

IL FUTURO DEI TRAPIANTI E' QUI:

Compatibilità Molecolare e Xenotrapianti

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Negli ultimi due anni **NON** ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

In questa presentazione, **NON** discuterò dell'utilizzo di medicinali fuori etichetta

LO STATO DEL TRAPIANTO DI ORGANI

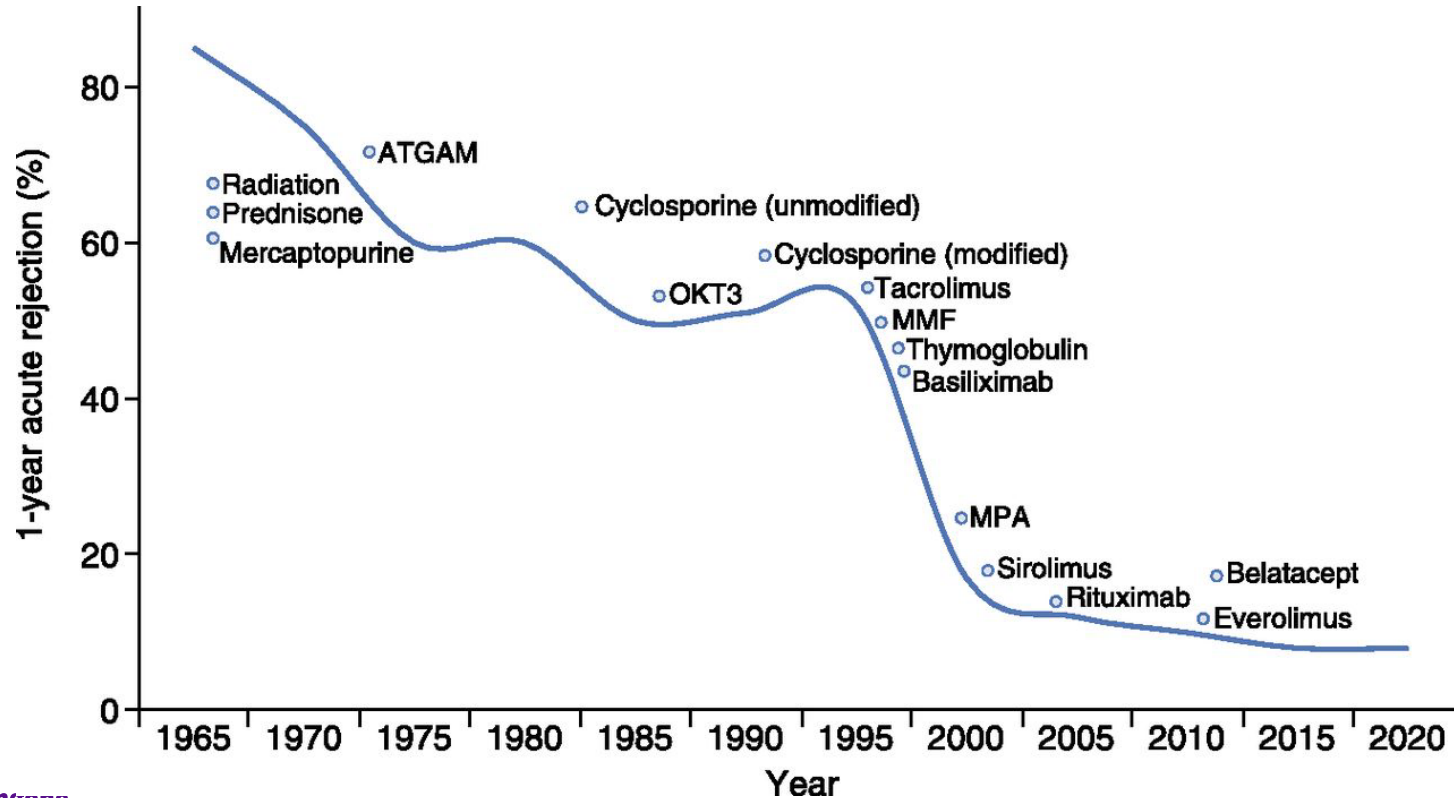
TRAPIANTI DI ORGANI: IL PROGRESSO

Reviews

Evaluation and Treatment of Acute Rejection in Kidney Allografts

James E. Cooper

CJASN March 2020, 15 (3) 430-438; DOI: <https://doi.org/10.2215/CJN.11991019>



TRAPIANTI DI ORGANI: IL SUCCESSO



TRAPIANTI DI ORGANI: IL SUCCESSO

BULLETIN

New Technologies, Approaches Help Surgeons Maximize the Use of Transplant Organs

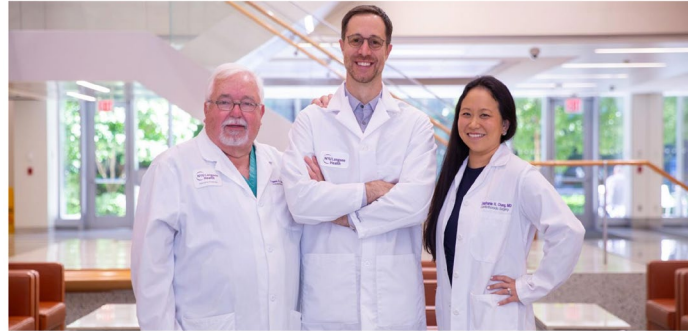
Jim McCartney
April 10, 2024

ACS
AMERICAN COLLEGE
OF SURGEONS



Dr. Zoe Stewart works with the surgical oncology team to successfully complete a portal vein reconstruction at the UH Cleveland Medical Center in Ohio.

NYU Langone Performs First Fully Robotic Lung Transplant in the United States



Dr. Travis C. Geraci and Dr. Eugene A. Grossi stand next to Dr. Stephanie F. Chang, who led the procedure.

Review

Robotic Surgical Techniques in Transplantation: A Comprehensive Review

Marco Di Pangrazio¹, Federico Pinto¹, Alessandro Martinino¹, Francesco Toti¹, Gioia Pozza¹ and Francesco Giovino^{2,3,*}

Research Letter

August 28, 2024

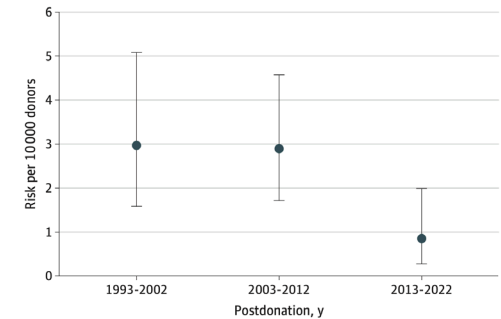
Thirty-Year Trends in Perioperative Mortality Risk for Living Kidney Donors

Allan B. Massie, PhD¹; Jennifer D. Motter, MHS¹; Jon J. Snyder, PhD²; et al

> Author Affiliations

JAMA. Published online August 28, 2024. doi:10.1001/jama.2024.14527

B 90-d Mortality risk by era

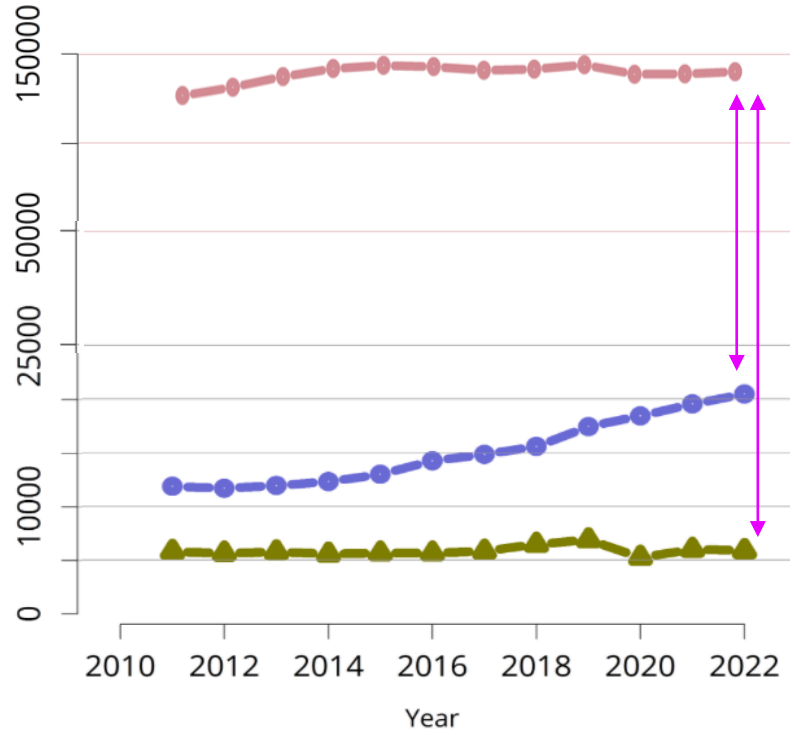


TRAPIANTI DI ORGANI: IL PROBLEMA

Adapted from:



SCIENTIFIC REGISTRY OF
TRANSPLANT RECIPIENTS



Differenza pazienti/organi

- Kidney waitlist candidates
- Deceased donor
- Living donor

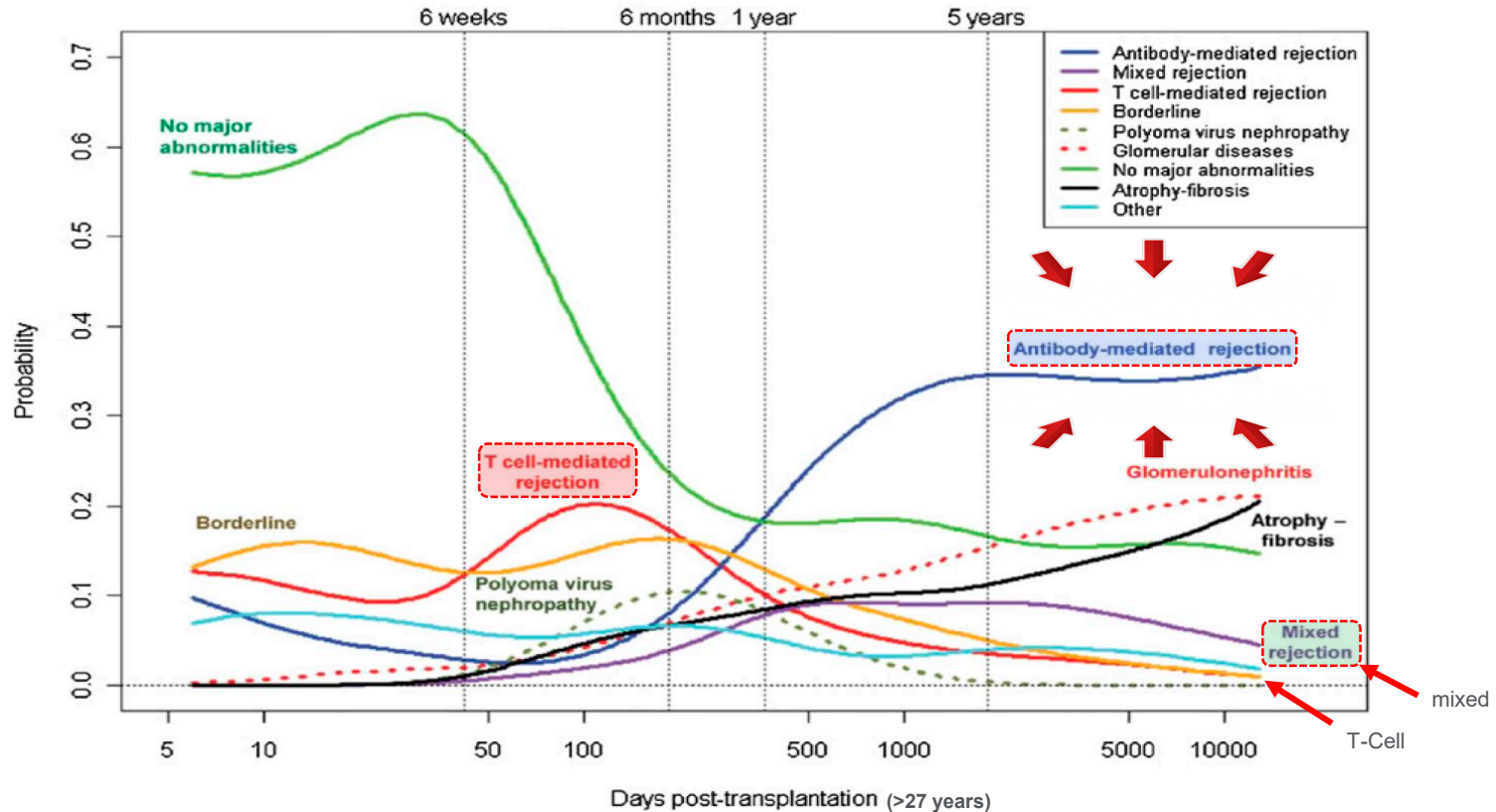


TRAPIANTI DI ORGANI: IL PROBLEMA

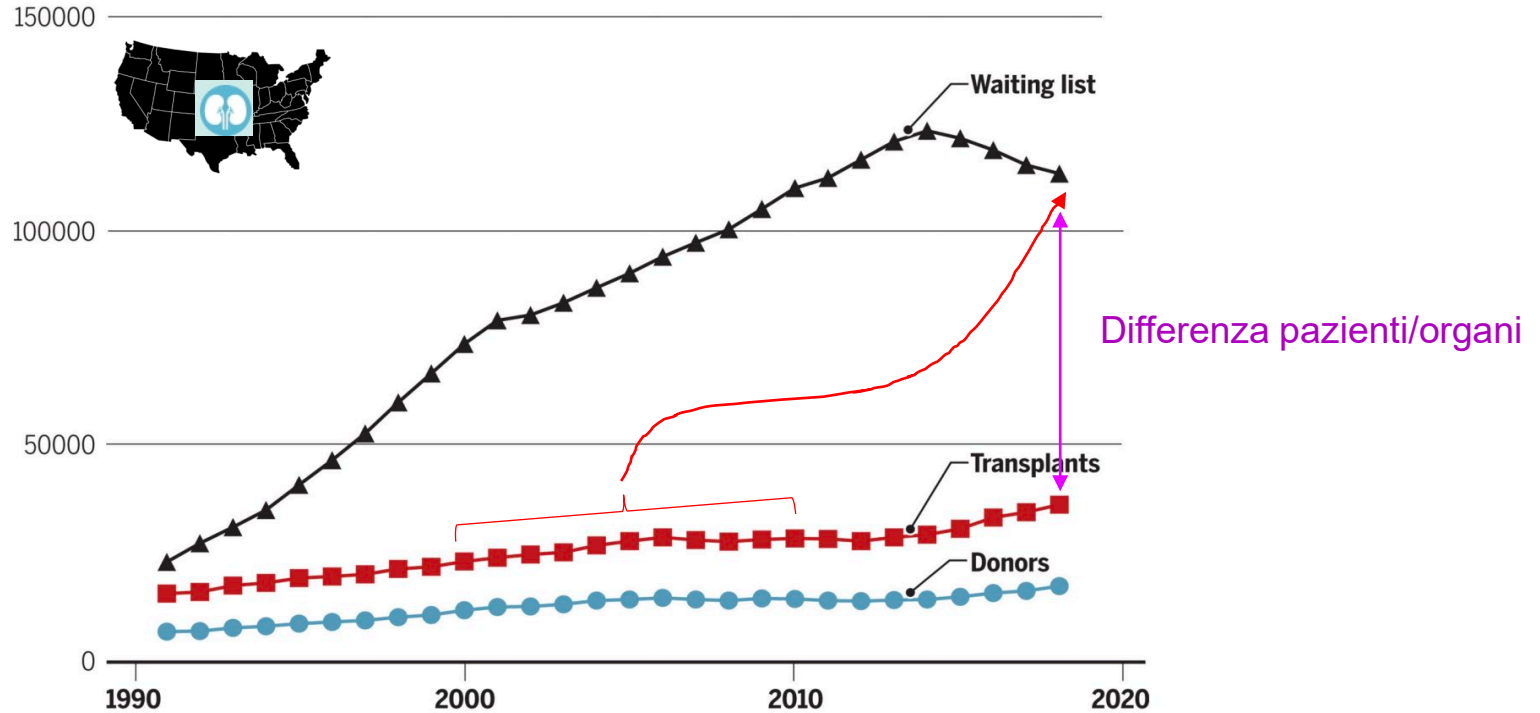
BRIEF REVIEW www.jasn.org

Through a Glass Darkly: Seeking Clarity in Preventing Late Kidney Transplant Failure

Mark D. Stegall,* Robert S. Gaston,[†] Fernando G. Cosio,[‡] and Arthur Matas[§]

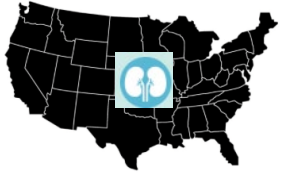


TRAPIANTI DI ORGANI: IL PROBLEMA



From: UNOS Database, 2019

TRAPIANTI DI ORGANI: LA CRUDA VERITÀ

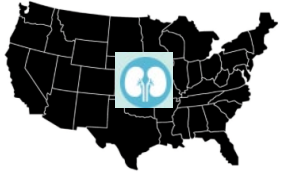


>800,000 pazienti in stato terminale di malattia renale (ESRD).

~10% (89,101) di pazienti entrano nella lista d'attesa.

<4% (27,332) di pazienti riceve un trapianto ogni anno.

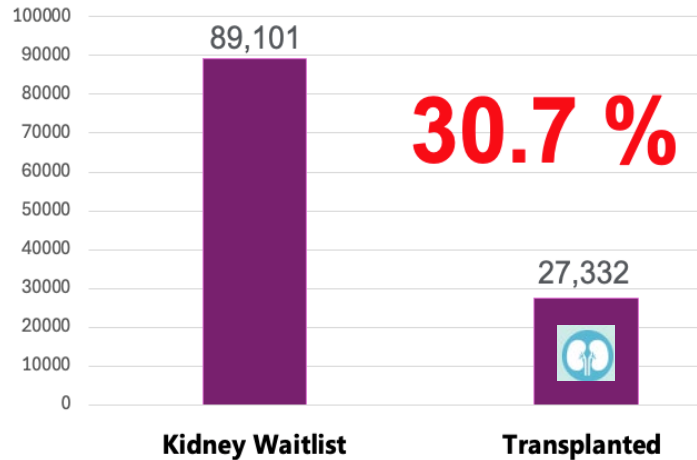
TRAPIANTI DI ORGANI: LA CRUDA VERITÀ



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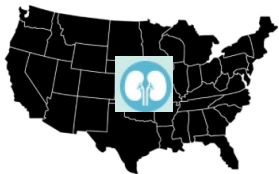
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(As of March 2024 – Source HRSA)

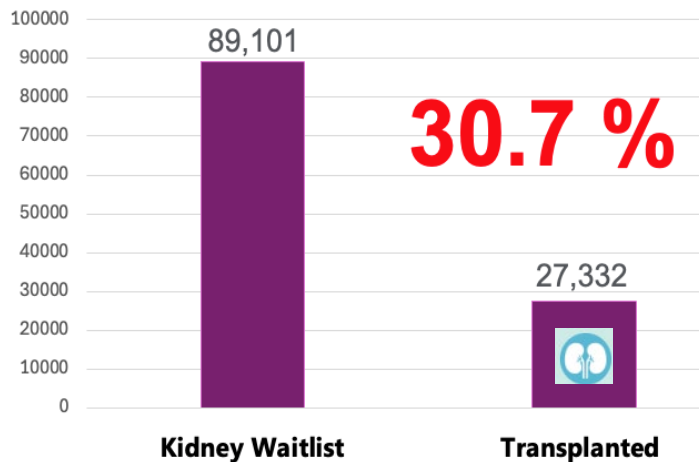
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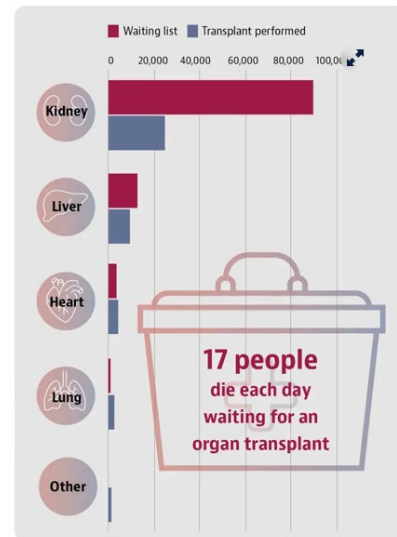


Figure. The Organ Shortage Crisis in the US
Number of patients on the waiting list vs. patients who have received transplants in 2021, by organ

UNOS

TRAPIANTI DI ORGANI: LA CRUDA VERITÀ

The New York Times

OPINION
GUEST ESSAY

My Transplanted Heart and I Will Die Soon

April 18, 2023



Amy Silverstein

“gratitude is not permission for status quo.”

TRAPIANTI DI ORGANI: LA SOLUZIONE

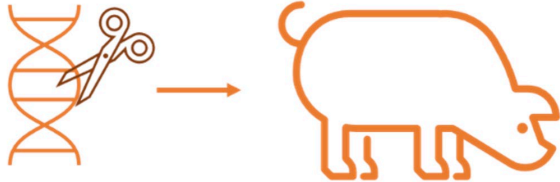


COMPATIBILITÀ MOLECOLARE

Prevenire il rigetto e migliorare la sopravvivenza a lungo termine

Genetic
modification

Donor
animal



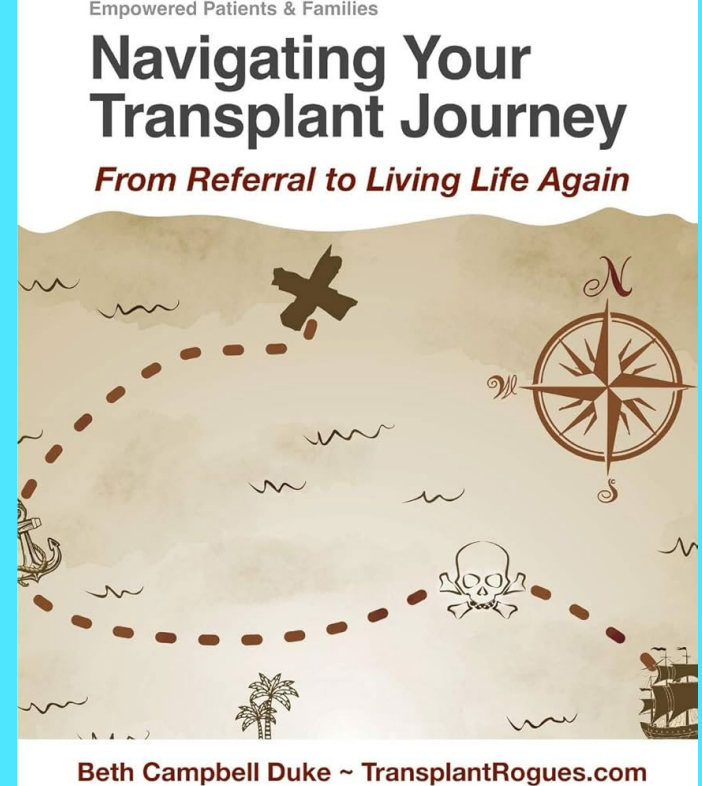
XENOTRAPIANTI

Aumentare il numero di organi disponibili soprattutto per pazienti critici

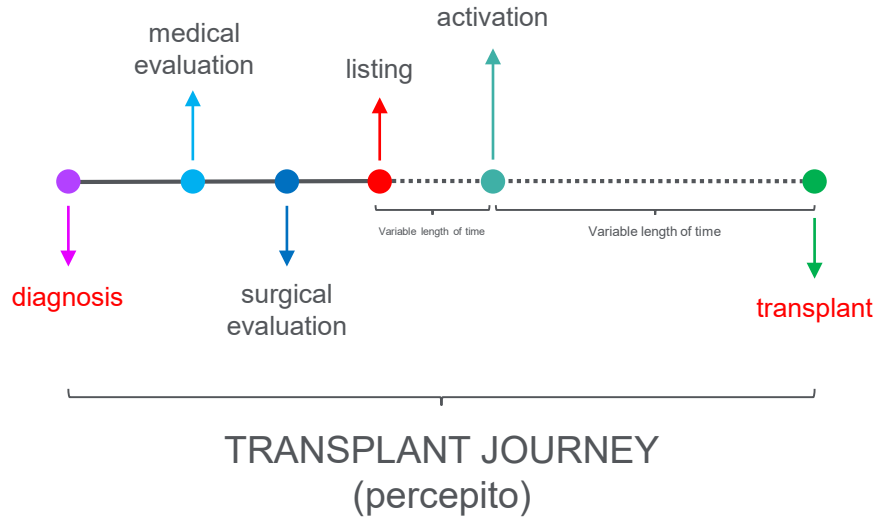
COMPATIBILITÀ MOLECOLARE

per prevenire il rigetto degli organi e migliorare la sopravvivenza a lungo termine.

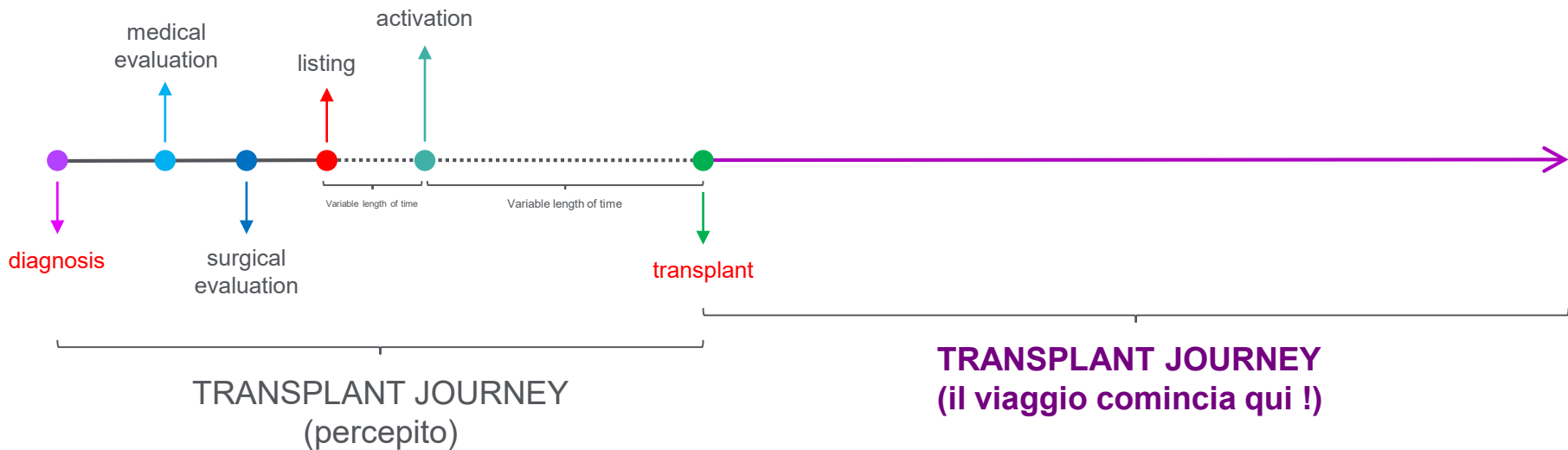
Il Viaggio del Trapianto



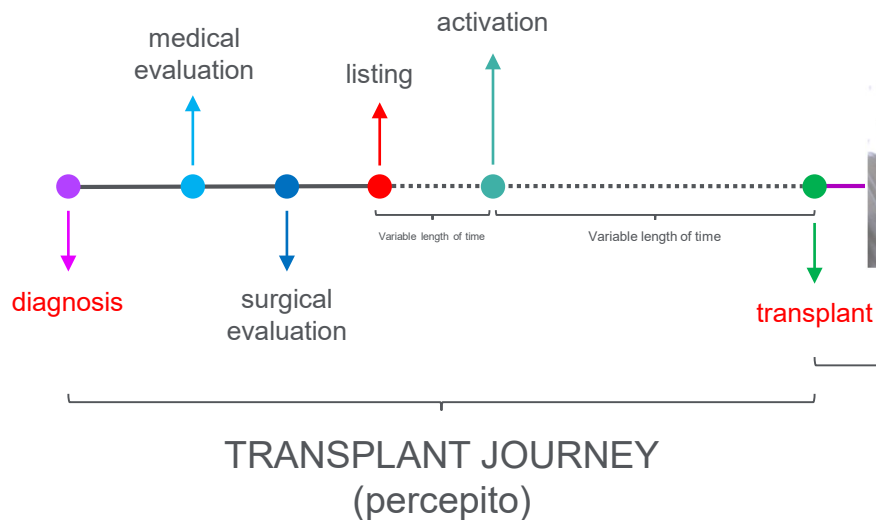
Il Viaggio del Trapianto



Il Viaggio del Trapianto



Il Viaggio del Trapianto



The Transplant Surgeon Needed a New Heart—Even if It Had Hepatitis C

A doctor advocating for his patients to have transplanted organs infected with the liver disease now uses himself as a living example



By Sumathi Reddy [Follow](#)
Jan. 28, 2019 at 10:58 am ET

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[41](#)



Change of Heart: Transplant Pioneer Uses Experience as Patient to Develop Landmark Innovation

Thomas J. McFeeley
September 1, 2022

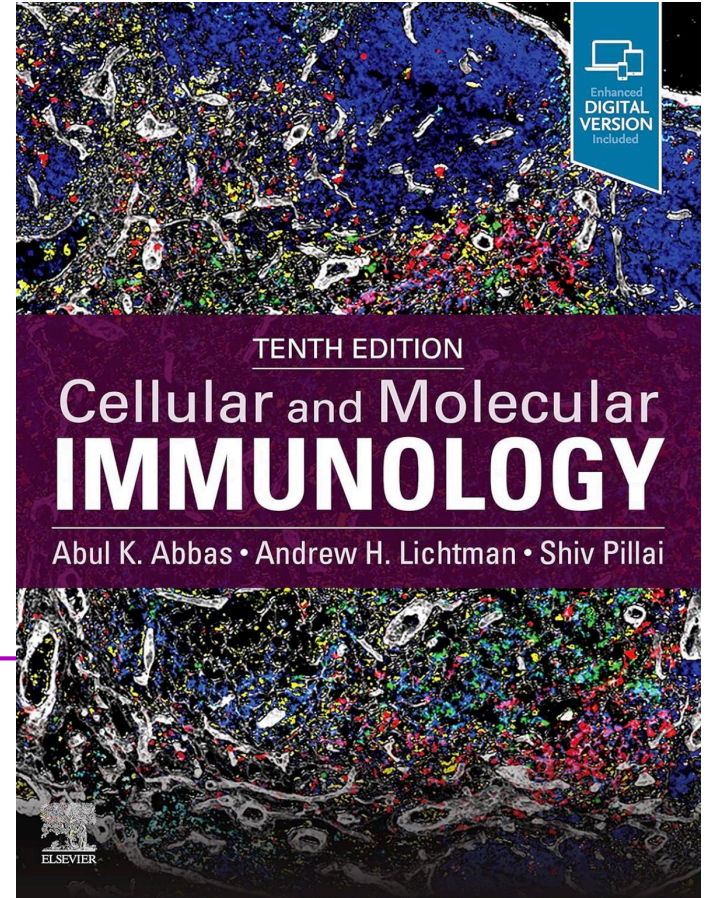


TRANSPLANT JOURNEY
(il viaggio comincia qui !)

Il VERO Viaggio del Trapianto



REAL TRANSPLANT JOURNEY

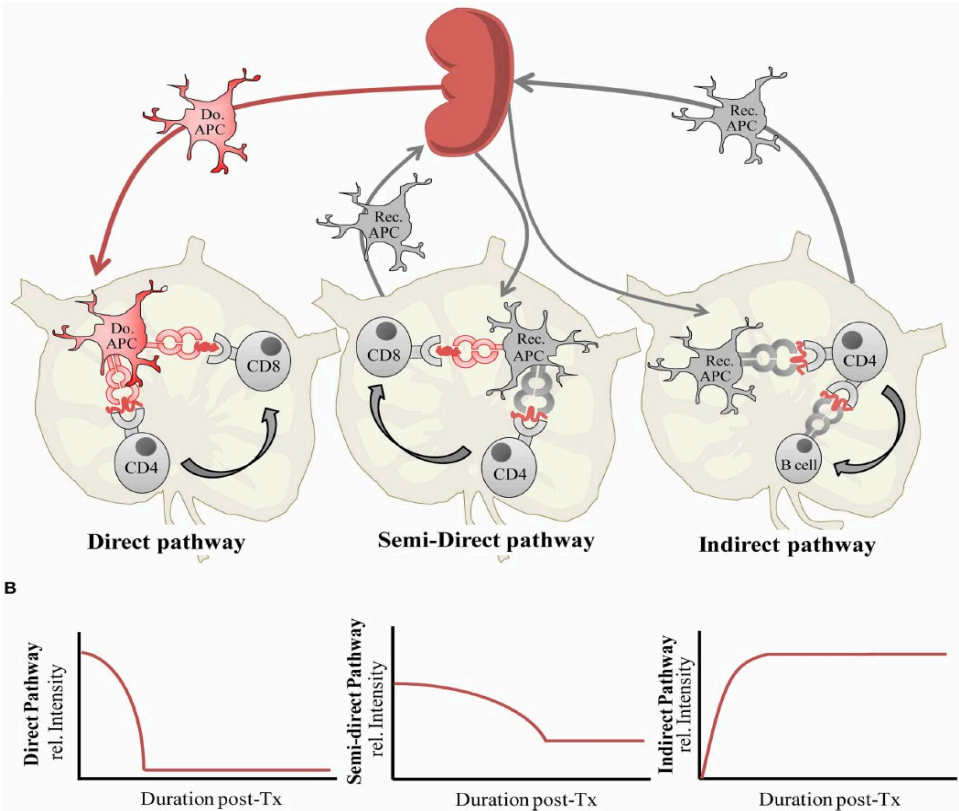


RISPOSTA ALLOIMMUNE PRIMARIA

frontiers in IMMUNOLOGY
REVIEW ARTICLE
published: 13 July 2012
doi: 10.3389/fimmu.2012.00084

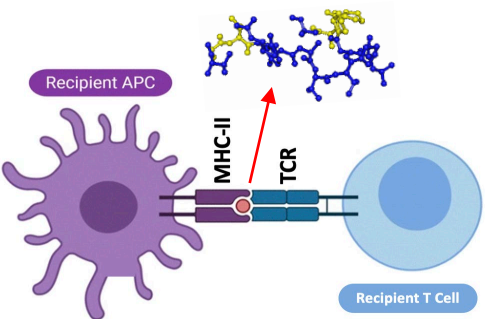
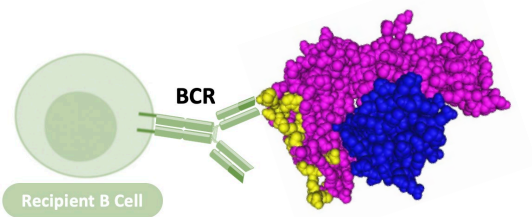
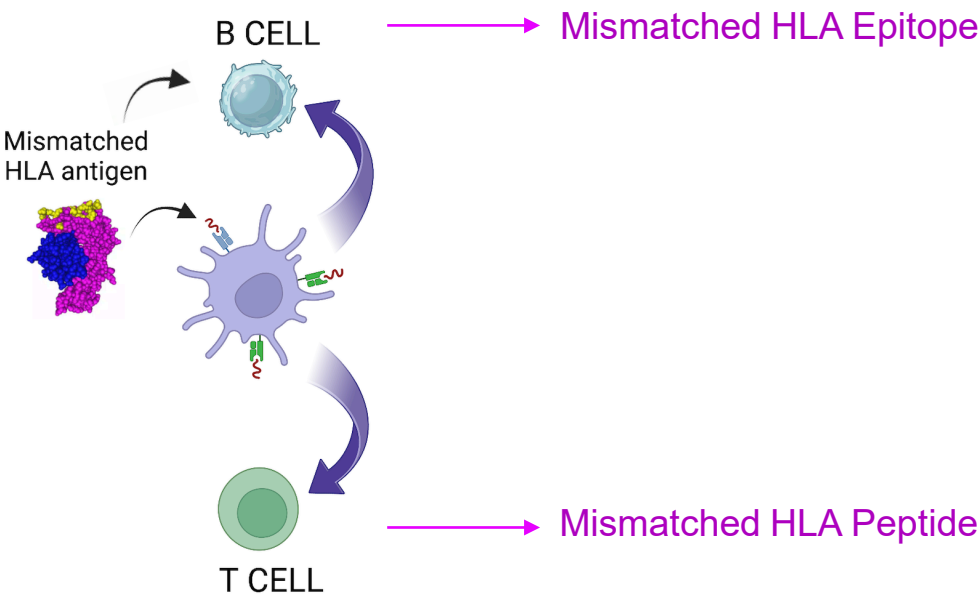
Relevance of regulatory T cell promotion of donor-specific tolerance in solid organ transplantation

Pervinder Sagoo^{1,2}, Giovanna Lombardi¹ and Robert I. Lechler^{1*}



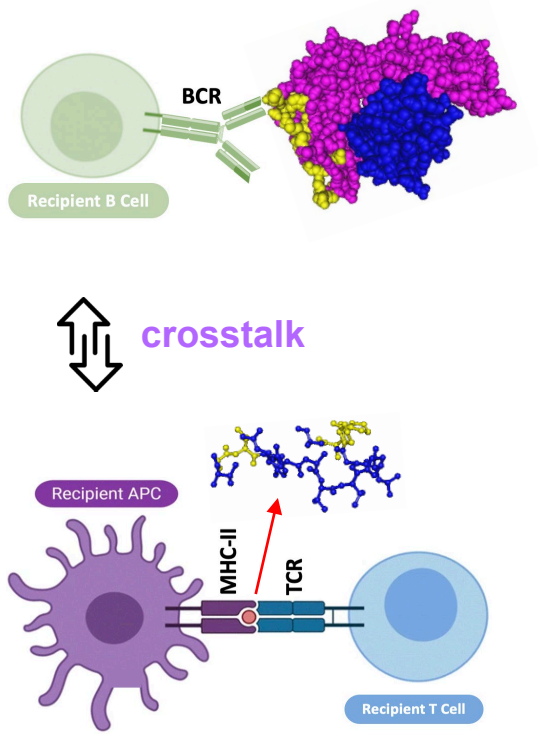
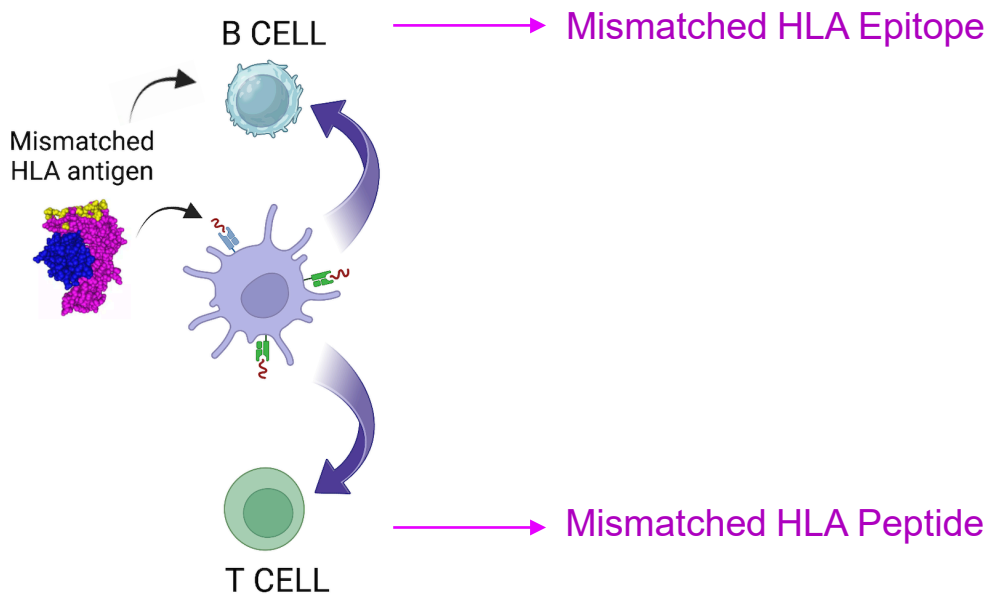
RISPOSTA ALLOIMMUNE PRIMARIA

T/B Cell Cooperation and generation of cellular and humoral responses



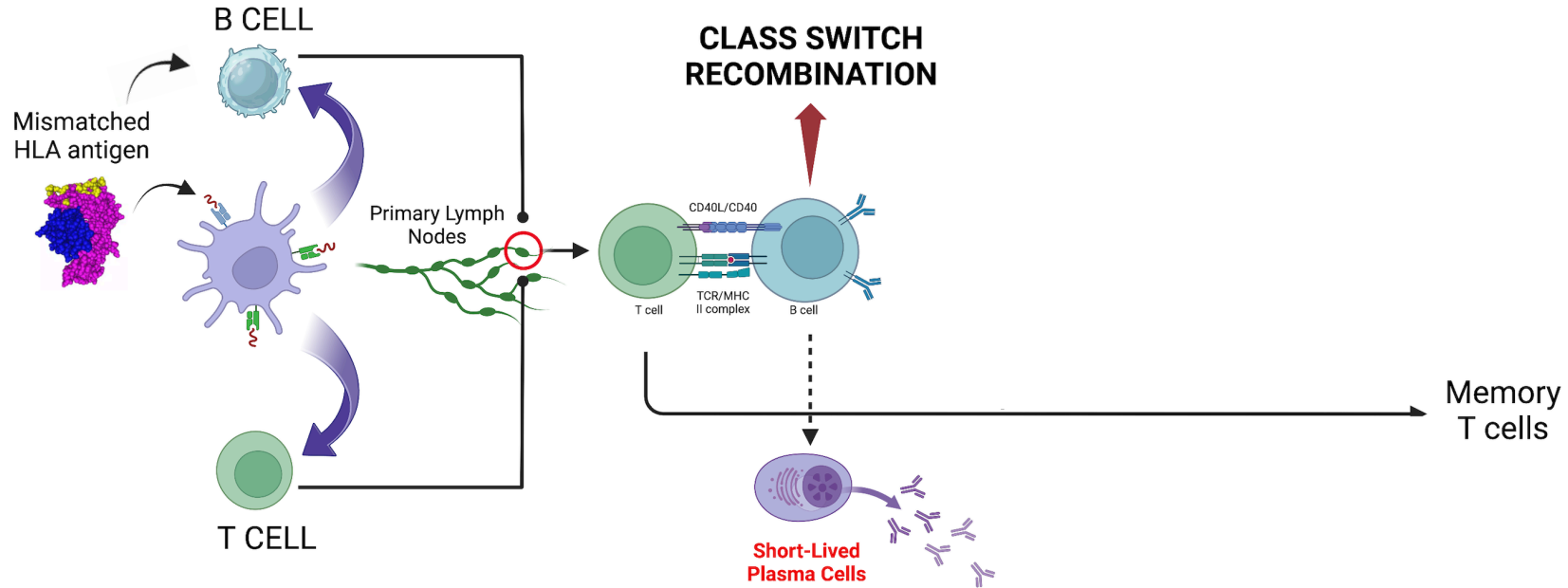
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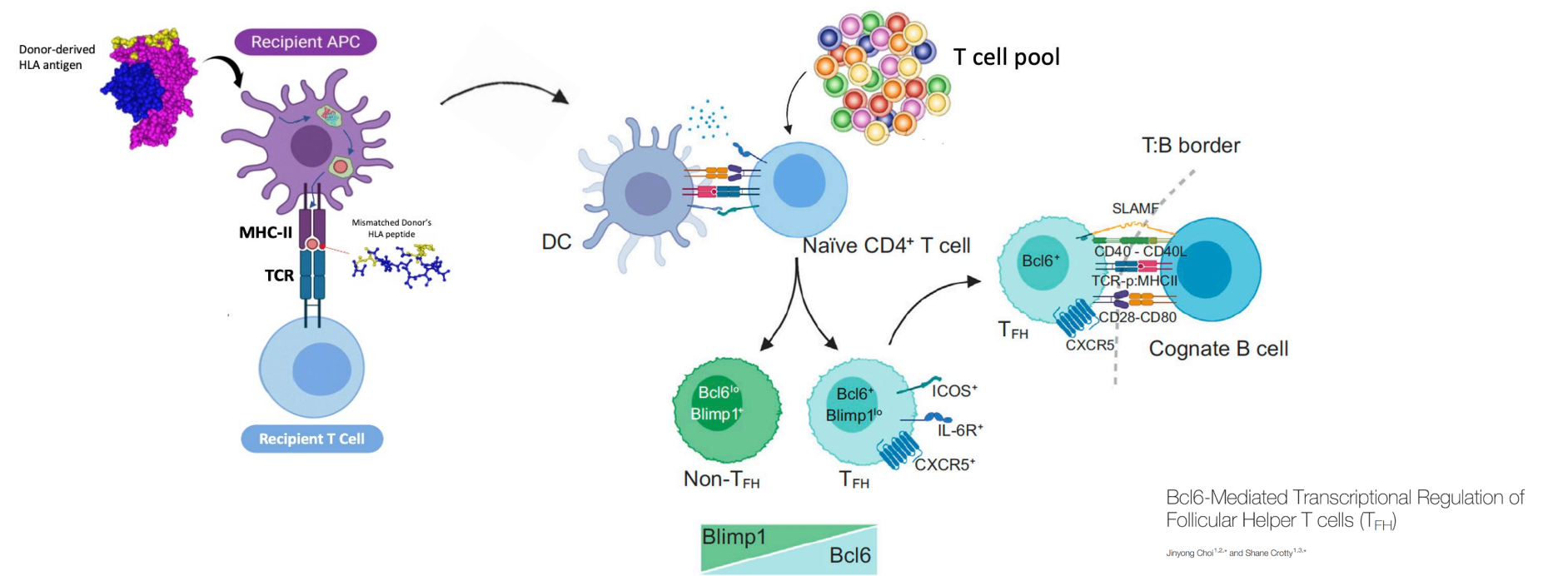
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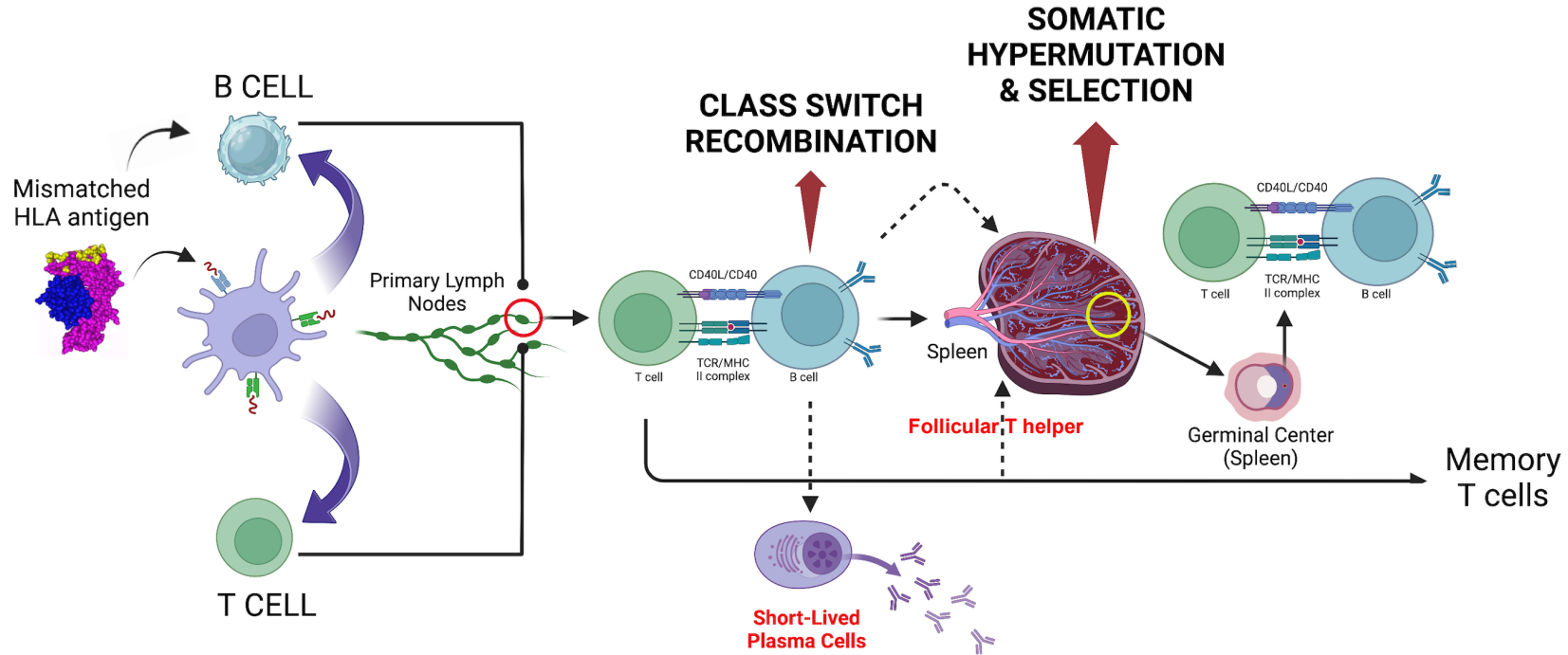
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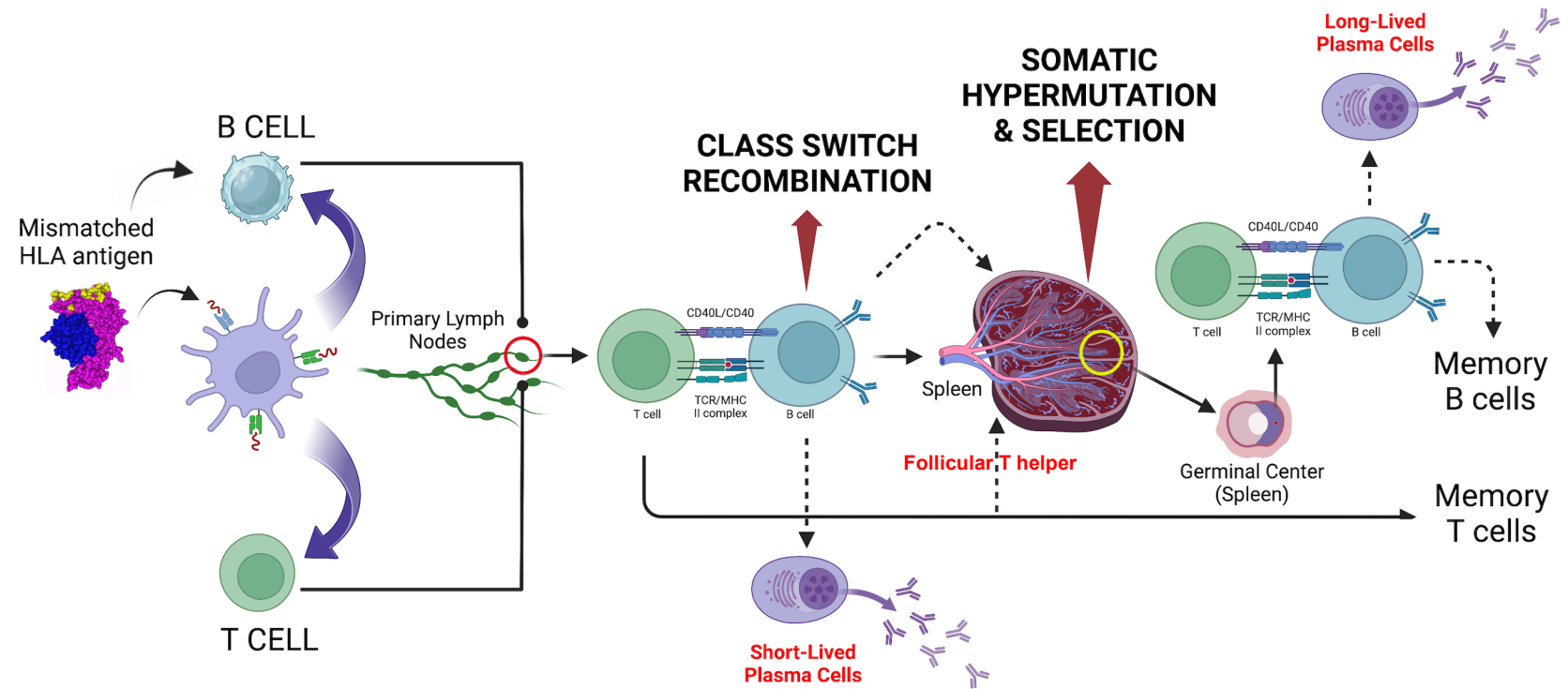
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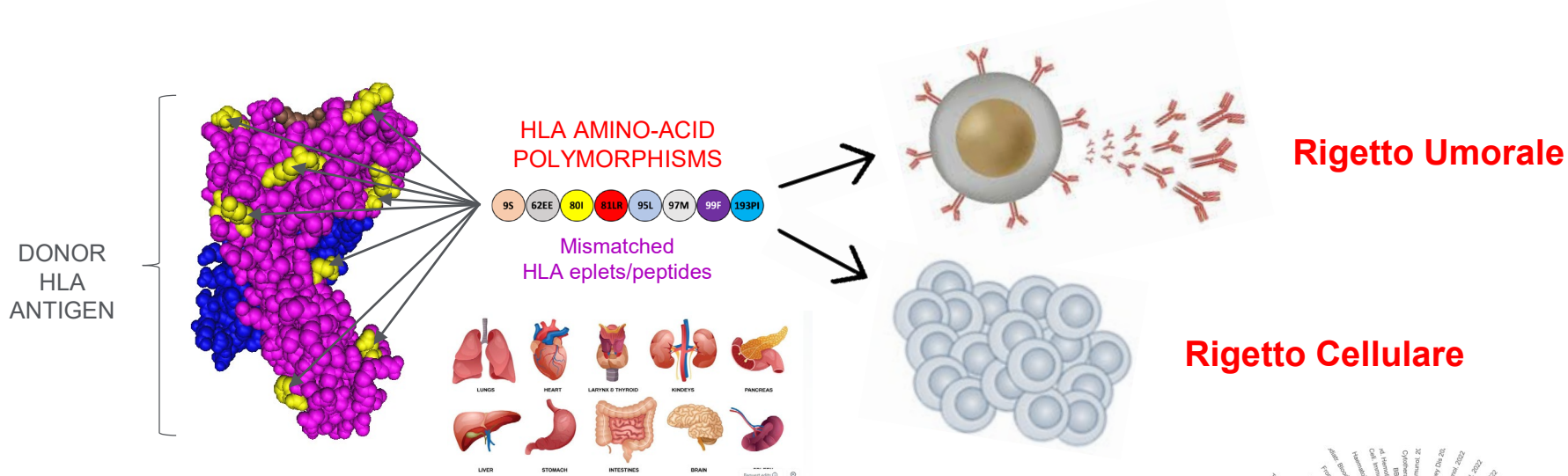


RISPOSTA ALLOIMMUNE PRIMARIA

T/B Cell Cooperation and generation of cellular and humoral responses



RUOLO DELL' HLA NEL RIGETTO DI ORGANI



ORIGINAL ARTICLE

HLA-DR/DQ molecular mismatch: A prognostic biomarker for primary alloimmunity

Chris Wiebe^{1,2} | Vasilis Kosmoliaptis^{3,4,5} | Denise Pochinco² | Ian W. Gibson^{2,6} | Julie Ho^{2,7} | Patricia E. Birk⁸ | Aviva Goldberg⁸ | Martin Karpinski¹ | Jamie Shaw¹ | David N. Rush¹ | Peter W. Nickerson^{1,2,7}

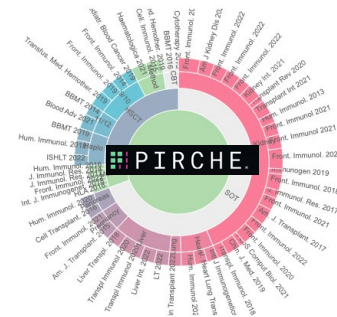
BRIEF COMMUNICATION

Adequate tacrolimus exposure modulates the impact of HLA class II molecular mismatch: a validation study in an American cohort

Scott Davis¹ | Christopher Wiebe² | Kristen Campbell¹ | Cheri Anobile³ | Michael Aubrey³ | Erik Stites¹ | Monica Grafals¹ | Elizabeth Pomfret⁴ | Peter Nickerson² | James E. Cooper¹

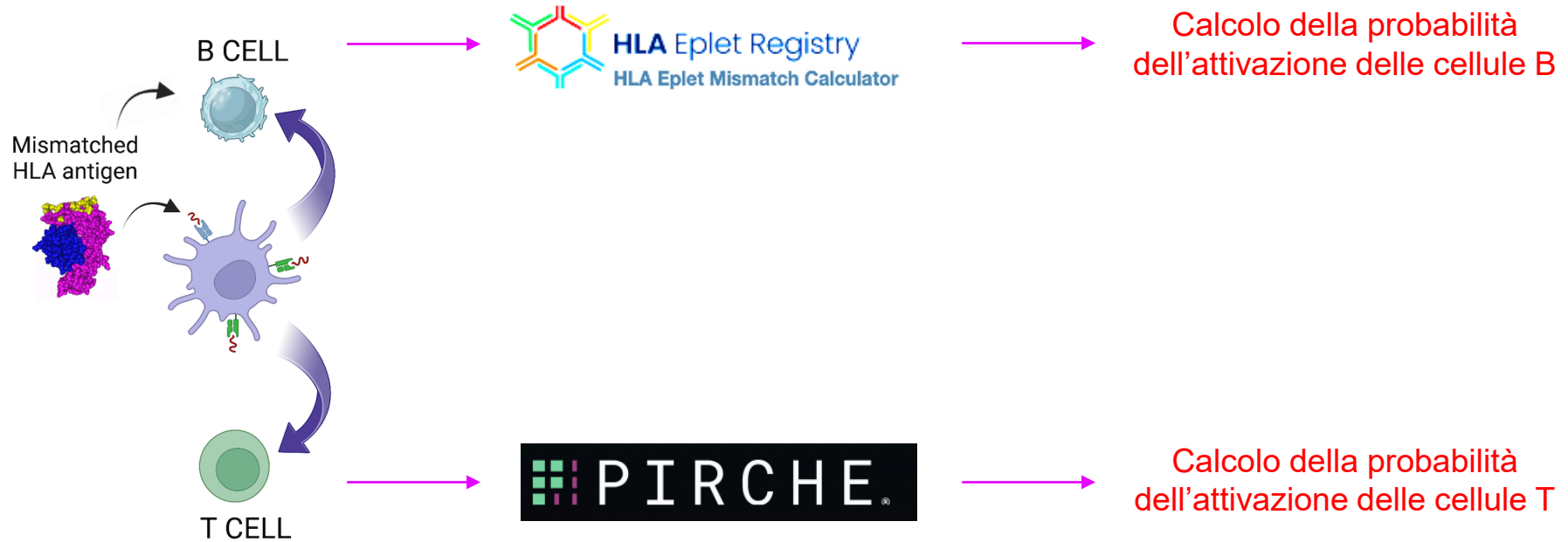
Eplet Mismatch Load and De Novo Occurrence of Donor-Specific Anti-HLA Antibodies, Rejection, and Graft Failure after Kidney Transplantation: An Observational Cohort Study

Aleksandar Senov^{1,2} | Maarten Coemans^{1,3} | Evelyn Lerut⁴ | Vicky Van Sandt² | Johan Kerkhofs² | Liesbeth Daniels² | Marleen Vanden Driessche² | Veerle Compennolle² | Ben Sprangers^{1,5} | Elisabeth Van Loon^{1,5} | Jasper Callemeyn^{1,5} | Frans Claas⁶ | Anat R. Tambur⁷ | Geert Verbeke² | Dirk Kuypers^{1,5} | Marie-Paule Emonds^{1,2} and Maarten Naessens^{1,5}



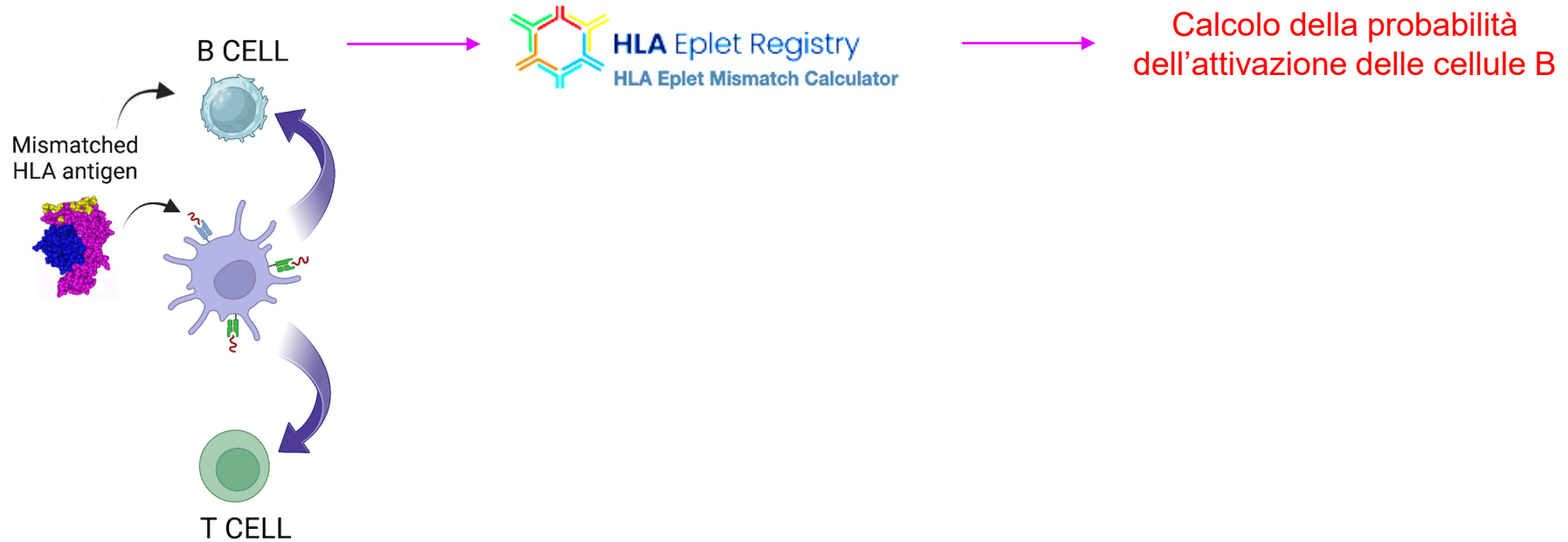
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T/B Cell Cooperation and generation of cellular and humoral responses



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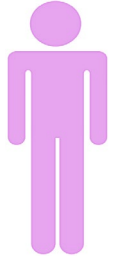


HLA EPLET: calcolo dell'attivazione delle cellule B



Recipient

HLA-A*02:01



Donor

HLA-A*24:02

HLA EPLET: calcolo dell'attivazione delle cellule B



Recipient

HLA-A*02:01 → 40 EPLETS

9F 44RM 44RME 62GE 62GK 65RA 65RK 66K 66KA 66KH 71HS 76VDT 77D 79GT 80T 80TL
95V 97R 99Y 105S 107W 109F 114H 116Y 127K 144K 144TKH 145KHA 149AH 150AAH
150AH 151AHV 151H 152V 156L 163T 184A 193AV 194V 207S 253Q



Donor

HLA-A*24:02 → 35 EPLETS

9S 44RM 44RME 62EE 65GK 66K 66KA 66KH 71HS 76EN 77N 80I 81ALR 82LR 95L 97M
99F 105S 109F 114H 116Y 127K 138MI 144K 144KR 149AH 150AAH 150AH 151AHV 151H
152V 156QA 163T 166DG 193PI

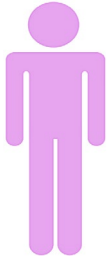
HLA EPLET: calcolo dell'attivazione delle cellule B



Recipient

HLA-A*02:01 → 40 EPLETS

9F 44RM 44RME 62GE 62GK 65RA 65RK 66K 66KA 66KH 71HS 76VDT 77D 79GT 80T 80TL
95V 97R 99Y 105S 107W 109F 114H 116Y 127K 144K 144TKH 145KHA 149AH 150AAH
150AH 151AHV 151H 152V 156L 163T 184A 193AV 194V 207S 253Q



Donor

HLA-A*24:02 → 35 EPLETS

9S 44RM 44RME 62EE 65GK 65K 66KA 66KH 71HS 76EN 77N 80I 81ALR 82LR 95L 97M
99F 106S 109F 114H 116Y 127K 138MI 144K 144KR 145AH 150AAH 150AH 151AHV 151H
152V 156QA 163T 166DG 193PI

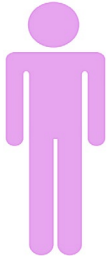
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9F 44RM 44RME 62GE 62GK 65RA 65RK 66K 66KA 66KH 71HS 76VDT 77D 79GT 80T 80TL
95V 97R 99Y 105S 107W 109F 114H 116Y 127K 144K 144TKH 145KHA 149AH 150AAH
150AH 151AHV 151H 152V 156L 163T 184A 193AV 194V 207S 253Q



Donor

HLA-A*24:02 → 35 EPLETS

9S 44RM 44RME 62EE 65GK 66K 66KA 66KH 71HS 76EN 77N 80I 81ALR 82LR 95L 97M
99F 106S 109F 114H 116Y 127K 138MI 144K 144KR 145AH 150AAH 151AHV 151H
152V 156QA 163T 166DG 193PI

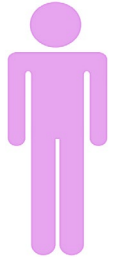
HLA EPLET: calcolo dell'attivazione delle cellule B



Recipient

HLA-A*02:01 → 40 EPLETS

9F 44RM 44RME 62GE 62GK 65RA 65RK 66K 66KA 66KH 71HS 76VDT 77D 79GT 80T 80TL
95V 97R 99Y 105S 107W 109F 114H 116Y 127K 144K 144TKH 145KHA 149AH 150AAH
150AH 151AHV 151H 152V 156L 163T 184A 193AV 194V 207S 253Q



Donor

HLA-A*24:02

9S 62EE 65GK 76EN 77N 80I 81ALR 82LR 95L 97M 99F 138MI 144KR 156QA 166DG 193PI

16 MISMATCHED EPLETS

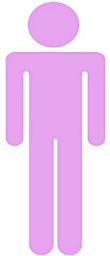
(EPLET è il nuova “valore” della compatibilità)

HLA EPLET: calcolo dell'attivazione delle cellule B



A*	B*	C*	DRB1*	DRB345*	DQA1*	DQB1*	DPA1*	DPB1*
02:01	15:03	02:10	03:01	3*02:02	05:01	02:01	02:02	01:01
33:01	53:01	04:01	08:04		04:01	03:19	03:01	105:01
Class I eplet mismatch			HLA-DR eplet mismatch		HLA-DQ eplet mismatch		HLA-DP eplet mismatch	
A*	B*	C*	DRB1*	DRB345*	DQA1*	DQB1*	DPA1*	DPB1*
24:02	18:01	07:01	04:07	4*01:03	03:01	03:02	01:03	02:01:02G
68:03	40:02	03:05	14:54	3*02:02	01:04	05:03	02:02	05:01:01G

HLA EPLET: calcolo dell'attivazione delle cellule B





HLA Eplet Registry

 Home

 Databases ▾

 Mismatch Calc.

 Publications

 New pattern

 Contact

Patient Vs. Donor 1

A/B/C

25

DRB1/3/4/5

11

DQA1/DQB1

11

DPA1/DPB1

10

MICA

TOTAL

57



HLA LOCI GROUP

MISMATCHES QTY.

MISMATCHES DETAILS

A/B/C

25

All mismatches: 9F, 9T, 12M, 14W, 16S, 45EE, [62GE], [62GK], 65RK, 66IF, 71TN, [73AN], 73ID, [80K], 94I, 95V, [107W], 113YN, 114Q, 116F, 156R, 156RA, 186R, 245AS, 275K
Single-allele mismatch load: A*02:01 6 A*33:01 5 B*15:03 2 B*53:01 4 C*02:10 2 C*04:01 8

DRB1/3/4/5

11

All mismatches: [16Y], 26Y, 37N, [47F], 67F, [70D], [70DA], 70DR, 70DRA, 74L, [74R]
Single-allele mismatch load: DRB1*03:01 4 DRB1*08:04 7 DRB3*02:02 0

DQA1/DQB1

11

All mismatches: [40GR], [45EV], [52LL], 55PPD, 66D, 66DR, 66IT, 75IL, [75S], 76L, 167H
Single-allele mismatch load: DQA1*04:01 4 DQA1*05:01 3 DQB1*02:01 3 DQB1*03:19 3

DPA1/DPB1

10

All mismatches: 8V, 8VG, 9Y, 33EA, 33EYA, 35YA, 36A, 55A, 66S, 76V
Single-allele mismatch load: DPA1*02:02 0 DPA1*03:01 1 DPB1*01:01 9 DPB1*105:01 0

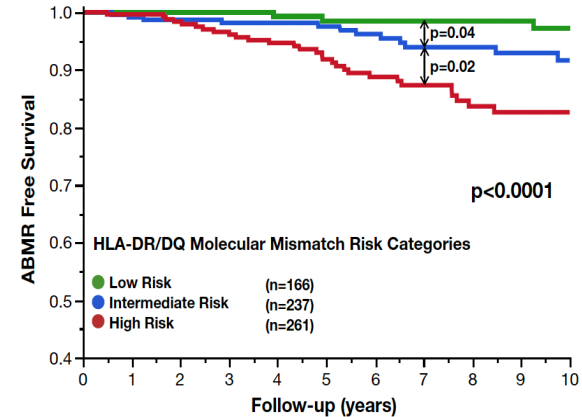
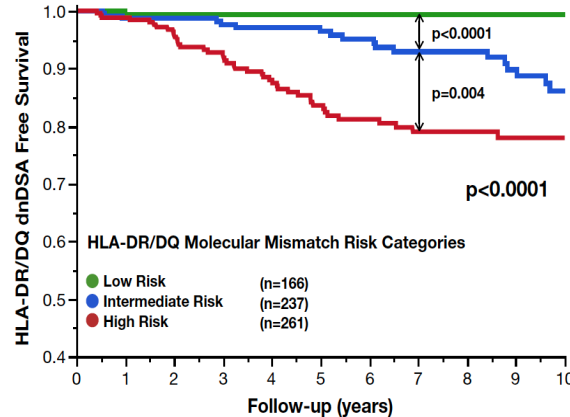
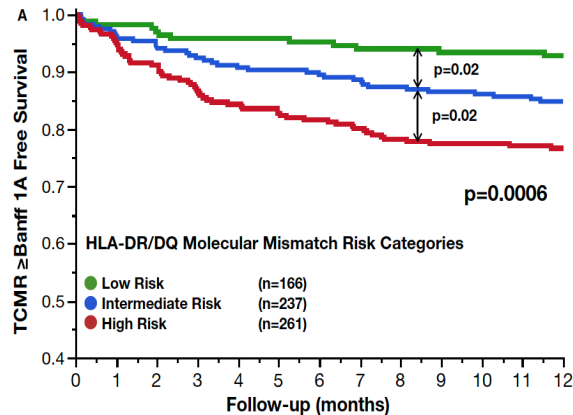
RISPOSTA ALLOIMMUNE PRIMARIA: cellule B

Am J Transplant. 2019;19:1708–1719.

HLA-DR/DQ molecular mismatch: A prognostic biomarker for primary alloimmunity

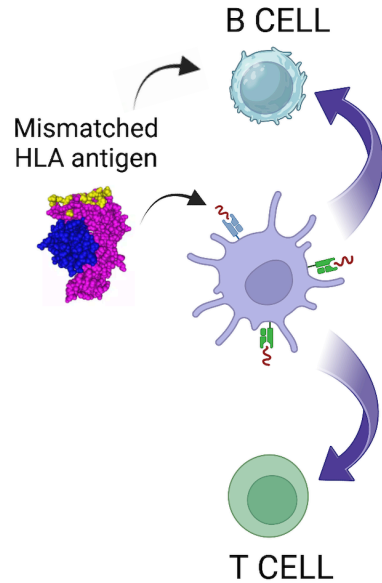
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Julie Ho^{1,7} | Patricia E. Birk⁸ | Aviva Goldberg⁸ | Martin Karpinski¹ | Jamie Shaw¹ |
David N. Rush¹ | Peter W. Nickerson^{1,2,7}

La differenza molecolare al livello delle cellule B
è un biomarker prognostico per il rigetto degli organi



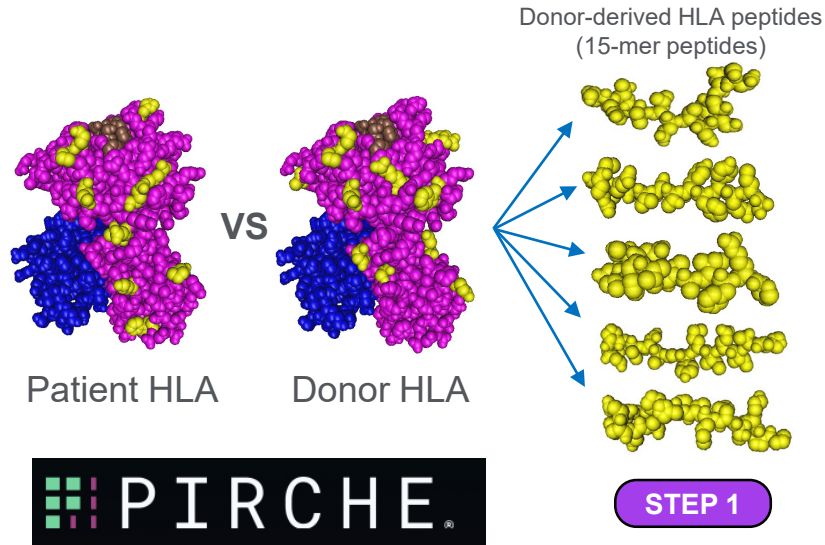
RISPOSTA ALLOIMMUNE PRIMARIA

T/B Cell Cooperation and generation of cellular and humoral responses

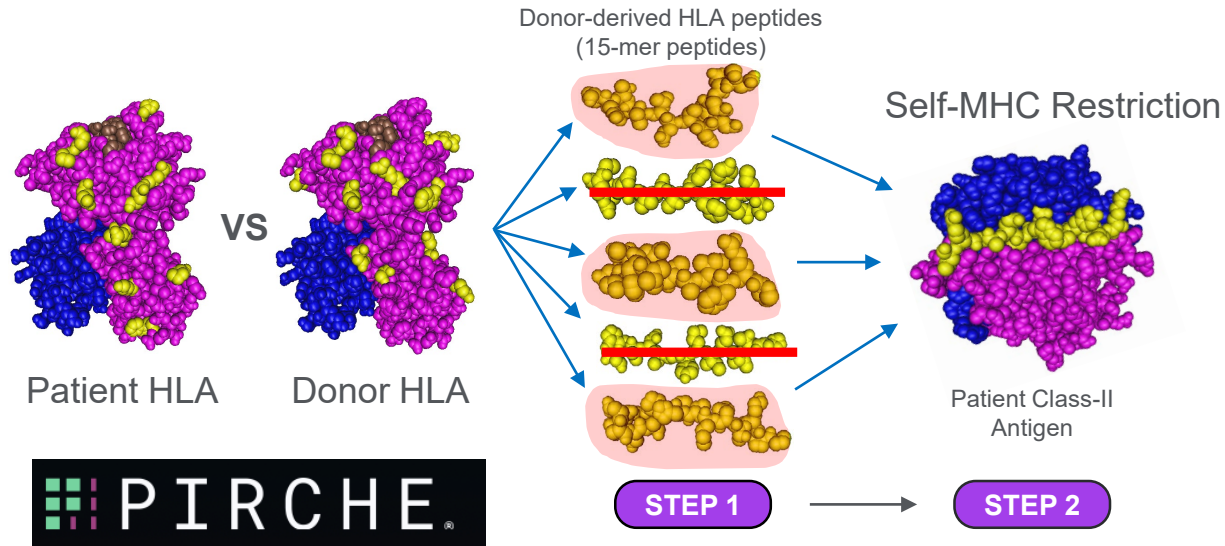


Calcolo della probabilità
dell'attivazione delle cellule T

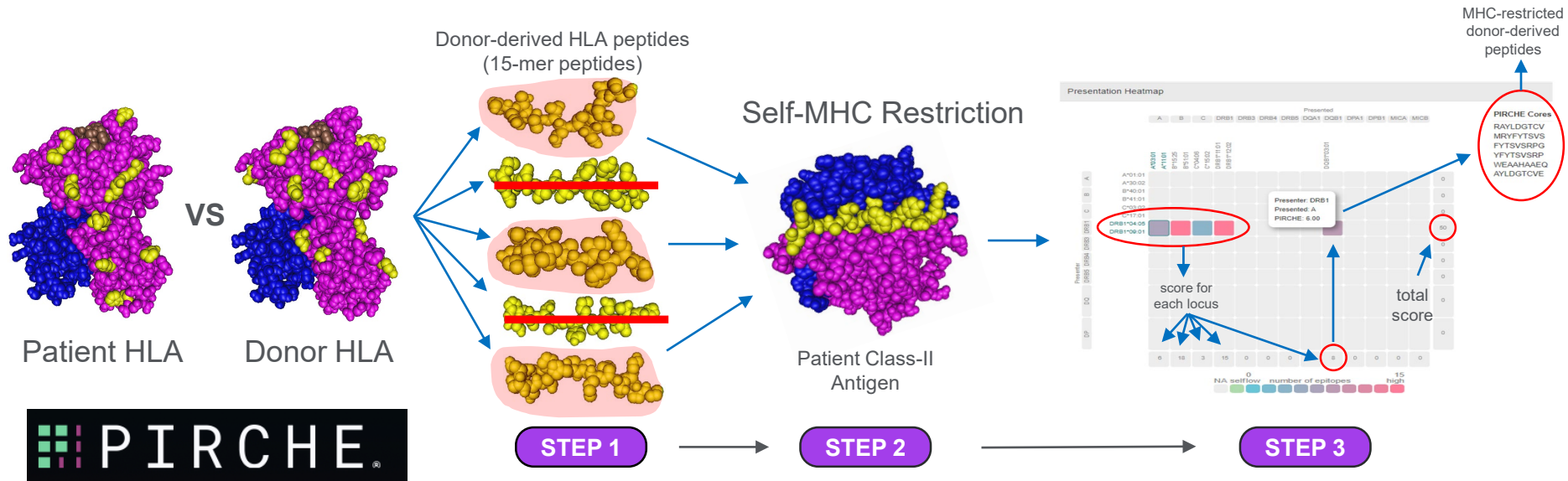
PIRCHE-II: calcolo dell'attivazione delle cellule CD4



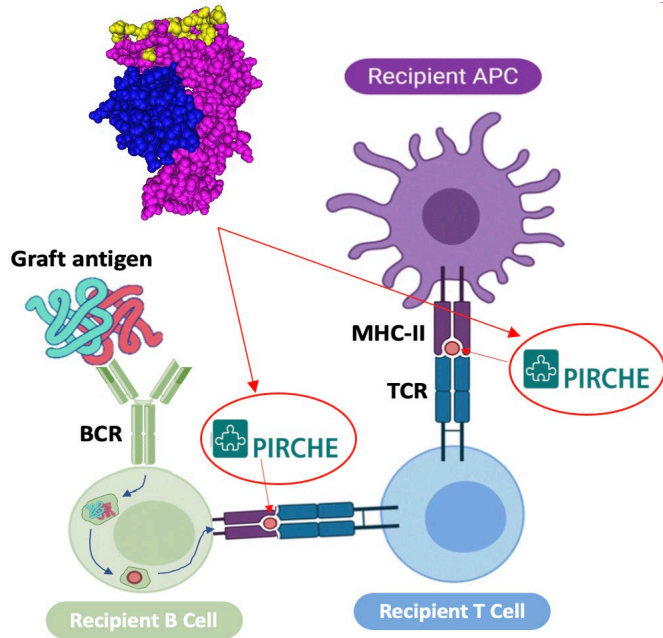
PIRCHE-II: calcolo dell'attivazione delle cellule CD4



PIRCHE-II: calcolo dell'attivazione delle cellule CD4



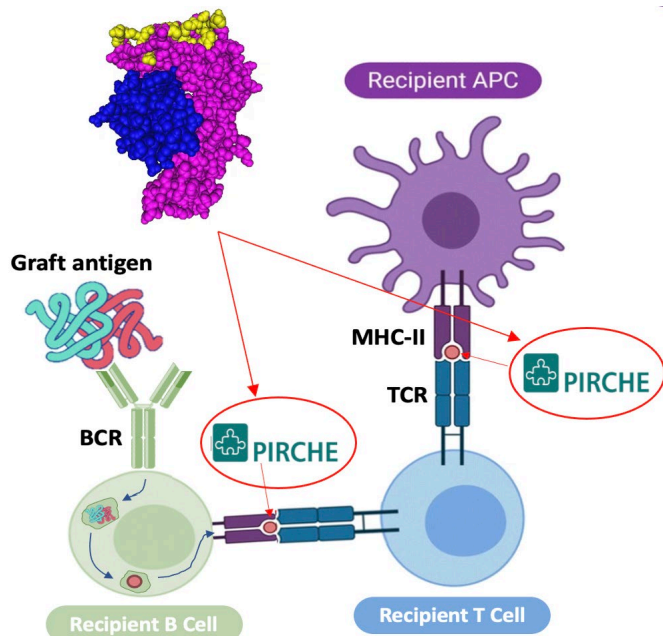
RUOLO DELLA RESTRIZIONE MHC



DQ7-DERIVED T-CELL PEPTIDES RESTRICTED BY RECIPIENT'S HLA-DRB1

DRB1*01:01 DRB1*15:01 DRB1*11:01 DRB1*04:01 DRB1*03:01

RUOLO DELLA RESTRIZIONE MHC



DQ7-DERIVED T-CELL PEPTIDES RESTRICTED BY RECIPIENT'S HLA-DRB1

DRB1*01:01

31 peptides

RTEALNHNHLLVCSV
LLVCSVDFYPAQIK
RFDSDEVYRAVTP
VYQFKAMCYFTNGTE
PEDFVYQFKAMCYFT
VTDYFPAQIKVRWFR
IFLGLGLIIHRSQK
HNLVCSVDFYPAQ
LGLIIHRSQKGLLH
KEVLERTRAELDTVC
FLGLGLIIHRSQK
VLGLIFLGLGLIIH
RTTLQRRVEPTVTIS
QLELRTTLQRRVEPT
MLSGIGGFVLGLIFL
ILVMLEMTPQHGDV
QSKMLSGIGGFVLGL
DTVCRHNYQLELRT
GTERVRYVTRYIYNR
SAQSKMLSGIGGFVL
QEETTGVSTPLIRN
LDTVCRHNYQLELRT
QKEVLERTRAELDTV
LVCSVDFYPAQIKV
YRAVTPLGPPDAEYV
EDFVYQFKAMCYFTN
FDSDDEVYRAVTP
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*15:01

22 peptides

QFKAMCYFTNGTERV
FYPAQIKVRWFRNDQ
YQFKAMCYFTNGTER
RDSPEFVYQFKAMC
VTDYFPAQIKVRWFR
LGLIIHRSQKGLLH
LGLIFLGLGLIIHHR
LGLGLIIHRSQKGL
GLGLIIHRSQKGLL
HNYQLELRTTLQRRV
GTERVRYVTRYIYNR
SKMLSGIGGFVLGL
FKAMCYFTNGTERV
QSKMLSGIGGFVLGL
GTERVRYVTRYIYNR
QILVMLEMTPQHGDV
ERVRYVTRYIYNREE
LVCSVDFYPAQIKV
EDFVYQFKAMCYFTN
VEVYRAVTPLGPPDA
VTRYIYNREEYARF
RHNYQLELRTTLQRR
RVRYVTRYIYNREEY

DRB1*11:01

18 peptides

YPAQIKVRWFRNDQ
FKAMCYFTNGTERV
PEDFVYQFKAMCYFT
VTDYFPAQIKVRWFR
LGLIFLGLGLIIHHR
LGLIIHRSQKGLLH
LGLGLIIHRSQKGL
GLGLIIHRSQKGLL
HNYQLELRTTLQRRV
GTERVRYVTRYIYNR
QILVMLEMTPQHGDV
TNGTERVRYVTRYIY
VYQFKAMCYFTNGTE
DVEVYRAVTPLGPPD
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*04:01

11 peptides

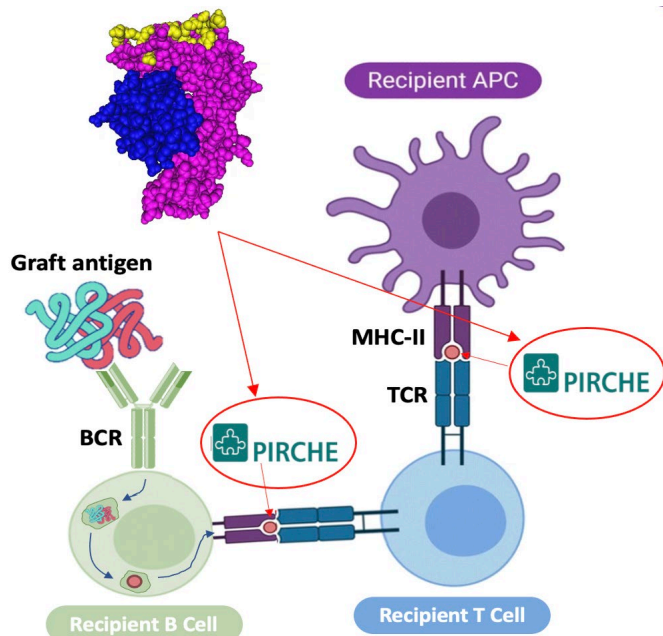
DFVYQFKAMCYFTNG
EDFVYQFKAMCYFTN
VTDYFPAQIKVRWFR
LGLIIHRSQKGLLH
GTERVRYVTRYIYNR
QILVMLEMTPQHGDV
DVEVYRAVTPLGPPD
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*03:01

9 peptides

RTRAELDTVCRHNYQ
FYPAQIKVRWFRNDQ
YARFDSDEVYRAV
VTDYFPAQIKVRWFR
LGLIIHRSQKGLLH
NYQLELRTTLQRRV
QILVMLEMTPQHGDV
GTERVRYVTRYIYNR
RHNYQLELRTTLQRR

RUOLO DELLA RESTRIZIONE MHC



DQ7-DERIVED T-CELL PEPTIDES RESTRICTED BY RECIPIENT'S HLA-DRB1

DRB1*01:01

31 peptides

RTEALNHNHLLVCSV
LLVCSVDFYPAQIK
RFDSDEVYRAVTP
VYQFKAMCYFTNGTE
PEDFVYQFKAMCYFT
VTDYPAQIKVRWFR
IFLGLGLIIHRSQK
HNLVCSVDFYPAQ
LGLIIHRSQKGLLH
KEVLERTRAELDTVC
FLGLGLIIHRSQK
VLGLIFLGLGLIIH
RTTLQRRVEPTVTIS
QLELRTTLQRRVEPT
MLSGIGGFVLGLIFL
ILVMLEMTPQHGDVY
QSKMLSGIGGFVLGL
DTVCRHNYQLELRTT
GTERVYVTRYIYNR
SAQSKMLSGIGGFVL
QEETGVSTPLIRN
LDTVCRHNYQLELRT
QKEVLERTRAELDTV
LVCSVDFYPAQIKV
YRAVTPLGPPDAEYV
EDFVYQFKAMCYFTN
FDSDDEVYRAVTP
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*15:01

22 peptides

QFKAMCYFTNGTERV
FYPAQIKVRWFRNDQ
YQFKAMCYFTNGTER
RDSPEDFVYQFKAMC
VTDYPAQIKVRWFR
LGLIIHRSQKGLLH
LGLIFLGLGLIIHHR
LGLIIHRSQKGLLH
LGLIIHRSQKGLLH
GLGLIIHRSQKGLLH
HNYQLELRTTLQRRV
GTERVYVTRYIYNR
SKMLSGIGGFVLGLI
FKAMCYFTNGTERV
QSKMLSGIGGFVLGL
GTERVYVTRYIYNR
QILVMLEMTPQHGDV
ERVYVTRYIYNREE
LVCSVDFYPAQIKV
EDFVYQFKAMCYFTN
VEVYRAVTPLGPPDA
VTRYIYNREEYARF
RHNYQLELRTTLQRR
RVRYVTRYIYNREEY

DRB1*11:01

18 peptides

YPAQIKVRWFRNDQ
FKAMCYFTNGTERV
PEDFVYQFKAMCYFT
VTDYPAQIKVRWFR
LGLIFLGLGLIIHHR
LGLIIHRSQKGLLH
LGLIIHRSQKGLLH
LGLIIHRSQKGLLH
LGLIIHRSQKGLLH
GLGLIIHRSQKGLLH
HNYQLELRTTLQRRV
GTERVYVTRYIYNR
QILVMLEMTPQHGDV
TNGTERVYVTRYIY
VYQFKAMCYFTNGTE
DVEVYRAVTPLGPPD
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*04:01

11 peptides

DFVYQFKAMCYFTNG
EDFVYQFKAMCYFTN
VTDYPAQIKVRWFR
LGLIIHRSQKGLLH
GTERVYVTRYIYNR
QILVMLEMTPQHGDV
DVEVYRAVTPLGPPD
VTRYIYNREEYARF
RHNYQLELRTTLQRR
VEVYRAVTPLGPPDA
RVRYVTRYIYNREEY

DRB1*03:01

9 peptides

RTRAELDTVCRHNYQ
FYPAQIKVRWFRNDQ
YARFDSDEVYRAV
VTDYPAQIKVRWFR
LGLIIHRSQKGLLH
NYQLELRTTLQRRV
QILVMLEMTPQHGDV
GTERVYVTRYIYNR
RHNYQLELRTTLQRR

BASSA PROBABILITÀ
DI ATTIVAZIONE

ALTA PROBABILITÀ DI ATTIVAZIONE

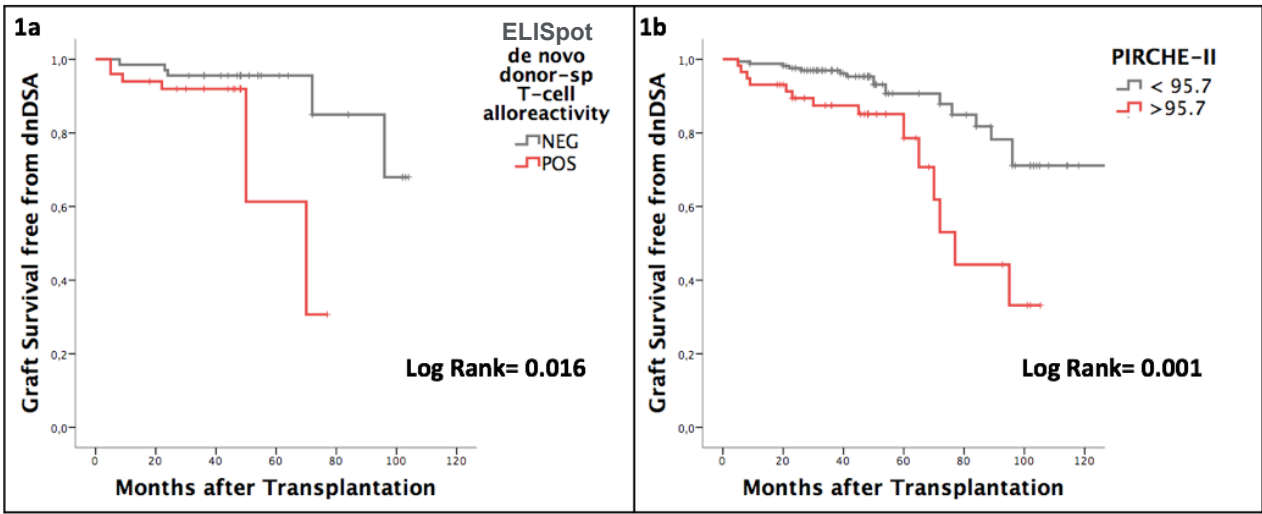
RISPOSTA ALLOIMMUNE PRIMARIA: cellule CD4

Donor-Recipient HLA Mismatched Peptides
Calculated by PIRCHE Algorithm Associate with De
Novo Donor-Specific Cellular and Humoral
Alloreactivity and Predicts Inferior Graft Outcome

M. Meneghini¹, E. Crespo², M. Niemann³, A. Torija², E. Melillo⁴, M. Jarque², N. Montero⁴, J. Cruzado³,
J. Grinyo⁵, O. Bestard¹

La differenza molecolare al livello delle cellule CD4
é un biomarker prognostico per il rigetto degli organi

N = 266

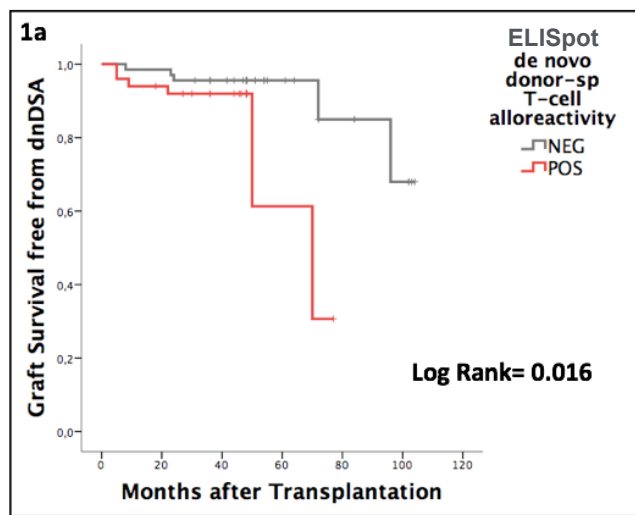


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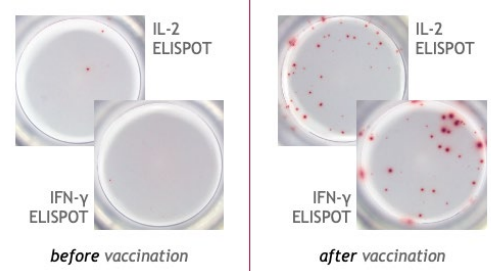
N = 266



La differenza molecolare al livello delle cellule CD4
é un biomarker prognostico per il rigetto degli organi

Enzyme-linked immune absorbent spot (Elispot) is a quantitative method for measuring relevant parameters of T cell activation. The sensitivity of Elispot allows the detection of low-frequency antigen-specific T cells that secrete cytokines and effector molecules, such as granzyme B and perforin.

CTL monitoring by Elispot is a gold standard for the evaluation of antigen-specific T cell immunity in clinical trials and vaccine candidates where the ability to detect rare antigen-specific T cells is of relevance for immune diagnostic.



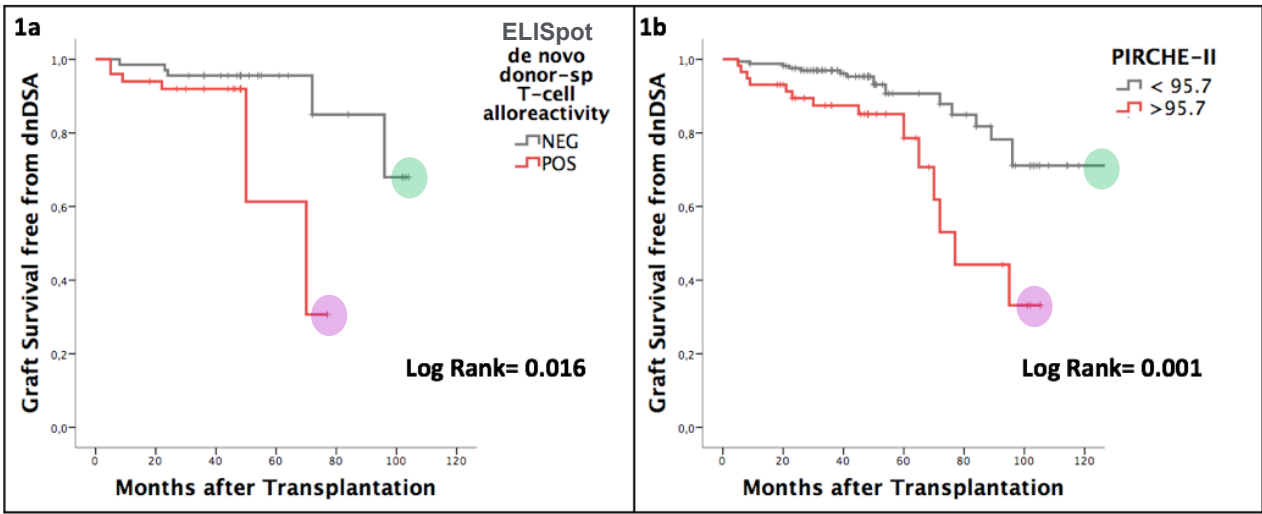
RISPOSTA ALLOIMMUNE PRIMARIA: cellule CD4

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La differenza molecolare al livello delle cellule CD4
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N = 266



PIRCHE-II può essere usato come un test in-silico per l'attivazione delle cellule T

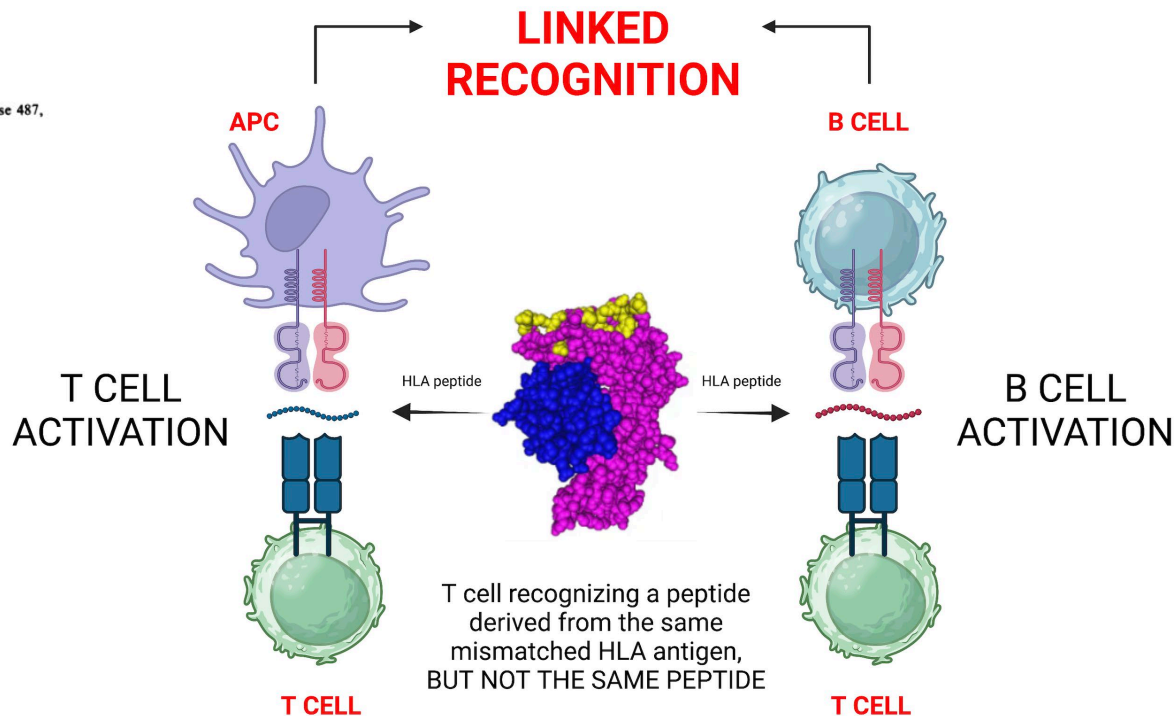
COOPERAZIONE CELLULARE T/B

NATURE VOL. 314 11 APRIL 1985

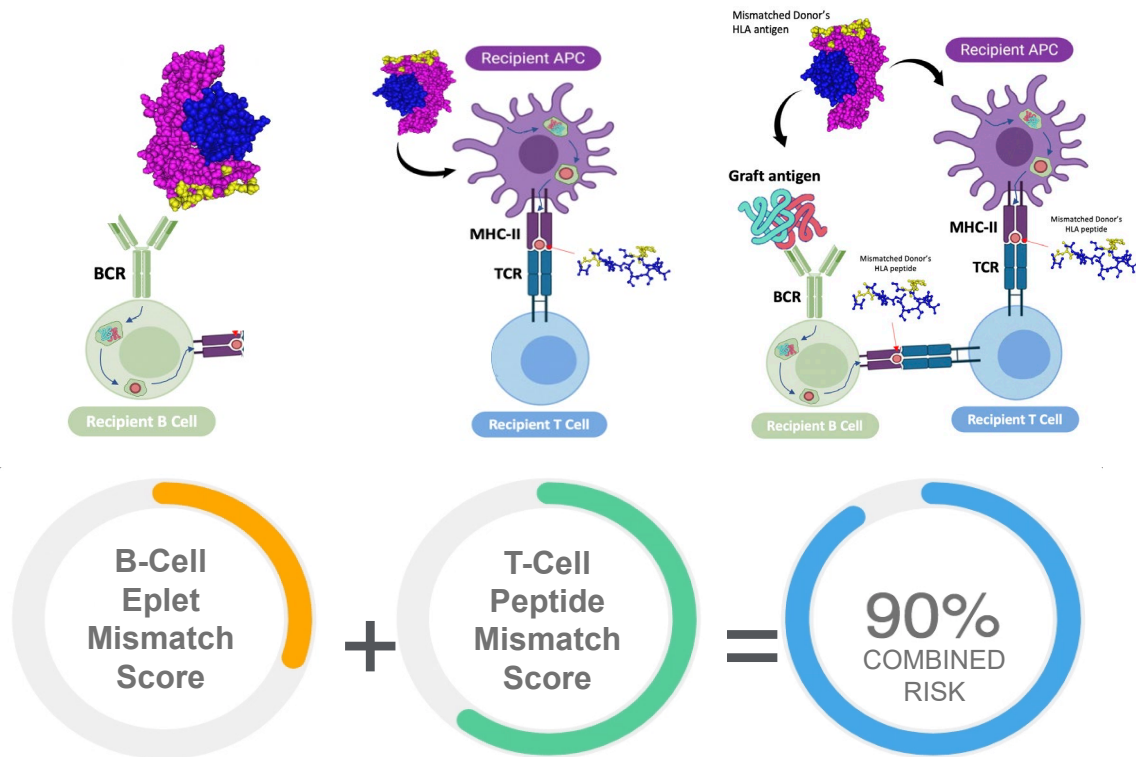
Antigen-specific interaction between T and B cells

Antonio Lanzavecchia

Basel Institute for Immunology, Grenzacherstrasse 487,
Postfach CH-4005, Basel, Switzerland



COMBINED T/B MOLECULAR MISMATCH



The Journal of
Heart and Lung Transplantation

The Official Publication of the International Society for Heart and Lung Transplantation

VOLUME 41, ISSUE 7, P952-960, JULY 01, 2022

01

ORIGINAL CLINICAL SCIENCE

Immunologic risk stratification of pediatric heart transplant patients by combining HLAMatchmaker and PIRCHE-II

Massimo Mangiola, PhD,^{a,1} Mitchell A. Ellison, PhD,^{b,1} Marilyn Marrari, MS,^c Carol Bentlejewski, MS,^c John Sadowski, MS,^b Dwayne Zern, MS,^b Matthias Niemann, MS,^d Brian Feingold, MD,^e Steve A. Webber, MD,^f and Adriana Zeevi, PhD^c, CTOTC-09 site investigators^g

frontiers | Frontiers in Immunology

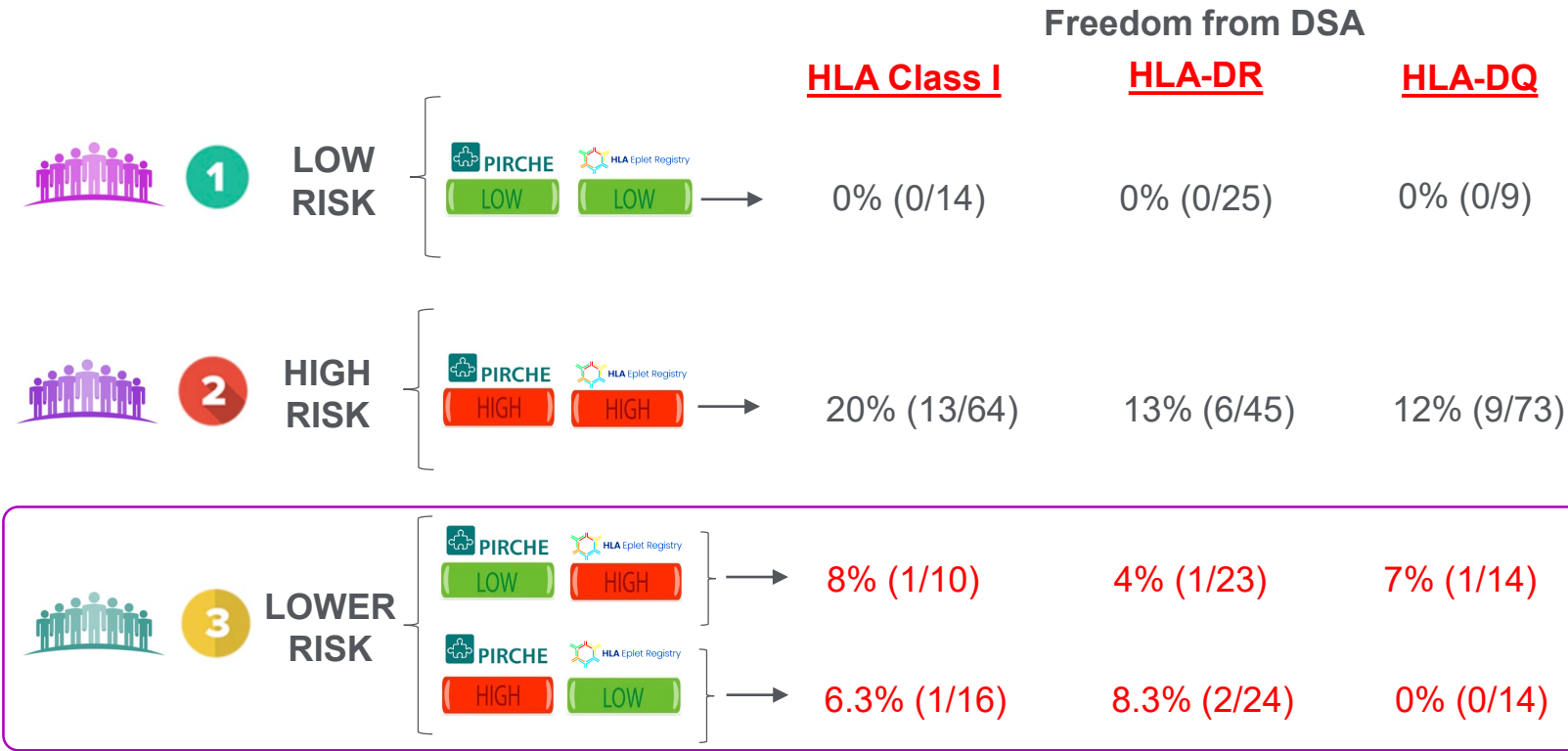
10.3389/fimmu.2023.1110292

02

Immunologic risk stratification of pediatric heart transplant patients by combining HLA-EMMA and PIRCHE-II

M. Ellison^{1*}, M. Mangiola², M. Marrari³, C. Bentlejewski³, J. Sadowski², D. Zern¹, Cynthia Silvia Maria Kramer⁴, S. Heidt⁴, M. Niemann⁵, Q. Xu³, A. I. Dipchand⁶, W. T. Mahle⁷, J. W. Rossano⁸, C. E. Canter⁹, T. P. Singh¹⁰, W. A. Zuckerman¹¹, D. T. Hsu¹², B. Feingold¹³, S. A. Webber¹⁴ and A. Zeevi³

COMBINED T/B MOLECULAR MISMATCH



COMPATIBILITÀ MOLECOLARE

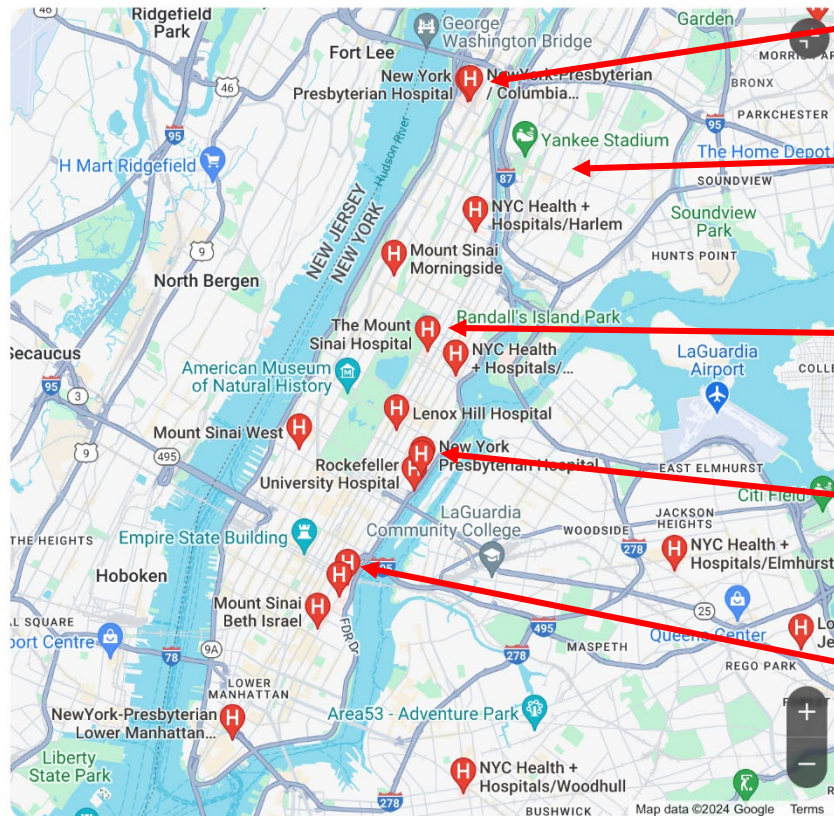
applicazione nei trapianti di organi

SELEZIONE DEL DONATORE

5 Centri Trapianti
nell'isola di Manhattan

8 Centri Trapianti
in NYC e periferia

17 Centri Trapianti
nel raggio di 160 km
da Manhattan



 **COLUMBIA**
COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER

Montefiore
HEALTH SYSTEM

 **Mount
Sinai
Hospital**

 **NewYork-Presbyterian**
The University Hospital of Columbia and Cornell

 **NYU Langone
Health**

SELEZIONE DEL DONATORE

DONATORI VIVENTI

[About](#)[For DONORS](#)[For PATIENTS](#)[For CENTERS](#)[Media](#)[Center Login](#)

Improving Living Kidney Donation & Transplantation

The National Kidney Registry is dedicated to increasing living kidney donation, ensuring better donor-recipient matches, and providing comprehensive support and protections for living donors.

[I need a kidney transplant](#)[I am considering donating my kidney](#)

9,316

*NKR-Facilitated
Transplants*

Why the National Kidney Registry:



Assistance, support and protections for living donors through **Donor Shield**



Resources for patients and their champions through **FindAKidney.org**



Better donor-recipient matches through the **Kidney for Life** initiative



Donor Care Network transplant centers that meet rigorous standards for excellence

ACTION CENTER

DONORS

RECIPIENTS

BILLING

REPORTS

SETTINGS

Donor Pre-Select

Voucher Holders

Recipients

NEW! Recipients

Recipient [PM9956746]

Import Waitlist

Patient Intake

List

Order Bulk Cheek Swabs

Add

NEW! Add

OLD Edit Recipient [PM9956746]

Edit Recipient [PM9956746]

Toolbox

Potential Donors [PM9956746]

Accepted 0

Preferred 1

Non-Preferred 203

Bio Matches 204

Zero PMP 35

ABO Incompatible 61

Avoid Conflict 0

All 306

Recipient: PM9956746

ABO: A

Age: 57

Avoids: 0

PMPc: 0

CPRA4: 0

EWT: 1 (D/R: 0%)

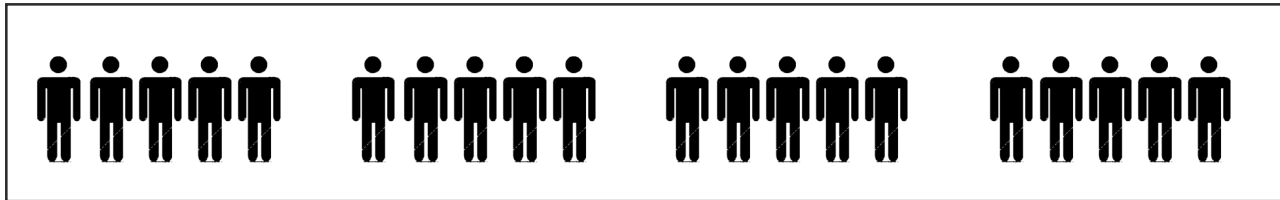
☐	Donor Center	Donor Alias	PMPc	State	ABO	Age	Wt	Lat	CC	E	C	HLA	LKDPI	plet MM	Allele M	Avoids	Notes	Match	Status	Review?	
☐	NYU	MM16794370		NY	O	28	0	—	0	⊖	⊖	0		MED	4/8	0			N/A		
☐	UCSF	D61952AA	88	CA	A?	29	79	L1	138	+	⊖	70	-31	LOW	2/8	0			Pending	--	Actions ▾
☐	StLouis	KRU12887	n/a	MO	O	37	111	L1(R)	173	+	+	50	-34	LOW	1/8	0			Pending	--	Actions ▾
☐	MayoAZ	AZJM1960	220.3	AZ	O	64	98	R1	93	+	⊖	50	11	LOW	1/8	0			Pending	--	Actions ▾
☐	Inova	02731117T	27.9	VA	O	41	88	L2	98	+	+	50	26	LOW	1/8	0			Pending	--	Actions ▾
☐	UCI	3505299CC	20.8	CA	O	41	89	L1	89	+	+	50	-3	LOW	1/8	0			Pending	--	Actions ▾
☐	MercyStMarys	BG01191979	n/a	MI	O	45	88	L1	106	+	+	45	-18	MED	2/8	0			Pending	--	Actions ▾
☐	UMiss	AF44336393	32.9	MS	A1	43	56	L2	107	+	+	35	20	MED	2/8	0			Pending	--	Actions ▾
☐	Inova	02600203R	26.2	VA	A2	53	68	L2	128	+	+	50	0	MED	2/8	0			Pending	--	Actions ▾
☐	Intermtn	MCFKEVDON	7	UT	A?	38	95	L2	145	⊖	⊖	35	3	MED	2/8	0			Pending	--	Actions ▾
☐	Chicago	AVI5333079	156.1	IL	A1	45	80	L1	132	+	+	40	-7	MED	2/8	0			Pending	--	Actions ▾
☐	UKentucky	LMT8225	80.7	KY	A1	53	78	L2	126	+	⊖	0	18	MED	1/8	0			Pending	--	Actions ▾
☐	Intermtn	RIGTAYDON	3.3	UT	A1	44	64	L2(R)	97	+	+	35	10	MED	2/8	0			Pending	--	Actions ▾

SELEZIONE DEL DONATORE

DONATORI VIVENTI

DONATORI ACCETTABILI

selezionati a random senza compatibilità molecolare

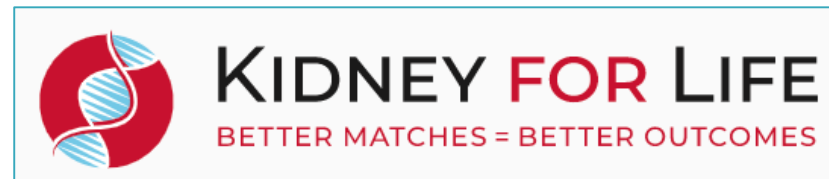
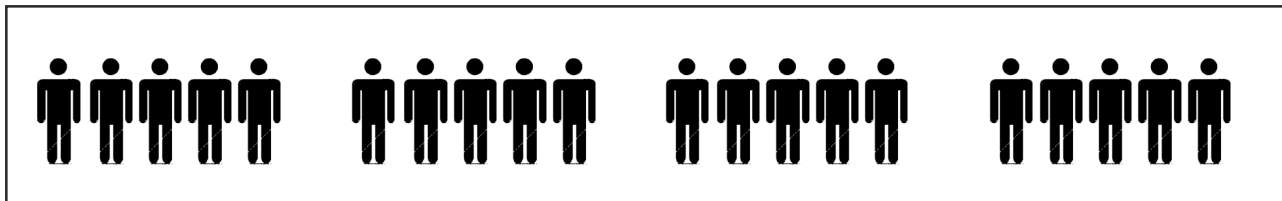


SELEZIONE DEL DONATORE

DONATORI VIVENTI

DONATORI ACCETTABILI

selezionati a random senza compatibilità molecolare



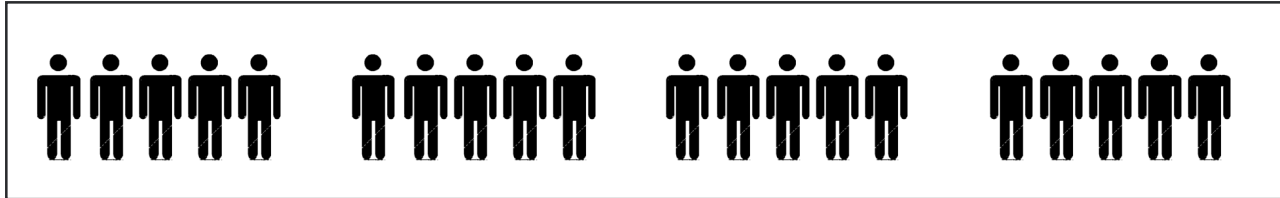
SELEZIONE DEL DONATORE

DONATORI VIVENTI



DONATORI ACCETTABILI

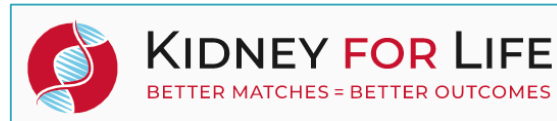
selezionati a random senza compatibilità molecolare



**I DONATORI POTENZIALI SONO SELEZIONATI CON GLI
STESSI CRITERI DI SEMPRE**
(accettabili dal punto di vista sociale, medico, e chirurgico)

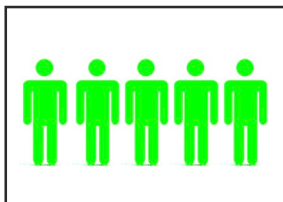
SELEZIONE DEL DONATORE

DONATORI VIVENTI

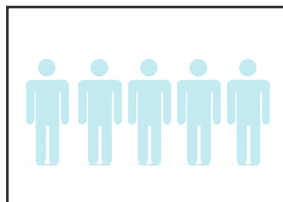


DONATORI ACCETTABILI

I donatori accettabili sono divisi in categorie di compatibilità molecolare



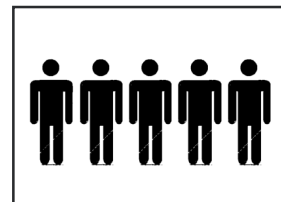
ZERO
Eplet Mismatch



LOW
Eplet Mismatch



MODERATE
Eplet Mismatch



HIGH
Eplet Mismatch

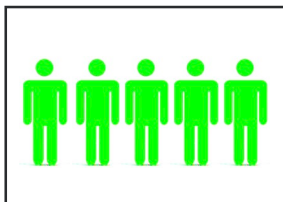


SELEZIONE DEL DONATORE

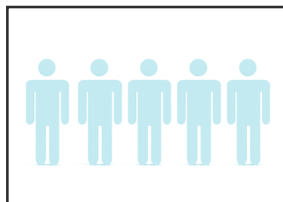
DONATORI VIVENTI

DONATORI ACCETTABILI

I donatori con ALTA compatibilità molecolare vengono selezionati per il trapianto



ZERO
Eplet Mismatch



LOW
Eplet Mismatch



MODERATE
Eplet Mismatch



HIGH
Eplet Mismatch

DONATORI "PREFERITI"

per ingegnerizzare trapianti a basso rischio di rigetto

 ACTION CENTER

 DONORS

 RECIPIENTS

 BILLING

 REPORTS

 SETTINGS

Donor Pre-Select

Voucher Holders

Recipients

NEW! Recipients

Recipient [PM9956746]

Import Waitlist

Patient Intake

List

Order Bulk Cheek Swabs

Add

NEW! Add

OLD Edit Recipient [PM9956746]

Edit Recipient [PM9956746]

Toolbox

Potential Donors [PM9956746]

Accepted 0

Preferred 1

Non-Preferred 203

Bio Matches 204

Zero PMP 35

ABO Incompatible 61

Avoid Conflict 0

All 306

Recipient: PM9956746

ABO: A

Age: 57

Avoids: 0

PMPc: 0

CPRA4: 0

EWT: 1 (D/R: 0%)

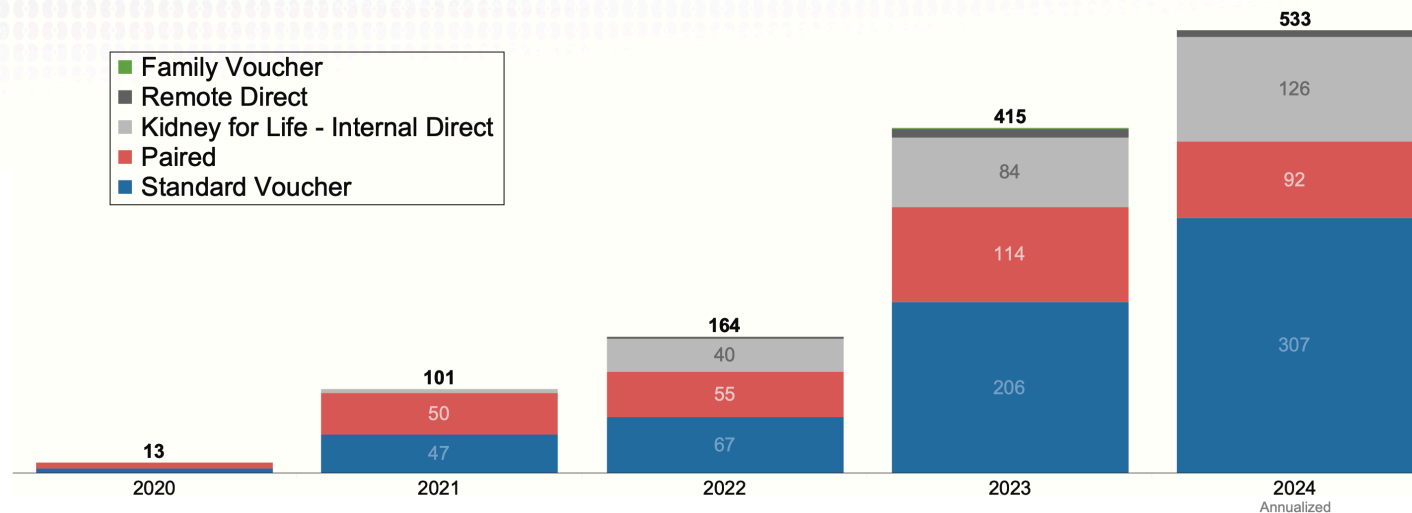
☐	Donor Center	Donor Alias	PMPc	State	ABO	Age	Wt	Lat	CC	E	C	HLA	LKDPI	Epit	MM	Allele M	Avoids	Notes	Match	Status	Review?	
☐	NYU	MM16794370		NY	O	28	0	—	0	⊖	⊖	0			MED	4/8	0			N/A		
☐	UCSF	D61952AA	88	CA	A?	29	79	L1	138	+	⊖	70	-31		LOW	2/8	0			Pending	--	Actions ▾
☐	StLouis	KRU12887	n/a	MO	O	37	111	L1(R)	173	+	+	50	-34		LOW	1/8	0			Pending	--	Actions ▾
☐	MayoAZ	AZJM1960	220.3	AZ	O	64	98	R1	93	+	⊖	50	11		LOW	1/8	0			Pending	--	Actions ▾
☐	Inova	02731117T	27.9	VA	O	41	88	L2	98	+	+	50	26		LOW	1/8	0			Pending	--	Actions ▾
☐	UCI	3505299CC	20.8	CA	O	41	89	L1	89	+	+	50	-3		LOW	1/8	0			Pending	--	Actions ▾
☐	MercyStMarys	BG01191979	n/a	MI	O	45	88	L1	106	+	+	45	-18		MED	2/8	0			Pending	--	Actions ▾
☐	UMiss	AF44336393	32.9	MS	A1	43	56	L2	107	+	+	35	20		MED	2/8	0			Pending	--	Actions ▾
☐	Inova	02600203R	26.2	VA	A2	53	68	L2	128	+	+	50	0		MED	2/8	0			Pending	--	Actions ▾
☐	Intermtn	MCFKEVDON	7	UT	A?	38	95	L2	145	⊖	⊖	35	3		MED	2/8	0			Pending	--	Actions ▾
☐	Chicago	AVI5333079	156.1	IL	A1	45	80	L1	132	+	+	40	-7		MED	2/8	0			Pending	--	Actions ▾
☐	UKentucky	LMT8225	80.7	KY	A1	53	78	L2	126	+	⊖	0	18		MED	1/8	0			Pending	--	Actions ▾
☐	Intermtn	RIGTAYDON	3.3	UT	A1	44	64	L2(R)	97	+	+	35	10		MED	2/8	0			Pending	--	Actions ▾

SELEZIONE DEL DONATORE

DONATORI VIVENTI

Low Eplet Mismatch Transplants

Compatible and Incompatible



Excludes waitlist.

As of 6/30/2024

Kidney for Life is an NKR initiative to provide opportunities for better donor matches.

Eplet mismatch categories are based on the definition provided by Wiebe C, Kosmoliaptis V, Pochinco D, et al. HLA-DR/DQ molecular mismatch: a prognostic biomarker for primary alloimmunity.

Am J Transplant. 2019;19:1708–1719. <https://doi.org/10.1111/ajt.15177>

SELEZIONE DEL DONATORE

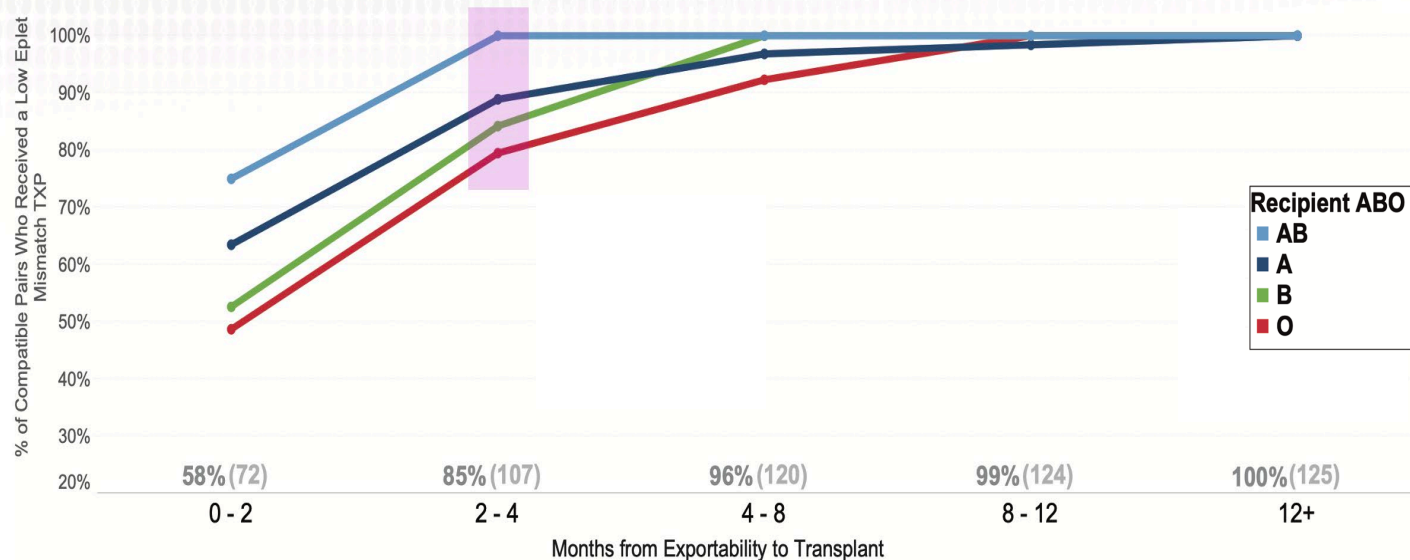
DONATORI VIVENTI



KIDNEY FOR LIFE
BETTER MATCHES = BETTER OUTCOMES

Actual Wait Times To Transplant

Compatible Pairs Who Received a Low Eplet Mismatch Transplant Total



Excludes KFL internal direct. Last 12 months to date. cPRA ≤ 99
As of 6/30/2024

SELEZIONE DEL DONATORE

DONATORI DECEDUTI

**L'APPLICAZIONE DELLA COMPATIBILITÀ MOLECOLARE
NON É POSSIBILE (1 organo/tanti pazienti)**

SELEZIONE DEL DONATORE

DONATORI DECEDUTI

L'APPLICAZIONE DELLA COMPATIBILITÀ MOLECOLARE NON É POSSIBILE (1 organo/tanti pazienti)



National Institutes
of Health

NIH grant per studiare l'impatto della compatibilità molecolare
nelle offerte di organi nel Sistema Nazionale dei Trapianti (UNOS)

- Fattibilità
- Equità
- Utilità (longevità degli organi)

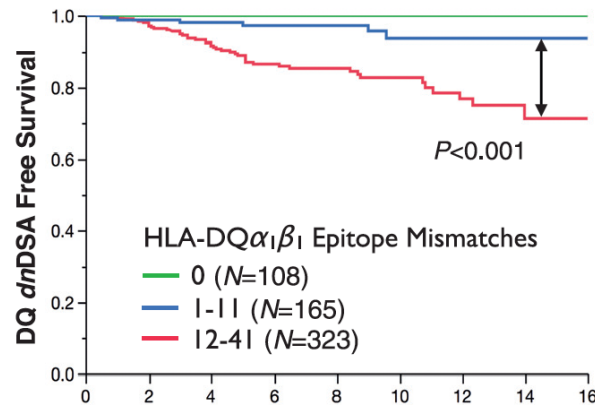
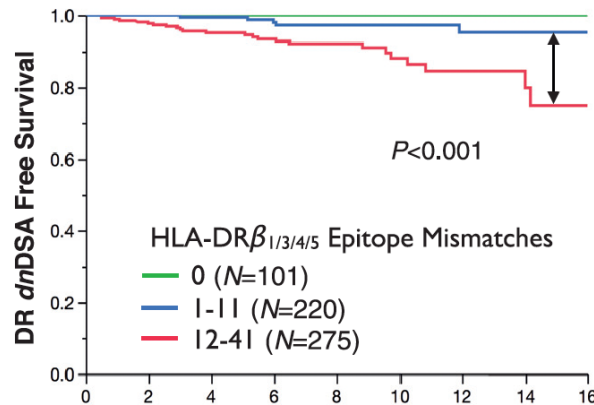
SELEZIONE DEL DONATORE

DONATORI DECEDUTI

J Am Soc Nephrol 28: 3353–3362, 2017. doi: <https://doi.org/10.1681/ASN.2017030287>

Class II Eplet Mismatch Modulates Tacrolimus Trough Levels Required to Prevent Donor-Specific Antibody Development

Chris Wiebe,^{*,†} David N. Rush,^{*} Thomas E. Nevins,[‡] Patricia E. Birk,[§] Tom Blydt-Hansen,^{||} Ian W. Gibson,^{†¶} Aviva Goldberg,[§] Julie Ho,^{***} Martin Karpinski,^{*} Denise Pochinco,[†] Atul Sharma,[§] Leroy Storsley,^{*} Arthur J. Matas,^{††} and Peter W. Nickerson^{*,†**}



Pazienti trapiantati con donatori ad alta compatibilità molecolare non hanno sviluppano anticorpi anche quando il livello di Tacrolimus era <2.5 ng/mL per almeno il 75% delle osservazioni

High Risk

HLA-DR or HLA-DQ >11 epMM

Low Risk

HLA-DR and HLA-DQ ≤11 epMM

SELEZIONE DEL DONATORE

DONATORI DECEDUTI

J Am Soc Nephrol 28: 3353–3362, 2017. doi: <https://doi.org/10.1681/ASN.2017030287>

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Pazienti trapiantati con donatori ad alta compatibilità molecolare non hanno sviluppano anticorpi anche quando il livello di Tacrolimus era <2.5 ng/mL per almeno il 75% delle osservazioni

**E' POSSIBILE ABBASSARE
L'IMMUNOSOPPRESSIONE
SENZA CAUSARE IL RIGETTO
DELL'ORGANO ?**

SELEZIONE DEL DONATORE

DONATORI DECEDUTI

L'APPLICAZIONE DELLA COMPATIBILITÀ MOLECOLARE NON É POSSIBILE (1 organo/tanti pazienti)



LIVING & DECEASED
KIDNEY DONORS
(single center study)



RIDUZIONE DELLA TERAPIA DI
IMMUNOSOPPRESSIONE
PER ZERO/LOW DR/DQ epMM

Planning Phase



LIVING KIDNEY DONORS
(multi-center study)

RIDUZIONE O ELIMINAZIONE DELLA
TERAPIA DI IMMUNOSOPPRESSIONE
PER ZERO/LOW DR/DQ epMM

SELEZIONE DEL DONATORE

DONATORI DECEDUTI



LIVING & DECEASED
KIDNEY DONORS
(single center study)



RIDUZIONE DELLA TERAPIA DI
IMMUNOSOPPRESSIONE
PER ZERO/LOW DR/DQ epMM



Dr. Bonnie Lonze, MD
(Chirurgia)

Massimo, non ti
dimenticare di dire che
questi sono dati
DAVVERO preliminari !

SELEZIONE DEL DONATORE

DONATORI DECEDUTI



LIVING & DECEASED
KIDNEY DONORS
(single center study)



RIDUZIONE DELLA TERAPIA DI
IMMUNOSOPPRESSIONE
PER ZERO/LOW DR/DQ epMM

44 PAZIENTI

(106 per completare lo studio)

6 ZERO
DR/DQ epMM

18 LOW
DR/DQ epMM

17 MODERATE
DR/DQ epMM

3 HIGH
DR/DQ epMM

RIDUZIONE DELLA TERAPIA
DOPO 90 GIORNI

Tacrolimus (5-6 ng/mL)

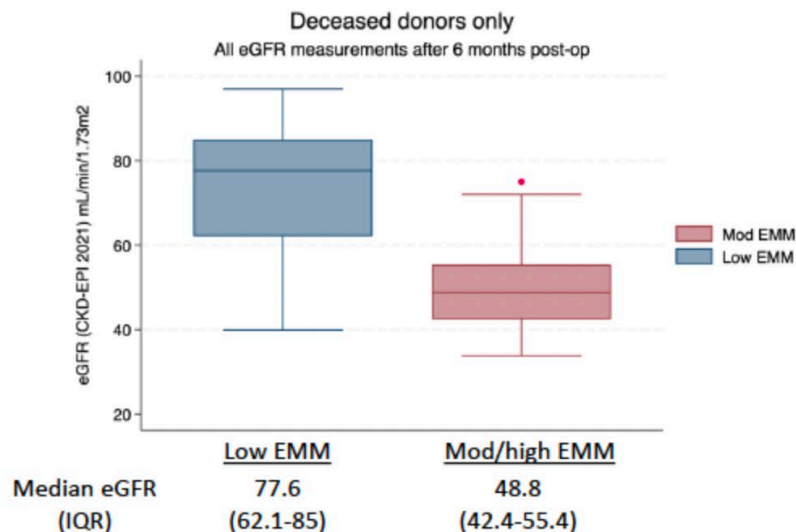
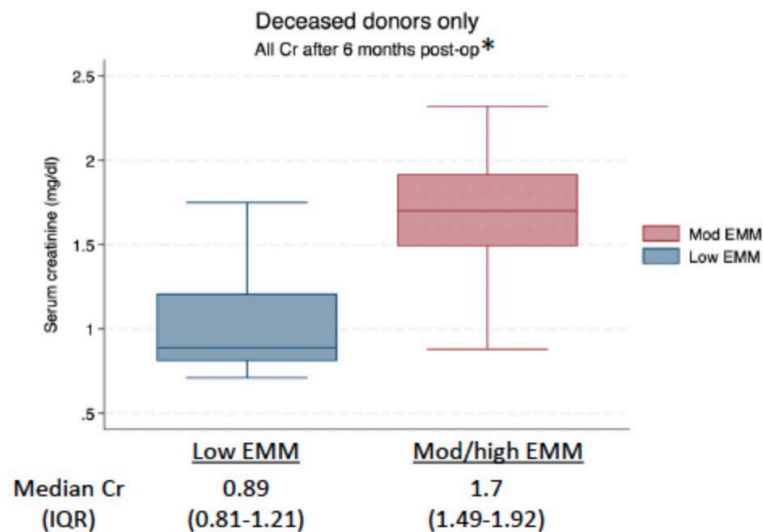
TERAPIA STANDARD

Tacrolimus (8-12 ng/mL)



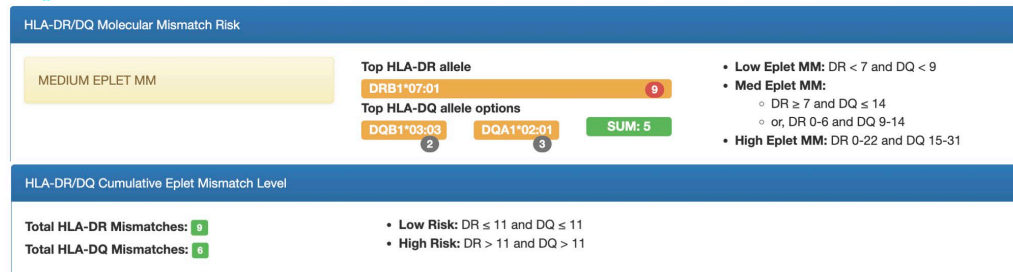
SELEZIONE DEL DONATORE

DONATORI DECEDUTI



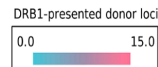
*excludes 3 patients who transitioned to bela (1 in low EMM group, 2 in mod/high EMM group)

Il VERO Viaggio del Trapianto

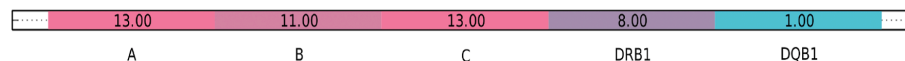


PIRCHE

Matching heatmap (DRB1 presentation)



PIRCHE-II Score: 44.00

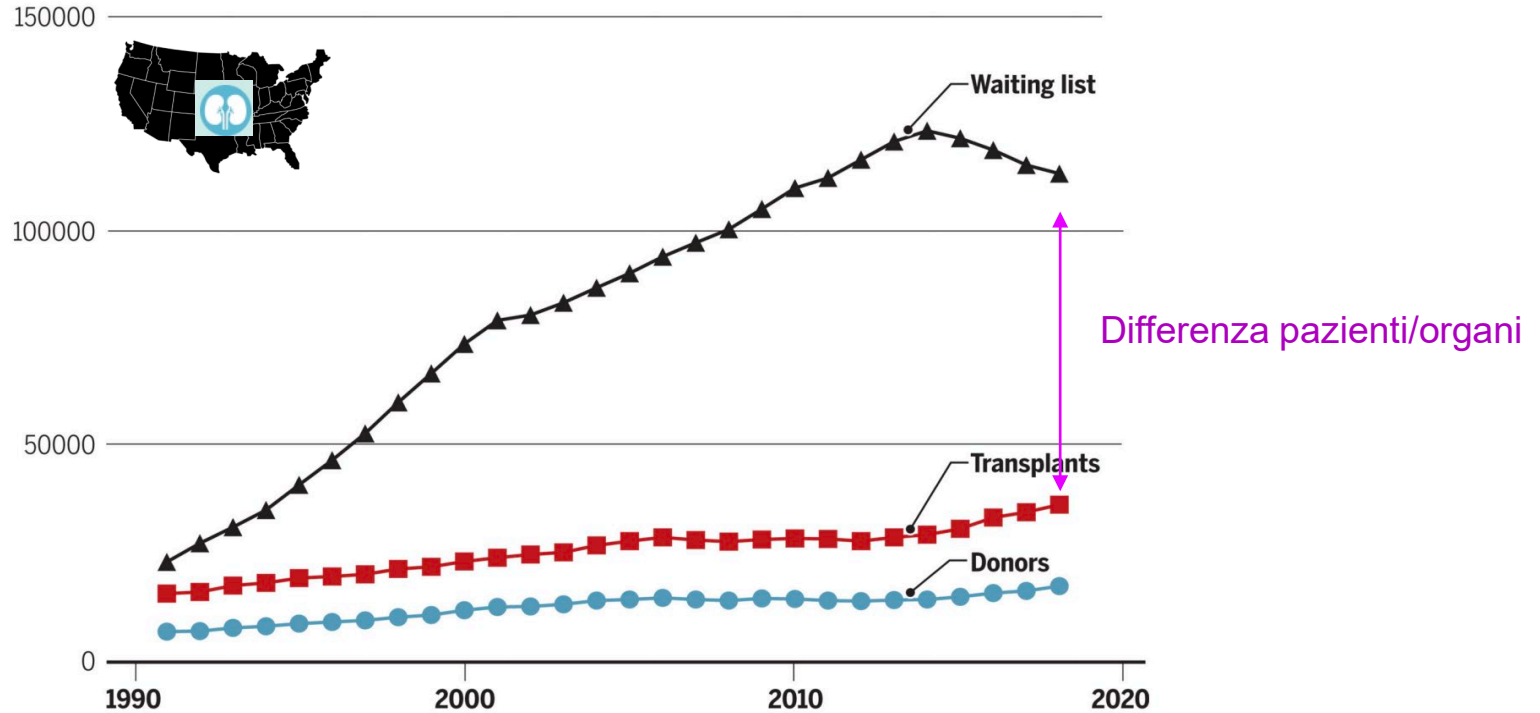


REAL TRANSPLANT JOURNEY

XENOTRAPIANTI

una nuova possibile risorsa di organi

PERCHE' XENOTRAPIANTI ?



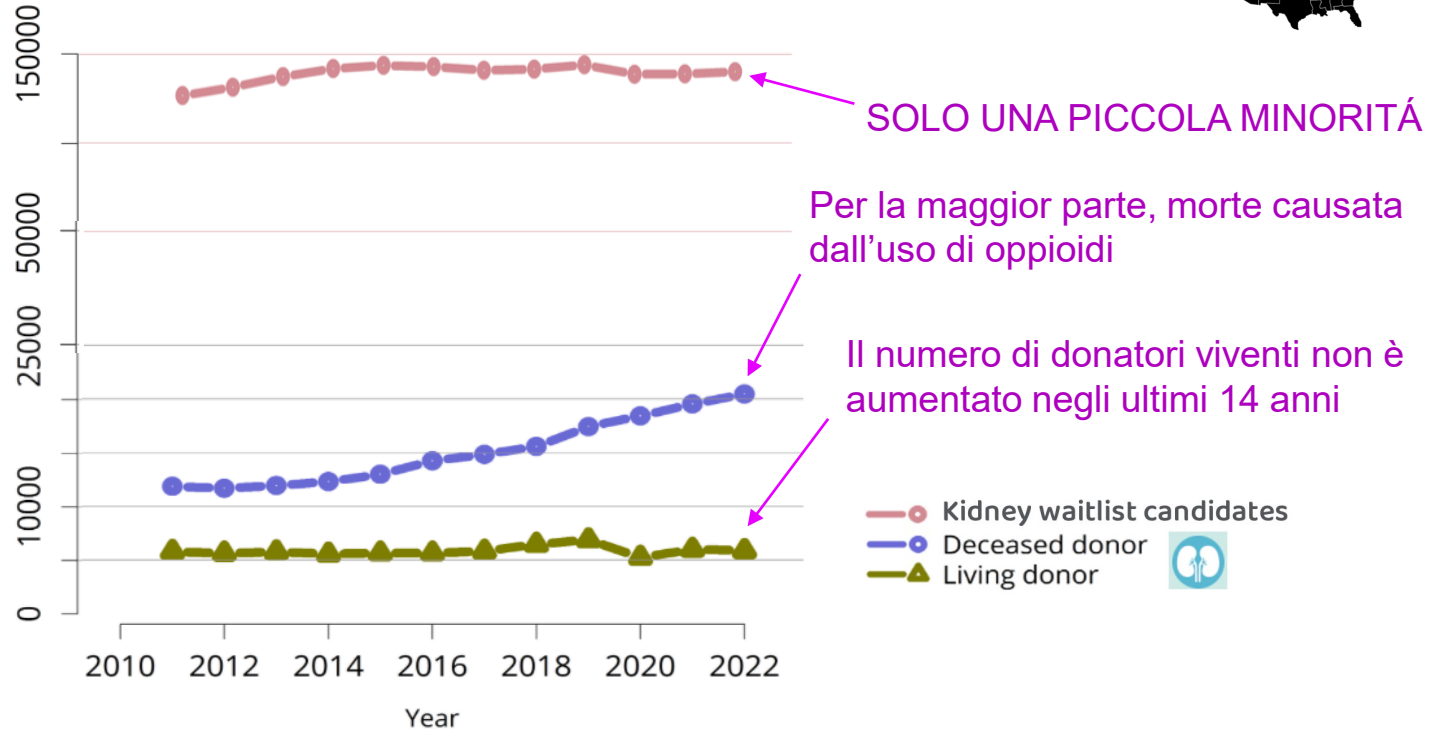
From: UNOS Database, 2019

TRAPIANTI DI ORGANI: IL PROBLEMA

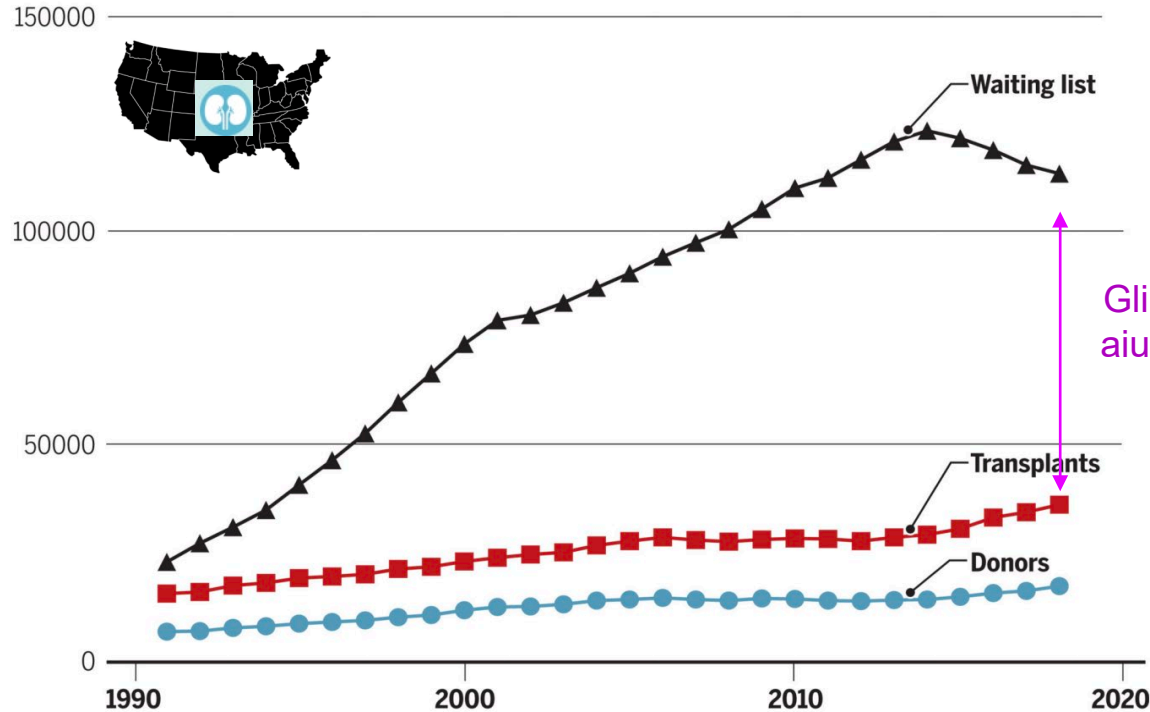
Adapted from:



SCIENTIFIC REGISTRY OF
TRANSPLANT RECIPIENTS



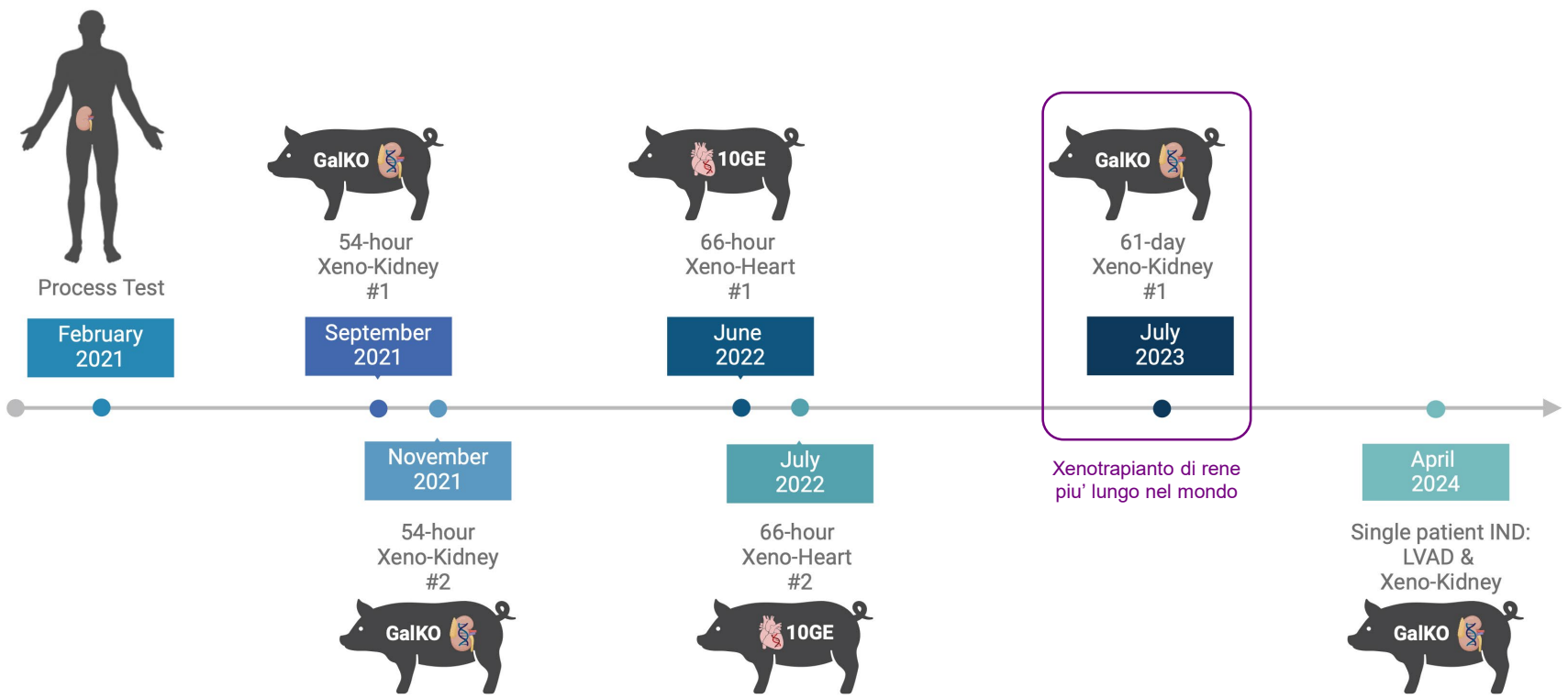
PERCHE' XENOTRAPIANTI ?



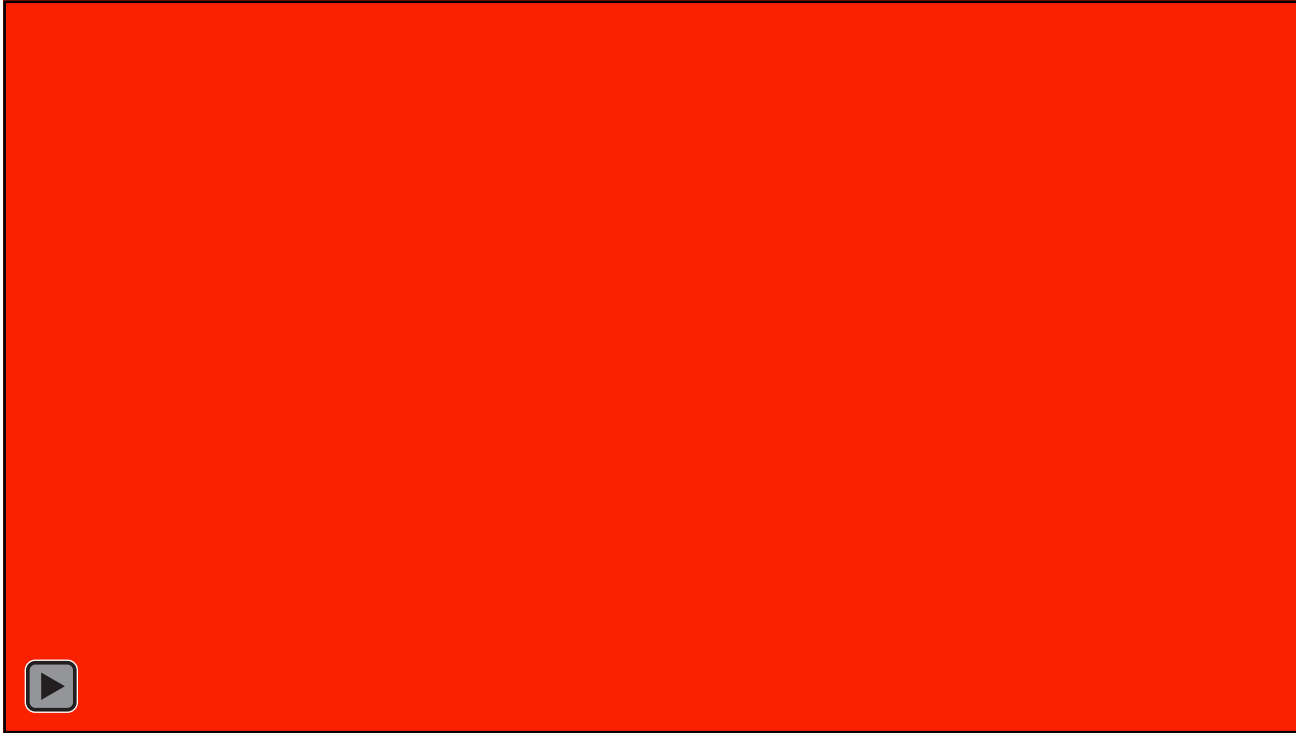
Gli organi di maiale possono aiutare a ridurre la differenza pazienti/organi

From: UNOS Database, 2019

PIG TO HUMAN XENOTRANSPLANTS AT NYU



THE "DECEDENT" MODEL



THE "DECEDENT" MODEL



Designated Xenotransplant Operating Room

THE "DECEDENT" MODEL

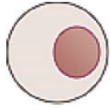


Designated Surgical Intensive Care Unit & Isolation Room

IMMUNOLOGIA DEI XENOTRAPIANTI

BARRIERE E CONSIDERAZIONI CLINCHE

BARRIERE IMMUNOLOGICHE

TYPE OF REJECTION	KEY IMMUNOLOGICAL PLAYERS	POSSIBLE STRATEGIES	TYPE OF REJECTION	KEY IMMUNOLOGICAL PLAYERS	POSSIBLE STRATEGIES
INNATE IMMUNITY	Complement	- Genetically engineered pigs (e.g. hCD55, hCD46, hCD59) - Soluble complement inhibitor (e.g. C1-inhibitor, Compstatin, Cp4, eculizumab) - Cobra Venom Factor	ADAPTIVE IMMUNITY	B-Lymphocytes	- Genetically engineered pigs (e.g. GalT-KO, CMAH-KO) - Soluble polymers (e.g. Gas914) - Immunosuppressive agents (e.g. anti-CD19, anti-CD20, bortezomib, BAFF/APRIL inhibitors) - B-cell tolerance
	Neutrophils	C3-complement inhibitors (e.g. Cp40)			
	NK Cells	Genetically engineered pigs (e.g. HLA-G, HLA-E/beta2 microglobulin)		T-Lymphocytes	- Genetically engineered pigs (e.g. CIITA-DN, MHC I-KO, CTLA4-Ig) - Immunosuppressive agents (e.g. ATG, CNl) - Co-stimulatory blockers (e.g. anti-CD154, anti-CD40, CTLA4-Ig) - T-cell tolerance / Tregs
	Macrophages	- Genetically engineered pigs (e.g. hCD47, hSIRPa) - Inhibitory receptor agonists (e.g. CD200-Ig)			

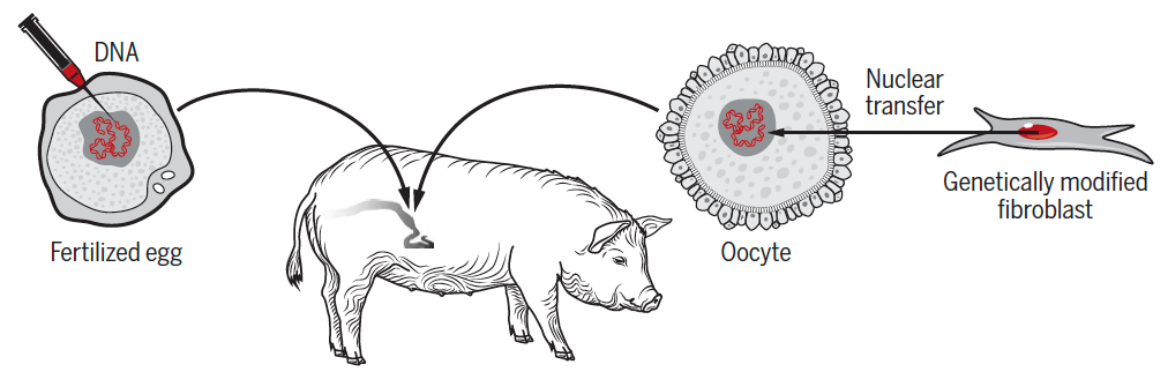
REVIEW ARTICLE

The immunological barriers to xenotransplantation

M. Vadori¹ & E. Cozzi^{1,2}

¹ CORIT (Consortium for Research in Organ Transplantation), Via dell'Università 10, 35020 Legnaro Padua, Italy
² Transplant Immunology Unit, Department of Transfusion Medicine, Padua University Hospital, Via Giustiniani, 2, 35128 Padua, Italy

MODIFICAZIONI GENETICHE



Transgenics		Knockouts
Complement inhibition	Immunosuppressive molecules	α 1,3-galactosyltransferase
hDAF	Anti-CD2	CMAH
hCD46	CTLA4Ig	B4GalNT2
hCD59	hCD47	vWF
Coagulation inhibition	PERV siRNA	PERVs
hCD39	MHC genes	
Human thrombomodulin	Class I (NK inhibition)	
Anti-inflammatory genes		
HO-1		
A20		

SCIENCE IMMUNOLOGY | REVIEW

XENOTRANSPLANTATION

Transplanting organs from pigs to humans

Megan Sykes^{1,2,3*} and David H. Sachs^{1,3}

GENETICS OF PIGS (knockouts/transgenes)



Gene KO: **GTKO**

Enzyme: α 1,3-galactosyltransferase

Carbohydrate: Galactose- α 1.3-galactose (α Gal)

GENETICS OF PIGS (knockouts/transgenes)



Gene KO: **GTKO**

Enzyme: α 1,3-galactosyltransferase

Carbohydrate: Galactose- α 1.3-galactose (**α GAL**)

- Circa l'1% degli anticorpi espressi sono anti- α GAL
- Gli anticorpi anti- α GAL causano un rigetto hyper-acuto

0041-1337/93/5606-1433\$03.00/0
TRANSPLANTATION
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Vol. 56, 1433-1442, No. 6, December 1993
Printed in U.S.A.

CARBOHYDRATE ANTIGENS OF PIG TISSUES REACTING WITH HUMAN NATURAL ANTIBODIES AS POTENTIAL TARGETS FOR HYPERACUTE VASCULAR REJECTION IN PIG-TO-MAN ORGAN XENOTRANSPLANTATION¹

RAFAEL ORIOL,^{2,5} YONG YE,³ EUGEN KOREN,⁴ AND DAVID K.C. COOPER³

INSERM U.178, Villejuif 94807 Cedex, France; and Oklahoma Transplantation Institute, Baptist Medical Center, and Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73112

Pig tissues were screened by immunofluorescence with lectins, mAb, and human natural antibodies for the presence of carbohydrate antigens, which may be potential targets for hyperacute vascular rejection in pig to man xenotransplantation. The unfluorescent monomorph linear B-antigen was found at the surface of all porcine vascular endothelial cells. This pig linear-B antigen reacts strongly with the anti- α Gal isolectin B₄ from *Griffonia simplicifolia* 1 and with human natural anti- α Gal antibodies specifically purified by affinity chromatography on synthetic oligosaccharides containing the terminal nonreducing α Gal1 $\rightarrow$ 3 β Gal-R disaccharide. This antigenic activity is destroyed by treatment of pig tissues with α -galactosidase. The localization of this linear-B epitope on vascular endothelium and its reactivity with natural human anti- α Gal antibodies suggest that it may play a major role in the hyperacute

vascular rejection of pig to man organ xenografts. The lectin from *Machaonia amurensis* reacting with α NeuAc2 $\rightarrow$ 3 β Gal1 $\rightarrow$ 4GlcNAc/Glc was also positive on pig vascular endothelium, but we do not know yet whether there are human natural antibodies reacting with the carbohydrate recognized by this lectin.

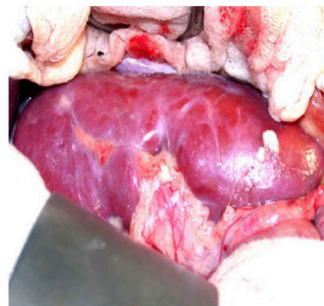
Epithelial cells of pig renal proximal convoluted tubules, respiratory epithelium, pancreatic ducts, and epidermis express the linear-B antigen, but they are less likely to trigger a hyperacute vascular rejection because they are not directly exposed to the blood.

The genetically defined pig A^{+/A} system controls the expression of A and B antigens in pig epithelial cells from renal distal and collecting tubules, biliary ducts, pancreatic ducts, large bronchi, and digestive mucosa. The pig A antigen may trigger an immune response in human O or B recipients if they are transplanted with organs from A⁺ pigs, but the pig A antigen is probably not involved in the hyperacute vascular rejection of a xenograft because it is not expressed on vascular endothelium.

¹This work was supported in part by the Centre National de la Recherche Scientifique (CNRS SD-401178) and the Institut National de la Santé et de la Recherche Médicale (INSERM U.178).

²INSERM U.178, Villejuif 94807 CEDEX, France.

Immediately post-reperfusion

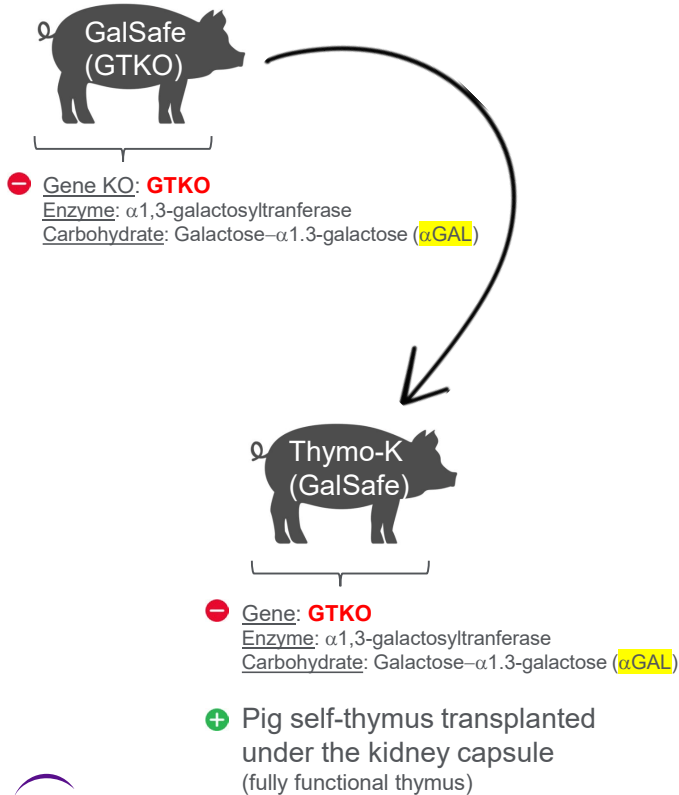


Okamoto, O. *Perit Bioeth J* 2, 38-41 (2006).

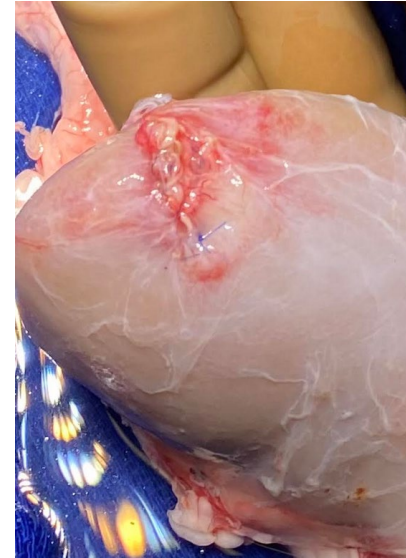
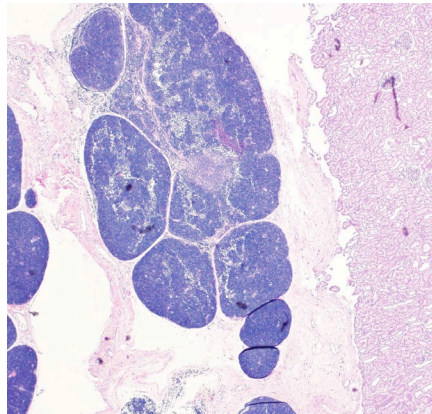
10 min post-reperfusion



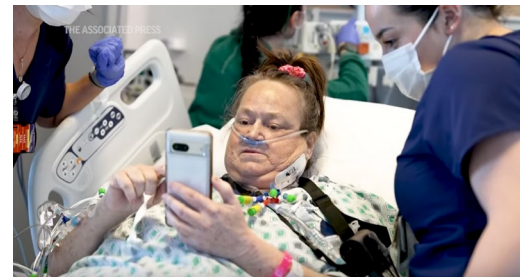
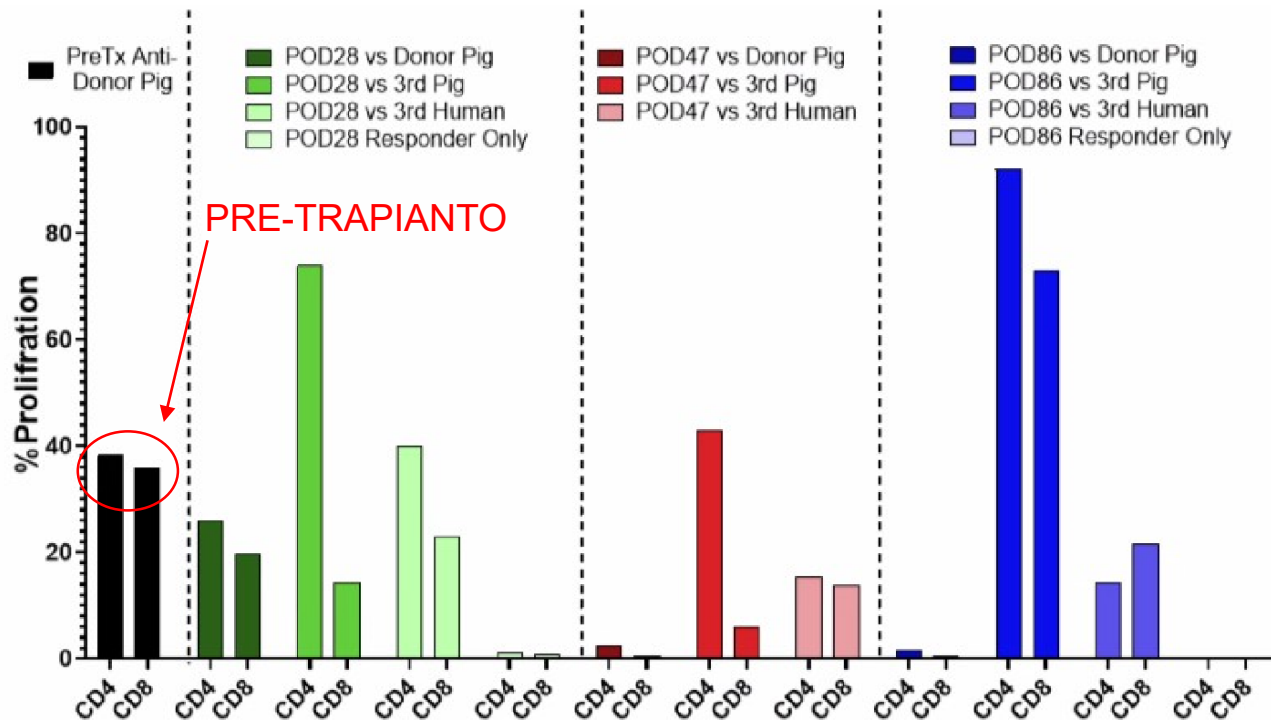
GENETICS OF PIGS (knockouts/transgenes)



Alpha-Gal KO, Thymokidney



LA PRIMA EVIDENZA DI TOLLERANZA CLINICA NEGLI XENOTRAPIANTI



Lisa Pisano

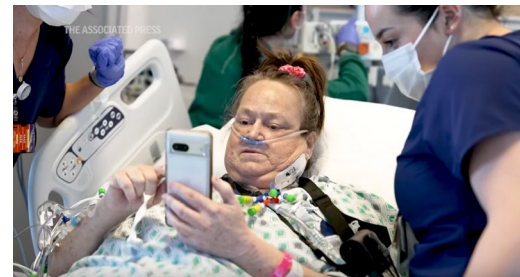
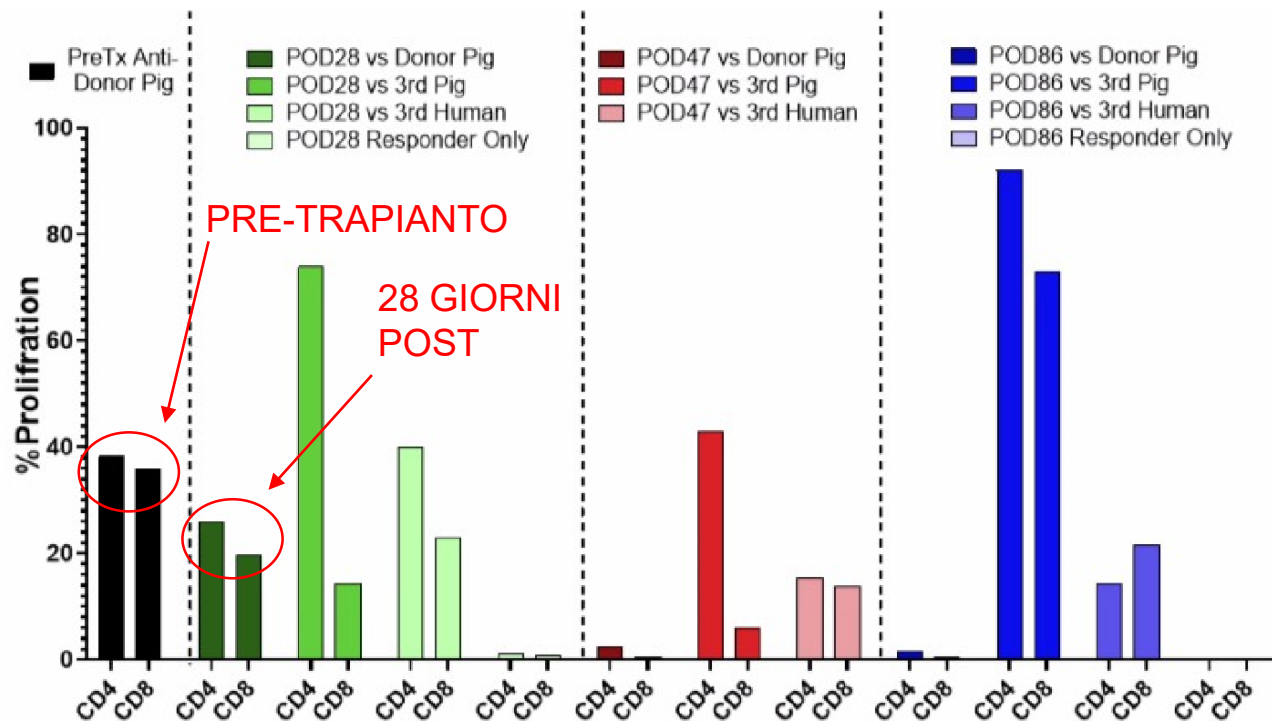


David H. Sachs, MD



Megan Sykes, MD

LA PRIMA EVIDENZA DI TOLLERANZA CLINICA NEGLI XENOTRAPIANTI



Lisa Pisano

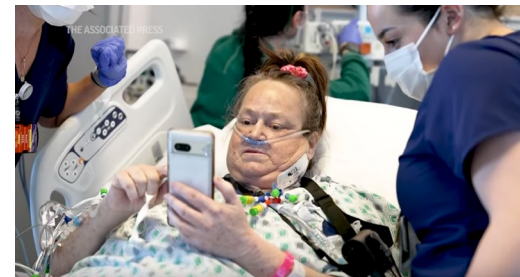
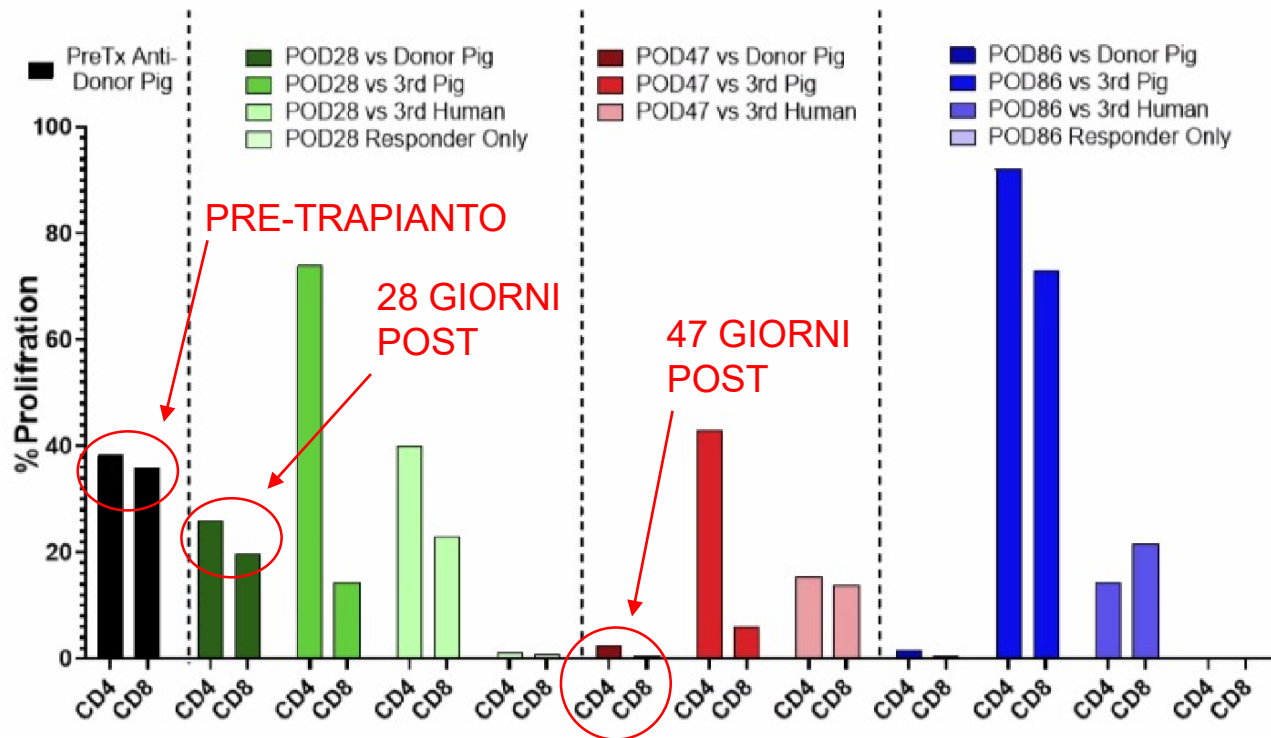


David H. Sachs, MD



Megan Sykes, MD

LA PRIMA EVIDENZA DI TOLLERANZA CLINICA NEGLI XENOTRAPIANTI



Lisa Pisano

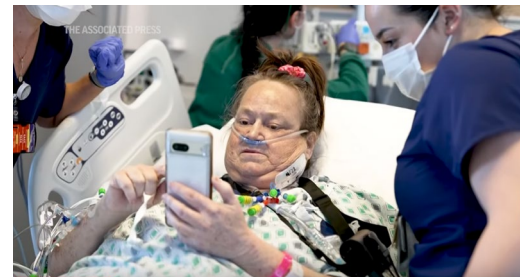
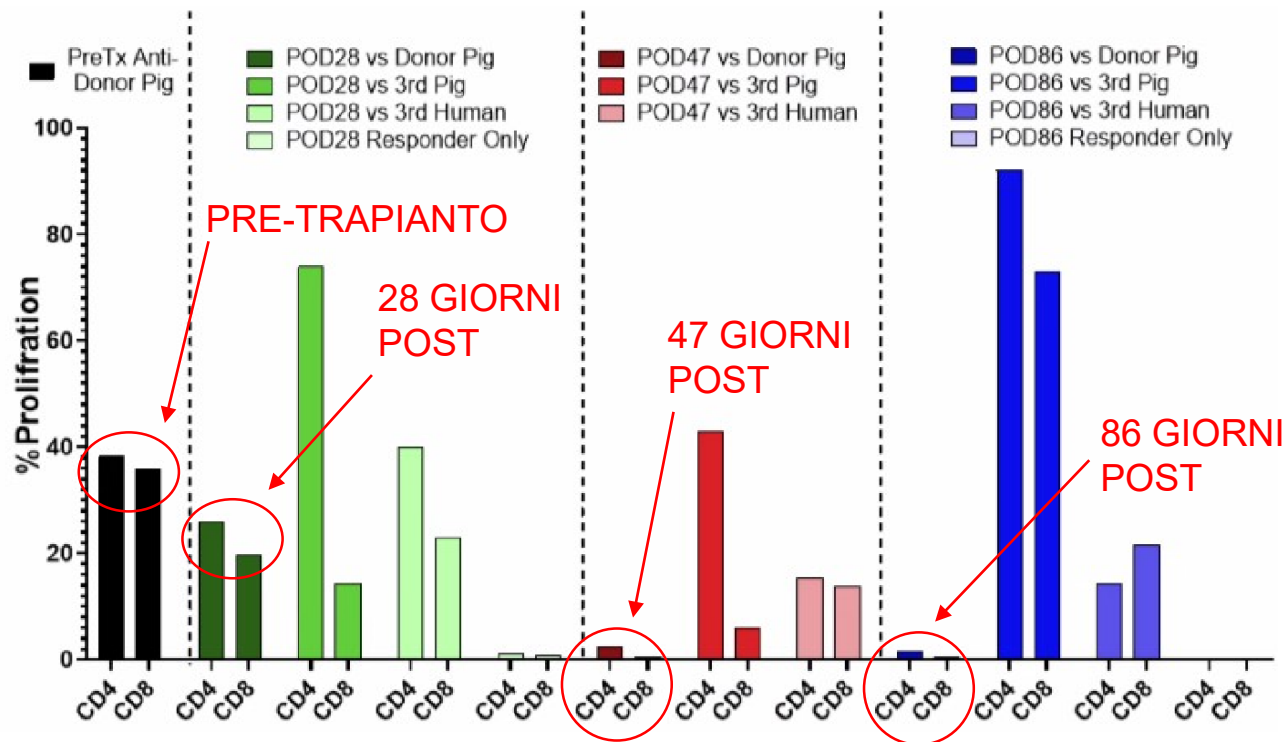


David H. Sachs, MD



Megan Sykes, MD

LA PRIMA EVIDENZA DI TOLLERANZA CLINICA NEGLI XENOTRAPIANTI



Lisa Pisano

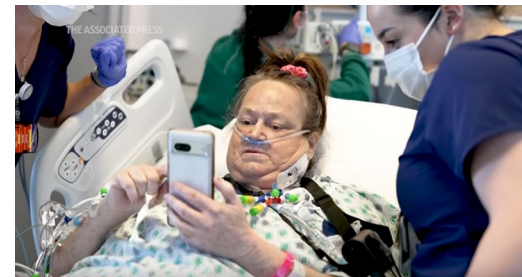
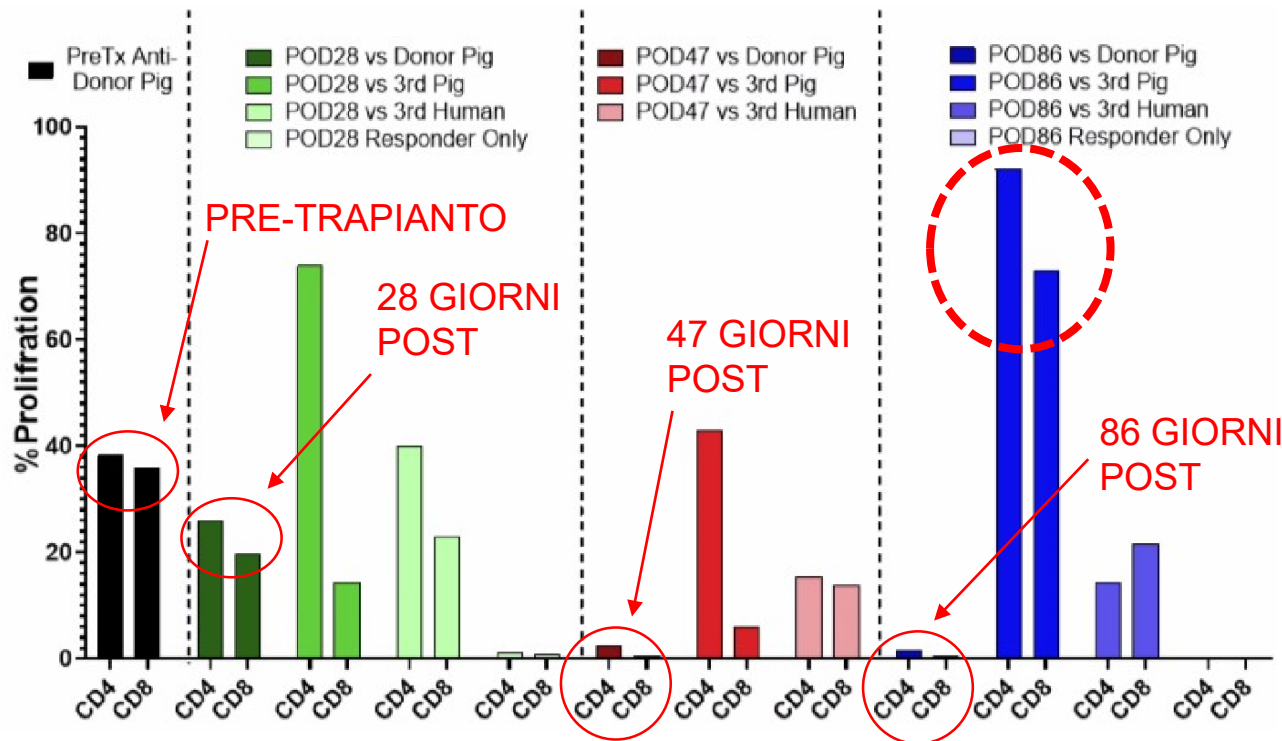


David H. Sachs, MD



Megan Sykes, MD

LA PRIMA EVIDENZA DI TOLLERANZA CLINICA NEGLI XENOTRAPIANTI



Lisa Pisano

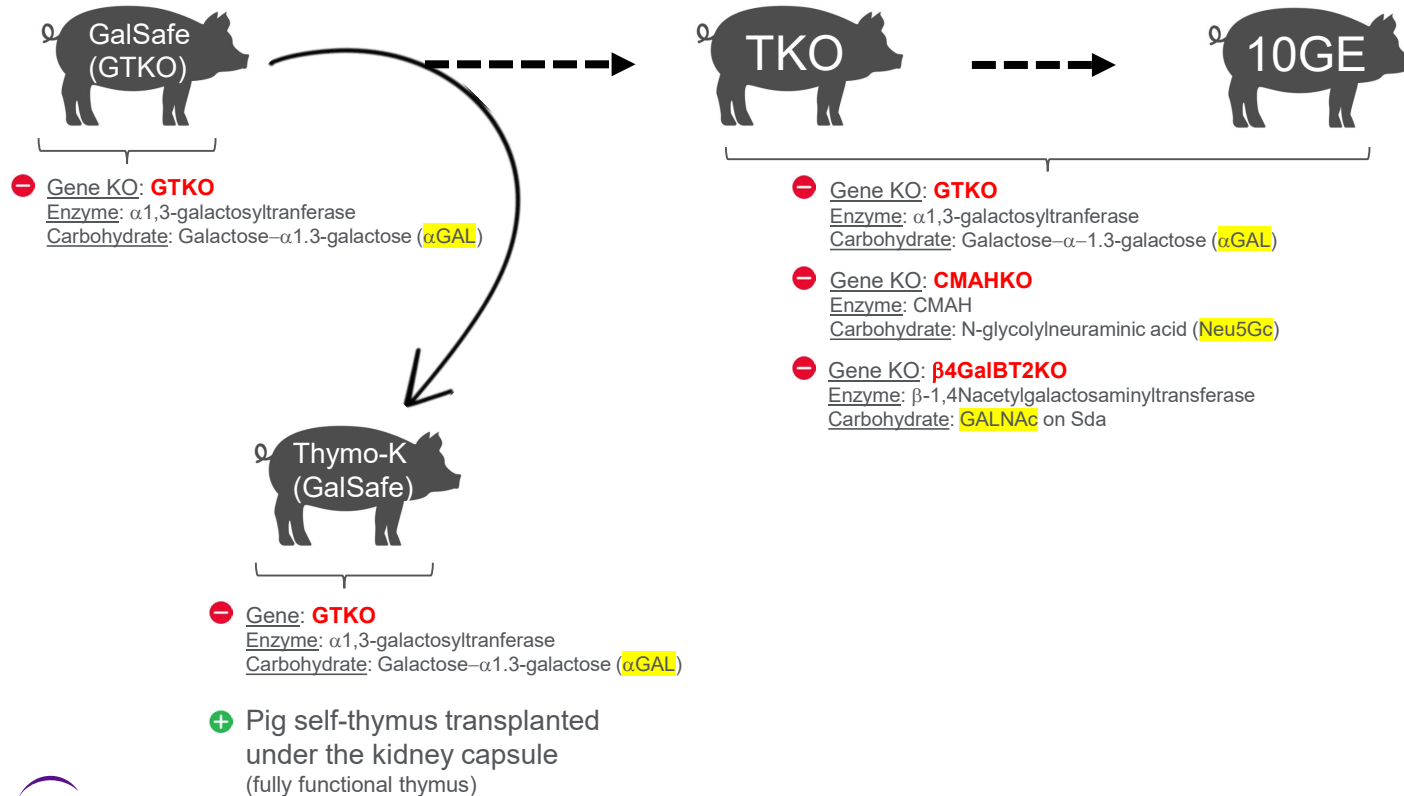


David H. Sachs, MD

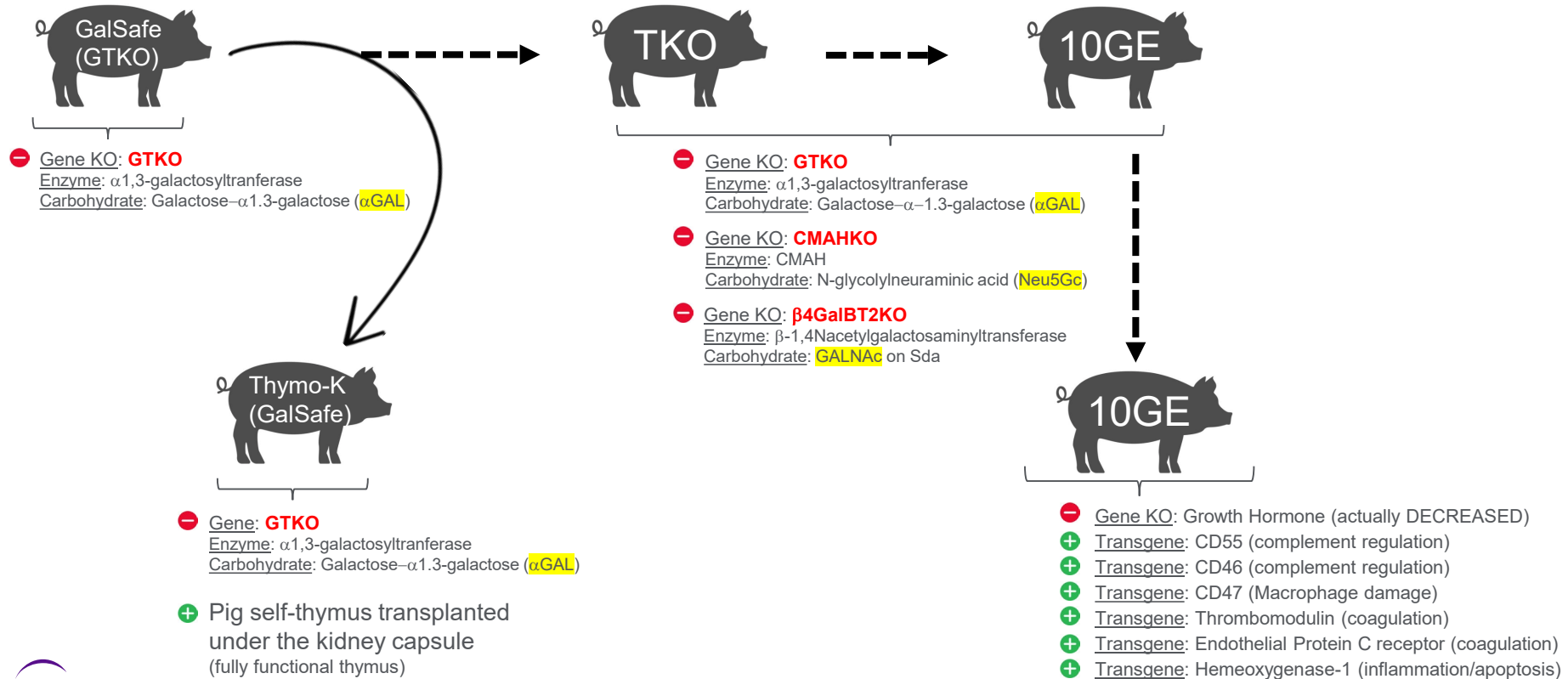


Megan Sykes, MD

GENETICS OF PIGS (knockouts/transgenes)

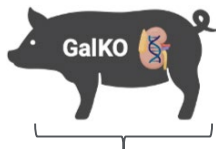


GENETICS OF PIGS (knockouts/transgenes)



NYU GENETICS OF CHOICE FOR KIDNEY XENOTRANSPLANT

GAL-SAFE THYMO-KIDNEY



– Gene: **GTKO**
Enzyme: α 1,3-galactosyltransferase
Carbohydrate: Galactose- α -1.3-galactose (α GAL)

+ Pig self-thymus transplanted
under the kidney capsule
(fully functional thymus)

Scalabile

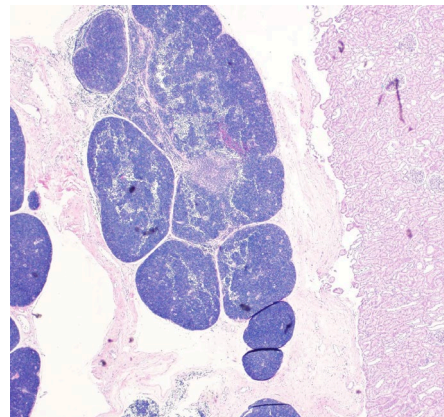
Capace di supplire il
numero di organi che
servono



Tollerogenico

Capace di produrre tolleranza
verso xeno-antigeni

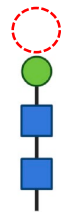
GTKO, Thymokidney



Gli anticorpi anti-Neu5Gc & -GALNAc
non sono necessariamente un problema

Anticorpi anti-carboidrati causano danno quando hanno un alto "titolo"

NYU GENETICS OF CHOICE FOR KIDNEY XENOTRANSPLANT

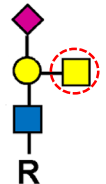
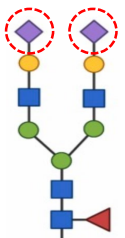


GTKO pigs lack expression of
Galactose- α -1,3-Galactose
(α -Gal-NEGATIVE)





ADDITIONAL KNOWN XENO-ANTIGENS

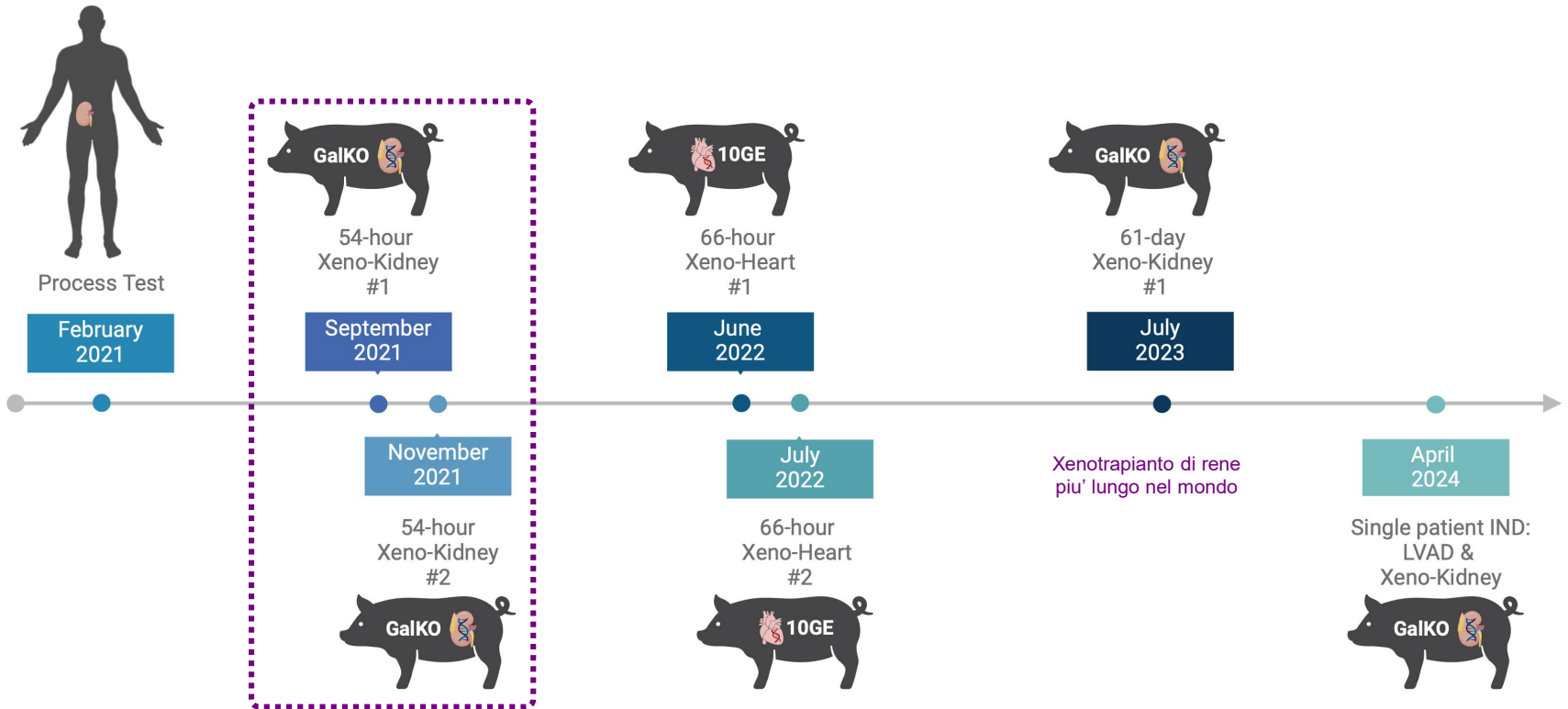


Glycolylneuraminic Acid
(**Neu5Gc**)

GALNAc on **Sd^a** Antigen

IMPATTO CLINICO ?

PIG TO HUMAN XENOTRANSPLANTS AT NYU



- 1- e' vero che non c'e rigetto hyper-acuto ?
- 2- quale e' l'impatto clinico degli anticorpi anti-Neu5Gc and GALNAc ?

PRIMI CASI DI XENOTRAPIANTO DEL RENE

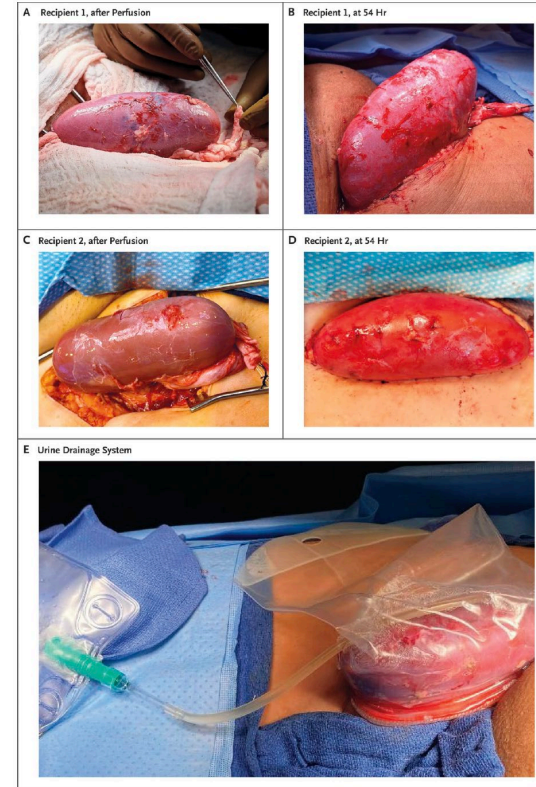
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

Robert A. Montgomery, M.D., D.Phil., Jeffrey M. Stern, M.D.,
Bonnie E. Lonze, M.D., Ph.D., Vasishta S. Tatapudi, M.D.,
Massimo Mangiola, Ph.D., Ming Wu, M.D., Elaina Weldon, M.S.N., A.C.N.P.-B.C.,
Nikki Lawson, R.N., Cecilia Deterville, M.S., Rebecca A. Dieter, Pharm.D., B.C.P.S.,
Brigitte Sullivan, M.B.A., Gabriella Boulton, B.A., Brendan Parent, J.D.,
Greta Piper, M.D., Philip Sommer, M.D., Samantha Cawthon, B.S.,
Erin Duggan, M.D., David Ayares, Ph.D., Amy Dandro, M.S.,
Ana Fazio-Kroll, Ph.D., Maria Kokkinaki, Ph.D., Lars Burdorf, M.D., Ph.D.,
Marc Lorber, M.D., Jef D. Boeke, Ph.D., Harvey Pass, M.D.,
Brendan Keating, Ph.D., Adam Griesemer, M.D., Nicole M. Ali, M.D.,
Sapna A. Mehta, M.D., and Zoe A. Stewart, M.D., Ph.D.

- Genetically modified pig kidney xenografts were transplanted into two brain-dead human recipients.
- The xenografts functioned immediately and showed no evidence of acute rejection on serial biopsy over a period of 54 hours.
- The serum creatinine level decreased in both recipients.



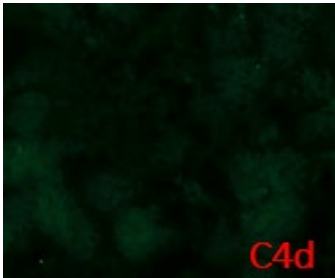
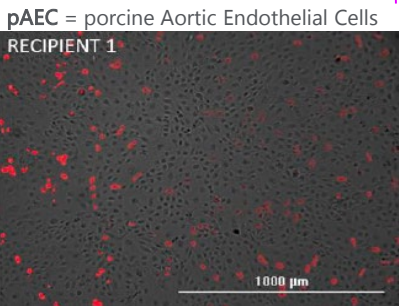
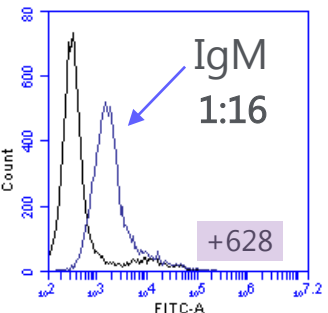
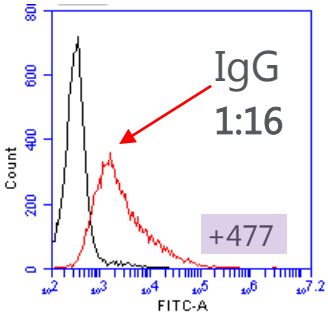
CORRELAZIONE ATTIVAZIONE DEL COMPLEMENTO

Flow cytometry on lymphocytes

CDCXM on endothelial cells

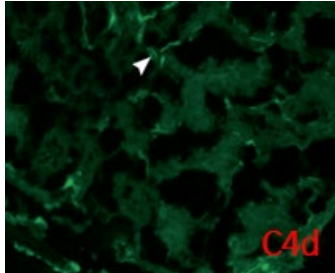
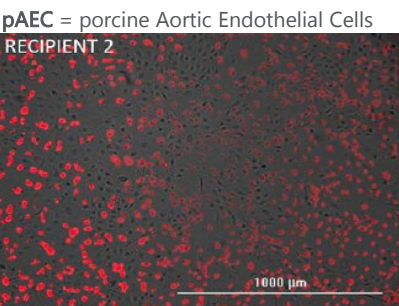
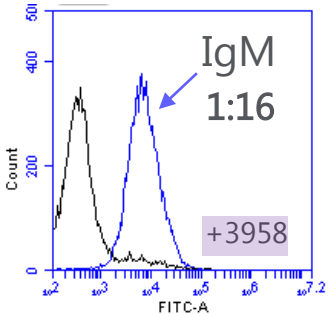
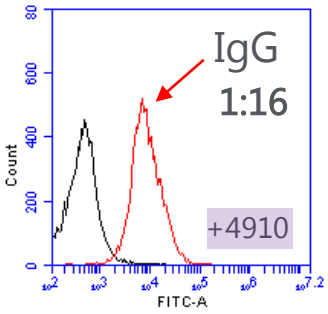
Pathology

LOW
TITER



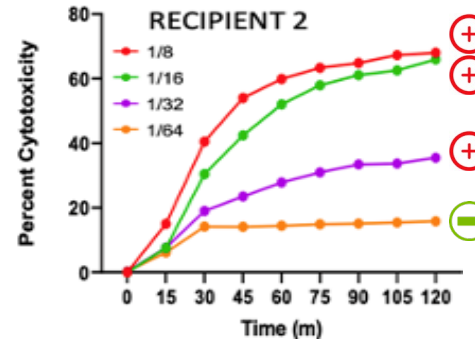
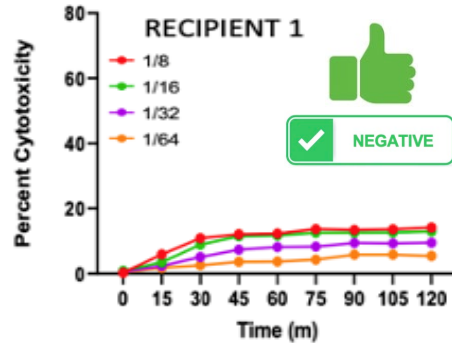
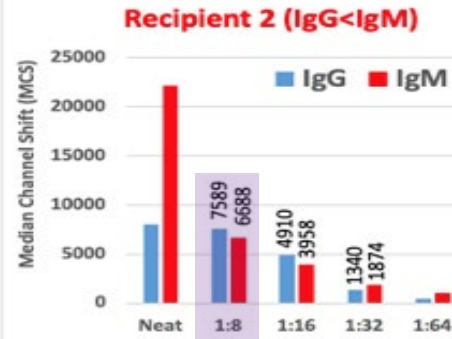
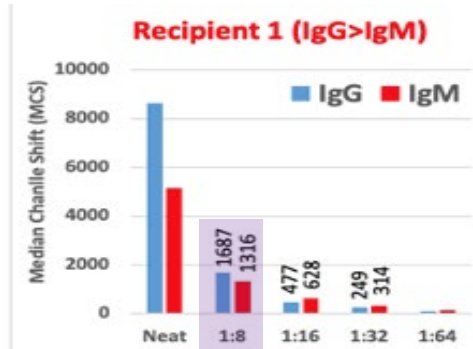
RECIPIENT 1

HIGH
TITER

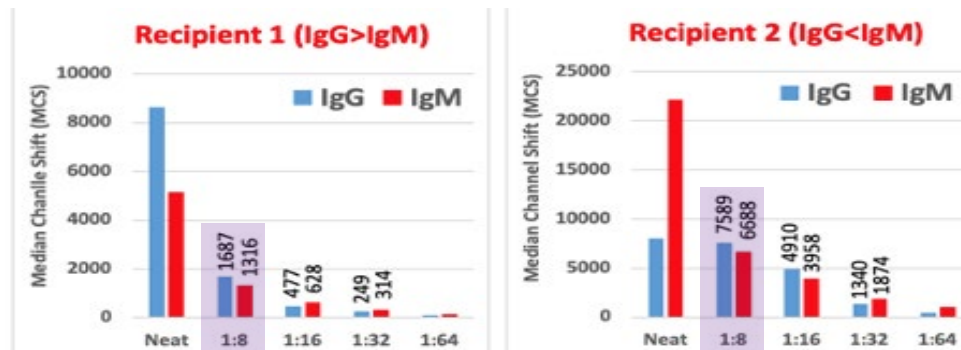


RECIPIENT 2

FLOW CROSSMATCH RISK CUT-OFF



FLOW CROSSMATCH RISK CUT-OFF

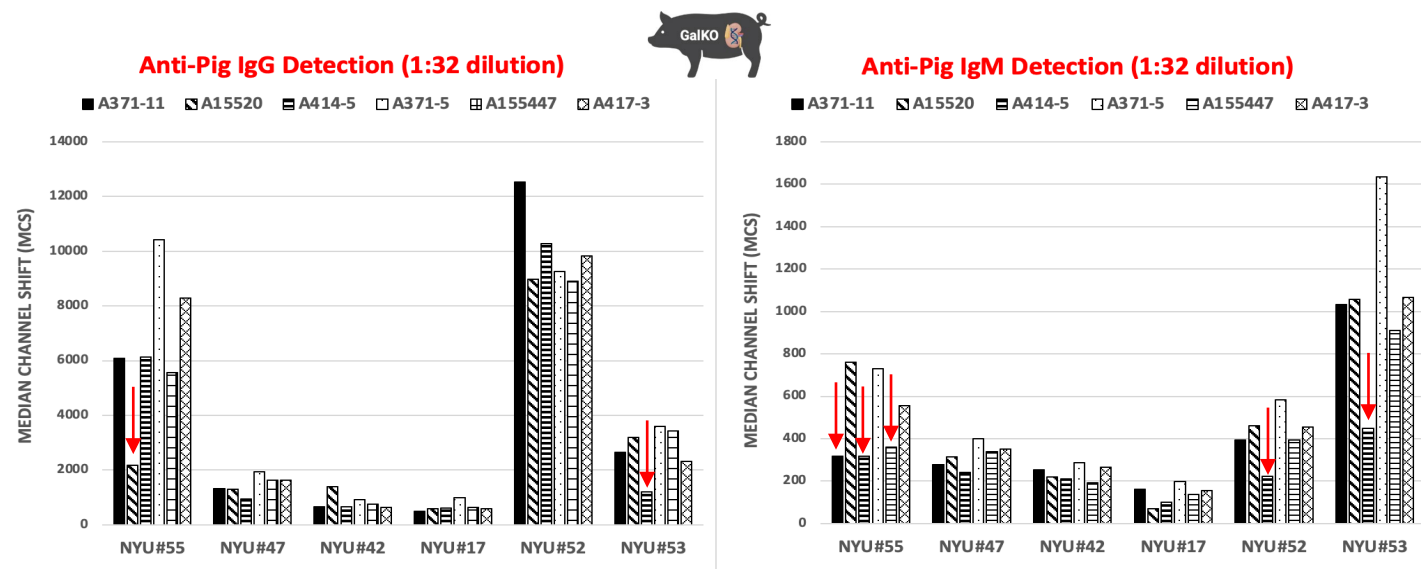


Anticorpi >1000 MCS sono a rischio di attivazione del complemento

- Pre-screening del candidato (FCXM)
- Identificazione candidato/donatore dove IgG ed IgM sono <1000 MCS
- Plasma Exchange quando IgG ed IgM sono >1000 MCS

DIFFERENTIAL EXPRESSION OF NON- α GAL EPIOTOPES

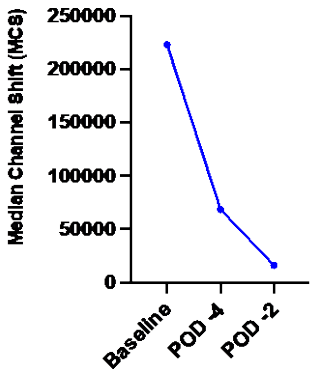
Prospective screening can help identifying best recipient/donor combination



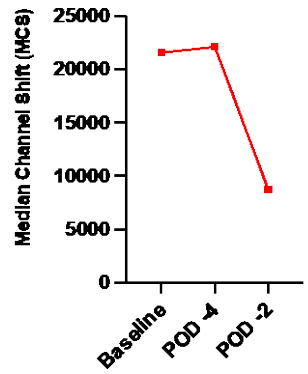
FCXM CONVERSION BY PLASMA EXCHANGE



IgG Reduction Following PLEX (pAEC)

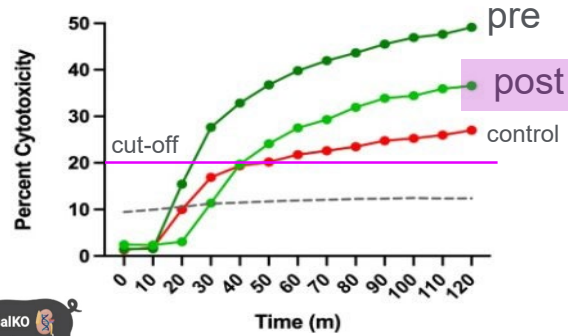


IgM Reduction Following PLEX (pAEC)

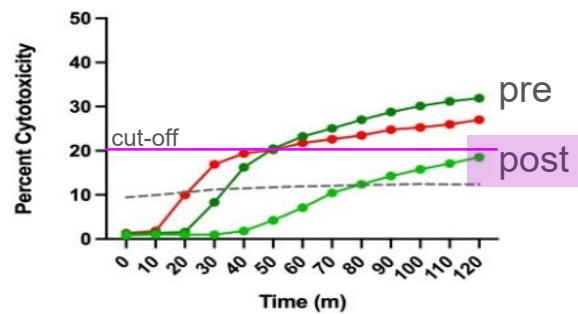


PLEX riduce gli anticorpi e converte il crossmatch

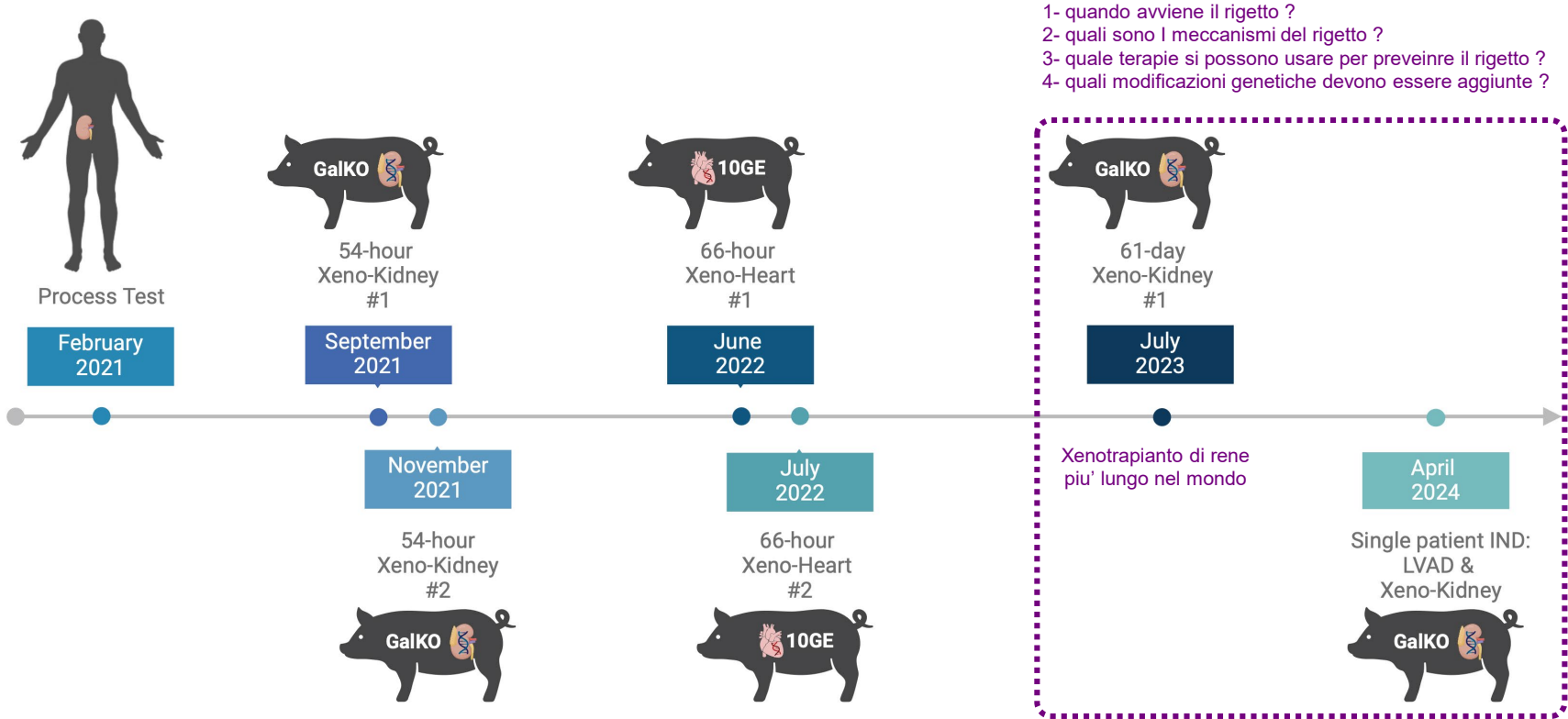
1:4 dilution PLEX#1



1:4 Dilution PLEX#2



POST-TRANSPLANT MONITORING



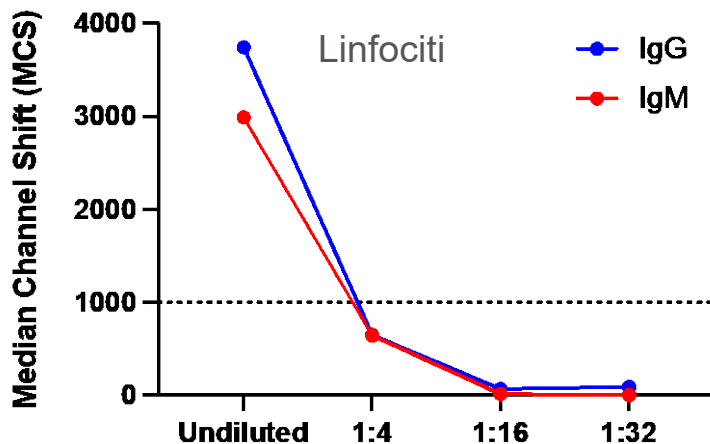
- 1- quando avviene il rigetto ?
- 2- quali sono i meccanismi del rigetto ?
- 3- quale terapie si possono usare per prevenire il rigetto ?
- 4- quali modificazioni genetiche devono essere aggiunte ?

LONGEST PIG TO HUMAN KIDNEY TRANSPLANT

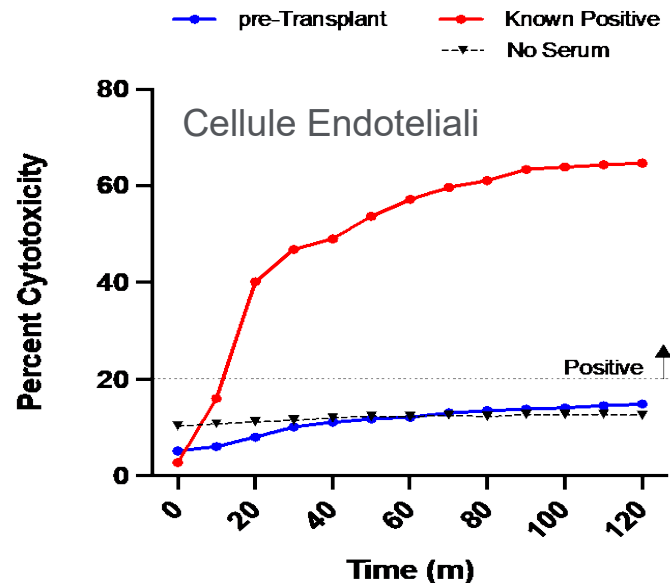


Pre-Transplant Flow and CDC Crossmatch

pre-Transplant IgG/IgM Titer



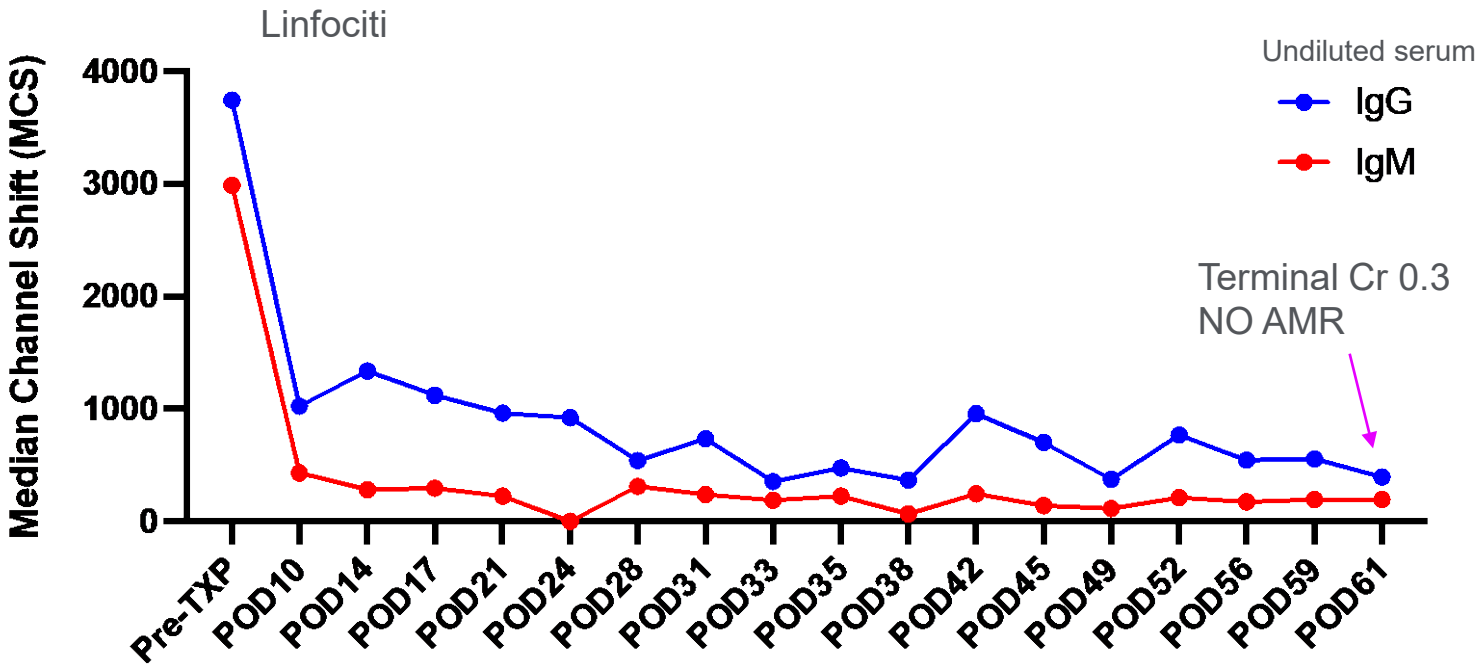
CDC Crossmatch on pAEC



LONGEST PIG TO HUMAN KIDNEY TRANSPLANT



IgG/IgM Flow Crossmatch Trend on PBMCs



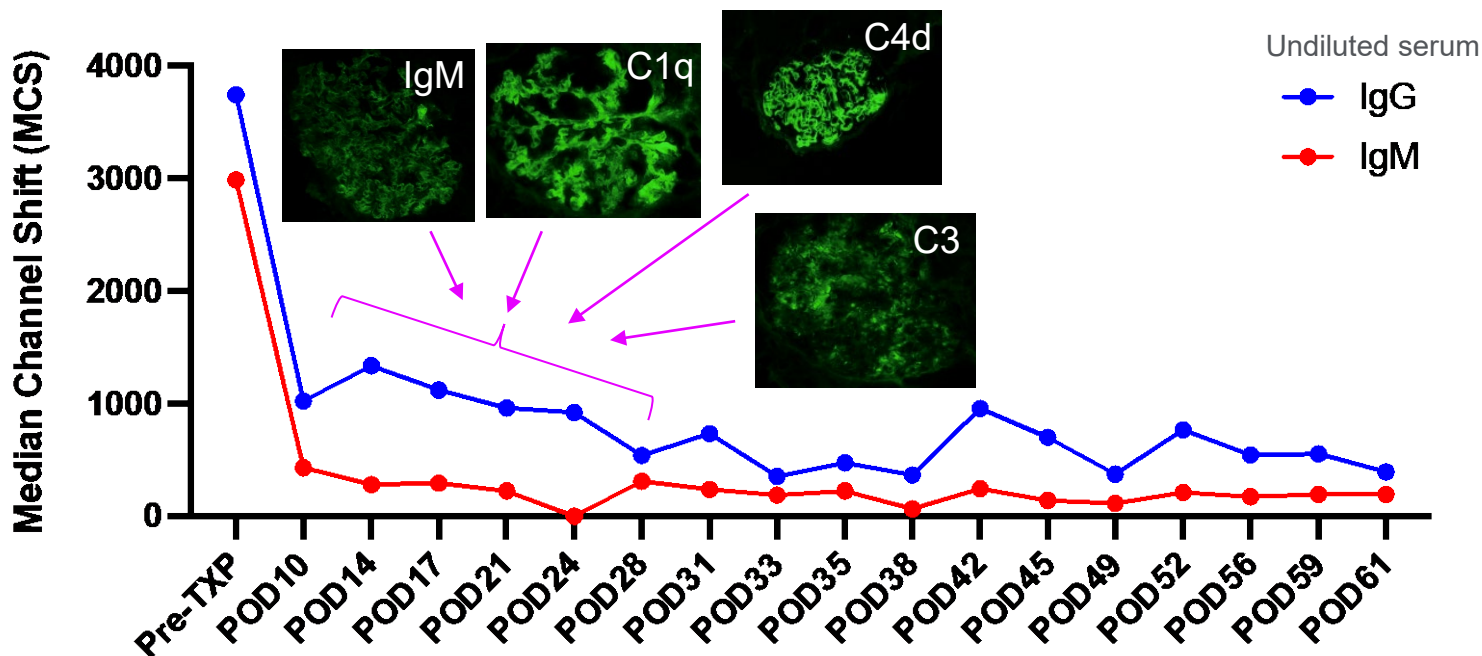
LONGEST PIG TO HUMAN KIDNEY TRANSPLANT



61-day
Xeno-Kidney
#1

July
2023

IgG/IgM Flow Crossmatch Trend on PBMCs



LONGEST PIG TO HUMAN KIDNEY TRANSPLANT

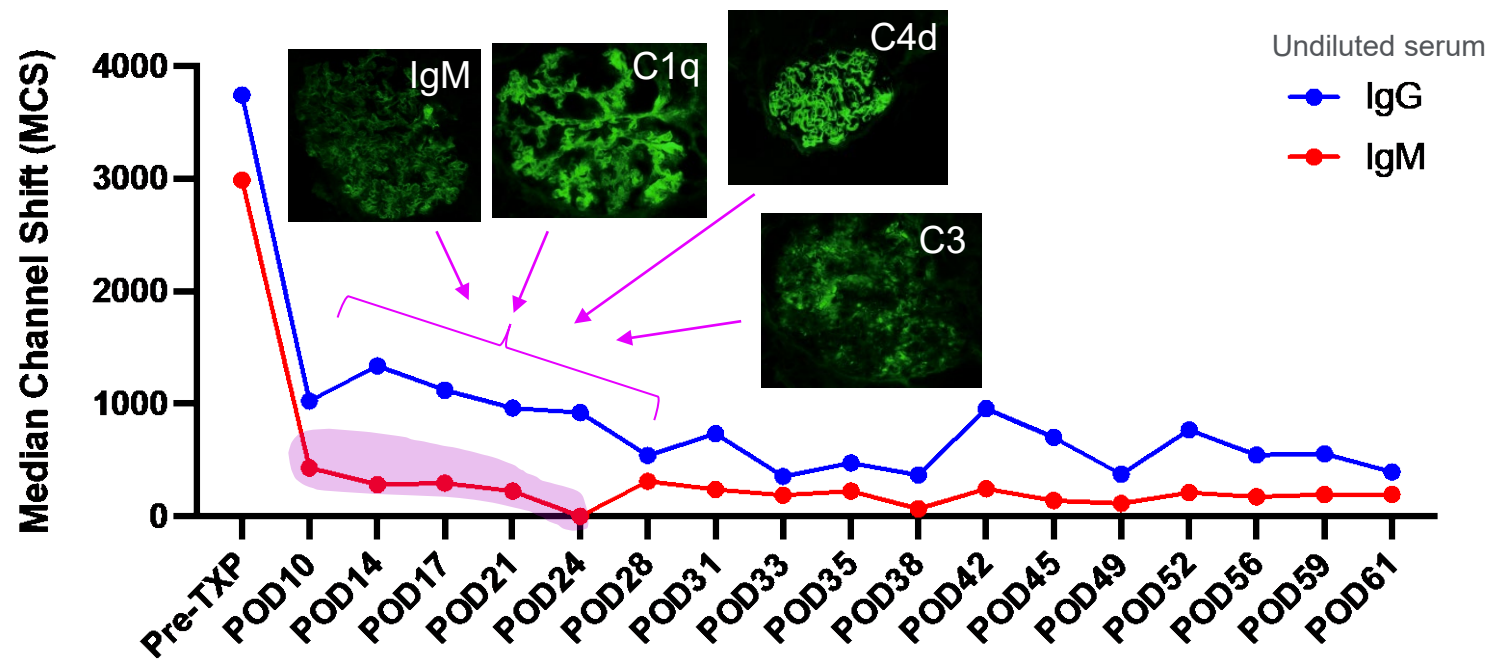


GalKO

61-day
Xeno-Kidney
#1

July
2023

IgG/IgM Flow Crossmatch Trend on PBMCs



LONGEST PIG TO HUMAN KIDNEY TRANSPLANT

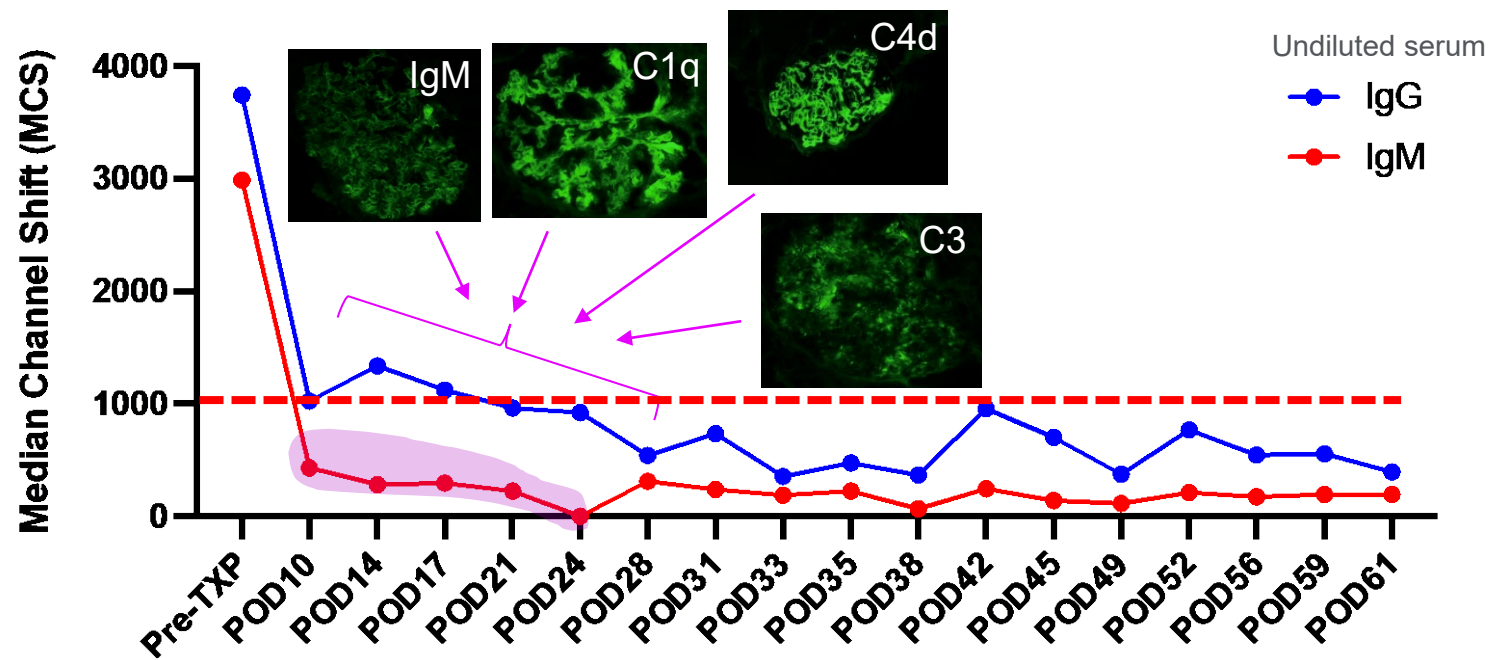


GalKO

61-day
Xeno-Kidney
#1

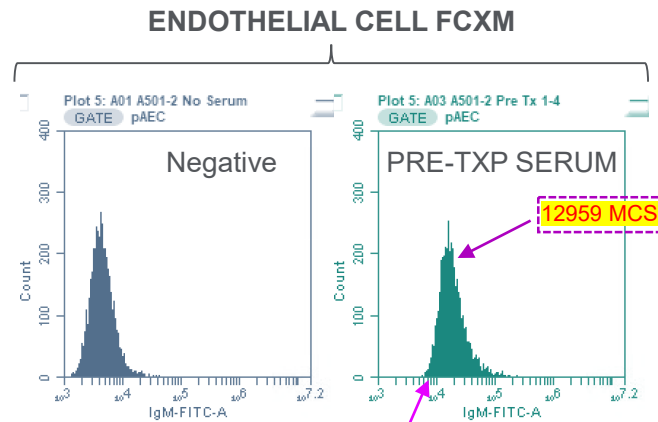
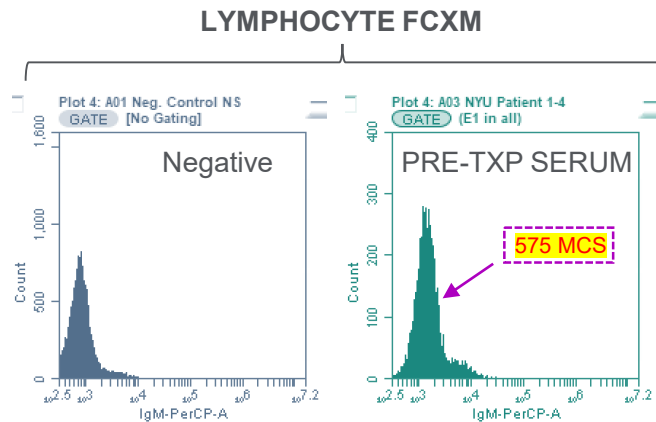
July
2023

IgG/IgM Flow Crossmatch Trend on PBMCs



DIFFERENTIAL EXPRESSION OF XENO ANTIGENS

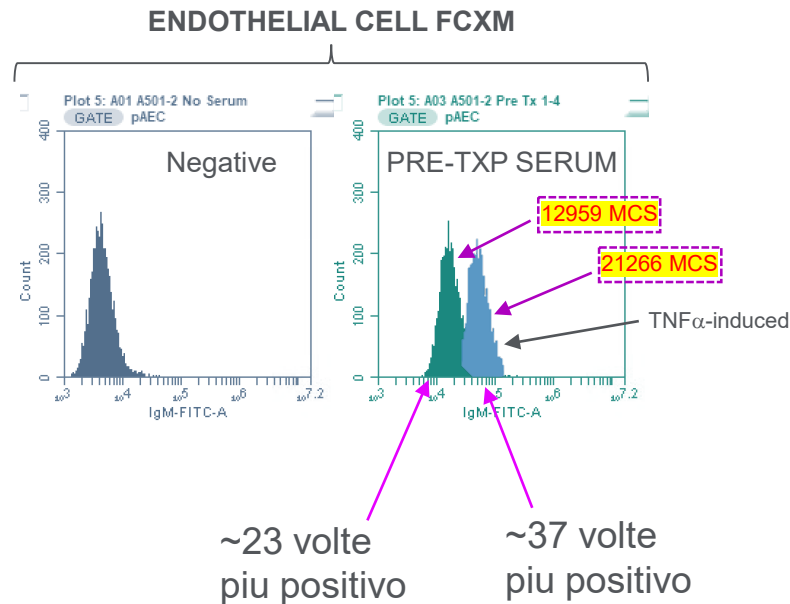
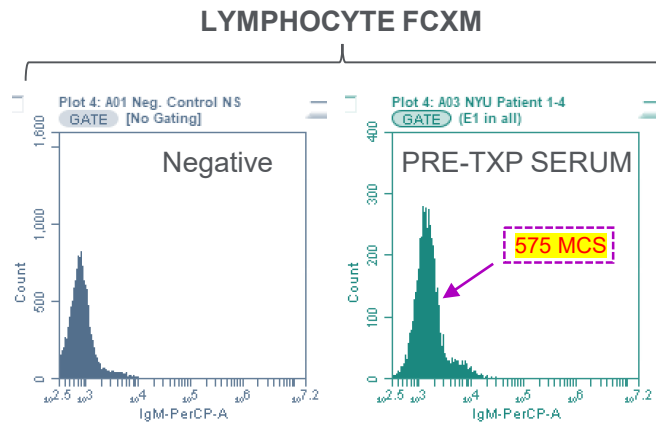
Linfociti vs Cellule Endoteliali



~23 volte
piu positivo

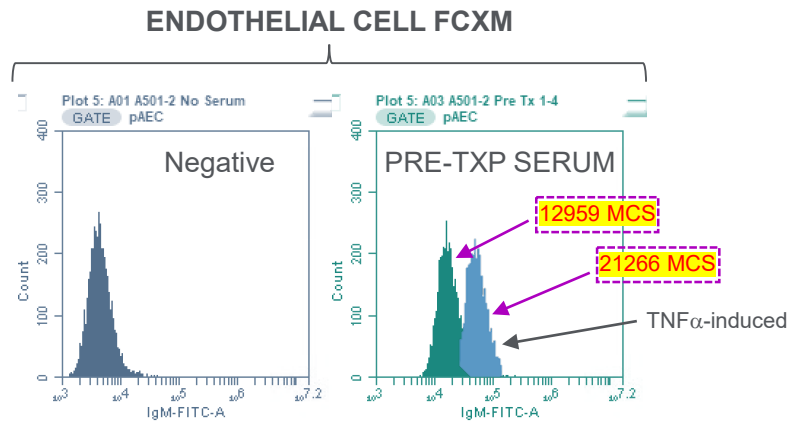
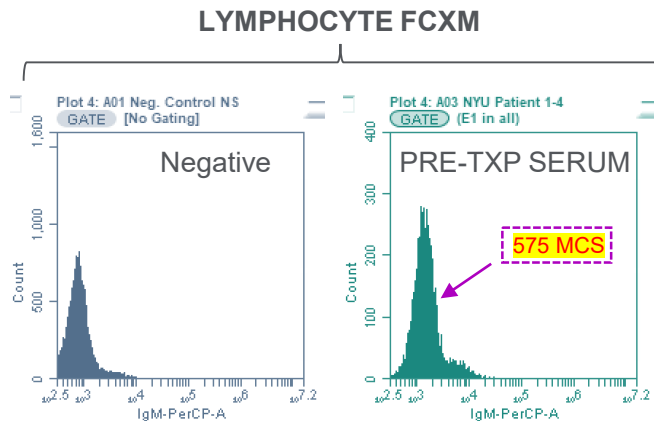
DIFFERENTIAL EXPRESSION OF XENO ANTIGENS

Linfociti vs Cellule Endoteliali



DIFFERENTIAL EXPRESSION OF XENO ANTIGENS

Linfociti vs Cellule Endoteliali



Le cellule endoteliali esprimono un antigene che è assente nei linfociti ?

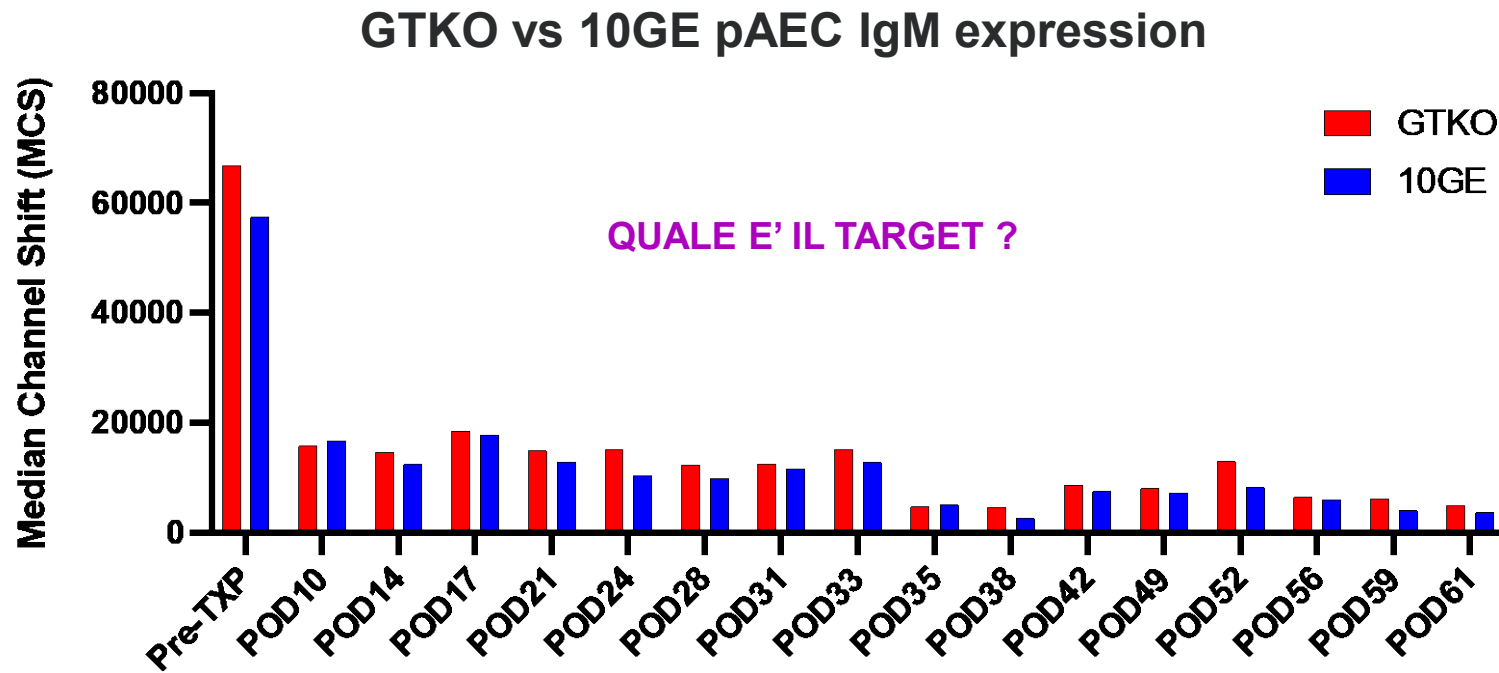
Le cellule endoteliali esprimono una quantità maggiore ?

in ogni caso

Il crossmatch con le cellule endoteliali correla meglio con in rigetto

L'ANTIGENE SCONOSCIUTO

L'antigene non è Neu5Gc o GALNAc (cellule 10GE non esprimono questi antigeni)



LIVING PIG TO HUMAN KIDNEY TRANSPLANT

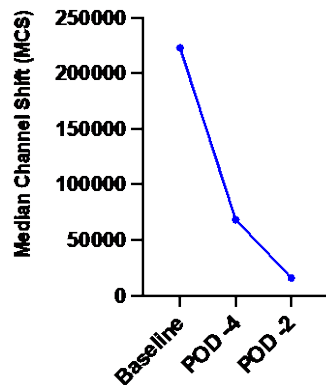
April
2024

Single patient IND:
LVAD &
Xeno-Kidney

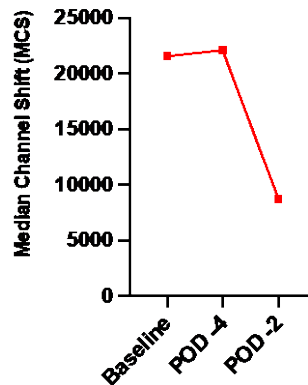


Riduzione degli anticorpi e conversione del crossmatch prima del trapianto

**IgG Reduction Following PLEX
(pAEC)**

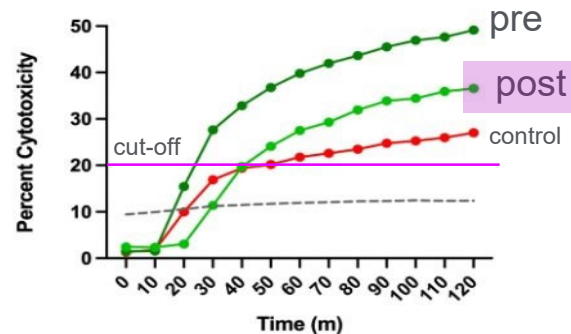


**IgM Reduction Following PLEX
(pAEC)**

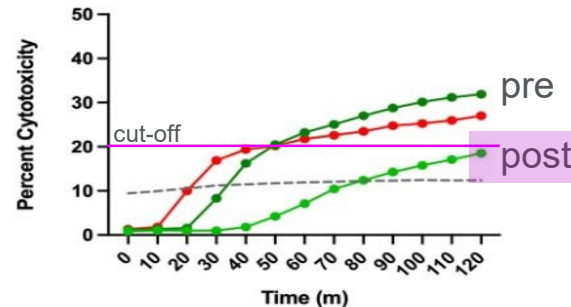


PLEX riduce gli anticorpi
e converte il crossmatch

1:4 dilution PLEX#1



1:4 Dilution PLEX#2

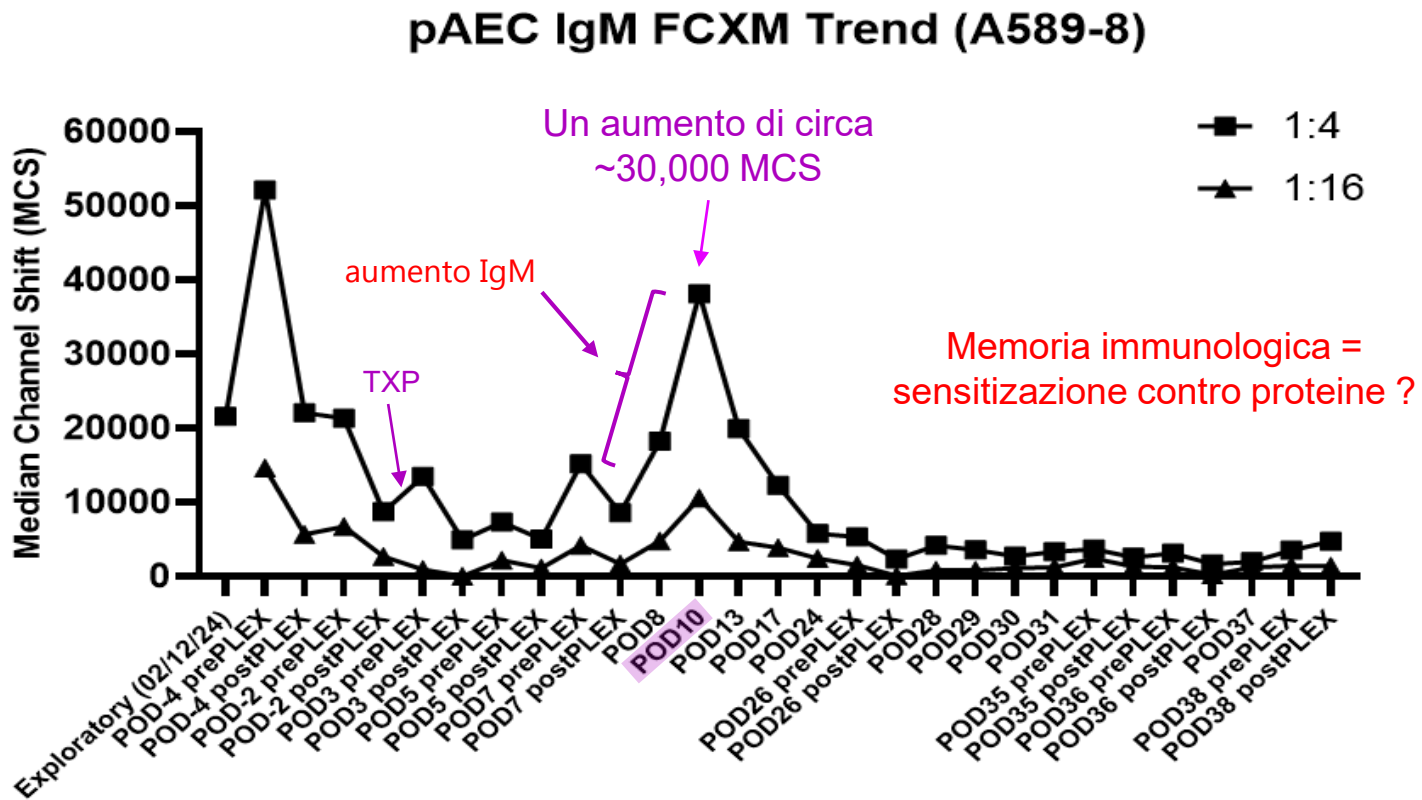


MEMORIA IMMUNOLOGICA E RIGETTO

April 2024

Single patient IND:
LVAD &
Xeno-Kidney


GalKO

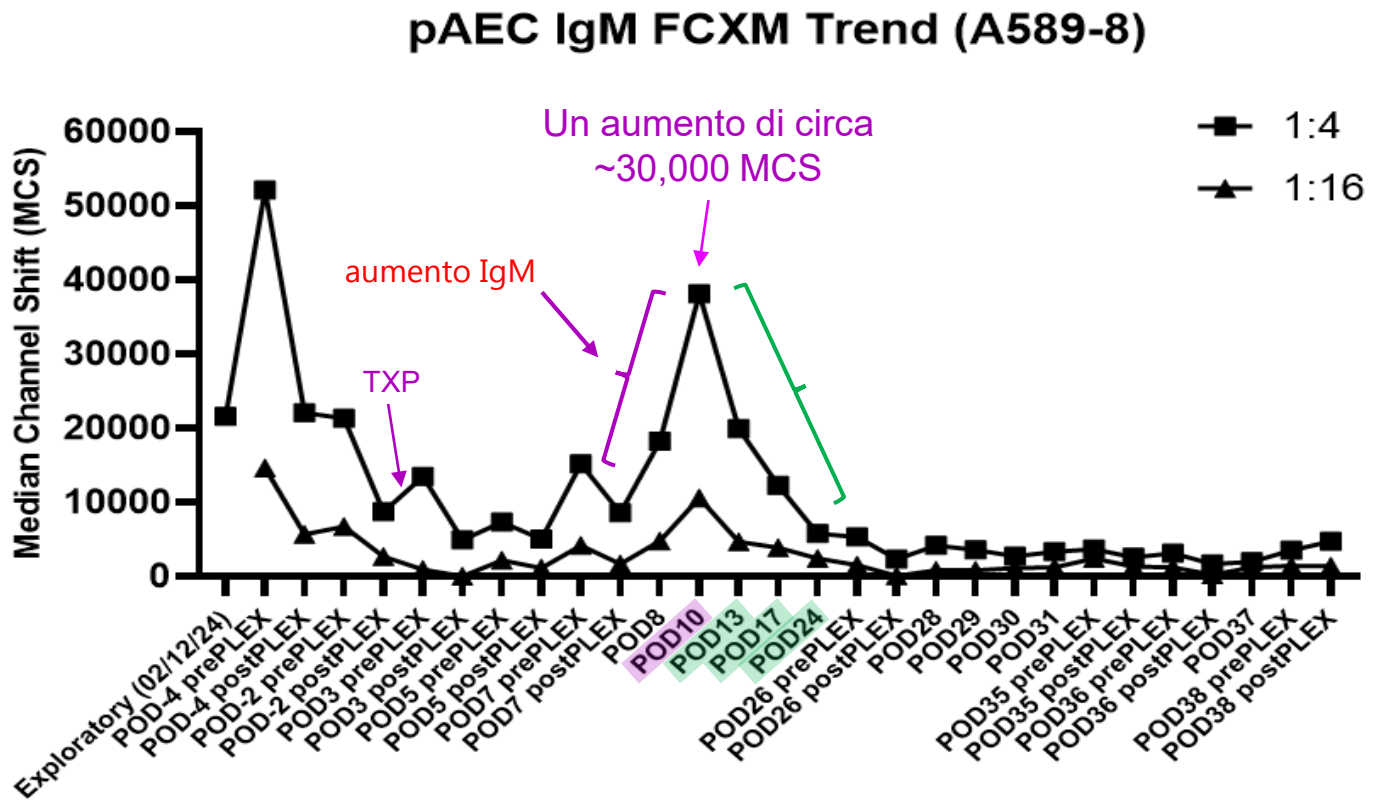


MEMORIA IMMUNOLOGICA E RIGETTO

April 2024

Single patient IND:
LVAD &
Xeno-Kidney

GalKO

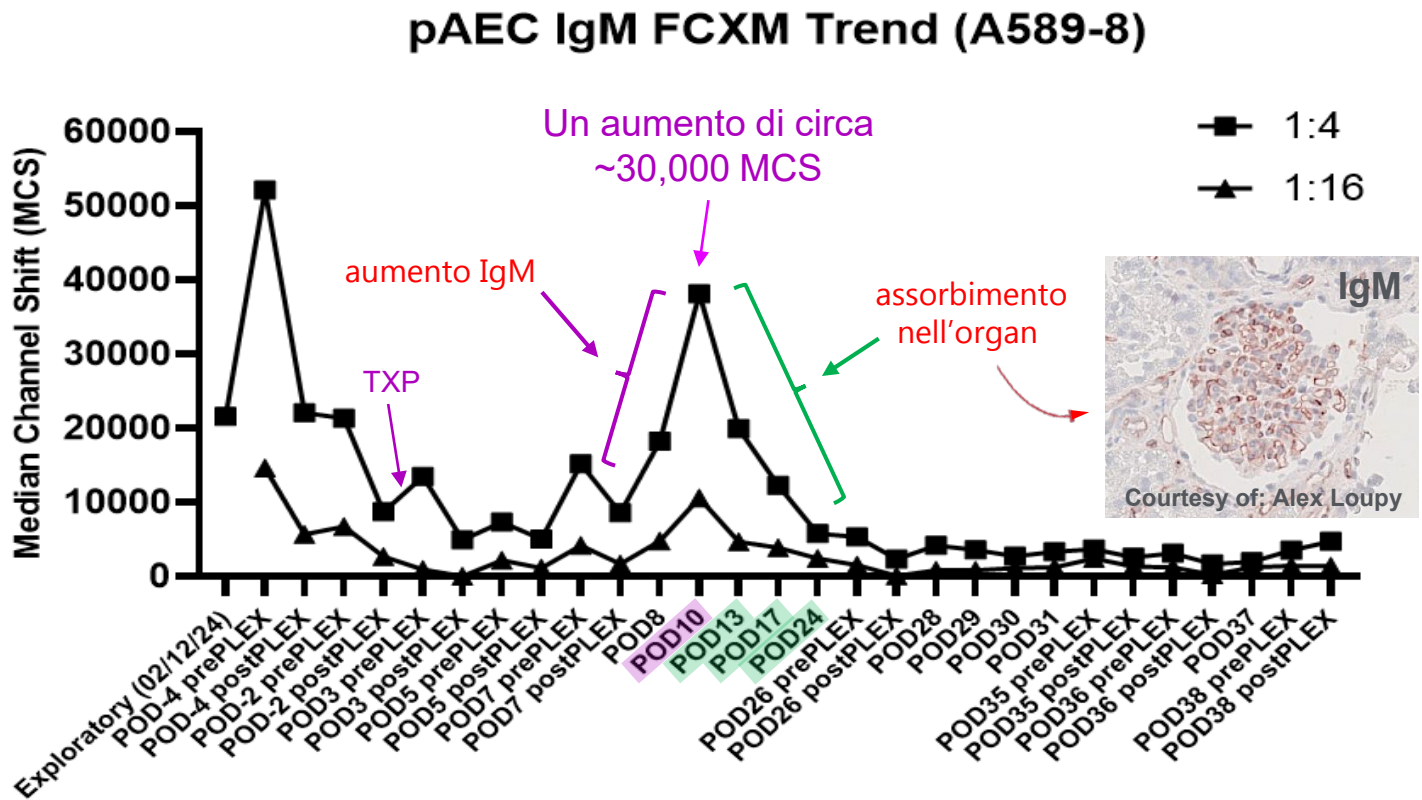


MEMORIA IMMUNOLOGICA E RIGETTO

April 2024

Single patient IND:
LVAD &
Xeno-Kidney


GalKO



PATOLOGIA DEL RIGETTO DELL'ORGANO



Alexandre Loupy, MD PhD



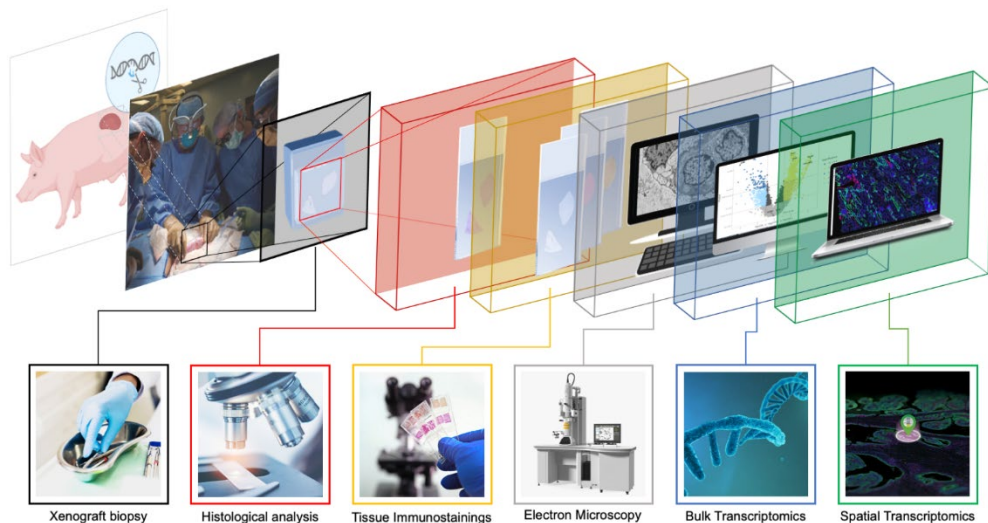
Paris Transplant Group
Kidney, Heart, Lung & Liver



Xeno-BANFF

PATOLOGIA DEL RIGETTO DELL'ORGANO

Pathologia Multimodale Fenotipica



Multimodality deep phenotyping of pig kidney xenografts.

A deep phenotyping of xenografts biopsies will be performed with a five-steps process combining i) a morphological evaluation by histological analysis, ii) an immunophenotyping with multiple immunostainings, iii) an ultrastructural assessment by electron microscopy analysis, iv) gene expression profiling with bulk transcriptomics, and v) whole-transcriptome digital spatial profiling and cell deconvolution.



Immune response after pig-to-human kidney xenotransplantation: a multimodal phenotyping study

Alexandre Loupy*, Valentin Goutaudier*, Alessia Giarraputo*, Fariza Mezine, Erwan Morgand, Blaise Robin, Karen Khalil, Sapna Mehta, Brendan Keating, Amy Dandro, Anaïs Certain, Pierre-Louis Tharaux, Navreet Narula, Renaud Tissier, Sébastien Graud, Thierry Hauet, Harvey I Pass, Aurélie Sannier, Ming Wu, Adam Griesemer, David Ayares, Vasishtha Tatapudi, Jeffrey Stern, Carmen Lefaucheur, Patrick Bruneval, Massimo Mangiola, Robert A Montgomery

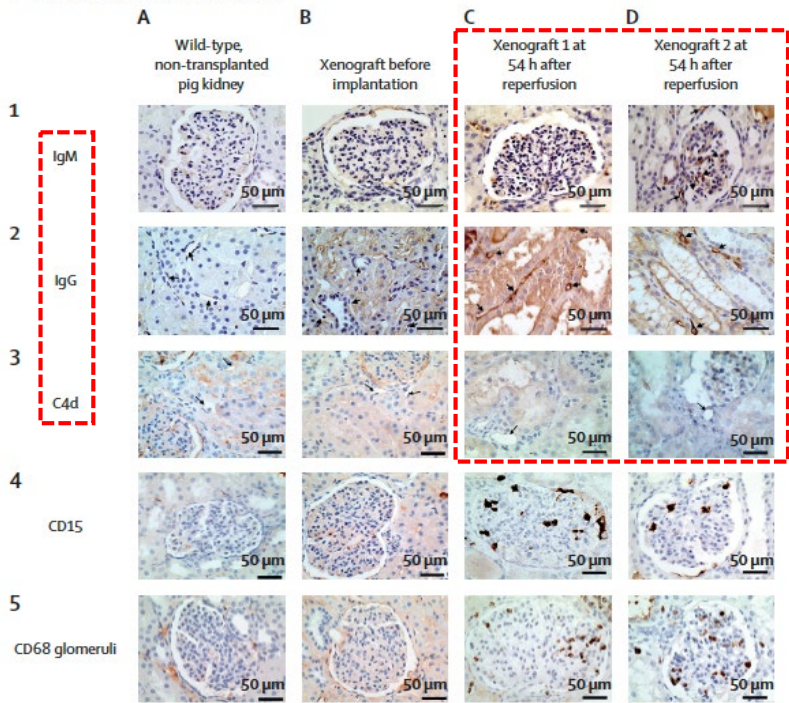
PATOLOGIA DEL RIGETTO DELL'ORGANO

Pathologia Multimodale Fenotipica

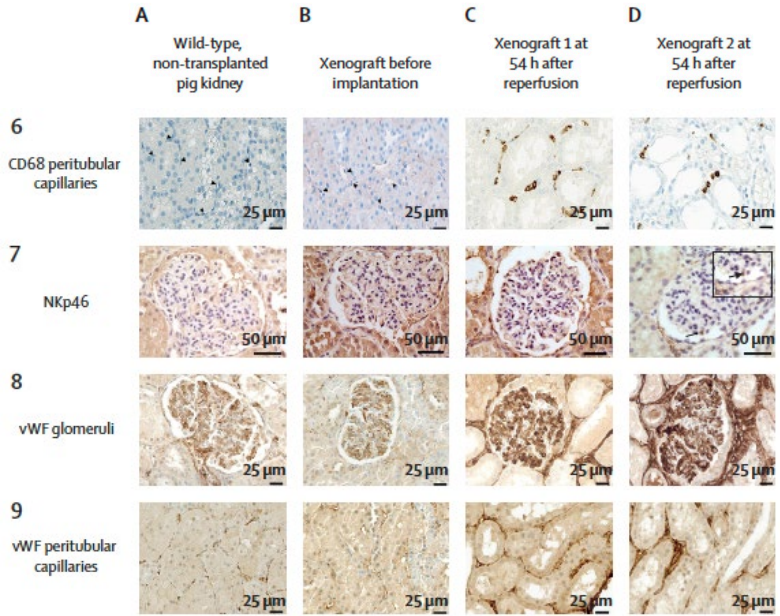
Immune response after pig-to-human kidney
xenotransplantation: a multimodal phenotyping study

Alexandre Lamy*, Valentin Gauthier*, Alessia Geronzi*, Fariza Mehin, Ewan Margend, Wahe Robin, Karen Khalil, Sagna Meltis, Brendan Keating, Amy Dando, Anais Certain, Pierre-Louis Thiauc, Noémie Nauda, Renaud Trisler, Sébastien Girard, Thierry Hauw, Harvey Pess, Aurélie Savinier, Ming Wu, Adam Giesemer, David Ayres, Vasilos Tzafopoulou, Jeffrey Stern, Carmen Lefebvre, Patrick Brunet, Massimo Mangiola, Robert A Montgomery

B Immune and endothelial activation



B Immune and endothelial activation



54 hours post-implant

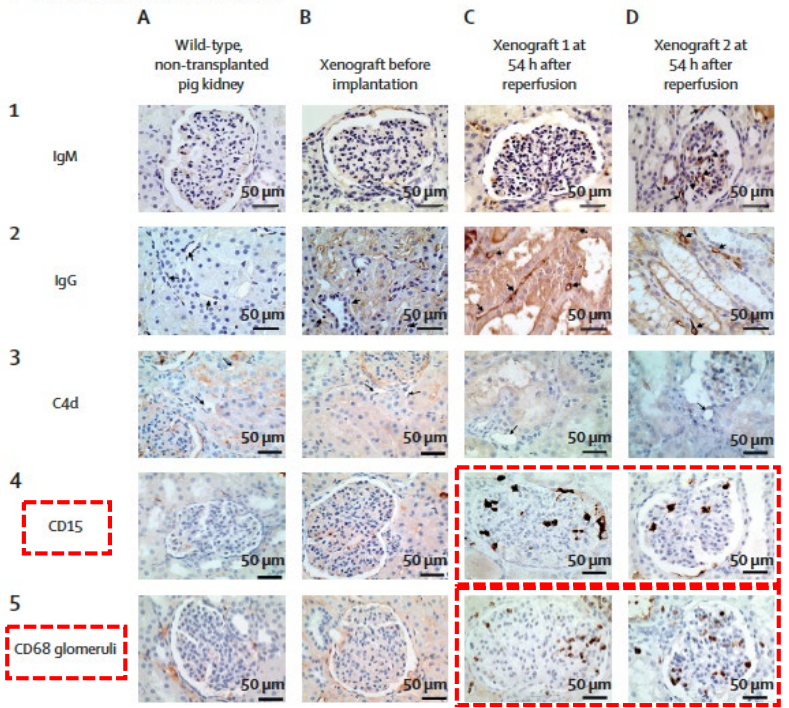
PATOLOGIA DEL RIGETTO DELL'ORGANO

Pathologia Multimodale Fenotipica

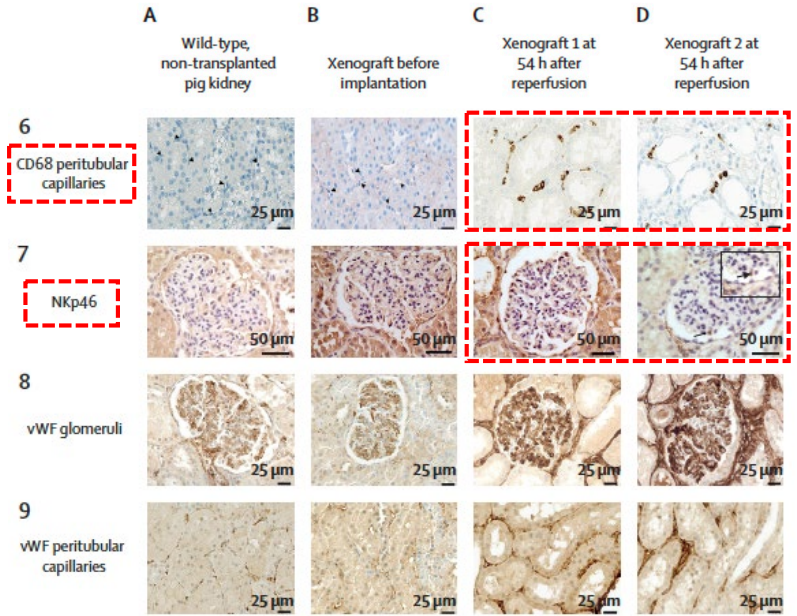
Immune response after pig-to-human kidney xenotransplantation: a multimodal phenotyping study

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B Immune and endothelial activation



B Immune and endothelial activation

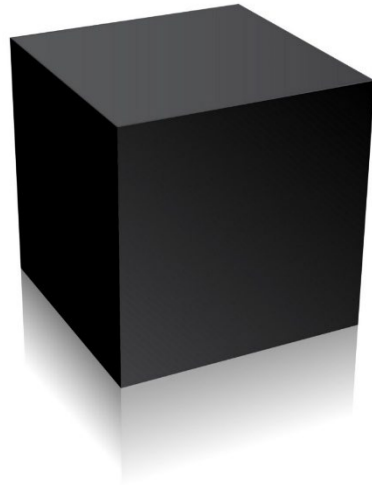


54 hours post-implant

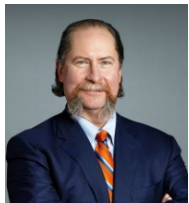
IL FUTURO DEI XENOTRAPIANTI

CONSIDERAZIONI PER IL SUCCESSO

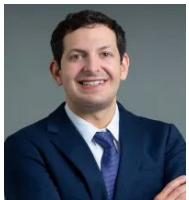
IL FUTURO DEL XENOTRAPIANTO



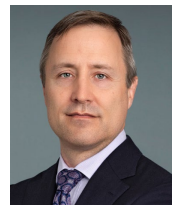
IL FUTURO DEL XENOTRAPIANTO



Robert Montgomery, MD



Jeff Stern, MD



Adam Griesemer, MD



TERAPIE

Quale trattamento terapeutico é il piú efficiente ?

GENETICA

Quale costrutto é Il migliore per lo sviluppo del programma ?

ZONOSIS

Sviluppo di assay per monitorare il rischio di infezioni

IMMUNOLOGIA CLINICAL

Sviluppo di assay per istocompatibilità e monitoraggio post-trapianto



Jef Boeke, PhD



Sapna Metha, MD



Massimo Mangiola, PhD

IL FUTURO DEL XENOTRAPIANTO



Brendan Keating, PhD

QUALI SONO
LE DIFFERENZE ?

PROTEOMICA
METABOLOMICA
GENOMICA

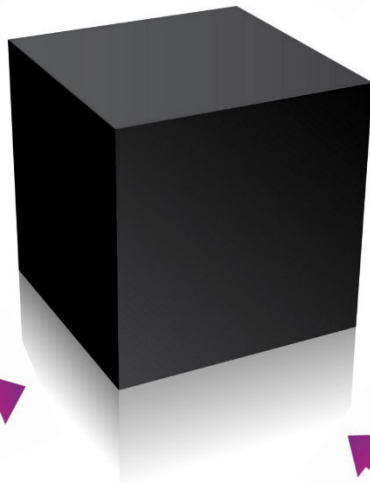


TOLLERANZA ?

Dimostrare che il
timo del donatore
induce tolleranza



Megan Sykes, MD



IMMUNOLOGIA
CELLULARE

Fenotipi
Funzionalità
Specificità



FISIOLOGIA

Puó il rene di
maiale sostituire
quello umano ?



Edward Y. Skolnik, MD Vasishta Tatapudi, MD

SUMMARY

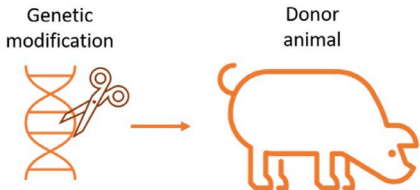


COMPATIBILITÀ MOLECOLARE

- Il livello di compatibilità molecolare correla con il rischio del rigetto
- Igegnerezare trapianti a basso rischio molecolare è possibile
- Abbassare l'immunosoppressione sembra possibile (work-in-progress)
- Trapianti ad alta compatibilità molecolare hanno il potenziale per una lunga sopravvivenza
- Questo programma migliorerà la qualità della vita dei pazienti

XENOTRAPIANTI

- Gli organi di maiale possono ridurre la differenza tra pazienti/organi
- I dati iniziali indicano che il rigetto inizia nei primi 10 giorni dal trapianto e ha un picco al 30simo giorno
- La terapia di desensitizzazione standard previene il rigetto
- L'immunità innata si attiva nei primi 2-3 giorni
- Molto deve essera fatto per capire come prolungare la sopravvivenza degli xeno-organi



Thank you

