Novel Immunosuppresssion in Kidney Transplantation

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Disclosures

Relevant Conflicts of Interest

Grant/Research support

(PI or Sub-I)

- CLS Behring
- Biogen
- Eledon Pharmaceuticals
- ITB-Med
- CareDx

I will be discussing off label uses of the following medications

- Abatacept
- Sipilizumab
- Tegoprubart
- Felzartamab
- Clazakizumab

Overview

Principles of immunosuppression for kidney transplantation

Benefits and limitations of current standard of care immunosuppression

Goals of improved immunosuppression

Novel immunosuppressive approaches*

- Costimulatory Blockage for prevention of rejection
- Treatment of antibody mediated rejection

*Focus on active Clinical Trials at UNMC

Immune Allorecognition

A high frequency of alloreactive T-cells are readily detectable in naïve humans

T-cells reacting to mismatched donor HLA can lead to T-cell activation (cellular immunity), B-cell activation and antibody production (humoral immunity), and allograft rejection

Immune suppression frequent targets T-cell activation

Here comes that picture from the New England Journal article from 20 years ago we see in EVERY SINGLE talk about transplant immunosuppression:

Signal 1

MHC/Peptide +T-Cell Receptor

- Calcineurin inhibitors (CNI)
  - Cyclosporine
  - Tacrolimus

Signal 2

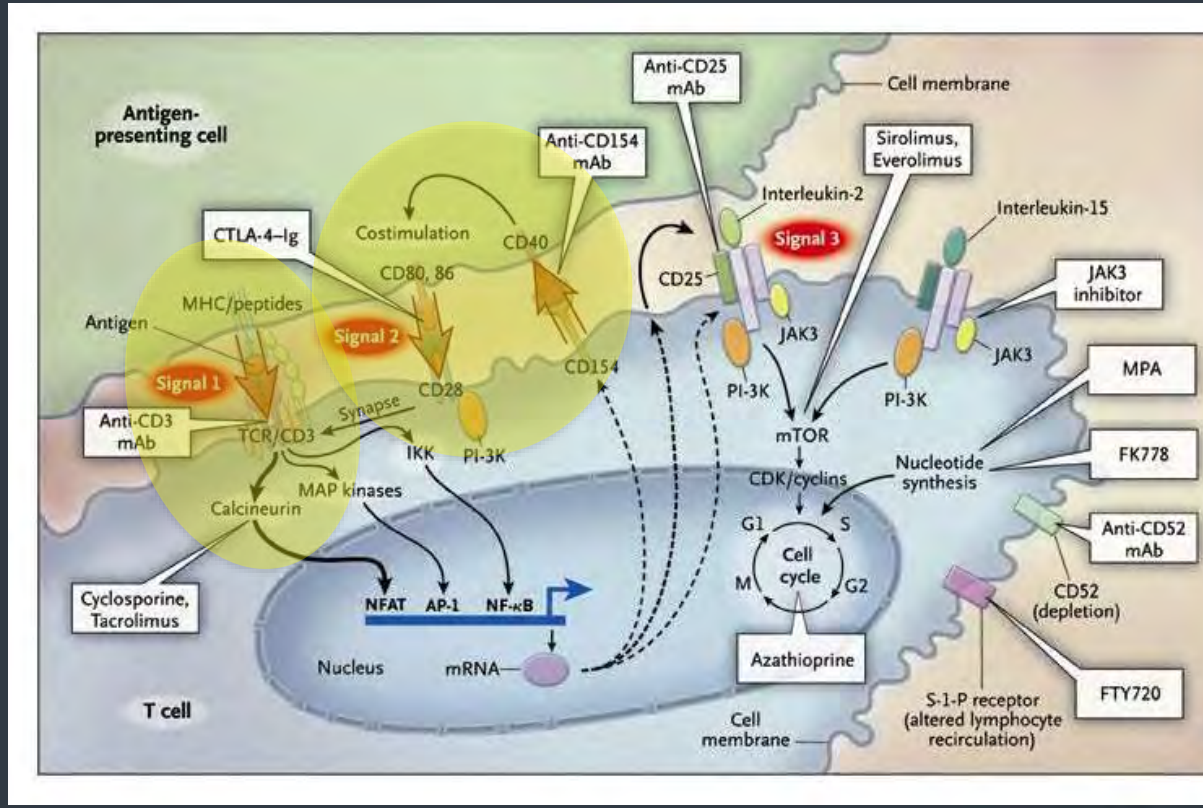
Co-Stimulation

- Co-stimulation blockade
  - Belatacept
  - Other biologic agents

Signal 3

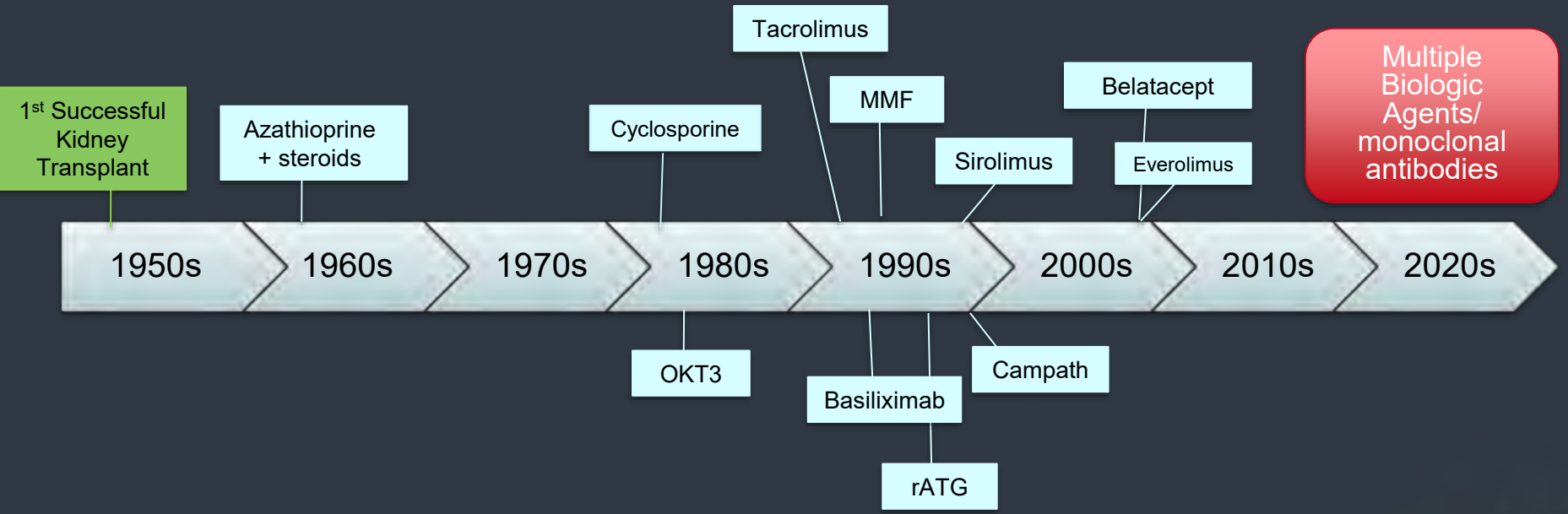
Cytokines and proliferation

- mTOR inhibitors (Sirolimus, Everolimus)
- Antiproliferatives (Mycopholate, Azathioprine)

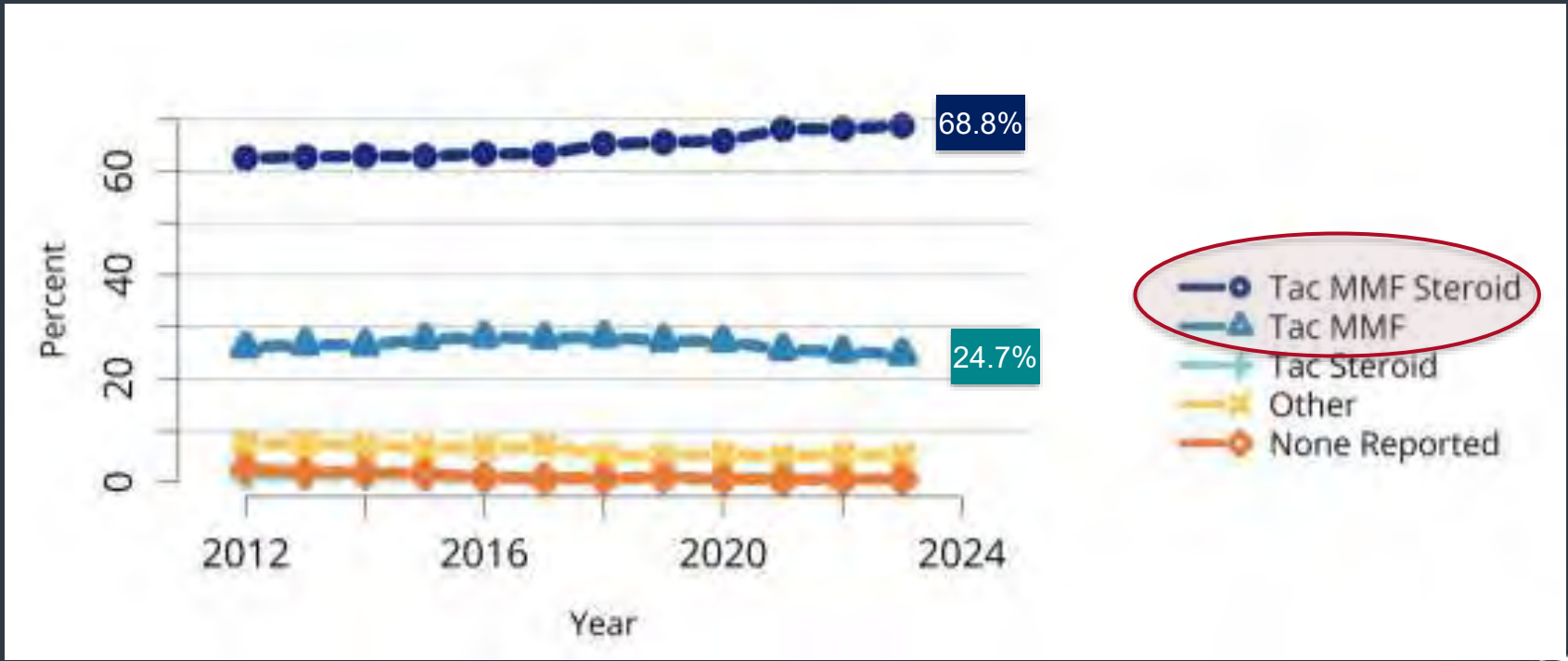


NEJM 2004;351:2715

IS Drug development timeline



Tacrolimus used in over 90% of US kidney transplant recipients



Neurotoxicity

Tremor

Memory Loss

Neuropathy

Diabetes

Nephrotoxicity

Acute tubular injury

Vasoconstriction

Thrombotic Microangiopathy

Endothelial injury/ dysfunction

Arteriolar hyalinosis

Tacrolimus

Side Effects

Hypertension

Immune Suppression

Infections

Cancers

Hair Loss

Hypo Mg+

Hyper K+

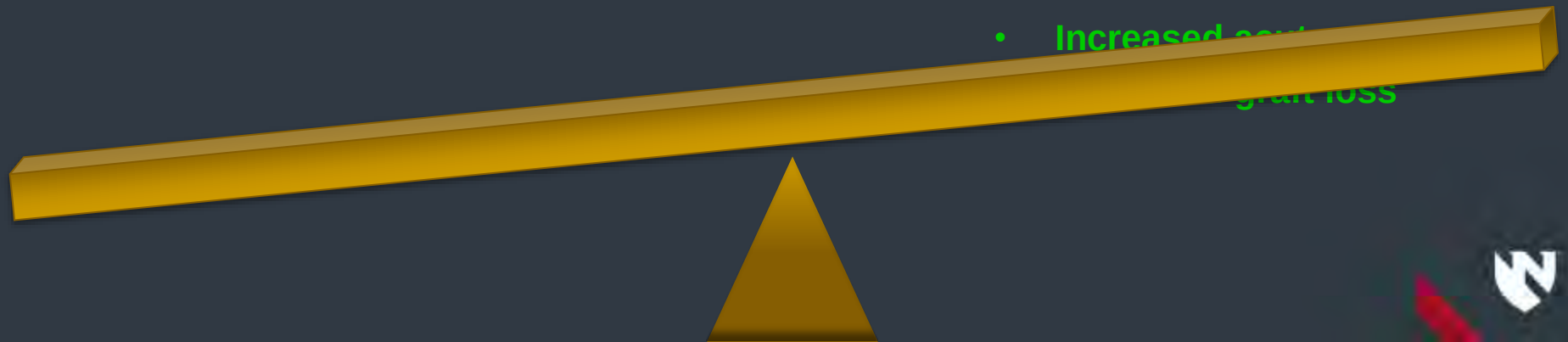
Hypercalciuria

Metabolic acidosis

Tacrolimus

- Narrow Therapeutic window
- Multiple off target side effects including Nephrotoxicity

- Effective at preventing acute rejection
  - > 90% one-year graft survival
- Weaning or replacing CNI with alternative drugs often resulted in:
  - Increased acu
    graft loss



Chronic Tacrolimus

Tacrolimus inhibits regulatory T-cells

May favor central memory effector T-cells

Donor specific antibodies remains significant cause of graft loss

especially with non-adherence or low tacrolimus levels

Chronic Alloimmune injury

Difficult to detect

Refractory to treatment

Risk of chronic immune activation may decrease opportunity to mitigate side effects

Tacrolimus prevents acute activation of T-cells and acute rejection

- Good short-term outcomes
- Limited effective alternatives

INTRODUCTION

Rejection is an inevitable consequence of allograft transplantation. The transplant community undertakes best efforts to manage this natural, sophisticated response of the host's immune system towards the allograft through reducing immunological risk at transplantation and administering immunosuppressive drug protocols. However, immunosuppression is not a 'cure' for rejection but rather an attempt to suppress the host response to a point where damage of the allograft is limited and allows it to function sufficiently. Although immunosuppressive drugs and protocols improved, and with that allograft survival, rejection still represents a major cause of allograft failure [1], especially if suppression of the host immune response is inadequate, for example due to noncompliance or medication side effects.

Curr Opin Organ Transplant 2024, 29; 97-103

How do I know when immunosuppression has been reduced too much?

Creatinine is an imperfect marker for kidney function/damage

Many nephrons can be damaged/destroyed without a change in serum creatinine

- Remaining nephrons can hyperfilter to compensate and keep creatinine stable

The Cheboygan Daily Tribune

FIRE TAKES HUGE TOLL

EARLY MORNING FIRE THREATENS SEVERAL BLOCKS

LOSS ESTIMATED OVER $50,000

We Thank You

CHEBOYGAN DAILY TRIBUNE GOES TO PRESS—AS USUAL

CITY NEWS

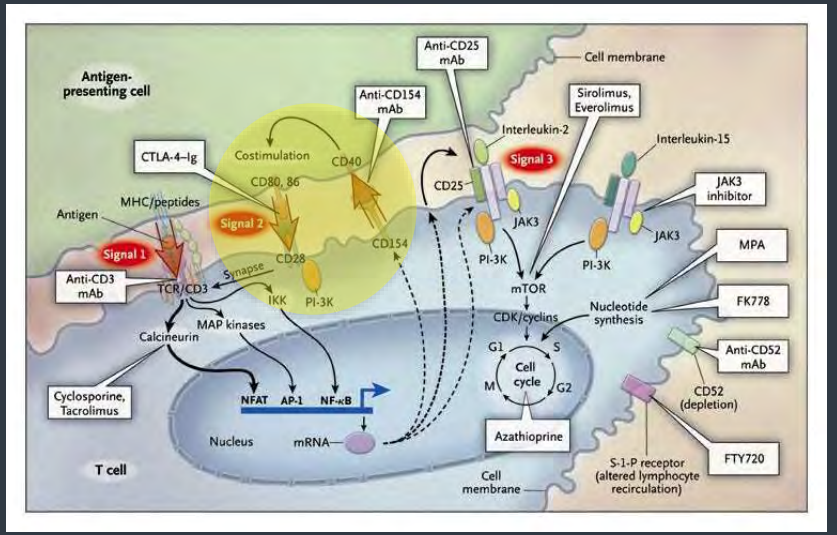
WIRE NEWS

Goals of immunosuppression

- Suppression of alloreactive immune cells
  - Prevents acute and chronic rejection
  - Promotes tolerance
- Limited suppression of non-alloreactive immune cells
  - Decreased risk of Infection and Cancer
- Limited off–target (Non-immune related) side effects

Co-stimulation Blockade *

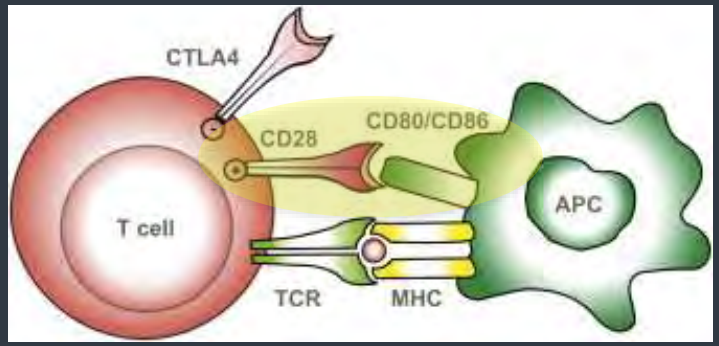
- Co-stimulation required second signal for T-cell activation
- T-cell receptor binding (Signal 1) without co-stimulation (Signal 2) results in T cell anergy

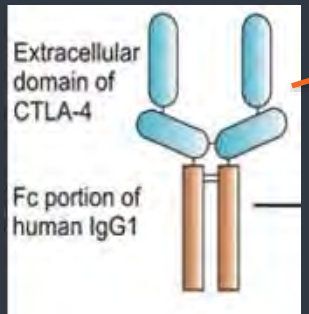


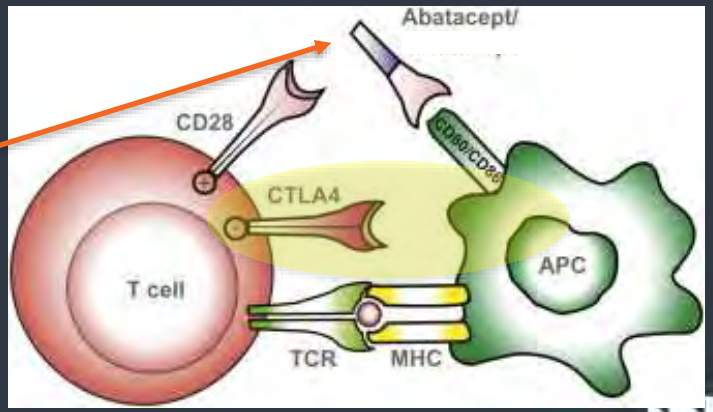
* Disclaimer: This is NOT the Holy Grail

Early Attempts at costimulation blockade in non-human primates

- Abatacept
  - CTLA4 Extracellular domain fused with Fc portion of human IgG
  - Non-human primate transplant model: Abatacept showed limited prevention of rejection or ability to prolong graft survival





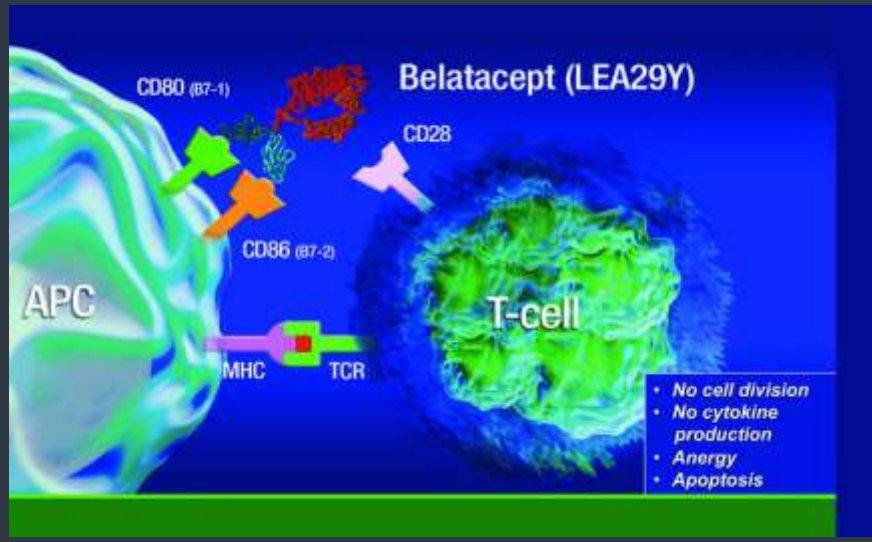


J All Clin Imm 2008, 121 (2) 299-306

Belatacept

2 Amino Acid substitution in Abatacept
- Improved CD80/86 binding

- IV infusions
  - Induction day 0, day 4, q 2 weeks
  - q28 day after induction

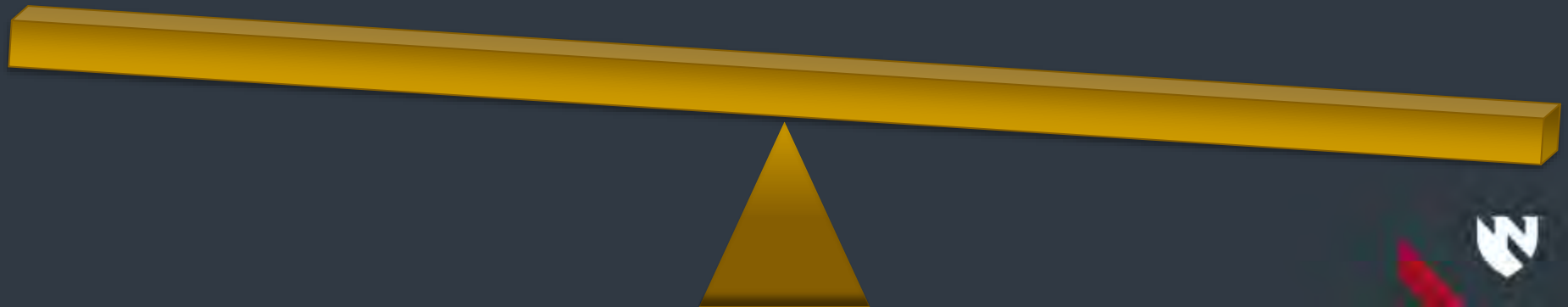


BENEFIT Trial
- Multicenter RCT
- Belatacept vs Cyclosporine
  - Increased early acute cellular rejection in belatacept group
  - Improved eGFR at one year – persisted at 7 and 10 yr

Belatacept

- Increased risk of early acute cellular rejection
  - Higher when compared to tacrolimus
- PTLD in EBV R-
- Refractory Infections (e.g CMV)
- IV infusion
- Cost

- eGFR similar to tacrolimus and better than cyclosporine despite early rejection
- Less off target side effects
  - Avoid tacrolimus related nephrotoxicity, vasoconstriction, and neurotoxicity
- No significant drug interactions
- No levels to monitor



Belatacept / Costimulation blockade

Increased risk of acute cellular rejection with either:

de novo belatacept
or
converstion to belatacept from CNI

Attempts to mitigate early ACR

- Additional maintenance immunosuppression
- Selecting patients with low immunologic risk
- Other co-stimulatory blockade agents

Despite early ACR risk, Belatacept may have a favorable chronic immunologic profile

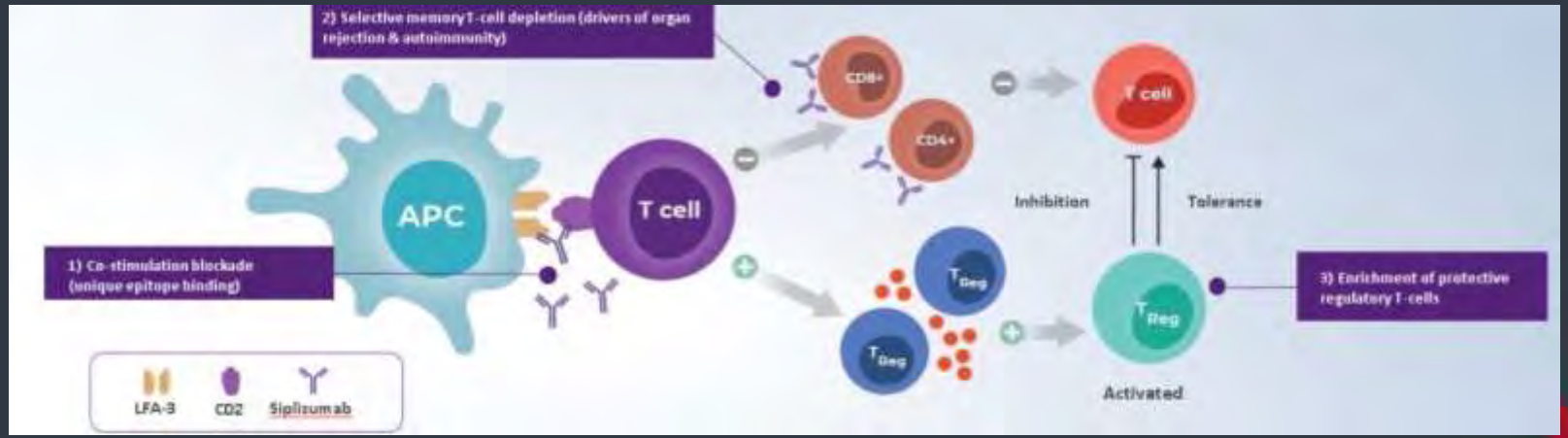
Decreased DSA
Costimulation required for germinal cell activation of B-cells and Isotype switching

Enhanced regulatory T-cells
in favor or effector memory T cells

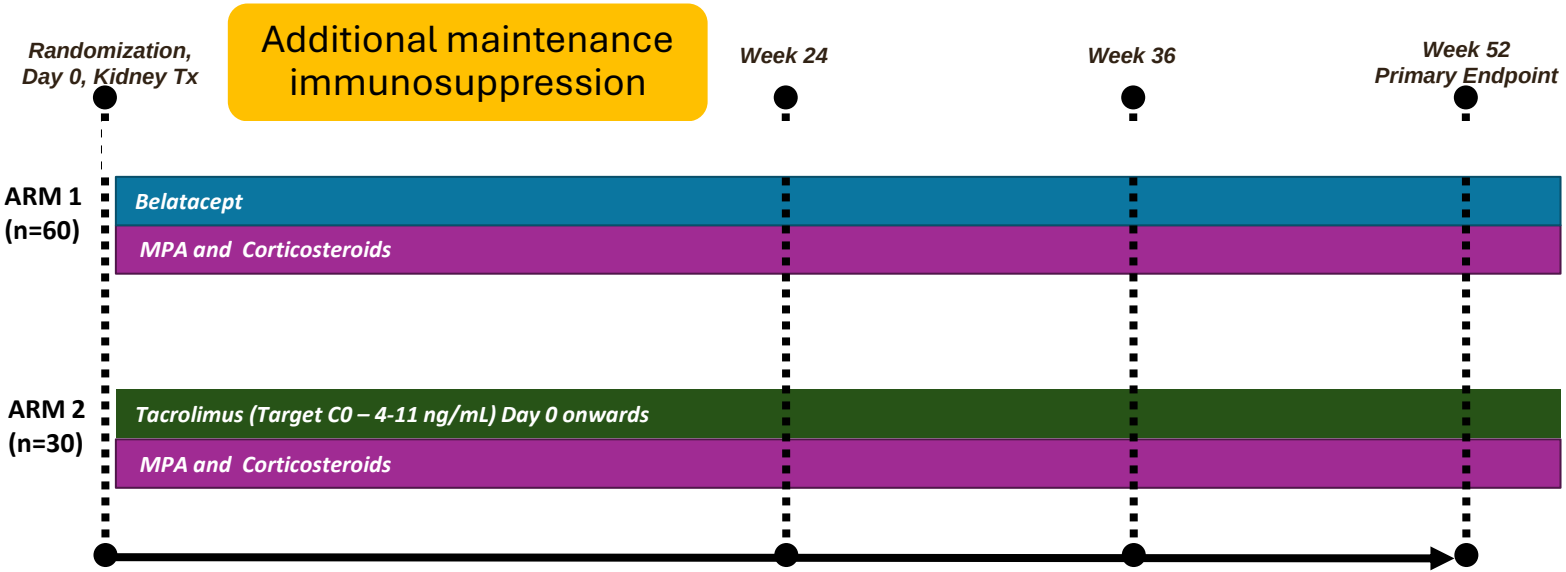
Sipilizumab

Anti CD2 Antibody

- CD2 expressed on T-cells and NK cells
  - Lower expression on Regulatory T cells
  - Selectively depletes effector memory T cells in vitro



ASCEND Study Design and Objective

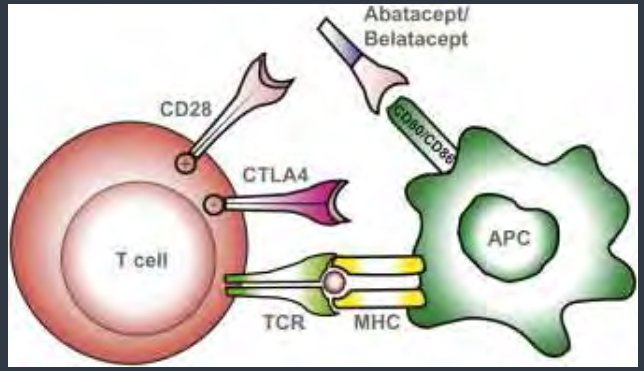


Does siplizumab allow for the use of belatacept (and deriving the benefit of CNI avoidance) while minimizing the risk of early rejection episodes observed in the belatacept trials?

Abatacept

- Non-human primate transplant models showed high rates of rejection
- Successfully used in transplant patients when belatacept was unavailable

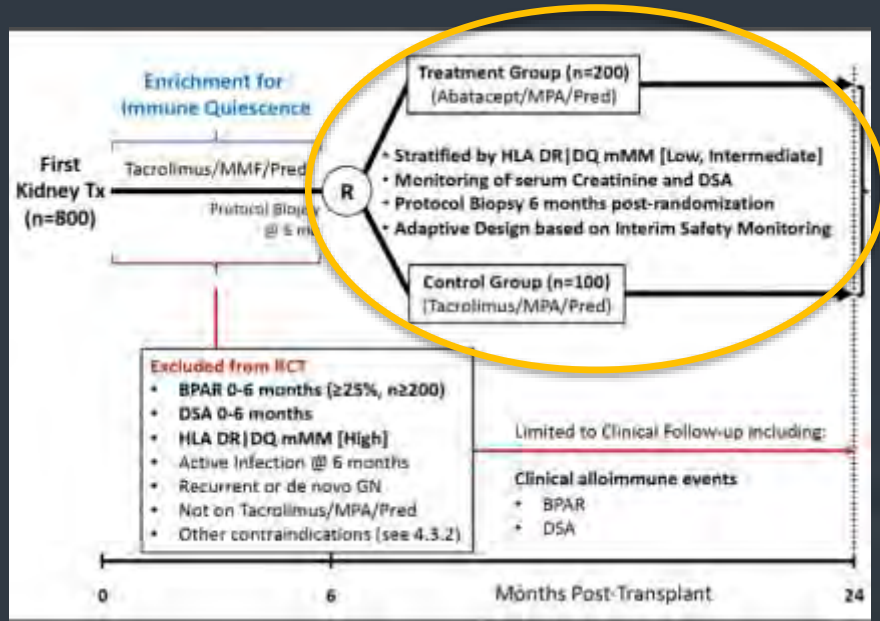
administered **subcutaneously**



ABC Trial

- RCT with low-risk patients with immune quiescence at 6 months

Selecting patients with low immunologic risk

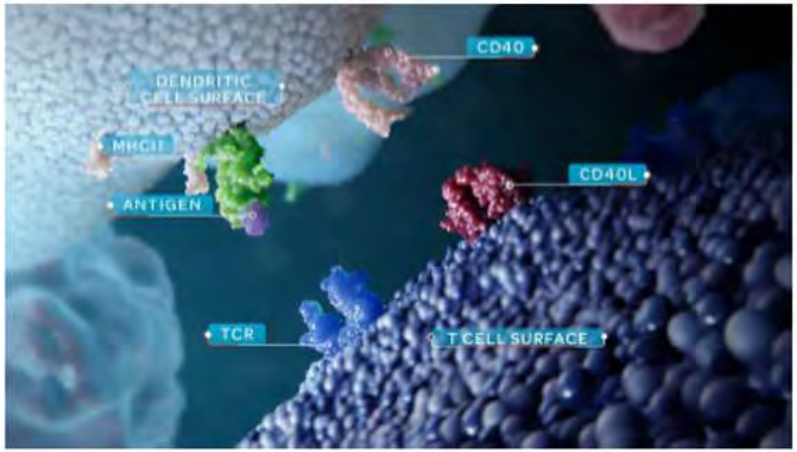


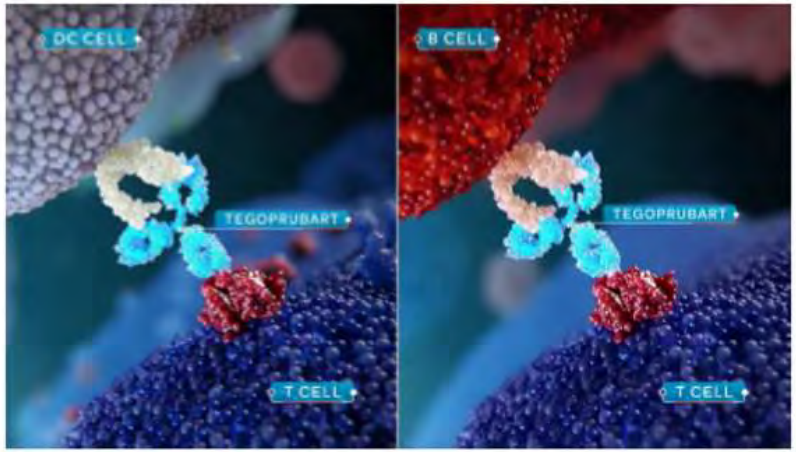
Tegoprubart (CD40-CD40Ligand)

Other co-stimulatory blockade agents

CD40L (T-cell) and CD40 (APC) is one of the vital costimulatory pathways required for T-cell activation

Tegoprubart binds CD40L to inhibit this pathway





BESTOW Study Design

Other co-stimulatory blockade agents

Arm 1:
*ATG
Tegoprubart
MPA
Prednisone

Arm 2:
*ATG
Tacrolimus
MPA
Prednisone

Primary endpoint: 12 month eGFR
Secondary endpoints: Graft survival, PTDM, BPAR

Belatacept / Costimulation blockade

Increased risk of early acute cellular rejection with costimulation blockade

Despite early ACR risk, Costimulation blockade may have a favorable chronic immunologic profile

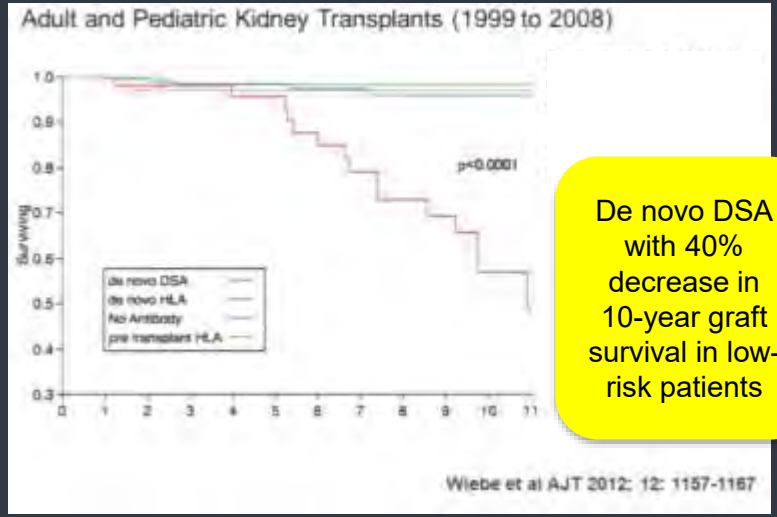
Attempts to mitigate early ACR

Additional maintenance immunosuppression	Belatacept, MPA, Pred + Sipilizumab (CD2 mAb)
Selecting patients with low immunologic risk	SQ Abatacept + MPA and Pred
Other co-stimulatory blockade agents	Tegoprubart (CD40L mAb) + MPA and Pred

Donor Specific HLA antibodies

- Despite maintenance immunosuppression, kidney transplant recipients can develop donor specific HLA antibodies

- Risk increased with
  - Immunologic memory (sensitization)
  - HLA mismatch
    - Higher with Class II HLA mismatch
  - Young Age
  - Decreased immunosuppression
    - Non-Adherence
    - Decreased due to side effects
      (or concern about side effects)



De novo DSA with 40% decrease in 10-year graft survival in low-risk patients

- Development of donor specific HLA antibodies with significant risk of graft loss
  - Early ABMR (<90 days) Graft loss HR 4.8
  - Late AMBR (>90 days) Graft loss HR 24

Hart et al Clin Trans 2021; 35 (7)

Treatment of Antibody Mediated Rejection (ABMR)

- Antibody mediated rejection is a cardinal cause of allograft failure

- Treatments used for early acute ABMR with modest success
  - Plasmapheresis
  - IVIG
  - Proteasome inhibition (Bortezomib)
  - CD20 monoclonal Ab (Rituximab)
  - IgG Degradation (IdeS/Inflimidase)
  - Compliment inhibition (Eculizumab)

- Chronic late AMBR due to long lived plasma cells
  - poor prognosis and refractory to treatments

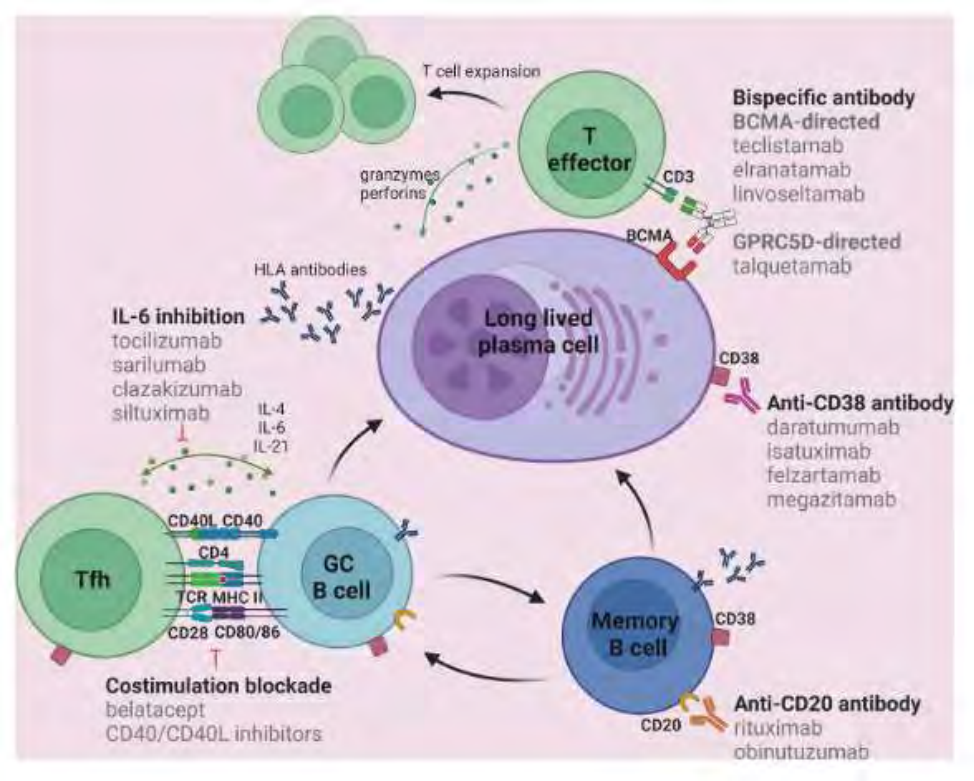
  - Expert guidelines recommend “optimizing maintenance immunosuppression”

Potential Targets for chronic AMBR

Plasmapheresis alone with rapid rebound of antibody production

Many therapies with no proven long-term benefit

Long lived plasma cells with limited targets



AJT 25 (2025) 19-26

Felzartamab

Anti-CD38 Monoclonal antibody

- CD38 expressed on plasma cells and NK cells
  - NK cells: important component of microvascular inflammation in AMR
- Phase 2 trial with Felzartamab
  - resolution of AMR in 82% (9/11) patients with AMR vs 20% in placebo
- TRANSCEND Clinical Trial
  - Double Blind Phase 3 RCT treated patients with biopsy proven late ABMR

Conclusions

- Goals of immunosuppression are to prevent organ rejection and preserve allograft function with minimal side effects

- CNI based immunosuppression
  - Good early outcomes
  - Off target side effects including nephrotoxicity, neurotoxicity, and increased cardiovascular risk factors

Alternates to calcineurin inhibitors have often resulted in increased rejection, graft loss or adverse effects

  - Chronic rejection remains the principle cause of graft loss

Conclusions

Co-stimulatory blockade

- Avoids many off target side effects of CNIs
- Increased risk for early acute rejection but may have improved chronic immunologic profile
- Clinical trials to determine if early rejection risk can be mitigated with

Additional maintenance immunosuppression

Selecting patients with low immunologic risk

Different co-stimulatory blockade agents

Chronic Antibody Mediated Rejection

- Poor prognosis and refractory to treatment
- Trials to mitigate antibody production from long lived plasma cells are ongoing

Questions?

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