Mass General Brigham

Immune Tolerance Through Combined Bone Marrow and Organ Transplantation

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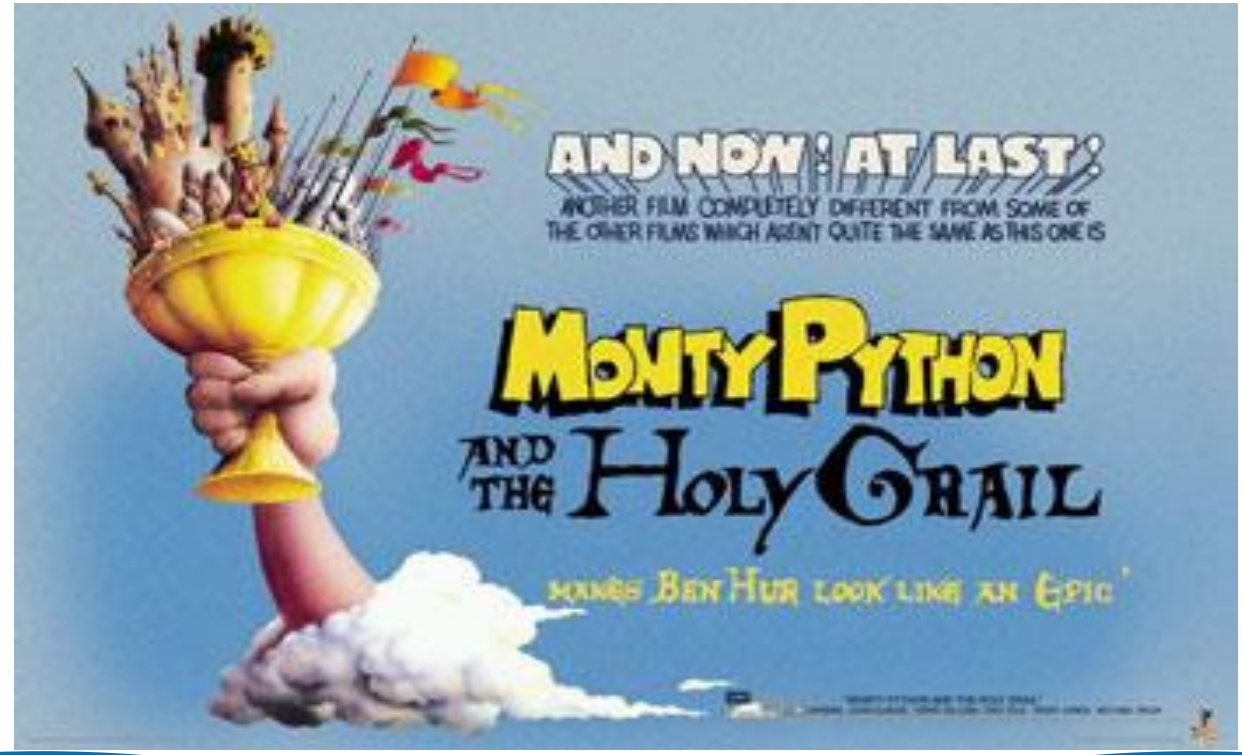
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School

Disclosures

BluebirdBio (DSMB member)
Qihan Biotech (SAB member)
Syneos Health (DSMB and Adjudication Committee member)
Ossium Health (SRC member)

The Holy Grail of Transplantation



BMT

Separation of GVHD and GVL

Organ Transplantation

Induction of specific tolerance

Immune Tolerance

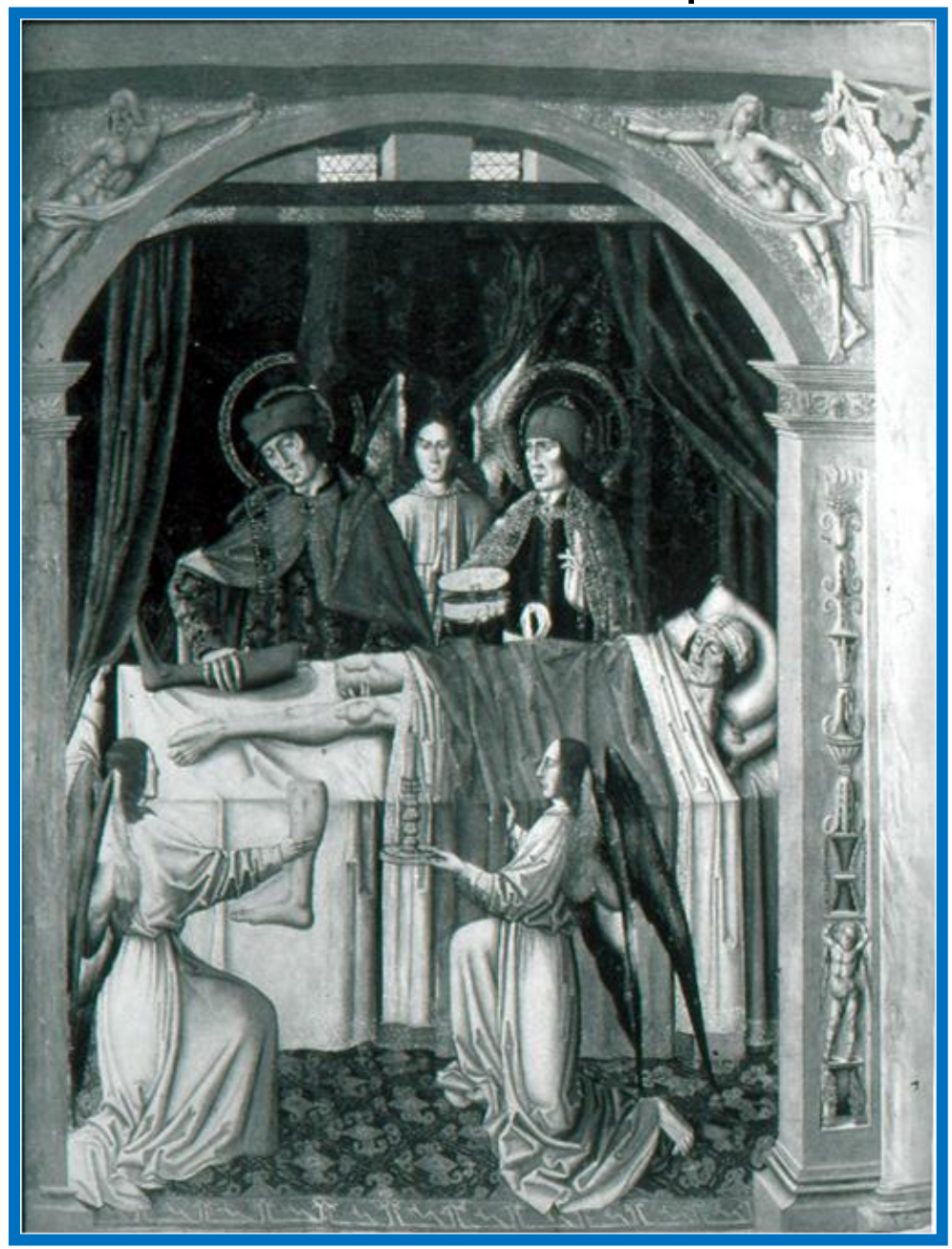
The absence of a destructive immune response after organ transplantation without systemic immunosuppression

Specific Tolerance

Preservation of third party immunity

Transplantation: An Historical Perspective

First Known Transplant

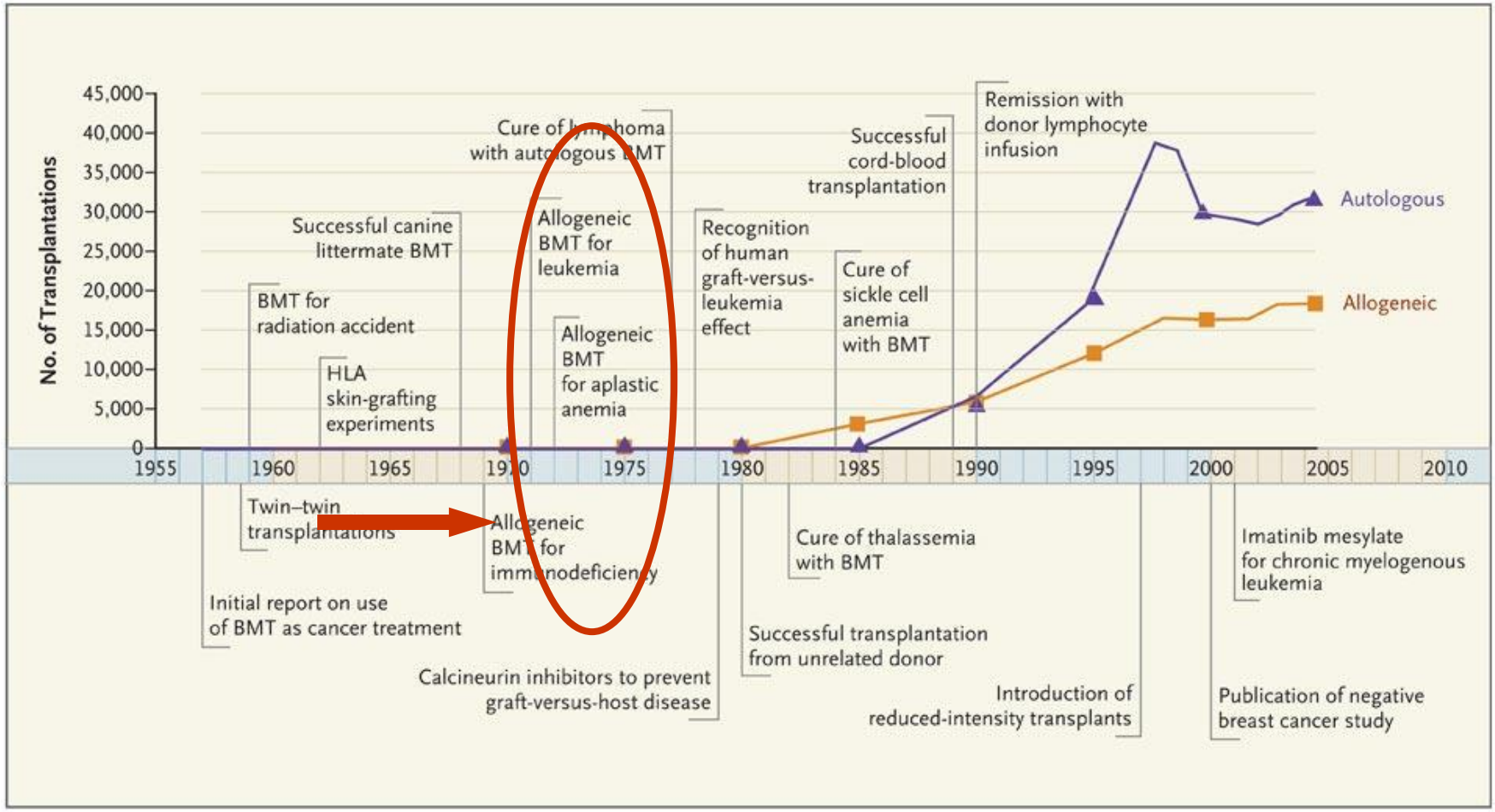


Gordon R. *The Alarming History of Medicine,*
St Martin's Press, NY 1993

First Successful Human Kidney Transplantation
Peter Bent Brigham Hospital - 1954

- Identical twin donor
- No post-transplant immunosuppression
- Feasibility, technical aspects established

Bone Marrow Transplantation: A Brief History



Appelbaum F. *N Engl J Med* 2007;357:1472-1475


Newsweek
DECEMBER 18, 1967 50c
NEW HEARTS FOR OLD
The Promise and Perils of
TRANSPLANT SURGERY
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LOYOLA COLLEGE LIBRARY
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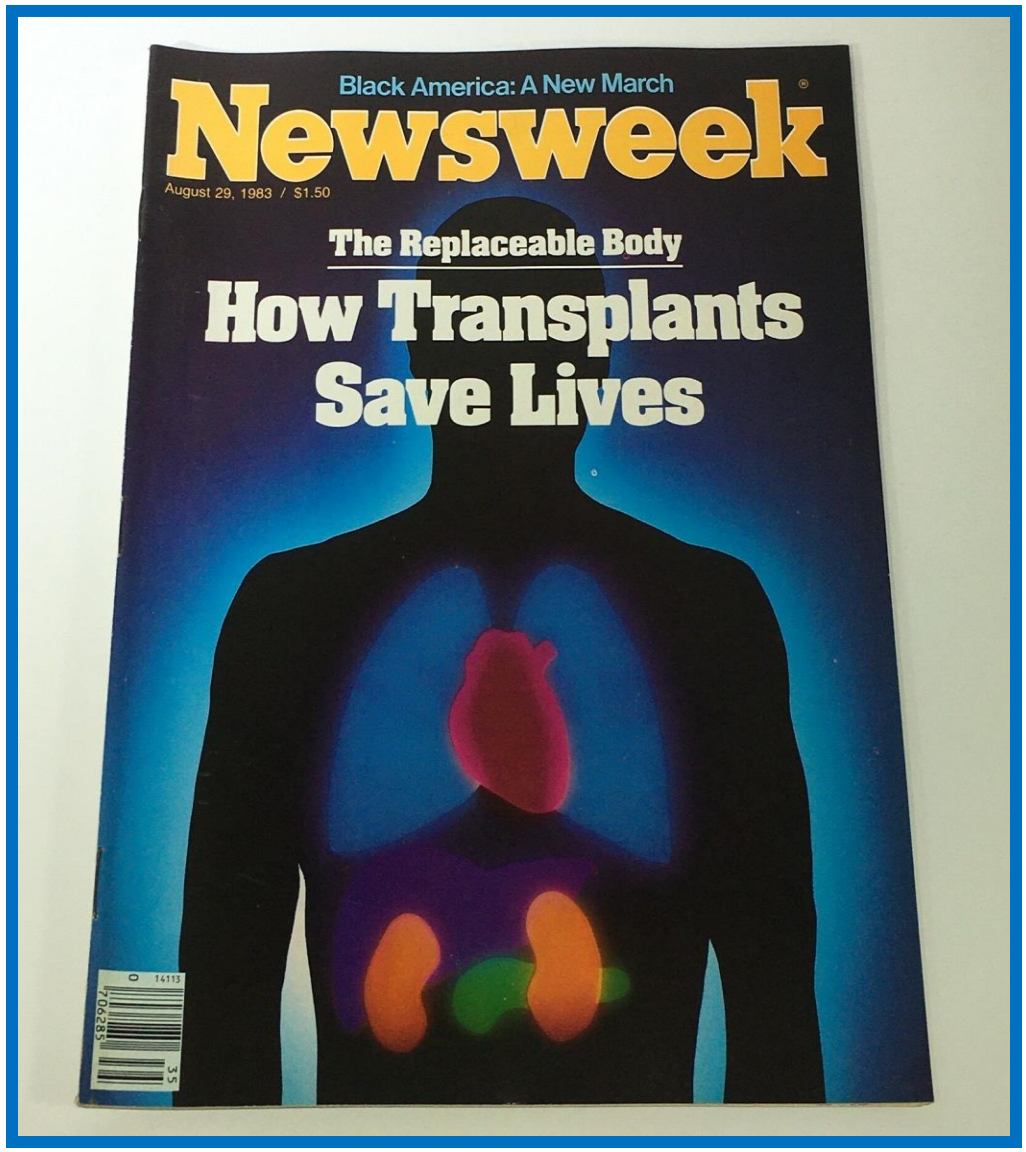
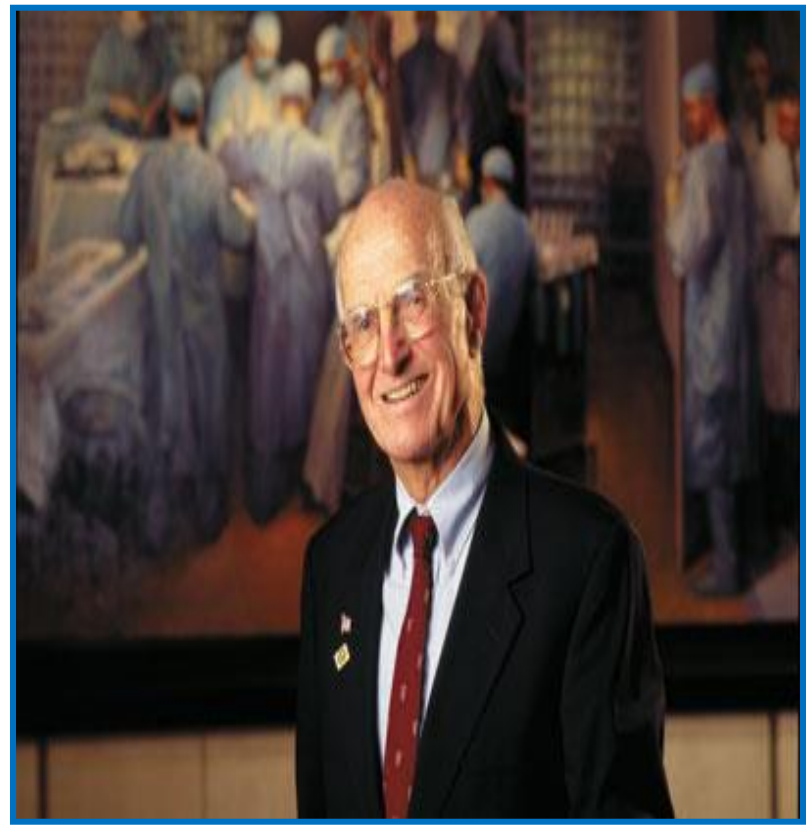

Black America: A New March
Newsweek
August 29, 1983 / $1.50
The Replaceable Body
How Transplants Save Lives

Dr E. Donnall Thomas (1920-2012)

Dr Joseph Murray (1919-2012)



Co-Awardees of the Nobel Prize in Medicine in 1990

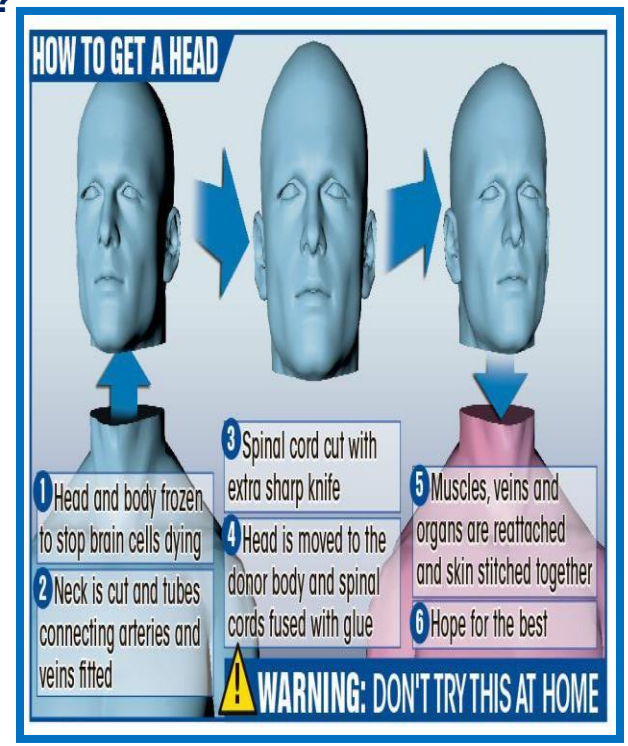
ADVANCES IN ORGAN TRANSPLANTATION

Has Dr. Sergio Canavero Already Performed a Human Head Transplant?
By the end of 2017, Italian doctor Sergio Canavero planned to carry out a highly controversial procedure: the first head human transplant between an anonymous recipient and a "brain-dead" body donor.

***Second Nexus* 1/18/18**

The World's First Head Transplant a Success After a Nineteen-Hour Operation? Reports that the world's first successful human head transplant has taken place in South Africa are fake news.

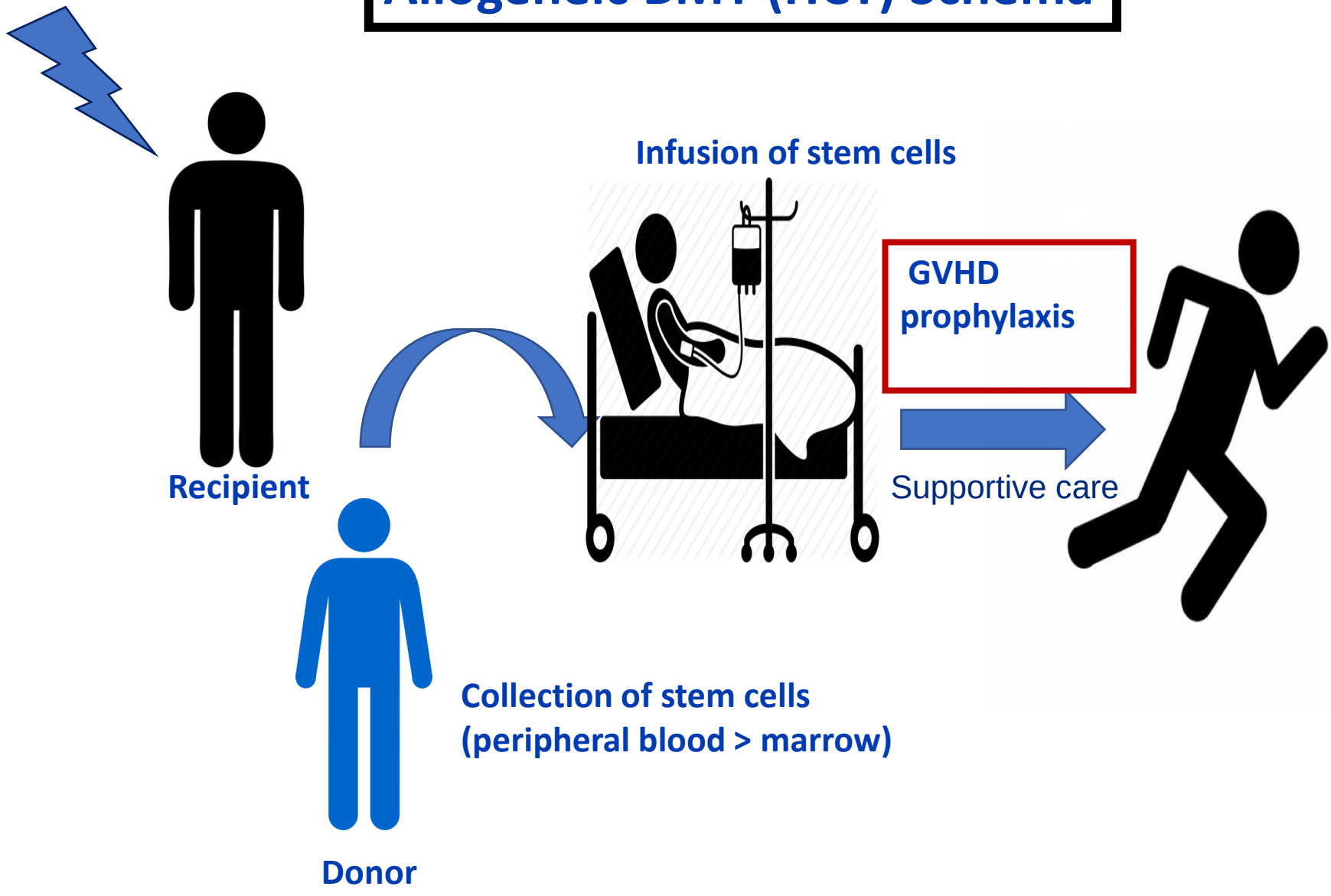
Good Morning Britain April 9, 2019



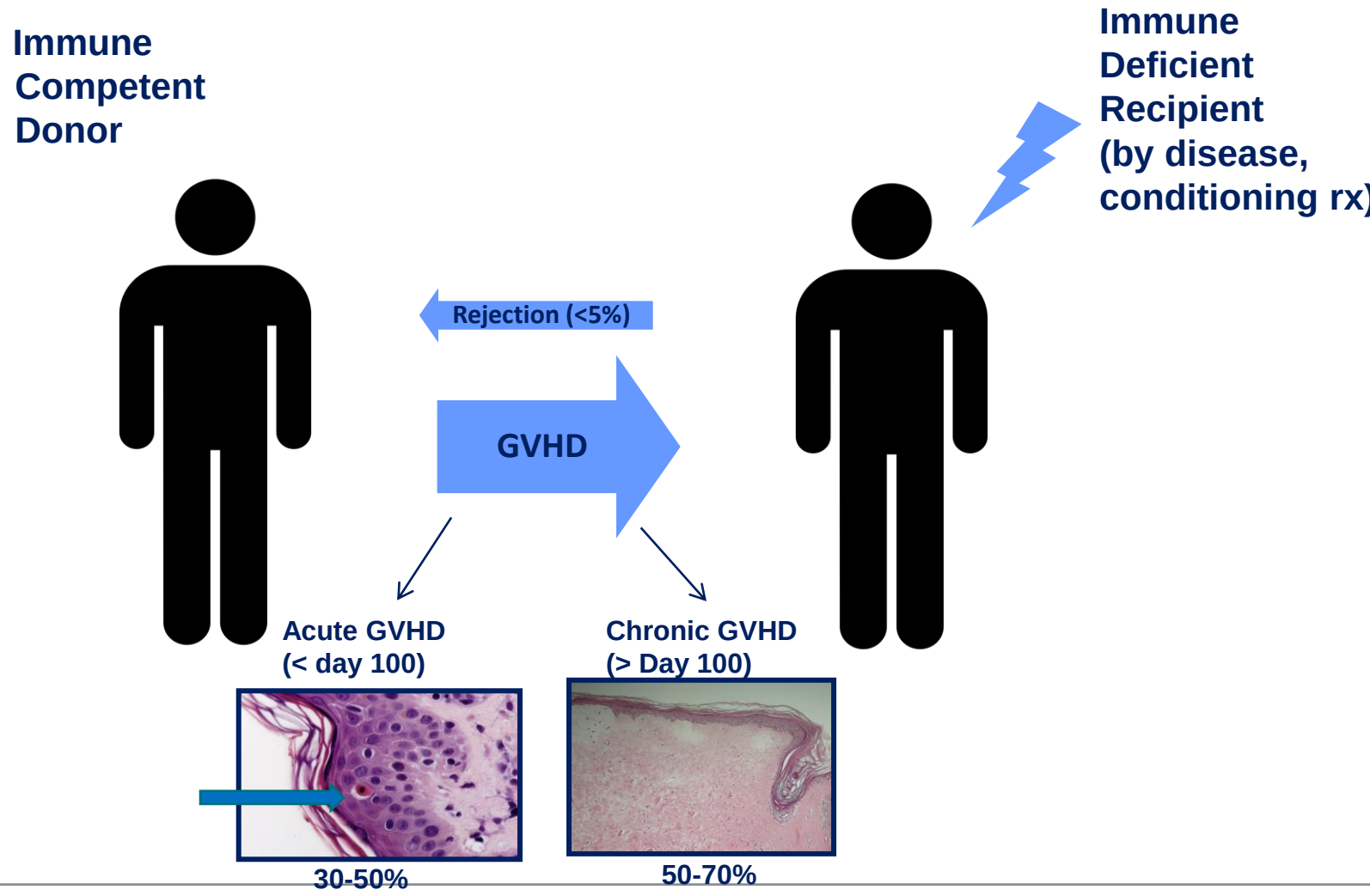
Not Every Cloud Has a Silver Lining

Principles of Transplantation and the Concept of Immune Vectors

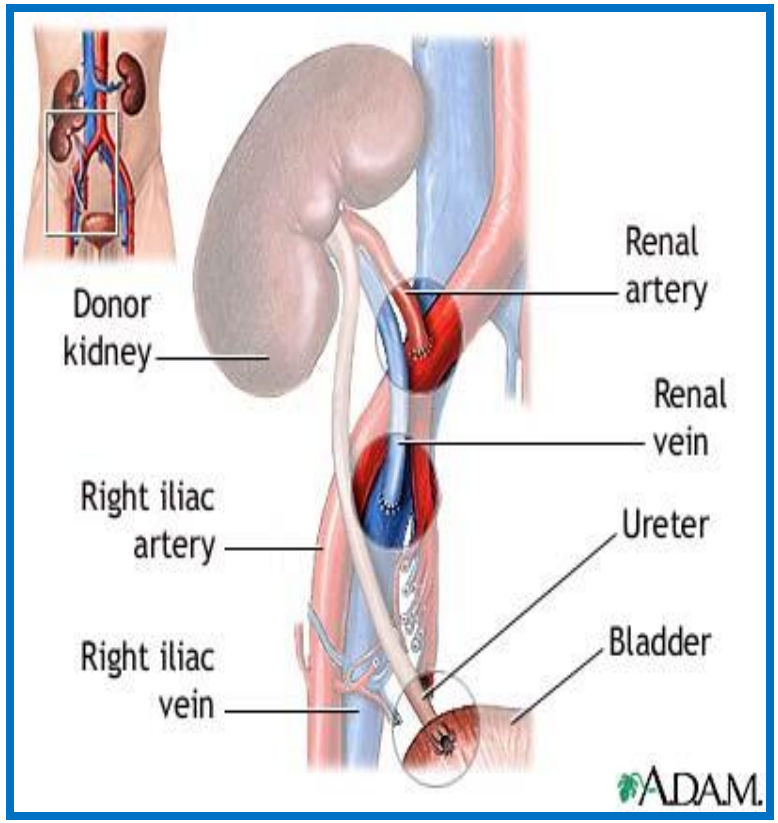
Allogeneic BMT (HCT) Schema



Hematopoietic Cell Transplantation (HCT) and the GVH Vector



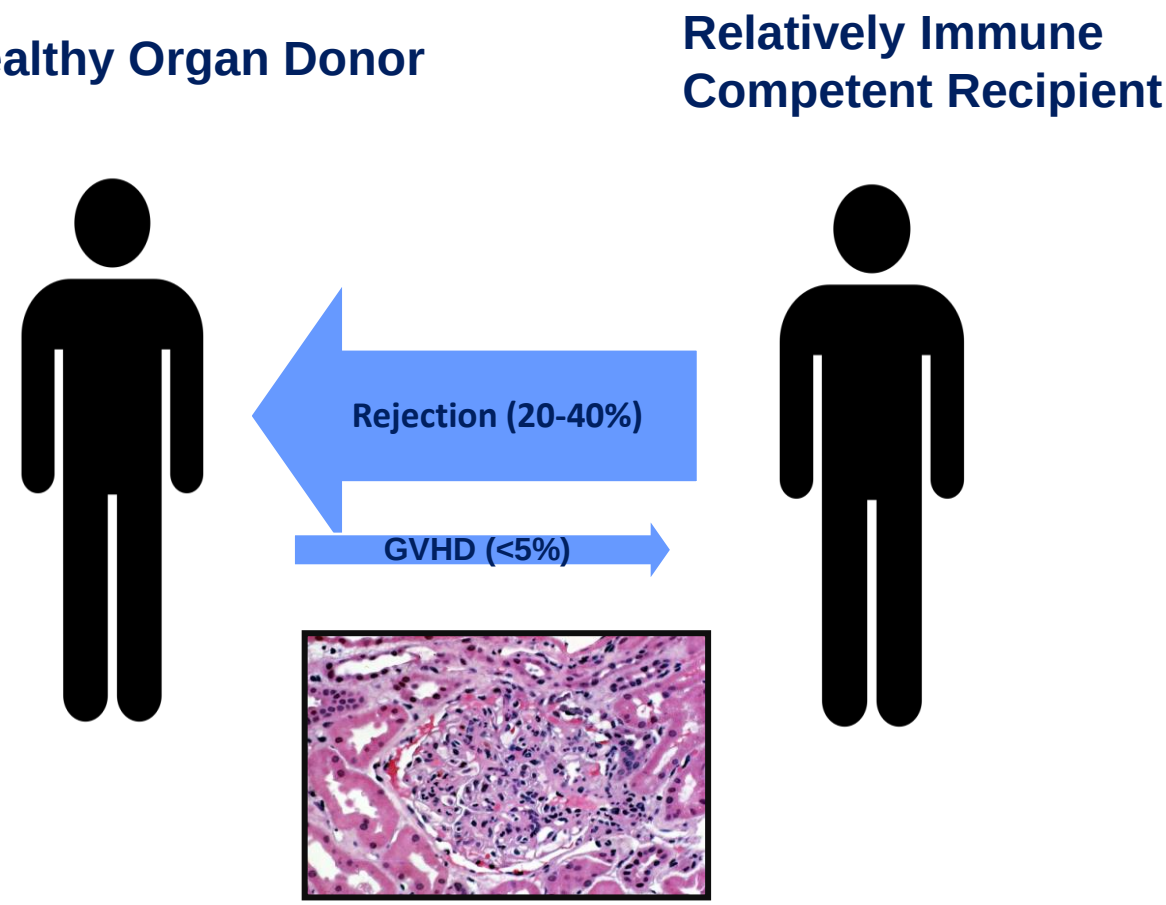
Organ (Kidney) Transplantation



Post-transplant immunosuppression

- Corticosteroids
- CNI (cyclosporine or tacrolimus)
- MMF
- ATG
- Belatacept

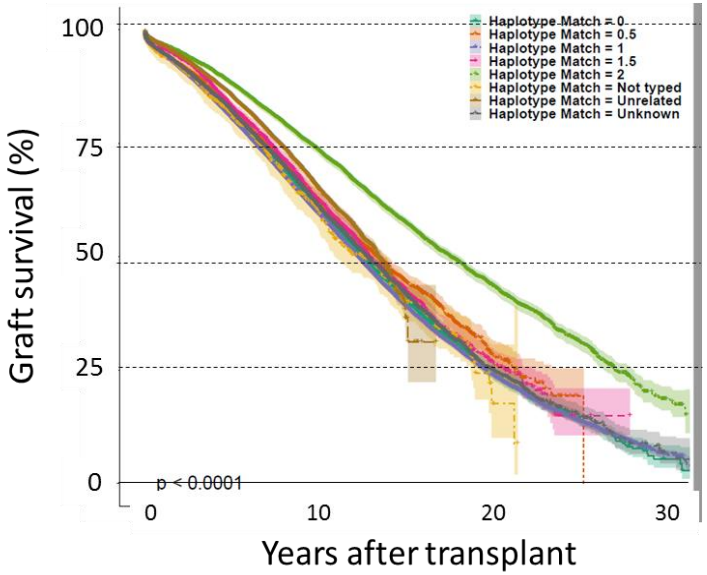
SOT and the HVG Vector

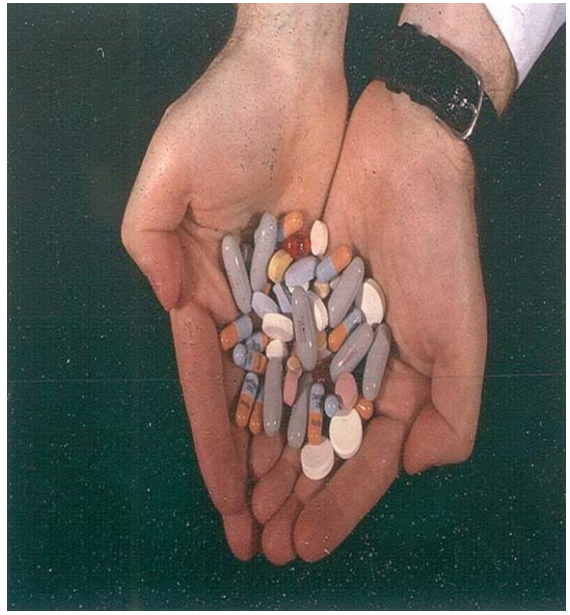


Why Pursue Tolerance?

Results of living donor kidney transplantation (HLA matched or mismatched) from UNOS data

Haplotype match 2= fully matched
Haplotype match 1=one haplotype match
Haplotype match 0= full mismatch





Courtesy of Nahel Elias, MD

One patient's daily pill burden

Side Effects of Lifelong Immunosuppression

- Opportunistic infection
- Nephrotoxicity
- Hypertension
- Hyperlipidemia
- Cataracts
- Osteoporosis/osteonecrosis
- Growth retardation
- Hirsutism
- Cushingoid habitus
- 2^0 malignancy

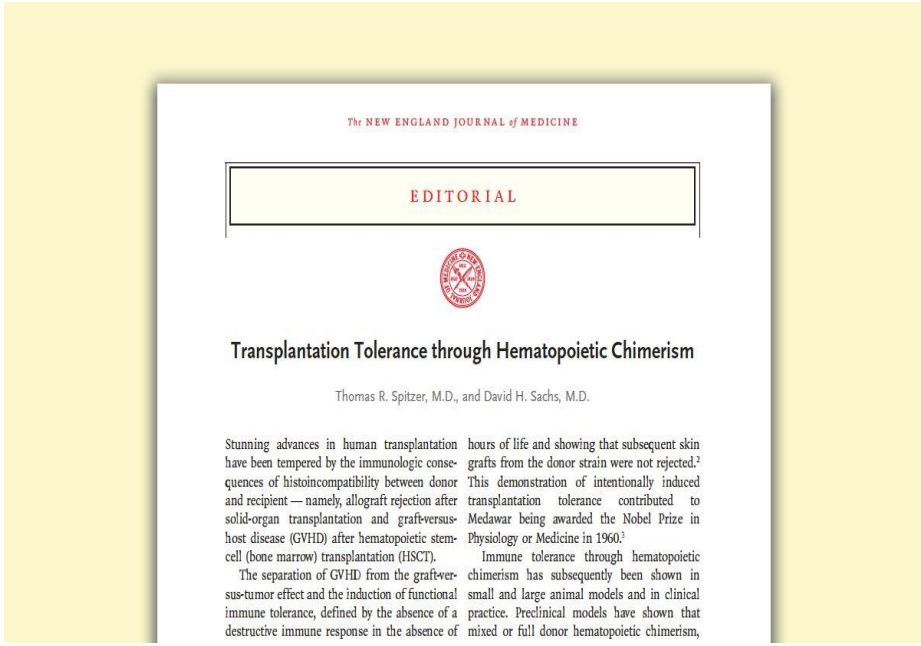
↓

Reduction of immunosuppression

↓

Allograft rejection or GVHD

Pathways to Transplantation Tolerance



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Transplantation Tolerance through Hematopoietic Chimerism

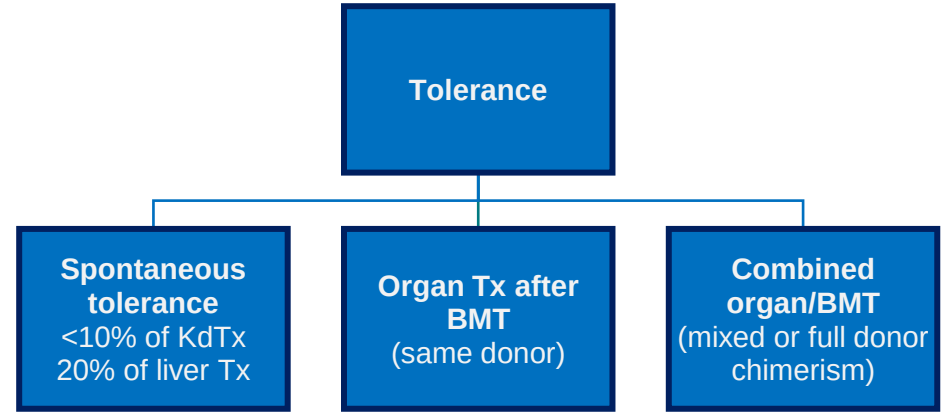
Thomas R. Spitzer, M.D., and David H. Sachs, M.D.

Stunning advances in human transplantation have been tempered by the immunologic consequences of histoincompatibility between donor and recipient — namely, allograft rejection after solid-organ transplantation and graft-versus-host disease (GVHD) after hematopoietic stem-cell (bone marrow) transplantation (HSCT).

The separation of GVHD from the graft-versus-tumor effect and the induction of functional immune tolerance, defined by the absence of a destructive immune response in the absence of hours of life and showing that subsequent skin grafts from the donor strain were not rejected.[2] This demonstration of intentionally induced transplantation tolerance contributed to Medawar being awarded the Nobel Prize in Physiology or Medicine in 1960.[3]

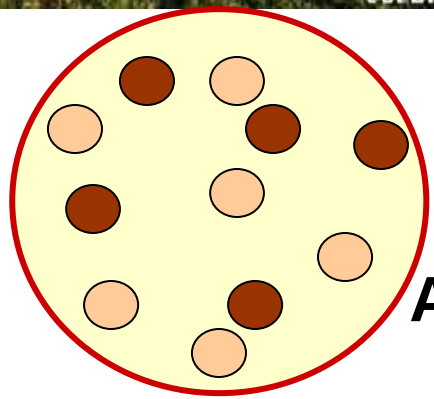
Immune tolerance through hematopoietic chimerism has subsequently been shown in small and large animal models and in clinical practice. Preclinical models have shown that mixed or full donor hematopoietic chimerism,

N Engl J Med 2022; 386:2332-2333

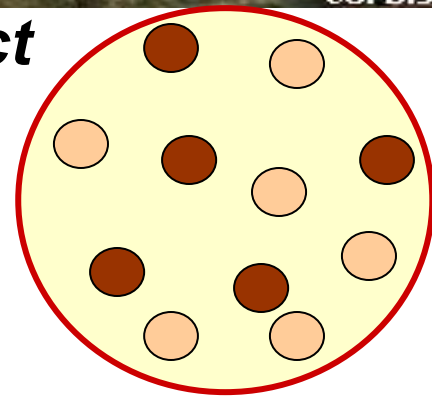


1945: Owen's Observation in Fraternal Bovine Twins

PLACENTA



"a mixture of two distinct types of erythrocytes"



A naturally occurring state of mixed chimerism

1951: Medawar showed that these chimeric twins were tolerant to skin grafts from their twin sibling

Can mixed chimerism be induced in man as a platform for tolerance induction?

Yes…..Although reliably induced in preclinical small and large animal models.....

Stable mixed chimerism has been difficult to achieve clinically, particularly across HLA barriers

Transient mixed chimerism may be sufficient to induce sustained specific tolerance

Full donor chimerism may be associated with GVHD but is likely the means to an optimal GVT effect

Can mixed chimerism be induced in man as a platform for tolerance induction?

Yes…..Although reliably induced in preclinical small and large animal models……..

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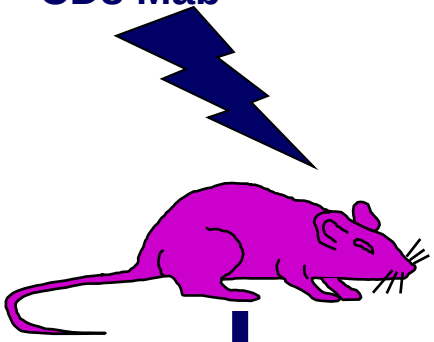
Transient mixed chimerism may be sufficient to induce sustained specific tolerance

Full donor chimerism may be associated with GVHD but is likely the means to an optimal GVT effect

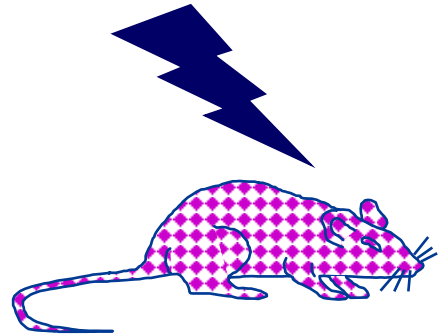
Conversion to full chimerism in CY/anti-T-cell mAb induced murine chimeras after administration of delayed DLI

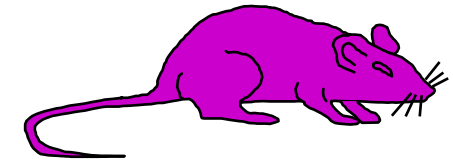
Cytoxan, Thymic XRT
Anti-CD4 and CD8 Mab



MHC mismatched BMT

DLI





Mixed chimerism

- Absence of GVHD
- Platform for DLI
- Donor specific tolerance

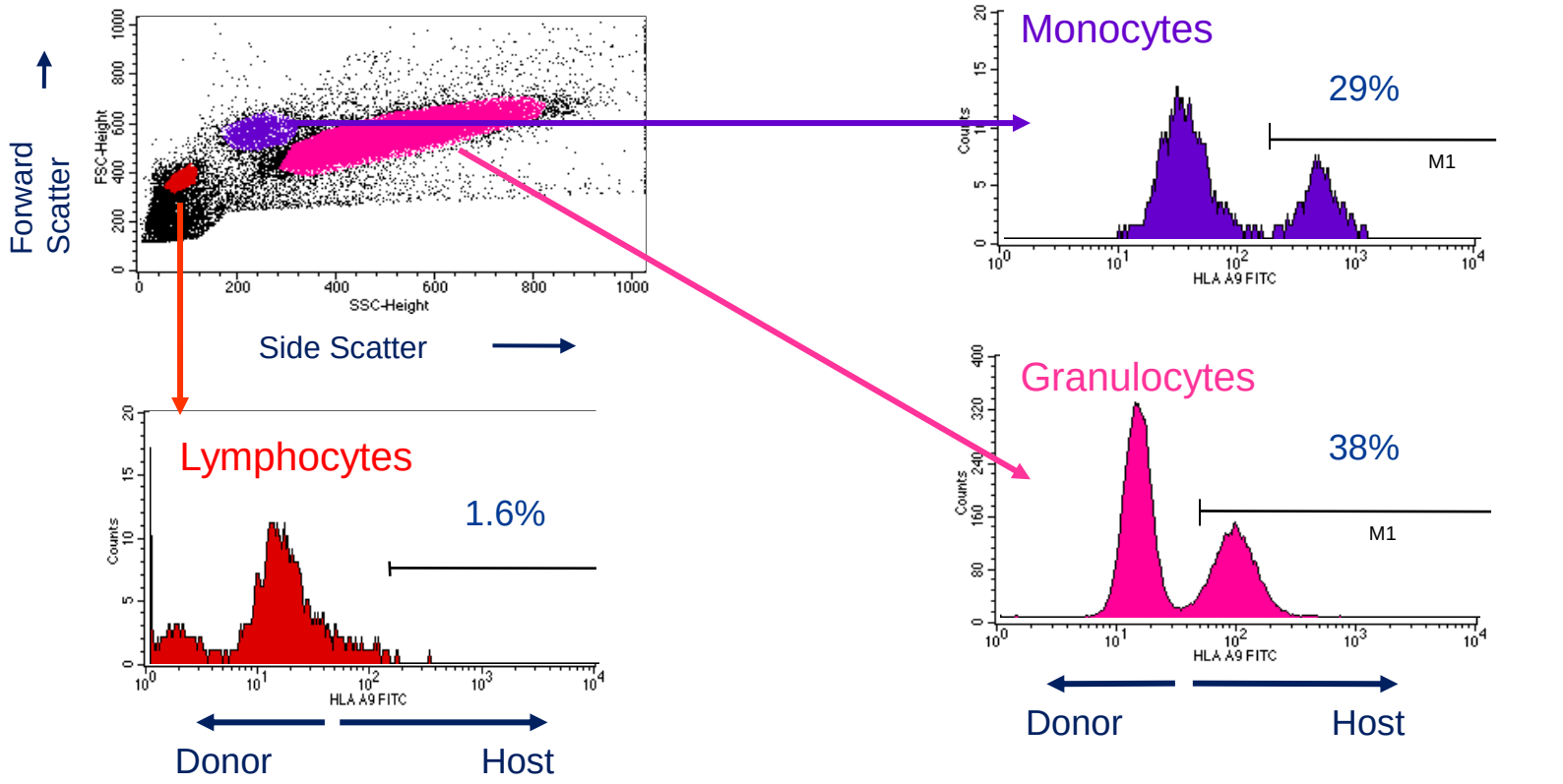
Full donor chimerism

- Lymphohematopoietic GVHR
- Absence of GVHD
- Potent GVL effect (host APCs)

Pelot MR…..Sykes M. BBMT 1999;5:133

Sustained Mixed Chimerism at 2 Years in a Patient Who Received Non-Myeloablative Conditioning and HLA Haploidentical Donor Allogeneic BMT

Sykes M…….Spitzer TR. *Lancet*, 1998



Clinical Tolerance Approaches

Reasons for Considering Tolerance Approaches

Hematologic Malignancy

- Pts with myeloma or other malignancy and ESRD are not eligible for kidney or bone marrow transplantation
- Tolerance through chimerism
- GVHD acceptable if not severe
- Optimal GVT effect likely mediated through sustained full donor chimerism

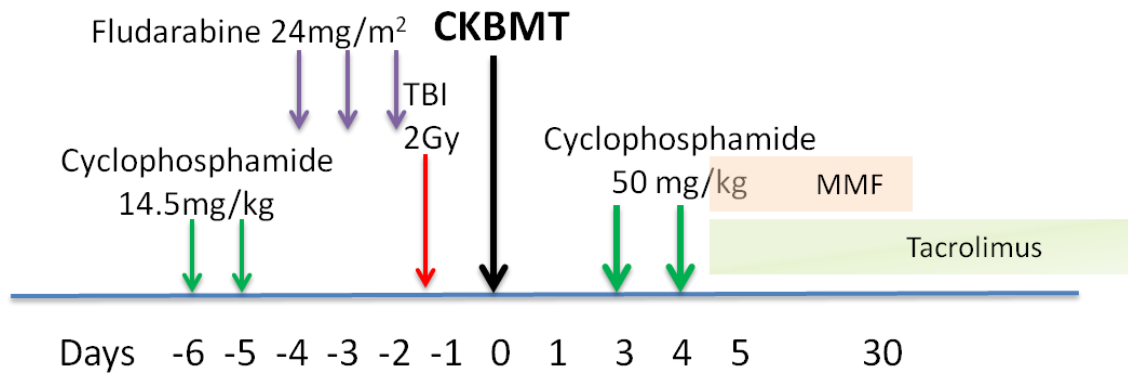
No Malignancy

- Avoidance of long term immunosuppression
- Transient mixed chimerism only to avoid GVHD
- Need for peripheral mechanisms for durable tolerance

Patient #1

- 55 y/o female with kappa light chain multiple myeloma and renal failure
- 9/22/98 – combined HLA matched bone marrow + kidney transplant
- Multi-lineage mixed chimerism for 105 days
- Cyclosporine stopped on day 73
- No GVHD or renal allograft rejection
- Subclinical relapse of myeloma in 2012 treated with multiple DLI (none since 2/17)
- Creatinine in 3/23: 0.80 mg/dl
- Went to college and received two degrees in art history
- Applied for a position in the Peace Corps but was rejected!

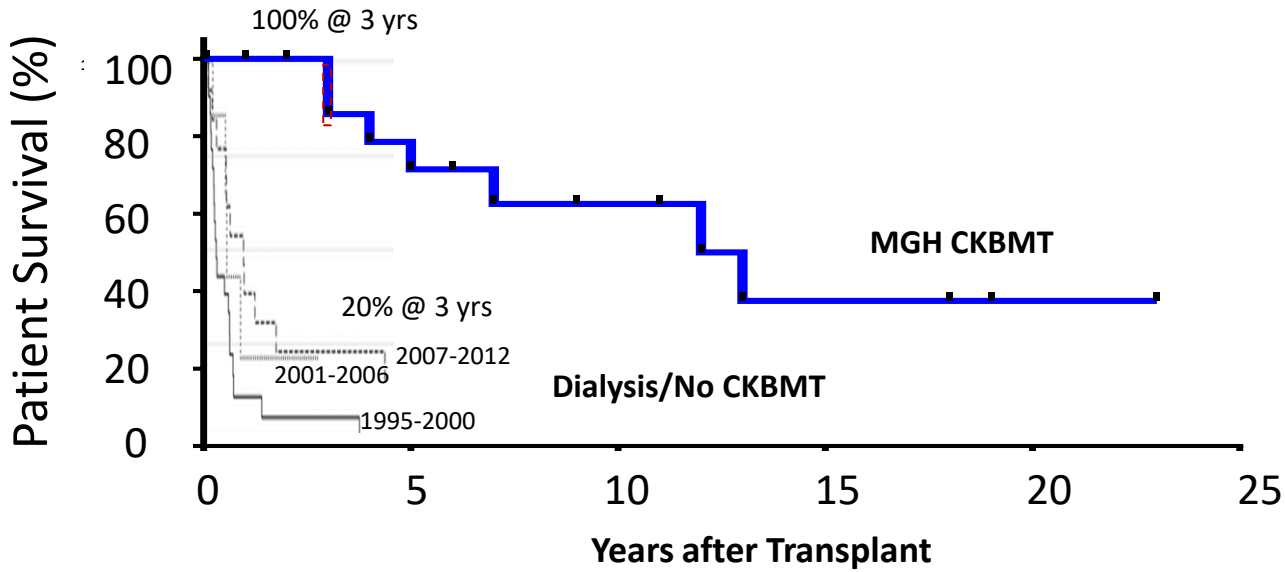
Current MGH CKBMT Transplantation for HM with ESRD



Eligibility Criteria

- Hematologic malignancy
- Related HLA-matched or haploidentical donor
- Acceptable organ function, performance status
- Insurance coverage

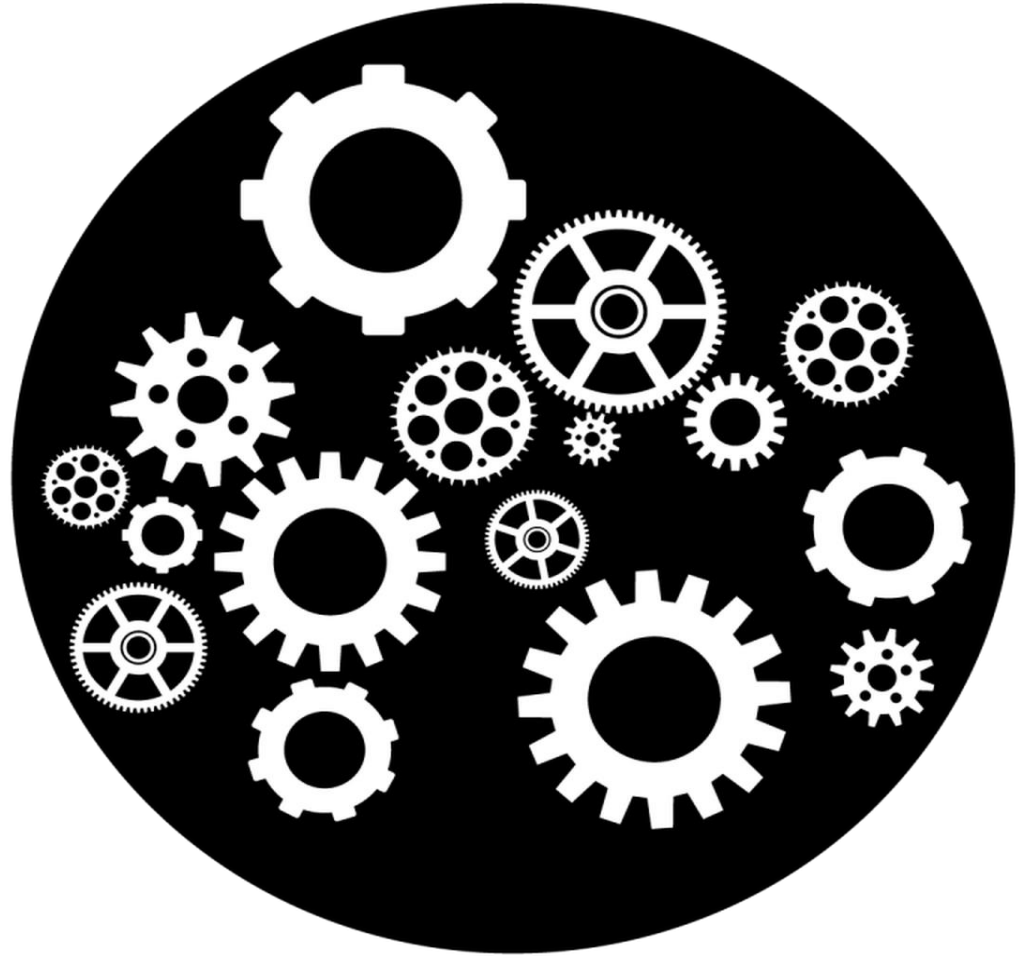
Survival of dialysis dependent myeloma patients vs. CKBMT



British Journal of Haematology
Volume 165, Issue 6, pages 890-891,

Courtesy of Tatsuo Kawai, MD

Shifting Gears: From ESRD With Malignancy to ESRD Without Malignancy



Reasons for Considering Tolerance Protocols

Hematologic Malignancy

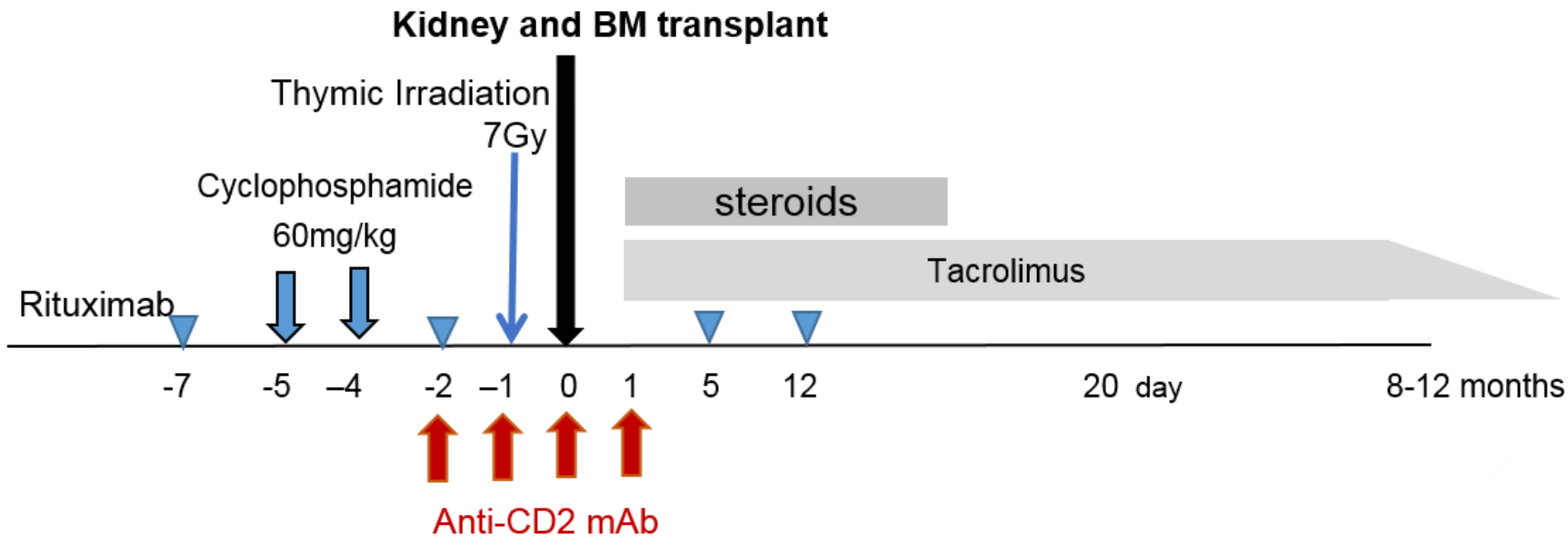
- Pts with myeloma and ESRD not eligible for renal or bone marrow transplantation
- Tolerance through chimerism
- GVHD acceptable if not severe
- Optimal GVT effect likely mediated through sustained full donor chimerism

No Malignancy

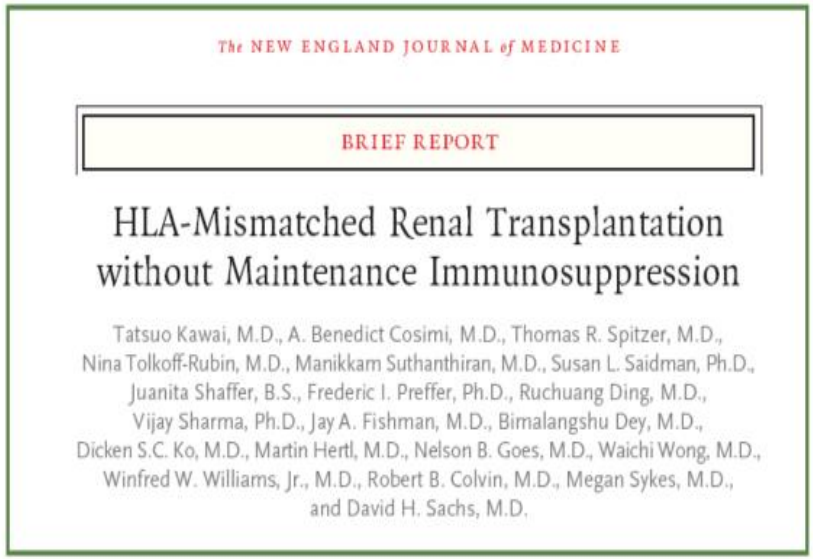
- Freedom from long term immunosuppression is the sole goal
- GVHD is not acceptable
- Transient mixed chimerism sufficient for tolerance induction

Renal Allograft Tolerance Can Be Induced By Transient Chimerism

MGH Tolerance Approach



Early Tolerance Outcomes



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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 358;4 January 24, 2008

7/10 patients off IST at 5 years

Principal problems:

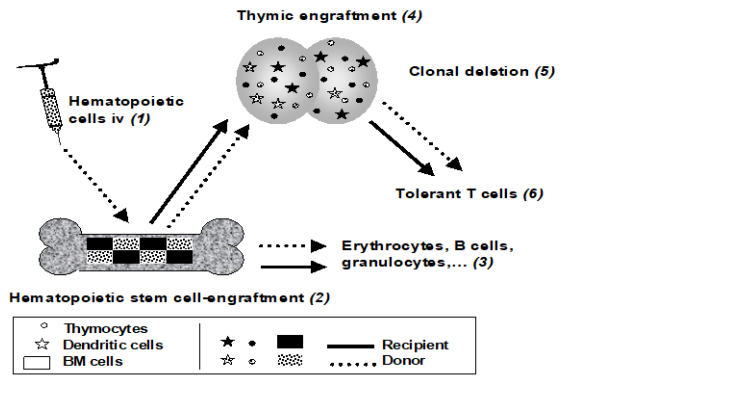
- Short duration of chimerism
- Cytokine release syndrome during chimerism transition
- Late humoral rejection in 4 patients
- Loss of availability of siplizumab (MEDI-507)

Mechanism(s) of Tolerance Induction

Central

Abundant pre-clinical evidence for role of intra-thymic mixed chimerism

Role of central tolerance in patients with transient chimerism less clear

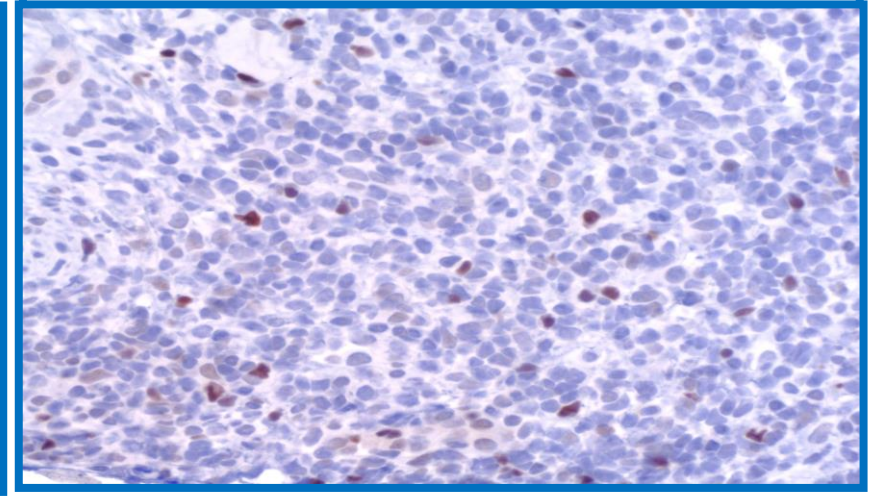


Peripheral

Increased intra-graft and peripheral Foxp3CD4+CD25+ donor specific T-regulatory cells

Gradual deletion of donor-reactive T cells

Role of the kidney allograft in tolerance induction



Wekerle T, Sykes M. Transplantation 1999; 68: 459-467

Sykes M, Griesemer AD. Bone Marrow Transplant 2019; 54: 815-821

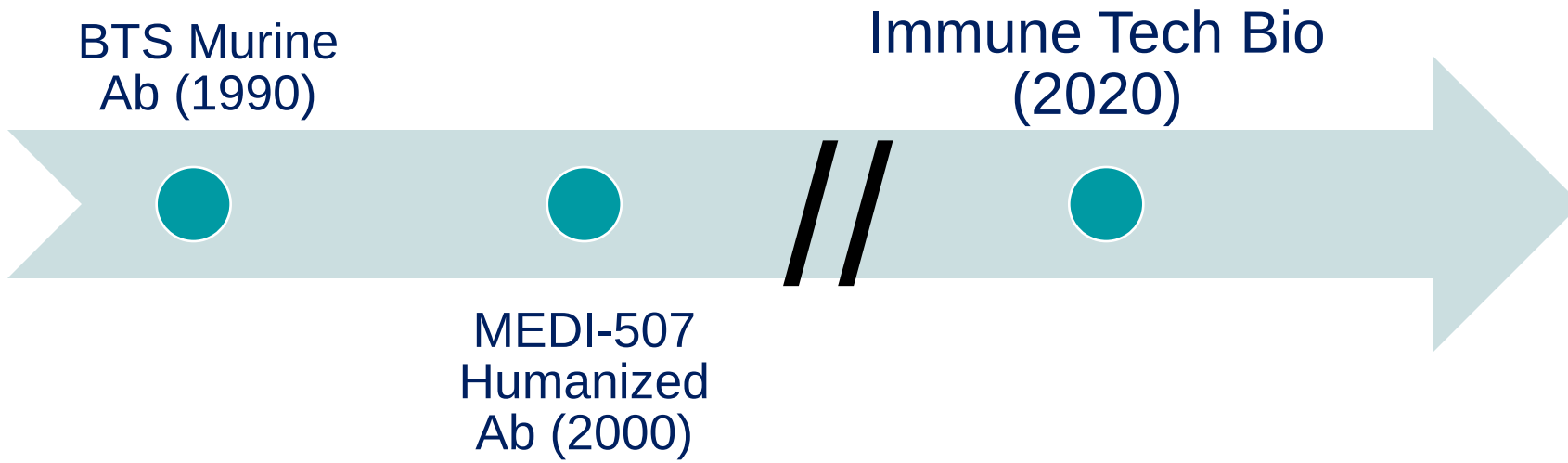
Advantages/Limitations of Tolerance Approaches

- Long IST free survival for the majority of patients
- Possible permanent specific tolerance
- Less IST related complications

- Early graft loss in 3/10 patients
- Short term chimerism (7-21 days)
- CRS (CTS) in the majority of patients with AKI
- Late rejection or recurrent disease

13 Year Anniversary of Tolerance Induction: 2014

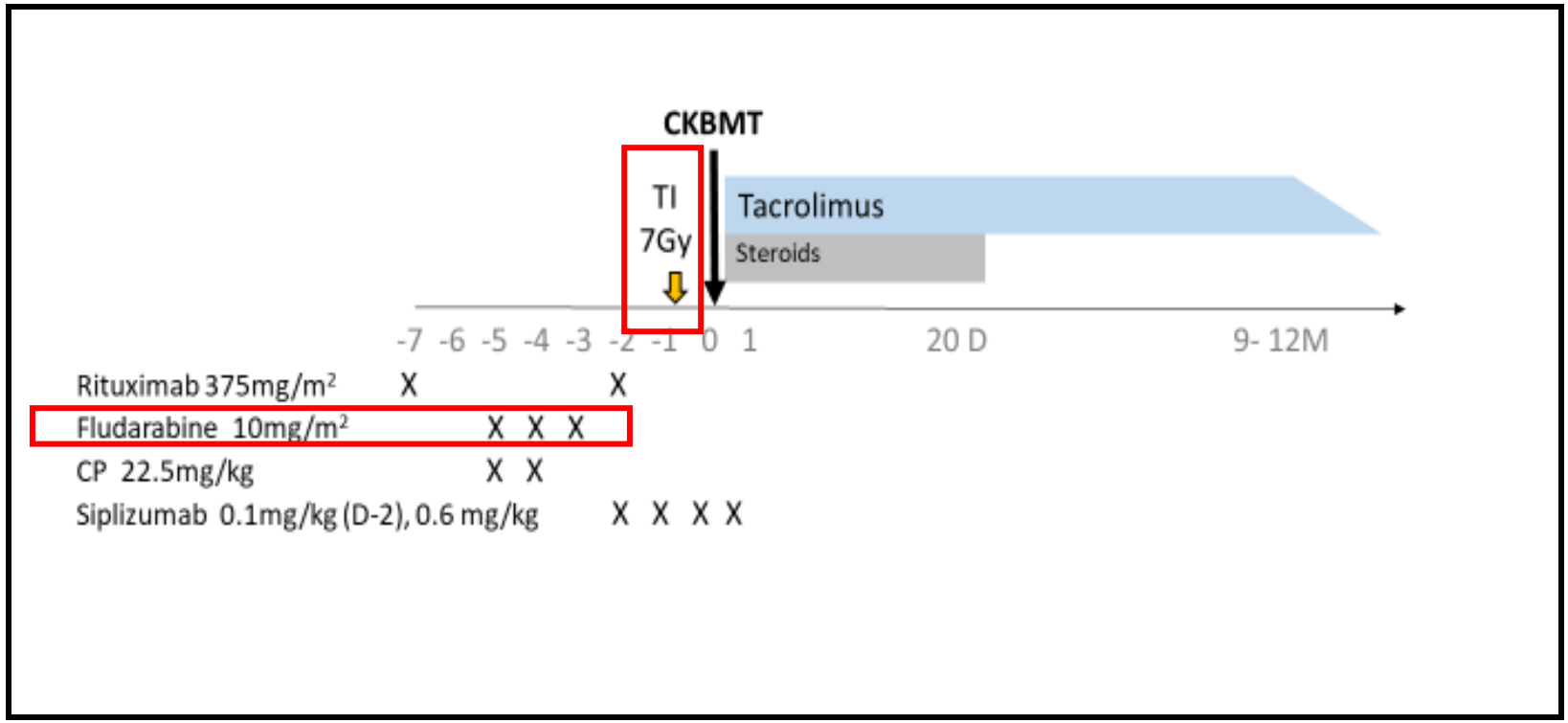
Siplizumab



Anti-CD2 monoclonal antibody

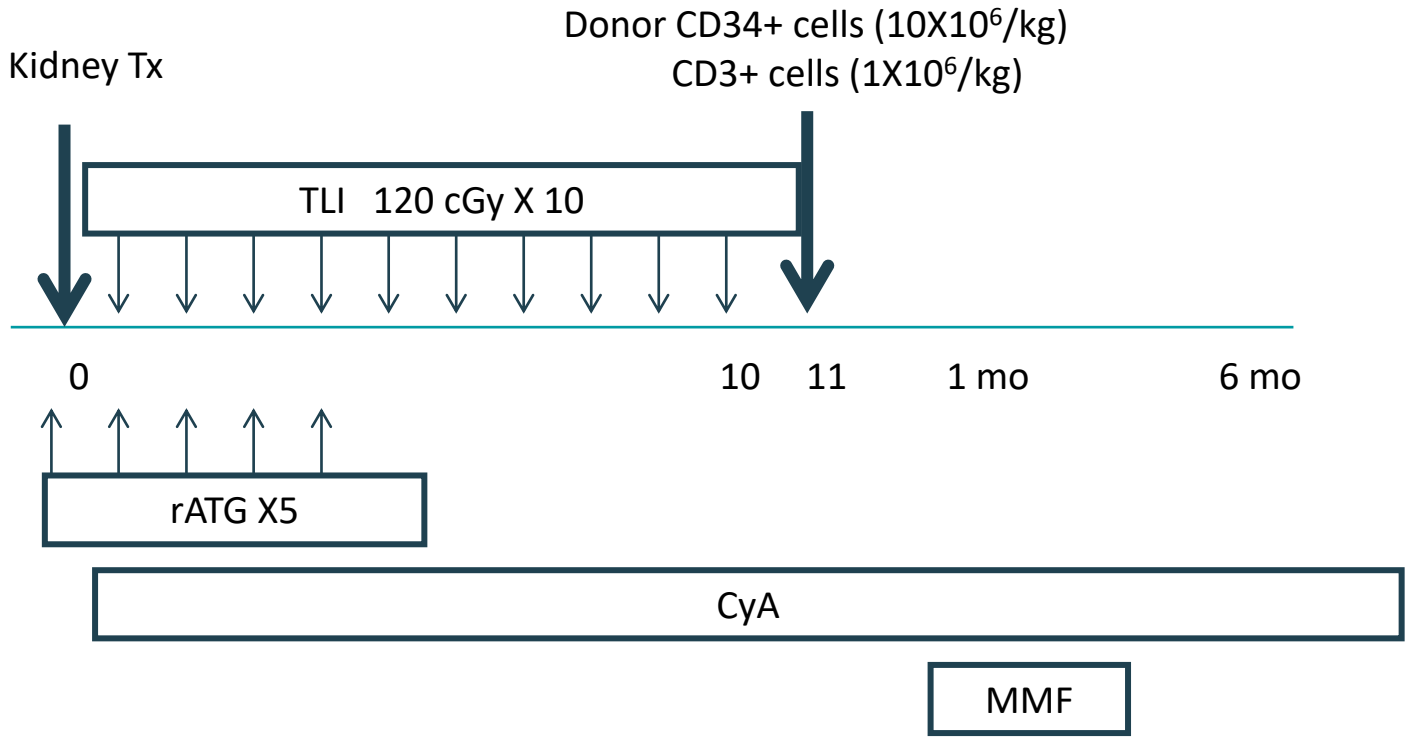
- Potent T-cell depletion
- Costimulatory blockade
- NK cell depletion
- T reg sparing

Current MGH Protocol



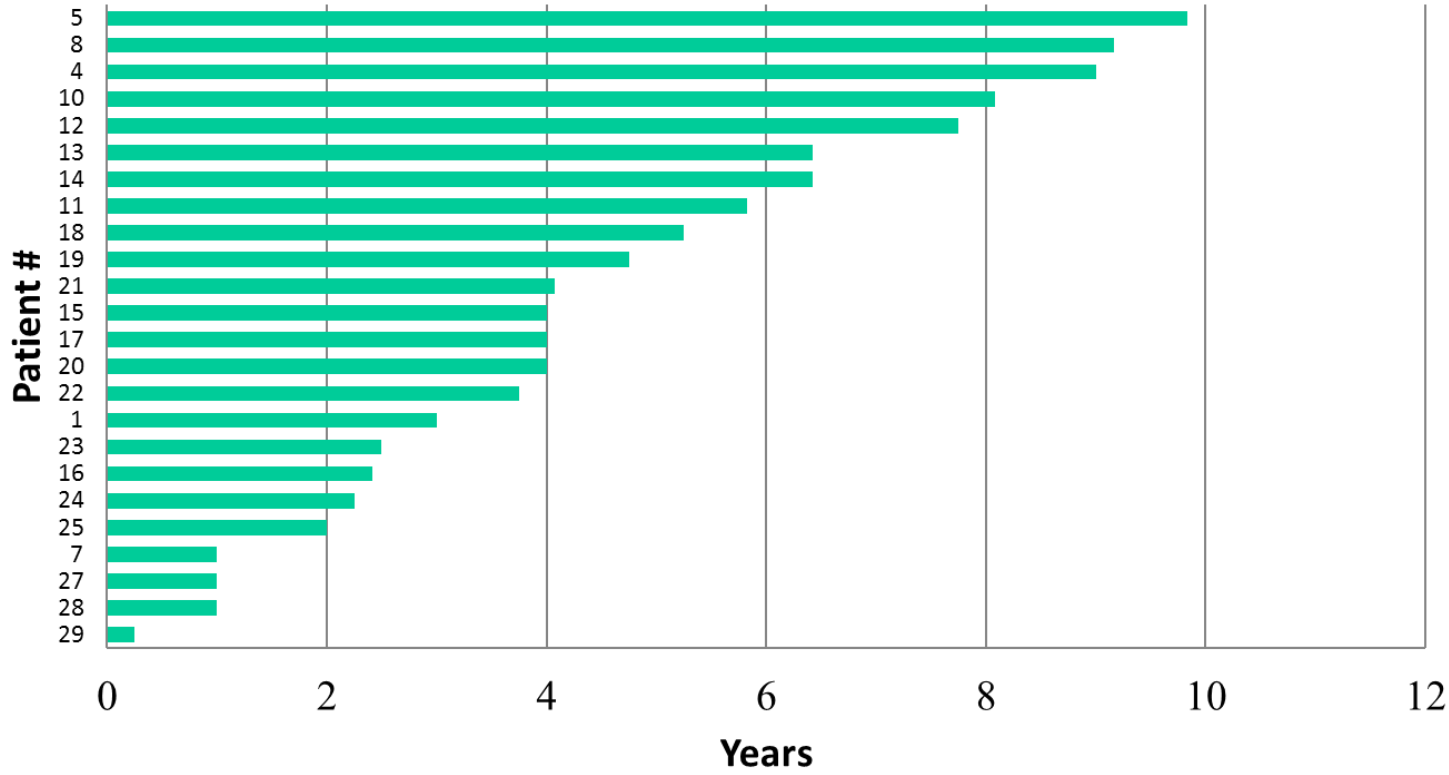
Tolerance Induction Elsewhere

Stanford Tolerance Protocol



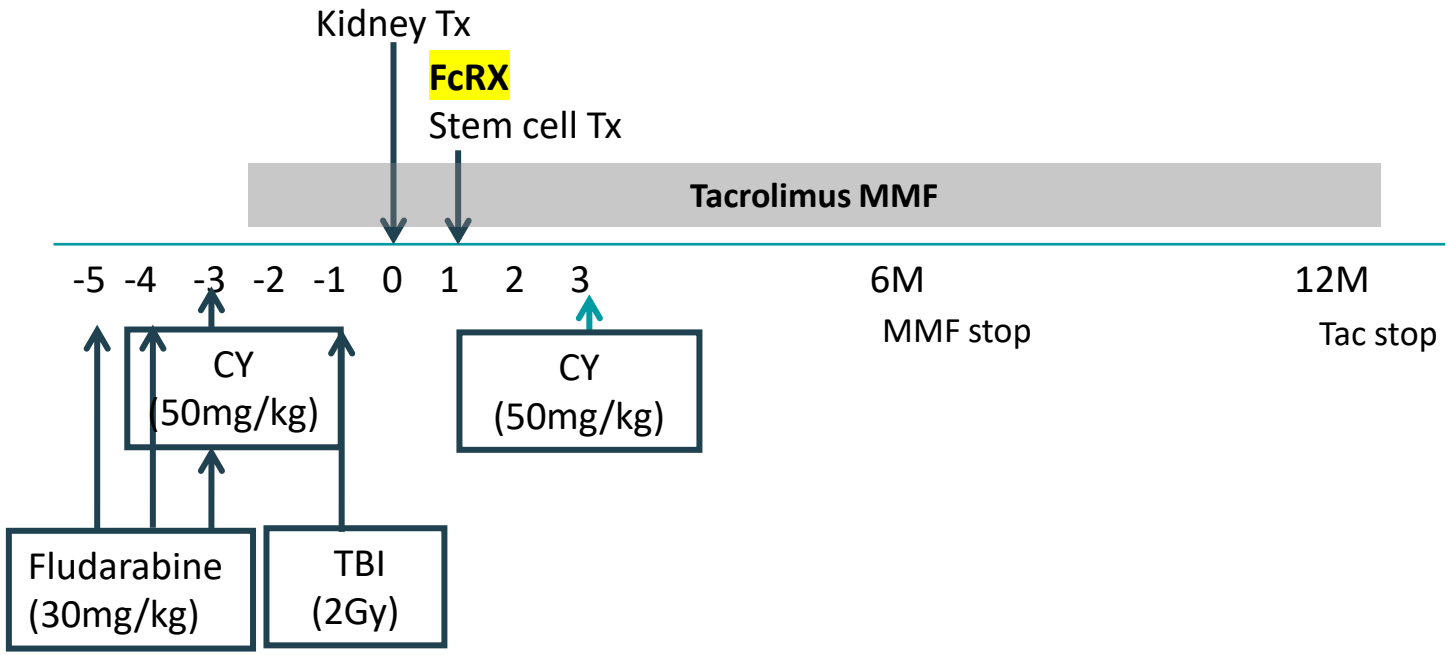
Stanford Tolerance Induction: HLA-Matched

Duration off Immunosuppression



Courtesy of Sam Strober, MD

Northwestern Tolerance Protocol



Tolerance Through Chimerism: Northwestern
The Role of the "Facilitating Cell"

- 37 HLA-mismatched combined transplants
- Of 31 patients @ >12months, 23 with durable chimerism (19 full) and 22 with tolerance
- Two lost the renal allograft due to infection
- 2 patients with GVHD, one fatal

Kawai T, Leventhal J, Wood K, Strober S. Am J Transplant 2018

Prospective Multicenter Clinical Trials for Tolerance Induction Through Hematopoietic Chimerism

Medeor Therapeutics

talaris THERAPEUTICS

ITBMed BIOPHARMACEUTICALS

Stanford Regimen

Randomization vs SOC

HLA matched donors

Goal of mixed chimerism without GVHD

Northwestern Regimen

Randomization vs SOC

Highly HLA mismatched donors

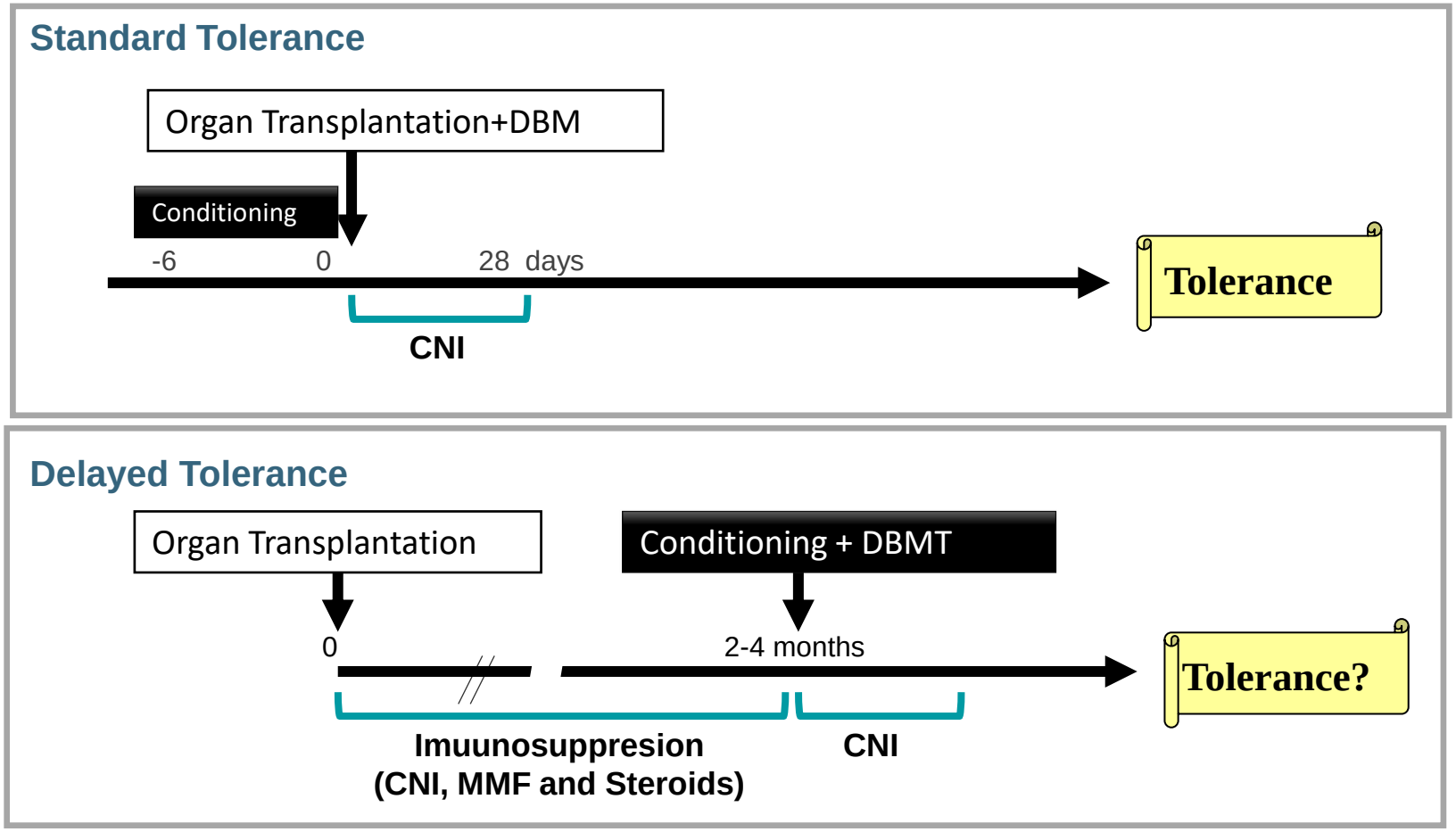
Use of FCR001 "facilitating cells" (Ildstadt)

Goal of full donor chimerism without GVHD

MGH Regimen

- PANORAMA and PERSPECTIVE pilot trials
- HLA haploidentical donors
- Siplizumab based
- Goal of transient mixed chimerism

Delayed Tolerance Induction



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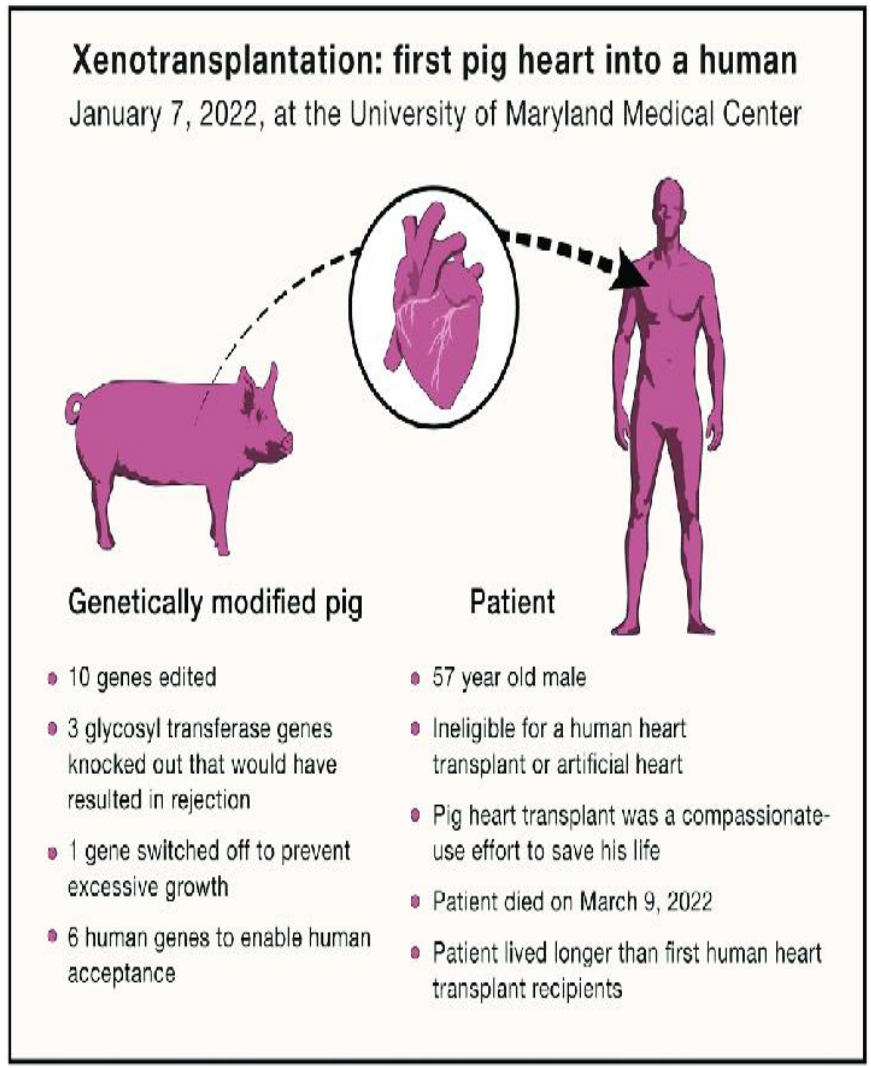
Expanding The Scope of Immune Tolerance Through Hematopoietic Chimerism

Application	Organ(s)	Strategy
Deceased donor	Kidney, liver, heart, etc.	Delayed BMT
VCA (vascularized composite allotransplantation)	Face, limb, etc.	Delayed BMT
Xenotransplantation	Heart, kidney, etc.	Genetically modified pig organs

Xenotransplantation: Crossing Species Barriers



ResearchGate

Bartley Griffith, MD

Combined KdBMT for the Induction of Immune Tolerance
Conclusions and Future Direction

Combined living donor bone marrow and kidney transplantation for patients with MM or other HM and ESRD is feasible and may lead to

- *Sustained tolerance even with transient mixed chimerism*
- *Long term anti-tumor responses*

The principles learned from the HM experience have provided a foundation for combined KdBMT protocols involving patients with ESRD without an underlying malignancy

Future tolerance protocol questions:

- *What is the optimal strategy and what level of chimerism is acceptable/desirable?*
- *Will a delayed tolerance approach allow for cadaveric organ transplantation including other organs/tissues*