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Nuovi agenti immunosoppressori

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INSTITUT
D'INVESTIGACIÓ
BIOMÈDICA
DE BELLVITGE

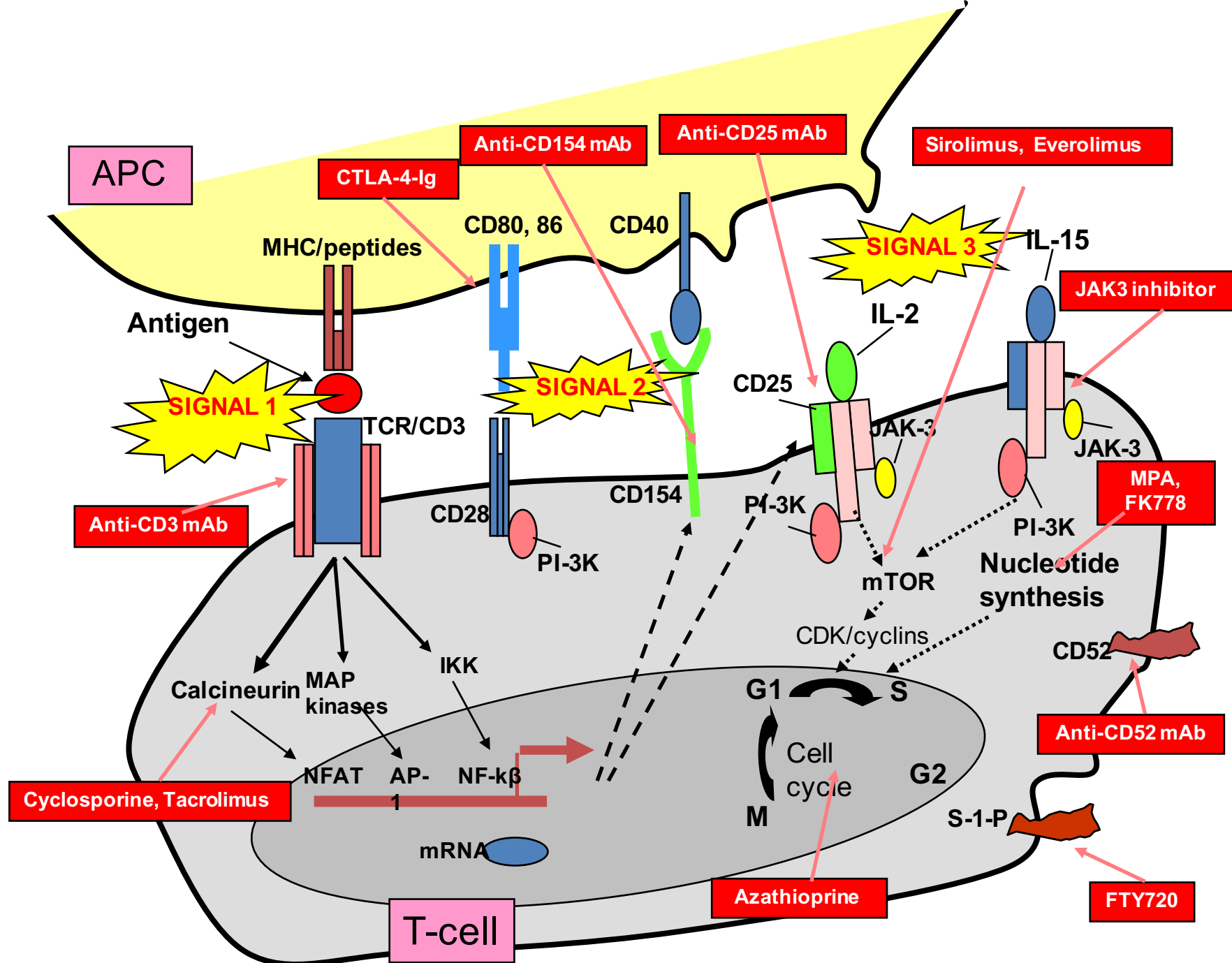
Current scenario on IS in renal transplantation

- CNI-based regimens
 - 90% RTR discharged with CNIs
- Low rates of acute rejection in low-risk KTR (10-15%)
- Low penetration of mTOR inhibitors-based regimens (2-5%).
- Gold standard: Almost Symphony-like IS regimens
- Resigned transplant community
- Off-label use of IS

Unmet clinical needs in RT

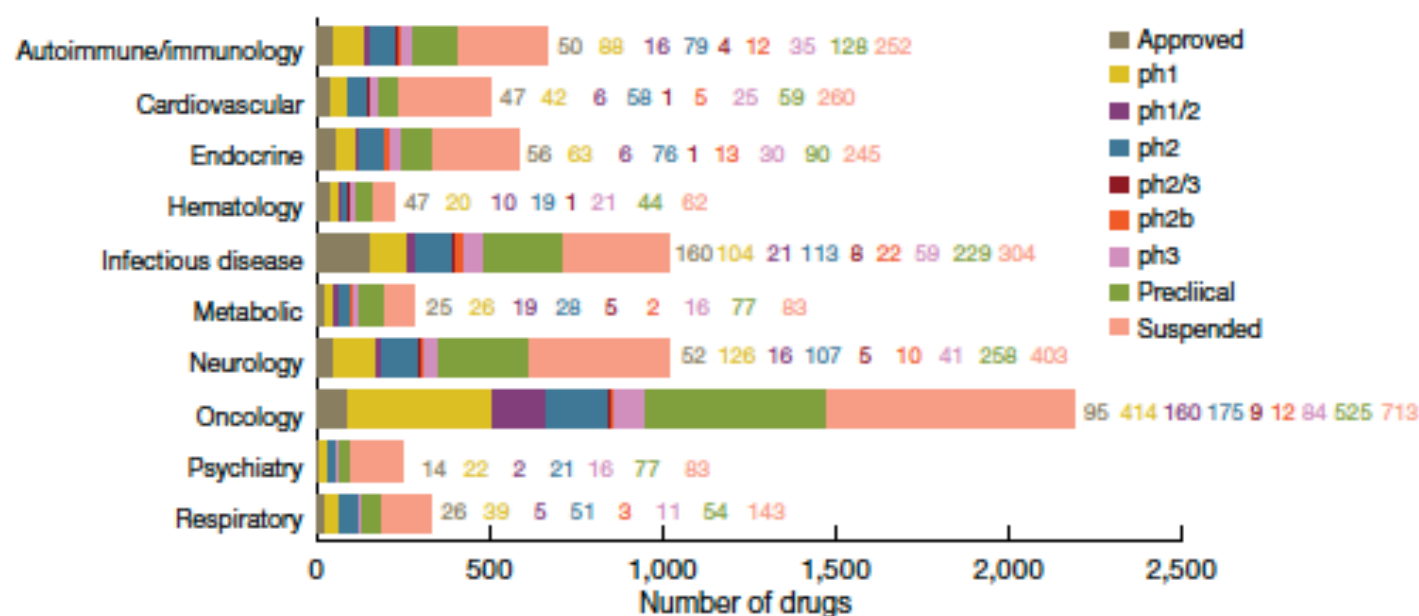
- Nephrotoxicity
- Metabolic complications
- Opportunistic infections (...BK)
- Long-term graft attrition
- CV morbi-mortality (DWFG)
- Malignancies
- Induction of donor-specific hyporesponsiveness (prope tolerance)?
- Antibody-mediated rejection

Targets of Immunosuppressants



Top ten disease groups by pipeline size

Oncology continues to dominate the drug pipeline



Drugs included are biologics, biosimilars, new molecular entities and vaccines. Approvals are cumulative; other phases are current. Source: BioMedTracker, a service of Sagient Research (<http://www.biomedtracker.com/>).

IS drug development in the last decade

- DSG analogues
- FK778
- FTY 720
- Anti-CD40L mAb
- Alefacept
- Sotrastaurin
- CsA analogues
- JAK3 inhibitors



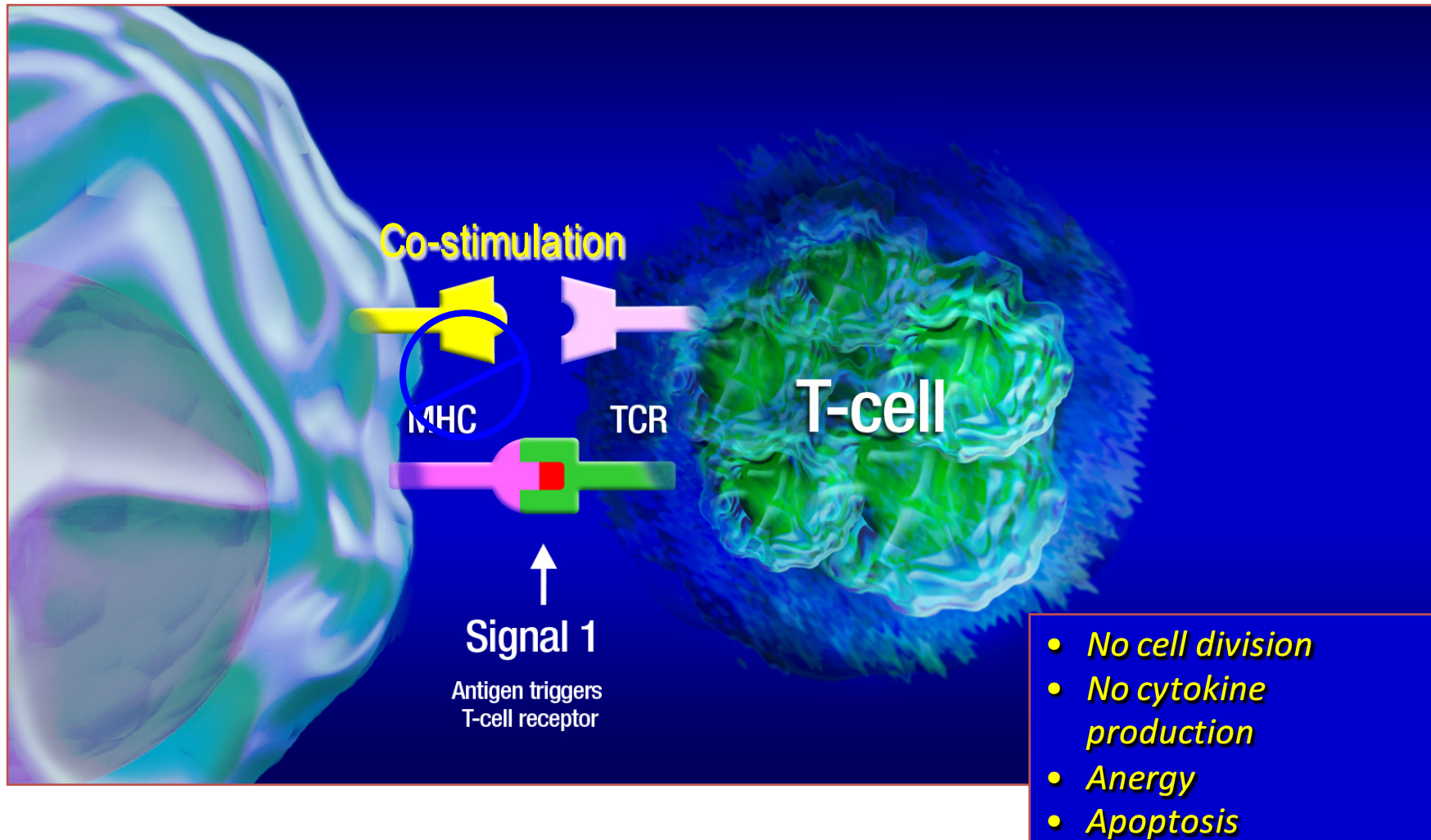
Higher interest in autoimmunity?
New core outcomes?

Core Outcome Measures in Effectiveness Trials (SONG-TX)



1. A systematic review to identify outcomes that have been reported in trials in kidney transplantation.
2. A three-round Delphi survey with stakeholder groups to distill and generate a prioritised list of core outcomes.
3. A consensus workshop to establish a core outcome set for kidney transplantation trials.

Belatacept: Costimulation blocker

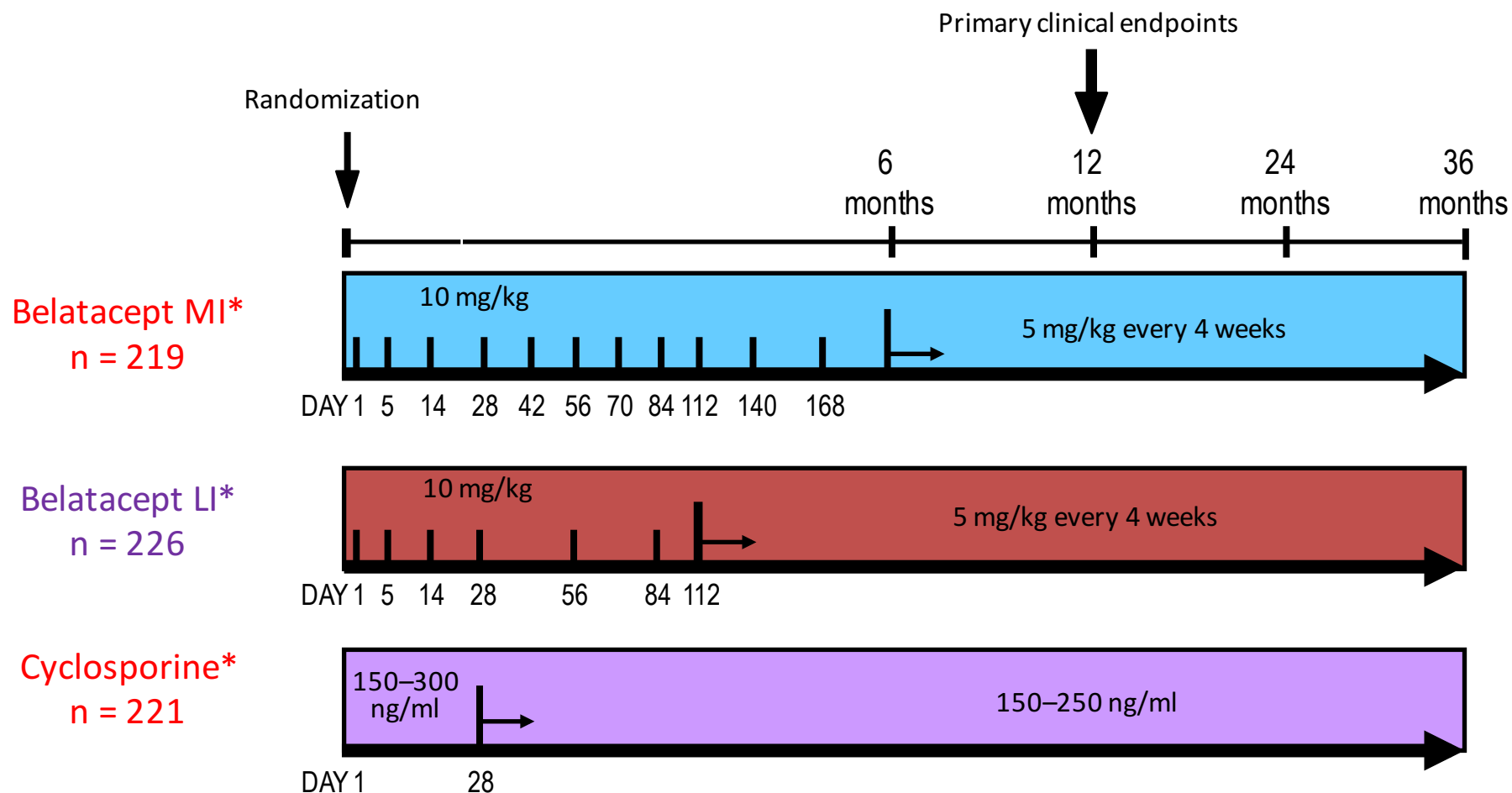


Phase 2 trial results at 12 months revealed better renal function and reduced incidence of chronic allograft nephropathy

Vincenti F, et al. *N Engl J Med.* 2005; 353:770-781

Belatacept in renal transplantation

BENEFIT and Benefit-EXT Study Designs. Phase III



*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids

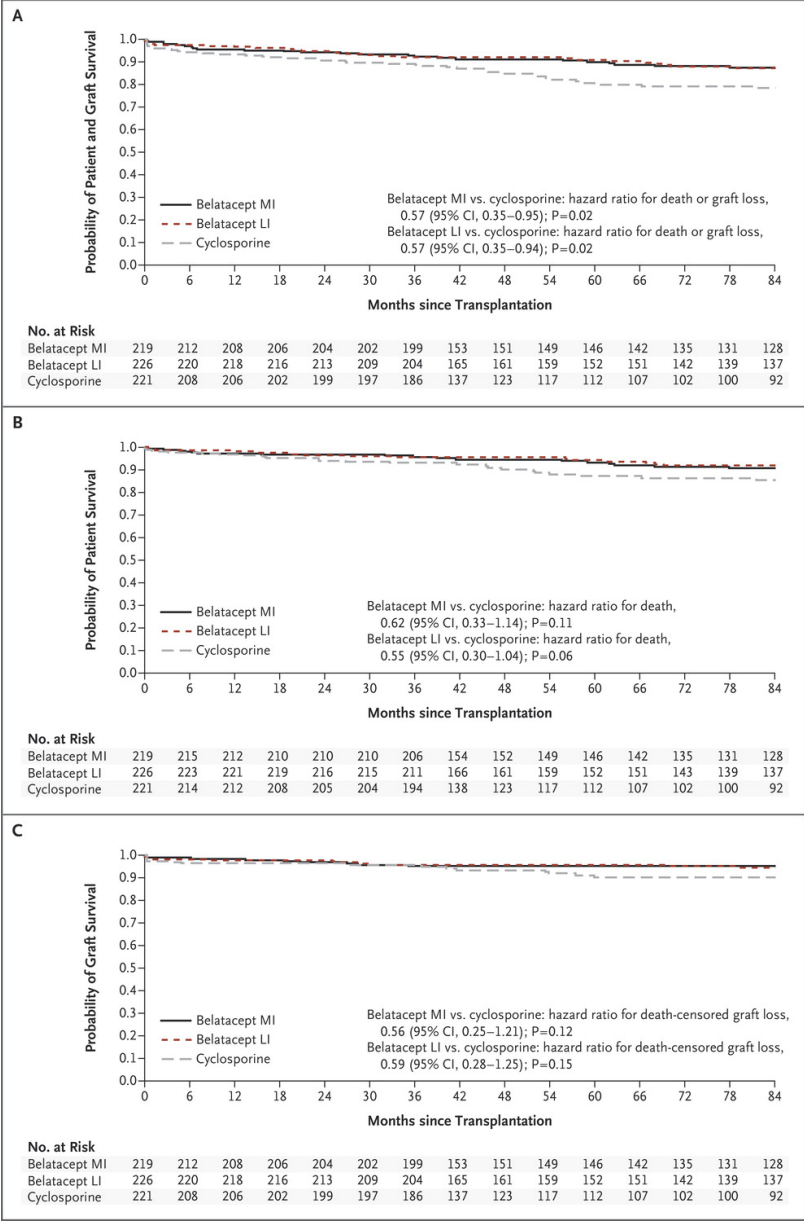
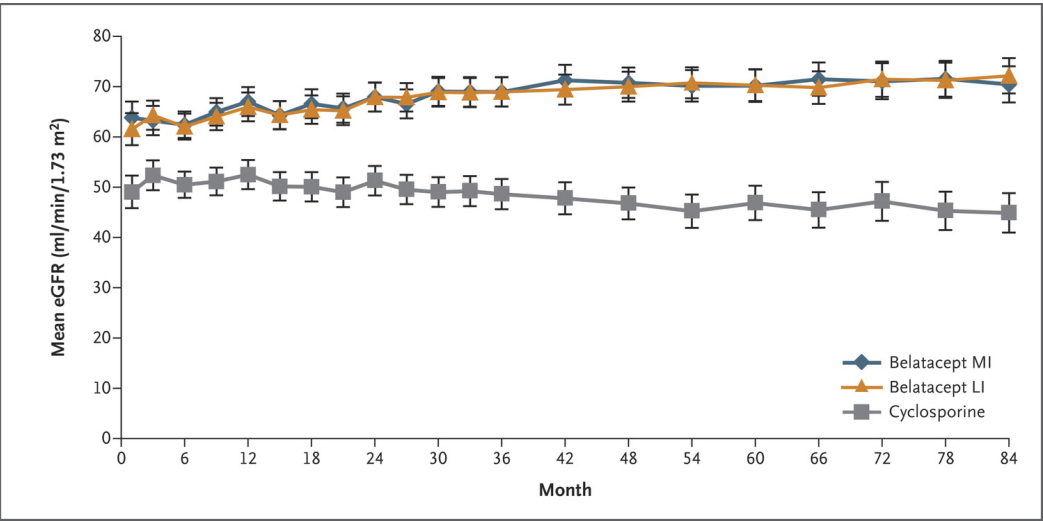
LI = less intensive; MI = more intensive.

Vincenti et al. Am J Transpl 2010; 10: 535-46.
Durrbach et al. Am J Transpl 2010; 10: 547-57

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

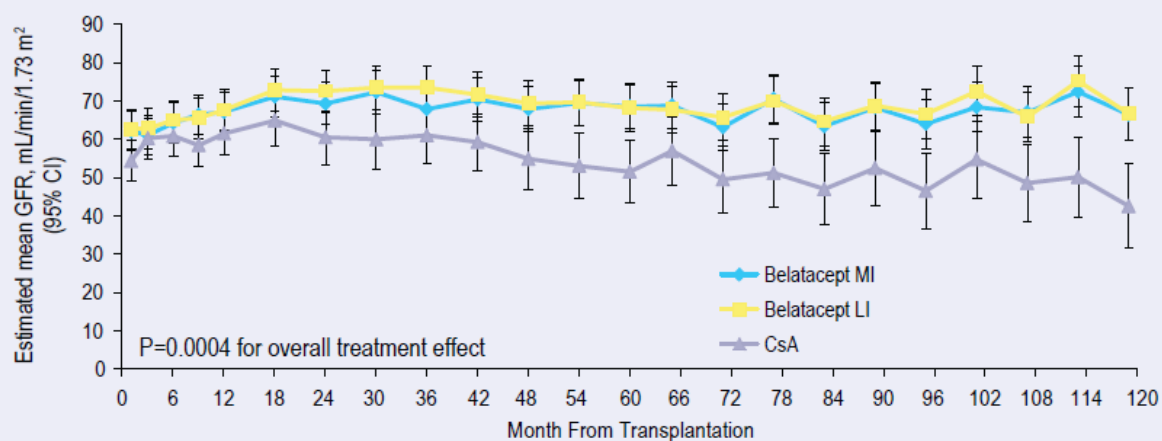
Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier,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



Optimal dosage? (cost?)

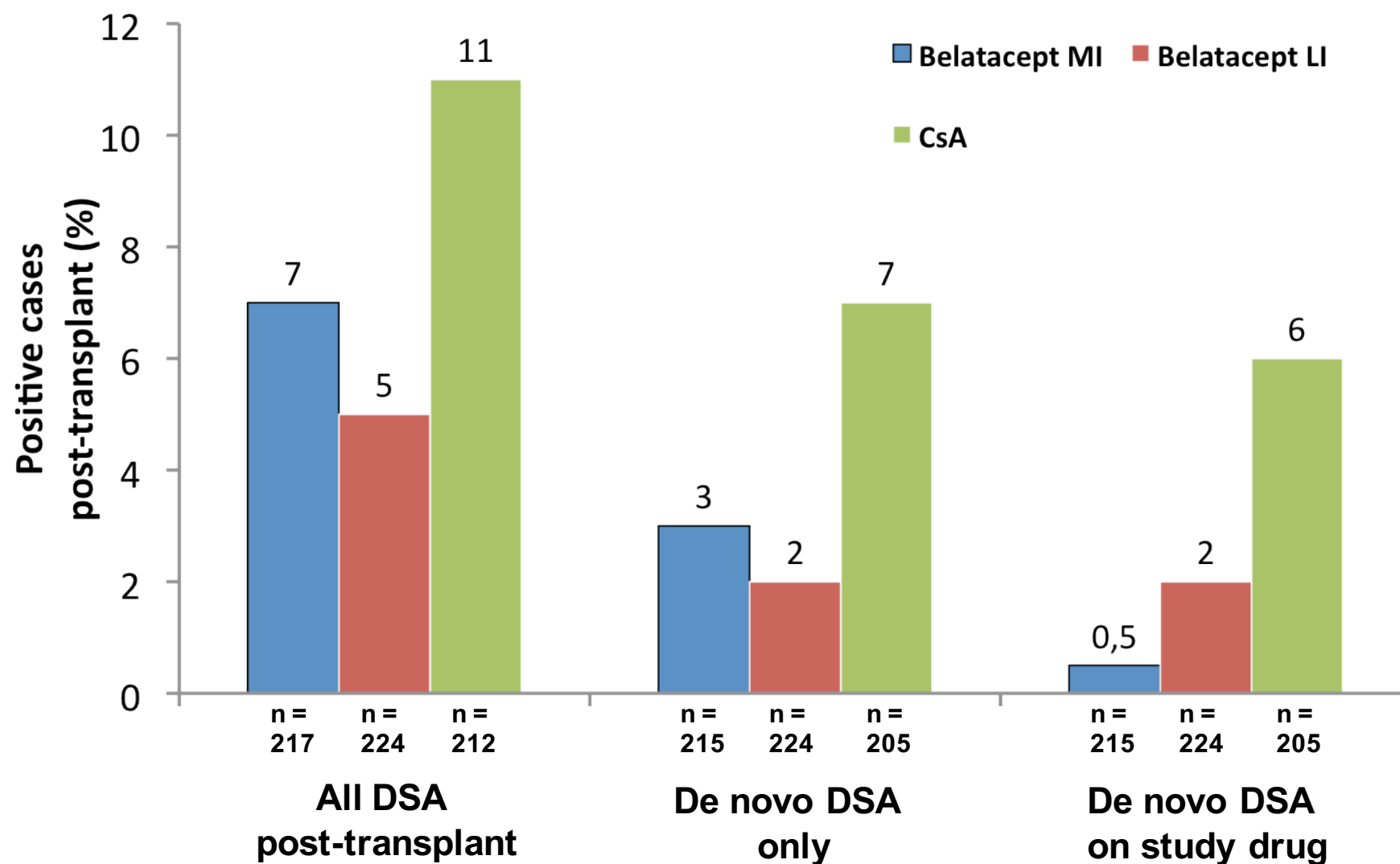
Belatacept phase II trial:

Renal function according to maintenance dose intervals at 10 years
(4 w or 8 w)

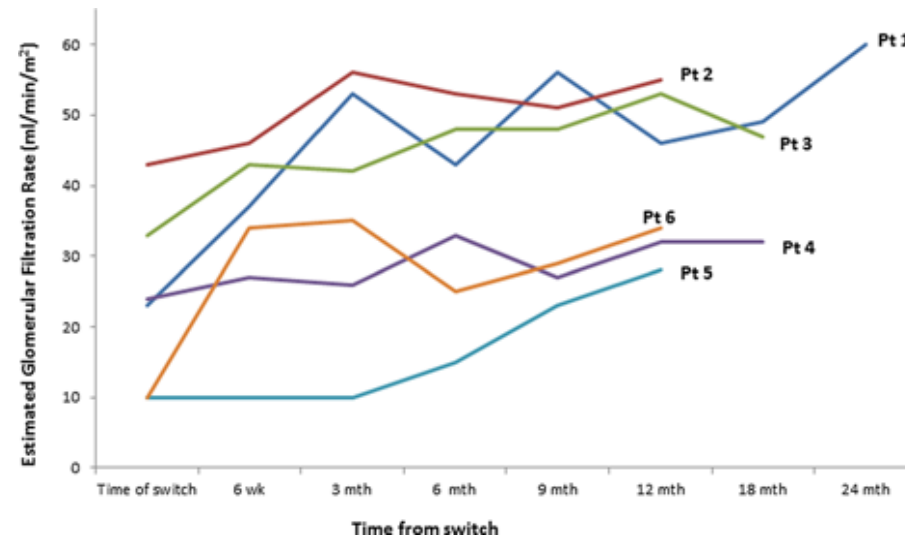


	Belatacept MI		Belatacept LI		CsA
	GFR	Difference vs. CsA	GFR	Difference vs. CsA	GFR
Year 1	67.1	5.7	67.6	6.2	61.4
Year 3	67.8	6.9	73.4	12.5	60.9
Year 5	68.4	17.0	68.1	16.7	51.4
Year 7	63.3	16.4	64.6	17.7	46.9
Year 10	66.3	23.9	66.6	24.2	42.4

BENEFIT: Prevalence of Donor-Specific Antibodies by Year 3 (SPA)

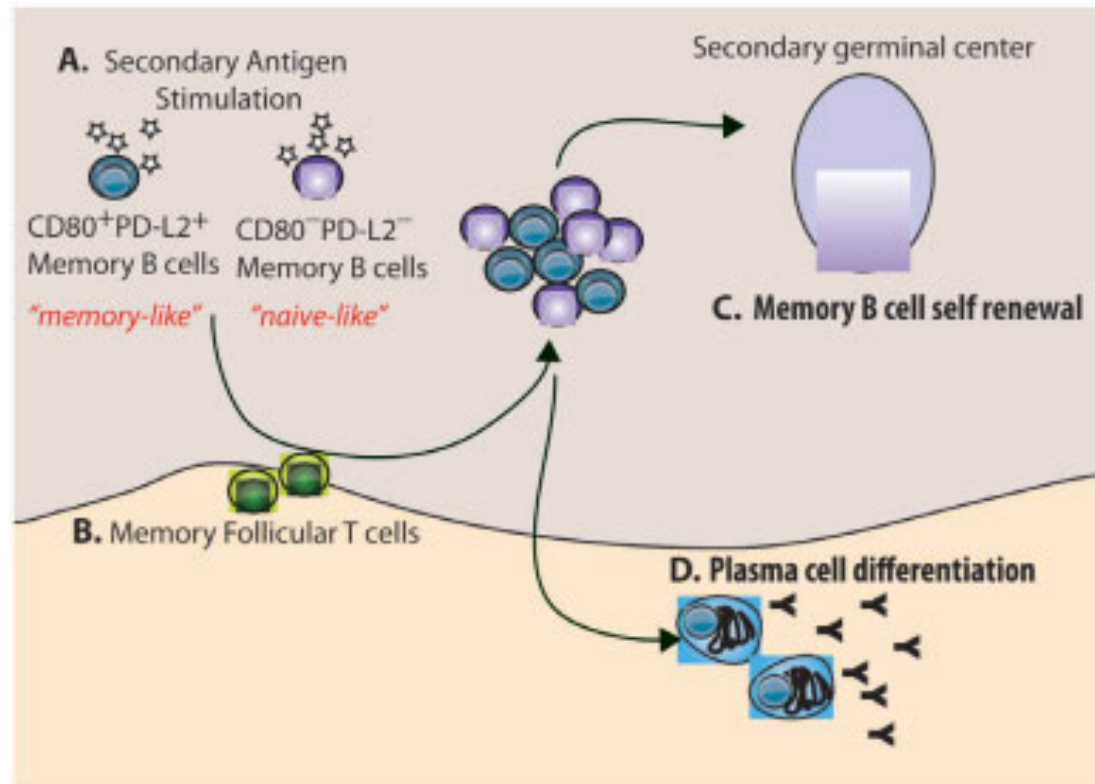


Safe Conversion From Tacrolimus to Belatacept in High Immunologic Risk Kidney Transplant Recipients With Allograft Dysfunction



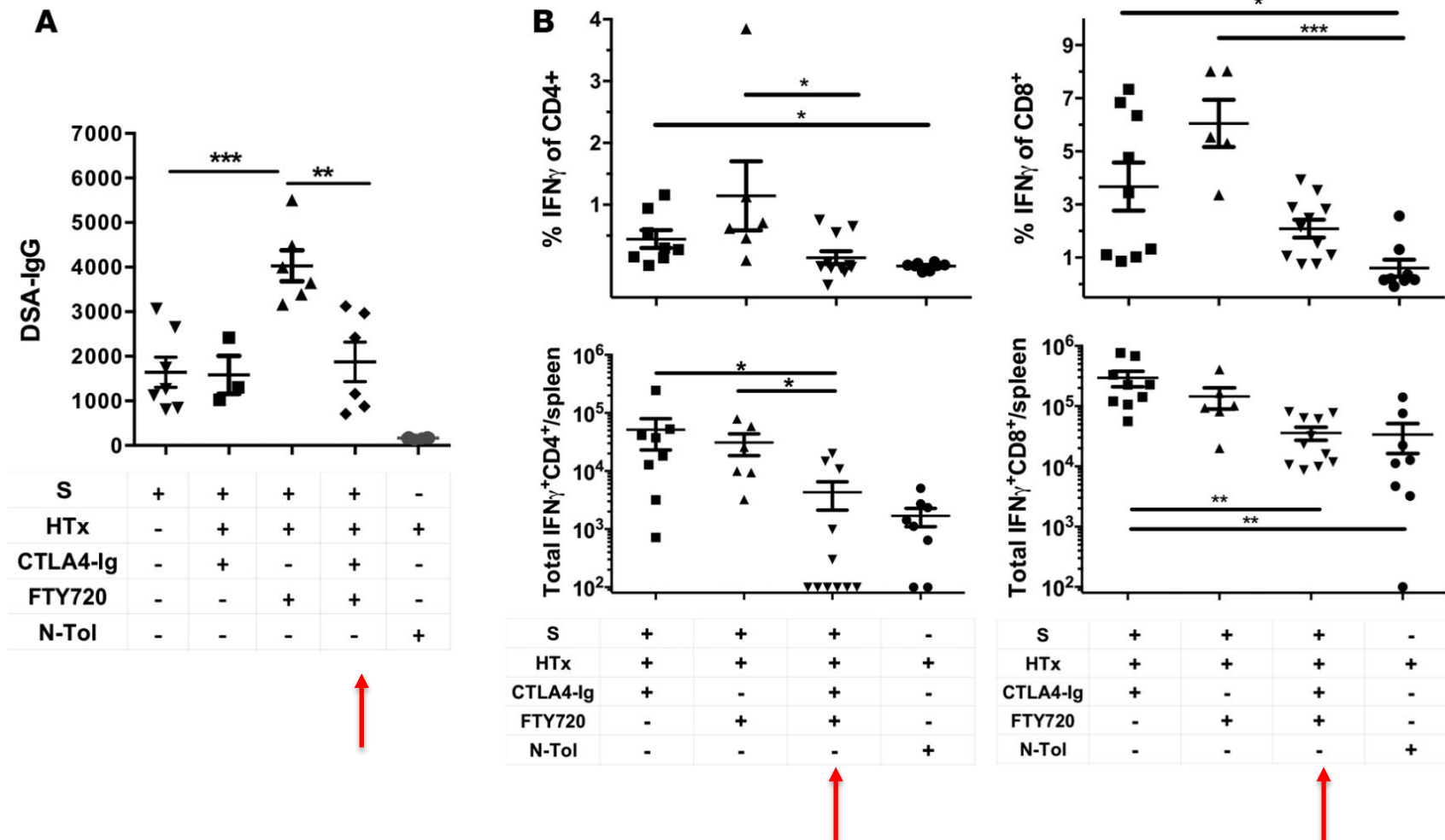
No development of DSA
No rejection episodes

Costimulation and memory B cell differentiation

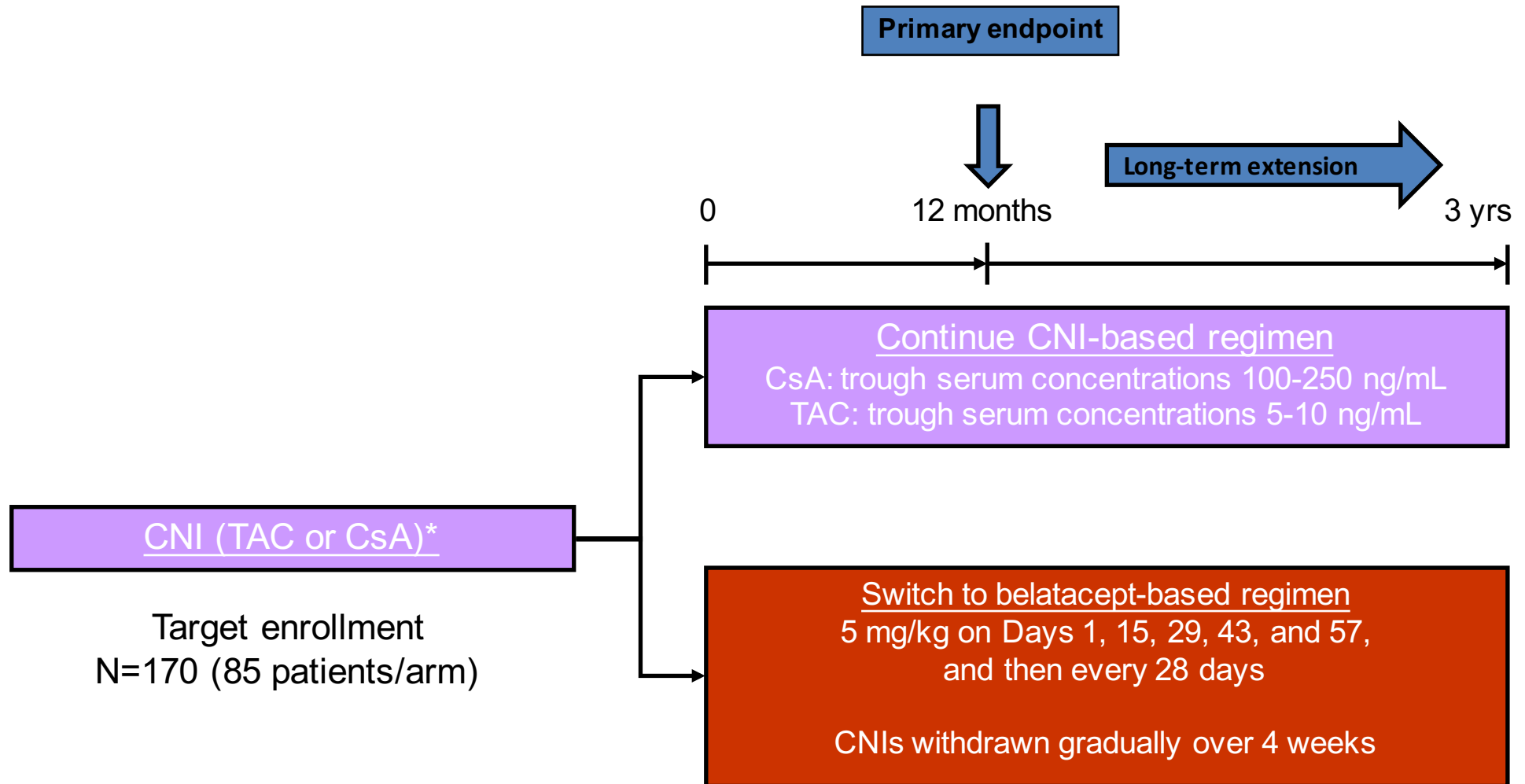


Belatacept (Abatacept): targeting mTfh cells?
(Bela in HS, de novo DSA, CABMR?)

CTLA4-Ig plus FTY720 combination therapy prevents rejection in sensitized recipients



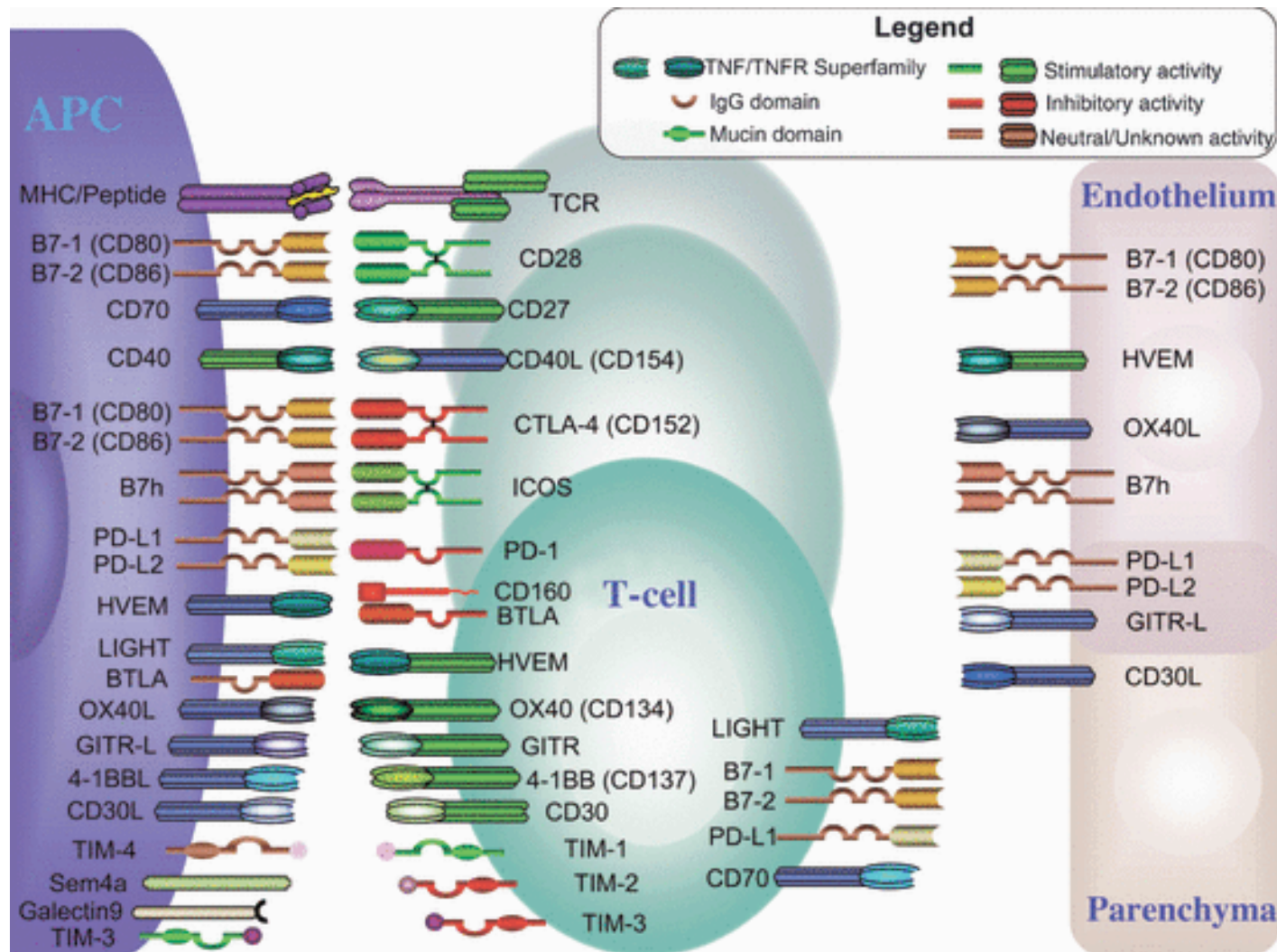
Switch from CNI to Belatacept



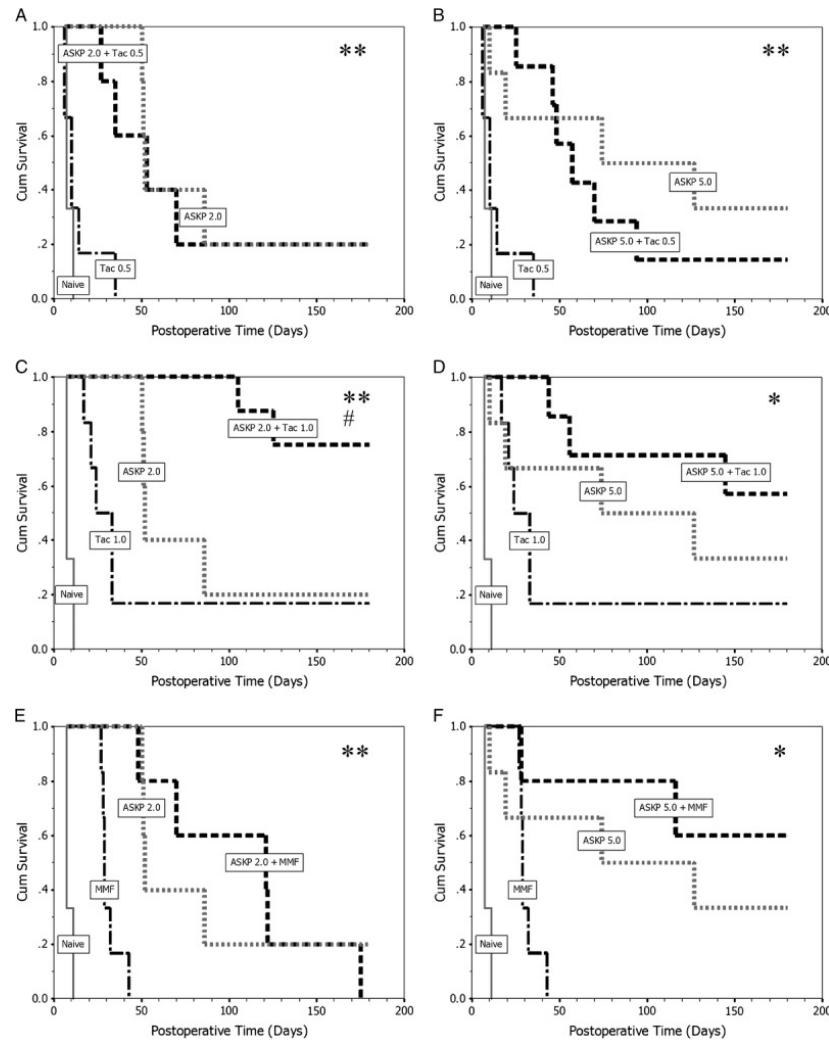
Belatacept Phase III conversion study.....?

Novel immunosuppressives

Costimulatory pathways (SOT and autoimmunity targets)



ASKP1240, a fully human anti-CD40 mAb combined with tacrolimus or MMF on renal allograft survival in Cynomolgus monkeys

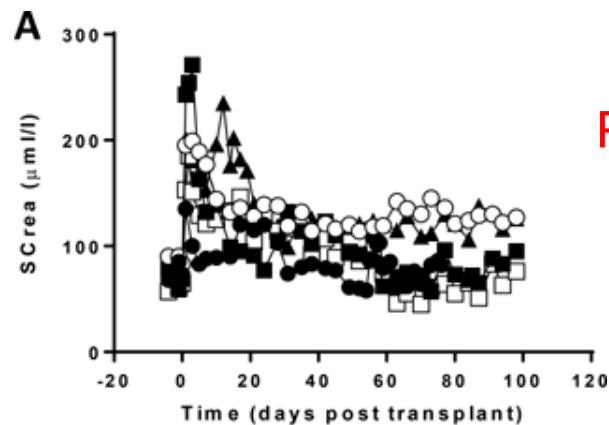


RCT: Phase IIa:
CNI avoidance
Basiliximab induction + **ASKP1240** + MMF + ST

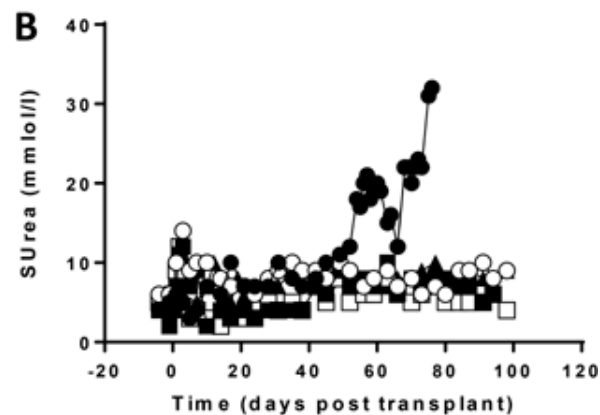


CD40–CD154 pathway blockade

CFZ533, Fc-Silent Anti-CD40 non-B-cell depleting mAb
prolongs KT survival in NHP



Phase II trial with and w/o tacrolimus vs SOC

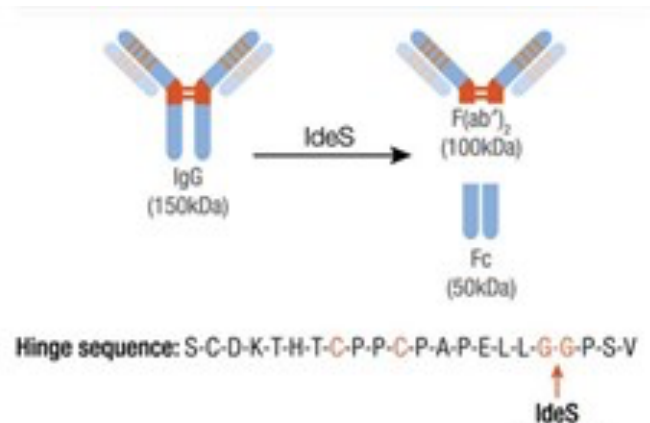


● 5535 ■ 5544 ▲ 5537
○ 5541 □ 5545

Cordoba et al. Am J Transplant. 2015;15:2825-36.

IdeS:

Protease (*S. pyogenes*) specifically inactivating IgG antibodies



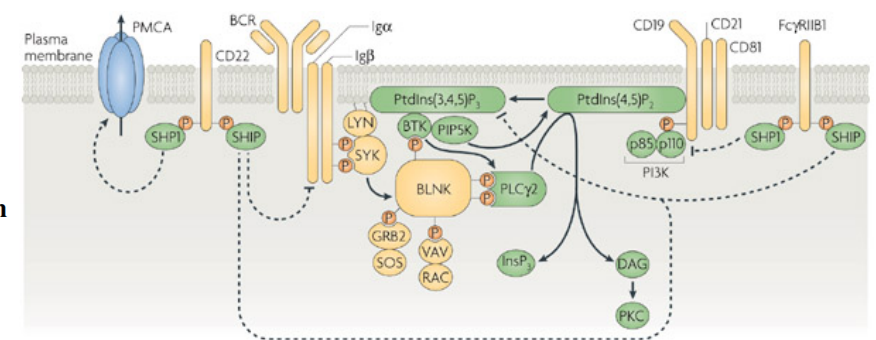
Phase I/II trial in highly sensitized patients:
Prevention of AMR and DSA elimination

The Journal of Immunology

The Bacterial Enzyme IdeS Cleaves the IgG-Type of B Cell Receptor (BCR), Abolishes BCR-Mediated Cell Signaling, and Inhibits Memory B Cell Activation

Sofia Järnum, Robert Bockermann, Anna Runström, Lena Winstedt, and Christian Kjellman

2015



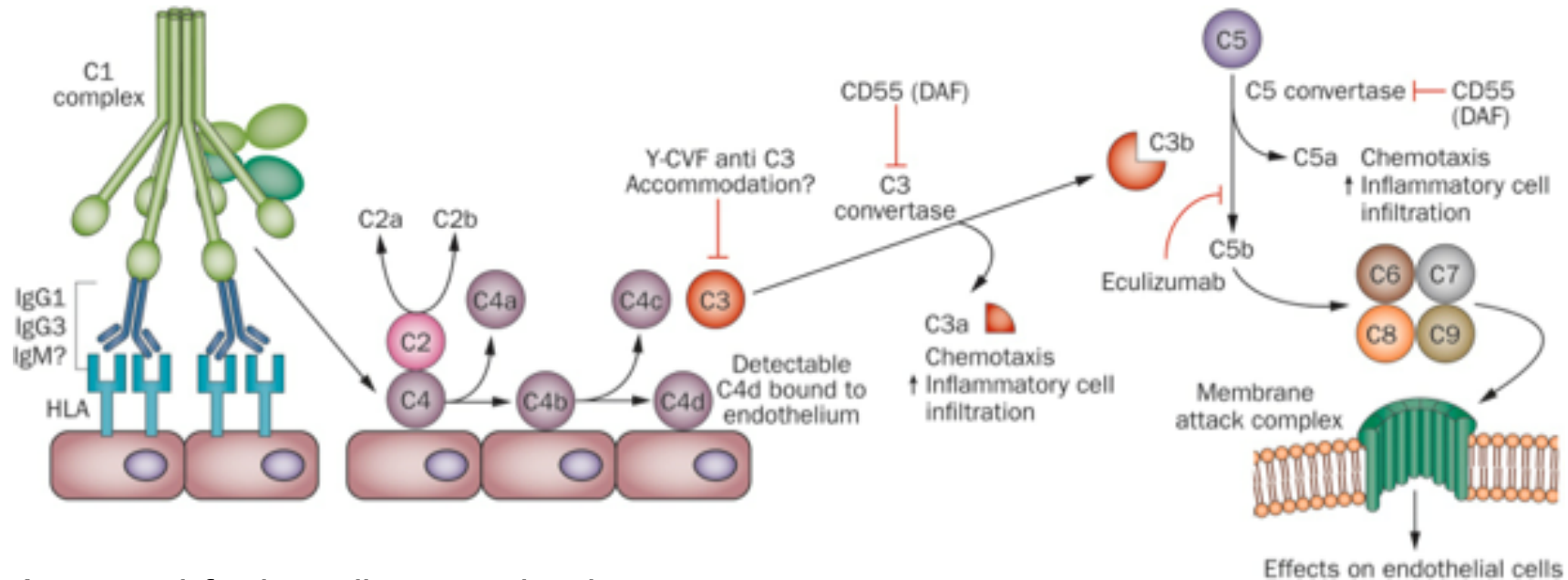
Nature Reviews | Immunology

Targeting complement cascade

C1 esterase inhibitors

BERINERT

CINRYZE



Approved for hereditary angioedema
Ongoing studies in AMR

Stegall et al. Nat Rev Nephrol 2012.

- Approved for PNH and atypical HUS
- Phase II trials in RT in highly sensitized pts:
- +XM, desensitization, CAMR
- Prevention of AAMR in HSP: 6.3% vs. to 30% expected for historical controls (Glotz et al. ATC 2015)

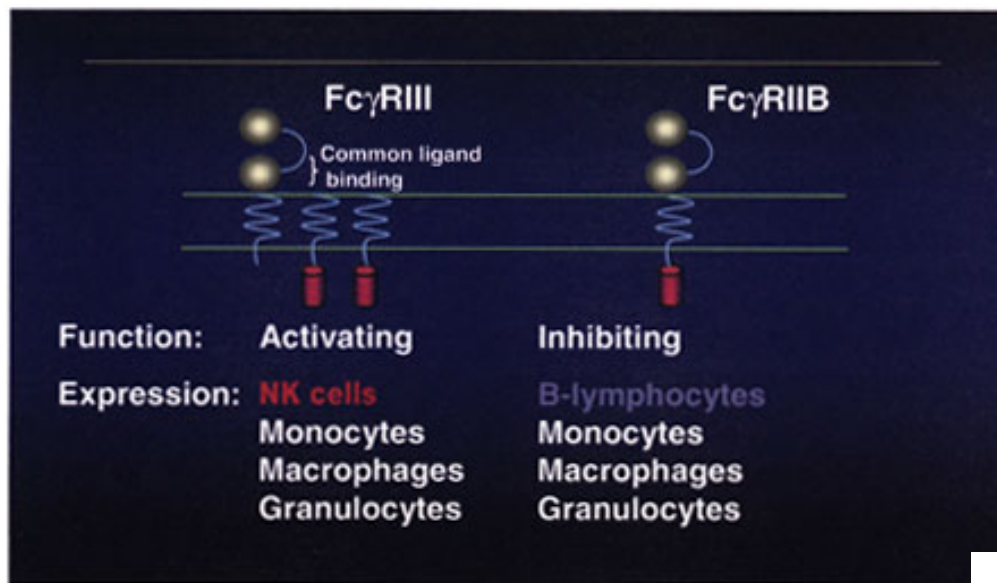
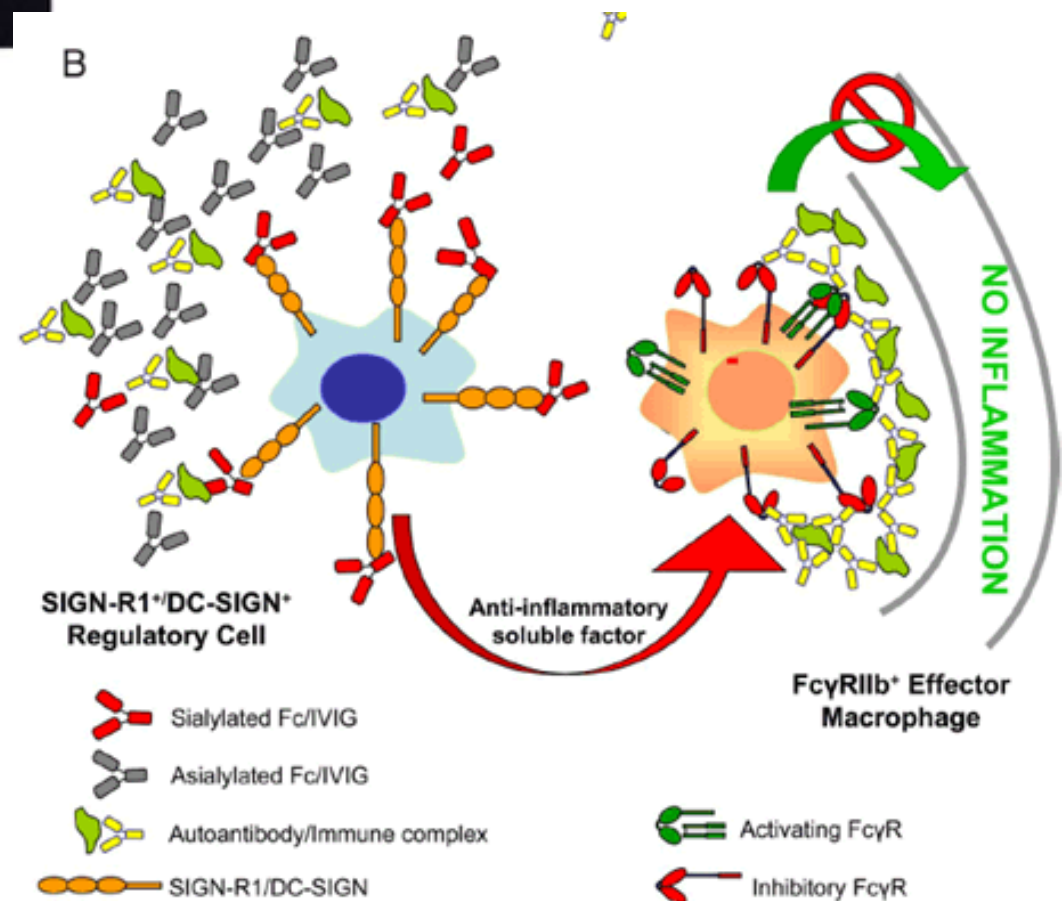


Figure 1. Activating and inhibiting Fc receptors.

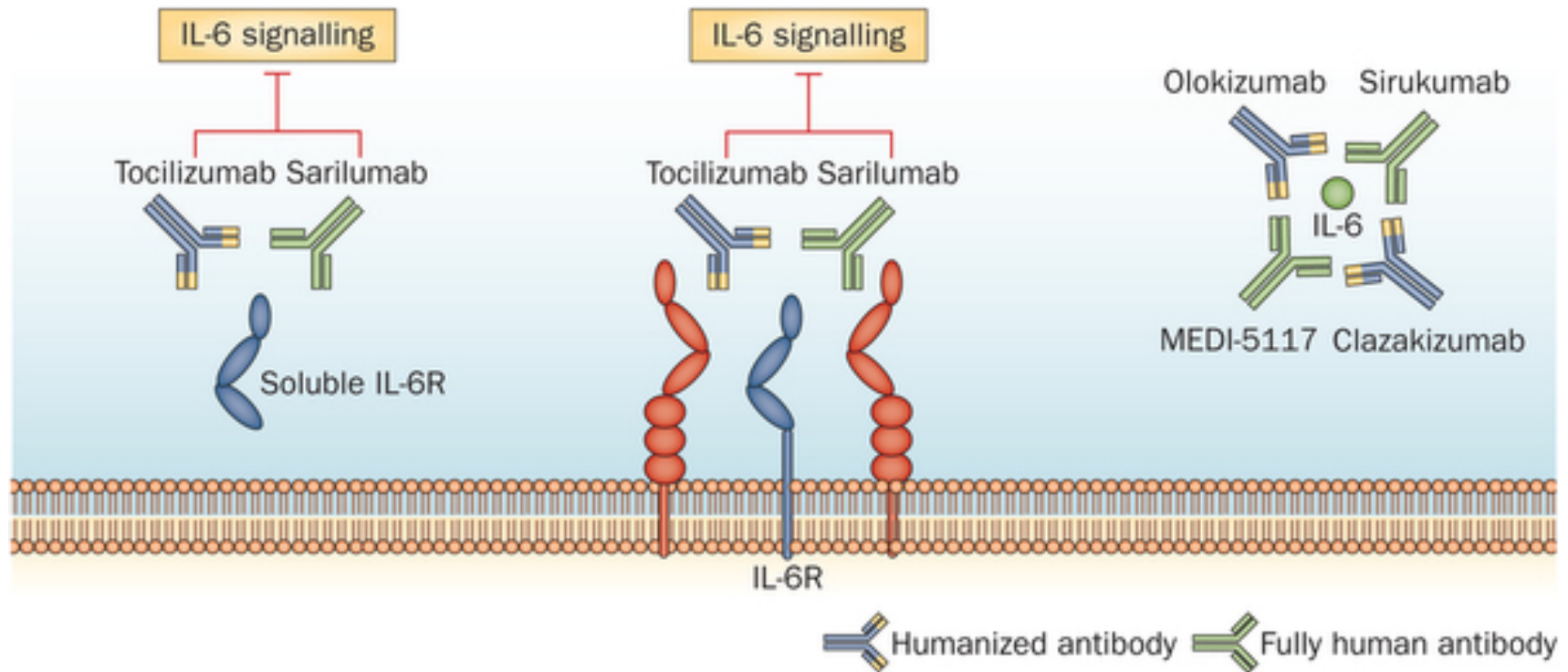
IVIg: New MOAs?



Second generation of anti-CD20 mAb: Ofatumumab (IG₁ human mAb) in RT?



Targeting IL-6 signalling



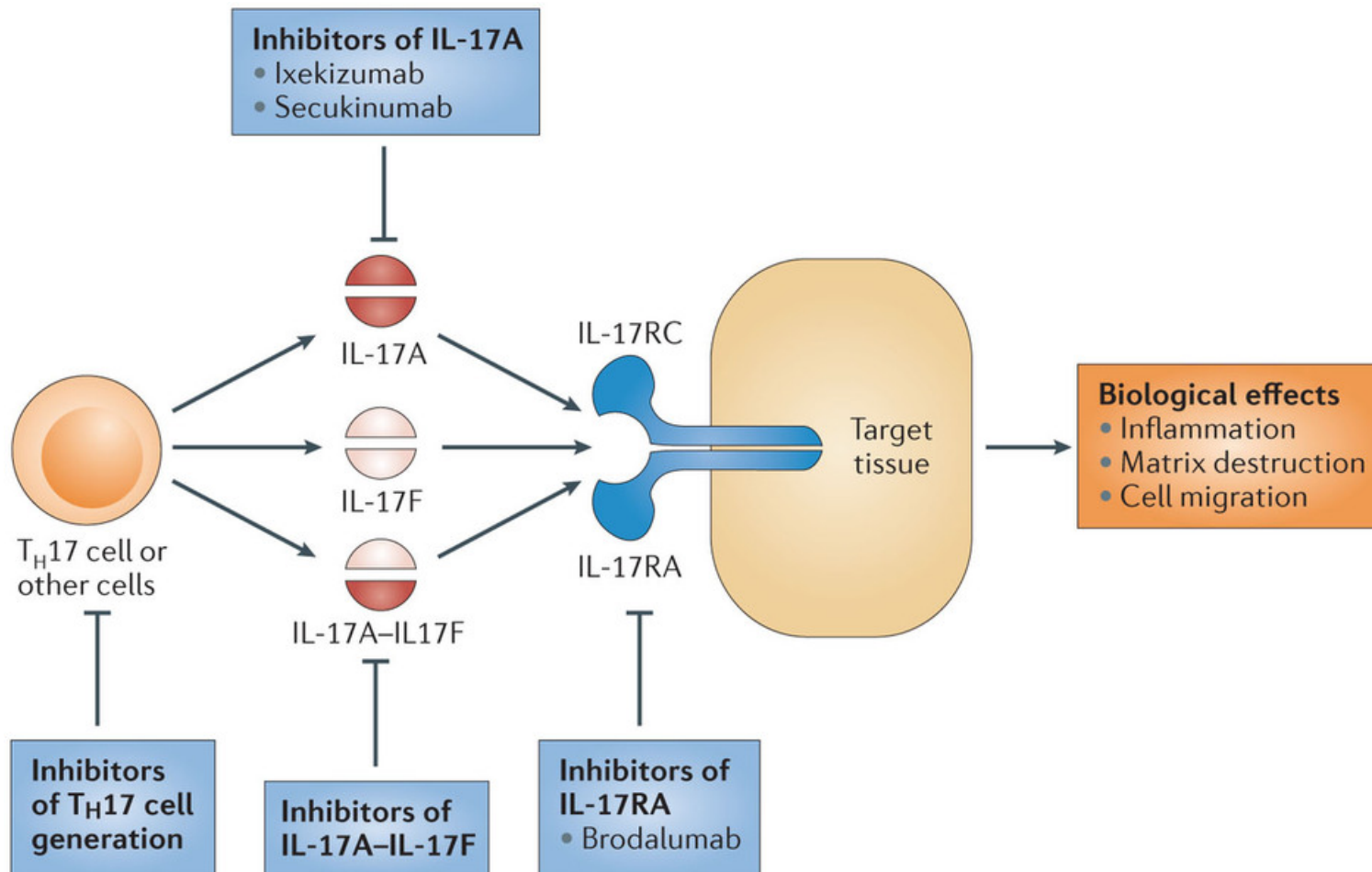
Nature Reviews | Rheumatology

Investigator-driven trials (Tocilizumab):

Treatment of SCR/Inflammation

Desensitization

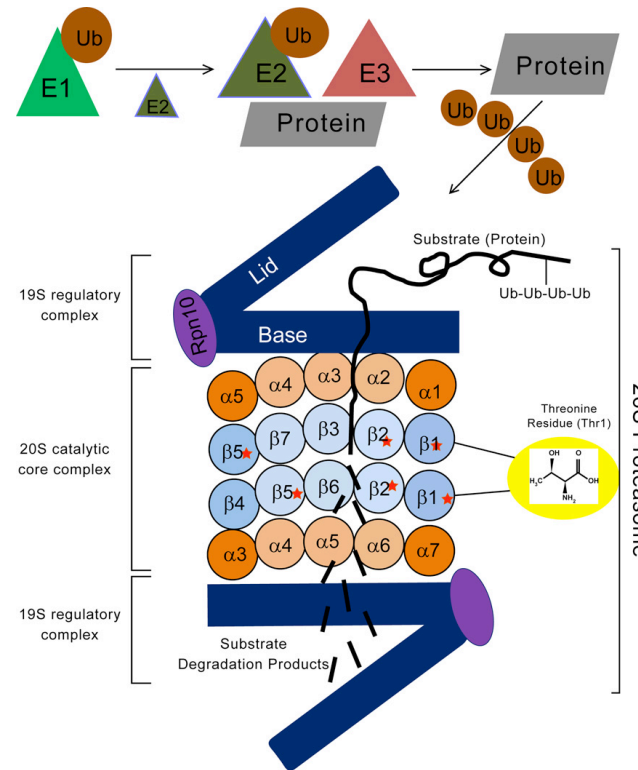
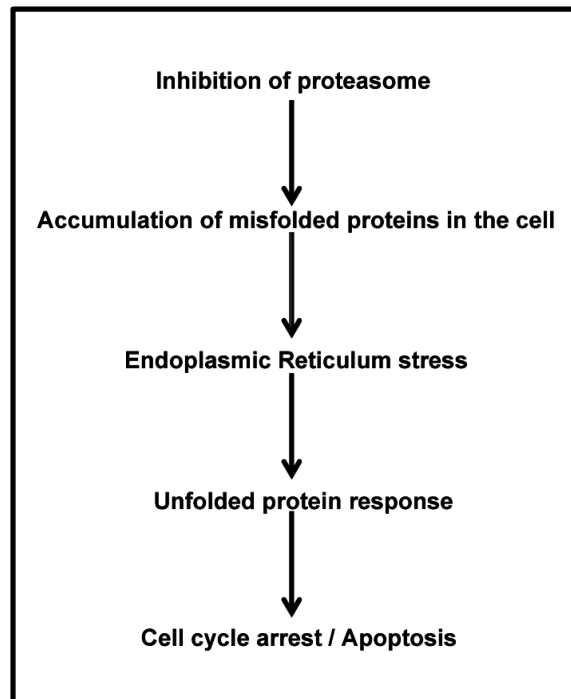
Targeting IL-17 axis?



Belimumab (anti-BAFF mAb) (IDT in RT)

- Desensitization (normalization of anti-HLA Ab)
- Prevention of AR (naïve and memory B cells)
- Belizumab vs Bortezomib

Proteasome inhibitors: Bortezomib, Carfilzomib.....

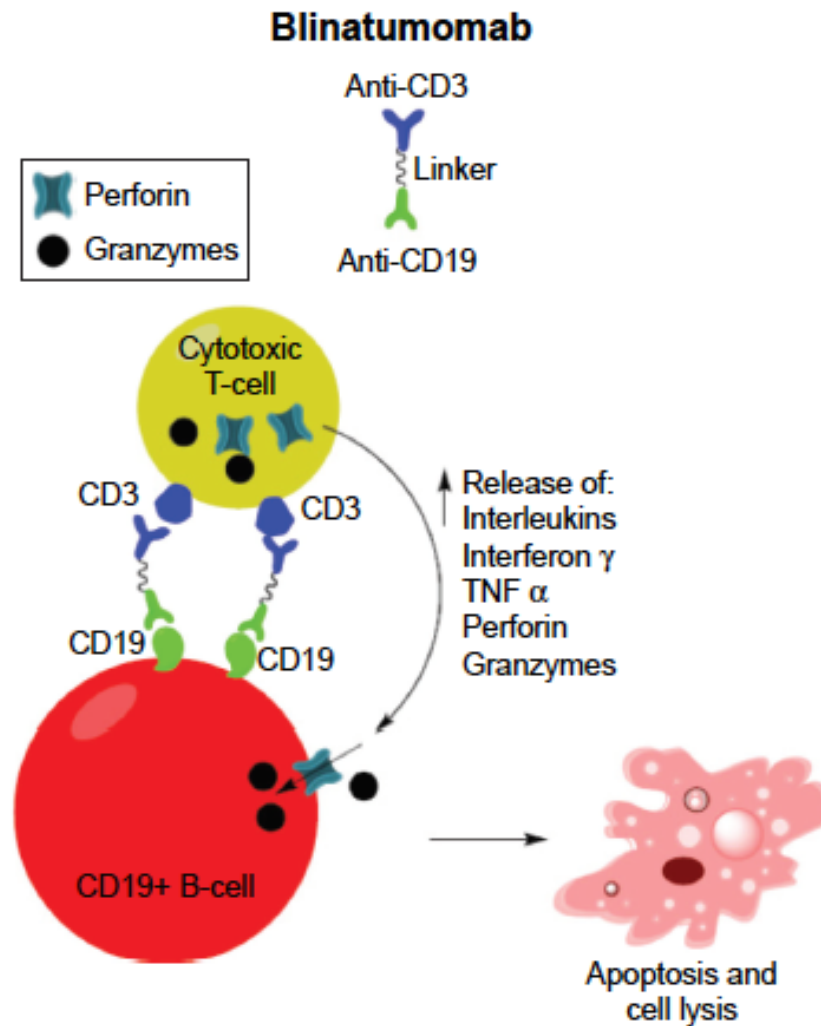


Desensitization
Treatment of AMR

Immunoproteasomes?

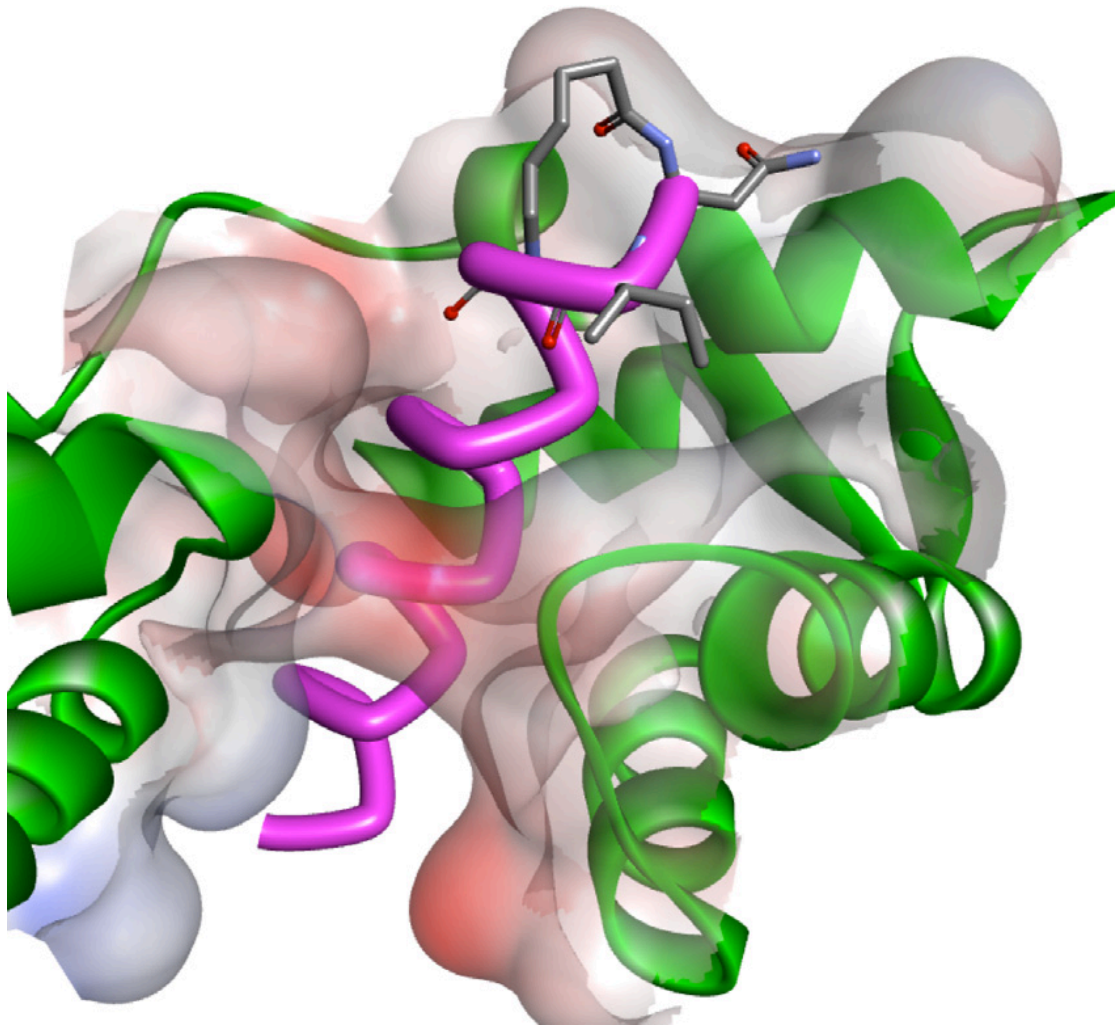
New classes of IS?

Bispecific Ab in TX? (Cell synapse engagers)



Protein-Protein Interaction (PPI) inhibitors?

Peptidomimetics
(in silico designs)



Cell products as new IS?

Tregs

DC

Mregs

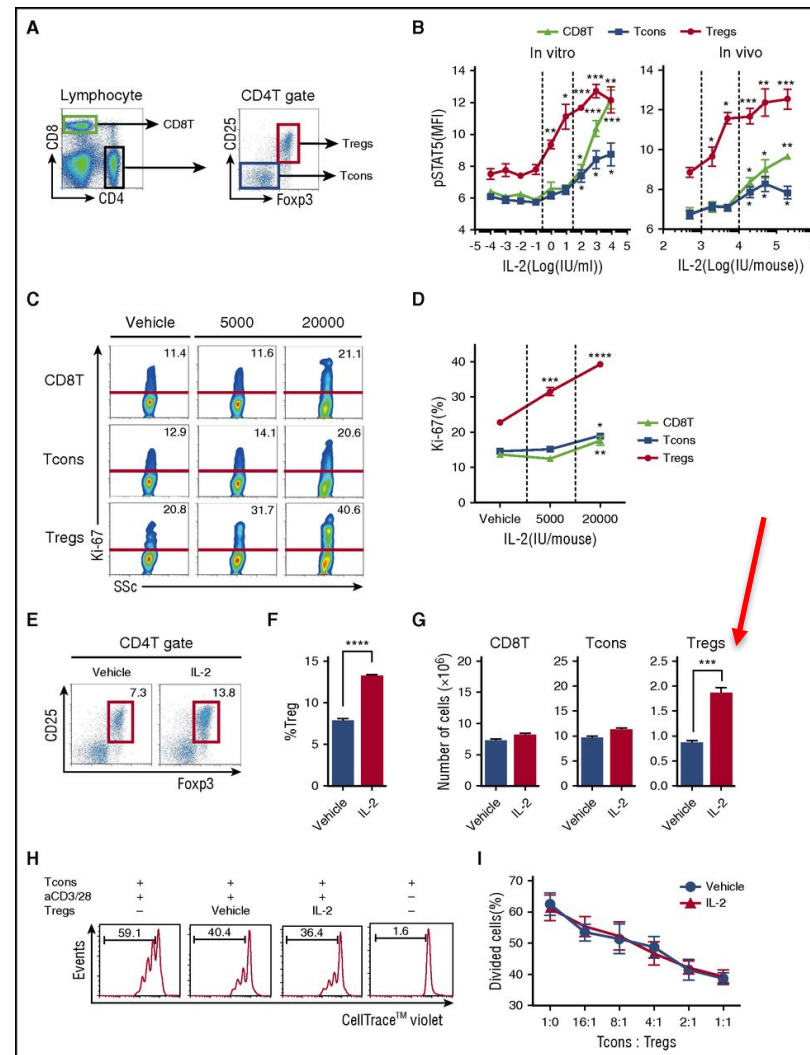
MSC



Low-dose rIL-2 to expand Tregs is SOT?

(NCT02417870)

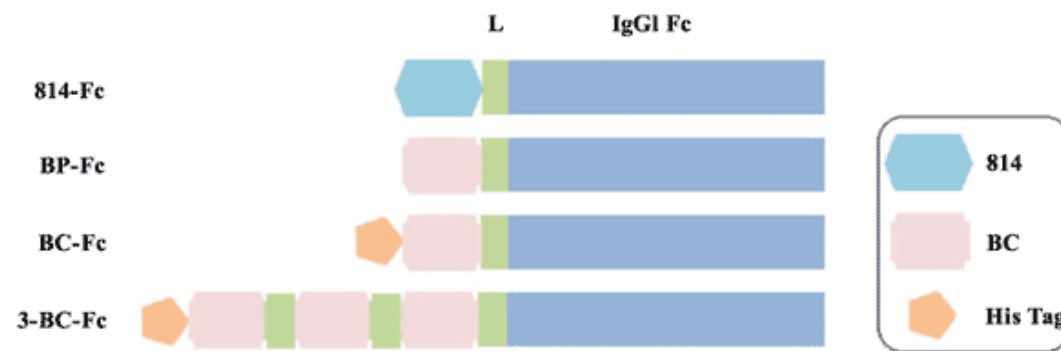
Selective expansion of CD4 Tregs in a murine model of low-dose IL-2 therapy.



Back-up slides

Peptibodies

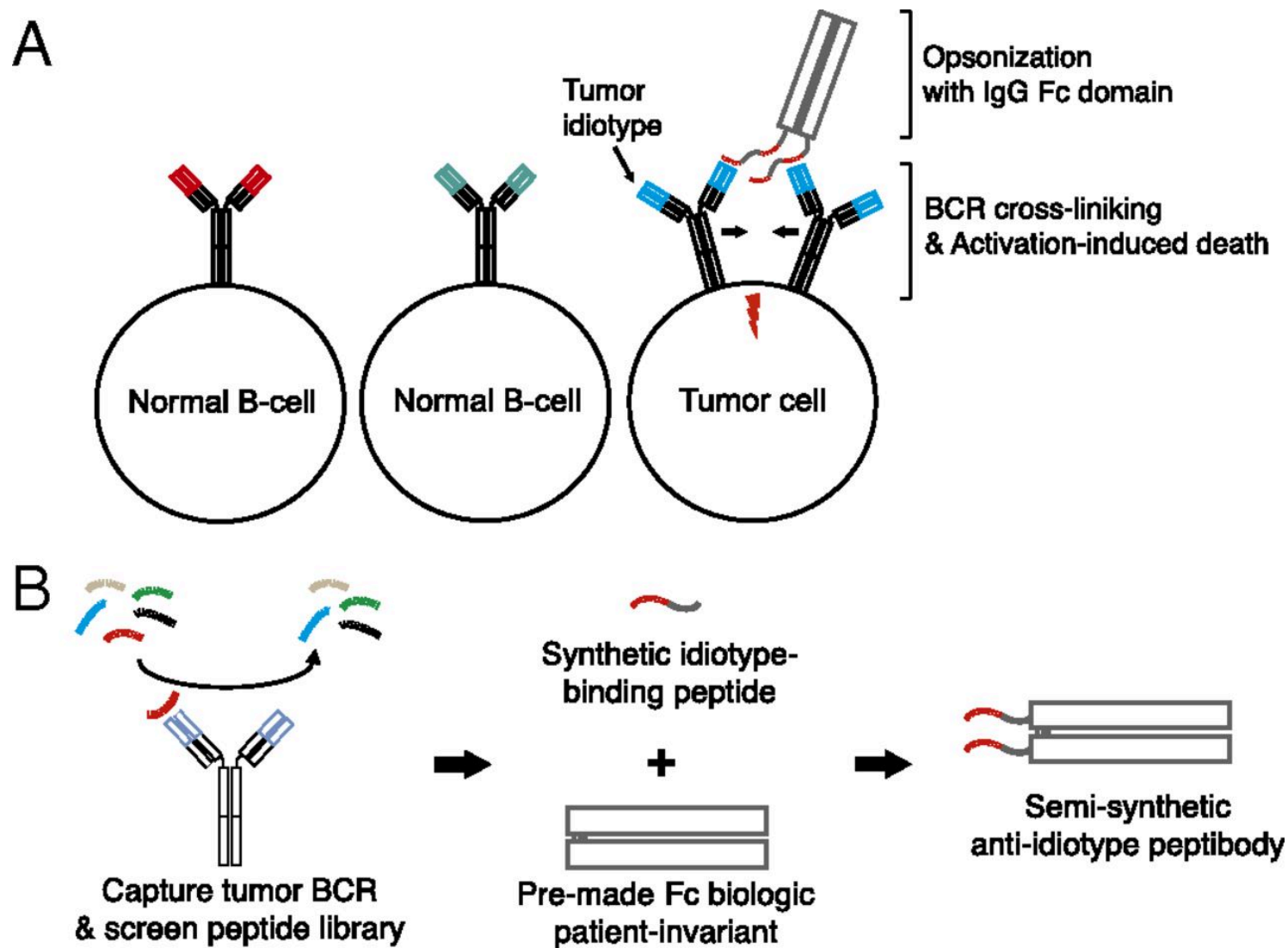
Peptide-Fc fusion proteins (Ig₁ Fc)
(Blys-binding peptides, ...)



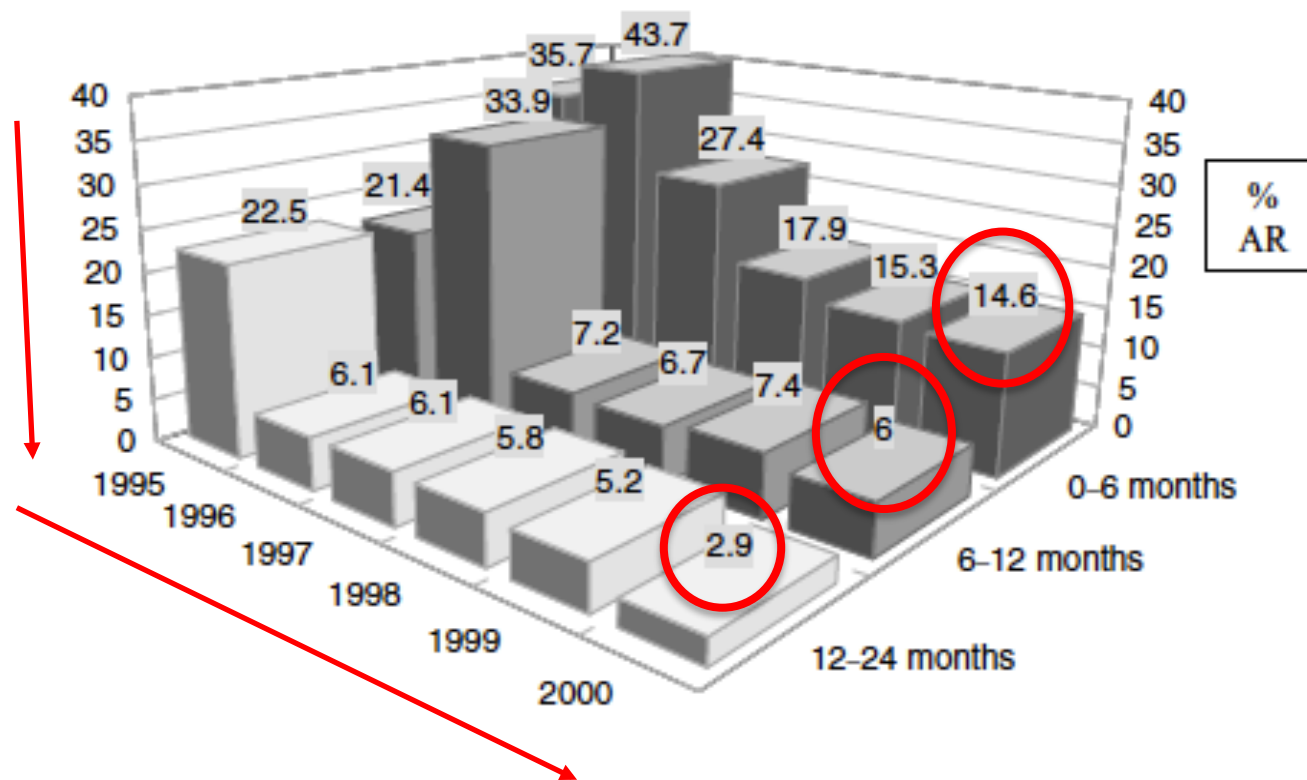
- ADCC
- NK enhanced cytotoxicity
- IFN- γ production

Semisynthetic anti-idiotypic peptibodies

Concept overview.

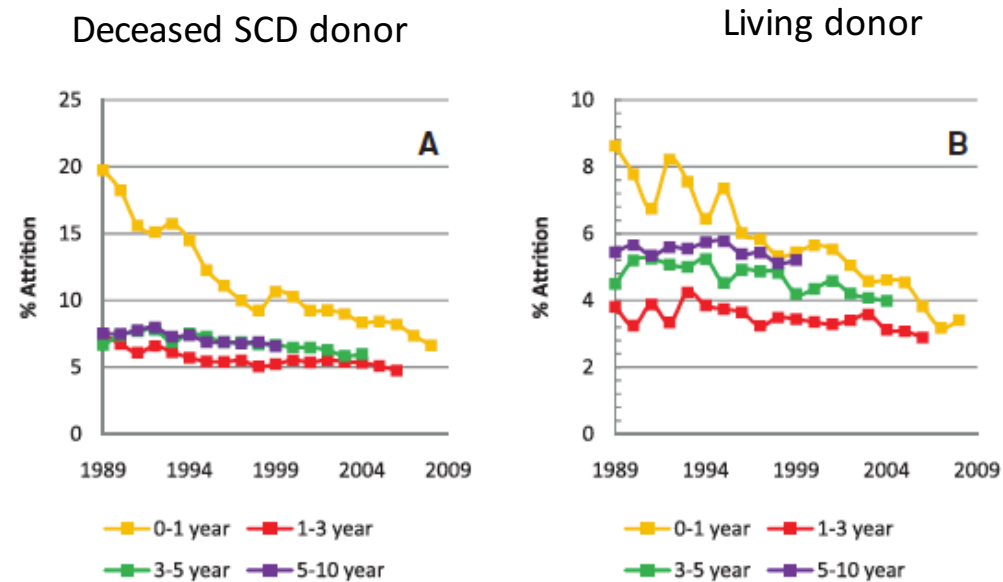


Acute rejection within the first 2 years after Kidney Transplantation

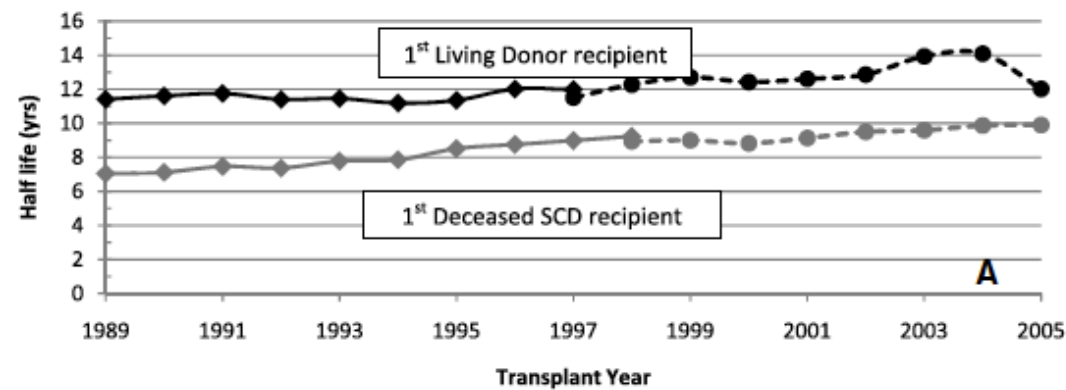


↓ Acute Rejection

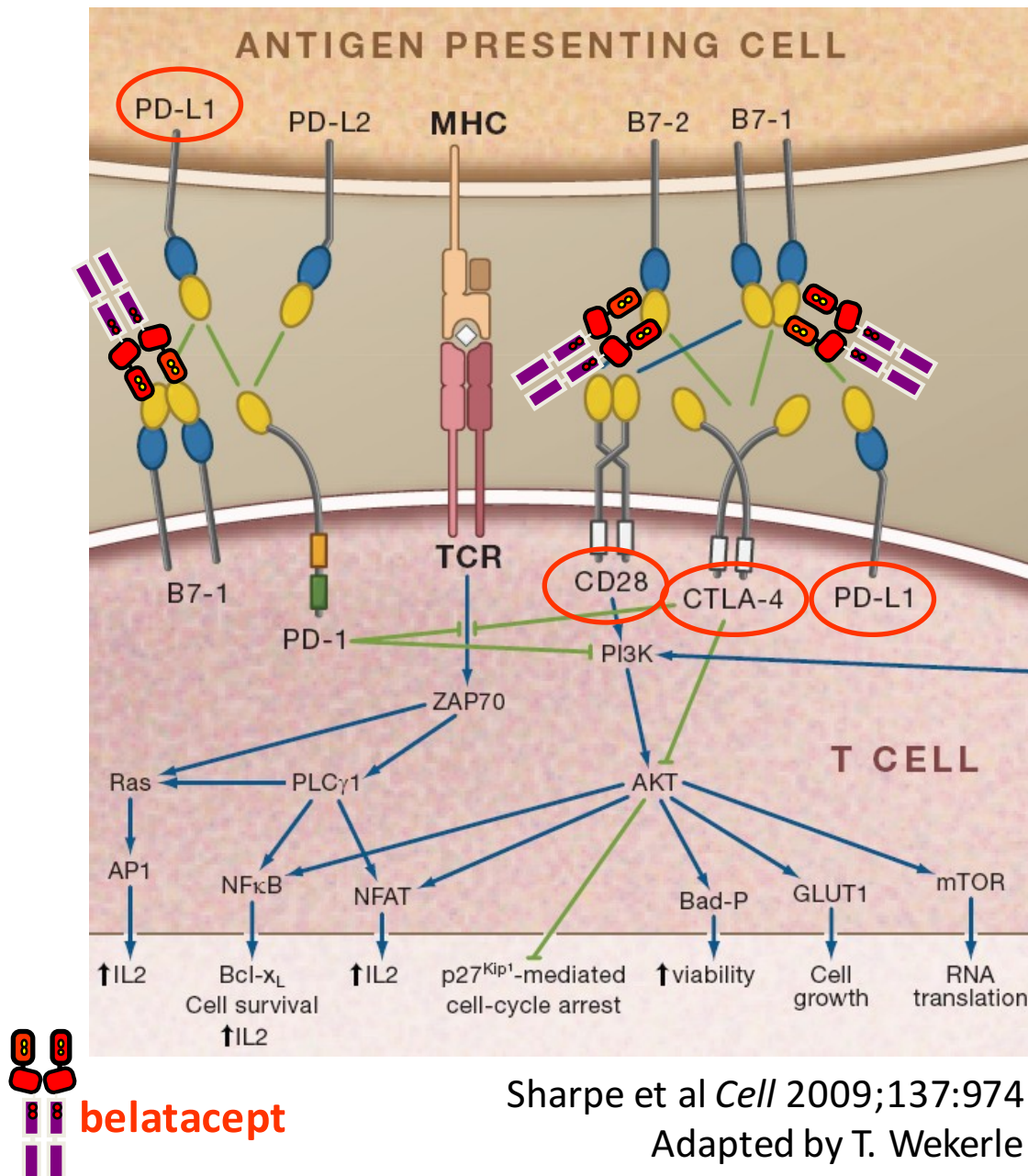
Cumulative graft failure yearly attrition rates of first kidney transplants



Actuarial and projected cumulative half-lives.



More AR in Belatacept MI regimen!?



Sharpe et al *Cell* 2009;137:974
Adapted by T. Wekerle

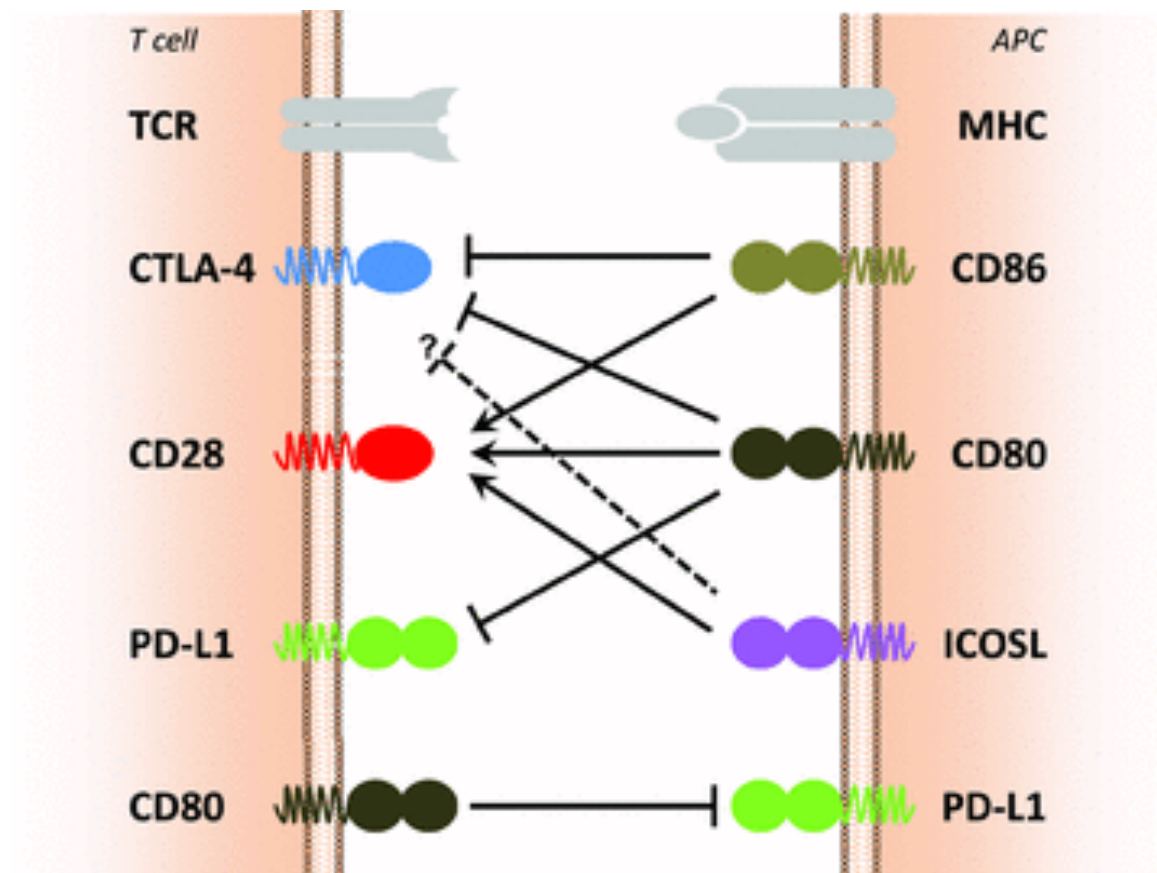
belatacept =
,anti-B7 compound'

APC function

T cell function

belatacept =
,CD28 blocker'

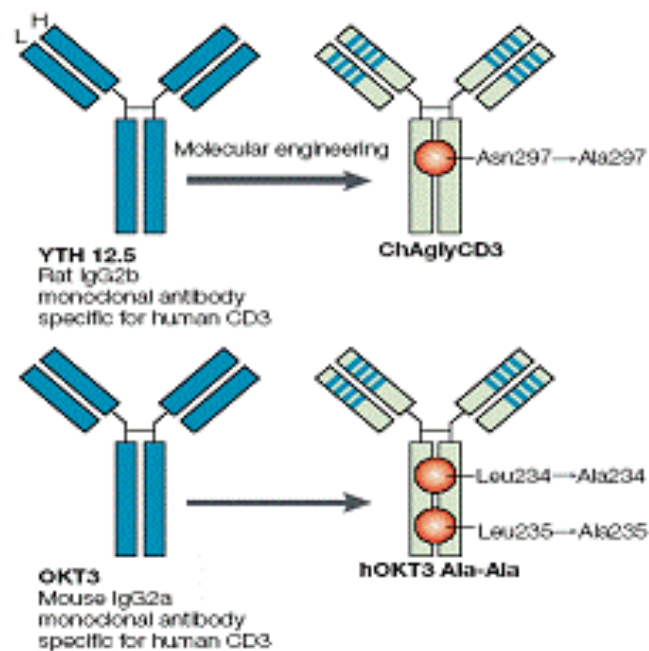
FR104, an antagonist anti-CD28 monovalent Fab' pegylated antibody



Preclinical efficacy and immunological safety
(phase II trial in RTI?)
(Autoimmunity)

Teplimumab

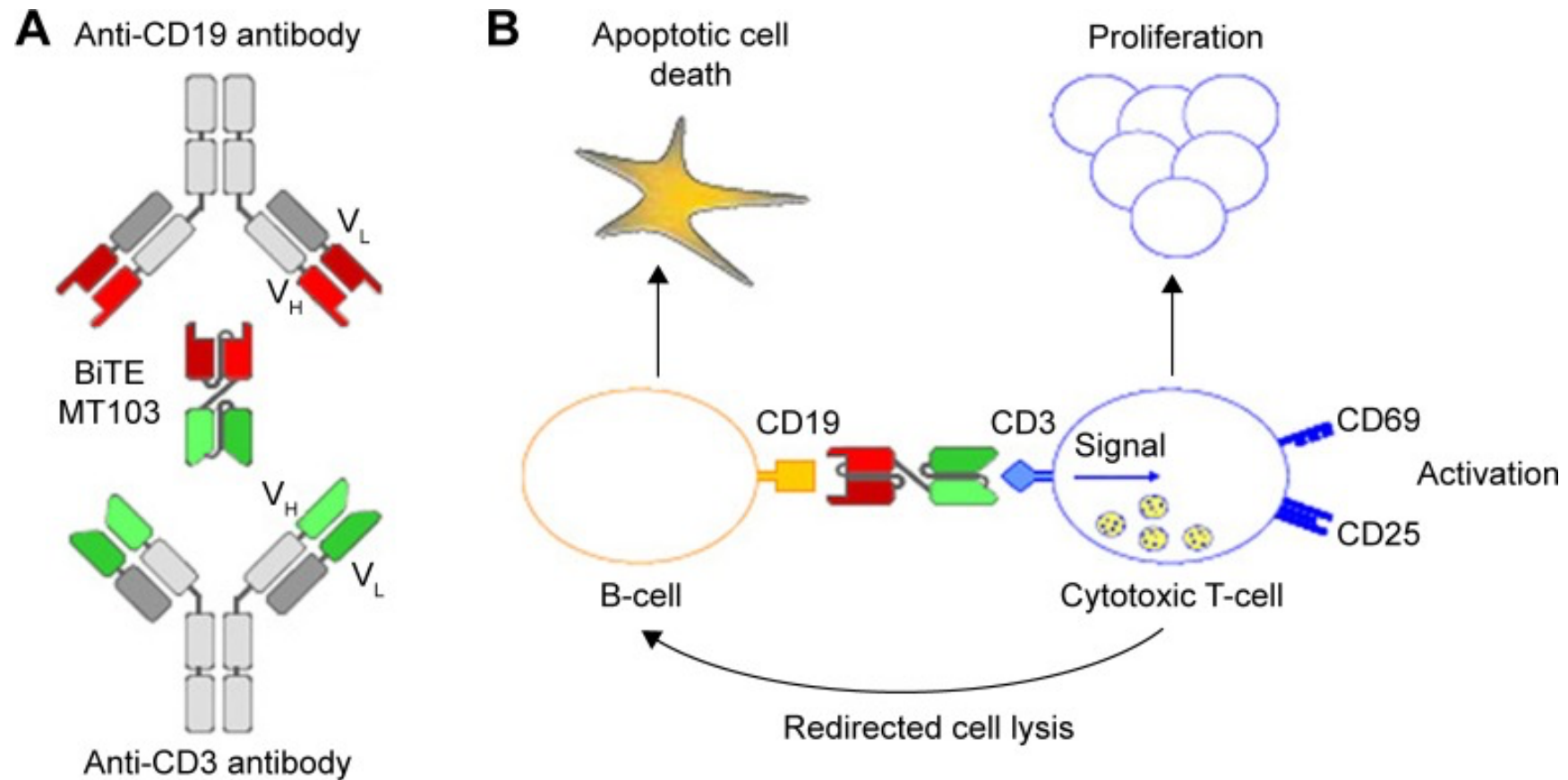
Anti-CD3 Antibodies Modified to block Fc Binding of Complement and Decrease Cytokine Stimulation



Type 1 diabetes
Transplantation?

Bispecific Ab in TX?

(Cell synapse engagers)



Specular lessons from checkpoint inhibitors?