



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
Policlinico S. Orsola-Malpighi



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EMILIA-ROMAGNA
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Policlinico S. Orsola-Malpighi
Dipartimento Attività Integrata
Dipartimento delle Insufficienze d'organo e dei trapianti
Unità Operativa Nefrologia, Dialisi e Trapianto - Prof. La Manna



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

SCUOLA DI SPECIALIZZAZIONE DI NEFROLOGIA DI BOLOGNA
DOTTORATO DI RICERCA IN SCIENZE CARDIO - NEFRO - TORACICHE

Il trapianto renale da vivente: tra sogno e realtà

Gaetano La Manna

**Università degli Studi di Bologna
U.O. di Nefrologia Dialisi e Trapianto**

Sabato 20 febbraio 2016

**Aula Magna Nuovo Arcispedale S. Anna
Cona, Ferrara**

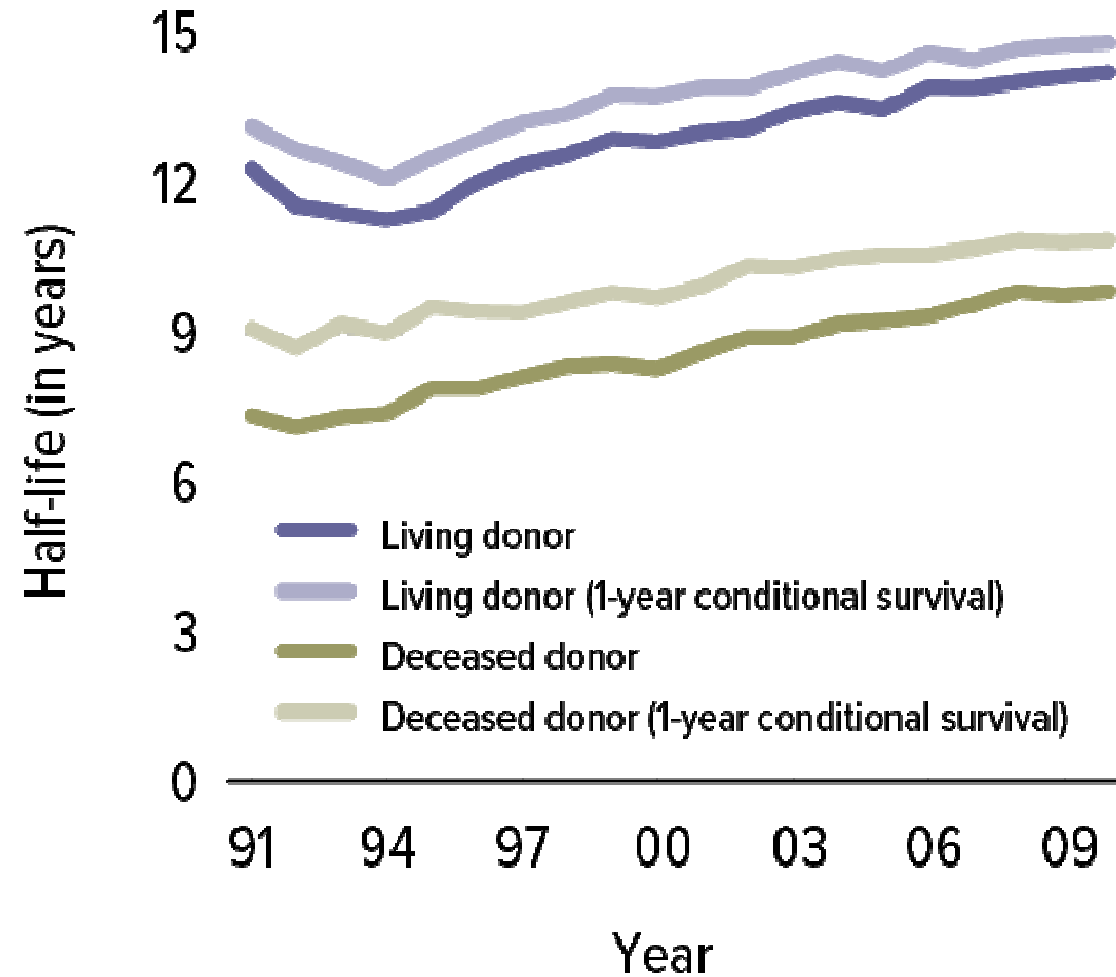
Il Segretario
Prof. C. Feo

Il Presidente
Prof. R. Manfredini





Half-lives for adult kidney transplant recipients



United States
Organ Transplantation
SRTR & OPTN Annual Data Report, 2012

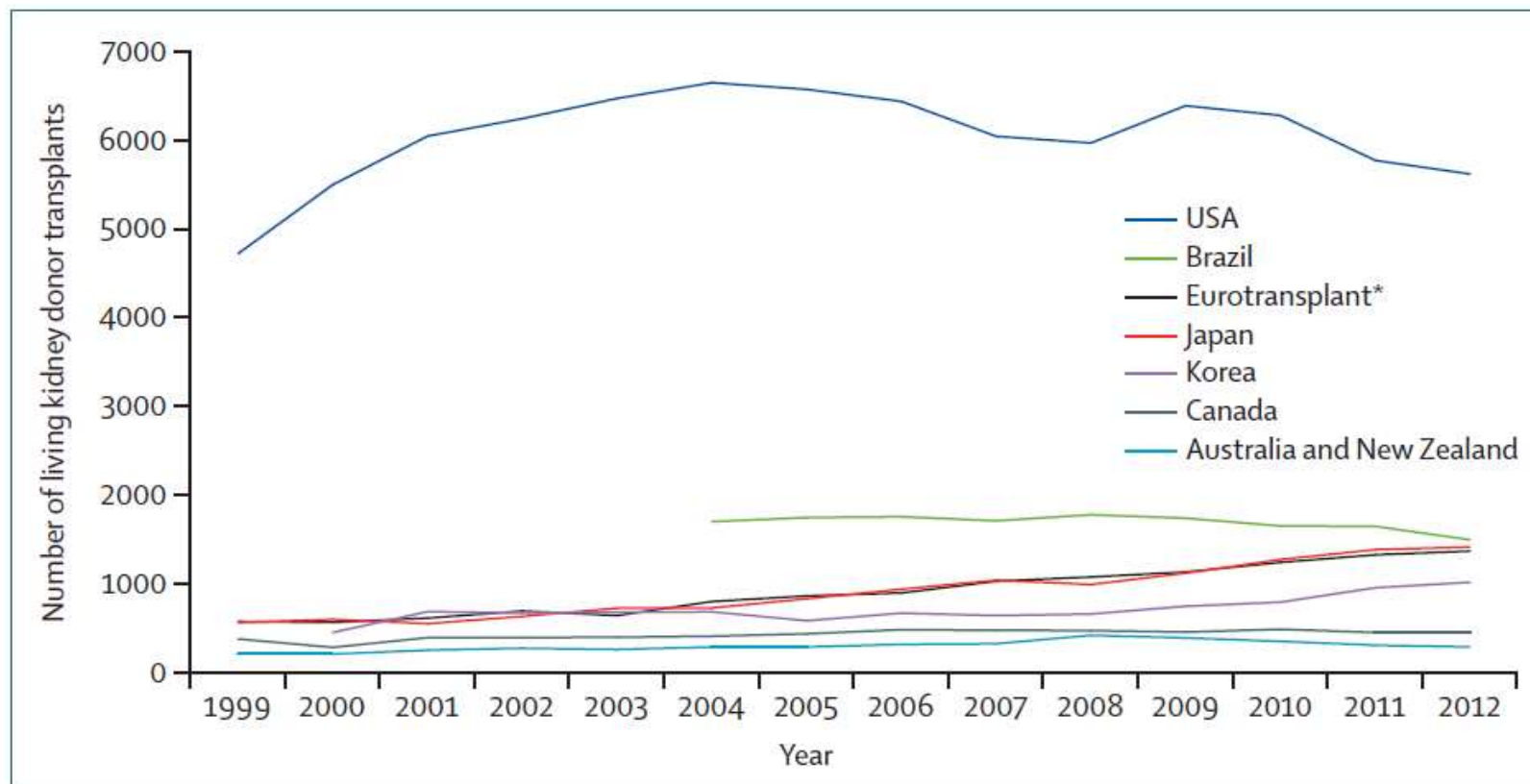


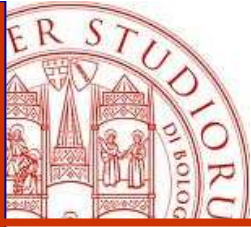


Trends in annual number of living kidney donation transplants

Living kidney donation: outcomes, ethics, and uncertainty

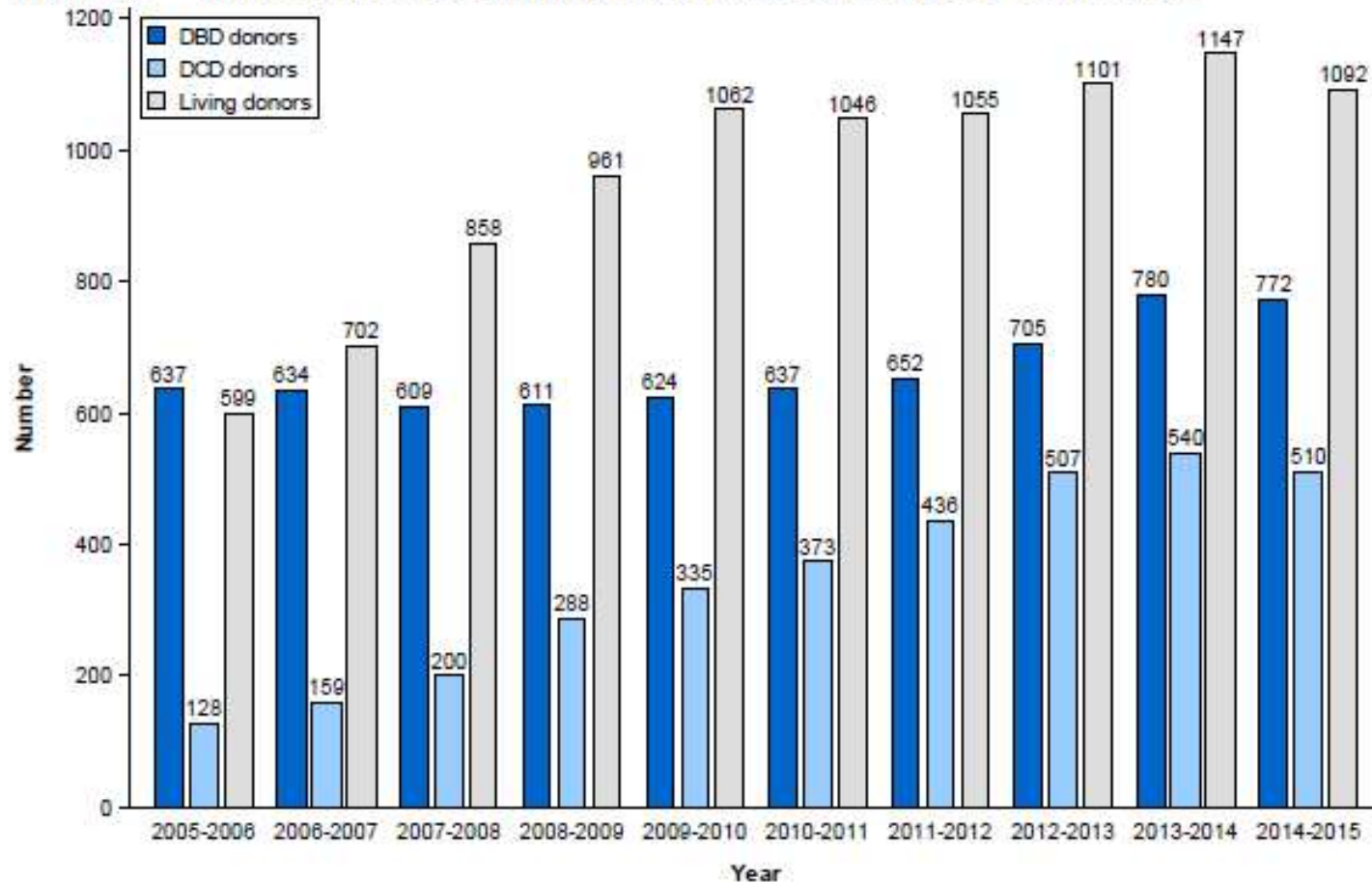
Peter P Reese, Neil Boudville, Amit X Garg





Transplant activity in the UK

Figure 2.2 Number of deceased and living donors in the UK, 1 April 2005 - 31 March 2015



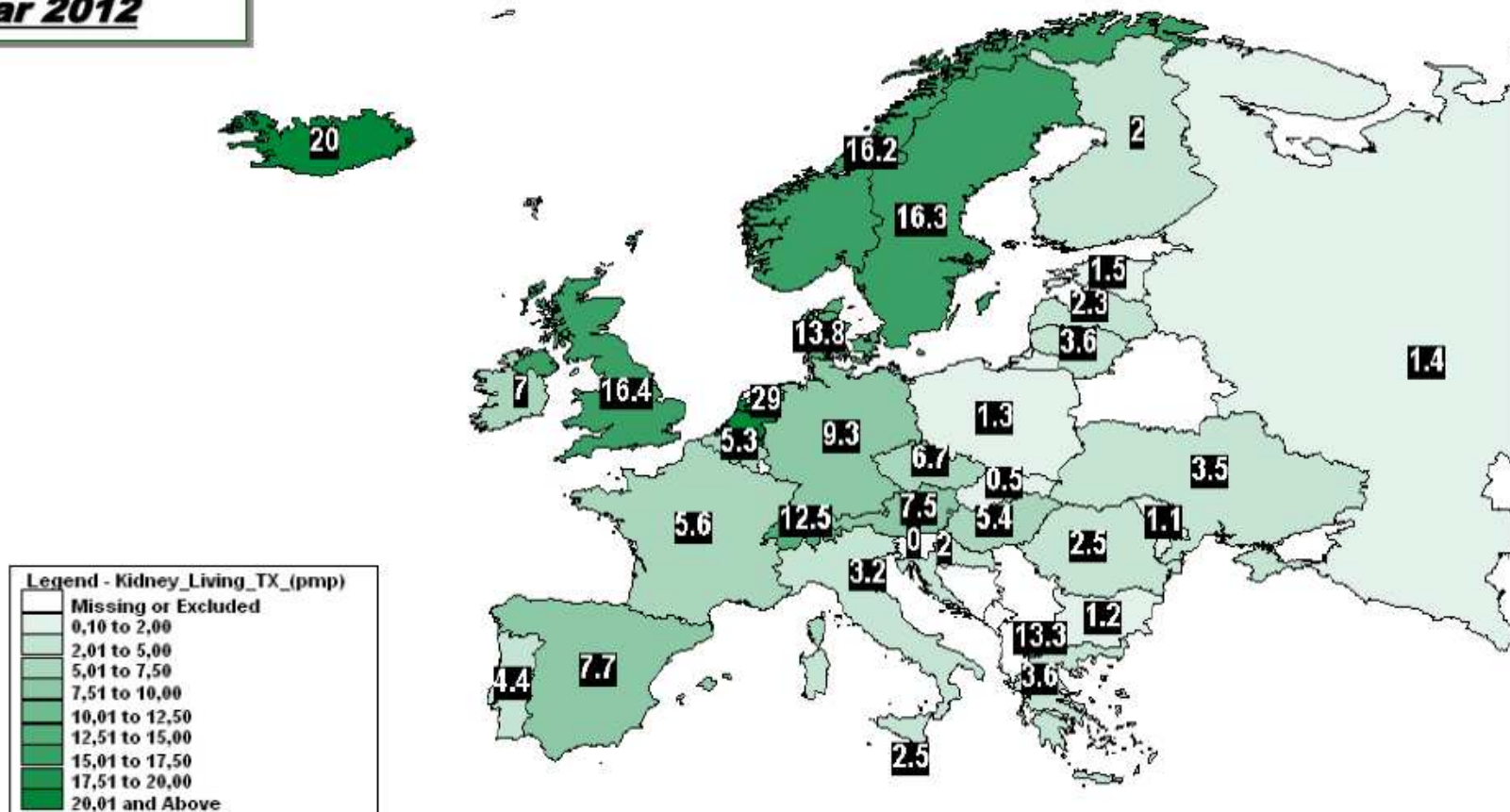
NHS Blood and Transplant

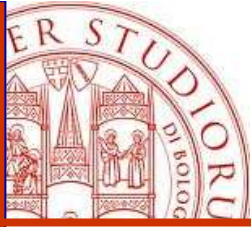


Europa

Living Kidney Transplant P.M.P.

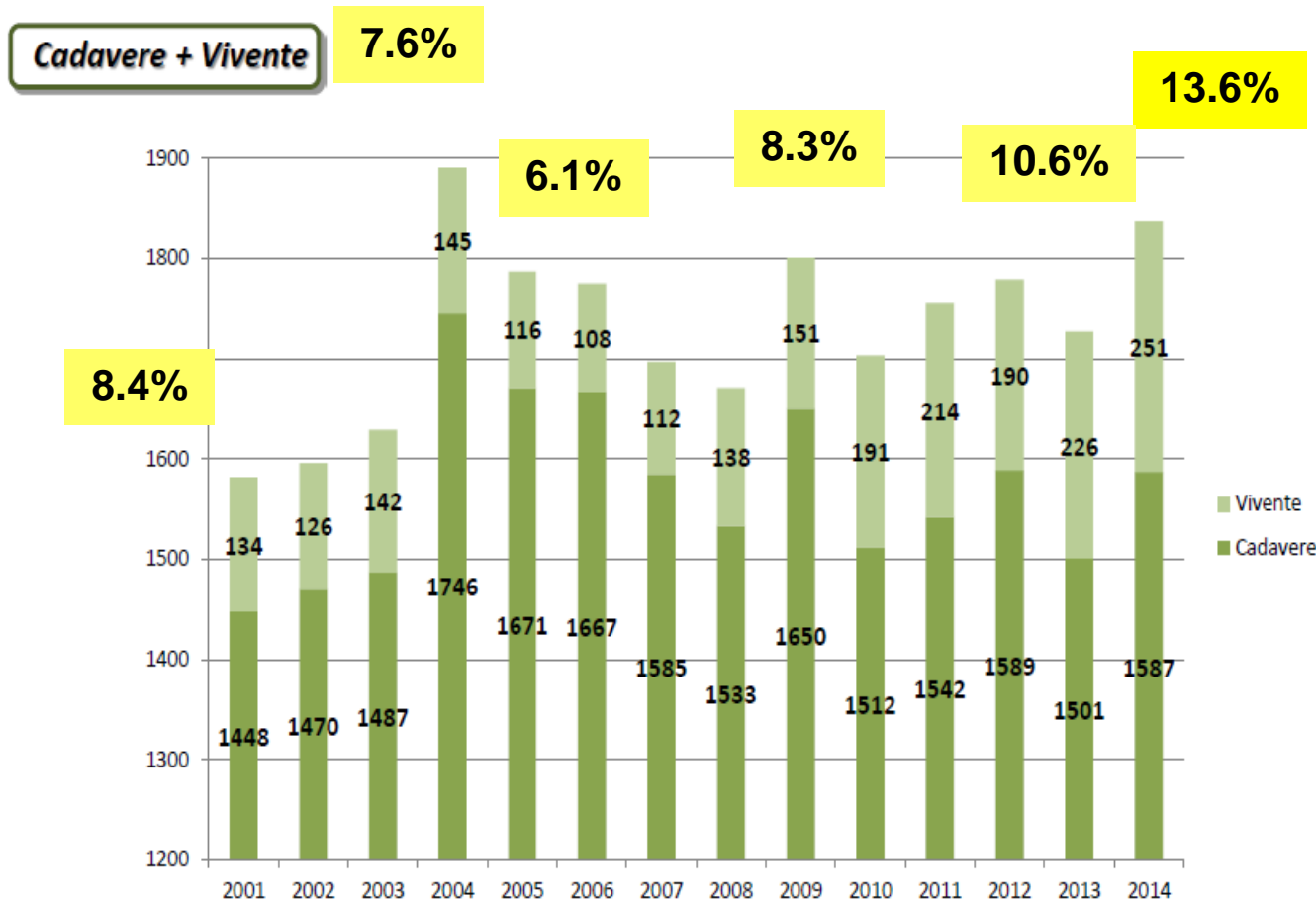
Year 2012

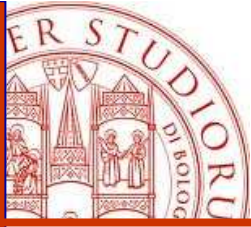




Italia

Trapianto di RENE – Anni 2001-2014*





23 December 1954

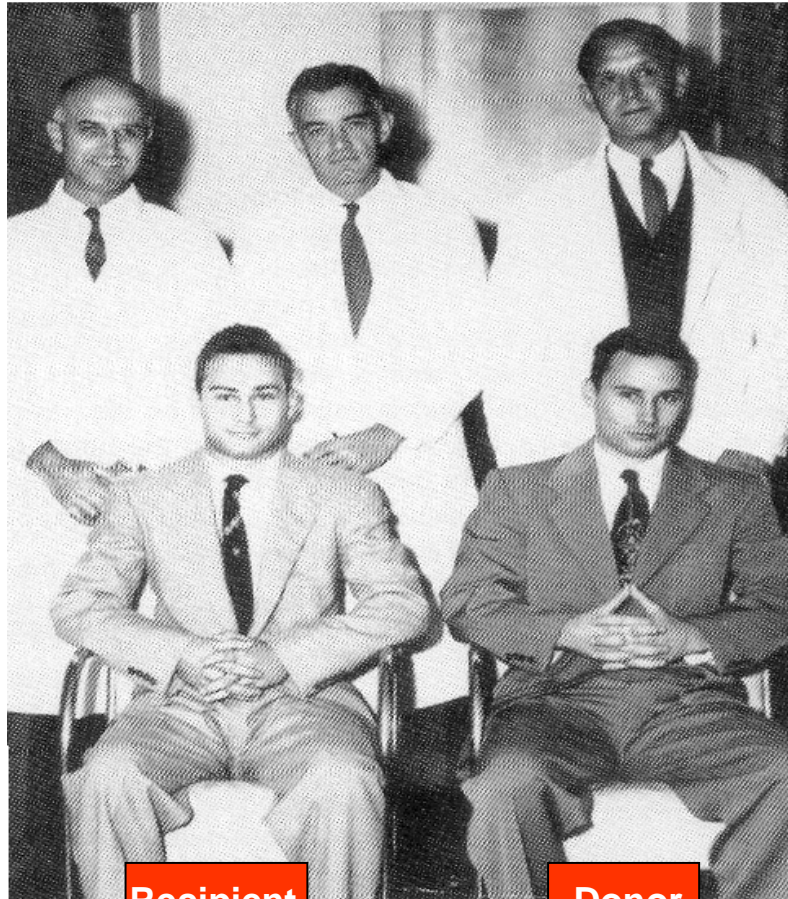
First Successful Kidney Transplant

The Brigham Transplant Team

J. E. Murray

J. P. Merrill

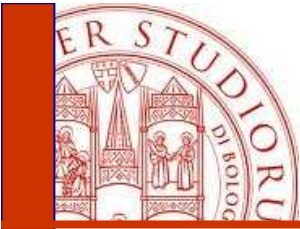
J. H. Harrison



Recipient

Donor

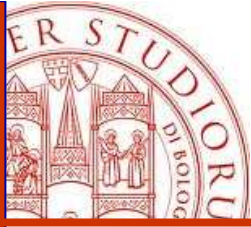




Come si sta modificando il panorama del dializzato?

- **Modificazioni del contesto epidemiologico**
- **Aumentata complessità immunologica**



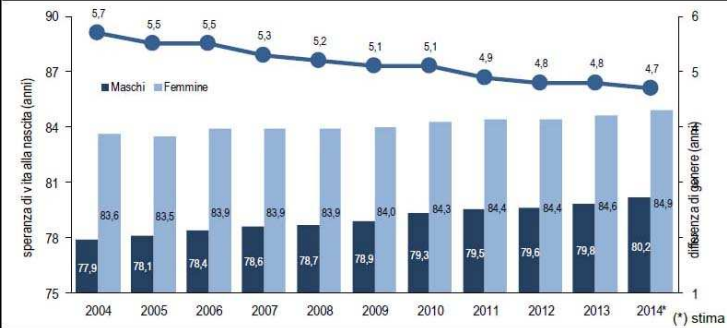


Trapianto da Vivente

Risposte alle marginalità donatore/ricevente

Età popolazione generale

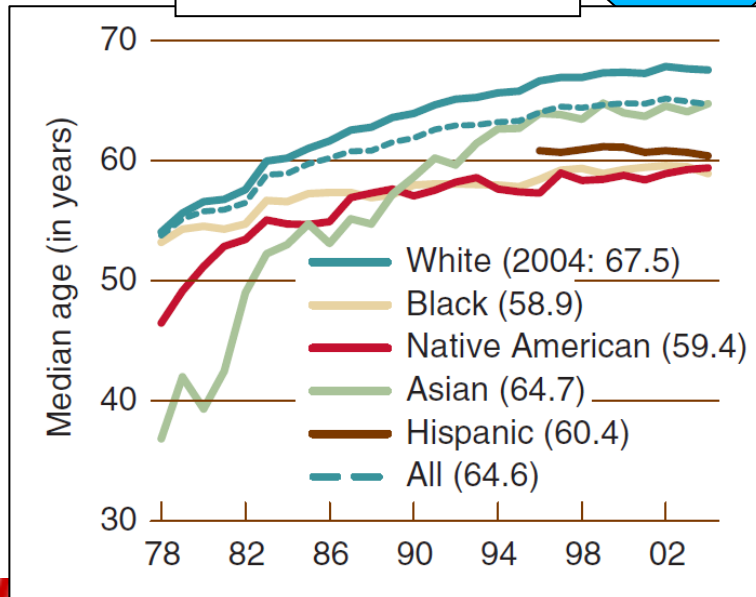
FIGURA 3. SPERANZA DI VITA ALLA NASCITA E DIFFERENZA DI GENERE - ITALIA. Anni 2004-2014



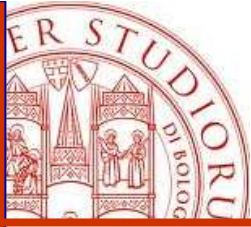
Maggiore efficacia conoscitiva

Superamento delle limitazioni

Età Incidenti in Dialisi

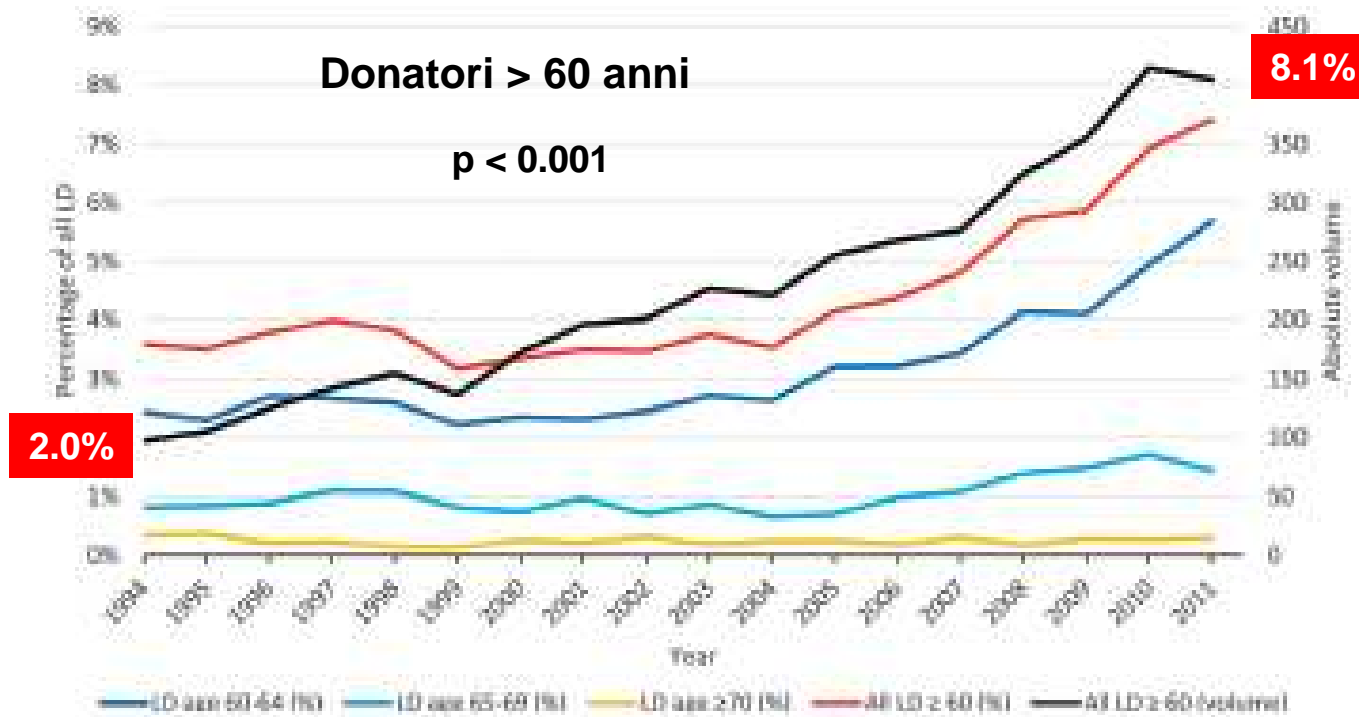


Fattori di rischio	IRC	1998	2008
		N = 2.286 %	N = 1.675 %
Diabete		14,7	16,3
Sindrome metabolica		28,3	33,0
BMI**			
Obesità		26,0	32,2
Sovrappeso		44,8	41,2
Normale		29,2	26,6
Iperensione arteriosa-stato del controllo^			
Non ipertesi		38,9	42,5
In trattamento efficace		5,7	11,5
Non adeguatamente trattati		24,1	22,4
Ipertesi non trattati		31,3	23,6
Abitudine al fumo di sigaretta			
Mai fumato		50,9	48,0
Ex fumatori		24,5	28,6
Fumatori correnti		24,6	23,3

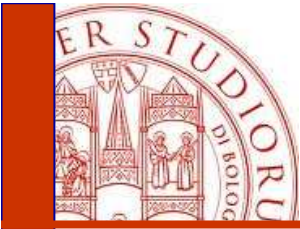


Donatori > 60 anni

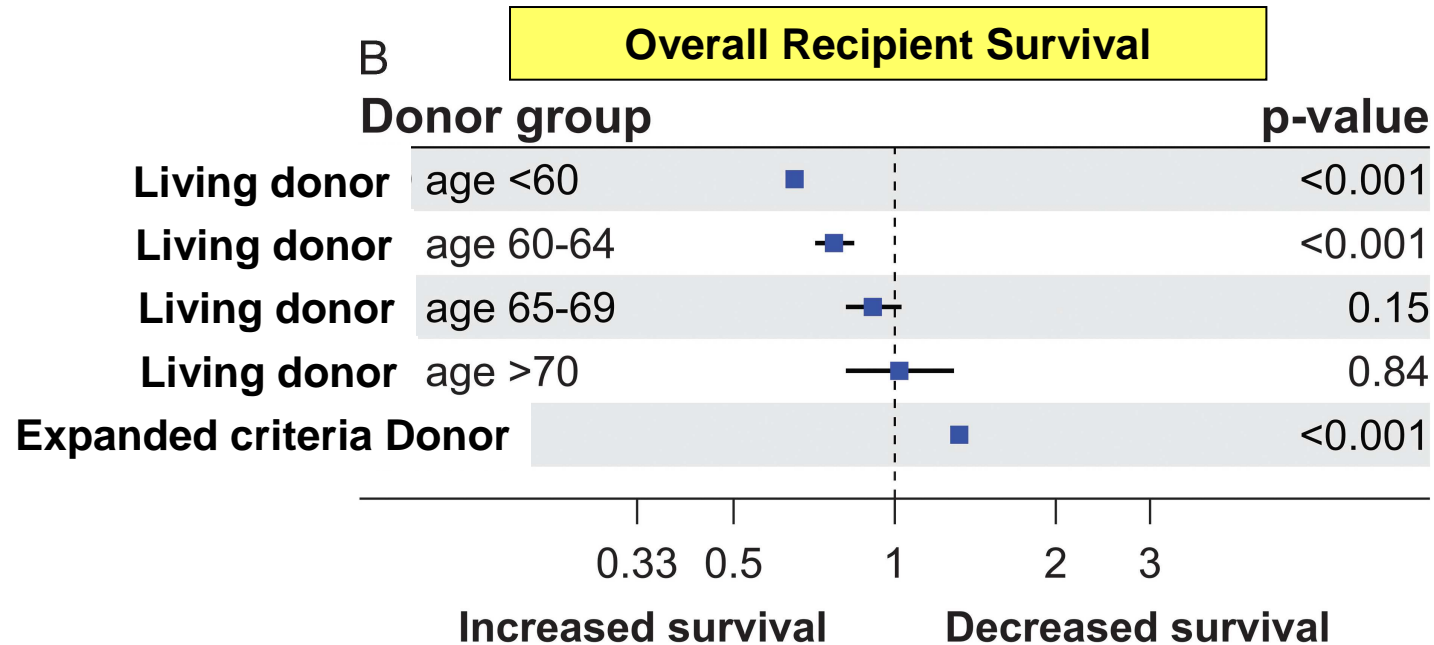
UNOS database
1994-2012 Tx vivente n= 92000



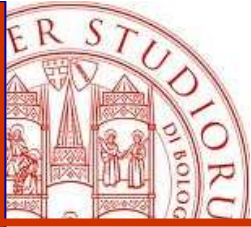
Englum B et al, Transplantation, 2015



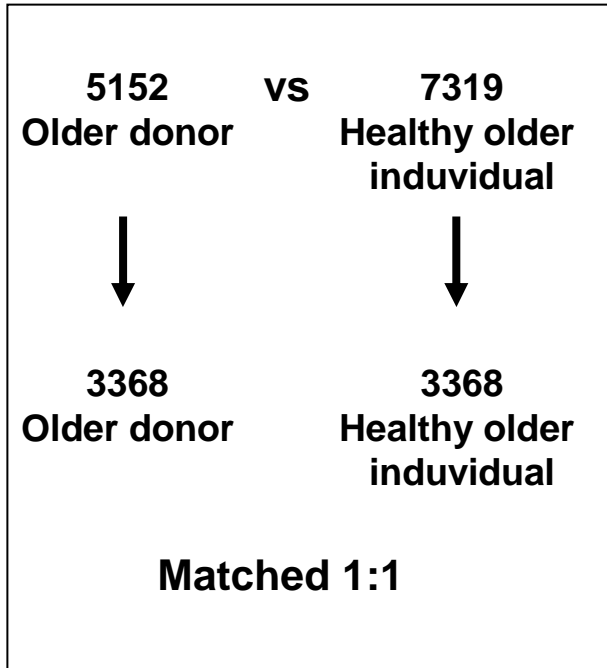
Sopravvivenza ed Età del Donatore



Englum B et al, Transplantation, 2015

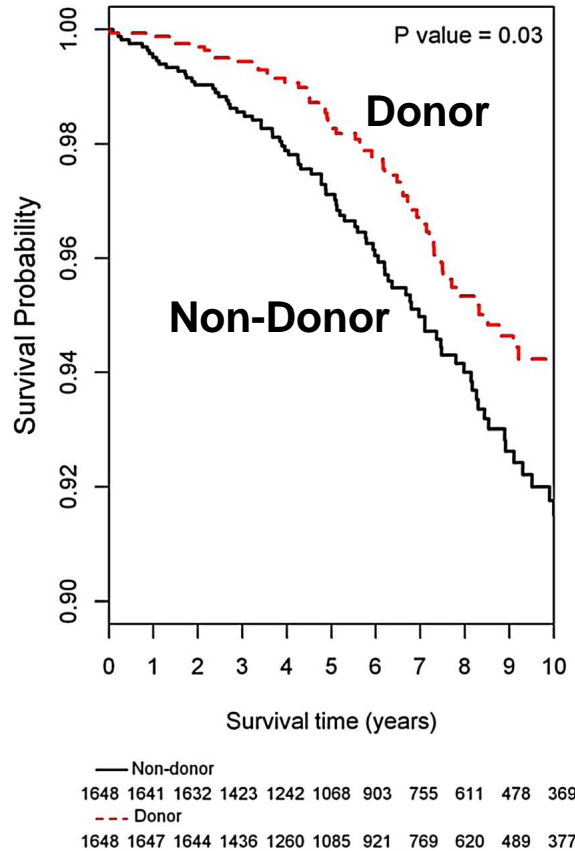


Donatore > 60 anni e Mortalità

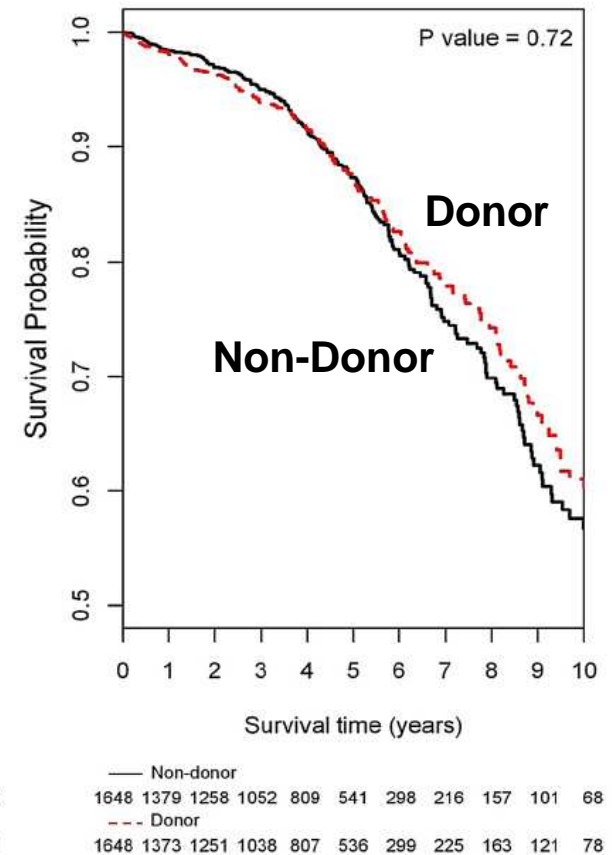


University of Pennsylvania
Dati UNOS

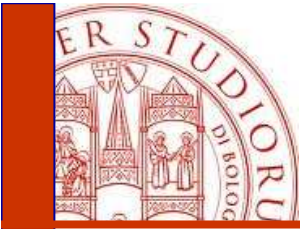
Survival



Cardiovascular outcomes



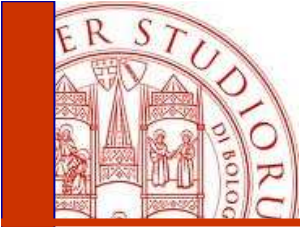
Reese PP B et al,
Am J Transplantation, 2014



Quali sono le condizioni che appaiono limitanti il trapianto da vivente?

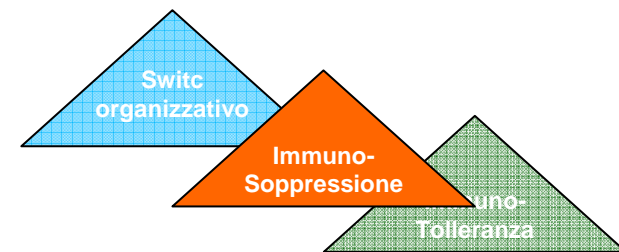
- **Modificazione del contesto epidemiologico della malattia renale cronica**
- **Aumentata complessità Immunologica**

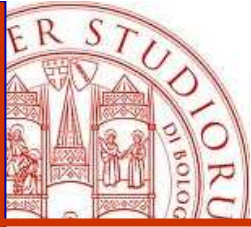




La complessità immunologica del trapianto da vivente?

- Recidiva della malattia immunologica
- Ritrapianti
- ABO incompatibile





Le risposte alla Complessità Immunologica

Swich organizzativo

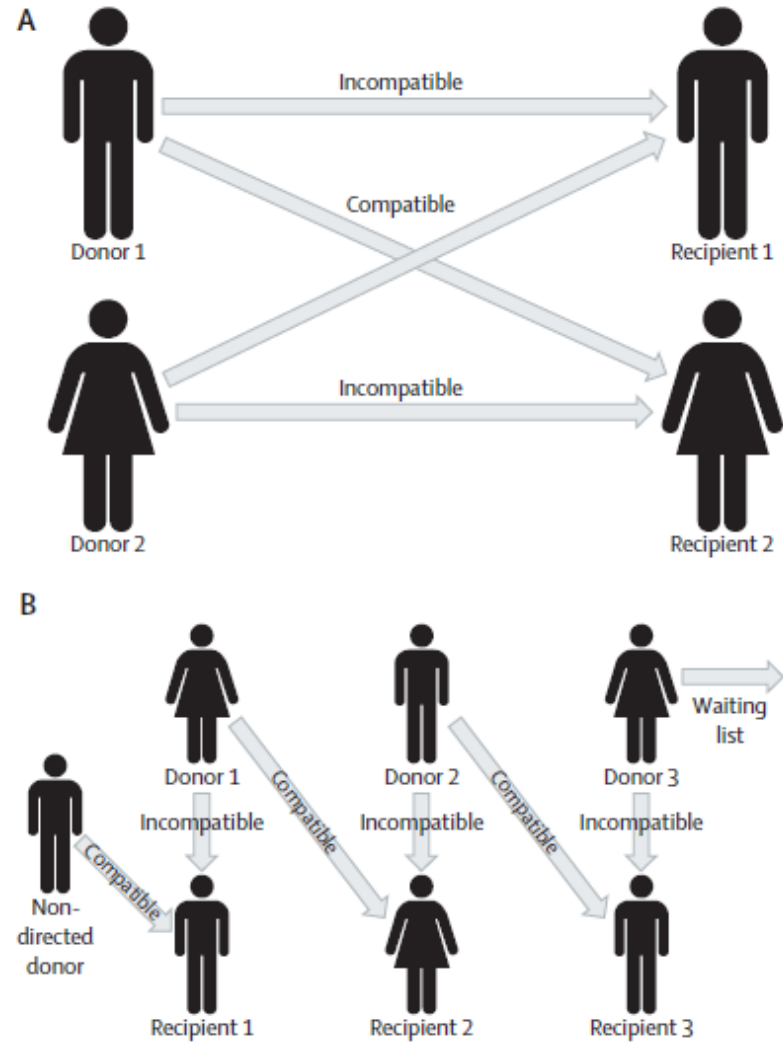
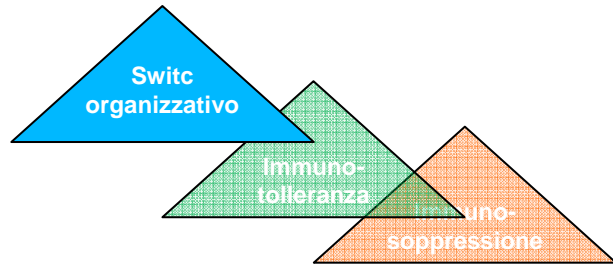
Immuno-Soppressione

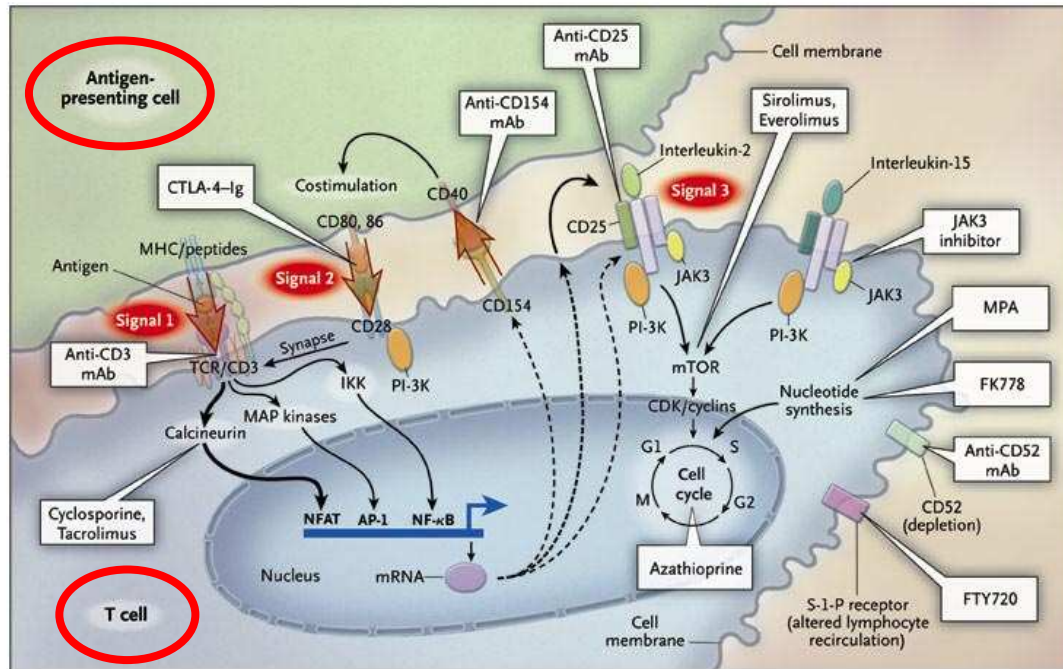
Immuno-Tolleranza



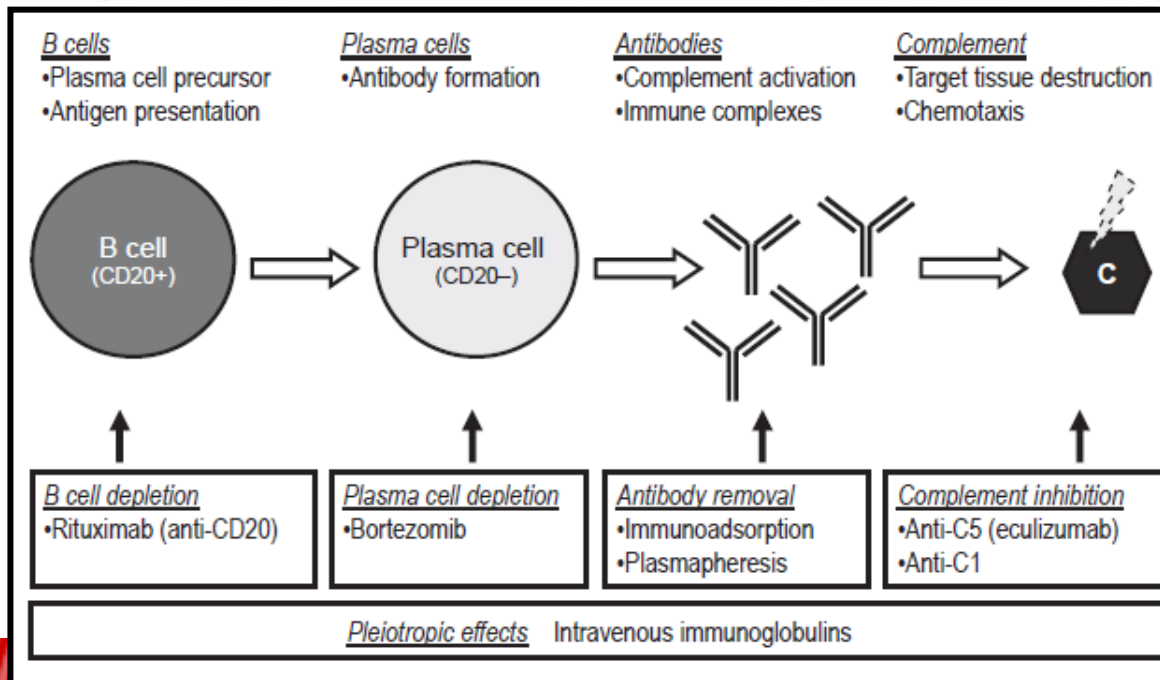
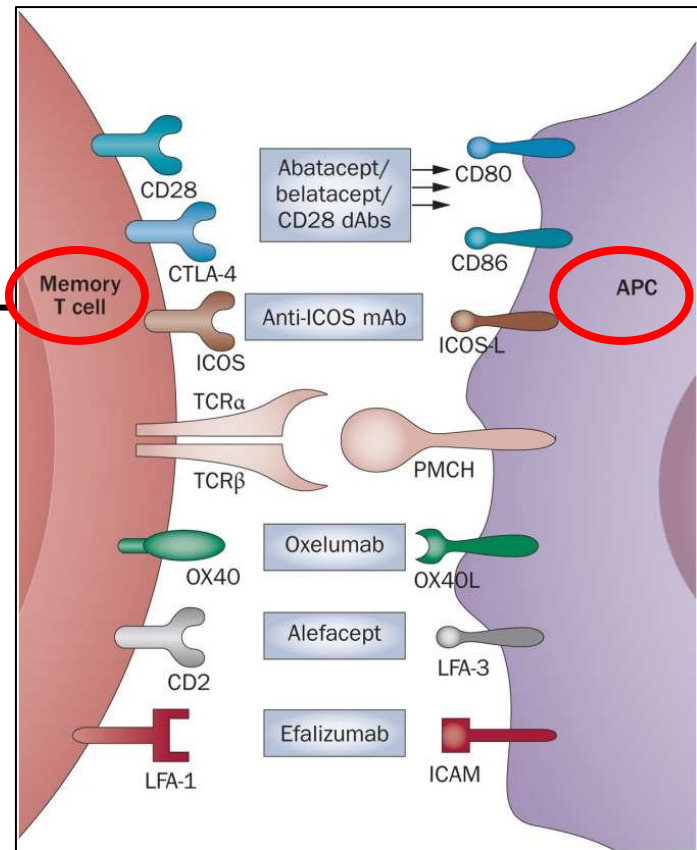


Kidney paired donation





Halloran, P. F. N Engl J Med 2004
 Ford, M. L. et al. (2013) Nat. Rev. Nephrol.
 Fehr T, Tr Int, 2012





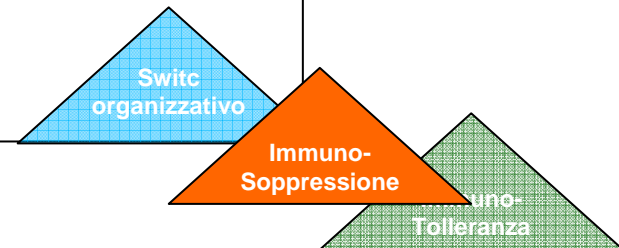
Glomerulosclerosi Segmentaria e Focale

Author Year	Overall	M	F	AA	Non-AA	LRD	DD
Masa 2013 [13]	30 % (28/94)	31 % (16/51)	28 % (12/43)			21 % (4/19)	32 % (24/75)
Nehra 2013 [12]	15 % (327/1,800)	12 % (194/1,305)	14 % (133/952)	13 % (95/721)	14 % (142/1,021)	1-10 yrs: 19 % (97/503) 11-20 yrs: 14 % (200/1,054)	17 % (1,968/899)
Hwang 2012 [8]	32 % (19/60)	29 % (10/35)	36 % (9/25)			<16 yrs: 27 % (11/41) >=16 yrs: 42 % (8/19)	31 % (12/38)
Starck 2011 [14]	39 % (19/49)	33 % (9/27)		43 % (10/23)	35 % (9/26)		38 % (8/21)
Schadner 2010 [9]	23 % (15/66)	16 % (6/37)		10 % (3/31)	29 % (13/45)		23 % (12/52)
Hickson 2009 [5]	55 % (6/11)	41 % (5/12)		100 % (3/3)	43 % (12/28)		48 % (13/27)
Sener 2009 [10]	23 % (5/22)	7 % (1/14)			50 % (4/8)		50 % (4/8)
Mabesh 2008 [6]	43 % (16/37)			39 % (7/18)	47 % (9/19)		41 % (7/17)
Hwang 2004 [7]	6 % (36/620)			5 % (13/258)	6 % (23/363)	2-12 yrs: 9 % (18/194) 13-17 yrs: 6 % (13/218) 18-21 yrs: 5 % (5/111)	10 % (27/271)

Incidenza di Recidiva 6-55 %

Approcci Terapeutici

- Plasmaferesi** 60% risposta favorevole
- Rituximab** 79% risposta favorevole
- Abatacept** Case report



Trachtman R et al, *Pediatr Nephrol*, 2015





Sindrome Emolitico Uremica

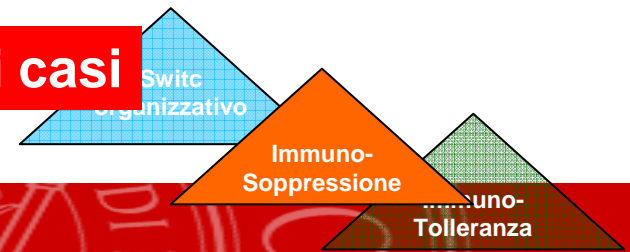
Mutation	aHUS incidence	Type of deficiency	C3 level	Risk of recurrence post-transplant
CFH	20-30%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	70-80%
MCP	10-15%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	Low (unless associated with other mutations)
CFI	5-10%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	70-80%
CFB	1-4%	-	Always low	100% (only 4 cases reported)
THBD	3-5%	-	Low in 50%	Unknown but probably very low
C3	2-10%	Majority are quantitative	Low in 80%	40%
Anti-CFH Abs	6%	N/A	Low in 40-60%	40-70% Depending on associated mutations
CFHR 1-5	Unknown	Usually qualitative	Normal unless it is associated with other mutations	Unknown
Combined mutations	10-12%	Variable	Variable	Variable

Incidenza di Recidiva 40-80 %

aHUS, atypical hemolytic uremic syndrome; C3, complement factor 3; CFH, complement factor-H; MCP, membrane co-factor protein; CFI, complement factor-I; CFB, complement factor B; THBD, thrombomodulin; CFHR, complement factor-H related proteins.

Terapia con Eculimzumab è efficace nell'80% dei casi

Alasfar S et al, Front Med, 2014



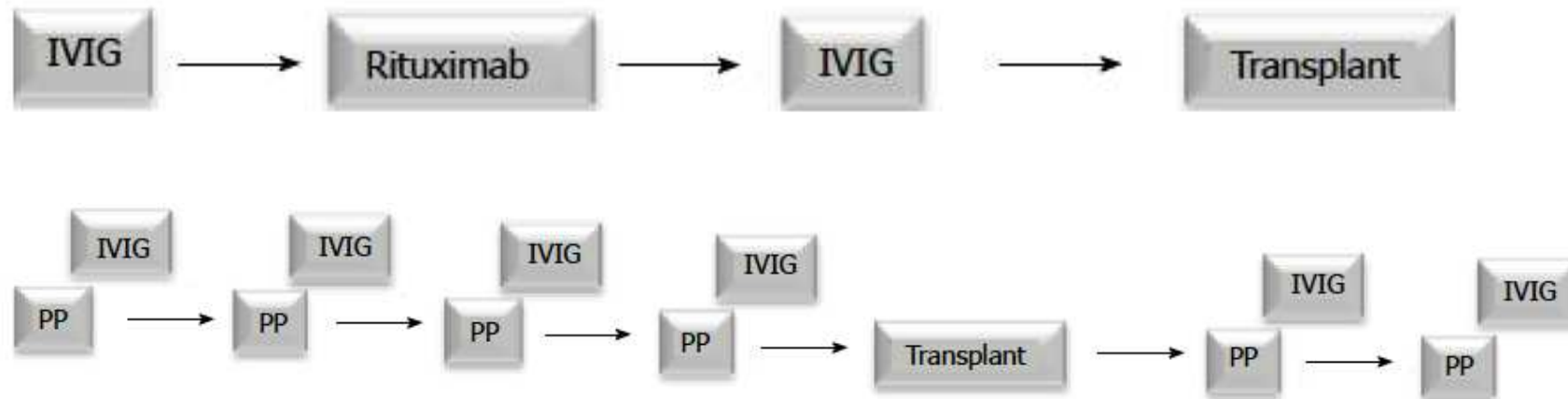
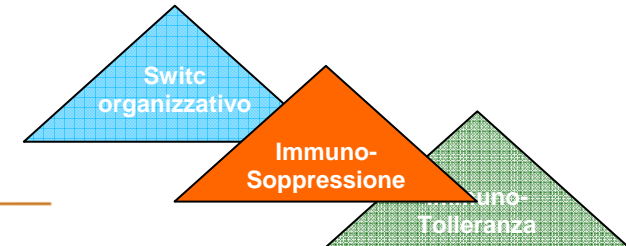


Incompatible kidney transplantation

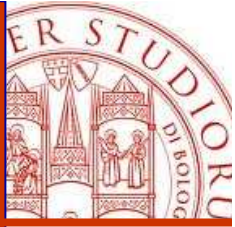
IVIG AND RITUXIMAB (ANTI-B CELL)

BORTEZOMIB (ANTI-PLASMA CELL)

ECULIZUMAB (COMPLEMENT INHIBITION)



Wongsaroj P et al, World J Nephrol, 2015

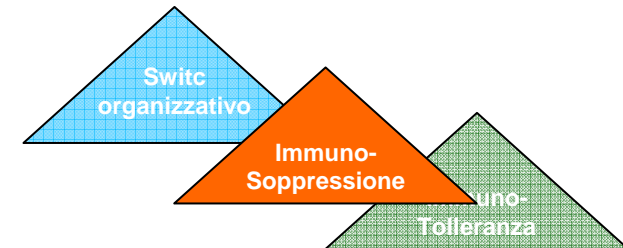


An update on ABO-incompatible kidney transplantation

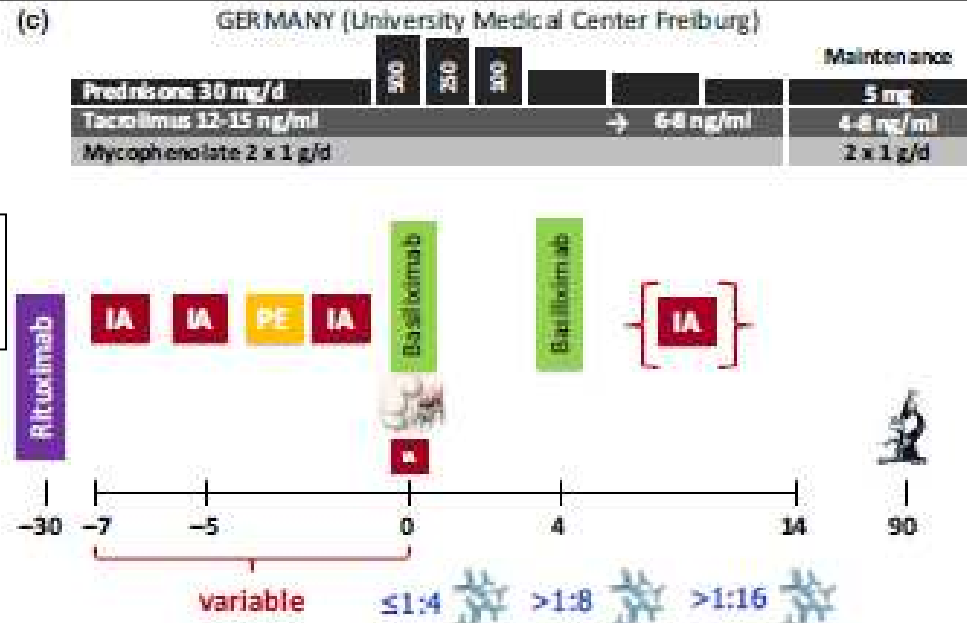
Stefan Zschiedrich,¹ Albrecht Kramer-Zucker,¹ Bernd Jänigen,² Maximilian Seidl,^{3,4} Florian Emmerich,⁵ Przemyslaw Pisarski² and Tobias B. Huber^{1,6,7}

Protocolli Terapeutici nel trapianto ABO-incompatibile

- Pre condizionamento della risposta B cellulare
- Eliminazione extracorporea delle isoemoagglutinine
- Marcata immunosoppressione pre e post trapianto



Esperienza di 10 anni, 100 Tx ABO i , Germania (Friburg)





An update on ABO-incompatible kidney transplantation

Stefan Zschiedrich,¹ Albrecht Kramer-Zucker,¹ Bernd Jänigen,² Maximilian Seidl,^{3,4} Florian Emmerich,⁵ Przemyslaw Pisarski² and Tobias B. Huber^{1,6,7}

Risultati

Graft survival 100% 1,3,5 anni
Graft survival 94 % a 10 anni

Complicanze chirurgiche: Nessuna differenza con tx ABO comp

transplantation.	Incidence
1. Vascular	0.2-30% [102-107]
-Bleeding	
-Arterial stenosis	
-Arterial obstruction	
2. Urological	2-10% [9, 103, 108, 109]
-Urinary leakage	
-Ureteral obstruction	
-Urinary retention	
3. Fluid collection	2-18% [107, 109-112]
-Seroma	
-Lymphocele	
-Lymph fistula	
4. Local infections	3-5% [110]
-Wound infection	
-Abscess	
-Impaired wound healing	

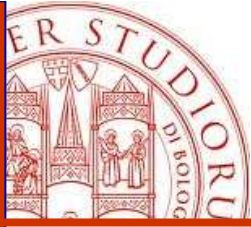
Risultati Letteratura

- **Giappone dal 1989 > 2000 tx**
Graft survival 95.8 % a 3 anni
- **USA dal 1995 > 700 tx**
Graft survival 89.6 % a 3 anni
Graft survival 82.6 % a 5 anni
Graft survival 72.9 % a 10 anni
- **Svezia dal 2001 > 274 tx**
Graft survival 97% a 3 anni

Swite
organizzativo

Immuno-
Soppressione

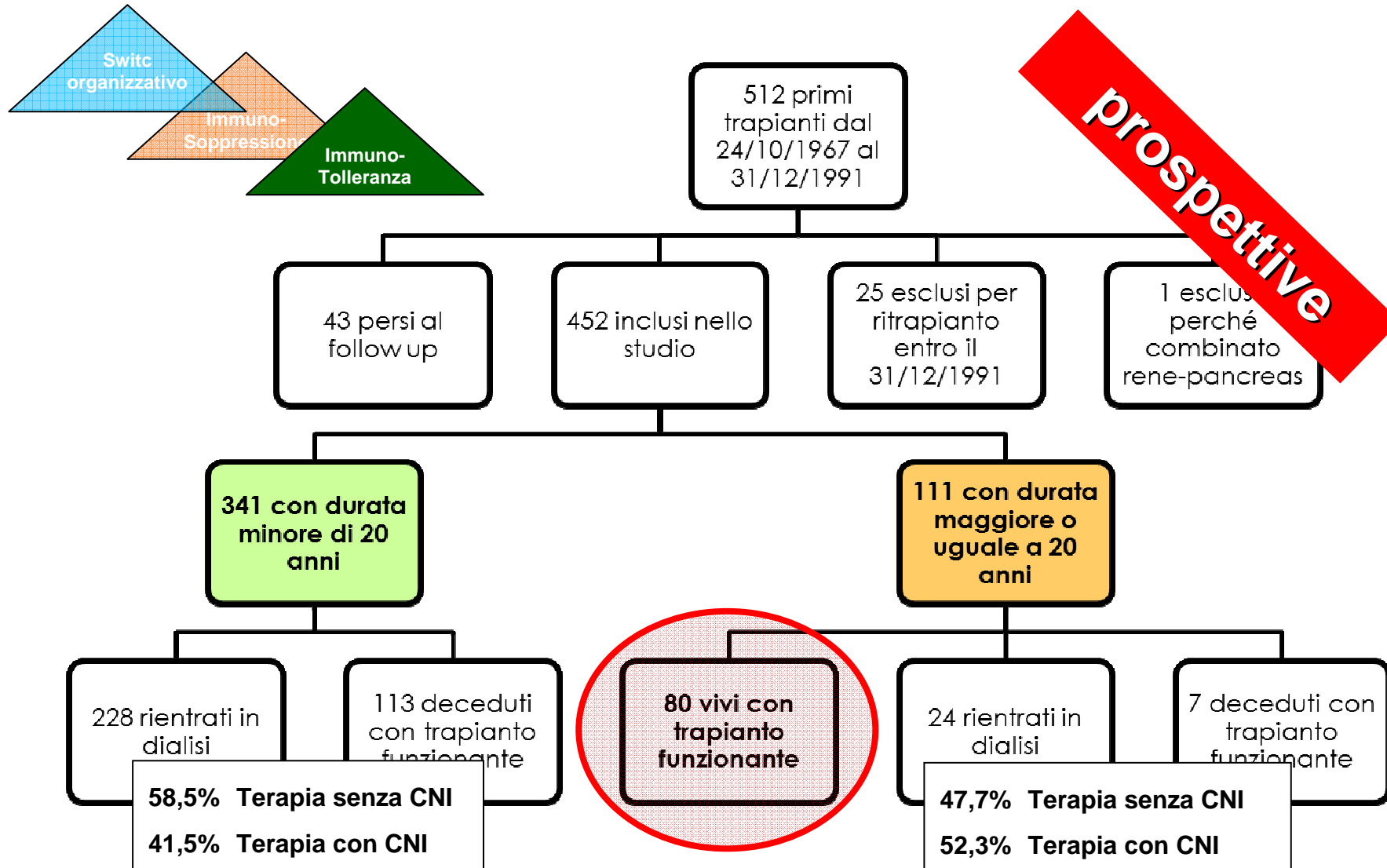
uno-
Tolleranza

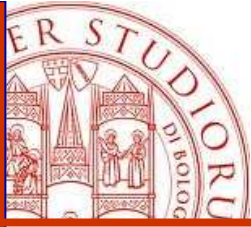


Immunotolleranza: Bologna experience

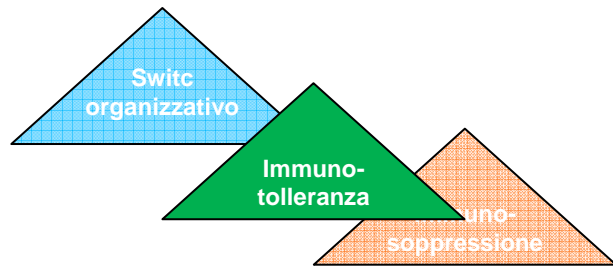
Long Survivors

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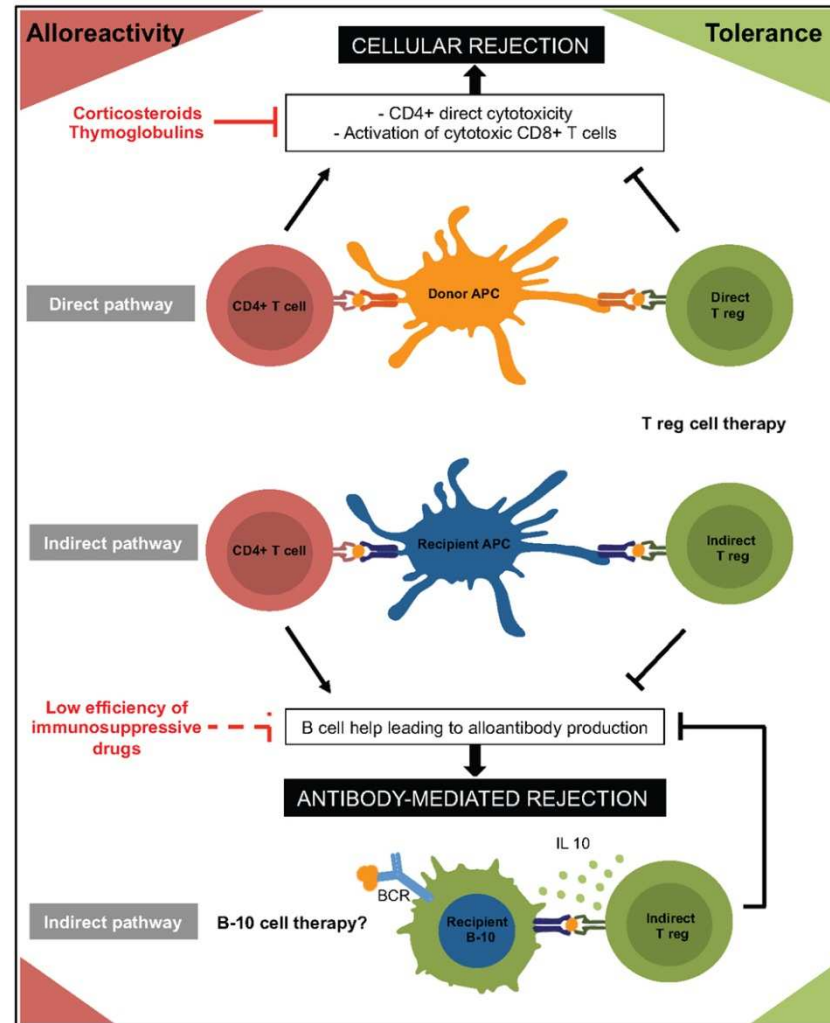




Immune mechanisms involved in rejection and tolerance to allograft



Regulatory cells are in green and effector cells in red. APC, antigen presenting cell; BCR, B cell receptor.



Ford, M. L. et al. (2013) *Nat Rev Nephrol*





Study of immunomodulatory cells HLA-G⁺ / FoxP3⁺ derived from patients on haemodialysis after immuno-conditioning

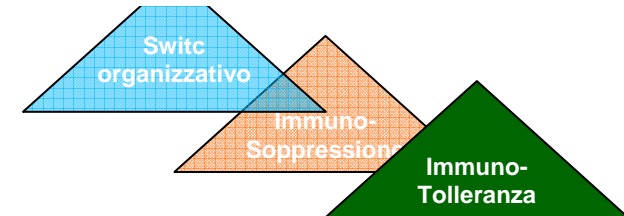
OPEN ACCESS Freely available online

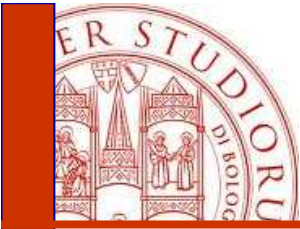
PLOS ONE



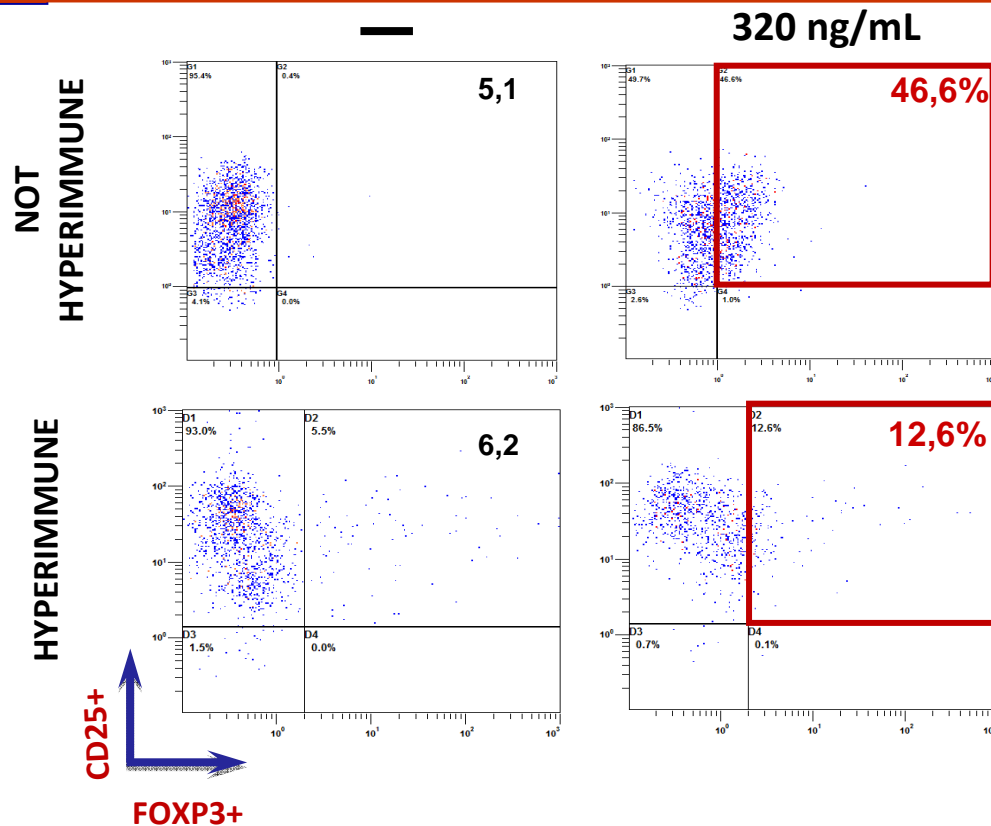
Neutrophil Gelatinase-Associated Lipocalin Increases HLA-G⁺/FoxP3⁺ T-Regulatory Cell Population in an In Vitro Model of PBMC

Gaetano La Manna^{1*}, Giulia Ghinatti², Pier Luigi Tazzari³, Francesco Alviano⁴, Francesca Ricci³, Irene Capelli¹, Vania Cuna¹, Paola Todeschini¹, Eugenio Brunocilla⁵, Pasqualepaolo Pagliaro³, Laura Bonsi⁴, Sergio Stefoni¹



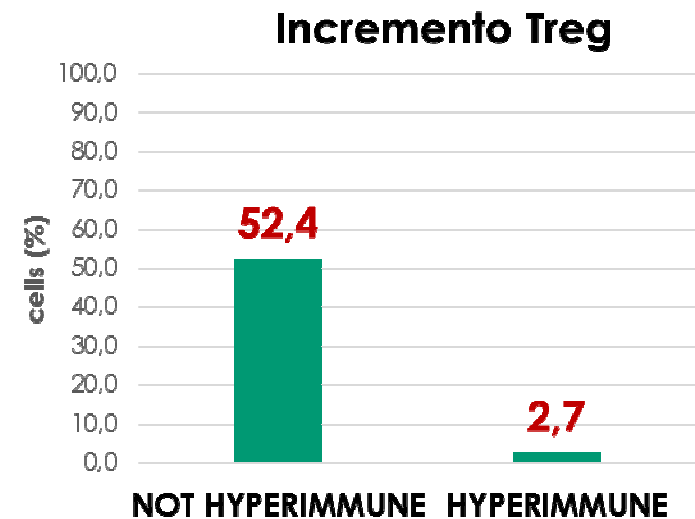


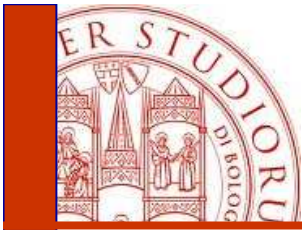
T regulatory cells



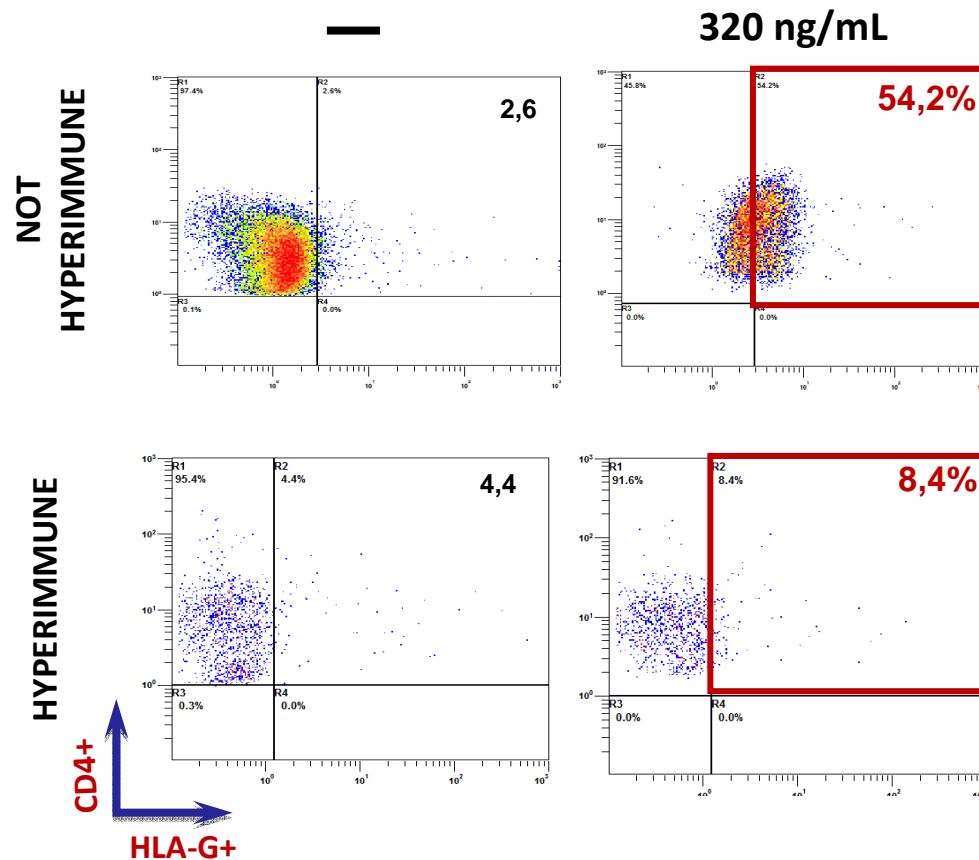
Nei soggetti non iperimmuni la % di Treg aumenta del 52,4% con l'aggiunta di NGAL

Nei soggetti iperimmuni aumenta solo del 2,7%



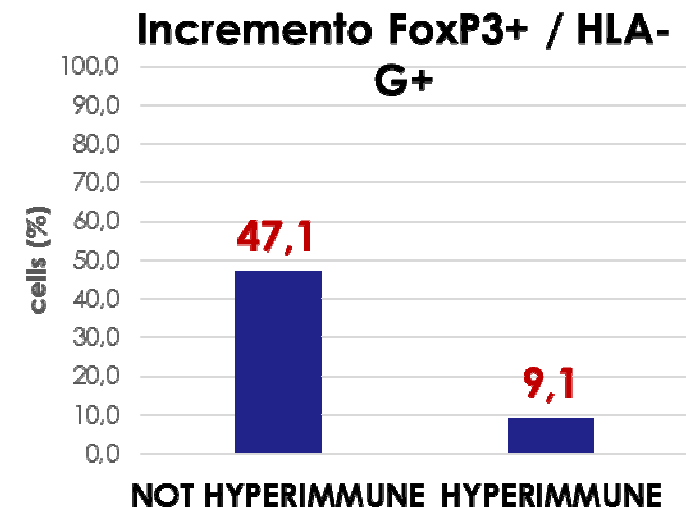


Immunomodulatory cells FoxP3+ / HLA-G+

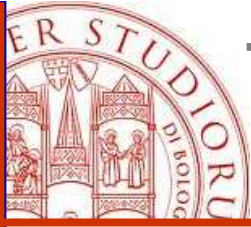


Nei soggetti non iperimmuni la % di HLA-G+ all'interno dei Treg aumenta del 47,1% con l'aggiunta di NGAL

Nei soggetti iperimmuni aumenta solo del 9,1%



La popolazione T regolatoria mostra anche un fenotipo immunomodulatorio dato dall'espressione di HLA-G



Trapianto di cellule T Reg per indurre tolleranza: Progetto finanziato dal Ministero della Salute

Policlinico S.Orsola-Malpighi

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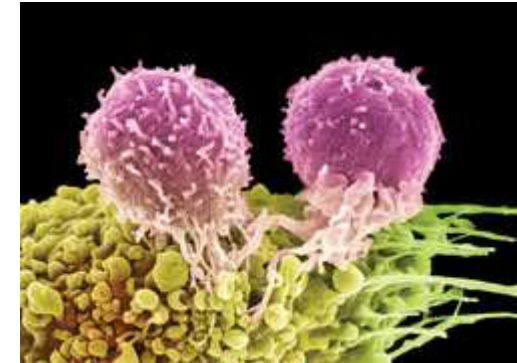
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Il Policlinico
Per il Professionista
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Il Policlinico
Chi siamo
L'organizzazione

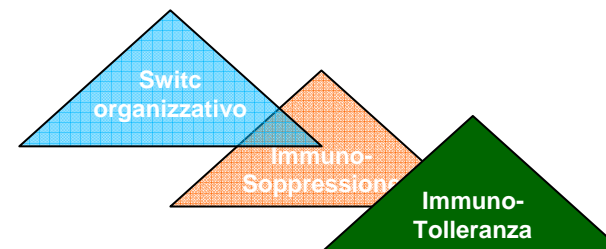
Home » Il Policlinico » L'organizzazione » Dipartimenti
Dipartimento delle Insufficienze d'organo e dei trapianti
Prof. Antonio Daniele Pinna



1 - Aferesi di cellule T reg del ricevente

2 - Espansione delle cellule T reg del ricevente

3 - Somministrazione in fase 0 (pre-trapianto) ed in fase 1 (6 giornata) delle sue stesse cellule T reg espanso in due dosaggi diversi.





Trapianto di cellule T Reg per indurre tolleranza: Progetto finanziato dal Ministero della Salute

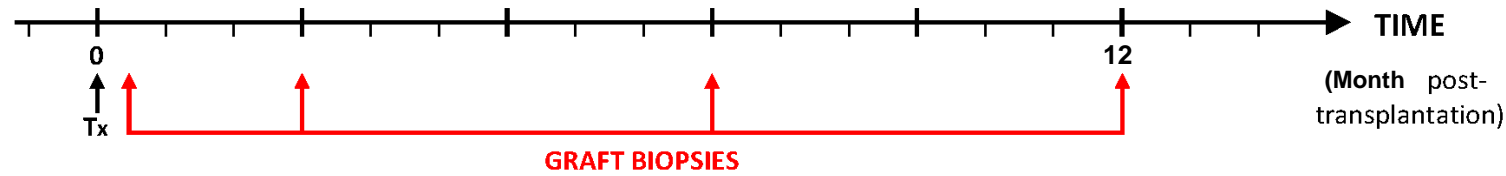
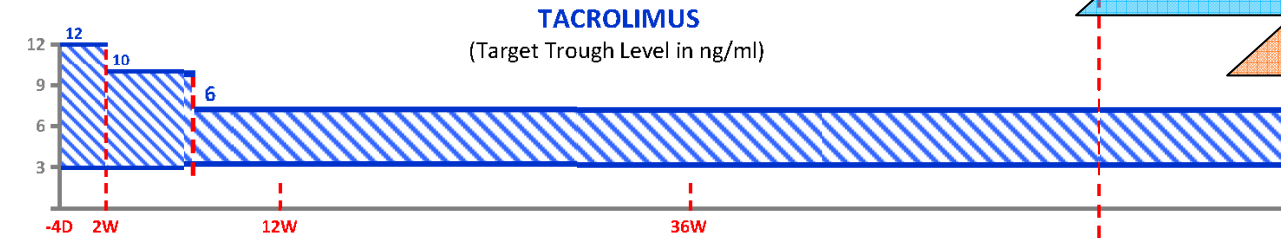
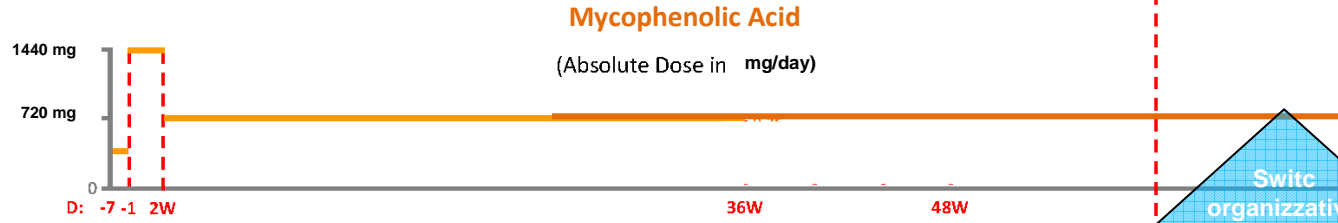
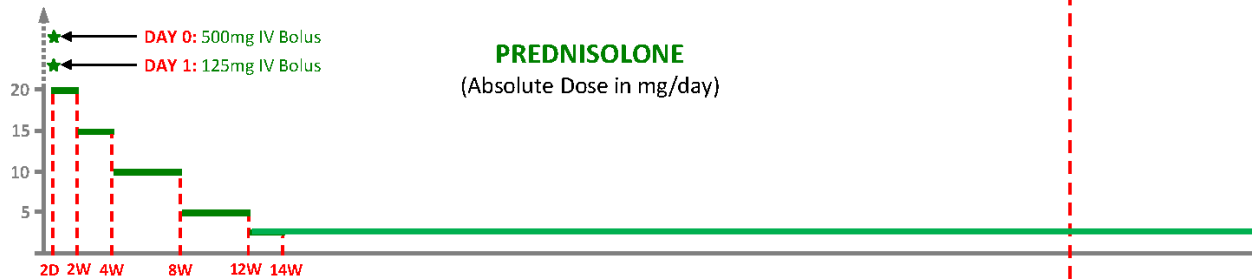
Immunosuppressive Regimen

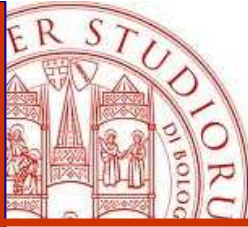


REGULATORY CELL THERAPY
(M_{reg}, Tol-DC, T_{reg}, Tr1)

**END OF TRIAL
FOLLOW-UP
PERIOD**

KEY:
h = hour(s)
D = day
W = week
g = gram(s)
mg = milligram(s)
ng = nanogram(s)
ml = millilitre
T_x = transplantation
IV = intravenous

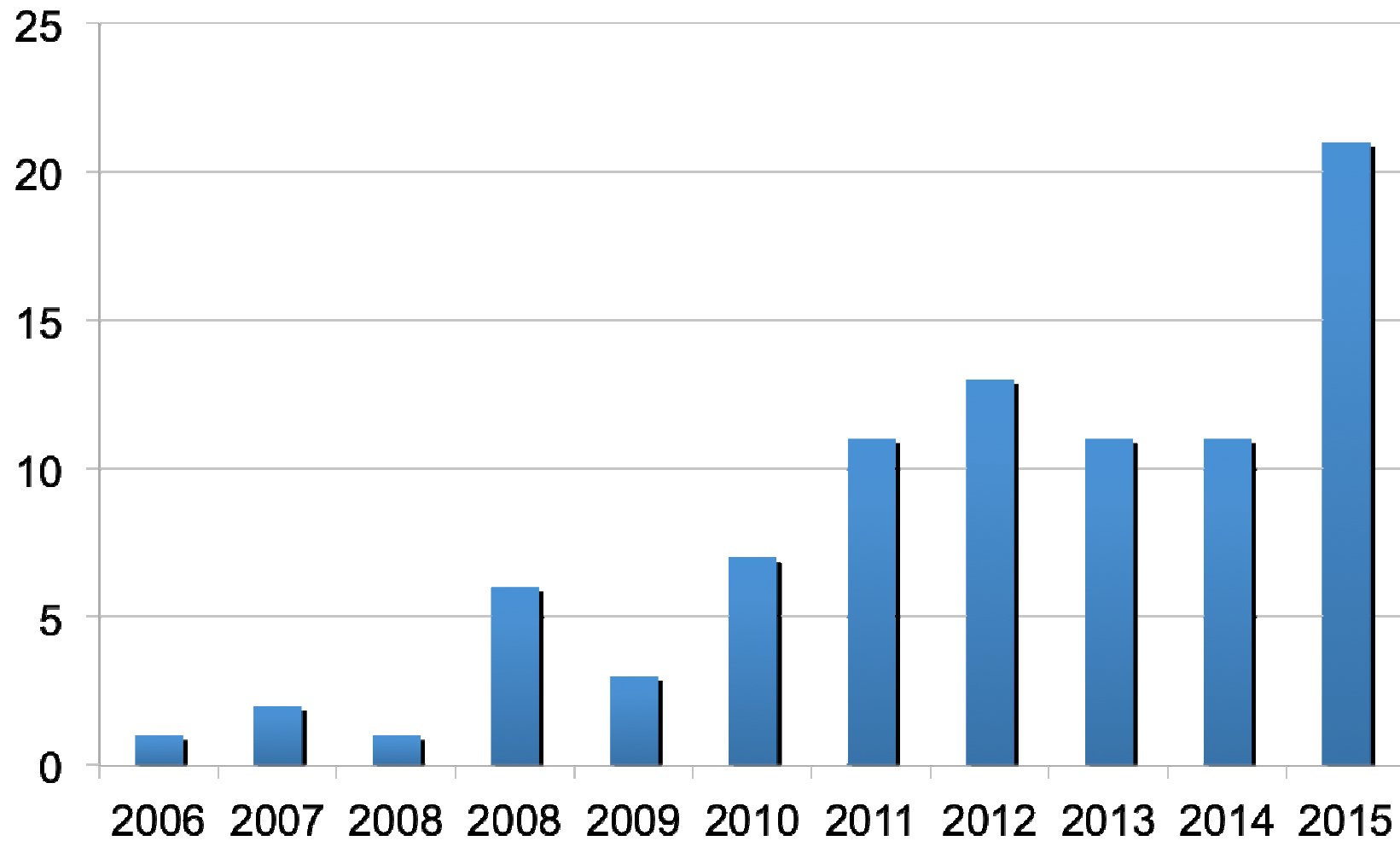




Centro Trapianti di Bologna

Trapianto da Vivente

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
Policlinico S. Orsola-Malpighi





**Il messaggio finale è che
Il trapianto da vivente è la prima
opzione da escludere e che il tempo
ha aperto nuove opportunità**

