La Medicina dei Trapianti

Antonio Amoroso

Centro Regionale Trapianti

REGIONE PIEMONTE

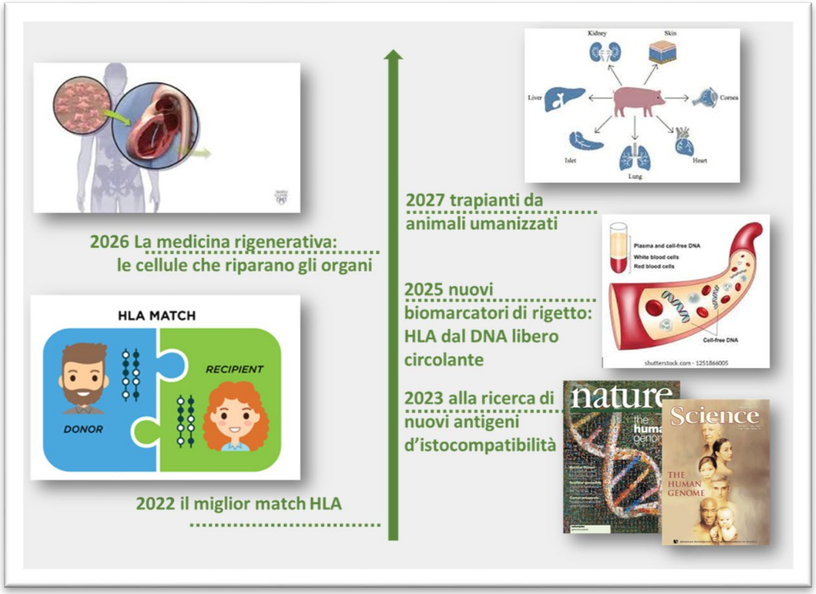
AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

28 maggio 2022

La Medicina dei Trapianti

- La storia dei Trapianti
- Le nuove prospettive
- Considerazioni finali

Sconosciuto - Landesmuseum Württemberg



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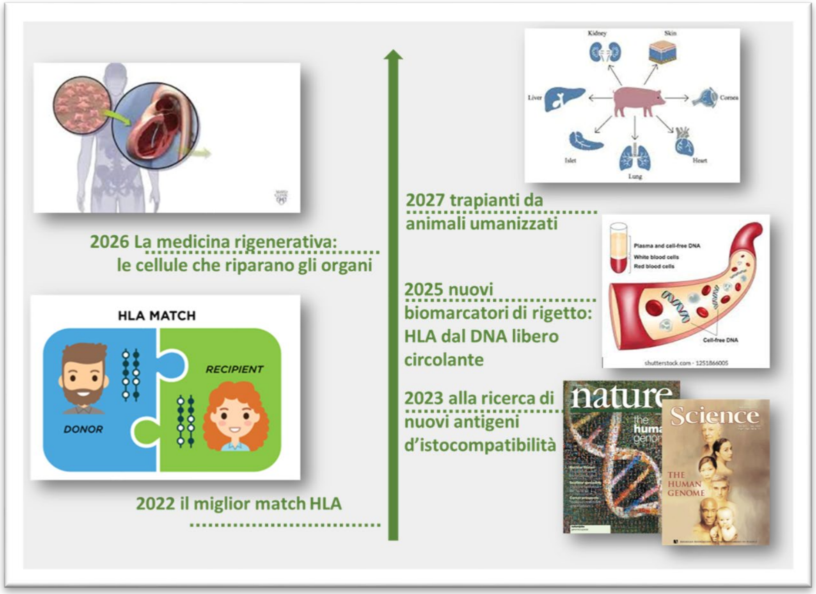


1964: Lung
Dr. James Hardy
University of Mississippi, Jackson

1954: Kidney
Dr. Joseph E. Murray
Brigham & Women's

1966: Pancreas/kidney
Drs. Richard Lillehei, William Kelly
University of Minnesota

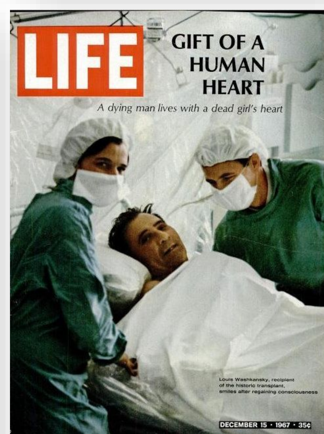
1981: Heart/lung
Dr. Bruce Reitz
Stanford University Hospital

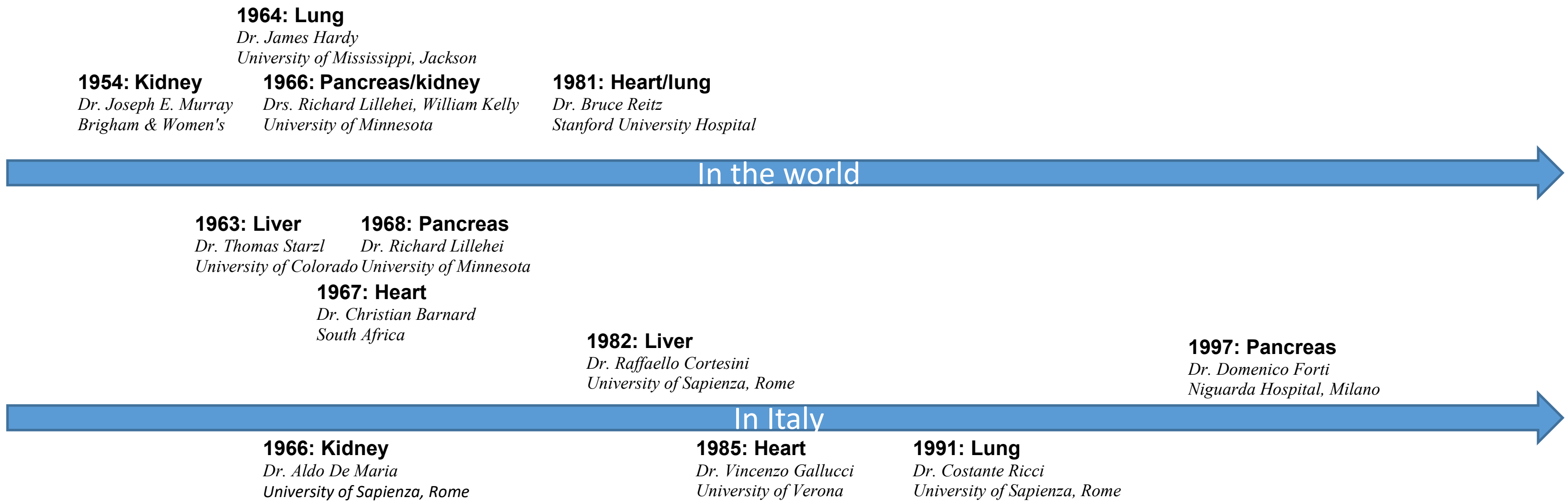
In the world

1963: Liver
Dr. Thomas Starzl
University of Colorado

1968: Pancreas
Dr. Richard Lillehei
University of Minnesota

1967: Heart
Dr. Christian Barnard
South Africa

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1982: Liver
Dr. Raffaello Cortesini
University of Sapienza, Rome
1997: Pancreas
Dr. Domenico Forti
Niguarda Hospital, Milano
In Italy
1966: Kidney
Dr. Aldo De Maria
University of Sapienza, Rome
1985: Heart
Dr. Vincenzo Gallucci
University of Verona
1991: Lung
Dr. Costante Ricci
University of Sapienza, Rome

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University of Verona

1991: Lung
Dr. Costante Ricci
University of Sapienza, Rome

1981: Kidney
Dr. Roberto Ferrero
Ospedale Molinette, Torino

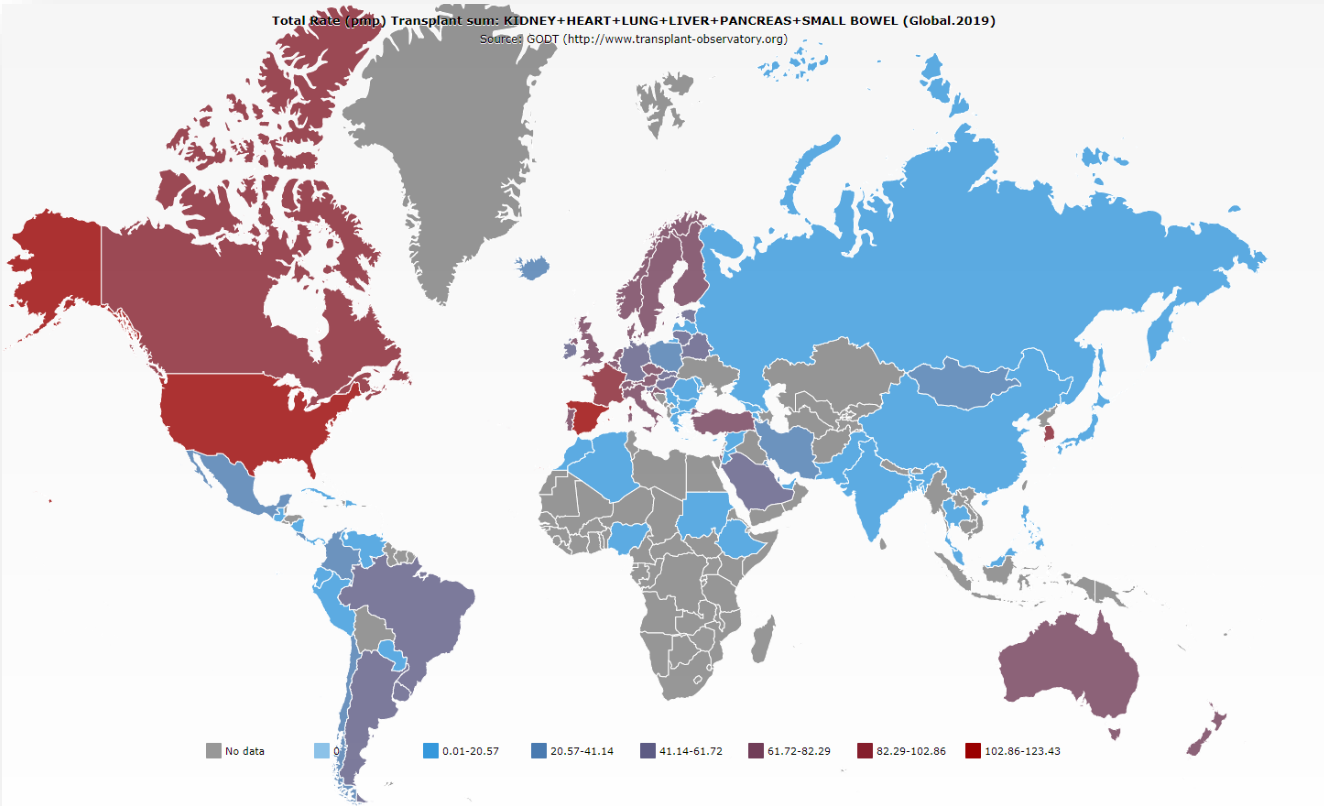
1990: Heart
Dr. Michele Di Summa
University of Torino

1993: Lung
Dr. Maurizio Mancuso
Ospedale Molinette, Torino

In Piedmont

1990: Liver
Dr. Mauro Salizzoni
University of Torino

1999: Pancreas
Dr. Mauro Salizzoni
Ospedale Molinette, Torino



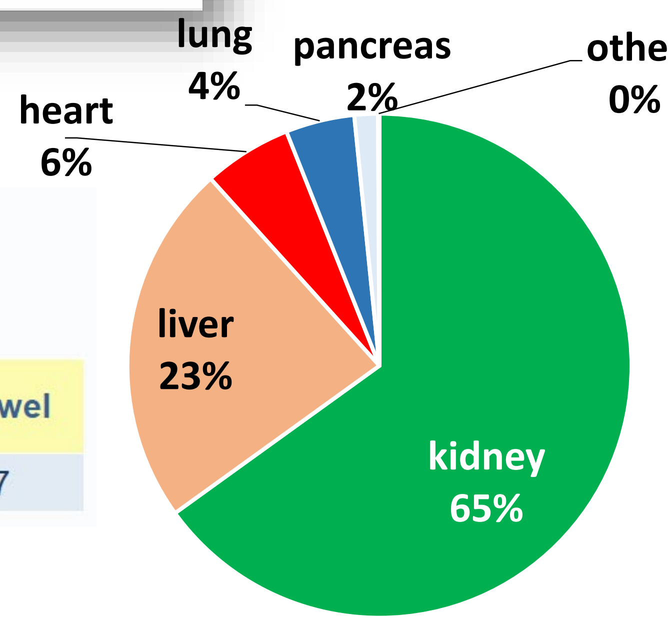
2019

40.608 deceased donors

153.863 solid organ transplants

Global activity in organ transplantation
Estimations 2019

Kidney	Liver	Heart	Lung	Pancreas	S. bowel
100 097	35 784	8 722	6 800	2 323	137



DONAZIONI E TRAPIANTI 2019

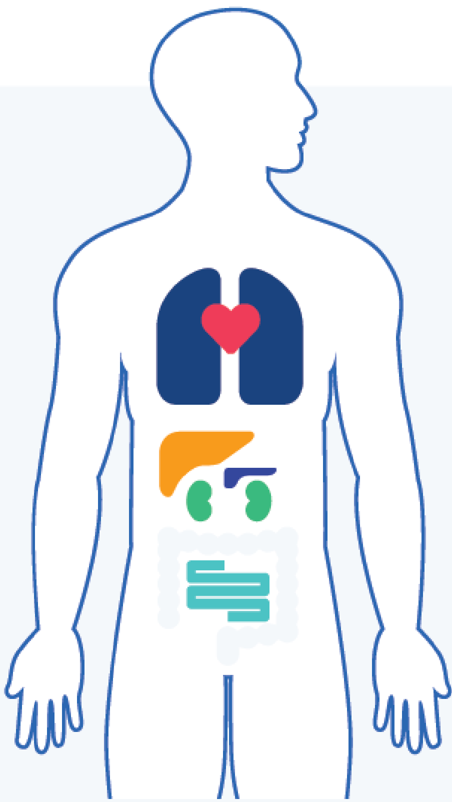
In Europa

NUMERO COMPLESSIVO DI DONATORI DECEDUTI*

11.346

9.686 con accertamento di morte cerebrale

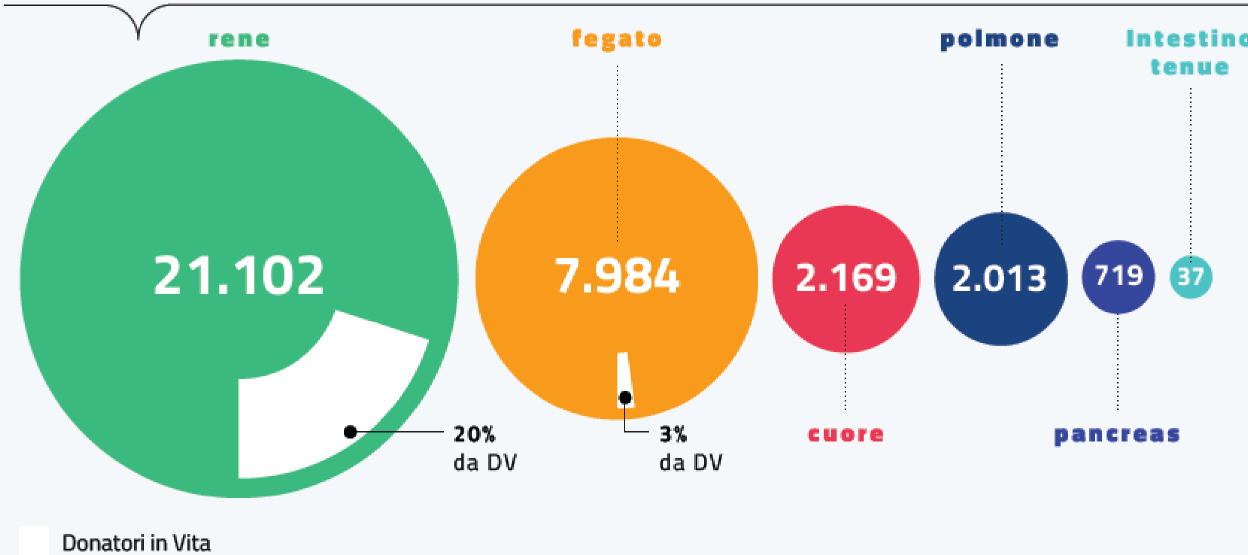
1.660 a cuore fermo



34.024

ORGANI TRAPIANTATI

Coinvolti 508,9 milioni di abitanti in Europa (28 stati membri)

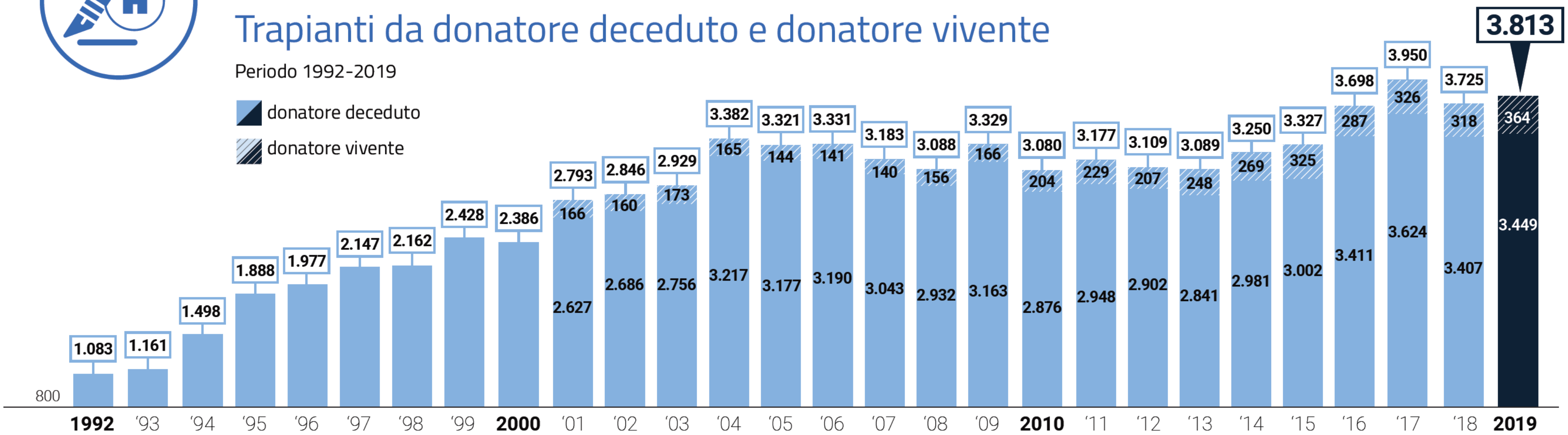


*I numeri si riferiscono a quei donatori a cui è stata applicata un'incisione chirurgica in sala operatoria indipendentemente dal prelievo dell'organo

ATTIVITÀ DI **TRAPIANTO** DI ORGANI 2019

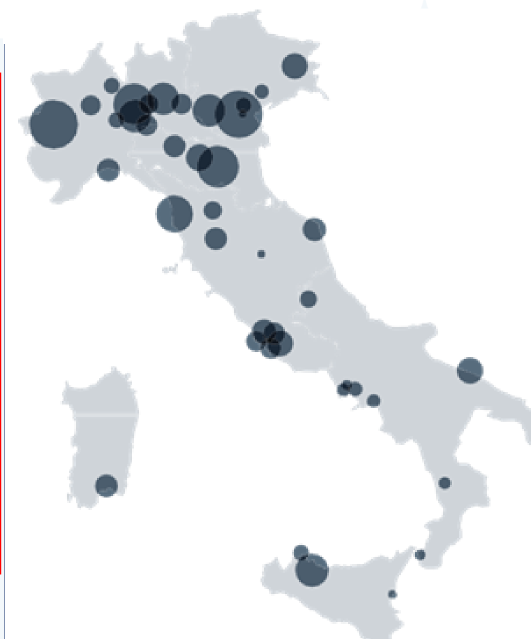
Trapianti da donatore deceduto e donatore vivente

Periodo 1992-2019

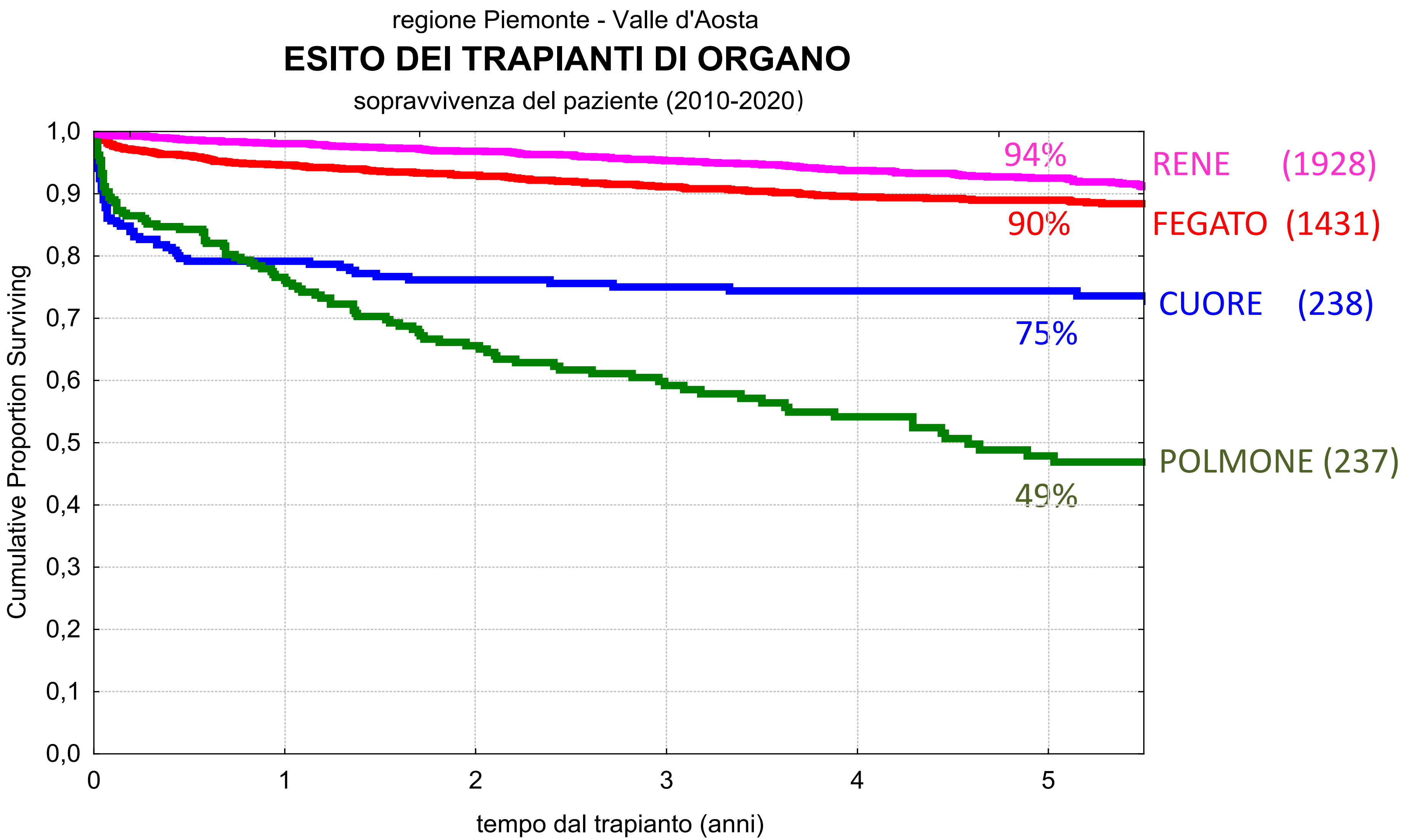


ATTIVITÀ PER OSPEDALE

Torino	360
Padova	335
Bologna	256
Milano - Niguarda	244
Pisa	205
Palermo - ISMETT	164
Milano - Policlinico	158
Verona	157
Bergamo	150
Modena	108
Bari	103
Udine	100
Roma - Tor Vergata	98
Roma - Gemelli	94
Ancona	82
Genova	78
Cagliari	76
Siena	75
Parma	74
Roma - Sapienza	70
Roma - San Camillo	66
Pavia	64
Roma - Bambin Gesù	63
Brescia	62
Novara	59
Milano - San Raffaele	56
Firenze	50
L'Aquila	44
Palermo - Civico	38
Varese	37
Milano - Tumori	36
Vicenza	36
Napoli - Cardarelli	35
Treviso	30
Salerno - San Giovanni	28
Napoli - Federico II	27
Cosenza	22
Reggio Calabria	18
Napoli - Monaldi	16
Catania	10
Padova - Pediatrico	9
Perugia	9

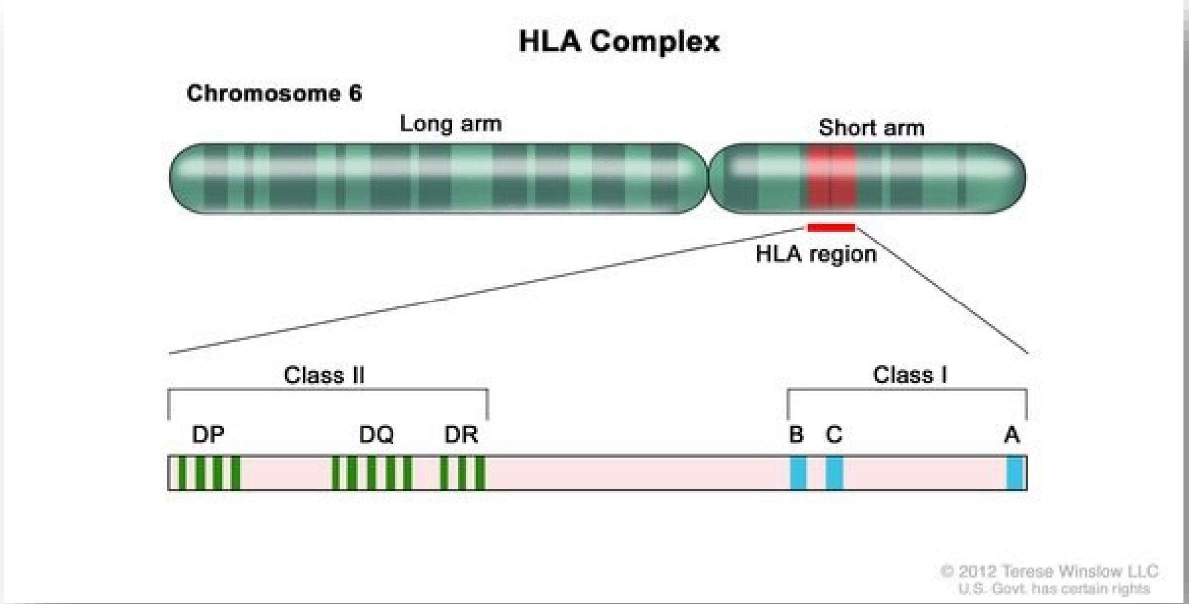


Come funzionano i trapianti fatti?



Centro Regionale Trapianti Piemonte – Valle d'Aosta the most important genes that address the immune response are the HLA genes

which encode membrane glycoproteins called HLA antigens



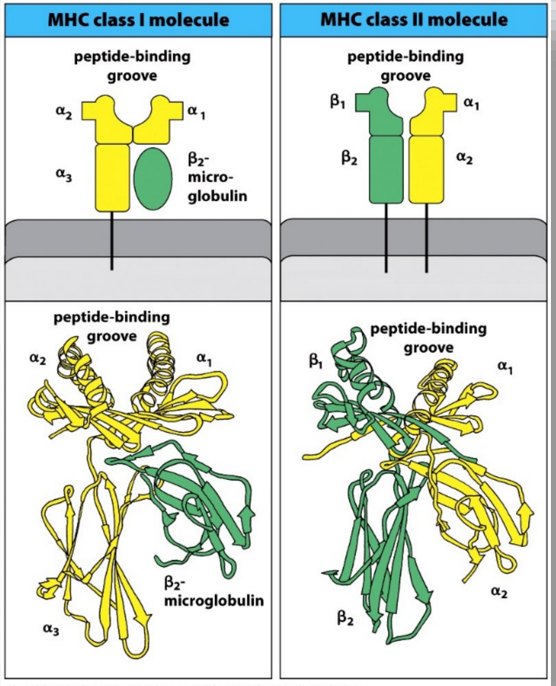
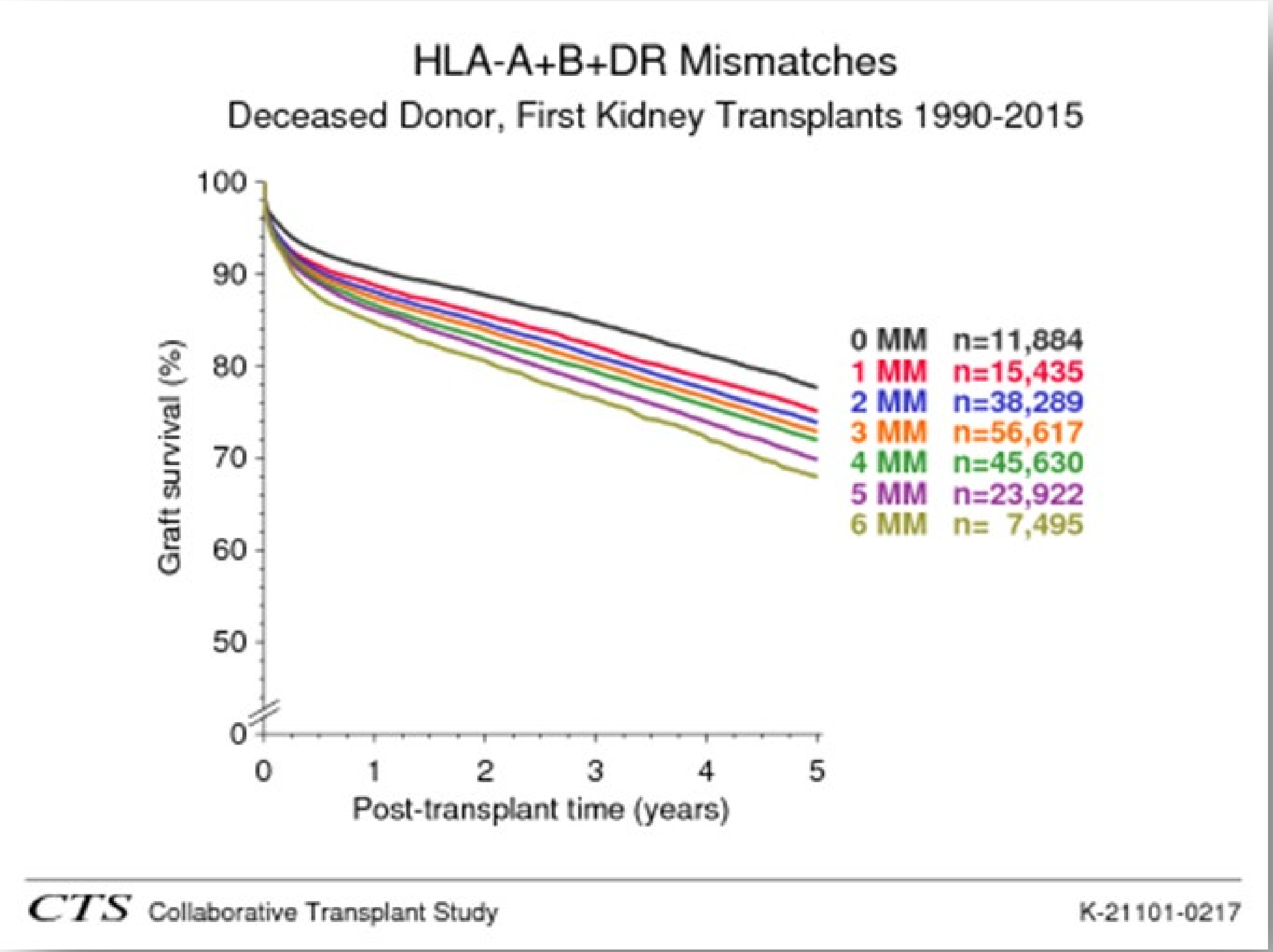


Figure 5.13 The Immune System, 3ed. (© Garland Science 2009)

- Il match HLA è uno dei predittori di successo più importanti per alcuni trapianti d'organo
- Per questo, almeno nel trapianto di rene, guida l'abbinamento tra donatore e ricevente



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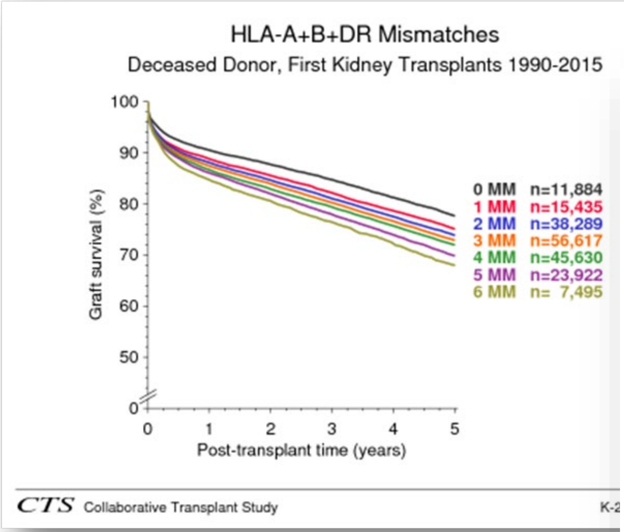
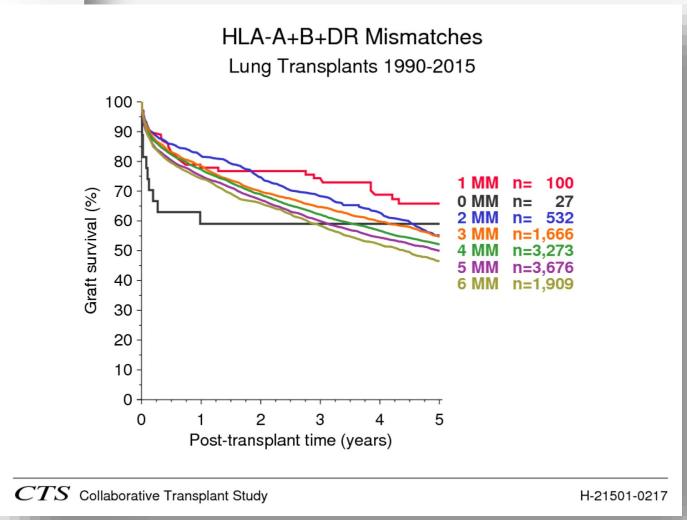
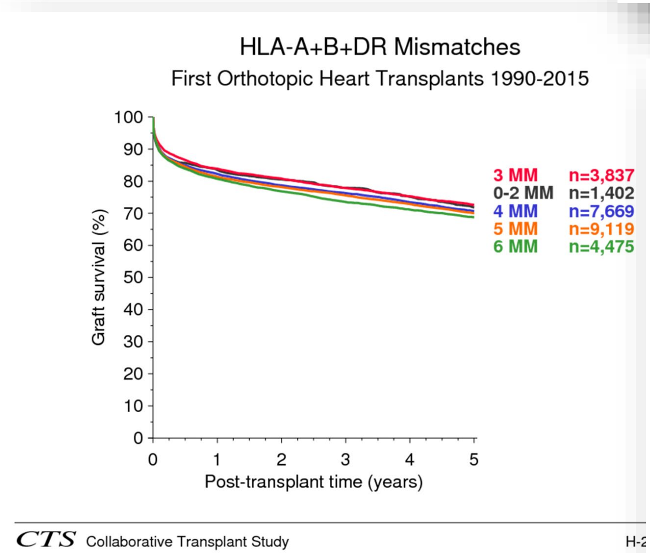
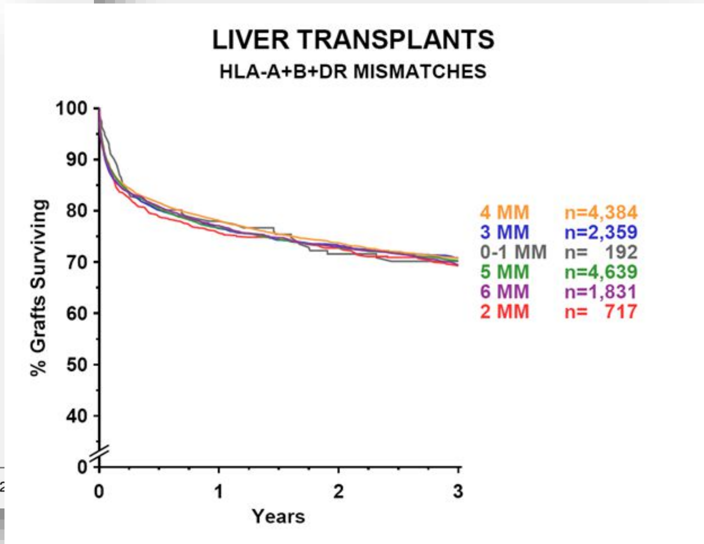
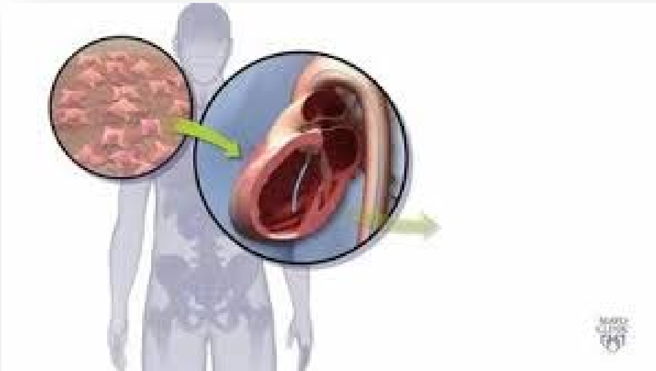


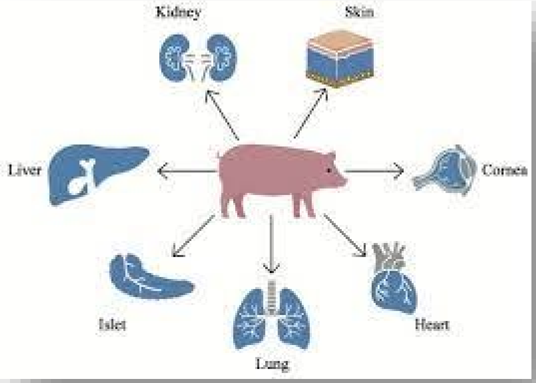






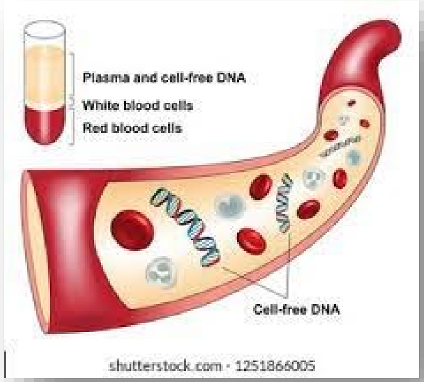
Medicina dei trapianti: prospettive future



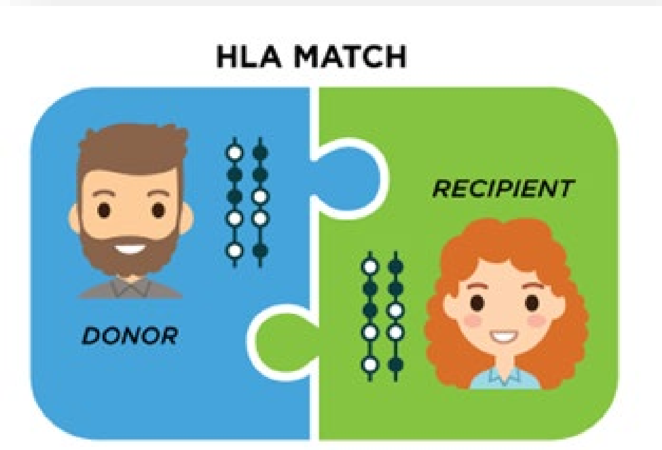


trapianti da animali umanizzati

La medicina rigenerativa: le cellule che riparano gli organi



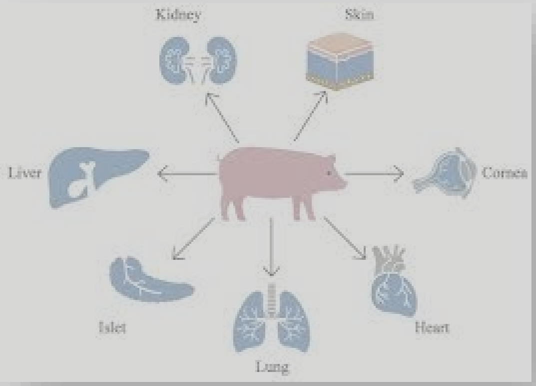
nuovi biomarcatori di rigetto: HLA dal DNA libero circolante



alla ricerca di nuovi antigeni d'istocompatibilità

2022 il miglior match HLA

Medicina dei trapianti: prospettive future



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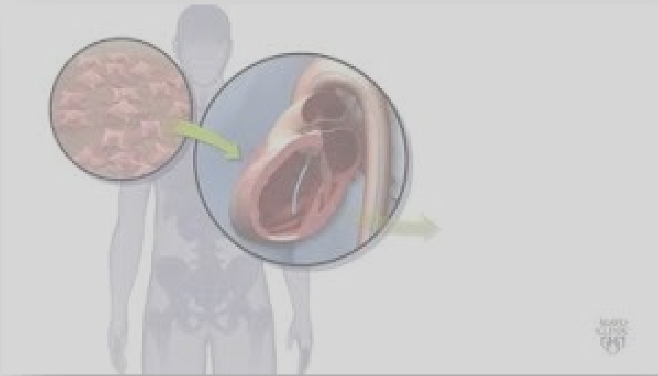

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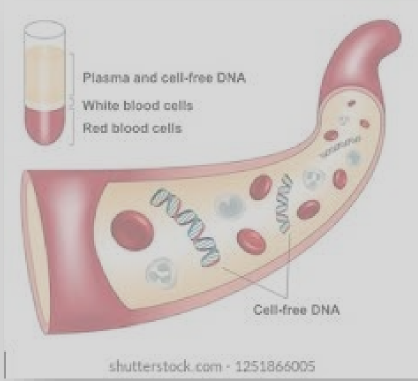

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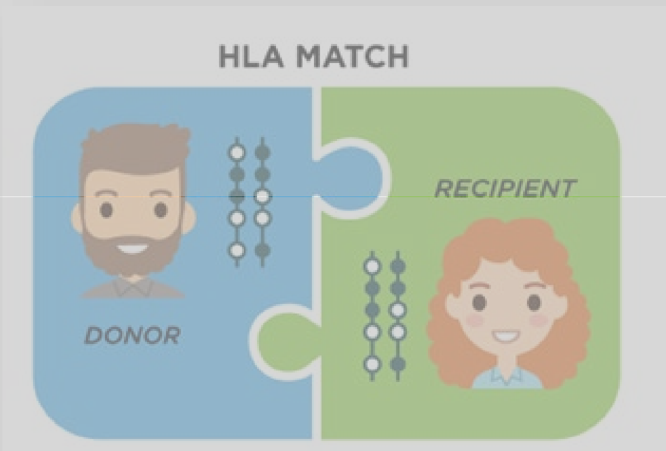

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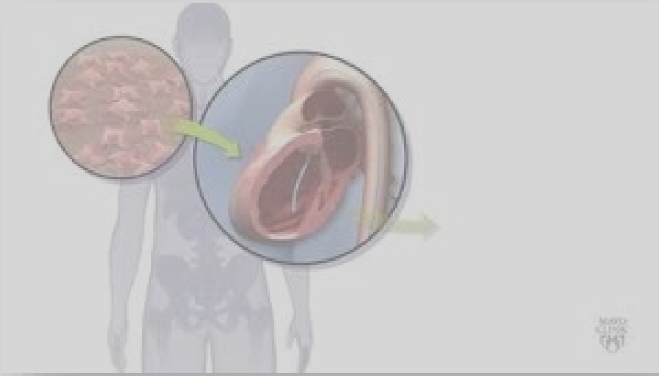
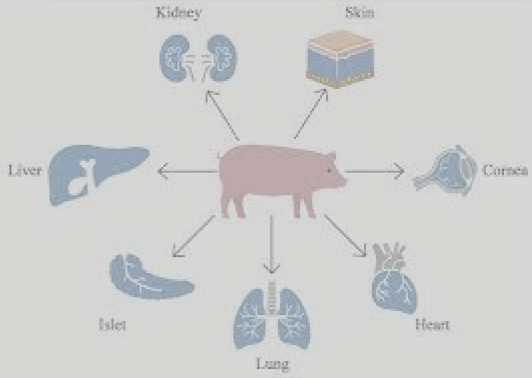
alla ricerca di nuovi antigeni d'istocompatibilità

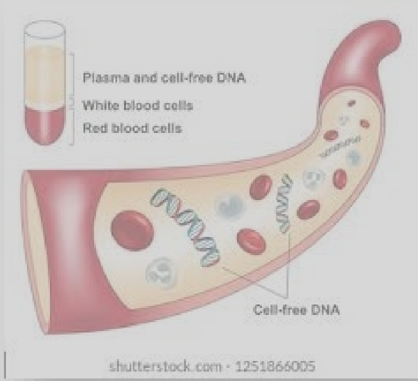
Storia dei trapianti: visioni future



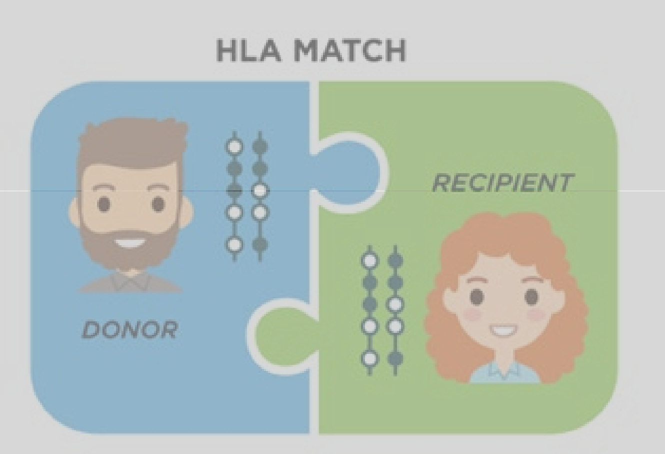


2027 trapianti da animali umanizzati

2026 La medicina rigenerativa: le cellule che riparano gli organi

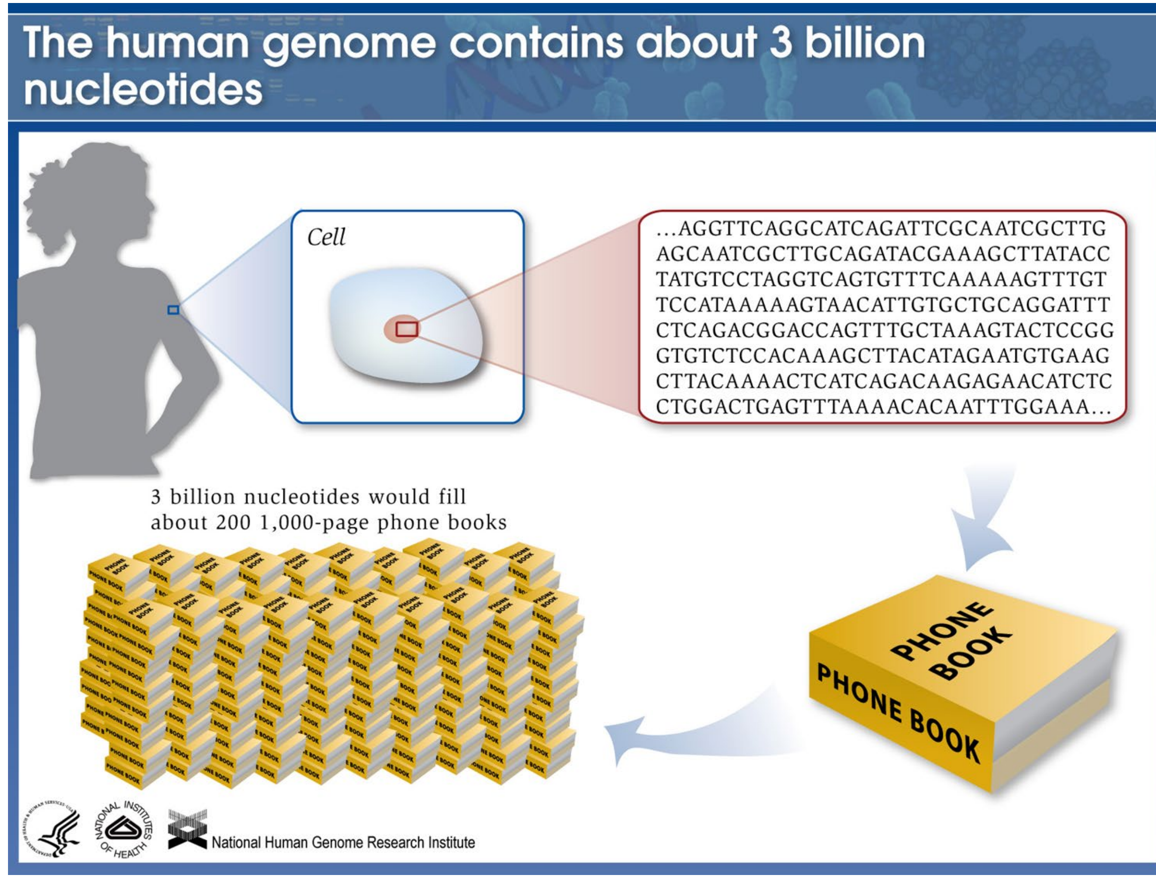


2025 nuovi biomarcatori di rigetto: HLA dal DNA libero circolante



2023 alla ricerca di nuovi antigeni d'istocompatibilità

2022 il miglior match HLA



From immunogenetics to immunogenomics: Applications in transplant medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomic Mismatch at *LIMS1* Locus and Kidney Allograft Rejection

N.J. Steers, Y. Li, Z. Drace, J.A. D'Addario, C. Fischman, L. Liu, K. Xu, Y.-J. Na, Y.D. Neugut, J.Y. Zhang, R. Sterken, O. Balderes, D. Bradbury, N. Ozturk, F. Ozay, S. Goswami, K. Mehl, J. Wold, F.Z. Jelloul, M. Rohanizadegan, C.E. Gillies, E.-R.M. Vasilescu, G. Vlad, Y.-A. Ko, S. Mohan, J. Radhakrishnan, D.J. Cohen, L.E. Ratner, F. Scolari, K. Susztak, M.G. Sampson, S. Deaglio, Y. Caliskan, J. Barasch, A.E. Courtney, A.P. Maxwell, A.J. McKnight, I. Ionita-Laza, S.J.L. Bakker, H. Snieder, M.H. de Borst, V. D'Agati, A. Amoroso, A.G. Gharavi, and K. Kiryluk

ABSTRACT

BACKGROUND

In the context of kidney transplantation, genomic incompatibilities between donor and recipient may lead to allosensitization against new antigens. We hypothesized that recessive inheritance of gene-disrupting variants may represent a risk factor for allograft rejection.

METHODS

We performed a two-stage genetic association study of kidney allograft rejection. In the first stage, we performed a recessive association screen of 50 common gene-intersecting deletion polymorphisms in a cohort of kidney transplant recipients. In the second stage, we replicated our findings in three independent cohorts of donor–recipient pairs. We defined genomic collision as a specific donor–recipient genotype combination in which a recipient who was homozygous for a gene-intersecting deletion received a transplant from a nonhomozygous donor. Identification of alloantibodies was performed with the use of protein arrays, enzyme-linked immunosorbent assays, and Western blot analyses.

RESULTS

In the discovery cohort, which included 705 recipients, we found a significant association with allograft rejection at the *LIMS1* locus represented by rs893403 (hazard ratio with the risk genotype vs. nonrisk genotypes, 1.84; 95% confidence interval [CI], 1.35 to 2.50; $P=9.8\times10^{-5}$). This effect was replicated under the genomic-collision model in three independent cohorts involving a total of 2004 donor–recipient pairs (hazard ratio, 1.55; 95% CI, 1.25 to 1.93; $P=6.5\times10^{-5}$). In the combined analysis (discovery cohort plus replication cohorts), the risk genotype was associated with a higher risk of rejection than the nonrisk genotype (hazard ratio, 1.63; 95% CI, 1.37 to 1.95; $P=4.7\times10^{-8}$). We identified a specific antibody response against LIMS1, a kidney-expressed protein encoded within the collision locus. The response involved predominantly IgG2 and IgG3 antibody subclasses.

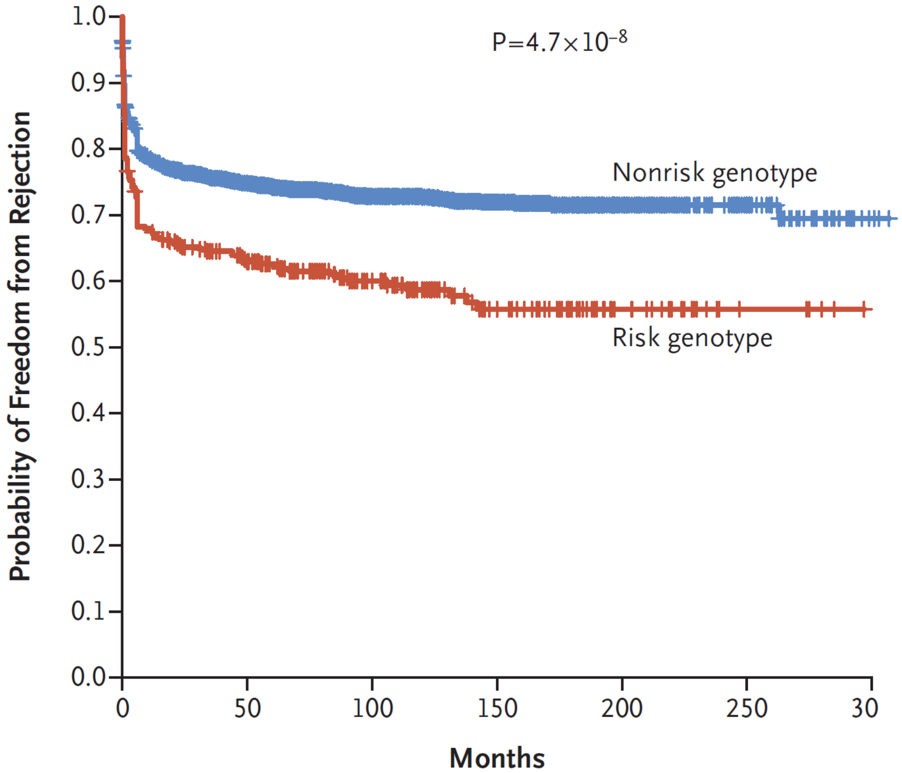
CONCLUSIONS

We found that the *LIMS1* locus appeared to encode a minor histocompatibility antigen. Genomic collision at this locus was associated with rejection of the kidney allograft and with production of anti-LIMS1 IgG2 and IgG3. (Funded by the Columbia University Transplant Center and others.)

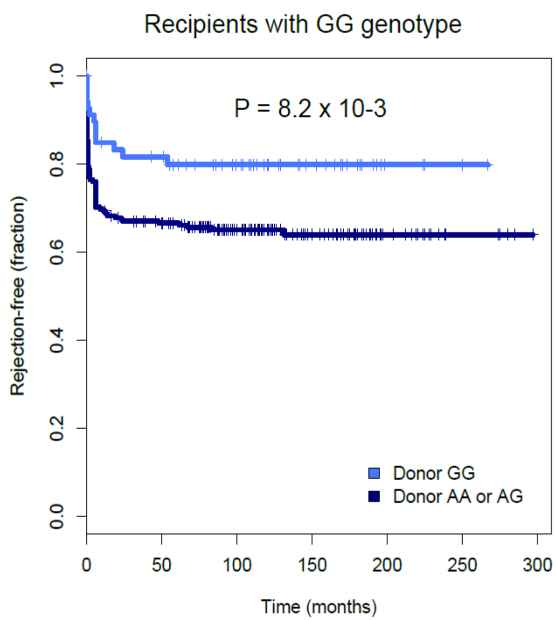
- Incompatibilità genomiche tra donatore e ricevente possono influenzare il rigetto acuto del trapianto di rene

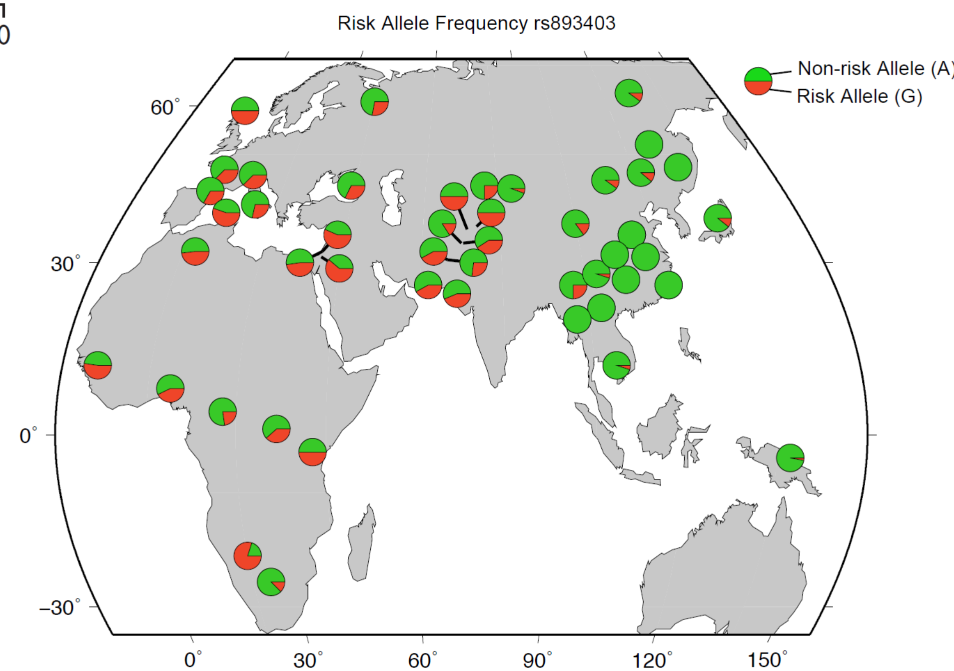
- Valutando tutte le incompatibilità genomiche tra donatori e riceventi, che correlavano con il rigetto, abbiamo identificato che quelle per il gene *LIMS1* erano importanti

- Abbiamo scoperto un nuovo "antigene minore d'istocompatibilità" fuori dalla regione HLA, che influenza l'esito del trapianto di rene



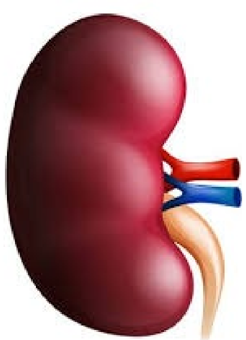
- Tutti noi possediamo un gene *LIMS*, che può avere una variante «G» o una variante «A». Coloro che portano 2 copie «G» producono meno proteina LIMS, che si trova espressa nel nostro organismo, anche nei reni ed altri organi
- I riceventi «GG» - genotipo a rischio – rigettano il rene più frequentemente.





Possible effects of *LIMS1* INS / DEL variants

«wild type» allele A	↑	Production of protein	+
Mutated or deleted allele G	↓	Reduction or absence of the protein	−



+/+

+/−

+/+

+/−

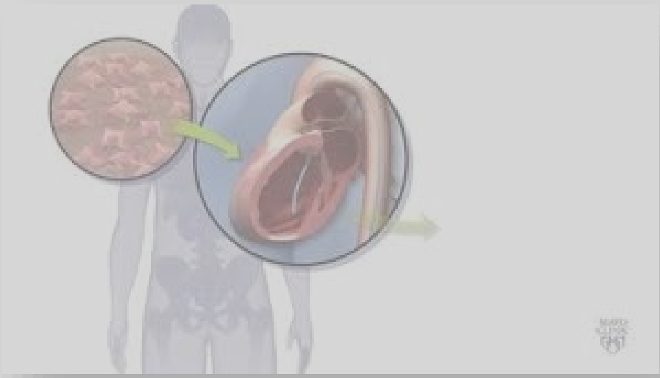
−/−

immune response

no

yes

Medicina dei trapianti: prospettive future



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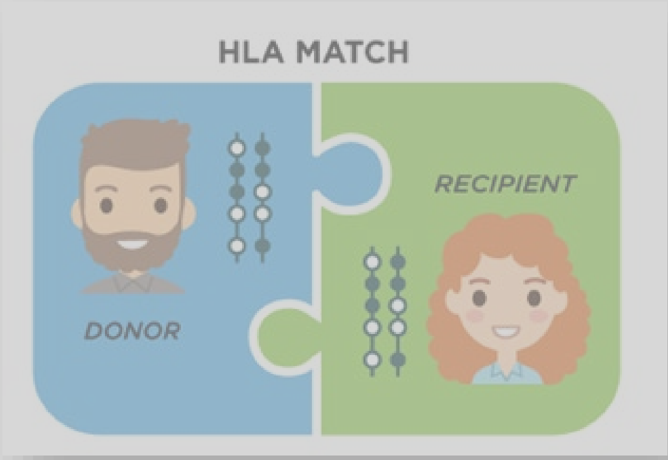

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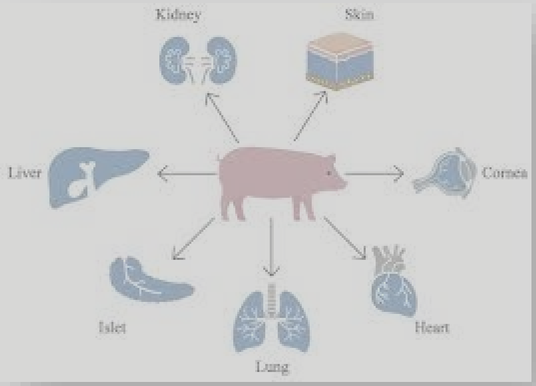

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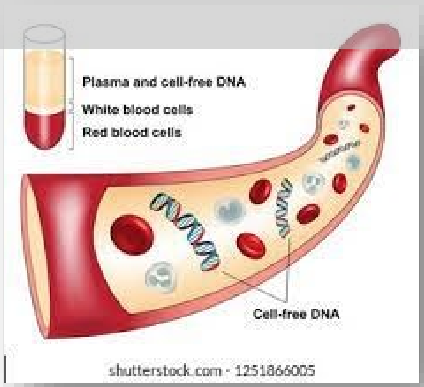
nuovi biomarcatori di rigetto: HLA dal DNA libero circolante



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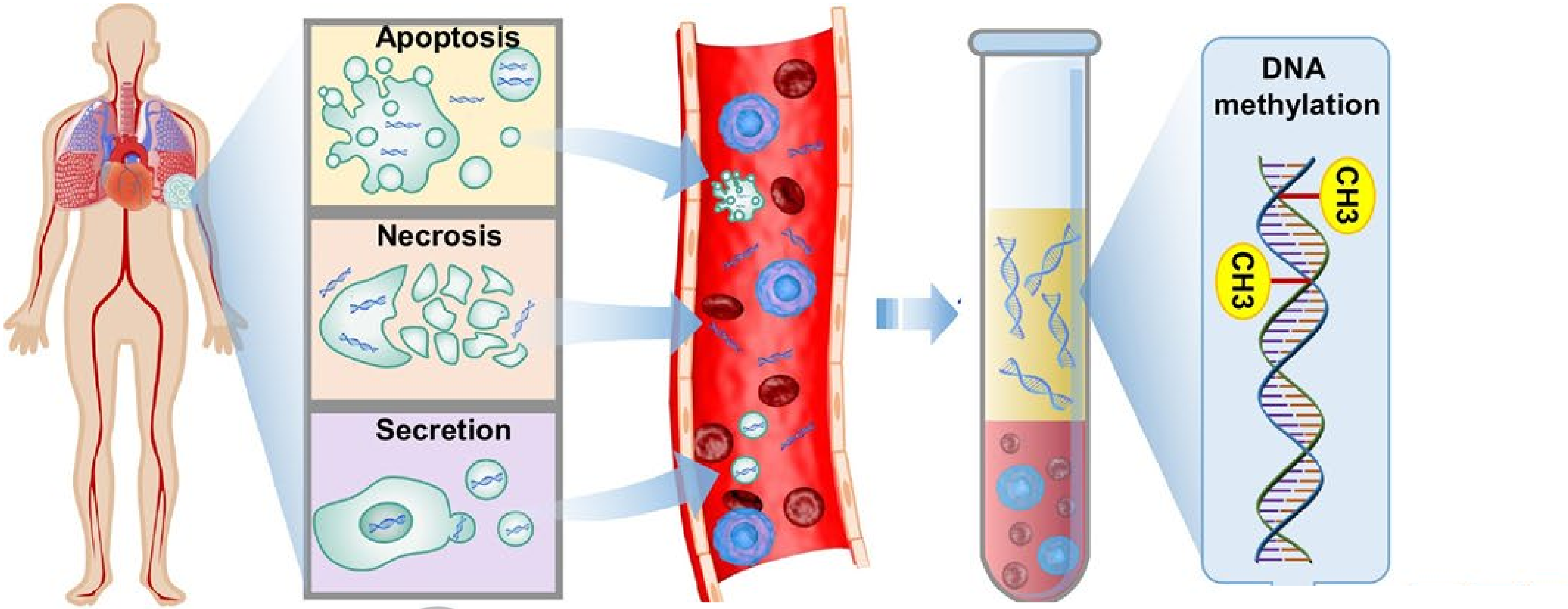
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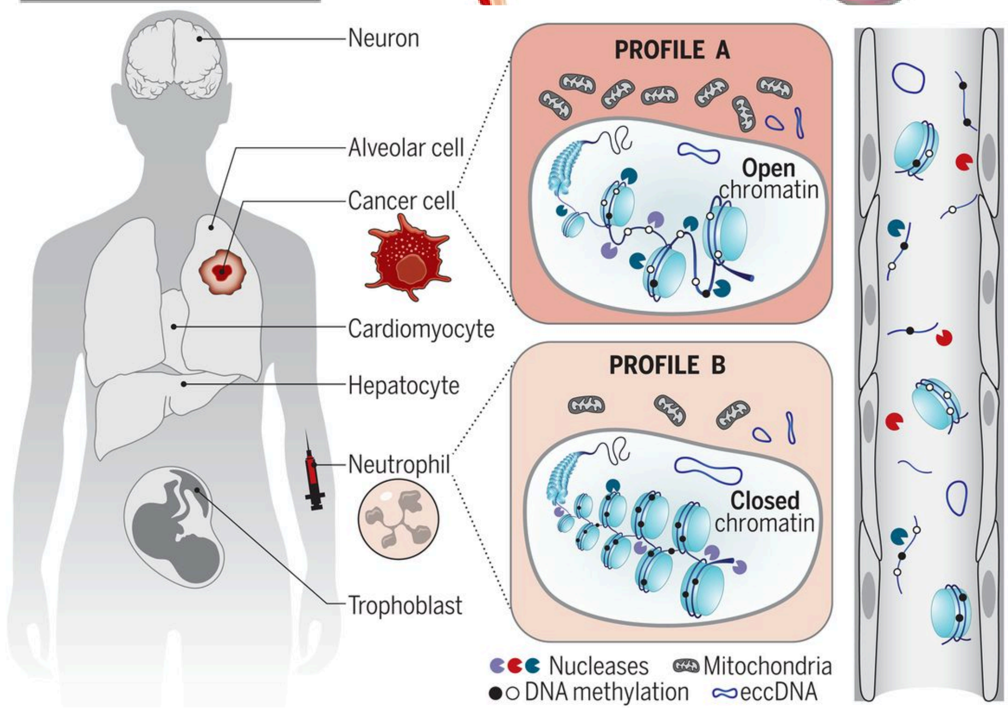
Necrosis
Secretion
DNA
methylation
CH3
CH3


Neuron
Alveolar cell
Cancer cell
Cardiomyocyte
Hepatocyte
Neutrophil
Trophoblast
PROFILE A
Open
chromatin
PROFILE B
Closed
chromatin
Nucleases
Mitochondria
DNA methylation
eccDNA

ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

CrossMark

HLA-DRB1 mismatch-based identification of donor-derived cell free DNA (dd-cfDNA) as a marker of rejection in heart transplant recipients: A single-institution pilot study

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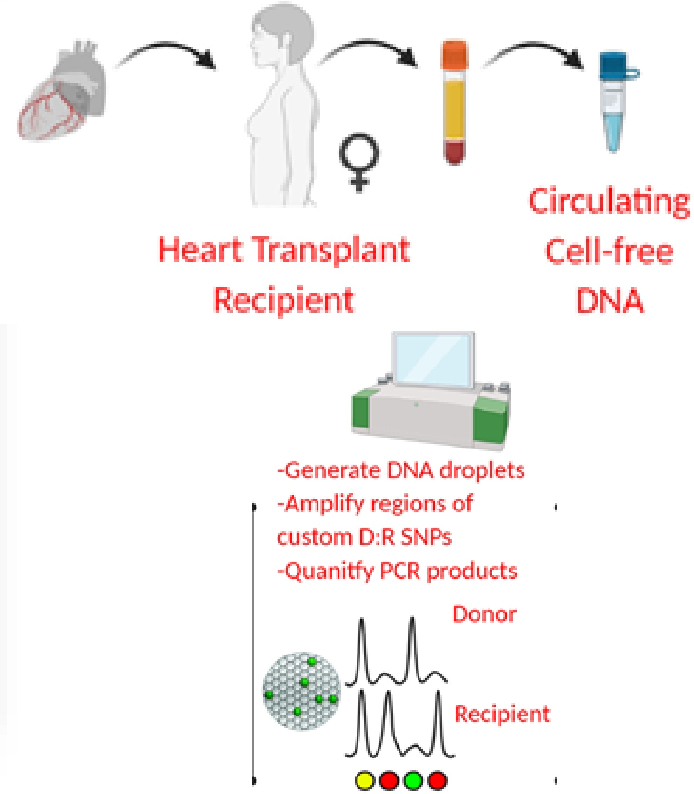
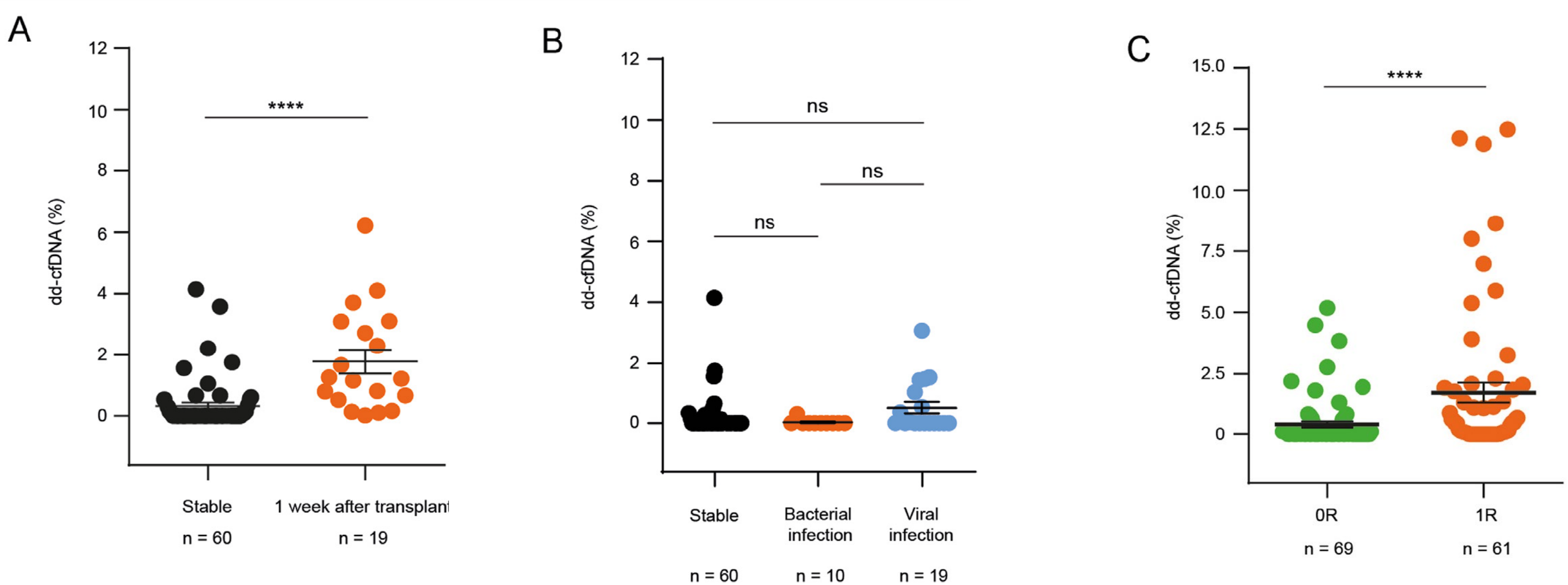
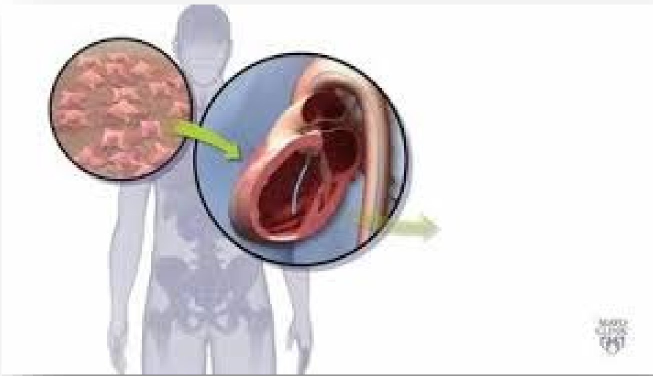
From the [a]Department of Medical Sciences, University of Turin, Turin, Italy; [b]Cardiac Surgery Division, Surgical Sciences Department, Heart and Lung Transplant Center, Città della Salute e della Scienza University Hospital of Torino, Torino, Italy; [c]Immunogenetics and Transplant Biology Service, Città della Salute e della Scienza University Hospital, Turin, Italy; and the [d]Department of Oncology, University of Turin and Pathology Unit, Città della Salute e della Scienza Hospital, Turin, Italy.

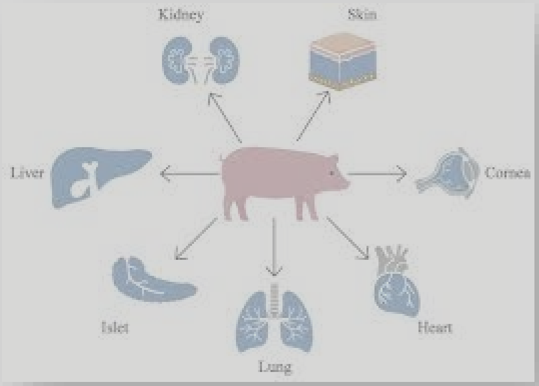




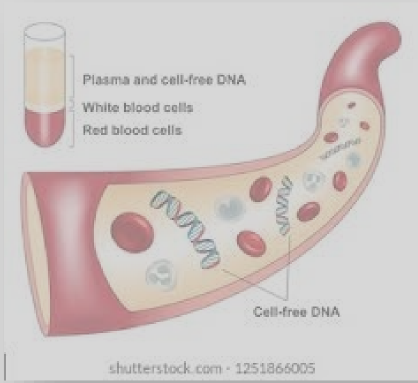
Medicina dei trapianti: prospettive future



La medicina rigenerativa: le cellule che riparano gli organi

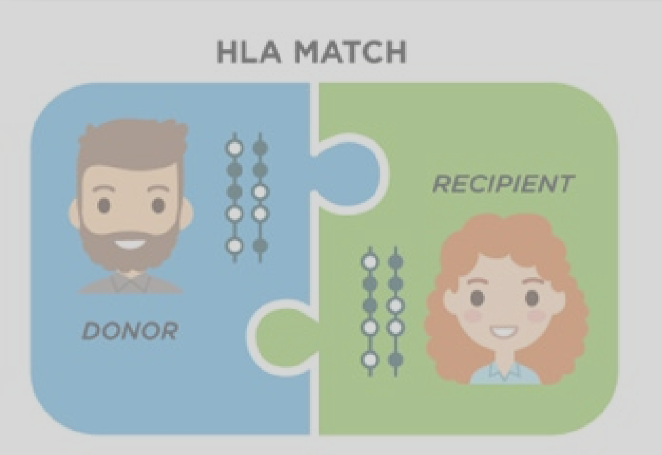


trapianti da animali umanizzati

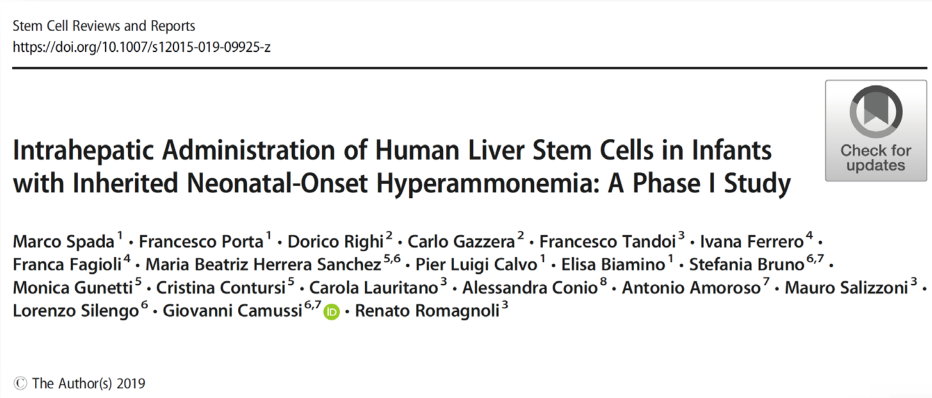


nuovi biomarcatori di rigetto: HLA dal DNA libero circolante

alla ricerca di nuovi antigeni d'istocompatibilità

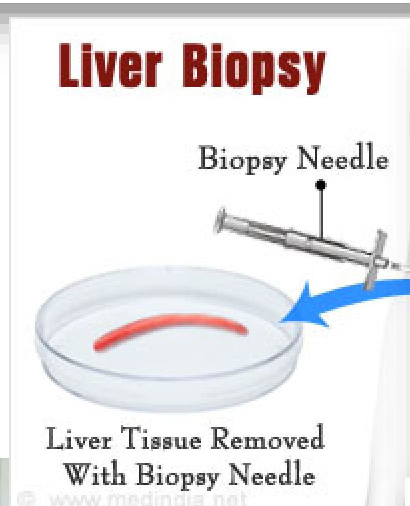


2022 il miglior match HLA


Stem Cell Reviews and Reports
https://doi.org/10.1007/s12015-019-09925-z

Intrahepatic Administration of Human Liver Stem Cells in Infants with Inherited Neonatal-Onset Hyperammonemia: A Phase I Study

Marco Spada[1] · Francesco Porta[1] · Dorico Righi[2] · Carlo Gazzera[2] · Francesco Tandoi[3] · Ivana Ferrero[4] · Franca Fagioli[4] · Maria Beatriz Herrera Sanchez[5,6] · Pier Luigi Calvo[1] · Elisa Biamino[1] · Stefania Bruno[6,7] · Monica Gunetti[5] · Cristina Contursi[5] · Carola Lauritano[3] · Alessandra Conio[8] · Antonio Amoroso[7] · Mauro Salizzoni[3] · Lorenzo Silengo[6] · Giovanni Camussi[6,7] · Renato Romagnoli[3]



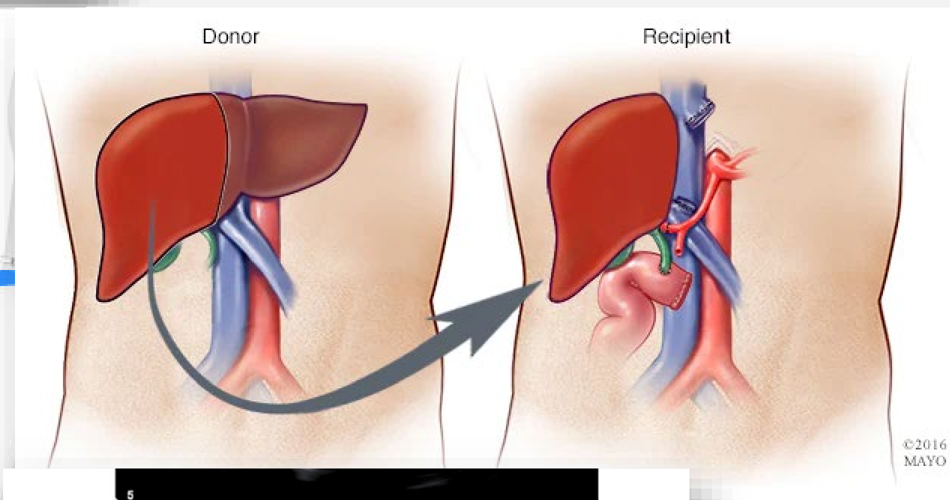
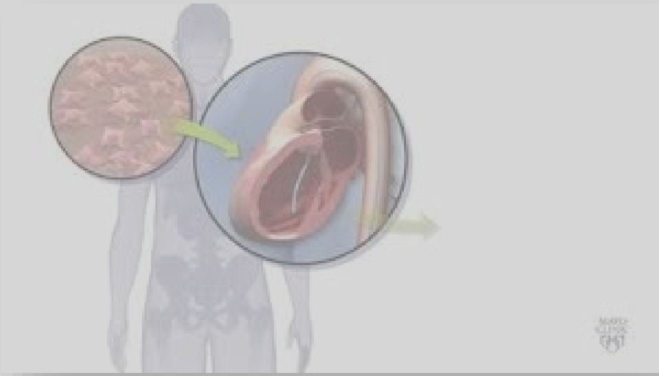
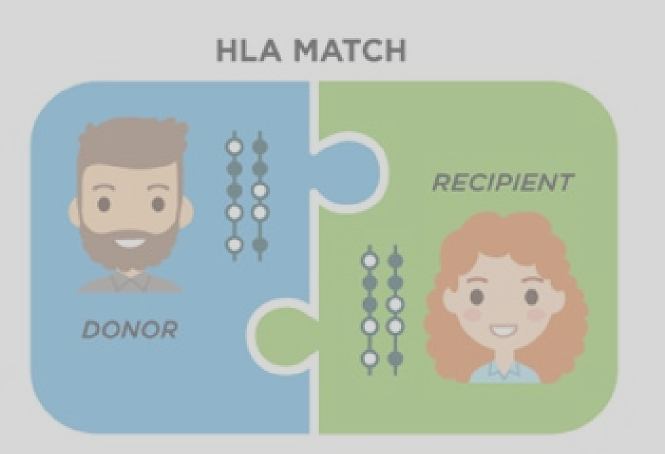


Fig. 3 Ultrasound-guided percutaneous intrahepatic injection of human liver stem cells (HLSCs) in an infant with neonatal-onset inherited hyperammonemia while in stable metabolic conditions. HLSCs injection and real-time ultrasound images are presented

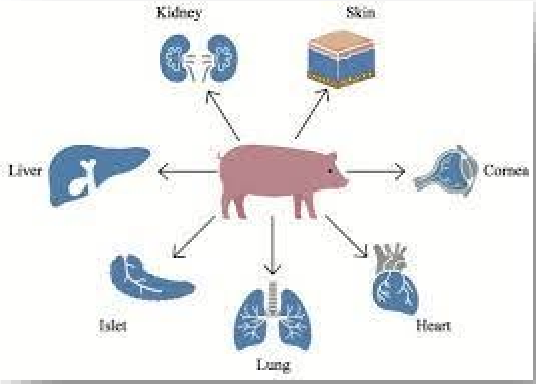
Medicina dei trapianti: prospettive future



La medicina rigenerativa:
le cellule che riparano gli organi



2022 il miglior match HLA



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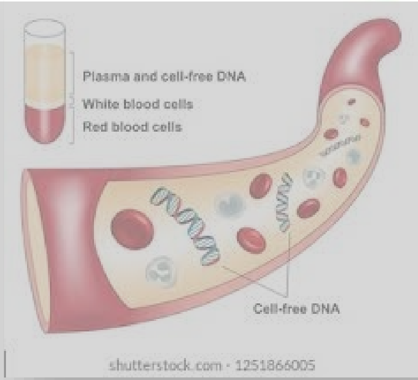
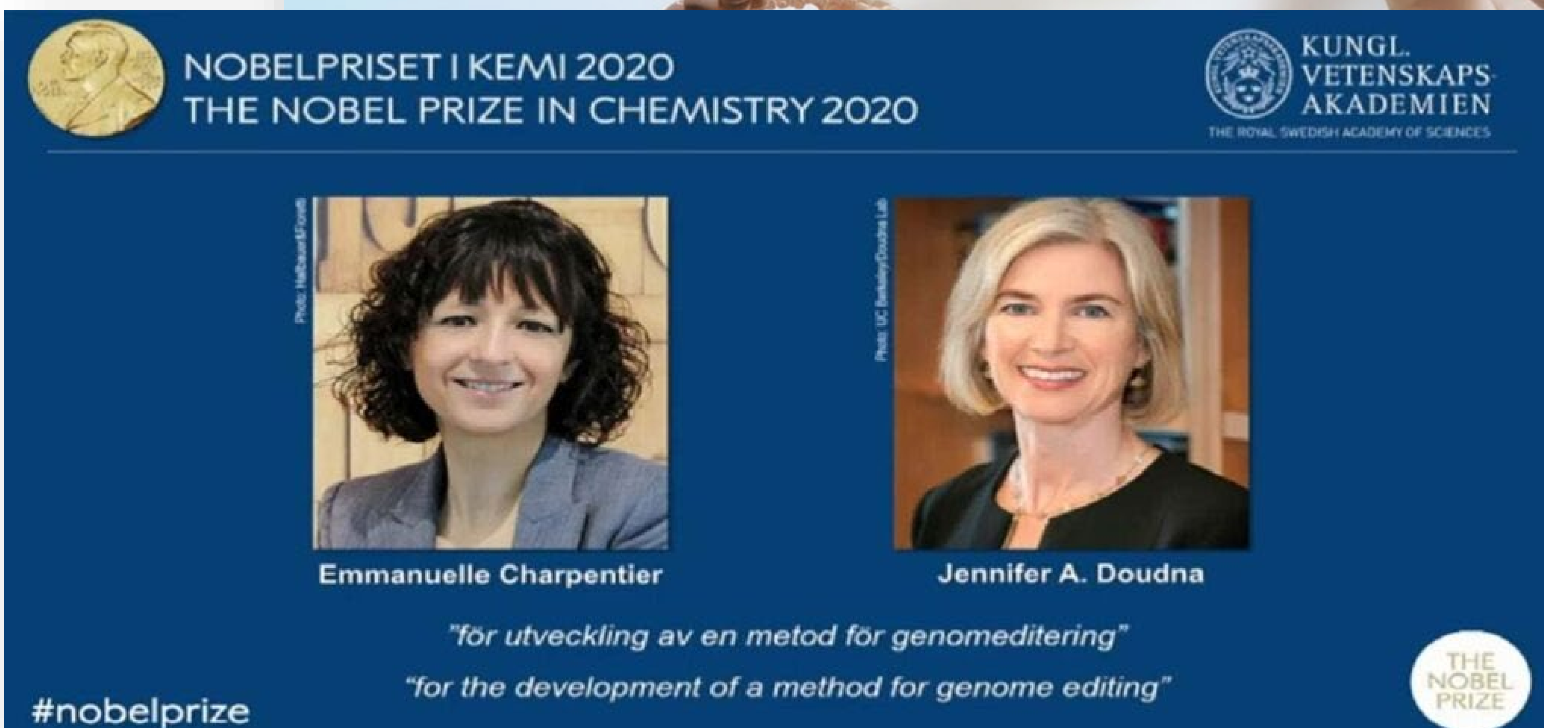


alla ricerca di nuovi antigeni d'istocompatibilità

CRISPR / CAS9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THE NOBEL PRIZE

XENOTRAPIANTI

La carenza di organi umani da trapiantare è un grosso problema. Negli Stati Uniti ci sono **> 100.000 individui in lista di attesa**. Ci sono **22 decessi al giorno** fra questi individui.

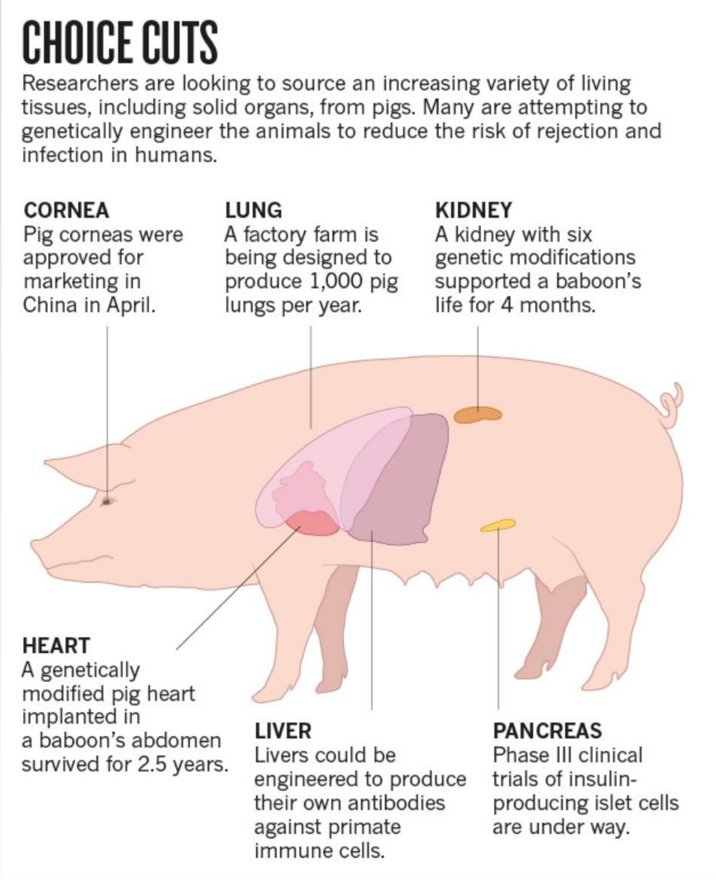
L'uso di CRISPR faciliterebbe l'uso di **organi di origine animale**, producibili su larga scala.

- Eliminazione di materiale retrovirale del virus PERVs inserito nel DNA suino che si riattiva una volta trapiantato in umano. Tramite CRISPR sono riusciti ad eliminare le 62 copie virali presenti nel genoma. *Yang, Luhan, et al., 2015*

- Il gene suino α-Gal è uno dei maggiori target della risposta immunitaria dell'ospite. Tramite CRISPR è possibile inattivare in maniera efficiente tale gene. *Sato, Masahiro, et al., 2014*

- Modifiche genetiche permettono di far esprimere immuni modulatori umani come il CTLA4 in isole pancreatiche suine da trapiantare in pazienti con DMI. *Hering BJ, Cozzi E, et al., 2016*

- Tramite CRISPR è possibile effettuare modifiche genetiche germinali permettendo di creare industrialmente linee di suini per xenotrapianti. *Feng, Wanyou, et al. 2015*



XENOTRAPIANTI

La carenza di organi umani da trapiantare è un grosso
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questi individu

The New York Times

In a First, Surgeons Attached a Pig Kidney to a Human, and It Worked

A kidney grown in a genetically altered pig functions normally, scientists reported. The procedure may open the door to a renewable source of desperately needed organs.

568

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.

ABSTRACT

BACKGROUND

Xenografts from genetically modified pigs have become one of the most promising solutions to the dearth of human organs available for transplantation. The challenge in this model has been hyperacute rejection. To avoid this, pigs have been bred with a knockout of the alpha-1,3-galactosyltransferase gene and with subcapsular autologous thymic tissue.

METHODS

We transplanted kidneys from these genetically modified pigs into two brain-dead human recipients whose circulatory and respiratory activity was maintained on ventilators for the duration of the study. We performed serial biopsies and monitored the urine output and kinetic estimated glomerular filtration rate (eGFR) to assess renal function and xenograft rejection.

RESULTS

The xenograft in both recipients began to make urine within moments after reperfusion. Over the 54-hour study, the kinetic eGFR increased from 23 ml per minute per 1.73 m^2 of body-surface area before transplantation to 62 ml per minute per 1.73 m^2 after transplantation in Recipient 1 and from 55 to 109 ml per minute per 1.73 m^2 in Recipient 2. In both recipients, the creatinine level, which had been at a steady state, decreased after implantation of the xenograft, from 1.97 to 0.82 mg per deciliter in Recipient 1 and from 1.10 to 0.57 mg per deciliter in Recipient 2. The transplanted kidneys remained pink and well-perfused, continuing to make urine throughout the study. Biopsies that were performed at 6, 24, 48, and 54 hours revealed no signs of hyperacute or antibody-mediated rejection. Hourly urine output with the xenograft was more than double the output with the native kidneys.

CONCLUSIONS

Genetically modified kidney xenografts from pigs remained viable and functioning in brain-dead human recipients for 54 hours, without signs of hyperacute rejection. (Funded by Lung Biotechnology.)

From the New York University (NYU) Langone Transplant Institute (R.A.M., J.M.S., B.E.L., V.S.T., M.M., E.W., N.L., C.D., R.A.D., B.S., G.B., G.P., N.M.A., S.A.M., Z.A.S.), the Departments of Pathology (M.W.), Anesthesia (P.S.), Biochemistry and Molecular Pharmacology (J.D.B.), and Cardiothoracic Surgery (H.P.), and the Institute for Systems Genetics (J.D.B.), NYU Langone Health, the Department of Population Health, Division of Medical Ethics (B.P.), NYU Grossman School of Medicine (S.C.), and the Columbia Center for Translational Immunology and the Department of Surgery, Columbia University (E.D., A.G.) — all in New York; Revivicor, Blacksburg, VA (D.A., A.D., A.F.-K., M.K., L.B.); United Therapeutics, Silver Spring, MD (M.L.); and the Department of Surgery, University of Pennsylvania, Philadelphia (B.K.). Dr. Montgomery can be contacted at robert.montgomery@nyulangone.org or at NYU Langone Health, 550 First Ave., New York, NY 10016.

N Engl J Med 2022;386:1889-98.
DOI: 10.1056/NEJMoa2120238

XENOTRAPIANTI

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568

CHOICE CUTS

Researchers are looking to source an increasing variety of living tissues, including solid organs, from pigs. Many are attempting to genetically engineer the animals to reduce the risk of rejection and infection in humans.

cells

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

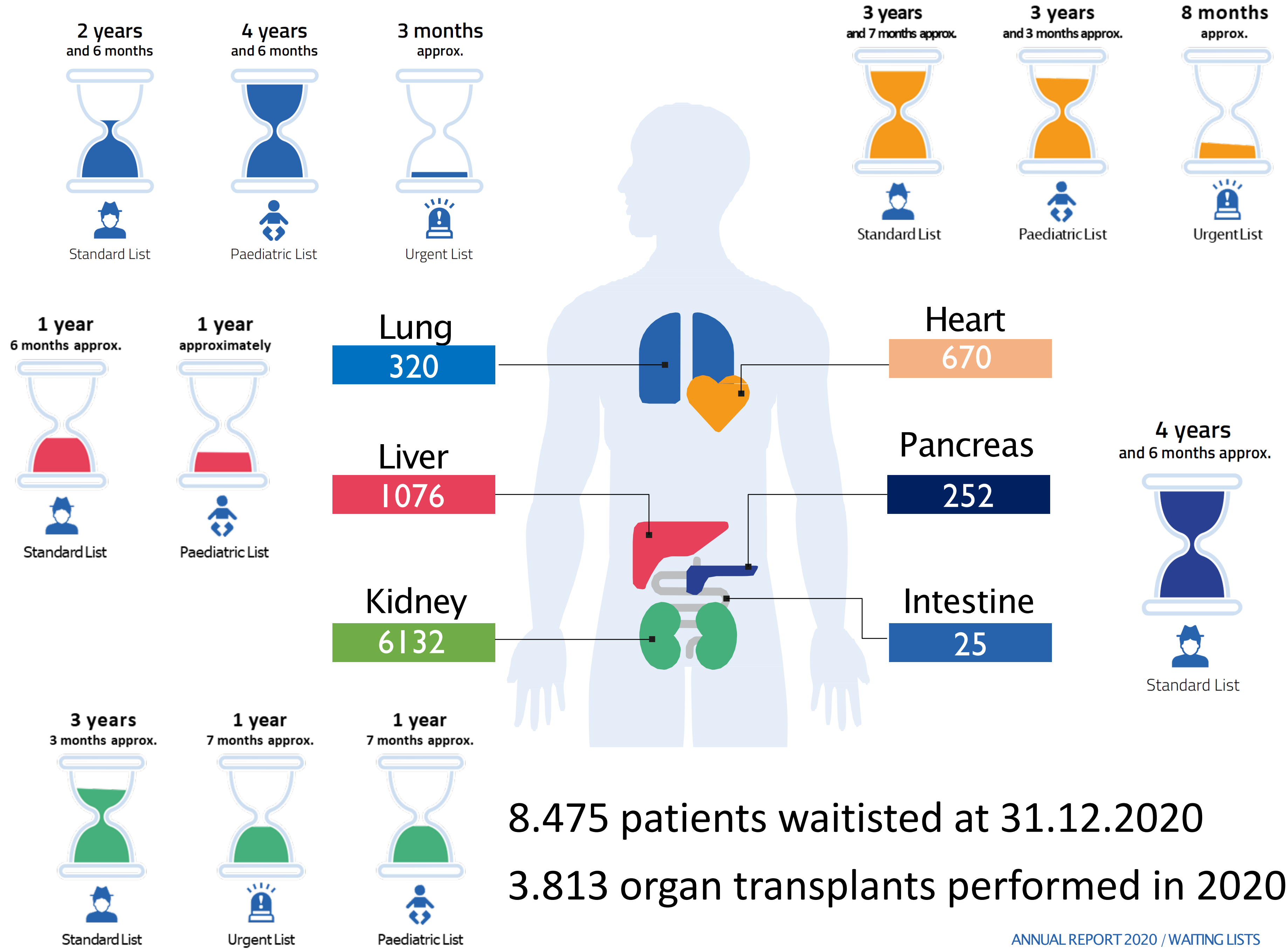
University of Maryland School of Medicine Faculty Scientists and Clinicians Perform Historic First Successful Transplant of Porcine Heart into Adult Human with End-Stage Heart Disease

January 10, 2022 | Deborah Kotz

First-of-Its-Kind Transplant at the University of Maryland Medical Center Was Patient's Only Option for Survival after Being Deemed Ineligible for Traditional Transplant

Conclusioni

- + donazioni = + trapianti
- Il trapianto non si fa solo in sala operatoria
- Un trapianto = un intero ospedale al lavoro
- Un trapianto = un rete nazionale al lavoro
- + trapianti = + salute e – spesa sanitaria
- Ancora troppo divario tra domanda e offerta


2 years
and 6 months
Standard List
4 years
and 6 months
Paediatric List
3 months
approx.
Urgent List
3 years
and 7 months approx.
Standard List
3 years
and 3 months approx.
Paediatric List
8 months
approx.
Urgent List
1 year
6 months approx.
Standard List
1 year
approximately
Paediatric List
Lung
320
Heart
670
Liver
1076
Pancreas
252
4 years
and 6 months approx.
Standard List
Kidney
6132
Intestine
25
3 years
3 months approx.
Standard List
1 year
7 months approx.
Urgent List
1 year
7 months approx.
Paediatric List
8.475 patients waitisted at 31.12.2020
3.813 organ transplants performed in 2020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