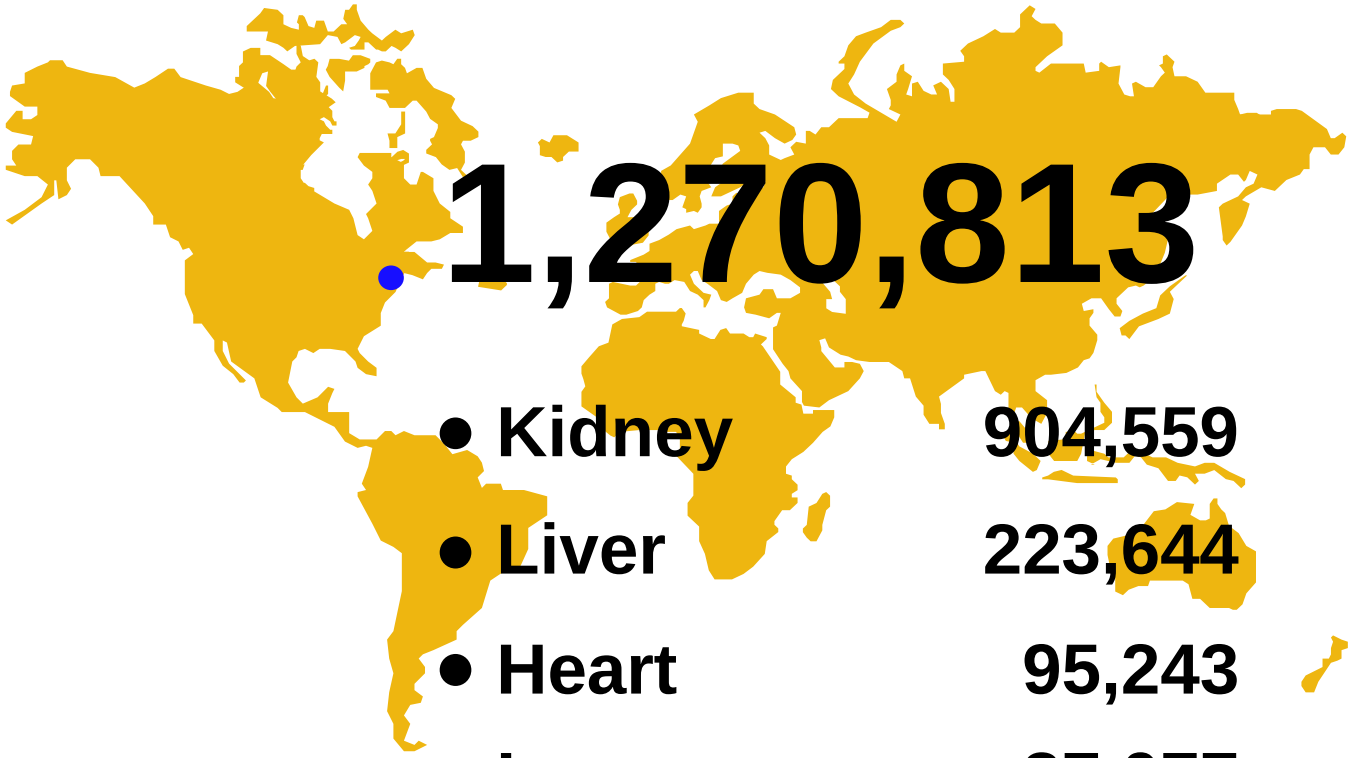
Trapianto di organi: da dove siamo partiti e dove vorremmo (forse) arrivare

NORBERTO PERICO

Pesaro – 13 novembre 2019

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

SOLID ORGAN TRANSPLANTS PERFORMED WORLDWIDE UP TO 2012



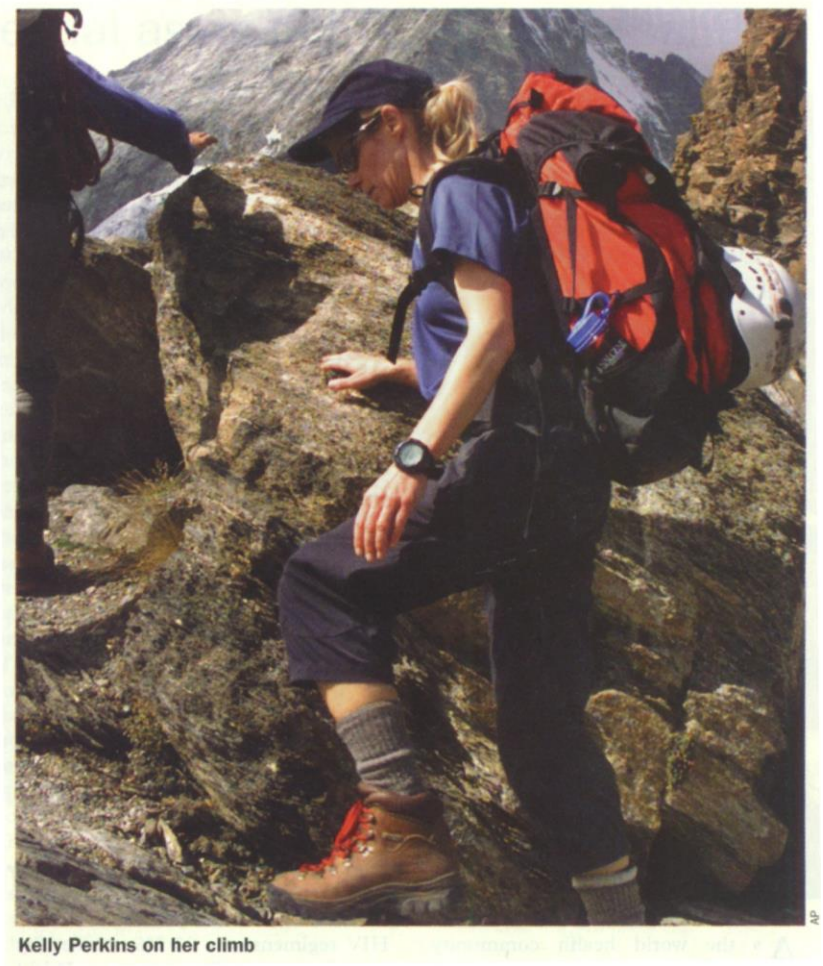
1,270,813

• Kidney	904,559
• Liver	223,644
• Heart	95,243
• Lung	37,077
• Pancreas	8,961
• Intestine	1,329

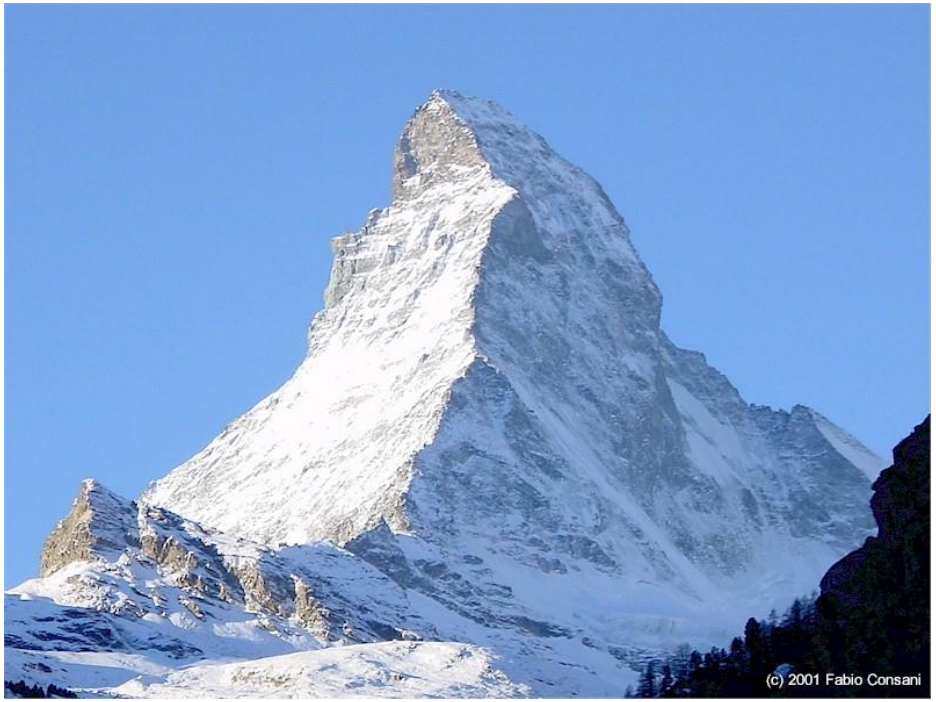
Clin Transplant, 2012

HEART TRANSPLANT RECIPIENT CLIMBS THE MATTERHORN (Swiss Alps)

42-year-old Kelly Perkins becomes the first person with a heart transplant to ascend the 4478-m peak



Kelly Perkins on her climb

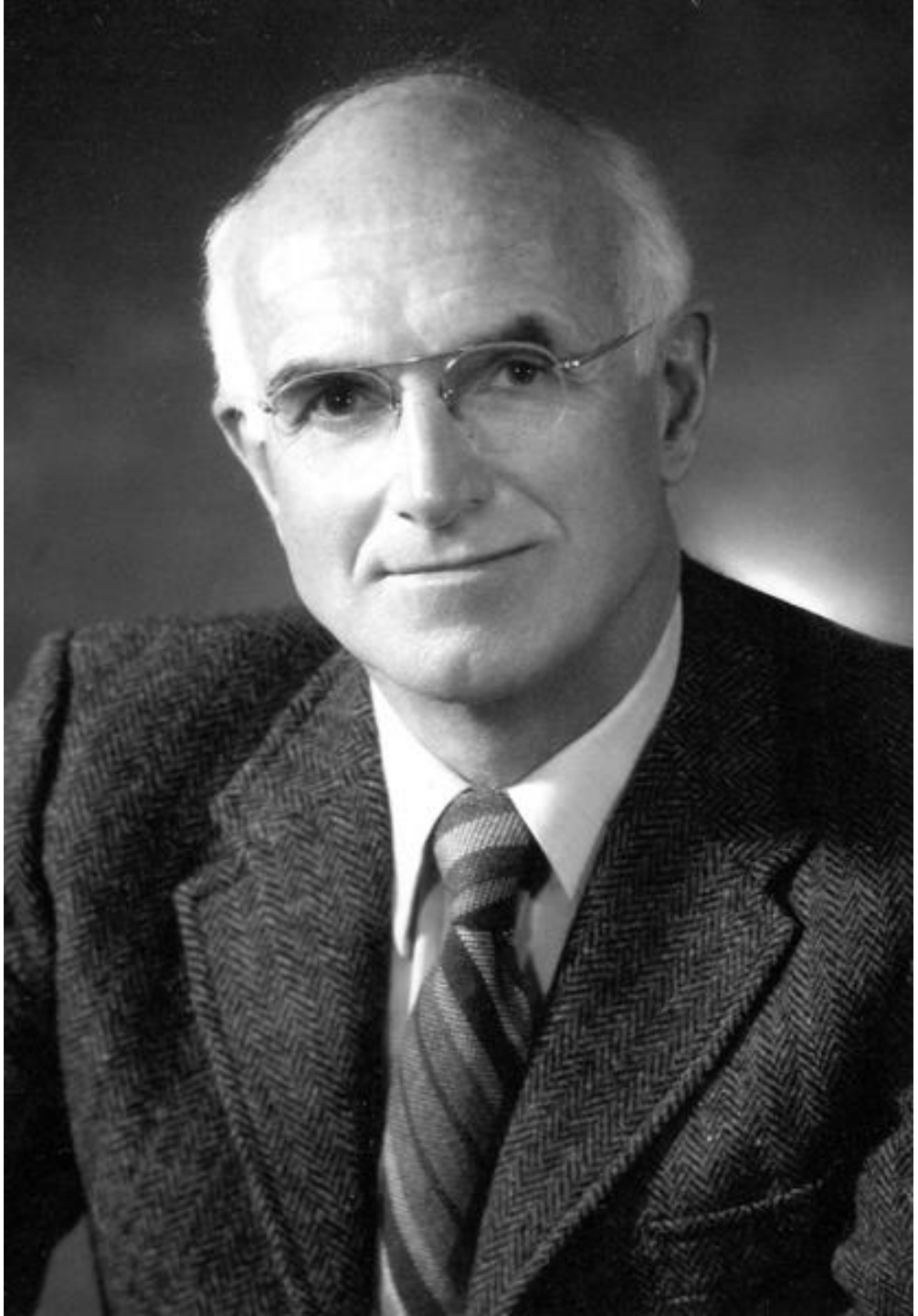


The Matterhorn in Zermatt, Switzerland

Lancet, 2003

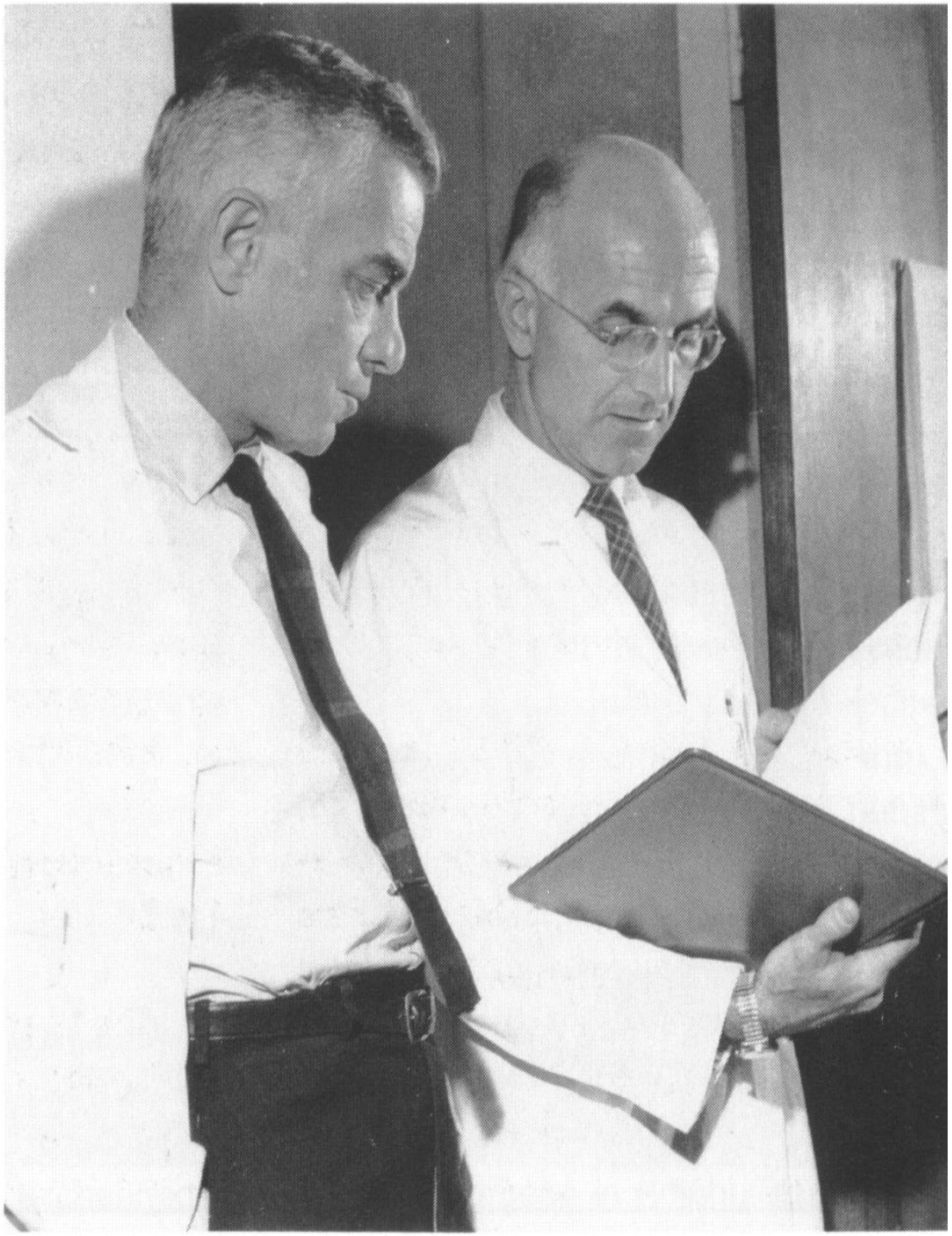
Nel 1951 il dottor David Hume e i suoi collaboratori all'Ospedale Peter Bent Brigham di Boston, eseguirono il primo trapianto di rene da un donatore cadavere, in un paziente che stava per morire per insufficienza renale acuta

In quell'anno e nel successivo Hume, in collaborazione con il dott Merrill, eseguì altri 9 trapianti da un soggetto ad un altro, posizionando il rene trapiantato nel braccio o nella coscia del ricevente



L'idea dei gemelli identici

A Boston nel 1954 il dottor J.P. Merril e il dottor J.E. Murray ragionarono che i gemelli identici, come non rigettavano il trapianto di cute, non avrebbero dovuto rigettare neppure il rene



“By the summer of 1954, we knew we’d solved the surgical barrier because we’d had dogs running around the labs with normally functioning transplanted kidneys for a couple of years”

Joseph E. Murray

The twins were Richard and Ronald Herrick (that they were identical was established with fingerprints with help of the police)

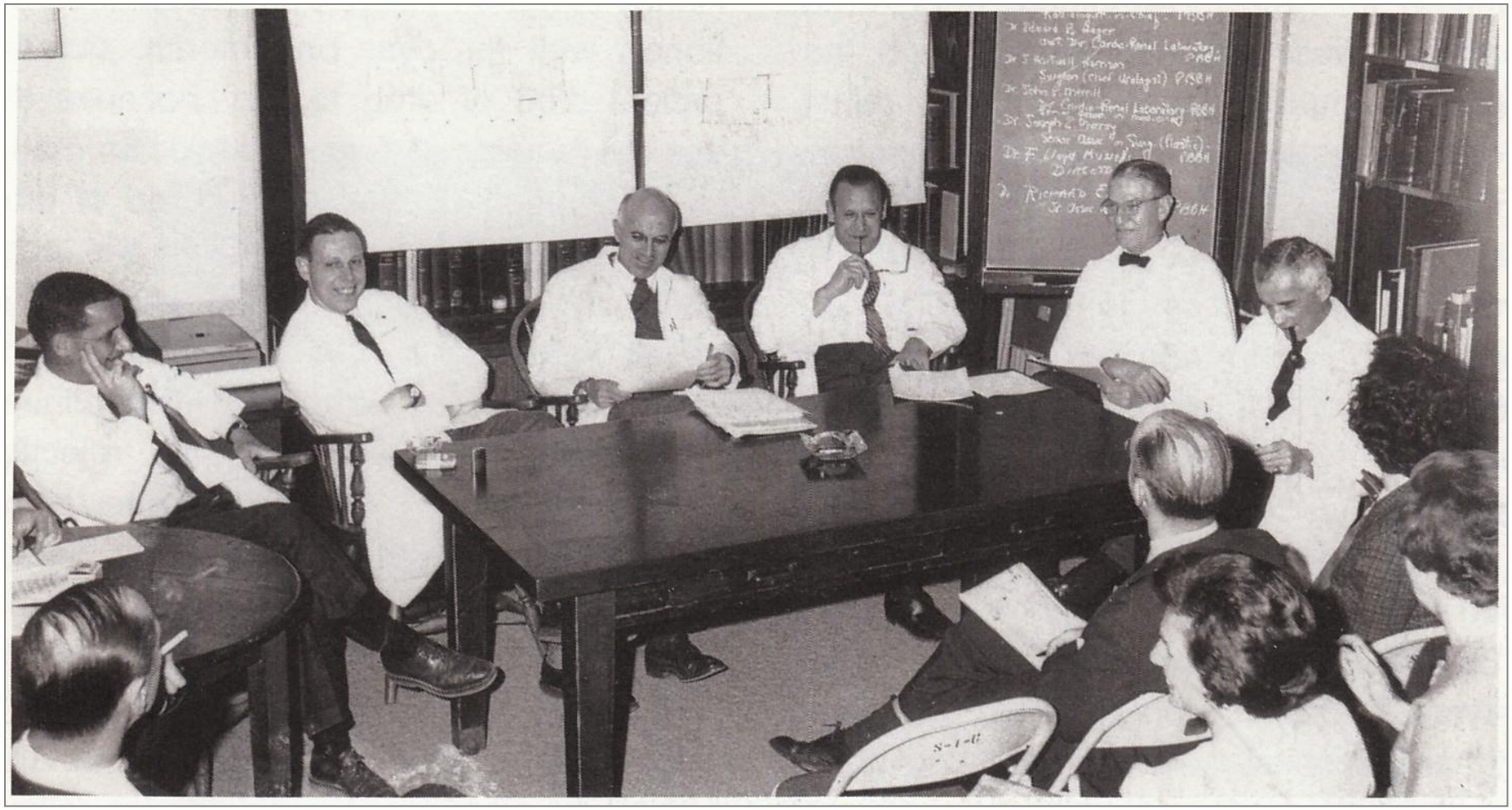
A DAUTING PROSPECT

"I was worried about taking a normal person and doing a major operation not for his benefit but for another person's

We were criticized for playing God"

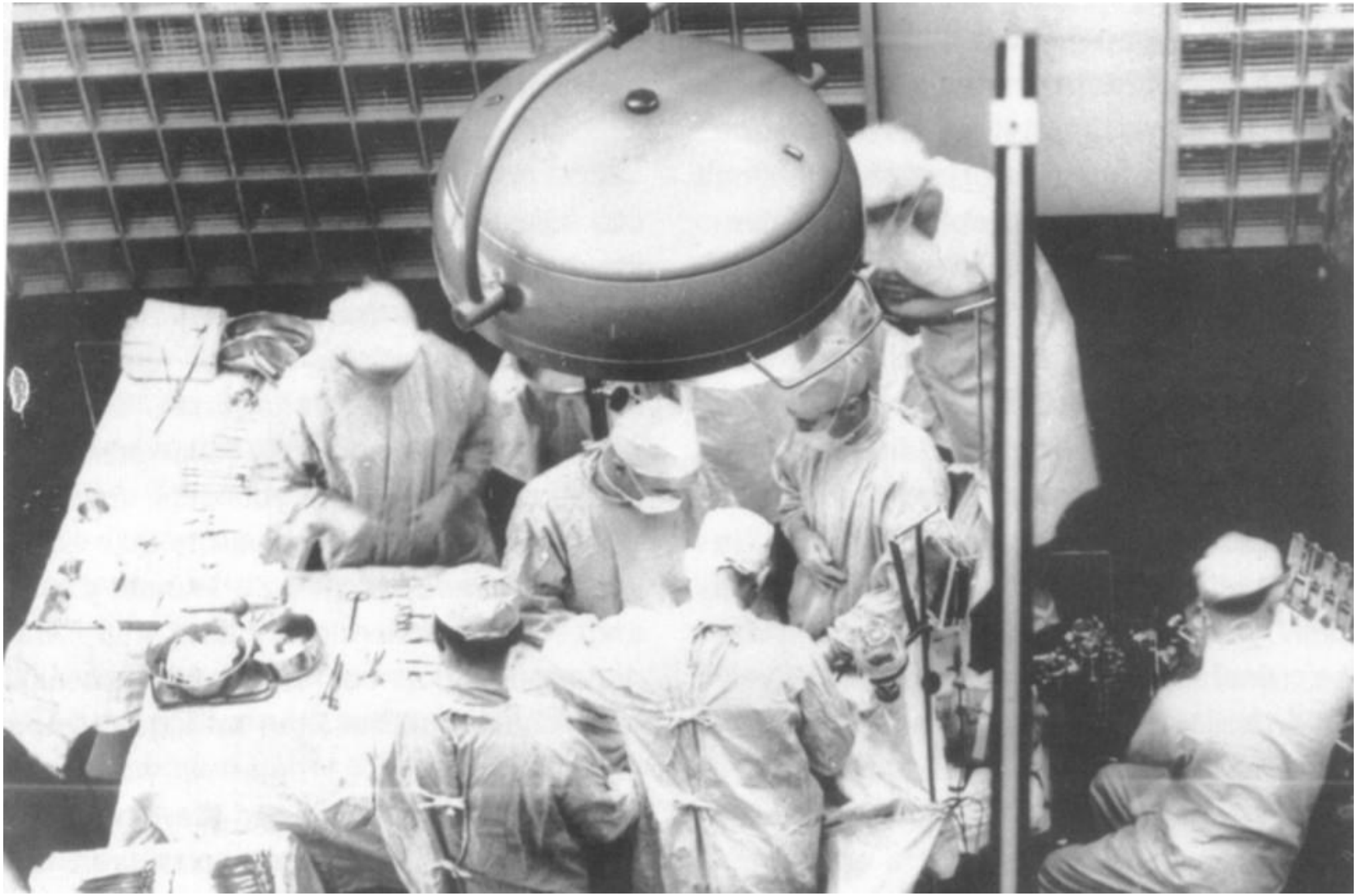
Joseph Murray, 2001

Ci fu una discussione pubblica



I più erano contrari. Così i dottori di Boston la decisione la presero da soli, con la famiglia Herrick

December 23, 1954



There was a collective hush in the operating room as blood began to flow into the implanted kidney and urine began to flow out of it

Joseph Murray, 2001

Q: Did your colleagues at the time question whether the information gained from work on dogs was applicable to humans?

A: Oh yes. Sure, everybody did. They'd say "Well, it'd work on the dog but not the human". But that doesn't make much sense because the physiology and the immunology are quite similar. I was a young surgeon then, and one of my close surgical friends said 'Joe, don't get involved with this, it will ruin your career"

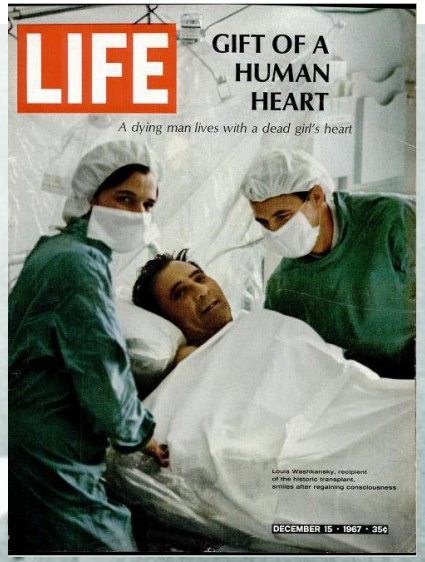
Si cominciano a fare trapianti anche tra fratelli che non erano gemelli

Per prevenire il rigetto si distruggeva con i raggi X gran parte del midollo osseo del ricevente, ma questo era un metodo molto pericoloso

Si avevano infezioni anche mortali e molti pazienti ebbero gravi emorragie

Elion e Hitchings, a Tuckahoe negli Stati Uniti, sintetizzarono la 6-mercaptopurina

Fra le righe di un lavoro pubblicato agli inizi degli anni '60, questi due ricercatori scrissero che il farmaco impediva anche la proliferazione dei linfociti

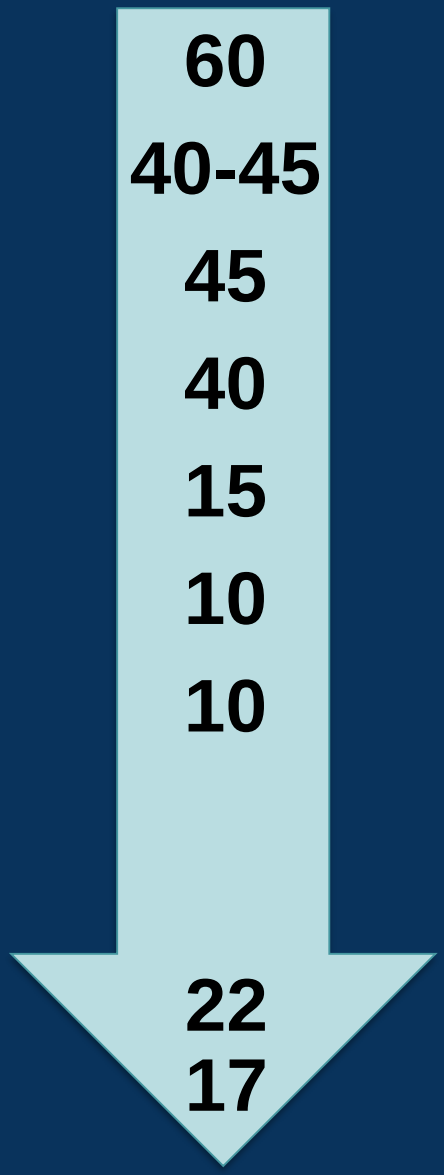

LIFE
GIFT OF A HUMAN HEART
A dying man lives with a dead girl's heart
Louis Washkansky, recipient of the historic transplant, smiles after regaining consciousness
DECEMBER 15 · 1967 · 35¢

Los Angeles Times
January 30, 2015

Organ donors gave more than 2 million years of life to sick patients

By KAREN KAPLAN

Acute rejection *(%)*



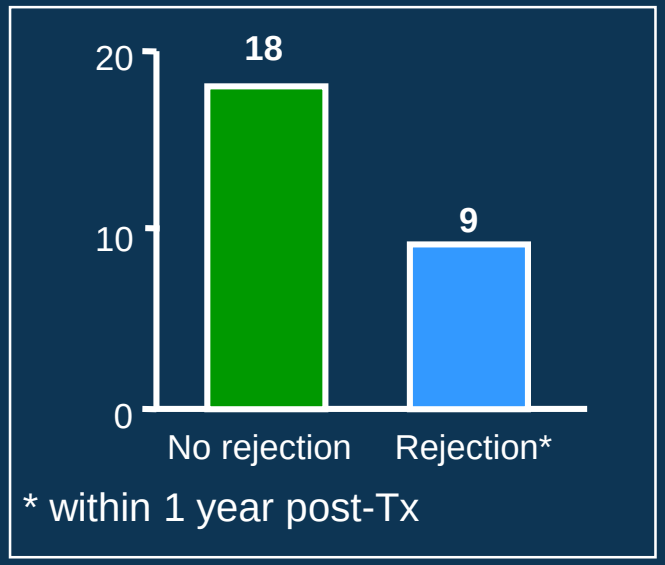
CsA		*1982*
CsA	+ ST	*1983*
FK	+ ST	*1991*
RAPA	+ ST + AZA	*1995*
CsA	+ ST + MMF	*1995*
FK	+ ST + MMF	*1996*
CsA	+ ST + RAPA	*1996*

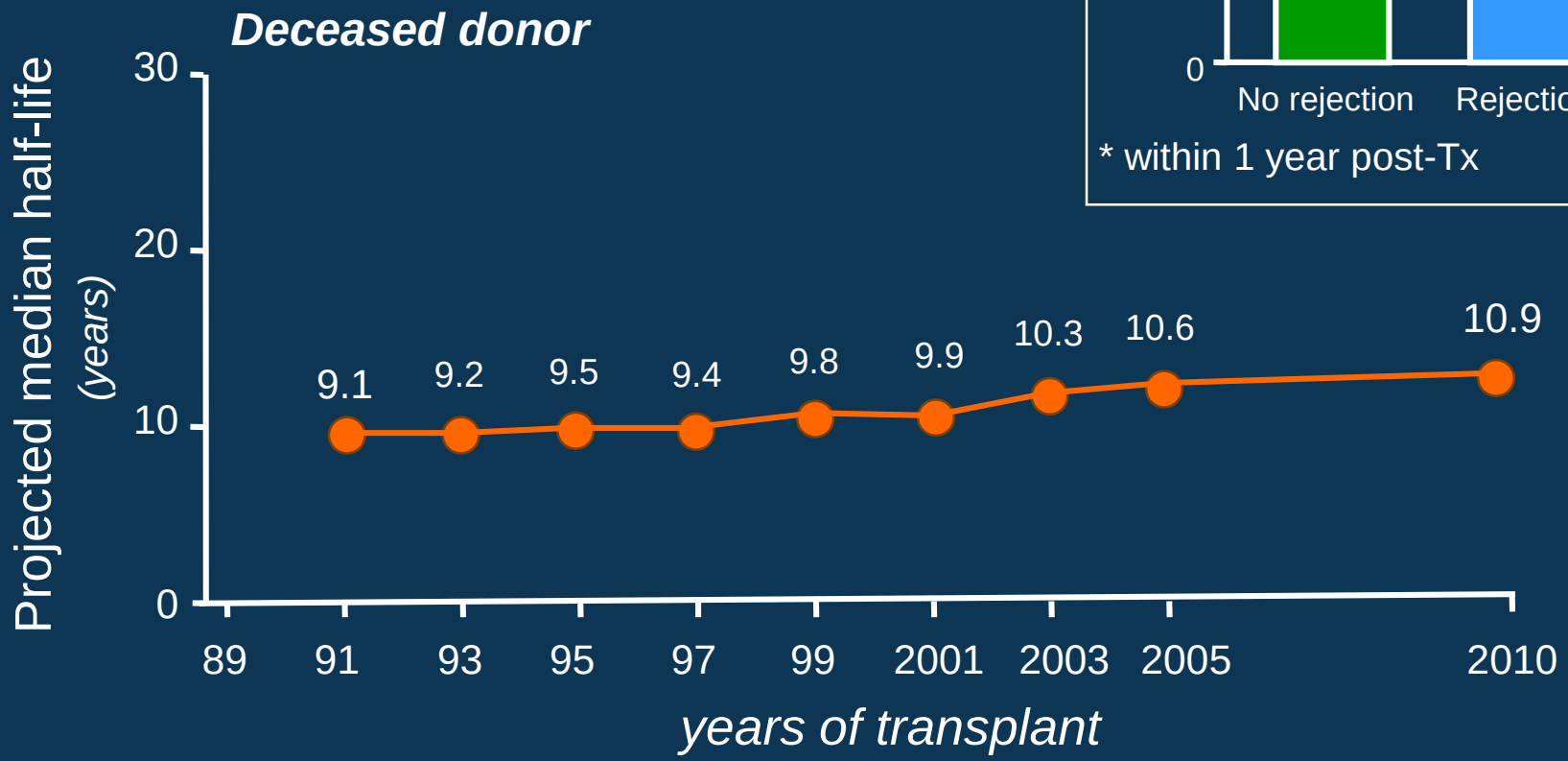
Bas + ST + Belatacept *2010*

(more intensive)

(less intensive)

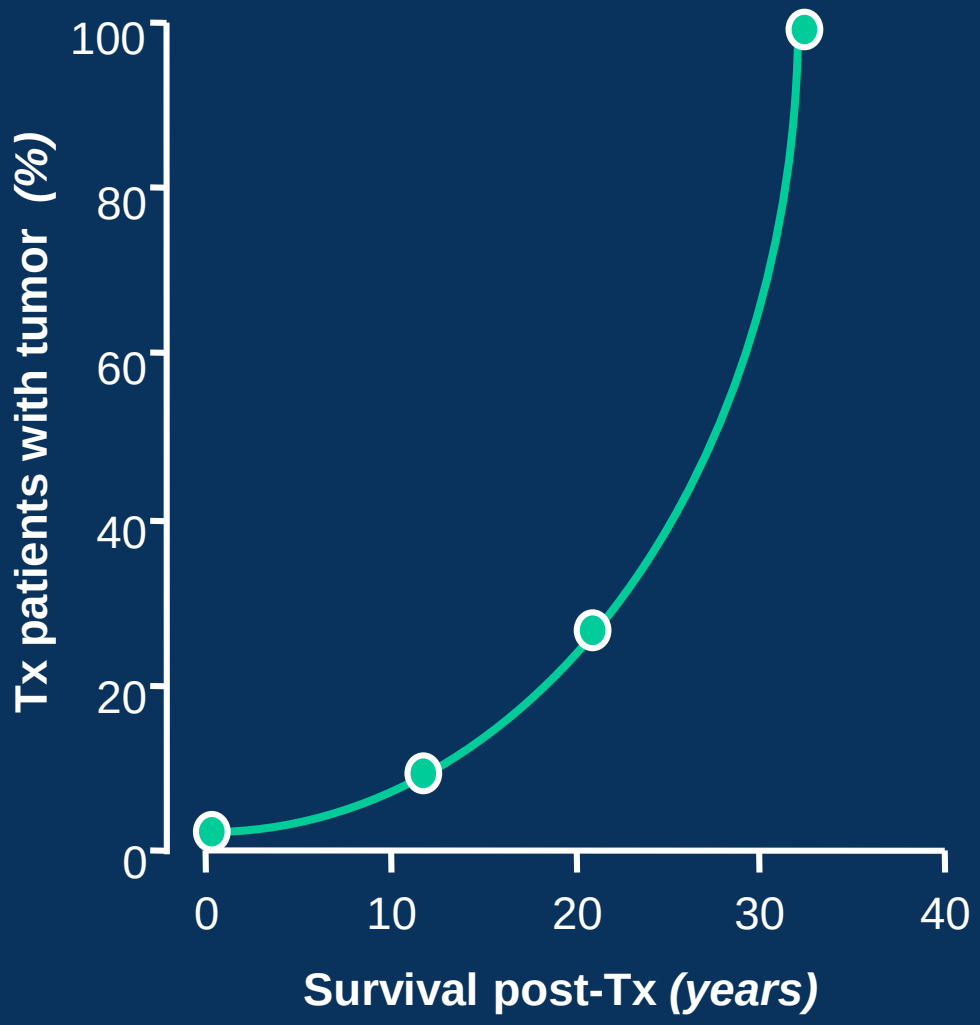
LONG TERM GRAFT SURVIVAL AFTER RENAL TRANSPLANTATION HAS NOT SIGNIFICANTLY IMPROVED IN THE PERIOD 1991-2010





OPNT/SRTR 2012 Annual Data Report

RISK OF DEVELOPING A TUMOR IN TRANSPLANT RECIPIENTS



THE PROMISE OF NOVEL IMMUNOSUPPRESSIVE AGENTS

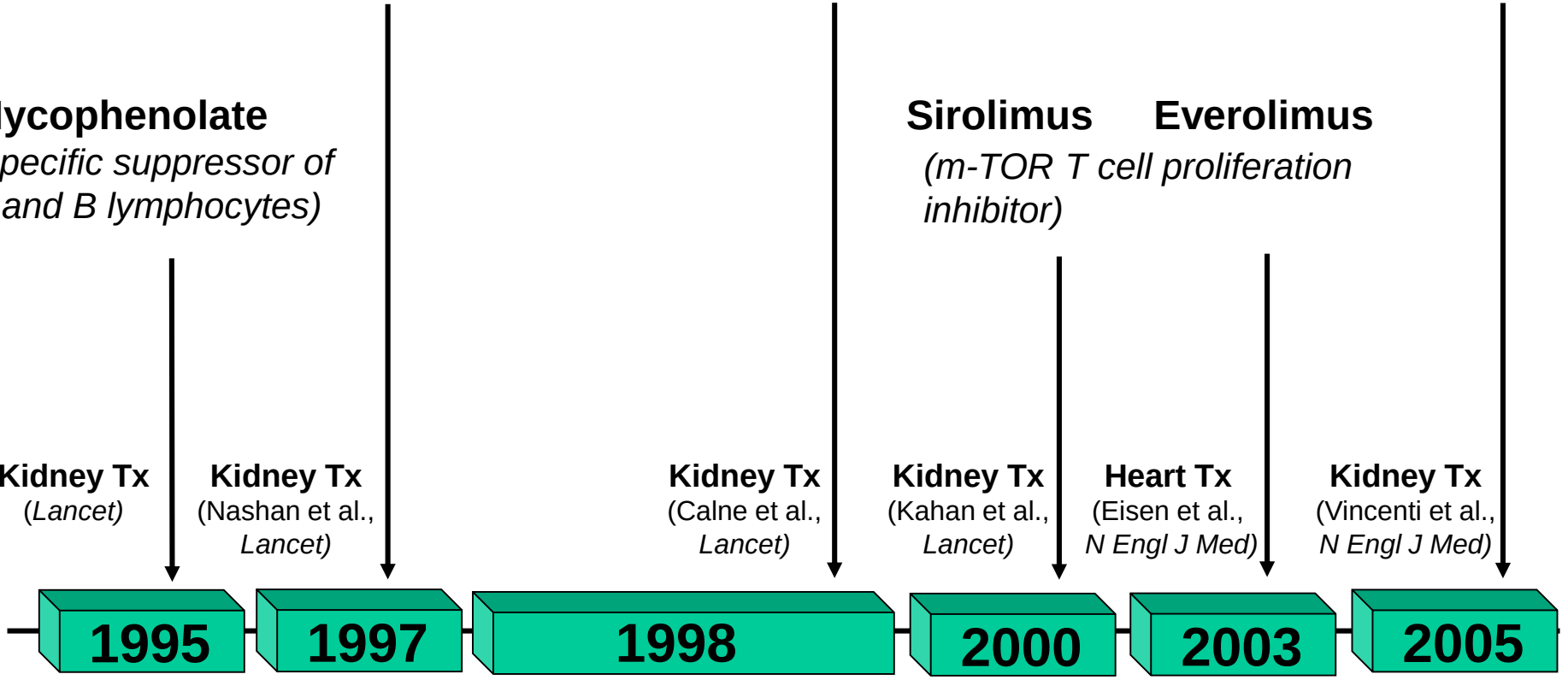
Basiliximab
(chimeric monoclonal antibody against IL-2 R)

CAMPATH-1H
(humanized anti-CD52 antibody - T and B cells depletion)

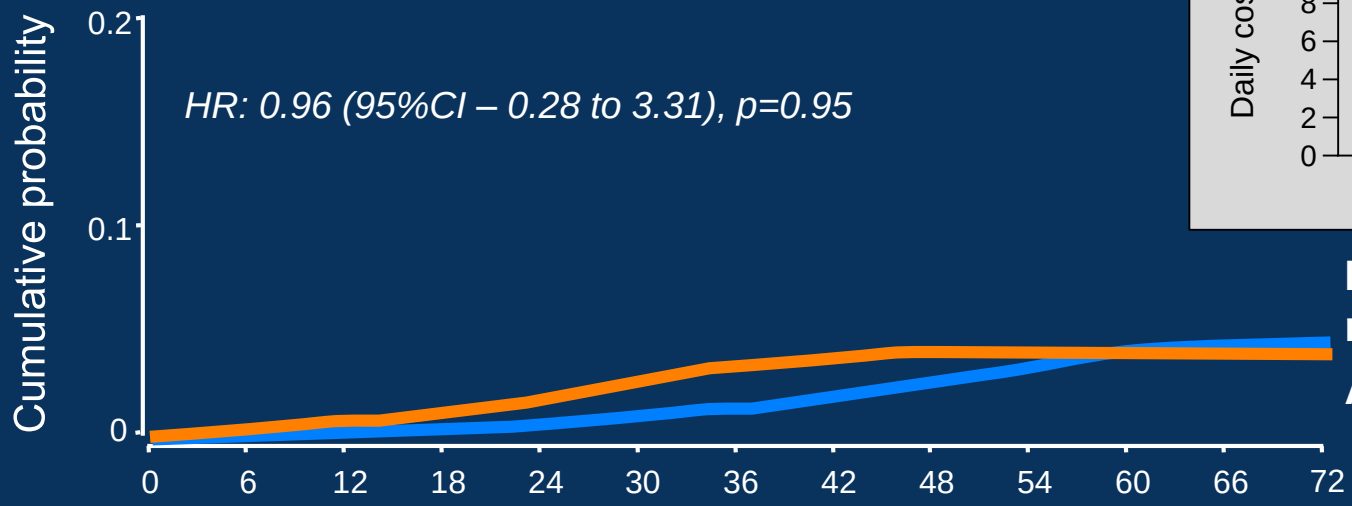
Belatacept
(IgG/CTLA4 fusion protein selective blocker of T cell activation)

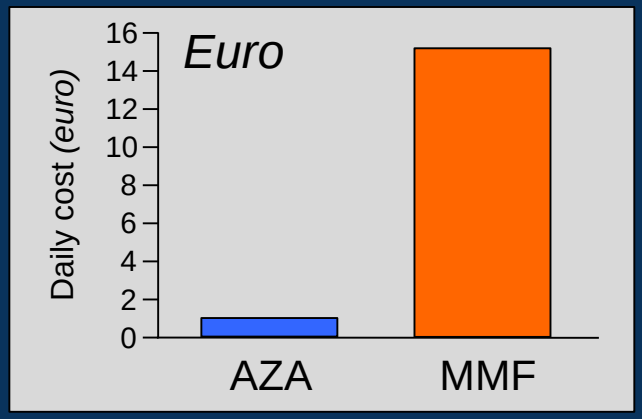
Mycophenolate
(specific suppressor of T and B lymphocytes)

Sirolimus **Everolimus**
(m-TOR T cell proliferation inhibitor)

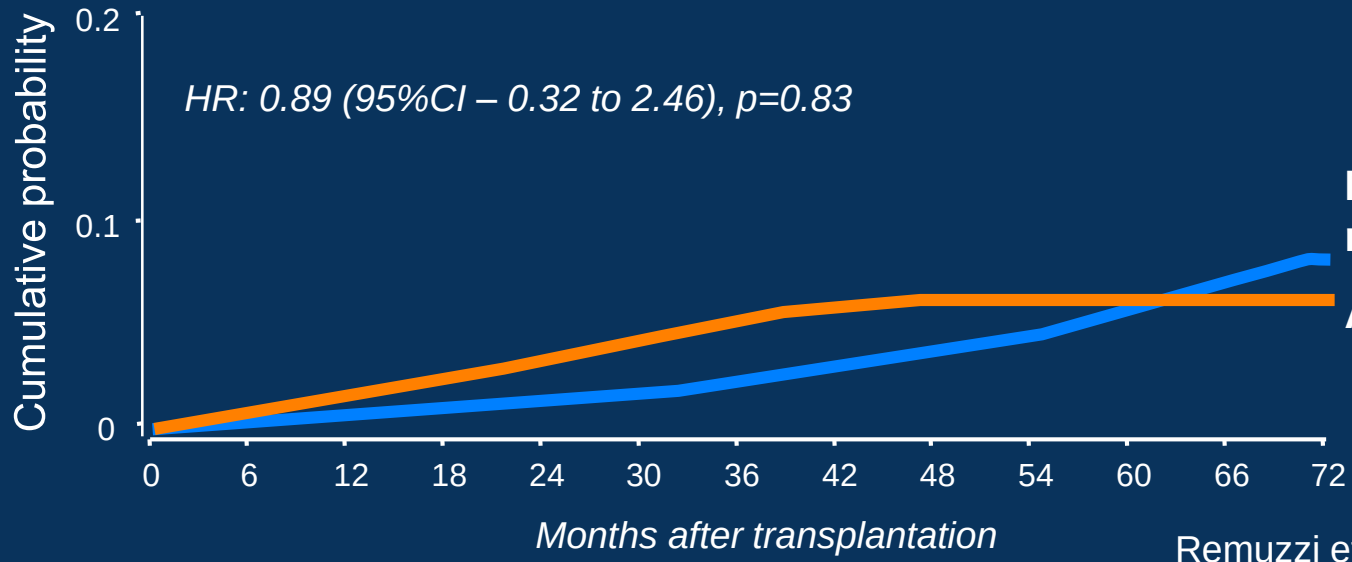


PATIENT DEATH





DEATH-CENSORED GRAFT LOSS

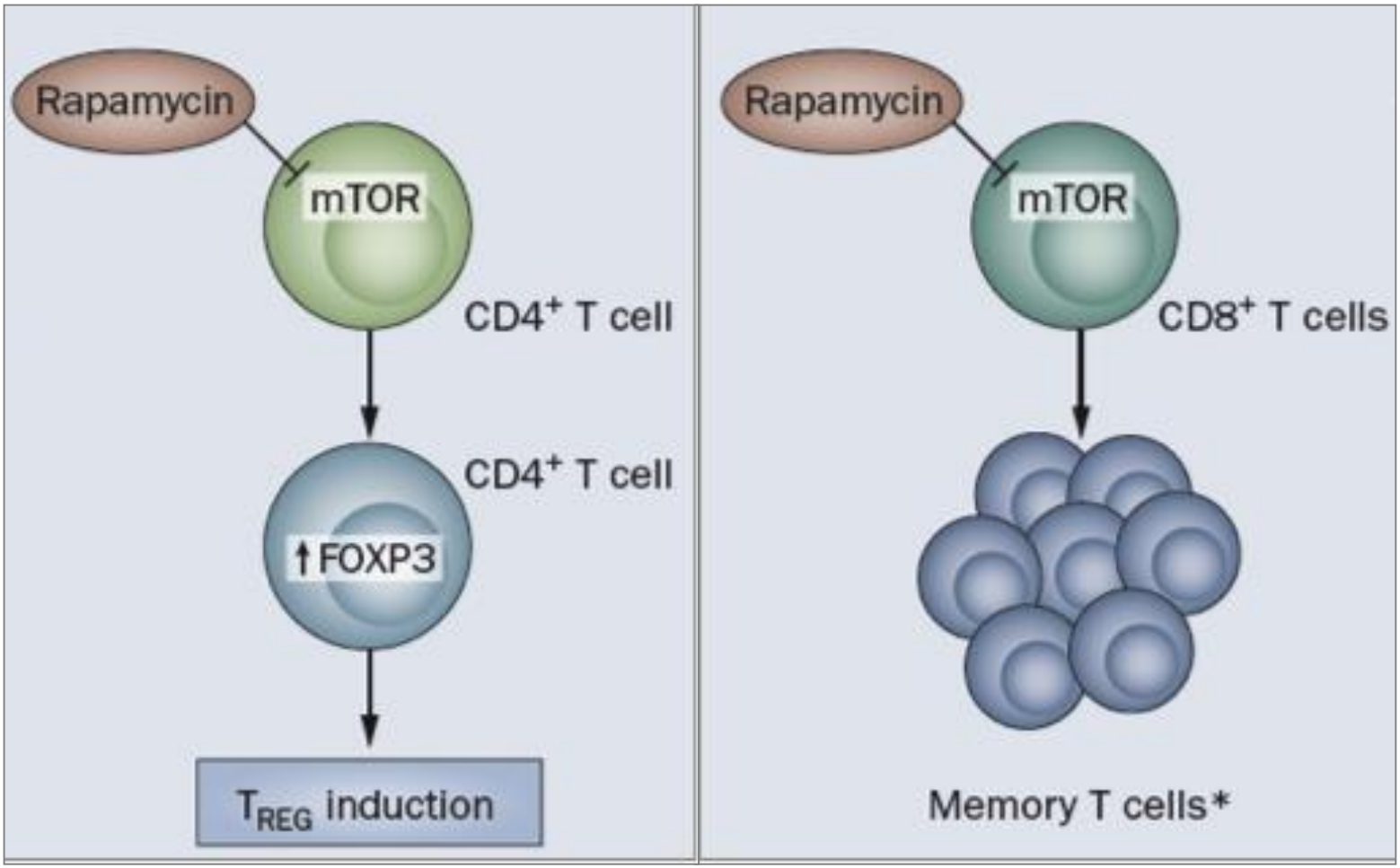


Remuzzi et al., *Lancet,* 2004
Remuzzi et al., *J Am Soc Nephrol,* 2007

NATURE REVIEWS | NEPHROLOGY VOLUME 5 | NOVEMBER 2009
TRANSPLANTATION

Time to rethink immunosuppression by mTOR inhibitors?

Marcus D. Säemann and Giuseppe Remuzzi

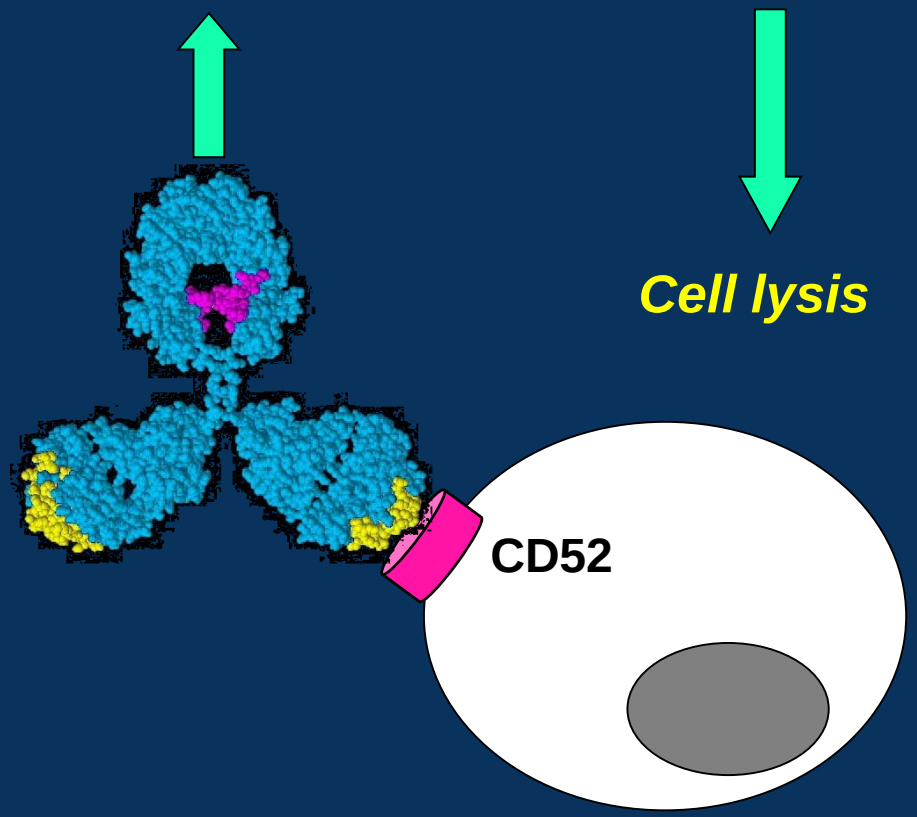


 Consequences of mTOR inhibition

TOLERANCE-PERMISSIVE ENVIRONMENT

Campath-1H *Humanized monoclonal antibody directed against the CD52 antigen expressed on B and T lymphocytes*

Classical pathway activation ----► C5b-9



- **T cells**
- **Mature B cells**
- **No memory B cells**
- **No plasma cells**

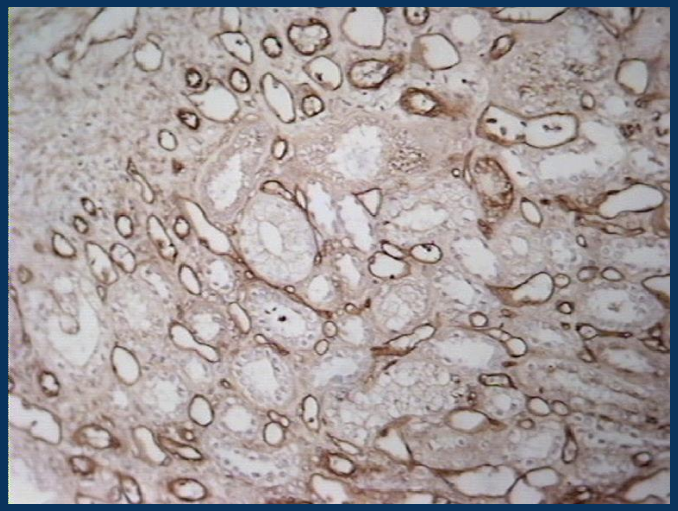
Hale et al., *Transplantation Rev,* 2003

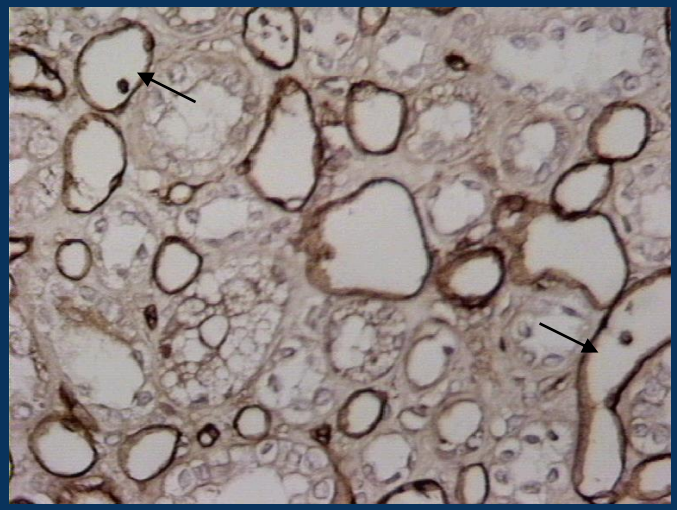
ACUTE HUMORAL REJECTION IN CAMPATH-1H BASED IMMUNOSUPPRESSION

Glomerular thrombosis

Acute tubular necrosis

C4d staining (glomerular peritubular capillaries)





C4d staining (peritubular capillary ectasia)

- Flow PRA test: In the recipient anti-HLA antibody against class I donor antigen B44

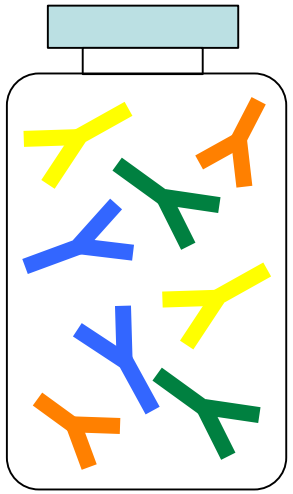
Hill et al., *Nephrol Dial Transpl*, 2005

B cell reconstitution in a B-cell activating factor rich environment allows preferential selection, survival and maturation of alloreactive B cells

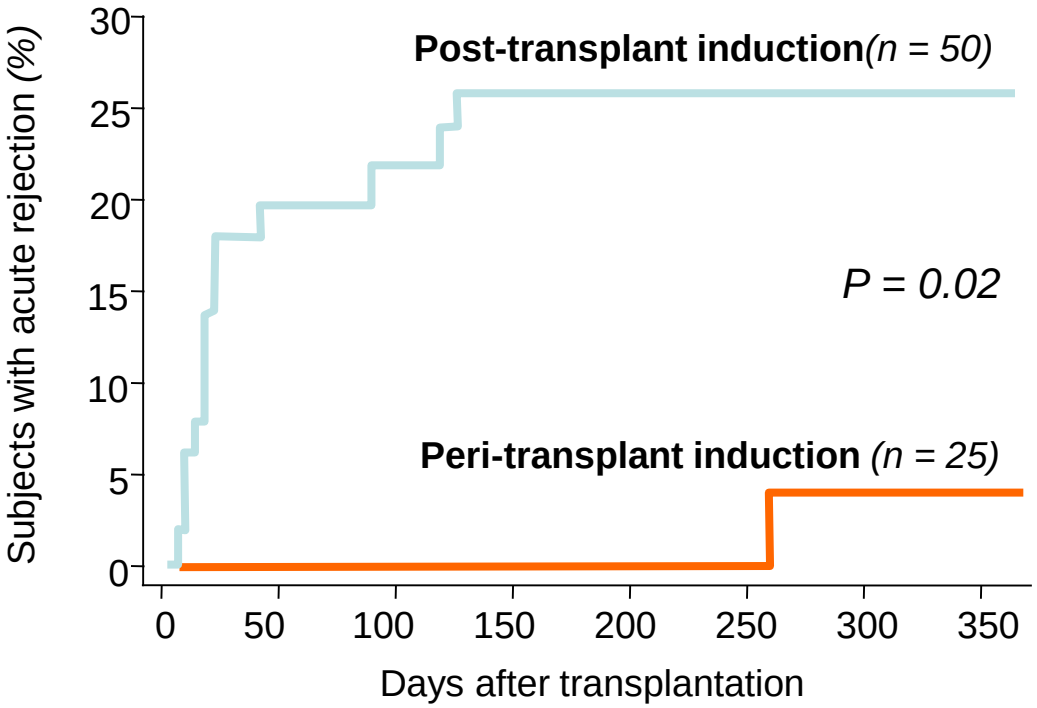
Todeschini M et al J Immunol, 2013

RATG induces cytokine release syndrome*, which may require dose reduction or even interruption

RATG



Basiliximab + Low-dose RATG



* fever, chills, leukopenia, and thrombocytopenia in 40 to 60% of patients

* Patients on steroid-free immunosuppression

Ruggenenti et al., *CJASN,* 2006

Gennarini et al., *J Transpl,* 2012

The NEW ENGLAND JOURNAL of MEDICINE 2016

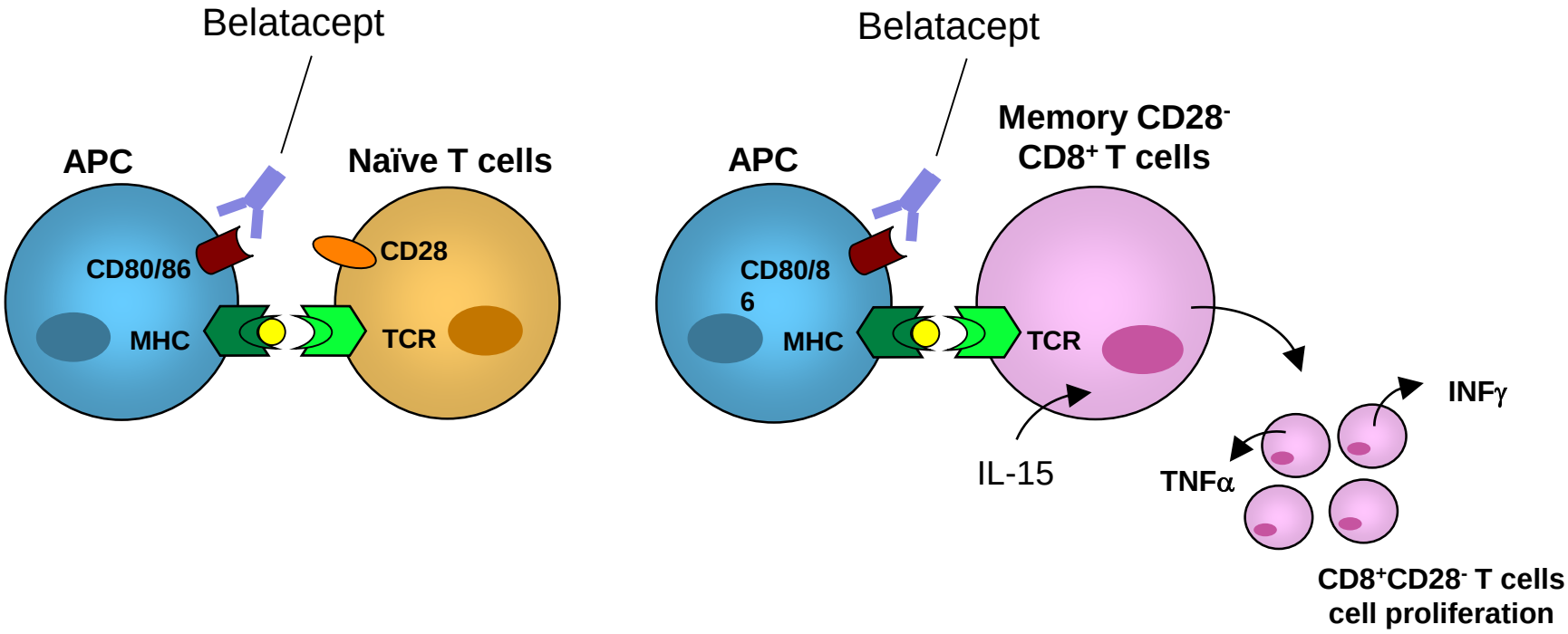
ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

BELATACEPT: a high affinity variant of CTLA4Ig

Belatacept-resistant memory T-cell activation



Traitanou et al., *Am J Transpl,* 2014

Antigen-experienced T cells, in particular CD8⁺T cells, upon antigen rechallenge lose CD28 expression and became memory T cells with increased capability of mounting a rapid response independent of CD80/86⁻ CD28 costimulation

Lo et al., *Am J Transpl,* 2011

HIGH ACUTE REJECTION RATE WITH BELATACEPT

	Biopsy-proven acute rejection* %
Belatacept MI	24.4
Belatacept LI	18.3
CsA	11.4

** At month 84 post-transplantation*

Vincenti et al., *N Engl J Med,* 2016

Belatacept

1,420 -11,300 euro per month depending on treatment phase

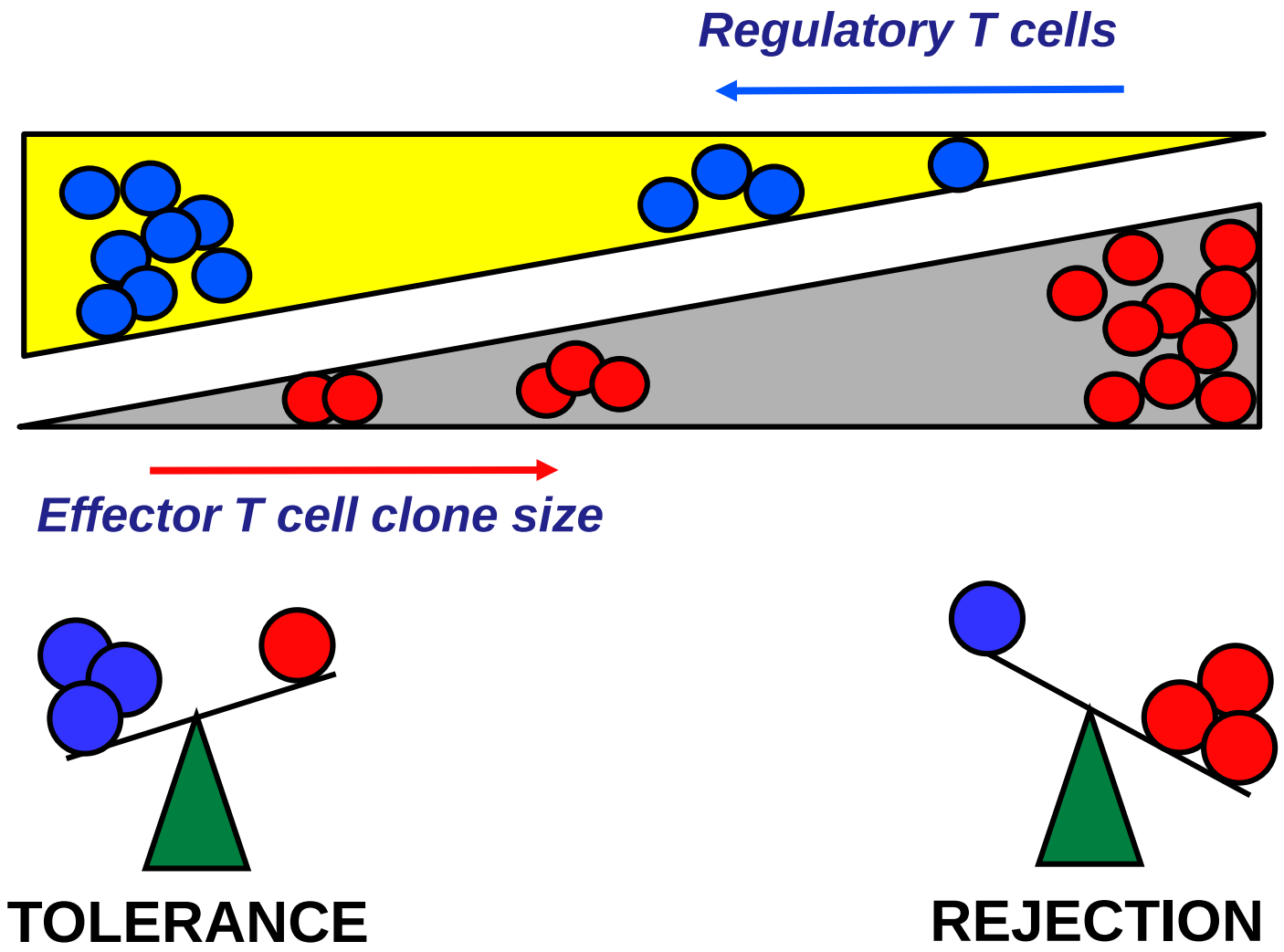
Because of generalized immunosuppression transplantation brings new problems that need to be addressed

- malignancies	*11-14 % at 10 year*	Navarro et al., Transplant Proc, 2008 Adami et al., Br J Cancer, 2003
- opportunistic infections	*40 % at 2 year*	Wujciuk eet al., Transplant Int, 2015
- cardiovascular disease	*12 % at 10 year*	Seoane-Pillado et al., BMC Cardiovascular Dis, 2017

One of the major questions remaining in clinical transplantation is whether it will be possible to induce states of true tolerance with little or no long-term drug therapy

…ideally one would like to alter the host's initial contact with the graft to promote a state of donor-specific unresponsiveness

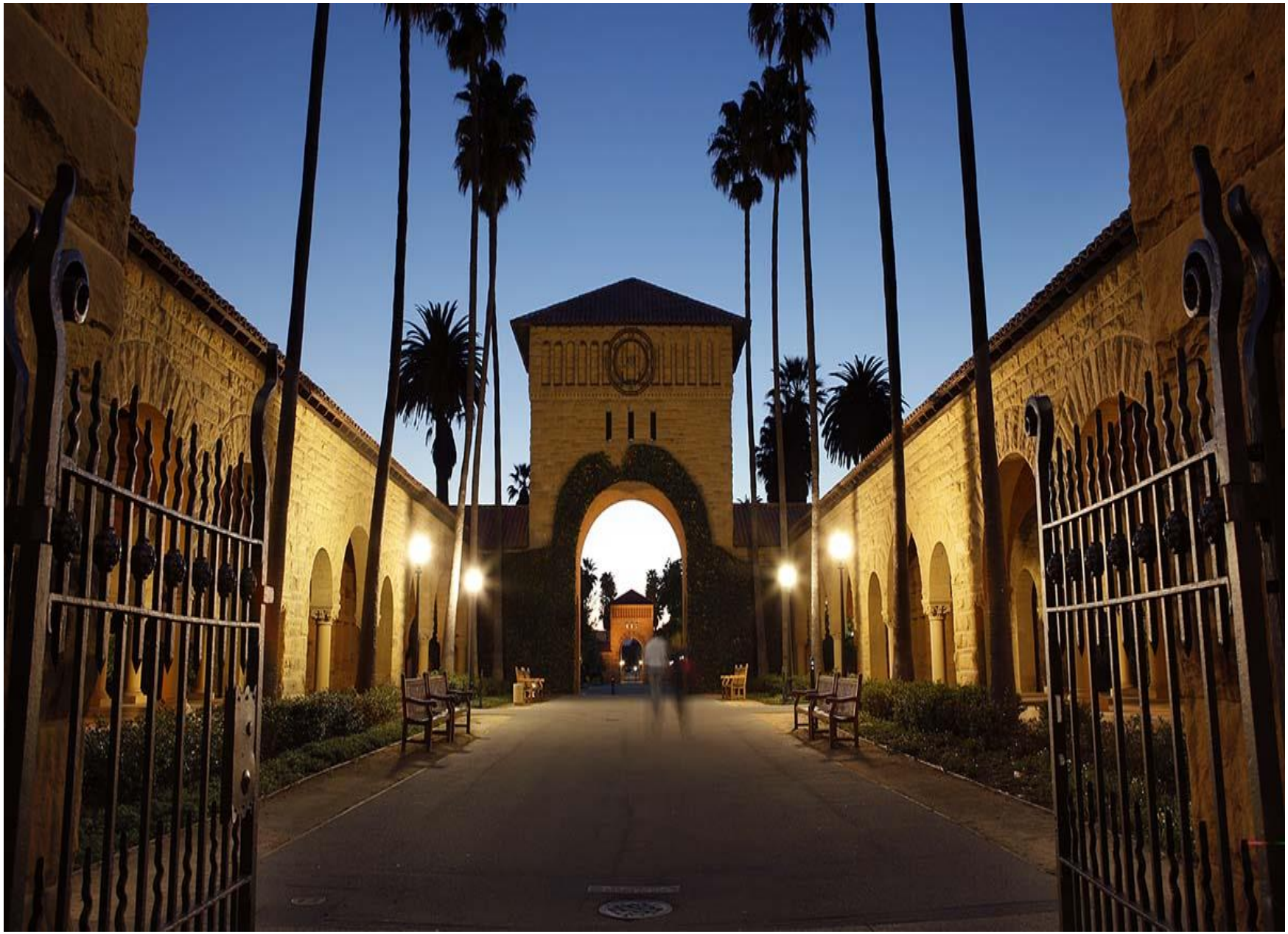
***Carpenter, N Engl J Med,* 1993**



Salama, Remuzzi, Harmon et al., *J Clin Invest,* 2001

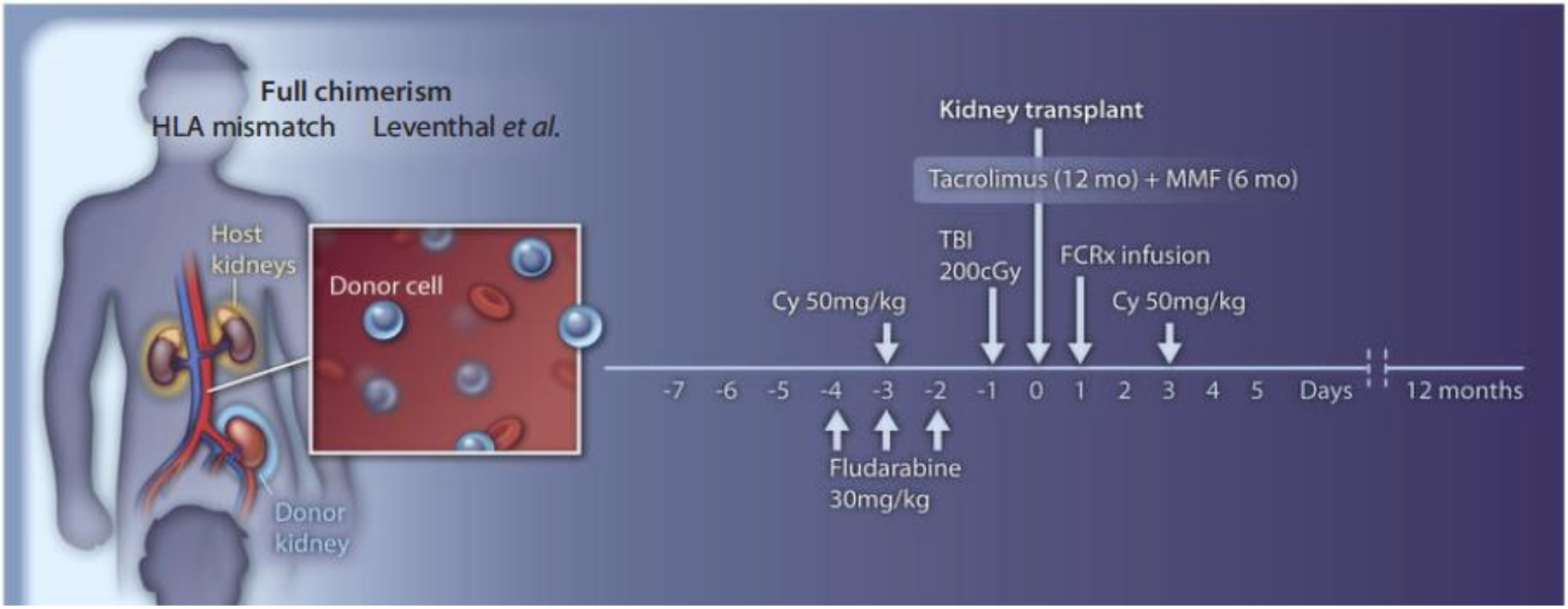
TOLERANCE AFTER RENAL AND BONE MARROW TRANSPLANTATION

Stanford University




Northwestern Medicine
Northwestern Memorial Hospital
EMERGENCY

DURABLE FULL CHIMERISM AND TOLERANCE AFTER RENAL AND HEMATOPOIETIC STEM CELL TRANSPLANTATION



- 37 recipients of HLA-mismatched kidneys from living related and unrelated donors
- FCRx infusion: a mixture of donor hematopoietic stem cells and tolerogenic graft facilitating cells from GCS-F-mobilized peripheral blood cells + donor T cells
- Immunosuppression discontinued at 1 year post-Tx

Leventhal et al., *Science Transl Med*, 2012
Markmann et al., *Science Transl Med*, 2012

2 patients lost their renal allografts within the first year post-transplant related to opportunistic infections

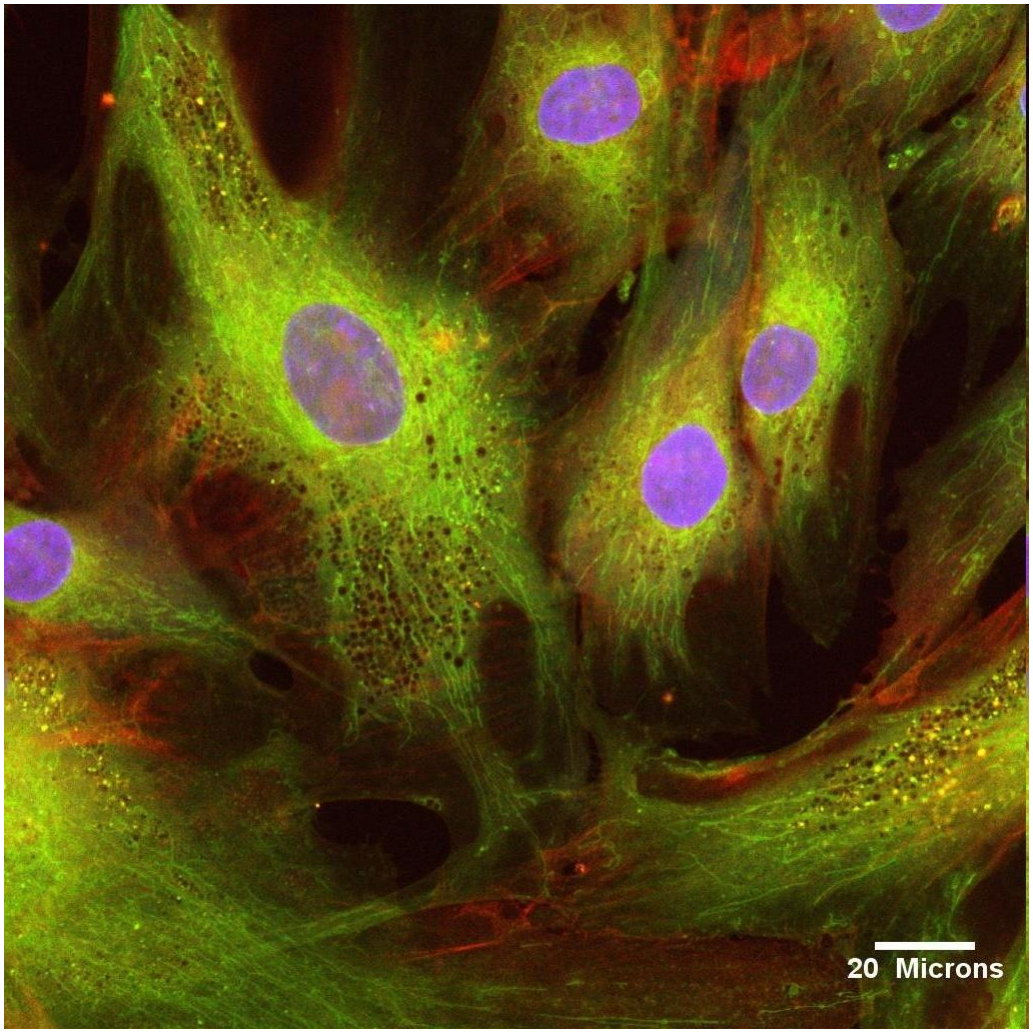
2 patients developed GVHD (one of them died due to grade 3 GVHD plus CMV colitis at 11 months after transplantation)

High incidence of infections including BK viremia, CMV activation, pneumonia, bacterial meningitis, disseminated histoplasmosis, aspergillosis

Kawai et al., *Am J Transplant,* 2019

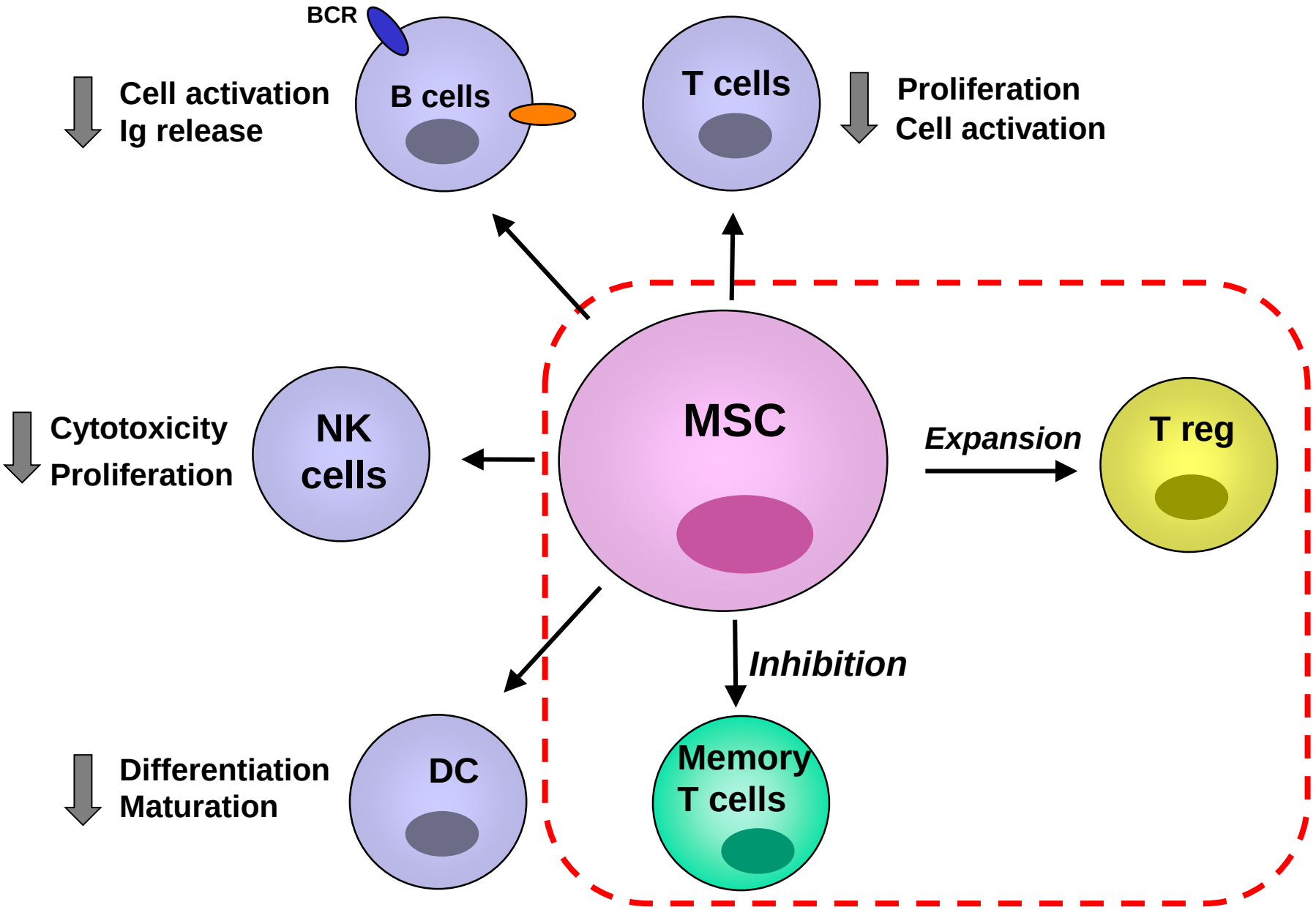
42

BONE MARROW-DERIVED MESENCHYMAL STROMAL CELLS FOR TOLERANCE INDUCTION



- *Unique for their low immunogenicity and immunoregulatory properties*

Casiraghi et al, *Curr Opin Organ Transpl*, 2010

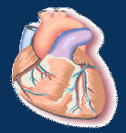


Nauta et al, *Blood*, 2007

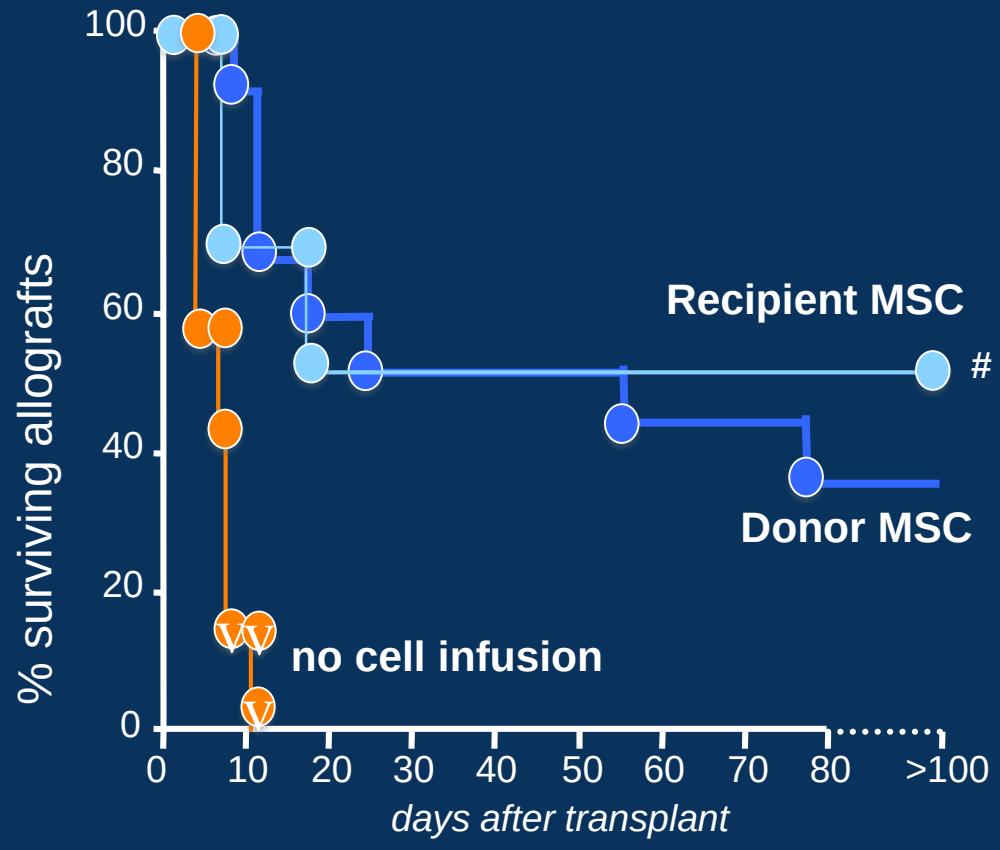
AUTOLOGOUS MSC PROLONG HEART TRANSPLANT SURVIVAL MEDIATED BY CD4$^+$CD25$^+$Foxp3$^+$ REGULATORY T CELLS

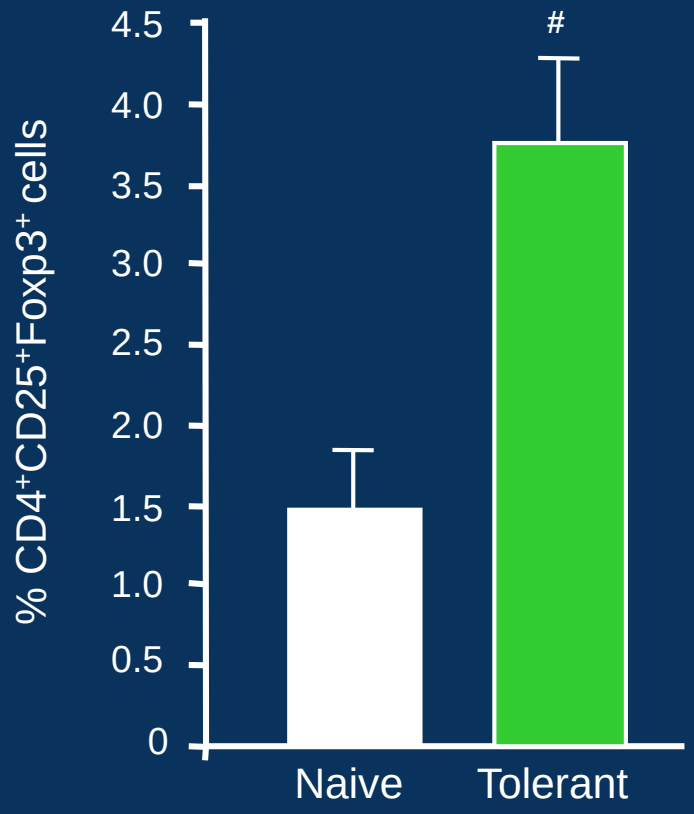
B6 MSC infusion
(0.5 x 10^6 cells)

B6 recipient mice



B6C3





# P<0.05

Casiraghi et al, *J Immunol*, 2008

AUTOLOGOUS BONE MARROW-DERIVED MSC TO INDUCE TOLERANCE IN LIVING-DONOR KIDNEY TRANSPLANT RECIPIENTS

Bergamo

• IRCCS, Mario Negri Institute
(coordinator/immunomonitoring)

• Azienda Ospedaliera Papa Giovanni XXIII

U.S.C. Chirurgia pediatrica
Kidney Tx

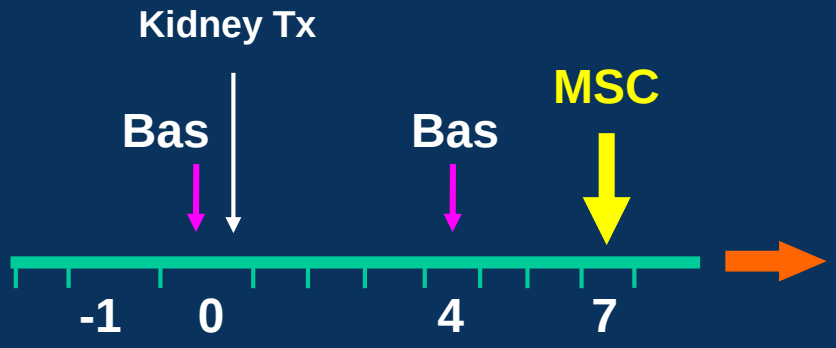
U.S.C. Ematologia
Bone marrow explants

Laboratorio Terapie Cellulari "G. Lanzani"
MSC preparation according to European GMP

U.S.C. Nefrologia
pre- and post-transplant patient monitoring and follow-up

LIVING TRANSPLANT RECIPIENTS

2 *

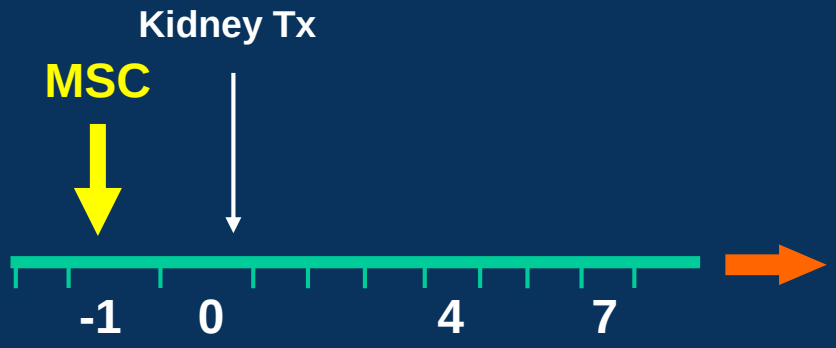


Engraftment syndrome: YES

Acute graft rejection: NO

IL-2 dependent Treg expansion ↑

2 *

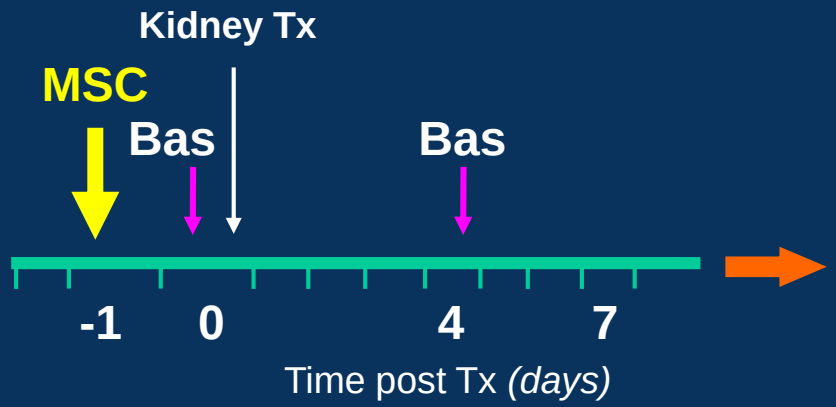


Engraftment syndrome: NO

Acute graft rejection: YES (1)

IL-2 dependent Treg expansion ↑

2 *



Engraftment syndrome: NO

Acute graft rejection: NO

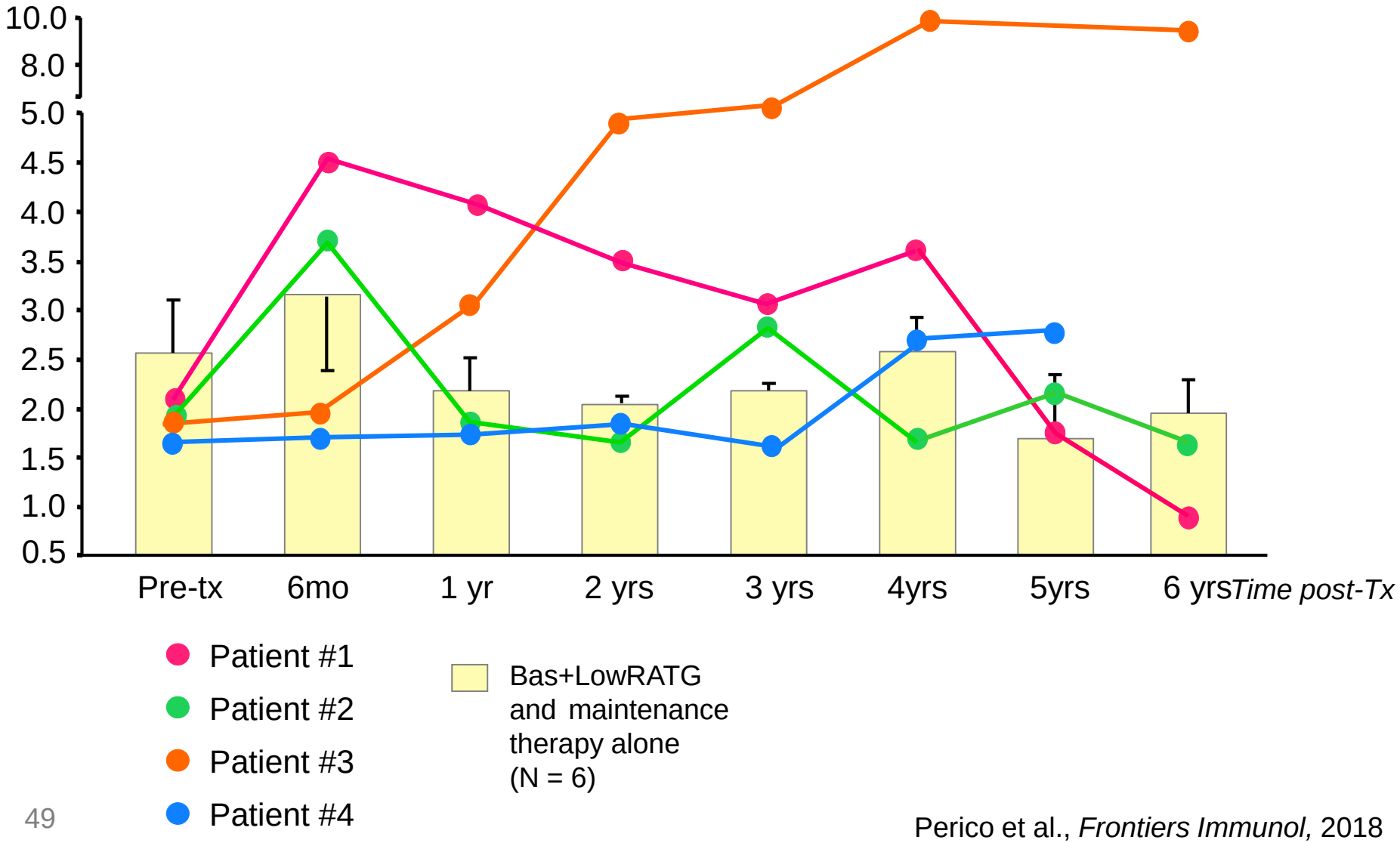
IL-2 dependent Treg expansion ↑

* *On top of RATG (0.5 mg/kg for 7 days)*


ZEISS
OPMI 6-CFR
Carl Zeiss

THE HIGH RATIO OF Treg/Tmemory COULD FAVOUR A STATE OF IMMUNE REGULATION

Treg/memory CD8⁺ T cells *(ratio)*



Perico et al., *Frontiers Immunol,* 2018

Patient #3 C.M.

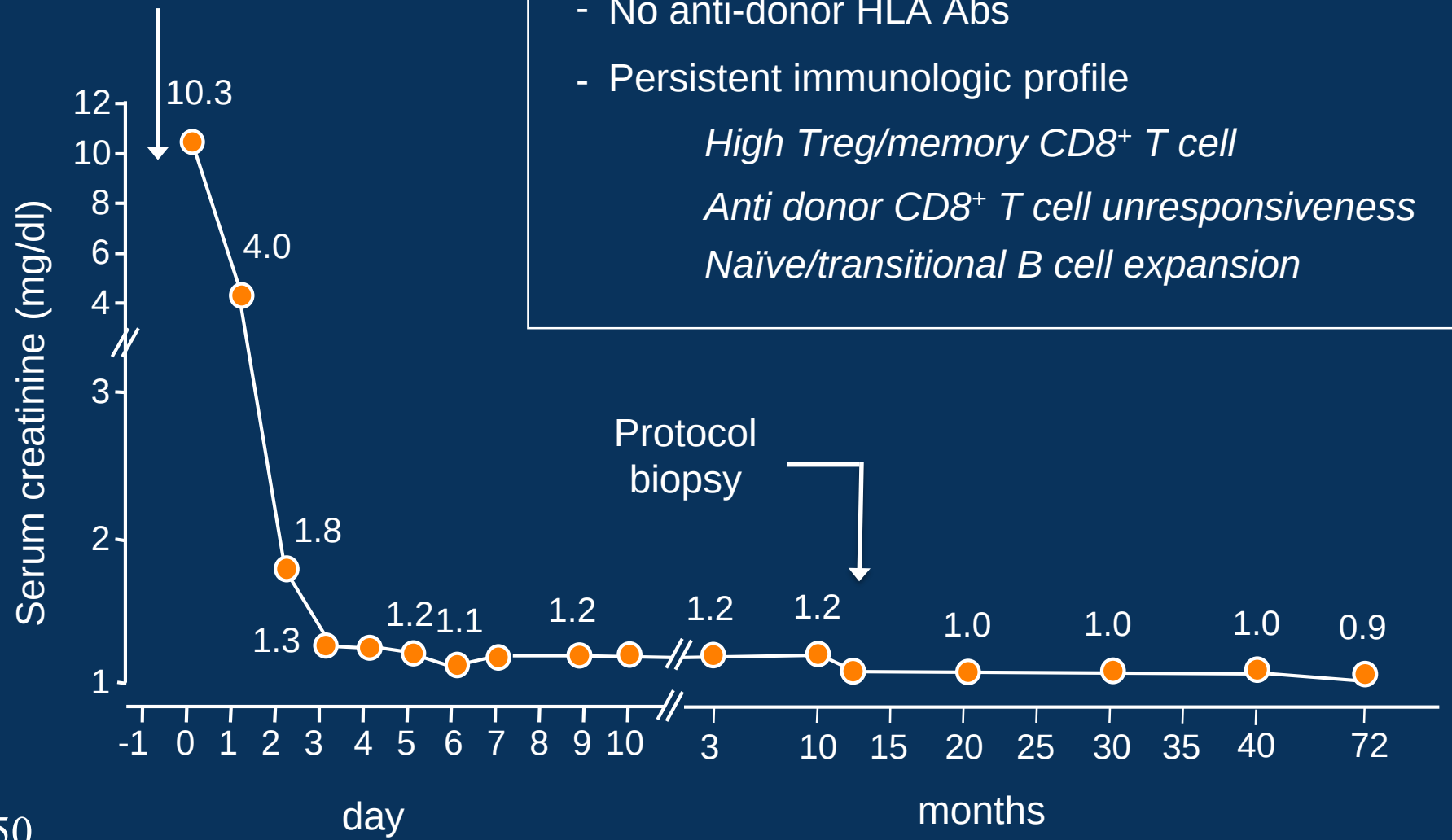
A pro-tolerogenic environment

- Stable graft function (S.creat <2.5 mg/dl)
- No proteinuria
- No anti-donor HLA Abs
- Persistent immunologic profile

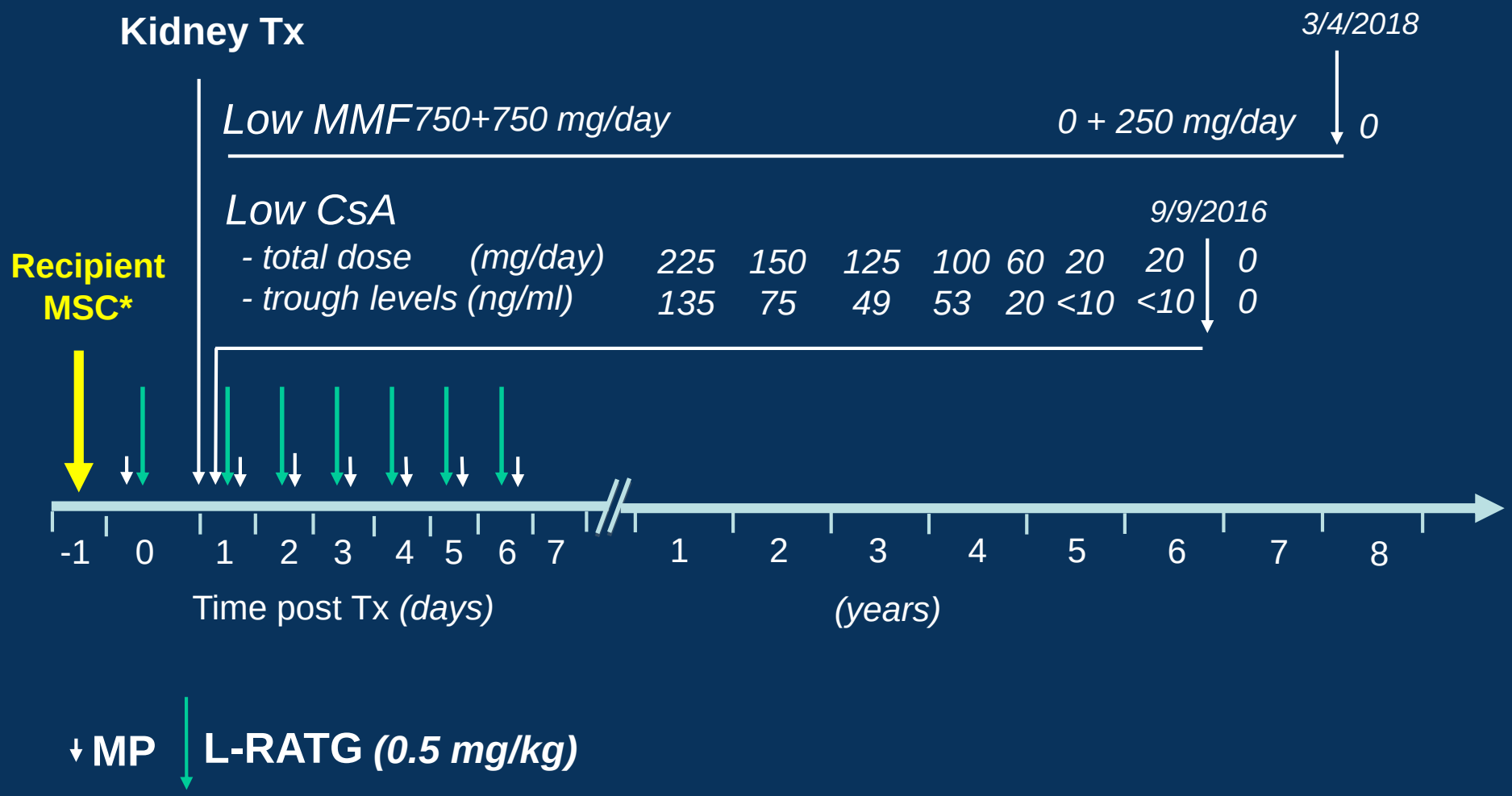
High Treg/memory CD8⁺ T cell

Anti donor CD8⁺ T cell unresponsiveness

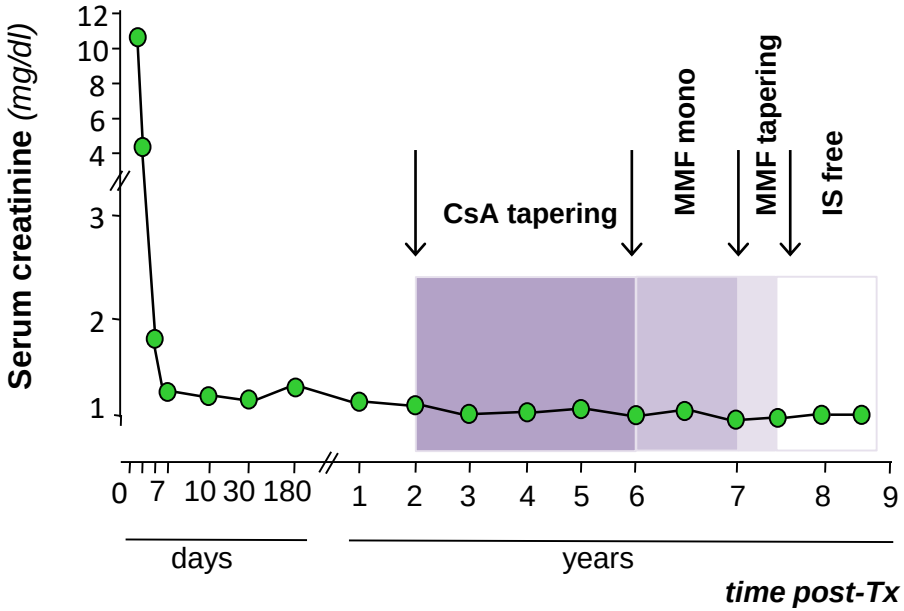
Naïve/transitional B cell expansion

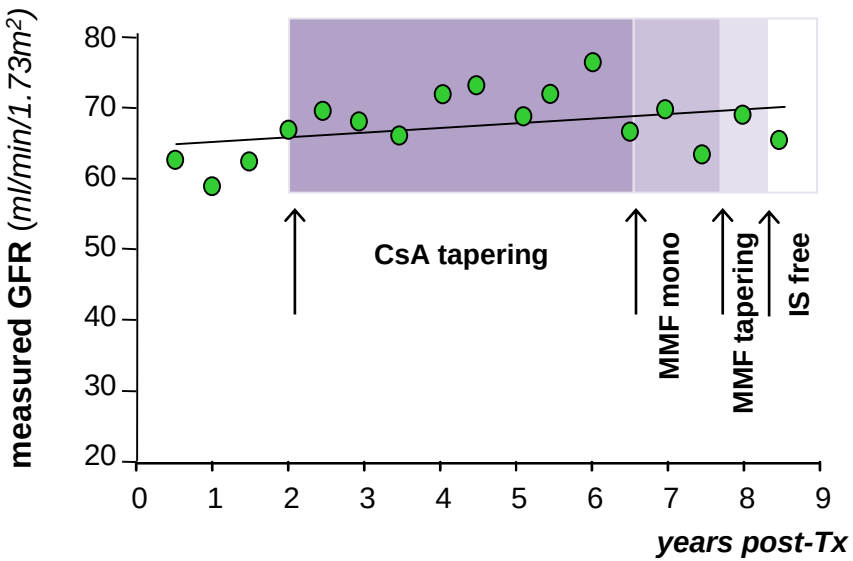


PATIENT #3: STOP IMMUNOSUPPRESSION



* Dose: 2 x 10^6/kg i.v.





Proteinuria (gr/day)

Start IS tapering

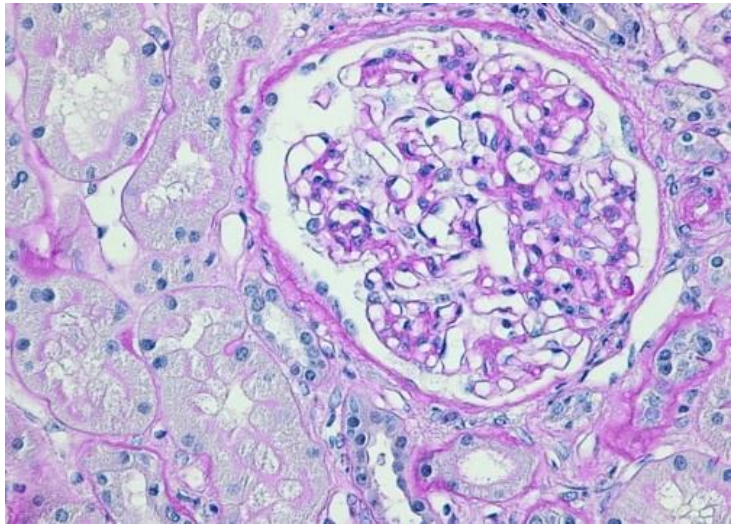
IS free

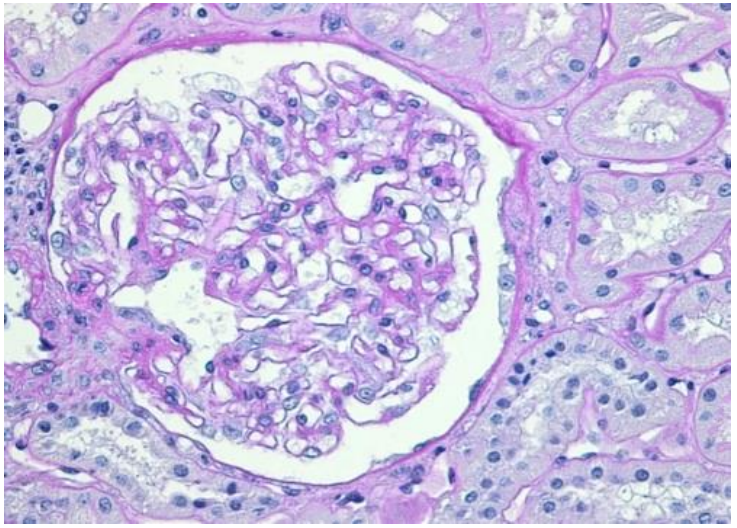
Years post-tx	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**
	0.17	0.09	0.06	0.09	0.06	0.07	0.15	0.13	0.26	0.12	0.13	0.22

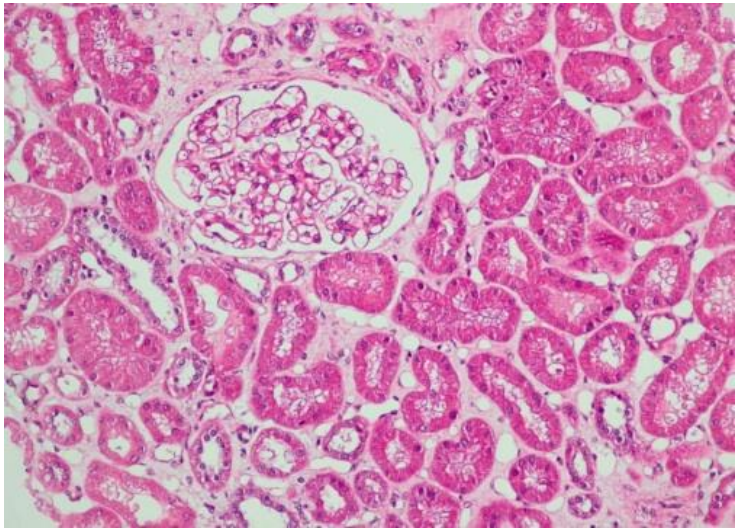
Casiraghi et al., *Personal Communication*

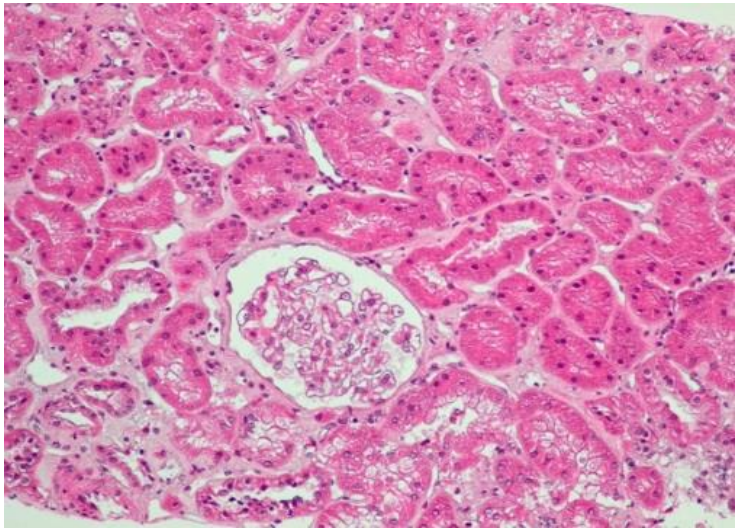
1 year post transplant

8 years post transplant









Casiraghi et al., *Personal Communication*

THIRD-PARTY BONE MARROW-DERIVED MSC TO INDUCE TOLERANCE IN CADAVERIC KIDNEY TRANSPLANTS RECIPIENTS

Bergamo

- **IRCCS, Mario Negri Institute**
  (coordinator/immunomonitoring)

Azienda Ospedaliera Papa Giovanni XXIII

- *U.S.C. Chirurgia pediatrica*
  Kidney Tx
- *U.S.C. Ematologia*
  Bone marrow explants
- *Laboratorio Terapie Cellulari "G. Lanzani"*
  MSC preparation according to European GMP
- *U.S.C. Nefrologia*
  pre- and post-transplant patient monitoring and follow-up

7 patients randomized (4 to MSC treatment)

THIRD-PARTY BONE MARROW-DERIVED MSC TO INDUCE TOLERANCE IN LIVER TRANSPLANT RECIPIENTS

Bergamo

- IRCCS, Mario Negri Institute
  (coordinator/immunomonitoring)
- Azienda Ospedaliera Papa Giovanni XXIII
  - U.O. Chirurgia III
    (Liver Tx)
  - U.O. Ematologia
    (Bone marrow explants)
  - Laboratorio Terapie Cellulari “G. Lanzani”
    (MSC preparation according to European GMP)

Bologna

- Azienda Ospedaliera Policlinico S. Orsola-Malpighi
  - U.O. Chirurgia Generale e Trapianto
    (Liver Tx)

New York Times

May 14, 2019

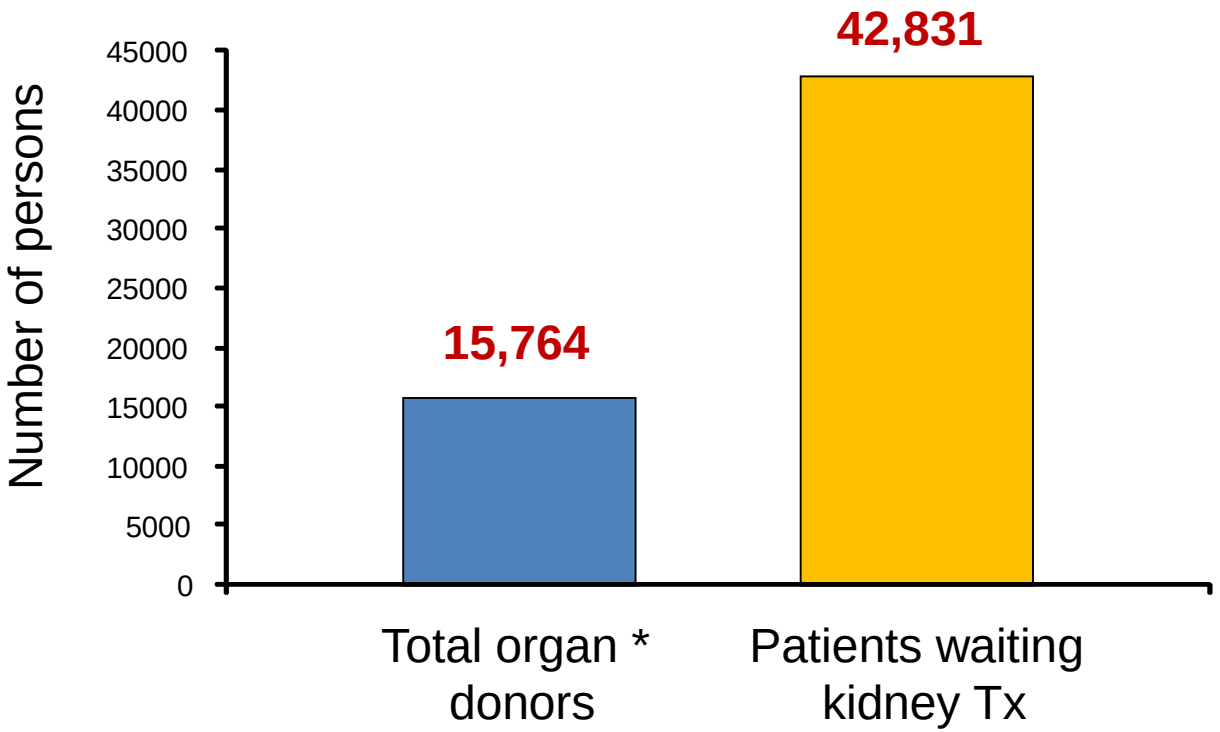
Stem Cell Treatments Flourish With Little Evidence That They Work

By Denise Grady and Reed Abelson

Many people have become captivated by the idea of using stem cells to fix their damaged joints, and some claim to have been helped

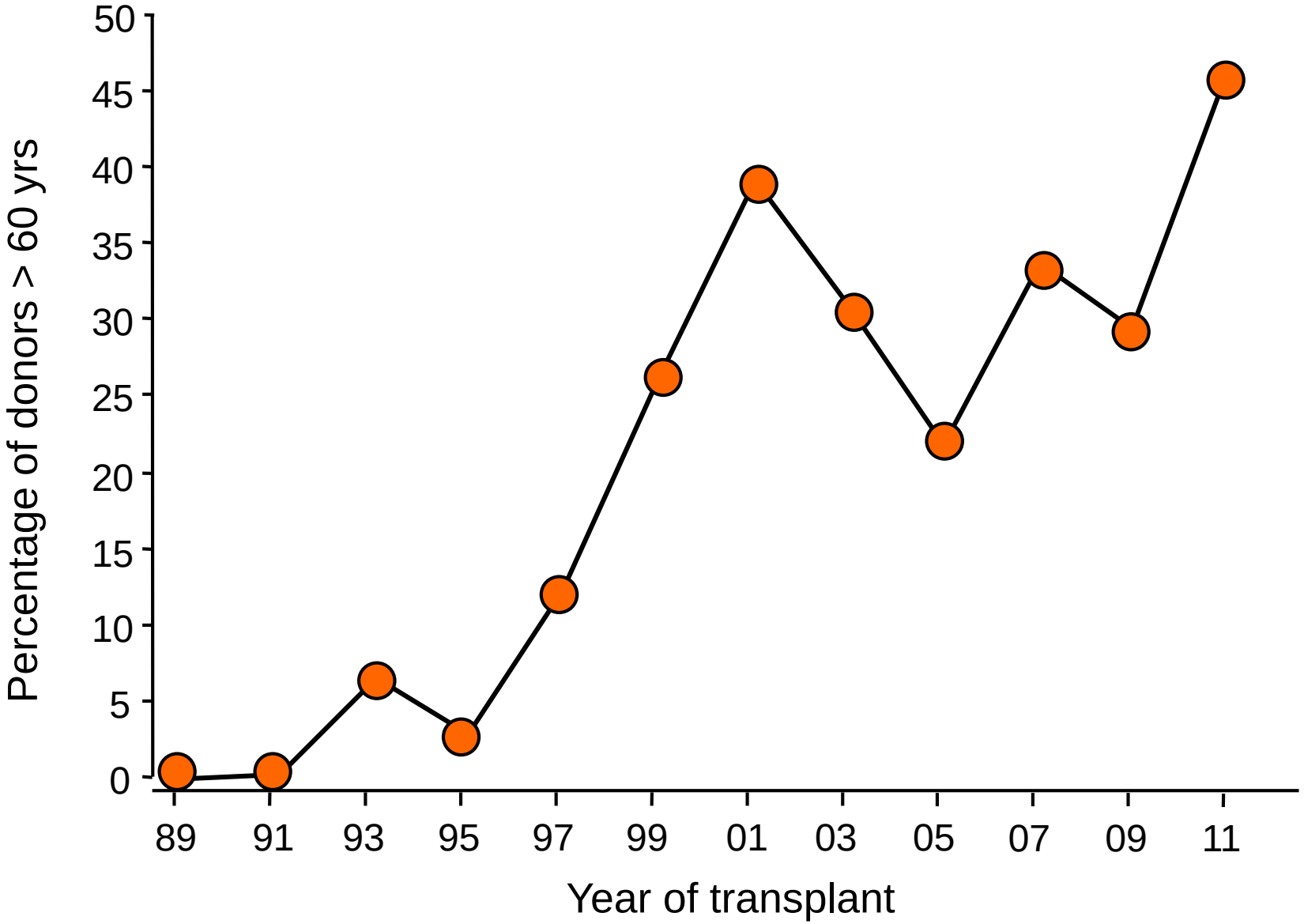
But there is no clear evidence that these treatments work, and their safety has yet to be established. Most researchers, including those at the National Institutes of Health, think that efforts to sell therapies involving adult stem cells, which can develop into different types of cells to replenish tissue, have gotten way ahead of the science

Discrepancy between organ donors and patients on waiting list for a kidney transplant in Europe (2017)



* Both deceased and living donors

WHO, Newsletter Transplant, 2018



Renal Transplant Unit, Bergamo

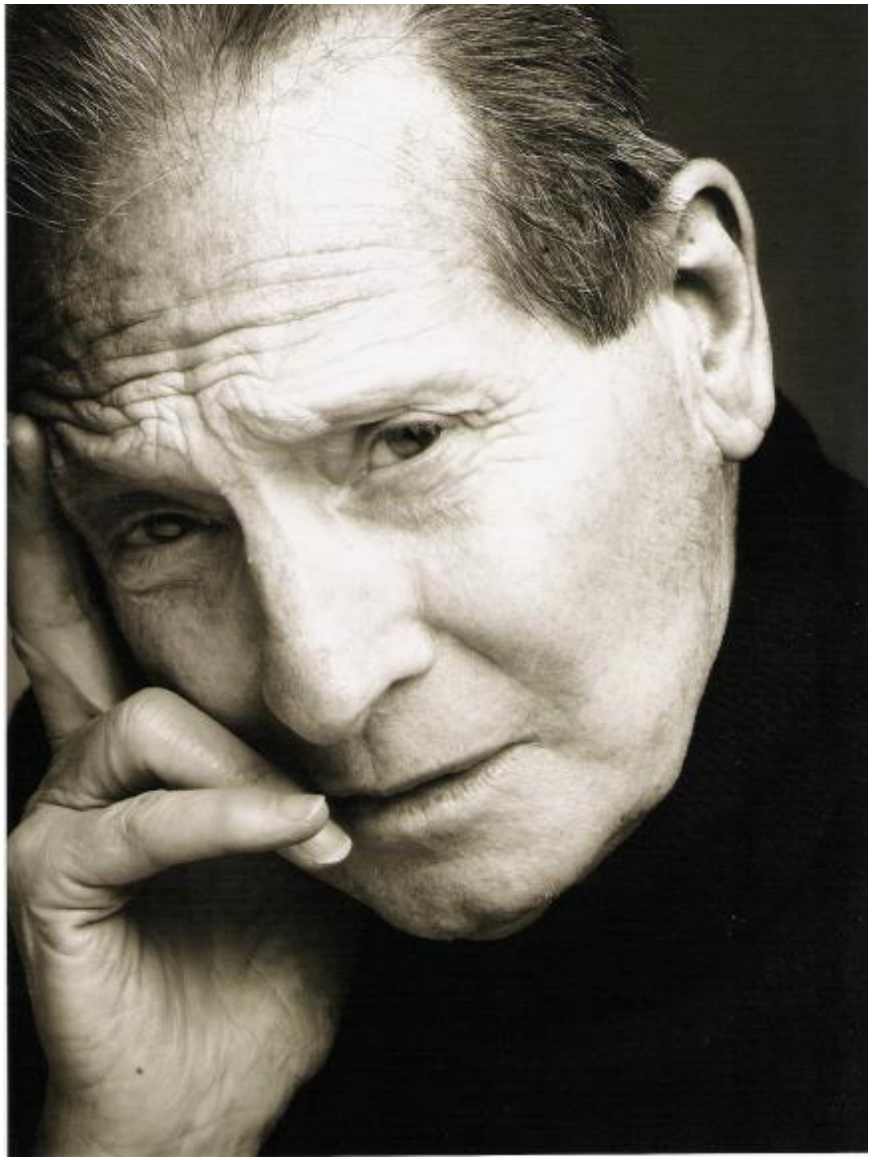
KIDNEY GRAFT OUTCOME ACCORDING TO DONOR CHARACTERISTICS AND PROCEDURE

	Dual transplants *(%)*	2-year survival *(%)*
Donor age *(years)*		
< 60 (ideal)*	0	95
60-69°	28	93
70-79°	78	92
≥ 80#	95	92

Remuzzi et al., *N Engl J Med,* 2006
Rigotti et al., *N Engl J Med,* 2009
Ruggenenti et al., *Am J Transplant, 2017*

Doctor, should I remain on dialysis or accept the expanded criteria donor kidney offered to me?

Heldal and Midtvedt, Am J Kidney Dis, 2012

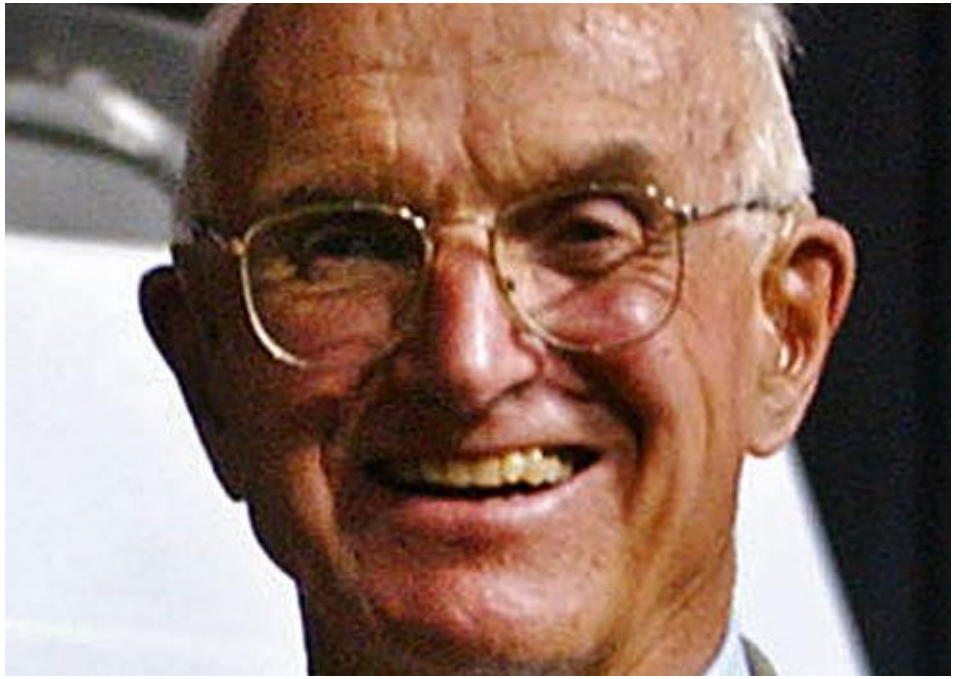


Conservatorio Teatrale, Roma
Dizione, Impostazione Vocale, Recitazione

New York Times
November 27, 2012

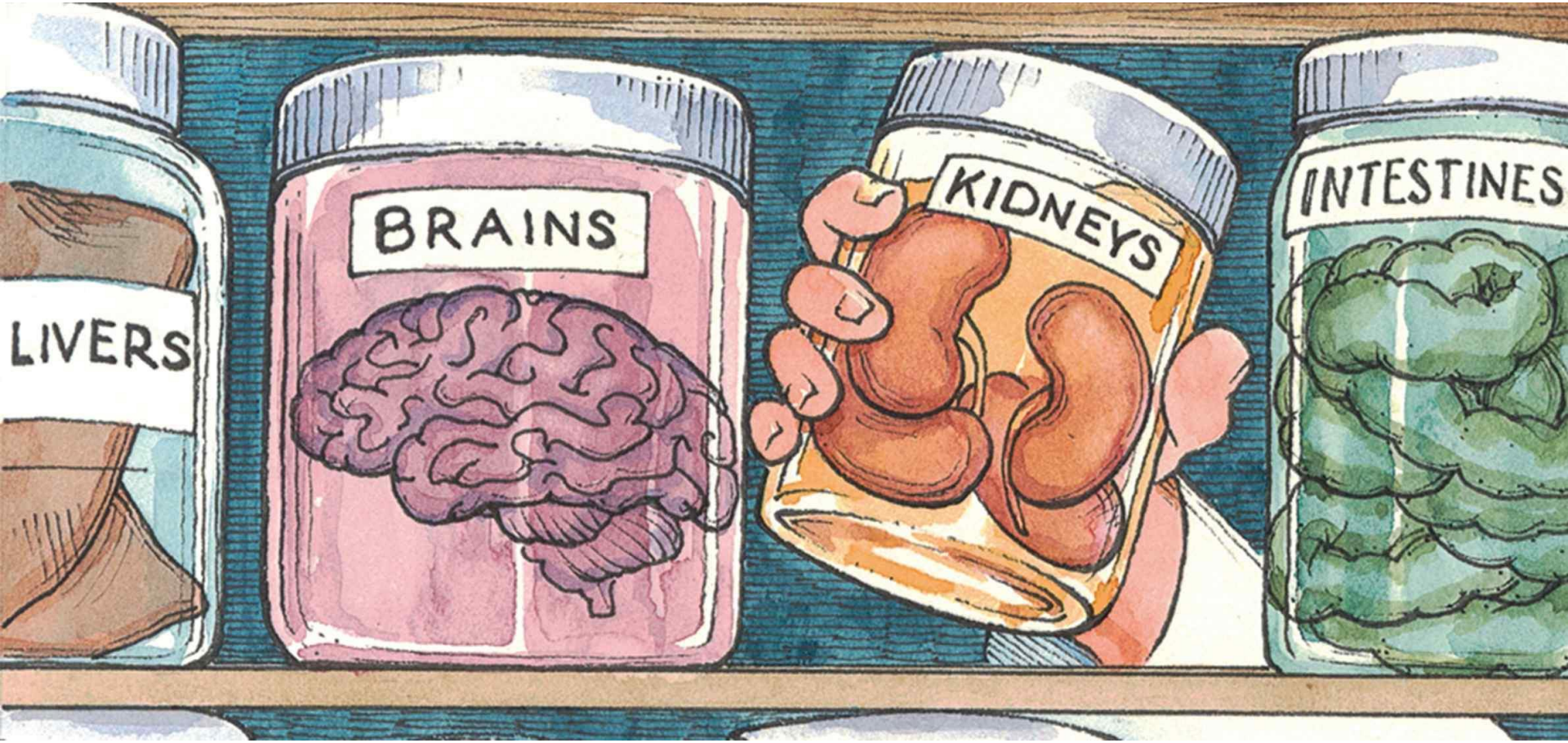
Joseph E. Murray, Transplant Doctor and Nobel Prize Winner, Dies at 93

By CORNELIA DEAN



We're victims of our success

Lack of donor organs is literally an insoluble problem until you can create organs in some other way



Geoffrey Carr, *The Economist*, 2017

- ***Will organs created in the lab be a solution?***

These slides belong to
Giuseppe Remuzzi, M.D.
Istituto di Ricerche Farmacologiche Mario Negri - IRCCS Bergamo

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FARMACOLOGICHE
MARIO NEGRI · IRCCS