Viruses and transplantation

13th of January 2025

Paris, France

Antiviral immunity in transplant patients –

Mechanisms of antiviral immune surveillance and risk of reactivation

Martina Sester, PhD

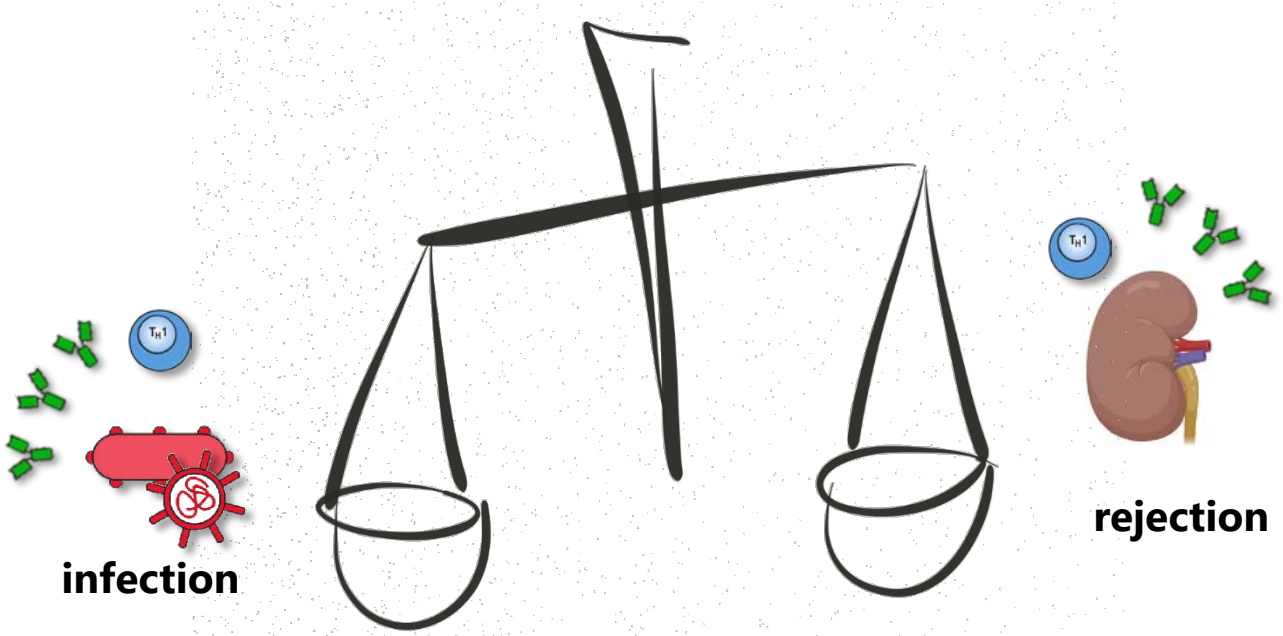
UNIVERSITÄT DES SAARLANDES

Transplantations- und Infektionsimmunologie

Conflicts of interest

- Research grants by Astellas, Biotest, Takeda (Institution)
- Honoraria, travel support, advisory boards by Novartis, Biotest, Astellas, Qiagen, Moderna, Takeda, MSD (personal)

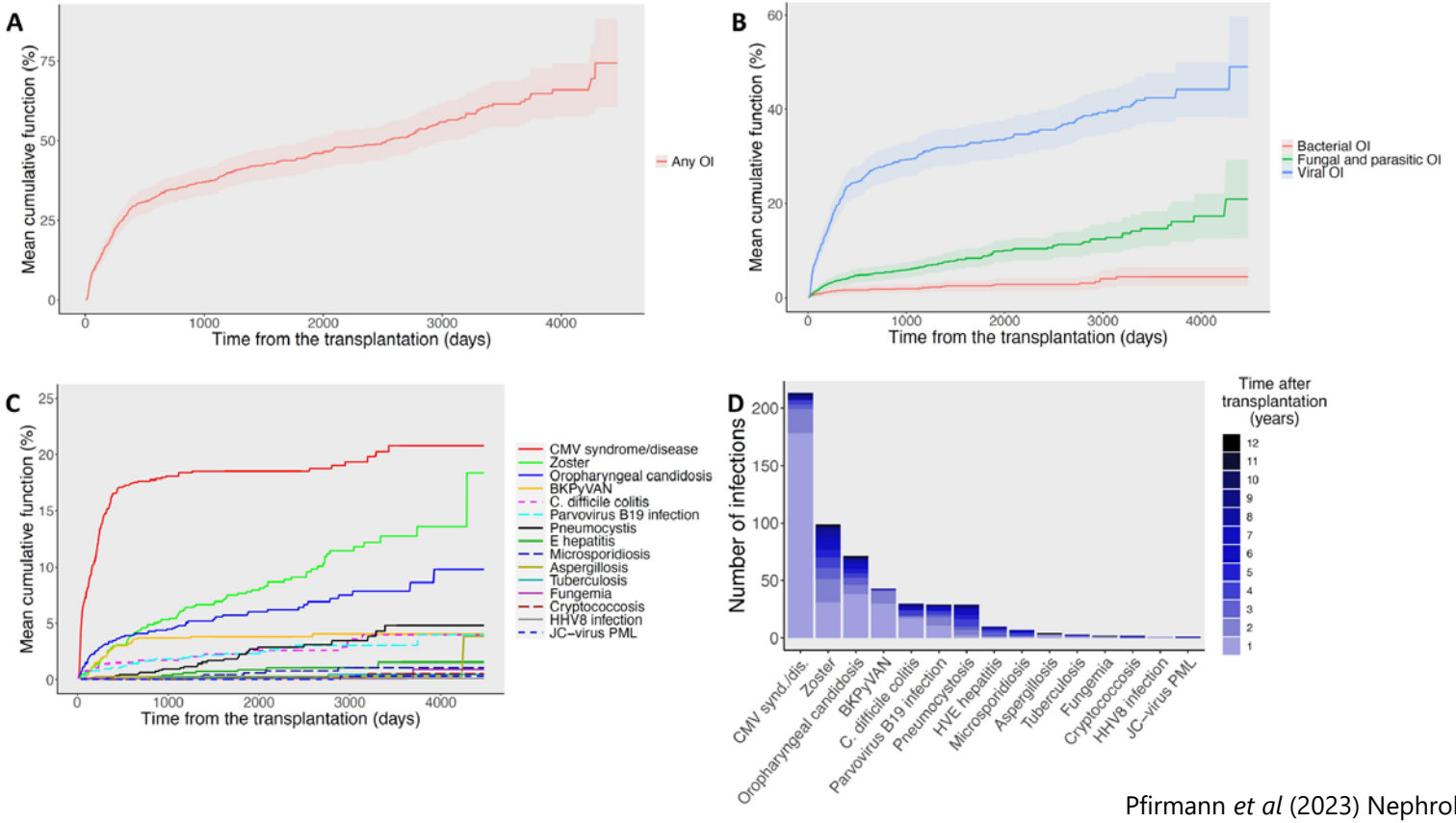
Immunosuppression



Control and monitoring of infectious complications

Control and monitoring of rejections

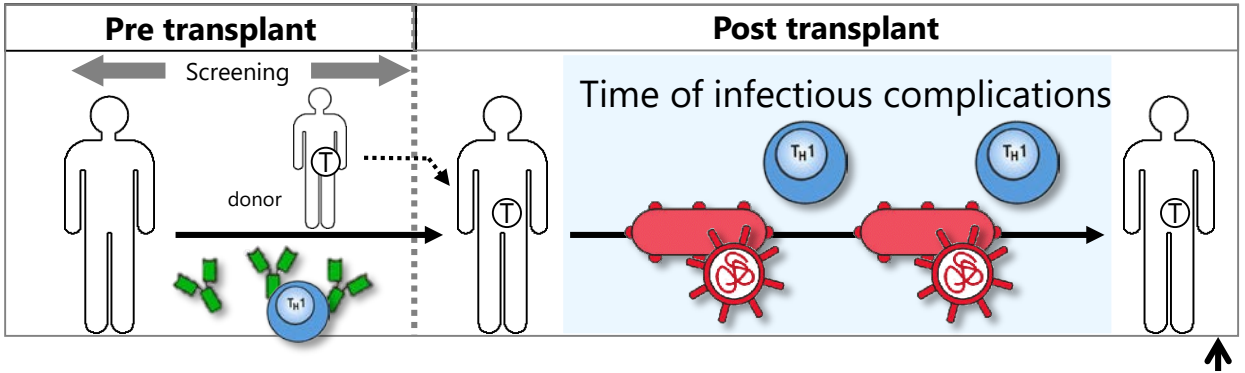
Infections after transplantation



Pfirmann *et al* (2023) Nephrol Dial Transplant

Monitoring of infectious complications

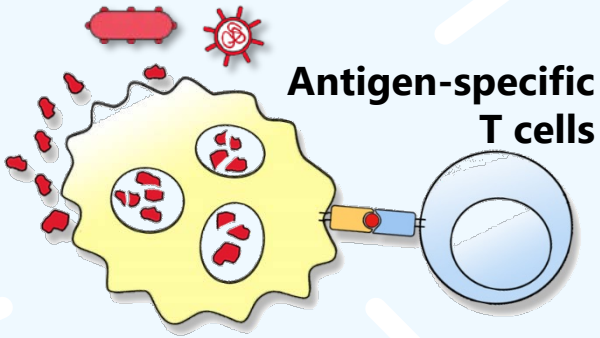
- Clinical symptoms
- Antibodies (IgG/IgM – avidity)
- Viral replication
- T cells



T-cell based monitoring of infectious complications

CMV
Monitoring of infectious complications
Guiding antiviral therapy

M. tuberculosis
Diagnosis of latent infections



BKPyV
Monitoring of infectious complications
Guiding of immunosuppression reduction

SARS-CoV-2
Monitoring of infectious complications and vaccine-induced immunity

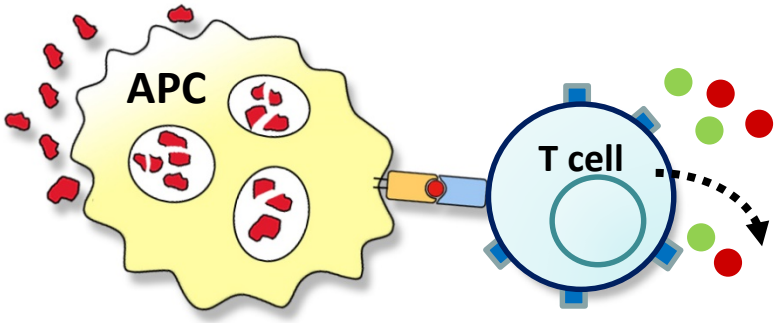
VZV
Monitoring of infectious complications and vaccine-responses

RSV
Monitoring of vaccine-induced cellular immunity

Characterization of antigen-specific T cells after stimulation

Stimuli
Antigens/Peptides
polyclonal
Stimuli

Whole blood/PBMC



6-24 hours

activation
cytokine-induction

Characterization of antigen-specific T cells after stimulation

Stimuli
Antigens/Peptides
polyclonal
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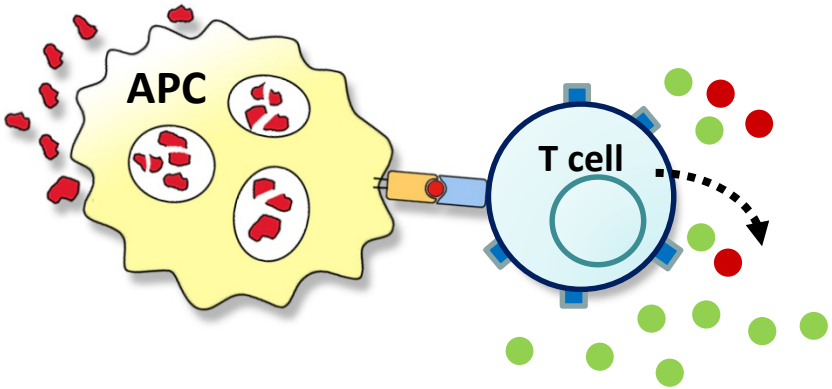
Whole blood/PBMC



6-24 hours

activation
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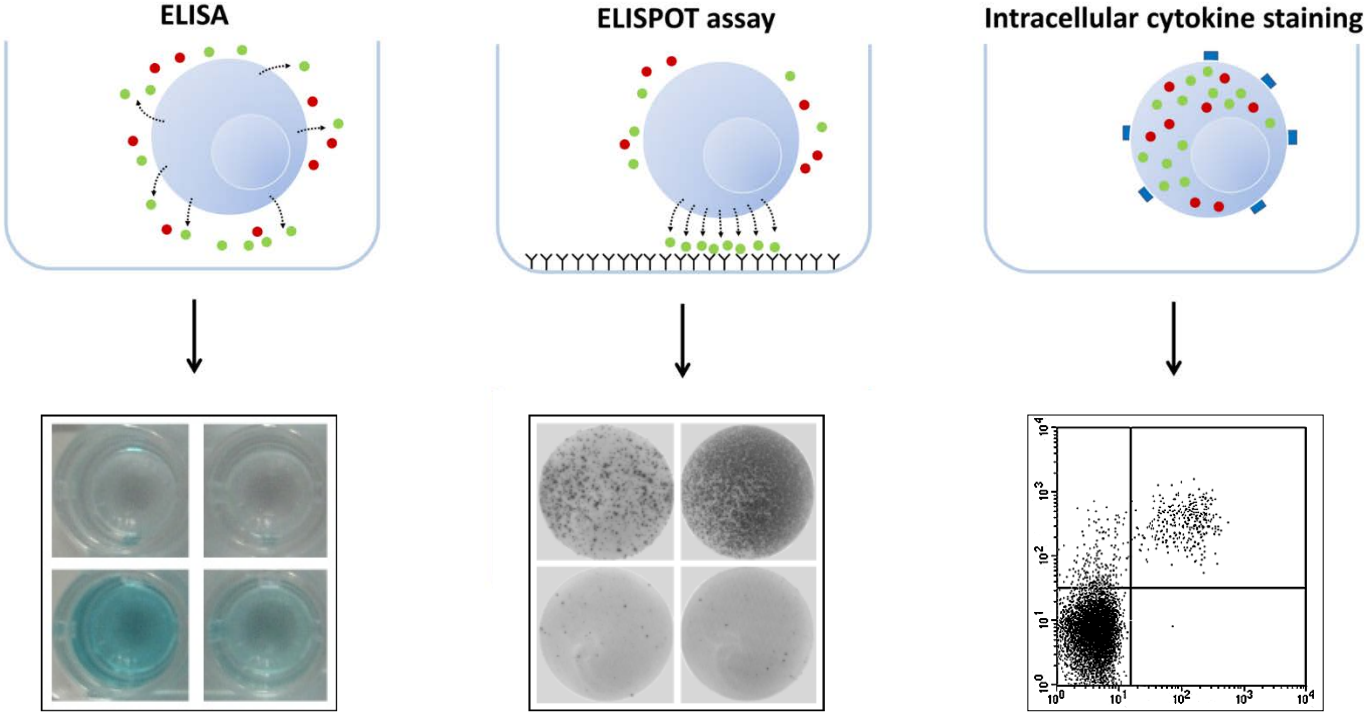
IFN-γ release assays

IFN-γ Release Assays



Sester *et al.* (2016) *Am J Transplant* 16: 1697

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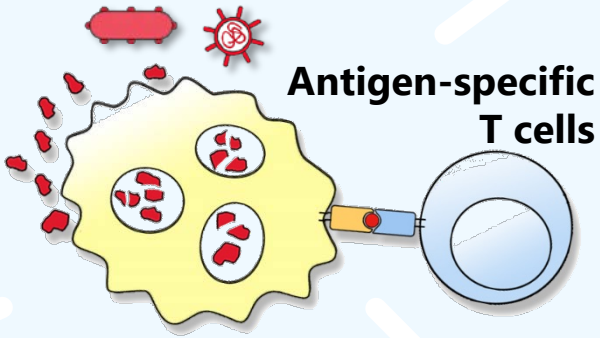

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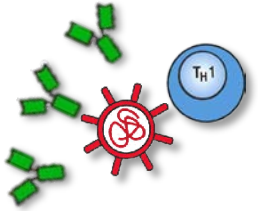
Areas of application in clinical practice

TTS consensus guidelines

Kotton *et al.* (2024) submitted

Areas of application in clinical practice



- Correct assignment of CMV infection status in individuals with potential passive immunity
- Early identification of patients at (low) risk in a pre-emptive setting
- Guidance on duration of antiviral prophylaxis
- Guidance on treatment duration

TTS
The Transplantation Society

CMV and Solid Organ Transplant Consensus Guidelines Meeting
2008 – Paris, France
2012 - Montréal, Canada
2017 – Toronto, Canada
2024 – Montréal, Canada

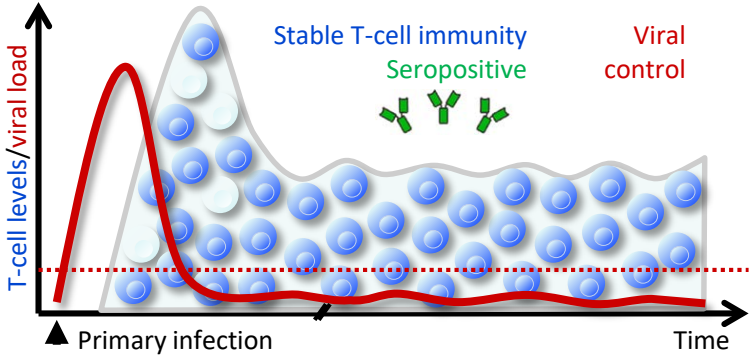
Sester *et al.* (2016) *Am J Transplant* 16: 1697; Kotton *et al.* (2018) *Transplantation* 102: 900; Kotton *et al.* (2024) submitted

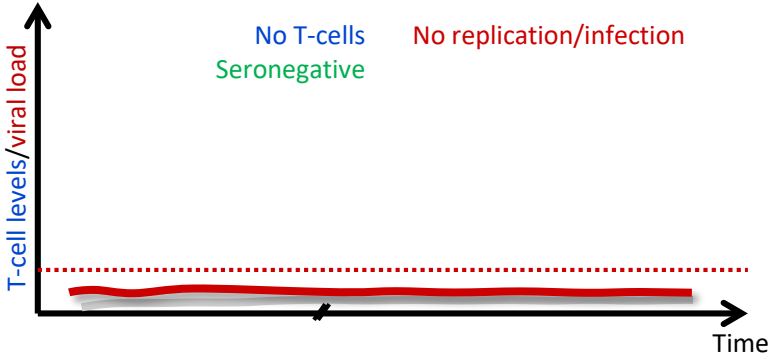
Risk of CMV infection after transplantation

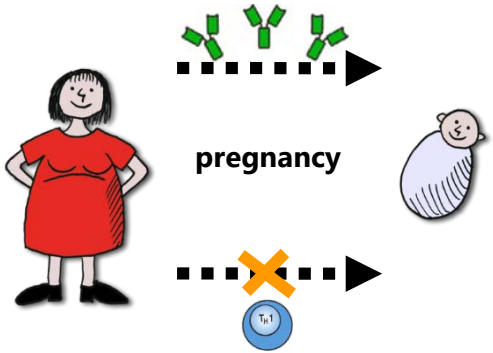
Donor	Recipient	Risk	+ T cell-depl. therapy
-	-	Low	Low
-	+	Intermediate	High
+	+	Intermediate	High
+	-	High	high

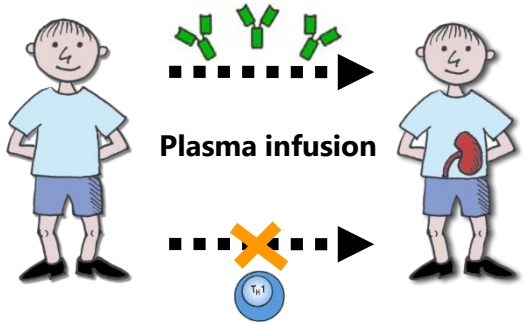
Kotton *et al.* (2018) *Transplantation* 102: 900

T-cell immunity as alternative to serology in individuals with passive immunity





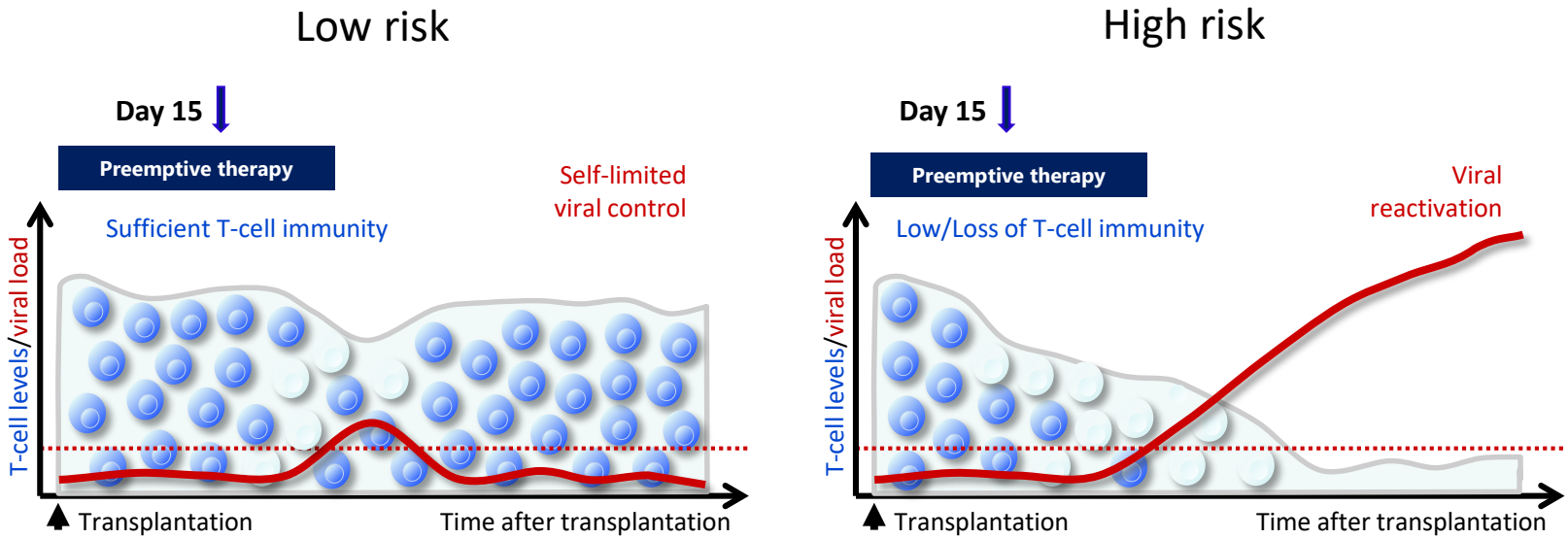




Burton *et al.* (2018) *J Infect Dis* 218: 1205; Burton *et al.* (2019) *J Clin Virol*
Schmidt *et al*. (2012) *J Clin Virol* 54: 272; Ritter *et al.* (2013) *Eur J Immunol* 43: 1099; Emery (2013) *Eur J Immunol* 43: 886

Use of immunomonitoring early after transplantation to identify patients at (low) risk

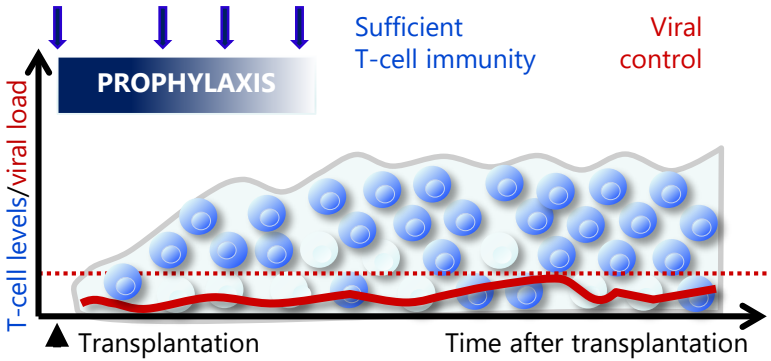
R+ patients on preemptive regimen

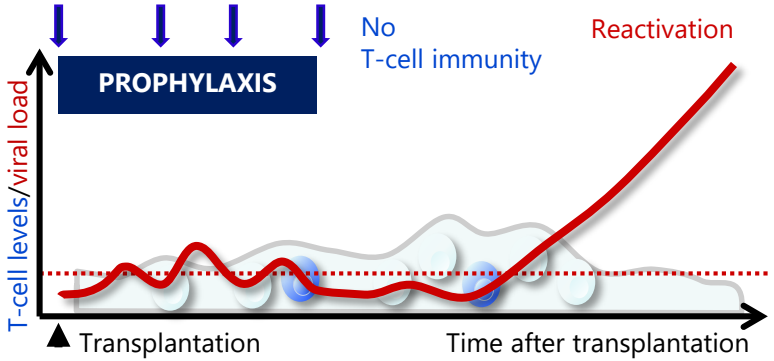


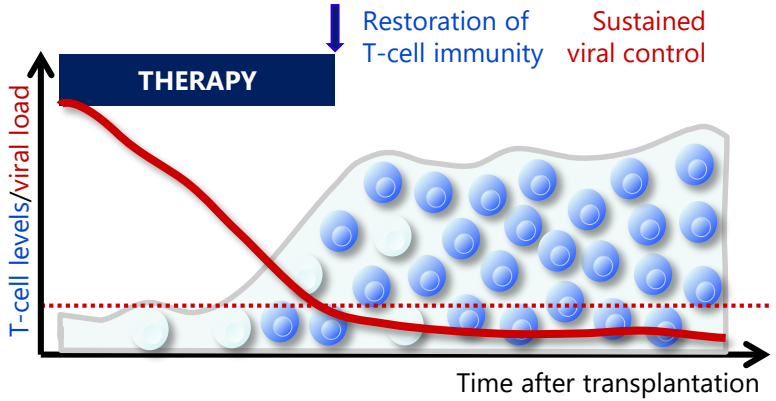
Jarque *et al.* (2020) *Clin Infect Dis* 71: 2375; Kotton *et al.* (2024) submitted

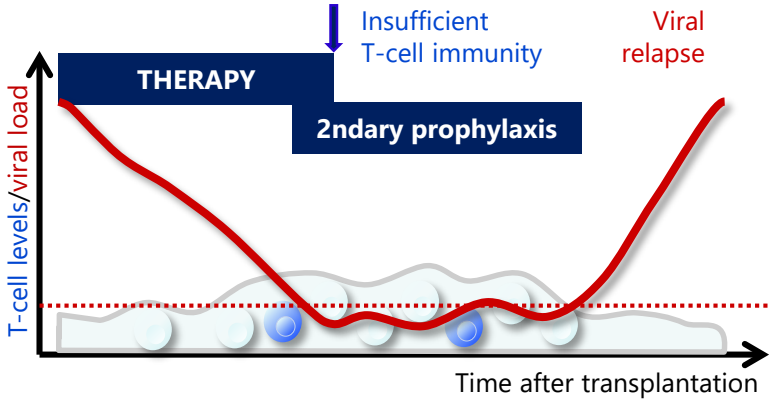
Use of immunomonitoring after transplantation to guide duration of prophylaxis and therapy

R+/ATG
R+









Sester *et al.* (2016) *Am J Transplant* 16: 1697; Kotton *et al.* (2024) submitted

HORUS: Casting light on **HO**st-cytomegaloviRUs interaction in **S**olid organ transplantation

CONSORTIUM

Viral Expertise	Clinical Expertise	Bioinformatics	Expertise in Immunology Protogenomics Genomics	Communication Dissemination
Universities (7)	Hospital Facilities (7)	Industry (1)	Research Teams (6)	Others (3)

Funded by the European Union

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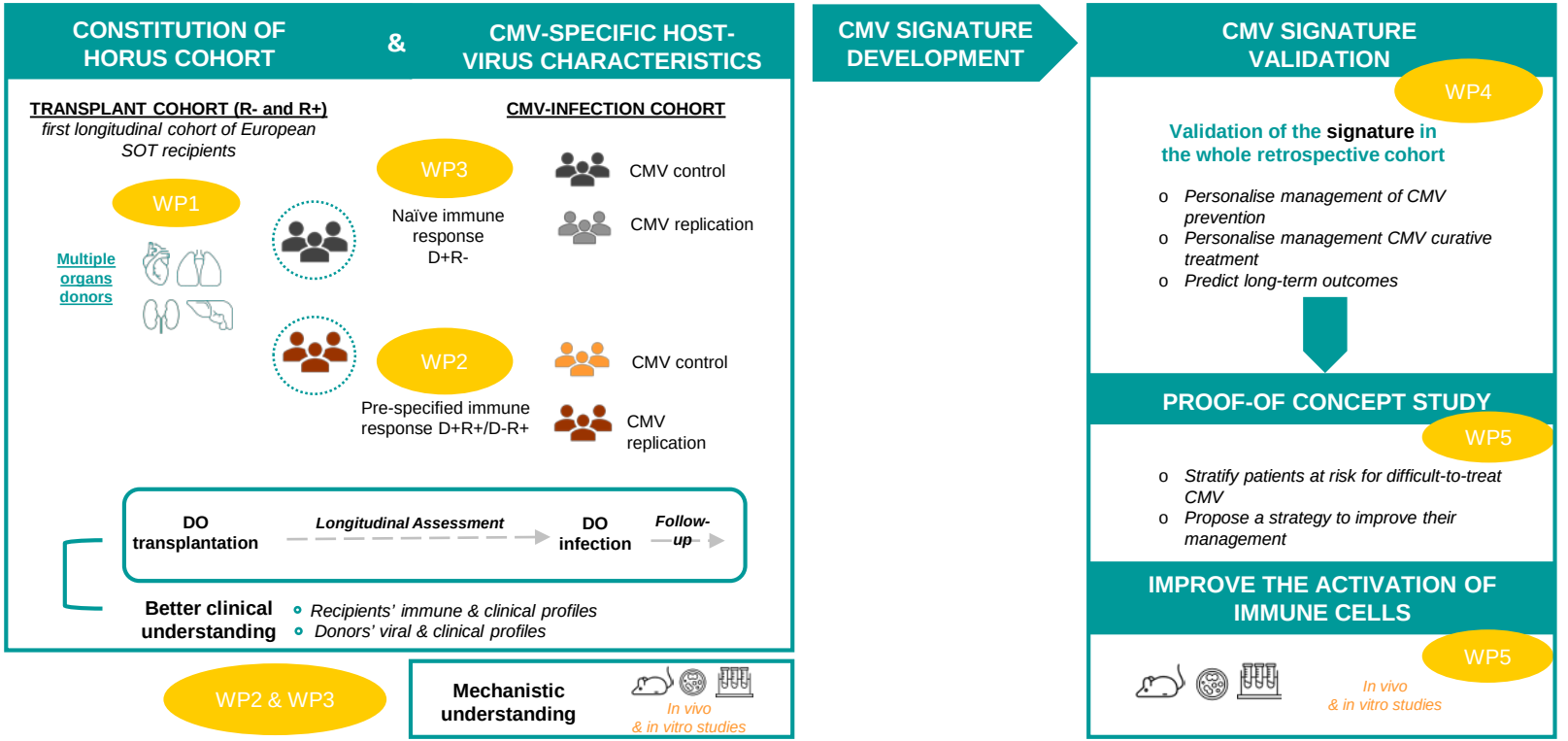
HORUS

HORUS: Casting light on **HO**st-cytomegalovi**RU**s interaction in **S**olid organ transplantation – 2022-2027



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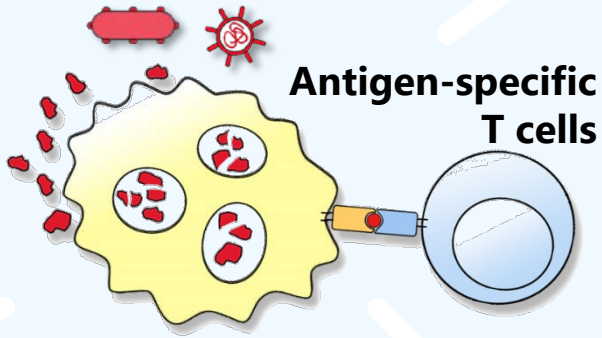

SARS-CoV-2
Monitoring of infectious complications and vaccine-induced immunity

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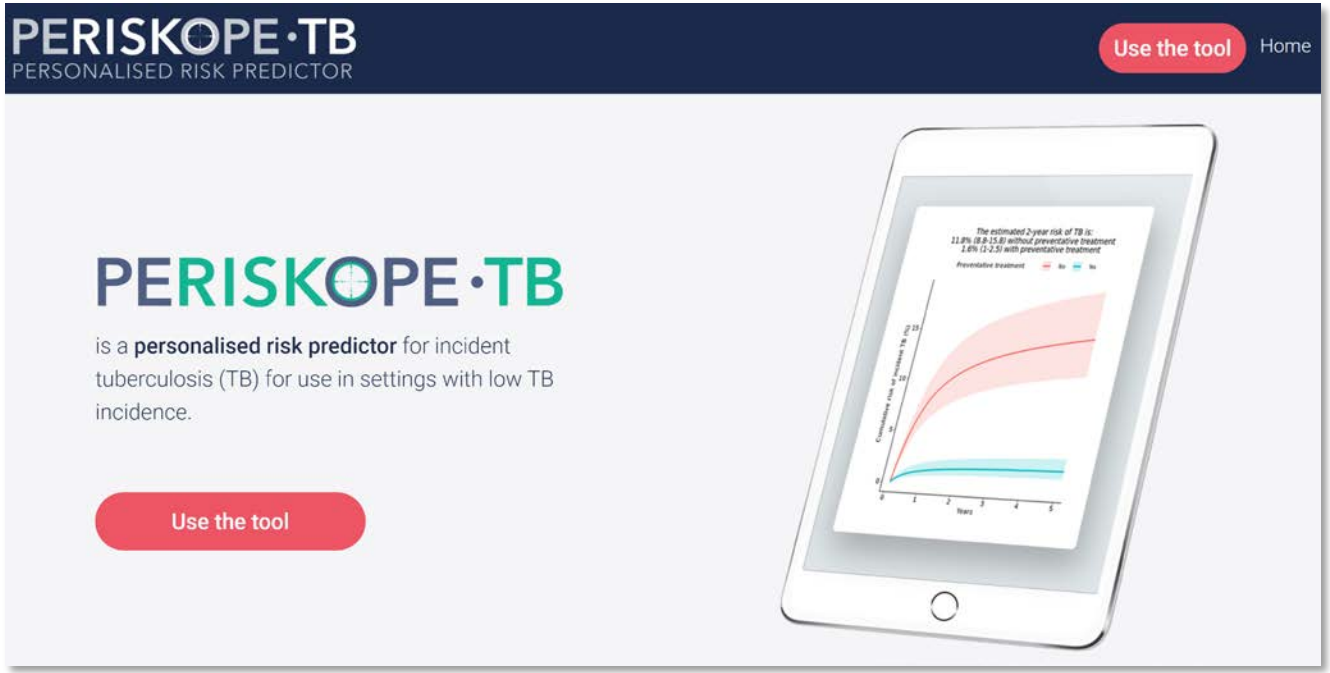
Individual risk assessment

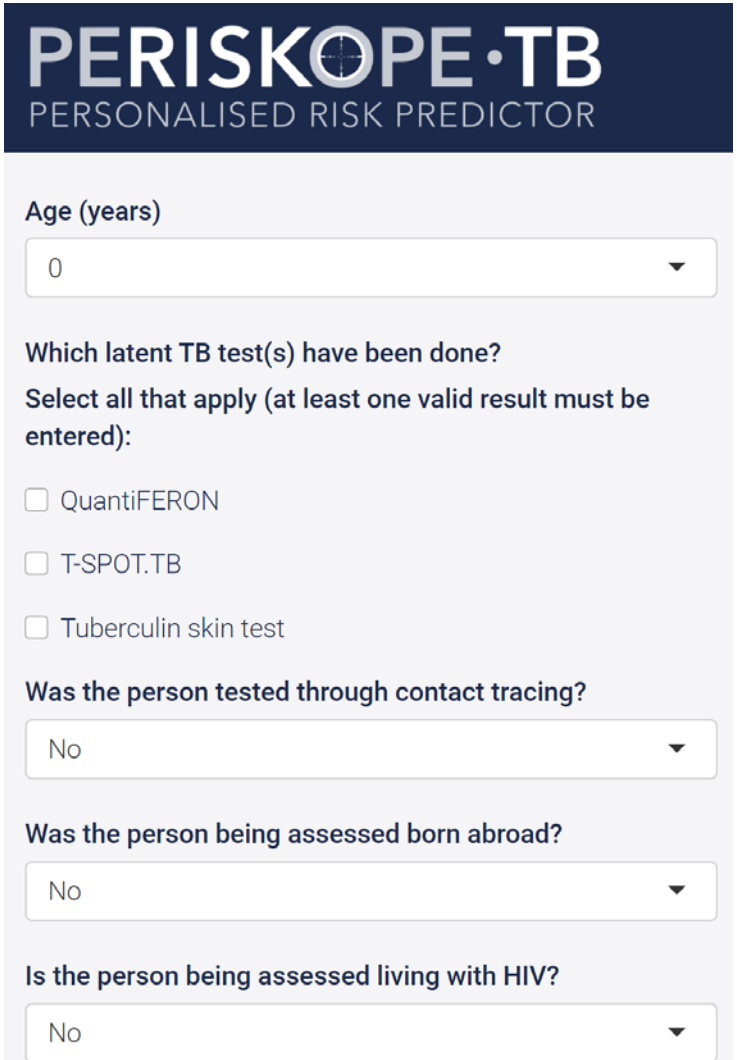
> 80.000 datasets from 15 studies from 20 low-incidence countries



University College London, UK

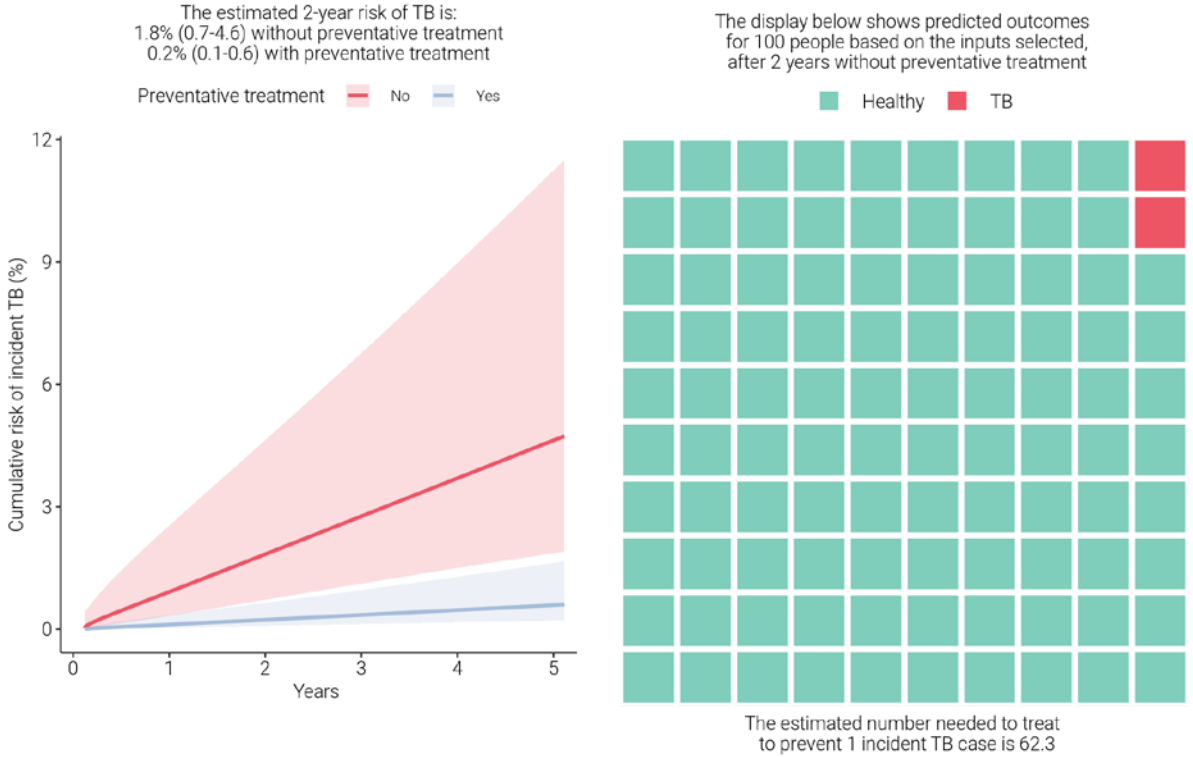
www.periskope.org

Gupta *et al.* (2020) *Nat Med* 26: 1941



Gupta *et al.* (2020) *Nat Med* 26: 1941

Individual risk assessment



Gupta *et al.* (2020) *Nat Med* 26: 1941

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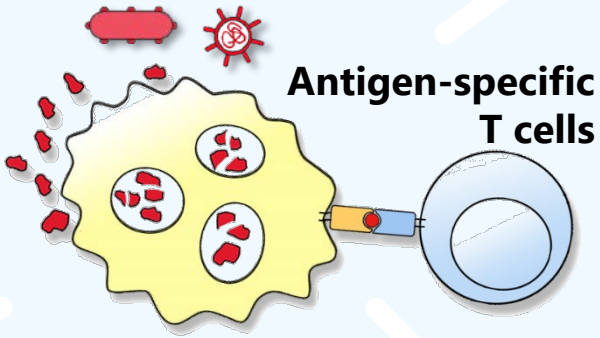

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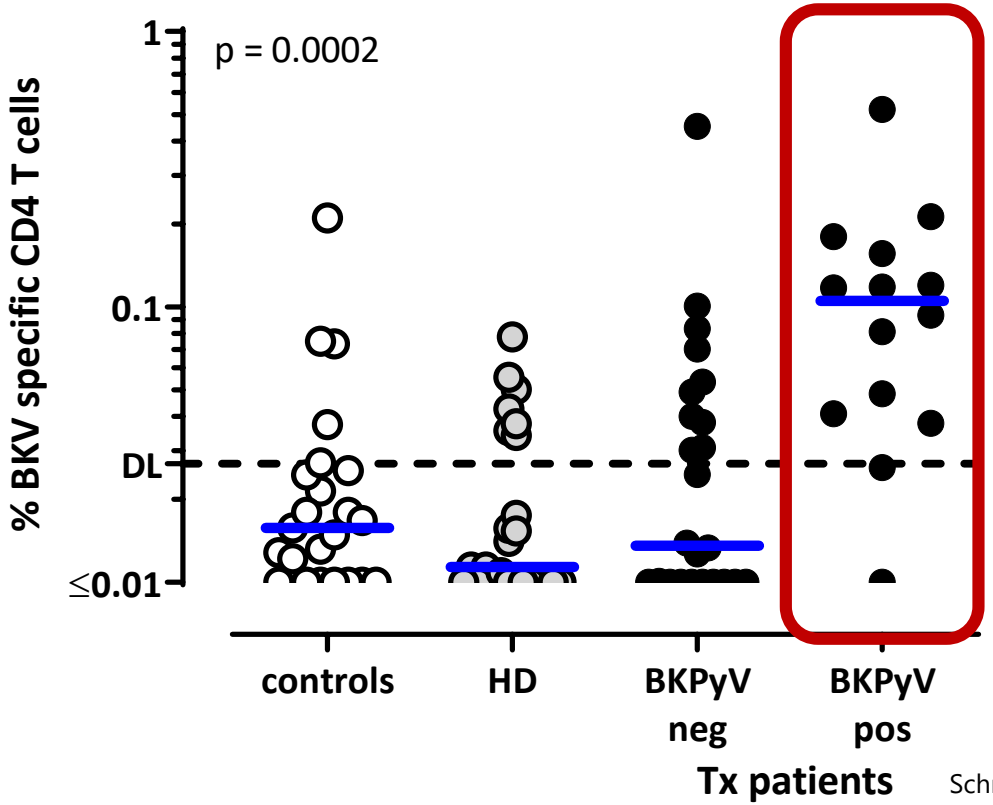
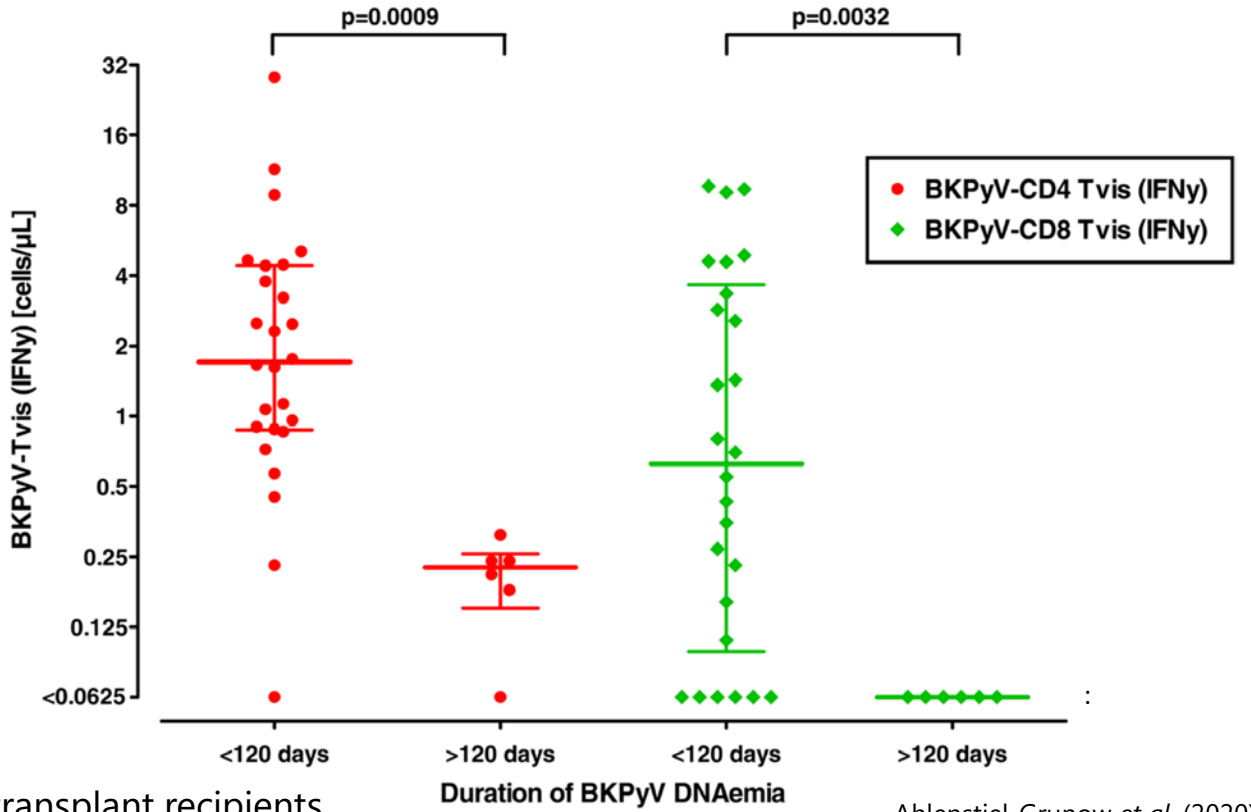
Increase of BKPyV specific T cells in patients with BKPyV viremia



Schmidt *et al.* (2014) Am J Transplant 14: 1334

BKPyV specific T cells correlate with duration of viremia



33 pediatric renal transplant recipients

Ahlenstiel-Grunow *et al.* (2020) *Transplantation* 104: 2393

International consensus recommendations

Reviews

OPEN

The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

Camille N. Kotton, MD,[1] Nassim Kamar, MD, PhD,[2] David Wojciechowski, MD,[3] Michael Eder, MD,[4] Helmut Hopfer, MD,[5] Parmjeet Randhawa, MD,[6] Martina Sester, PhD,[7] Patrizia Comoli, MD,[8] Helio Tedesco Silva, MD, PhD,[9] Greg Knoll, MD,[10] Daniel C. Brennan, MD,[11] Jennifer Trofe-Clark, PharmD,[12,13] Lars Pape, MD, PhD,[14] David Axelrod, MD, MBA,[15] Bryce Kiberd, MD,[16] Germaine Wong, MBBS, MMed, PhD,[17,18,19] and Hans H. Hirsch, MD[20,21]; on behalf of The Transplantation Society International BK Polyomavirus Consensus Group*

International BKPyV consensus meeting
Basel, Switzerland 6.-8.4.2022

Kotton *et al.* (2024) *Transplantation*

International consensus recommendations

Reviews

OPEN

The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

- Further data are needed:
  - before pretransplant BKPyV serology of donor or recipient can be recommended for risk stratifying kidney transplant recipients for posttransplant BKPyV-DNAemia/-nephropathy
  - before pretransplant BKPyV-specific CMI measurement can be recommended for routine clinical use to predict posttransplant BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV serology can be recommended for routine clinical use to predict the course of BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV-specific CMI can be recommended for routine clinical use to predict the course of posttransplant BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV-specific CMI can be used to safely guide changes in immunosuppression

Kotton *et al.* (2024) *Transplantation*

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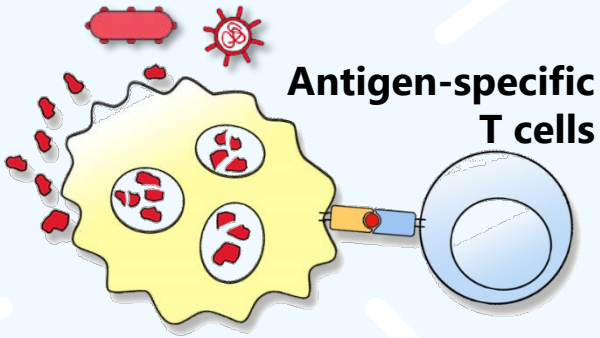

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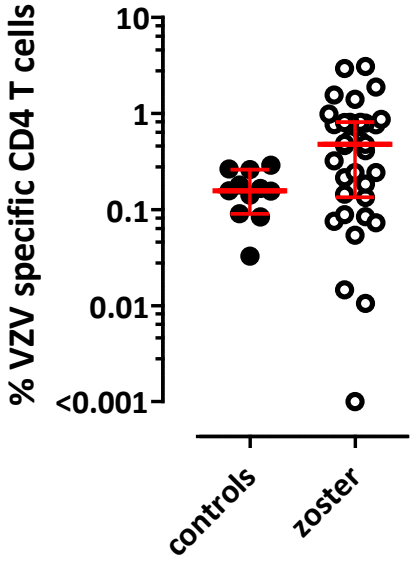
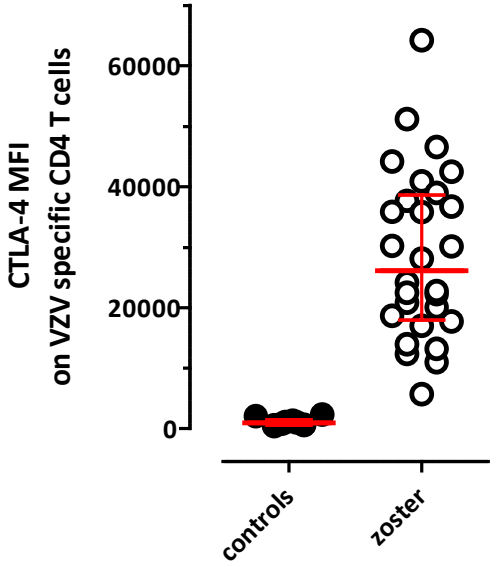
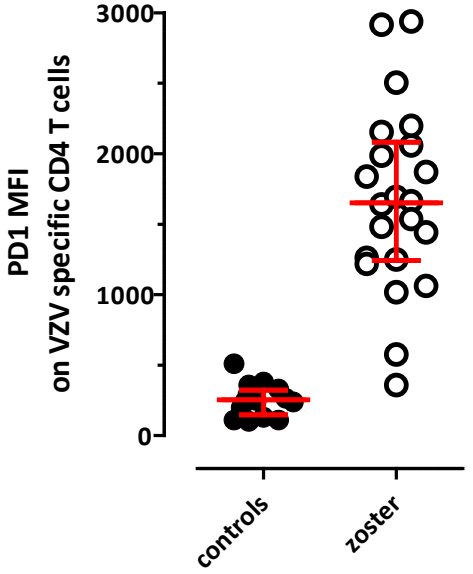
Alterations of VZV specific T cells in patients with acute herpes zoster



T-cell levels ↑



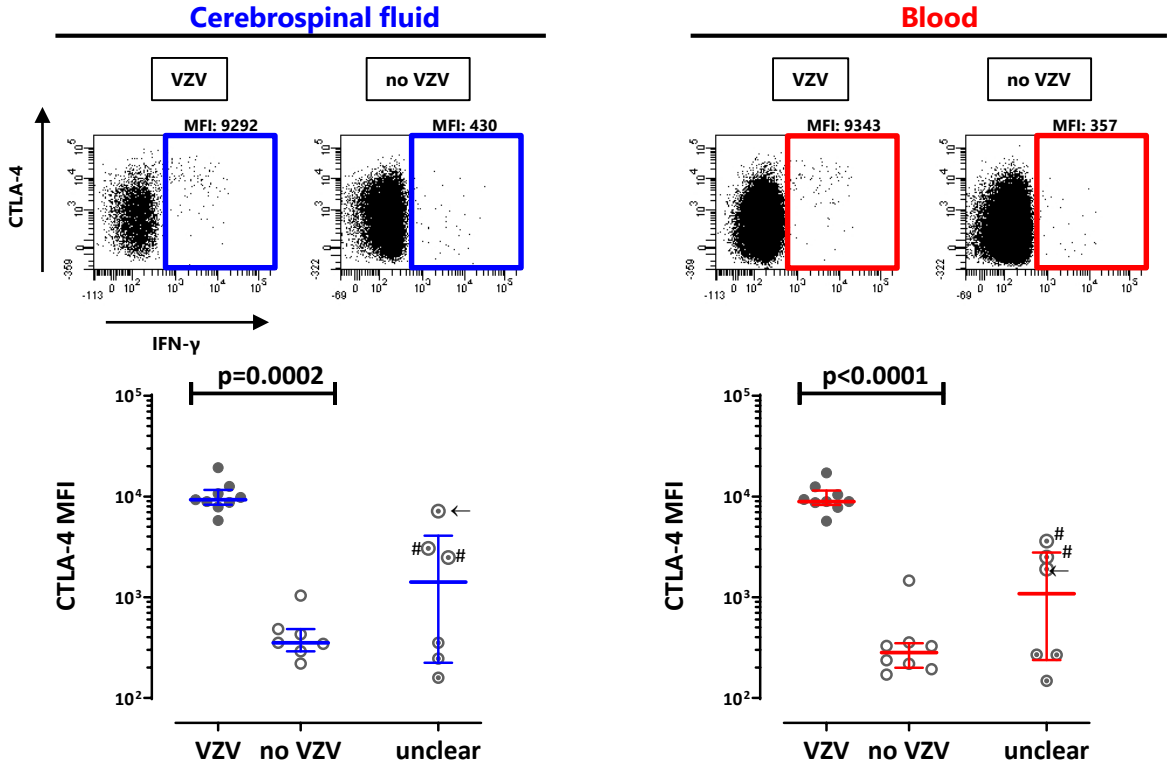
CTLA-4 ↑



PD-1 ↑

Schub *et al.* (2015) *J Infect Dis* 211: 600

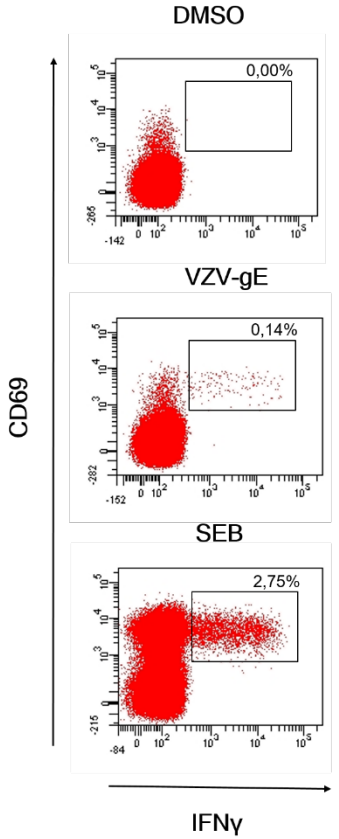
Strong CTLA-4 expression on VZV specific T cells in patients with VZV meningitis



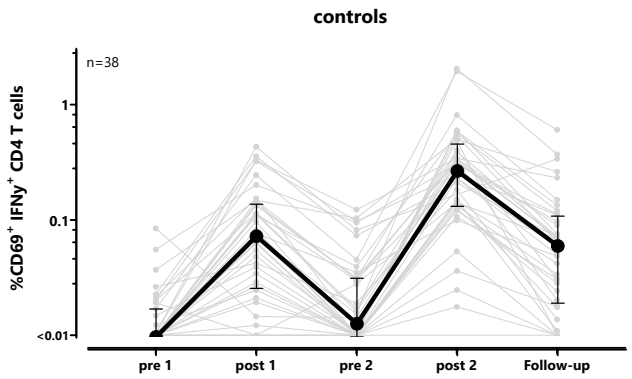
Also applies for patients with VZV-associated facial palsy

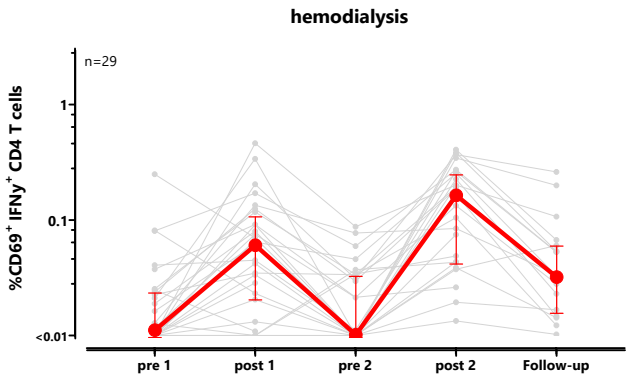
Schub *et al.* (2018) *Eur J Immunol* 48: 151; Schub *et al.* (2018) *Eur J Immunol* 48: 1412; Mohammad *et al.* (2023) *J Neuroinflammation* 20: 246

Induction of VZV-specific CD4 T cells by the recombinant Herpes zoster vaccine in dialysis patients

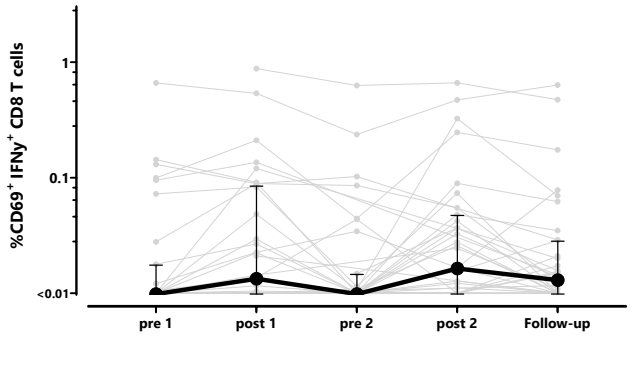


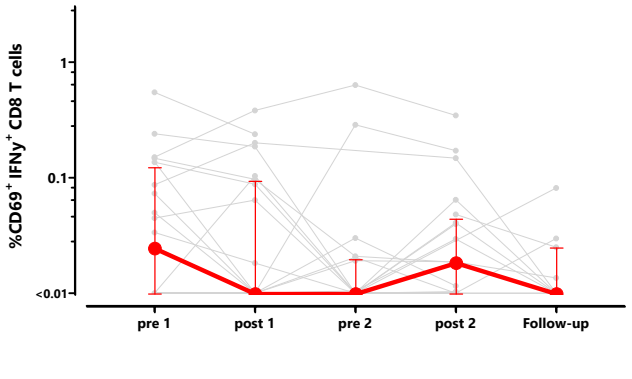
CD4





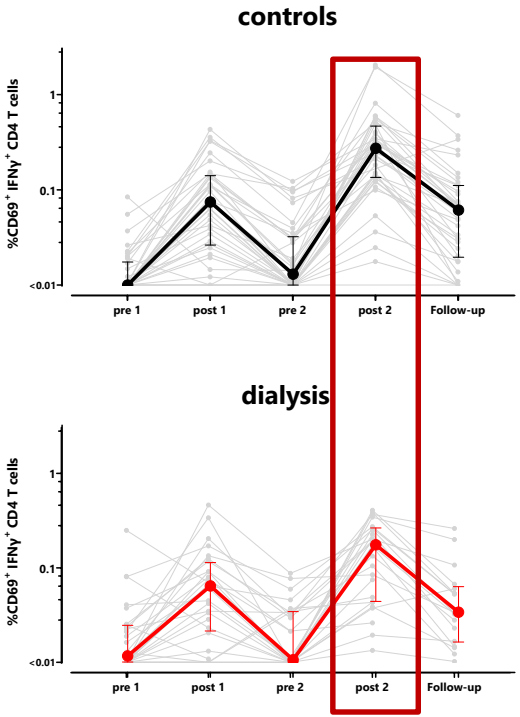
CD8

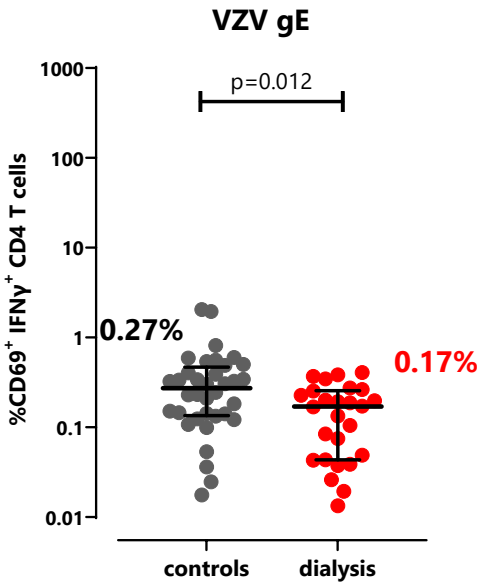




Hielscher *et al* (2024) EBioMedicine 108:105335

Less pronounced increase of VZV-specific CD4 T cells in patients





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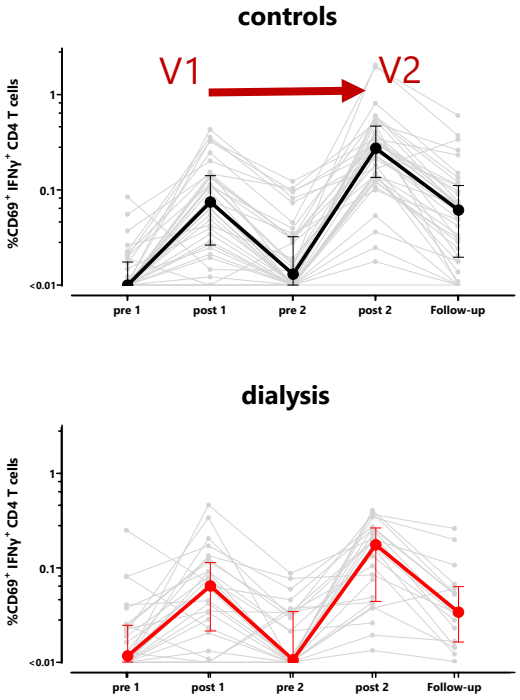
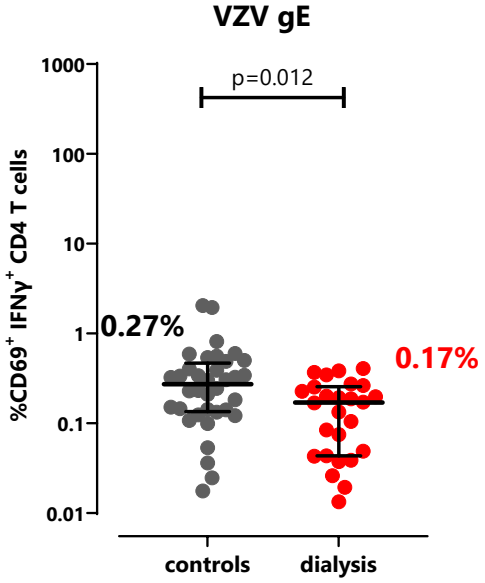
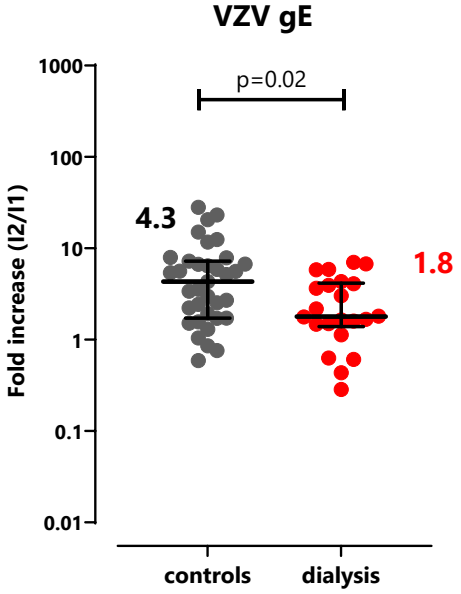
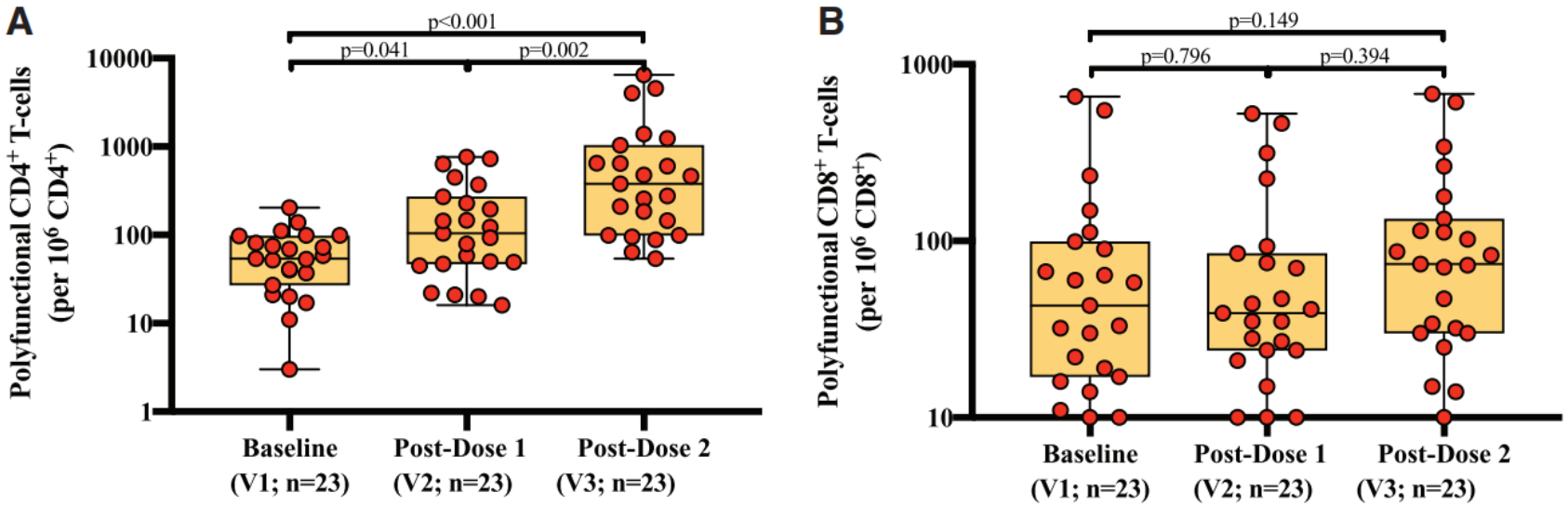






Hielscher *et al* (2024) EBioMedicine 108:105335

Induction of VZV-specific T cells after organ transplantation



- Induction of CD4 T cells
- No induction of CD8 T cells

L´Huillier *et al* (2021) *Transplantation* 105: 2613; Hirzel *et al.* (2021) *Am J Transplant* 21:2246

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M. tuberculosis
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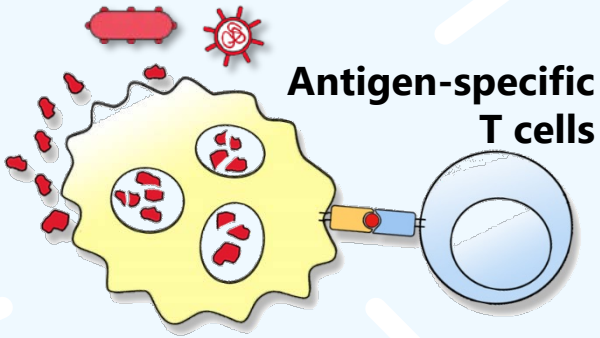


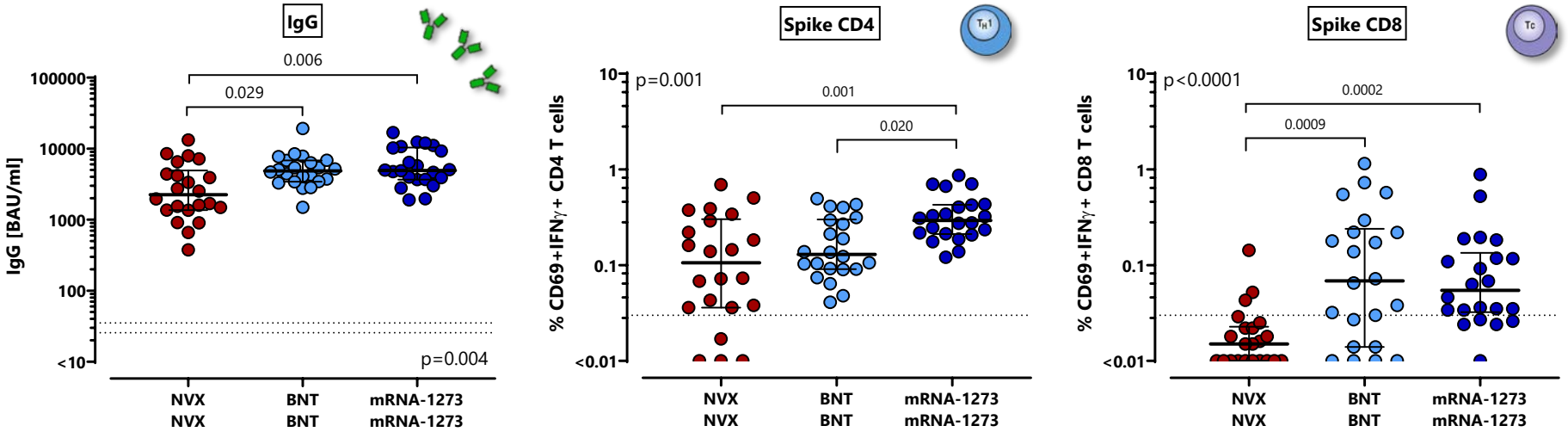
BKPyV
Monitoring of infectious complications
Guiding of immunosuppression reduction

SARS-CoV-2
Monitoring of infectious complications and vaccine-induced immunity

VZV
Monitoring of infectious complications and vaccine-responses

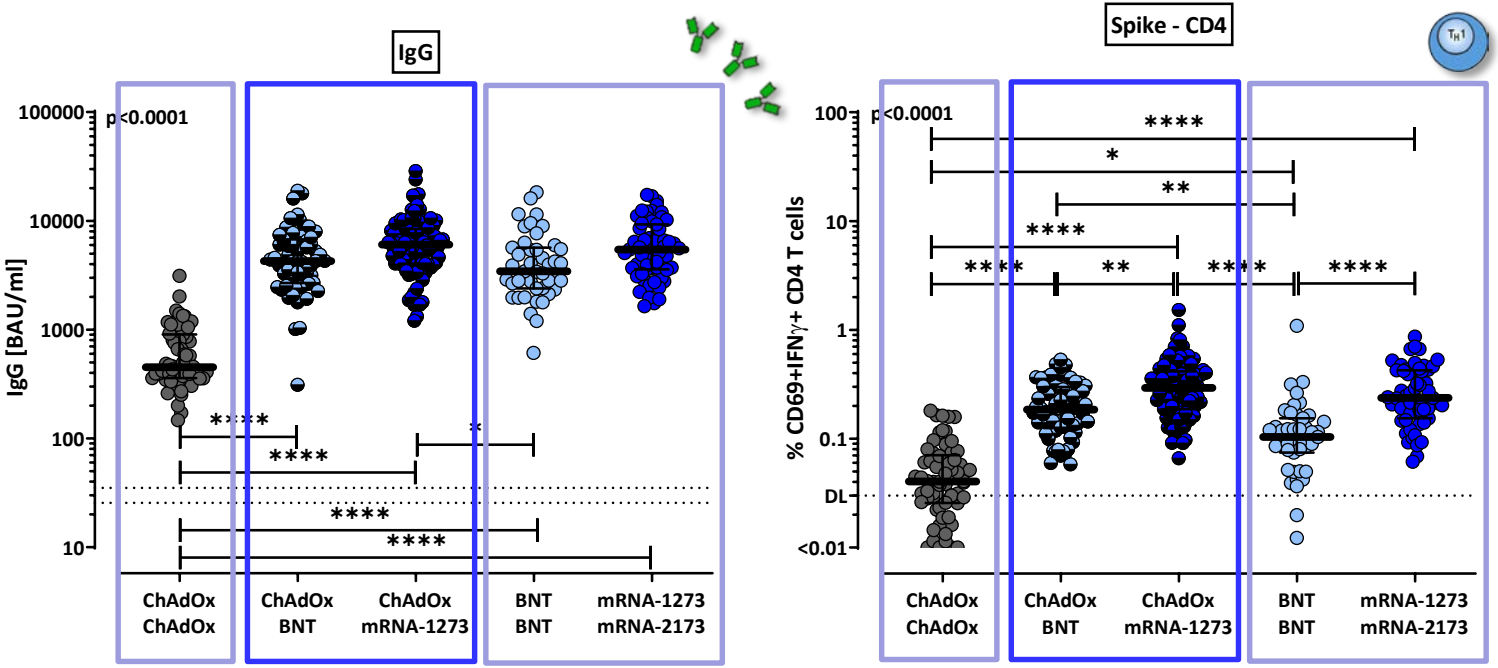
RSV
Monitoring of vaccine-induced cellular immunity

Outcome of immune response determined by vaccine type



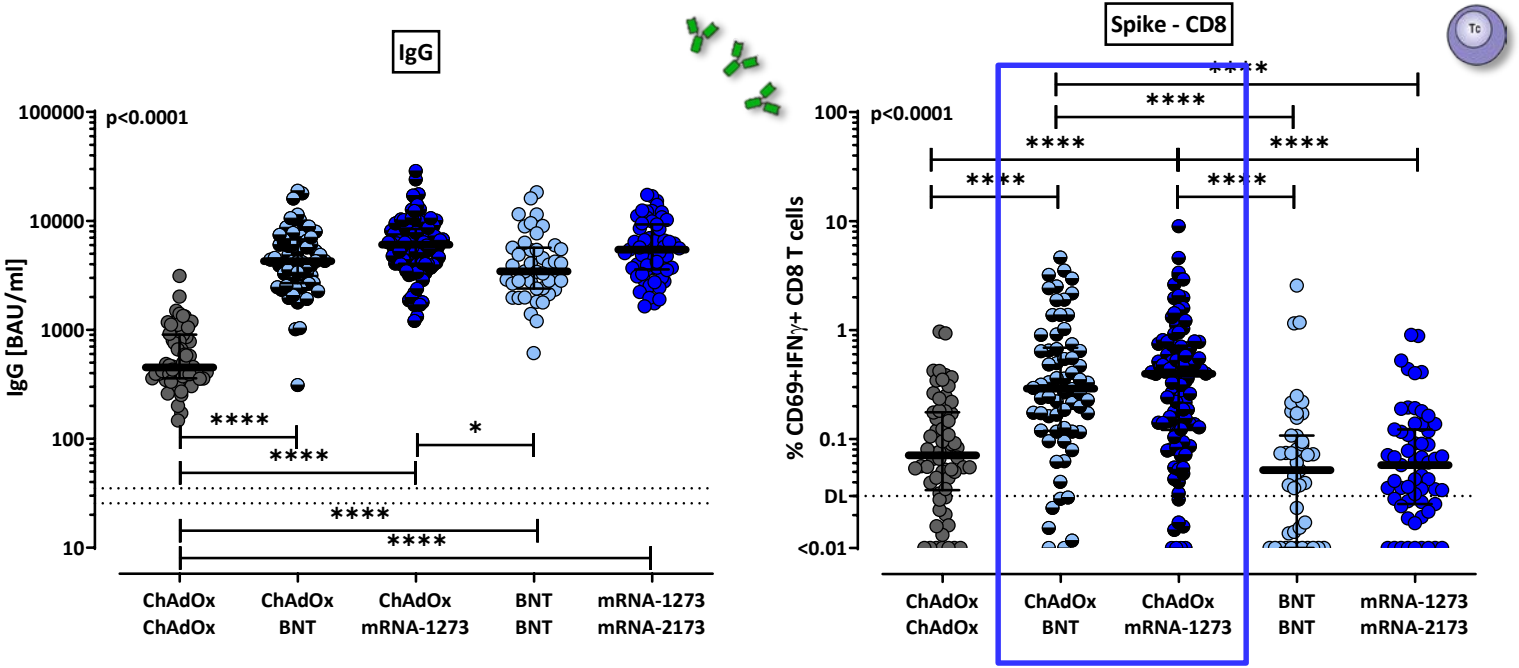
Hielscher *et al.* (2022) *Journal of Clinical Virology* 157

Outcome of immune response determined by vaccine combination and dosage



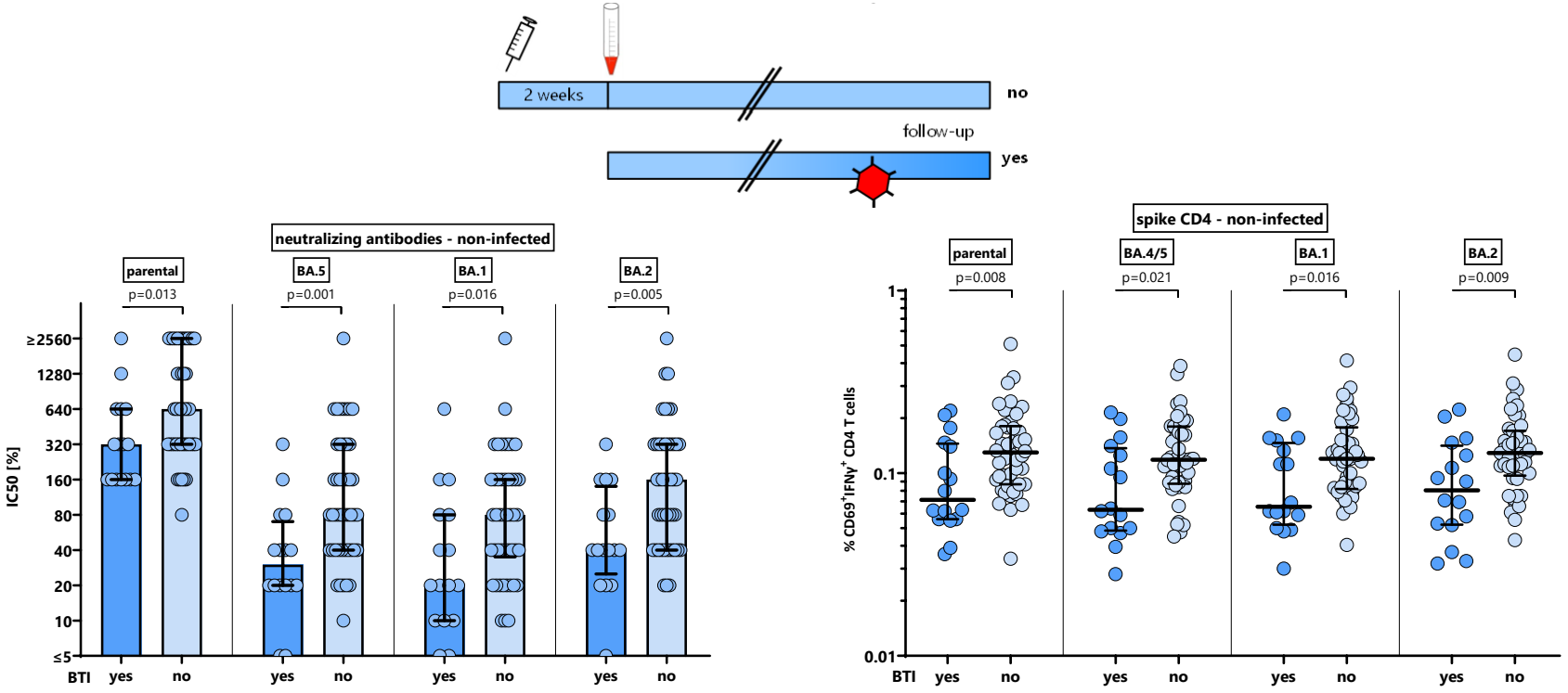
Schmidt *et al.* (2021) *Nat Med* 27: 1530, Klemis *et al.* (2022) *Nat Commun* 13: 4710

Outcome of immune response determined by vaccine combination and dosage



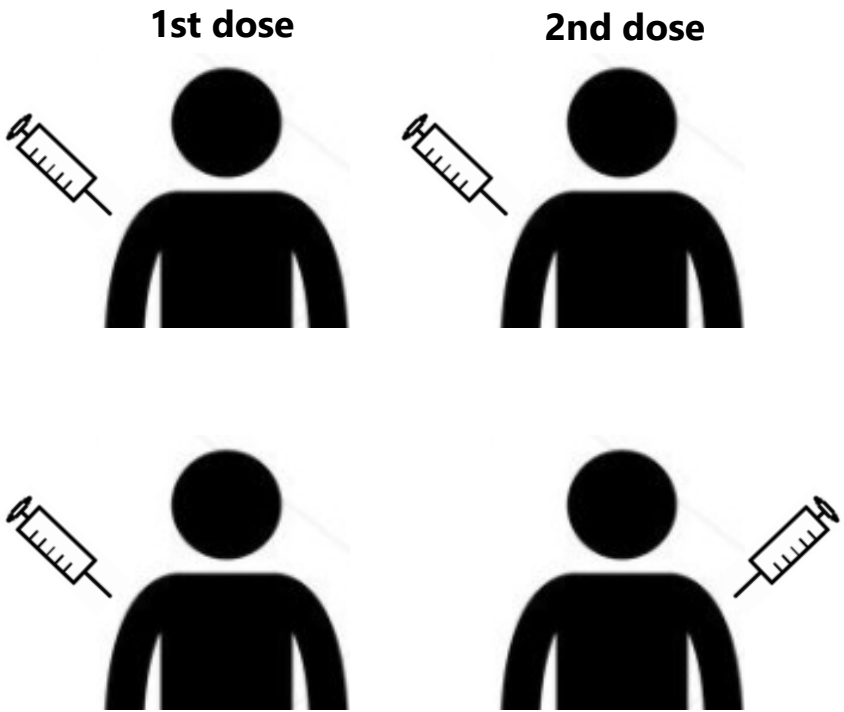
Schmidt *et al.* (2021) *Nat Med* 27: 1530, Klemis *et al.* (2022) *Nat Commun* 13: 4710

Lower neutralizing antibody titers and CD4 T-cell levels in individuals with subsequent infection



Urschel *et al.* (2024) *Nat Commun* 15: 3077

Does the vaccine side matter?

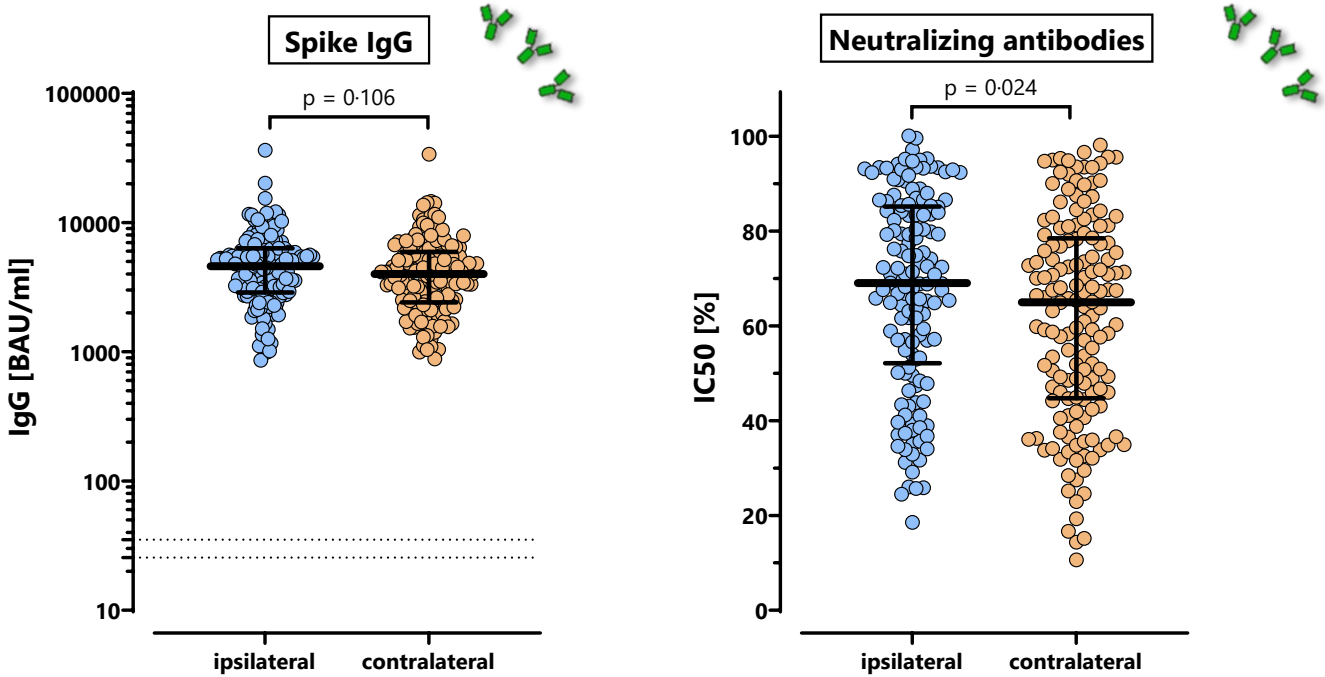


ipsilateral

contralateral

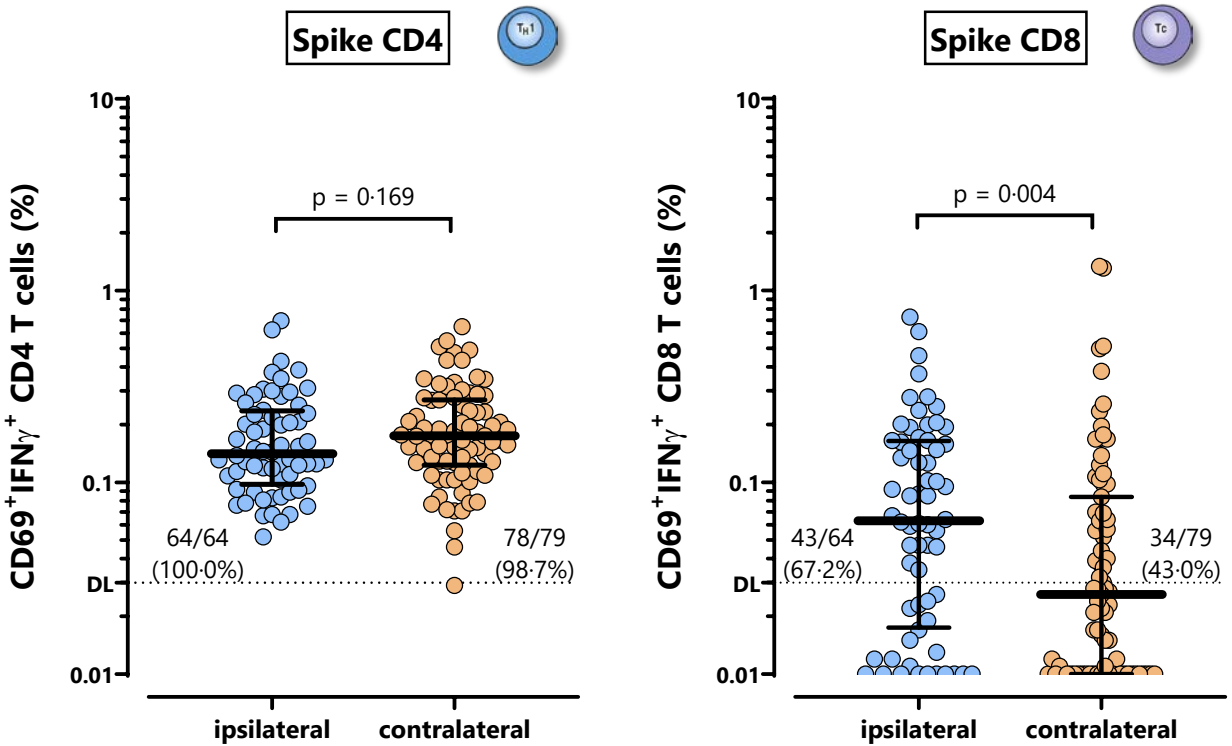
Ziegler et al. (2023) EBioMedicine 95:104743

Lower neutralizing antibody activity after contralateral vaccination



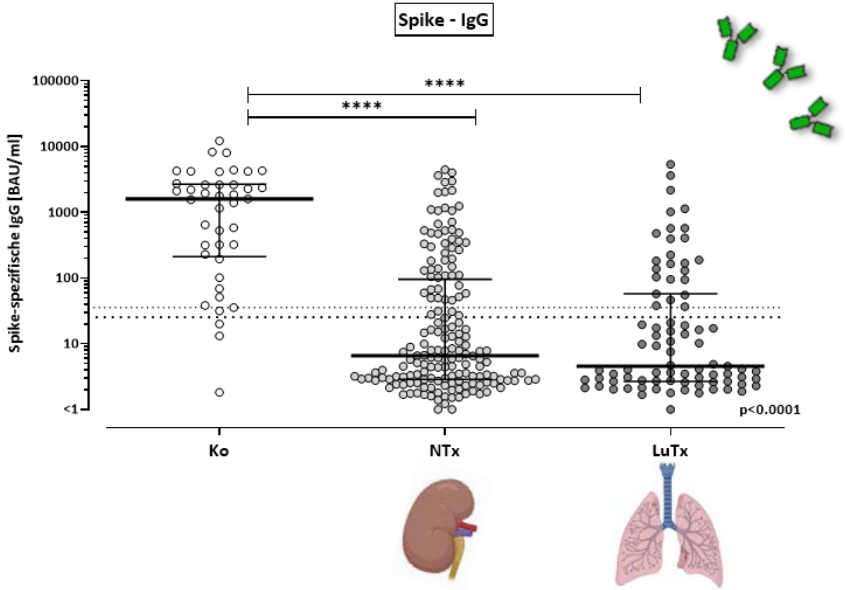
Ziegler et al. (2023) EBioMedicine 95:104743

Lower CD8 T-cell levels after contralateral vaccination



Ziegler et al. (2023) EBioMedicine 95:104743

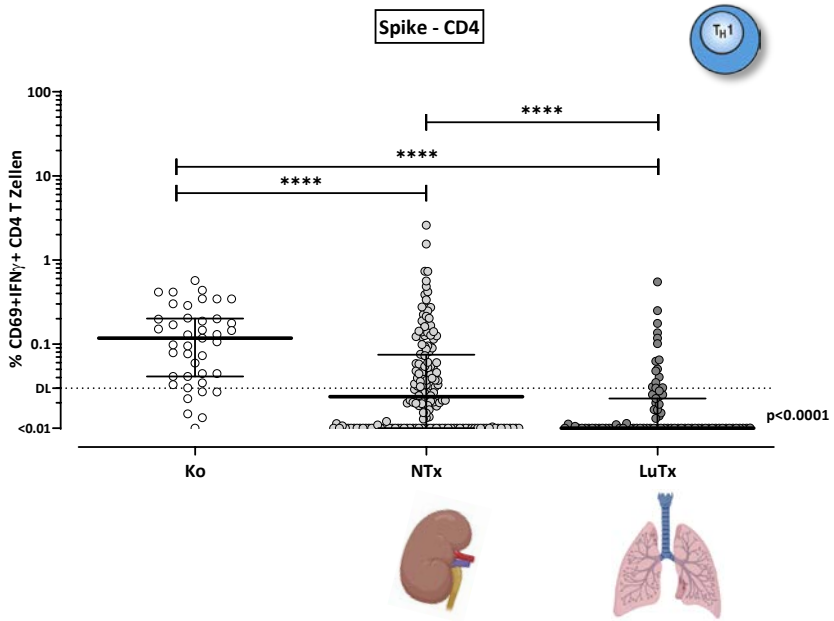
Lower antibody levels after renal and lung transplantation

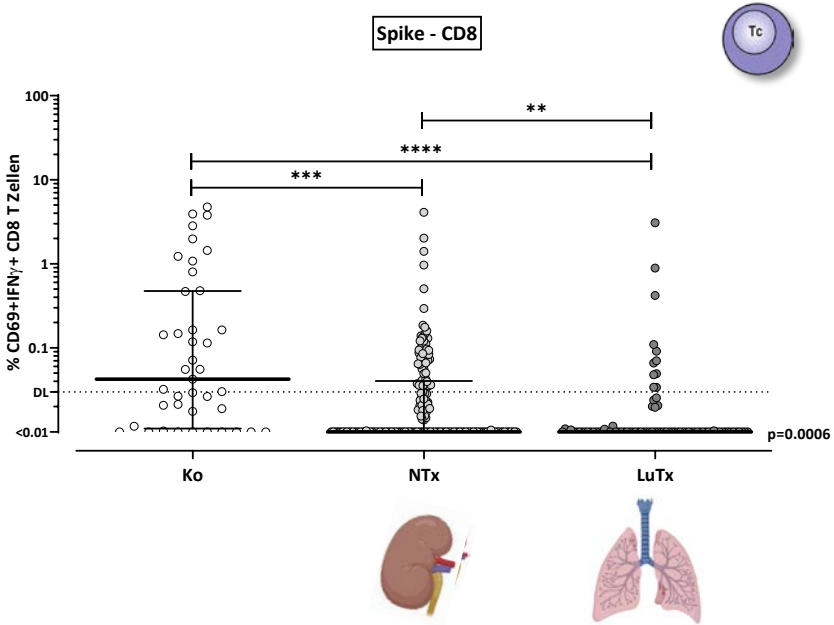


Response rate above detection limit (%)	90,2	31,0	30,1

)

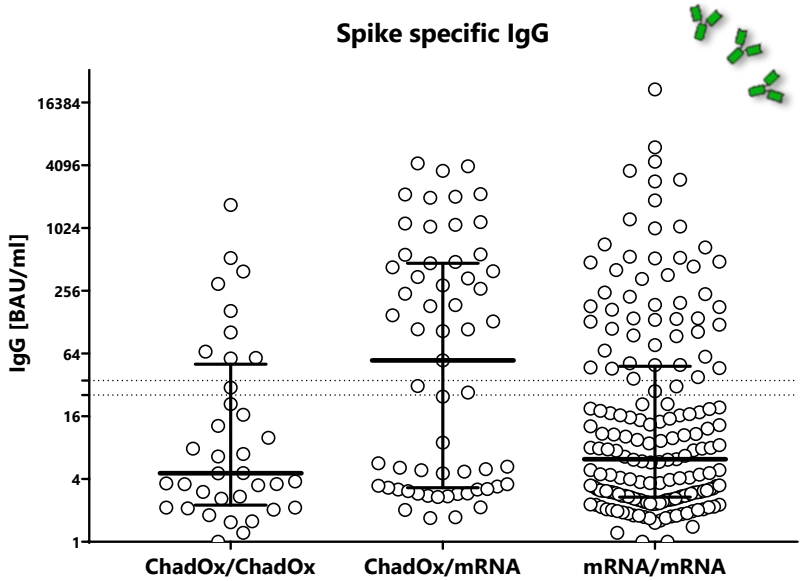
Lower T-cell levels after renal and lung transplantation





Response rate (%)	85,4	45,6	19,3	56,1	29,6	13,3

Most pronounced induction of immunity after heterologous vaccination in transplant recipients

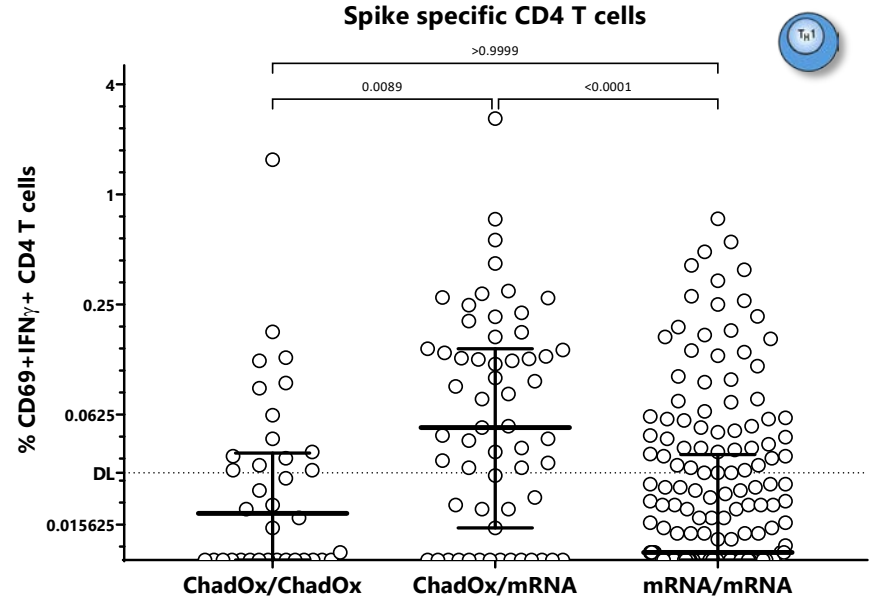


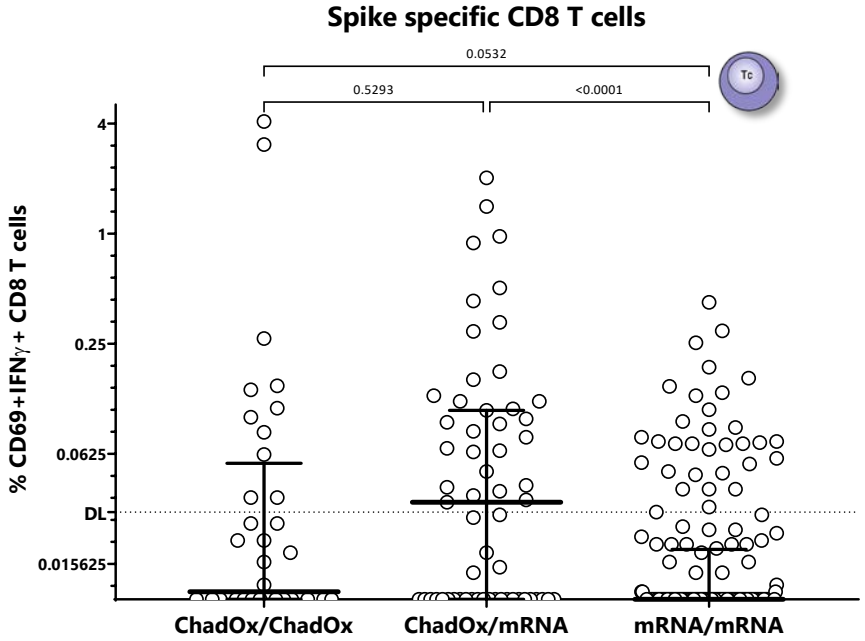
% of Responders	25.0%	32.6% 51.7%	27.4%

273 patients after solid organ transplantation

Schmidt et al. (2021) Am J Transplant; Schmidt *et al.* unpublished

Most pronounced induction of immunity after heterologous vaccination in transplant recipients





% of Responders	**38.9%**	**39.2%** **65.5%**	**30.9%**	**30.6%**	**26.7%** **51.7%**	**18.0%**

Schmidt et al. (2021) Am J Transplant; Schmidt *et al.* unpublished

Most pronounced induction of immunity after heterologous vaccination in transplant recipients

Response defined by	Total	ChAdOx ChAdOx	ChadOx mRNA	mRNA mRNA
antibodies 	**32.6%**	25.0%	51.7%	27.4%
T cells 	**46.8%**	50.0%	69.0%	39.2%
antibodies and/or T cells	**50.9%**	52.8%	72.4%	43.8%

- Antibodies underestimate vaccine response rates in transplant recipients

Schmidt et al. (2021) Am J Transplant; Schmidt *et al.* unpublished

Most pronounced induction of immunity after heterologous vaccination in transplant recipients

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Most pronounced induction of immunity after heterologous vaccination in transplant recipients

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- Antibodies underestimate vaccine response rates in transplant recipients
- Most pronounced response rate after heterologous vaccination
- Patients benefit from heterologous regimen in subsequent vaccinations

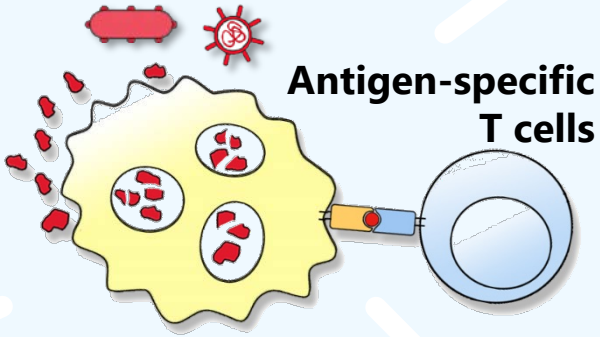
Schmidt et al. (2021) Am J Transplant; Schmidt *et al.* unpublished

T-cell based monitoring of infectious complications

CMV
Monitoring of infectious complications
Guiding antiviral therapy

M. tuberculosis
Diagnosis of latent infections

BKPyV
Monitoring of infectious complications
Guiding of immunosuppression reduction



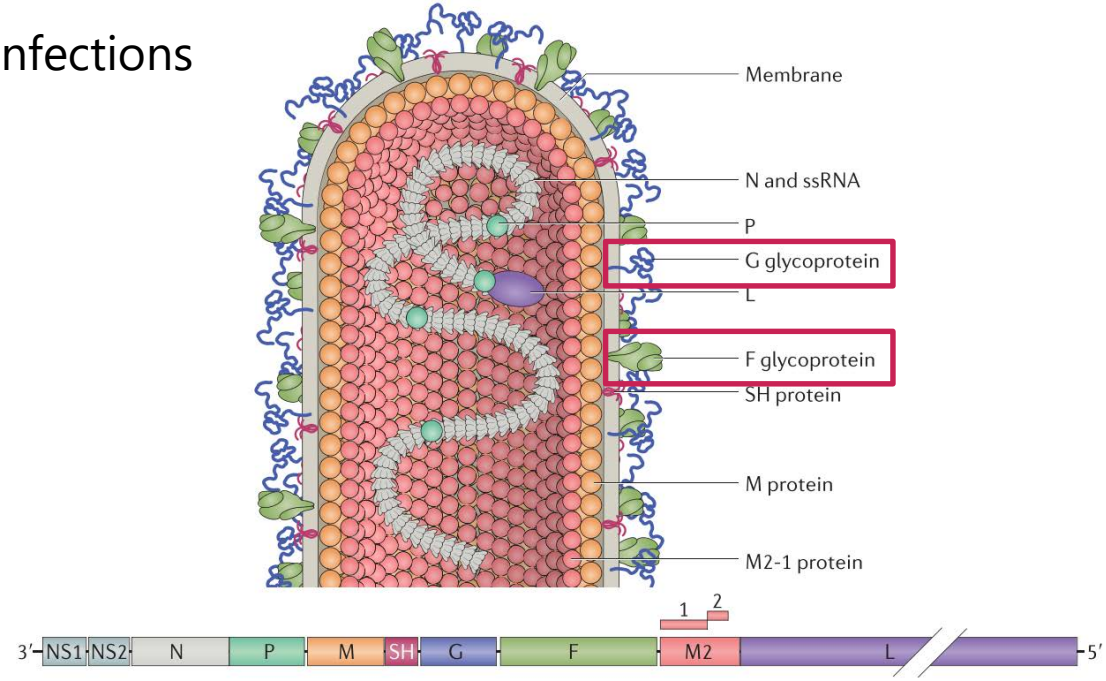
SARS-CoV-2
Monitoring of infectious complications and vaccine-induced immunity

VZV
Monitoring of infectious complications and vaccine-responses

RSV
Monitoring of vaccine-induced cellular immunity

Respiratory syncytial virus RSV

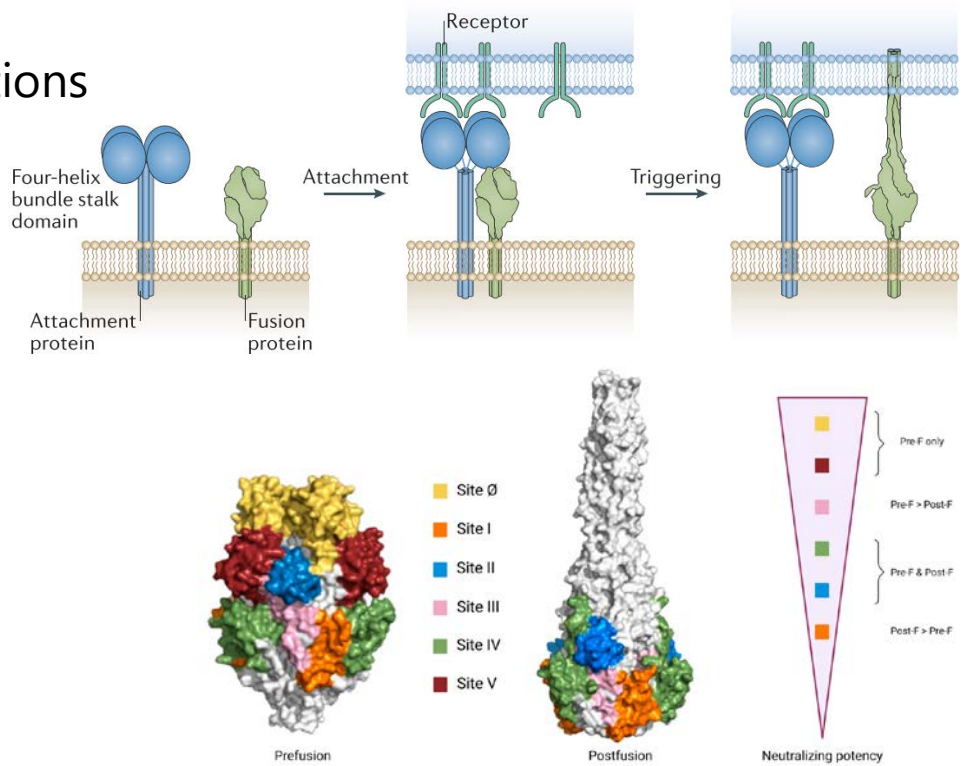
- Causes lower respiratory tract infections
- 2 subtypes
  - RSV-A
  - RSV-B
- Membrane proteins
  - Adhesion protein
  - Fusion (F) protein



Battles and McLellan (2019) *Nat Rev Microbiol* 17: 233

RSV vaccine

- Causes lower respiratory tract infections
- 2 subtypes
  - RSV-A
  - RSV-B
- Membrane proteins
  - Adhesion protein
  - Fusion (F) protein
- Vaccine contains „pre-fusion F protein“
- Vaccine recommended as one dose
  - For adults >75 years
  - Für adults > 60 years with risk factors

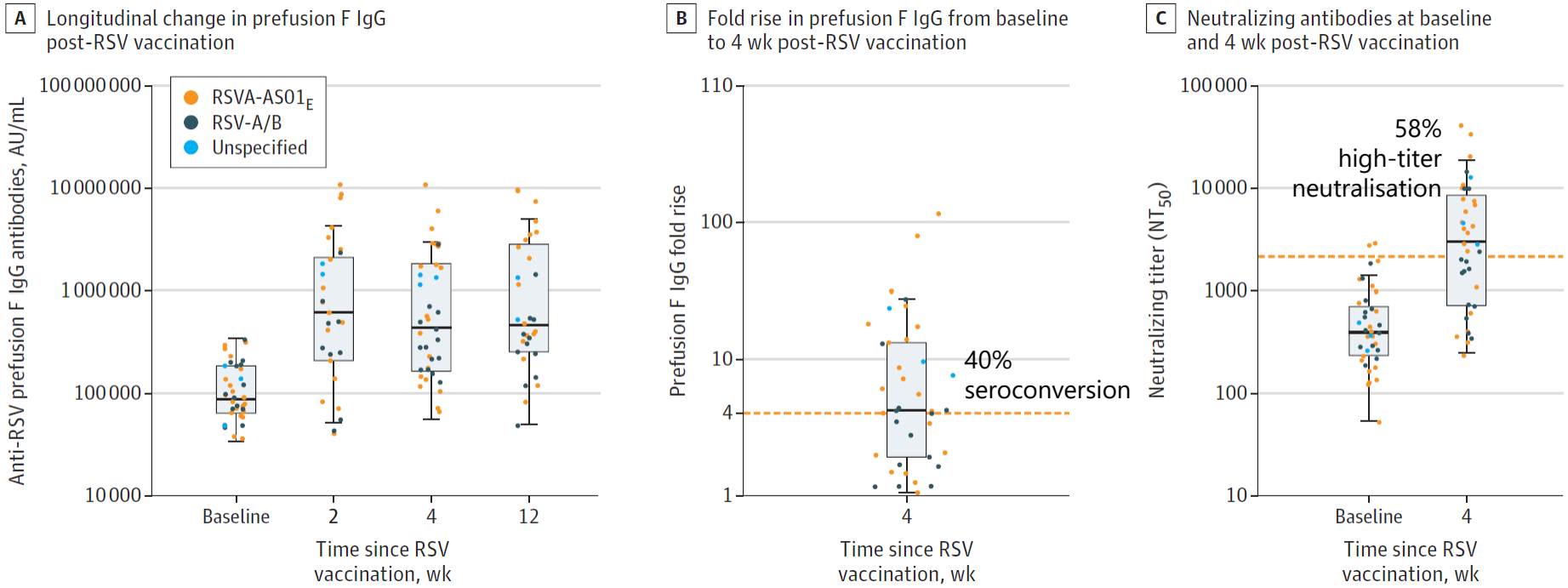


Battles and McLellan (2019) *Nat Rev Microbiol* 17: 233

RSV vaccines

	Standard Protein	Protein with adjuvant	mRNA
vaccine type	Recombinant protein	Recombinant protein	mRNA
Antigens	Pre-Fusion F **Type A, Type B**	Pre-Fusion F **Type A only**	Pre-Fusion F **Type A only**
adjuvant	Standard	$AS01_E$ (50% Shingrix)	
Dosage per Ag	60µg (=120µg)	120µg	50µg mRNA
Approved for	>60 years Pregnant women	>60 years	>60 years
Vaccine name	Abrysvo	Arexvy	mRESVIA
Efficacy (3 symptoms)	**85.7** (32.0-98.7)	**94.1** (62.4-99.9)	**82.4** (34.8-95.3)
reference	Walsh *et al.* (2023) *N Engl J Med* 388: 1465	Papi *et al.* (2023) *N Engl J Med* 388: 595	Wilson *et al.* (2023) *N Engl J Med* 389: 2233

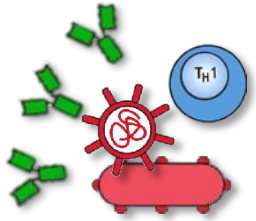
Induction of RSV-induced antibodies in immunocompromised patients



38 patients with immunodeficiencies (82% SOT recipients)

Karaba *et al.* (2024) *JAMA*

Summary
Immunomonitoring



- Pathogen-specific T cells may be analysed in a clinical setting
- Pathogen-specific T cells provide individual insights into the immune response towards infections or vaccinations
- Adjunct application of immunomonitoring in association with viral load assays
- Contribution towards personalized antimicrobial therapy and immunosuppressive drug treatment

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UNIVERSITÄT DES SAARLANDES

SHG Klinik für Nephrologie Völklingen
Urban Sester
Janine Mihm

Transplantations- und Infektionsimmunologie

Merci pour l'attention
Thank you for your attention
Vielen Dank für die Aufmerksamkeit

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Transplantations- und Infektionsimmunologie