SYLVESTER

Comprehensive Cancer Center

Present and future trends in immunosuppression

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ASBMT CIBMTR

Learning Objectives

- Explain principles of immunosuppression and historic and current standards of care for graft-versus-host disease (GVHD) prophylaxis and therapy in the setting of allogeneic stem cell transplantation.
- Identify risks of adverse outcomes due to GVHD after allogeneic transplantation as well as the risks and side effects of commonly used immunosuppressive medications.
- Describe how advances in T cell biology and signaling are leading to the discovery of novel approaches to immunosuppression that are likely to be translated to the clinical arena.

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My center most commonly uses which of the following regimens to prevent GVHD:

A. Tacrolimus combined with methotrexate (MTX)

B. Cyclosporine combined with methotrexate

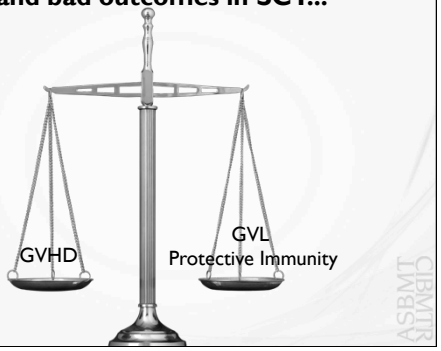
C. Tacrolimus combined with sirolimus

D. Cyclosporine combined with mycophenolate mofetil (MMF)

E. Other

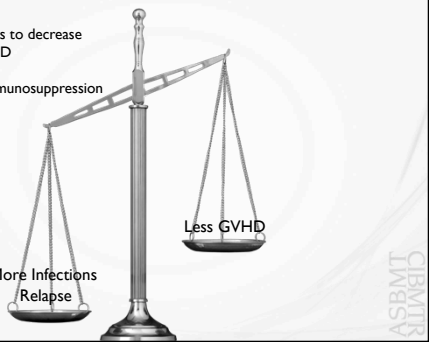
ASBMT CIBMTR

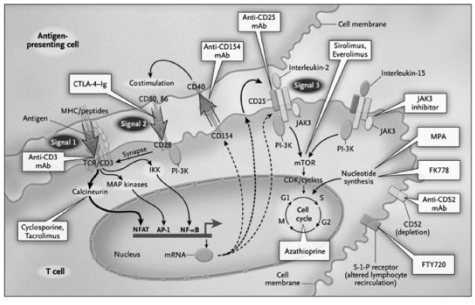
Since T cells mediate both good and bad outcomes in SCT...



...nonspecific targeting of T cells has a catch

Removal of T cells to decrease GVHD
or
More aggressive immunosuppression





Halloran P, et al. N Engl J Med 2004;351:2715-2729

The NEW ENGLAND JOURNAL of MEDICINE

ARS question: Which of the following is considered the standard of care for first line treatment of acute GVHD?

a) Methylprednisolone 10 mg/kg/day
b) Prednisone 0.5 mg/kg/day
c) Methylprednisolone 2 mg/kg/day
d) Methylprednisolone 2 mg/kg/day plus mycophenolate mofetil 15 mg/kg BID
e) Prednisone 2.5 mg/kg/day plus pentostatin 1.5 mg/m^2/day on day 1,2,3,15,16,17

ASBMT acute GVHD treatment guidelines

Martin P, et al, Biol Blood Marrow Transplant. 2012;18:1150-1163

- First line: The use of 6-methylprednisolone or prednisone alone...remains the standard of care for initial treatment of acute GVHD. The survival and response data from studies combining the use of other immunosuppressive agents together with glucocorticoid treatment do not support this approach as the standard of care.
- Second-line: Enrollment in well-designed clinical trials should be encouraged, since no standard, effective second line therapy for steroid-refractory acute GVHD has been identified, and since no treatment has been definitively demonstrated to be superior to any others.

Appendix A. *Evidence-Based Rating System for Ancillary Therapy and Supportive Care Guidelines in Chronic Graft-versus-Host Disease*

Category	Definition
Strength of the recommendation	
A	Should always be offered.
B	Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against, or evidence for efficacy might not outweight adverse consequences, or cost of the approach. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Quality of evidence supporting the recommendation	
I	Evidence from ≥1 properly randomized, controlled trial.
II	Evidence for ≥1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center), or from multiple time series or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive.
Qualifier for categories I and II	
a	Evidence derived directly from study(s) in graft-versus-host disease.
b	Evidence derived indirectly from study(s) in analogous or other pertinent disease.

Couriel D, et al, *Biol Blood Marrow Transplant. 2006; 12:375*

Consensus Conference on Clinical Practice in Chronic Graft-versus-Host Disease (GVHD): First-Line and Topical Treatment of Chronic GVHD

Daniel Wolff,[1] Armin Gerbitz,[2] Francis Ayuk,[3] Alexander Kiani,[4] Gerhard C. Hildebrandt,[1] Georgia B. Vogelsang,[5] Sharon Elad,[6] Anita Lawitschka,[7] Gerard Socie,[8] Steven Z. Pavletic,[9] Ernst Holler,[1] Hildegard Greinix[10]

Table 4. First-Line Treatment Options in cGVHD

Agent	Recommendation (citation number of references)	Evidence	Side effects	Comments
Steroids	A [16-18]	I	Osteoporosis, avascular necrosis of the bone, diabetes	Important but need to spare steroids because of side effect profile, generally sufficient in primary treatment of mild cGVHD as single agent, may be used in combination with CNI in moderate or severe cGVHD
CNI	C [16,17]	II	Renal toxicity, hypertension	Only be used in combination with steroids, spares steroids, lower rate of avascular necrosis of the bone, may be considered in combination with steroids in primary treatment of severe cGVHD as well as in CNI dependent moderate cGVHD
MMF in triple agent combinations	D [19]	II	GI complaints, infectious and relapse risk	Failure to improve efficacy in a randomized trial documented
Azathioprine	D [18]	II	Hematologic toxicity, infectious risk	Adverse outcome in a randomized trial in combination with steroids
Thalidomide	D [20,21]	II	Neurotoxicity, sedation, constipation, thrombosis	May be used in concomitant relapse of multiple myeloma

CNI indicates calcineurin inhibitors; MMF, mycophenolate mofetil; GI, gastrointestinal; cGVHD, chronic graft-versus-host disease.

Wolff D, et al, *Biol Blood & Marrow Transplant.* 2010; 16:1611-1628

Summary of Monitoring Recommendations as Proposed by the National Institute of Health Consensus Development Project for Clinical Trials in Chronic Graft-Versus-Host Disease

SYSTEM	FREQUENCY	DETAILS
General history & physical exam	1–12 months	Physical exam, weight, height, nutritional status, psychosocial, medication review
Laboratory	1–12 months	CBC, chemistry, LFTs, therapeutic drug monitoring, IgG level, lipid profile, iron studies
Pulmonary	3–12 months	Pulmonary function tests
Endocrine	Yearly	TFTs, bone densitometry, calcium levels, vitamin D levels
Ophthalmologic	3–4 months	Schirmer's test and glaucoma assessment
Dental	6–12 months	Comprehensive soft- and hard-tissue examination, biopsy of lesions as indicated
Dermatologic	Variable	Skin assessment for GVHD but also skin cancer
Gynecologic	Variable	Assess for GVHD as clinically indicated
Physiotherapeutic	Variable	Assess range of motion if sclerotic features are present
Neuropsychiatric	Yearly	Assess for depression as clinically indicated; EMG testing as indicated

Abbreviations: CBC = complete blood count; LFT = liver function tests; IgG = immunoglobulin G; TFT = thyroid function test; GVHD = graft-versus-host disease; EMG = electromyogram

Chronic Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation: Challenges in Prevention, Science, and Supportive Care

Richard B. Joseph, MD, Daniel R. Couriel, MD, and Krishna V. Komanduri, MD

The Journal of Supportive Oncology
Volume 6, Number 8 ■ November/December 2008

Level A and B Ancillary and Support Care Recommendations as Proposed by the National Institutes of Health Consensus Development Project for Clinical Trials in Chronic Graft-Versus-Host Disease

ORGAN SYSTEM	LEVEL A AND B RECOMMENDATIONS FOR ANCILLARY AND SUPPORTIVE CARE
Skin	Avoidance of sun exposure, sunscreen, topical emollients and antipruritics, stretching exercises
Hepatic	Ursodeoxycholic acid
Mouth and oral cavity	Topical steroids on lips, steroid rinses, topical analgesia, salivary stimulants (gum) and sialogues, frequent water sipping
Ocular	Lubrication with artificial tears and ointments, topical steroid drops, punctal occlusion, protective eyewear
Respiratory	Supplemental oxygen
Gastrointestinal	Esophageal dilation, pancreatic enzyme replacement, lactase tablets, dietary modifications
Immunologic	Vaccines for encapsulated organisms, pneumocystis prophylaxis, influenza vaccination
Hematologic	Transfusions as necessary
Vaginal	External emollients, topical estrogen, topical steroids and tacrolimus, surgical dilation
Neurologic	Anticonvulsants, tricyclic antidepressants, intravenous immunoglobulin

Level A: Consistent randomized controlled clinical trial, cohort study, all or none, clinical decision rule validated in different populations
Level B: Consistent retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study; or extrapolations from level A studies
Level C: Case-series study or extrapolations from level B studies
Level D: Expert opinion without explicit critical appraisal or based on physiology, bench research or first principles

Chronic Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation: Challenges in Prevention, Science, and Supportive Care

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GVHD Therapy: many trials, little progress

- Standard of care in GVHD prophylaxis (calcineurin inhibitors (CNI) + methotrexate) defined in 1986 (articles by Storb and Thomas in *Blood, NEJM*)
- Steroids remain the mainstay of primary therapy for GVHD.
- Some progress with novel agents, though many have proven efficacious yet toxic.
- Patients almost always die of infection rather than GVHD-related end organ damage.
- *Can we identify potential approaches to selectively target alloreactive T cells while sparing pathogen and cancer-specific memory cells?*

Review of recent trials of alternate regimens

- Recent Randomized Controlled Trials (RCT) of GVHD Prophylaxis:
  - CTN0402 (tacrolimus/MTX vs. tacrolimus/sirolimus)
  - Randomized trials adding sirolimus to CNI-based GVHD prophylaxis for patients with lymphoma
- RCT of standard vs. lower starting steroid dose for acute GVHD

ARS Question

Sirolimus (rapamycin):

A. May cause thrombotic microangiopathy/thrombotic thrombocytopenia purpura and hyperlipidemia

B. Has been proven superior to methotrexate (when combined with tacrolimus)

C. May spare regulatory T cells capable of suppressing GVHD

D. Improves overall survival when added to either tacrolimus/ methotrexate or cyclosporine/MMF after allogeneic transplantation for lymphoid malignancies

E. Answers A and C

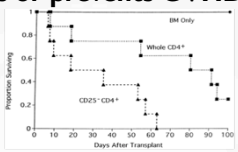
Sirolimus (rapamycin)

- Naturally occurring compound isolated from *Streptomyces hygroscopicus* on Easter Island (Rapa Nui).
- A Canadian expedition collected soil samples in1964; Ayerst's microbiology department isolated sirolimus in 1972.
- Properties:
  - Antifungal
  - Antiviral
  - Antineoplastic
  - Immunosuppressive

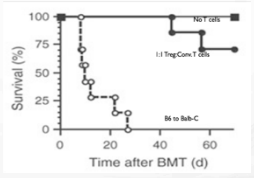
from Corey Cutler, DFCI

Regulatory T cell enrichment in mice delays or prevents GVHD

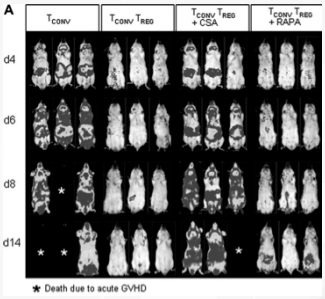
Taylor PA, Lees CJ, Blazar BR. The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality. *Blood*. 2002 May 15;99(10):3493-9.



Edinger M, Hoffmann P, Ermann J, Drago K, Fathman CG, Strober S, Negrin RS. CD4+CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation. *Nat Med*. 2003 Sep;9(9):1144-50.



Sirolimus spares regulatory T cells



Zeiser R, et al. *Blood* 2006; 108:390-399

from Corey Cutler, DFCI

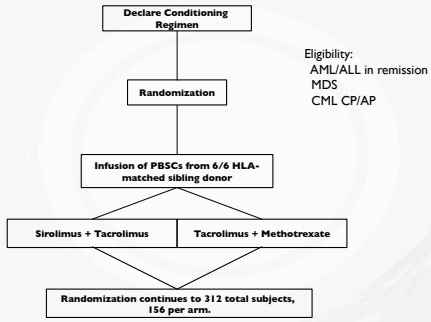
BMT CTN Protocol 0402
A Phase III Randomized, Multicenter Trial of GVHD Prophylaxis Regimens After HLA-Matched, Related PBSCT

Sirolimus / Tacrolimus
Versus
Tacrolimus / Methotrexate

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

from Corey Cutler, DFCI

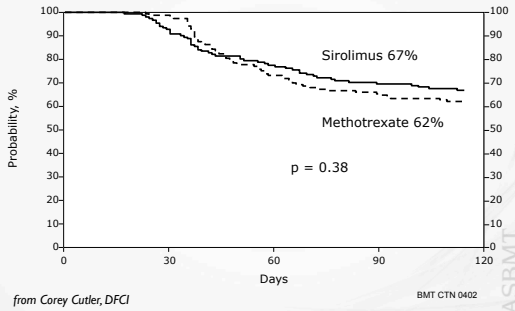
BMT CTN 0402: Schema



Eligibility:
AML/ALL in remission
MDS
CML CP/AP

from Corey Cutler, DFCI

CTN 0402: Probability of Grade II-IV Acute GVHD-Free Survival



from Corey Cutler, DFCI

RCT: sirolimus added for GVHD prophylaxis in NHL *Methods*

- **GVHD Prophylaxis**
- **Arm A *("experimental")***
  - **Tacrolimus**
    - **0.05mg/kg PO bid starting day -3**
    - **Trough goal 5-10ng/ml**
  - **Sirolimus**
    - **12mg/4mg PO daily starting day -3**
    - **Trough goal 4-12 ng/ml**
  - **Methotrexate**
    - **5mg/m² IV days 1,3,6**
  - **Taper**
    - **Tacrolimus day 100-180**
    - **Sirolimus day 180-365**

RANDOMIZE

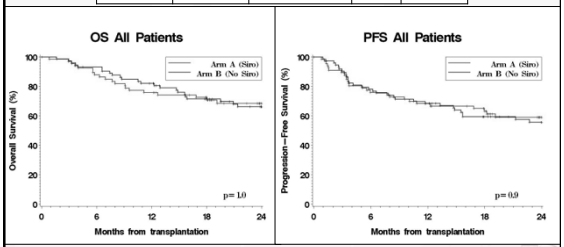
Arm B1 *("control")*
- **Tacrolimus**
- **Methotrexate (+day 11 for MUD)**

Arm B2 *("control UMN")*
- **Cyclosporine (CSA)**
  - **6mg/kg PO bid starting day -3**
  - **Trough goal 200-400 ng/ml**
- **MMF**
  - **3g/d PO/IV divided day 3-30**
- **Taper**
  - **CSA day 100-180**

from Philippe Armand, DFCI (ASH 2013)

RCT: sirolimus added for GVHD prophylaxis in NHL *Survival*

Outcome	Arm A Tac+Siro+Mtx	Arm B Tac+Mtx/CSA+MMF	*p*	All patients
2-year OS	*68% (55-78)*	*66% (53-76)*	*1.0*	*67% (58-75)*
2-year PFS	59% (46-70)	56% (43-67)	0.9	57% (48-65)

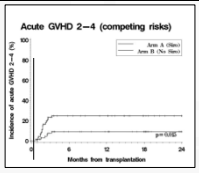


from Philippe Armand, DFCI (ASH 2013)

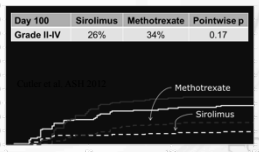
RCT: sirolimus added for GVHD prophylaxis in NHL *Conclusions*

- **Outcome with addition of sirolimus**
- **Generalizability of acute GVHD benefit**
  - **Addition versus substitution of MTX**

Outcome	Arm A Tac+Siro+Mtx	Arm B Tac+MTX/CSA+MMF	*p*
6m aGVHD 2-4	*9% (4-18)*	*25% (15-35)*	*0.015*
6m aGVHD 3-4	3% (1-9)	4% (1-11)	0.7



Day 100	Sirolimus	Methotrexate	Pointwise p
Grade II-IV	26%	34%	0.17



from Philippe Armand, DFCI (ASH 2013)

RCT with Sirolimus: Conclusions

- Despite compelling intellectual and preclinical rationale, randomized trials substituting sirolimus for methotrexate/MMF have not demonstrated superiority (at least in terms of progression free survival/overall survival)
- There is a suggestion of benefit in secondary endpoints (e.g., grade 2 GVHD) but also some toxicities (thrombotic microangiopathy/ Thrombotic Thrombocytopenia Purpura, hyperlipidemia)
- >25 years later, no prophylaxis strategy better than CNI/MTX

Can we identify potential approaches to selectively target alloreactive T cells while sparing pathogen and cancer-specific memory cells?

ASBMT acute GVHD treatment guidelines

Martin P, et al, Biol Blood Marrow Transplant. 2012;18:1500-1163

- Prophylaxis using cyclosporine A or tacrolimus, in addition to methotrexate (MDACC: 5 mg/m^2 on d +1, +3, +6, ± 11)
- Initiate methylprednisolone (2 mg/kg) for documented acute or chronic GVHD, taper based on response and other clinical manifestations
- No standard of care beyond first-line therapy (other agents include infliximab, daclizumab (no longer available in the U.S.), anti-thymocyte globulin (ATG))

Standards of care for GVHD

- First line: The use of 6-methylprednisolone or prednisone alone...remains the standard of care for initial treatment of acute GVHD. The survival and response data from studies combining the use of other immunosuppressive agents together with glucocorticoid treatment do not support this approach as the standard of care.
- Second-line: Enrollment in well-designed clinical trials should be encouraged, since no standard, effective second line therapy for steroid-refractory acute GVHD has been identified, and since no treatment has been definitively demonstrated to be superior to any others.

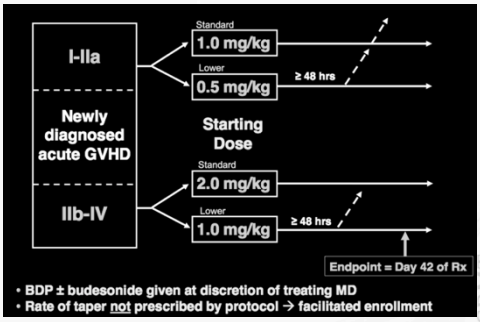
Which of the following regimens does your center use as first-line treatment of acute GVHD occurring despite prophylaxis (in a patient presenting with both skin and lower GI GVHD):

A. Steroids (equivalent of prednisone 0.5 mg/kg/day)
B. Steroids (equivalent of prednisone 1 mg/kg/day)
C. Steroids (equivalent of prednisone 2 mg/kg/day)
D. ATG or other biological therapy
E. Steroids combined with another agent

Efficacy and Safety of Lower-Dose Glucocorticoids for Initial Treatment of Acute GVHD: A Randomized Controlled Trial

Marco Mielcarek, MD
Fred Hutchinson Cancer Research Center
University of Washington
Seattle, WA

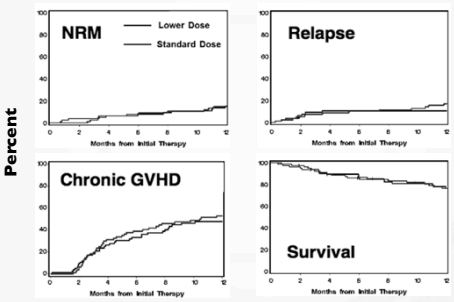
Stratification and Randomization



Mielcarek M, et al. *Blood*. 2013;122: 703 (Abstract)

Outcomes: Overall Group

Median Follow-Up: 27 (1-48) months



Mielcarek M, et al. *Blood.* 2013;122: 703 (Abstract)

Summary

- Primary endpoint (≥ 33% ↓ of day-42 AUC) not reached
  - Due to evolving practice of rapid prednisone taper in responding patients treated initially at higher dose
- Grade IIa at onset + lower initial dose (0.5 mg/kg/d)
  - Safe and effective
- Grade IIb-IV at onset + lower initial dose (1 mg/kg/d)
  - Increased risk of requiring 2° systemic immunosuppressant therapy *without* adversely affecting survival
  - Rash > 50% BSA associated with increased risk of 2° therapy
- No statistically significant differences in risks of NRM, relapse, OS or toxicity metrics

NRM - non-relapse mortality
OS - overall survival

Mielcarek M, et al. *Blood.* 2013;122: 703 (Abstract)

Recommended Initial Prednisone Dose for Newly Diagnosed acute GVHD

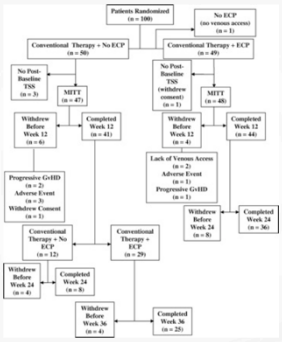
GVHD Grade at Onset	Initial Prednisone Dose (mg/kg/d)*
IIa ("upper gut syndrome")	0.5
≥ IIb (rash ≤50% BSA)	1
≥ IIb (rash >50% BSA)	Consider 2

*** Add oral beclomethasone dipropionate ± budesonide if gastrointestinal symptoms present**

How can we more selectively inhibit T cells?

- Photopheresis
- Regulatory T cells
- Targeting T cell deacetylases
- Targeted inhibitors of T cell activation

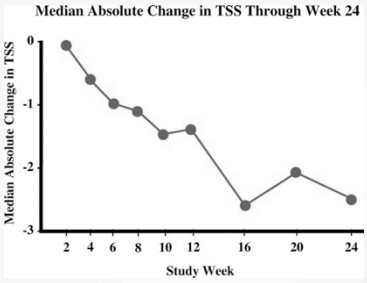
Randomized study of ECP in chronic GVHD



Flowers, et al. *Blood* 2008;112:2667-2674

ECP = extracorporeal photopheresis

Efficacy of ECP in chronic GVHD



Flowers, et al. *Blood* 2008;112:2667-2674

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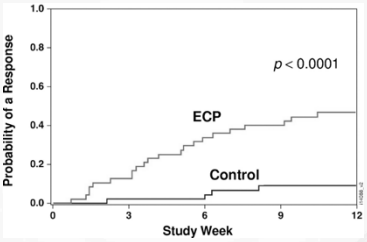
Cumulative incidence of complete or partial skin response



Flowers, et al. *Blood* 2008;112:2667-2674

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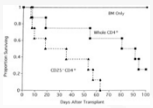
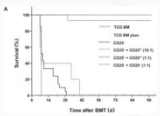
Enrichment of donor grafts with regulatory T cells prevents murine GVHD

Taylor PA, Lees CJ, Blazar BR.
The infusion of ex vivo activated and expanded CD4(+)CD25(+) immune regulatory cells inhibits graft-versus-host disease lethality.
Blood. 2002 May 15;99(10):3493-9.



Blazar 2002 Blood

Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S.
Donor-type CD4(+)CD25(+) regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation.
J Exp Med. 2002 Aug 5;196(3):389-99.



Strober 2002 JEM

Edinger M, Hoffmann P, Ermann J, Drago K, Fathman CG, Strober S, Negrin RS.
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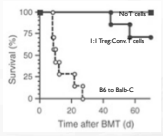
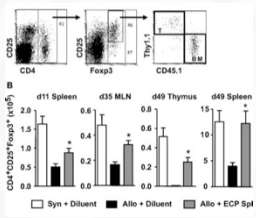


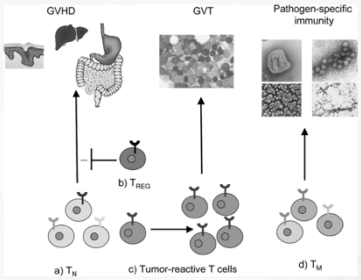
Negrin 2003 Nat.Med.

Putative mechanism of ECP: Induction of regulatory T cells in mice



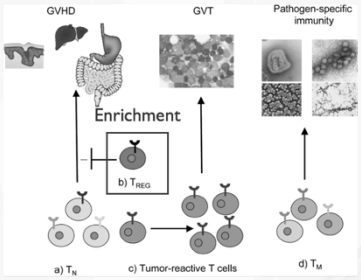
Gatza E, et al. *Blood*. 2008;112:1515-1521

T cells in allogeneic SCT: Good and Bad



Graft-Versus-Host Disease: A Surge of Developments
Stanley R. Riddell, Frederick R. Appelbaum PLoS MEDICINE July 2007 | Volume 4 | Issue 7 | e198

The goal: Eliminating GVHD while sparing beneficial T cells



Graft-Versus-Host Disease: A Surge of Developments
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Human T Regulatory Cell Therapy: Take a Billion or So and Call Me in the Morning

Immunity
Review
Immunity 30, May 22, 2009 ©2009 Elsevier Inc.

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DOI 10.1016/j.immuni.2009.04.006

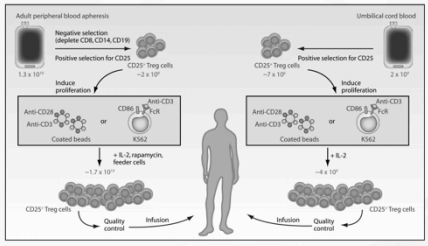

Figure 1. Clinical Applications of Human Treg Cells in Allo-HSCT

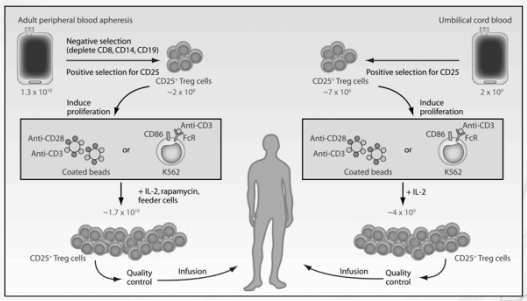

Figure 1. Clinical Applications of Human Treg Cells in Allo-HSCT

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Promising SCT graft manipulation strategies

- Regulatory T cell therapy (e.g., Blazar, et al., U of MN) is safe and may have therapeutic benefit
- Chimeric antigen receptor (CAR) therapy uses engineered T cells directed at specific tumor targets (June, et al., Penn; multiple other groups treating ALL, CLL, NHL, others)

ARS question: Which of the following modalities has been shown to decrease the cumulative incidence of grade II to IV acute GVHD in phase I/II trials?

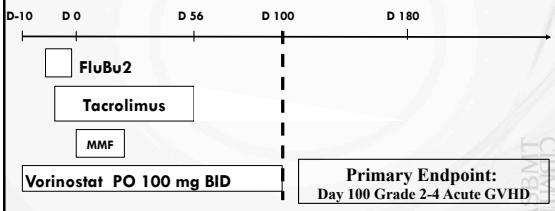
A. Selumetinib
B. Vorinostat
C. Chimeric antigen receptor (CAR) infusions
D. Pentostatin
E. None of the above

Targeting Deacetylases As a Novel Strategy for Prevention of Acute Graft Versus Host Disease

- **Sung Choi, M.D.**
- **Blood and Marrow Transplantation Program**
- **University of Michigan**

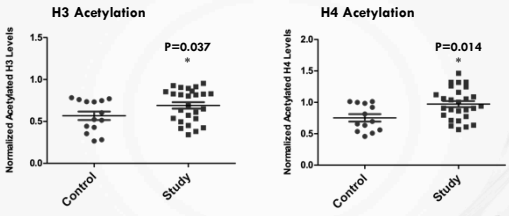
Study Schema

- **STUDY DESIGN:** IRB-approved Phase I/II trial (two-center)
- **STUDY DRUG:** Vorinostat 100 mg twice daily (D-10 to D100)



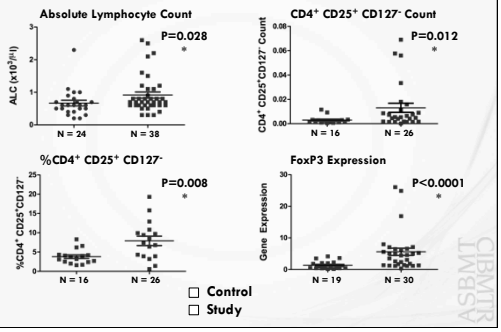
FluBu2 = fludarabine + busulfan IV

Acetylation Of Histones H3/H4

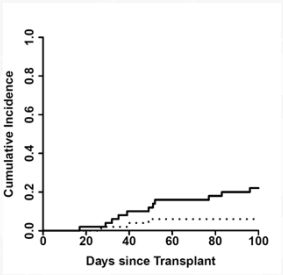


- Control (N = 13)
- Study (N = 26)

T Cells



Primary Endpoint: Acute GVHD

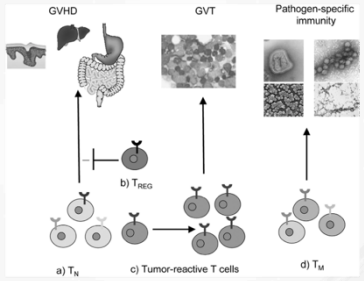


Grade 2-4 Acute GVHD (22%)
Grade 3-4 Acute GVHD (6%)

Conclusions

- Safe & feasible to administer vorinostat (D-10 thru D100) at a dose that inhibited histone deacetylase activity & had good bioavailability.
- Correlative laboratory data were consistent with experimental studies.
- Vorinostat combined with standard GVHD prophylaxis reduced the cumulative incidence of grade 2–4 acute GVHD by D100.
- Demonstrate translation of our experimental observations into a phase I/II clinical trial of GVHD prevention.

Eliminating GVHD while sparing beneficial T cells



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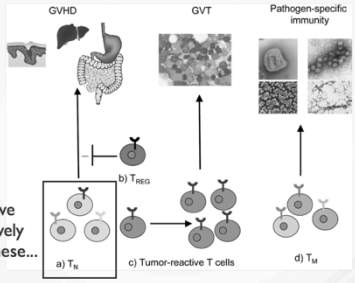
Eliminating GVHD while sparing beneficial T cells



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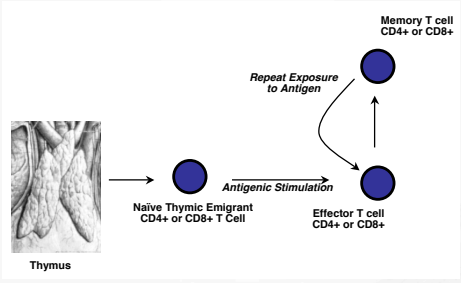
The thymus generates a naive T cell pool from which the memory repertoire is derived



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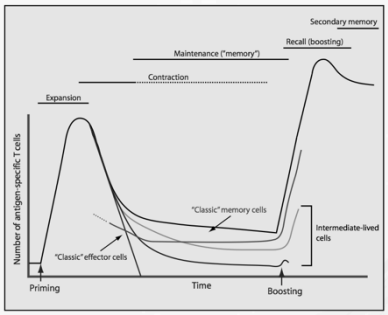
Kinetics of memory T cell development

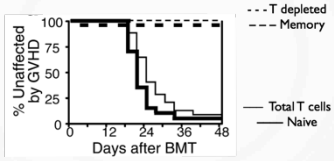


S Jameson, et al., *Immunity* 2009; 31(6):859-71

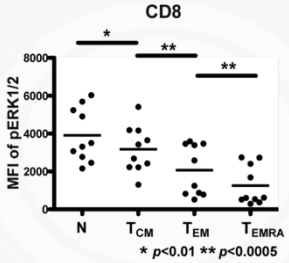
Memory CD4⁺ T cells do not induce graft-versus-host disease

Britt E. Anderson,[1] Jennifer McNiff,[2] Jun Yan,[3] Hester Doyle,[3] Mark Mamula,[3] Mark J. Shlomchik,[1,4] and Warren D. Shlomchik[1,5]

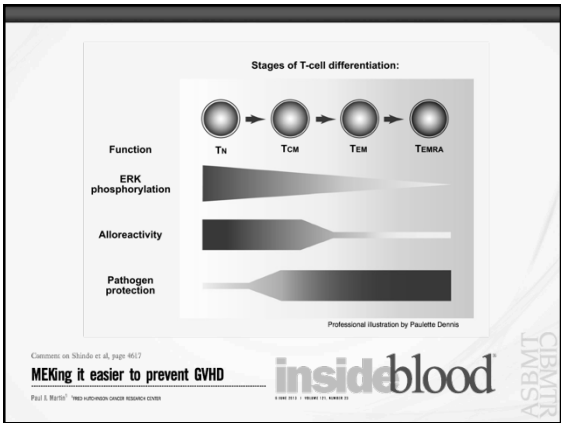
The Journal of Clinical Investigation | July 2003 | Volume 112 | Number 1

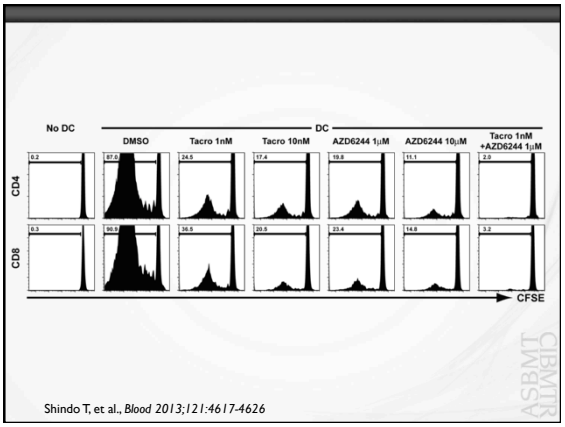


T cell signaling differs in "naive" and more mature T cells

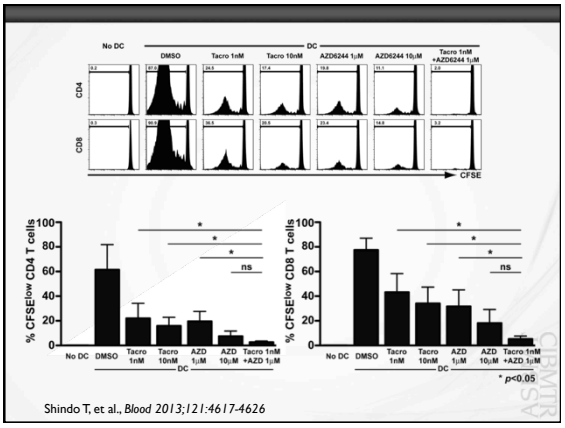


Shindo T, et al., *Blood 2013;121:4617-4626*

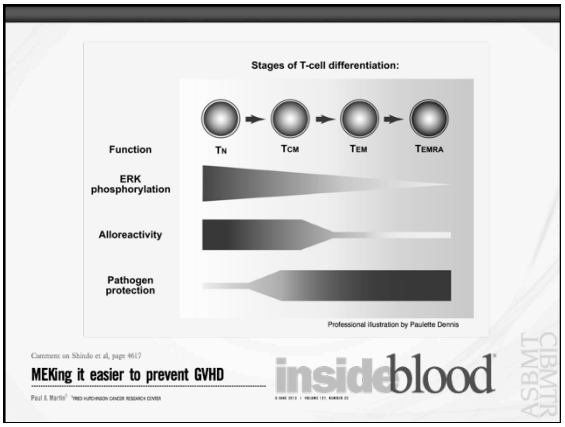


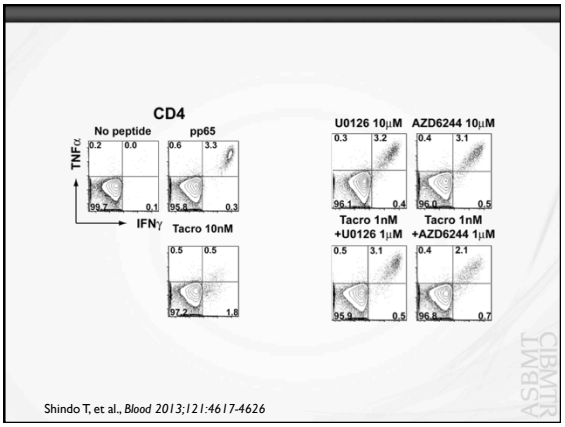


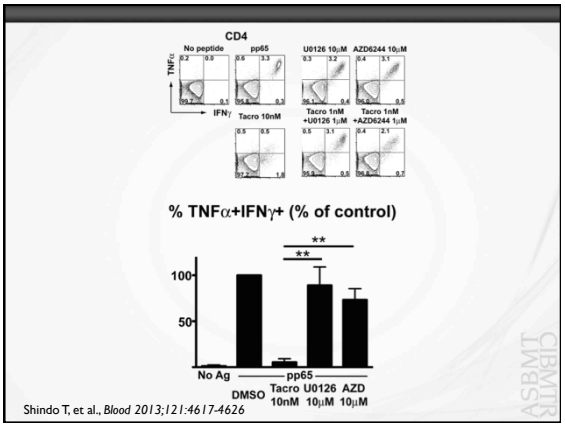
Shindo T, et al., *Blood 2013;121:4617-4626*



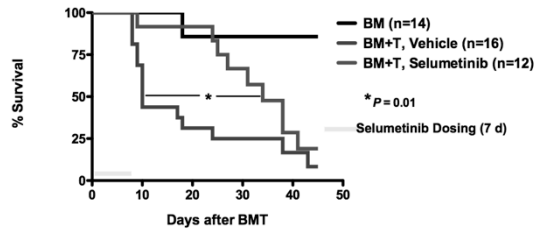
Shindo T, et al., *Blood 2013;121:4617-4626*


Stages of T-cell differentiation:
Function
TN
TCM
TEM
TEMRA
ERK phosphorylation
Alloreactivity
Pathogen protection
Professional illustration by Paulette Dennis
Comment on Shindo et al, page 4617
MEKing it easier to prevent GVHD
Paul J. Martin
insideblood


CD4
No peptide
pp65
TNFα
IFNγ
Tacro 10nM
U0126 10μM
AZD6244 10μM
Tacro 1nM +U0126 1μM
Tacro 1nM +AZD6244 1μM
Shindo T, et al., Blood 2013;121:4617-4626

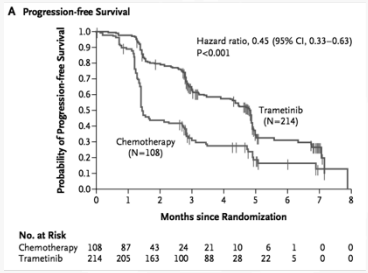

CD4
% TNFα+IFNγ+ (% of control)
100
50
No Ag
pp65
DMSO
Tacro 10nM
U0126 10μM
AZD 10μM
Shindo T, et al., Blood 2013;121:4617-4626

Short term MEK inhibition significantly delays murine GVHD



Shindo T, et al., *Blood 2013;121:4617-4626*

Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma



Flaherty KT, et al. *N Engl J Med* 2013; 367: 107-114

Selective immunosuppression

- We have identified an approach that may selectively target cells that can cause GVHD while sparing cells that protect patients from potentially lethal infection
- Drugs developed with another rationale (in this case, safely used to treat melanoma and other solid tumors) may be repurposed for benefit in SCT

Summary

- We have seen dramatic advances in systems biology, cellular therapy and immunology, but to date these have not significantly influenced therapeutic approaches, including for GVHD.
- Novel approaches including cellular therapies and novel targeted agents are likely to yield more selective immunosuppression
- Controlled studies of novel approaches will be required, with the likelihood that we will be able to more selectively prevent and more effectively treat acute and chronic GVHD.

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Acknowledgments

- Tae Kon Kim (Yale)
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- Philippe Armand (DFCI)
- Marco Mielcarek (University of Washington)
- Sung Choi (University of Michigan)

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