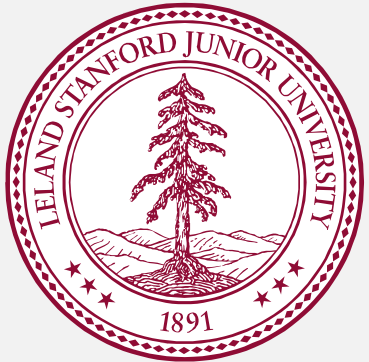
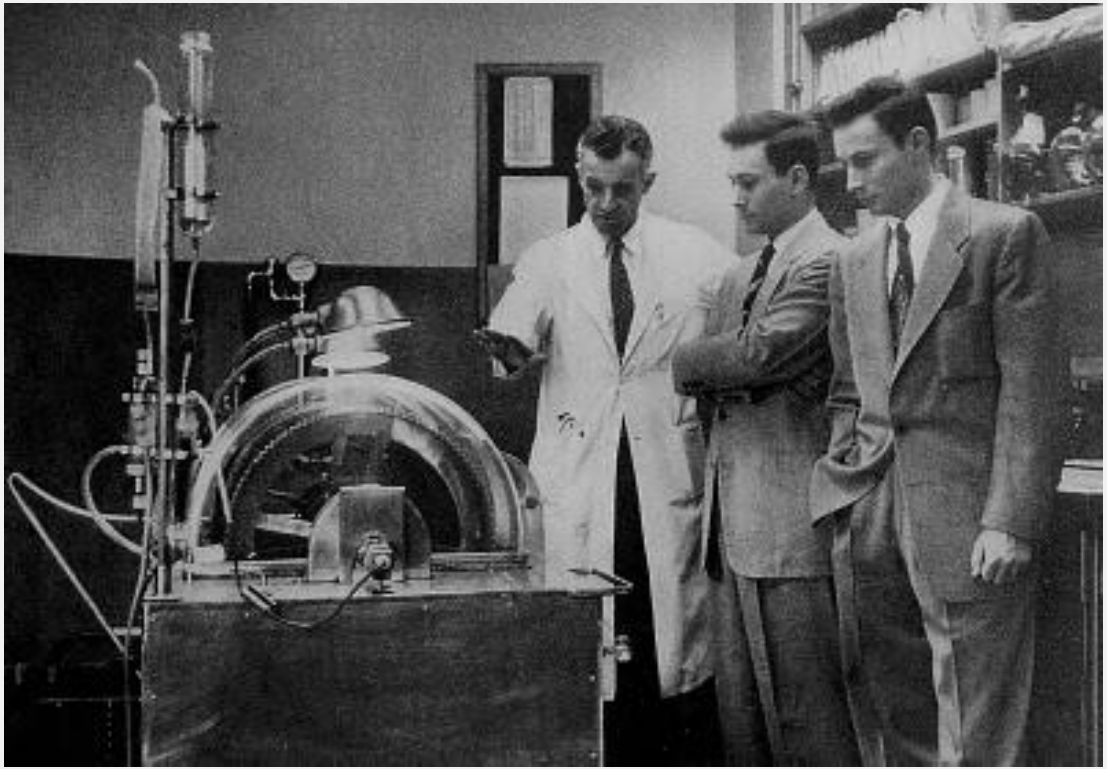
Sequential hematopoietic stem cell transplantation (HSCT) followed by kidney transplant
If successful patient is free of immunosuppression

- Paul Grimm,
- Pediatrics, Stanford University, Stanford, California, USA,

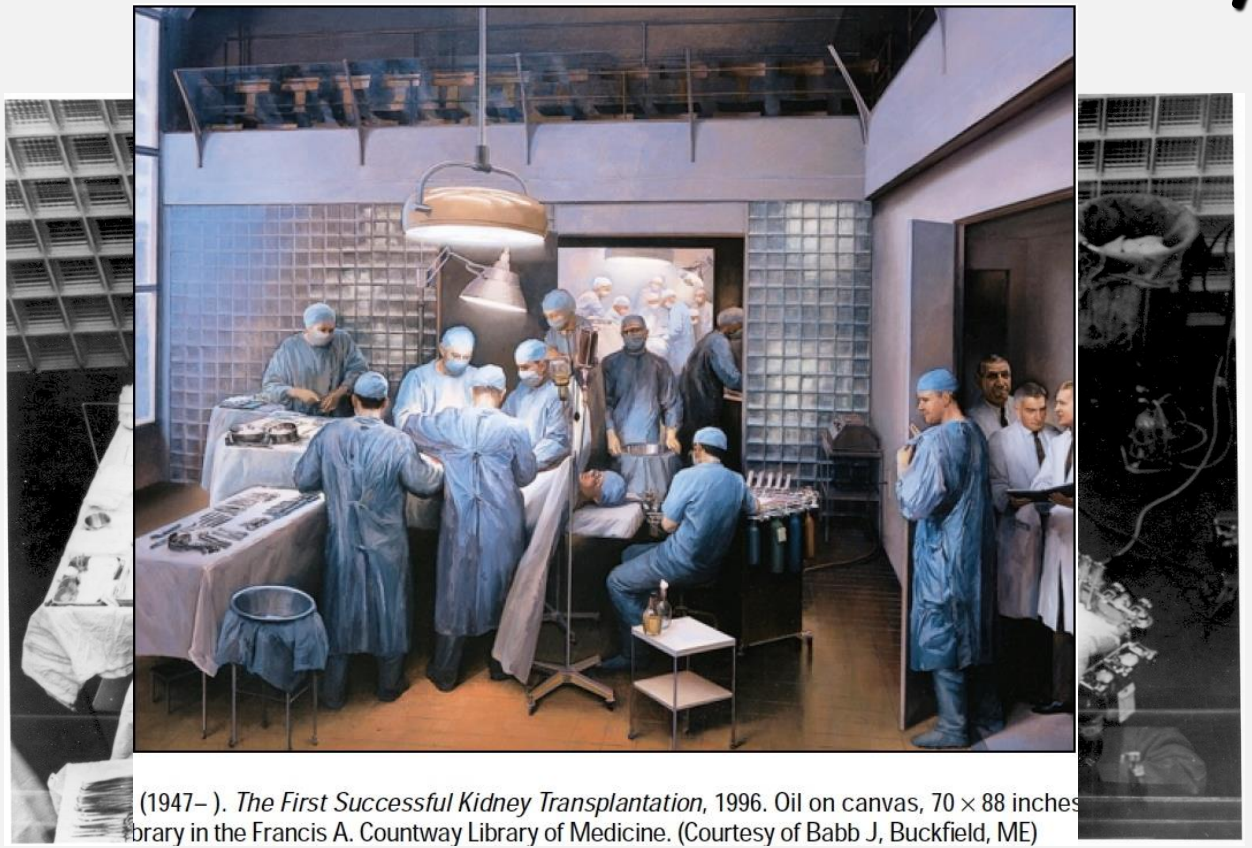


Stanford Children's Health

Dec, 23, 1954

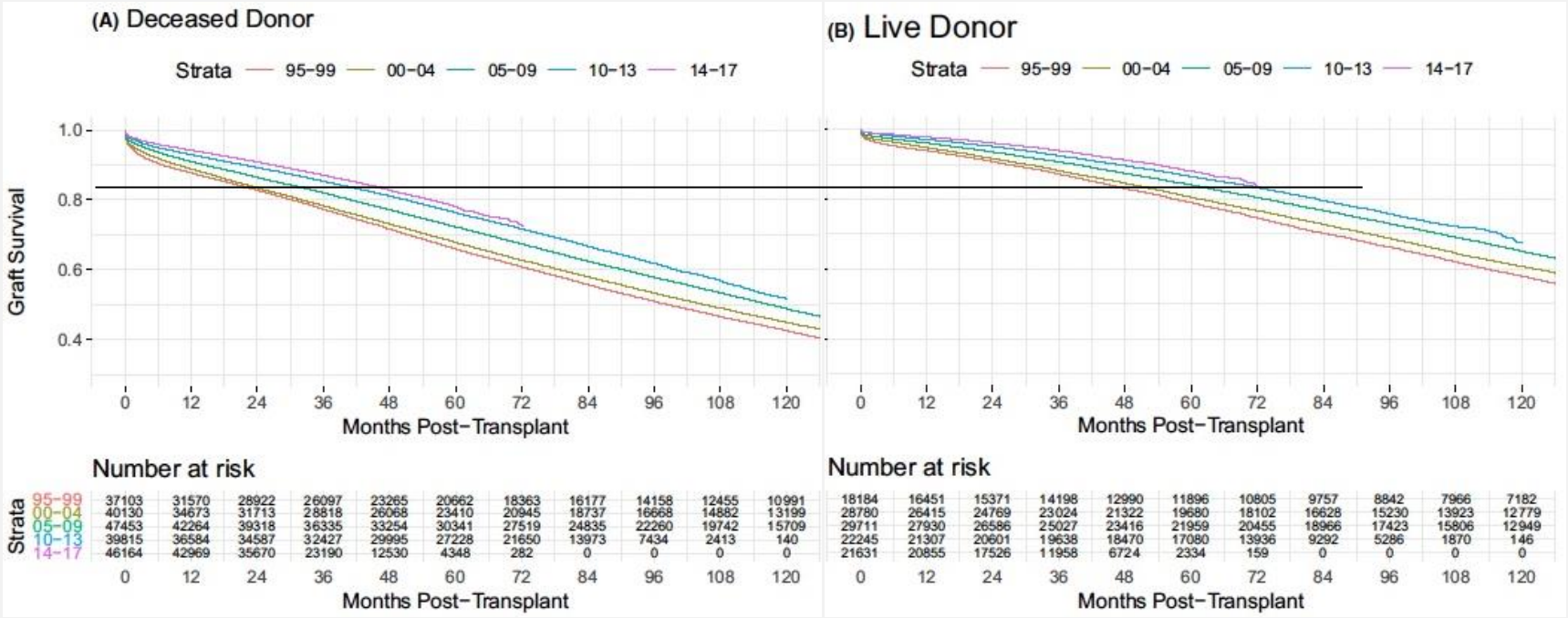


First successful identical twin kidney



(1947–). *The First Successful Kidney Transplantation*, 1996. Oil on canvas, 70 × 88 inches
brary in the Francis A. Countway Library of Medicine. (Courtesy of Babb J, Buckfield, ME)

Current Kidney Graft Outcome



ORIGINAL ARTICLE AJT

Long-term kidney transplant graft survival—Making progress when most needed

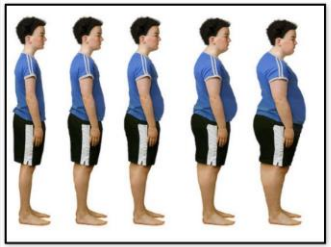
Emilio D. Poggio[1,2] | Joshua J. Augustine[1,2] | Susana Arrigain[3,4] | Daniel C. Brennan[5] | Jesse D. Schold[2,3,4]

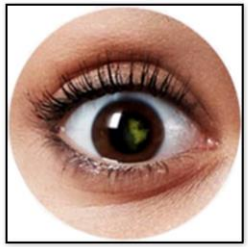
Median Kidney Transplant Survival is
11.7 years for deceased donor &
19 years for Living Donor

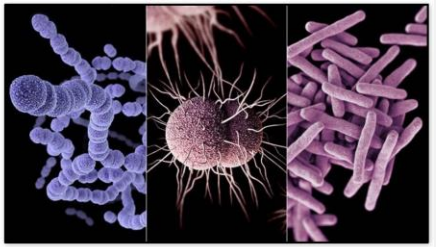
Am J Transplant. 2021;00:1–9.

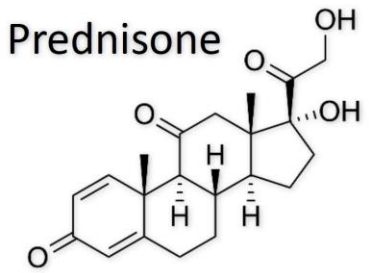
Post Transplant Problems

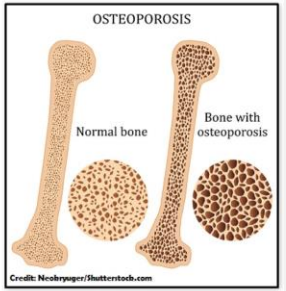
- Drug toxicity

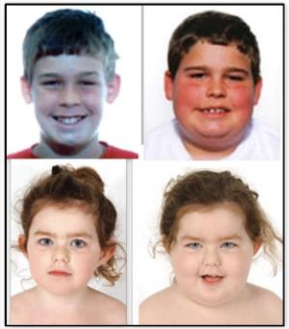


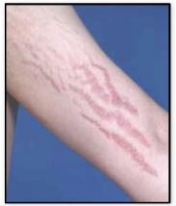


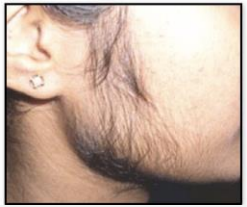


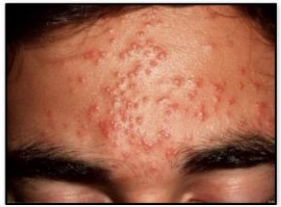












Post Transplant Problems

- Drug toxicity
- Viruses
  - EBV, CMV, BK
- New Onset Post Transplant Diabetes mellitus

Long term outcome of Pediatric Kidney Transplant

- All SOT Hospital for Sick Children, Toronto 1991-2014, 42% kidney
- Ontario Cancer Registry does NOT include non-melanoma skin cancer

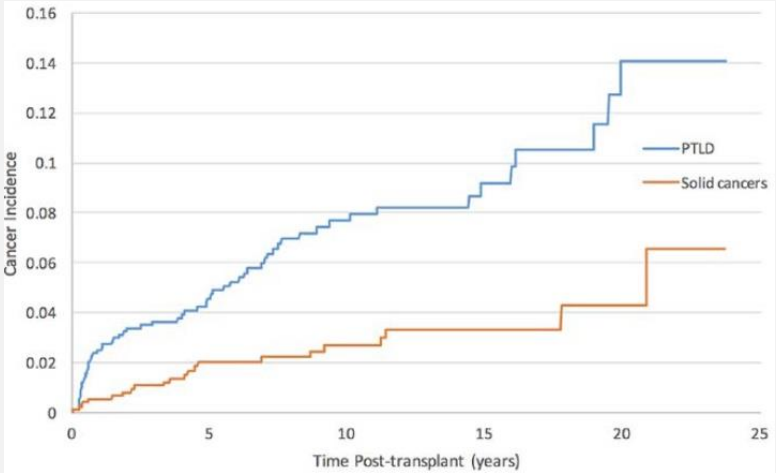
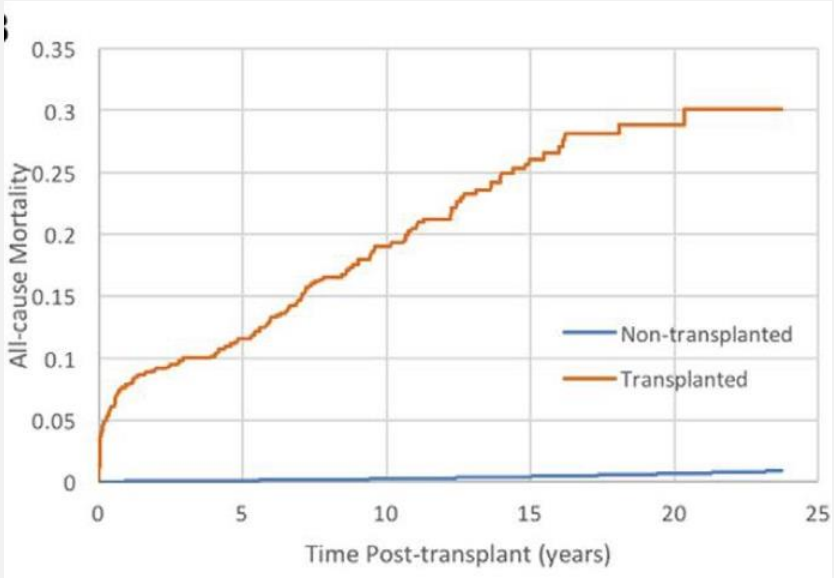


FIGURE 3. Incidence curves of solid cancers and posttransplant ymphoproliferative disorders (PTLD) among childhood transplant ecipients.



Elevated Risk of Cancer After Solid Organ Transplant in Childhood: A Population-based Cohort Study

Abhijat Kitchlu, MD,[1] Stephanie Dixon, PhD,[2,3] Jade S. Dirk,[2] Rahul Chanchlani, MD,[1,4] Jovanka Vasilevska-Ristovska, MD,[4] Karlota Borges,[4] Anne I. Dipchand, MD,[5,6] Vicky L. Ng, MD,[7] Diane Hebert, MD,[1,4] Melinda Solomon, MD,[7] J. Michael Paterson,[2,8] Sumit Gupta, MD, PhD,[2,9] S. Joseph Kim, MD, PhD,[1,2,8] Paul C. Nathan, MD,[2,4] and Rulan S. Parekh, MD, FRCPC[1,4,7]

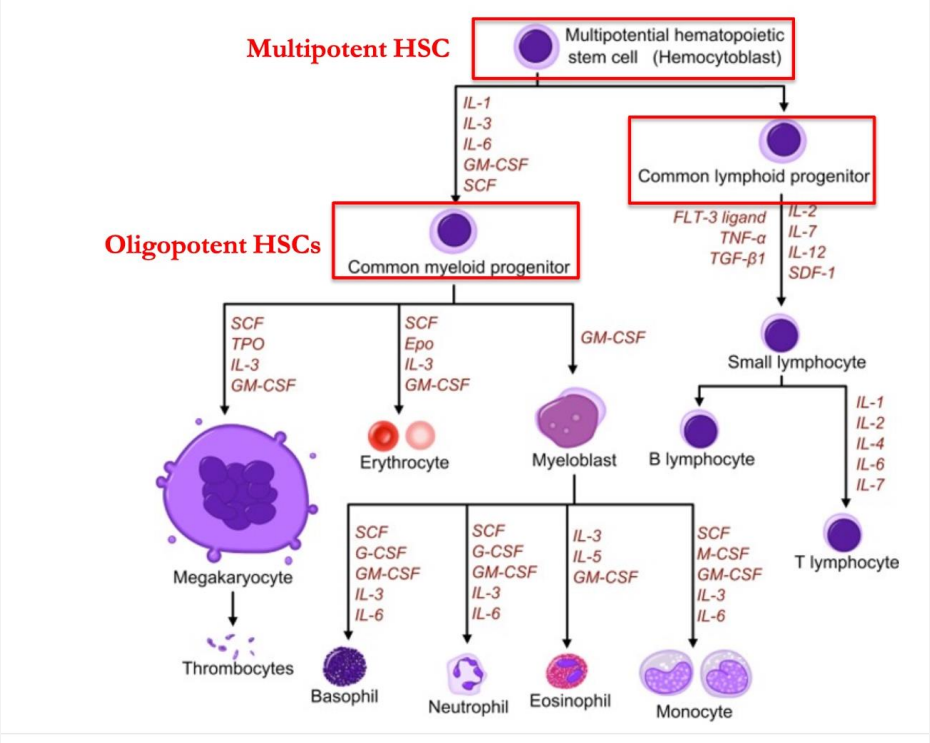
PROBLEM

- Immunosuppression prevents rejection
- ALSO reduces the body's defenses
  - Cancer
  - Infection
- Immunologic processes that cause rejection are the same ones that protect from infection and cancer

Tolerance through Chimerism

Stem Cells

- Only about 10,000 in your body
- Divide maybe once every year or so



Goal of Stem Cell Transplantation->Chimerism

- Mixed-
  - Stem cells of donor and recipient coexist
  - Little risk of Graft vs Host Disease (GvHD) and low risk of infection

-

Mixed Chimerism for Kidney Transplant
The ONE Study

- 8 Centers
- 6 different cell recipes

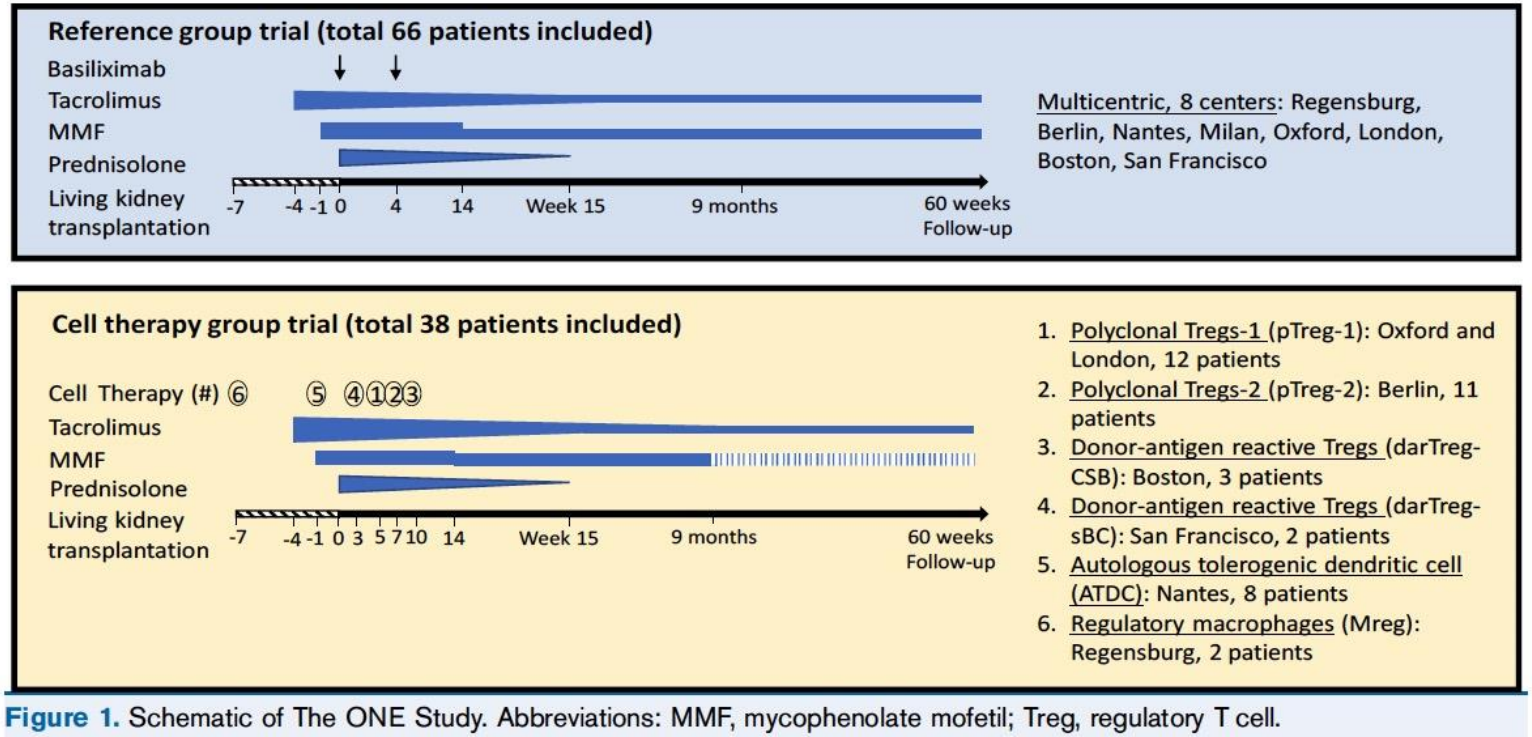
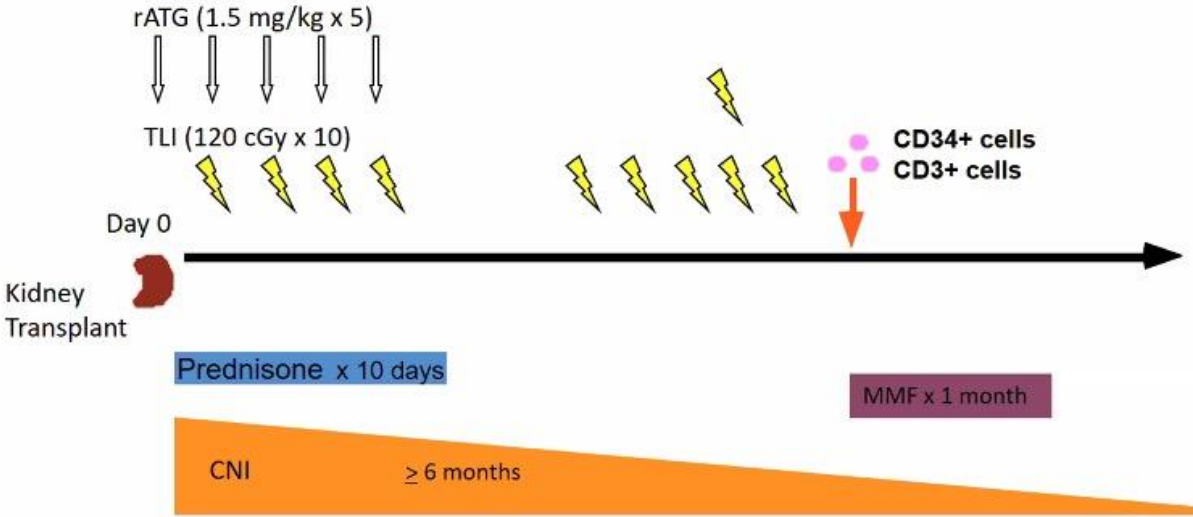


Figure 1. Schematic of The ONE Study. Abbreviations: MMF, mycophenolate mofetil; Treg, regulatory T cell.

Mixed Chimerism-Stanford Adult Tolerance Protocol

Stanford Tolerance Induction

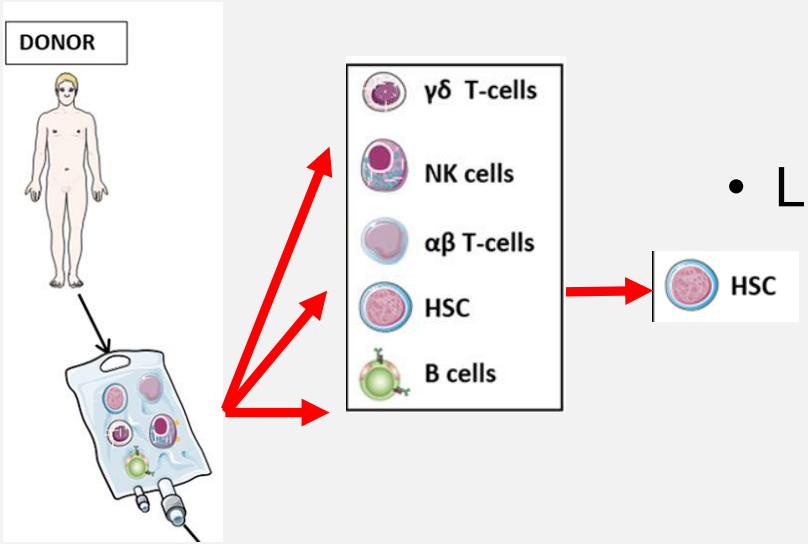
HLA-matched Kidney and Hematopoietic Cell Transplantation



Withdraw immunosuppression if:
-stable mixed chimerism >180 days
-no evidence of rejection
-no GVHD

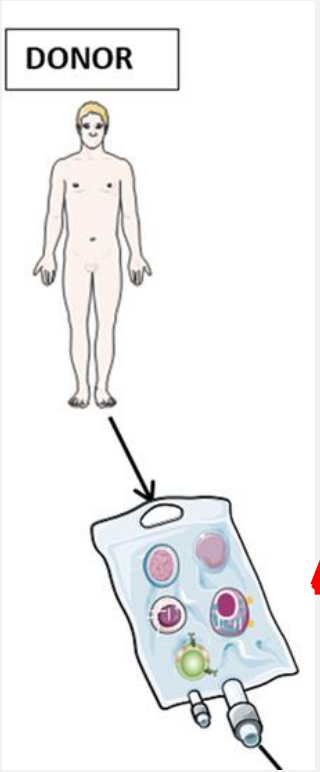
Stanford MEDICINE

GvHD is caused by cells that are NOT the stem cells…
So why not just give the stem cells?



- Lonely Stem cells need a village
  - Don’t grow well
  - Get rejected
  - Patient gets infections

What cells cause GvHD?



γδ T-cells

NK cells

αβ T-cells

HSC

B cells

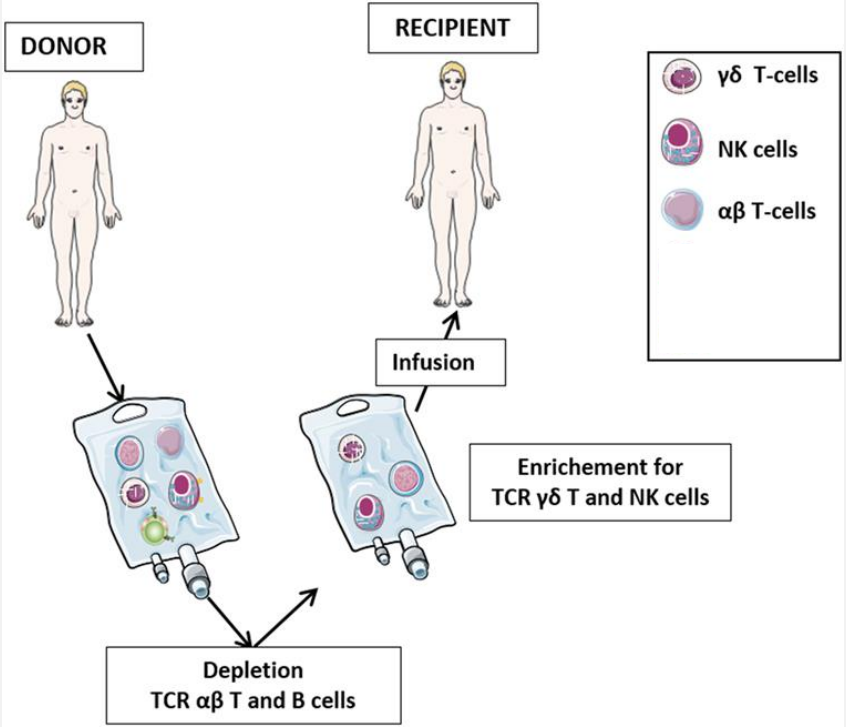
Protect against infection AND support the new stem cells

Cause GvHD

Carry EBV and cause PTLD

Stanford Children's

- αβ T-cell depletion: decrease risk of GvHD
- CD19+ B-cell depletion/Rituximab: to prevent EBV reactivation and PTLD



Engineered Stem Cell Infusion

- >70 Patients
- Metabolic disease, immune deficiency, bone marrow failure, genetic disease
- Very low rates of infection/graft failure/ need for retransplant or death

TCRαβ/CD19 depleted HSCT from an HLA-haploidentical relative to treat children with different nonmalignant disorders

Pietro Merli,[1] Daria Pagliara,[1] Federica Galaverna,[1] Giuseppina Li Pira,[1] Marco Andreani,[2] Giovanna Leone,[3] Donato Amodio,[4] Rita Maria Pinto,[1] Alice Bertaina,[1] Valentina Bertaina,[1] Angela Mastronuzzi,[1] Luisa Strocchio,[1] Emilia Boccieri,[1] Daniela Pende,[5] Michela Falco,[6] Matteo Di Nardo,[7] Francesca Del Bufalo,[1,*] Mattia Algeri,[1,*] and Franco Locatelli[1,8,*]

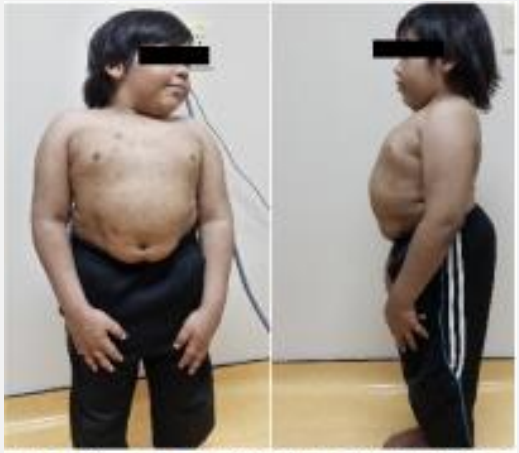
[1]Department of Pediatric Hematology/Oncology, Cell and Gene Therapy, [2]Laboratory of Transplantation Immuno-genetics, [3]Transfusion Unit, Department of Laboratories, [4]Academic Department of Pediatrics, Clinical Immunology and Vaccinology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [5]Laboratory of Immunology, IRCCS San Martino Hospital, Genoa, Italy; [6]Laboratory of Clinical and Experimental Immunology, Integrated Department of Services and Laboratories, IRCCS Giannina Gaslini Institute, Genoa, Italy; [7]Pediatric Intensive Care Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; and [8]Sapienza, University of Rome, Rome, Italy

Aβ T-Cell/CD19 B-Cell Depleted Haploidentical Stem Cell Transplantation: A New Platform for Curing Rare and Monogenic Disorders

Alice Bertaina MD, PhD[1], Rosa Bacchetta MD[1], David B. Lewis MD, PhD[2], Paul C. Grimm MD[3], Ami J. Shah MD[4], Rajni Agarwal MD[1], Waldo Concepcion MD[5], Agnieszka Czechowicz MD, PhD[6], Neehar Bhatia PhD[7], Premanjali Lahiri PhD[8], Kenneth I Weinberg MD[9], Robertson Parkman MD[1], Matthew Porteus MD, PhD[10], Maria Grazia Roncarolo MD[1,11]. [1] Division of Stem Cell

Schimke Immuno-Osseous Dysplasia (SIOD)

- Autosomal recessive disorder, mutation of the SMARCAL1 gene
  - SMARCAL1 -annealing helicase important for DNA repair
- 1/ 10^6 to $3x10^6$ births
- Progressive, multisystem disorder
- Short stature with spondyloepiphyseal dysplasia (dwarfism),
- T-cell deficiency
- Kidney failure before age 10
- Bone marrow failure
- Strokes and death in the 20's
- Kidney Transplant outcome- POOR
  - Infection
  - Rejection
  - Cancer
  - GVHD



Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

Stem Cell & Kidney Transplant Protocol for Schimkes

- Stem cell transplant
- If 100% chimeric (i.e. the donor bone marrow has “taken”)
- Living donor kidney transplant from donor who gave stem cells.
- No immunosuppression needed
- No risk of rejection
- No risk of PTLD, Cancer, Nonadherence
- No “countdown to the next kidney transplant”

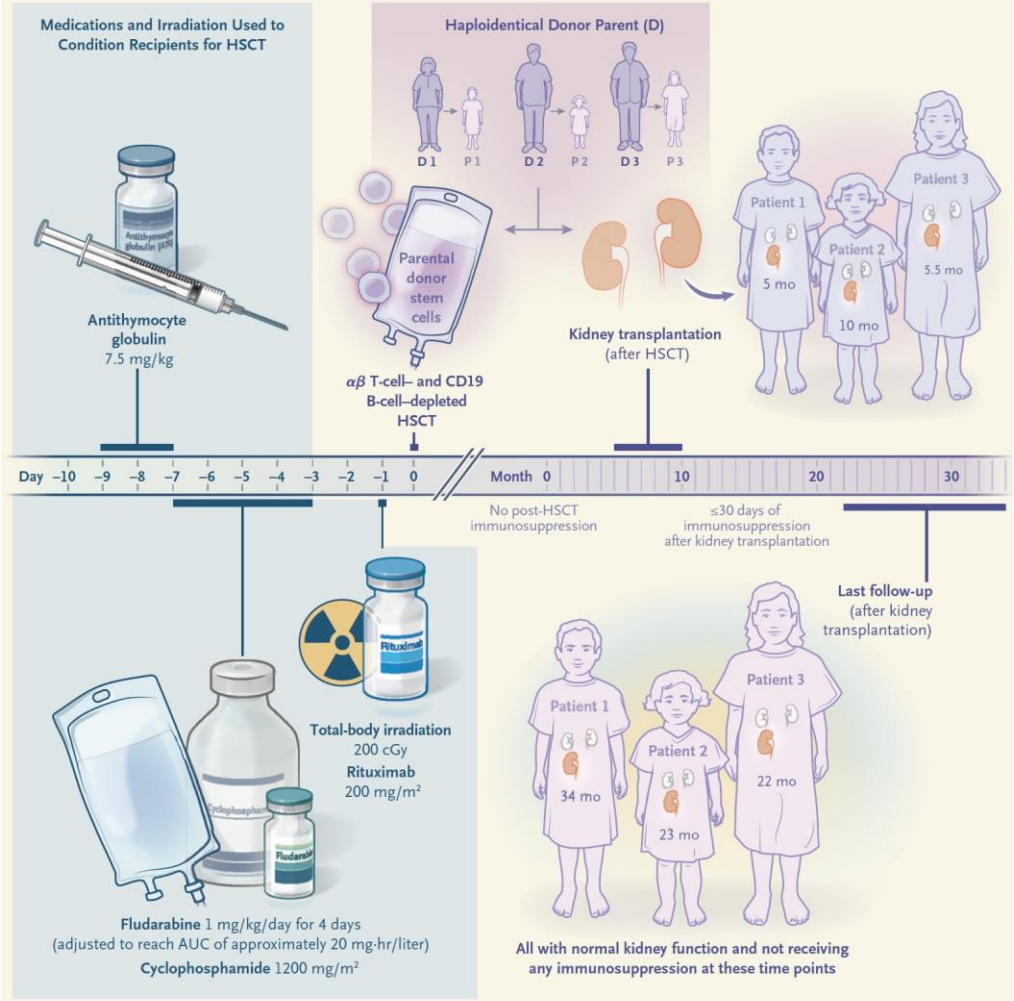


Figure 1. Sequential αβ T-Cell–Depleted and CD19 B-Cell–Depleted Haploidentical HSCT and Kidney Transplantation in Three Patients with SIOD.

Outcome- Short Term

- Engraftment by day 15 for WBC and platelets
- 1 patient mild skin GVHD
  - Treated with burst of prednisone & fully recovered
- Kidney transplant from SCT donor
  - 5-10 months post SCT
  - Steroid and tacrolimus taper withdrawn by 1 month post transplant

Outcome- Long Term

- 20, 21, 32 months, after kidney transplant
  - GFR> 100,
  - no immunosuppression
  - no complications
  - 100% chimerism
- Mixed Lymphocyte Culture
  - Donor specific- nonresponse ~ tolerance
  - 3rd party and Mitogen- Normal response

3 Schimke Patients

Milestone

- The first time pediatric SCT was performed with the express purpose of immunosuppression for an organ transplant
- Benefits seem to outweigh the risks
- Long term follow-up needed

- Moving Forward
  - FDA Approved expanded indication (IDE)

Working toward the future

- Is this safe???
- Genetic disease like Cystinosis
- Diseases which may come back in the transplanted kidney (FSGS, IgA nephropathy and Lupus)
- Otherwise normal children and teens with high risk of nonadherence
- Resource limited areas of the world?
- Other organs like living donor liver?
- Maybe any transplant?

4th patient- Focal Segmental GlomeruloSclerosis

- **First** kidney transplant from mom
  - Lost in 3 months from recurrent FSGS
- On HD for 10 years… considering stopping dialysis
- α/βT cell depleted, CD19 depleted stem cell transplant.
  - Conditioning was with 7.5 mg/kg rabbit anti-thymocyte globulin, 100 mg/kg cyclophosphamide, fludarabine (27.5mg initial dose & pharmacokinetics determined subsequent 3 doses) melphalan 100 mg/m², rituximab 200 mg/m² and a single dose of 200 cGy total body irradiation
  - 13.6×10^6/kg CD34 positive stem cells and 0.1×10^5/kg TCR α/β T cells
  - Platelets and neutrophils engrafted day 14.
- Readmitted for Graft vs Host Disease (Skin Grade 4, Liver Grade 2) which responded to therapy
- Readmitted for intensive nutrition and rehabilitation.

4th patient- FSGS

- On SCT day #362 he received a living donor kidney transplant from the SCT donor dad
- Post Transplant course uneventful
- Last followup, 4.25 months after kidney transplant, normal kidney function

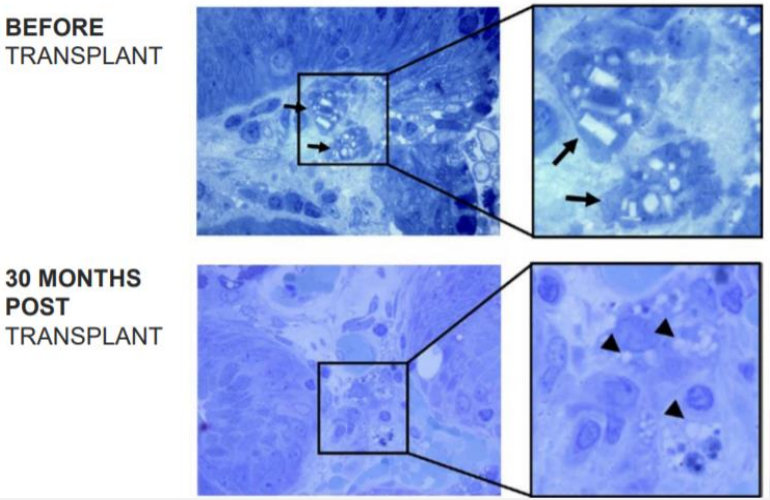
First SCT for human cystinosis

Allogeneic transplant demonstrated stabilized renal function, corrected polyuria and improved photophobia

Allogenic HSC Transplant
University Hospital Leuven

- 16 year old male
- Diagnosed at 2.7 years old, started on cysteamine
- Age 15 years – cysteamine toxicity
- Age 16 years – fully matched HLA transplant
- Acute GvHD
- **First few months**
  - **Kidney function stabilized**
  - **Polyuria resolved**
- **6 months**
  - **Photophobia score reduced from 5 (unable to open eyes even inside dark room) to 0 (no photophobia)**

Cystine crystal reduction (31%) in macrophages in gastric mucosa at 30 months post transplant



Mohamed A. Elmonem[1,2] | Koenraad Veys[1] | Fanny Oliveira Arcolino[1] | Maria Van Dyck[1] | Maria C. Benedetti[3] | Francesca Diomedi-Camassei[3] | Gert De Hertogh[4] | Lambertus P. van den Heuvel[1,5] | Marleen Renard[6] | Elena Levtchenko[1]

Am J Transplant. 2018;18:2823–2828.

First SCT for human cystinosis

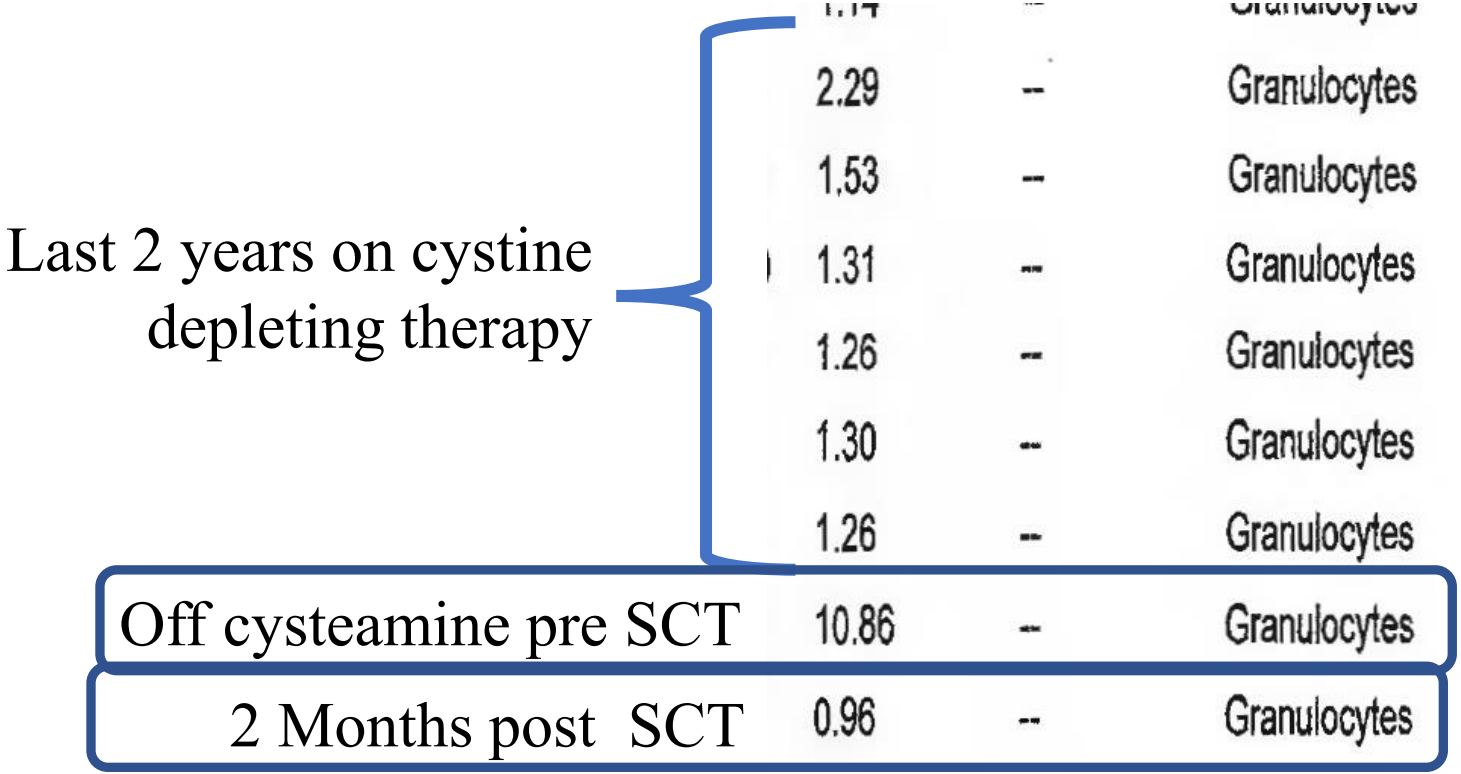
- Moderate to severe GvHD
- Adenovirus & Parvovirus Infections
- Brain injury (pontine myelinolysis) with seizure, reduced level of consciousness
- Salvage stem cell transplant
- Kidney failure-> dialysis
- Pneumonia and died at age 19

5th Patient- Cystinosis

- 15 year old, CKD 4
- Central catheter, Testicular sperm harvest, stored pheresis stem cells for rescue
- The following month started conditioning
  - TBI 200cGy, Melphalan, Fludarabine, Cyclophosphamade, ATG, Rituximab
- Engrafted day 12, discharged from hospital day 21

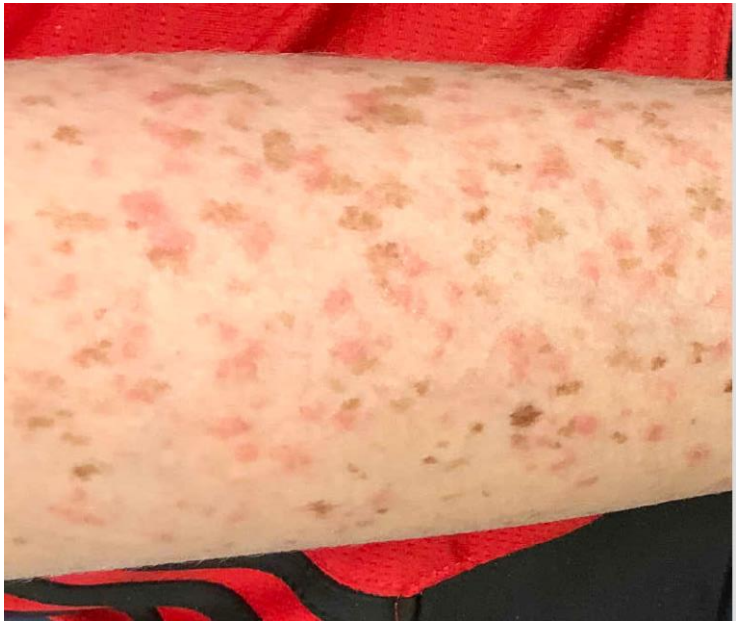
- Plan Kidney Transplant at 6 months post SCT

5th Patient- Cystinosis- Granulocyte Cystine (<1.9)



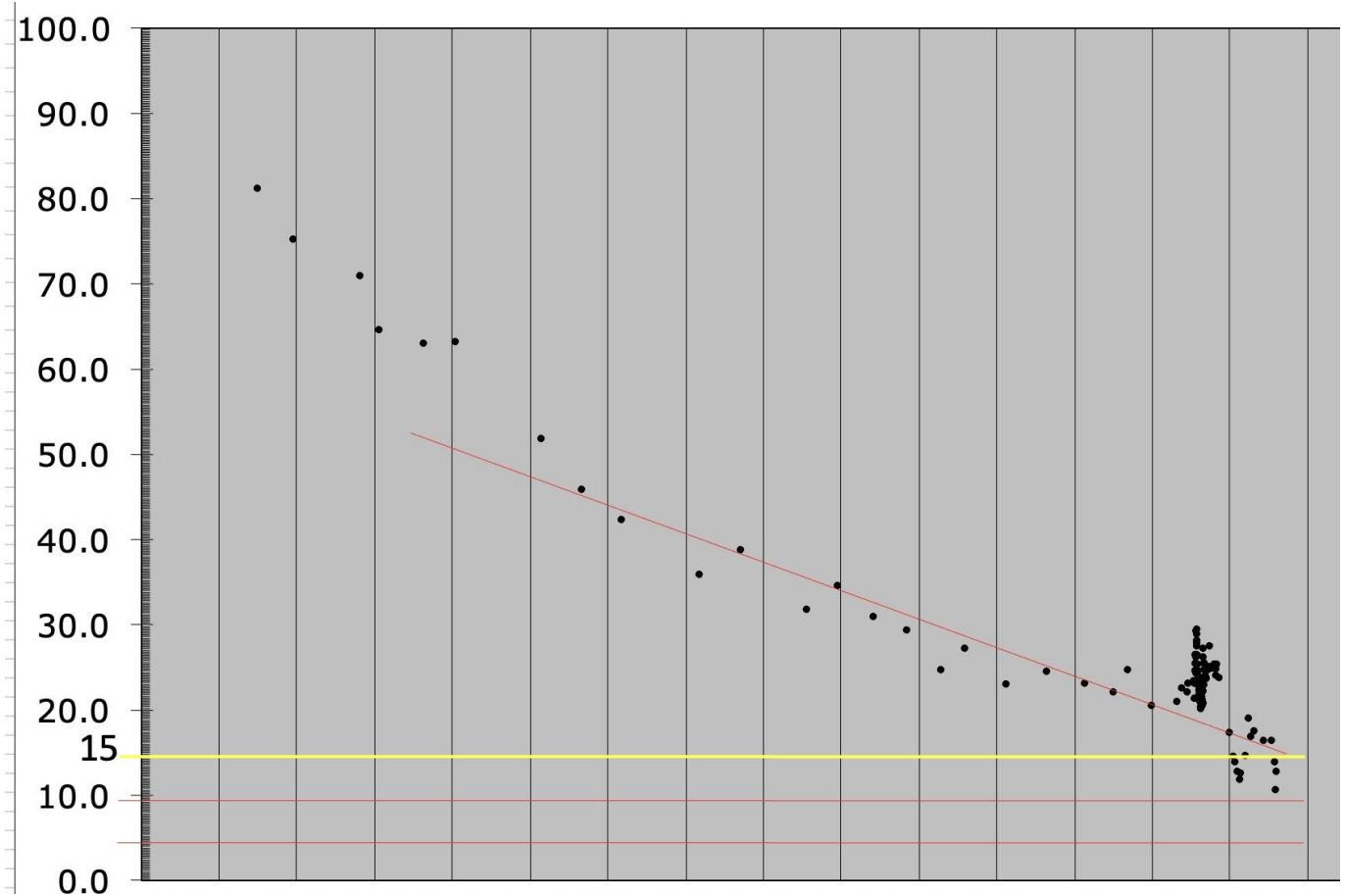
5th Patient- Cystinosis, Skin Problems

- Month 0.5- Biopsy #1 maybe drug induced spongiotic dermatitis
- Month 5- Biopsy #2 maybe GVHD or phototoxicity
  - Started steroids,
- Month 6, rash better but HHV6 positive so started valganciclovir and weaned steroids
- Month 6.5 rash worse, Biopsy #3 maybe GVH, maybe drug induced
  - added tacrolimus



No cystine crystals in 2 month biopsy using glutaraldehyde fixation

5th Patient- Cystinosis- GFR



5th Patient- Cystinosis

- Month 7 rash better but now uremic & hypertensive, trilineage bone marrow suppression, ill with infected line
- Admit to hospital, antibiotics, change line, start dialysis
- Within few days, back to himself, feeling well, appetite great and labs improving
- Rash nicely improved with no other sign of GVHD
  - wean steroids

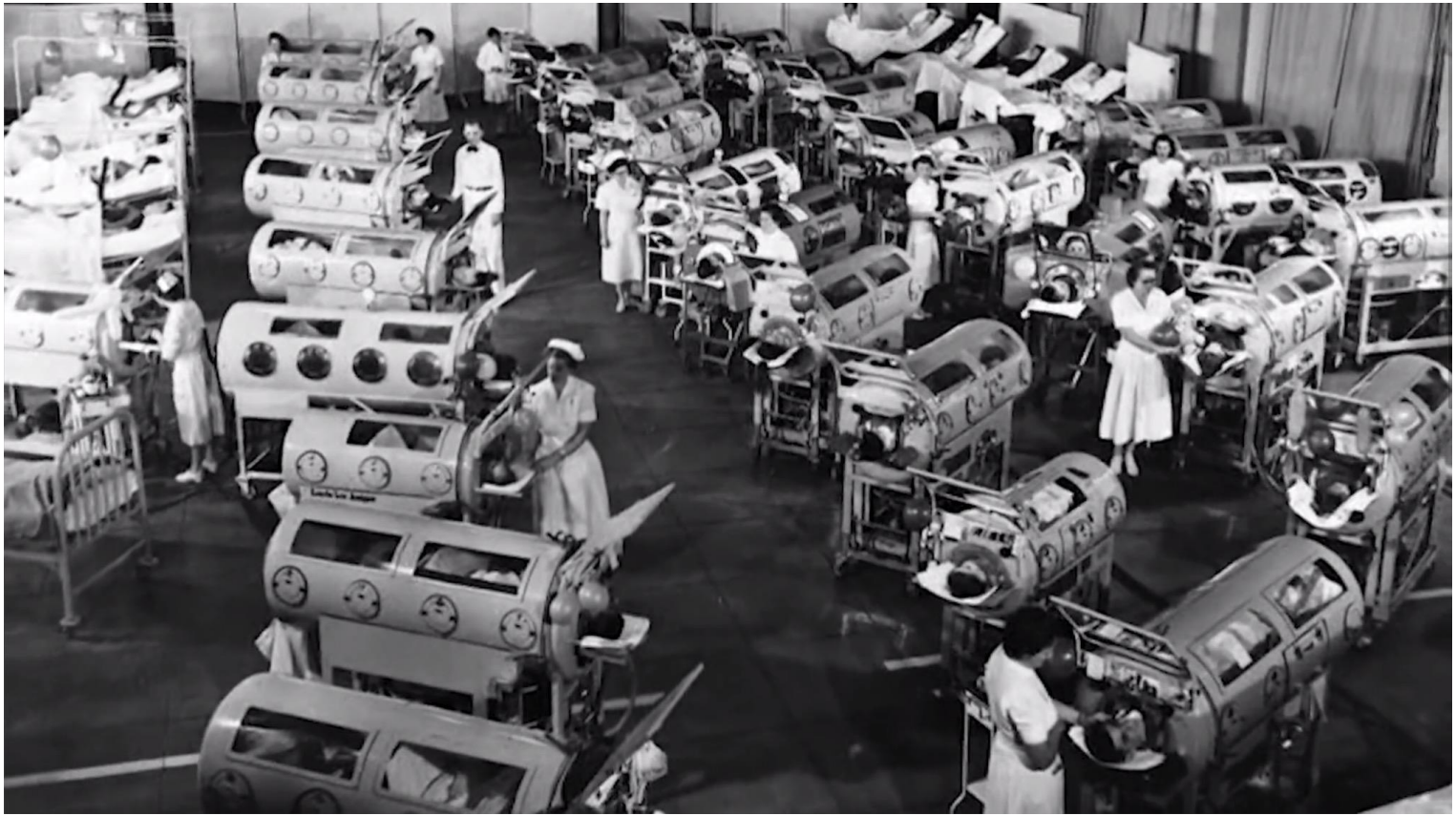
5th Patient- Cystinosis

- When does he get to the Kidney Transplant?

Goal of the Research

“Once a idney patien lways a kid y patient”

Why Research?



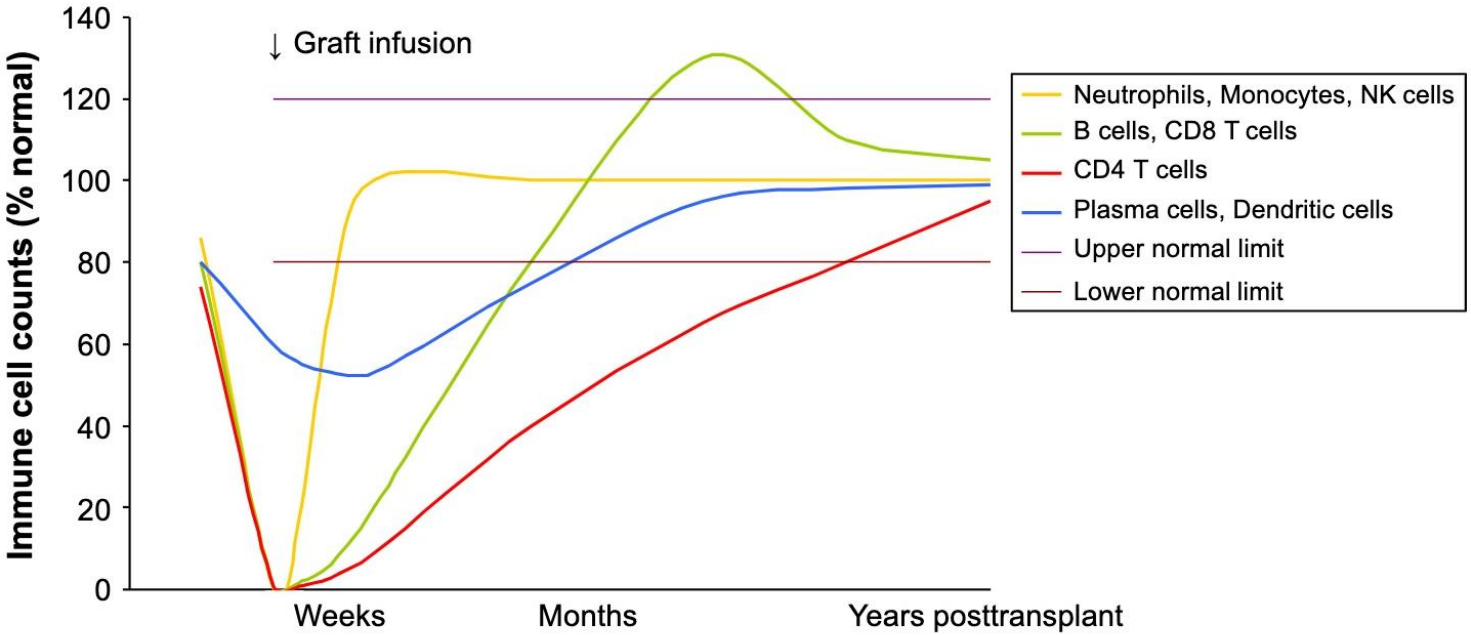
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Sequential Stem Cell–Kidney Transplantation in Schimke Immuno-osseous Dysplasia

Alice Bertaina, M.D., Ph.D., Paul C. Grimm, M.D., Kenneth Weinberg, M.D., Robertson Parkman, M.D., Karen M. Kristovich, P.N.P., Giulia Barbarito, M.S., Elizabeth Lippner, M.D., Girija Dhamdhere, Ph.D., Vasavi Ramachandran, M.S., Jordan M. Spatz, M.D., Ph.D., Sahar Fathallah-Shaykh, M.D., T. Prescott Atkinson, M.D., Ph.D., Amira Al-Uzri, M.D., Geraldine Aubert, Ph.D., Kim van der Elst, Ph.D., Sean G. Green, Pharm.D., Rajni Agarwal, M.D., Priscila F. Slepicka, Ph.D., Ami J. Shah, M.D., Maria G. Roncarolo, M.D., Ph.D., Amy Gallo, M.D., Waldo Concepcion, M.D., and David B. Lewis, M.D.

It may take years for the immune system to completely return to normal after HSCT



Expert Opin Biol Ther (Informa). 2008;8:583-597.

Stanford Children's Stem Cell & Kidney Transplant Protocol (3)

- Offering to pediatric genetic disease patients (including cystinosis)
- Haploidentical or fully matched living donor
  - (Unmatched maybe/some day)
- Pre dialysis or on dialysis acceptable
- No strong DSA