Columbia Center for Translational Immunology

COLUMBIA UNIVERSITY

Immune Tolerance and Graft Acceptance: Lessons learned from transplant immunology

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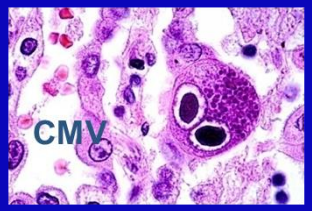
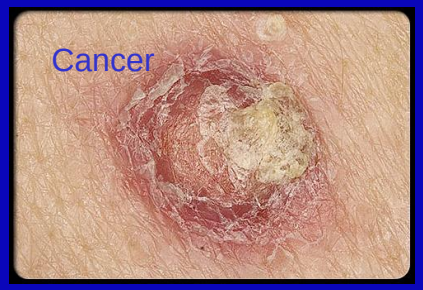
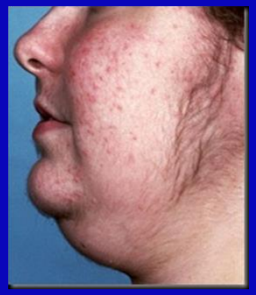
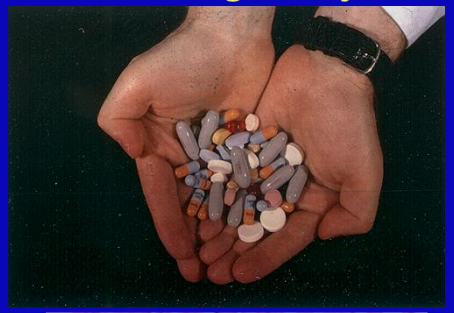
The Problems with Immunosuppressive Drugs

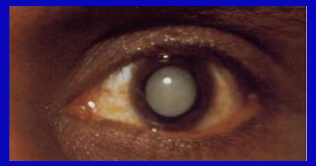


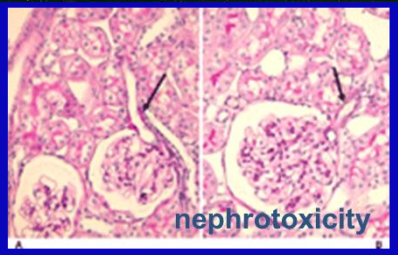


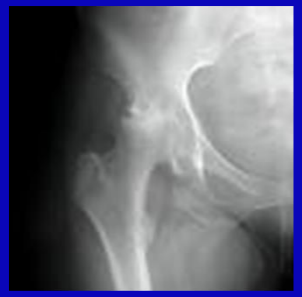


What Patients Take in One Day to Prevent Organ Rejection









Current Limitations to Successful Organ Transplantation

- Drug treatment-related complications
- Chronic rejection

Both limitations can be avoided by induction of immune tolerance

Tolerance

Long-term graft acceptance without immunosuppressive therapy, with immunocompetence.

- Ability to resist infection and cancer is preserved.
- Chronic rejection does not occur.

Cell Engineering to Avoid PSC-Derived Graft Rejection: Concerns

- HLA-deficient grafts would be subject to NK cell-mediated rejection.
- HLA-deficient grafts would evade T cell immunity. Consequences: 1) loss of tumor surveillance mechanism; 2) inability to protect graft from infection.
- Similar concerns apply to graft engineering to express immunosuppressive molecules.

Induction of tolerance bypasses these concerns, leaving the immune system intact.

Mechanisms of Tolerance

- Clonal deletion– Cells are gone. Can be central (thymus) or peripheral
- Anergy– Cells persist but don't respond to antigen.
- Suppression– Cells persist but are actively suppressed (eg Tregs).

Approaches to Allograft Tolerance Induction

- Thousands in the literature.
- Most in rodent models of vascularized allografts, which are themselves highly tolerogenic.
- Rodent vascularized allografts have a strong ability to induce regulatory T cell responses. Partial/temporary immunosuppression allows this regulatory response to dominate, leading to graft acceptance.
- Extension to large animals has, with few exceptions, been unsuccessful.

Regulatory Cell Therapies in Clinical Trials of Organ Transplantation

Tregs- polyclonal

-donor-specific

-CAR-Tregs

DCregs

Mesenchymal Stem Cells

Tolerogenic Monocytes

None of these trials assess allograft tolerance, as complete immunosuppression withdrawal is not planned.

These approaches have generally not been shown to achieve allograft tolerance in large animal models.

Ideal Achievements Before Clinical Trials of Tolerance Induction

- Efficacy data in stringent rodent models (MHC-mismatched skin grafts)
- Efficacy and safety data in large animal models
- Safety data with proposed drugs/biological agents in humans

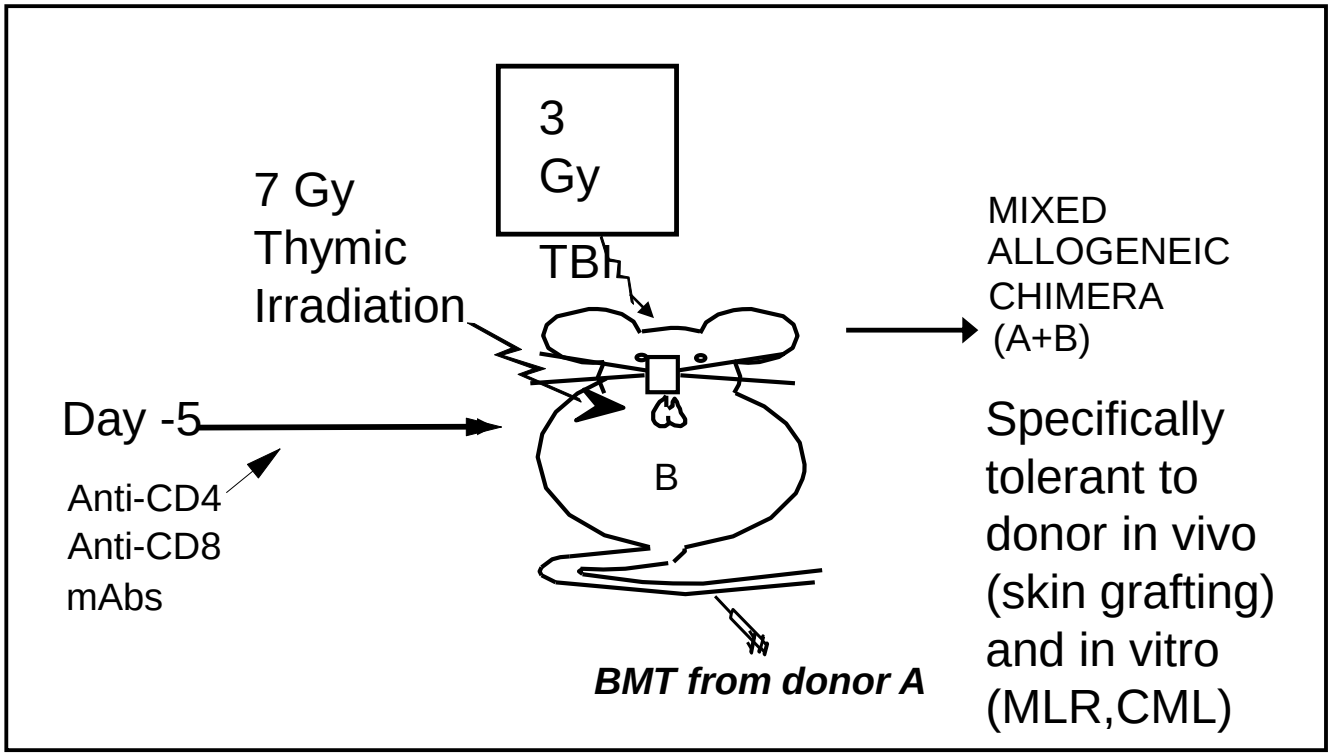
Hematopoietic cell transplantation/mixed chimerism comes closest to meeting these criteria

Hematopoietic Cell Transplantation for Tolerance Induction: Requirements

- Conditioning must be minimally toxic (non-myeloablative)
- Conditioning must overcome host-vs-graft T cell barrier to allow mixed chimerism induction *across HLA barriers*.
- Graft-vs-host disease (GVHD) unacceptable-must be reliably avoided.

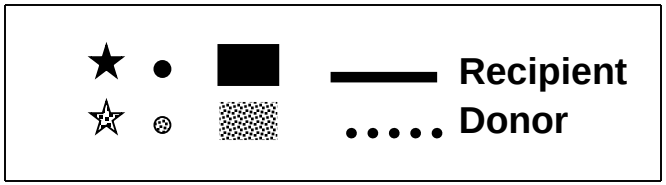
Non-Myeloablative Mixed Chimerism Protocol

Sharabi and Sachs, JEM 169:493, 1989



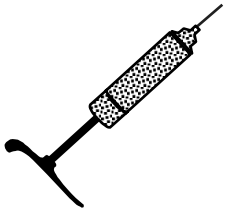
Pure Deletional Tolerance in Murine Mixed Chimeras Prepared with Non-Myeloablative Conditioning

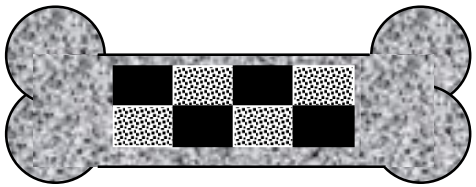
3) New T cells mature and become "educated" in the recipient thymus gland.



1) T cell depleting antibodies and thymic irradiation , or costimulatory blockade, prevent peripheral and intrathymic rejection of donor hematopioetic cells. Donor stem cells cells are given i.v.

4) The emerging T cells that repopulate the immune system are tolerant of donor and recipient. A donor organ is accepted and there is no GVHD.





Blood cells are a mixture of donor and host (mixed chimera)

2) Donor stem cells go to recipient marrow.
Stem cells in the marrow send progeny to the recipient thymus.

Pure deletional tolerance, with no long-term role for regulatory mechanisms, is observed when durable mixed chimerism is achieved with either:

- 1) Complete, global T cell ablation in the periphery and thymus. ;

  Sharabi JEM 1990; Tomita, JI 1994; Khan Transplantation 1996; Nikolic BBMT 2001

- 2) Specific deletion of pre-existing donor-reactive T cells in the periphery and thymus, without global depletion (e.g. BMT with costimulatory blockade).

Takeuchi, AJT 2004; Kurtz, Blood 2004; Fehr, EJI 2005; Fehr, JI 2008; Haspot, Blood 2008; Fehr, Blood 2010; Lucas, Blood 2011

However, Tregs Have Been Implicated in Several Mixed Chimerism Models in Which Complete Deletion of Donor-Reactive Cells is Never Achieved

- Bemelman et al, JI 160:2645, 1998
- Domenig et al, JI 175:51, 2005: CTLA4Ig,anti-CD40L, rapamycin, high dose marrow
- Bigenzhan et al, AJT 5:1237, 2005: CTLA4Ig, anti-CD40L, TBI
- Yamazaki et al, AJT 7:1710, 2007: DST, anti-CD154, high dose marrow

Clinical Trials of HSCT for Kidney Allograft Tolerance

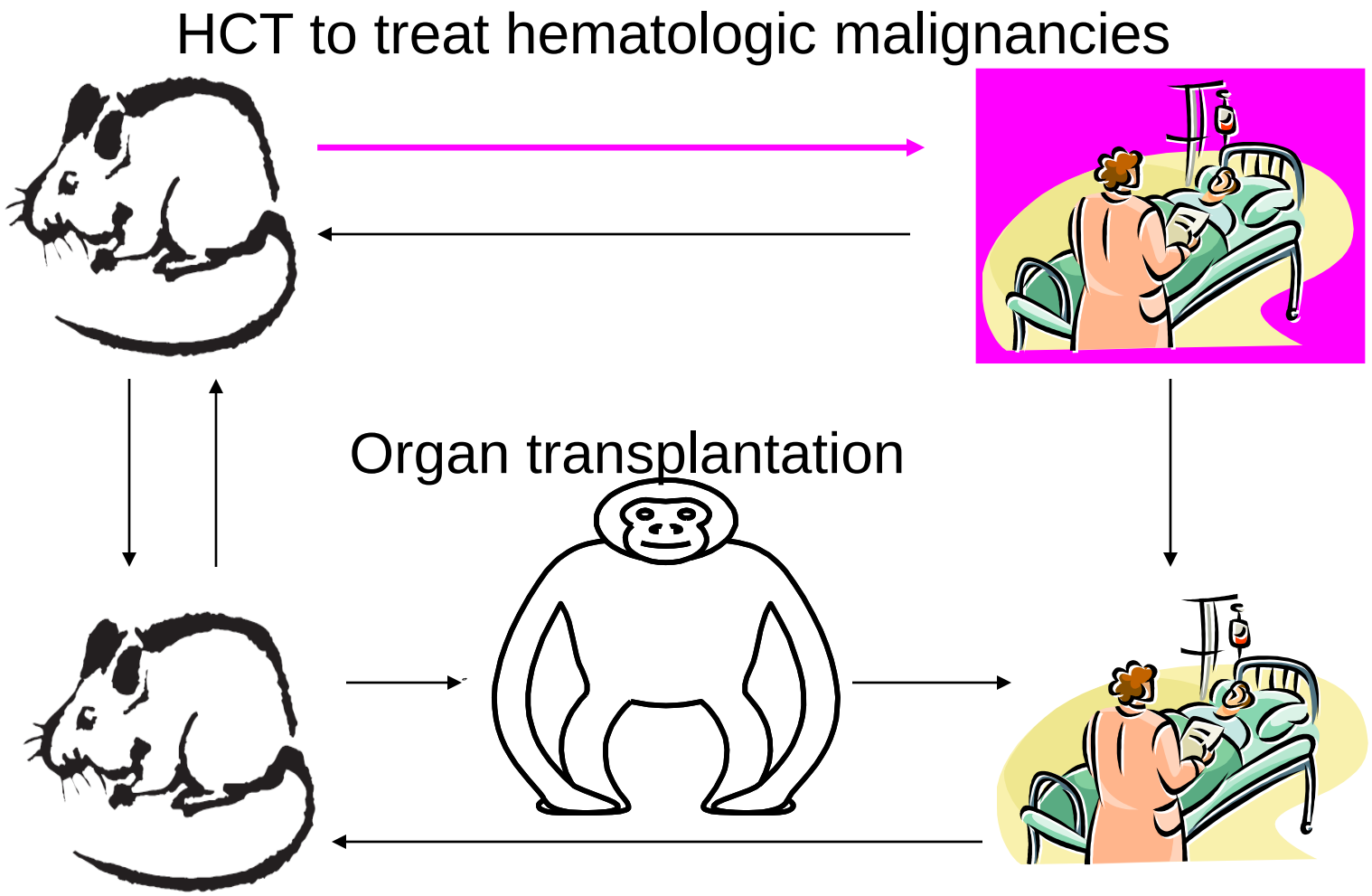
MGH: CTX/ATG or anti-CD2/TI +KTx: Tolerance in HLA-identical or **mismatched** transplants with transient (or durable) chimerism. Long (up to 18 yrs) follow-up.

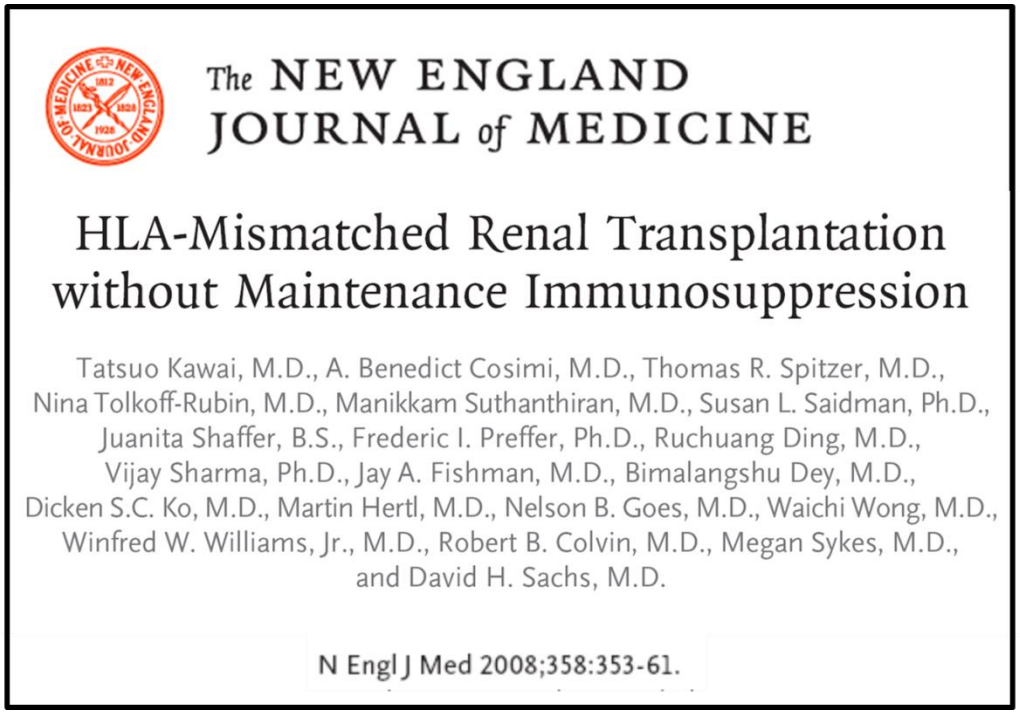
Northwestern: CTX (Pre-and post-tx)/Flu +BMT+ FC +KTx: Tolerance in HLA-**mismatched** full chimeras. 23/31 patients off immunosuppression. Tolerance only in durable chimeras. Significant GVHD and infectious complications. Now in Phase III trial.

Stanford: TLI/ALS/BMT +KTx: Tolerance so far only in HLA-identical transplants.

Samsung Medical Center: CTX/ATG/fludarabine/TI, rituximab: Transient mixed chimerism and i.s. discontinuation in 3/3 HLA-**mismatched** transplants. BK nephritis in 2.

Translational Studies Between HCT and Organ Transplantation



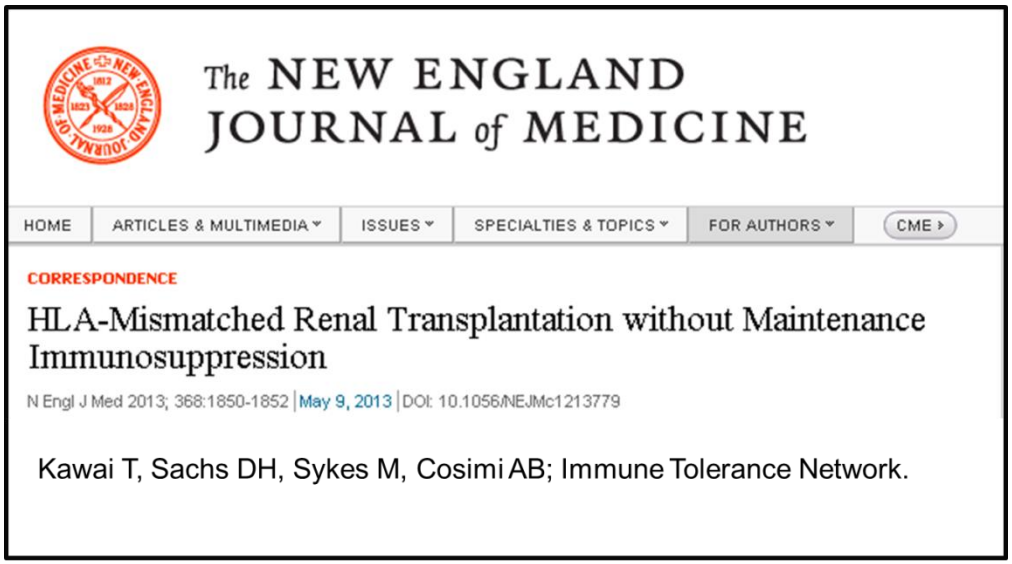


The NEW ENGLAND JOURNAL of MEDICINE

HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

Tatsuo Kawai, M.D., A. Benedict Cosimi, M.D., Thomas R. Spitzer, M.D., Nina Tolkoff-Rubin, M.D., Manikkam Suthanthiran, M.D., Susan L. Saidman, Ph.D., Juanita Shaffer, B.S., Frederic I. Preffer, Ph.D., Ruchuang Ding, M.D., Vijay Sharma, Ph.D., Jay A. Fishman, M.D., Bimalangshu Dey, M.D., Dicken S.C. Ko, M.D., Martin Hertl, M.D., Nelson B. Goes, M.D., Waichi Wong, M.D., Winfred W. Williams, Jr., M.D., Robert B. Colvin, M.D., Megan Sykes, M.D., and David H. Sachs, M.D.

N Engl J Med 2008;358:353-61.



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

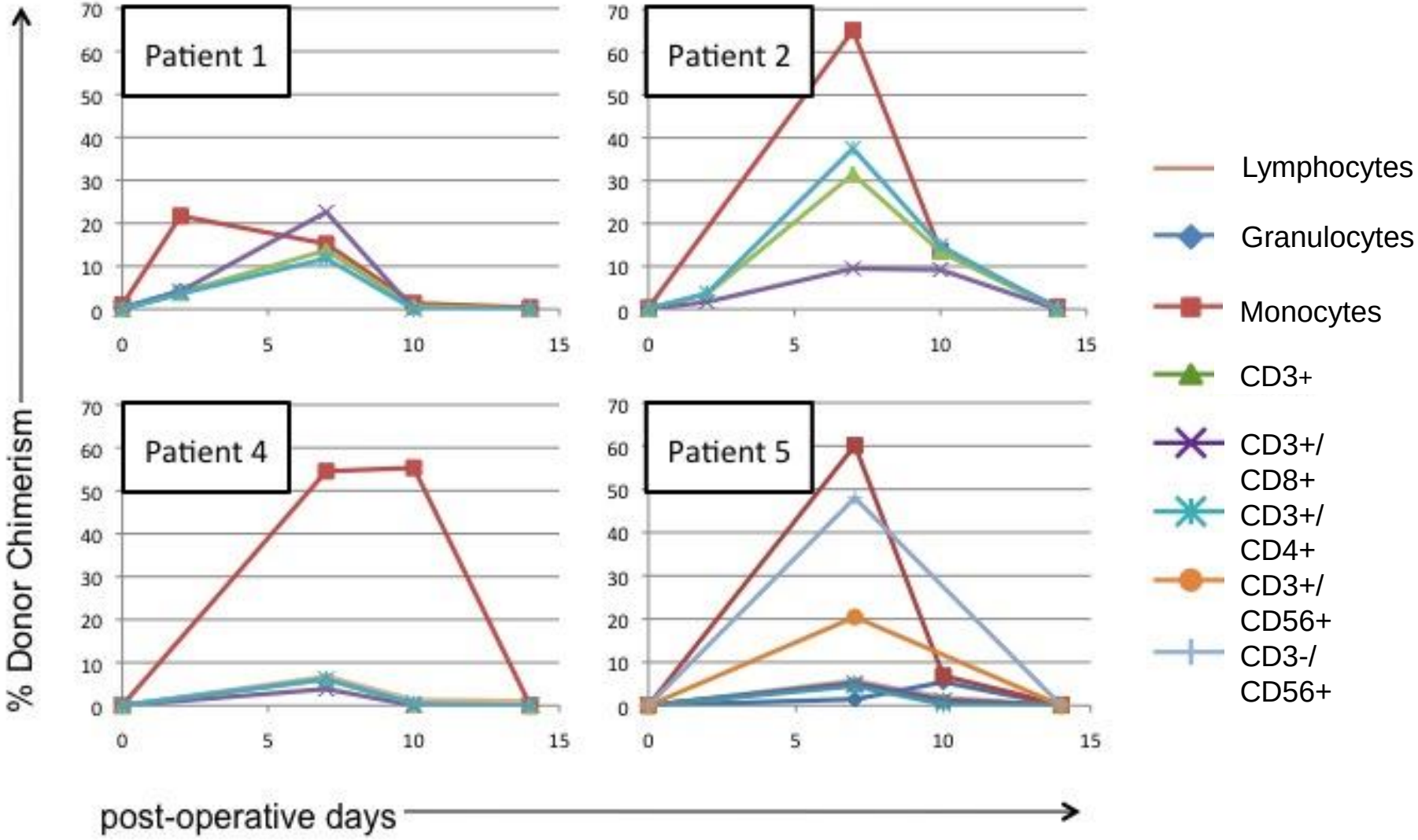
HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

N Engl J Med 2013; 368:1850-1852 | May 9, 2013 | DOI: 10.1056/NEJMc1213779

Kawai T, Sachs DH, Sykes M, Cosimi AB; Immune Tolerance Network.

(2013 - update on all 10 patients)

Chimerism is Transient in Recipients of CKBMT

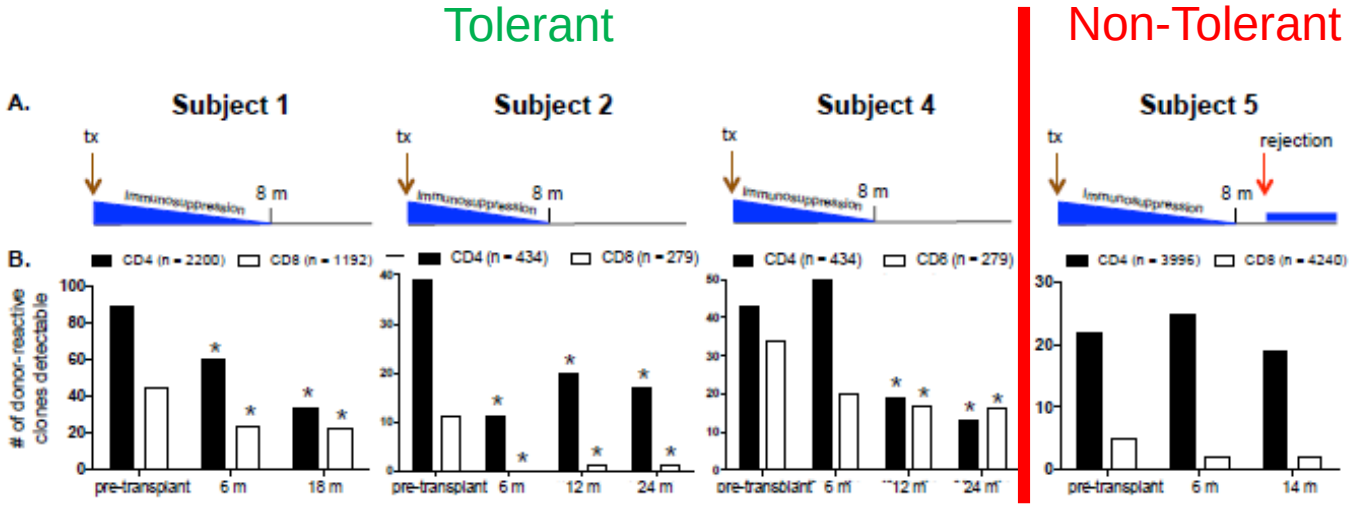


Locascio et al, Transplantation 90:1607, 2010

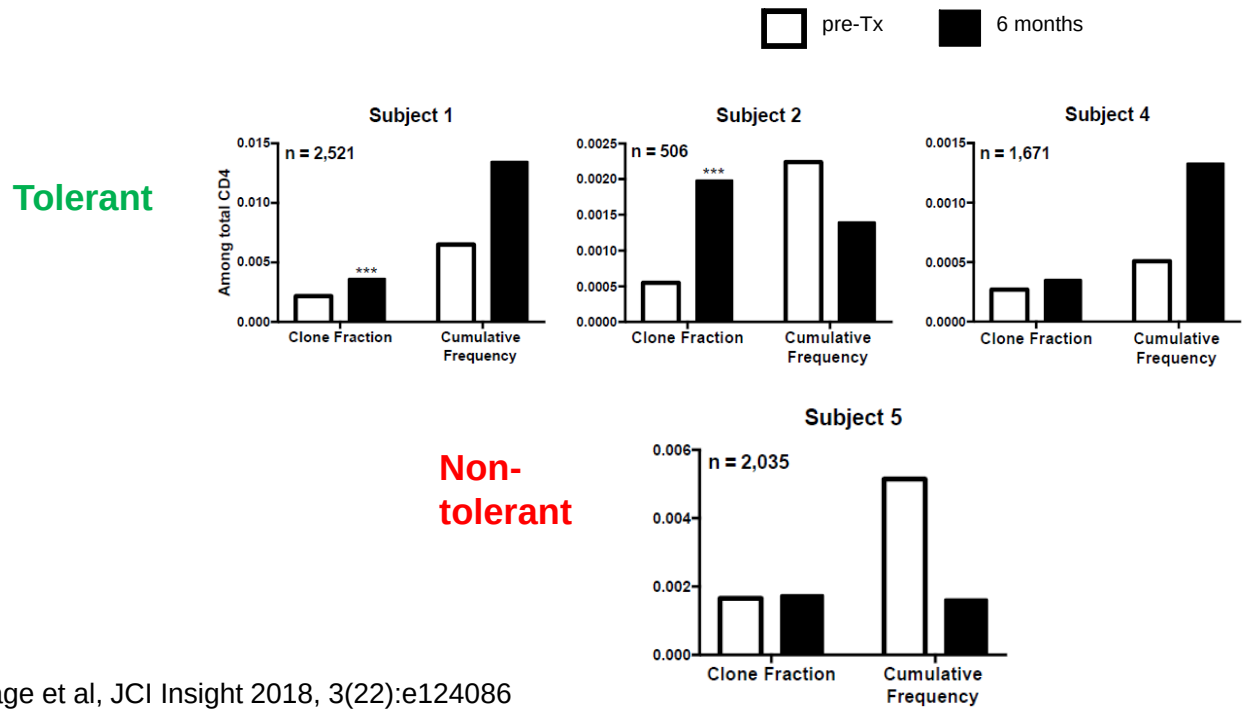
TRANSPLANTATION

Tracking donor-reactive T cells: Evidence for clonal deletion in tolerant kidney transplant patients

Heather Morris,[1]* Susan DeWolf,[1]* Harlan Robins,[2] Ben Sprangers,[1] Samuel A. LoCascio,[1] Brittany A. Shonts,[1] Tatsuo Kawai,[3] Waichi Wong,[1] Suxiao Yang,[1] Julien Zuber,[1] Yufeng Shen,[1†] Megan Sykes[1†]



Increased Circulating Donor-Specific Treg Clones (detected by activated B cell expansion method) at 6 Months Only in Tolerant Patients



T. Savage et al, JCI Insight 2018, 3(22):e124086

Summary: Mechanisms of Tolerance in Patients With Transient Chimerism Following CKBMT (MGH ITN Protocols)

- Early role for expanded donor-specific Tregs
- Long-term deletion of pre-existing donor-reactive T cells

Limitations of Transient Chimerism

- The kidney plays an important role in promoting tolerance (must be grafted with the BMT)
- Not all organs are tolerogenic like the kidney
- No success yet with regimen that would be relevant for cadaveric donation

A priority of the new program at Columbia has been the establishment of a non-human primate transplant program aimed at overcoming these limitations.

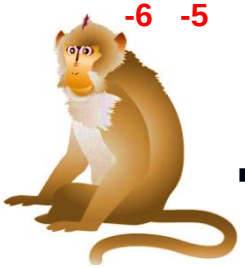
Non-human primate BMT + Treg protocol

Day 0: bone marrow transplantation

150 cGy TBI

-6 -5

-1



28 days CyA or

Ktx/ Skin (d+120-140)

Autologous Tregs 0,2,5,7

ATGAM 20mg/kg

aCD40L

day 0,2 20mg/kg

Day 5,9,12 10mg/kg

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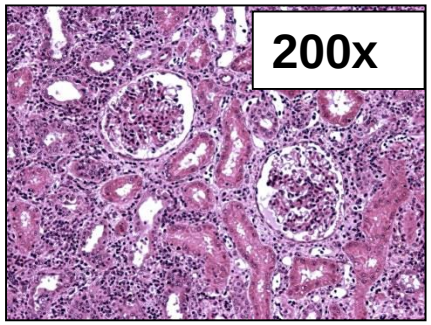
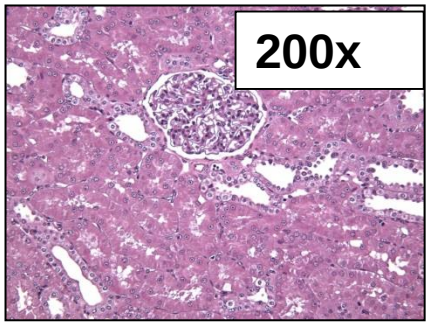
BMT plus Treg cell recipient is tolerant to donor kidney transplanted 4 months post-BMT

No Tregs: Acute cellular rejection



Tregs: No evidence of rejection



Duran-Struuck et al, Transplantation 2017, 101:274

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Summary

Treg infusion resulted in several "first time" outcomes, without GVHD:

- Multilineage chimerism lasting 1 year
- T cell chimerism
- Acceptance of a donor kidney grafted after a marked delay (4 months)
- Prolongation of donor skin grafted at 4 months

These results demonstrate that the combination of a low-intensity conditioning regimen and Tregs can achieve more robust tolerance than has ever been seen previously. This tolerance does NOT depend upon the presence of the donor kidney and therefore should be applicable to other types of transplants.

Relevance to Regenerative Medicine

- Several groups are working on the development of pluripotent hematopoietic stem cells from human pluripotent stem cells.
- Advances will continue to be made in the achievement of durable mixed chimerism with relatively non-toxic conditioning regimens.
- With success in the two areas above, off-the-shelf PSC-derived donor HSCT can be used to achieve tolerance for organs and tissues derived from the same PSCs.
- In my view, this approach is optimal.

Concerns About Cell Engineering to Avoid PSC-Derived Graft Rejection

- HLA-deficient grafts would be subject to NK cell-mediated rejection
- HLA-deficient grafts would evade T cell immunity. Consequences: 1) loss of tumor surveillance mechanism; 2) inability to protect graft from infection.
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