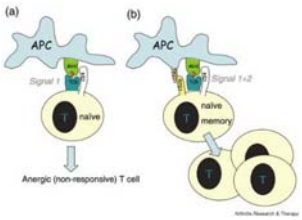
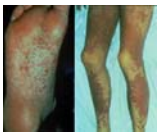
# Costimulation blockade for prevention of acute GVHD



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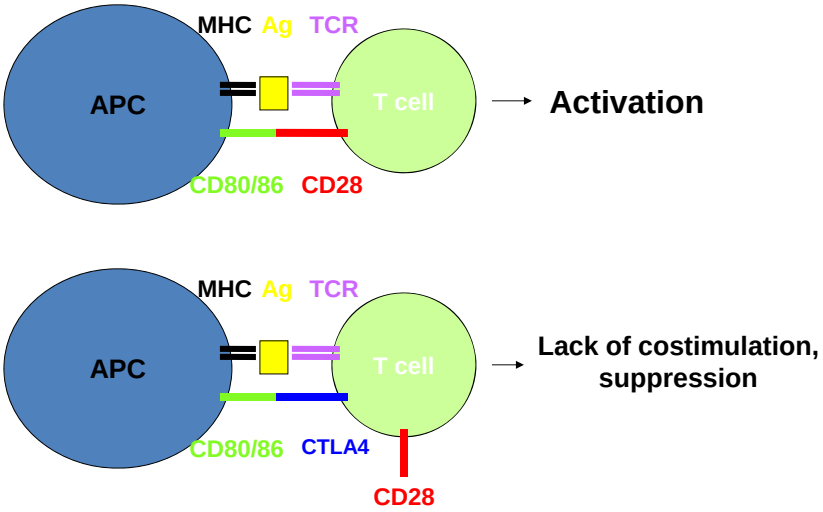
## Lack of costimulation leads to tolerance

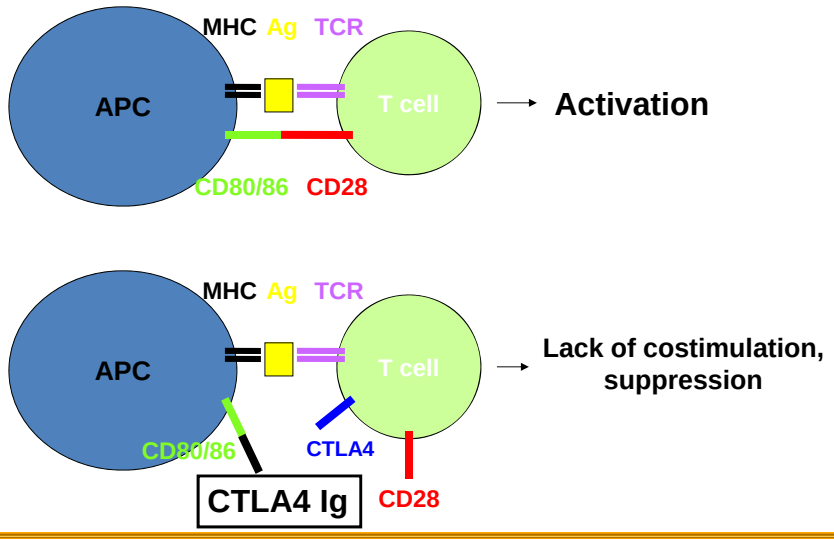


## Rationale for condsideration of costimulation blockade as part of GVHD Prophylaxis

- Blockade of the required "second signal" may prevent alloreactive donor T cell activation and clonal expansion
  - Effect may be additive with conventional immunosuppressive approaches
  - Possibility of induction of donor-host tolerance
  - Theoretically should be less suppressive of protective immune reconstitution and GVL effects



## Abatacept--CTLA4 Ig



## Costimulation blockade in renal transplantation

- Goals
  - Eliminate the need for long term CNI use
  - Promote long term graft tolerance that might permit d/c of all immune suppression
- BENEFIT and BENEFIT-EXT studies
  - Multicenter RCTs comparing 2 non-CNI Belatacept containing regimens with a standard CSA-based regimens for prevention of rejection
  - Similar rates of pt and graft survival
  - Early T cell mediated rejection was more common in Belatacept-treated arms, but was generally treatable
  - Belatacept arms had better renal function and markers of CV risk
  - Belatacept arms had higher incidence of PTLD (still only ~1% @ 1 yr)
  - No difference in clinically significant infections

**Vincenti et al. *Am J Transpl* 2010, and Durrbach et al. Am J Transpl 2010**

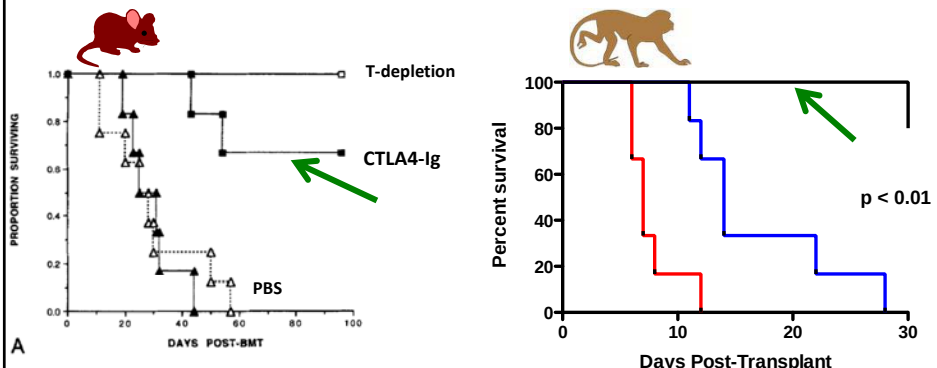


## CD28/B7 Costimulation Blockade

Slow translation into the HSCT setting

- Abatacept: FDA approved for RA
- Belatacept: FDA approved for prevention of rejection post renal transplantation
- Mixed results in preclinical models of HSCT
  - Human CTLA4 not fully cross reactive with canine and rodent targets
  - Redundancy in mechanisms producing the second signal

## Abatacept Prevents GVHD in Both Murine and Non-Human Primate Models




In Vivo Blockade of CD28/CTLA4: B7/BB1 Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatibility Complex Barrier in Mice

By Bruce R. Blazar, Patricia A. Taylor, Peter S. Linsley, and Daniel A. Vallera

Miller and Kean, 2010

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## Pilot study of costimulation blockade for prevention of GVHD

- Single arm, single center pilot study of Abatacept (CTLA4Ig) added to CSP + MTX for GVHD prophylaxis
- Conditioning with Bu-CY, TBI (12Gy) - CY, or Flu-Mel
- Endpoints
  - Safety
  - PK/PD
  - Incidence and severity of aGVHD and cGVHD
  - Opportunistic infections
  - Immune reconstitution

**Koura et al. BBMT 2013, 19: 1638-49**

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## Inclusions

- Patients (adults and children) with hematologic malignancies receiving an allogeneic transplant from an ***unrelated*** **donor**
  - *Preference for patients with a one locus mismatched donor*
- Normal renal, hepatic and cardiac function
- No active infection or other active malignancy
- No concurrent participation in other therapeutic trials for which GVHD or infection was a primary endpoint

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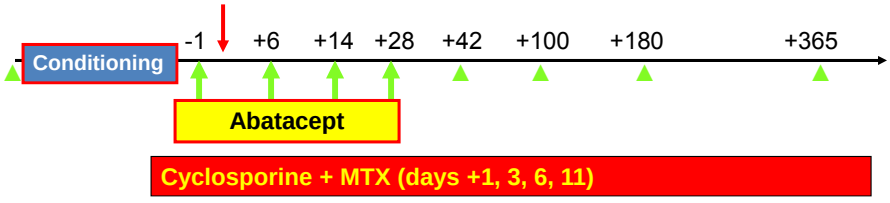
## Abatacept Pilot Study




▲ **Correlative studies:** Aba PK, qualitative immune reconstitution, EBV and CMV-specific T cell recovery, cytokine profiles

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# Patient Population

n=10

| UPN | Age, yr/sex | Disease and Status | HLA Matching (Mismatch) | CMV Status (R/D) | Preparative Regimen | Graft Source |
|---|---|---|---|---|---|---|
| 001-001 | 46/M | AML, CR2 | 7/8 (C allele) | +/+ | Bu/Cy | PBSCs |
| 001-002 | 61/F | AML, CR1 | 7/8 (B antigen) | −/− | Flu/Mel | PBSCs |
| 001-004 | 74/F | AML, CR2 | 7/8 (C antigen) | +/− | Flu/Mel | PBSCs |
| 001-005 | 59/F | MDS →AML | 8/8 matched | −/− | Flu/Mel | PBSCs |
| 001-006 | 43/M | Biphenotypic $Ph^+$ leukemia, CR1 | 8/8 matched | +/− | TBI/Cy | PBSCs |
| 001-007 | 46/M | ALL, CR1 | 7/8 (A antigen) | +/+ | TBI/Cy | PBSCs |
| 001-008 | 39/M | AML, CR1 | 8/8 matched | +/+ | Bu/Cy | PBSCs |
| 001-009 | 40/M | CML, extramedullary disease | 7/8 (A antigen) | +/− | Bu/Cy | PBSCs |
| 002-001 | 22/F | ALL, CR3 | 8/8 match | +/+ | TBI/Cy | BM |
| 002-002 | 17/M | ALL, induction failure | 7/8 (DRB1 antigen) | +/− | TBI/Cy | BM |



# Engraftment and early toxicities

- All patients engrafted
  - Median time to neutrophil engraftment- 17 d (11-47)
- Full donor chimerism in T cell and myeloid compartments
- Abatacept delivered safely--no infusional events
- No unanticipated early toxicities or events

# Viral infections

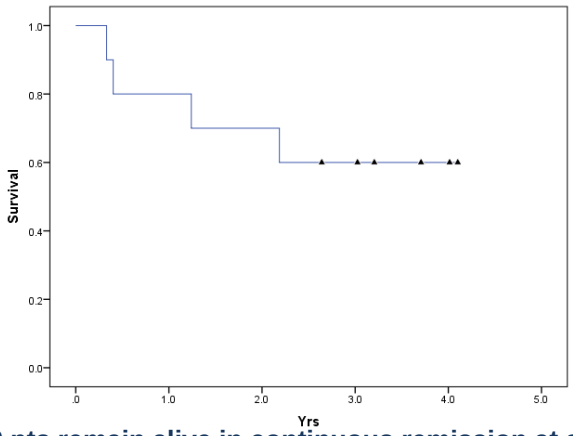
- CMV
  - 5 of 8 pts at risk reactivated CMV
  - No CMV disease
- EBV
  - 1 pt - low level reactivation (PCR)
  - 1 pt - EBV related plasmacytic hyperplasia (PCR neg)—resolved without therapy
- BK virus HC: 1 pt
- Adenoviremia: none
- *No life-threatening viral infections*



# GVHD, relapse, and survival

- Acute GVHD
  - Gr 2: 2 pts (one late aGVHD during CSA withdrawal)
  - Gr 3: 1 pt (gut)
- Chronic GVHD
  - Mild-2, moderate-3, severe-2
  - Two cGVHD-related deaths
- Deaths
  - Relapse has occurred in 2 pts (both with MRD prior to HPCT), and both pts died on days +121 and +147
  - Two late non-relapse deaths with ongoing cGVHD

## Overall Survival




**6 of 10 pts remain alive in continuous remission at a median of 3.5 yrs post-transplant**

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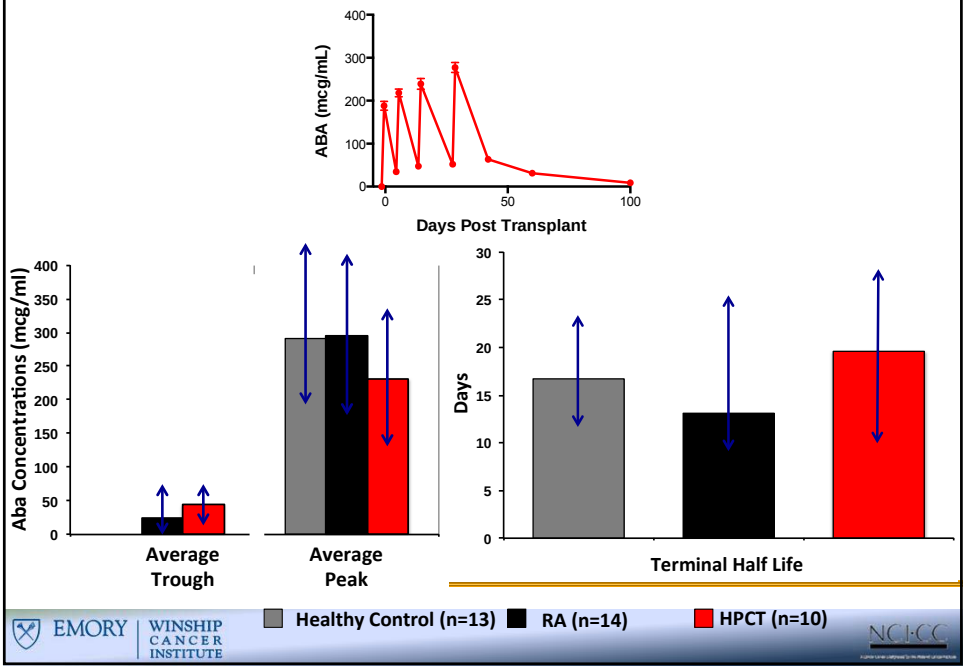
## Abatacept Pharmacokinetics in HSCT

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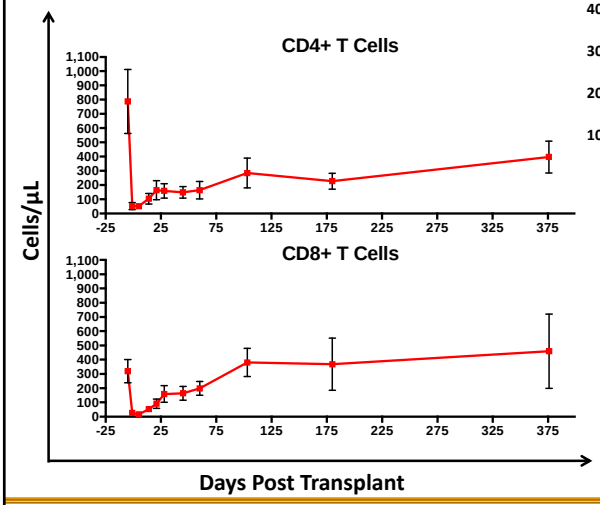
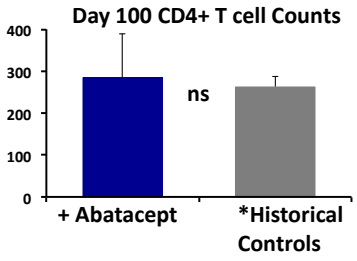
## Reconstitution of CD4+ and CD8+ T cells




***Historical Controls:**
**43 patients transplanted at EUH between 2007-2011 who met eligibility criteria for Aba trial**

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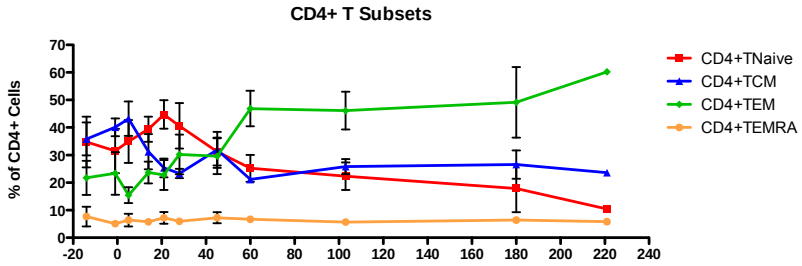
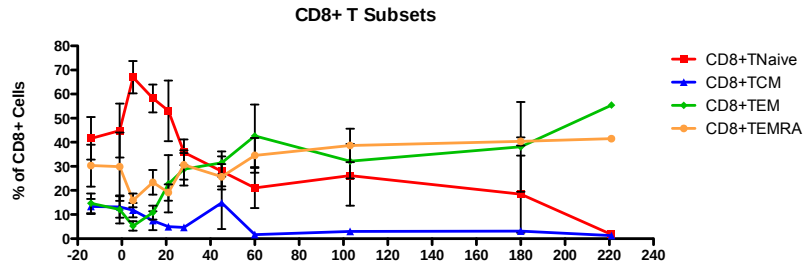
## A shift toward T cell effector memory

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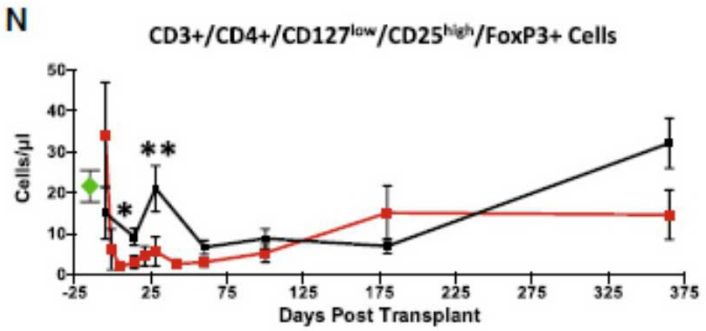
## Treg recovery overlaps with untreated controls

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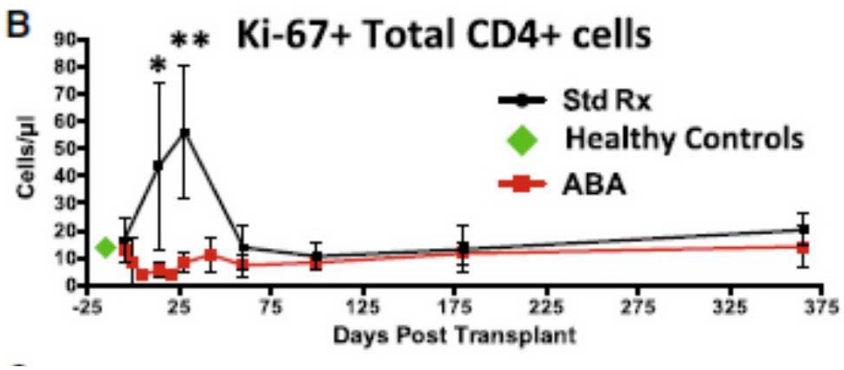
## Reduced proliferation of CD4+ T cells at early time points

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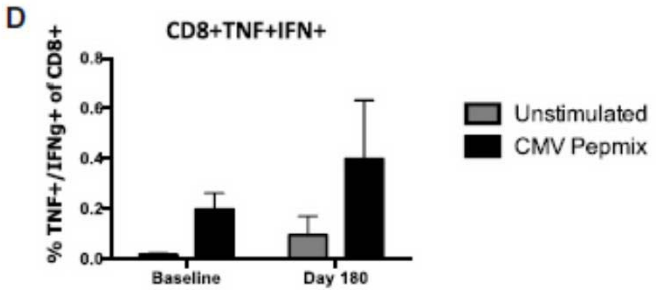
## The ability of CD8 effector cells to respond appropriately to CMV is preserved






## Conclusions

- **Murine and non-human primate studies laid the foundation for a 'first-in disease' trial investigating CD28-directed costimulation blockade with Abatacept for GvHD prevention.**
- **Feasibility established in this trial.**
- **First demonstration of the pharmacokinetic and pharmacodynamic impact of abatacept in HSCT patients.**
- **Encouragingly low rates of early severe GvHD.**
- **At day 100, CD4+ and CD8+ T cell reconstitution is similar to patients not treated with abatacept.**
- **Viral disease has not been a major clinical problem.**
- **These results have led to the design of a randomized, double-blind, placebo controlled multi-center phase 2 trial**

## Phase 2 Trial: Abatacept combined with CNI + MTX for GVHD prophylaxis

- **Design:** Phase II multicenter , randomized, double blind, placebo controlled trial
- **Primary Objective**
  - To determine if the addition of costimulation blockade to standard GVHD prophylaxis can reduce the incidence of *gr II-IV aGVHD* in pts receiving URD transplants for hematologic malignancies
- **Secondary Objective**
  - To characterize the impact of Abatacept on post-transplant reconstitution of protective antiviral immunity



## Phase II Study Design

- Eligibility
  - >5 yrs old
  - High –risk leukemia
  - Lack of an HLA matched related donor
  - Availability of a volunteer donor matched at 7/8 or 8/8 HLA loci by high resolution allele level typing
- Conditioning: Bu/Cy, TBI/Cy, Flu/Mel, Bu/Flu
- Two Strata
  - 8/8 match: Randomization (n=75)
    - CNI + MTX + Aba/placebo (blinded)
  - 7/8 match: all pts will receive CNI + MTX + Aba (n=35)
    - Comparison with a case-control CIBMTR cohort (n=70)

## Safety

- Stopping rules
  - Day 100 transplant-related mortality: The trial may continue as long as the hypothesis that 100-day TRM is less than or equal to 20% is not rejected
  - PTLD: The development of malignant PTLD will be monitored in the 2 arms, and the trial may continue as long as the hypothesis that the incidence of malignant PTLD is less than or equal to 5% is not rejected



## Correlative Biology

- PK and pharmacodynamic analysis
- Immune reconstitution of T, B, NK subsets
- Quantitative and qualitative analysis of T cell activation and regulation
- Quantitative analysis of CMV-specific, EBV-specific, and BK-specific CD8+ T cells
- Functional analysis of anti-CMV, EBV, and BK immunity
- PCR-based monitoring for viral replication
- Serum cytokine and chemokine analysis

## Implementation

- NIH funding and IND in place (PI: L. Kean)
- Bristol-Meyers Sqibb providing study drug
- PBMTC is coordinating the study
- Biorepository receiving samples
- Open sites
  - Emory, CHOA, FHCRC, Florida, Cincinnati, Michigan, Utah, Wash U, DC Children's, Hackensack
- *Accrual to date: 29 subjects*
- DSMB monitoring ongoing

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**PBMTC PROTOCOL GVH 1201: Abatacept Combined with a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis: A Randomized Controlled Trial**

**FDA IND#:** 111738 **SPONSOR:** Leslie S. Kean, M.D., PhD
**PRODUCT NAME(S)**: CTLA4lg, abatacept, Orencia

**Protocol Chair:** Leslie Kean
**Protocol Vice Chair, Clinical Oversight:** John Horan
**Protocol Vice Chair PBMTC:** David Jacobsohn
**PBMTC Chair:** Mike Pulsipher
**Protocol Vice Chair, Adult BMT:** Amelia Langston
**Study Statistician:** Andre Rogatko
**Statistical Lead Clinician:** Muna Qayed
**Study Coordinator:** Chiani Shelman
**Study CRN:** Audrey Grizzle
**Committee Members:** Mark Atlas, Paul Carpenter, Cindy Couture, Christine Duncan, Mike Grimley, Jean Khoury, Eneida Nemecek,Tal Schechter-Finkelstein

***Emory study Nurse**: Rebecca Gerkin*
***Former fellows:** Divya Koura and Ben Watkins*

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**Thanks!**

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