Antoni Caralps

Josep Maria Subirachs (1927–2014)

1985

Lessons and consequences in the evolution of immunosuppression in organ transplantation

UNIVERSITAT DE BARCELONA

Josep M. Grinyó

Emeritus Professor of Medicine

Eras in Immunosuppression in Transplantation

- Conventional IS (AZA-ST)
- Calcineurin inhibitor era : CsA and tacrolimus
- Rationally designed IS (MOA)

Conventional Immunosuppression (AZA+ ST) (1964- 1980)

Adrenal cortical steroids: Kendall's compound E: 'cortisone' (1953)

- anti-inflammatoty effects (Rheumatology…)
  - A 'wonder drug'
  - Medicine before and after steroids

From 6- mercaptopurine (antineoplastic drug) to azathioprine

National Research Council Conference (Washington 1963)

- AZA + steroids (Starzl 1963)

REVIEW

Diamonds are forever: the cortisone legacy

Stephen G Hillier 2007

Very well known limitations

CNI and MMF

- Reduction of rejection rates
- Toxicities
- Metabolic and CV morbidity
- Malignancies (+BKVi)
- Transplantation: from an ‘acute’ to a ‘chronic’ clinical entity
- Need for improved outcomes in the mid, long-term
- Acute rejection: not enough appropriate for evaluating the benefits of a new drug/ IS regime
- Endpoints

Empirical IS minimization strategies

- ST withdrawal
- CNI minimization
- CNI withdrawal
- Trial and error approach

The success of the Symphony trial

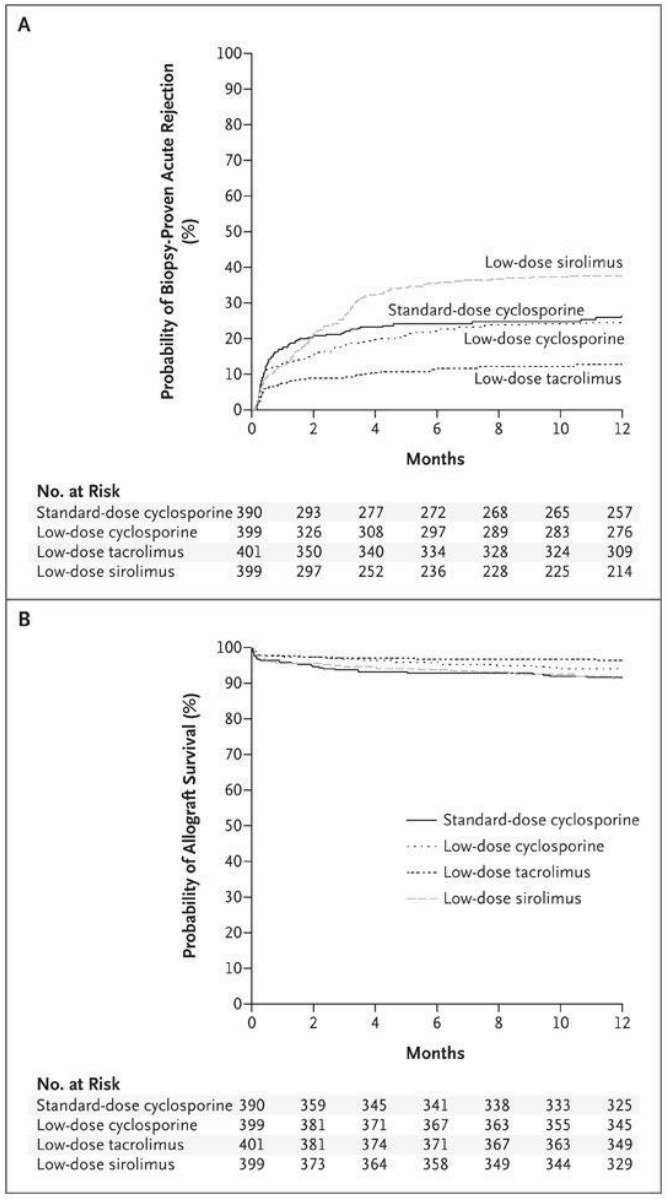
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

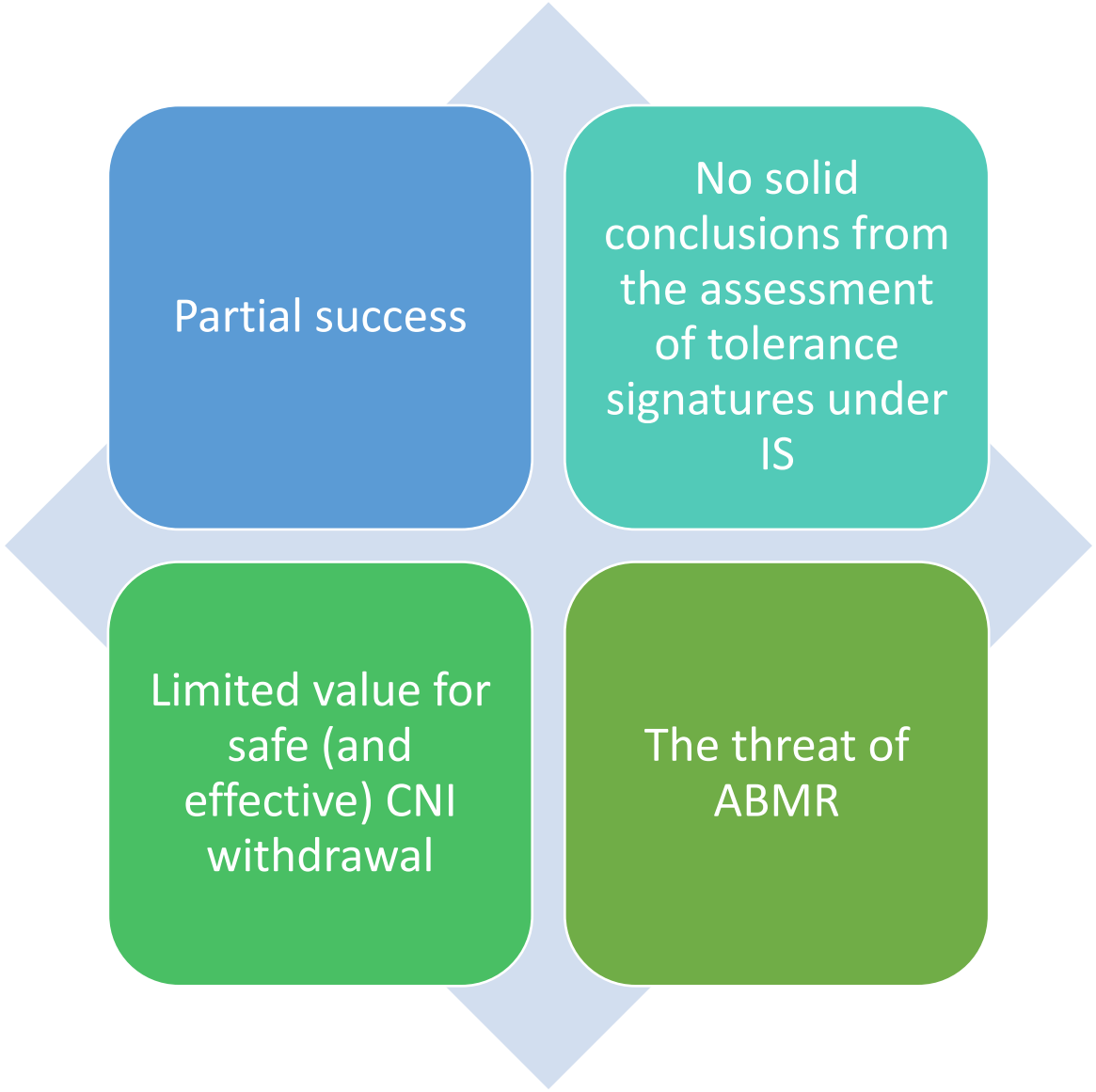
Tac levels 3-7 ng/ml



The threat of ABMR

Back to more conventional CNI doses and exposures?

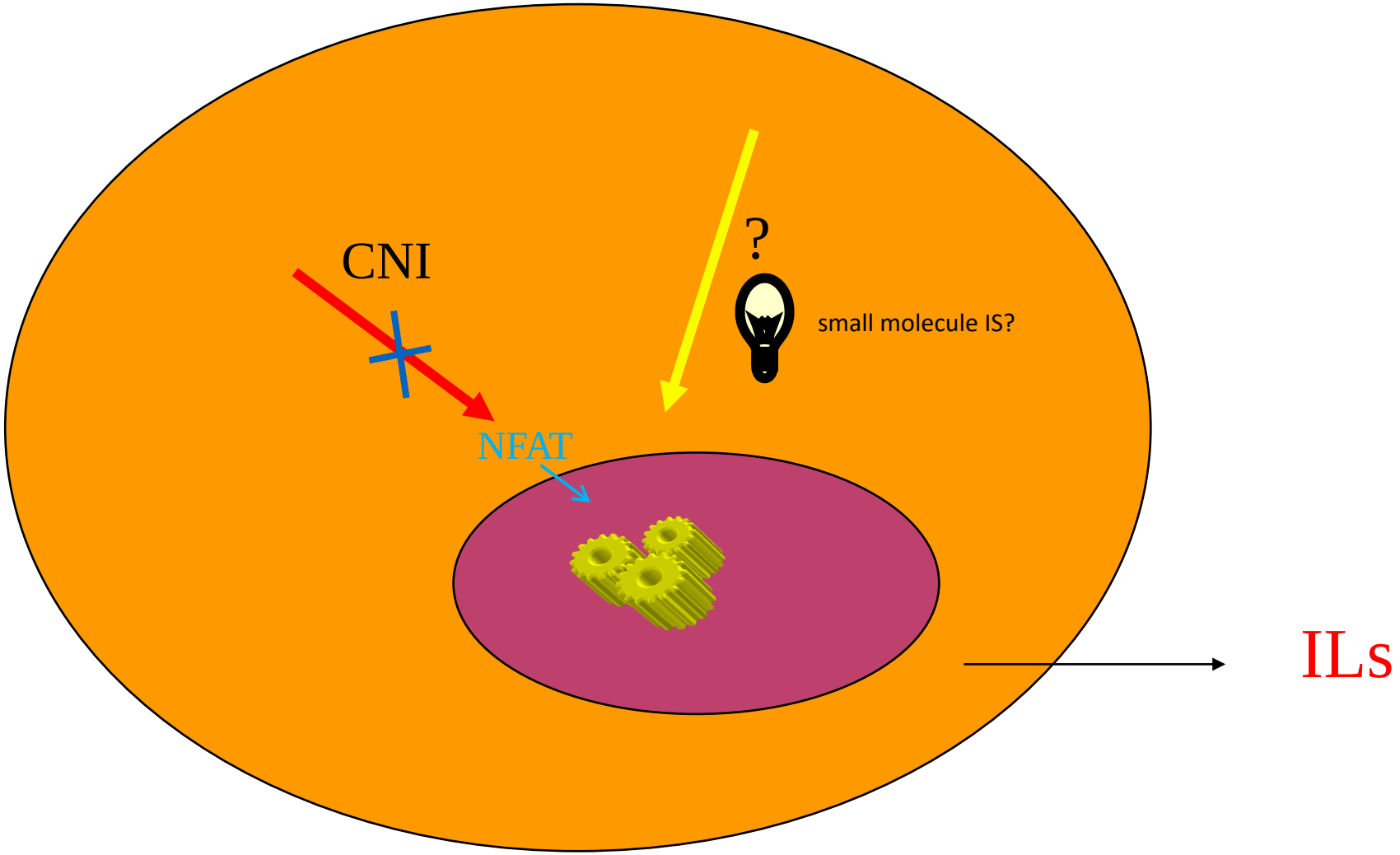
Biomarker-driven IS minimization/withdrawal



IS drug development in transplantation in the last decade

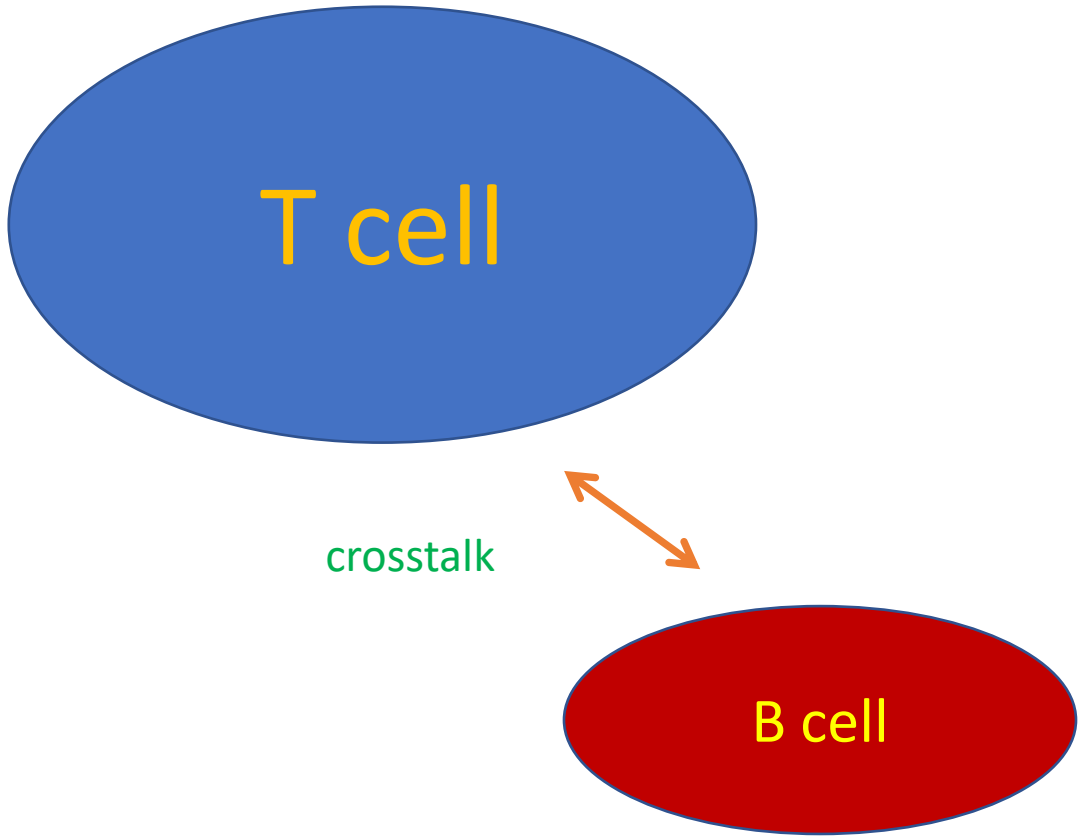
- DSG analogues
- FK778
- FTY 720
- Anti-CD40L mAb
- Alefacept
- Sotrastaurin
- CsA analogs
- JAK3 inhibitors

Sotrastaurin (PKCi): inhibition of T cell activation



Efficacy failure in RT

Historical imbalance between T and B cells



- Pathophysiology of allograft reaction
- BMK development for transplant monitoring (beyond anti-HLA Ab)
- IS drug development
- IS borrowed from myeloma
- Better knowledge of B cell effects of T–cell-oriented IS agents

mAbs: antagonism or agonism?

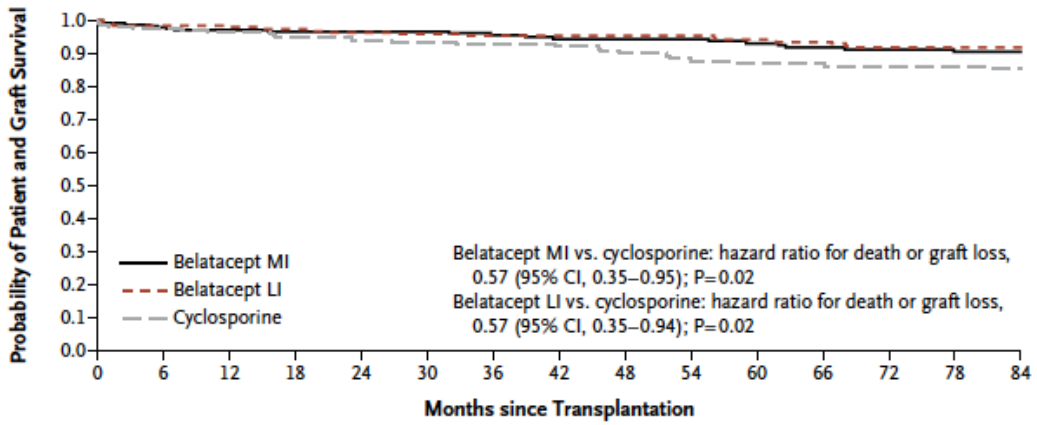
The NEW ENGLAND JOURNAL of MEDICINE

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.

The story of Belatacept
(after phase III BENEFIT trials)

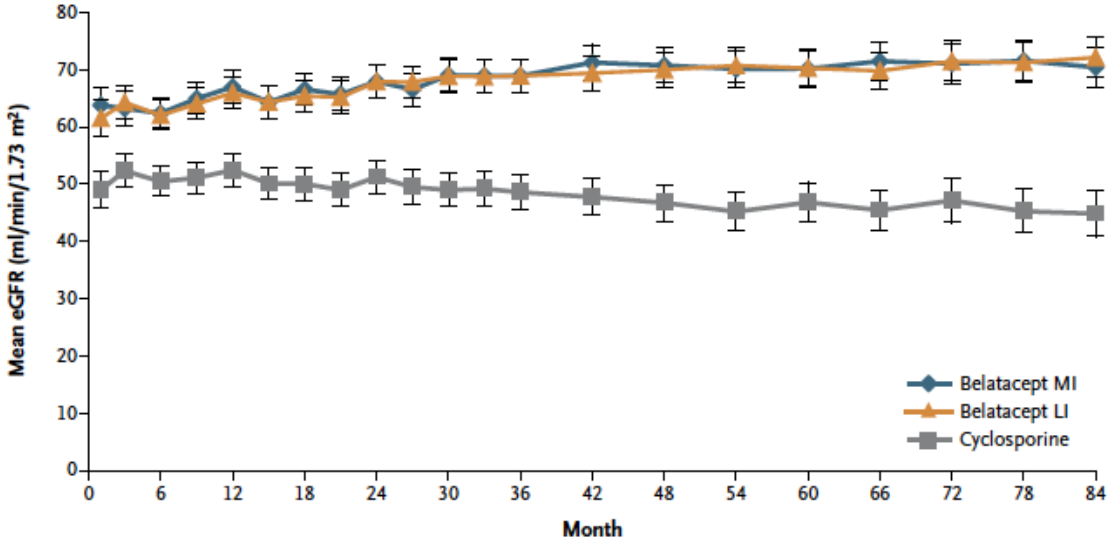


No. at Risk

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

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.



The story of Belatacept

Inconveniencies

- Cost
- IV route administration
- Early TCMR

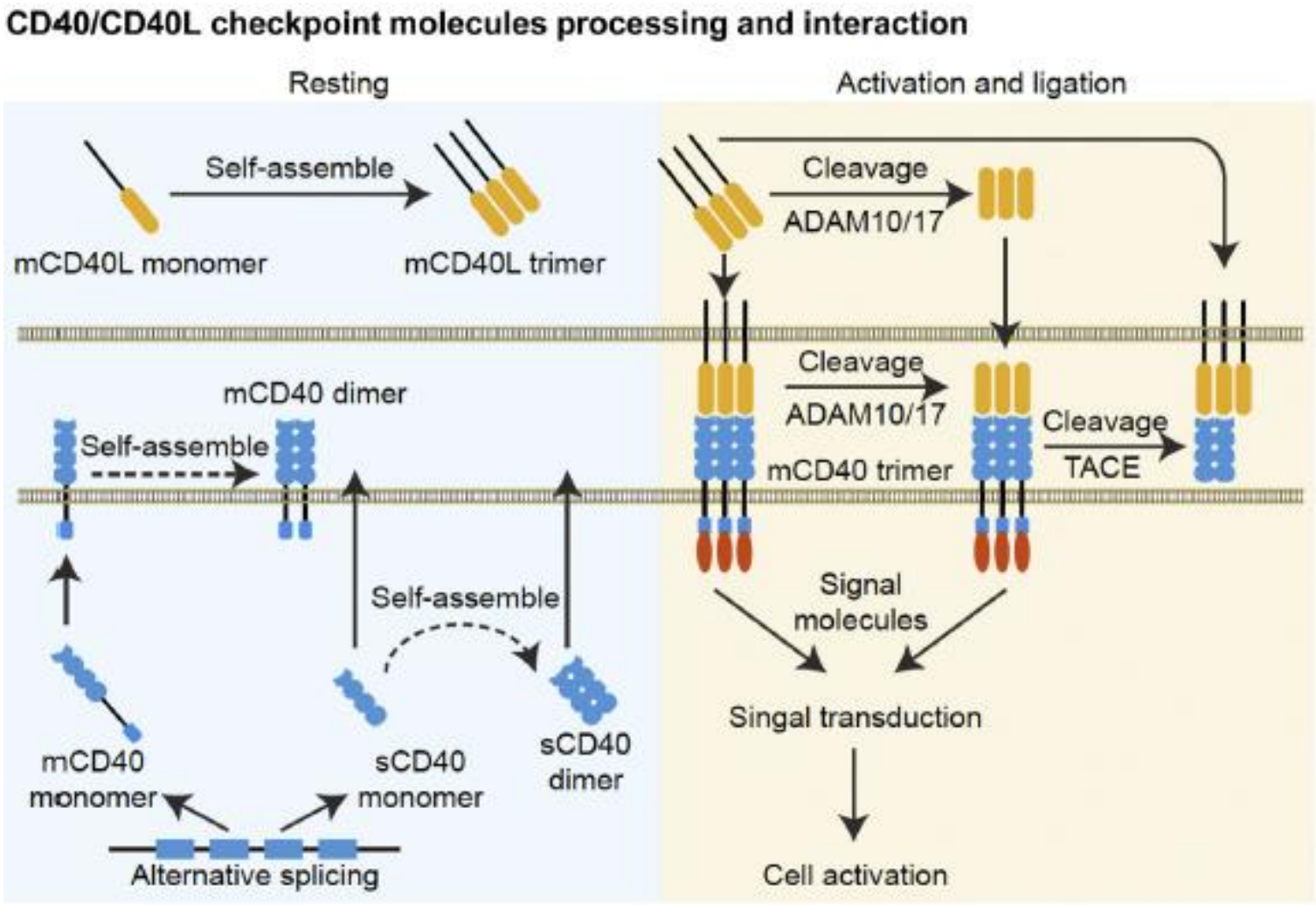
Advantages

- Improved outcomes
- Safety profile
- Reduction of the novo DSA
- Mechanistic properties
- Compliance

Belatacept

- De novo use trials in DGF (PNF)
- High KDPI kidneys of high risk patients
- Desensitization studies/ABMR with MOA-supported drug combinations.
- Conversion studies.
- Support Investigator-driven studies (dosage, PD)
- Consensus guidelines

The targeting of CD40/CD40L pathway



Tang et al. doi:10.1016/j.pharmthera.2020.107709

αCD40L mAbs

- hu5c8 (Ruplizumab)
- ABI793
- BG9588

Thrombosis

Fc dependent (FcγRs)

The Journal of Immunology
2014

Engineering of a Novel Anti-CD40L Domain Antibody for Treatment of Autoimmune Diseases

Jenny H. Xie,* Aaron P. Yamniuk,† Virna Borowski,* Robert Kuhn,* Vojkan Susulic,* Sandra Rex-Rabe,* Xiaoxia Yang,* Xiadi Zhou,* Yifan Zhang,* Kathleen Gillooly,* Ruth Brosius,* Rathna Ravishankar,* Kimberly Waggie,‡ Kathy Mink,‡ Laura Price,* Robert Rehfuss,* James Tamura,† Yongmi An,† Lin Cheng,† Bozena Abramczyk,† Olga Ignatovich,§ Philip Drew,§ Steven Grant,§ James W. Bryson,† Suzanne Suchard,* Luisa Salter-Cid,* Steven Nadler,* and Anish Suri*,1

Fc mutation

Lupus (2015) 24, 1045–1056
http://lup.sagepub.com

PAPER

First-in-human trial of the safety, pharmacokinetics and immunogenicity of a PEGylated anti-CD40L antibody fragment (CDP7657) in healthy individuals and patients with systemic lupus erythematosus

A Tocoian[1], P Buchan[1], H Kirby[1], J Soranson[1], M Zamacona[1], R Walley[1], N Mitchell[1], E Esfandiari[1], F Wagner[2] and R Oliver[1]
[1]UCB Pharma, Slough, UK; and [2]Charité Research Organisation GmbH, Germany

Pegylation

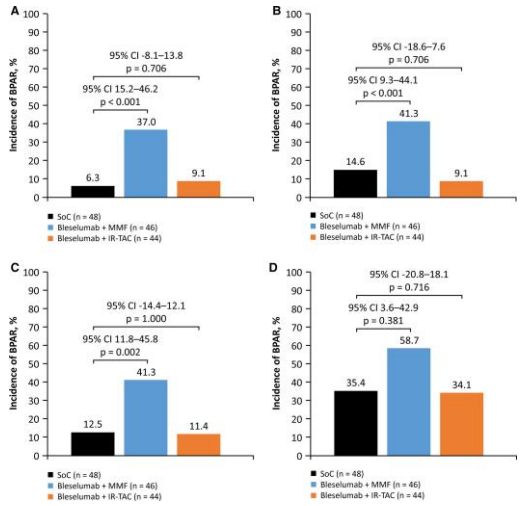
Unconclusive results

αCD40 mAbs

Bleselumab (non-depleting IgG_4 mAb)

6 mos w/o LTFU

36 mos w/o LTFU



6 mos with LTFU
(as BPAR)

36 mos with LTFU
(as BPAR)

Harland et al. Am J Trans, 2019, DOI: (10.1111/ajt.15591)

Iscalimab (non-depleting IgG_1 N297A mutation)

Efficacy failure in Cirrus study (2021)

Development halted in transplantation

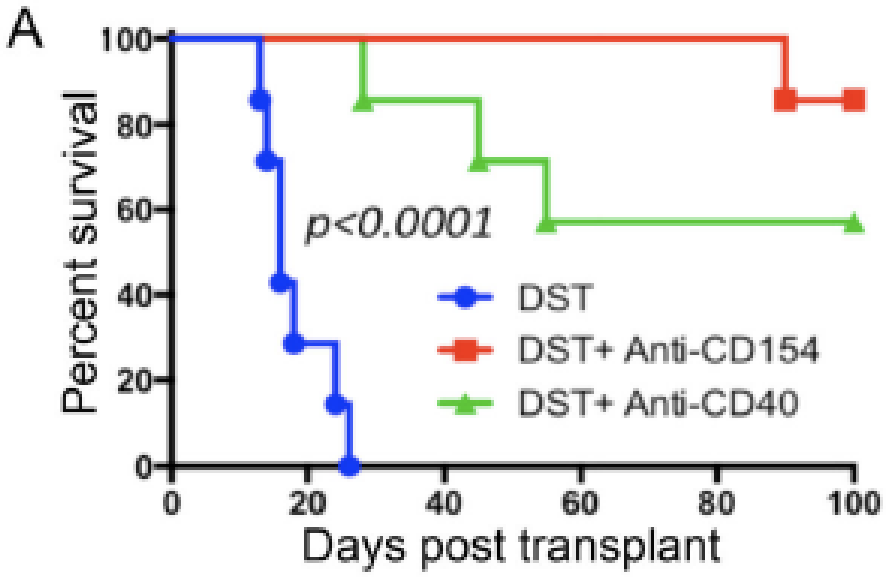
DOI: 10.1111/ajt.15835

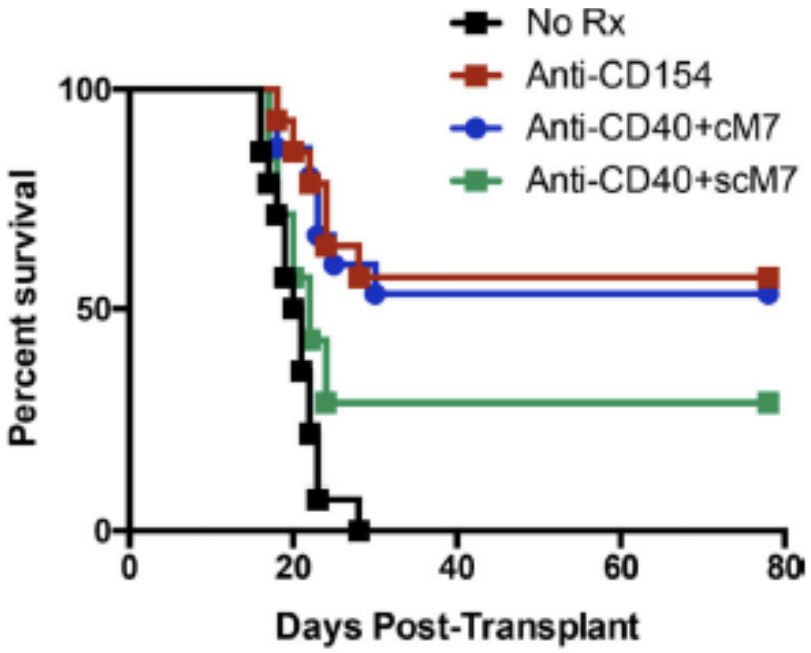
BRIEF COMMUNICATION

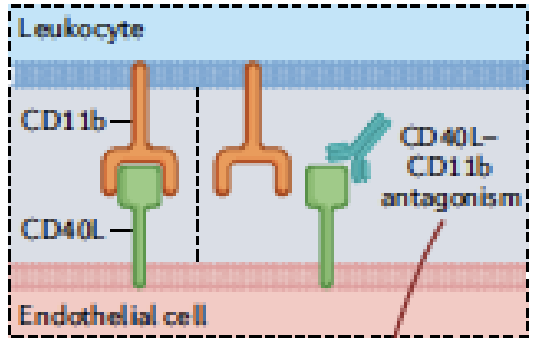
AJT

CD11b is a novel alternate receptor for CD154 during alloimmunity

Danya Liu | Mandy L. Ford



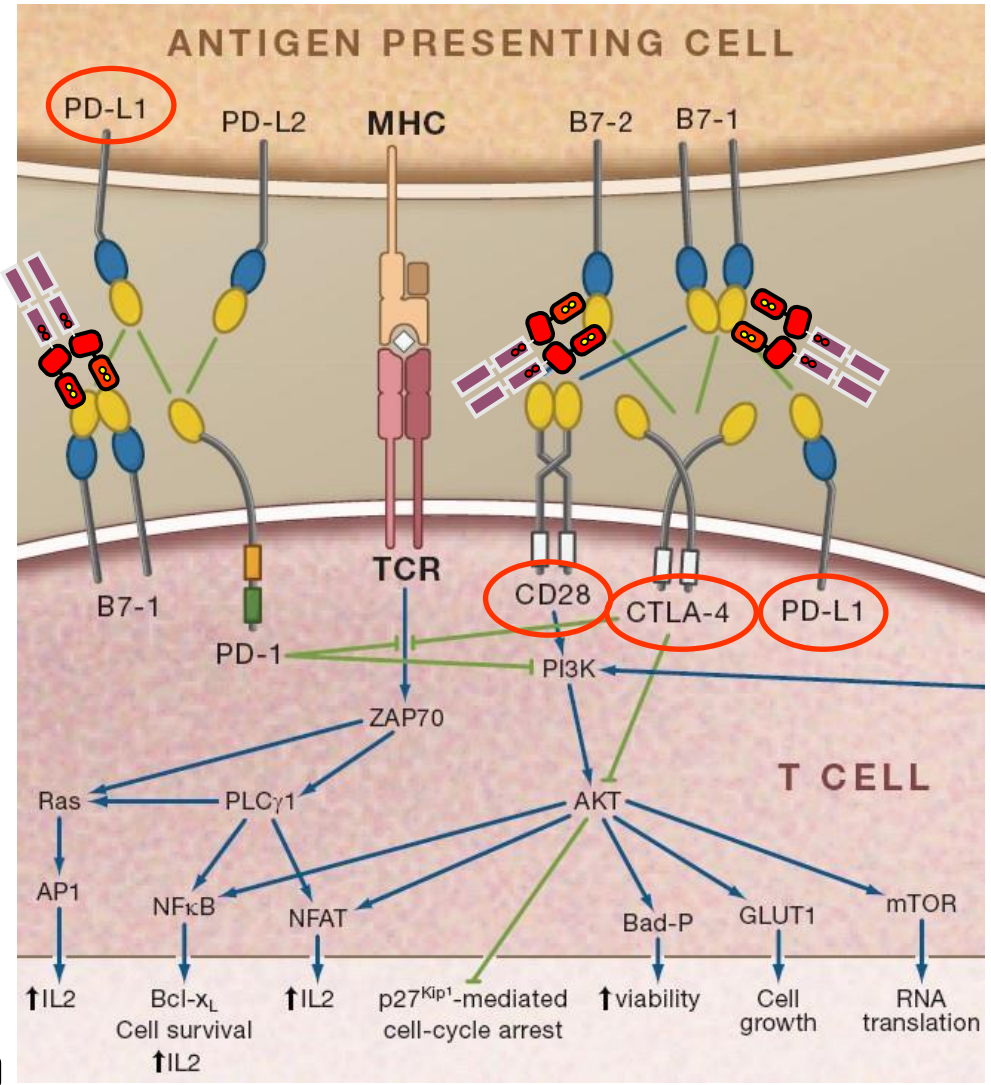




Blocking CD154 interactions with both CD40 and CD11b is required for optimal inhibition of alloimmunity?

Dual targeting for effective immunosuppression?

More AR in Belatacept MI regimen!?



belatacept

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

belatacept =
‚anti-B7 compound‘

APC function

↑

—

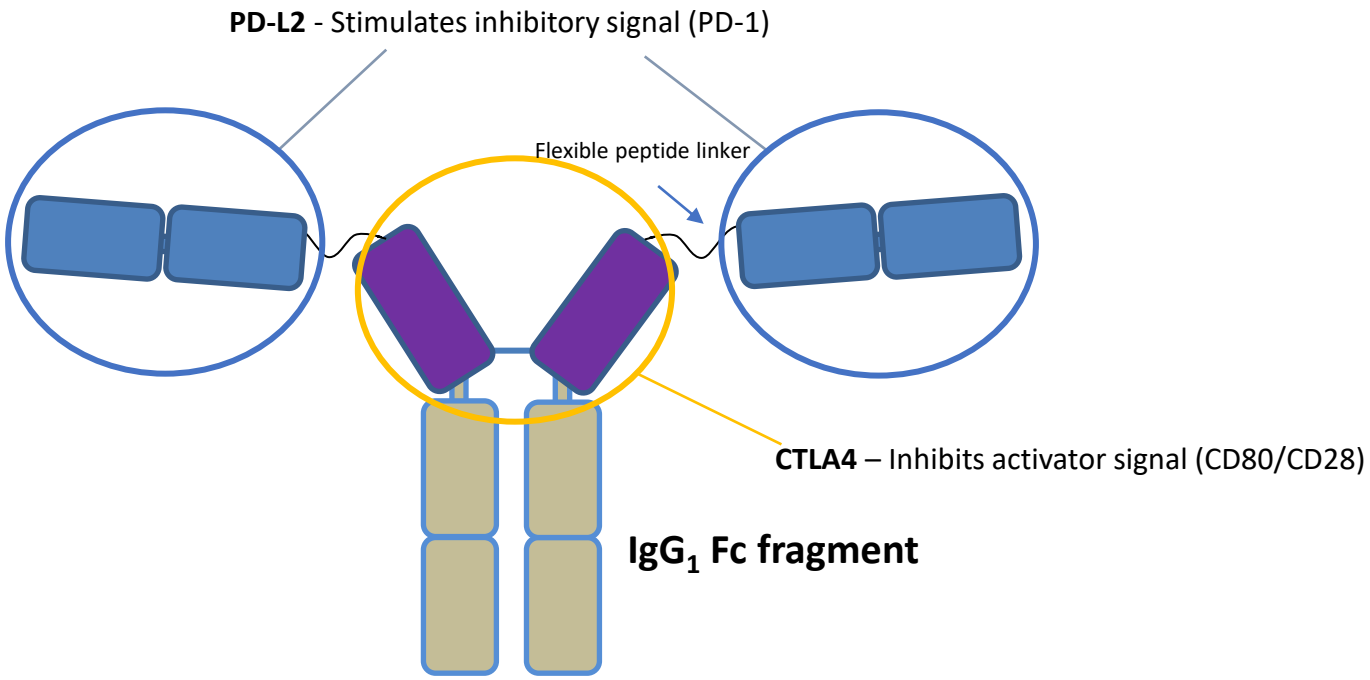
↓

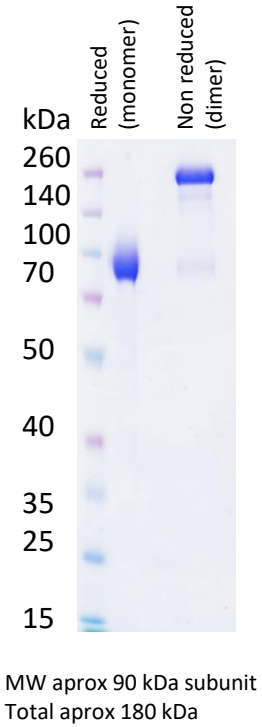
T cell function

belatacept =
‚CD28 blocker‘

A Human Hybrid Fusion Protein Construct

Dual and opposite costimulatory/coinhibitory targeting





MW aprox 90 kDa subunit
Total aprox 180 kDa

Therapeutic efficacy in experimental models:

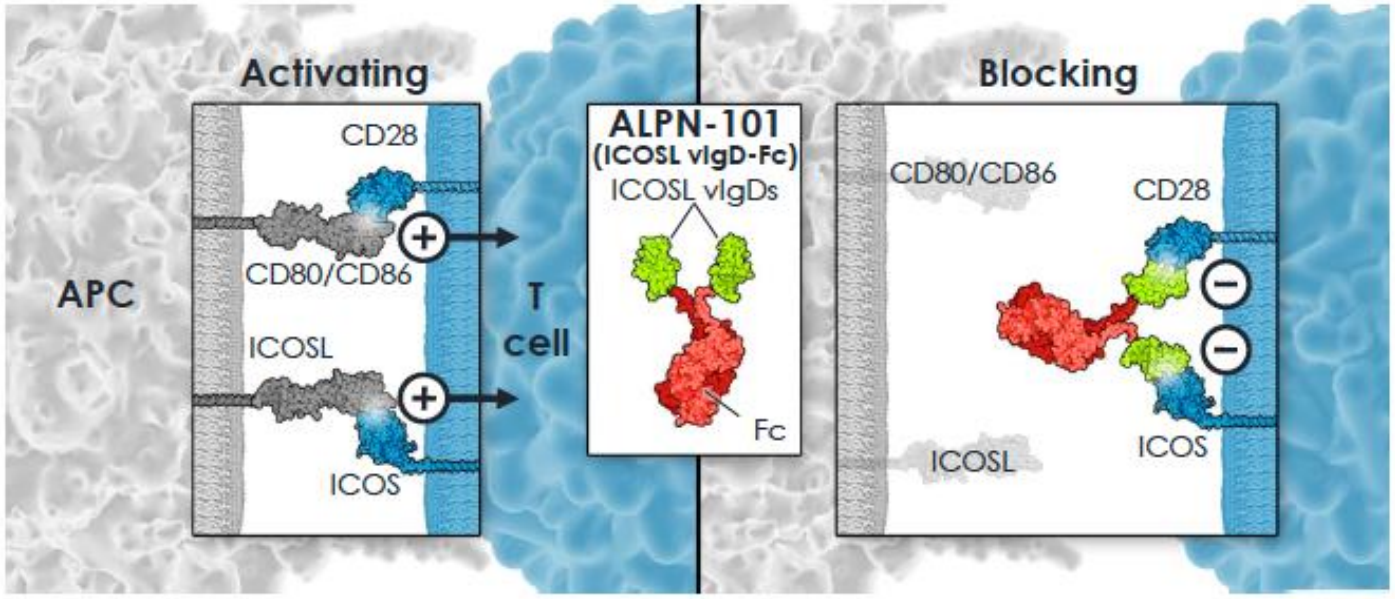
- Ischemia reperfusion injury
- Renal allotransplantation
- Murine lupus nephritis

(Guiteras et al. Int J Mol Sci. 2021; 22: 1216)
(Guiteras et al. Int J Mol Sci. 2022; 23: 8411).

Purification > 95%
Estable in human and animal plasma

ExpiCHO cells and transient transfection

Acazicolcept: ICOS ligand and variant Ig domain (ICOSL vIgD-Fc)
(Dual ICOS/CD28 antagonist)



Therapeutic efficacy in murine models of RA, MS, SS

Yang et al. Clin Transl Sci. 2021;14:1314-1326

Serendipity for IS discovery more rewarding than rational design of new IS?

Gaston Bachelard (1884-1962)

L’obstacle épistémologique:

Ce qui vient se placer entre le désir de connaître du scientifique et l'objet qu'il étudie …..

et l'induit en erreur quant à ce qu'il croit pouvoir savoir du phénomène en question

Jeroni Alsina †

Narcís Serrallach †

Joan Torras

Alberto M. Castelao

Antoni Caralps

Núria Lloberas

Rosa Pérez

Oriol Bestard