

Was gibt es Neues in der Transplantation? 10. März 2023 Christian Morath



	1	2	3	4	5	6
Xeno-Tx	X	x	X		x	
MIC-Zelltherapie/CAR-Treg	X	x		X	x	
Idefirix/CD38-Antikörper	X	x				x
NK-Zell-Immunität		x	x			
SolKid LSP-Register/RiLi Spenderschutz	X					X
Natriumbicarbonat nach Tx		X			X	
iBox		X			X	
Letermovir/Maribavir bei CMV		X			X	
TTV		x				x
SGLT-2 Inhibitoren nach Tx	X					
Check-point Inhibitoren nach Tx		x				
Best Fluid Trial/Maschinenperfusion					X	
HLA Epitope Matching					X	

Agenda

- Neue pathophysiologische Konzepte
- Neue klinische Endpunkte
- Neues immunologisches Monitoring
- Neue immunsuppressive Therapien
- Verschiedenes

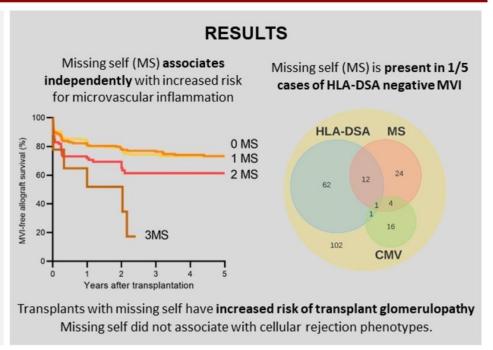


Missing Self Induced Microvascular **Rejection of Kidney Allografts:** a Population-based Study



METHODS 924 kidney transplantations 3476 post-transplant biopsies Impact of missing self (MS) on microvascular inflammation (MVI)? Missing self Self recognition Recipient NK cell Recipient NK cell inhibition activation HLA class I Donor endothelium Donor endothelium

stressed



Conclusion:

unaltered

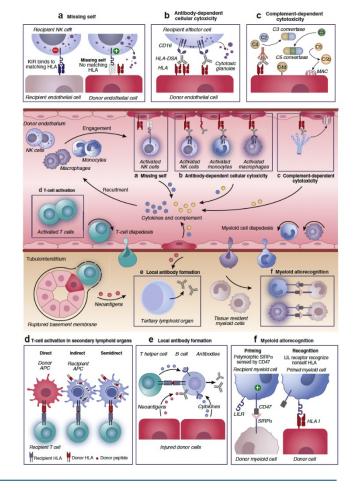
Missing self is a cumulative, independent and specific risk factor for the occurrence of microvascular inflammation after kidney transplantation. JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

doi: 10.1681/ASN.2020111558

Callemeyn J Am Soc Nephrol 2021

Abstoßung 2023

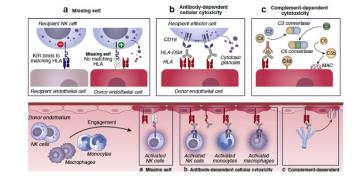
- Mehr als TCMR und ABMR
- Mikrovaskulärer Schaden (ptc+g)
 - CDCC (AK+, C4d+)
 - ADCC (AK+, C4d-)
 - Missing self (AK-, C4d-)

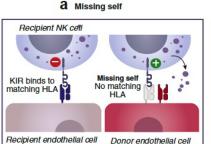


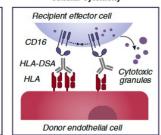


Abstoßung 2023

- Mehr als TCMR und ABMR
- Mikrovaskulärer Schaden (ptc+g)
 - CDCC (AK+, C4d+)
 - ADCC (AK+, C4d-)
 - Missing self (AK-, C4d-)

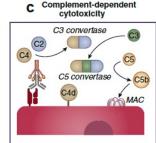


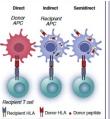


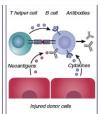


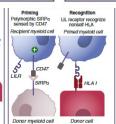
Antibody-dependent

cellular cytoxicity

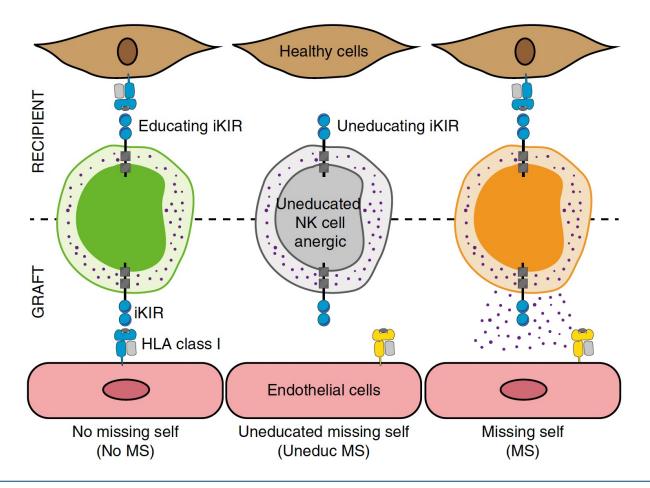










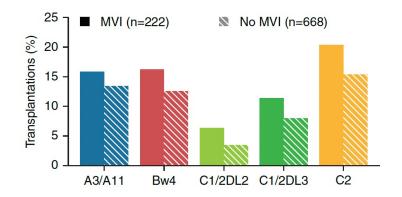


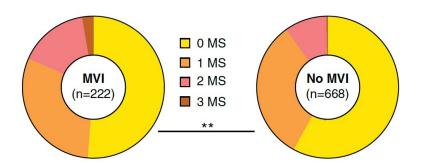


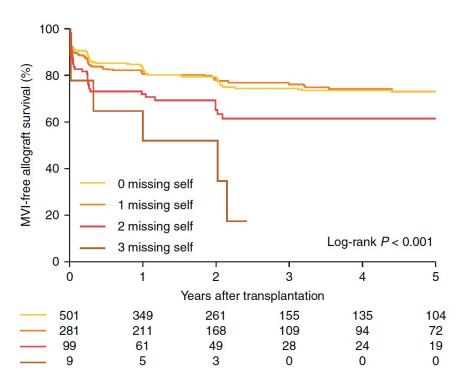
Studiendesign

- Prospektive Observationsstudie in Leuven (2004-2013)
- N = 924 konsekutive Nierentransplantatempfänger
- Hochauflösende Spender- und Empfänger-HLA-Typisierung, Empfänger KIR-Genotypisierung
- "Missing self" definiert als Abwesenheit von A3/A11, Bw4, C1 oder C2 Spendergenotyp bei Anwesenheit des entsprechenden "educated/licensed" inhibitorischen Empfänger KIR-Gen

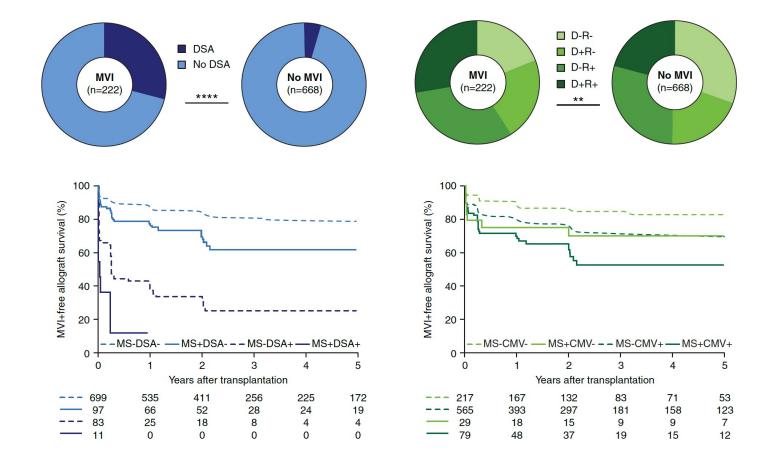














Agenda

- Neue pathophysiologische Konzepte
- Neue klinische Endpunkte
- Neues immunologisches Monitoring
- Neue immunsuppressive Therapien
- Verschiedenes



Integrated immunologic monitoring in solid organ transplantationthe road towards Torque Teno virus guided immunosuppression



Narrative review on



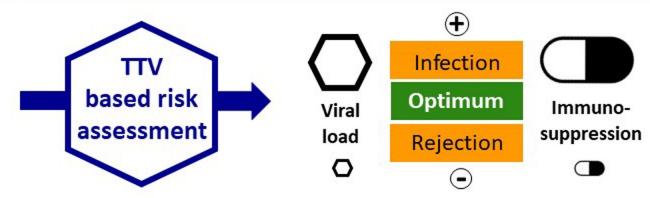
TTV-based immunologic monitoring in



Solid organ transplant recipients

Torque Teno Virus (TTV)

- non-pathogenic
- ~ 99% prevalence in SOT
- plasma load associates with host's immune status

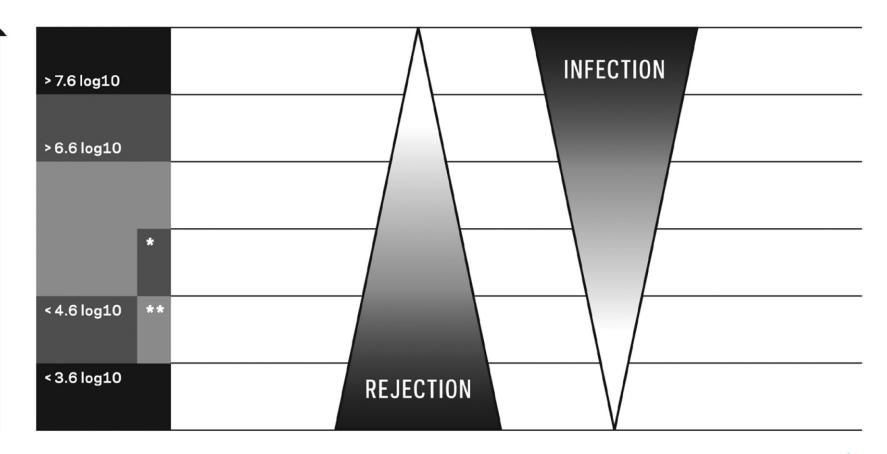


Conclusion: TTV might be useful for guiding immunosuppression in SOT

Jaksch et al. Transplantation. 2022.

@TransplantJrnl



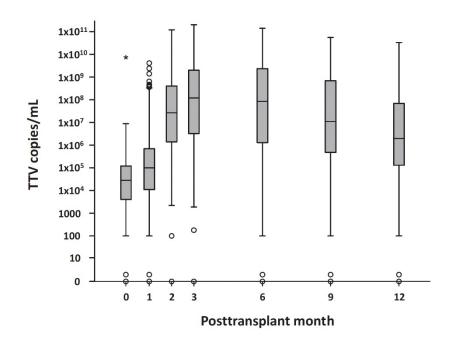




Studiendesign

- Prospektive Observationsstudie in Wien (2016-2018)
- N = 386 konsekutive Nierentransplantatempfänger: Biopsie-Kohorte N = 37, Infektions-Kohorte N = 274
- TTV Monitoring für 12 Monate nach Transplantation





TTV Level

Ideal 10⁶ bis 10⁹?

Aktuell Überprüfung in TTV Guide Projekt

 TABLE 3
 Diagnostic accuracy to detect rejection by TTV level

TTV ^a	NPV ^b	PPV^b	Sensitivity ^b	Specificity ^b
10 ⁴	0.74-0.76	0.76-1.00	0.09-0.18	1.00-1.00
10 ⁵	0.77-0.82	0.57-0.85	0.18-0.36	0.93-0.96
10 ⁶	0.77-0.85	0.47-0.56	0.36-0.64	0.75-0.89
10 ⁷	0.84-0.87	0.40-0.50	0.64-0.73	0.61-0.71
10 ⁸	0.80-0.89	0.30-0.41	0.73-0.91	0.18-0.57
10 ⁹	0.67-1.00	0.28-0.30	0.91-1.00	0.07-0.14

 TABLE 5
 Diagnostic accuracy to detect infection by TTV level

TTV ^a	NPV ^b	PPV^b	Sensitivity ^b	Specificity ^b
10 ⁴	0.83-1.00	0.25-0.25	0.93-0.97	0.05-0.10
10 ⁵	0.79-0.83	0.25-0.26	0.85-0.92	0.10-0.22
10 ⁶	0.82-0.84	0.26-0.29	0.74-0.85	0.22-0.42
10 ⁷	0.82-0.84	0.29-0.33	0.63-0.73	0.43-0.59
10 ⁸	0.80-0.83	0.33-0.36	0.41-0.62	0.59-0.76
10 ⁹	0.75-0.80	0.36-0.43	0.10-0.41	0.77-0.96
10 ¹⁰	0.75-0.76	0.43-0.67	0.01-0.10	0.96-0.99



Agenda

- Neue pathophysiologische Konzepte
- Neue klinische Endpunkte
- Neues immunologisches Monitoring
- Neue immunsuppressive Therapien
- Verschiedenes



Received: 21 March 2021

Revised: 11 June 2021

Accepted: 4 July 2021

DOI: 10.1111/ajt.16754

ORIGINAL ARTICLE

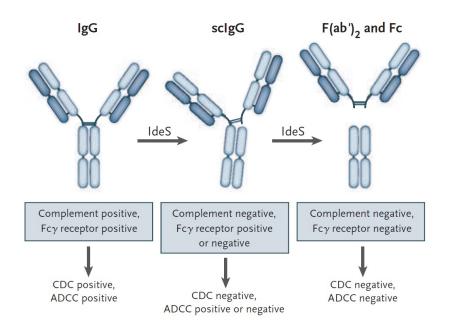
AJT

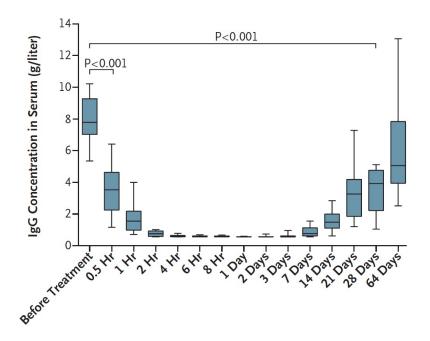
Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients

Christian Kjellman¹ | Angela Q. Maldonado¹ | Kristoffer Sjöholm¹ | Bonnie E. Lonze² | Robert A. Montgomery² | Anna Runström¹ | Tomas Lorant³ |

Niraj M. Desai⁴ | Christophe Legendre⁵ | Torbjörn Lundgren⁶ | Bengt von Zur Mühlen³ |

Ashley A. Vo⁷ | Håkan Olsson¹ | Stanley C. Jordan⁷







Studiendesign

- Vier einarmige Phase-II Studien (-02, -03, -04, -06) an 6 Zentren
- N = 39: 82% Verstorbenennierentransplantation, hohes immunologisches Risiko (XM positiv), behandelt mit Imlifidase
- Keine Desensibilisierung
- Einmalgabe Imlifidase vor Transplantation
- Induktionstherapie mit Pferde-ATG oder Alemtuzumab, später IVIg und Rituximab



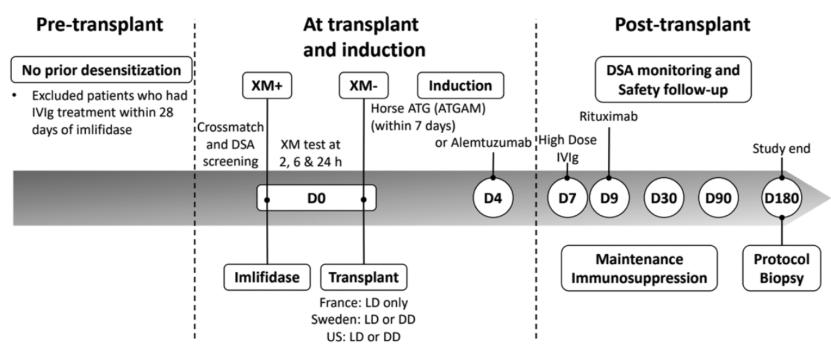
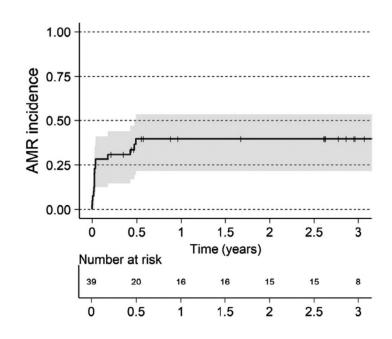


FIGURE 1. Study design. DD, deceased donor; DSA, donor-specific antibody; IVIg, intravenous immune globulin; LD, living donor.

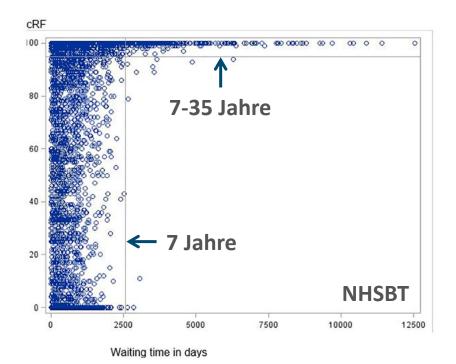


Ergebnisse nach 3 Jahren

- Patientenüberleben 90%
- Für Tod zensiertes
 Überleben 84%
 - AMR-neg. 77%
 - AMR-pos. 93%
- DGF 44%
- eGFR 55 mL/min/1,73m²







Heidelberg 01/2023, vPRA ≥98%

Wartezeit (Jahre)	N (=36)
<3 Jahre	15
>3 Jahre	10
>5 Jahre	3
>8 Jahre	5
>10 Jahre	2
>20 Jahre	1

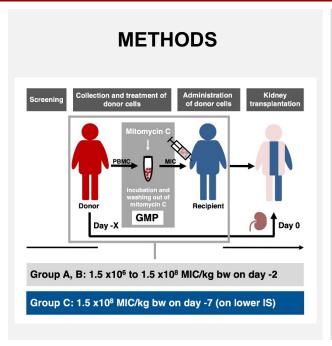
Warum ist das relevant?

Besonderes Verfahren im AM-Programm für "höchstsensibilisierte" Patienten: Entfernung von unakzeptablen HLA-Antigenen, Transplantation unter Imlifidase



Induction of Long-lasting Regulatory B Lymphocytes by Modified Immune Cells in Kidney Transplant Recipients



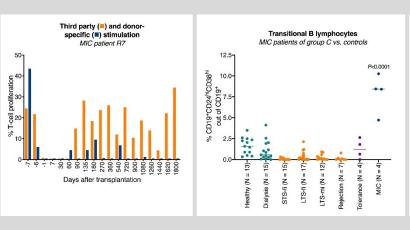


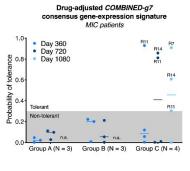


Donor-specific unresponsive-ness in patient R7 of group C

Strongly increased regulatory B lymphocyte frequencies

Gene expression signature of operational tolerance



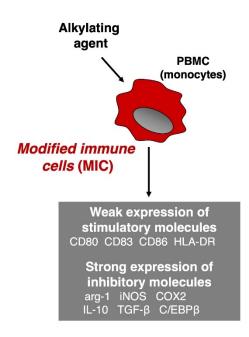


Conclusion

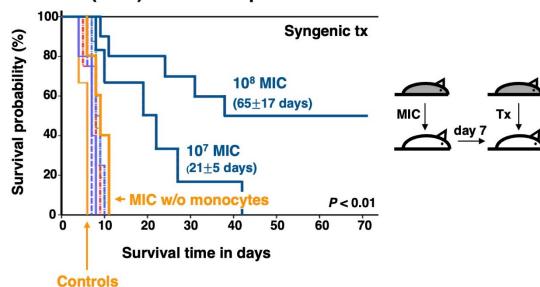
Donor-specific immunosuppression after MIC infusion is long-lasting and associated with a striking increase in regulatory B lymphocytes. MIC appear to be an immunoregulatory cell population which, when administered to recipients prior to transplantation, carry the promise of exerting a beneficial effect on kidney transplants.

Morath J Am Soc Nephrol 2023

doi: 10.1681/ASN.



Dark Agouti (DA) to Piebald Virol Glaxo (PVG) heart transplantation

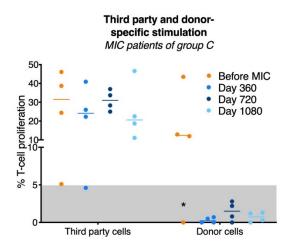


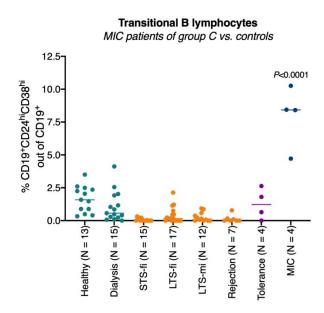


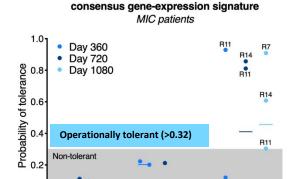
Studiendesign

- Monozentrische, einarmige Phase-I Studie in Heidelberg
- N = 10: Lebendnierentransplantation, niedriges immunologisches Risiko, **MIC-Zelltherapie** an Tag (-2 und) -7
- Immunsuppression mit CyA, EC-MPS, Urbason (N = 10), niedrig dosiertes CyA und EC-MPS ohne Urbason im Verlauf (N = 4)
- 79% Männer, im Median 45 Jahre, Follow-up 3 Jahre









Group B (N = 3)

Group A (N = 3)

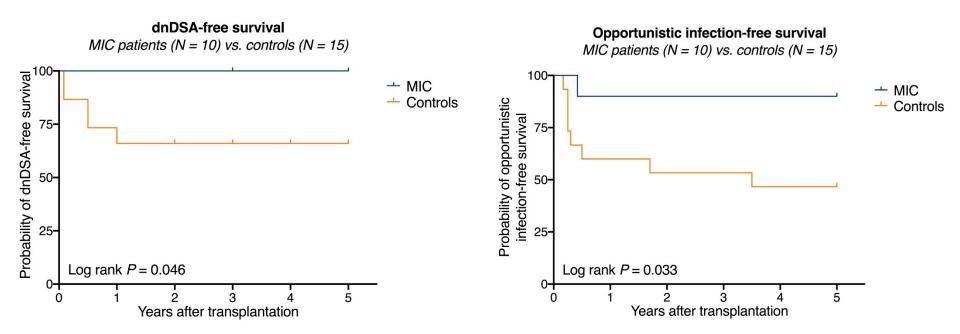
Drug-adjusted COMBINED-g7

MIC induzieren einen operational toleranten Phänotyp

Reduzierte Spender-T-Zellantwort, vermehrt regulatorische B-Lymphozyten (TrB), Nachweis der *COMBINED-q7* Konsensus-Genexpressionssignatur



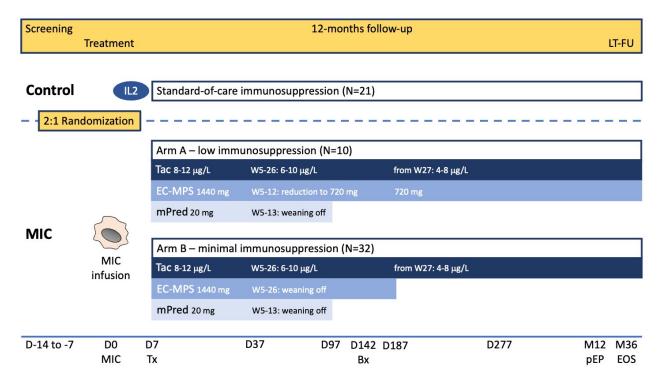
Group C (N = 4)



Retrospektive Analyse klinischer Endpunkte

Keine DSA, keine akuten Abstoßungen, "keine" opportunistischen Infektionen, höherer anti-S1 IgG Index (53 vs. 2, P = 0.16) von MIC vs. Kontrolle





Multizentrische Phase-IIb Studie

Primärer Endpunkt: Operationale Toleranz, zwei herausgehobene sekundäre Endpunkte u.a. Patienten-relevante Infektionen



Agenda

- Neue pathophysiologische Konzepte
- Neue klinische Endpunkte
- Neues immunologisches Monitoring
- Neue immunsuppressive Therapien
- Verschiedenes



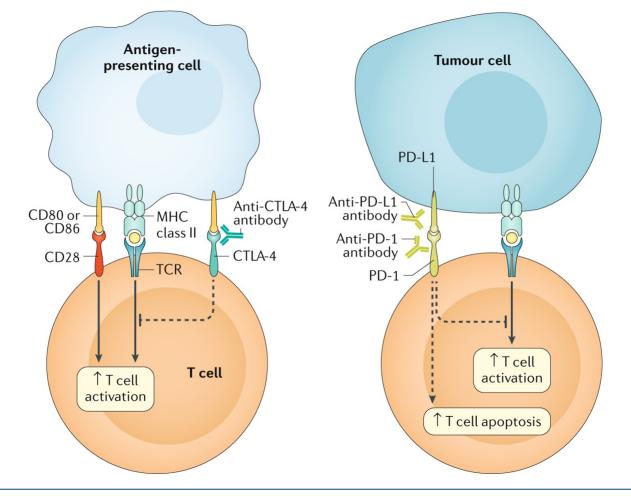
Carroll Lancet Oncol 2022





Immune checkpoint inhibitors in kidney transplant recipients: a multicentre, single-arm, phase 1 study

 $Robert\ P\ Carroll,\ Michael\ Boyer,\ Val\ Gebski,\ Bronwyn\ Hockley,\ Julie\ K\ Johnston,\ Svjetlana\ Kireta,\ Hsiang\ Tan,\ Anne\ Taylor,\ Kate\ Wyburn,\ John\ R\ Zalcberg$





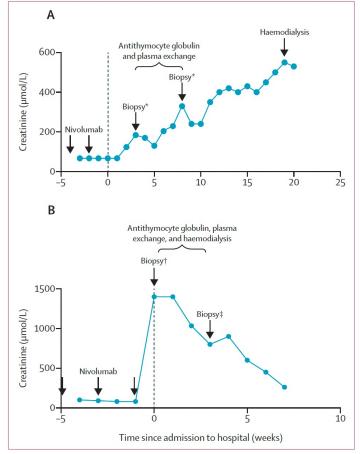
Studiendesign

- Multizentrische, einarmige Phase-I Studie in Australien
- N = 22, fortgeschrittenes Tumorleiden, ECOG 0-2, Kreatinin
 ≤180 μmol/L, keine/wenig HLA-Antikörper
- N = 17 in Auswertung, 65% Männer, im Median 67 Jahre, 3
 Infusionen, Follow-up 28 Monate
- N = 9 Plattenepithel-Ca von Haut oder Oropharynx
- Frühzeitige Beendigung aufgrund COVID-19-Pandemie



Ergebnisse

- Nivolumab-Therapie
- Immunsuppression: Tac/MPA
- CR/PR: N = 9 (4+5)
- 1 Abstoßung ohne Tx-Verlust mit ATG und PP behandelt
- 1 Abstoßung mit Tx-Verlust
- 1 Tx-Verlust aufgrund OP





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.

Urine Drainage System





Corrected: Author Correction

https://doi.org/10.1038/s41586-018-0765-z

Consistent success in life-supporting porcine cardiac xenotransplantation

Matthias Längin^{1,2,18}, Tanja Mayr^{1,2,18}, Bruno Reichart^{2*}, Sebastian Michel³, Stefan Buchholz³, Sonja Guethoff^{2,3}, Alexey Dashkevich³, Andrea Baehr⁴, Stefanie Egerer⁴, Andreas Bauer¹, Maks Mihalj³, Alessandro Panelli², Lara Issl², Jiawei Ying², Ann Kathrin Fresch², Ines Buttgereit², Maren Mokelke², Julia Radan², Fabian Werner¹, Isabelle Lutzmann², Stig Steen⁵, Trygve Sjöberg⁵, Audrius Paskevicius⁵, Liao Qiuming⁵, Riccardo Sfriso⁶, Robert Rieben⁶, Maik Dahlhoff⁴, Barbara Kessler⁴, Elisabeth Kemter⁴, Mayuko Kurome⁴, Valeri Zakhartchenko⁴, Katharina Klett^{7,8,9}, Rabea Hinkel^{7,8,9}, Christian Kupatt^{7,9}, Almuth Falkenau¹⁰, Simone Reu¹¹, Reinhard Ellgass³, Rudolf Herzog³, Uli Binder¹², Günter Wich¹³, Arne Skerra¹⁴, David Ayares¹⁵, Alexander Kind¹⁶, Uwe Schönmann¹⁷, Franz-Josef Kaup¹⁷, Christian Hagl³, Eckhard Wolf⁴, Nikolai Klymiuk⁴, Paolo Brenner^{2,3,19} & Jan-Michael Abicht^{1,2,19}