



Northwestern University Feinberg School of Medicine

Trends in Kidney Transplantation

John J. Friedewald

National Kidney Foundation of Illinois 2011





Overview

Trends in transplant type and donors

Incompatible and Kidney Paired Donations

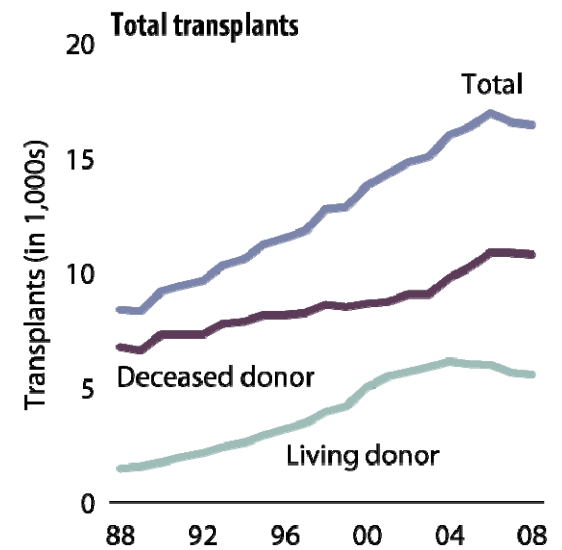
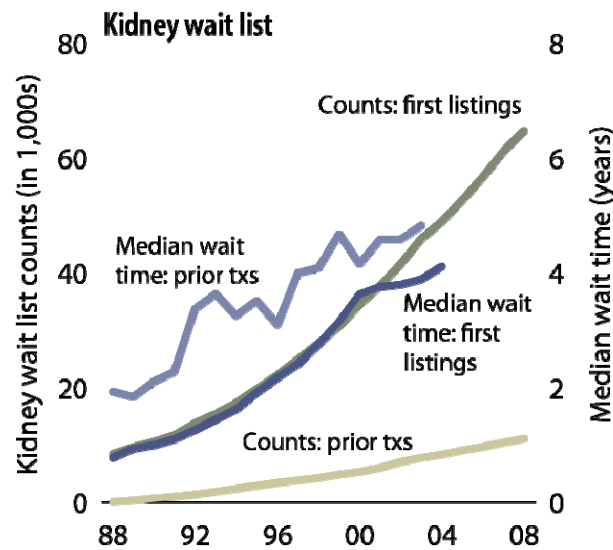
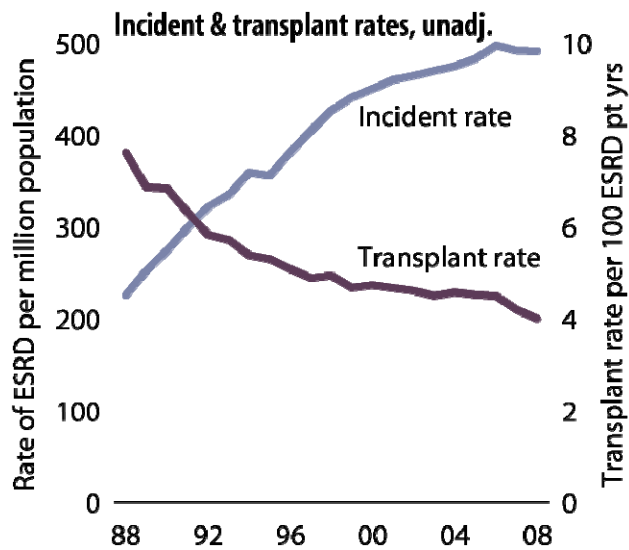
Transplant Medications

Research

Stem Cells, Tolerance, Biomarkers, Personalized therapies

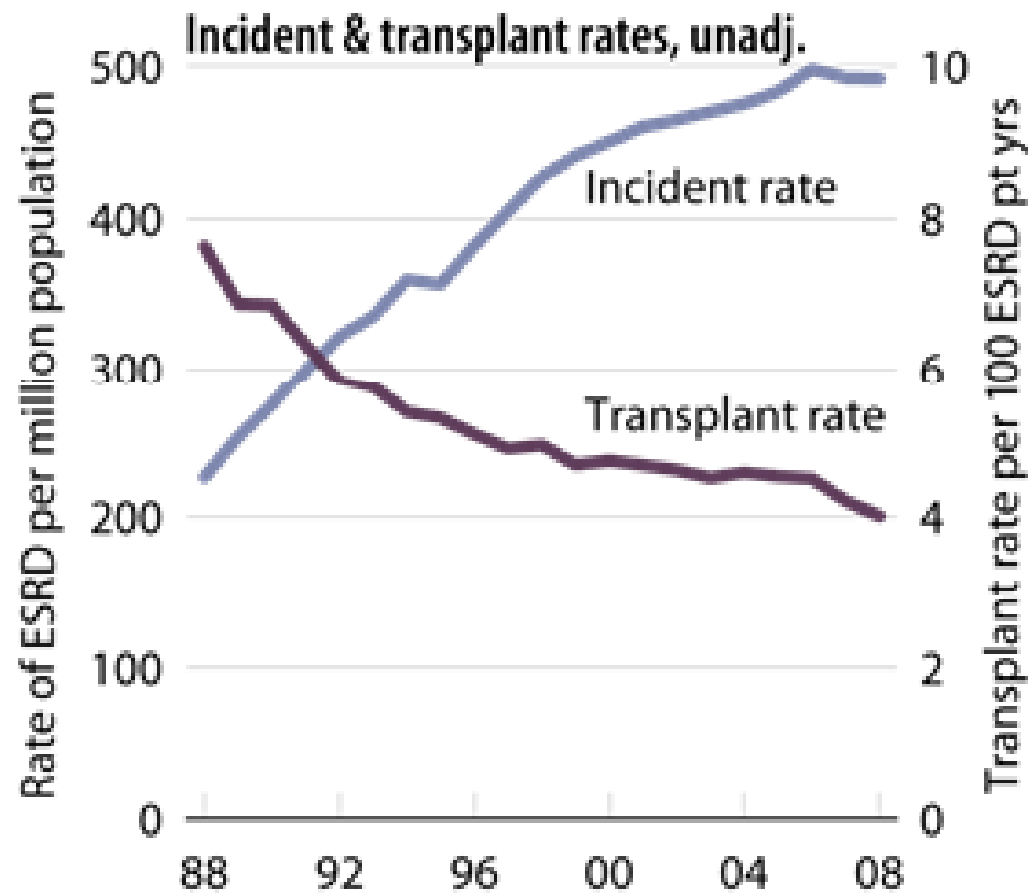


Trends in transplantation: unadjusted rates, wait list, & total transplants, patients age 20 & older



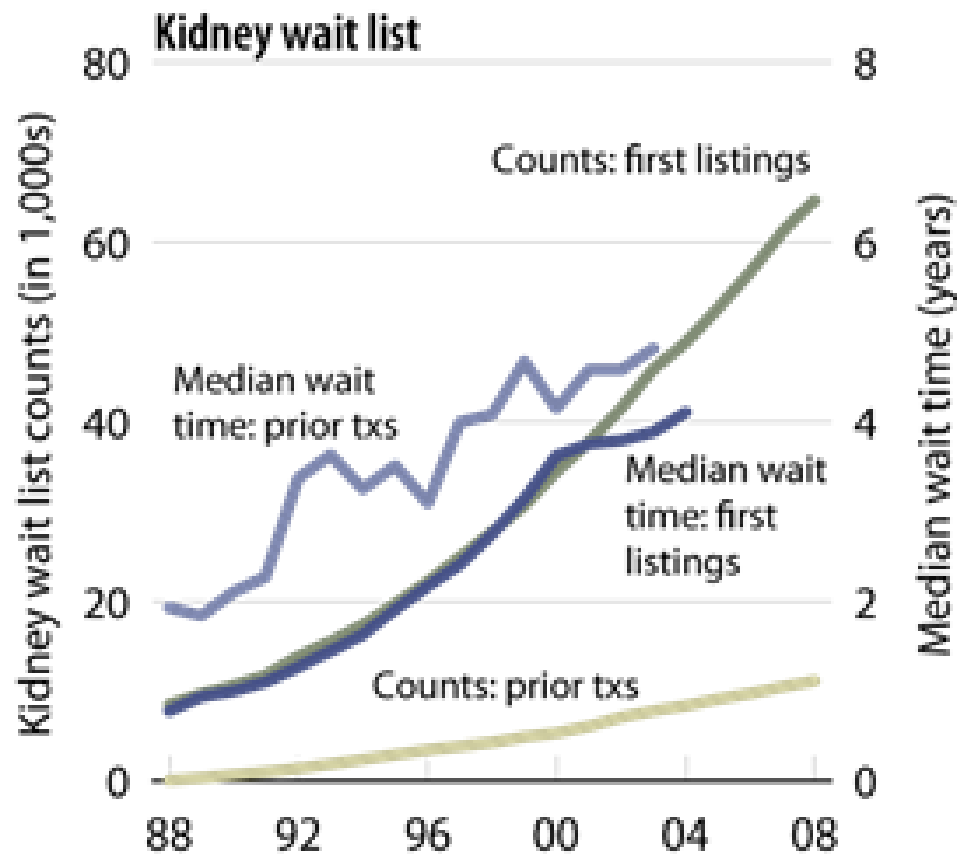


Incident ESRD Rate and Transplant Rate



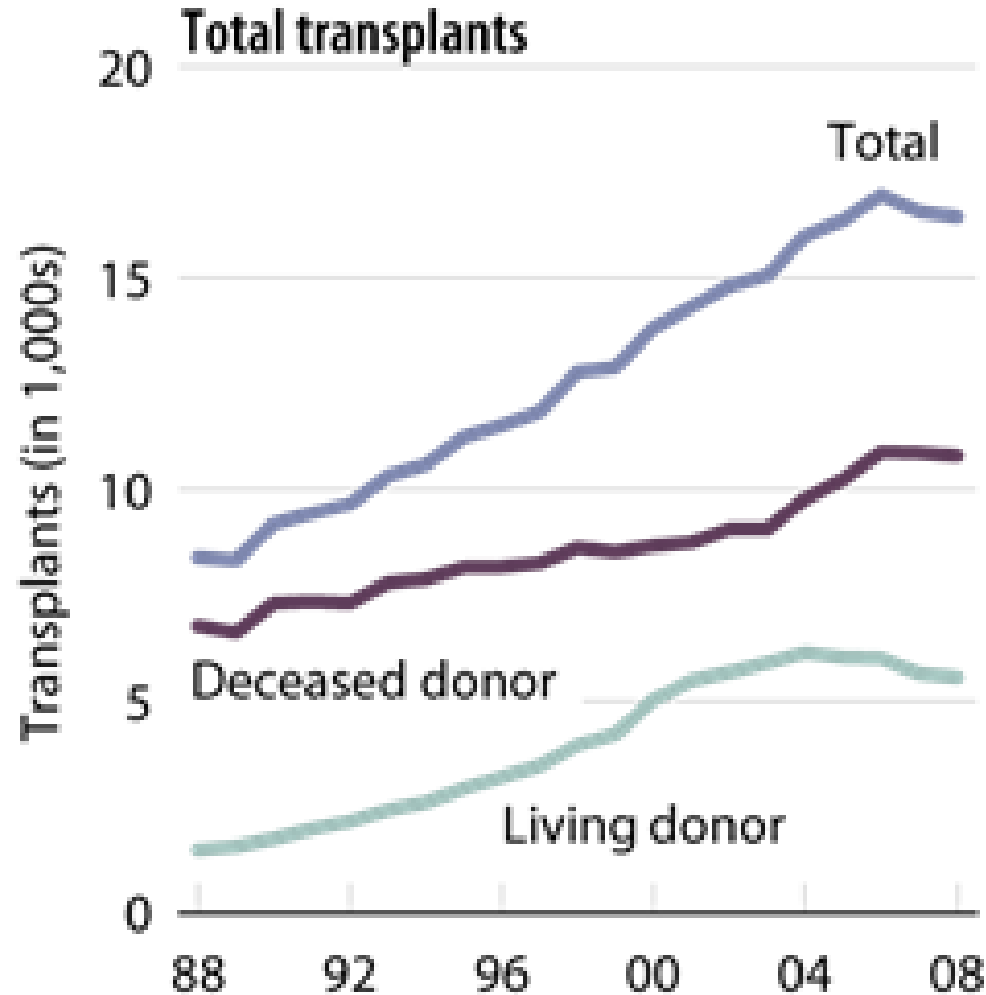


Kidney Transplant Wait List



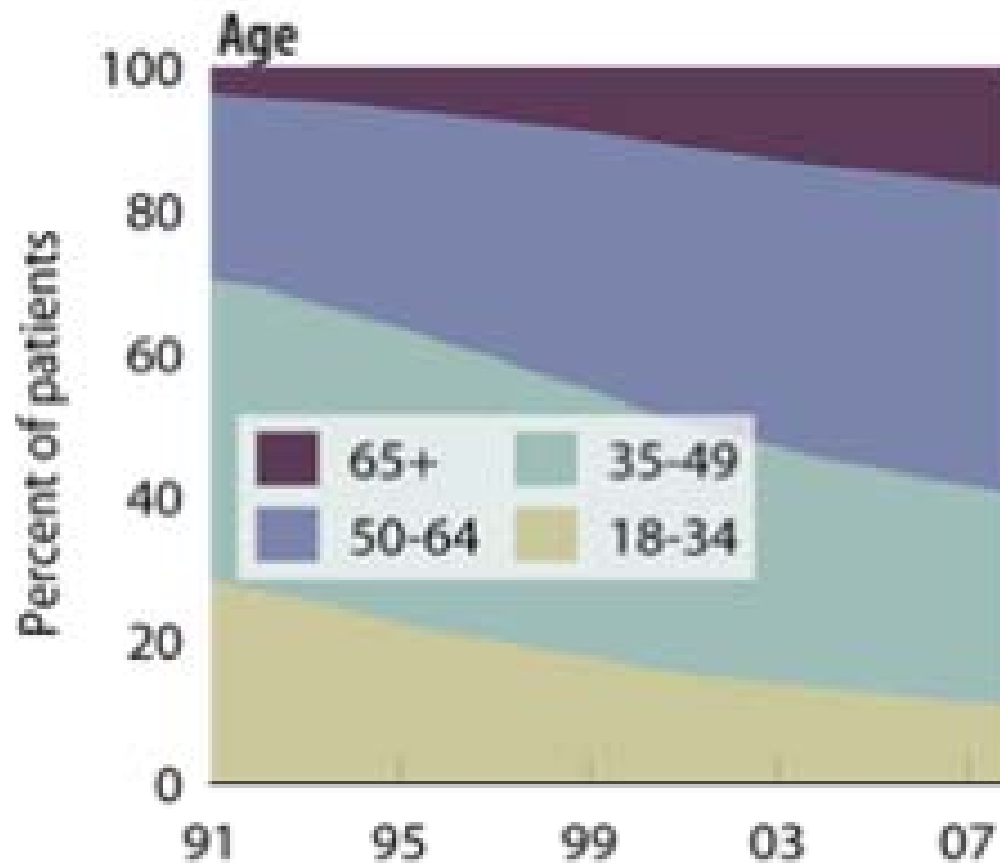


Total Kidney Transplants



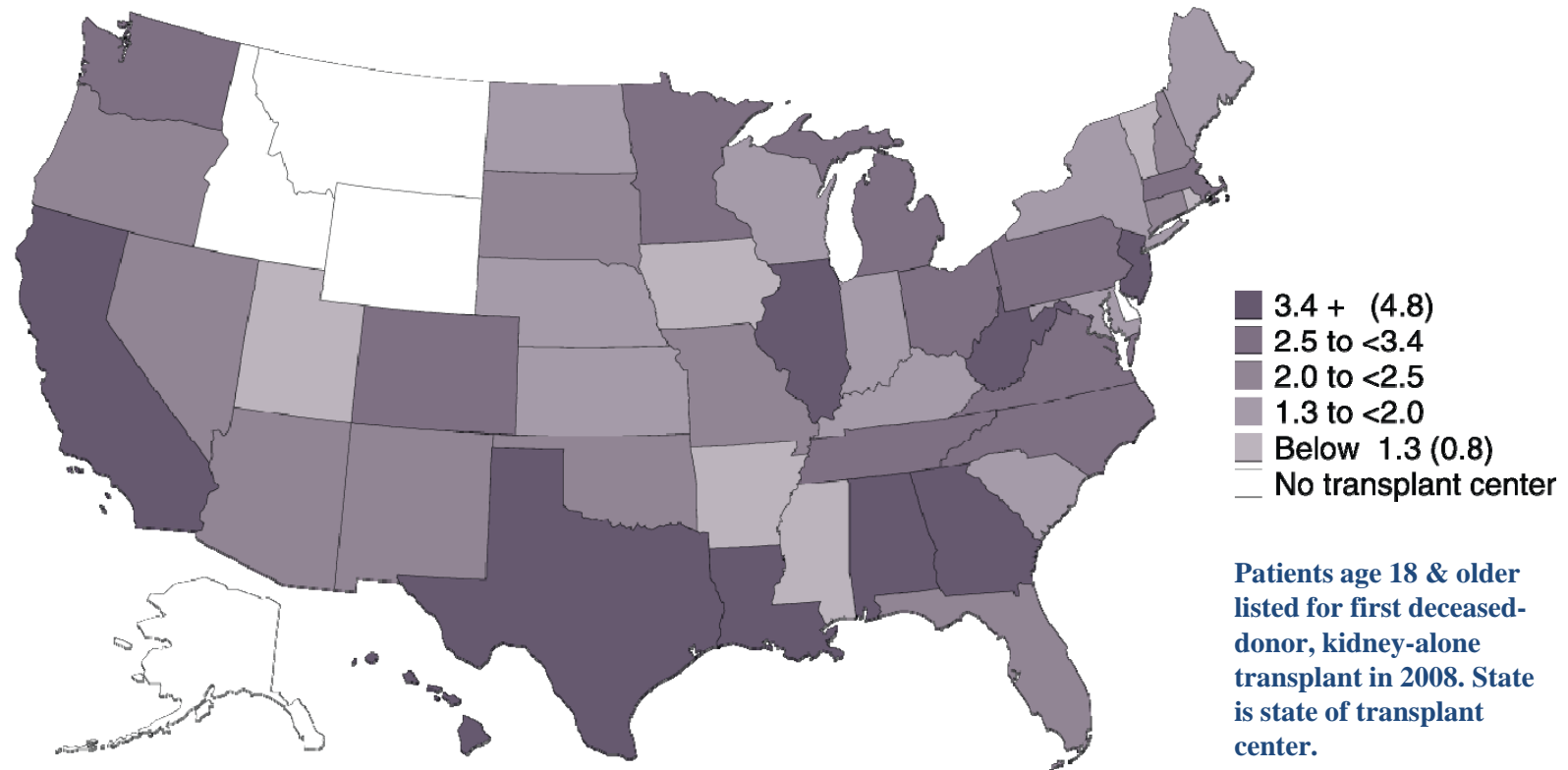


Distribution of wait-listed patients by age



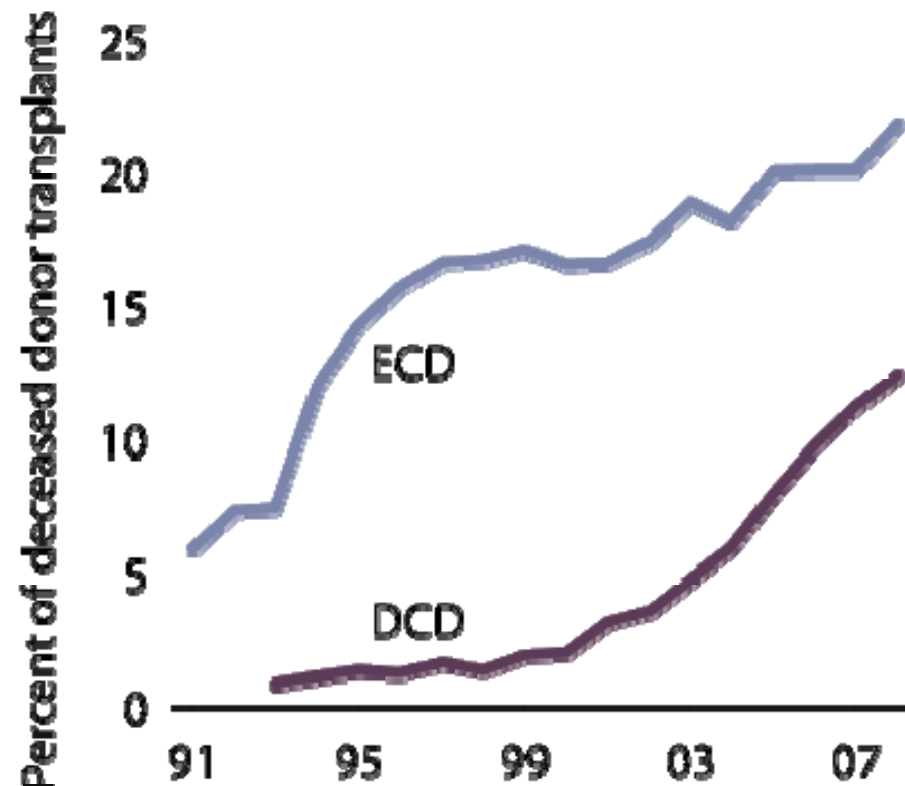


Unadjusted projected median wait times (years) for adults listed in 2008, by state





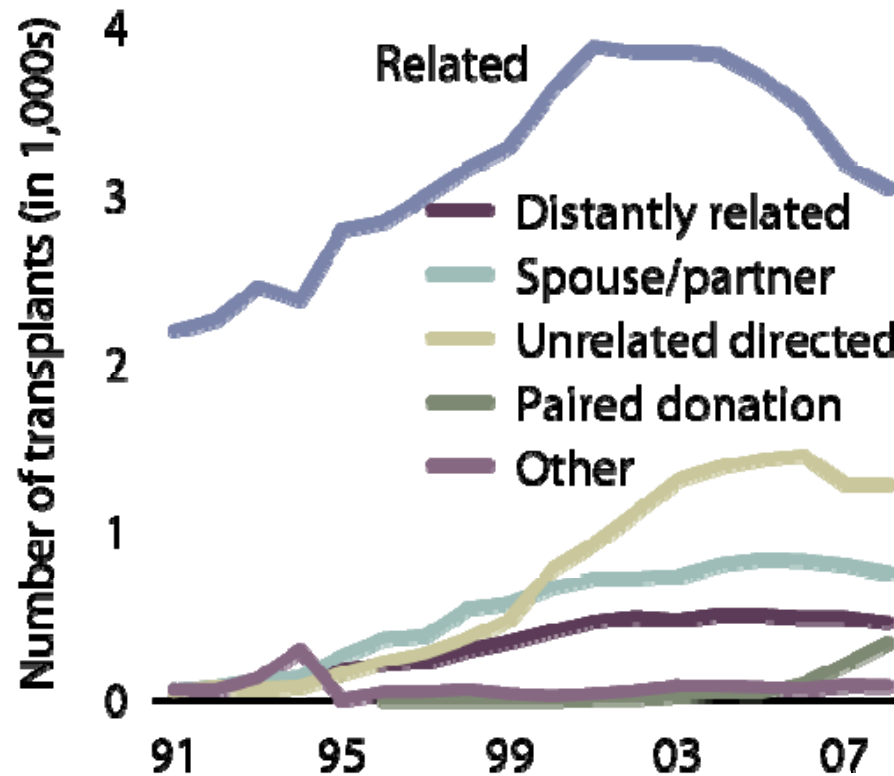
Deceased donor transplants from ECD & DCD donors



Patients age 18 & older receiving a first-time, kidney-only, deceased donor transplant, 1991–2008.



Number of transplants from living donors, by donor relation



All patients receiving a living donor kidney transplant.



Incompatible Transplants

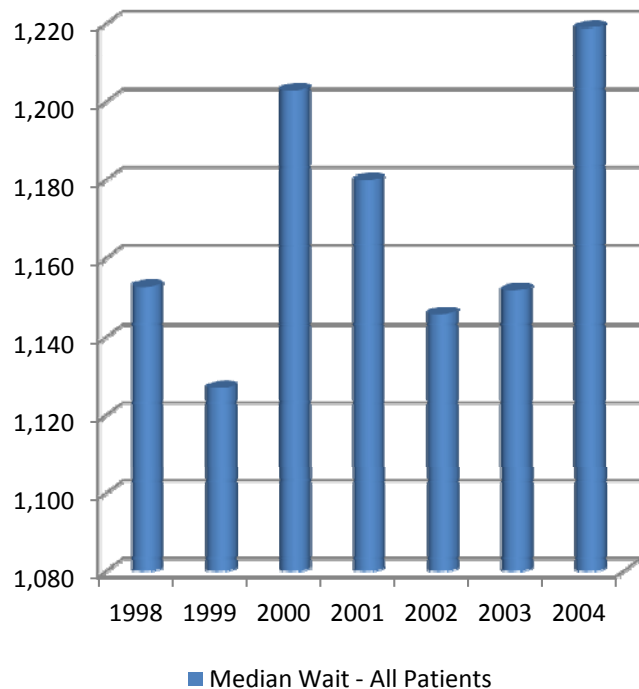
Kidney paired donation

Desensitization

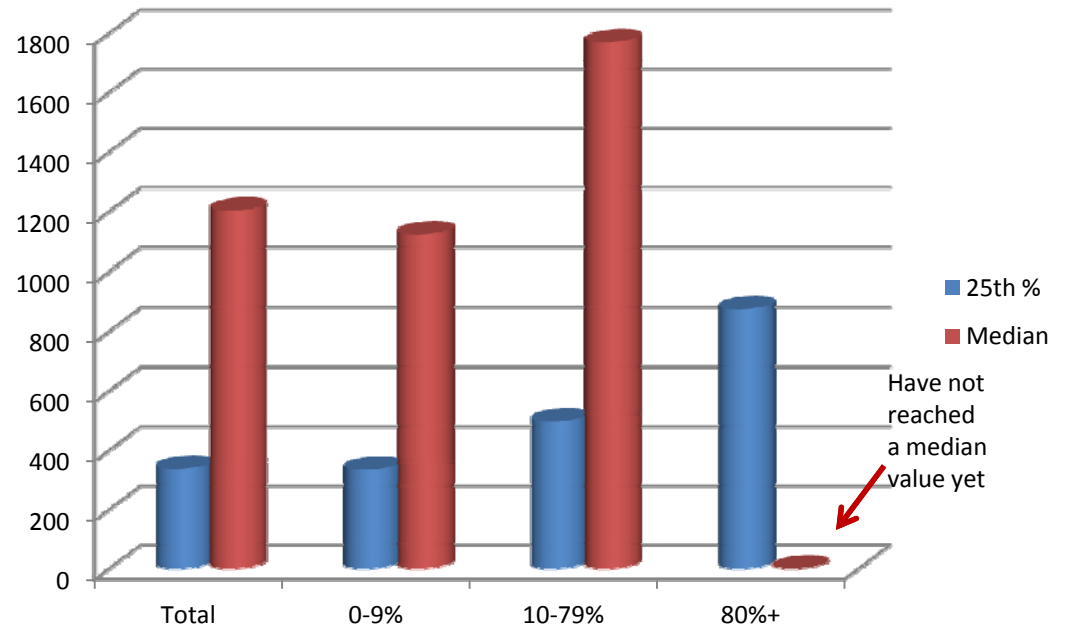


Waiting Times for Sensitized Patients - National

Median Wait - All Patients

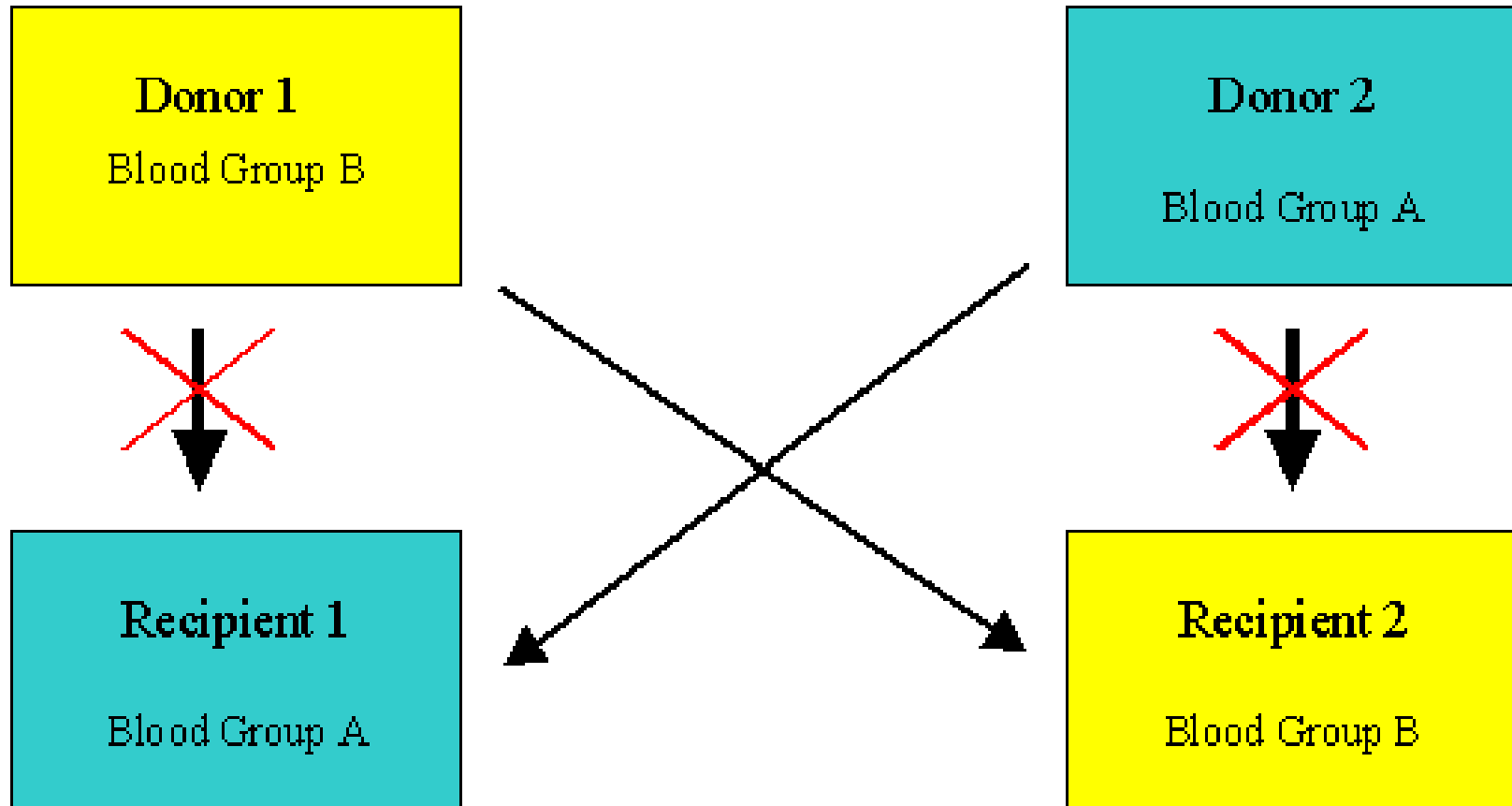


25% & Median Waits in 2001 – by PRA

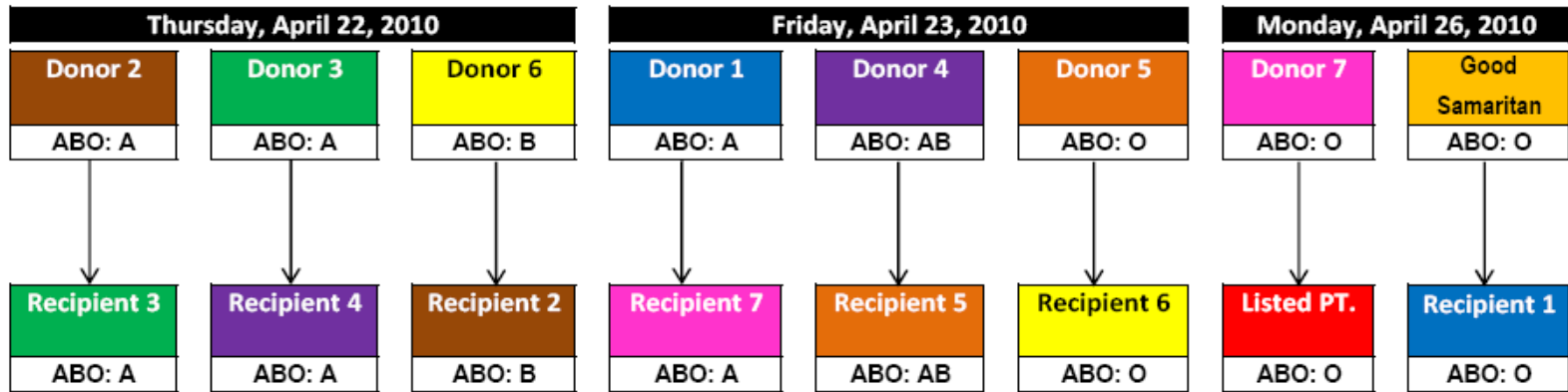
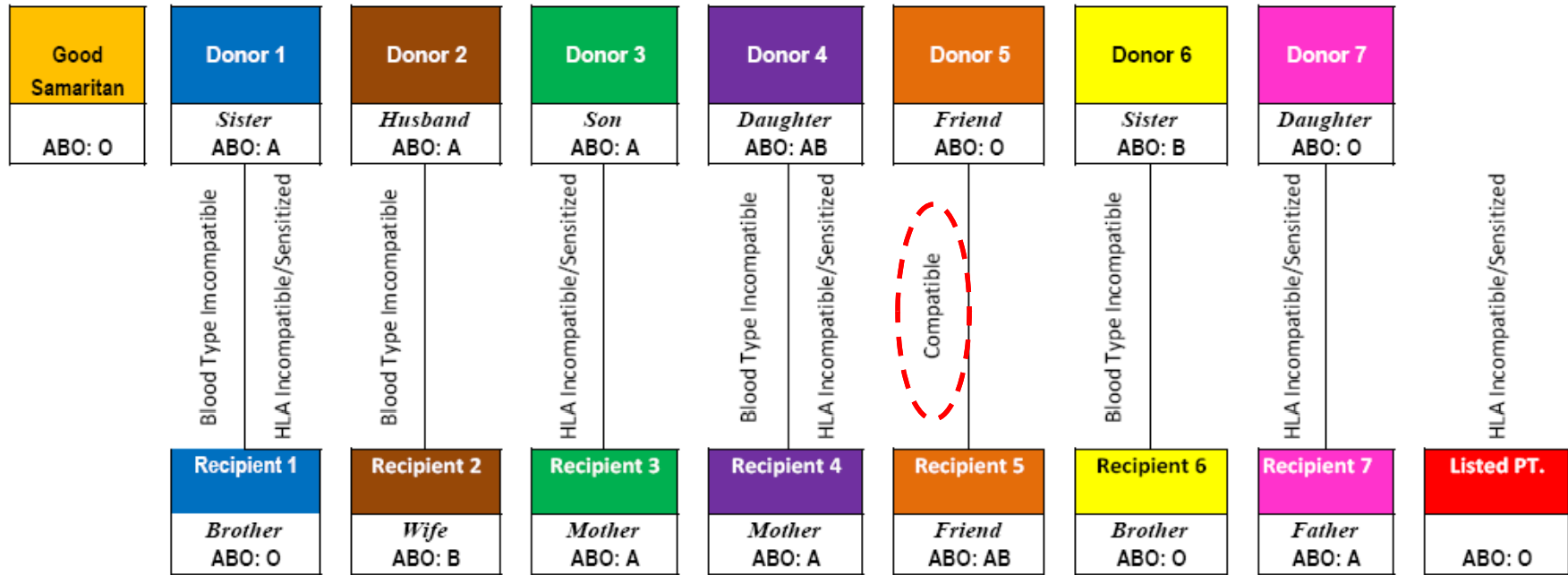


PRA 80%+ median wait time was > than the current follow up time of 6 years

Basic Kidney Paired Donation (KPD)



Eight-Way Paired Exchange - Non Simultaneous Chain



Non-Simultaneous Altruistic Donor Chains (NEADS)

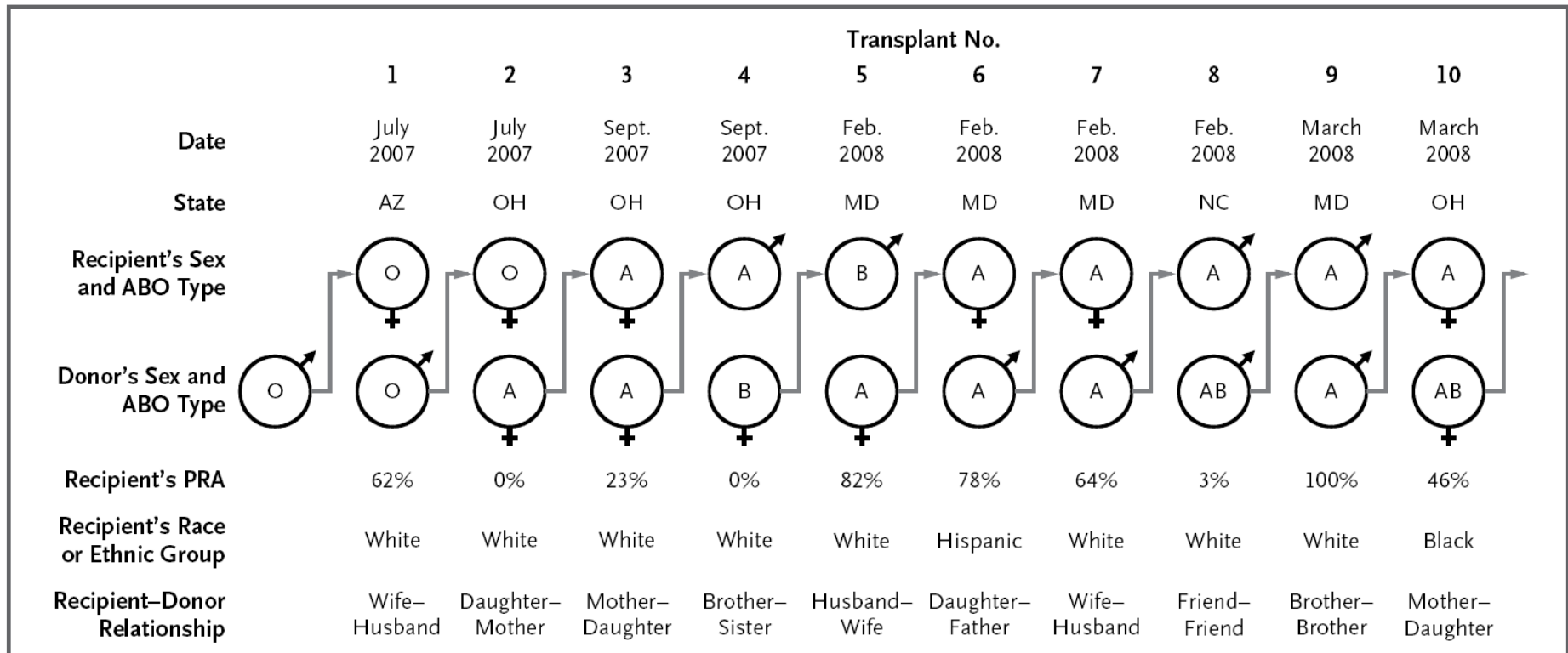


Figure 1. A Nonsimultaneous, Extended, Altruistic-Donor Chain.

In less than 1 year, 10 patients (5 with panel-reactive antibodies [PRAs] >60%) were given a transplant; an 11th transplantation is possible. The initiating donor was an unpaired altruistic donor from Michigan. To date, none of the bridge donors have reneged. The recipient of transplant 6 required desensitization of HLA donor-specific antibodies by T-cell and B-cell flow cytometry. The recipient of transplant 9 had an anti-B antibody titer of 1:8 (as assessed with the use of an antihuman globulin reagent) and required desensitization to blood group.



Desensitization

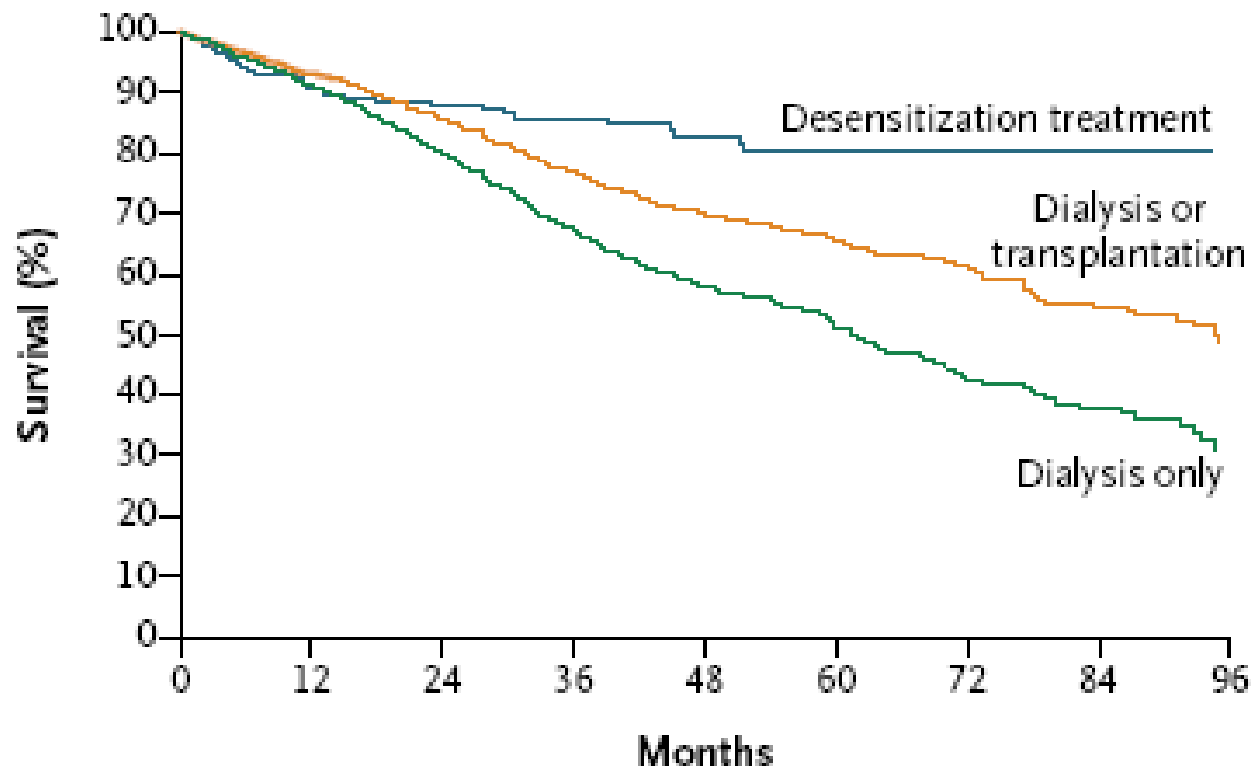
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ORIGINAL ARTICLE

Desensitization in HLA-Incompatible Kidney
Recipients and Survival



Desensitization



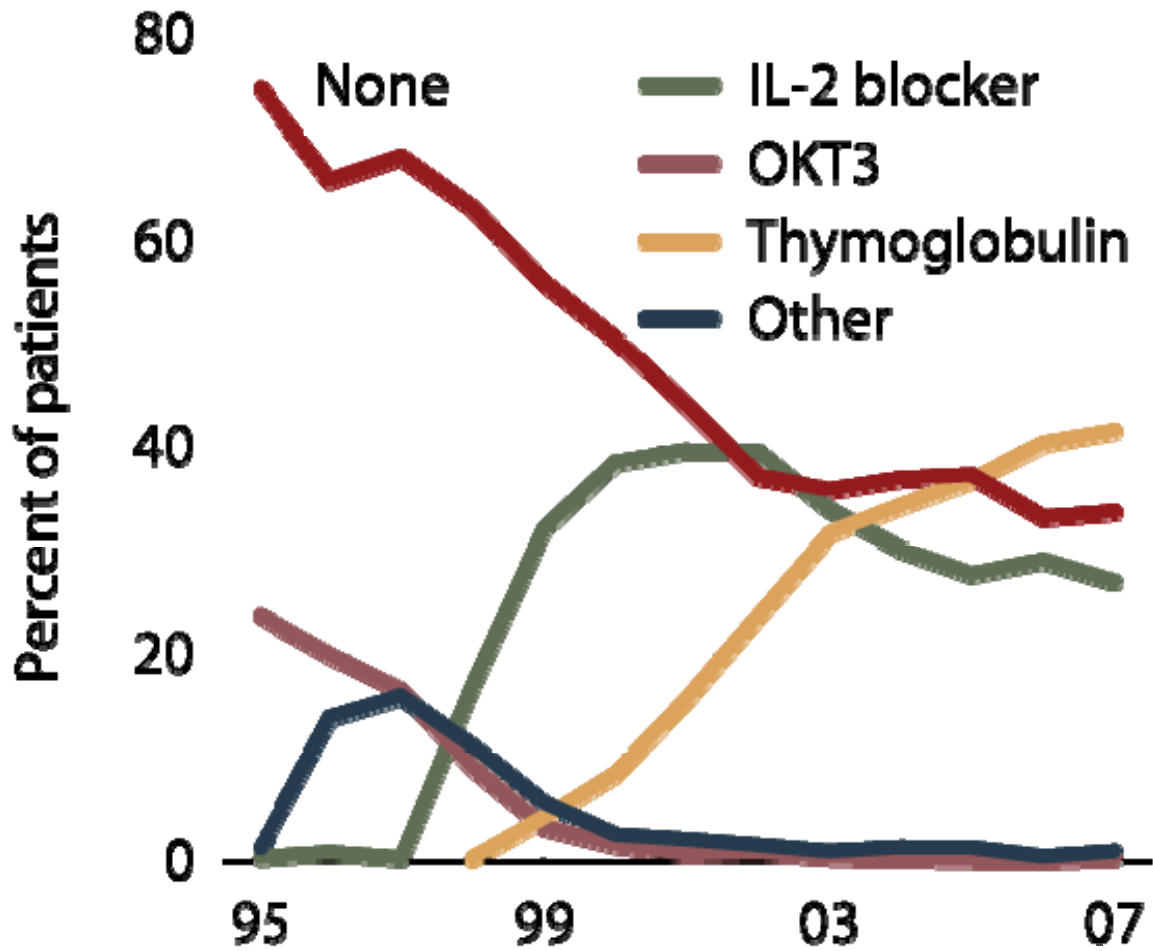
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Trends in Transplant Medications



Antibody Induction: Adults

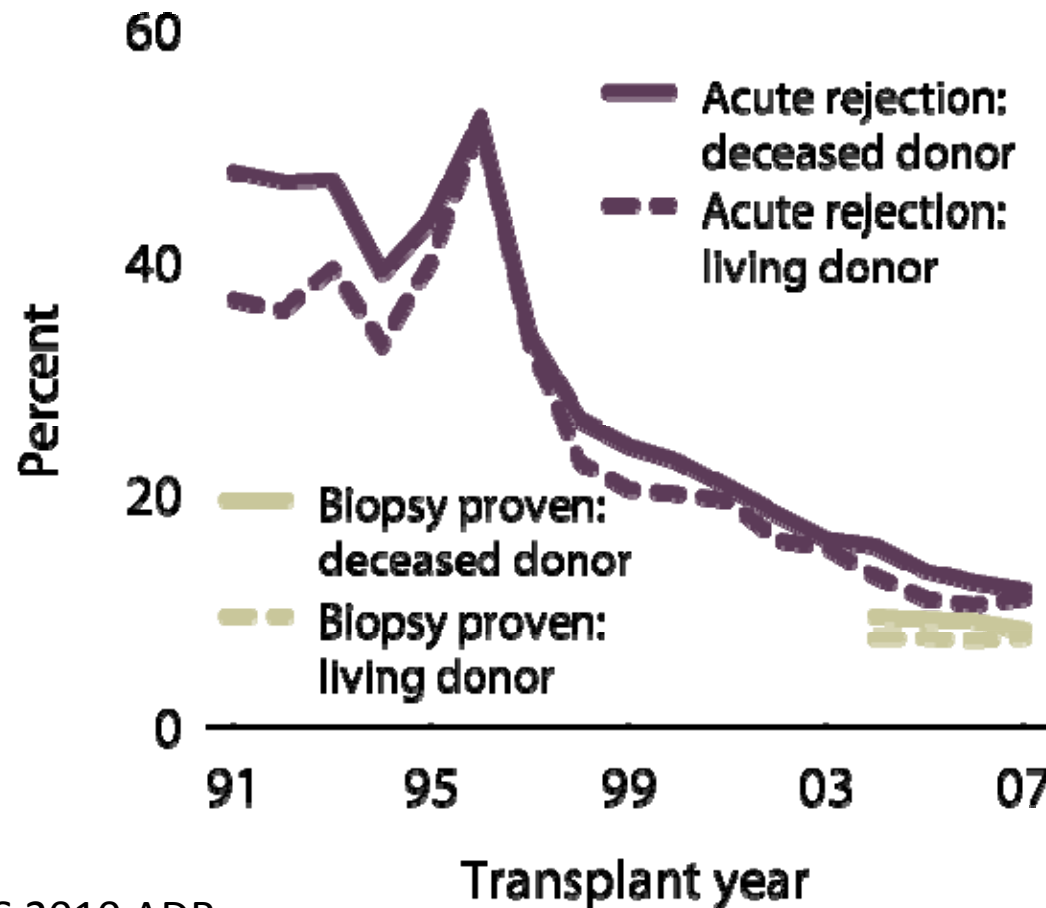


First-time, kidney-only transplants, age 18 & older, 1997–2007. Immunosuppression as identified to OPTN.

Source: USRDS 2009 ADR



Acute rejections within the first year post-transplant

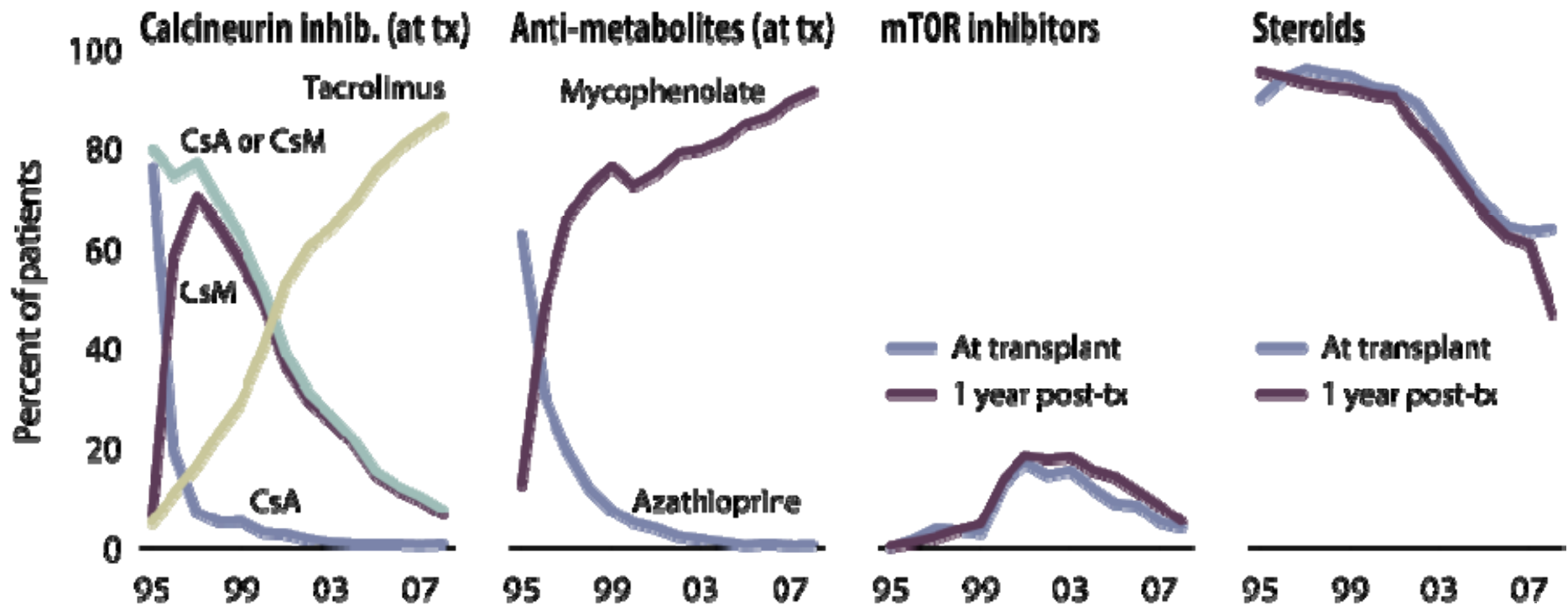


First-time, kidney-only transplant recipients, age 18 & older, with functioning graft at discharge.

Source: USRDS 2010 ADR



Immunosuppression use

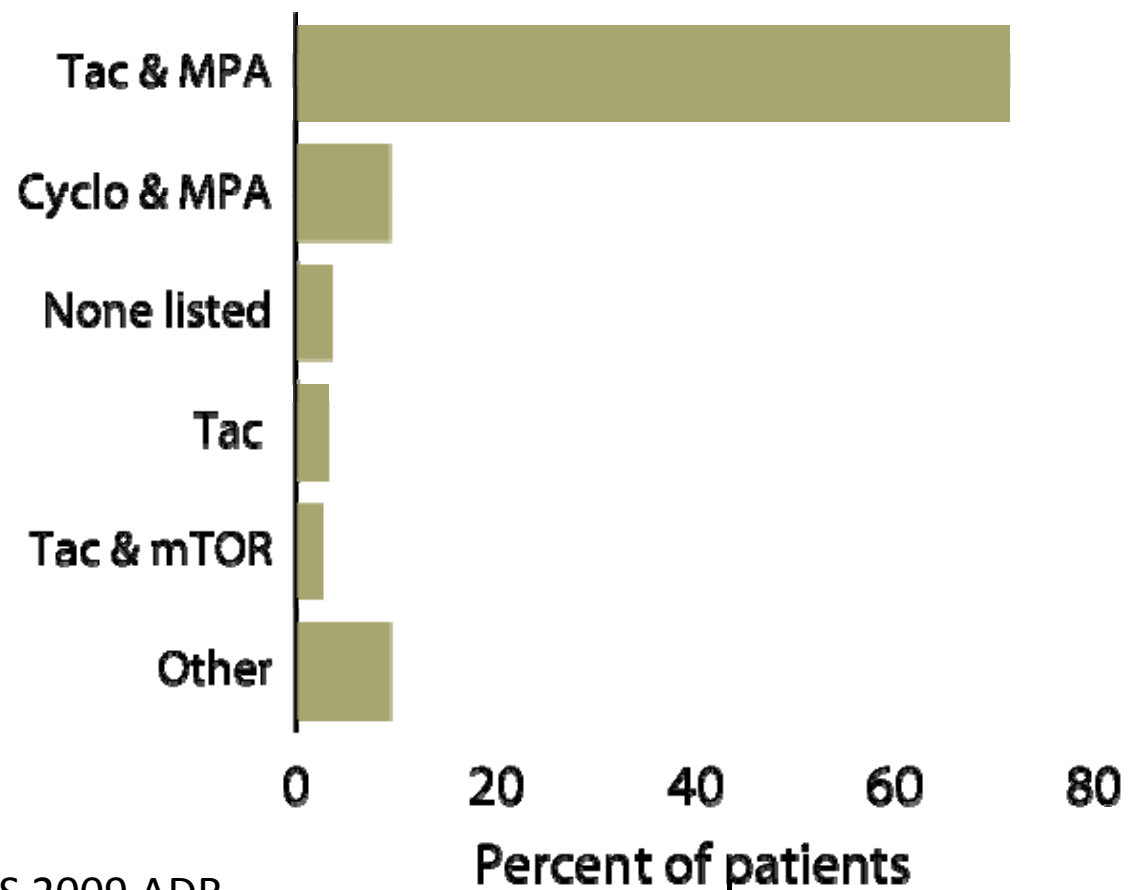


Patients age 18 & older receiving a first-time, kidney-only tx. CsA: cyclosporine A; CsM: cyclosporine microemulsion.

Source: USRDS 2010 ADR



Most common immunosuppression regimens at time of transplant: 2005–2007

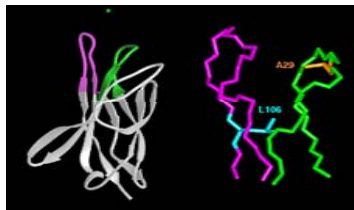
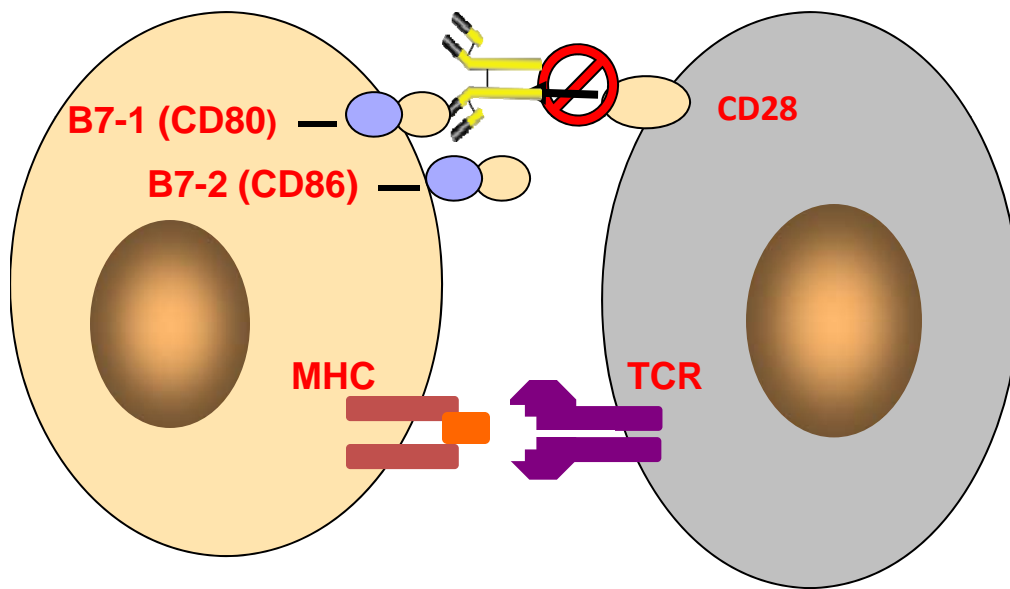


Source: USRDS 2009 ADR

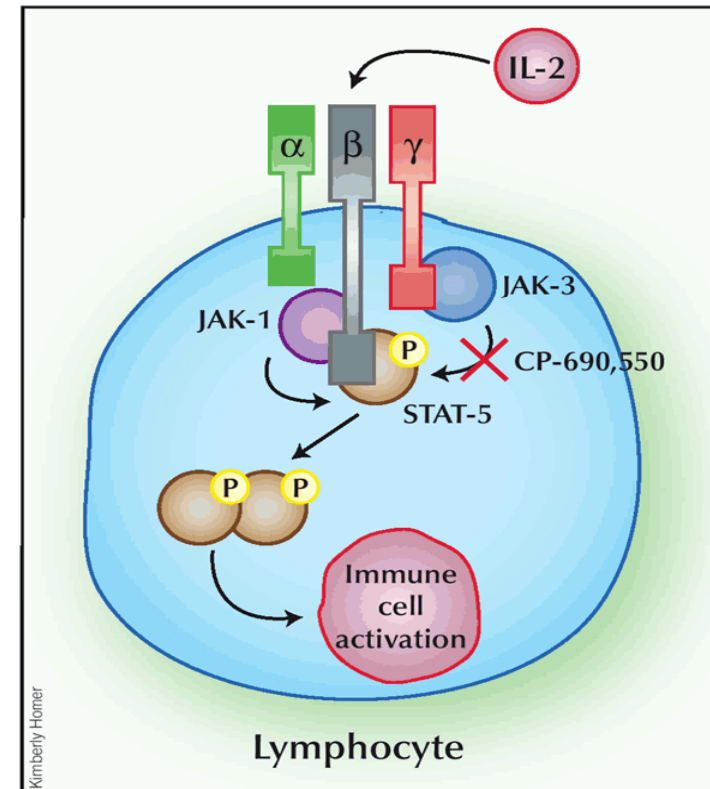
Novel Approaches



LEA29Y (Belatacept)
Anti B7 Blockade



JAK-3 inhibition



Kimberly Horner



Belatacept

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Costimulation Blockade with Belatacept in Renal Transplantation

N Engl J Med 2005;353:770-81.

Belatacept



Recently approved for use in the US

Concern over PTLD cases with Belatacept

-restricted in EBV naïve recipients

Approved for use in de novo kidney transplant recipients along with mycophenolate and steroids



Belatacept – Downsides and Ongoing Work

Currently given intravenously, monthly

Ongoing studies for subcutaneous administration

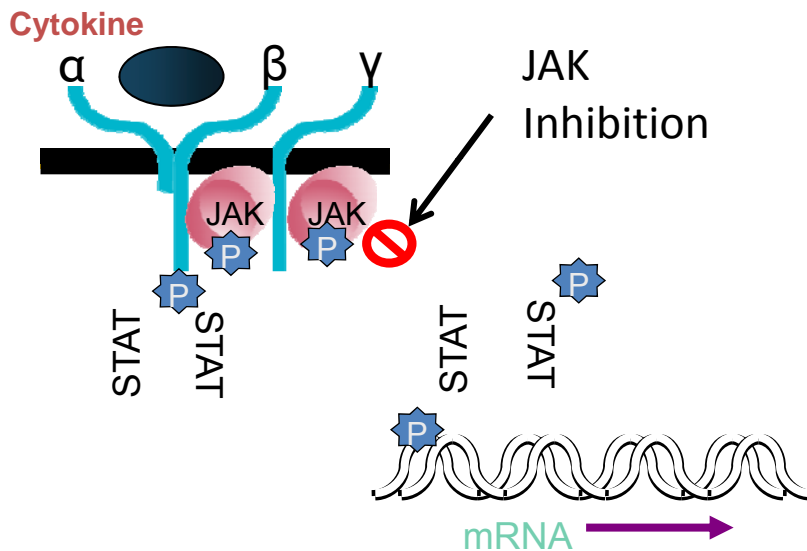
Ongoing studies for late conversion from CNI

Looking for its place in transplantation



JAK Inhibitors

➤ JAK inhibition suppresses the signaling of multiple cytokines



Cytokine	Effects on the immune system
IL-2	Stimulate the proliferation and differentiation of Th, Tc, B and NK cells
IL-4	Induce the differentiation of Th0 to Th2 Induce Ig switching
IL-7	Promote the development, proliferation and survival of T, B and NK cells
IL-9	Stimulate Intrathymic T cell development
IL-15	Promote the proliferation, cytotoxicity and cytokine production of NK cells
IL-21	Enhance T and B cell function

Not yet approved for transplantation



Trends in Transplant Research

Mixed Chimeras



The co-existence of two genetically different components in one organism



Chimerism induces tolerance

How can we make it safe?



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BRIEF REPORT

Tolerance and Chimerism after Renal and Hematopoietic-Cell Transplantation

John D. Scandling, M.D., Stephan Busque, M.D., Sussan Dejbakhsh-Jones, M.S.,
Claudia Benike, B.S., Maria T. Millan, M.D., Judith A. Shizuru, M.D., Ph.D.,
Richard T. Hoppe, M.D., Robert Lowsky, M.D., Edgar G. Engleman, M.D.,
and Samuel Strober, M.D.

N Engl J Med 2008;358:362-8.



Northwestern Clinical Tolerance Protocols

Sequential kidney/HSC in HLA matched related

Simultaneous kidney/HSC in HLA mismatched



HLA-Matched Protocol

PI: Joshua Miller

Current Enrollment – 18/20 now 2 to 38 months
post transplant

First patient enrolled January 2008

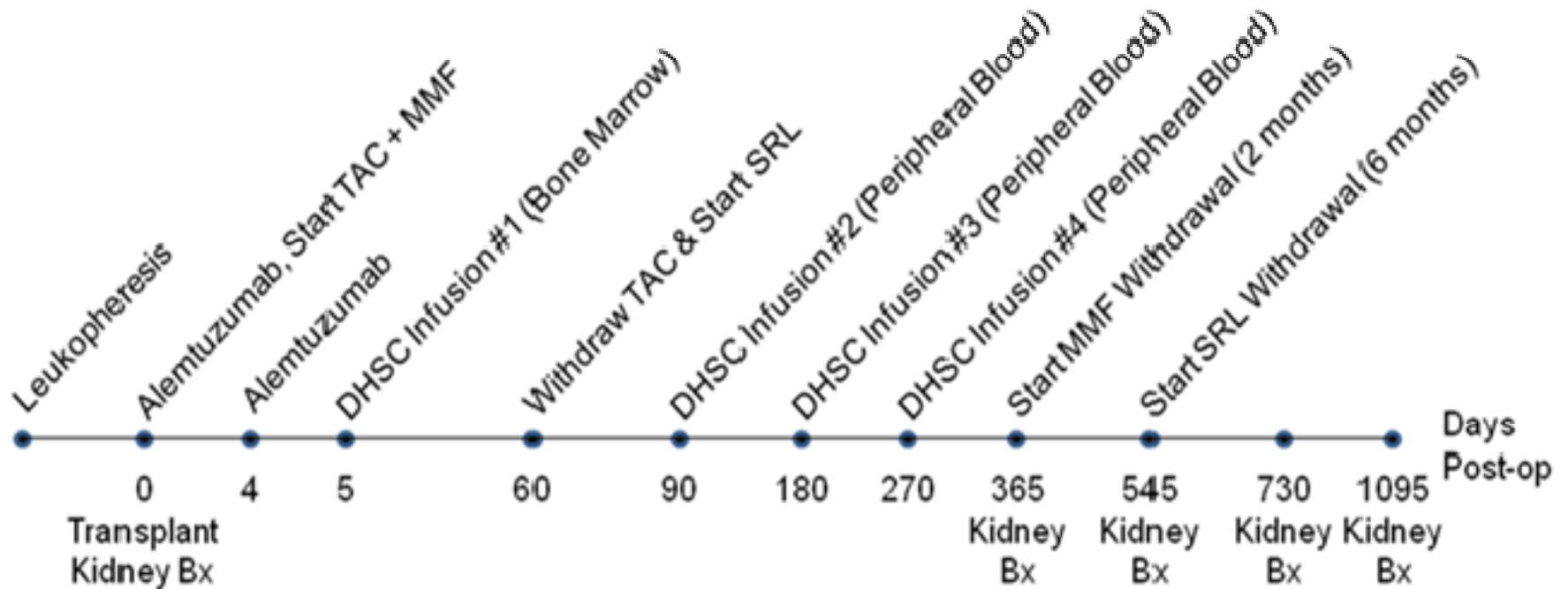
HLA identical siblings

Excluded if high risk of recurrent disease in the
allograft (role of immunosuppression in
preventing disease recurrence)



HLA-Matched Protocol

PI: Joshua Miller





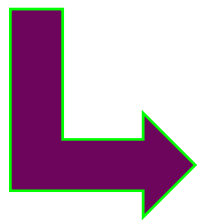
Simultaneous kidney/HSC in HLA mismatched protocol

PI: Joseph Leventhal & Suzanne Ildstad

Simultaneous FCRx +Kidney Transplant

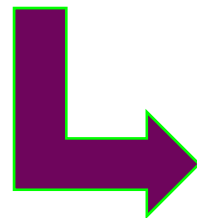
Processed donor leukopheresis product/marrow enriched for HSC, FC and progenitors (FCRx)

HSCT mobilized, collected, processed, & cryopreserved (> 2 wks before Tx)

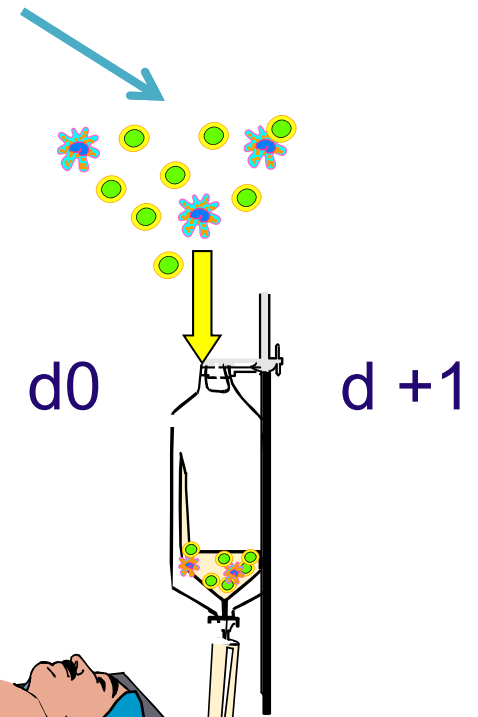
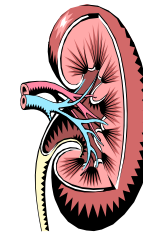
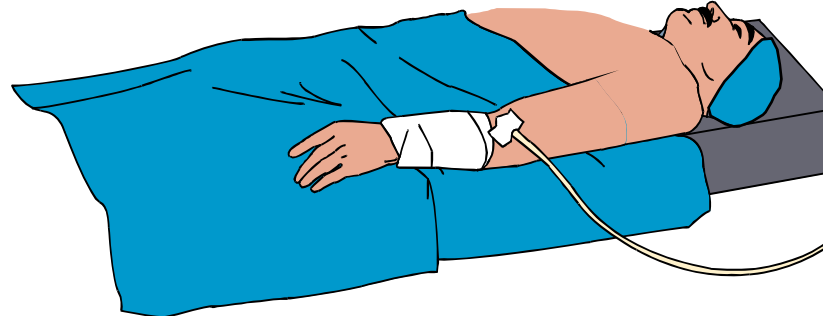


Conditioning

Fludarabine, cytoxan, 200 cGy TBI



Perform Transplant

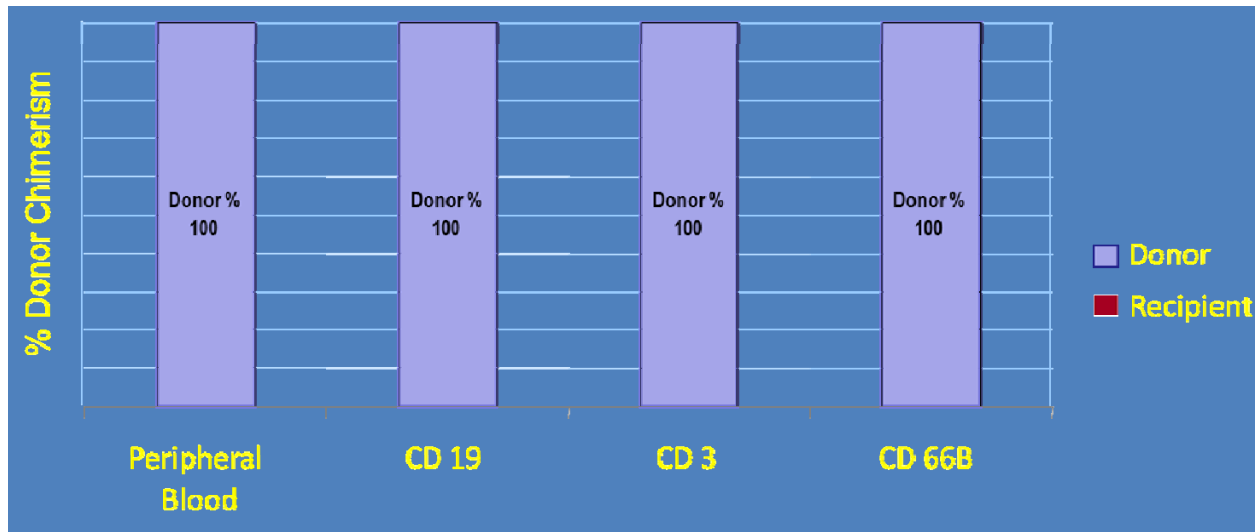
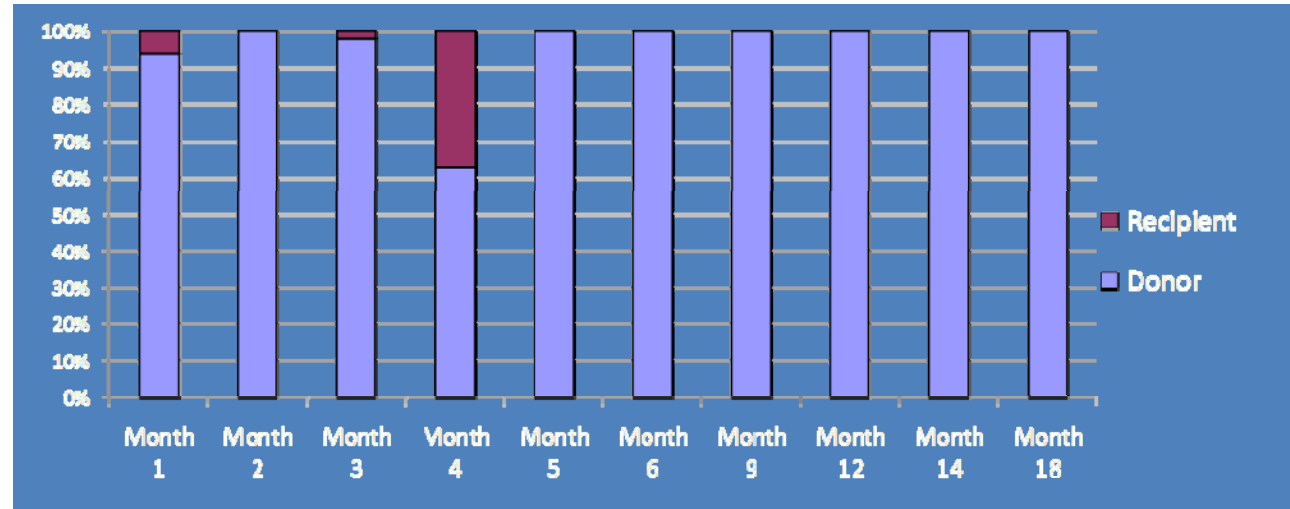


Tapering of Immunosuppression



- ❖ Discontinue MMF at 6 months if protocol Bx normal, no DSA, evidence of chimerism and/or *in vitro* donor-specific hyporesponsiveness
- ❖ Taper Prograf to subtherapeutic levels (≤ 3.0 ng/ml) by 9 months
- ❖ Discontinue Prograf at 12 months if protocol Bx normal, no DSA, evidence of chimerism and/or *in vitro* donor specific hyporesponsiveness

Subject #3 - Chimerism



Multilineage
Chimerism Testing –
Month 12



Biomarkers for Transplant

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ORIGINAL ARTICLE

Messenger RNA for *FOXP3* in the Urine of Renal-Allograft Recipients

Thangamani Muthukumar, M.D., Darshana Dadhania, M.D.,
Ruchuang Ding, M.D., Catherine Snopkowski, B.S., Rubina Naqvi, M.D.,
Jun B. Lee, M.D., Choli Hartono, M.D., Baogui Li, Ph.D., Vijay K. Sharma, Ph.D.,
Surya V. Seshan, M.D., Sandip Kapur, M.D., Wayne W. Hancock, M.D., Ph.D.,
Joseph E. Schwartz, Ph.D., and Manikkam Suthanthiran, M.D.

CTOT



Clinical Trials in Organ Transplantation

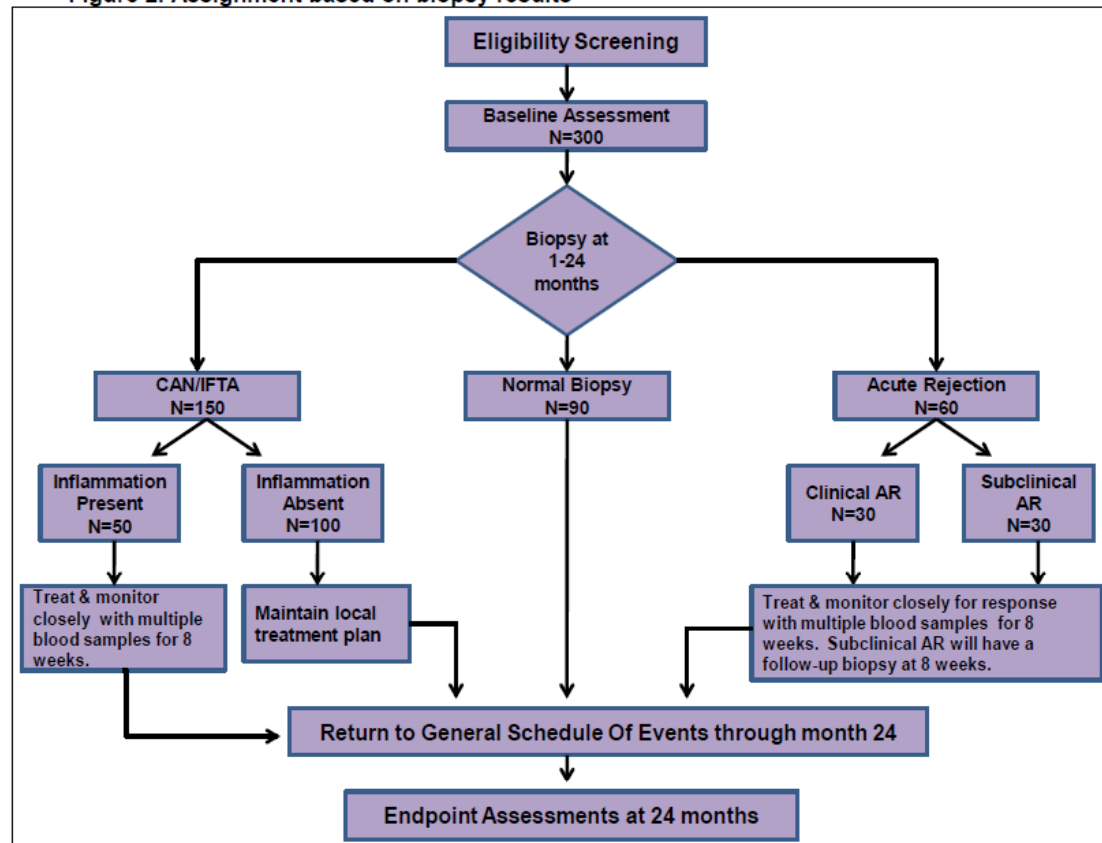
NIH sponsored clinical trials in transplantation
across organ types

Basic mechanisms of transplant immunology



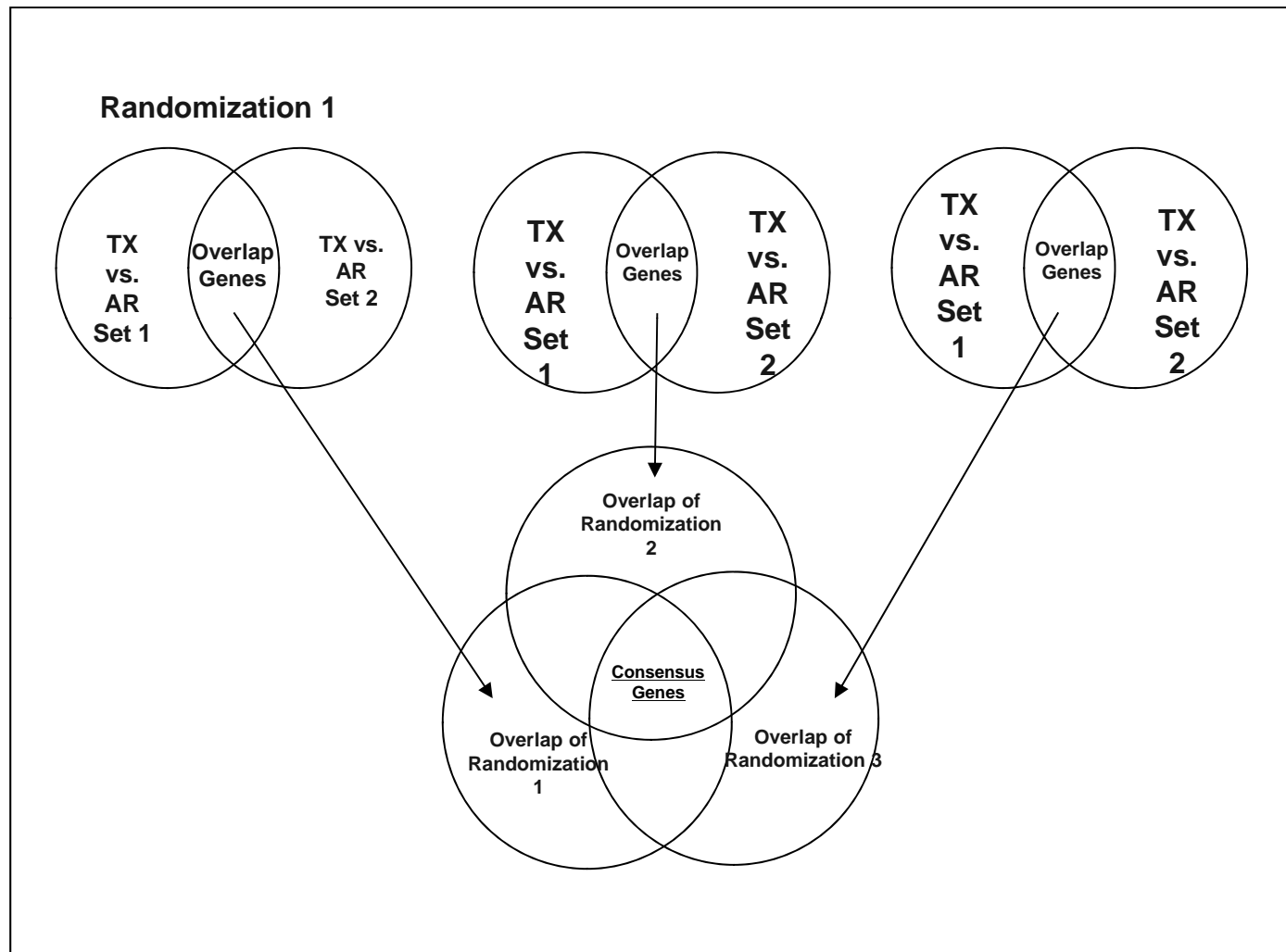
CTOT 08 – Proteogenomic Biomarkers

Figure 2. Assignment based on biopsy results





Gene Discovery Process





Goals of Better Biomarkers

More individualized therapies

-No more “one size fits all approach”

Less invasive diagnostics (fewer or no biopsies)

Better monitoring of tolerance trials

Better pre-emptive therapies promoting longer graft survival



Thank You

Questions?