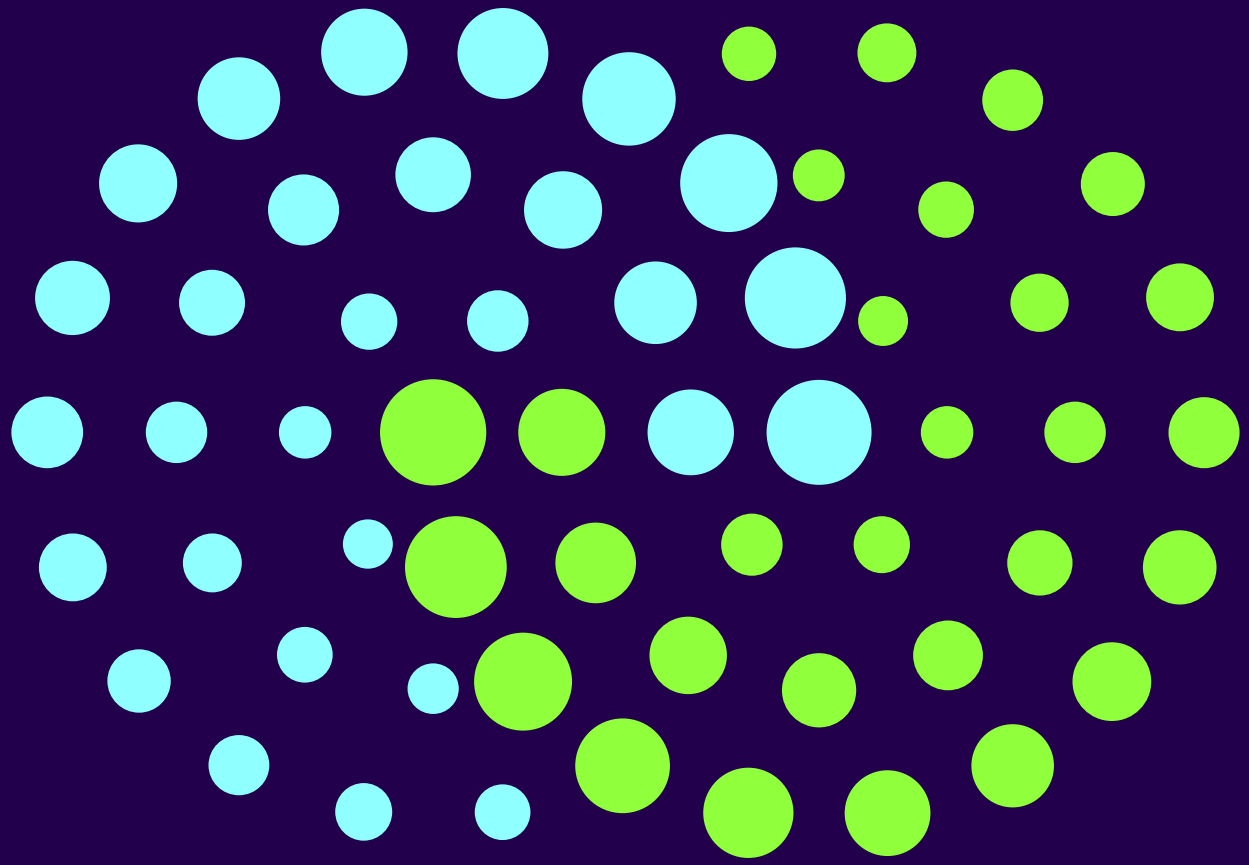

Nuevas dianas biológicas en el trasplante renal

Oriol Bestard

Servicio de Nefrologia, Dialisis y Trasplante Renal
Hospital Universtari Vall d'Hebron
Barcelona

MAT-ES-2401498-1.0-05/2024

sanofi

Disclosures

- Fees for this presentation and travel grants
- Research grant from Sanofi
- Participated in Advisory boards from Sanofi

Vall d'Hebron

Outline

- **New costimulation blockade-targeting Immunosupressants**
  - CTLA4Ig (abatacept / belatacept)
  - Anti-CD154 (CD40L)
  - Anti-CD28

- **New selective anti-Plasma Cell desensitization therapy**
  - Anti-C1s
  - Anti-CD38

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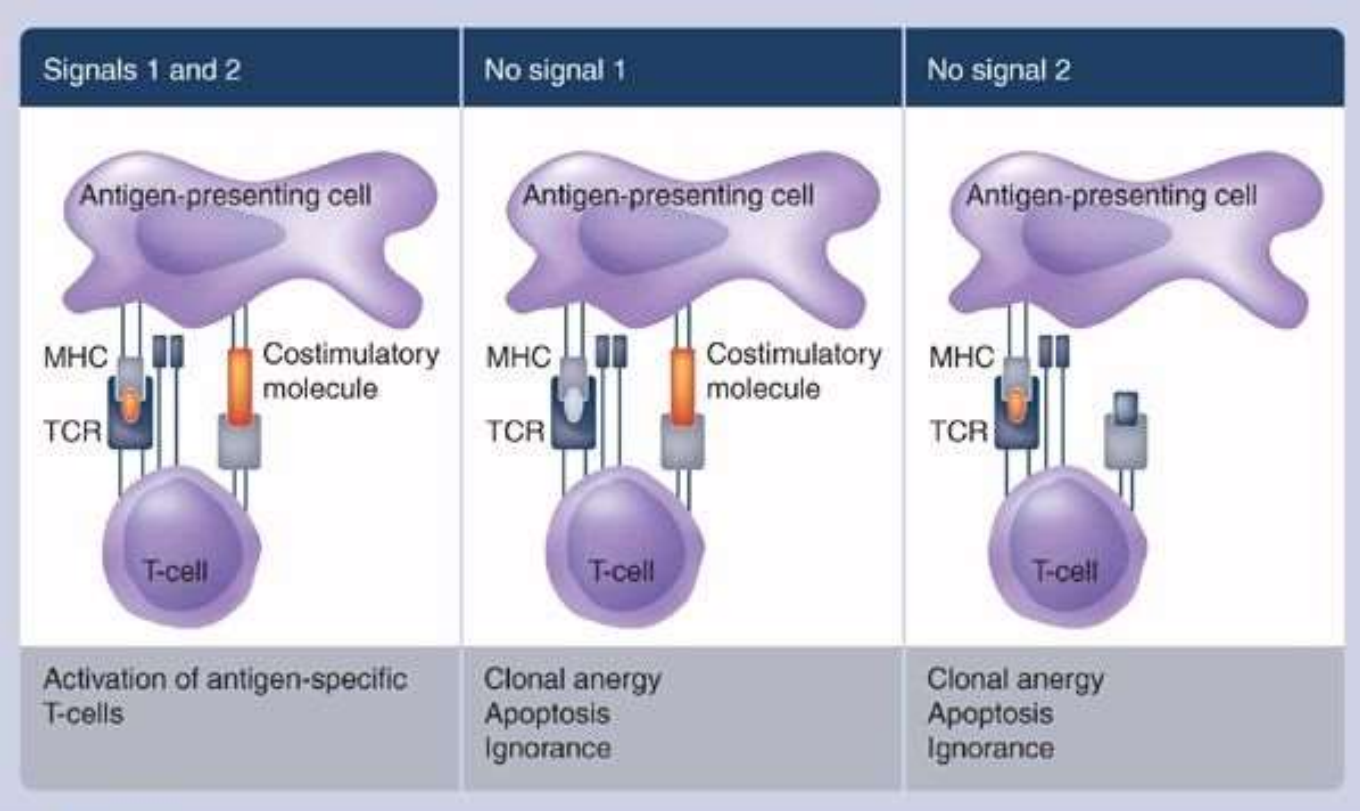
T-cell activation signaling



Li, Rothstein and Sayegh. Immunol Rev 2009

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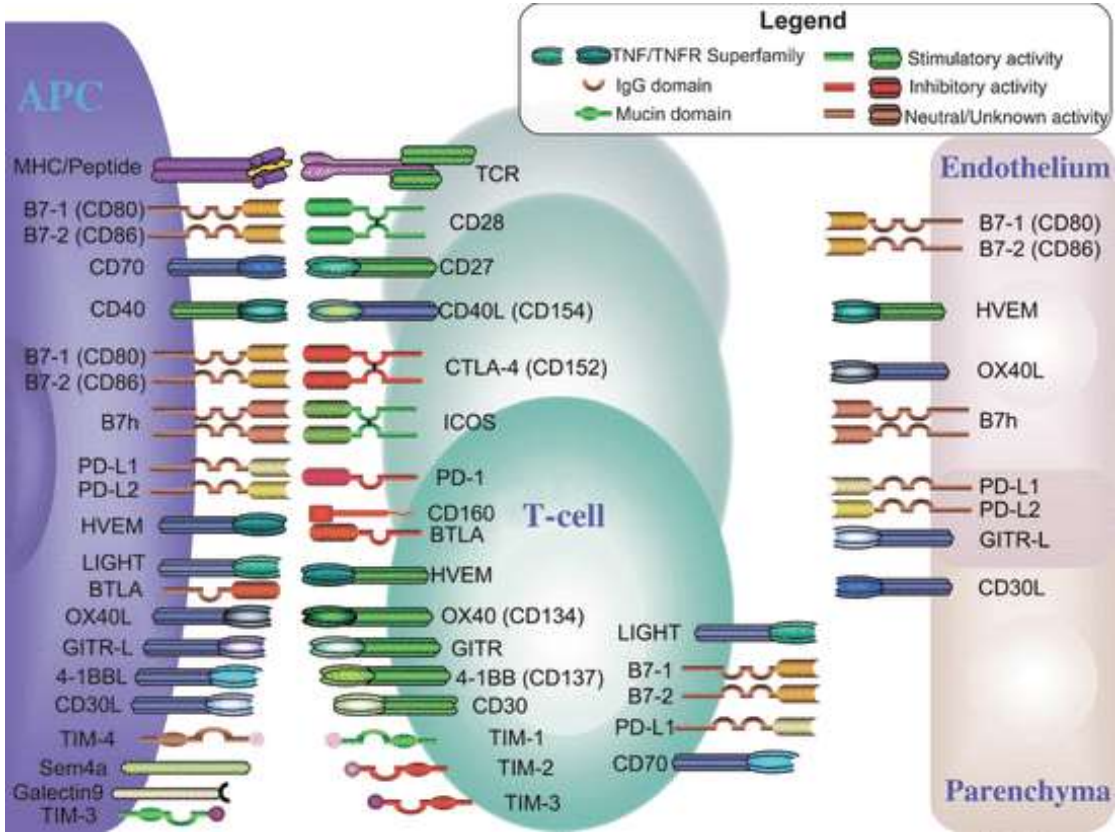
Costimulation pathways: New known interactions



Negative signals:

- CTLA4-CD80/CD86 (B7)
- PD1-PD-L1/PD-L2
- BTLA/LIGHT-HVEM
- B7-H4

↓

T-cell inhibition

Positive signals:

- CD28-CD80/86 (B7)
- CD40-CD154 (CD40L)
- ICOS-B7h (ICOSL)
- OX40-OX40L
- CD134-CD134L
- CD27-CD70
- CD137-CD137L

↓

T-cell activation

Li, Rothstein and Sayegh. Immunol Rev 2009

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Aims, Rationale and Agents targeting costimulatory pathways

Aims of costimulatory targeting:

- Antagonize positive costimulatory pathways
- Agonize negative costimulatory pathways
- Both ?

Agents

- Antibodies
- Fusion proteins
- siRNA ?

Rationale to select a costimultory target

- Hierarchy?
- Timing?
- Combined blockades? (CD40 and CD28?)
  - Redundancies/Synergisms?
- Concomitant therapy (immunosuppressants, cell therapies?)
- Mechanisms abrogating “tolerance induction” (CNIs, TLR engagement?)
- Safety

Van der Zwan M et al. Drugs 2019

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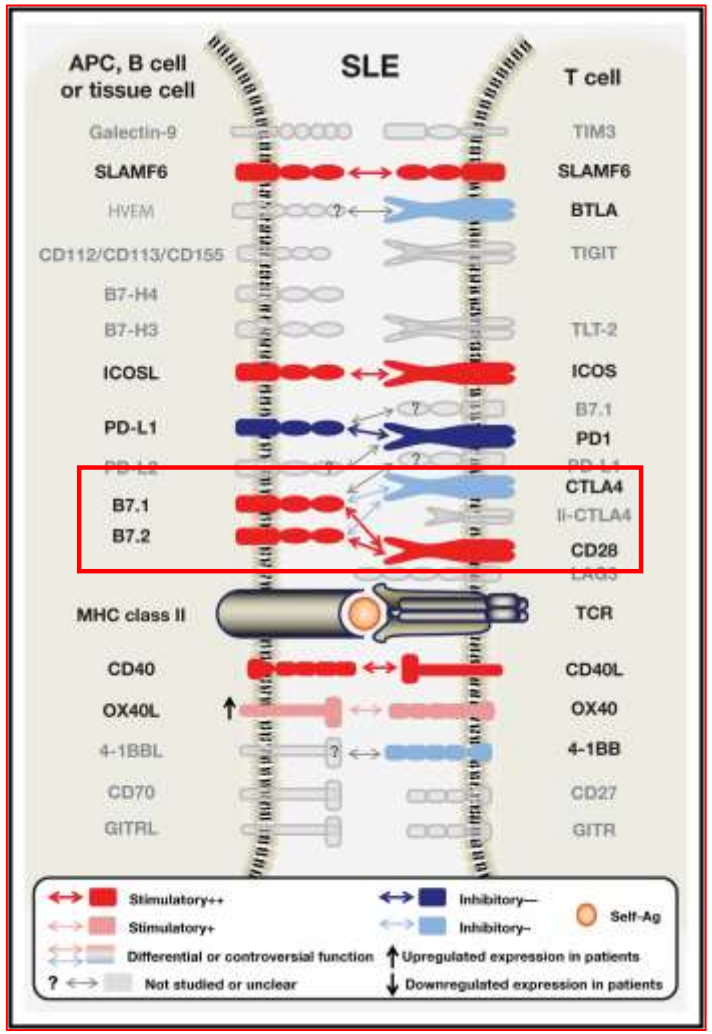
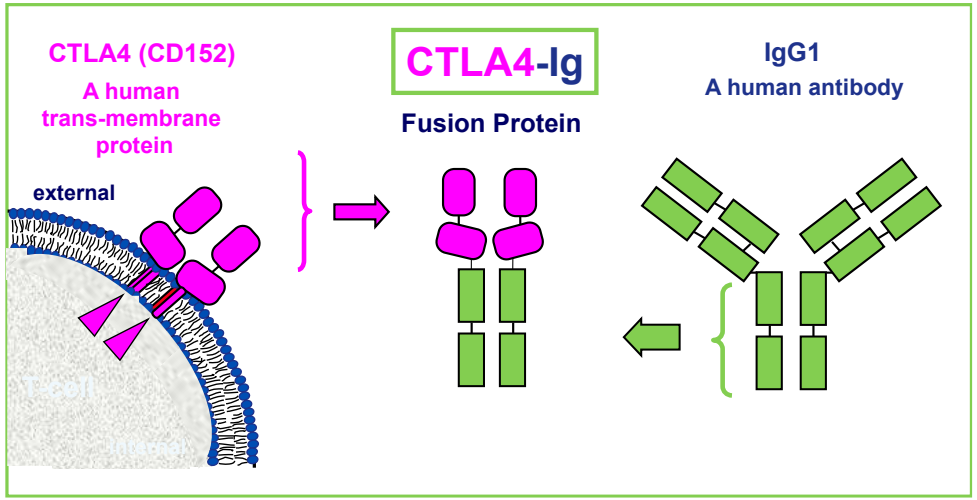
I. The CD28/CTL4 and B7 (CD80/CD86). *A story of success*



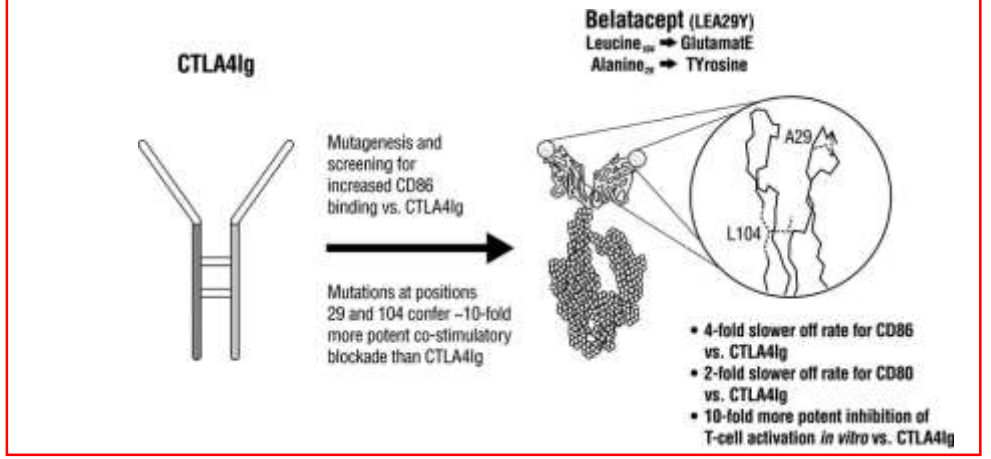
Zhang and Vignali. Immunity 2016

CD28-B7 high avidity → **POS**

CTLA4-B7 low avidity → NEG



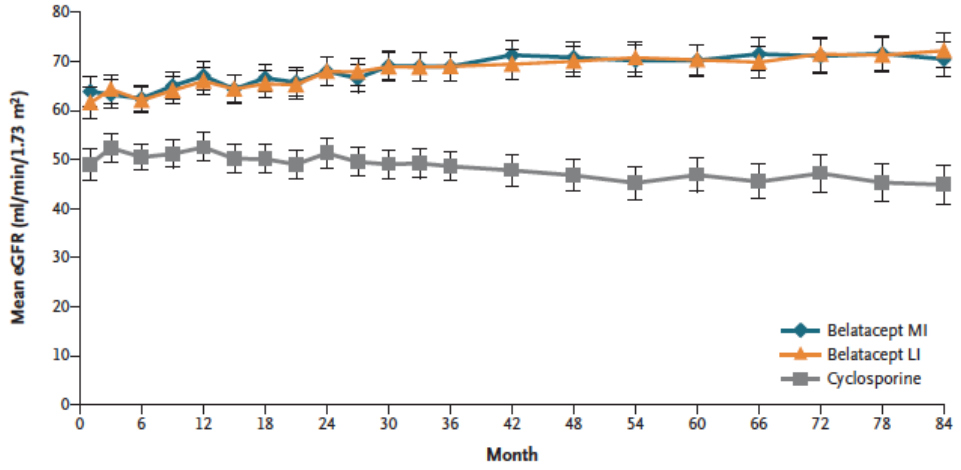
Belatacept

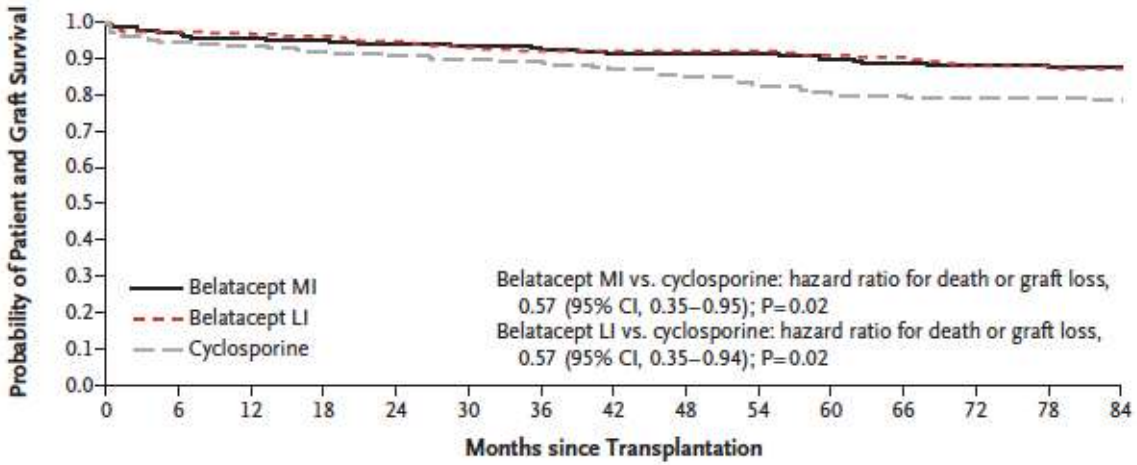


Larsen C et al. Am J Transplant 2005

Belatacept and long-term outcomes

Long-term Graft and Patient survival

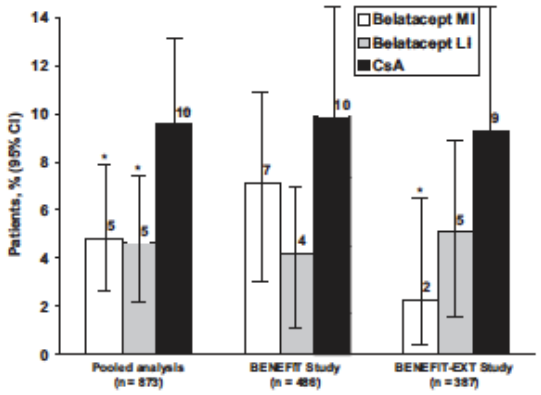




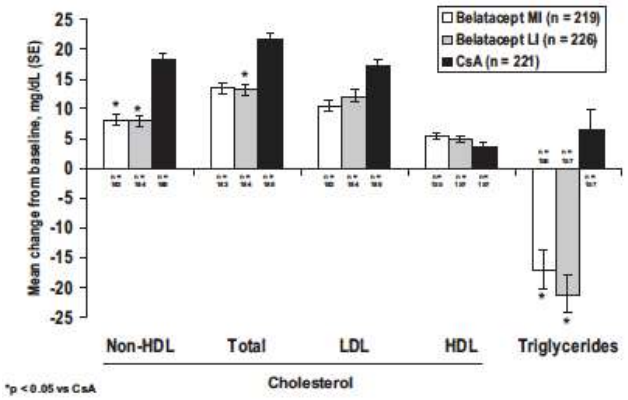
Vincenti F et al N Eng J Med 2016

Improved Cardiovascular profile

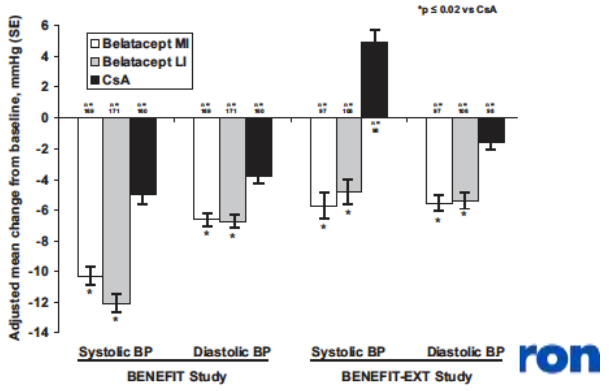
NODAT



DISLIPIDEMIA



BLOOD PRESSURE



Vanrenterghem Y et al Transplant 2011

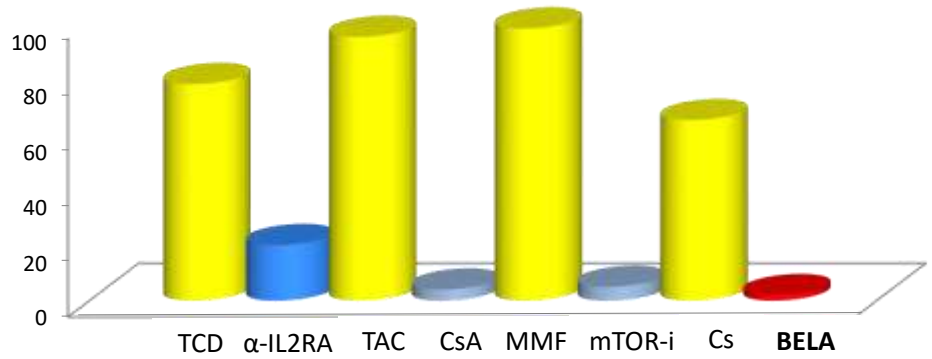
But…higher rates of acute TCMR (*de novo*) and production shortage

De novo BPAR rates

	Belatacept MI n = 219	Belatacept LI n = 226	CsA n = 221
Baseline ⟶ Month 24	24		
Number of cases, Month 24⟶ Month 36	(		
Baseline ⟶ Month 36	24		

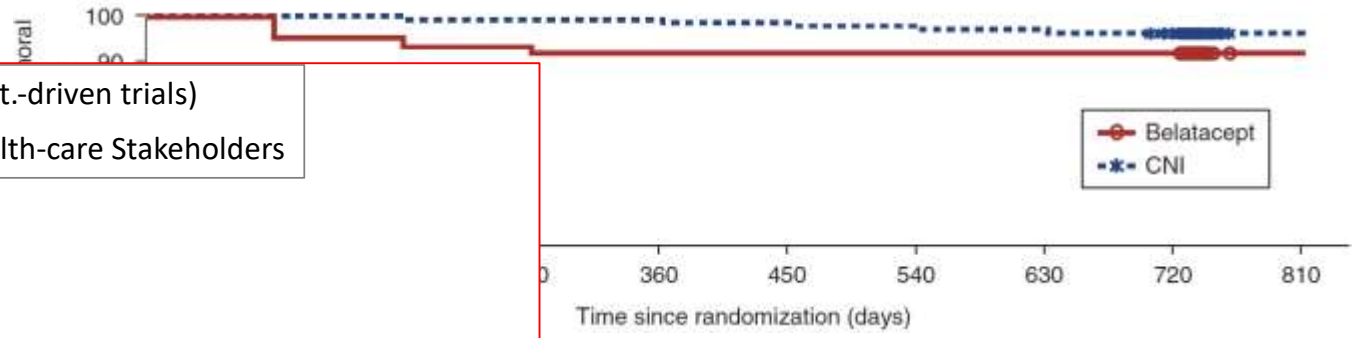
Very Low use (Invest.-driven trials)

No reimbursement by health-care Stakeholders



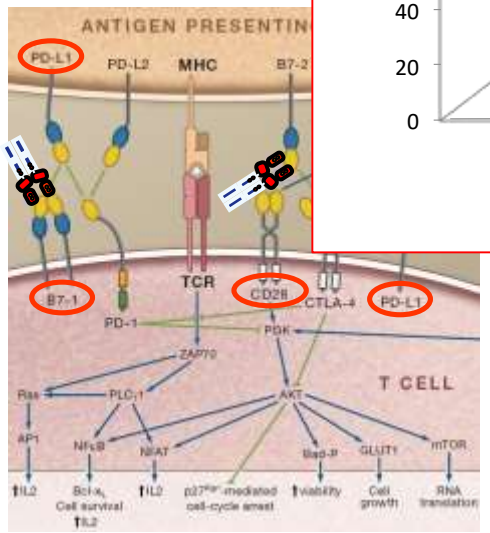
OPTN/SRTR Annual Report 2021

Conversion BPAR rates



Budde K et al J Am Soc Nephrol 2021

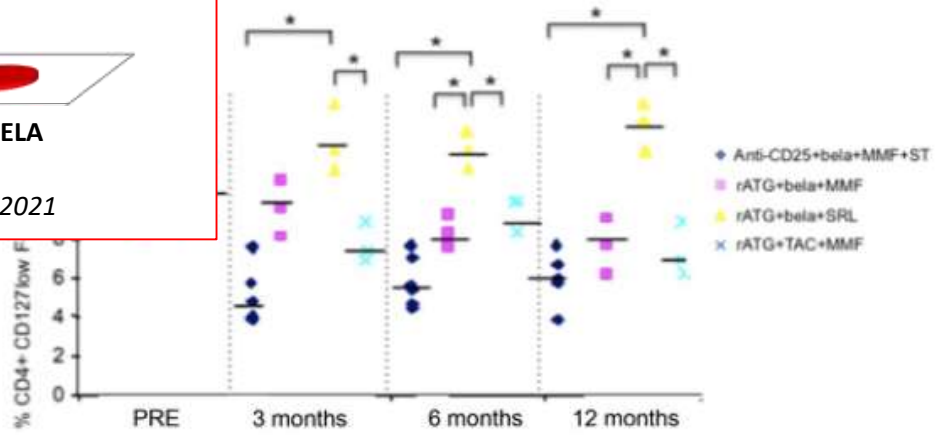
Redundant costimul



belatacept

Sharpe et al *Cell 2009*
Extracted by T. Wekerle

wn-regulation of Treg function



Bluestone J Am J Transplant 2011
Cassis L et al Transpl Int. 2011

CTLA4Ig; alternative to belatacept ?

ESOT | Transplant International

ORIGINAL RESEARCH

Conversion From Intravenous In-Hospital Belatacept Injection to Subcutaneous Abatacept Injection in Kidney Transplant Recipients During the First COVID-19 Stay-at-Home Order in France

Dominique Bertrand[1,†], Mélanie Brunet[2†], Ludivine Lebourg[1], Anne Scemla[2], Mathilde Lemoine[1], Lucile Amrouche[2], Charlotte Laurent[1], Christophe Legendre[2], Dominique Guerrot[1,3], Dany Anglicheau[2] and Rebecca Sberro-Soussan[2]*

Received: 9 October 2018 | Revised: 23 January 2019 | Accepted: 11 February 2019

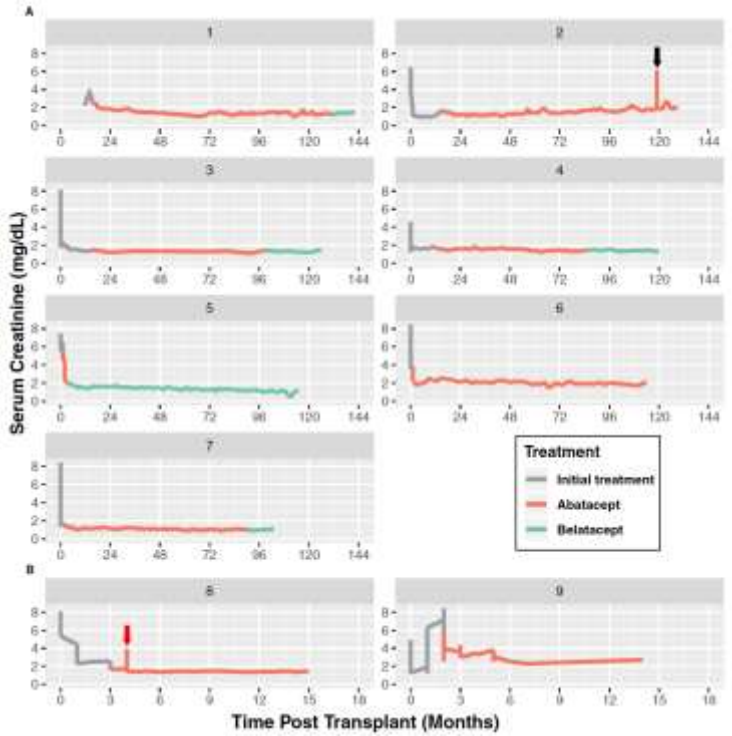
DOI: 10.1111/ajt.15319

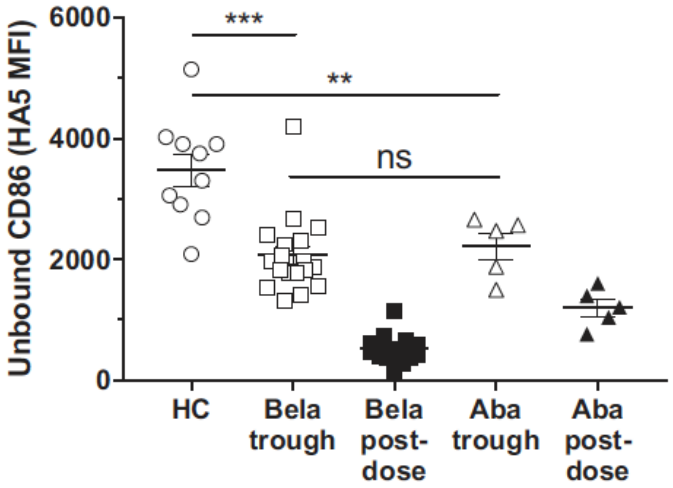
BRIEF COMMUNICATION

AJT

Abatacept as rescue immunosuppression after calcineurin inhibitor treatment failure in renal transplantation

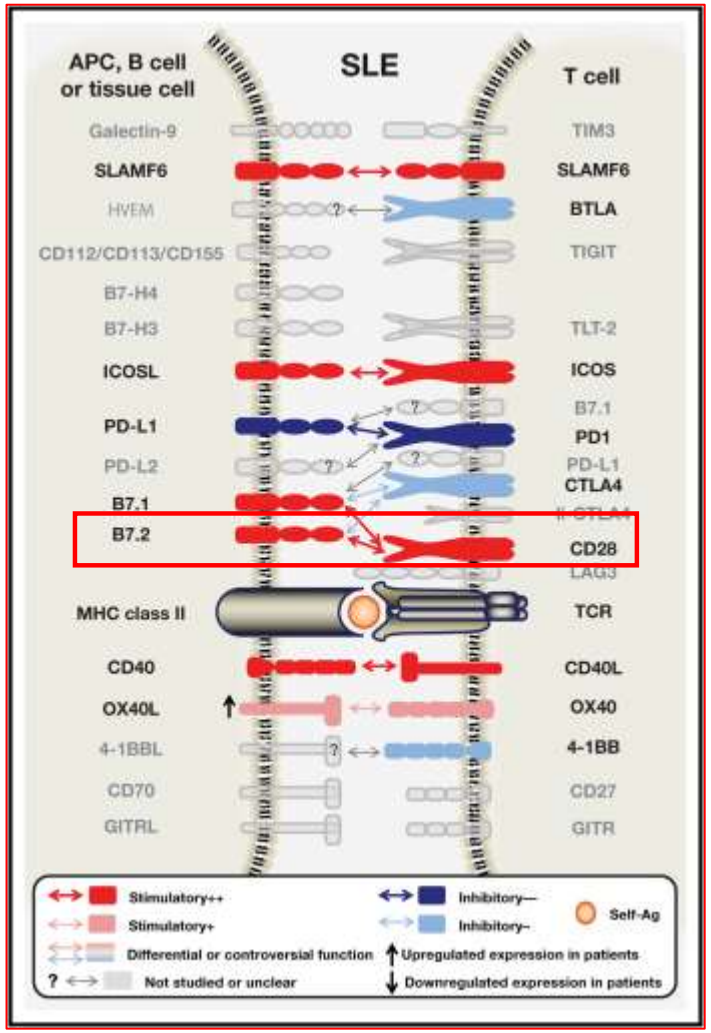
Idelberto Raul Badell[1] | Geeta M. Karadkhele[1] | Payaswini Vasanth[1] | Alton Brad Farris III[2] | Jennifer M. Robertson[1] | Christian P. Larsen[1]





Badell IR et al Am J Transplant 2018

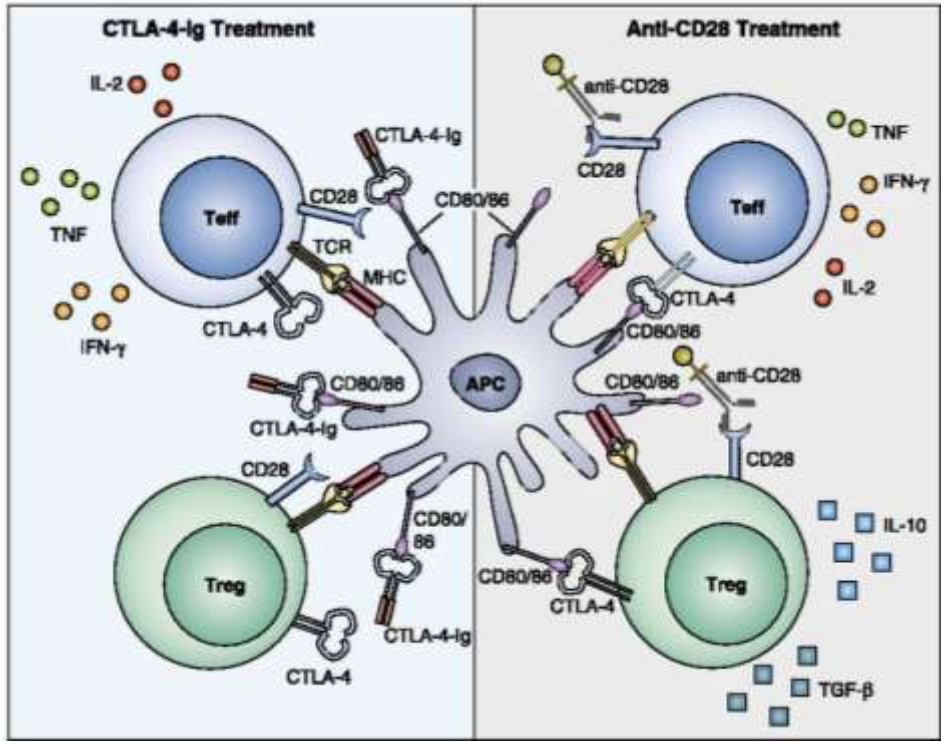
II. Alternative costimulatory signals promoting higher regulation. The CD28/B7 axis



Zhang and Vignali. Immunity 2016

Selective blockade of the costimulatory CD28 may overcome CTLA4Ig/B7

- Robust T-cell inhibition (proliferation and cytokine profile)
- Preserves Treg function by maintaining inhibitory signal of intact CTLA-4 ligation



Adams AB et al J Immunol. 2016

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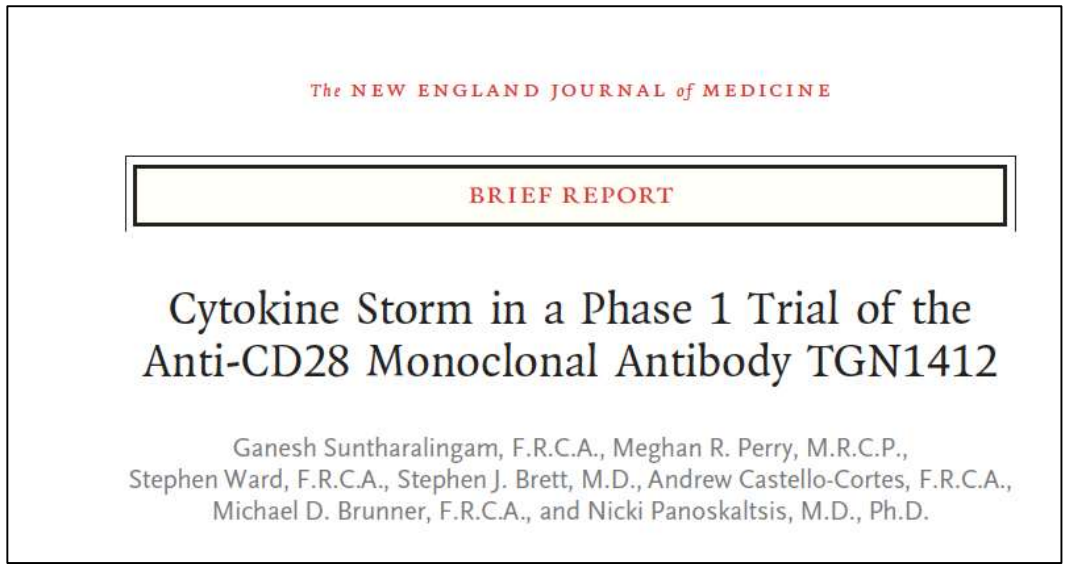
II. Alternative costimulatory signals. The CD28/B7 axis



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

Humanized superagonist anti-CD28 mAb that stimulated and expanded T cells independently of TCR ligation

- **Systemic inflammatory response** characterized by a rapid induction of proinflammatory cytokines

Monovalent anti-human CD28 domain antibody antagonist

- Preclinical efficacy and immunological safety
- Safety in a Phase I clinical trial
- On-going Phase II RCT in autoimmunity (SLE, Sjögren)

Suchard S et al J Immunol 2013
Shin R et al J Clin Pharmacol 2017

Selective antagonist anti-CD28 monovalent Fab' PEG antibody (VEL-101)

- Preclinical efficacy and immunological safety
- Safety in a Phase I clinical trial
- On-going Phase I/II RCT (FIRST study; NCT04837092)

Poirier et al. Am J Transplant 2012

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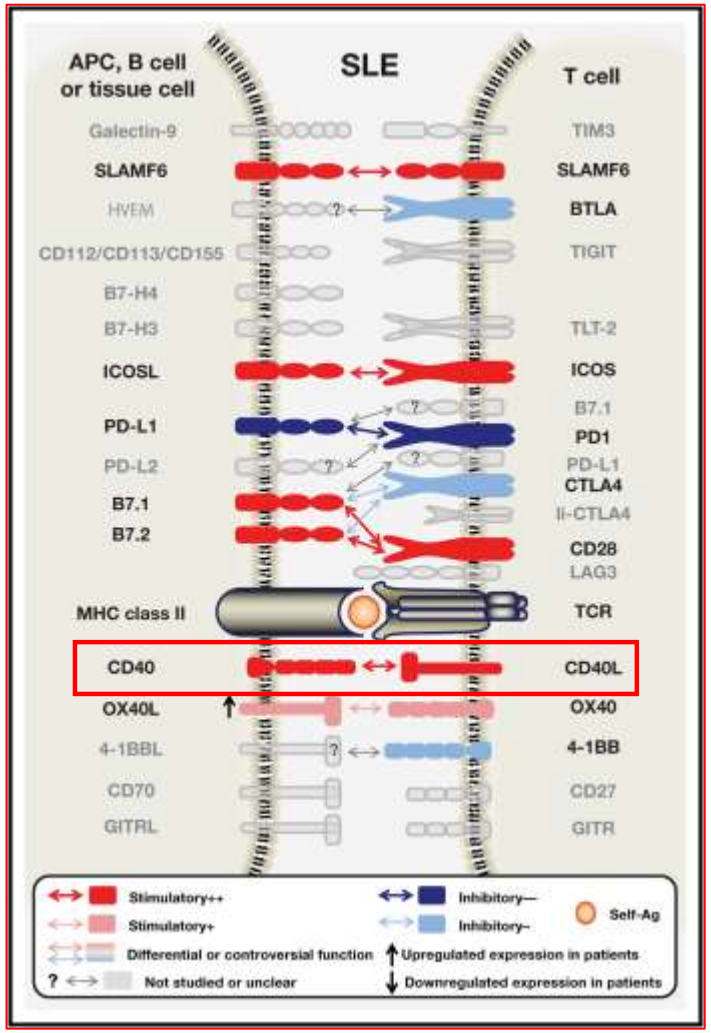
III. Alternative costimulatory signals. The CD40/CD40L axis

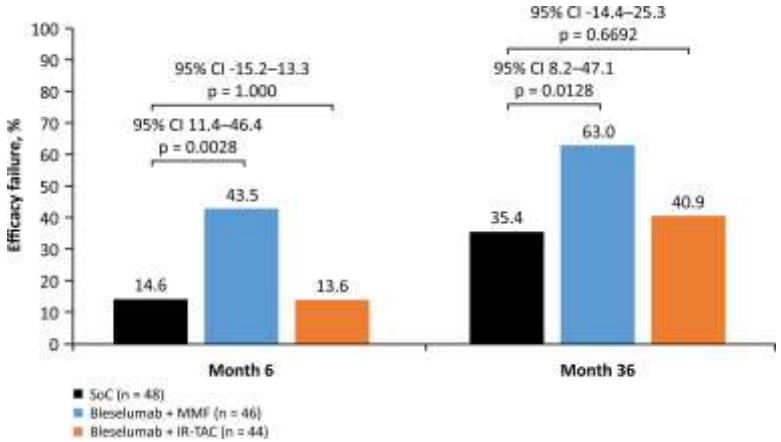


Zhang and Vignali. Immunity 2016

Anti-CD40 mAb

- **Success** in Experimental transplantation (NHP),
- **Failed** experience targeting CD40 with anti-CD40 mAbs

I. Non-depleting IgG_4 mAb KPL-404 (Bieselumab)



Harland et al. Am J Transplant, 2019

II. Non-depleting IgG1 mAb N297A mutation (iscalimab)

Trial halted → Efficacy failure due to high rejection rates

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Suboptimal alloimmune control of CD40 blockade due to CD11b / CD40L activation

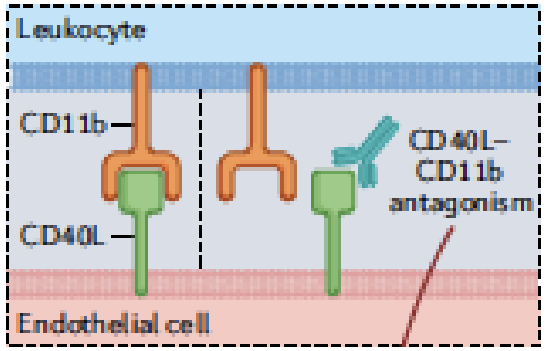
DOI: 10.1111/ajt.15835

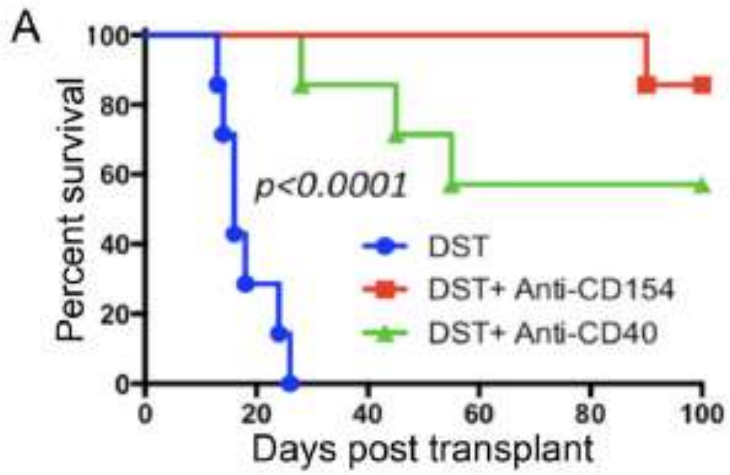
BRIEF COMMUNICATION

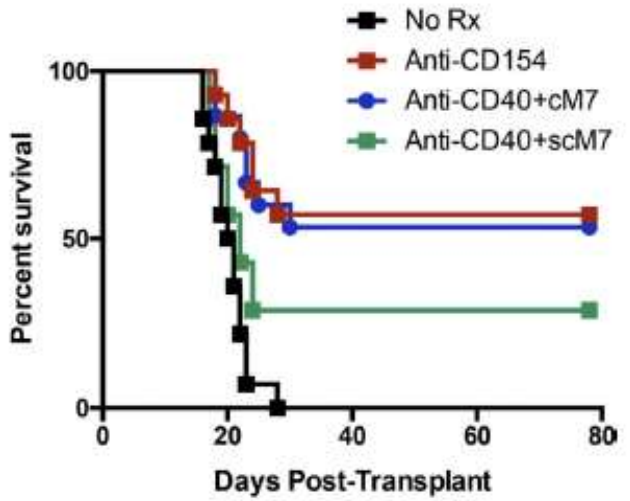
AJT

CD11b is a novel alternate receptor for CD154 during alloimmunity

Danya Liu | Mandy L. Ford







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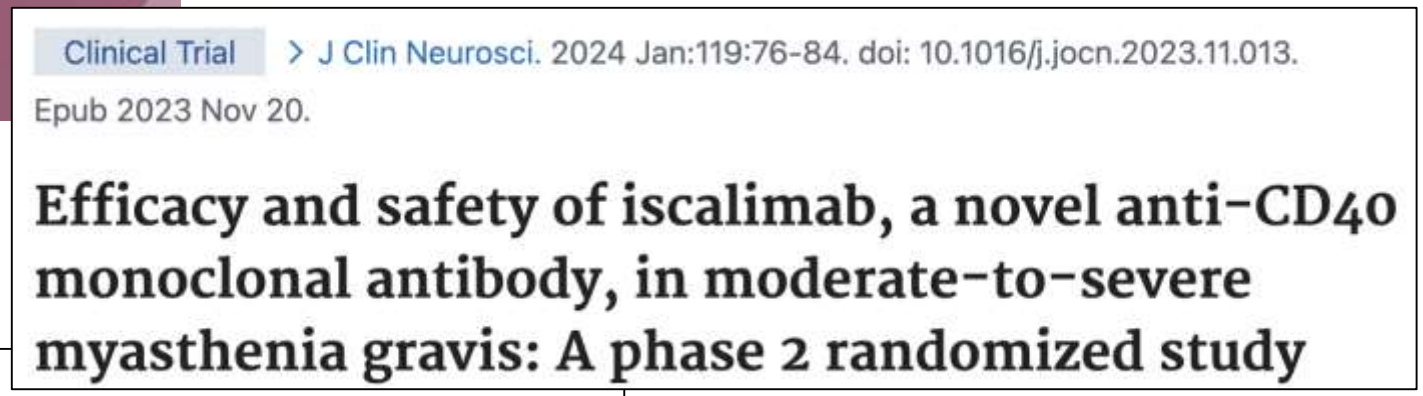
Liu D et al. Am J Transplant, 2020

CD40 blockade in autoimmunity. Importance of the biological hierarchy of the immune response

ARTICLES | VOLUME 2, ISSUE 3, E142-E152, MARCH 2020 Download Full Issue

Assessment of the anti-CD40 antibody iscalimab in patients with primary Sjögren's syndrome: a multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study

Benjamin A Fisher, MD • Antonia Szanto, MD • Prof Wan-Fai Ng, MD • Michele Bombardieri, MD • Maximilian G Posch, MD • Prof Athena S Papas, MD • et al. Show all authors • Show footnotes



Clinical Trial > J Clin Neurosci. 2024 Jan:119:76-84. doi: 10.1016/j.jocn.2023.11.013. Epub 2023 Nov 20.

Efficacy and safety of iscalimab, a novel anti-CD40 monoclonal antibody, in moderate-to-severe myasthenia gravis: A phase 2 randomized study

Premium Insights | January 9, 2024

Iscalimab by Novartis for Lupus Nephritis: Likelihood of Approval

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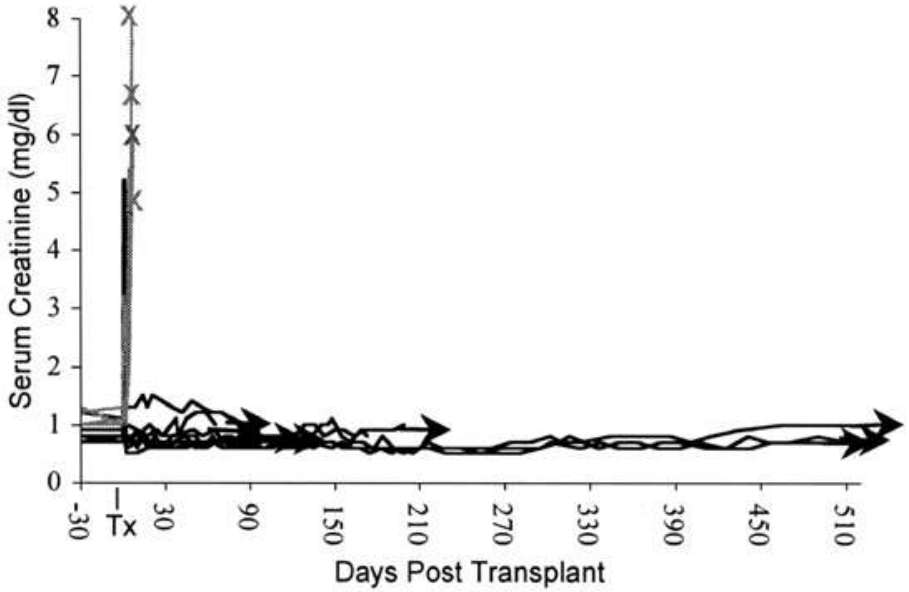
II. Alternative costimulatory signals. The CD40/CD40L axis

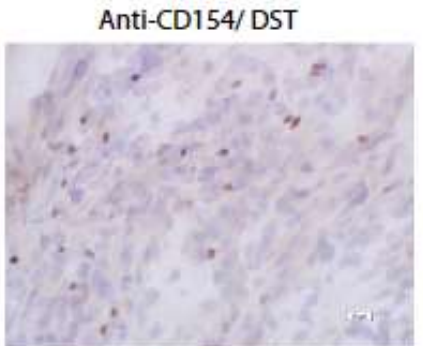
Anti-CD40L (CD154) mAbs

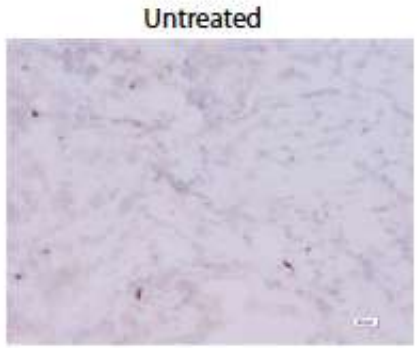
Anti-CD40L mAb (hu5C8) prevents acute rejection in NHP

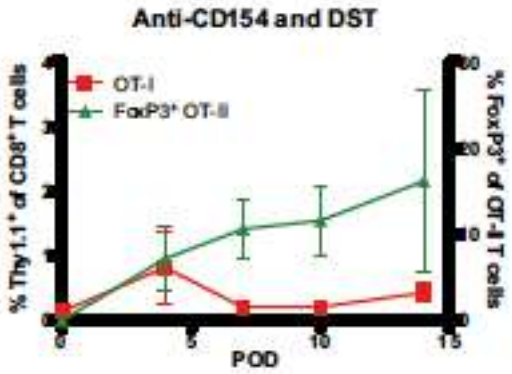


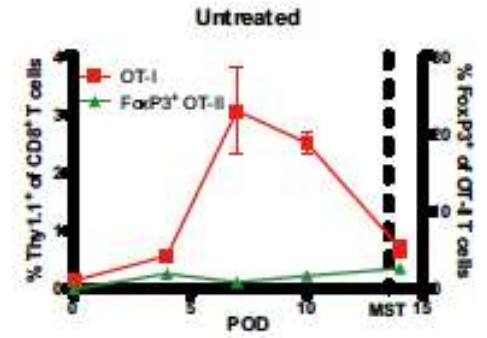
Kirk et al. Nat Med 1999; 5: 686-93.

Ag-sp Foxp3+ Treg generation after anti-CD40L









Ferrer IR, et al. PNAS 2012

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Alternative costimulatory signals. The CD40/CD40L axis

Anti-CD40L (CD154) mAbs

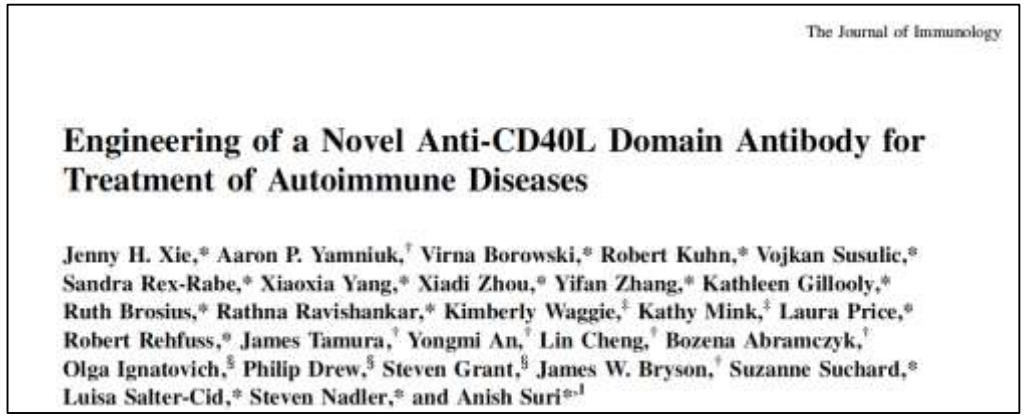
- hu5c8
- ABI793
- BG9588

Thromboembolic effect

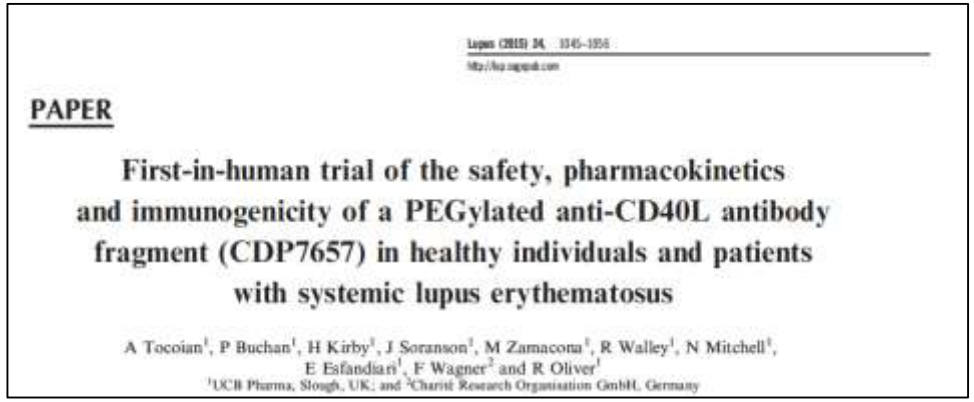
Fc dependent (FcγRs)

(CD154 Platelet expression)

Fc mutation



Pegylation



Xie et al. J Immunol 2014;192(9):4083-92

Tocoian et al. Lupus 2015; 24(10):1045-56

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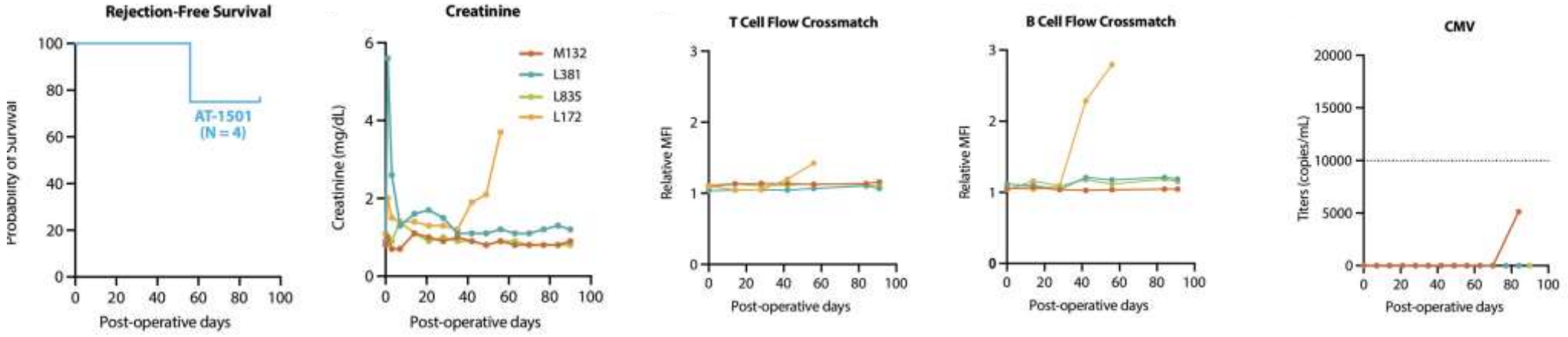
A new anti-CD40L mAb in clinical Transplantation

- Novel humanized IgG1 mAb targeting CD154
- Devoid of FcgRII functions* to avoid binding to Platelets

*(substitutions into the Hu5C8 heavy chain hinge and hinge-proximal CH2)

- Promotes **islets** and **renal allograft** survivals in **Non-Human Primates**



Anwar et al., Sci. Transl. Med 2023

Vall d'Hebron

A new anti-CD40L mAb in clinical Tx.

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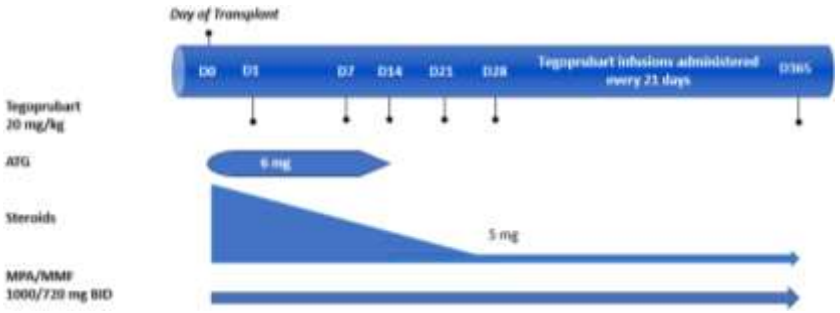
Anwar et al., Sci. Transl. Med 2023

- Safety of a **Phase I trial** (n=10) in **kidney transplant recipients** (NCT05983770)
  - ATG-MMF-CS- anti-CD40L



Curtesy from Eledon Pharma, abstract ASN 2023

SAES

- 1 TCMR IA, remains on the study
- No DSA
- 4 BK viremia, No PVAN
- No CMV infection
- No graft loss patients death

A new anti-CD40L mAb in clinical Tx.

- Novel humanized IgG1 mAb targeting CD154
- Devoid of FcgRII functions* to avoid binding to Platelets

*(substitutions into the Hu5C8 heavy chain hinge and hinge-proximal CH2)

- Promotes islets and renal allograft survivals in Non-Human Primates

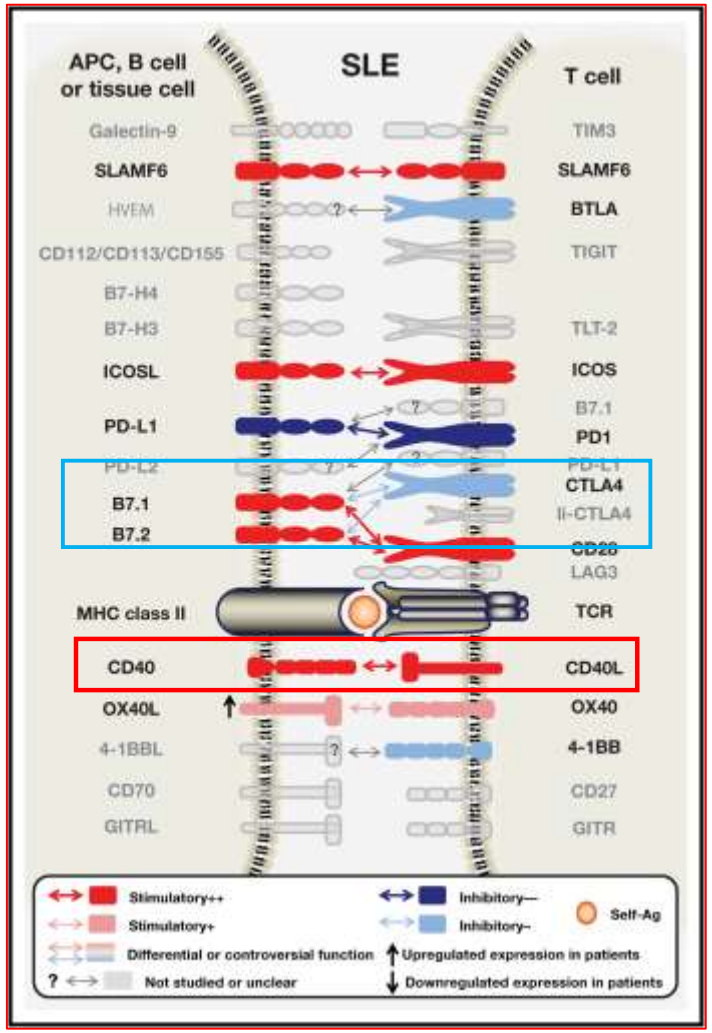
Anwar et al., Sci. Transl. Med 2023

- Safety of a Phase I study (n=10) in kidney transplant recipients (NCT05983770)
  - ATG-MMF-CS- anti-CD40L

- **On-going Phase II study (n=120) (NCT05983770)**
  - Safety & Efficacy
  - ATG+MMF-CS -Tac vs. ATG-MMF-CS- anti-CD40L

Vall d'Hebron

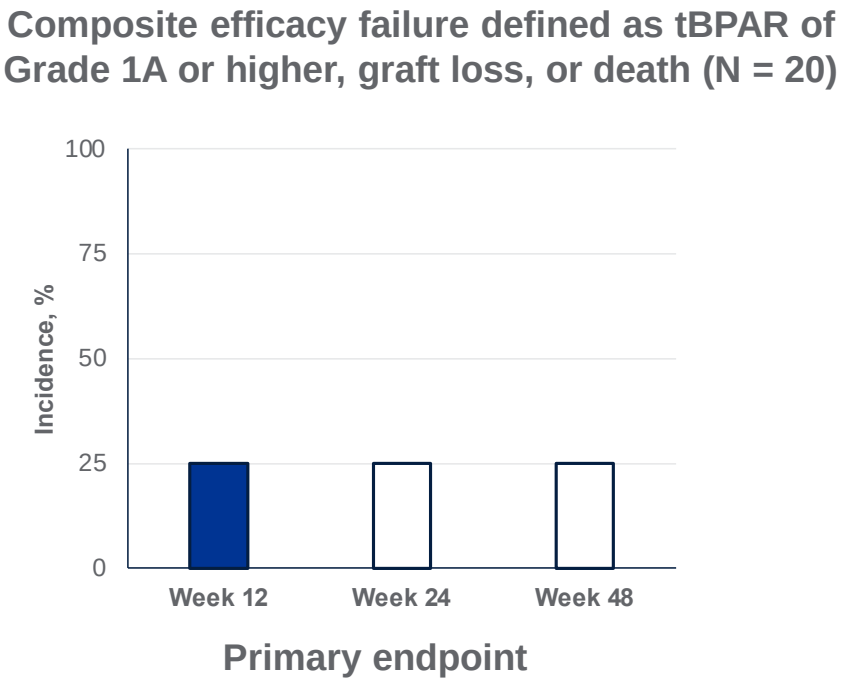
Dual targeting of costimulatory signals



Zhang and Vignali. Immunity 2016

- **Pilot study with Belatacept and a CD40L antagonist fusion protein**

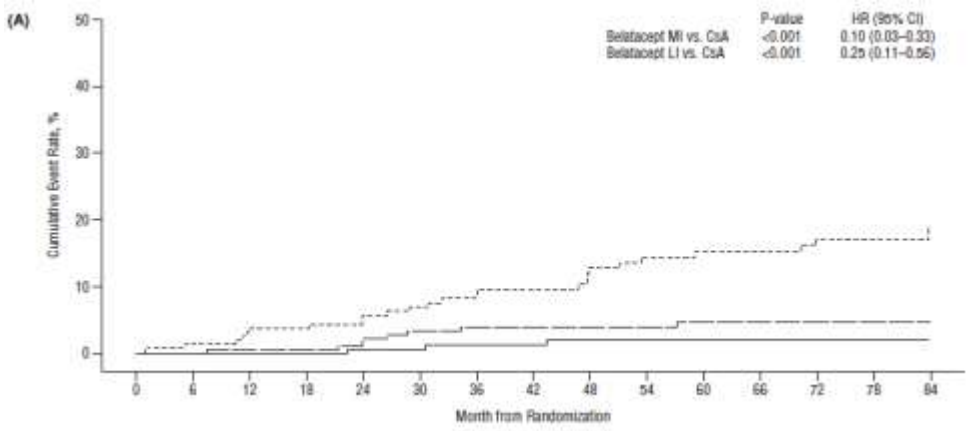
	D0	D1	D2	D3	D4	D5–D7	W2	W3	W4 ±2 days	W6 ±2 days	W8 ±2 days	W10 ±2 days
Thym (mg/kg)	1.5[a]	1.5[a]	1.5[a]	1.5[a]		—	—	—	—	—	—	—
MP (mg)	500	250	125	60	30[b]	30[b]	20[b]	10[b]	5[b]	—	—	—
DAZ (mg)	—	1500	—	1500[c]		—	1500	—	1500	1500	1500	1500
Bela (mg/kg)	—	10[d]	—	10[c]		—	10	—	10	—	10	—



Vincenti F et al. ESOT congress 2024

Costimulation blockade-driven B-cell Immune control

De *novo* DSA inhibition



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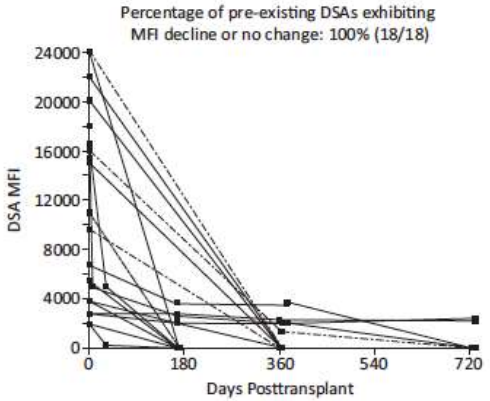
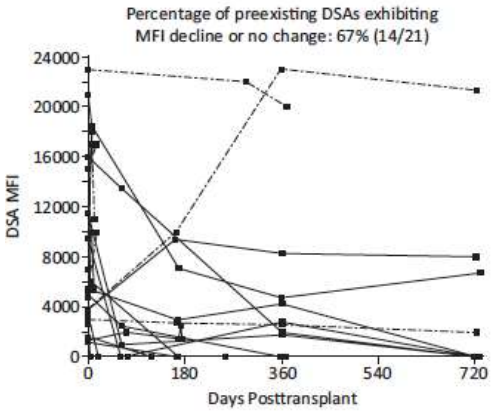
Preformed DSA inhibition

BELA



CsA



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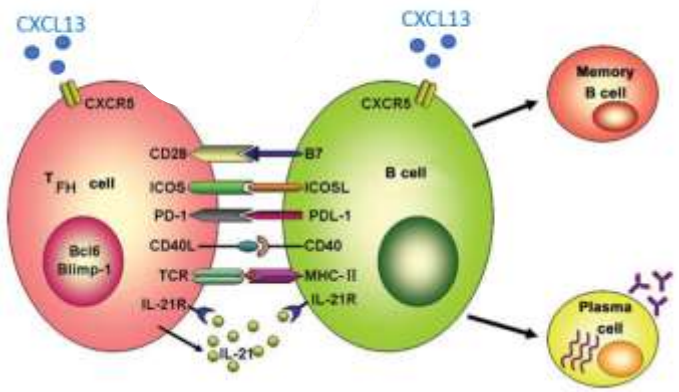
CD28/B7 and CD40/CD154 Costimulation dependent GC B-cell activation



Ongoing trials using Bela combined with other anti-B/PC agents as desensitization therapy

- Bela + anti-CD38 mAb (NCT05145296; NCT04827979)
- Bela + anti-CD40L (NCT04046549)

ClinicalTrials.gov. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05145296
ClinicalTrials.gov. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04827979
ClinicalTrials.gov. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04046549

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Outline

- New costimulation blockade-targeting Immunosupressants
  - CTLA4Ig (Belatacept)
  - Anti-CD154 (CD40L)
  - Anti-CD28

- **New selective Plasma Cell-targeting desensitization therapy**
  - Anti-C1s
  - Anti-CD38

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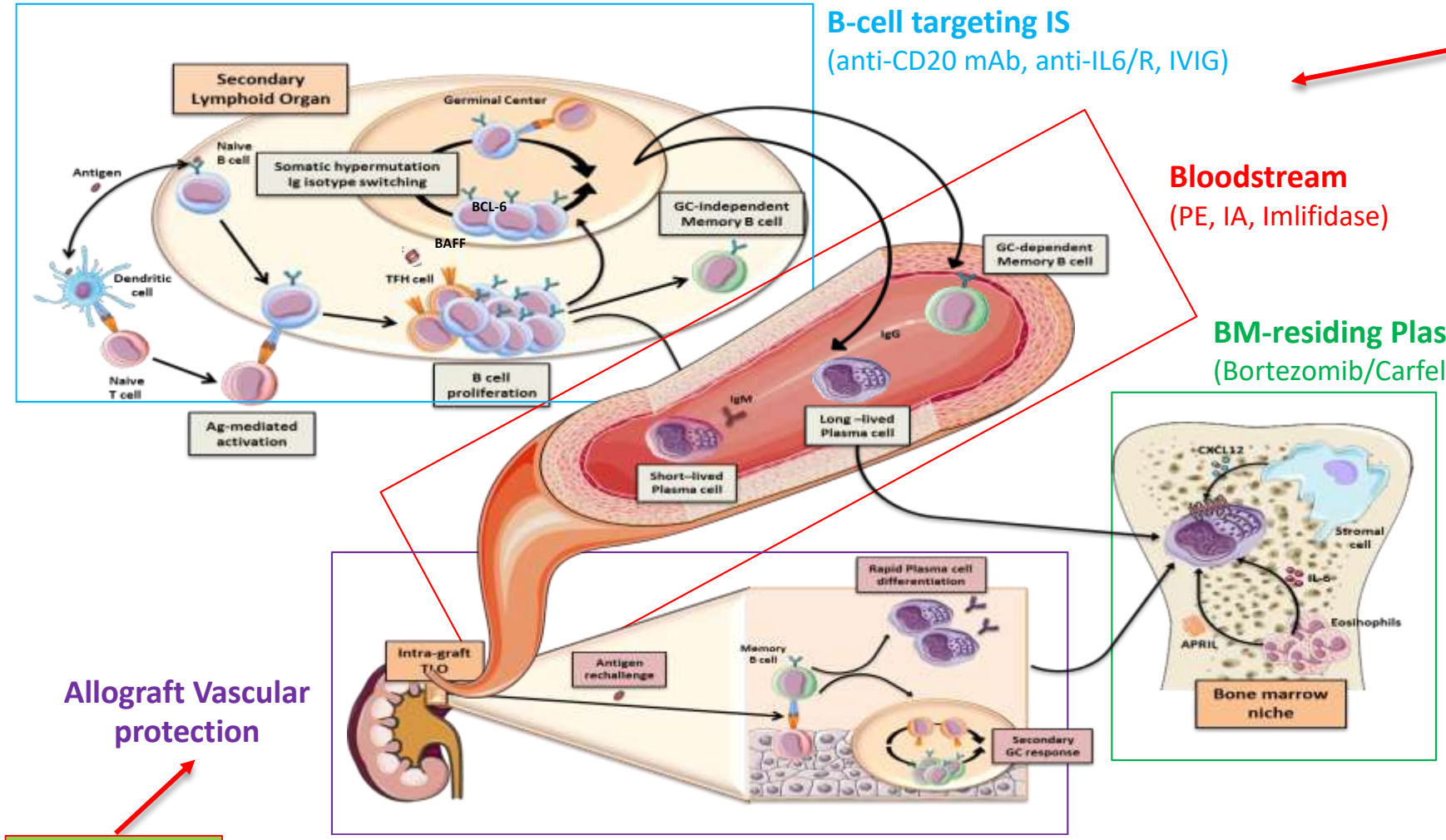
Desensitization therapies to improve access to transplantation



B-cell targeting IS
(anti-CD20 mAb, anti-IL6/R, IVIG)

Anti-CD38 mAb

Bloodstream
(PE, IA, Imlifidase)

BM-residing Plasma cells
(Bortezomib/Carfelzomib)

Allograft Vascular protection

Anti-C1s mAb

Extracted Luque S et al. Transplant Int 2017

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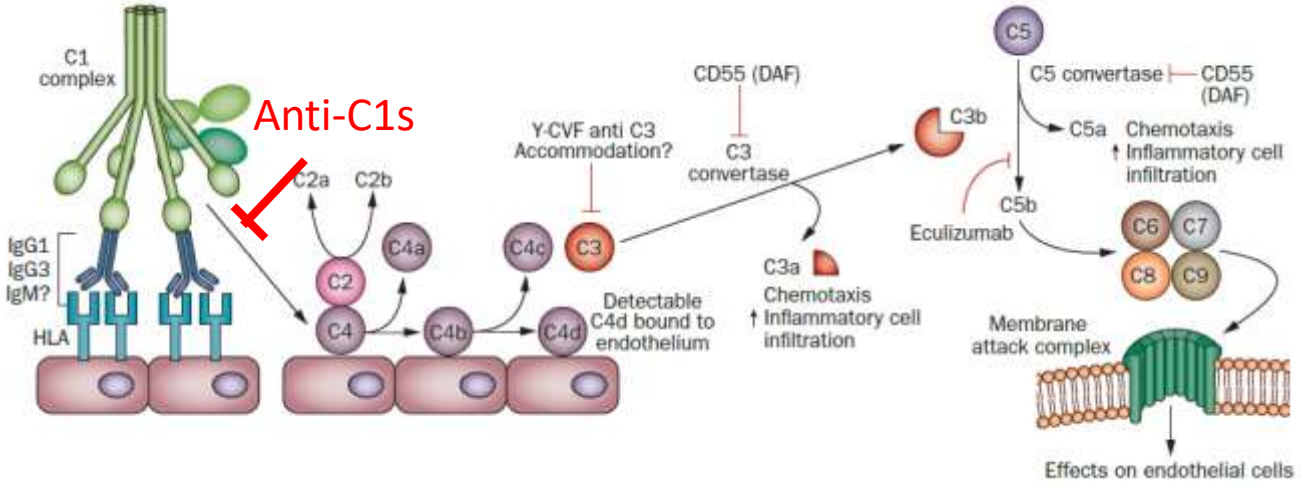
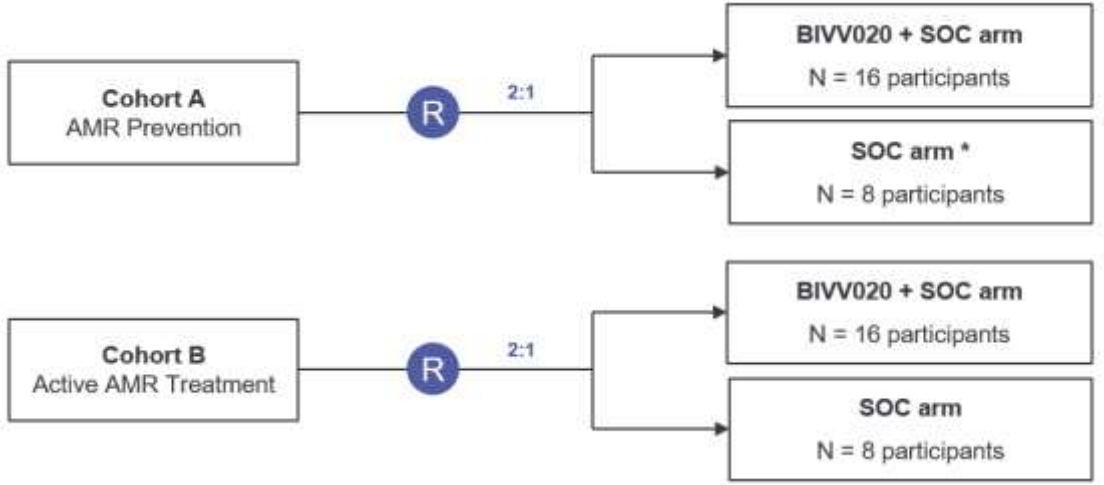
Blocking anti-C1s classical CP (BIVV02)



BIVV020 (Anti-C1s mAb:

- Selecive blockade of active C1s CP
- Preserves alterative pathway activation to fight against pathogens
- Improved efficacy than terminal C5 inhibition.
- C1INH lacks specificity against C1
- Sustained and effective CP inhibition at a tolerable dose in healthy adult subjects.

Phase 2 RCT with BIVV020 for prevention and treatment of ABMR in kidney Tx recipients.



CD38-targeting therapy for anti-HLA Ab desensitization

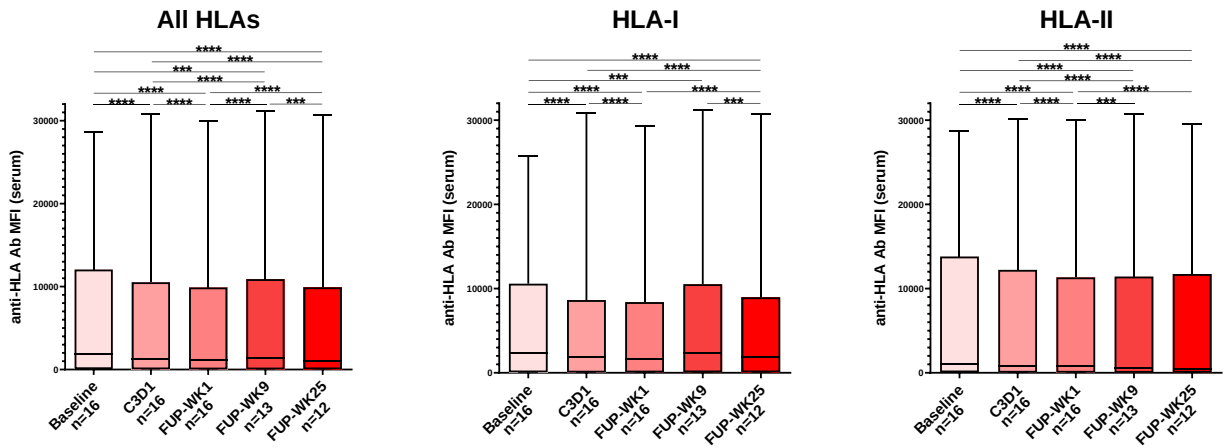
Anti-CD38 Efficacy (NCT04294459)**: Response Rates**

No. (%)	Cohort A (*n*=12)	Cohort B (*n*=11)	All (*N*=23)
No. of participants assessed	12	11	23
RR based on criterion 1	4 (33.3)	5 (45.5)	9 (39.1)
RR based on criterion 2	7 (58.3)	4 (36.4)	11 (47.8)
RR based on criterion 3	10 (83.3)	9 (81.8)	19 (82.6)
Overall RR	10 (83.3)	9 (81.8)	19 (82.6)
95% CI	51.6 to 97.9	48.2 to 97.7	61.2 to 95.0

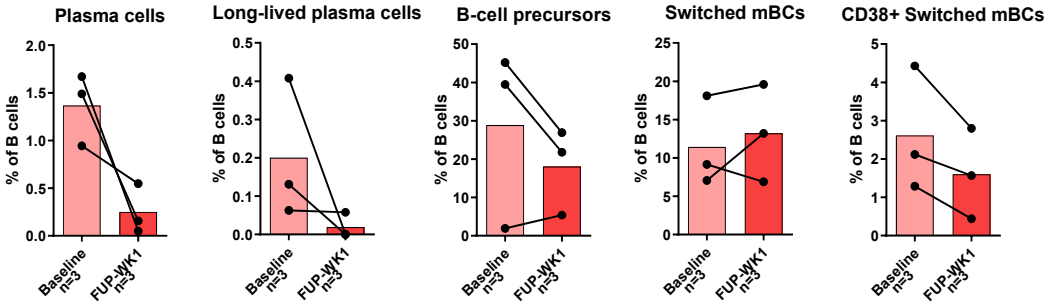
CI, confidence interval; RR, response rate.

- **Criterion 1:** cPRA to target levels (doubling the likelihood of finding a compatible donor).
- **Criterion 2:** reduction of >2 Ab titers to reach target cPRA
- **Criterion 3:** elimination of anti-HLA Ab as MFI <2000

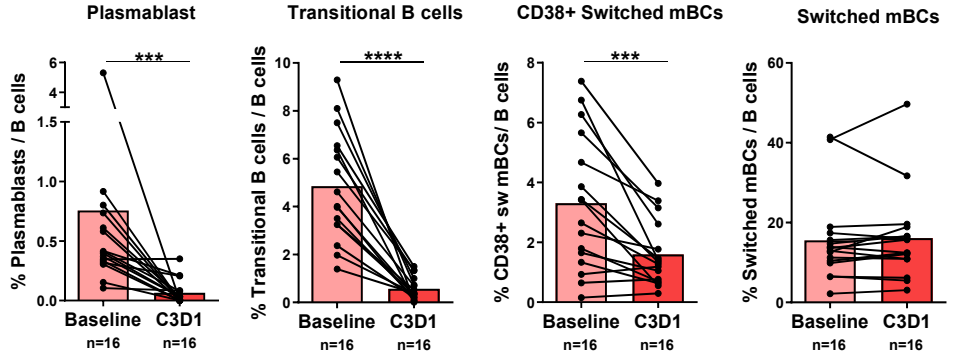
Serum anti-HLA Ab reduction



Bone Marrow

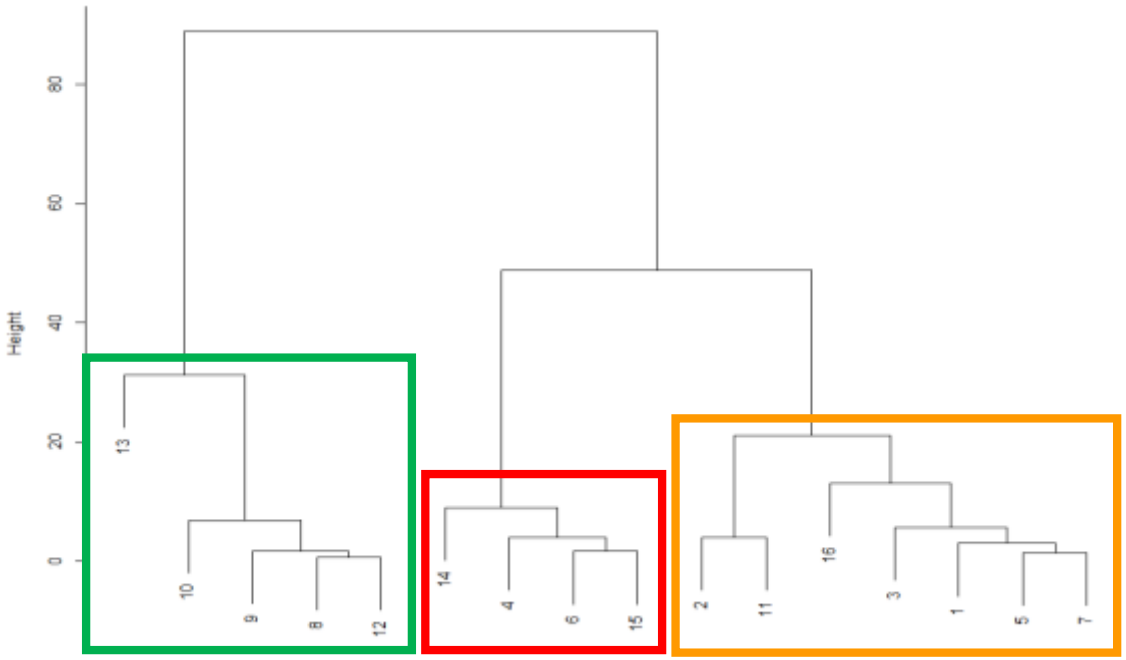


Periphery



Vinicenti F et al. J Am Soc Nephrol 2024

Clusters of patients regarding reduction of serum anti-HLA Abs (MFI and titers)



High responders (HR)

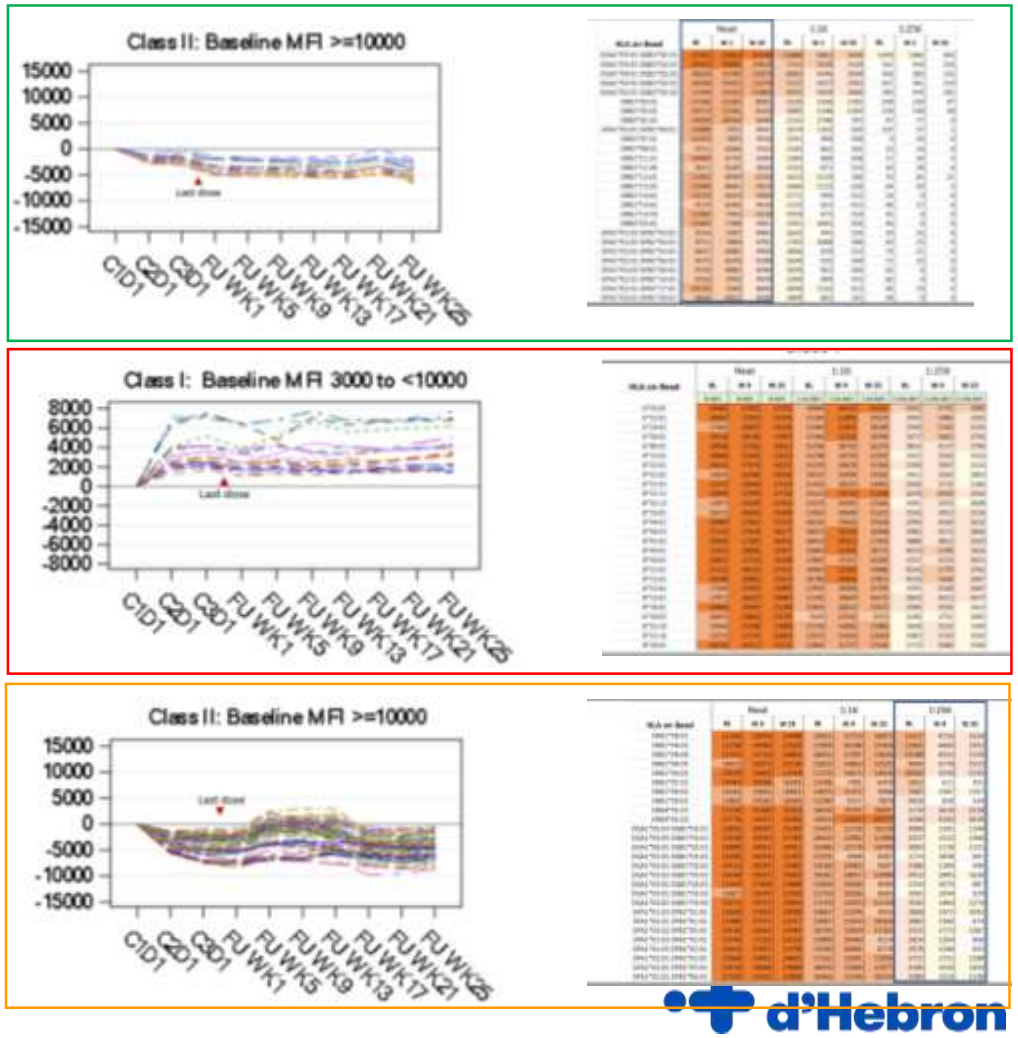
Larger decrease of 35-66% of anti-HLA Ab MFI

Non-responders (NR)

No change or increase of anti-HLA Ab MFI

Intermediate-low responders (LR)

Slight decrease of 36-5% of anti-HLA Ab MFI



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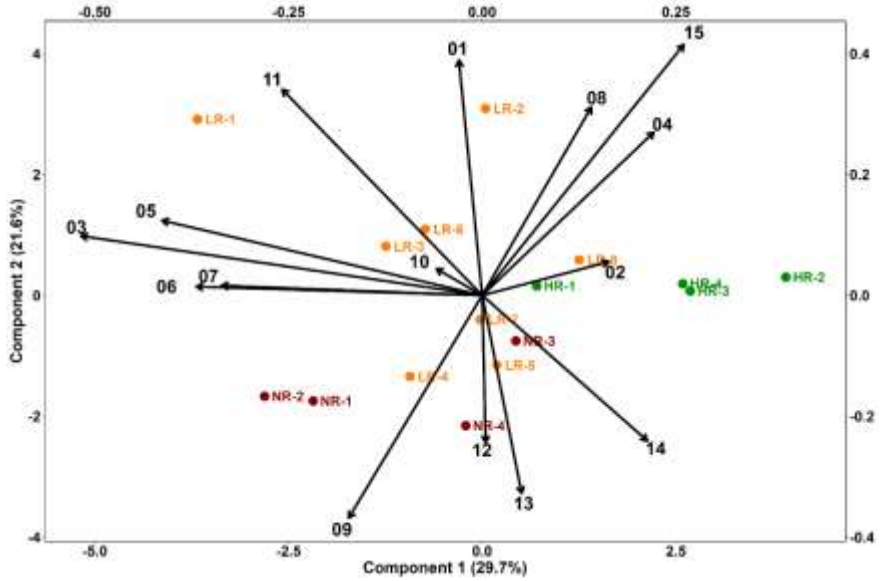
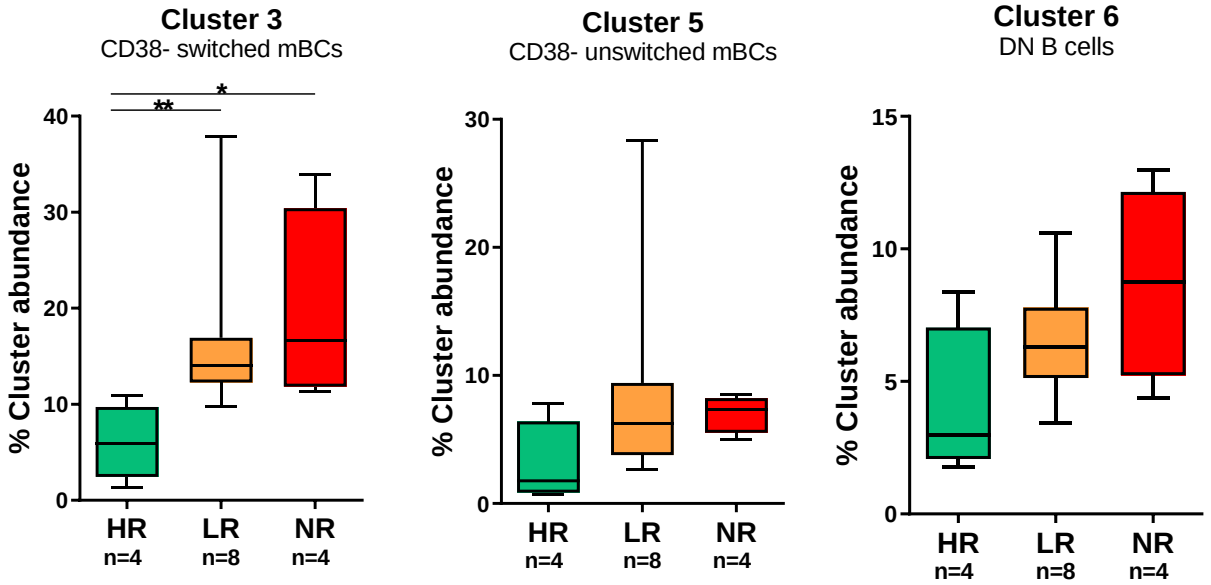
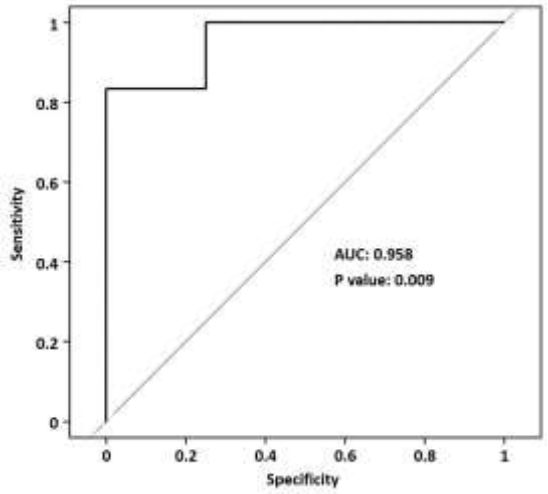
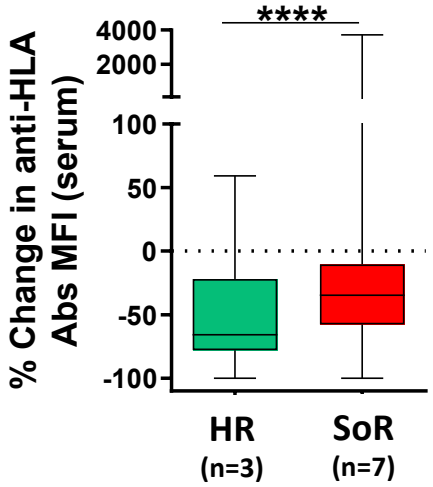
Pre-treatment cellular phenotypes of response to anti-CD38 therapy

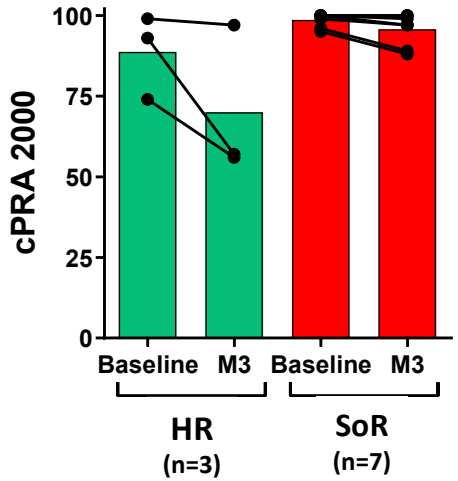




External validation (anti-CD38; NCT04294459)







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Summary

- Costimulation-targeting immunomodulation continues to have high interest as IS strategies to prevent Tx rejection while avoiding off-target side effects
- The short-term drawbacks and lack of supply has dramatically impacted a wider implementation of belatacept, hampering its long-term benefits to a broader transplant population
- New costimulation-targeting agents are on their way to the clinic, aiming to improve safety and efficacy
- New CD38-targeting agents for anti-HLA desensitization have showed high inter-patient efficacy variability for depleting anti-HLA antibodies
- A biological cellular signature prior to treatment may stratify responders from non-responder patients to CD38-targeting therapy

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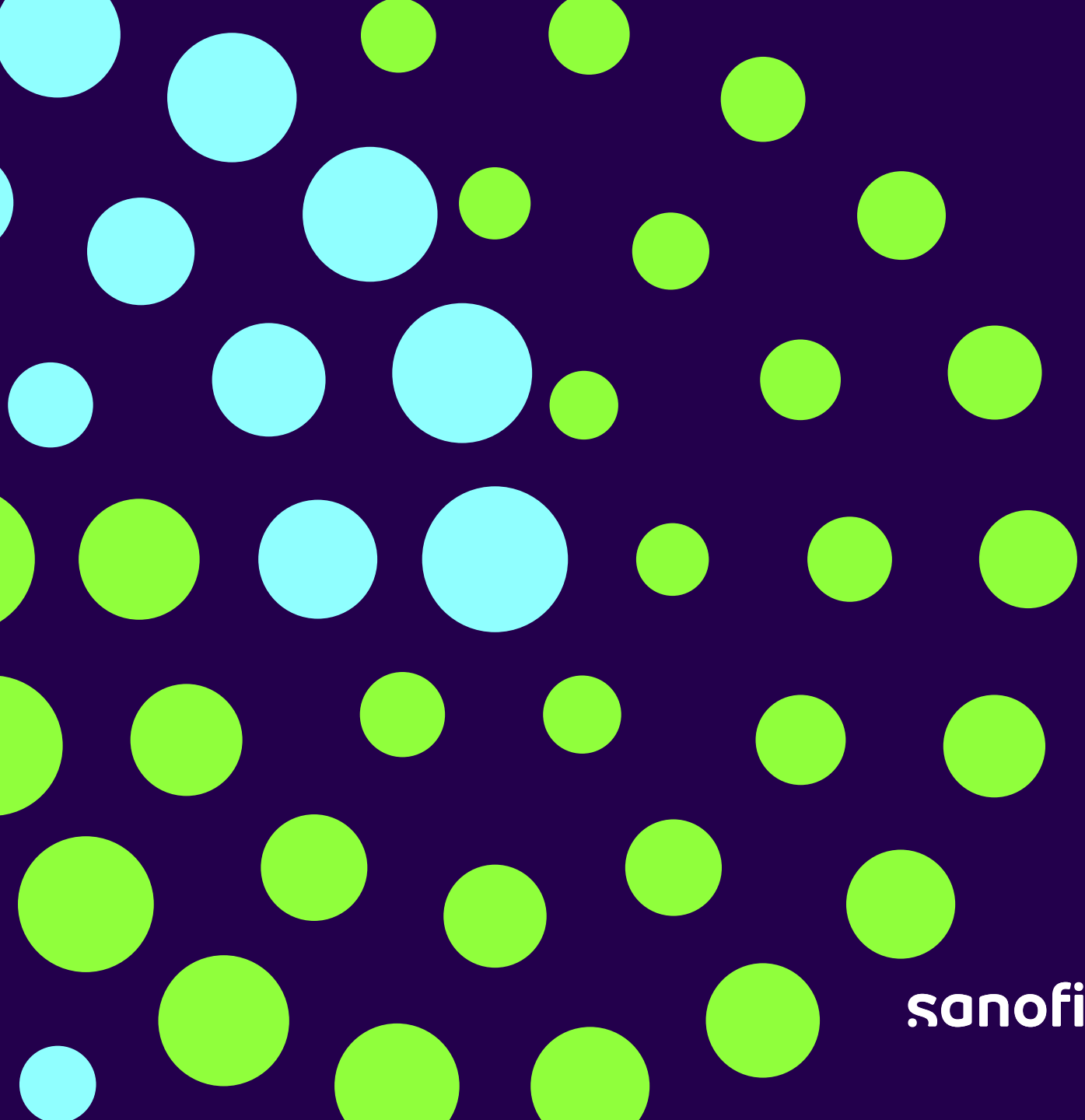

Thank you

sanofi