AST AMERICAN SOCIETY OF TRANSPLANTATION

Belatacept: An Opportunity to Personalize Immunosuppression?

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Emory Transplant Center

CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Disclosure

Research Funding from BMS.

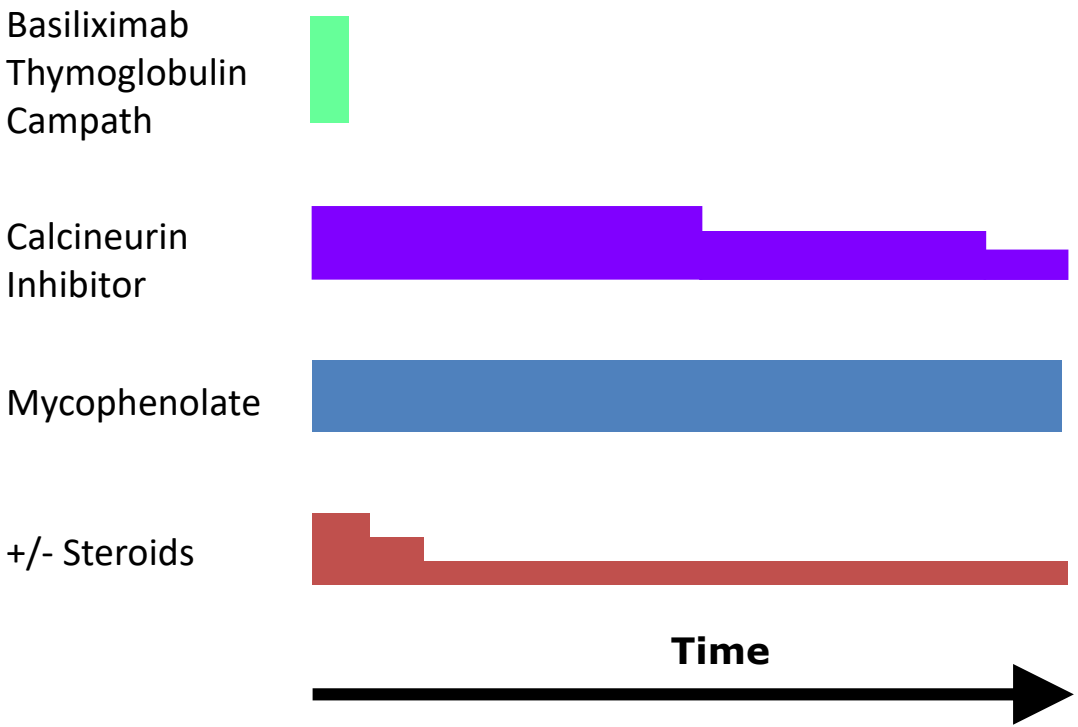
Learning Objectives

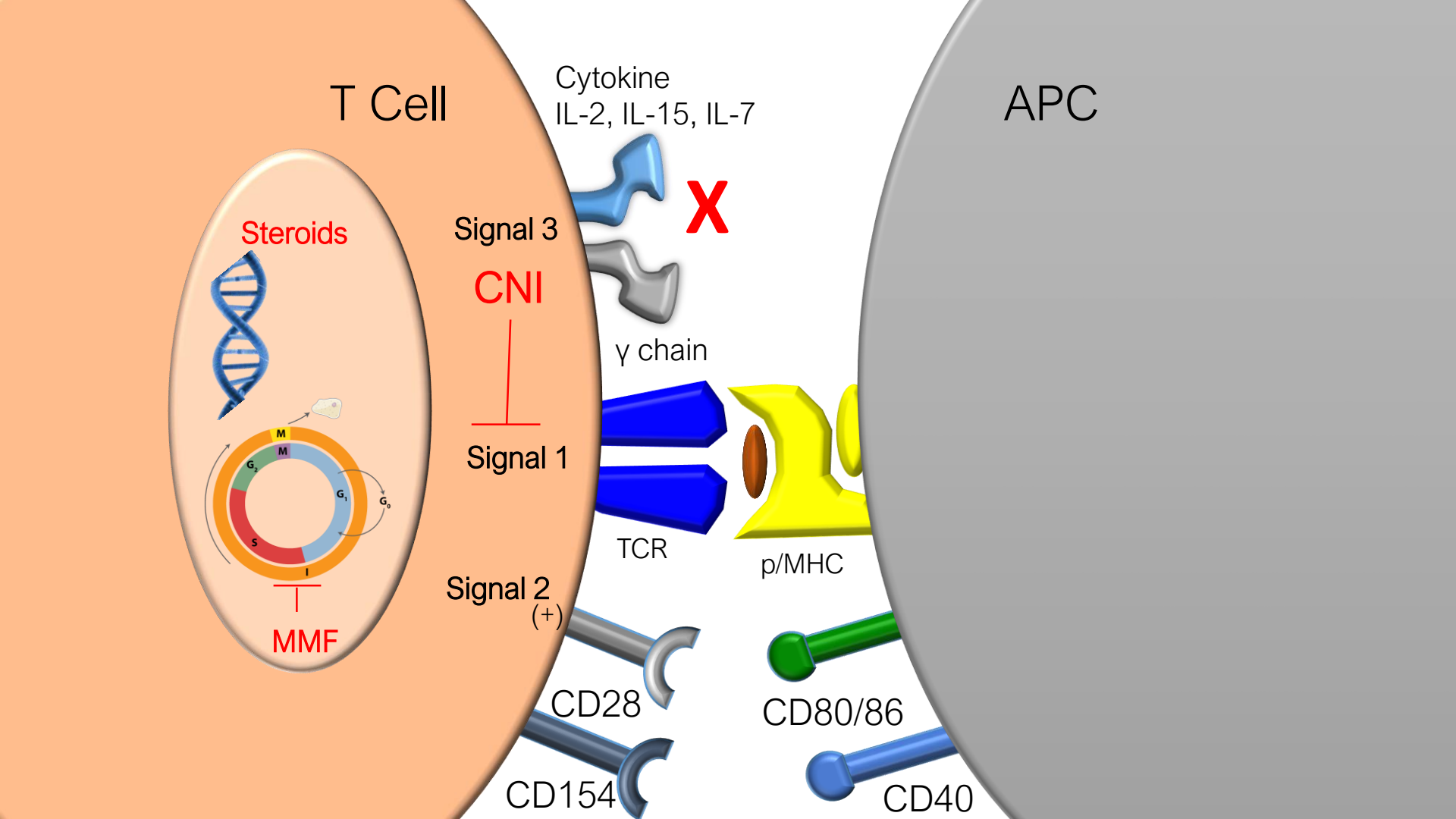
-Define belatacept-resistant rejection

- Identify pathways and cell subsets involved in belatacept-resistant rejection

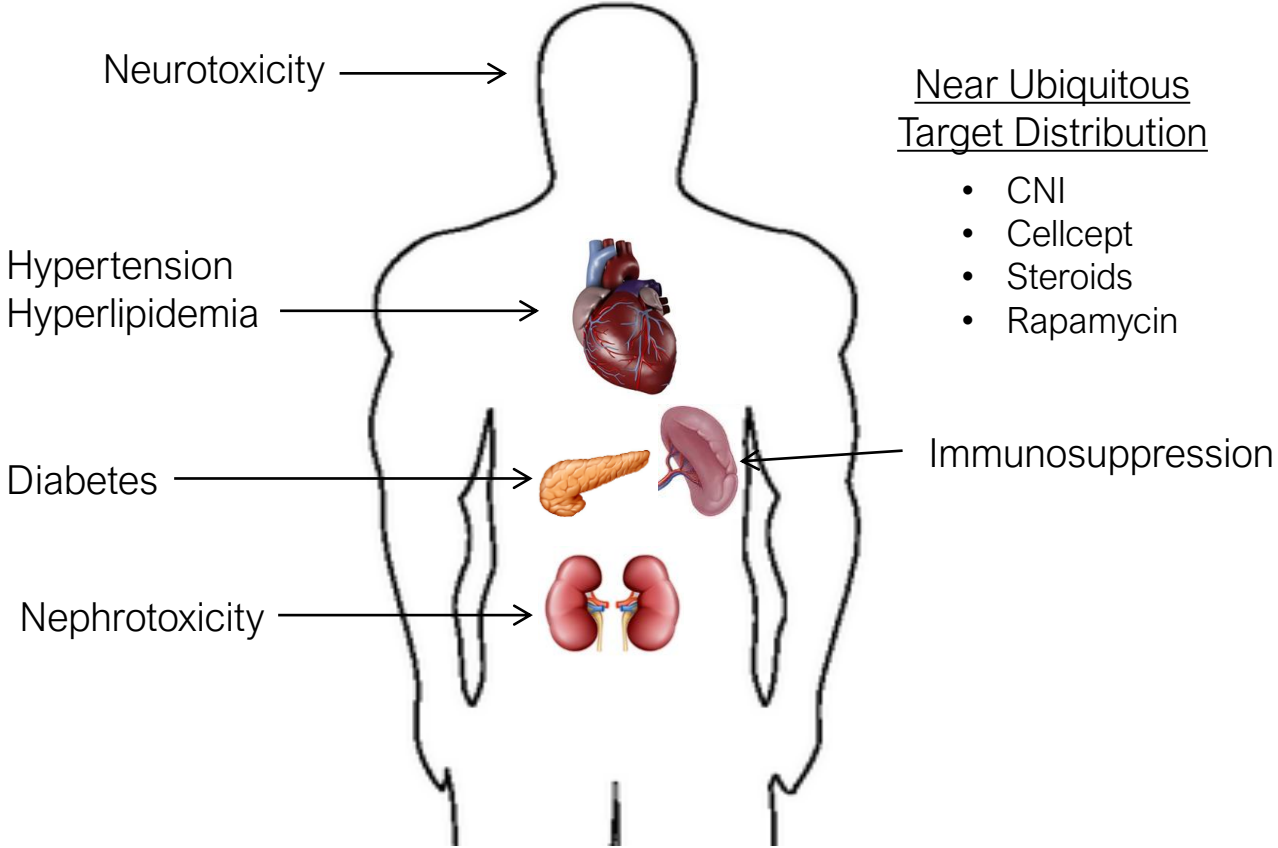
-Propose possible therapeutic interventions to prevent belatacept-resistant rejection

Current Immunosuppressive Strategies




T Cell
Cytokine
IL-2, IL-15, IL-7
APC
Steroids
Signal 3
X
CNI
γ chain
Signal 1
TCR
p/MHC
Signal 2
(+)
MMF
CD28
CD80/86
CD154
CD40

Targeted immunosuppression



Near Ubiquitous Target Distribution

- CNI
- Cellcept
- Steroids
- Rapamycin

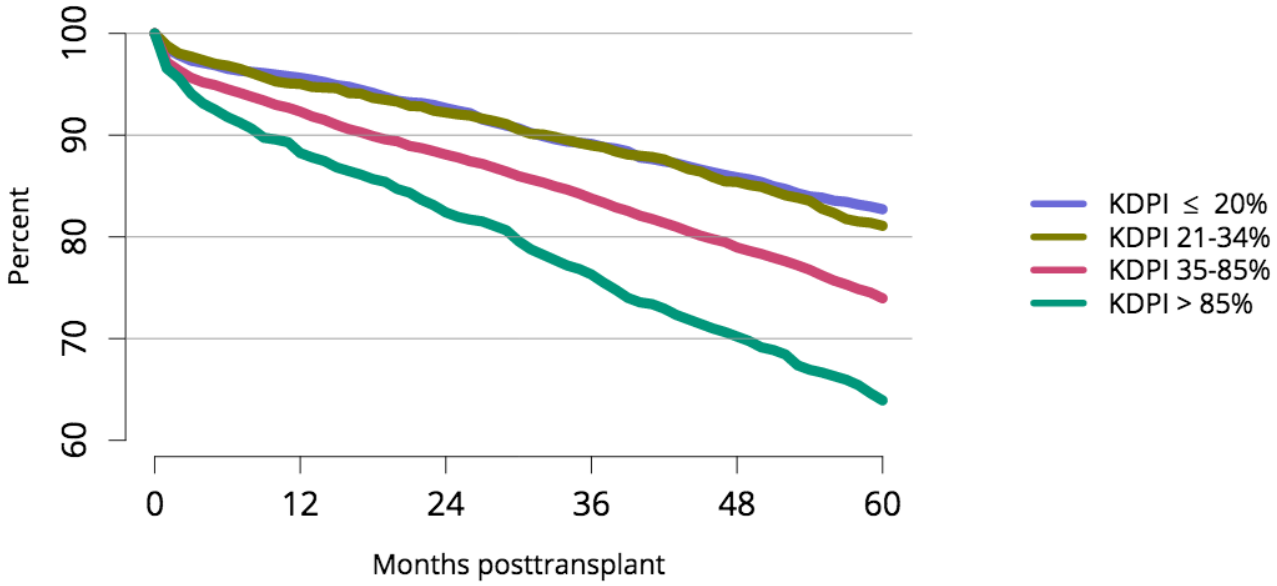
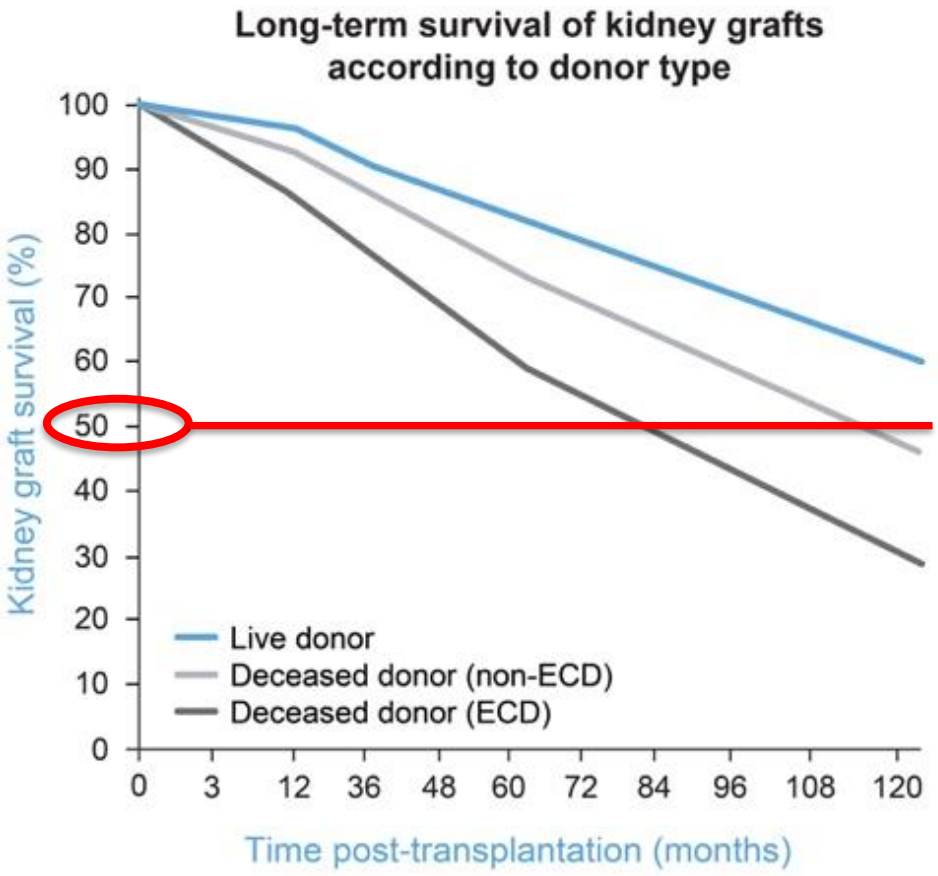


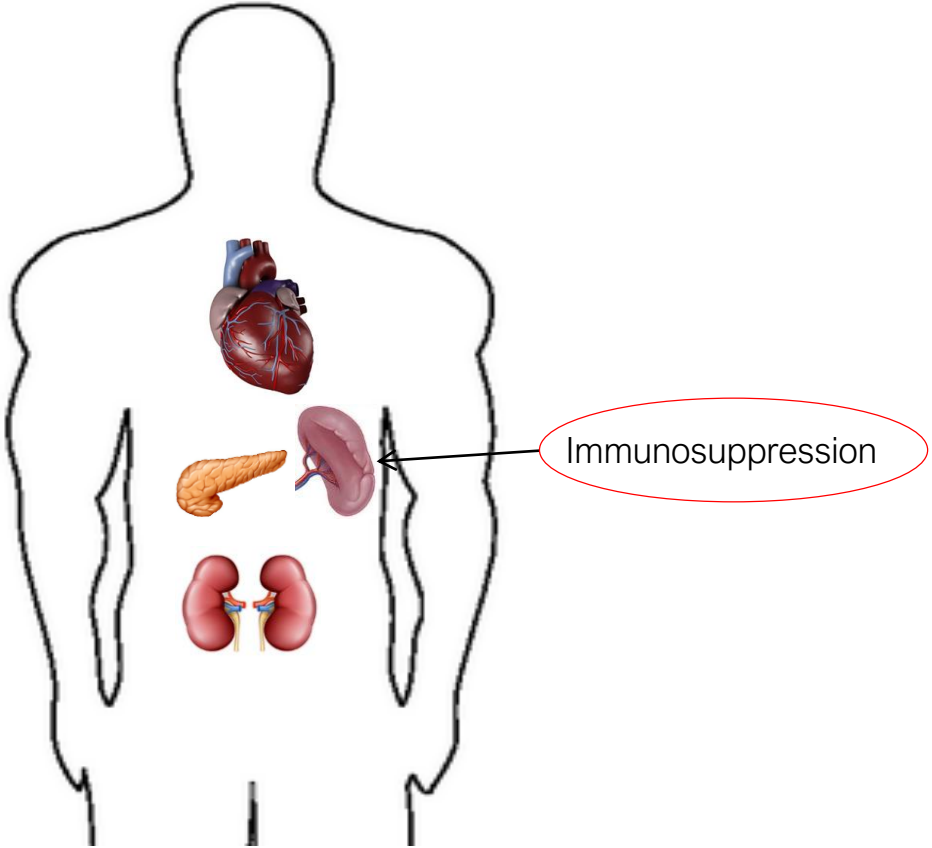
Figure KI 71. Graft survival among adult deceased donor kidney transplant recipients, 2011, by KDPI. Graft survival estimated using unadjusted Kaplan-Meier methods. The reference population for the KDRI to KDPI conversion is all deceased donor kidneys recovered for transplant in the US in 2016. KDPI, kidney donor profile index.

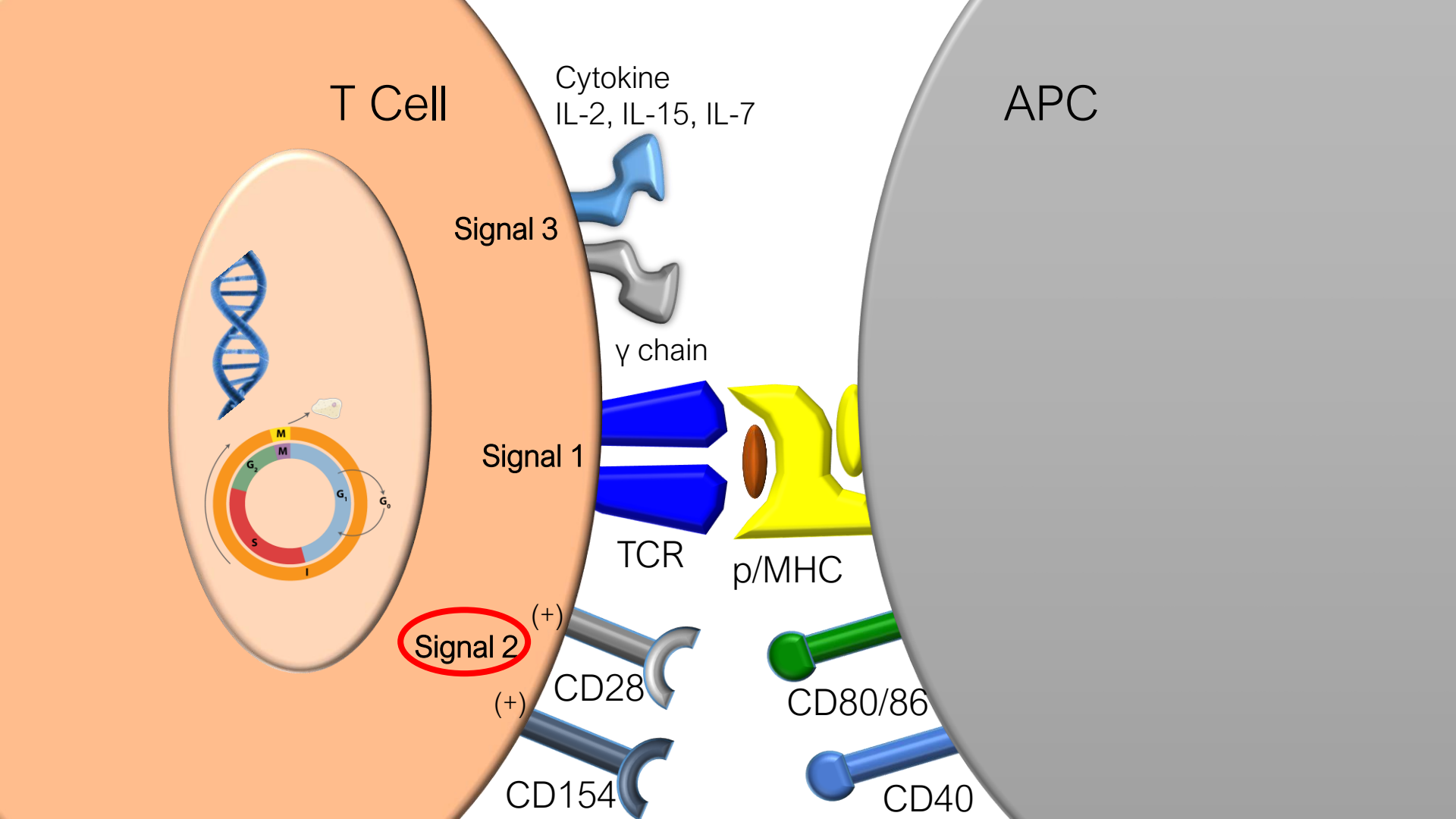


ECD: Expanded criteria donor

http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/01_kidney_12.pdf.

Targeted immunosuppression

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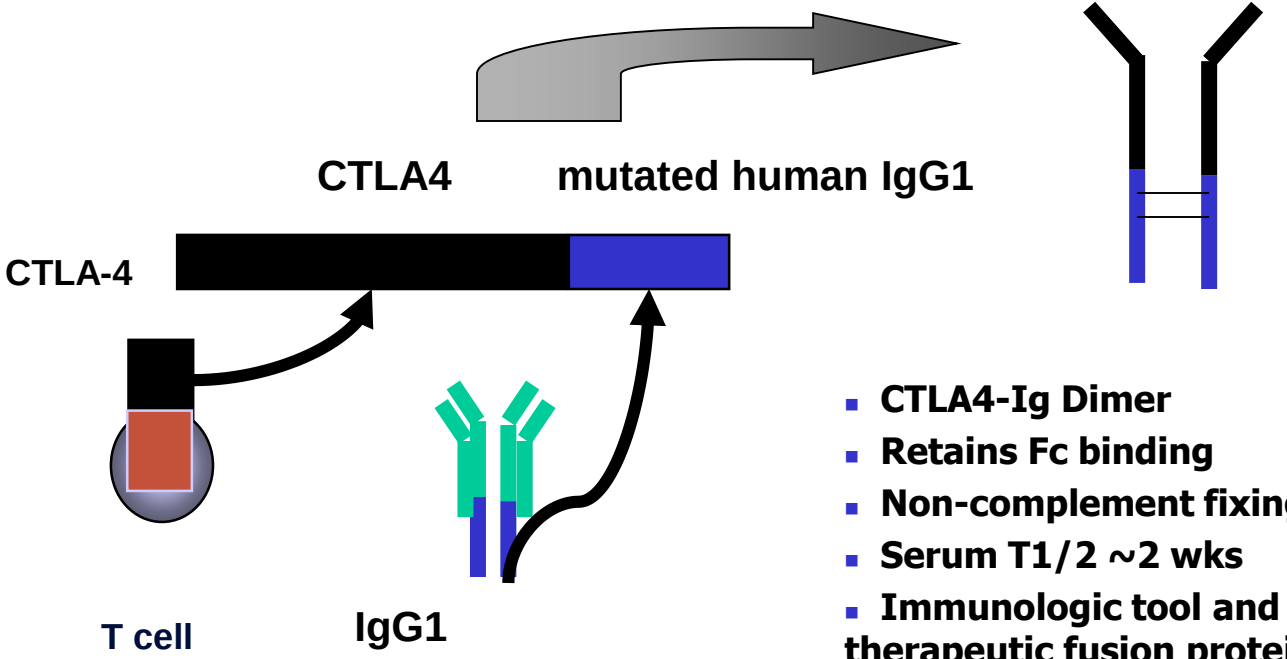
Signal 3
γ chain
Signal 1
TCR
p/MHC
(+)
Signal 2
CD28
CD80/86
(+)
CD154
CD40

CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7

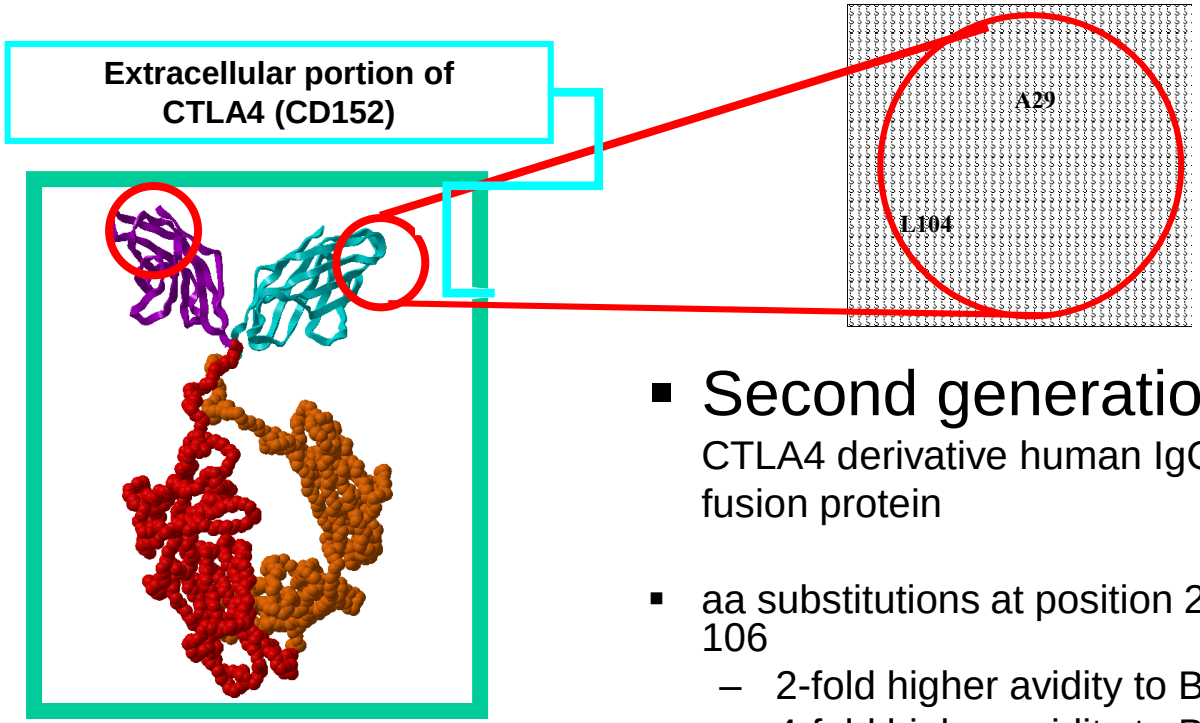
By Peter S. Linsley, William Brady, Mark Urnes, Laura S. Grosmaire, Nitin K. Damle, and Jeffrey A. Ledbetter

From the Oncogen Division, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121



- CTLA4-Ig Dimer
- Retains Fc binding
- Non-complement fixing
- Serum T1/2 ~2 wks
- Immunologic tool and therapeutic fusion protein

Belatacept (LEA29Y): Engineered for more potent co-stimulation blockade



- Second generation
  CTLA4 derivative human IgG1 Fc fusion protein

- aa substitutions at position 29 and 106
  - 2-fold higher avidity to B7-1
  - 4-fold higher avidity to B7-2 than parent CTLA4-Ig molecule
  - 10-fold higher biologic potency in vitro

Larsen et al AJT 2005

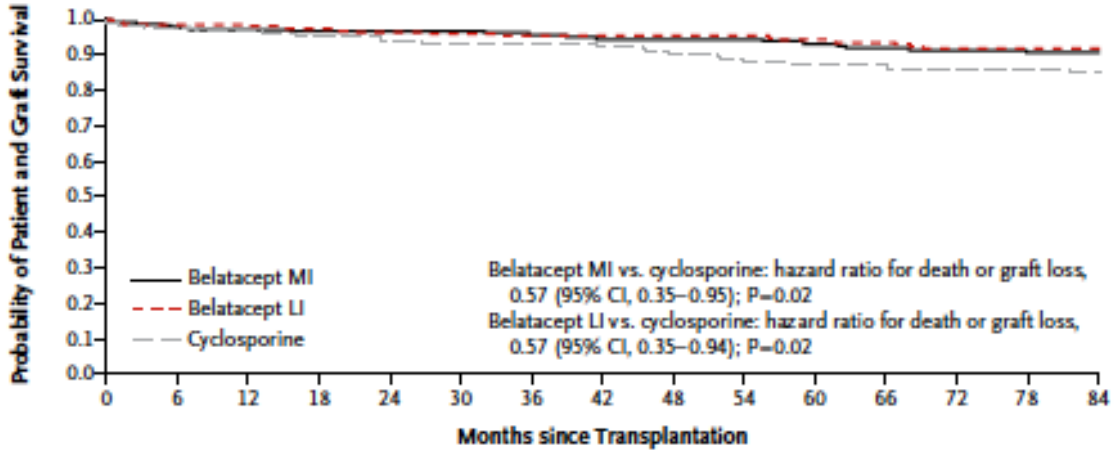
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

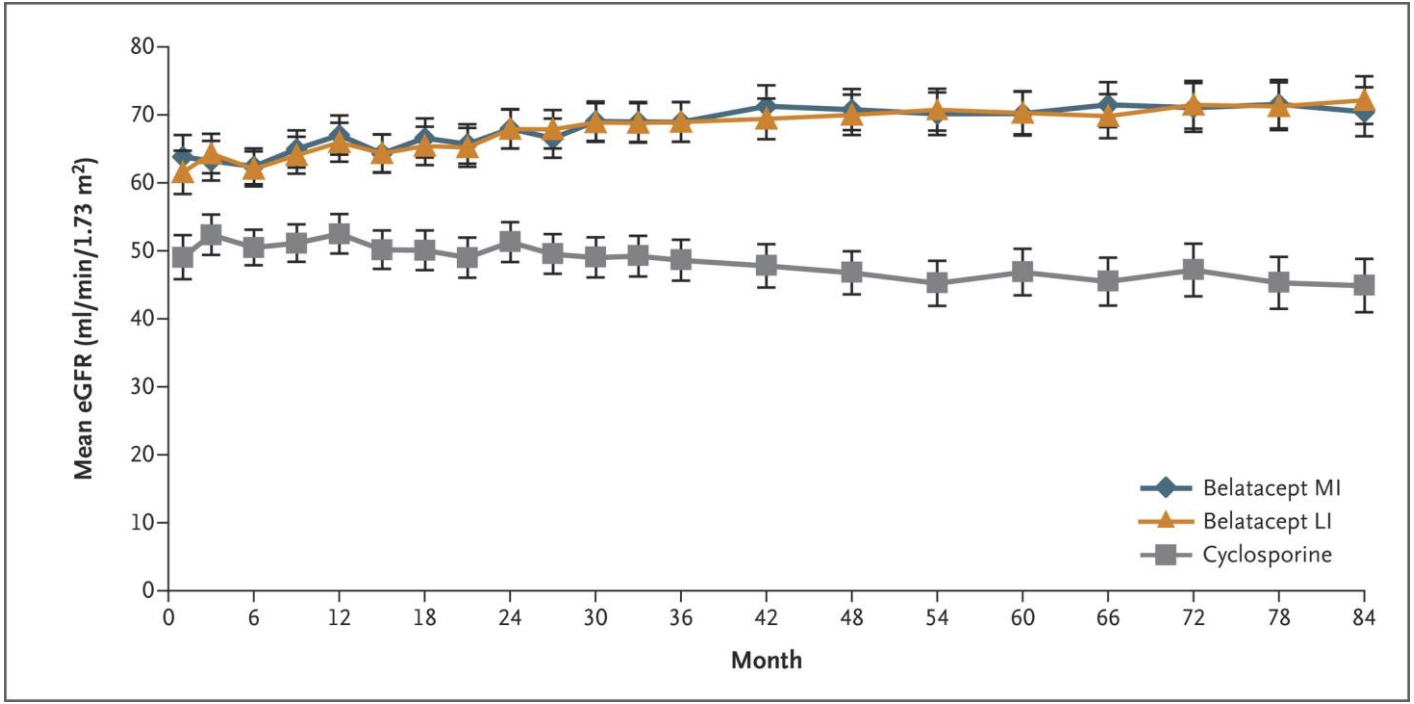
Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

7yr Patient/Graft Survival



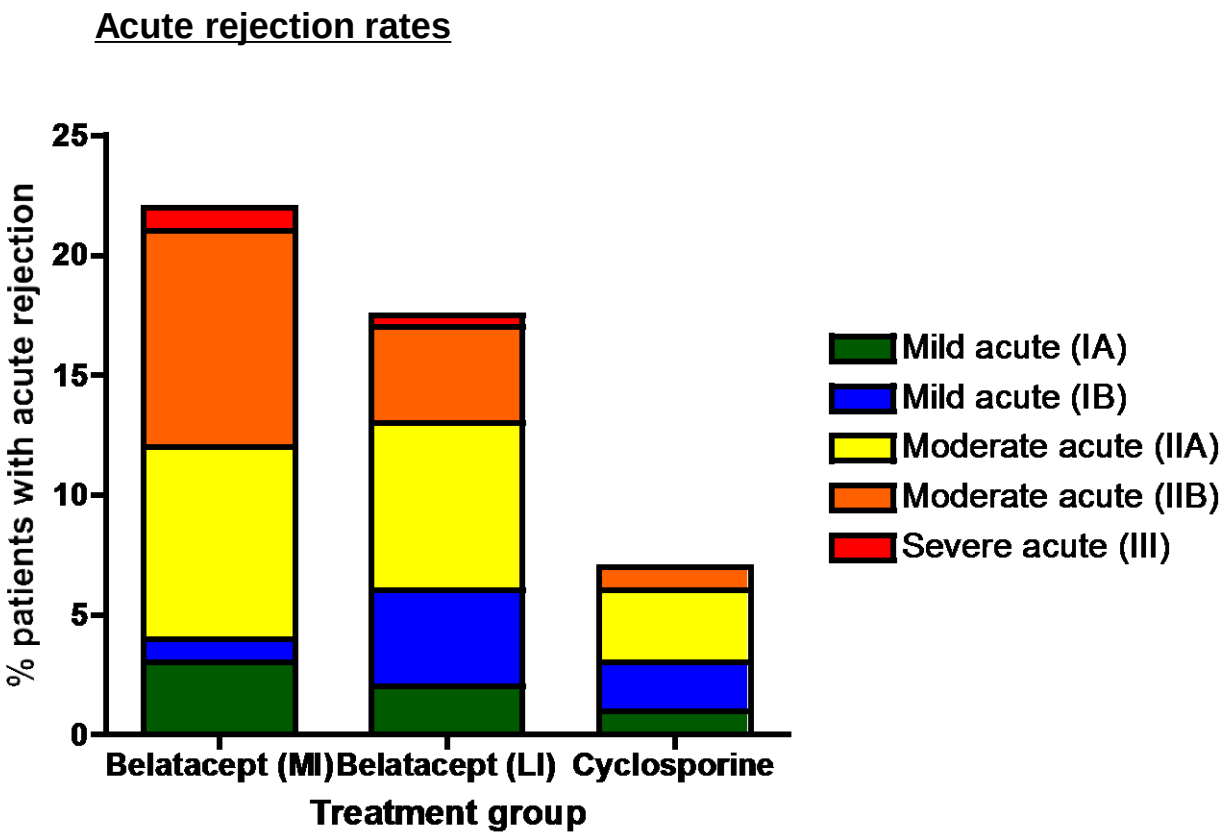
No. at Risk															
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

BENEFIT-Trial: Improved Cardiovascular, Metabolic and Renal health



NEJM 2016

Belatacept & Rejection



FDA Approval 2011

FDA NEWS RELEASE

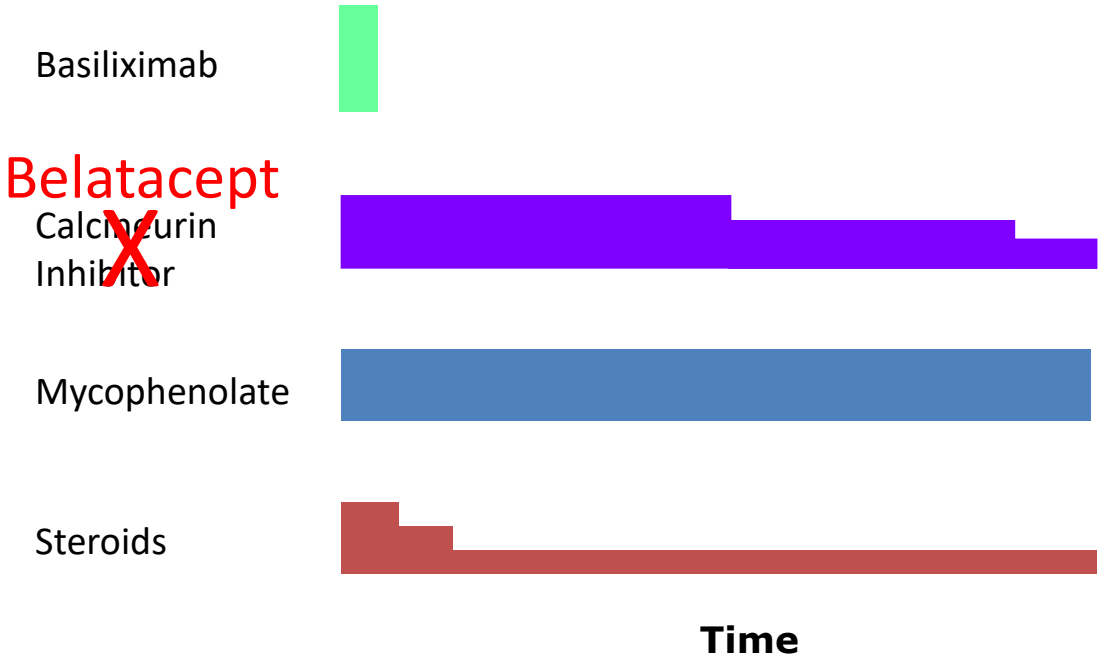
For Immediate Release: June 15, 2011
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Nulojix for kidney transplant patients

The U.S. Food and Drug Administration today approved Nulojix (belatacept) to prevent acute rejection in adult patients who have had a kidney transplant. The drug is approved for use with other immunosuppressants (medications that suppress the immune system) -- specifically basiliximab, mycophenolate mofetil, and corticosteroids.

Nulojix is a type of drug called a selective T-cell costimulation blocker. The drug helps to prevent organ rejection after a kidney transplant. Without immunosuppression, the body can reject a transplanted organ because the immune system recognizes the new organ as foreign (transplant rejection). By preventing rejection, Nulojix, given through 30 minute intravenous infusions, works with other immunosuppressants to keep the new kidney working.

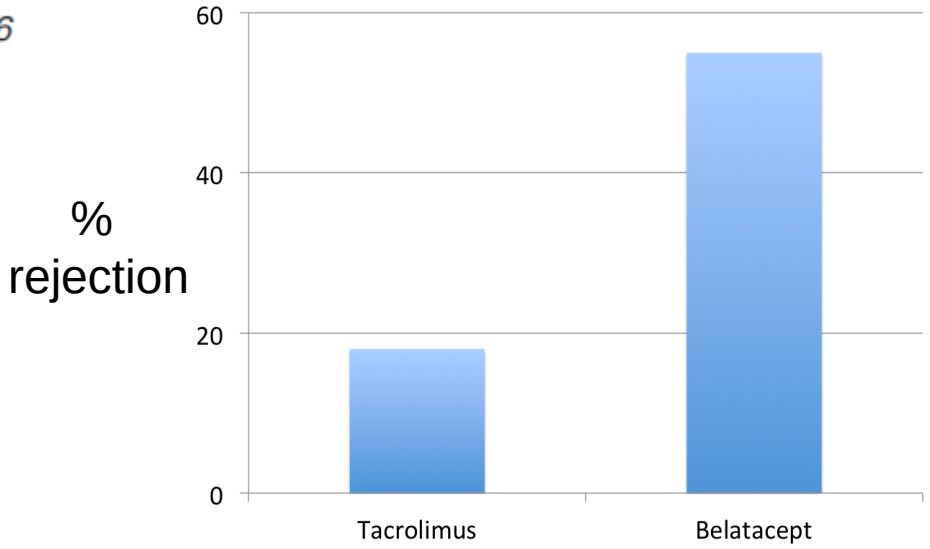
Current Immunosuppressive Strategies



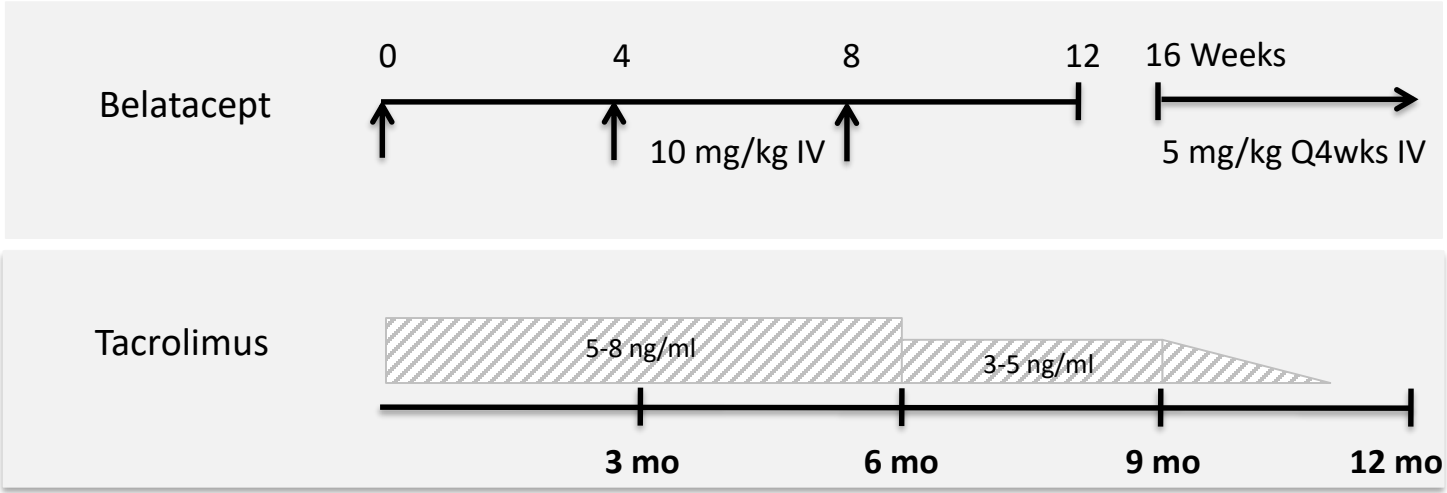
Belatacept Combined With Transient Calcineurin Inhibitor Therapy Prevents Rejection and Promotes Improved Long-Term Renal Allograft Function

A. B. Adams[1], J. Goldstein[1], C. Garrett[1], R. Zhang[2], R. E. Patzer[1,2], K. A. Newell[1], N. A. Turgeon[1], A. S. Chami[1,3], A. Guasch[1,3], A. D. Kirk[4], S. O. Pastan[1,3], T. C. Pearson[1] and C. P. Larsen[1,*]

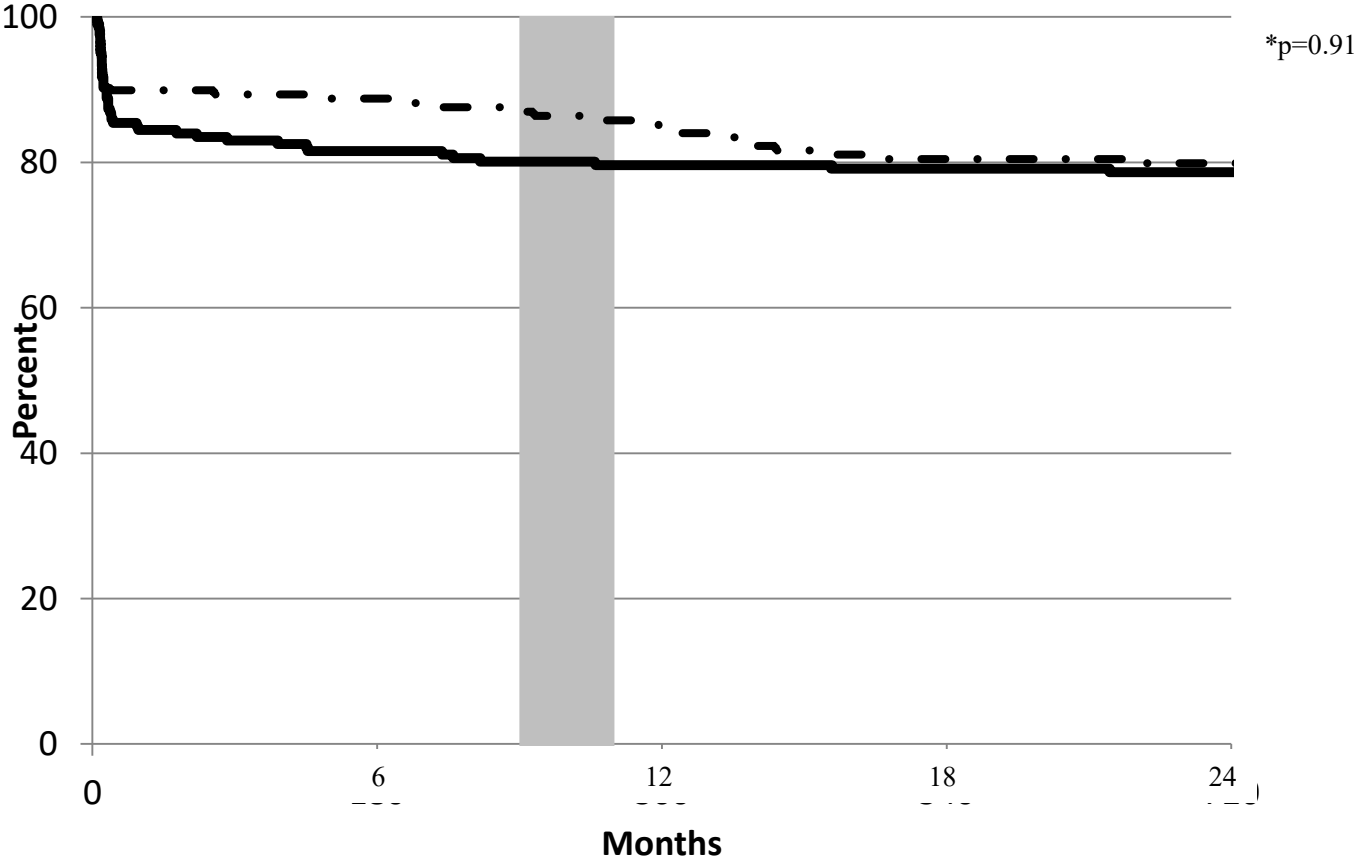
American Journal of Transplantation 2017; 17: 2922–2936
Wiley Periodicals Inc.



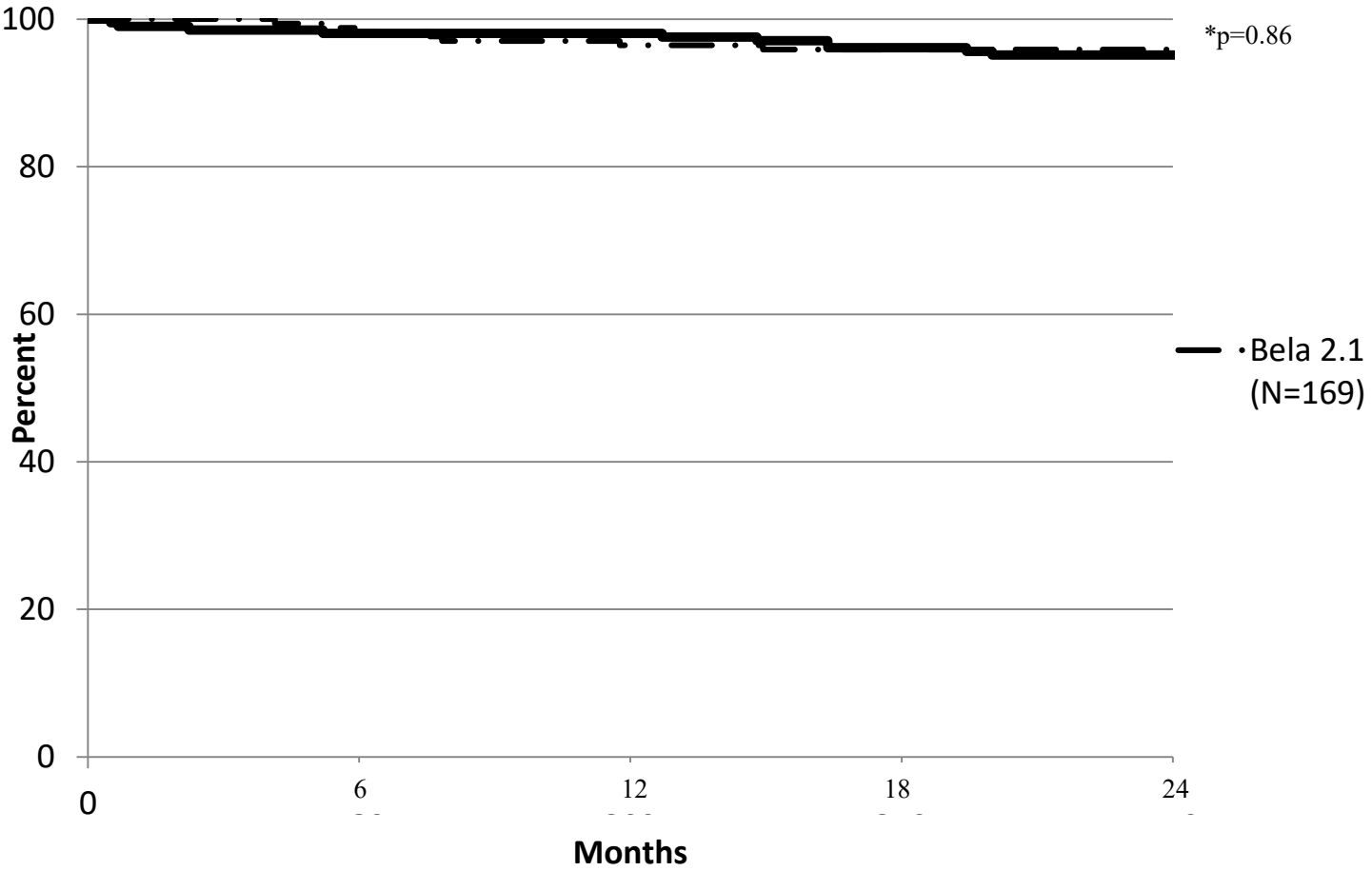
Update Belatacept Protocol



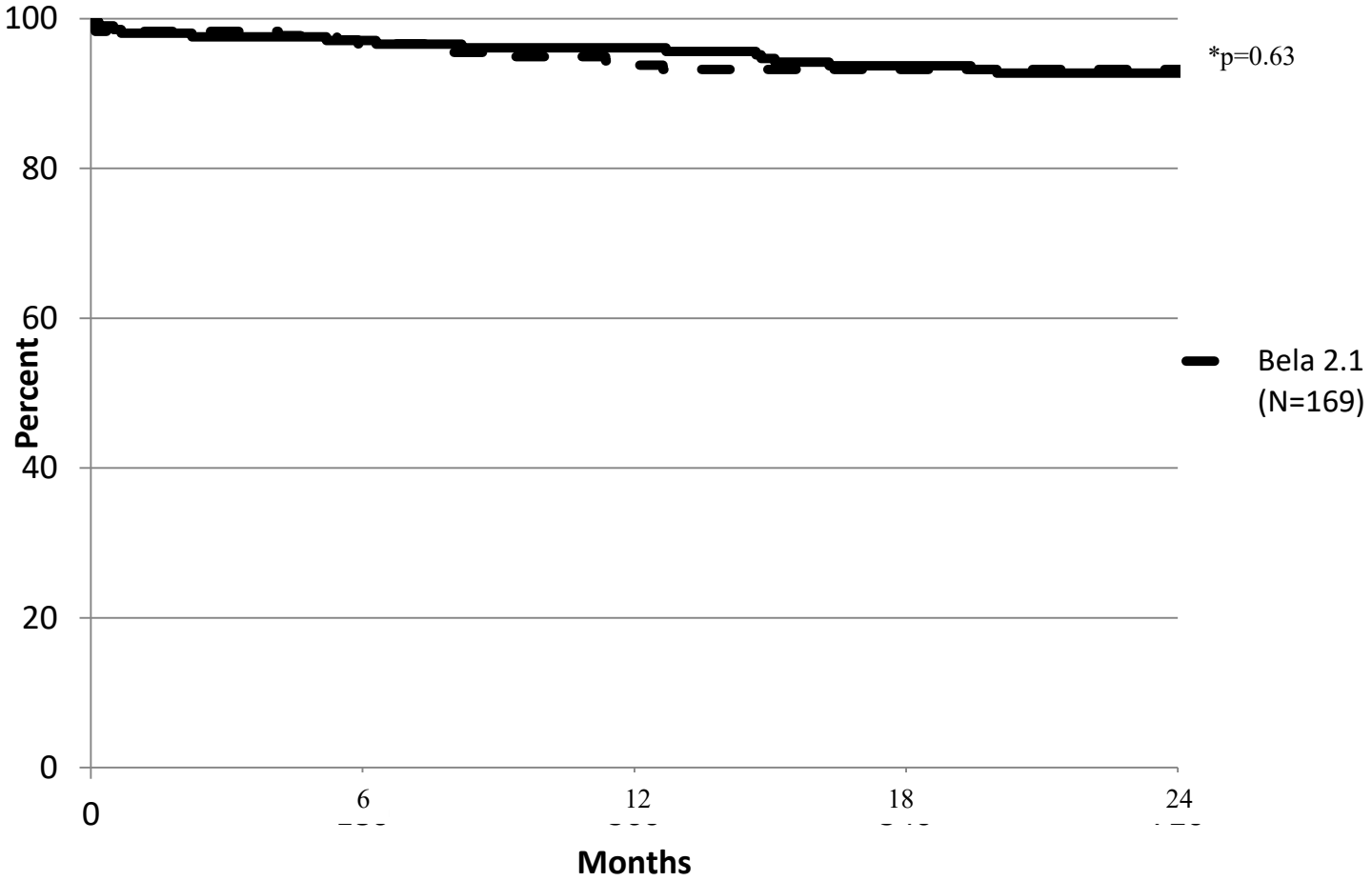
Freedom from Rejection



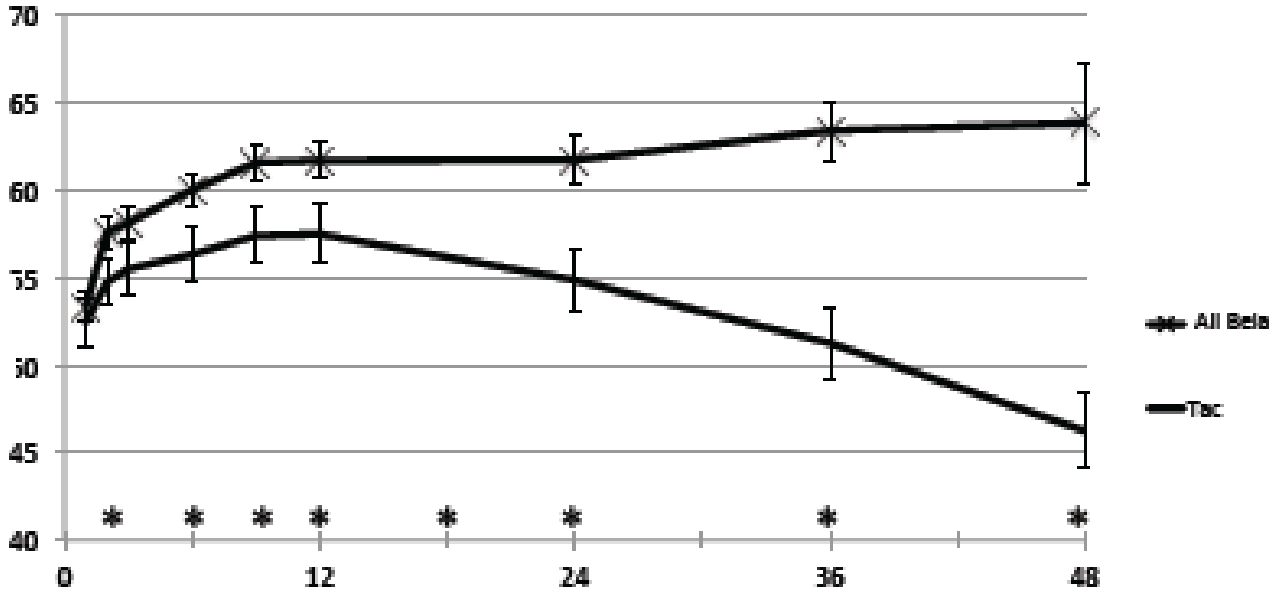
Patient Survival



Graft Survival

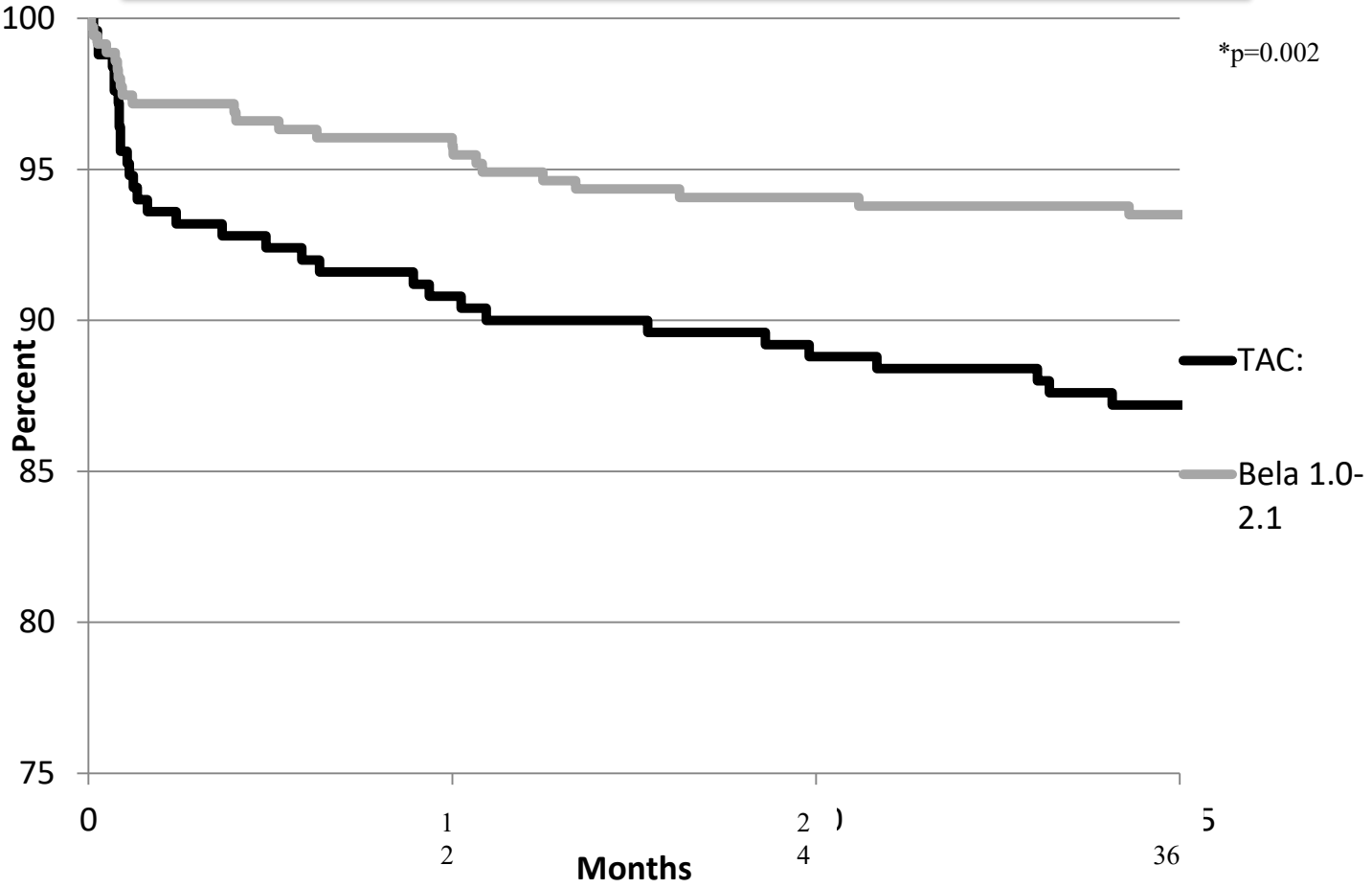


Renal Function
On Treatment Analysis- Combined



	1 mo	3 mo	3 mo	6 mo	9 mo	12 mo	24 mo	36 mo	48 mo
Bela(N=540)	528	521	517	494	479	446	316	179	46
Tac(N=200)	205	205	204	203	202	201	186	130	125

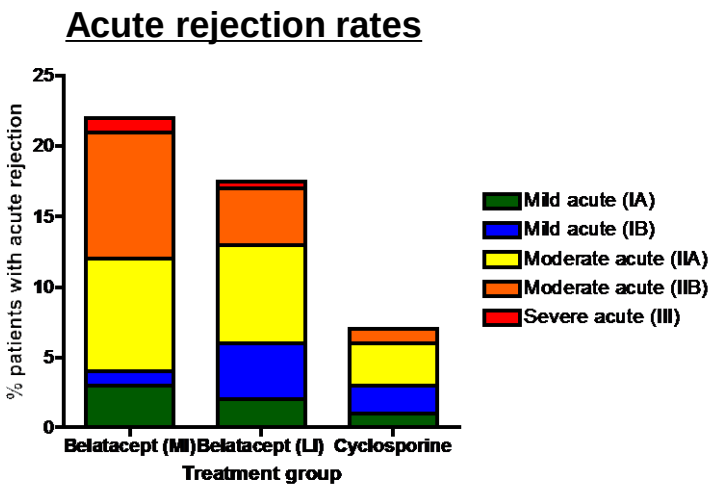
Freedom From DSA

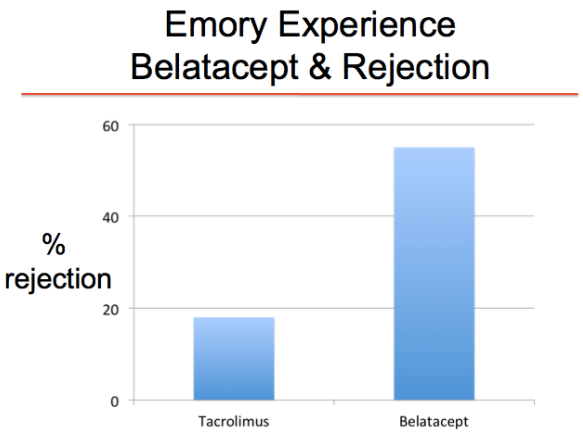


Belatacept and Rejection

- Better long-term renal function post-transplant
- Higher acute rejection rate and more severe pathology

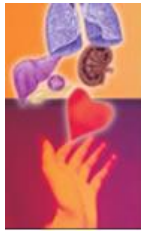
Why does belatacept-resistant rejection occur?





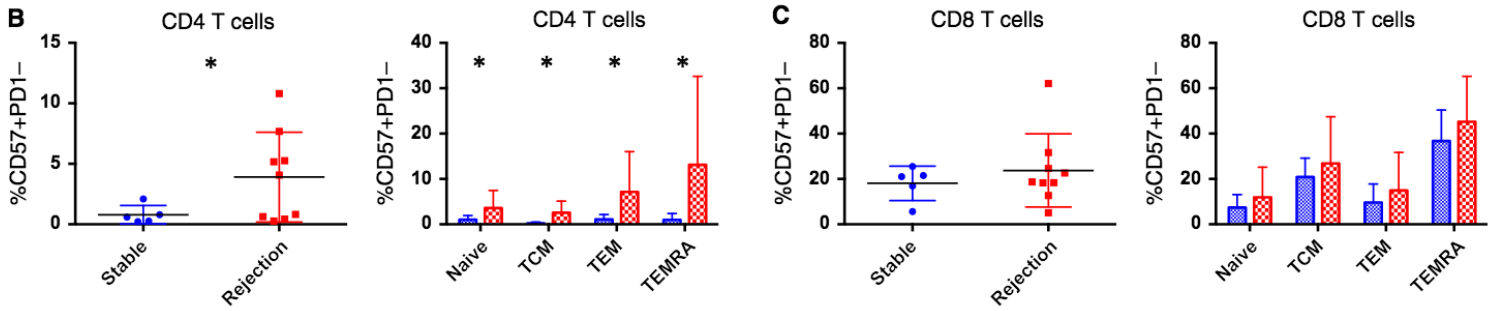
Costimulation Blockade Resistant Rejection

- alternative costimulatory molecules provide escape signals
- certain T cell subsets are less dependent on "traditional" costimulatory signals
  - Memory T cells
    - acquired directly vs via heterologous response
  - ? Other cell subsets



CD57+ CD4 T Cells Underlie Belatacept-Resistant Allograft Rejection

J. Espinosa[1,2], F. Herr[3], G. Tharp[4], S. Bosinger[4], M. Song[1], A. B. Farris III[5], R. George[1], J. Cheeseman[1,2], L. Stempora[1,2], R. Townsend[6], A. Durrbach[3,7] and A. D. Kirk[1,2,*]



Editorial

CD4+ CD28-Negative Cells: Armed and Dangerous

American Journal of Transplantation 2017; 17: 2285–2299
Wiley Periodicals Inc.

doi: 10.1111/ajt.14349

Belatacept-Resistant Rejection Is Associated With CD28+ Memory CD8 T Cells

D. V. Mathews[1,†], W. C. Wakwe[1,†], S. C. Kim[1],
M. C. Lowe[1], C. Breeden[1], M. E. Roberts[2],
A. B. Farris[1], E. A. Strobert[3], J. B. Jenkins[3],
C. P. Larsen[1,3], M. L. Ford[1], R. Townsend[2] and
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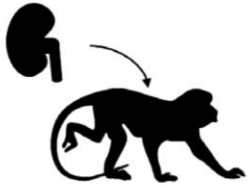
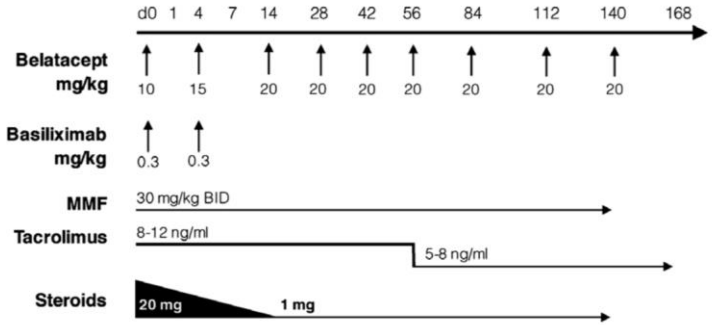
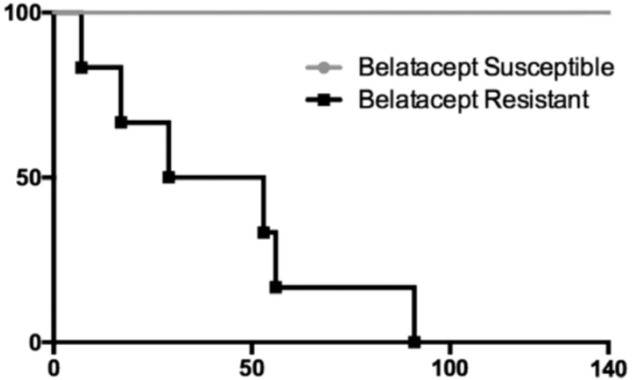
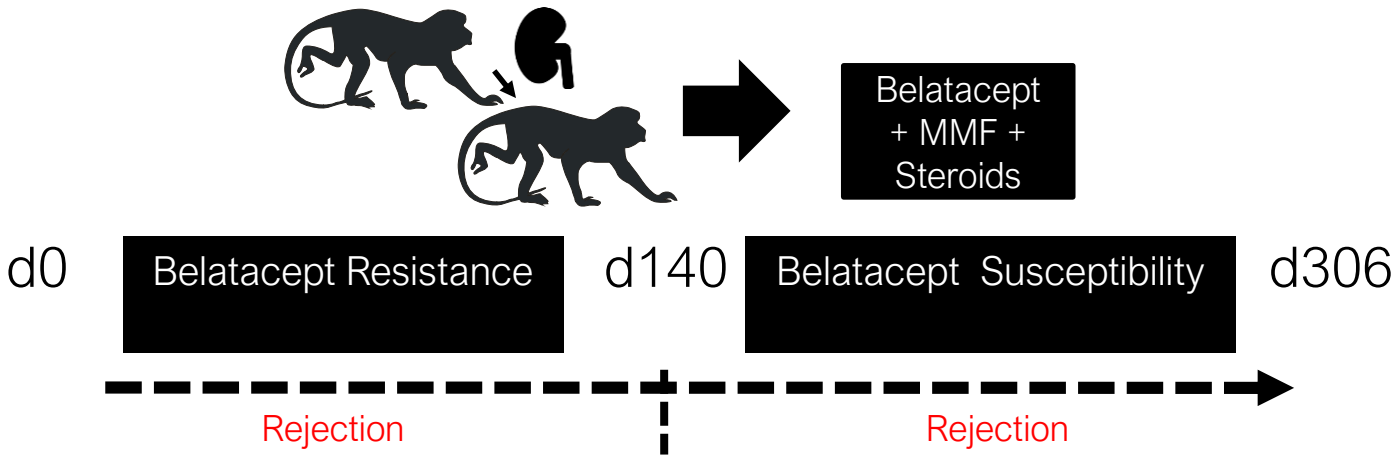




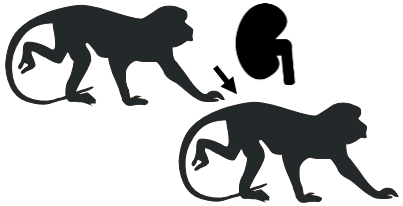


Understanding Mechanisms of Costimulation Independence



Understanding Mechanisms of Costimulation Independence

Pre-Transplant Immune Phenotype?

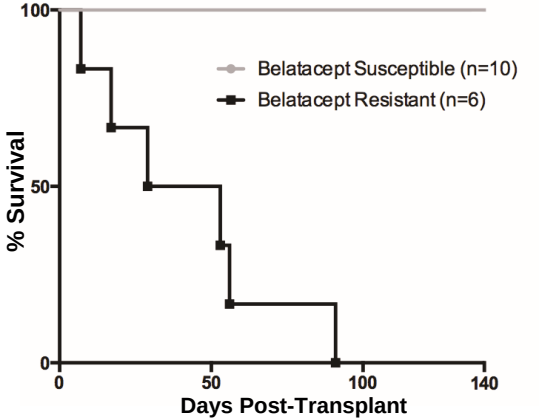


Belatacept + MMF + Steroids

d0 — Belatacept Resistance — d140 — Belatacept Susceptibility — d306

Rejection

Rejection



Understanding Mechanisms of Costimulation Independence

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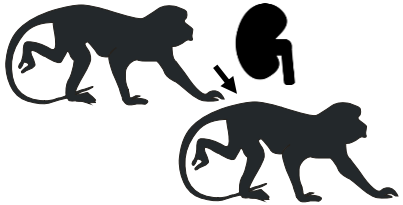

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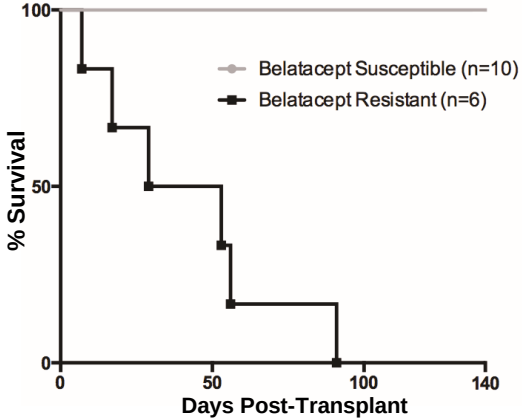
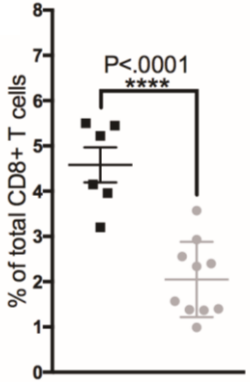
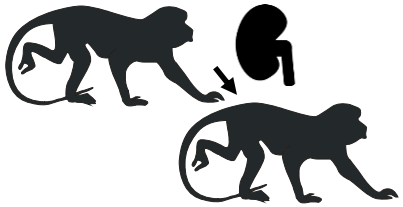




Understanding Mechanisms of Costimulation Independence

Pre-Transplant Immune Phenotype?



Belatacept + MMF + Steroids

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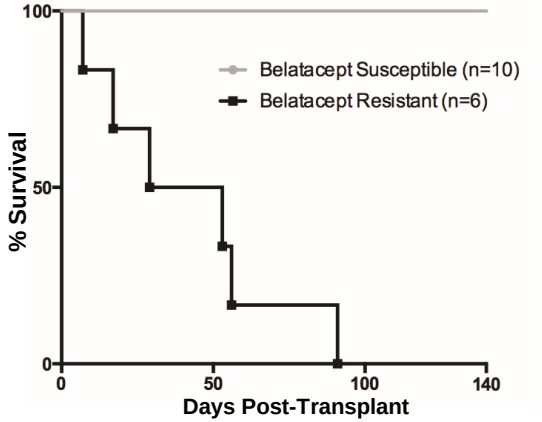
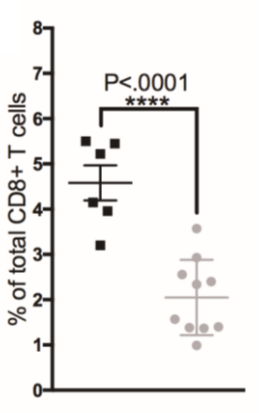
Rejection





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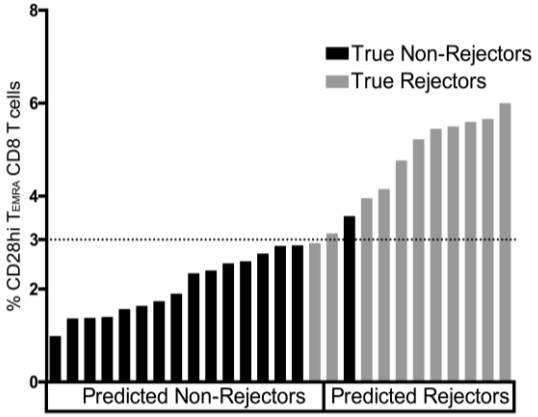
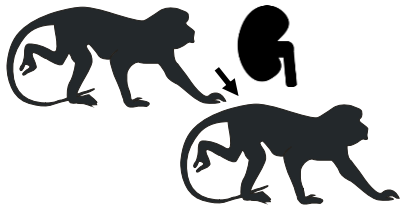
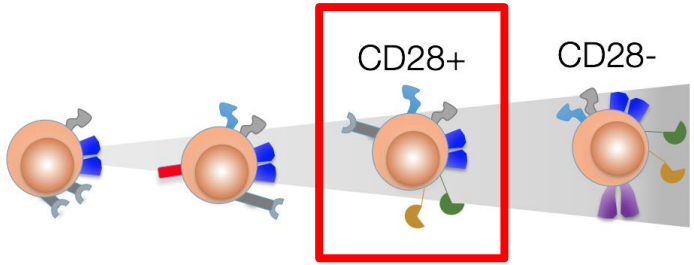
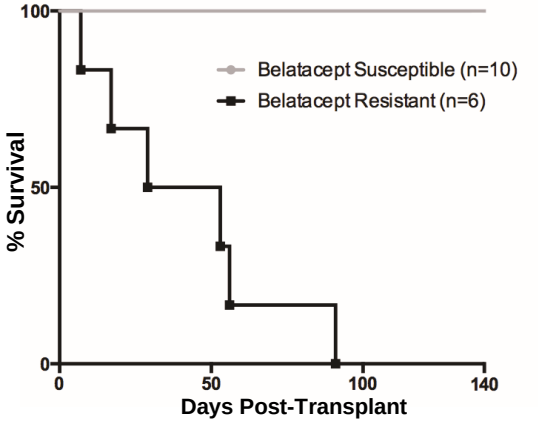
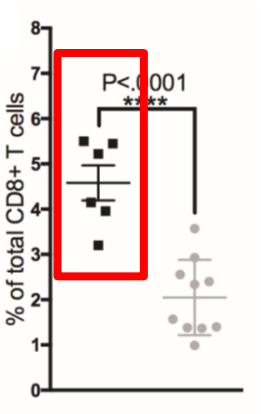


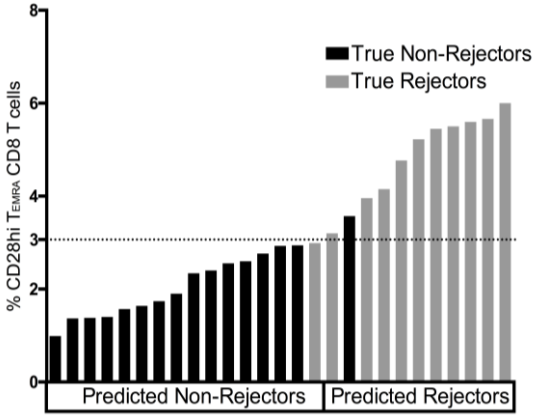
Understanding Mechanisms of Costimulation Independence





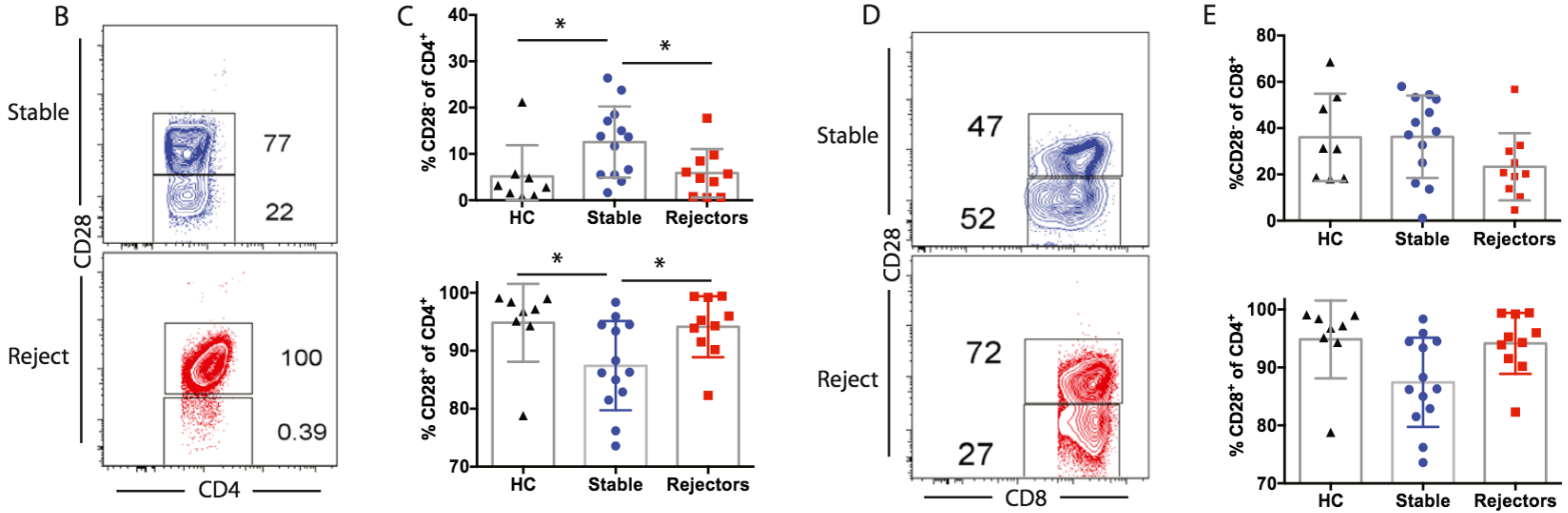




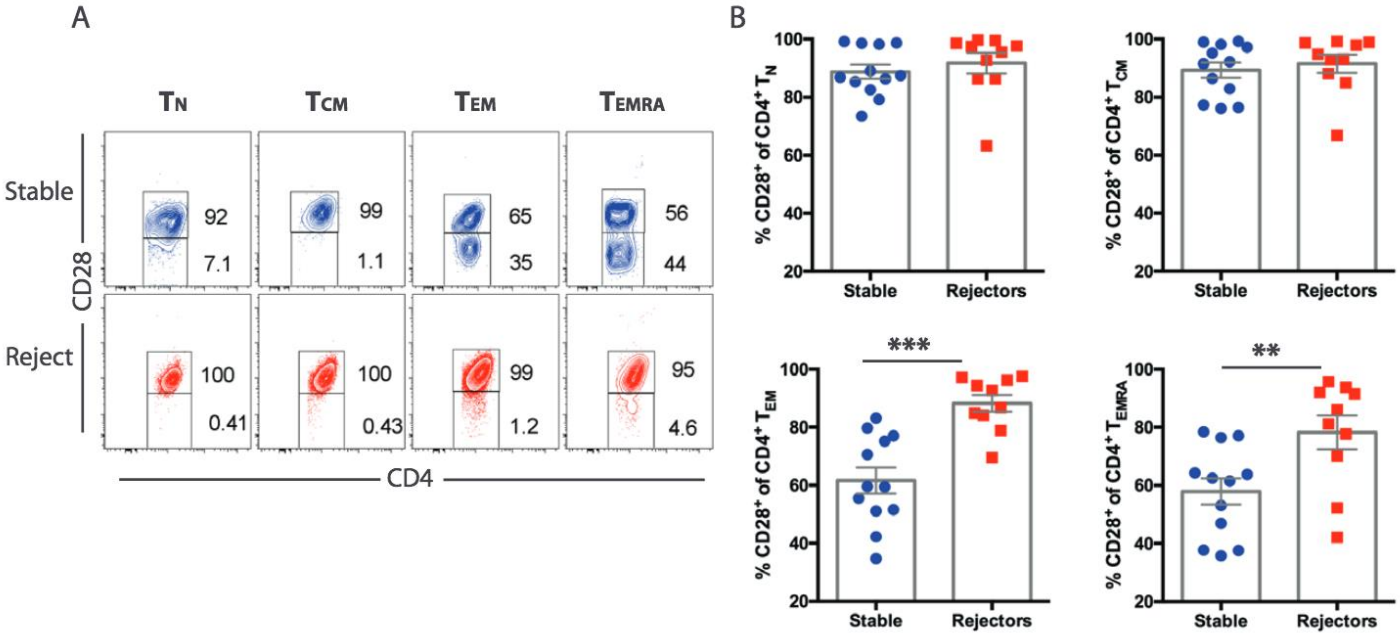


Increased Pretransplant Frequency of CD28$^+$ CD4$^+$ T_{EM} Predicts Belatacept-Resistant Rejection in Human Renal Transplant Recipients

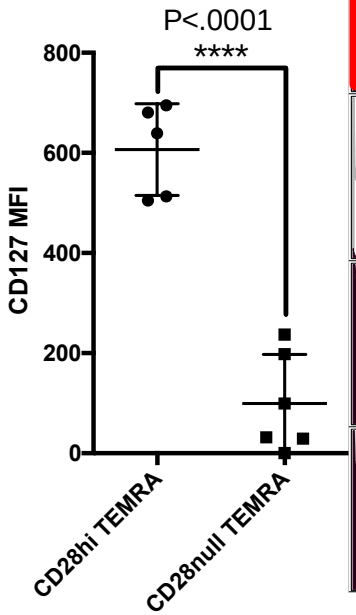
M. Cortes-Cerisuelo, S. J. Laurie,
D. V. Mathews, P. D. Winterberg, C. P. Larsen,
A. B. Adams and M. L. Ford*

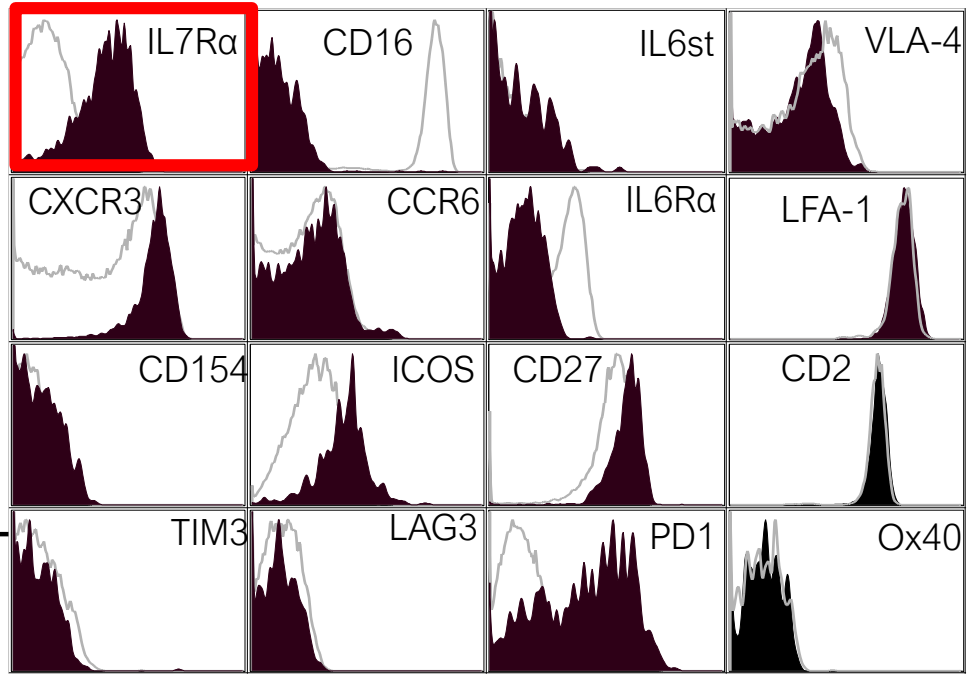


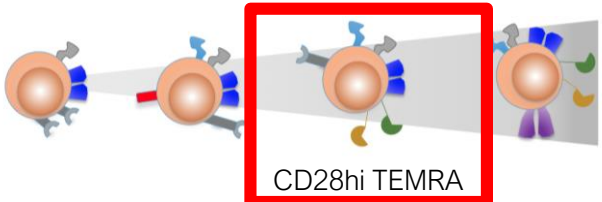
Increased Pretransplant Frequency of CD28$^+$ CD4$^+$ T_{EM} Predicts Belatacept-Resistant Rejection in Human Renal Transplant Recipients



CD28hi TEMRA Cells Express High Levels of IL-7Rα

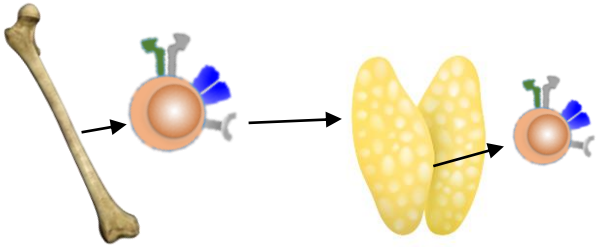


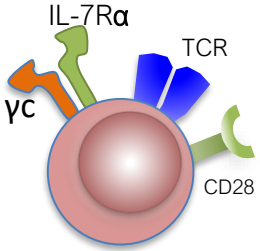




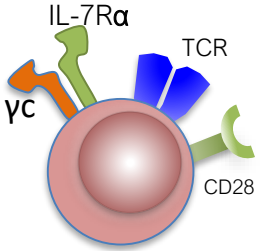
The Role of IL-7Rα Signaling in Transplantation

Lymphopoiesis

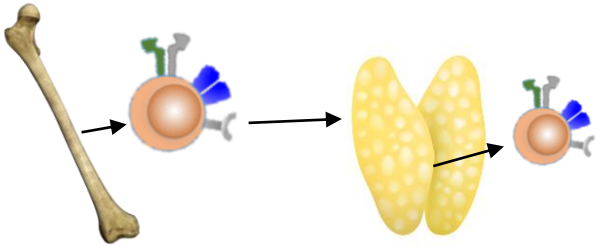




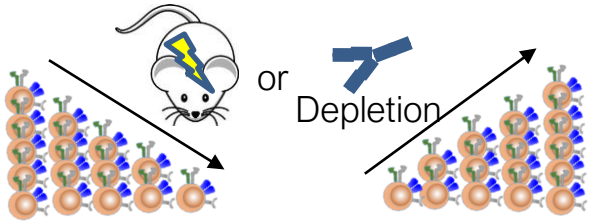
The Role of IL-7Rα Signaling in Transplantation



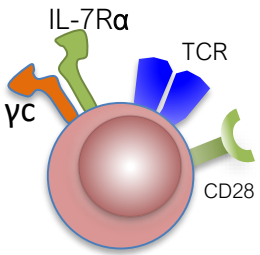
Lymphopoiesis



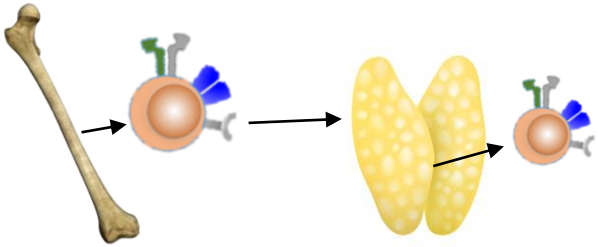
Homeostatic Proliferation



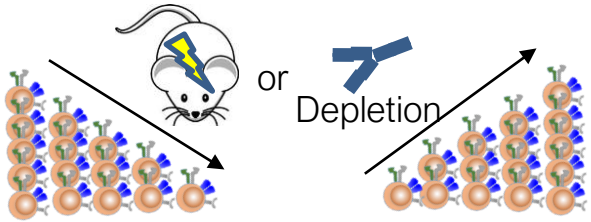
The Role of IL-7Rα Signaling in Transplantation



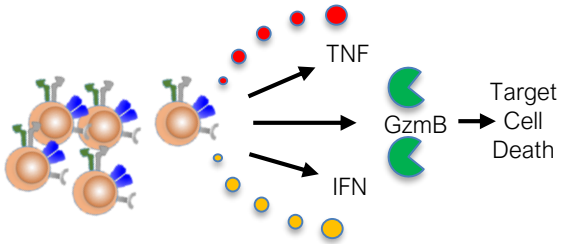
Lymphopoiesis



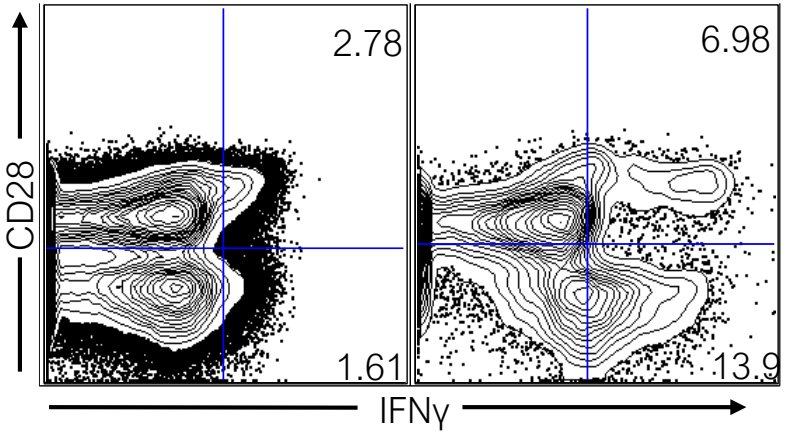
Homeostatic Proliferation

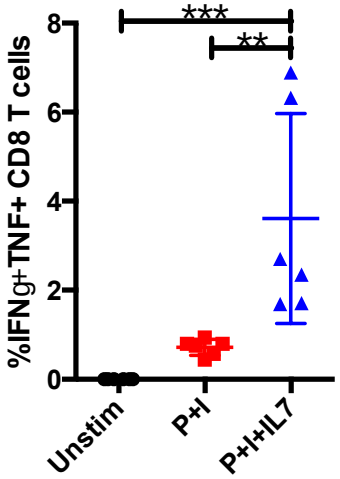


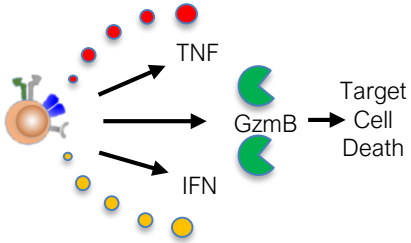
Signal 3 Cytokine?



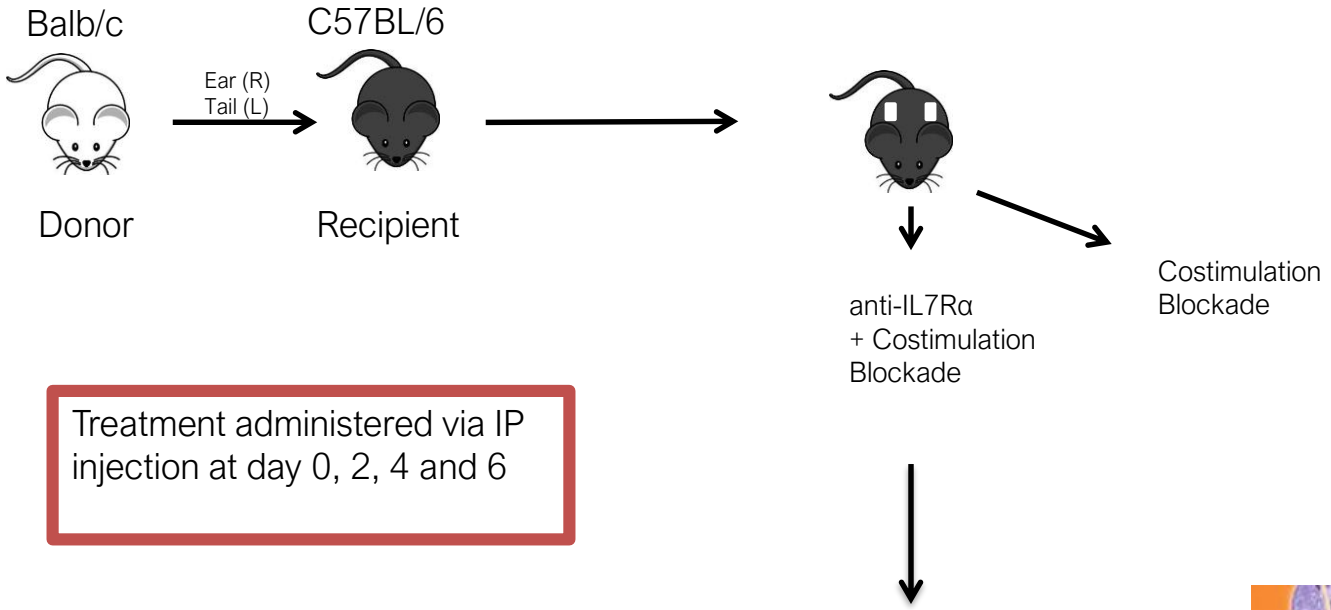
Addition of IL-7 Augments Effector Function





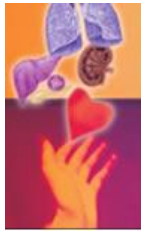


Mouse Allogeneic Skin Graft Experimental Design



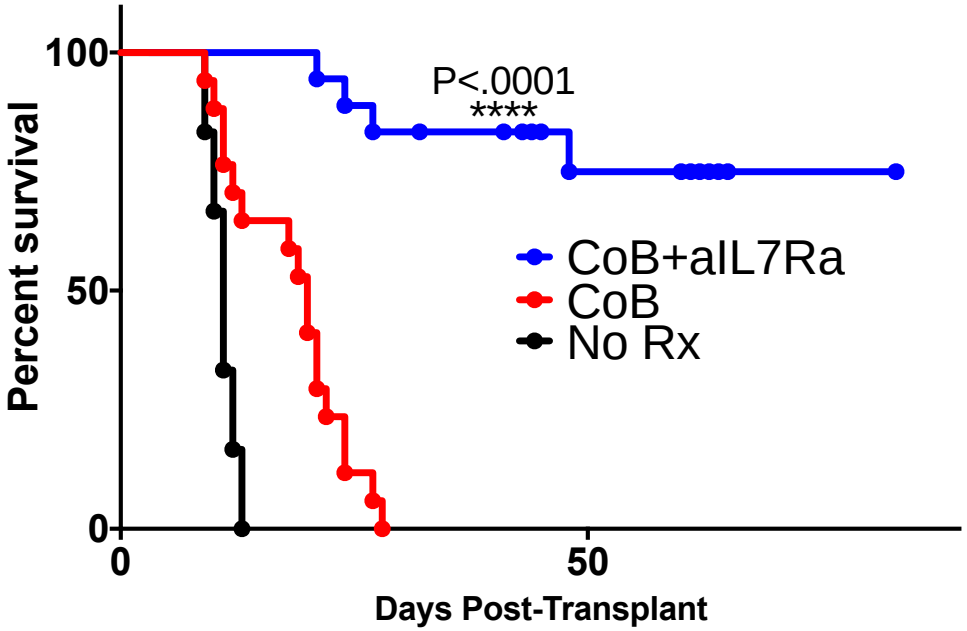
Treatment administered via IP injection at day 0, 2, 4 and 6

Assess Skin Graft Survival

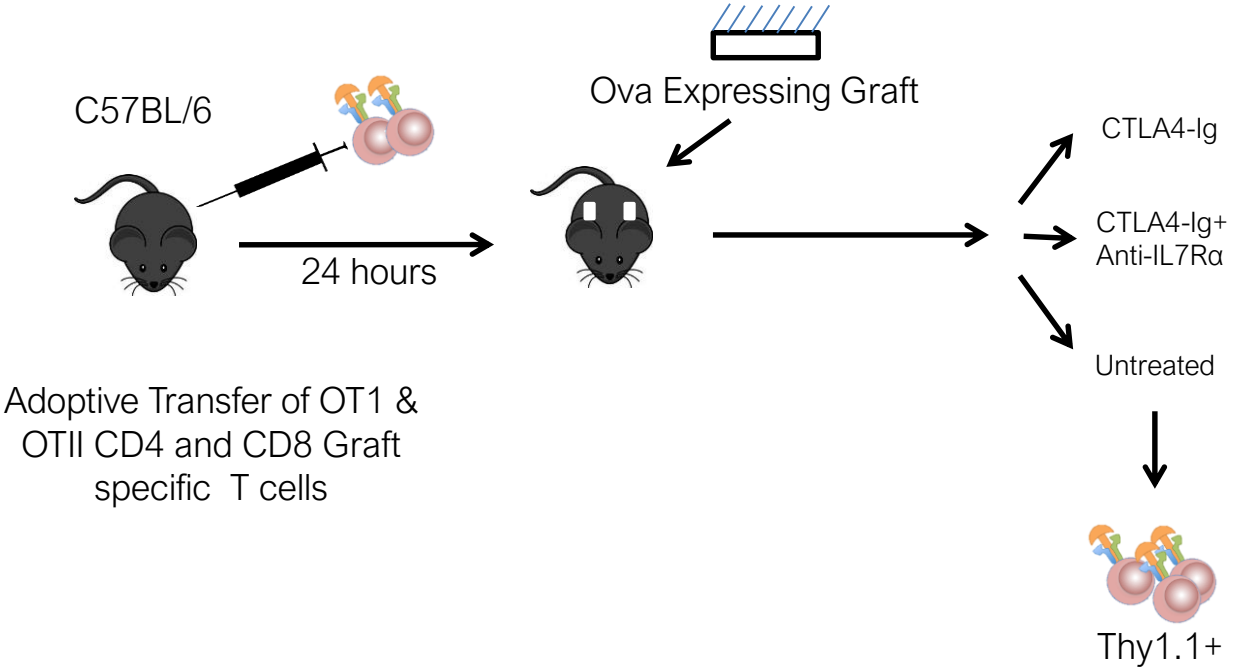


DEPARTMENT OF SURGERY
EMORY

Blocking IL-7Rα Prevents Costimulation Independent Rejection

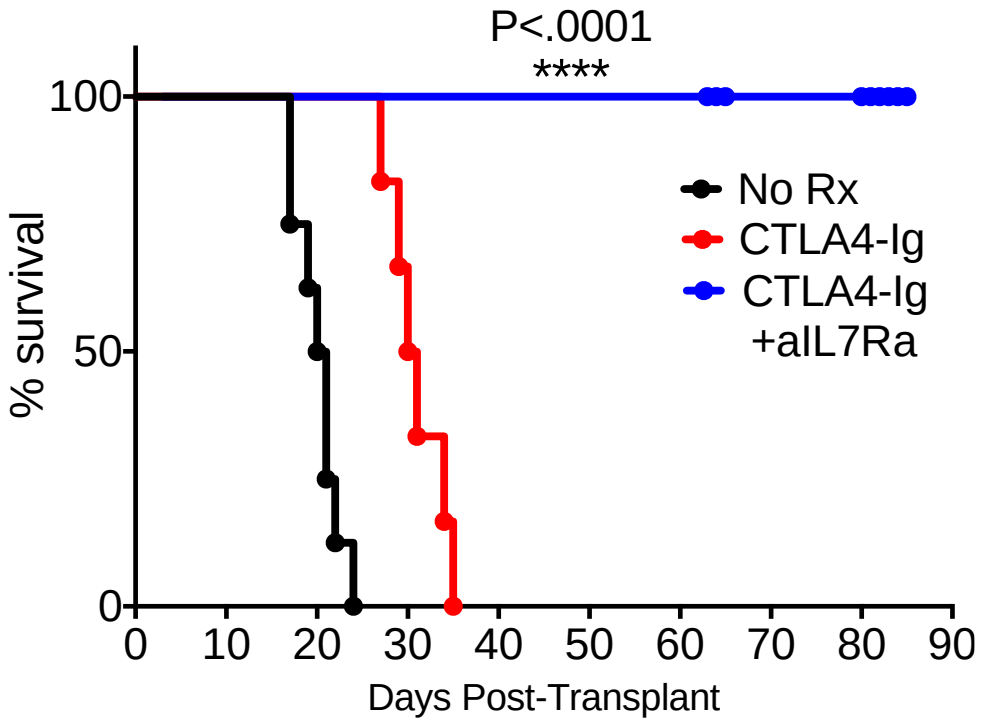


Role of IL-7Rα in Costimulation Independent Rejection

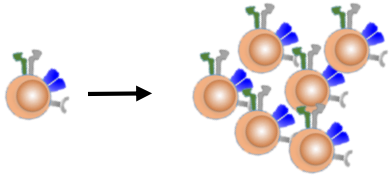


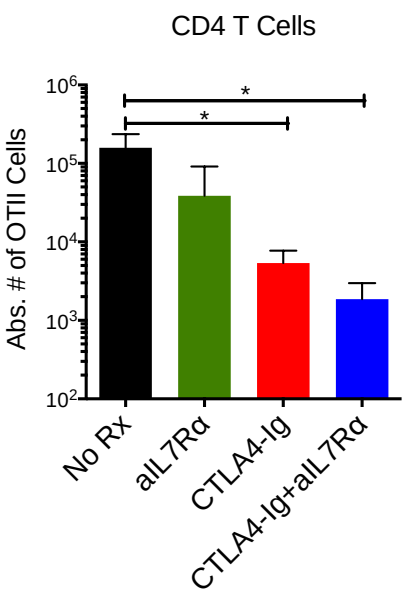
Tracking Graft Specific T cells

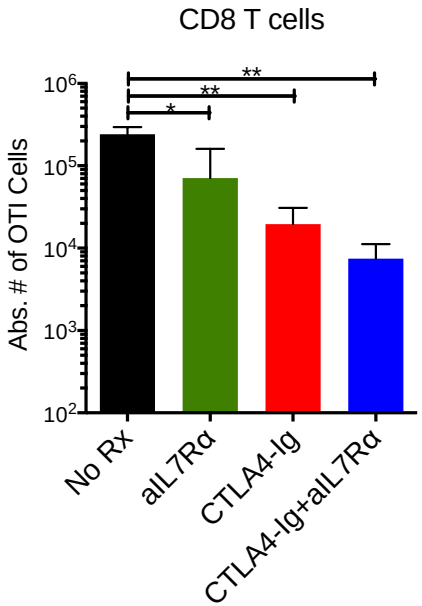
Addition of Anti-IL-7Rα Synergistically Prevents Costimulation Independent Rejection



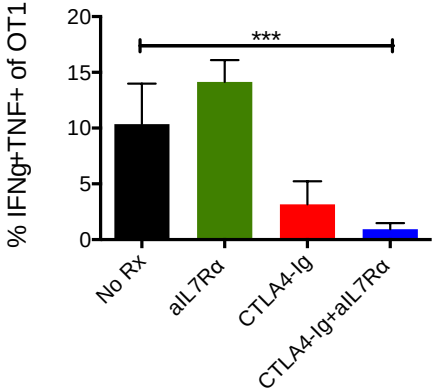
Anti-IL-7Rα + CoB Results in Decreased Expansion of Graft Reactive T cells

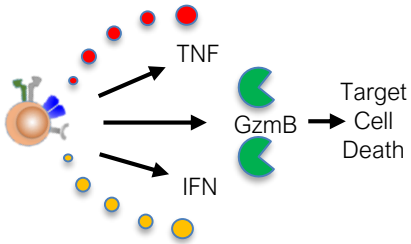


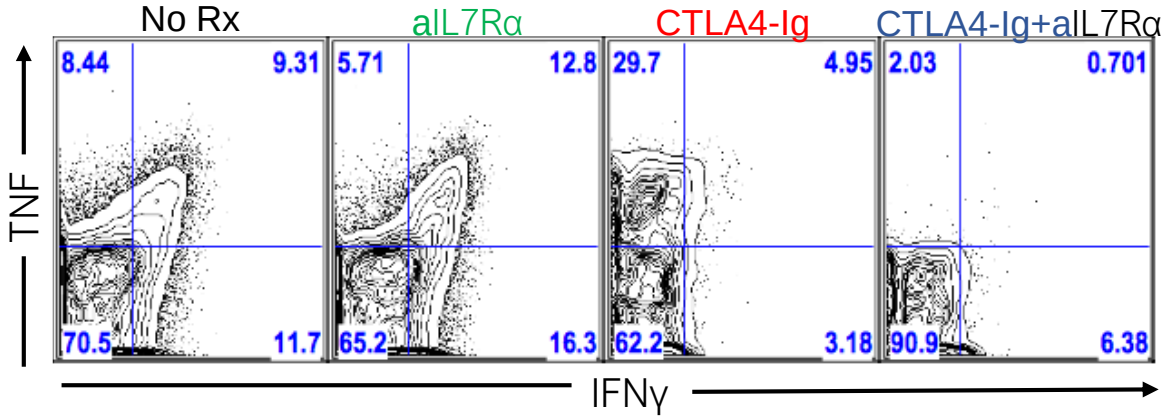




Anti-IL-7Rα+CoB Decreased Effector Function of Graft Reactive T cells







Inflammation, Vol. 35, No. 6, December 2012 (© 2012)
DOI: 10.1007/s10753-012-9496-8

$CD4^{+}CD25^{+}CD127^{low/-}$ T Cells: A More Specific Treg Population in Human Peripheral Blood

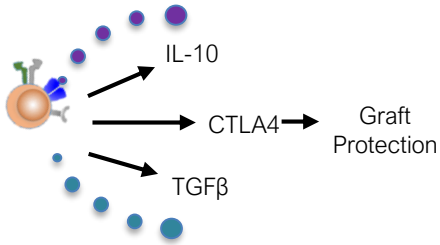
- $CD4^{+}$ $CD25^{+}$ $CD127^{lo/-}$ cells express highest level of Foxp3
- Strongest correlation with functional activity
- Used as phenotype in clinical trials

Anti-IL-7Rα + Costimulation Blockade Impact on Graft Specific CD4 T cells

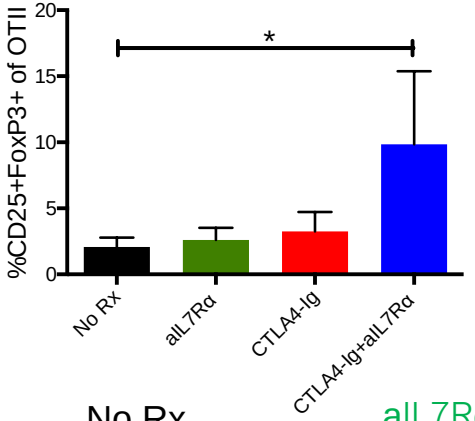
Treg Phenotype

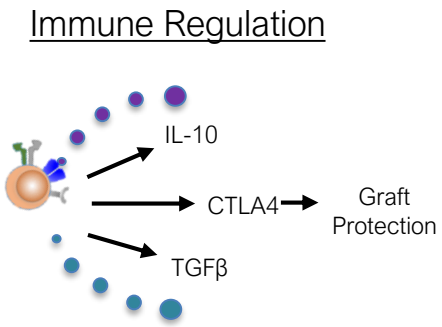
IL7Rα (CD127) Negative, CD25 (IL2Rα) Positive

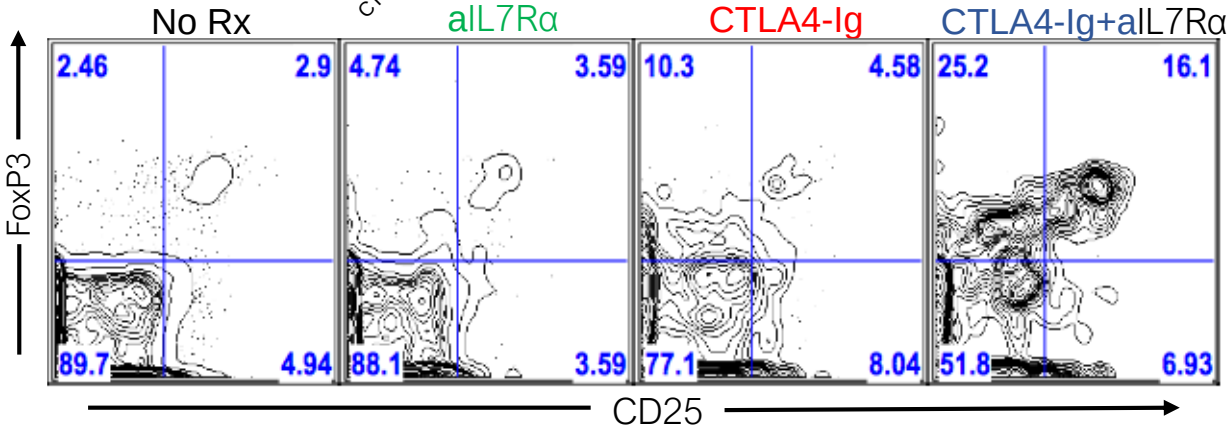
Immune Regulation



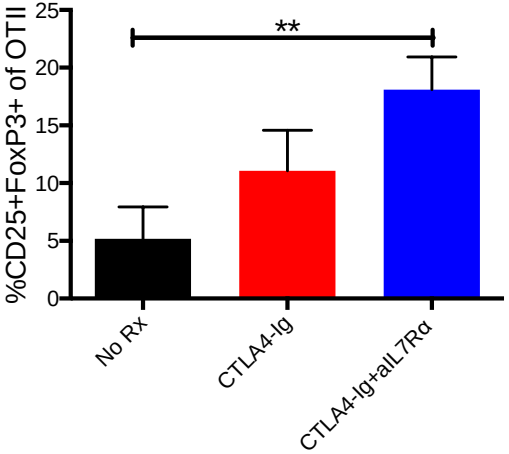
Anti-IL-7Rα + Costimulation Blockade increased Frequency of Tregs

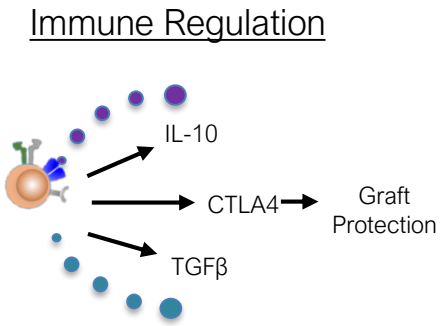


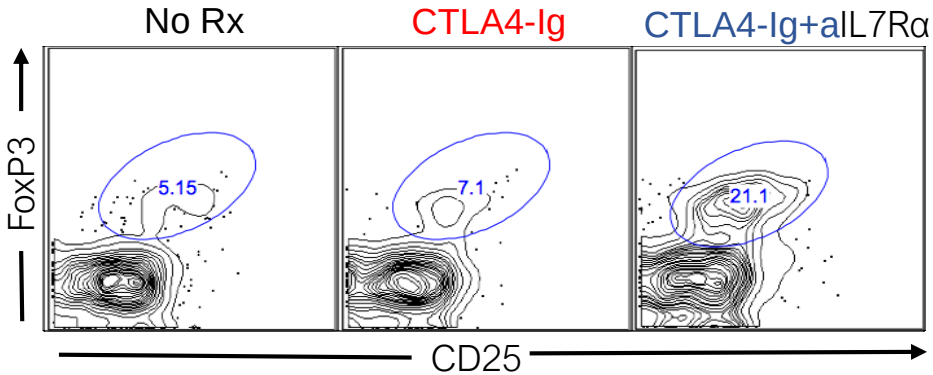




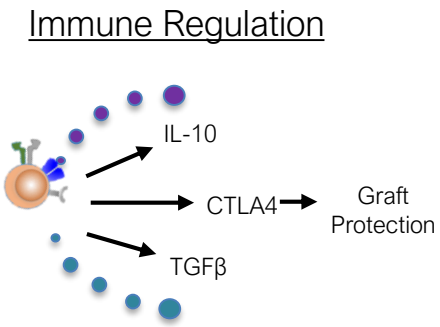
Anti-IL-7Rα + CoB increased Frequency of Tregs Sustained at Day 20

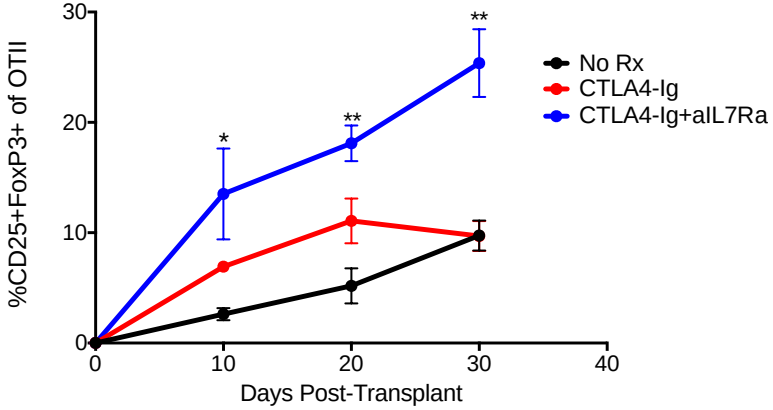


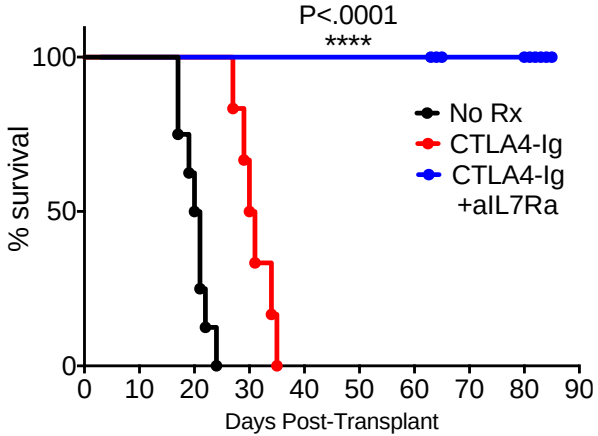




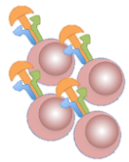
Anti-IL-7Rα + CoB increased Frequency of Tregs Sustained at Day 30



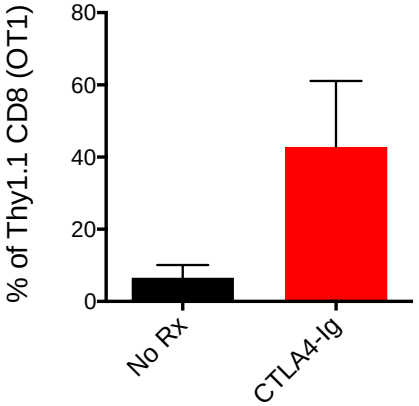


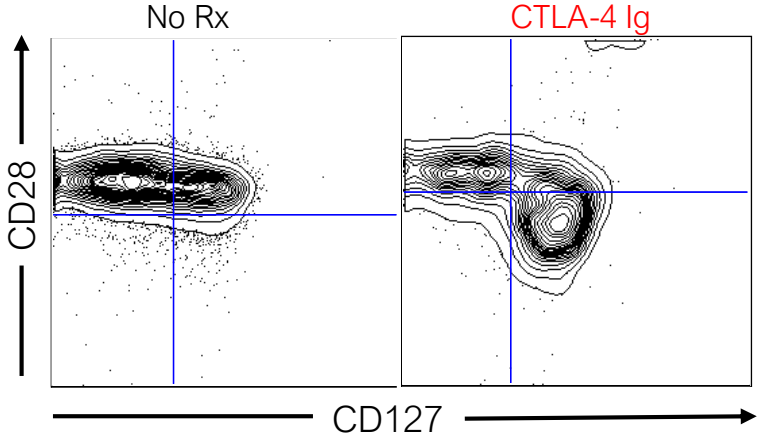


Costimulation Independent CD8 T cells Decrease CD28 Expression, Increase IL-7Rα



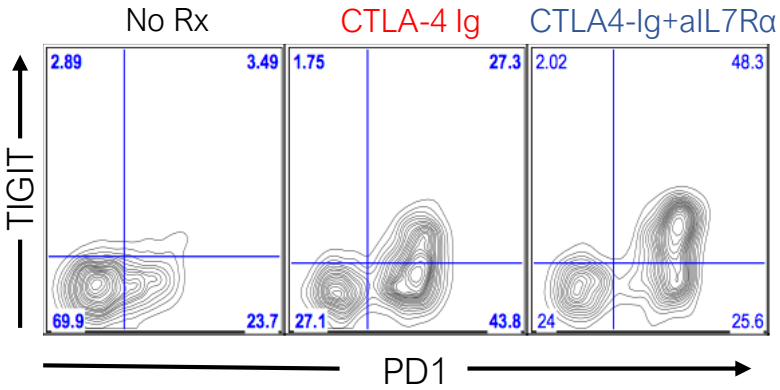
CD8 OTI
Thy1.1

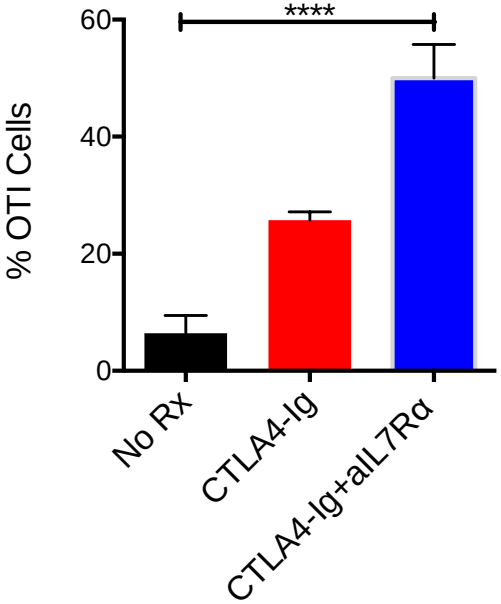




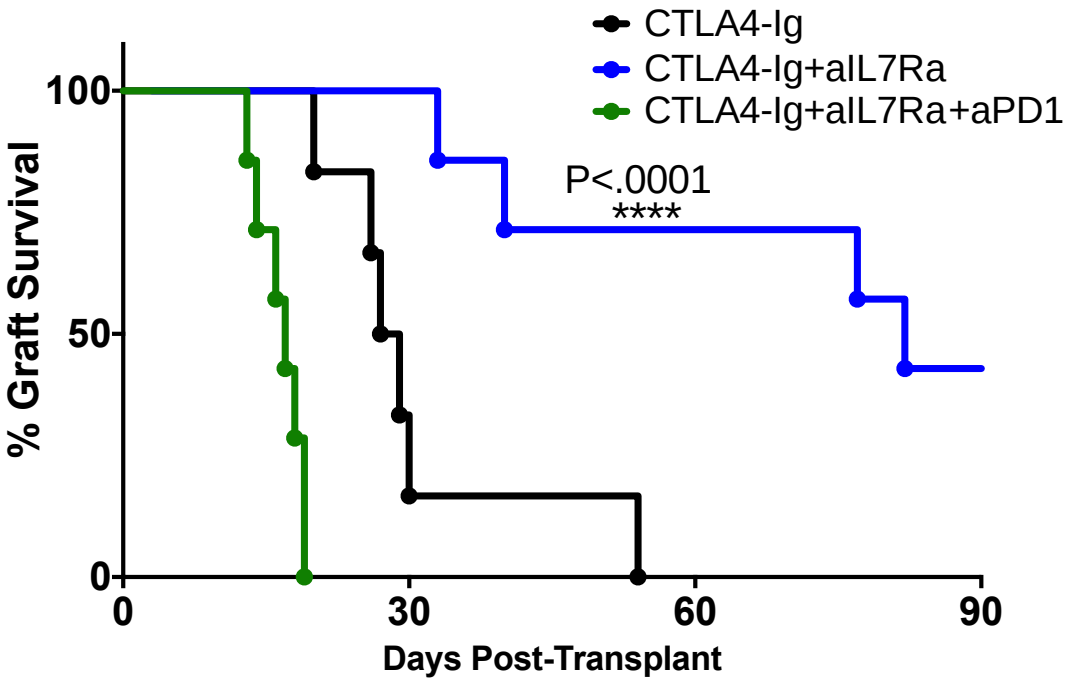
Anti-IL-7Rα + CoB Induces an Exhaustion-like Phenotype in Graft Reactive T cells

CD8 OTI
Thy1.1



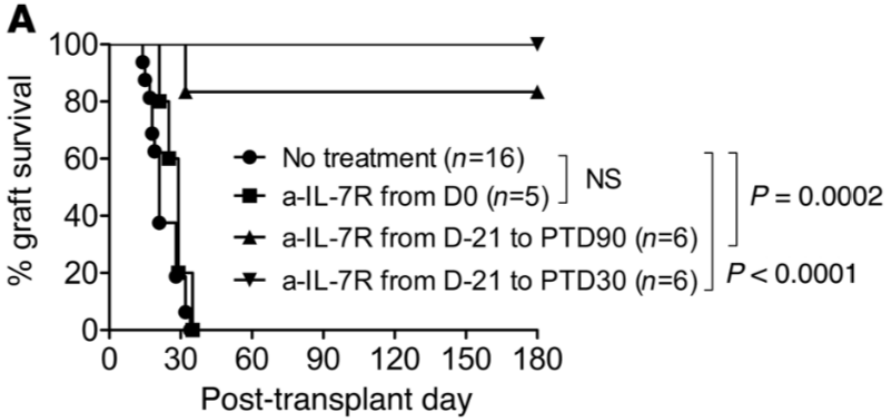


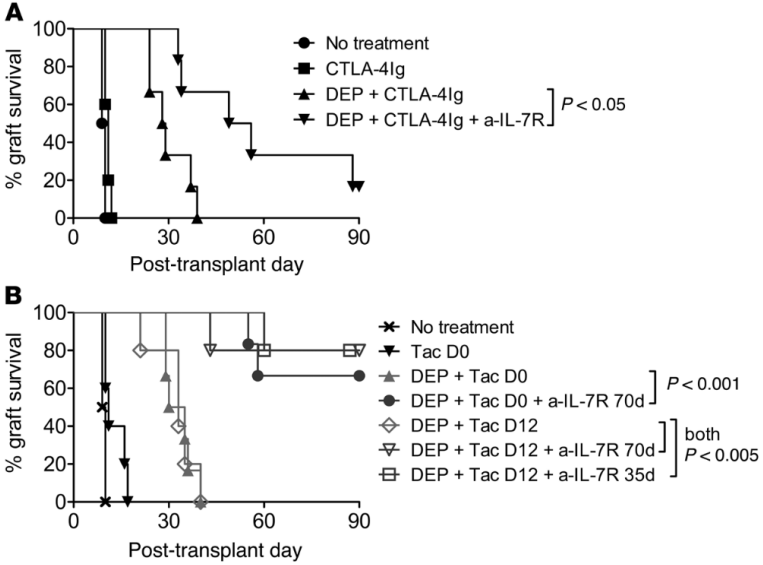
Anti-IL7Ra+CoB Mediated Graft Survival is PD1 Dependent



IL-7 receptor blockade following T cell depletion promotes long-term allograft survival

Hoa-Le Mai,[1] Françoise Boeffard,[1] Julie Longis,[1] Richard Danger,[1] Bernard Martinet,[1] Fabienne Haspot,[1] Bernard Vanhove,[1,2] Sophie Brouard,[1] and Jean-Paul Soulillou[1,2]



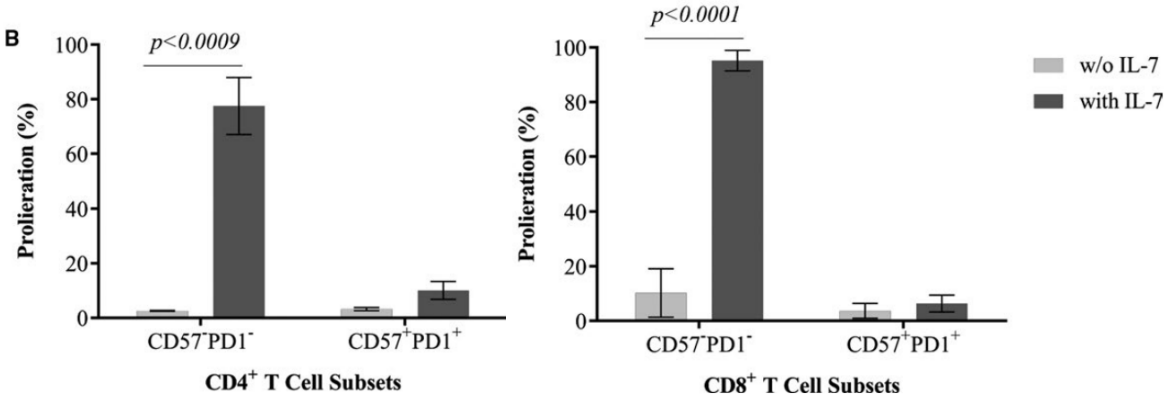


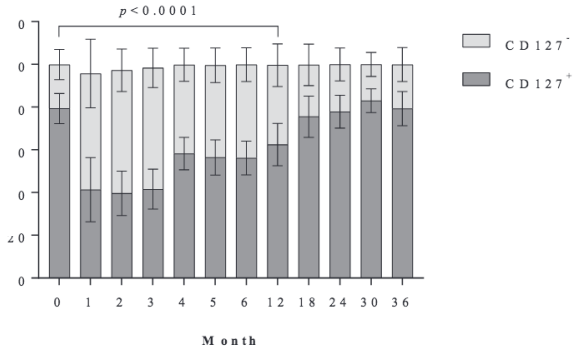
BRIEF COMMUNICATION

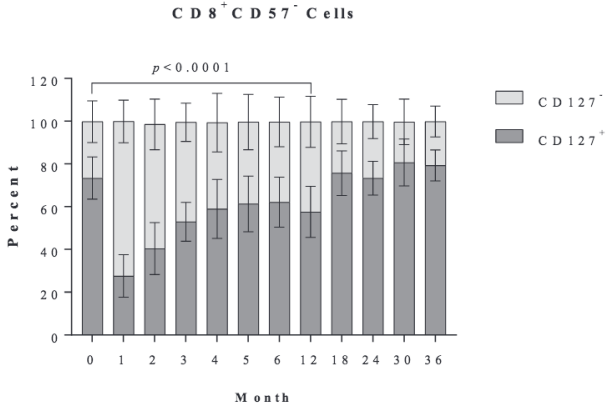
AJT

IL-7 receptor heterogeneity as a mechanism for repertoire change during postdepletional homeostatic proliferation and its relation to costimulation blockade–resistant rejection

He Xu | Victoria A. Bendersky | Todd V. Brennan | Jaclyn R. Espinosa | Allan D. Kirk





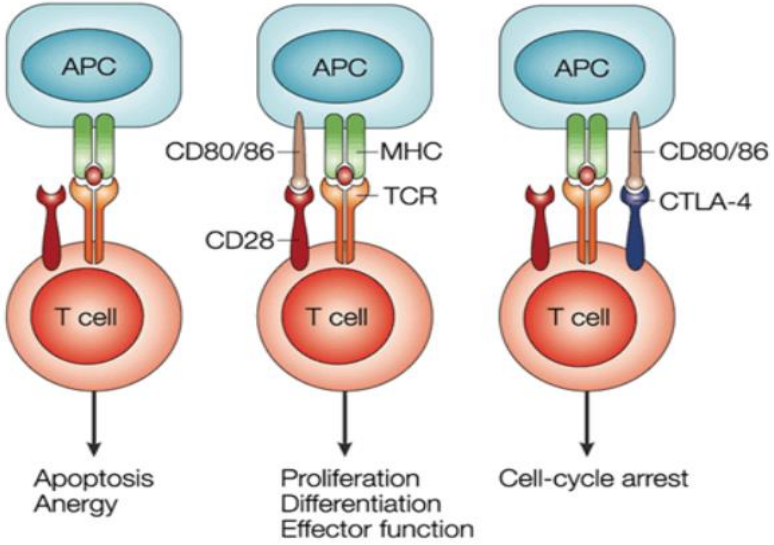


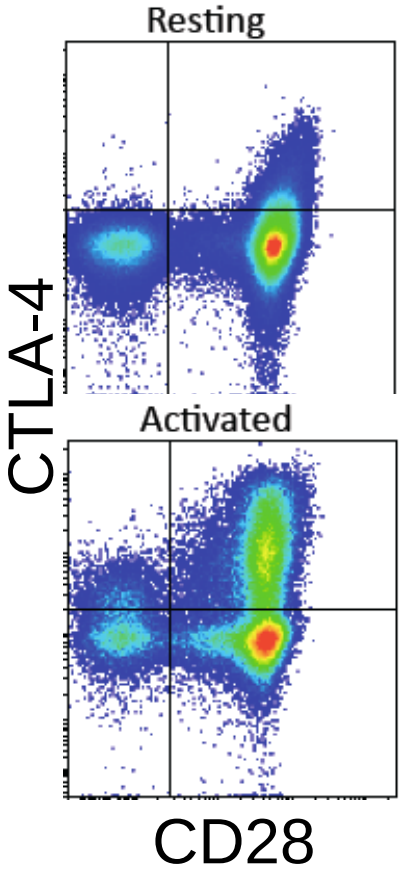
nature COMMUNICATIONS

IL-7 receptor blockade blunts antigen-specific memory T cell responses and chronic inflammation in primates

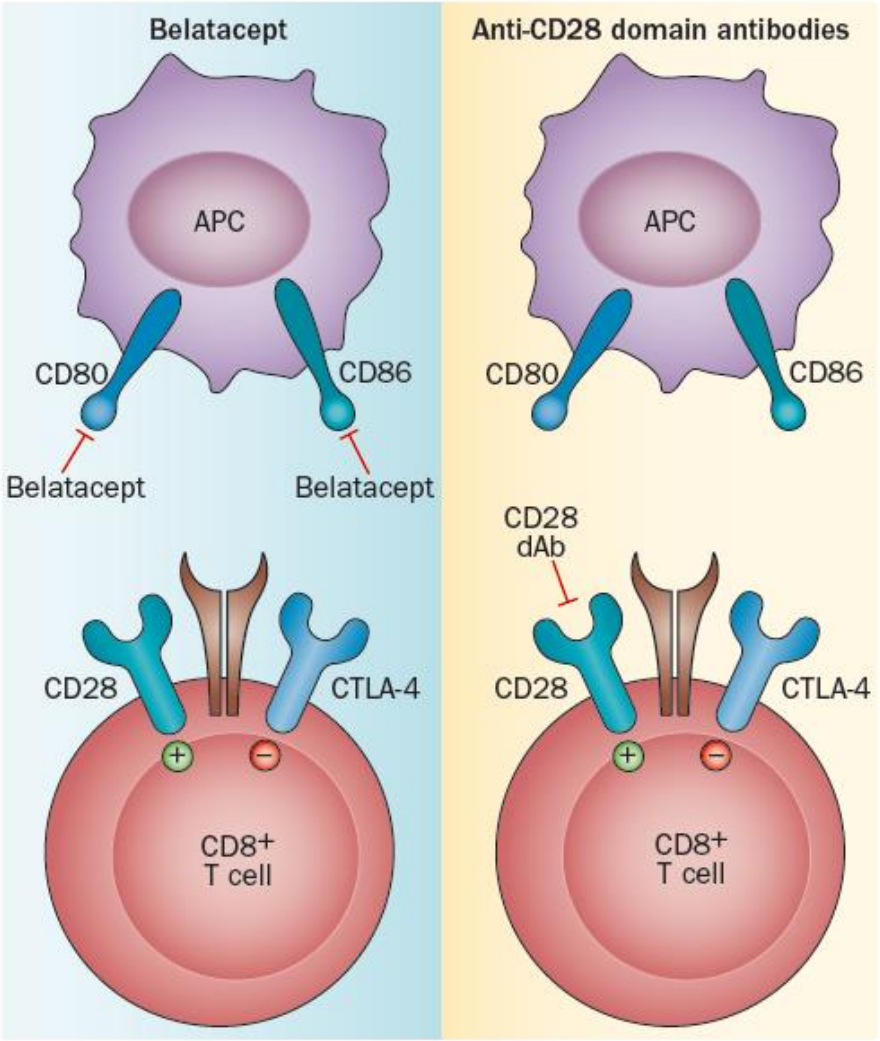
Lyssia Belarif[1,2], Caroline Mary[1,2], Lola Jacquemont[1], Hoa Le Mai[1], Richard Danger[1], Jeremy Hervouet[1], David Minault[1], Virginie Thepenier[1,2], Veronique Nerrière-Daguin[1], Elisabeth Nguyen[1], Sabrina Pengam[1,2], Eric Largy[3,4], Arnaud Delobel[3], Bernard Martinet[1], Stéphanie Le Bas-Bernardet[1,5], Sophie Brouard[1,5], Jean-Paul Soulillou[1], Nicolas Degauque[1,5], Gilles Blancho[1,5], Bernard Vanhove[1,2] & Nicolas Poirier[1,2]

Next Generation Costimulation Blockade

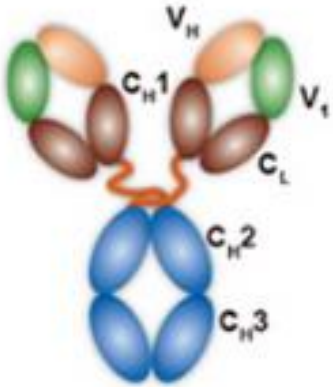




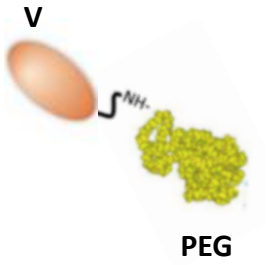
T cell function is tightly regulated by a fine balance of costimulatory and coinhibitory signals

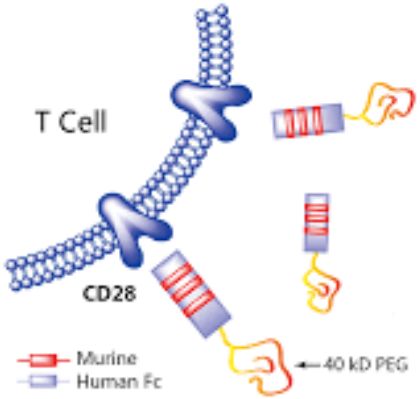

Belatacept
APC
CD80
CD86
Belatacept
Belatacept
CD28
CTLA-4
CD8+
T cell
Anti-CD28 domain antibodies
APC
CD80
CD86
CD28
dAb
CD28
CTLA-4
CD8+
T cell

Lulizumab- a domain antibody



traditional antibody (IgG)

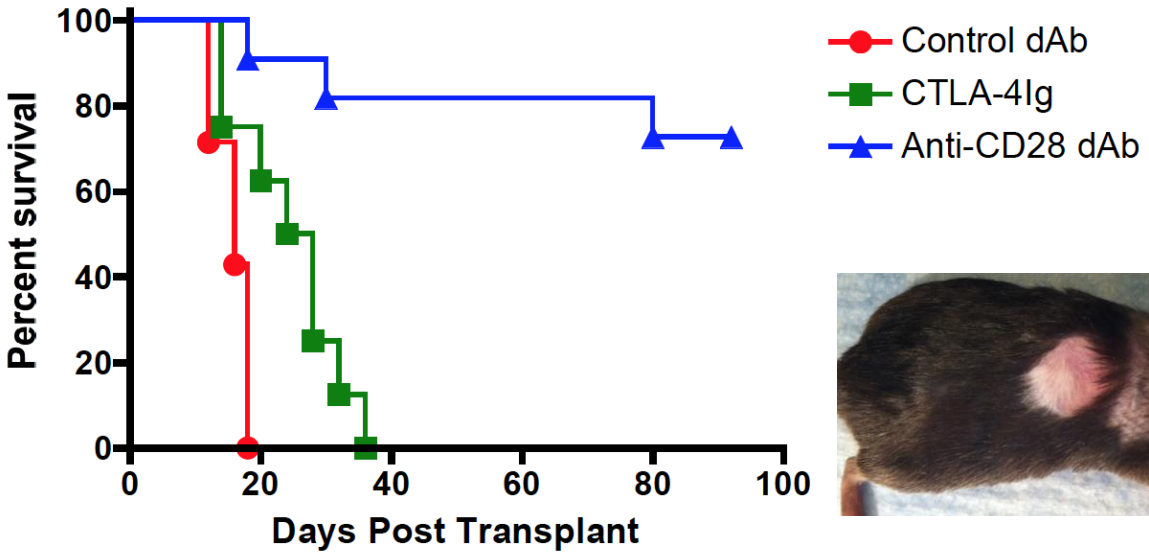


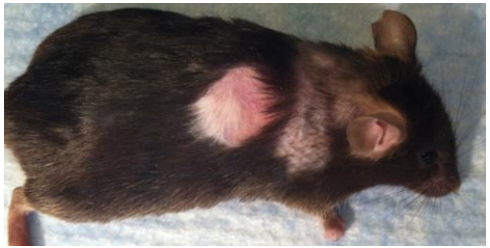


monovalent, pegylated

- **non-activating**
- **no evidence of “cytokine release syndrome”**

Selective blockade of CD28 is superior to CTLA4-Ig



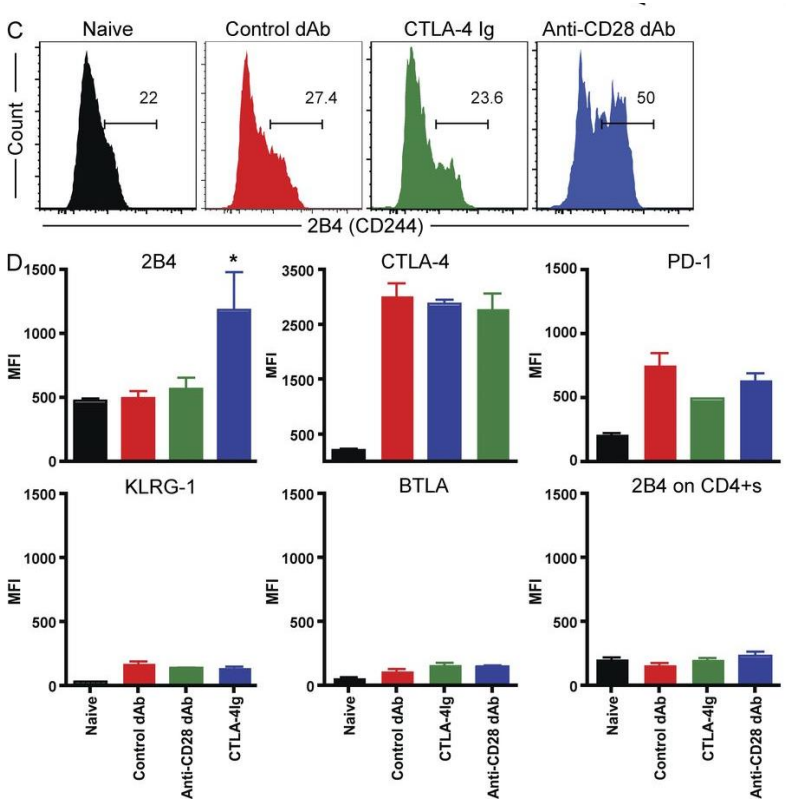


Control dAb	MST= 16 d
CTLA-4 Ig	MST= 26 d
CD28 dAb	MST= >100 d

} *p<0.0001*

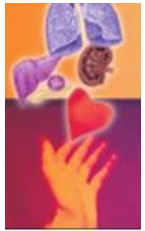
Liu et al., 2014 *J Exp Med*

2B4 Upregulation after CD28 dAb

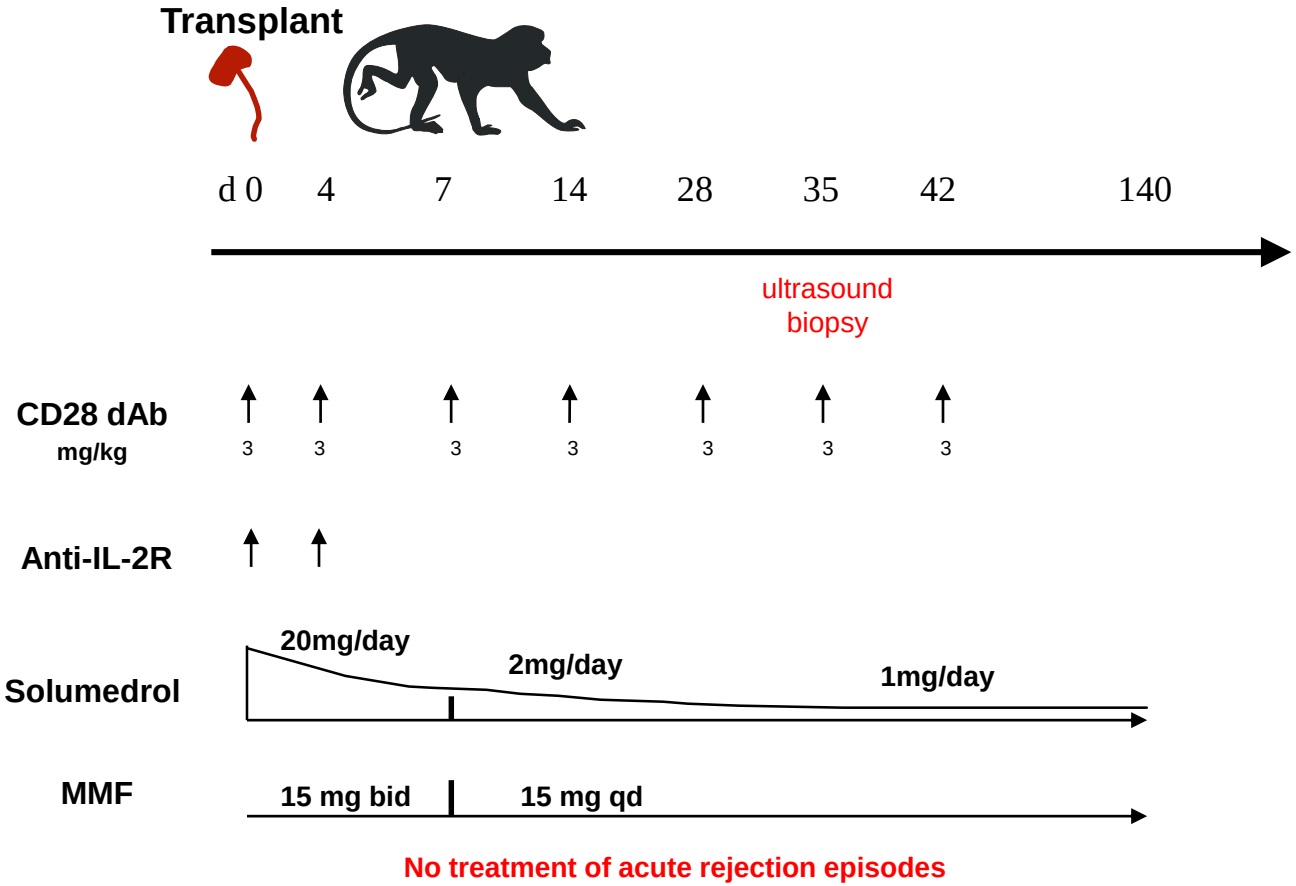


DEPARTMENT OF SURGERY
EMORY

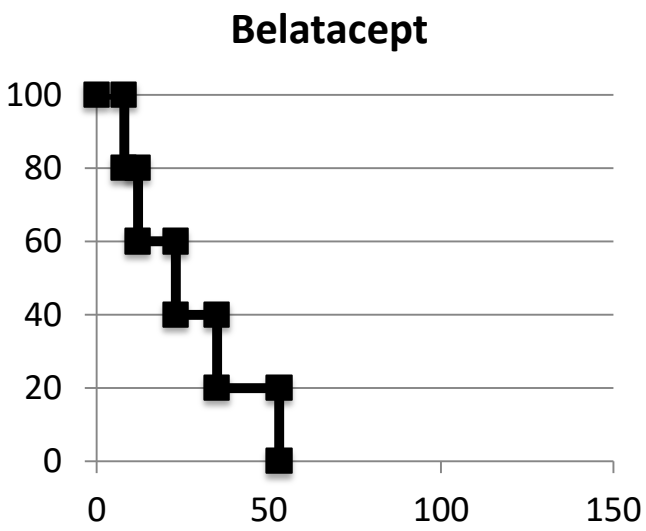
The Emory Transplant Center

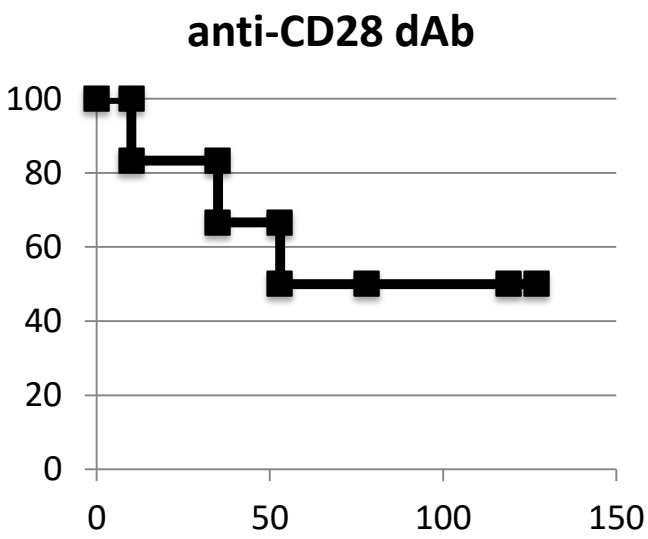


CD28 dAb Renal allograft Protocol



Belatacept vs CD28-specific Rx





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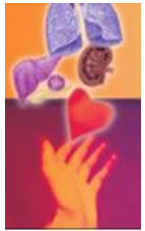
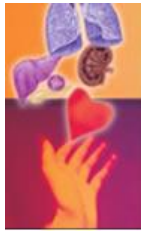
Emory
Transplant
Center

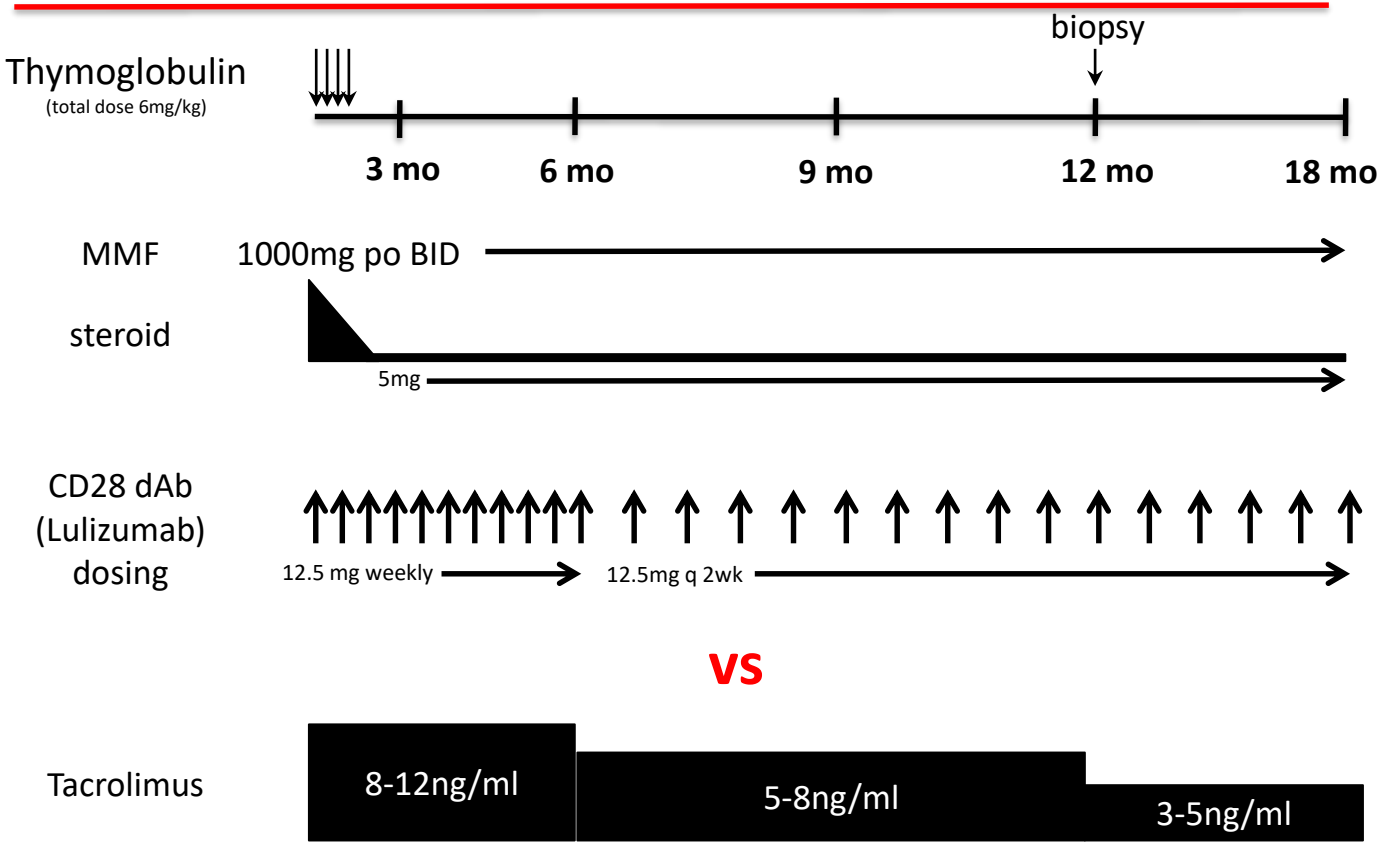


Next Generation Costimulation Blockade

- CD28 selective therapy
- Primate studies supportive,
  - superior to belatacept
  - Mechanistic studies, ? Increase in Treg activity
- Appears safe and efficacious
- No overt safety signal in clinical trial for SLE
- Next Step- Clinical Trial(s) in Renal Transplant recipients



Proposed Immunosuppression Protocol



Conclusions

- Belatacept holds promise for improved outcomes
- Pre-transplant phenotyping may be able to identify patients at risk of rejection
- Adjunct therapies may improve outcomes
  - blockade of IL-7 pathway, IL-15
  - CD28 selective therapy