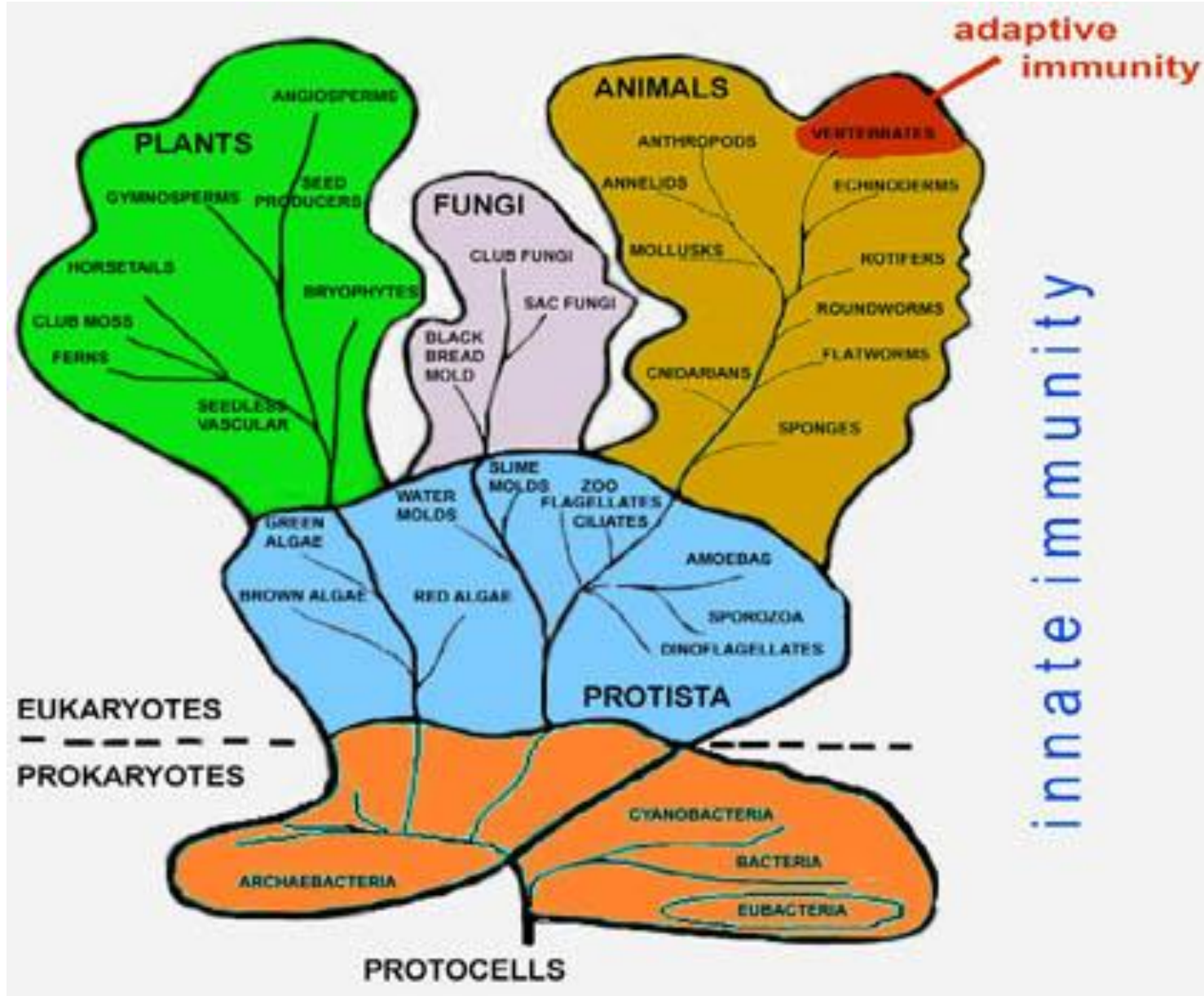
Sistema Innato

- Rápido
- No Especifico
- No tiene memoria

Sistema Adaptativo

- Necesita 10-14 días
- Antígeno específico
- Tiene memoria inmunológica

Vertebrados representan el 5% de las especies animales

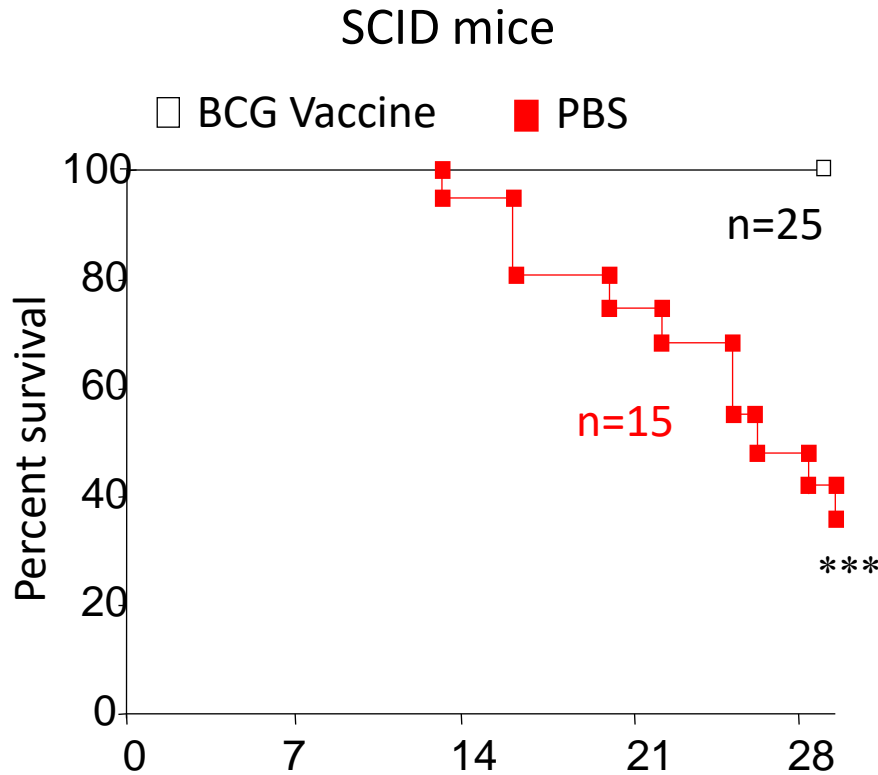


Memoria Inmunológica en Invertebrados y Vertebrados

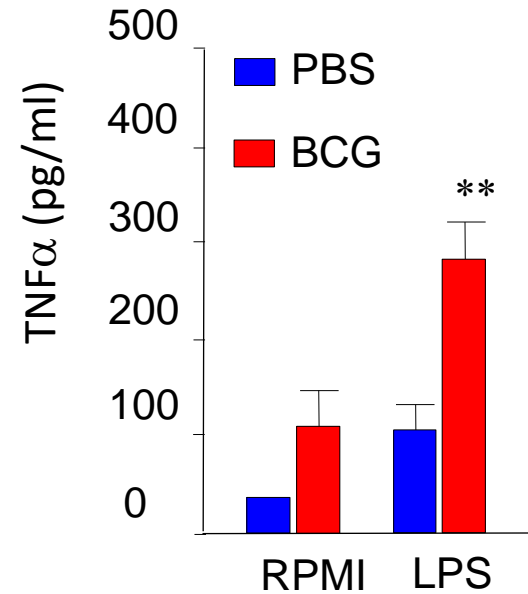
Organism	Experimental Model	Biological Effect	Specificity	References
Plants—Systemic Acquired Resistance				
Large variety of plants	Viruses, bacteria, fungi	Protection against reinfection	Variable	Durrant and Dong, 2004; Sticher et al., 1997
Nonvertebrates				
Mealworm beetle	LPS, or bacterial prechallenge	Protection against secondary infection	No	Moret and Siva-Jothy, 2003
<i>Drosophila</i>	<i>S. pneumoniae</i> prechallenge	Protection against <i>S. pneumoniae</i>	Uncertain	Pham et al., 2007
<i>Anopheles gambiae</i>	<i>Plasmodium</i> prechallenge	Protection against <i>Plasmodium</i>	No	Rodrigues et al., 2010
Vertebrates				
Mice	BCG	Protection against candidiasis	No	Van 't Wout et al., 1992
Mice	<i>Candida</i> vaccination	T/B cell-independent protection	No	Bistoni et al., 1986, 1988
Mice	Murine CMV infection	NK-dependent protection	No	Sun et al., 2009
Humans	BCG	Nonspecific protection to secondary infections	No	Garly et al., 2003

Netea et al: Cell Host and Microbe 2011

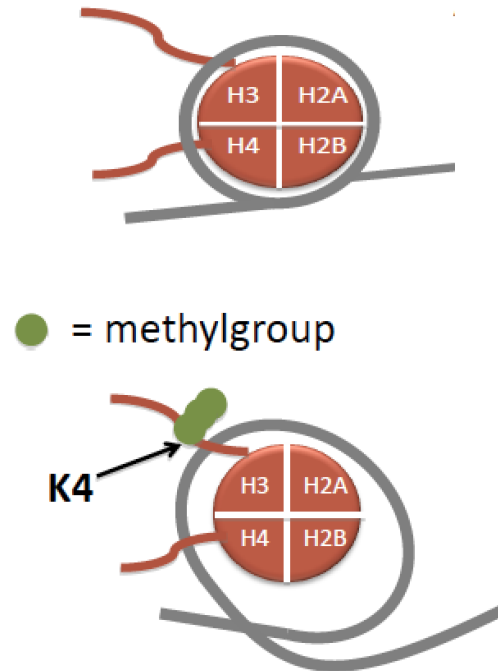
Los Macrófagos Tienen Memoria Inmunológica



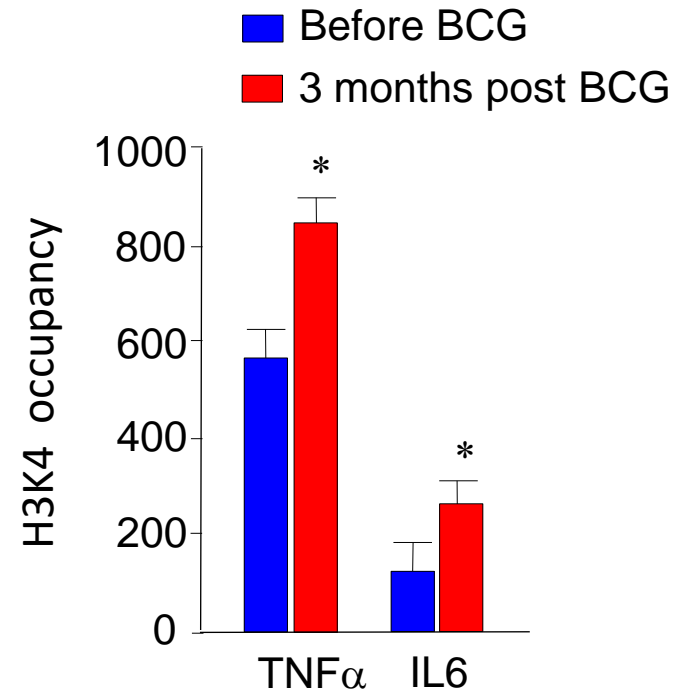
Days post *C. albicans* infection (14 days after vaccination)



Protección de BCG esta asociada a cambios epigenéticos



Trimethylation of histone 3 and lysine 4
(H3K4me3: euchromatin (open))



Conclusiones

1. Introducción “Inmunidad Entrenada”

1.1 Inmunidad entrenada representa una forma de memoria innata

1.2 Inmunidad entrenada induce macrófagos pro-inflamatorios

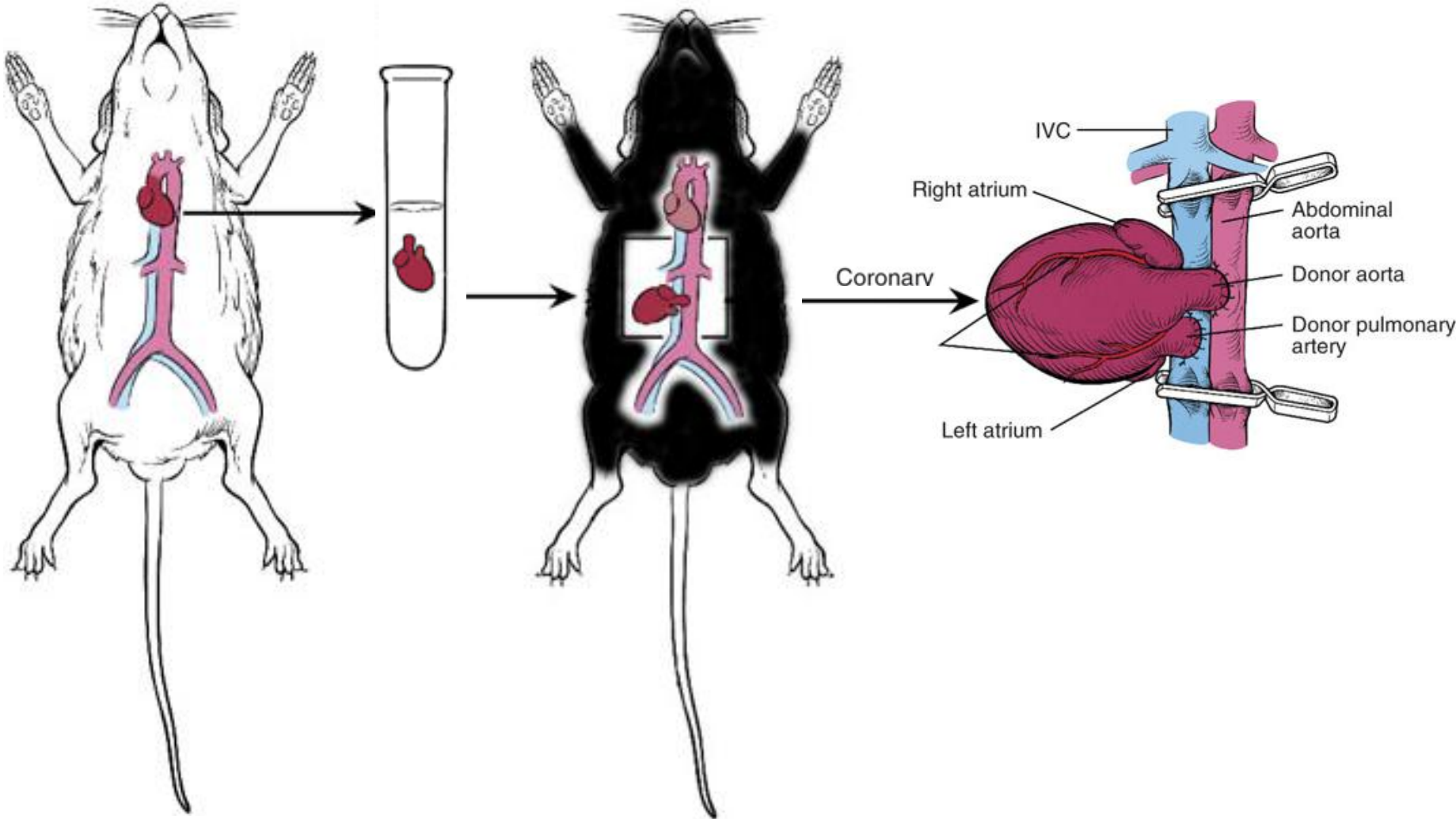
1.3 Inmunidad entrenada está asociada a cambios epigenéticos

Existe Inmunidad Entrenada en Trasplante de Órganos?

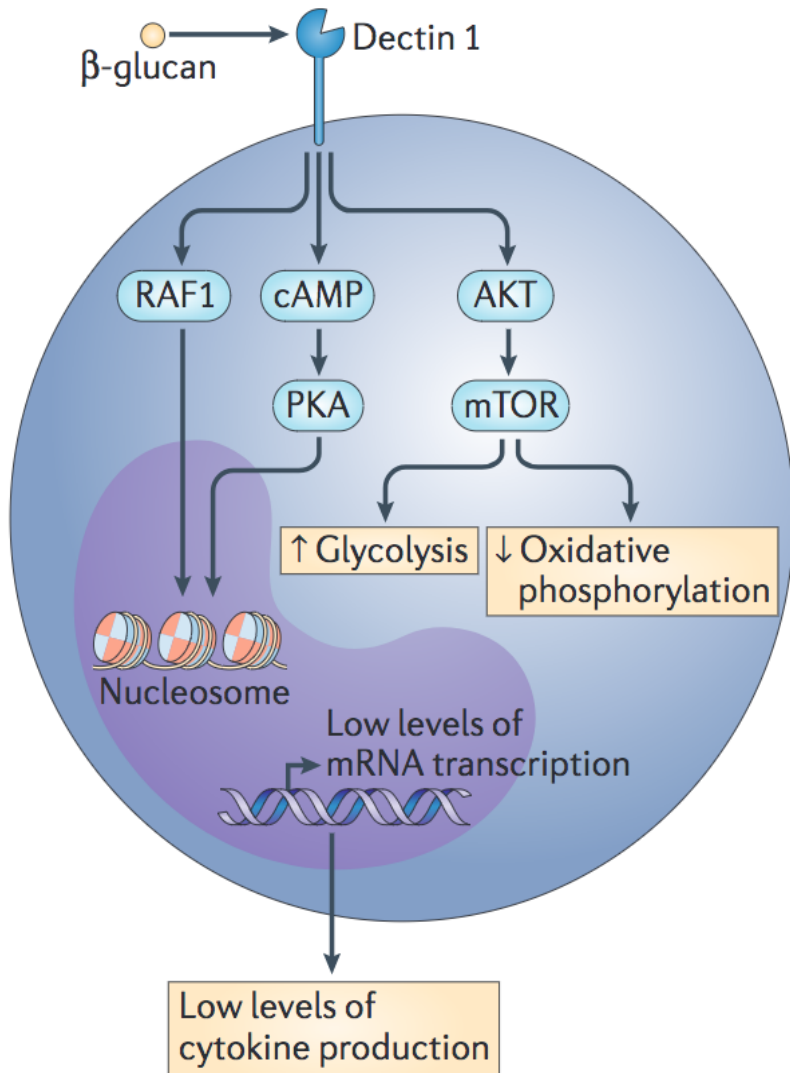
Experimental Heart Transplant Model in mice

BALB/c donor
(H-2d)

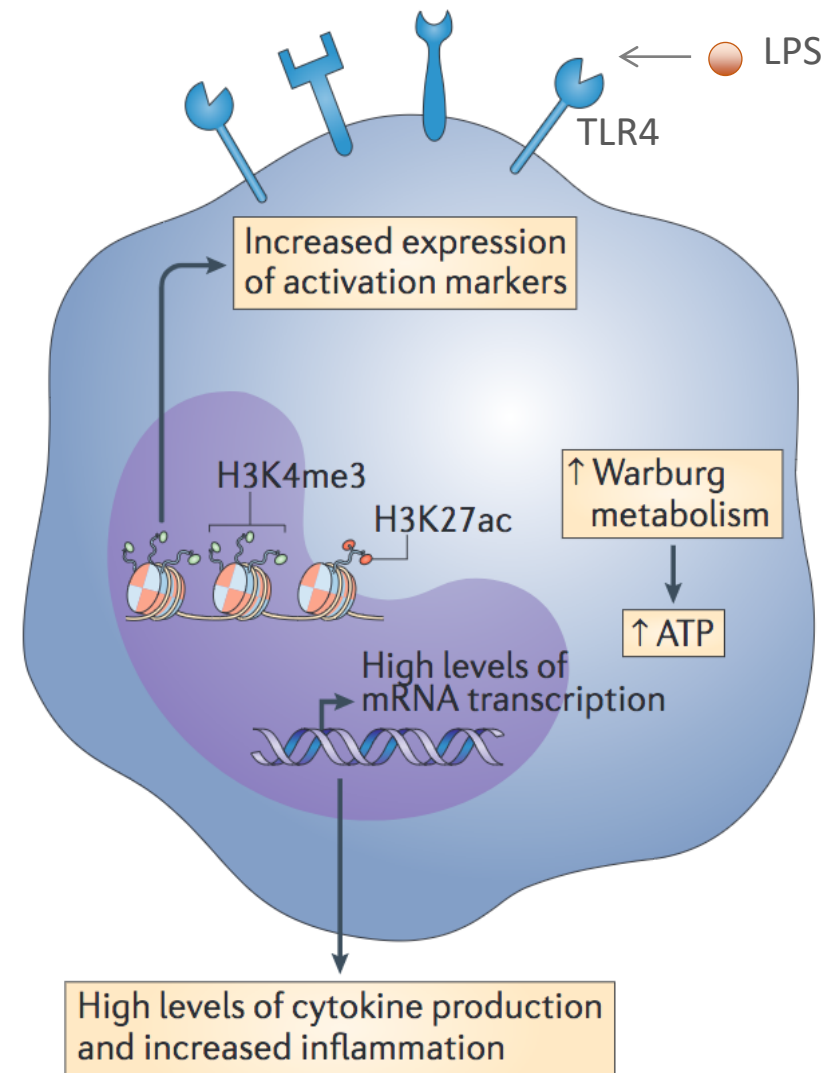
C57BL6 recipient
(H-2b)



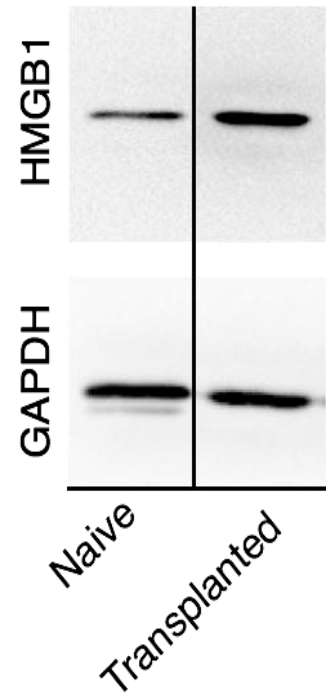
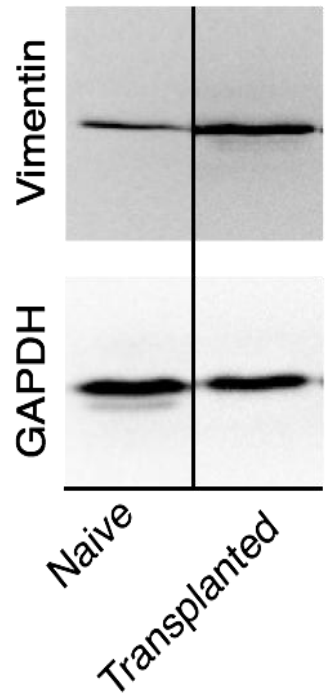
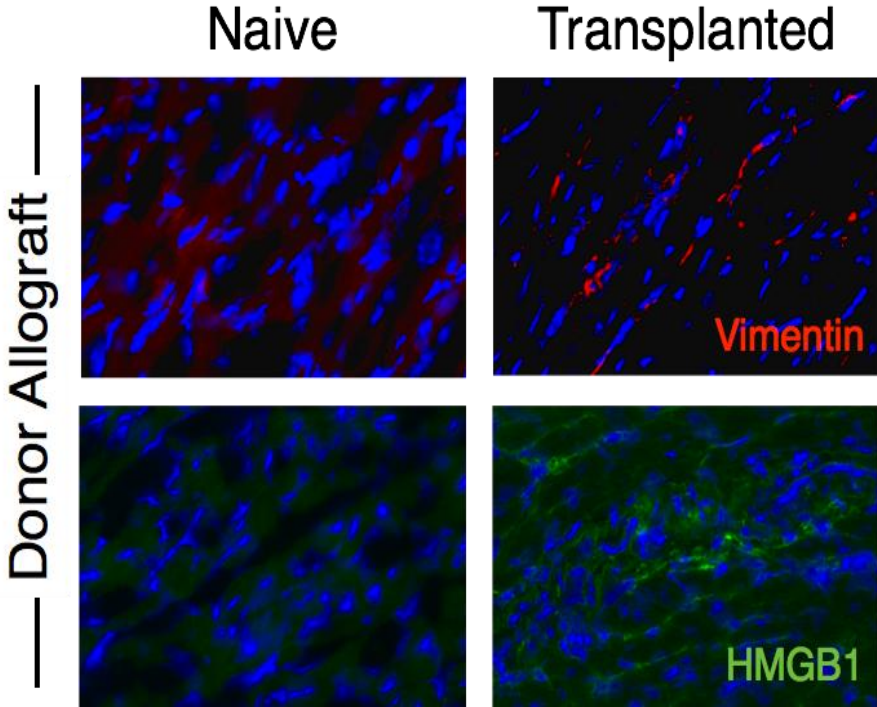
Naive monocyte



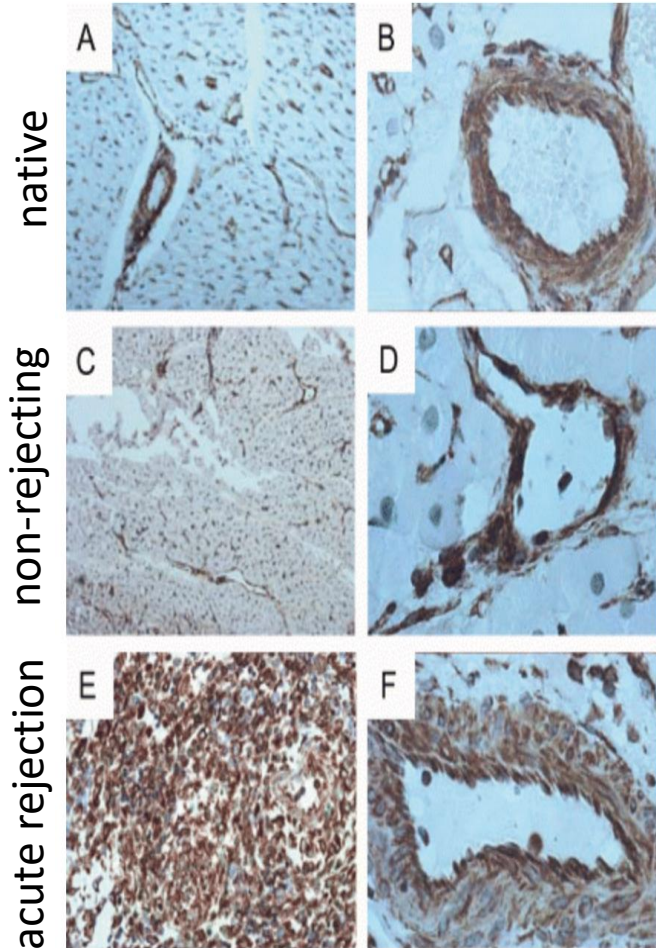
Trained monocyte



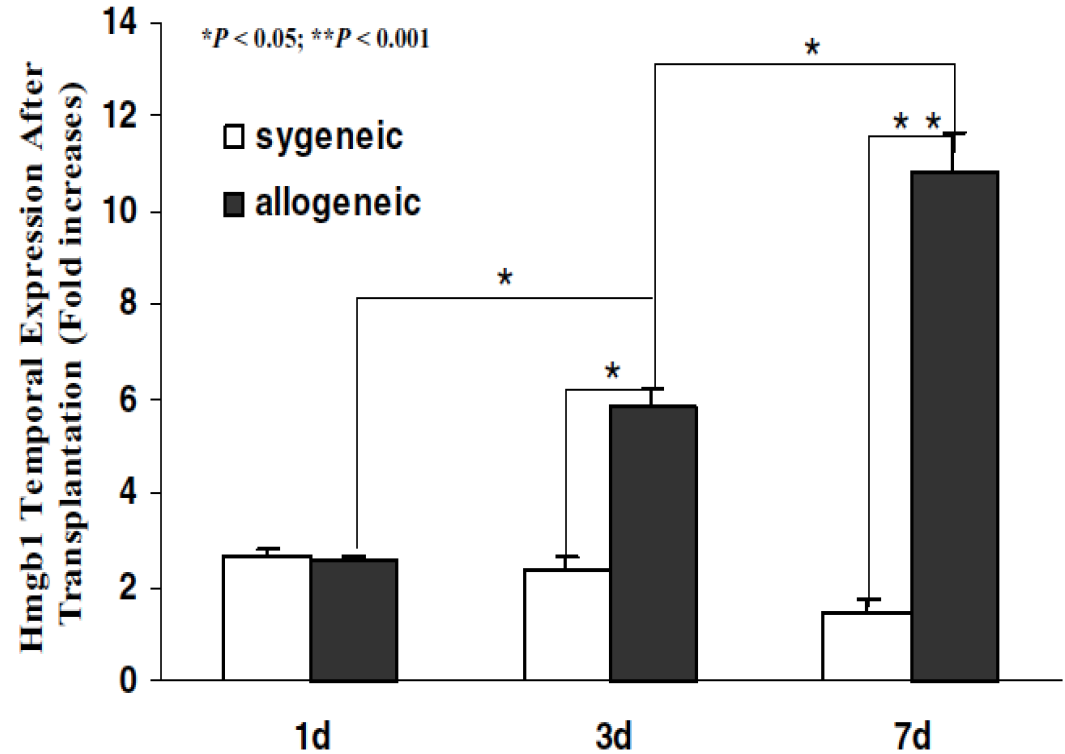
Increased Vimentin/HMGB1 in the transplanted organ



Increased Vimentin/HMGB1 in the transplanted organ

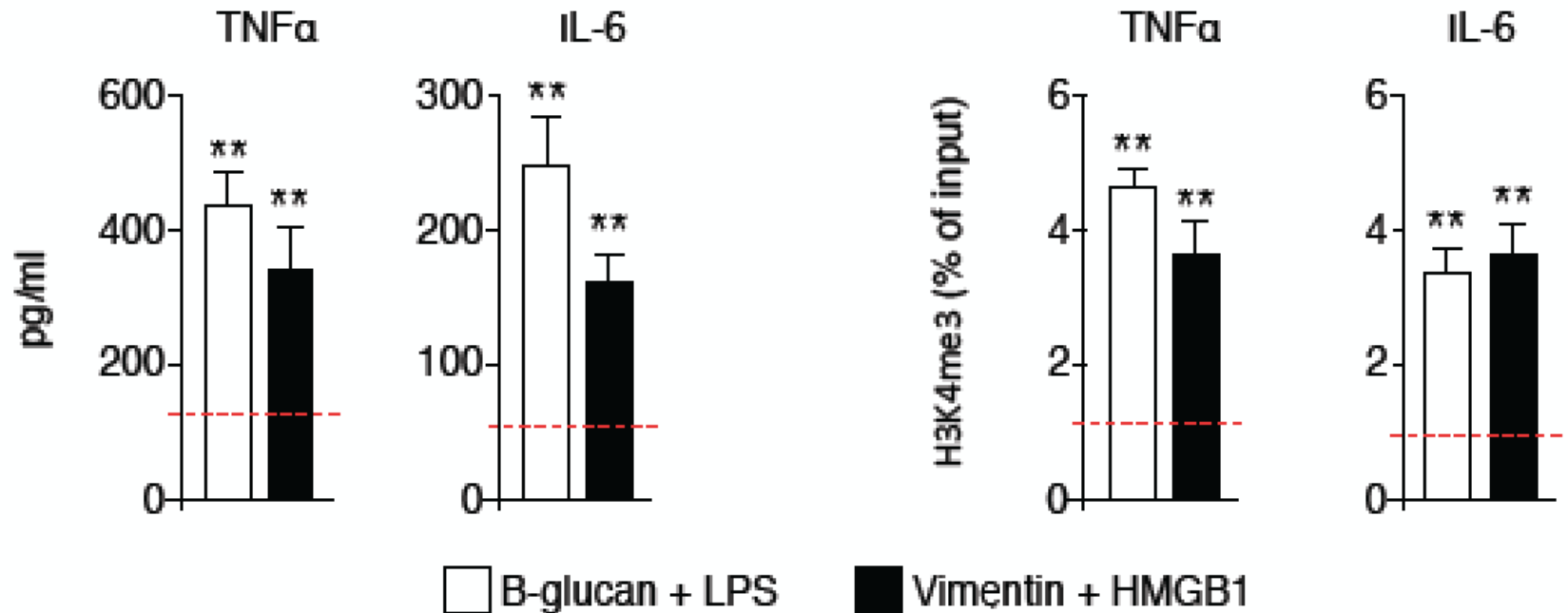
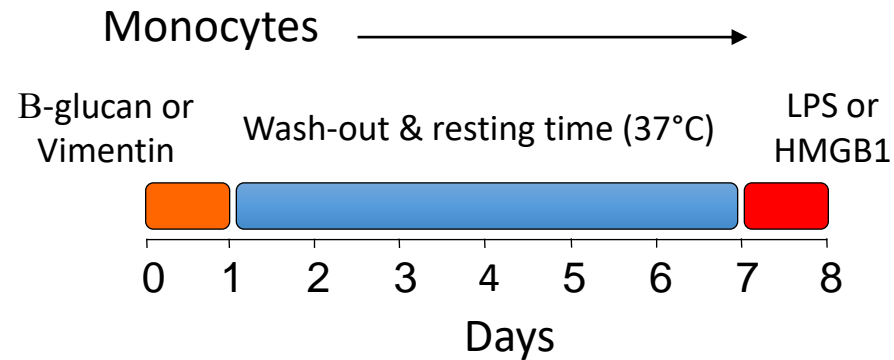


Azimzadeha A et al, AJT 2005

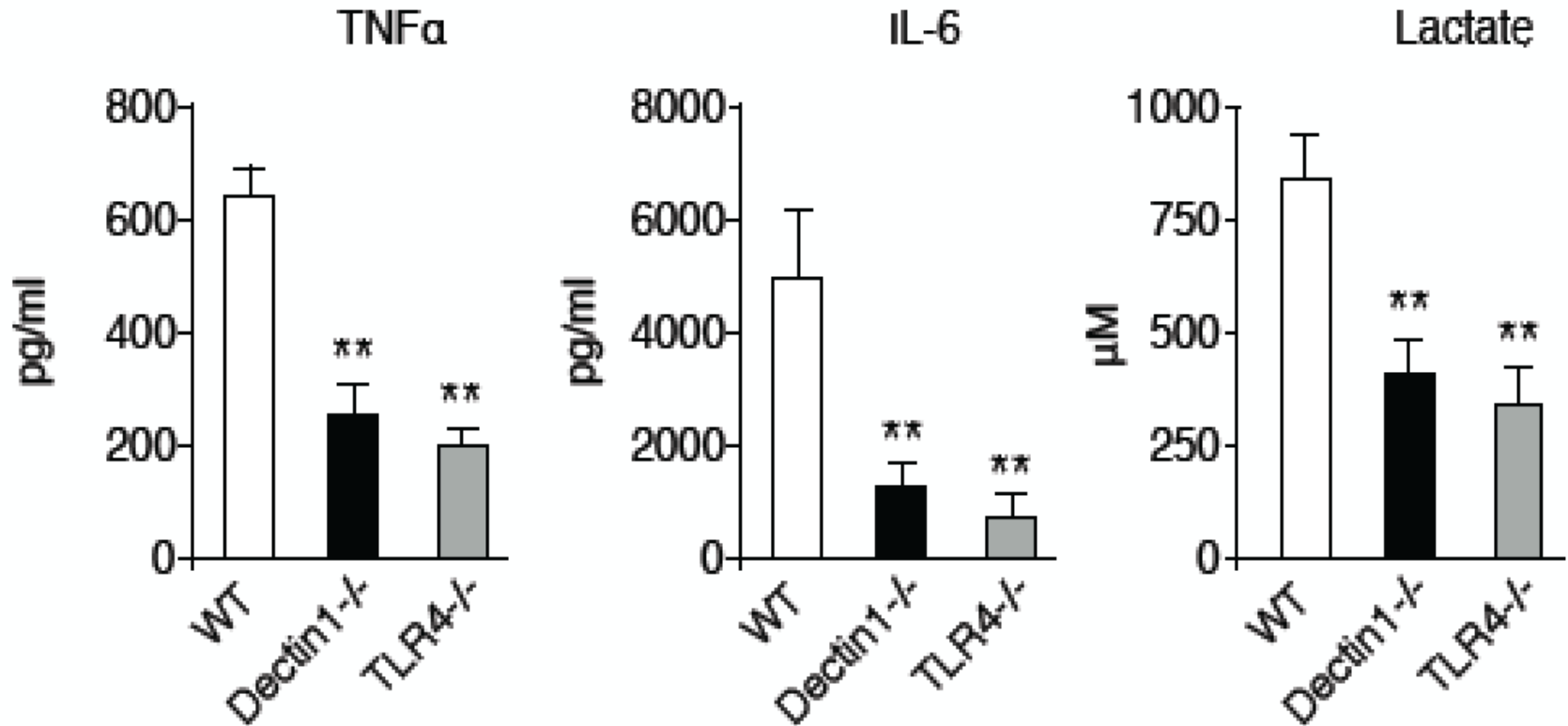


Huang Y et al, AJT 2007

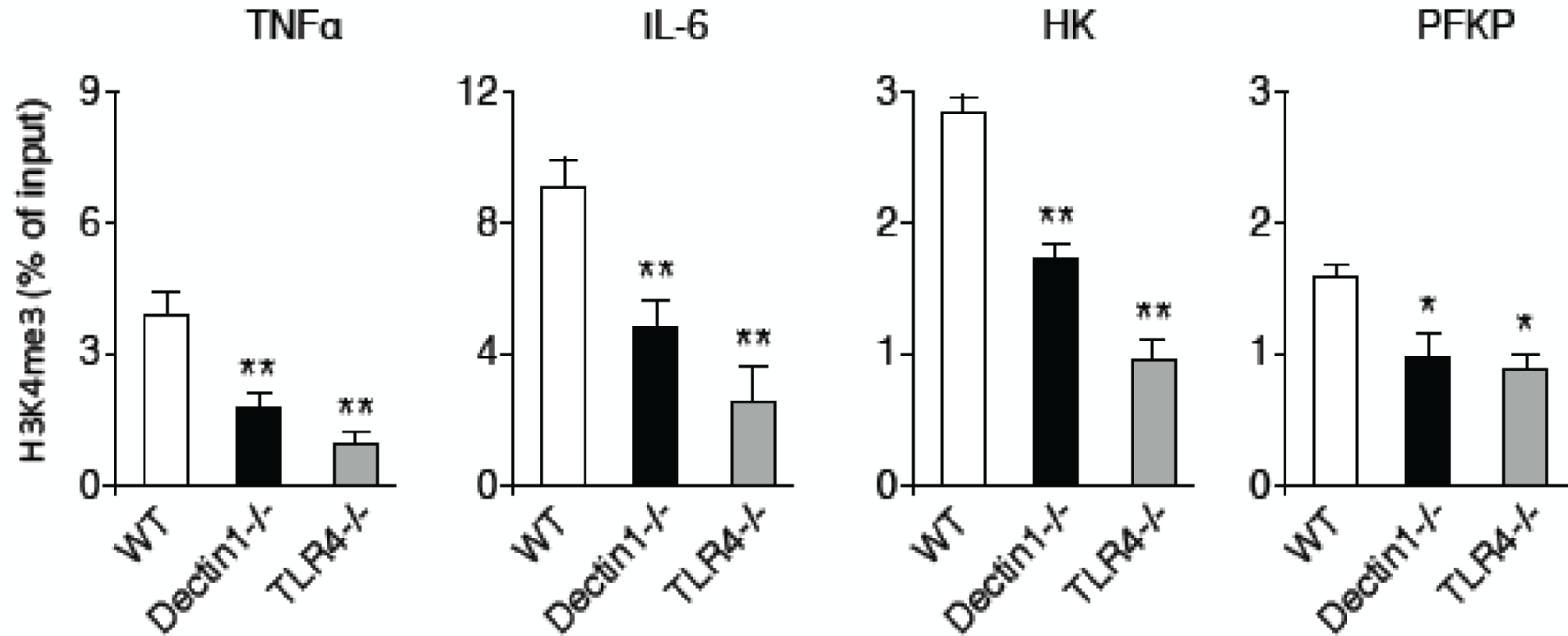
Vimentin/HMGB1 induce Trained Immunity in vitro



Vimentin/HMGB1 contribute to Trained Immunity in vivo



Vimentin/HMGB1 contribute to Trained Immunity in vivo



Conclusiones

1. Los macrófagos en el órgano trasplantado están entrenados

1.1 Macrófagos entrenados cambian su metabolismo (glicólisis)

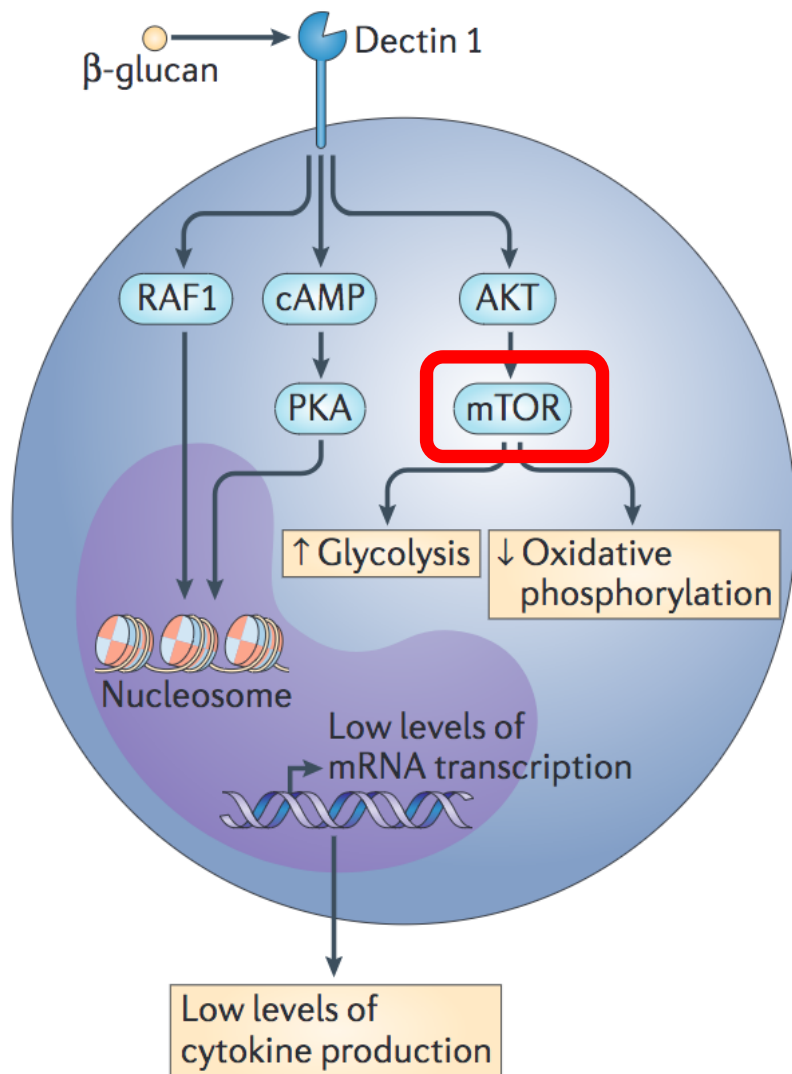
1.2 Macrófagos entrenados presentan cambios epigenéticos

1.3 Macrófagos entrenados producen citoquinas pro-inflamatorias

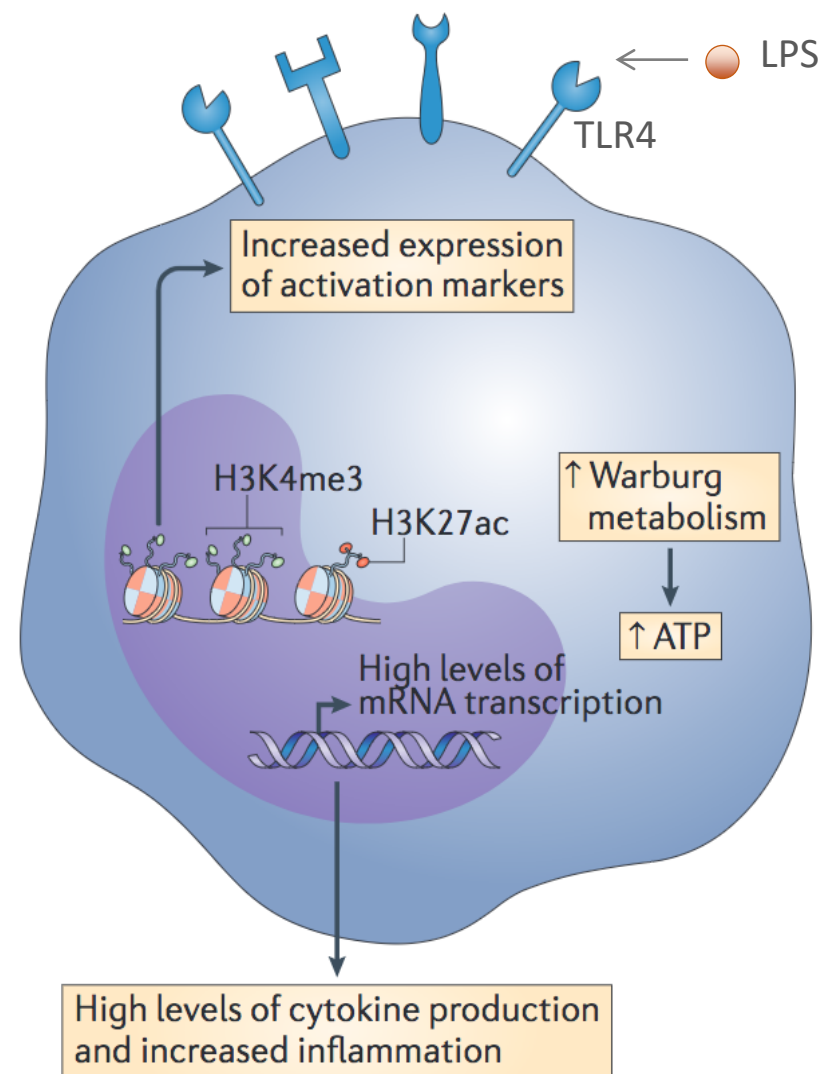
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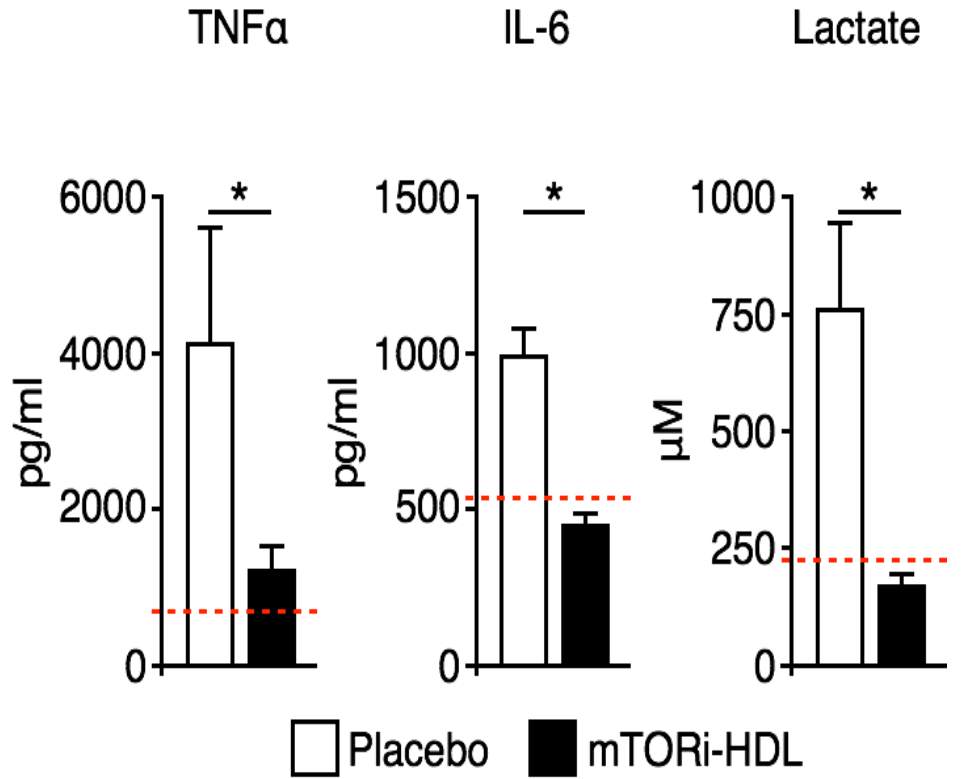
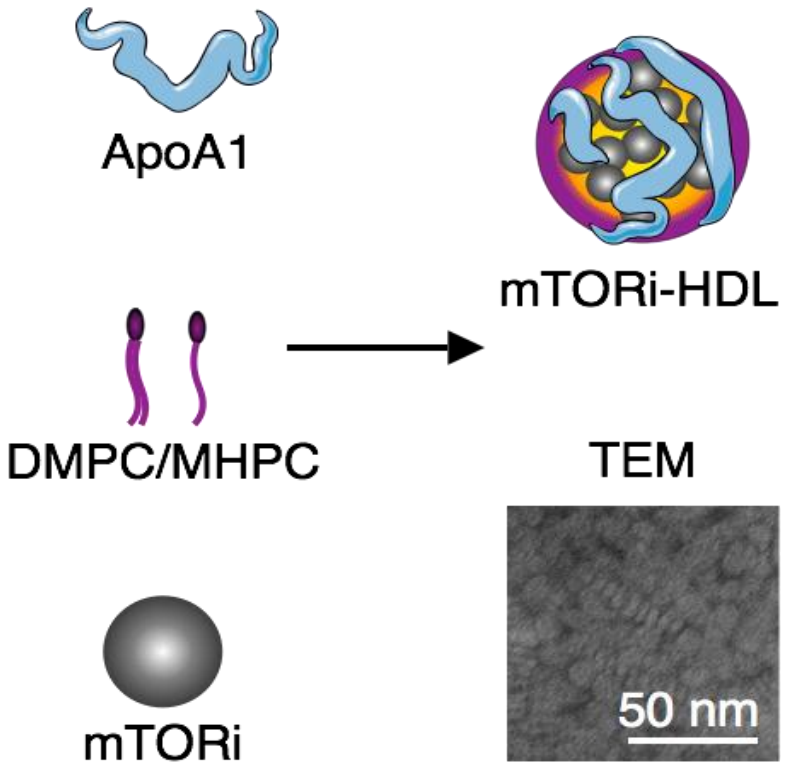
Naive monocyte



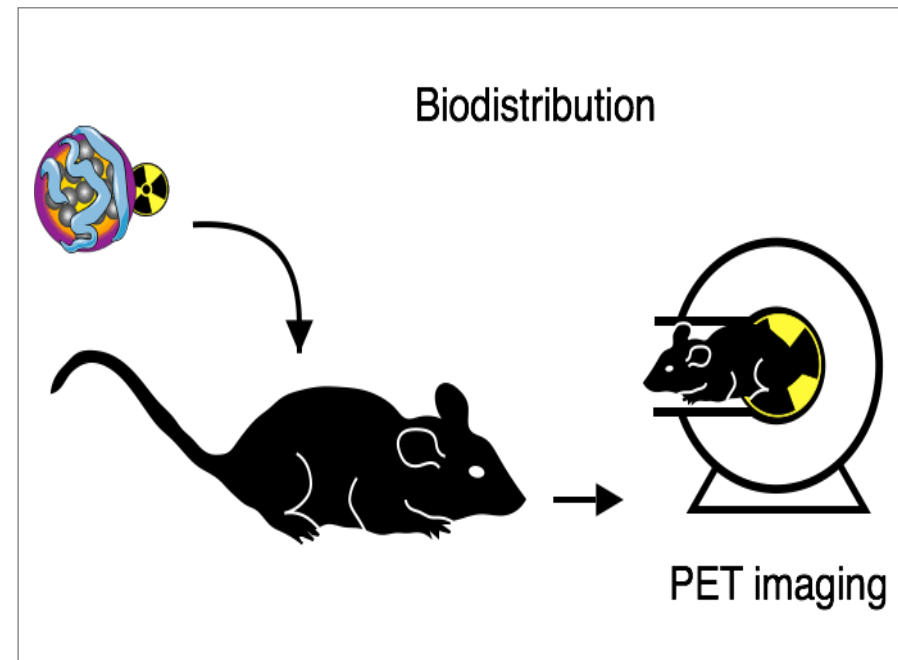
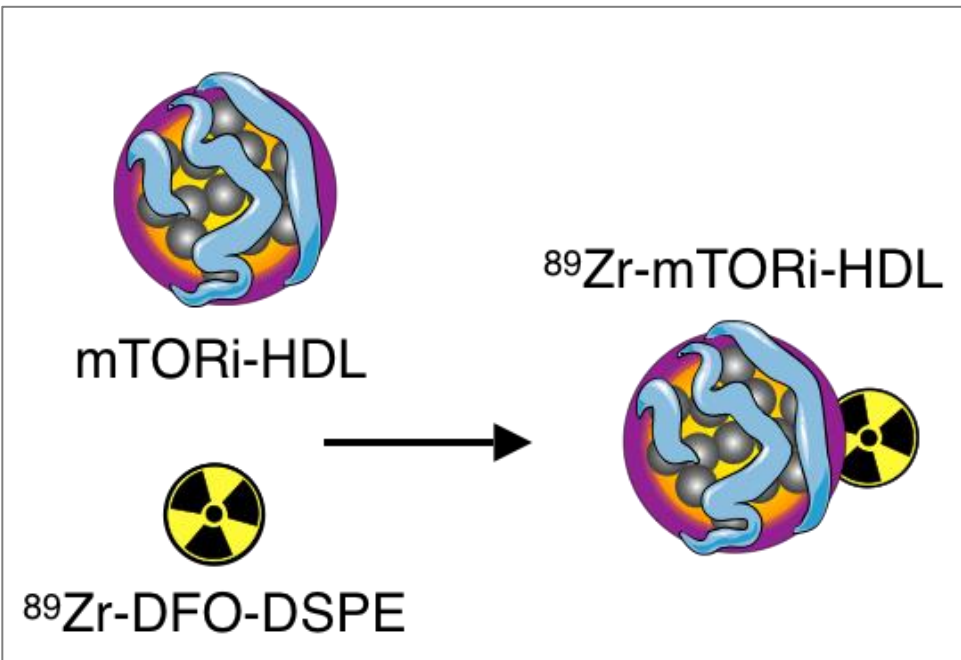
Trained monocyte



mTORi-HDL Nanobiologics prevent trained immunity in vitro



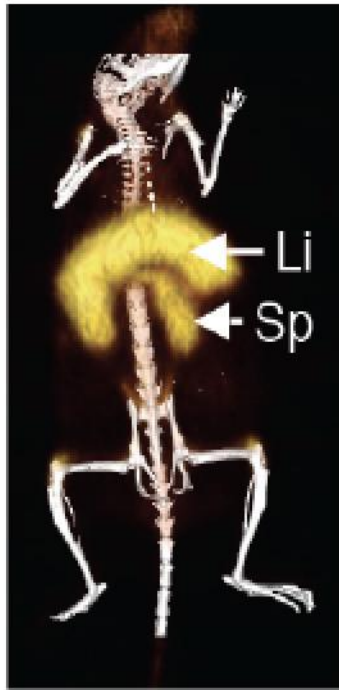
mTORi-HDL Nanobiologics biodistribution



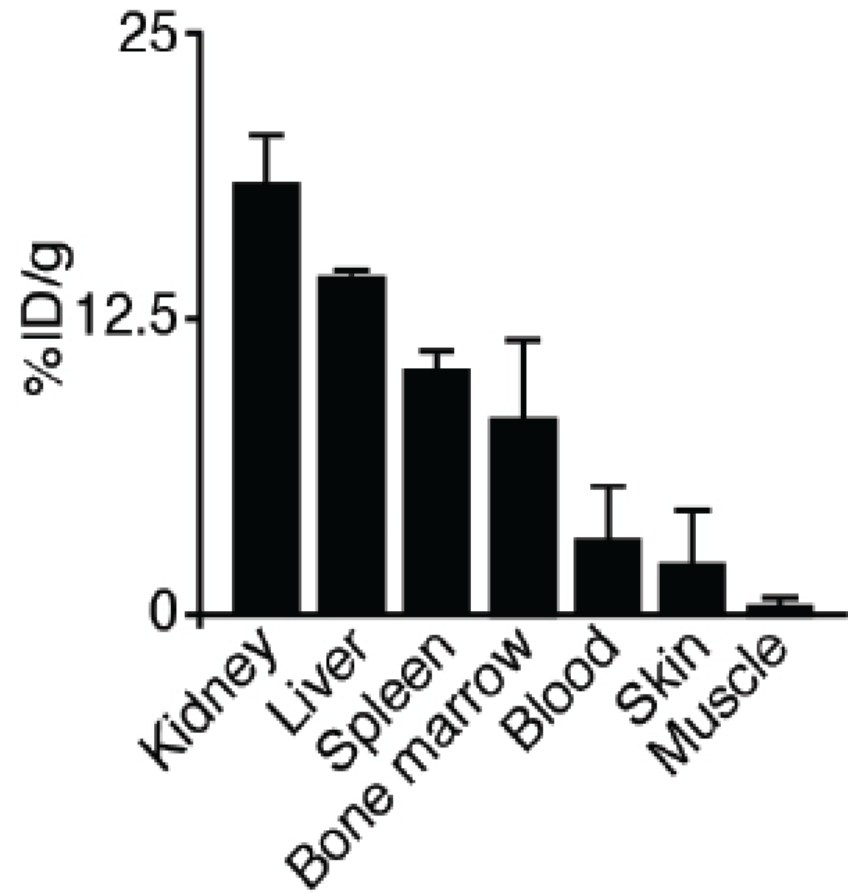
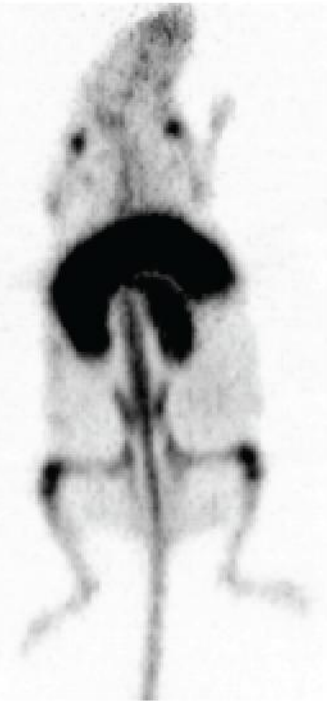
mTORi-HDL Nanobiologics biodistribution

In vivo PET

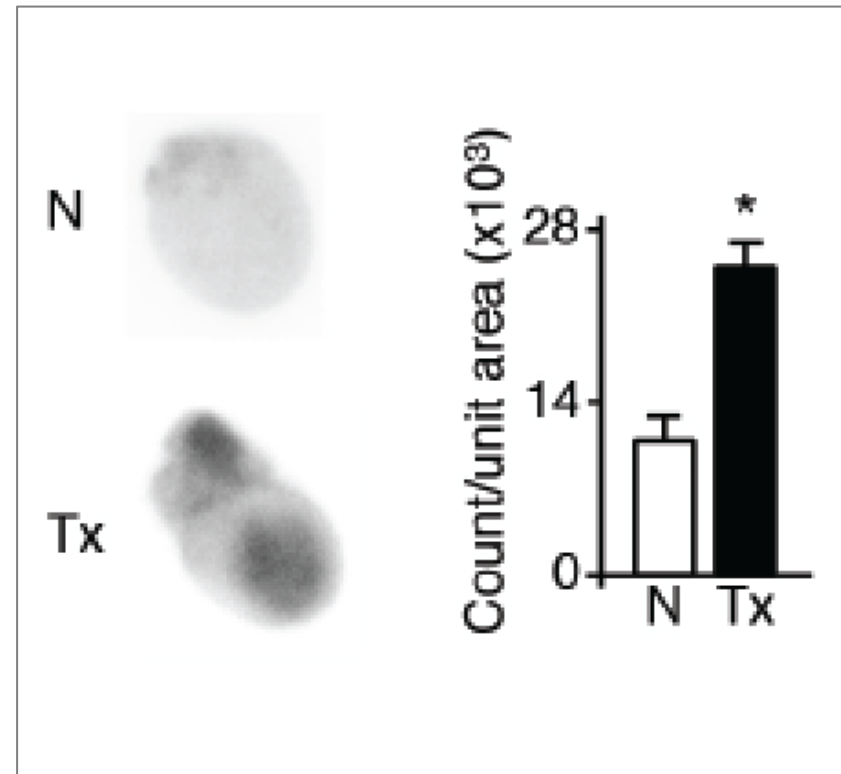
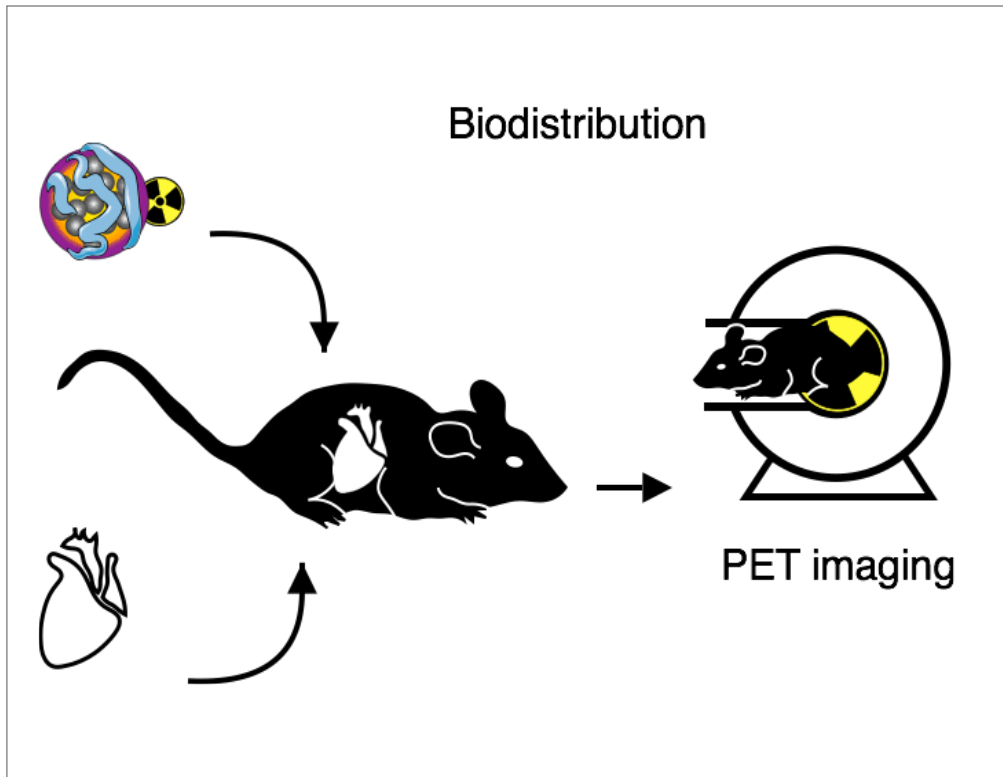
PET/CT



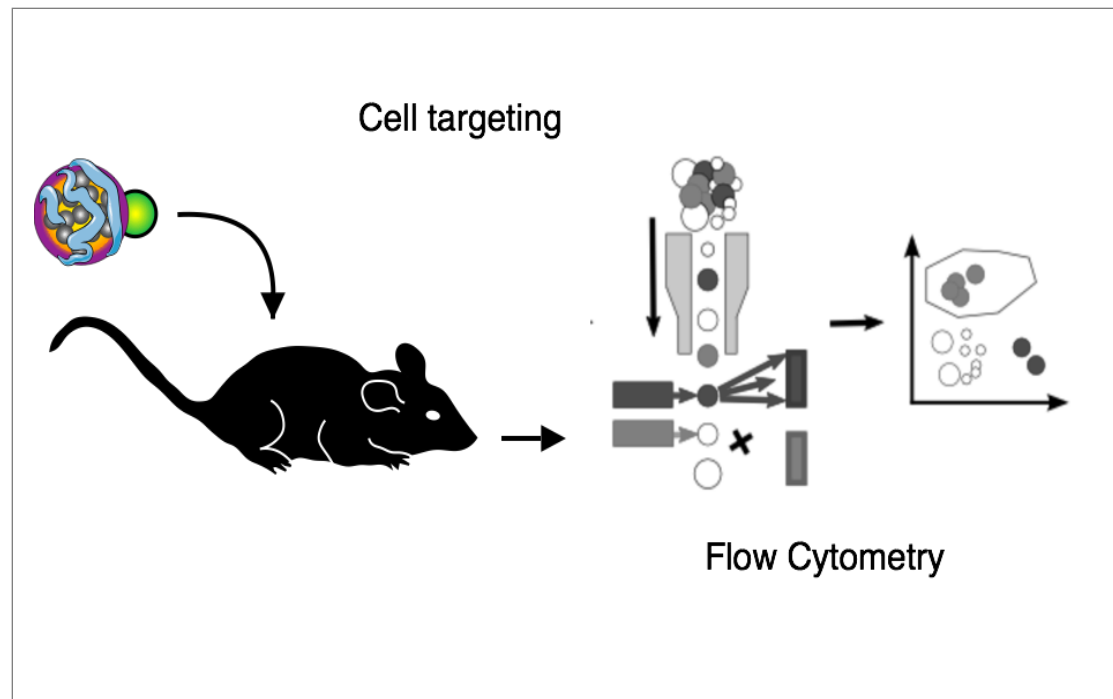
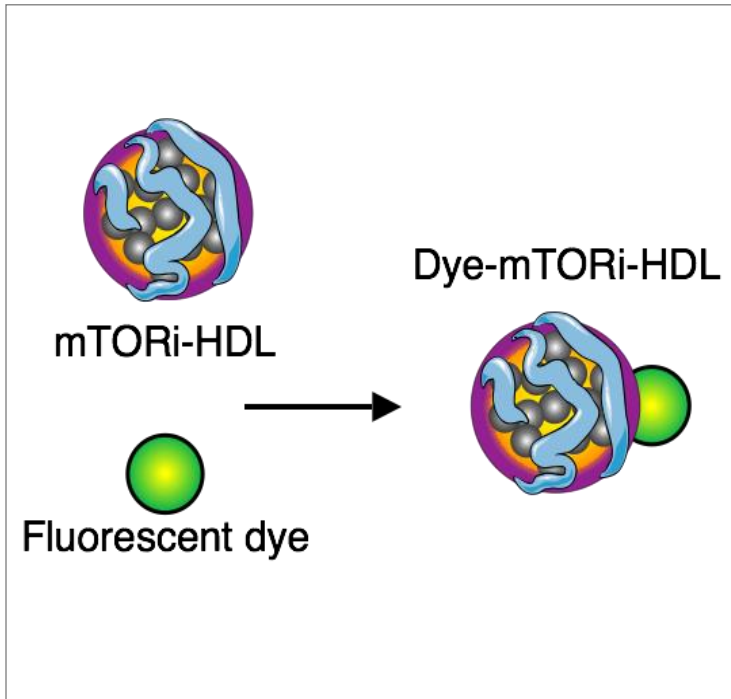
MIP



mTORi-HDL Nanobiologics accumulate in the allograft

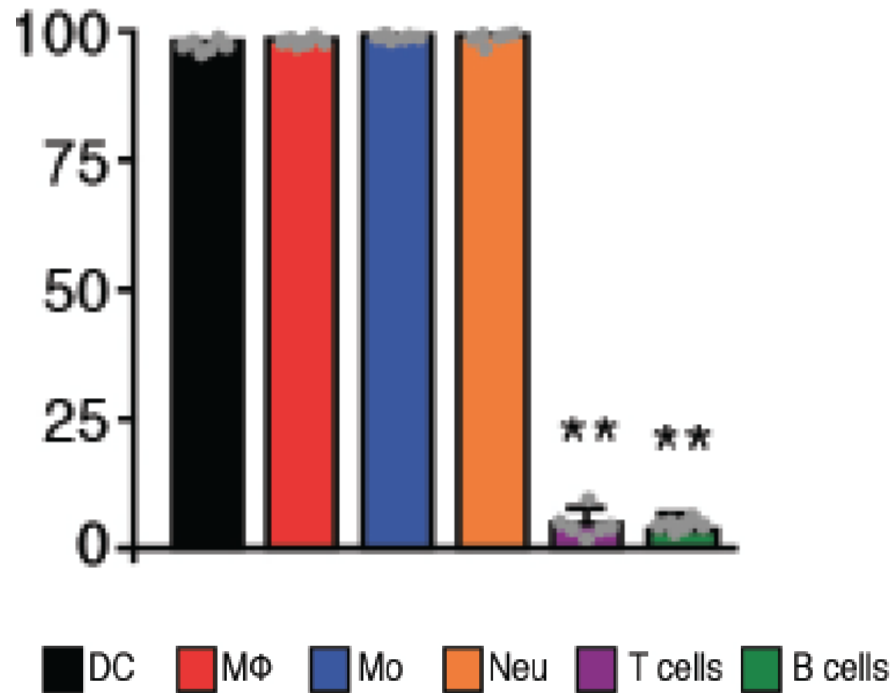


mTORi-HDL Nanobiologics cell targeting

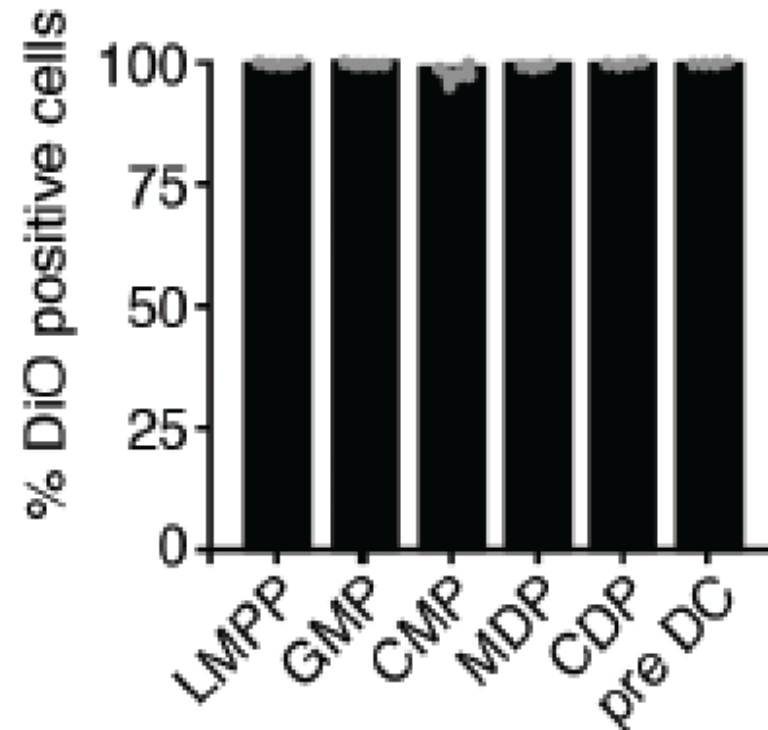


mTORi-HDL Nanobiologics cell targeting

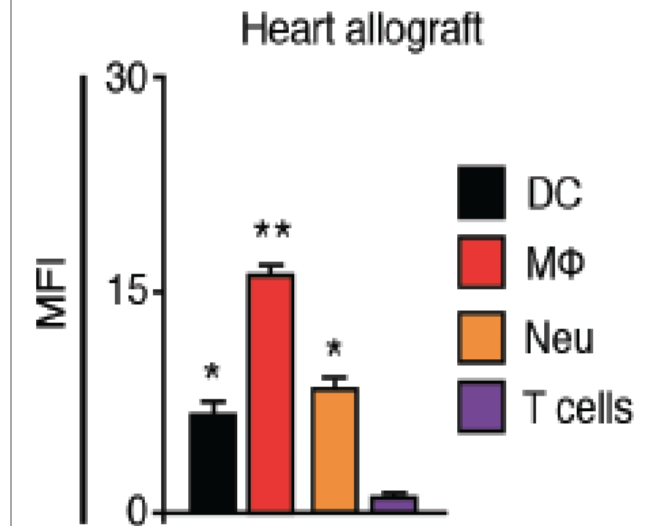
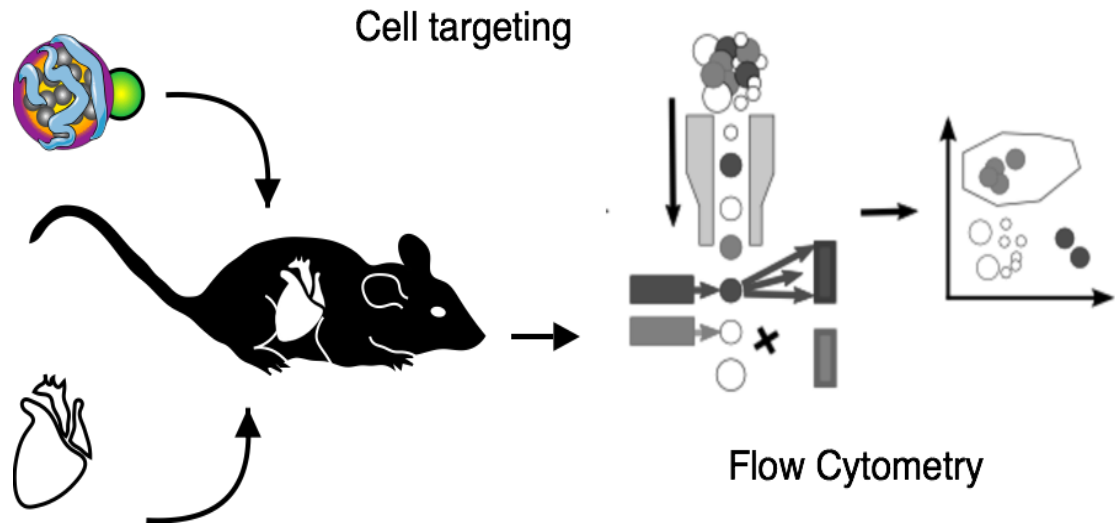
Bone marrow



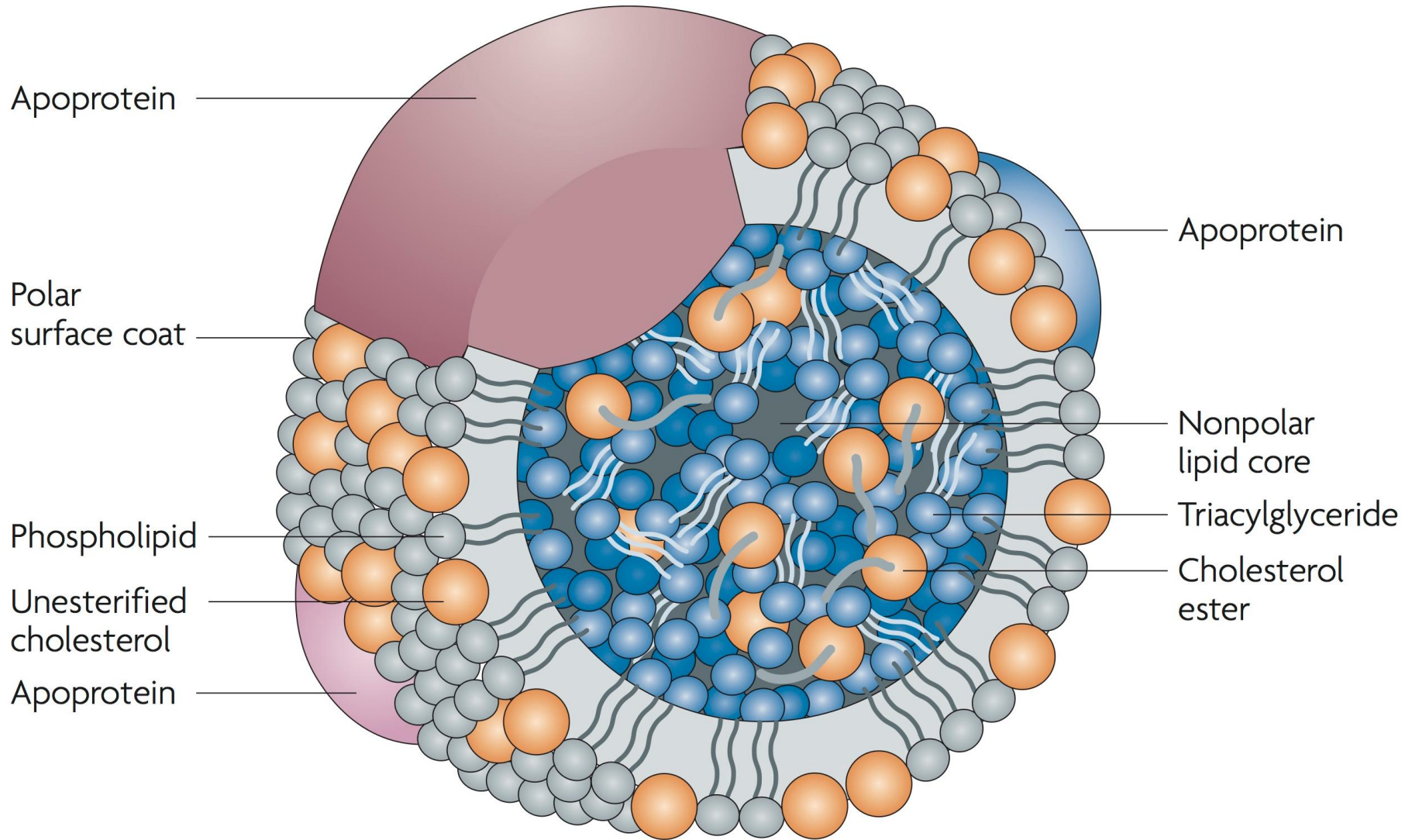
Bone marrow progenitors



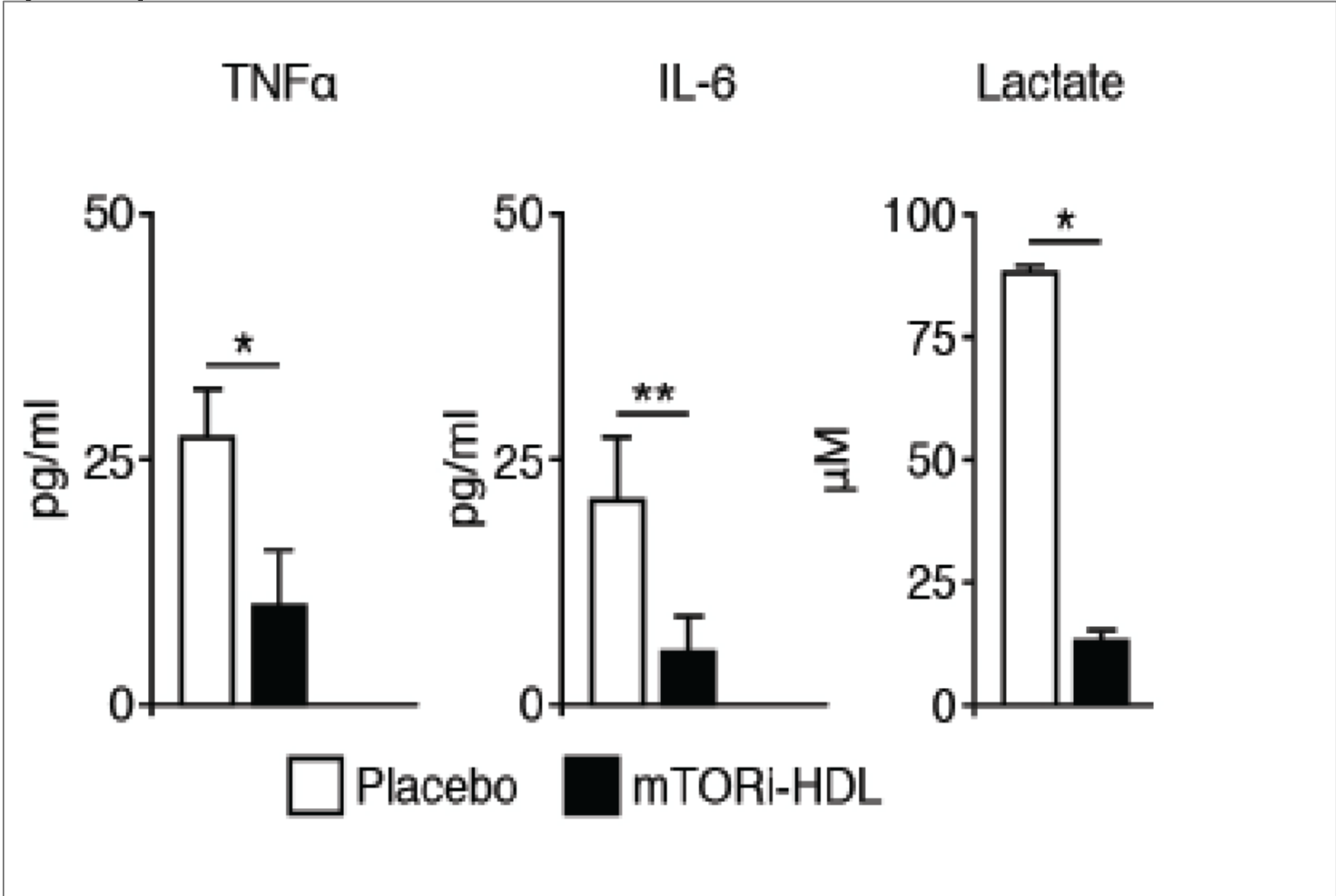
mTORi-HDL Nanobiologics target myeloid cells in the allograft



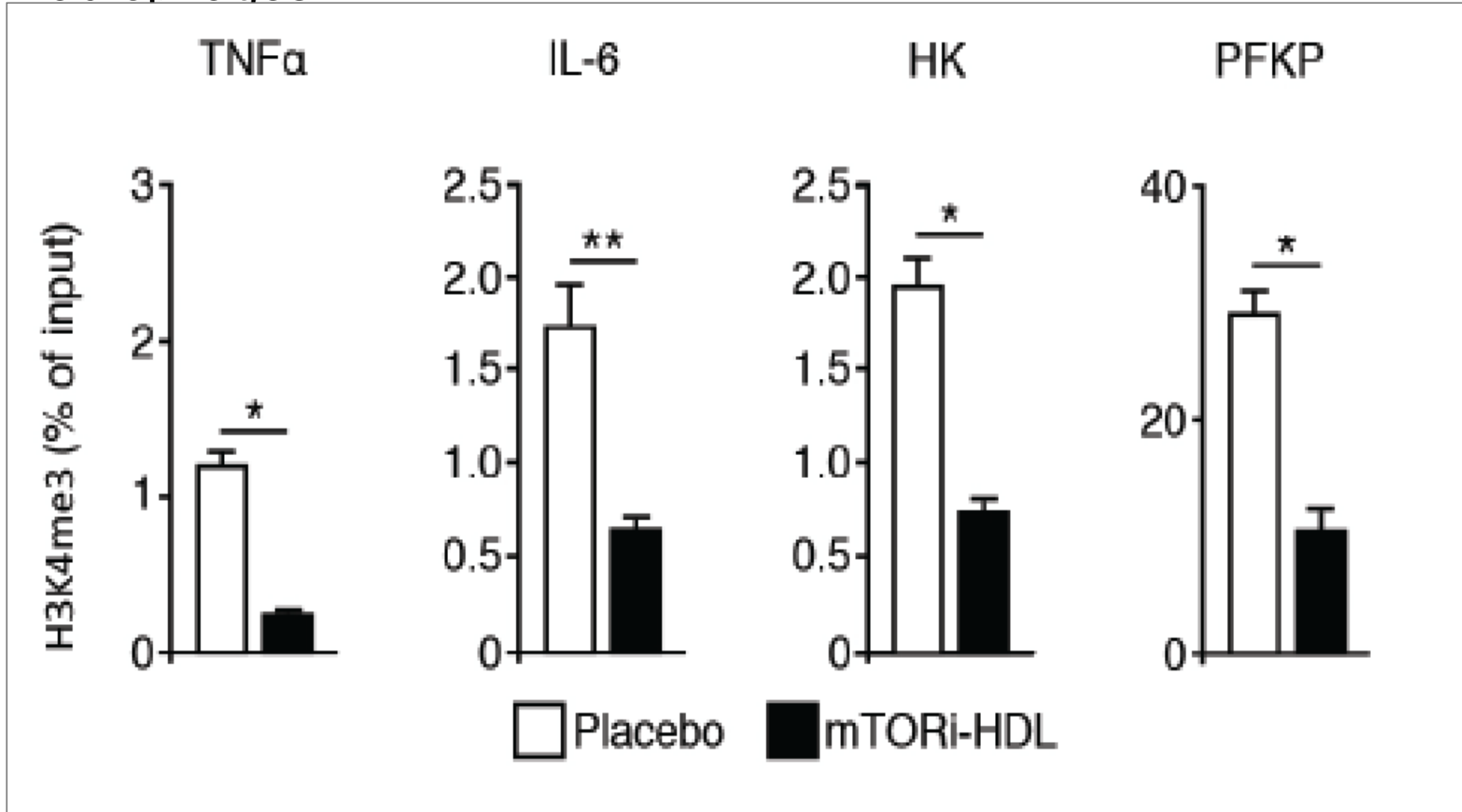
mTOR-HDL nanobiologics



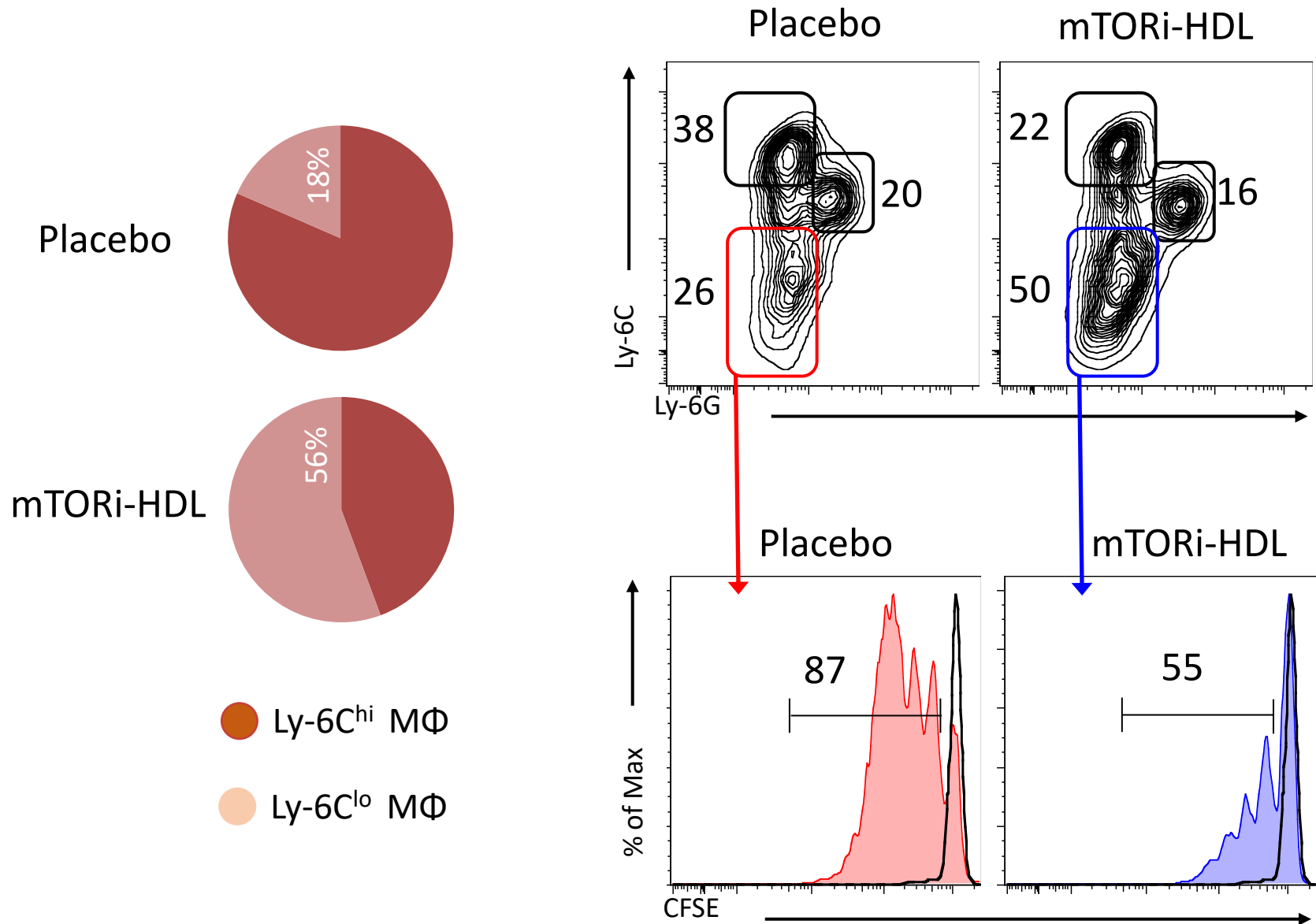
mTORi-HDL Nanobiologics prevent training of graft macrophages



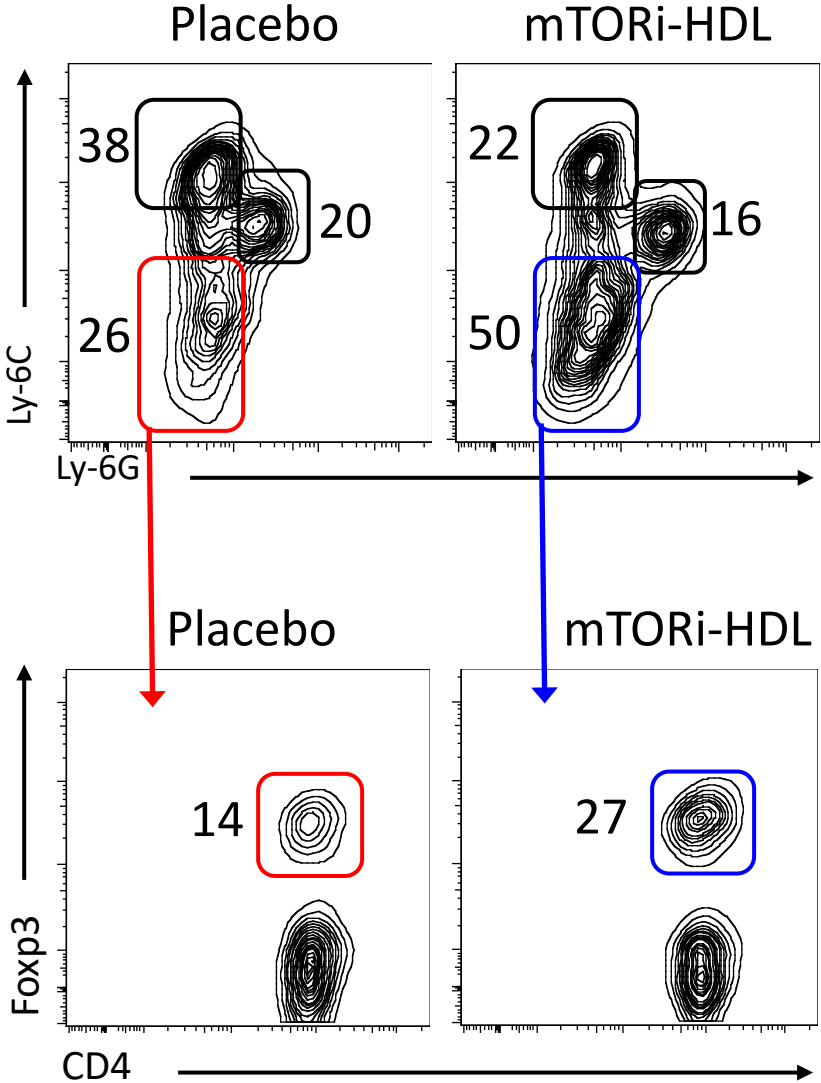
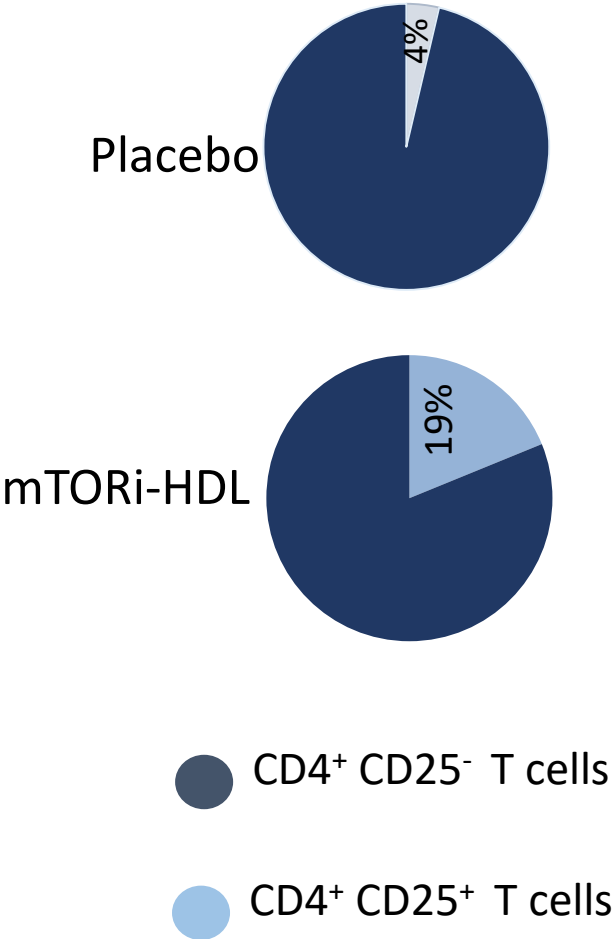
mTORi-HDL Nanobiologics prevent training of graft macrophages



mTORi-HDL promotes suppressive macrophage accumulation



mTORi-HDL promotes Treg accumulation

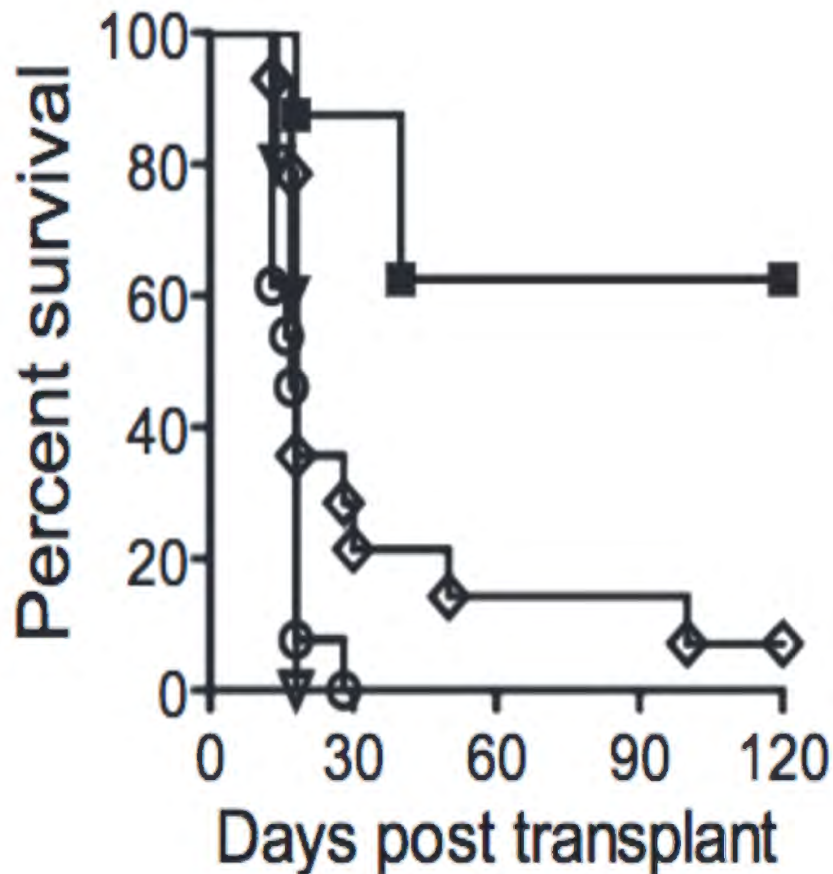


IL-6 and TNF- α Synergistically Inhibit Allograft Acceptance

Hua Shen and Daniel R. Goldstein

J Am Soc Nephrol 20: 1032-1040, 2009.

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut



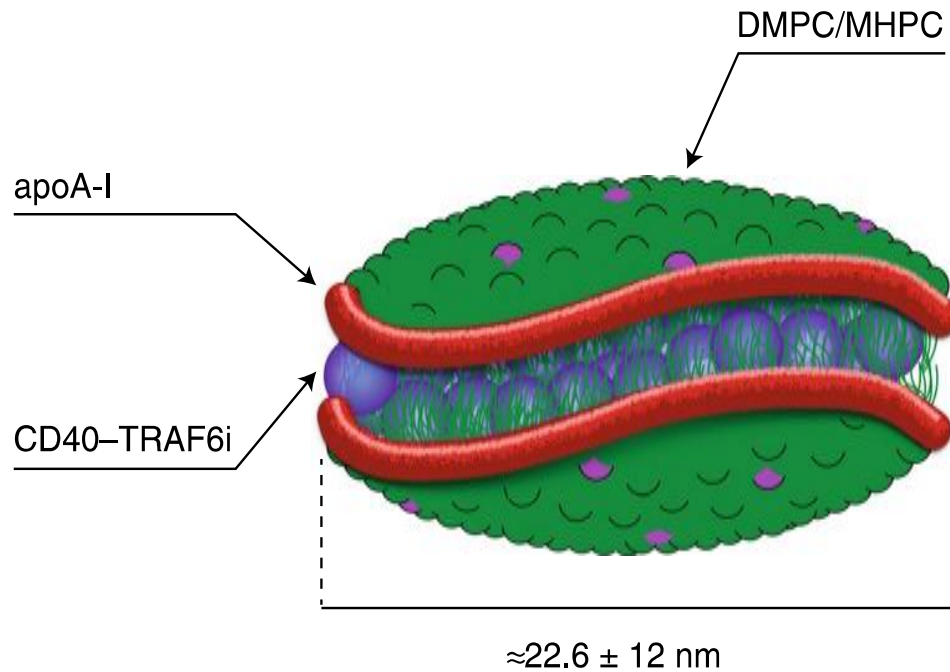
- WT w/CB (n = 13)
- ◇ IL-6^{-/-} w/CB (n = 14)
- ▽ TNF- α ^{-/-} w/CB (n = 5)
- IL-6^{-/-}TNF- α ^{-/-} w/CB (n = 8)

Absence of IL-6 and TNF- α Synergizes with Co-stimulatory Blockade to Induce Allograft Acceptance

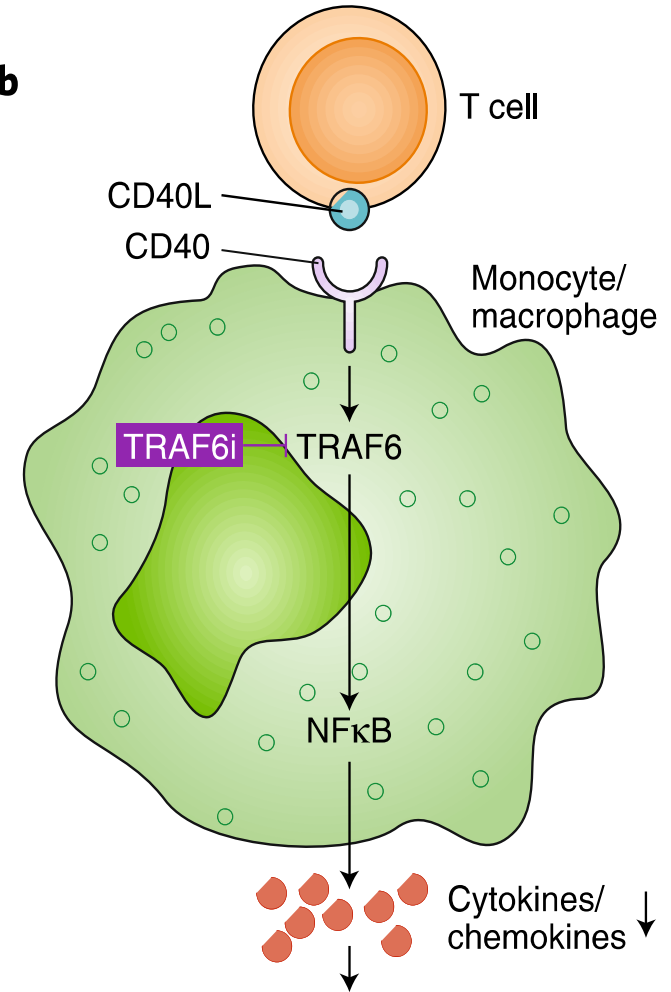
IRAK-M^{-/-} Macrophages Produce Augmented IL-6 and TNF- α upon TLR Activation, which Promotes T Cell Alloimmunity

CD40-TRAF6-HDL Nanobiologics

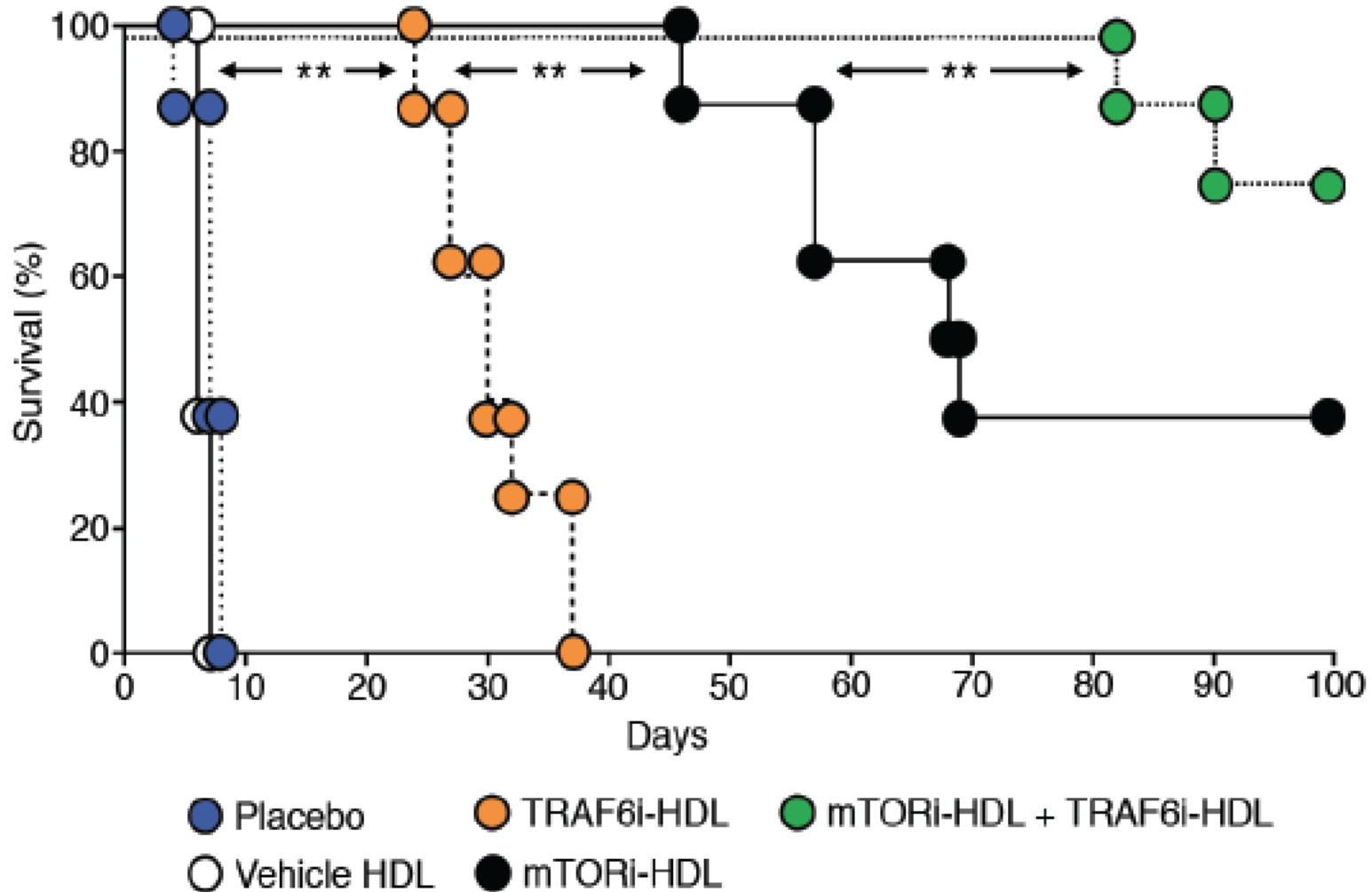
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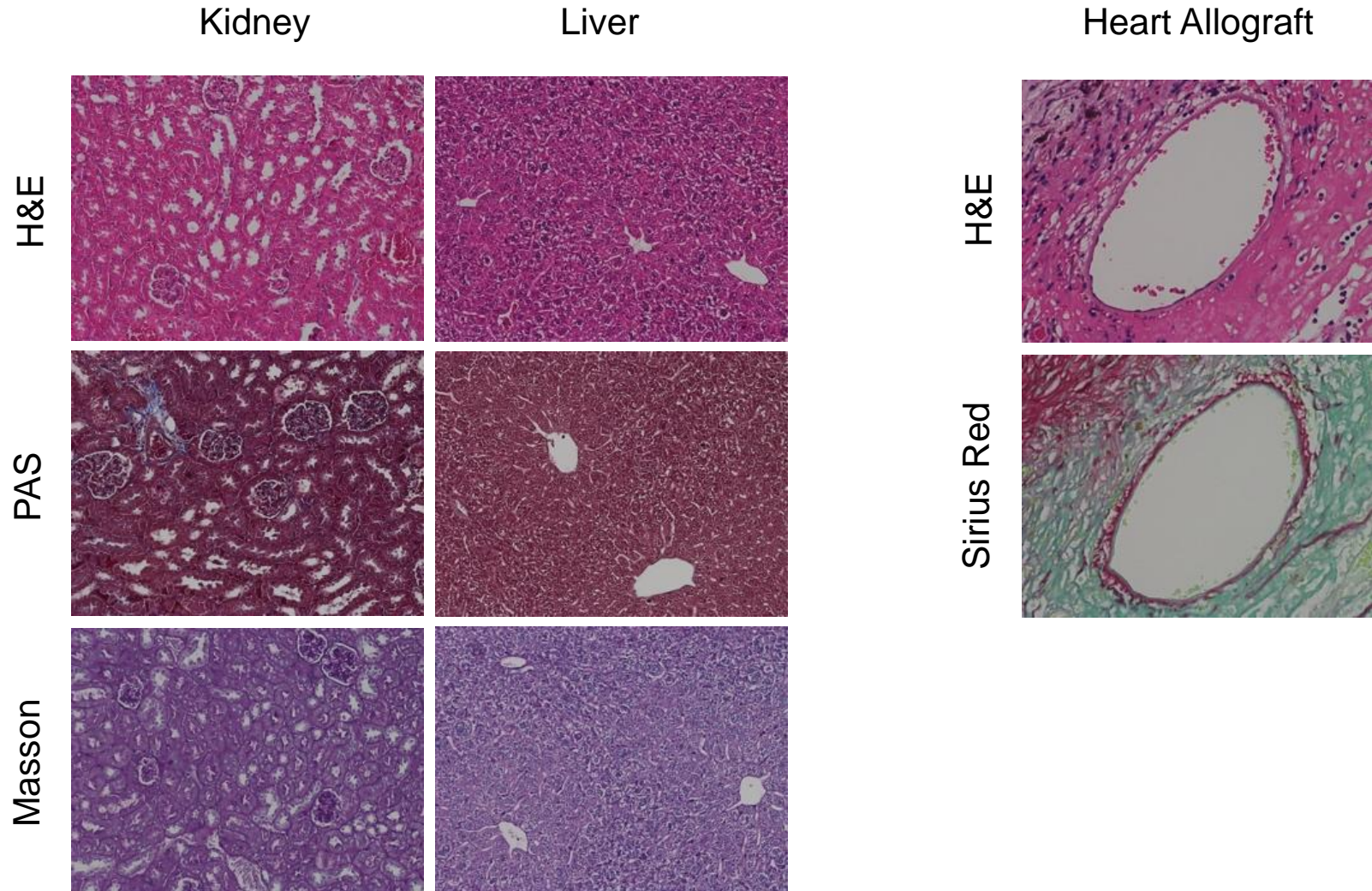
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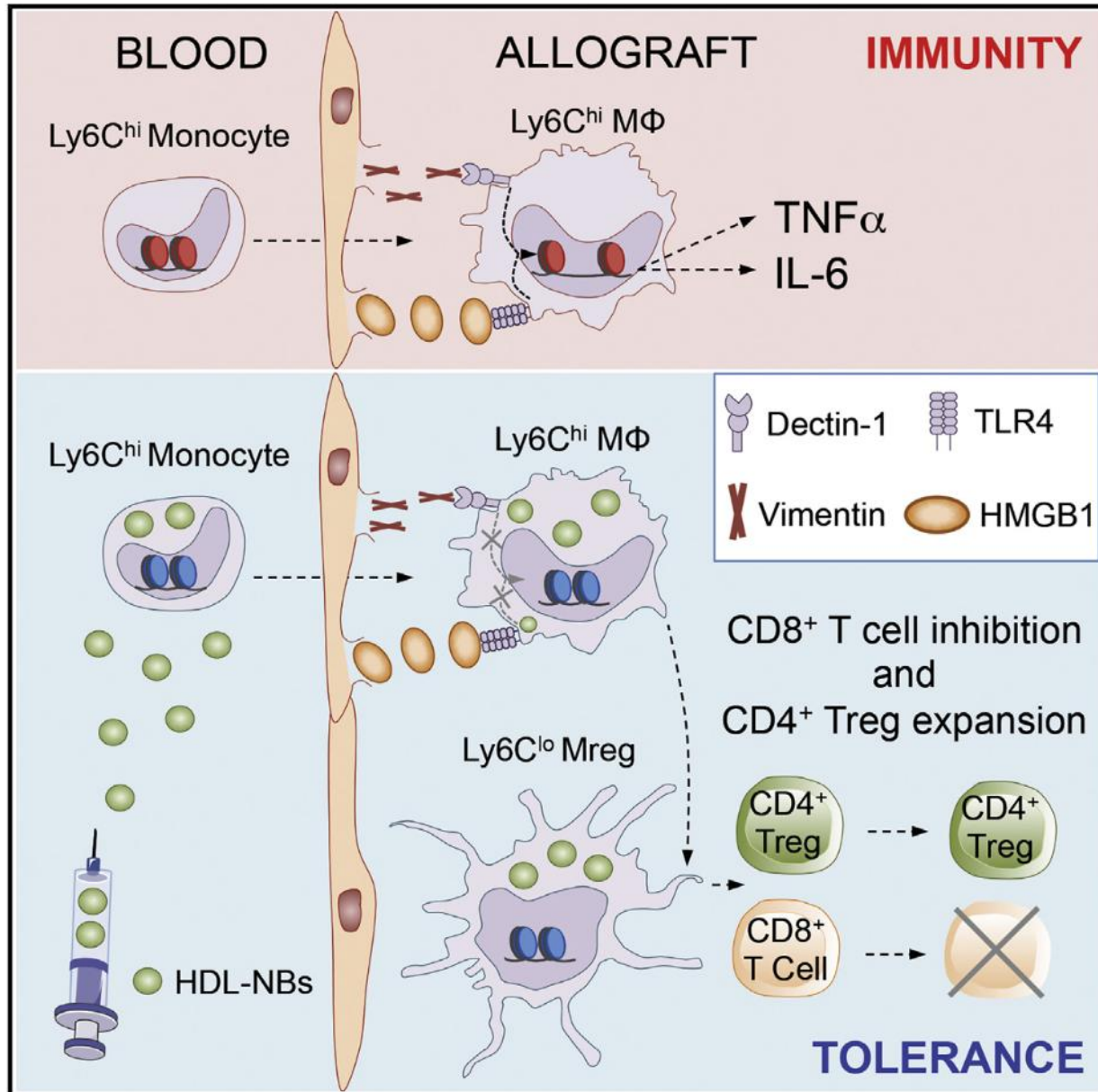
Combined Targeted Nanobiologics Promotes Organ Transplant Acceptance



Nanobiologic treatment exhibits no signs of toxicity 100 days post-transplant and no signs of chronic allograft vasculopathy



Graphical Abstract



Acknowledgements

Immunity
Report

CellPress

Inhibiting Inflammation with Myeloid Cell-Specific Nanobiologics Promotes Organ Transplant Acceptance

Mounia S. Braza,^{1,2} Mandy M.T. van Leent,¹ Marnix Lameijer,³ Brenda L. Sanchez-Gaytan,¹ Rob J.W. Arts,⁴ Carlos Pérez-Medina,¹ Patricia Conde,⁵ Mercedes R. Garcia,⁵ Maria Gonzalez-Perez,⁵ Manisha Brahmachary,² Francois Fay,¹ Ewelina Kluza,³ Susanne Kossatz,⁶ Regine J. Dress,⁷ Fadi Salem,⁸ Alexander Rialdi,⁹ Thomas Reiner,^{6,10} Peter Boros,² Gustav J. Strijkers,^{1,11} Claudia C. Calcagno,¹ Florent Ginhoux,⁷ Ivan Marazzi,⁹ Esther Lutgens,^{3,12} Gerry A.F. Nicolaes,¹³ Christian Weber,¹³ Filip K. Swirski,¹⁴ Matthias Nahrendorf,¹⁴ Edward A. Fisher,¹⁵ Raphaël Duivenvoorden,^{1,16,17} Zahi A. Fayad,¹ Mihai G. Netea,^{4,18} Willem J.M. Mulder,^{1,2,3,19,20,21,*} and Jordi Ochando^{2,5,20,*}