Trapianti di organi solidi: come si è partiti e dove vogliamo arrivare

Giuseppe Remuzzi

Palermo, 12 settembre 2011

1,132,617 ORGAN TRANSPLANTS PERFORMED WORLDWIDE UP TO 2008*

	Transplants n°
Kidney	793,479
Liver	186,234
Heart	87,689
Lung	28,712
Kidney/pancreas	23,653
Pancreas/Islet	7,513
Heart/lung	4,096
Intestine	1,243

* October 2008

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

Sempre 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

"Nothing is more ridiculous than saying that all this could have been done with computers or with tissue cultures. That's like saying you can live without breathing or without having blood. It's absolutely the most anti-intellectual thinking that ever existed"

Joseph Murray, Nobel Prize Lecture, 1990

Ci fu una discussione pubblica

I più erano contrari - a Ronald l'intervento non avrebbe portato alcun vantaggio - Chiedono al comitato etico, ma quelli non sanno che pesci prendere (succede spesso quando si chiede ai comitati etici di rispondere o si o no)

Così i dottori di Boston la decisione la presero da soli, con la famiglia Herrick

- Si provarono anche a fare trapianti fra fratelli e sorelle non gemelli

- Quasi sempre il rene smetteva di funzionare dopo 5-10 giorni e la maggior parte dei pazienti moriva

- 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

“nel frattempo Gertrude Elion e George Hitchings, a Tuckahoe negli Stati Uniti, sintetizzarono la 6-mercaptopurina”

Fra le righe di un lavoro pubblicato agli inizi degli anni ‘60, c’era scritto che il farmaco impediva anche la proliferazione dei linfociti

Questo particolare non sfuggì a un giovane e brillante dottore inglese, Roy Calne, che lavorava al Royal Free Hospital di Londra per prolungare la sopravvivenza del trapianto negli animali

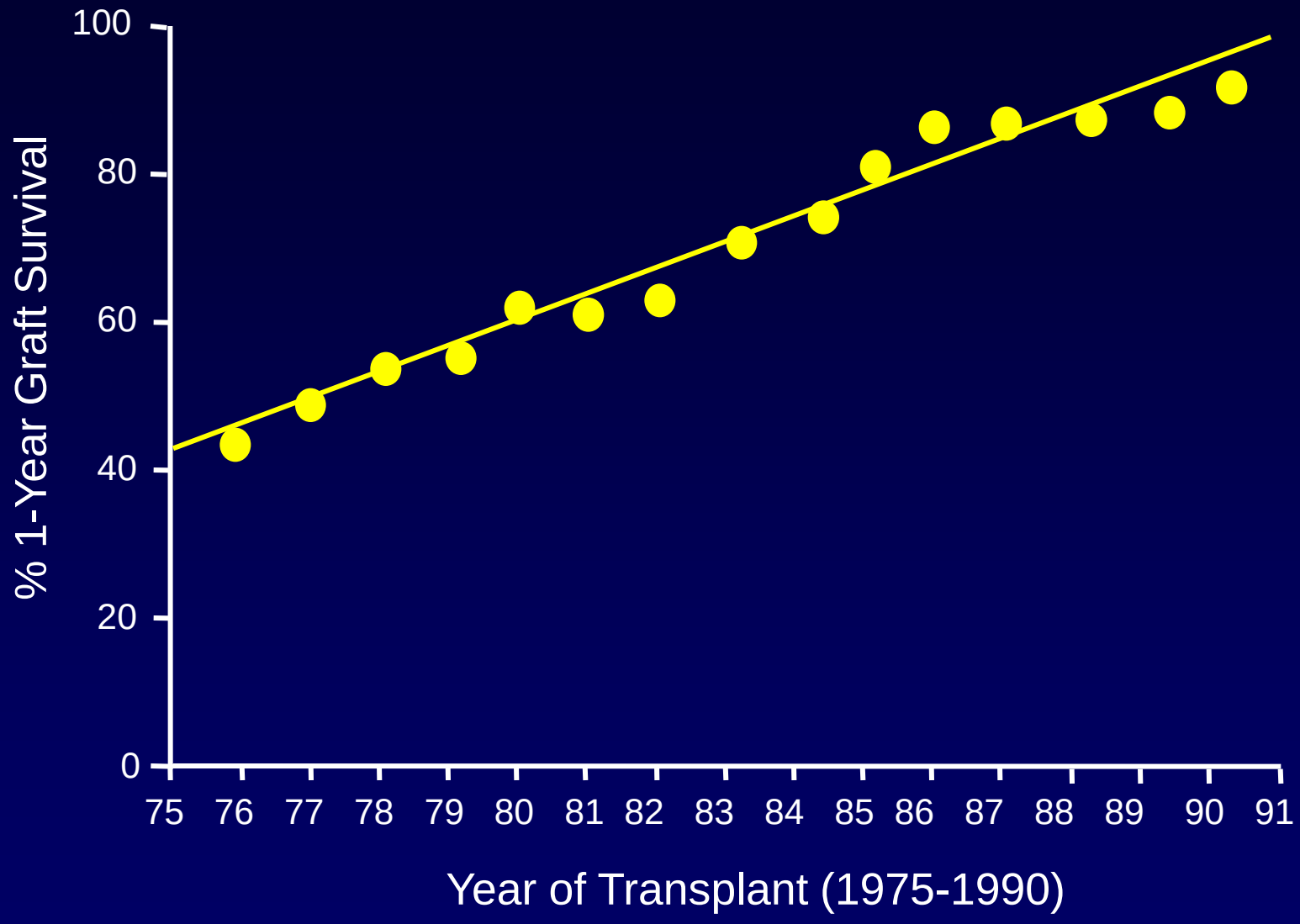
1962

- Calne si convinse a provare l’azatioprina nell’uomo dopo molti mesi di esperimenti nel cane
- Fra i primi pazienti, uno, operato nel 1962, ebbe una vita normale per moltissimi anni

1972

Le speranze di risolvere definitivamente il problema sembrarono ad un certo punto legate ad un'altra scoperta

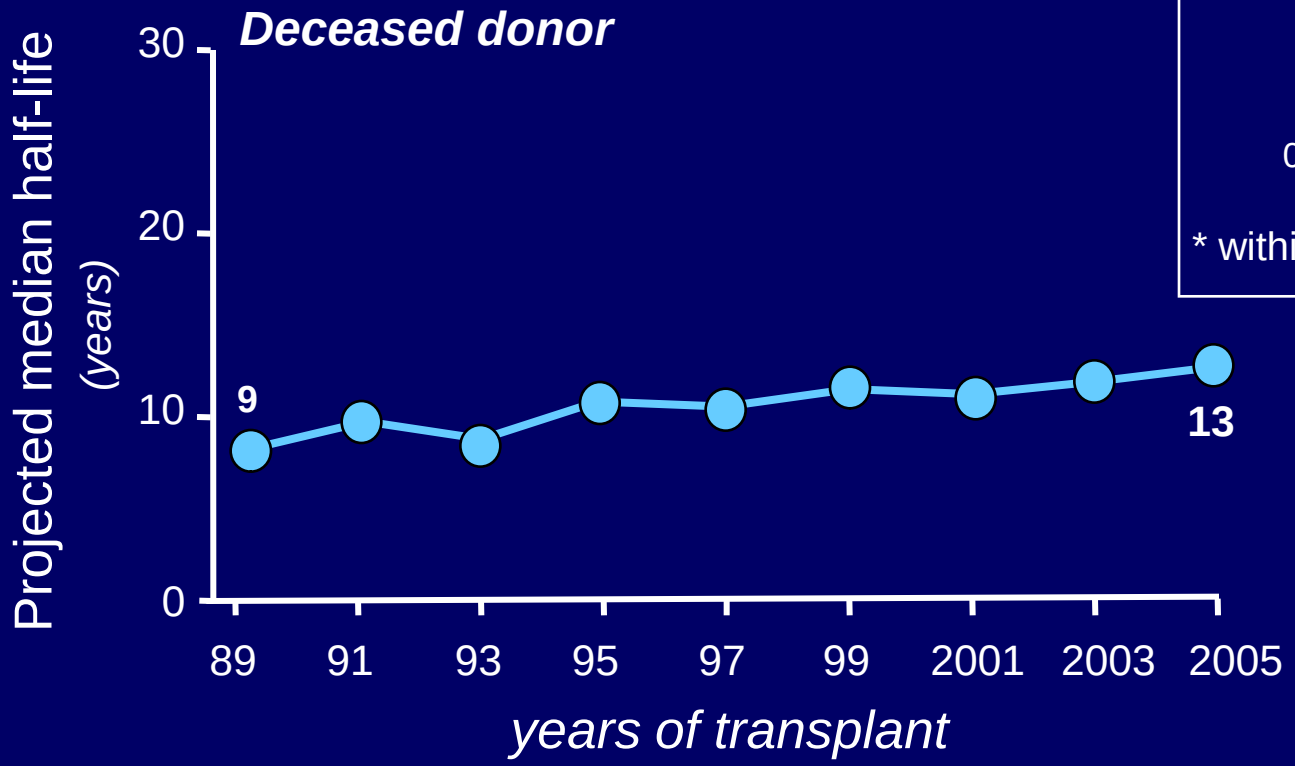
A Basilea nel 1972 ricercatori impegnati nel cercare nuovi antibiotici ottennero, da un fungo, una sostanza chiamata *ciclosporina*

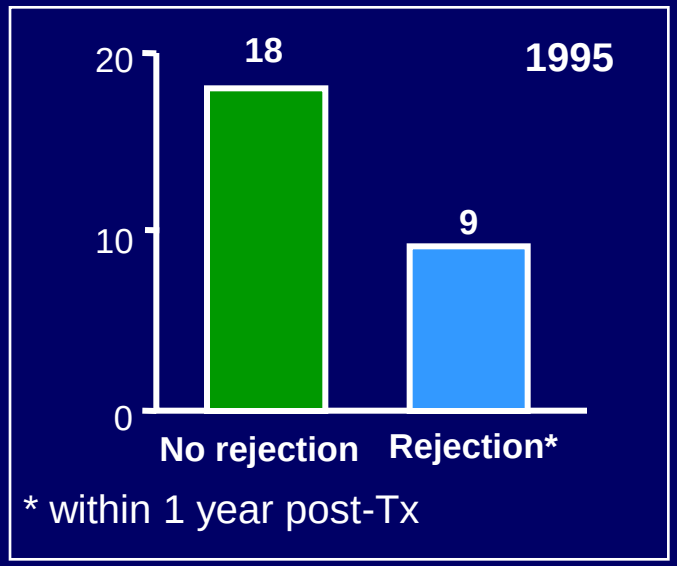


Gjertson et al., *1992*

GRAFT SURVIVAL AFTER RENAL TRANSPLANTATION IN THE PERIOD 1989-2005

Analysis of UNOS data on patients with functioning kidney 1 year post transplant





Hariharan et al., *N Eng J Med*, 2000
USRDS, *Am J Kidney Dis*, 2009

THE PROMISE OF NOVEL IMMUNOSUPPRESSIVE AGENTS

Basiliximab
(chimeric monoclonal antibody against IL-2 R)

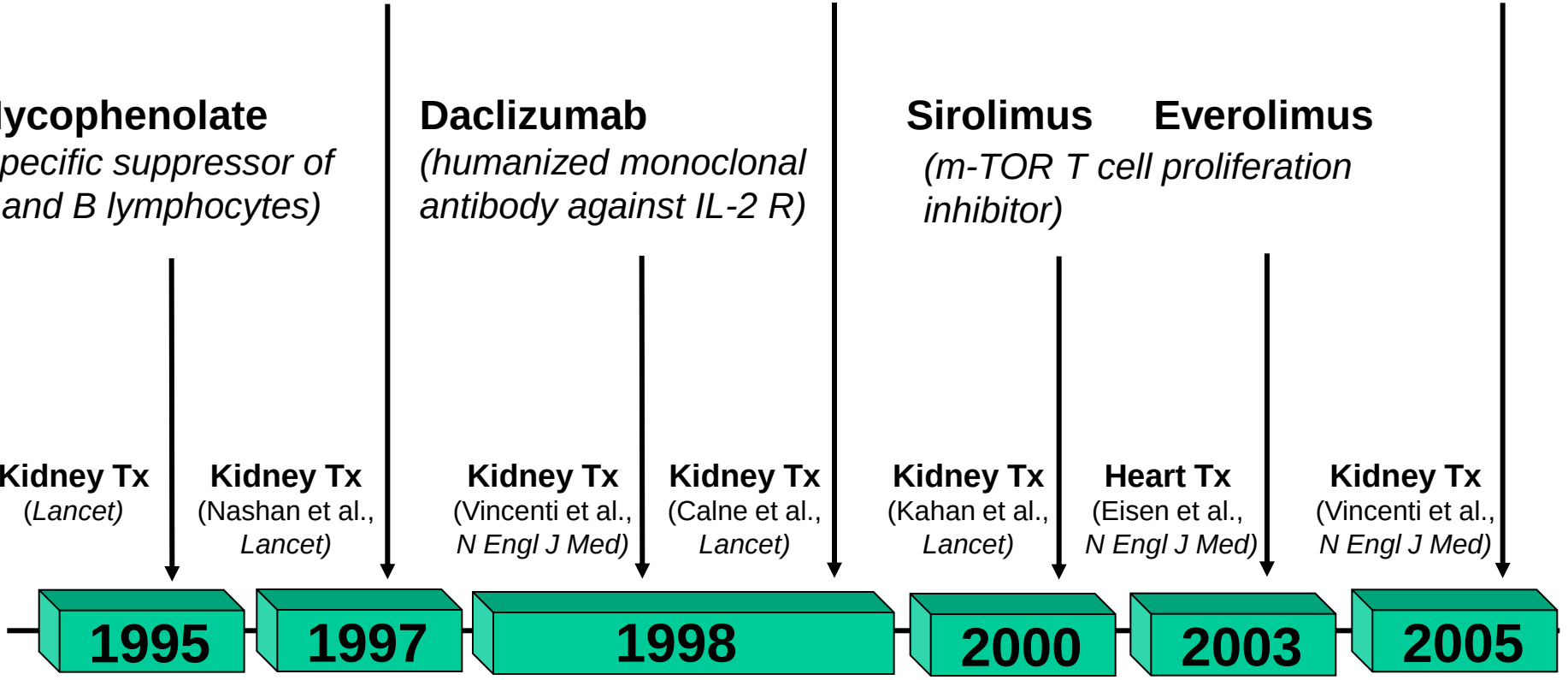
CAMPATH-1H
(humanized anti-CD52 antibody - T and B cells depletion)

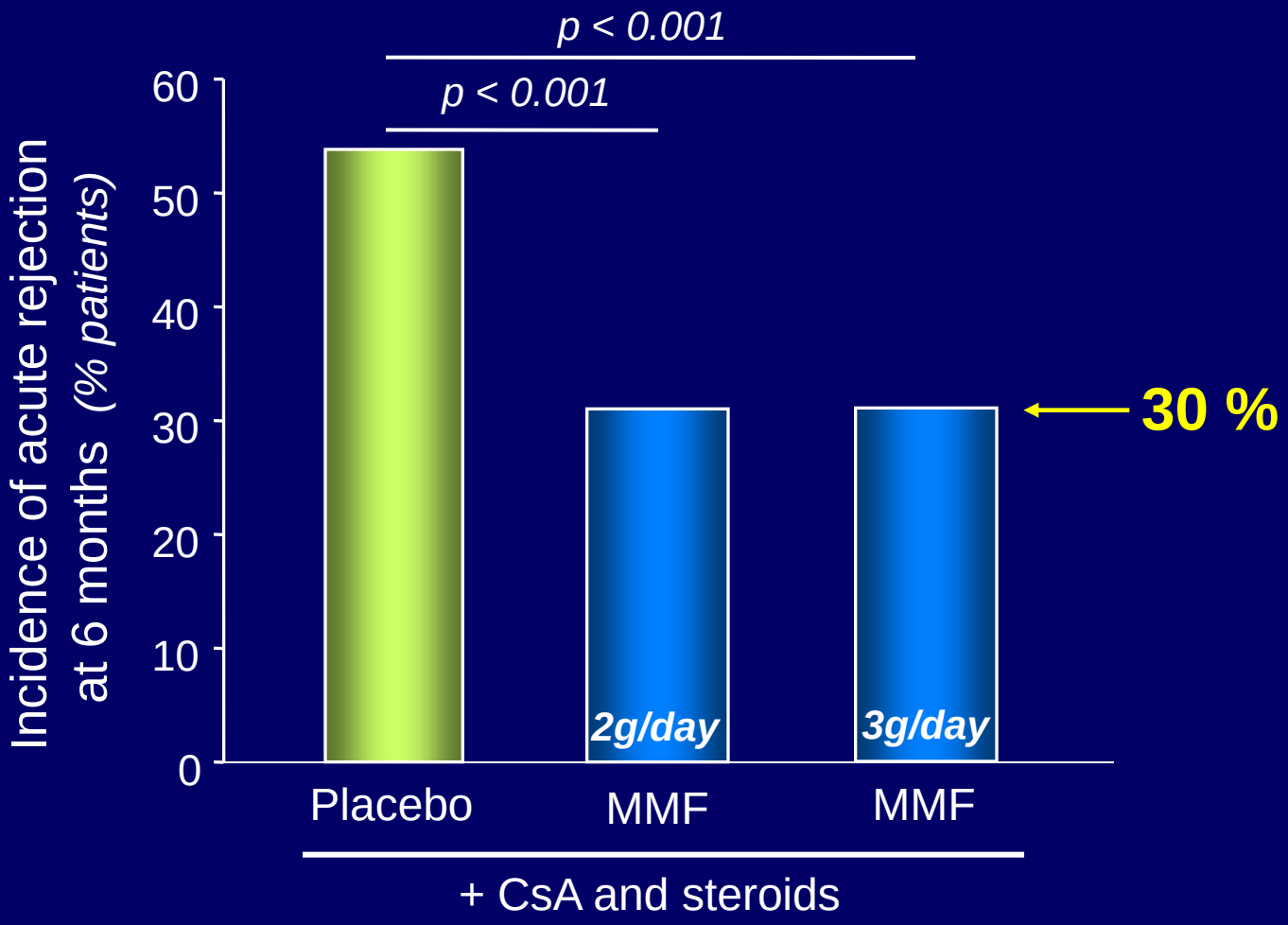
Belatacept
(IgG/CTLA4 fusion protein selective blocker of T cell activation)

Mycophenolate
(specific suppressor of T and B lymphocytes)

Daclizumab
(humanized monoclonal antibody against IL-2 R)

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





491 recipients of first or second cadaveric renal allograft

More specific suppression of T and B lymphocytes leaving unchanged hematopoiesis and neutrophil number and activity

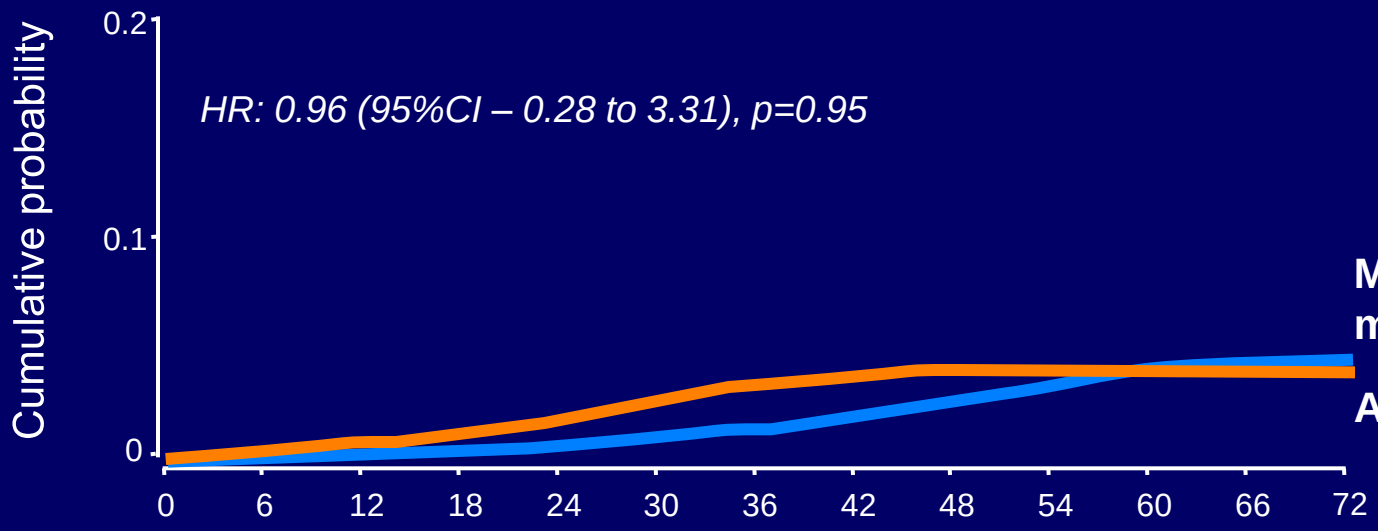
European Mycophenolate Mofetil Cooperative study Group, Lancet, 1995

Acute rejection episodes

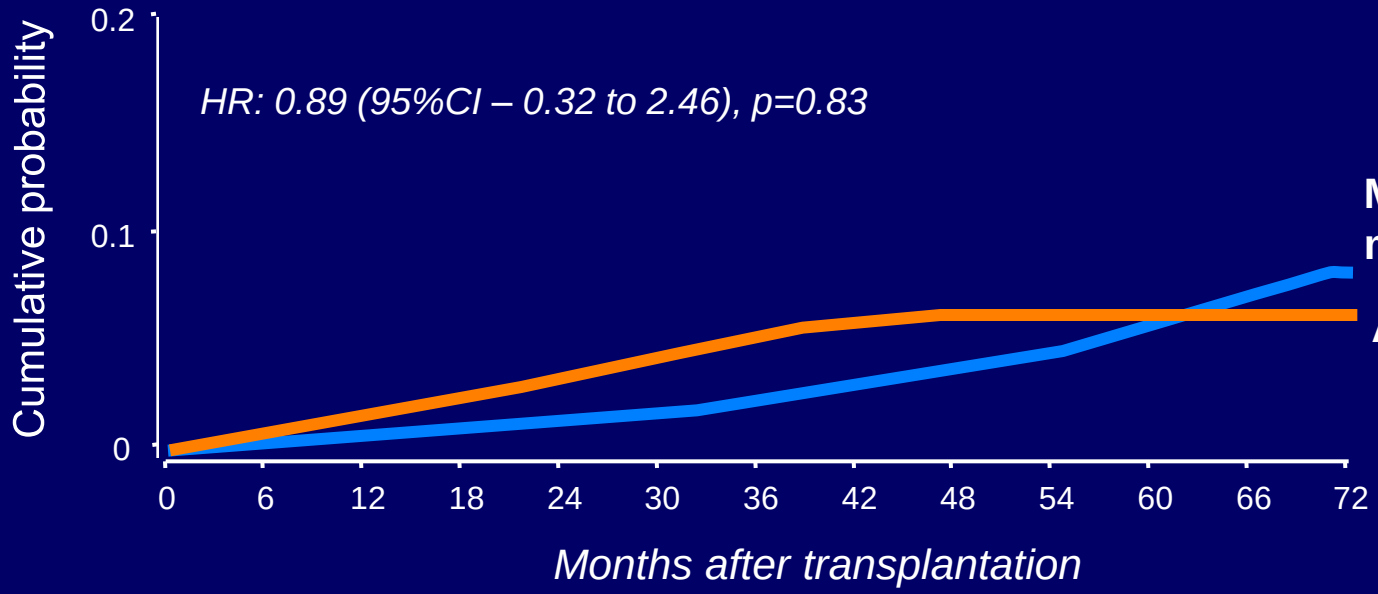
	Overall *(%)*	MMF *(%)*	AZA *(%)*	p
Clinical diagnosis	34	34	**35** ⬅	0.91
Biopsy proven	20	18	23	0.34
Steroid resistant	8	5	11	0.11

Remuzzi et al., *Lancet,* 2004

PATIENT DEATH

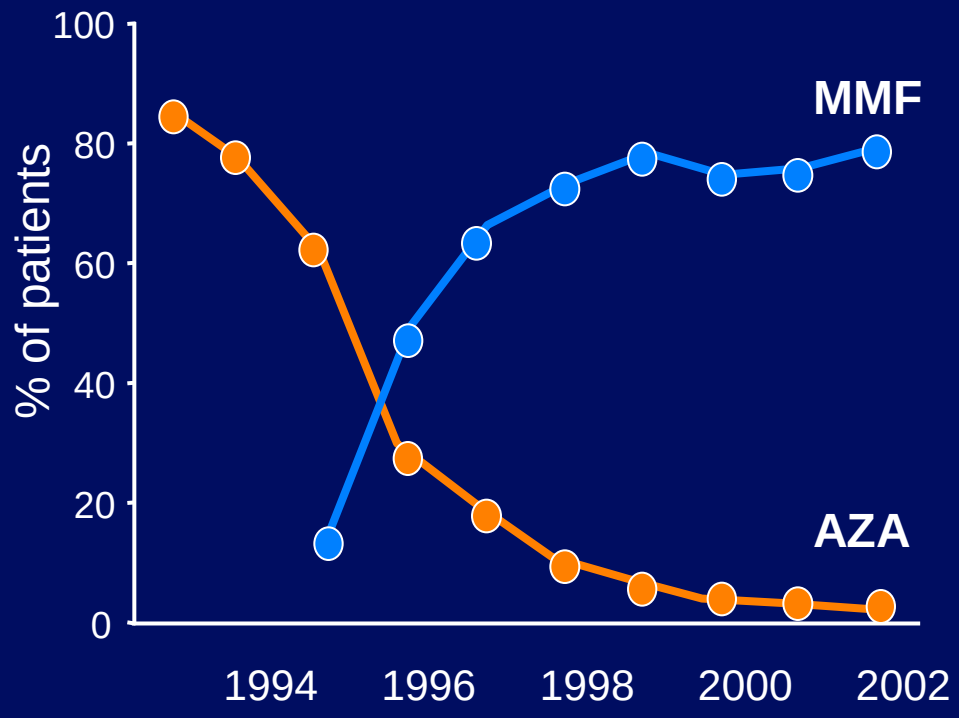


DEATH-CENSORED GRAFT LOSS

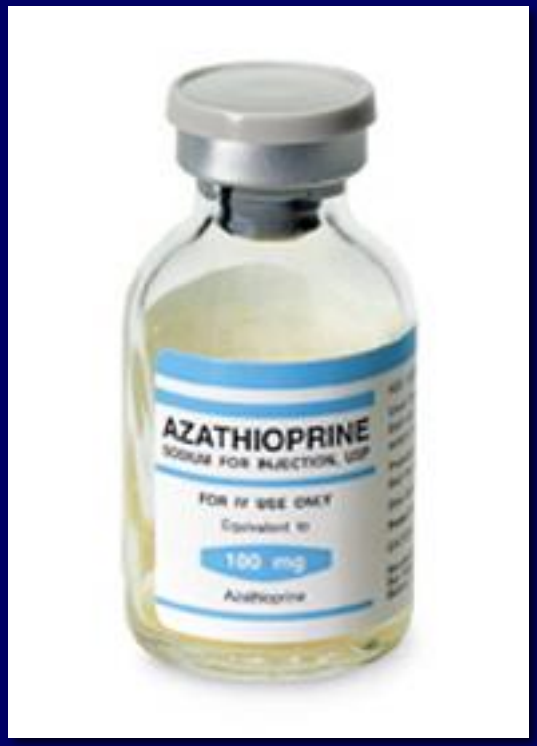


Remuzzi et al., *J Am Soc Nephrol,* 2007

In 2004 MMF (CellCept®) was in the 5 top-selling products worldwide



Higher incidence of tuberculosis in MMF- than azathioprine-based immunosuppressive regimens in India kidney transplant scenario



0,62 euro **15,12 euro**

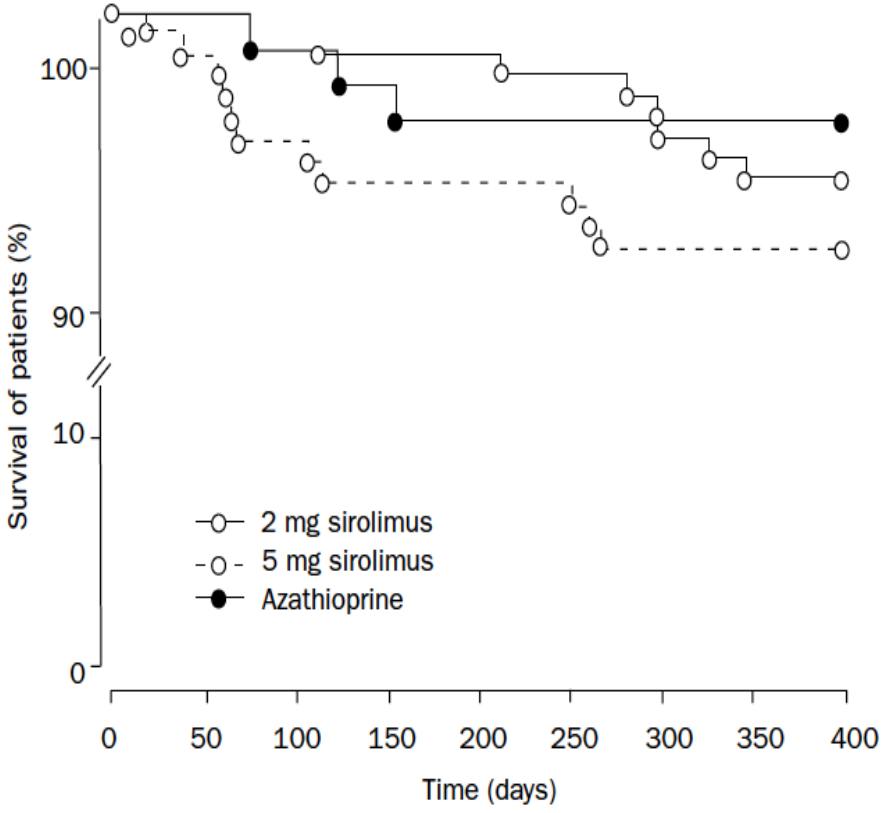
Costo dose giornaliera

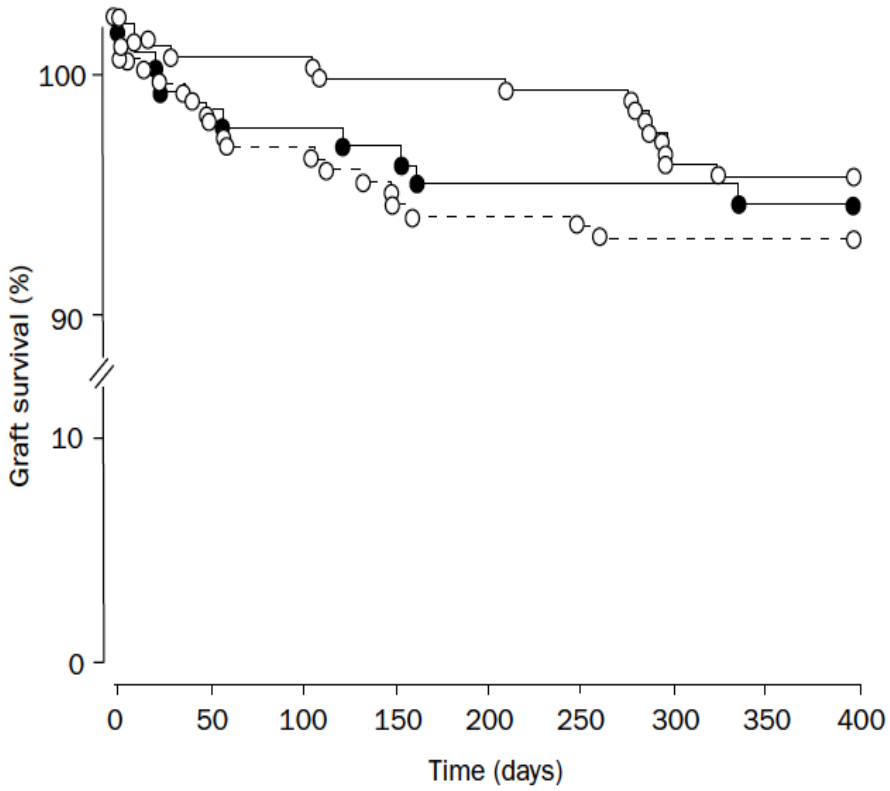
Lancet 2000

Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study

*Barry D Kahan for The Rapamune US Study Group**

Use of sirolimus reduced occurrence and severity of biopsy-confirmed acute rejection episodes with no increase in complications



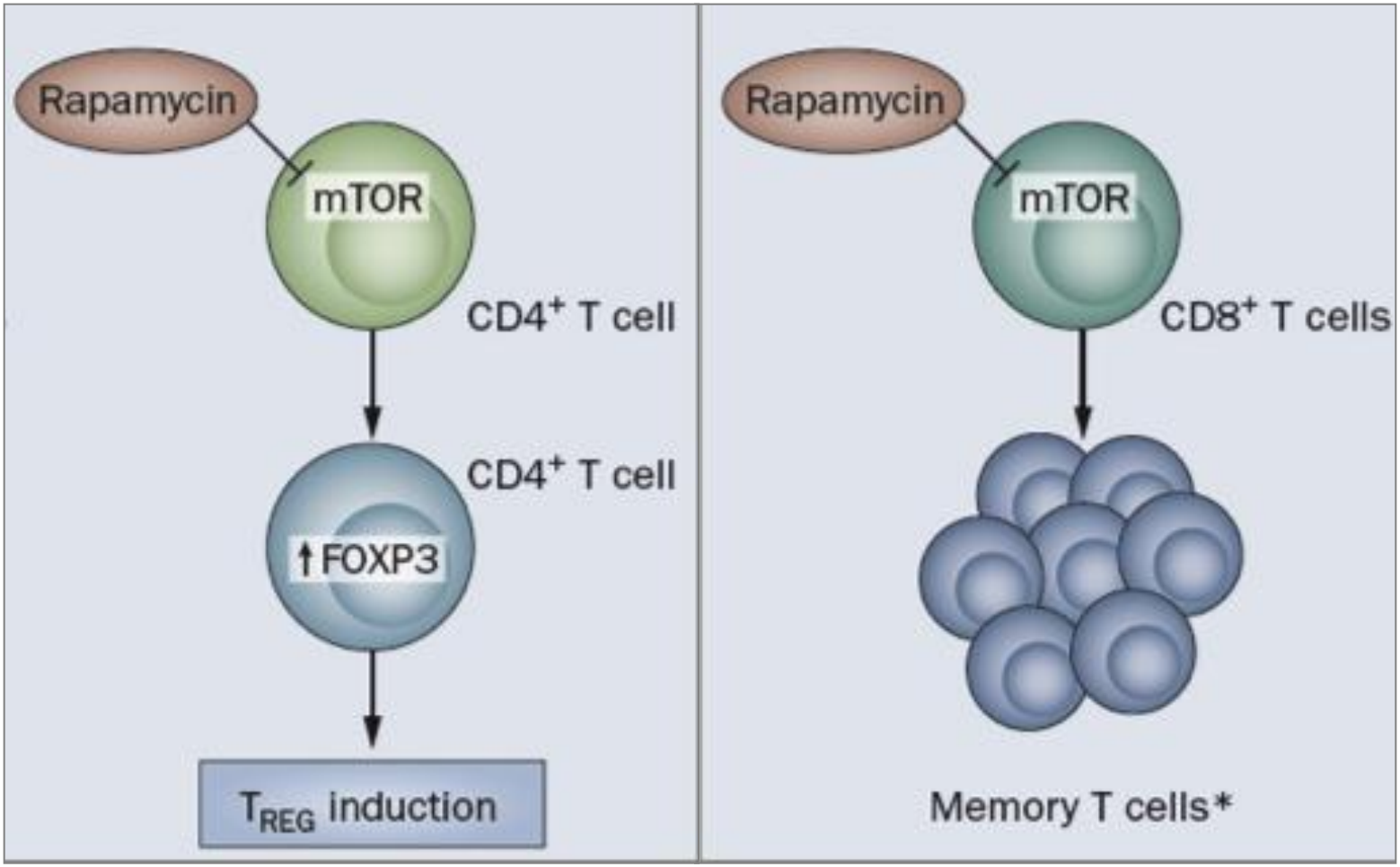


Kahan et al., *Lancet,* 2000

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

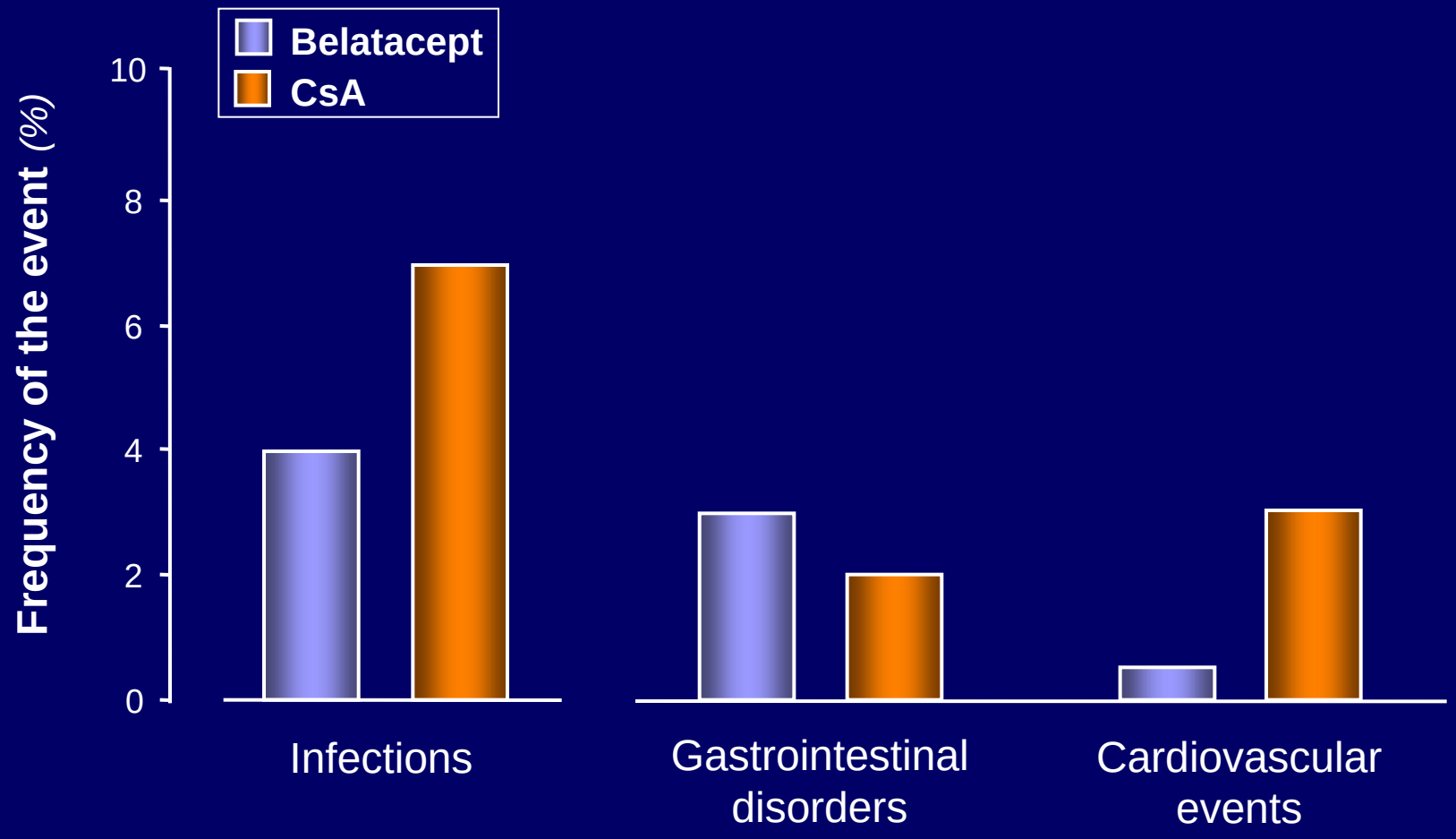
New England Journal of Medicine, 2005

Costimulation Blockade with Belatacept in Renal Transplantation

Flavio Vincenti, M.D., Christian Larsen, M.D., Ph.D., Antoine Durrbach, M.D., Ph.D., Thomas Wekerle, M.D., Björn Nashan, M.D., Ph.D., Gilles Blancho, M.D., Ph.D., Philippe Lang, M.D., Josep Grinyo, M.D., Philip F. Halloran, M.D., Ph.D., Kim Solez, M.D., David Hagerty, M.D., Elliott Levy, M.D., Wenjiong Zhou, Ph.D., Kannan Natarajan, Ph.D., and Bernard Charpentier, M.D., for the Belatacept Study Group*

- 102 kidney transplant recipients receiving Belatacept (10-5 mg/kg i.v.) infusion compared with 26 patients on CsA, both in addition to Basiliximab, MMF and steroids
- At six months, the incidence of acute rejection was similar among the groups (7 vs 8 %)

FIVE-YEAR SAFETY OF BELATACEPT IN RENAL TRANSPLANTATION



Vincenti et al, *J Am Soc Nephrol*, 2010

Few subjects treated with more intensive Belatacept regimen, developed post-transplant lymphoproliferative disease

UNEXPECTED HIGH REJECTION RATE IN PHASE III CLINICAL TRIAL WITH BELATACEPT

The case of BENEFIT trial with Belatacept (living or standard deceased donors)

Three arms:
- Intensive belatacept dose *(n = 225)*
- Less-intensive belatacept dose *(n = 230)*
- CsA *(n = 231)*

] Basiliximab + Steroids + MMF

	Acute rejection *(%)*	Graft loss at 1 year post-Tx *(%)*
Intensive Belatacept	22	2
Less-intensive Belatacept	17	2
CsA	7	4

Vincenti et al., *Am J Transpl,* 2010

Belatacept

1350 euro for each treatment

(5-8 fold within 3 months post transplant)

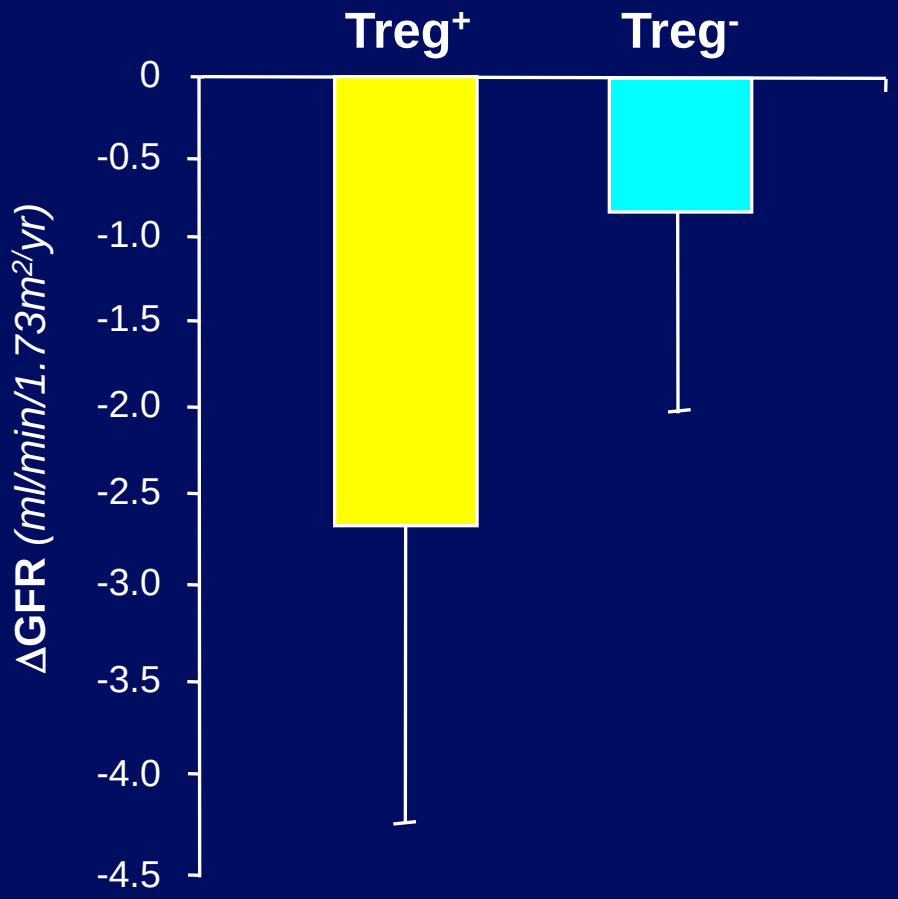
CAMPATH-1H ALONE FAILS TO INDUCE RENAL ALLOGRAFT TOLERANCE IN HUMANS

7 nonsensitized recipients of living-donor kidneys

Patient *(sex)*	**CAMPATH dosing** *(days)*	**Rejection** *(day of onset)*
M	-5, -3, -1	21
M	-5, -3, -1	18
F	-5, -3, -1	15
M	-5, -3, -1	14
M	-3, -1, 2	18
F	-3, -1, 2	24
M	-1, 1, 3, 5	28

Kirk et al., *Transplantation,* 2003

HIGH CIRCULATING T REG COUNTS UNDER CAMPATH-1H DO NOT CONFER APPRECIABLE PROTECTION AGAINST GRAFT FUNCTION LOSS AND CHRONIC ALLOGRAFT REJECTION



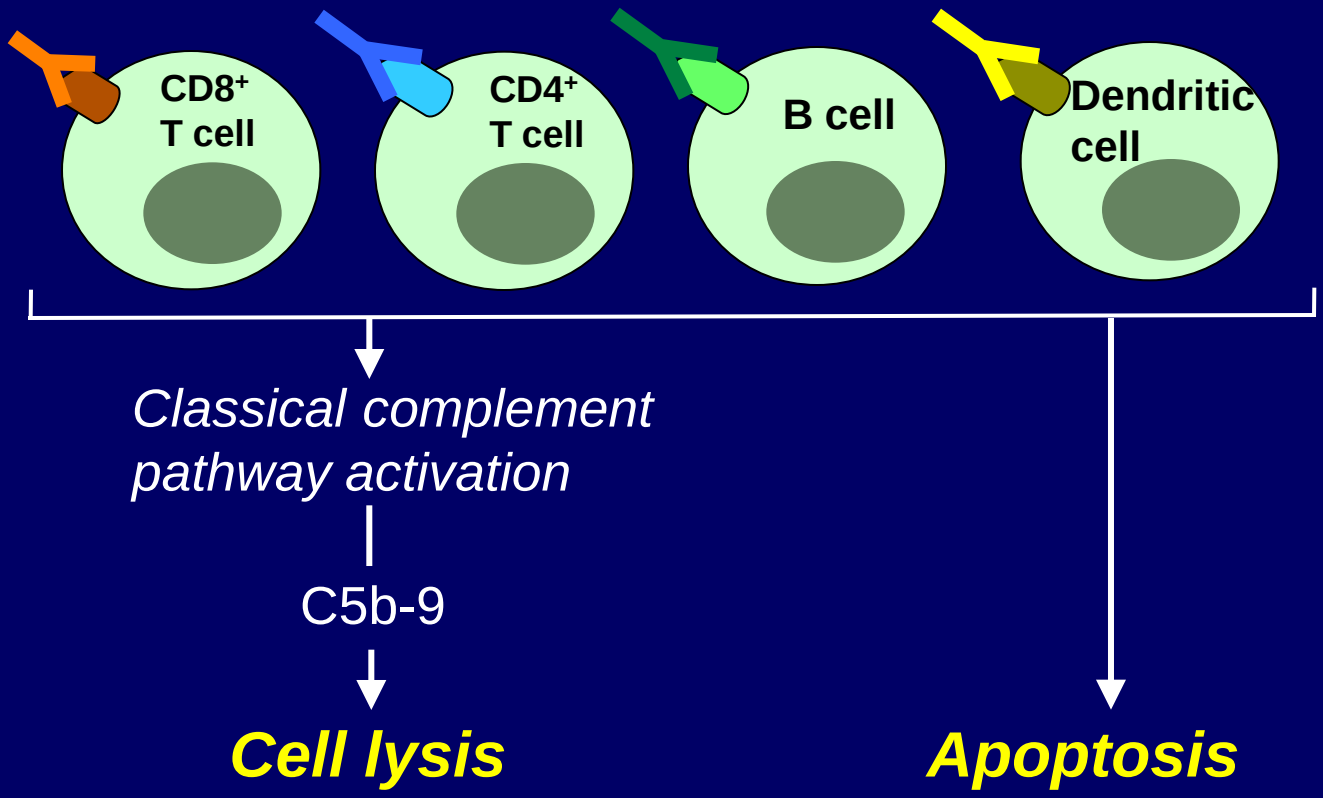
From months 6 to 30 post transplant

	Treg+	Treg-
	(mean)	
CADI score*	**5.2**	**4.3**
C4d staining*	**1.0**	**0.4**

**2 yrs post Tx*

Ruggenenti et al., *Transplantation,* 2008

POLYCLONAL ANTI-THYMOCYTE GLOBULINS *(ATG)*

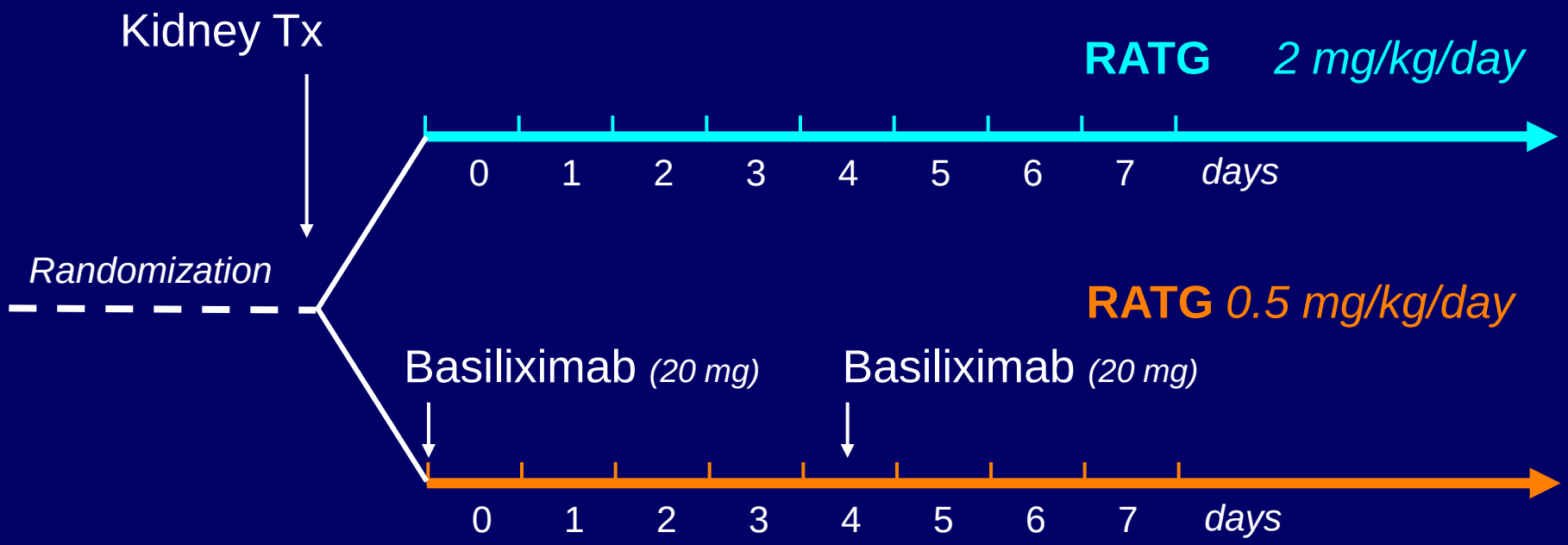


Zand et al., *Transplantation,* 2006

- Cytokine release syndrome (anemia, leukopenia and thrombocytopenia)

- Opportunistic infections, lymphoproliferative disorders, or malignancies

BASILIXIMAB COMBINED TO LOW-DOSE RATG IN HIGH RISK KIDNEY TRANSPLANT RECIPIENTS



Maintenance therapy with CsA, ST, MMF

- 1 episode of biopsy-proven acute rejection on low-dose RATG plus basiliximab, and 2 on standard-dose RATG
- Less side effects* with the combined low-dose RATG and basiliximab

* fever, elukopenia, anemia, CMV reactivation

Ruggenenti et al., *C J Am Soc Nephrol,* 2006

ATHENA *Study design*

Phase A *Phase B* *Extension*

CsA
+ low-dose MMF
(n=112)

CsA*
tapering/
withdrawal

Low dose MMF as the sole immunosuppressant

Day 0

CsA
+ low-dose AZA
(n=112)

CsA*
tapering/
withdrawal

Low dose AZA as the sole immunosuppressant

12 24 36 48 60

Graft Biopsy *Graft Biopsy*

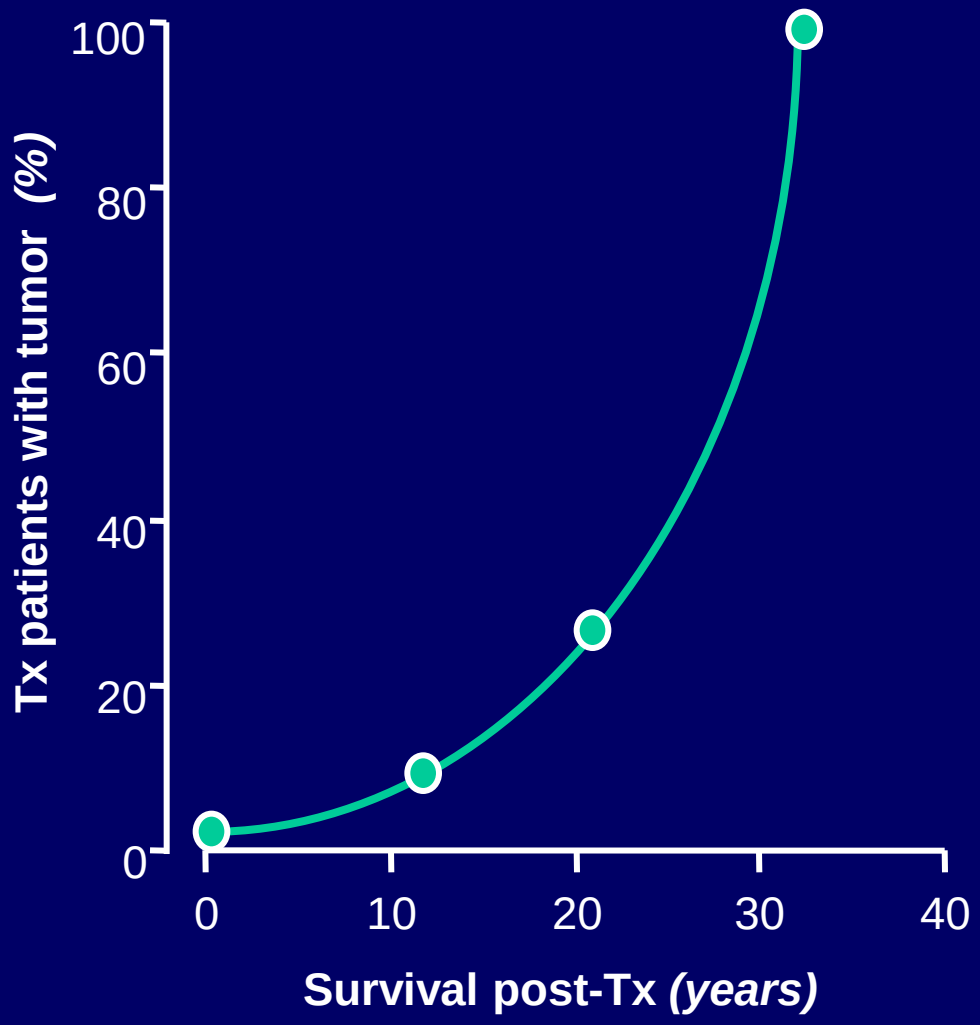
Time post-transplant *(months)*

Induction therapy:
Basiliximab + Low RATG

*In patients without previous biopsy-proven acute rejections

http://clinicaltrials.gov

RISK OF DEVELOPING A TUMOR IN TRANSPLANT RECIPIENTS



CHIMERISM AND TOLERANCE AFTER RENAL AND BONE MARROW TRANSPLANTATION

- *5 subjects with ESRD: Alport's syndrome (2), MPGN, PKD (2)*
  Bone marrow (day 0) and kidney from one-haplotype-mismatched, living-related donors

Preparative regimen

Cyclophosphamide	**60**	**mg/kg**
Thymic irradiation	**700**	**cGy**
Anti-CD2 mAb	**0.1**	**mg/kg**
CsA	**5**	**mg/kg i.v.**
Rituximab	**375**	**mg/m^2 BSA**

Post-Tx immunosuppression

CsA	**8-12 mg/d orally**
Prednisone	**2 mg/kg**

Follow-up after discontinuation of immunosuppression: 5 - 7 years

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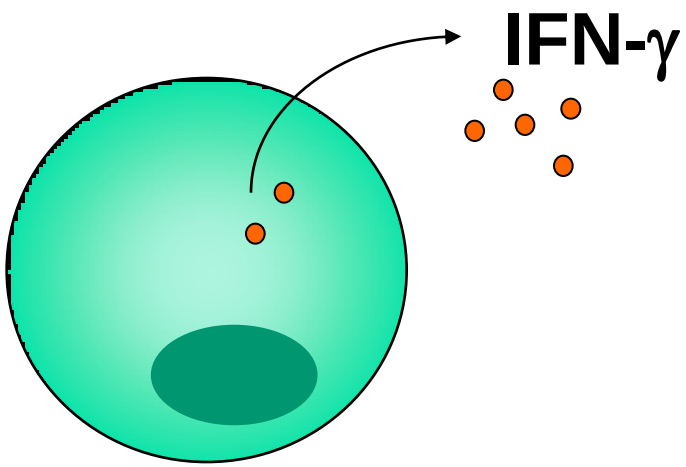
Kawai et al., *N Engl J Med,* 2008

Unusually high incidence of acute humoral rejection despite the combined conditioned regimen of thymic irradiation, cyclophosphamide, anti-CD2 mAb, cyclosporine and rituximab

Risk of infections and aplasia and ultimately death outweigh the potential benefit of tolerance

THE SPECIAL PROBLEM OF MEMORY



Activated CD8$^+$ memory

Memory T cells contribute to allograft rejection through:

- *Activation endothelial cells*
- *Help naive CD8, CD4 T cells and B cells*

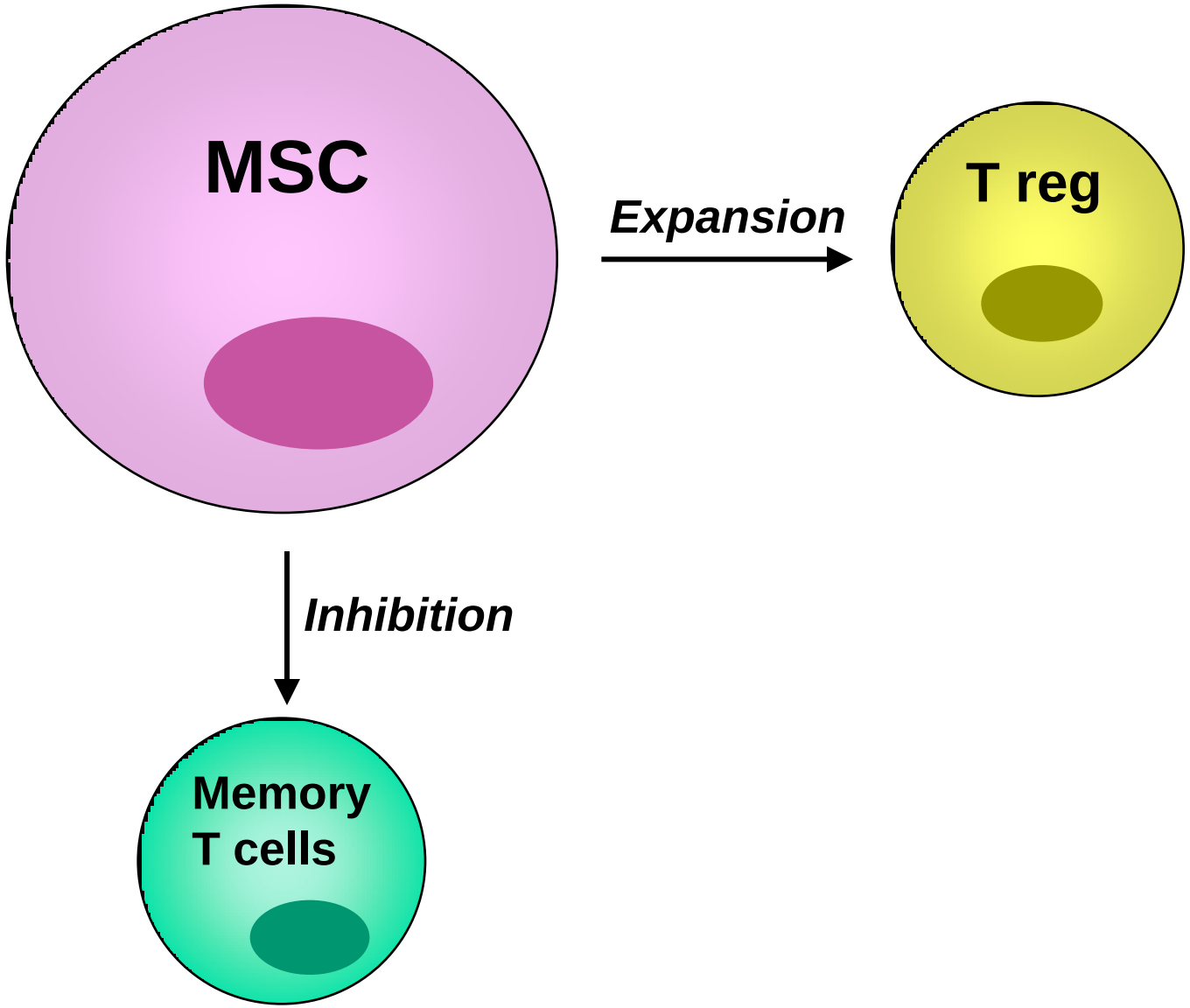
IFN-γ blockade (in vitro)

● Calcineurin inhibitors	*complete**
● Hydrocortisone	*partial*
● Sirolimus, MMF, azathioprine	*negligible*

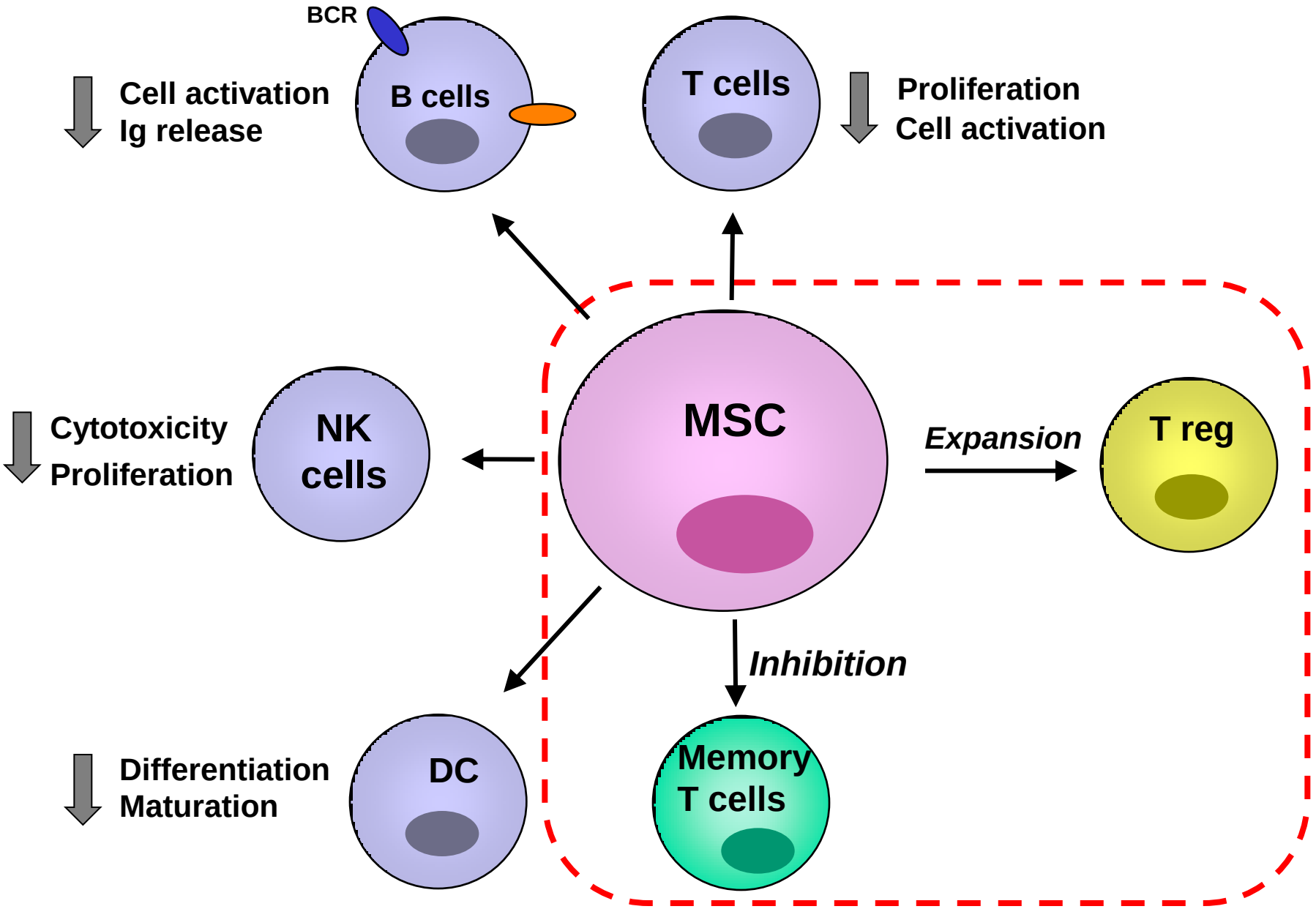
Jones et al., *Transplantation,* 2006

* When present at low level during T cell priming, CsA promotes the T cell commitment to a memory state

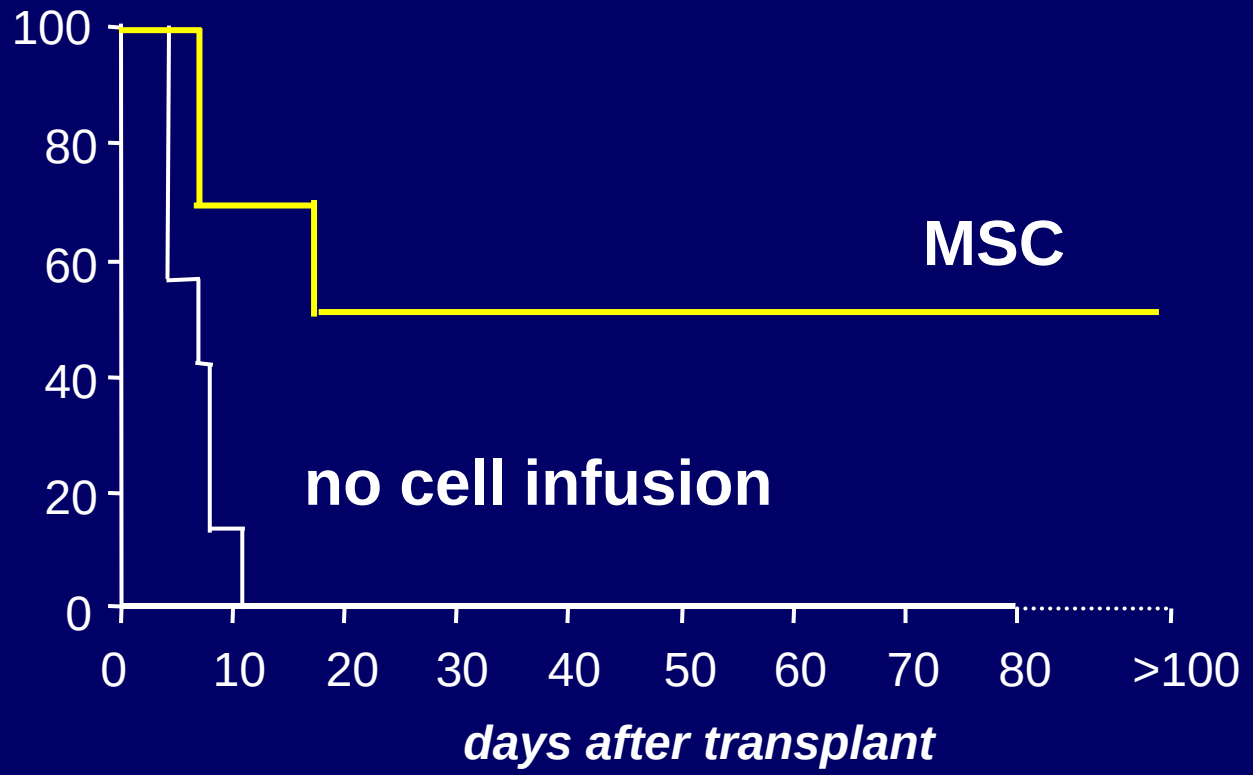
Valujskikh et al J Am Soc Nephrol, 2007



Nauta et al, *Blood*, 2007



Nauta et al, *Blood*, 2007

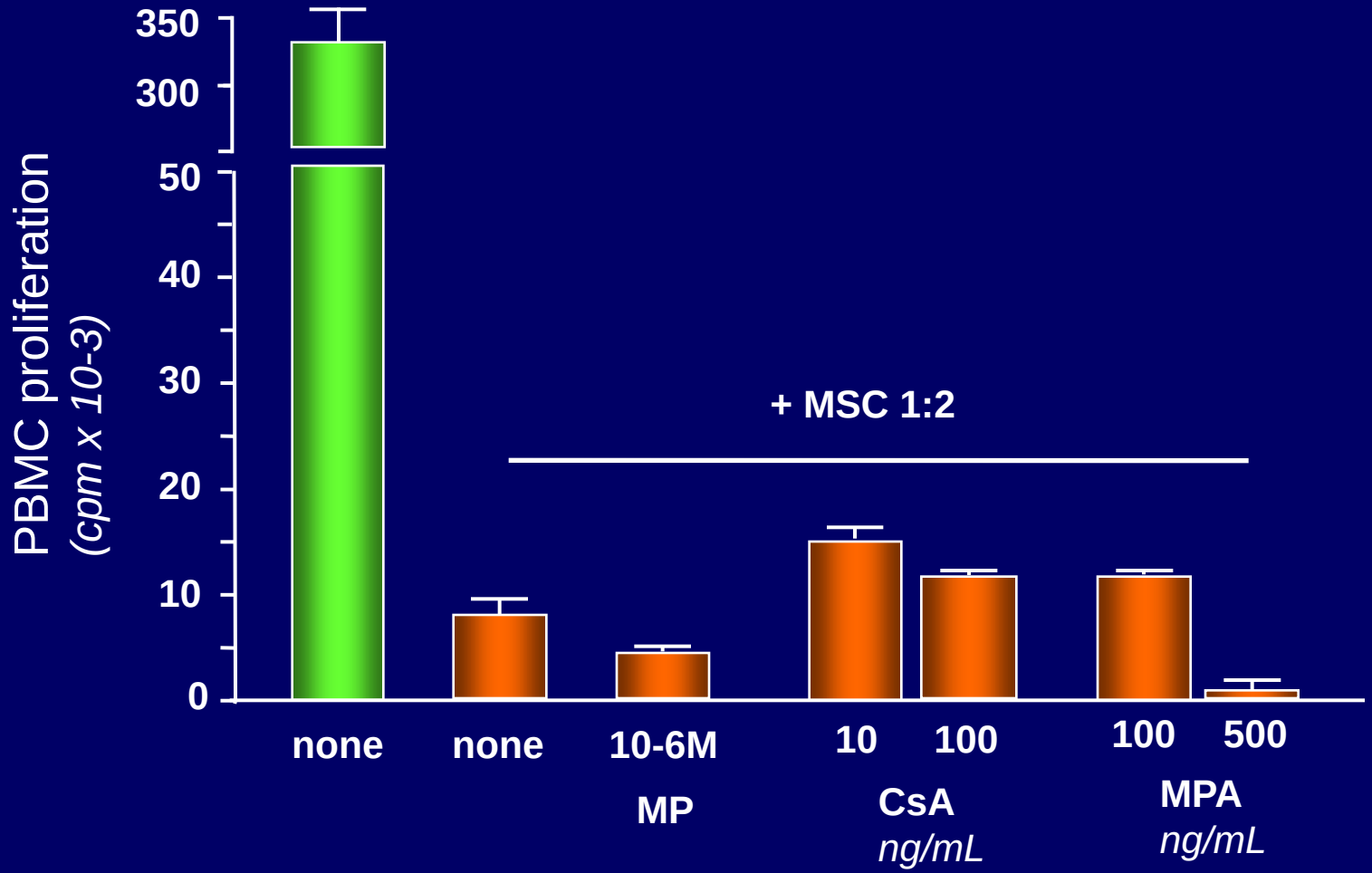


In a semi-allogeneic heart transplant pretransplant infusion of syngeneic MSC prolongs the survival of the graft through the expansion of donor-specific $CD4^+CD25^+Foxp3^+$ T-regulatory cells

Casiraghi et al., J Immunol, 2008

Timing of MSC infusion?

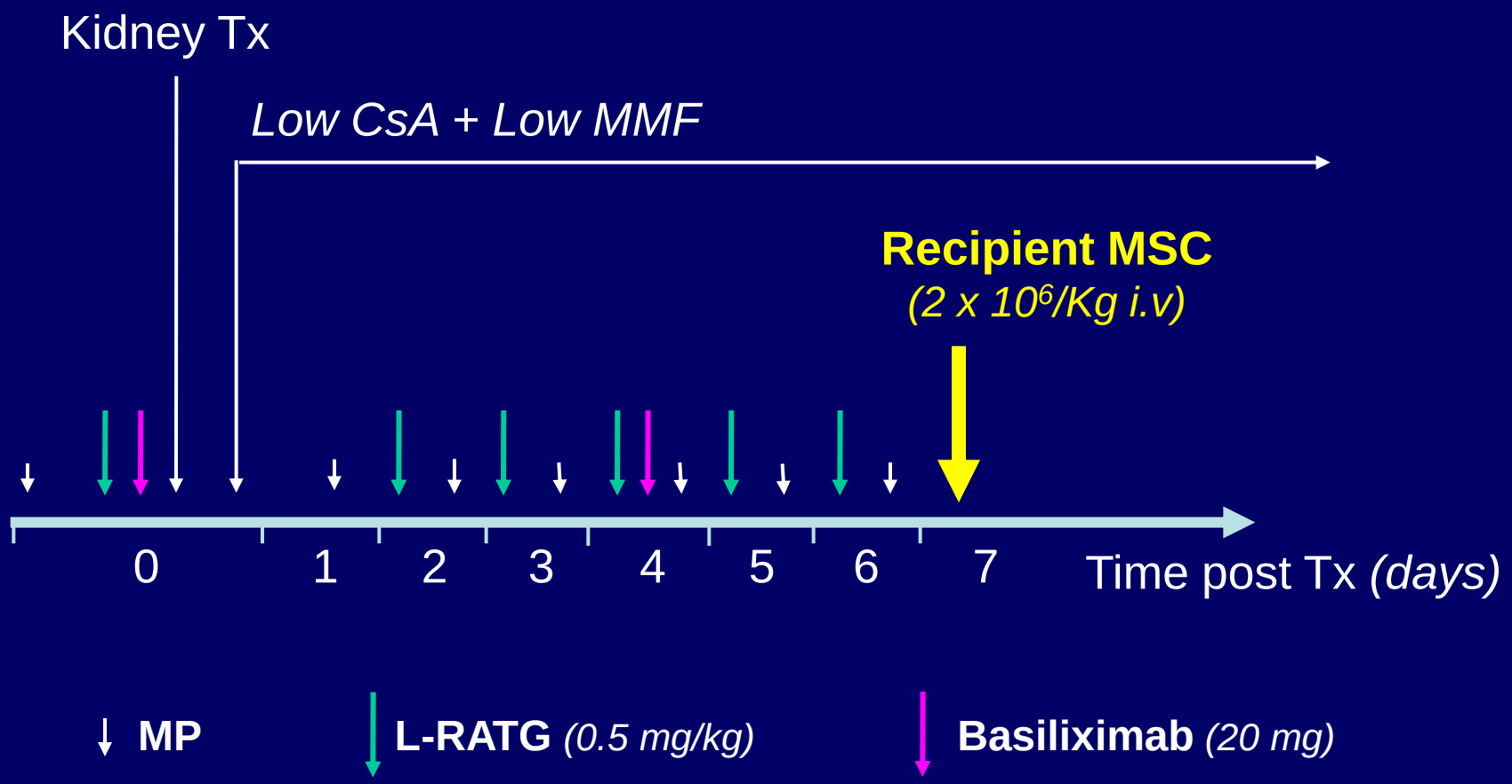
MSC IMMUNOMODULATORY FUNCTION ARE NOT IMPAIRED BY IMMUNOSUPPRESSIVE DRUGS



Casiraghi et al., 2009

MSC TO PROMOTE RENAL TRANSPLANT TOLERANCE

A pilot explorative study (start with 3 patients)



Perico et al., *C J Am Soc Nephrol,* 2011

LIVING-RELATED KIDNEY TRANSPLANTS COMBINED WITH RECIPIENT MSC INFUSION

Patient #1: D.D

- Male, 22 years old
- ESRD: unknown etiology (proteinuric nephropathy)
- RRT: hemodialysis *(July 2007)*
- ABO compatible (Rec: A, Rh^+ Donor: 0, Rh^+)
- 2 HLA mismatches (HLA- A24, B35)
- Negative cross-match (FCXM)
- Negative anti-donor Abs (Bead Array Technique – Luminex)

Patient #2: G.U.

- Male, 34 years old
- ESRD: IgA nephropathy
- Pre-emptive transplant
- ABO compatible (Rec: A, Rh^+ Donor: 0, Rh^+)
- 2 HLA mismatches (HLA- A30, B57)
- Negative cross-match (FCXM)
- Negative anti-donor Abs (Bead Array Technique – Luminex)

Perico et al., *C J Am Soc Nephrol,* 2011

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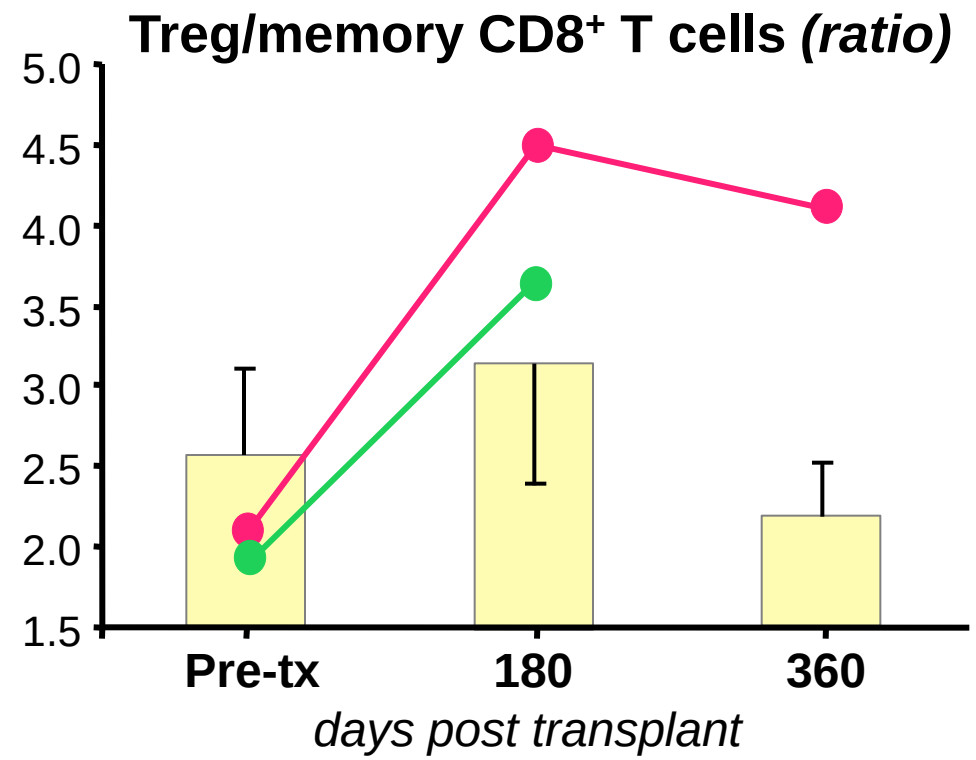
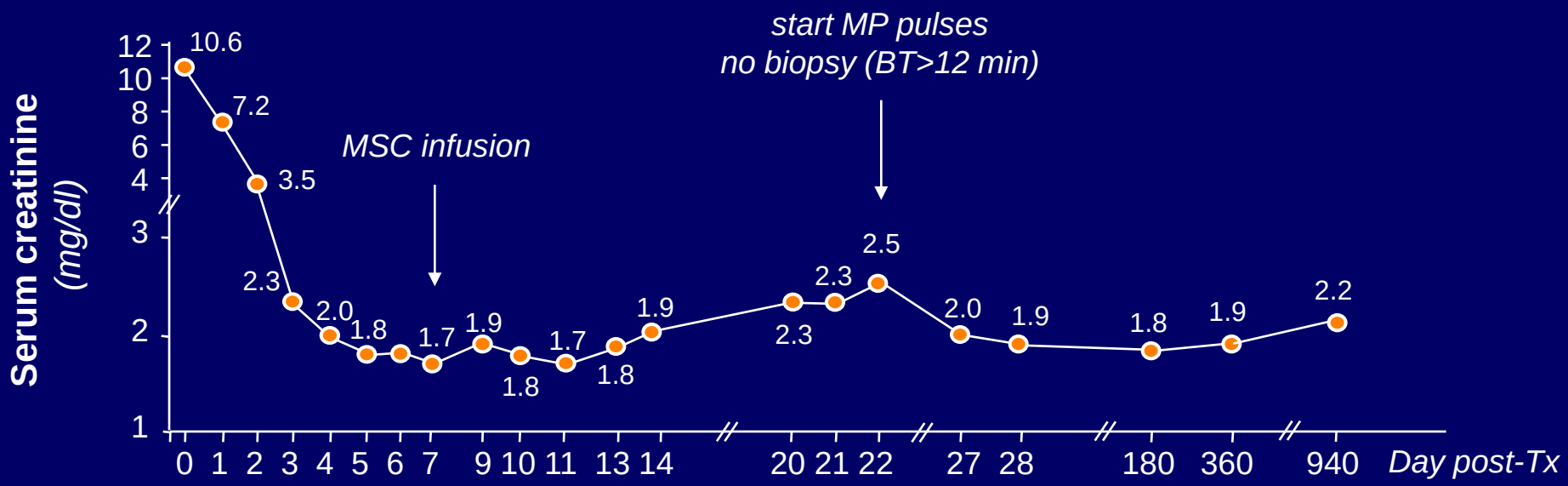
THE HIGH RATIO OF Treg/Tmemory COULD FAVOUR A STATE OF IMMUNE REGULATION



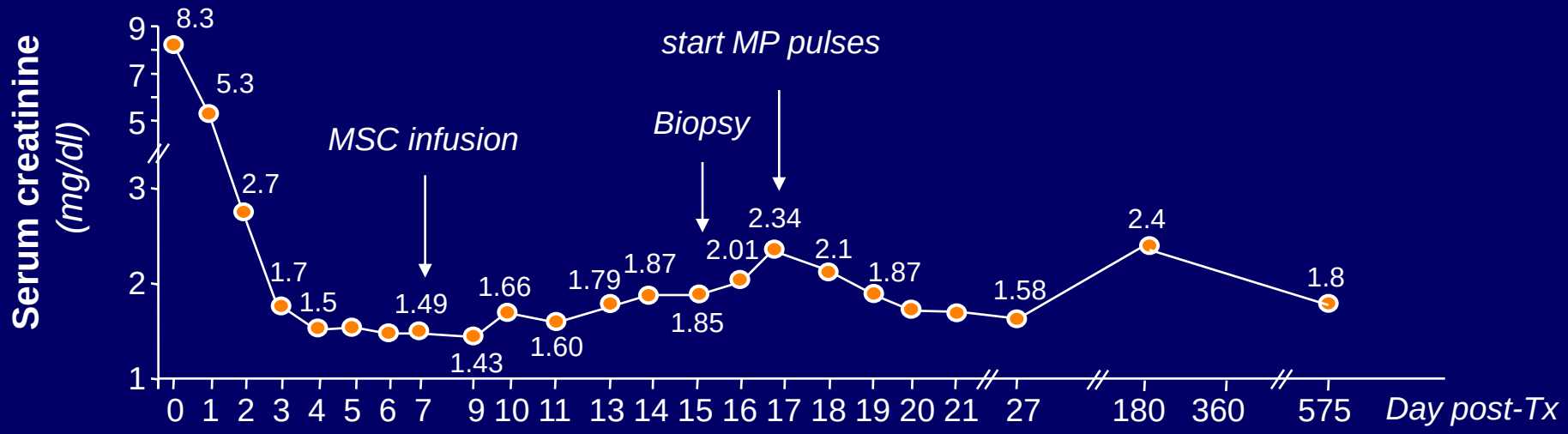
- Less anti-donor memory T cell activation
- Complete suppresses anti-donor $CD8^+$ T cell cytotoxicity

Perico et al., *C J Am Soc Nephrol,* 2011

Patient #1 D.D.



Patient #2 G.U.



Perico et al., *C J Am Soc Nephrol,* 2011

GRAFT INFILTRATING CELLS *(day +15)*

	CD4$^+$ T cells	*CD8$^+$ T cells*	*CD14$^+$ monocytes*
		(cells/field)	
Patient #2: G.U.	1.5	9.8	6.4
Controls			
Acute rejection (n=3)	80 ± 35	103 ± 35	39 ± 12

Values are mean of 30 fields

Perico et al., *C J Am Soc Nephrol,* 2011

GRAFT INFILTRATING CELLS *(day +15)*

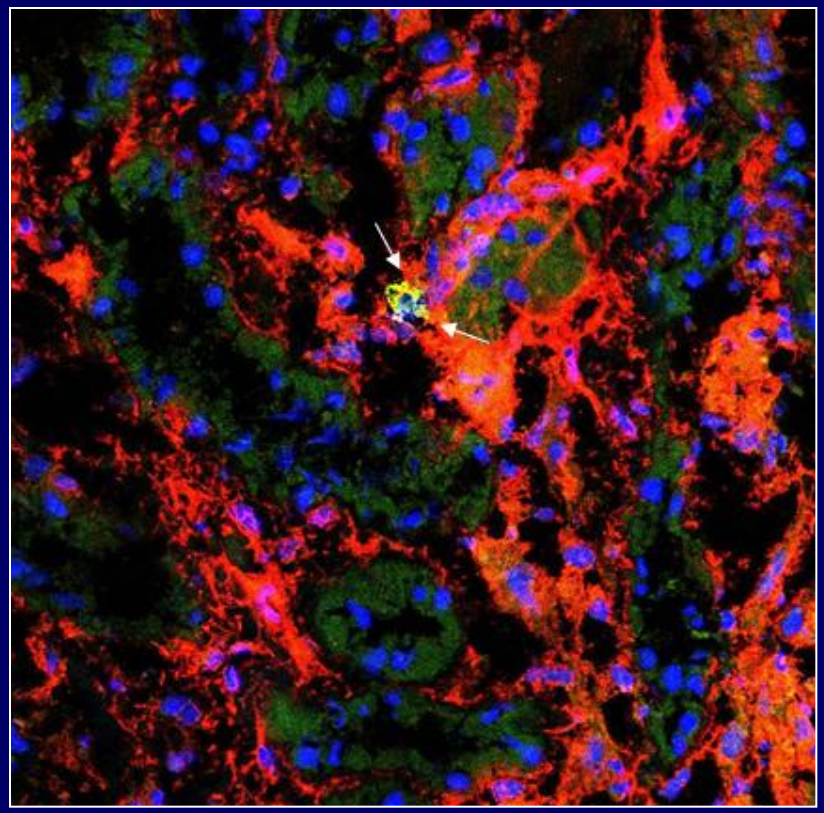
	CD20^{+} *B cells*	*CD68*$^{+}$ *macrophages*	*Granulocytes*
		(cells/field)	
Patient #2: G.U.	1.2	26.1	30.7
Controls			
Acute rejection (n=3)	20 ± 16	58 ± 2	5.5 ± 1.2

Values are mean of 30 fields

Perico et al., *C J Am Soc Nephrol,* 2011

MSC INFILTRATE THE GRAFT *(day +15)*

	CD105⁺ CD44⁺ cells (cells/3 mm²)
Patient #2: G.U.	17
Controls	
Acute rejection:	
15 day post-tx	0
Native control kidneys (n=4)	1.5 ± 2.6



Perico et al., *C J Am Soc Nephrol,* 2011

GRAFT INFILTRATING CELLS *(1 year)*

	CD4⁺ T cells	*CD8⁺ T cells*	*CD14⁺ monocytes*
		(cells/field)	
Patient #1: D:D.	6.5	5.5	1.6
Controls *Per-protocol biopsy (n=3)*	9.5 ± 6	14 ± 7	1.7 ± 1

Values are mean of 30 fields.

Perico et al., *C J Am Soc Nephrol,* 2011

GRAFT INFILTRATING CELLS *(1 year)*

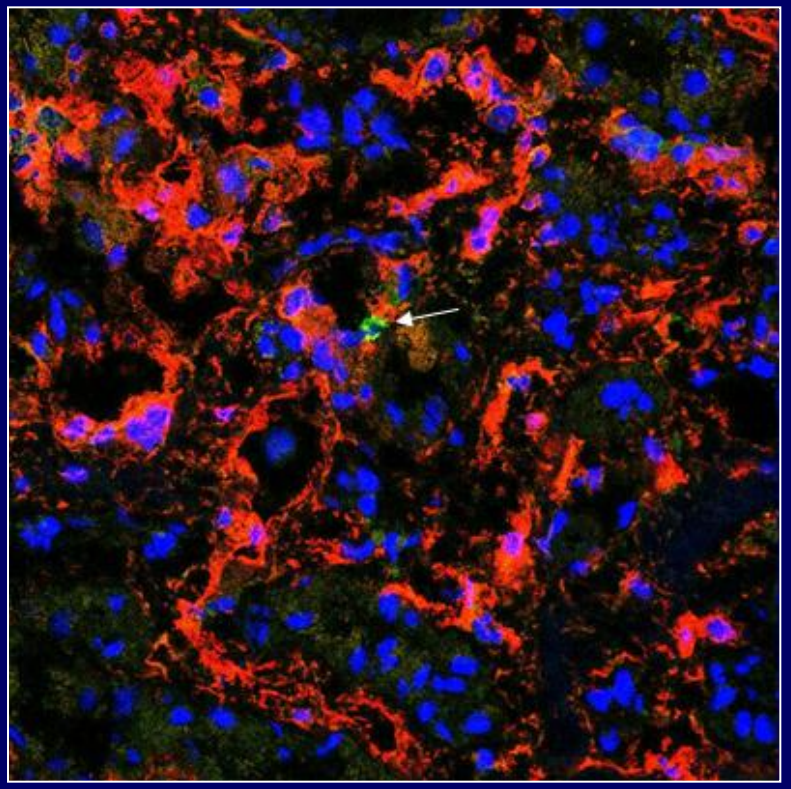
	CD20^{+} *B cells*	*CD68*$^{+}$ *macrophages*	*Granulocytes*
		(cells/field)	
Patient #1: D.D.	0.3	12.2	14.1
Controls			
Per-protocol biopsy (n=3)	3 ± 2.4	12 ± 5	5.8 ± 4.2

Values are mean of 30 fields.

Perico et al., *C J Am Soc Nephrol,* 2011

MSC INFILTRATE THE GRAFT *(1 year)*

	CD105⁺ CD44⁺ cells (cells/3 mm²)
Patient #1: D.D.	1.3
Control	
Per-protocol biopsy:	
2 years post-tx	1.36



Perico et al., *C J Am Soc Nephrol,* 2011

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