

Accelerated immune senescence in Patients with CKD: Can and should we individualize immunosuppressive therapies?

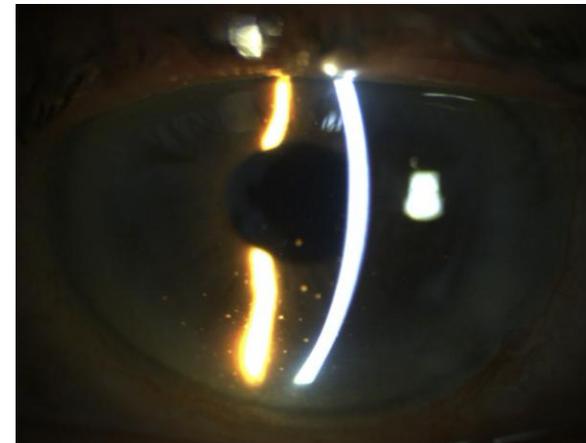
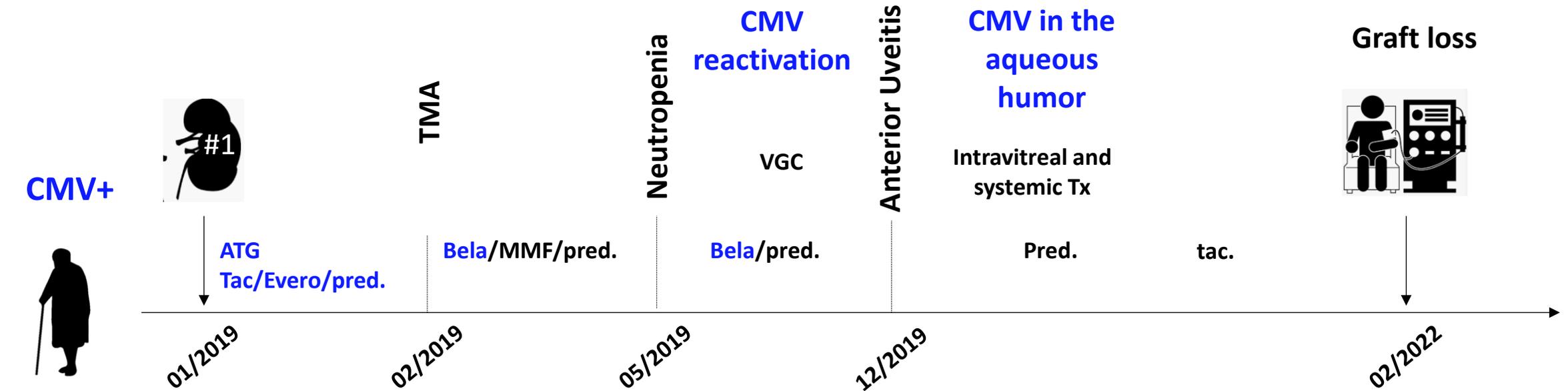
Julien Zuber

Maladies du rein et du métabolisme, transplantation et immunologie clinique
Hôpital Necker

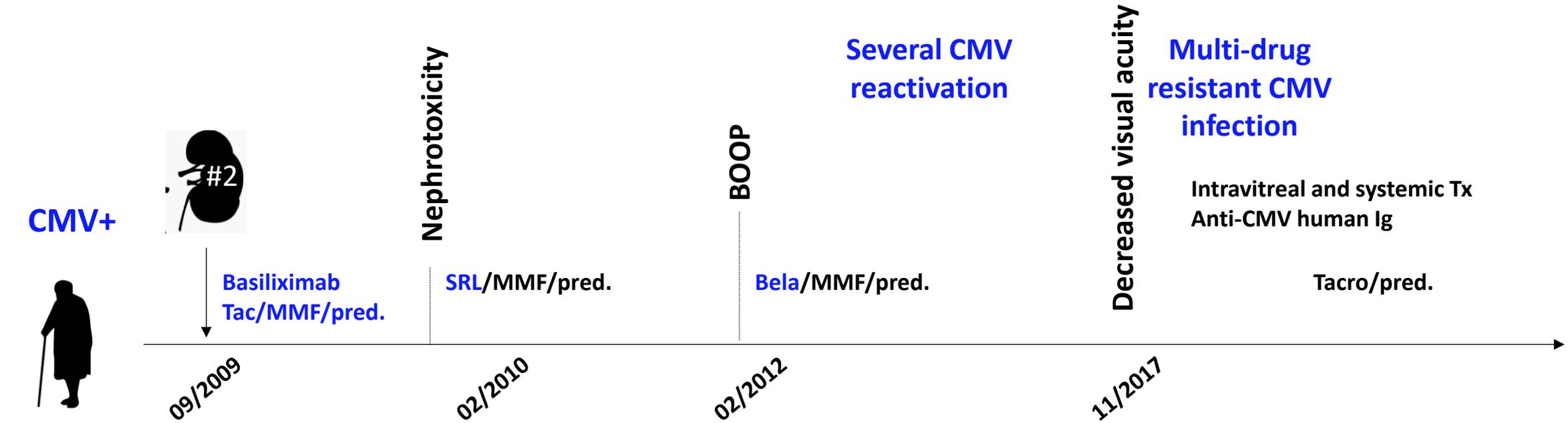
Henry Ford

**« The only real mistake is the one from
which we learn nothing »**

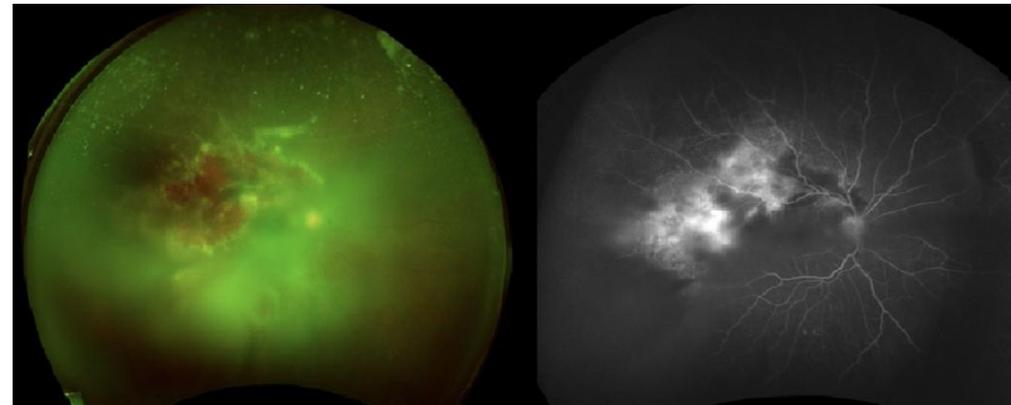
CASE 1: CMV reactivation in an elderly kidney Tx recipient



Late CMV infection in seropositive elderly KTx treated with belatacept



76-yr-old

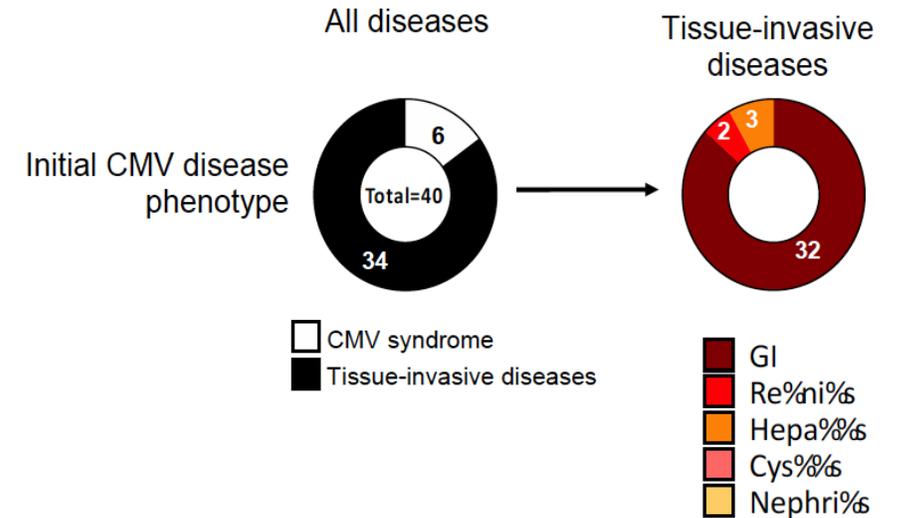


Late CMV infection in seropositive elderly KTx treated with belatacept



N. Chavarot

| Variables ^a | N=40 |
|---|-------------------|
| CMV disease characteristics | |
| Time between conversion and CMV disease (months), <i>median (IQR)</i> | 9.0 (0.23-54.8) |
| Age at CMV disease (yr), <i>median (IQR)</i> | 67.3 (56.1- 73.9) |
| CMV serostatus, <i>n (%)</i> | |
| D-/R- | 2 (5) |
| D-/R+ | 8 (20) |
| D+/R+ | 19 (47.5) |
| D+/R- | 11 (27.5) |
| Clinical manifestations of the initial CMV disease, <i>n (%)</i> | |
| CMV syndrome | 6 (15) |
| Gastrointestinal involvement | 32 (80) |
| Retinitis | 2 (5) |
| Hepatitis | 3 (7.5) |



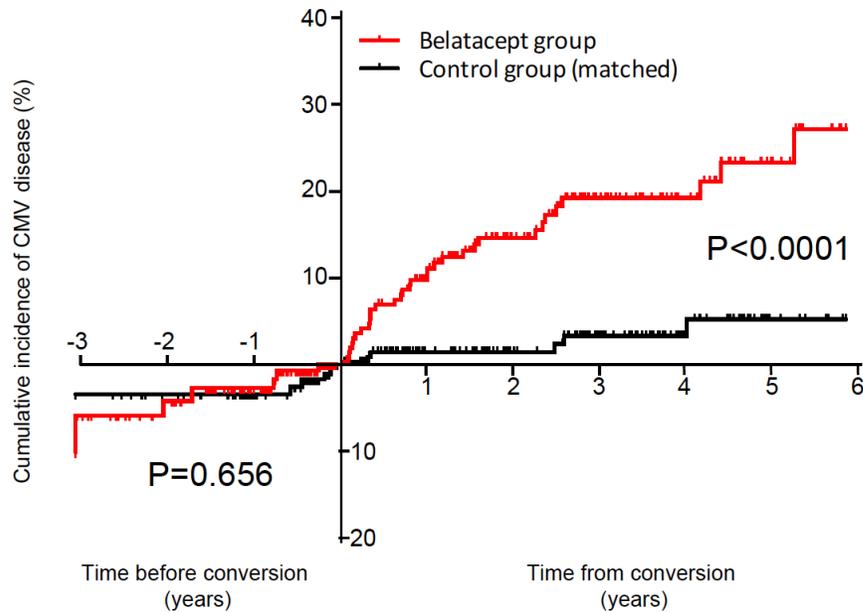
40/223 (17.9%) developed CMV disease

Late CMV infection in seropositive elderly KTx treated with belatacept



N. Chavarot

Propensity score matching revealed a 7-fold increased risk of CMV disease under belatacept, whose independent risk factors included increased age, D+/R- serostatus, and eGFR at conversion



Number at risk:

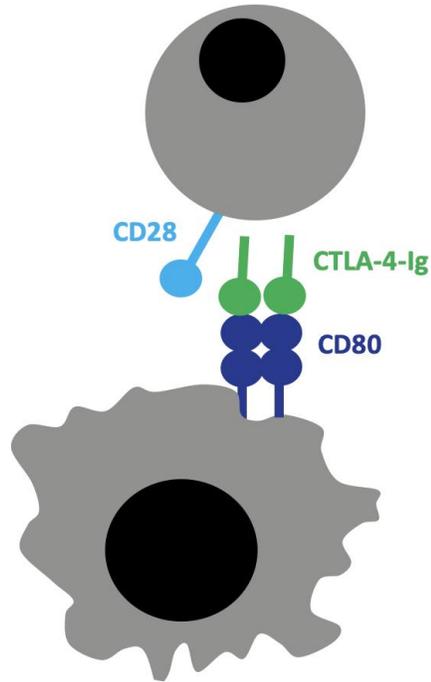
| | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|------------------|----|----|----|-----|-----|-----|----|----|----|----|
| Belatacept Group | 44 | 58 | 87 | 181 | 141 | 106 | 69 | 46 | 26 | 10 |
| Control Group | 29 | 37 | 98 | 181 | 141 | 113 | 88 | 56 | 32 | 19 |

Table 2: Factors associated with CMV disease in belatacept-treated patients: univariable and multivariable Cox analysis

| Variables | Univariable Cox analysis | | | | | Multivariable Cox analysis | | | | |
|--|--------------------------|-------------|-------|-------------------|--------|----------------------------|-------------|-------|-------------------|--------|
| | # of patients | # of events | HR | 95% CI | p | # of patients | # of events | HR | 95% CI | p |
| Age at conversion (per 1-year increment) | 222 | 40 | 1.041 | [1.014 to 1.068] | 0.0024 | 218 | 40 | 1.032 | [1.006 to 1.058] | 0.0164 |
| Gender | | | | | | | | | | |
| Female | 86 | 19 | 1 | - | - | - | - | - | - | - |
| Male | 137 | 21 | 0.614 | [0.329 to 1.144] | 0.1241 | - | - | - | - | - |
| CMV serostatus | | | | | | | | | | |
| D-/R- | 36 | 2 | 1 | - | - | 36 | 2 | 1 | - | - |
| D+/R+ | 94 | 19 | 4.343 | [1.011 to 18.659] | | 94 | 19 | 3.876 | [0.900 to 16.685] | |
| D-/R+ | 50 | 8 | 3.256 | [0.691 to 15.340] | | 50 | 8 | 2.713 | [0.571 to 12.890] | |
| D+/R- | 40 | 11 | 7.909 | [1.745 to 35.843] | 0.0325 | 39 | 11 | 7.703 | [1.693 to 35.047] | 0.0220 |
| eGFR (mL/min/1.73 m ²) | 221 | 40 | 0.969 | [0.946 to 0.993] | 0.0123 | 218 | 40 | 0.973 | [0.948 to 0.998] | 0.0355 |
| Proteinuria (g/g creat) (log transformation) | 218 | 40 | 1.357 | [1.007 to 1.829] | 0.0451 | - | - | - | - | - |

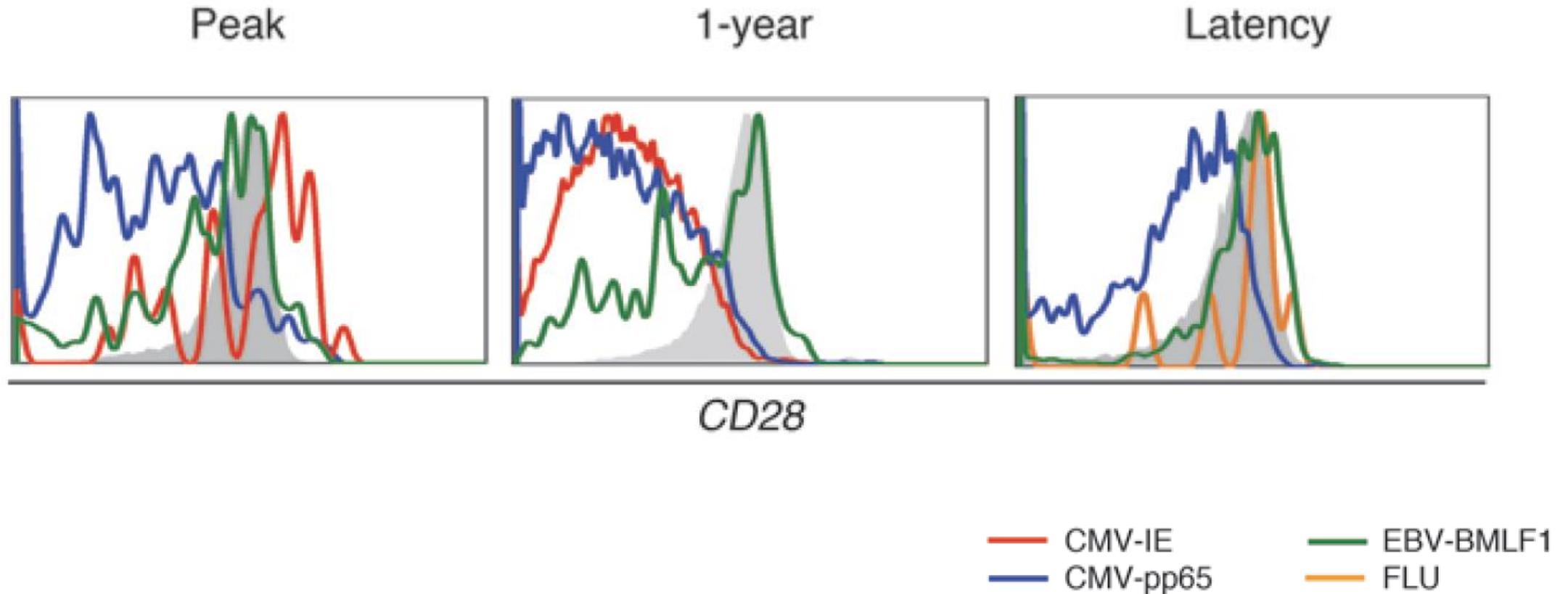
CI, confidence interval; HR, hazard ratio; HLA, human leukocyte antigen; eGFR, estimated glomerular filtration rate.

Anti-CMV memory immune responses appear to be overly sensitive to CTLA-4-Ig in **elderly individuals** with **graft dysfunction**



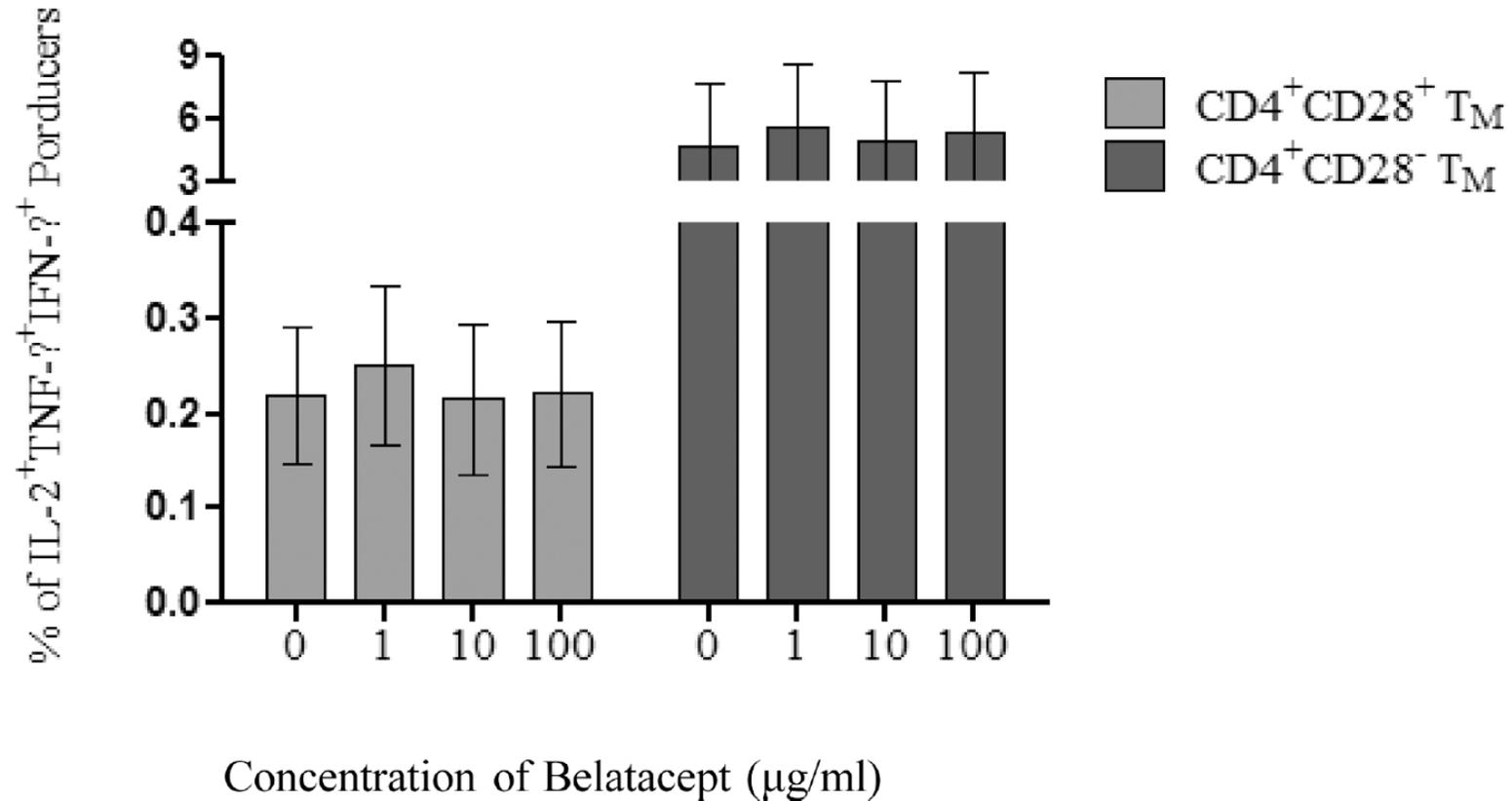
1- Is **CD28 signal essential** for maintaining an effective CMV-specific T cell response?

CMV-specific CD8+ memory T cells do not express CD28



Belatacept does not inhibit CMV-specific memory T cells

CMV stimulation



CMV infection is contained despite dysfunctional CD28



Vivien Beziat



Giant cutaneous horns (« Tree man syndrome »)



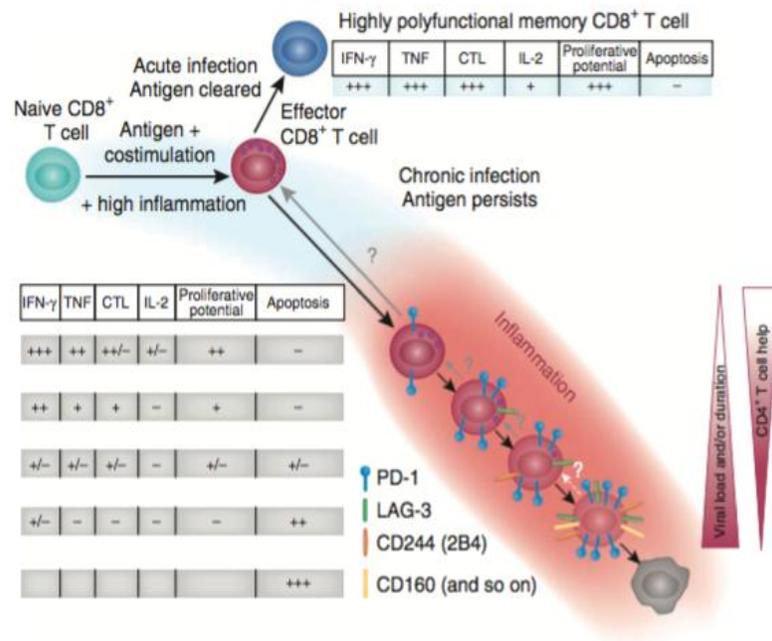
Humans with inherited T cell CD28 deficiency are susceptible to skin papillomaviruses. They are otherwise healthy, **yet exhibit moderate EBV and CMV replication.**

| | P1 (30 yo) | P2 (40 yo) | P3 (12 yo) | Normal range |
|--------------------------------------|------------|------------|------------|--------------|
| PCR pathogens | | | | |
| Toxoplasmosis (whole blood) | Neg | NT | NT | - |
| <i>Aspergillus fumigatus</i> (serum) | Neg | NT | NT | - |
| HIV-1 RNA (plasma) | Neg | NT | NT | - |
| CMV (whole blood; copies/mL) | 2979 | 1537 | <500 | <446 |
| EBV (whole blood; copies/mL) | 20922 | 2312 | 1460 | <90 |
| Adenovirus (whole blood) | Neg | NT | NT | - |
| HSV-1 (whole blood) | Neg | NT | NT | - |
| HSV-2 (whole blood) | Neg | NT | NT | - |
| VZV (whole blood) | Neg | NT | NT | - |

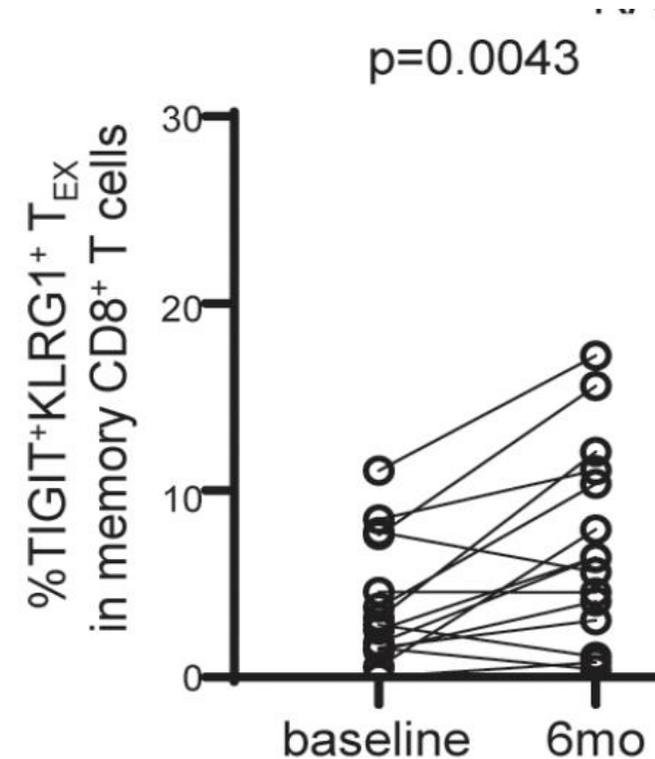
CTLA-4-Ig may induce exhaustion in chronically-stimulated T-cells

Late-onset CMV reactivation suggests that anti-CMV T-cell responses gradually wane under belatacept therapy

T cell exhaustion



CTLA-4, LAG-3, Tim-3, TIGIT, KLRG1, PD-1

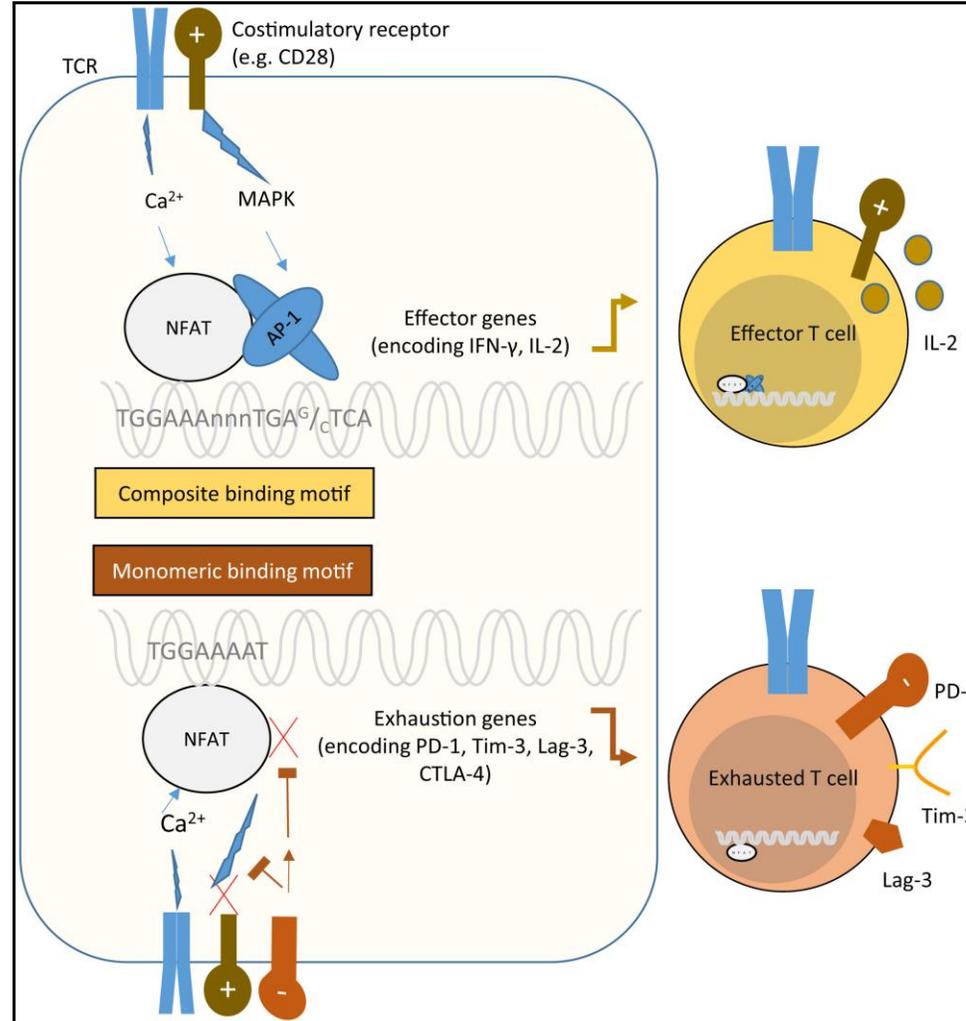


TIGIT+ KLRG1+ exhausted CD8+ T cells are increased in rheumatoid arthritis patients following abatacept treatment

Lack of CD28 signal may induce exhaustion in chronically-stimulated T-cells

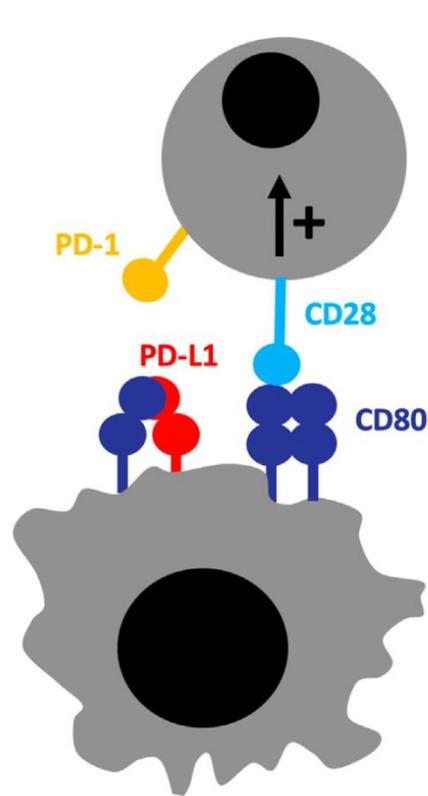


J. Wherry

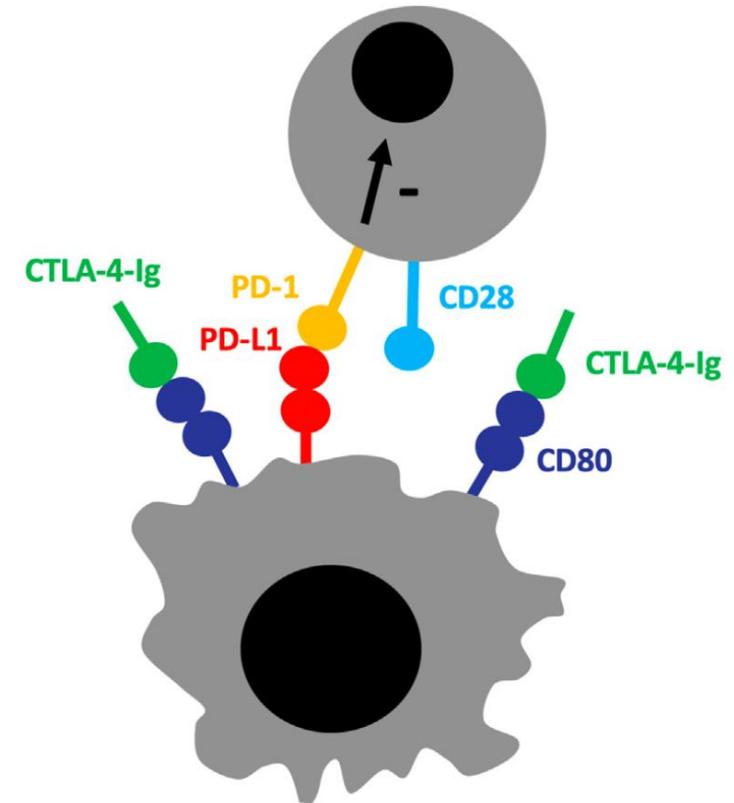


Partnerless NFAT drives the T cell exhaustion program

CTLA-4-Ig increases the level of free PD-L1 on dendritic cells



The interaction of CD80 with PD-L1 in cis restricts the transbinding between PD-1 and PD-L1



CD80 occupancy by belatacept might liberate PD-L1 from PD-L1/CD80 heterodimers, thereby promoting CD28-independent PD-1-mediated T cell suppression

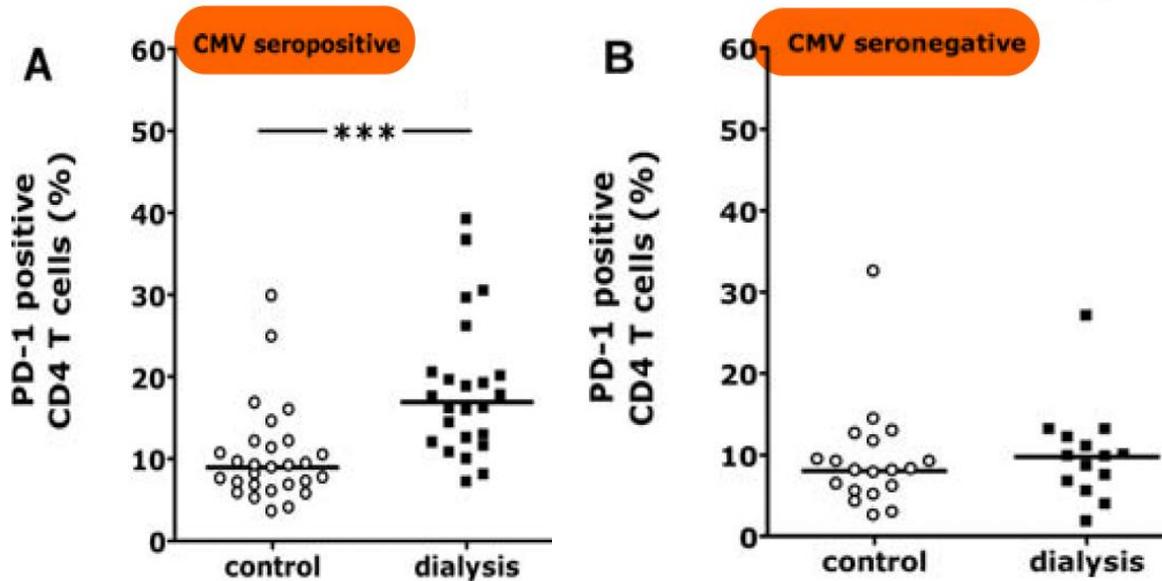
Terminally differentiated PD-1+ CD28- T cells accumulate in CMV-seropositive patients with chronic kidney disease



M. Sester

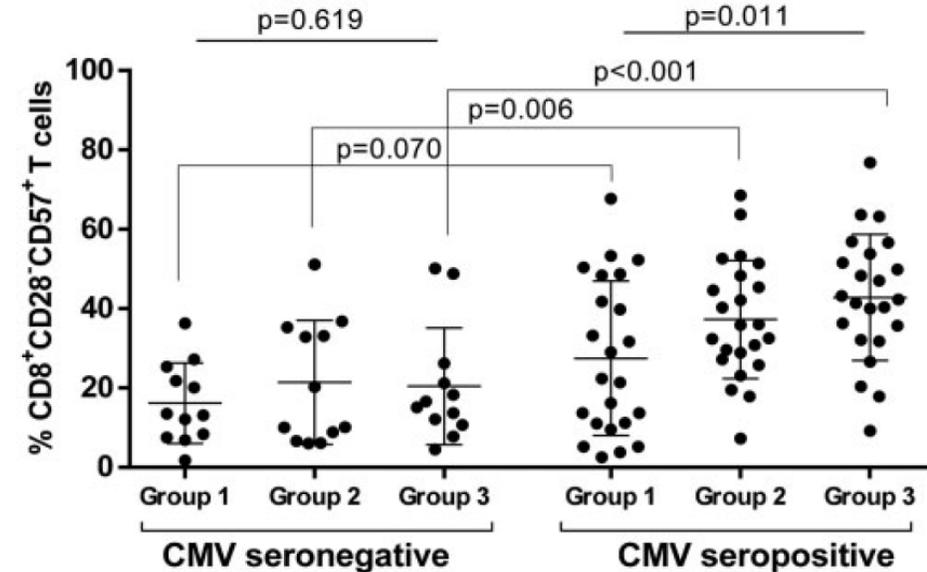


D. Ducloux



CMV-seropositive, yet not CMV-seronegative, dialysis patients had significantly higher frequencies of PD-1+ CD4+ T cells compared to controls

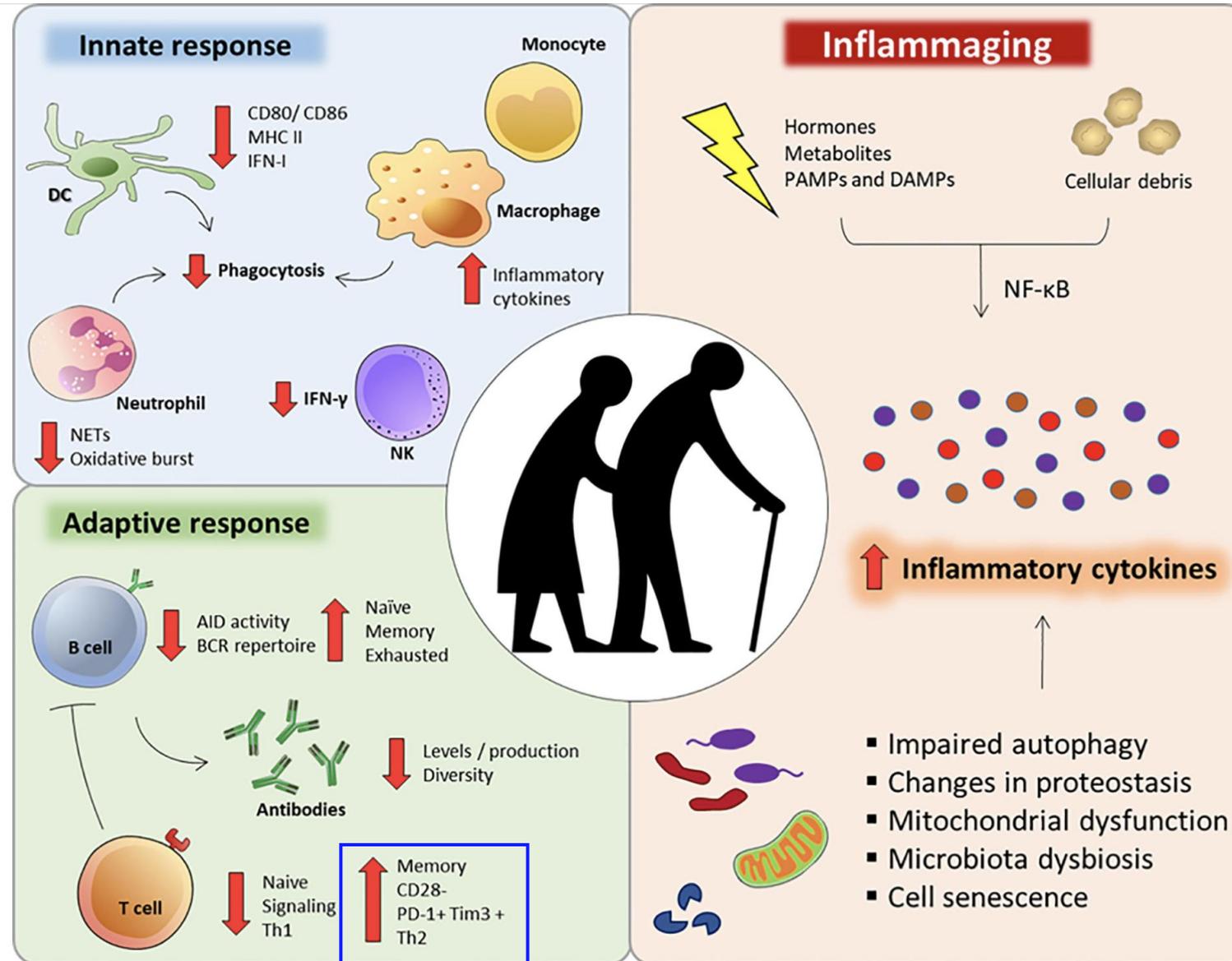
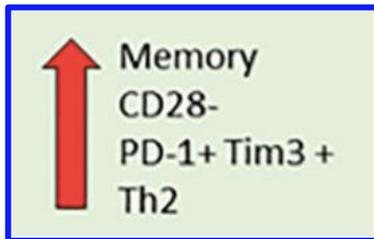
Increased frequency of terminally differentiated CD8+ CD57+ T cells



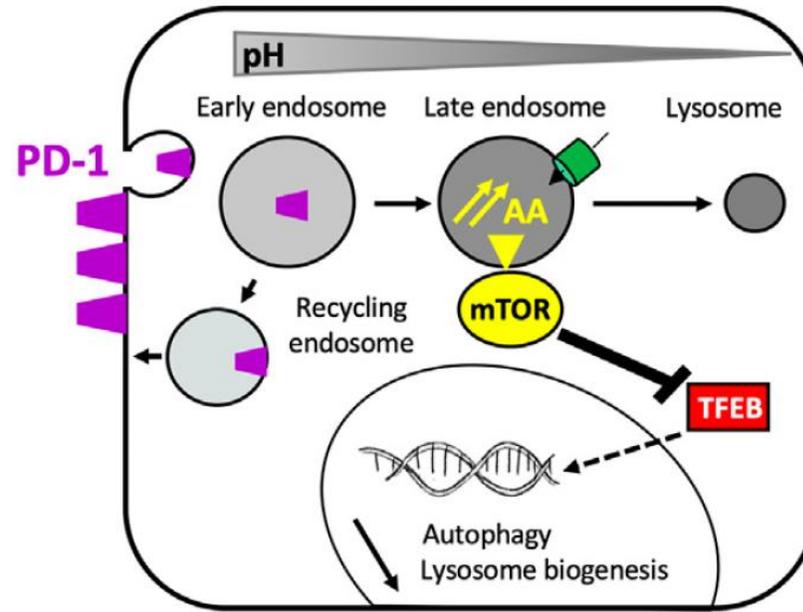
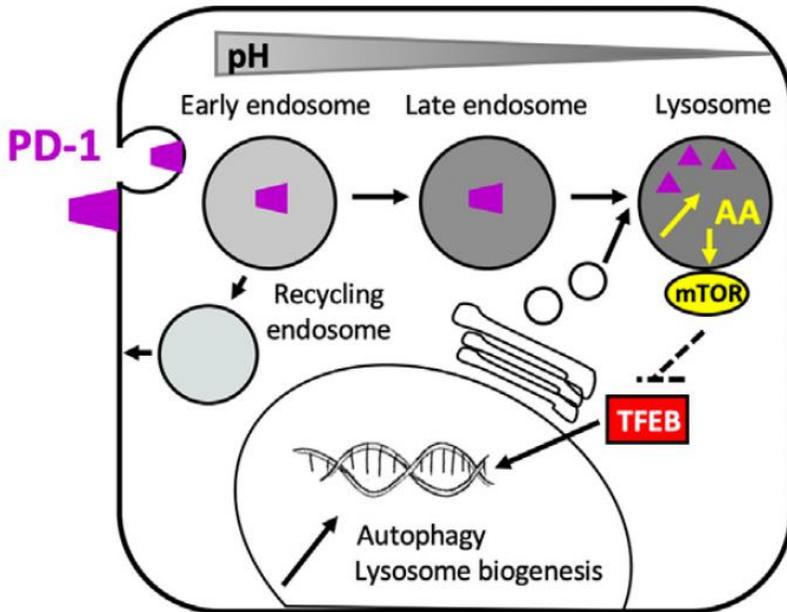
Gr 1: eGFR > 60 ml/mn **Gr 2:** eGFR: 15-30 ml/mn **Gr 3:** dialysis

Immunosenescence and inflammaging

Accumulation of CD28- PD-1+ memory T cells is a hallmark of immune ageing



Mechanisms underlying PD-1 accumulation in the elderly



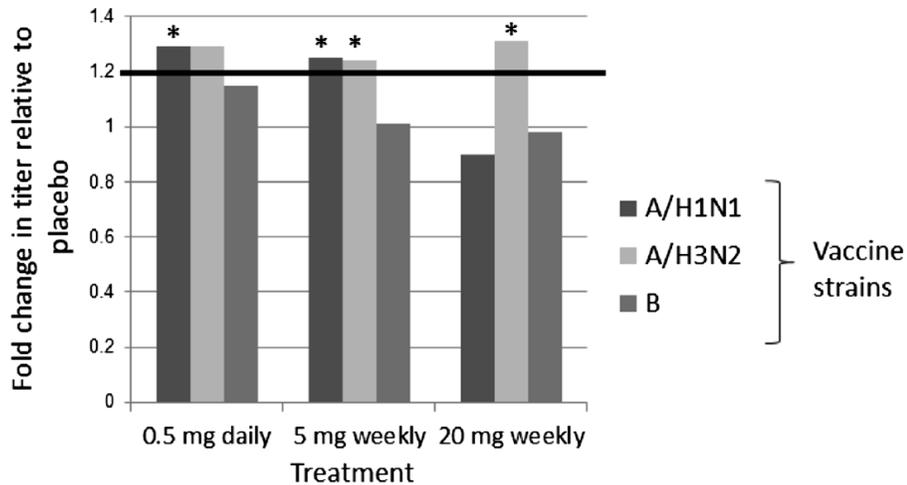
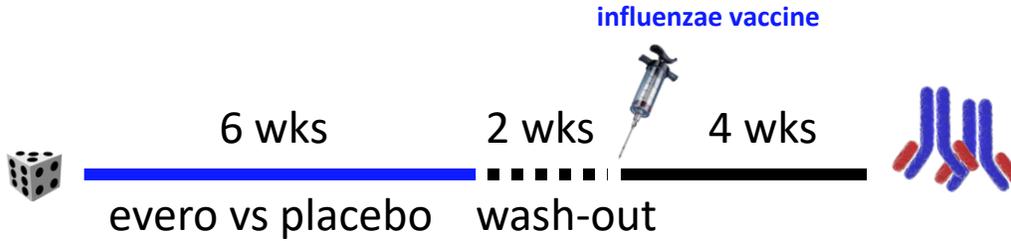
Adapted from Jin et al. *Sci Immunol* 2021

mTOR inhibition rescues age-related T cell dysfunction

Everolimus

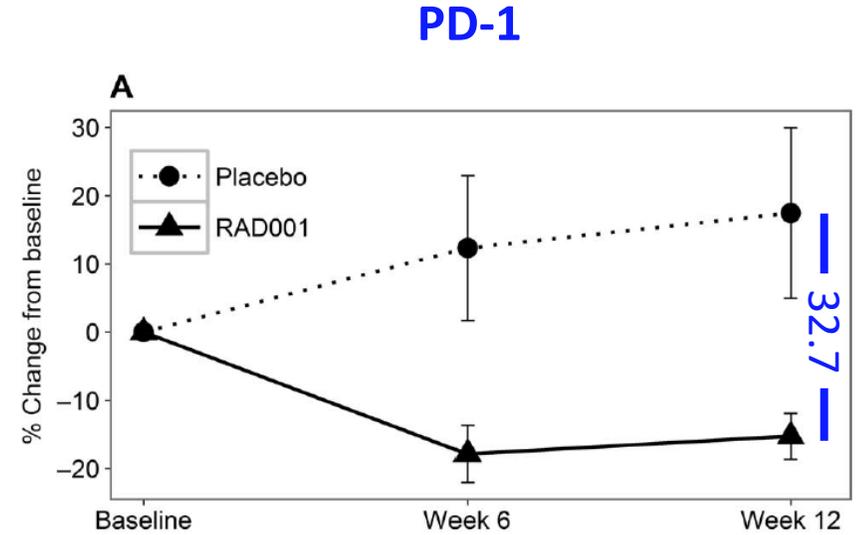


> 65 years
(n=218)

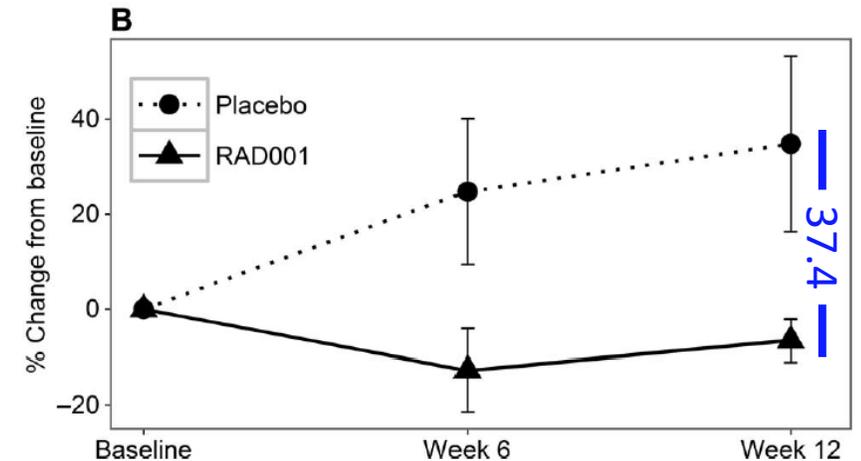


The 1.2-fold increase in the influenza GMT ratio was chosen as endpoint because this level of improvement induced by the MF59 vaccine adjuvant was associated with a decrease in influenza illness

CD4



CD8

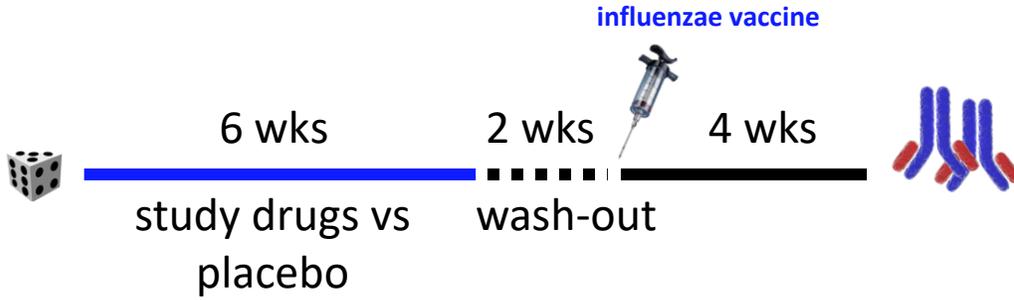


Low-dose mTOR inhibition protects from viral respiratory tract infection

Everolimus
and/or RTB101



> 65 years
(n= 264)



Phase 2a clin. trial

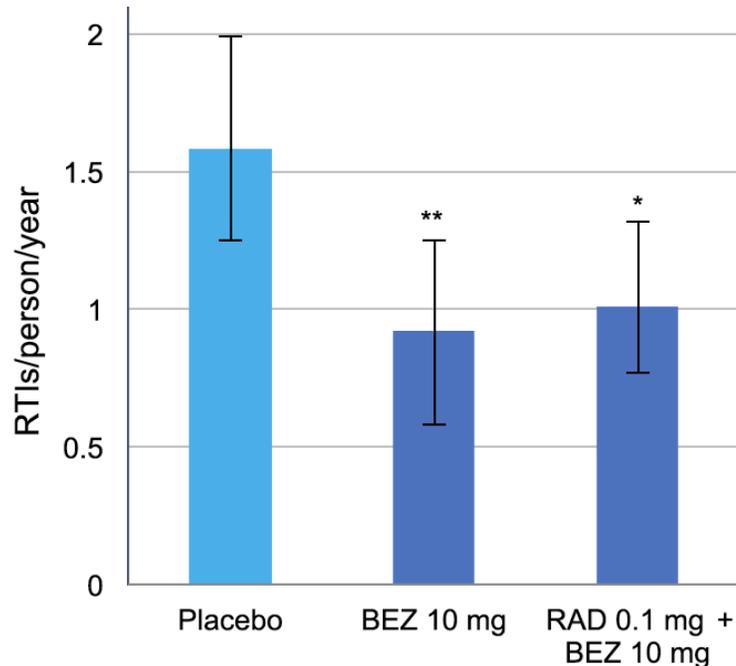


Table 2. Pathways and genes up-regulated after RAD001 + BEZ235 treatment as determined by gene expression analysis of whole blood.

| Pathway | Mean FC of genes in pathway | P value | Up-regulated genes* |
|-------------------------------------|-----------------------------|--------------|--|
| IFN α/β signaling | 0.08 | $10^{-21.8}$ | <i>IFI27, IFIT2, IFIT1, IFIT3, MX1, OAS3, ISG15</i> |
| IFN signaling | 0.04 | $10^{-36.7}$ | <i>IFI27, IFIT2, IFIT1, IFIT3, MX1, OAS3, HERC5, ISG15</i> |
| Cytokine signaling in immune system | 0.02 | $10^{-43.5}$ | <i>IFI27, IFIT2, IFIT1, IFIT3, MX1, OAS3, HERC5, ISG15</i> |

*Listed up-regulated genes are those determined to be outliers by the Tukey method of outlier detection.

... through enhanced Interferon responses

Mitigation of CMV reactivation risk with mTOR inhibitors



H. Kaminski



J. Déchanet-Merville



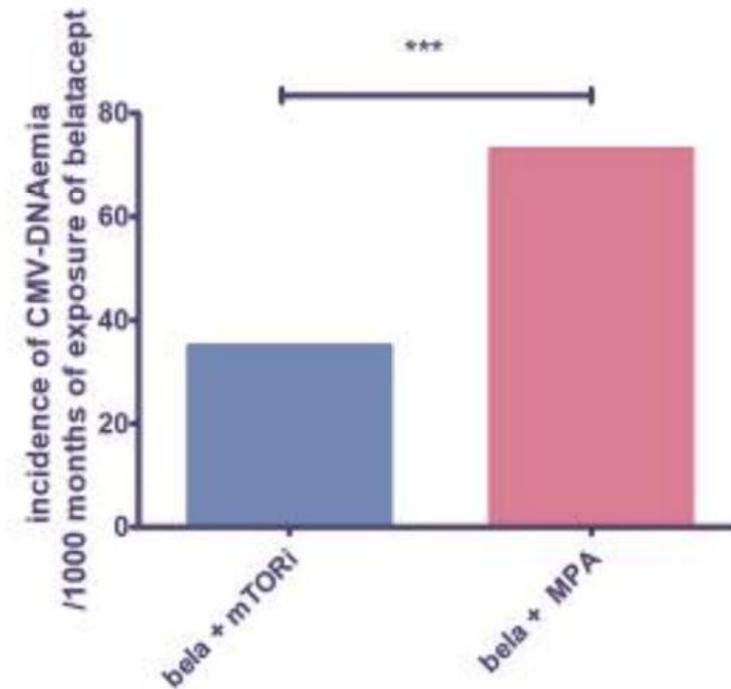
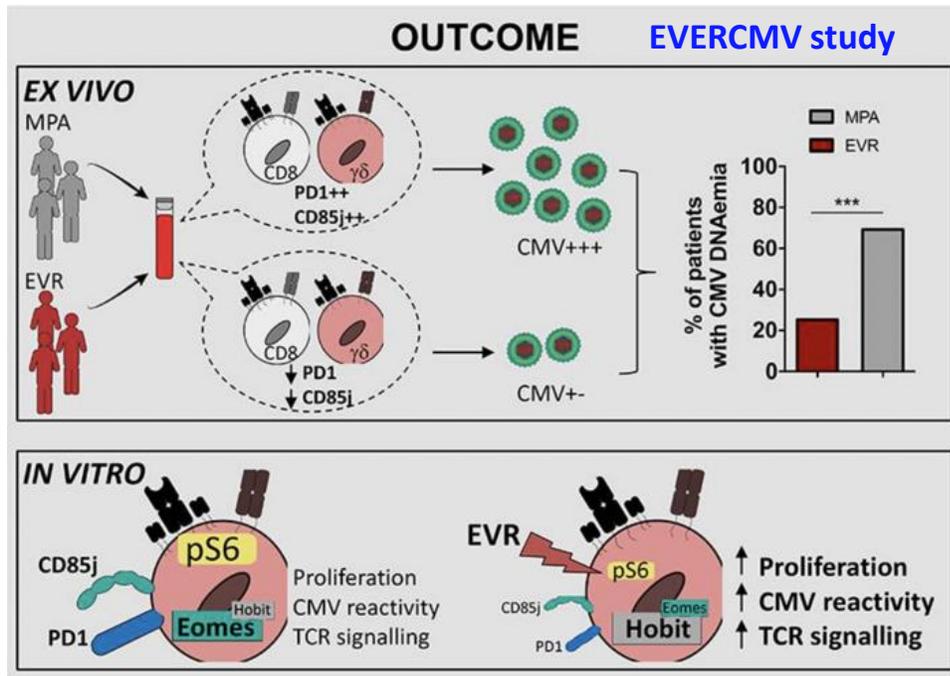
L. Couzi



A. Del Bello



N. Kamar



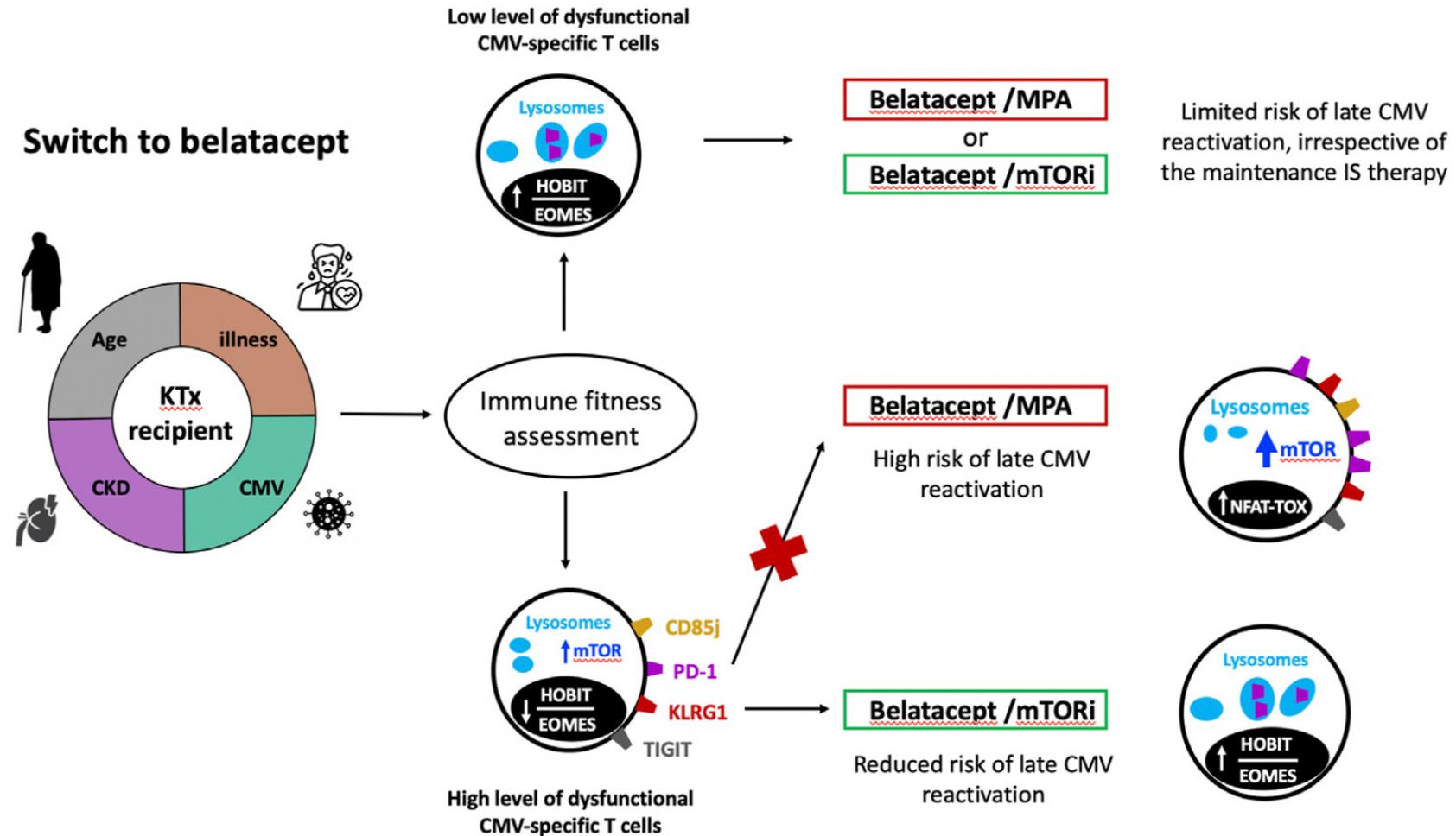
mTORi improve T-cell fitness and function, decreased PD-1 expression in T cells, along with better control of CMV

Belatacept-related cytomegalovirus infection: Advocacy for tailored immunosuppression based on individual assessment of immune fitness

Julien Zuber^{1,2,*}, Juliette Leon^{1,2}, Julie Déchanet-Merville³, Hannah Kaminski^{3,4,**}

American Journal of Transplantation

Conclusion-1



CASE 2: Early-onset and recurrent SCCs in a young kidney Tx recipient

LD: 65-year-old mother



BL rejection
Chronic diarrhea
Episodes of recurrent AKI



ATG
Tac/MMF

Tac/MMF/Pred.

Bela/Aza/Pred.

Tac/Pred.

Pred.

04/2018

11/2021

02/2022

04/2022

08/2022

10/2022

01/2023

05/2023

11/2023

01/2024

04/2024

10/2024

12/2024

02/2025

04/2025

Skin SCCs

iSCC (x2)

Bowen (x3)

Bowen (x2)

Bowen (x2)

Bowen (x2)

Bowen (x2)

Bowen (x2)

Bowen (x2)

Bowen (x1)

PVB19-related RC aplasia

11 8.4 5.5 5.1 log

PVB19

IGIV

iSCC (x1)

Bowen (x4)

Bowen (x2)

Bowen (x1)

38-yr-old

Lysinuric protein intolerance
Non-AA, non-AL amyloidosis

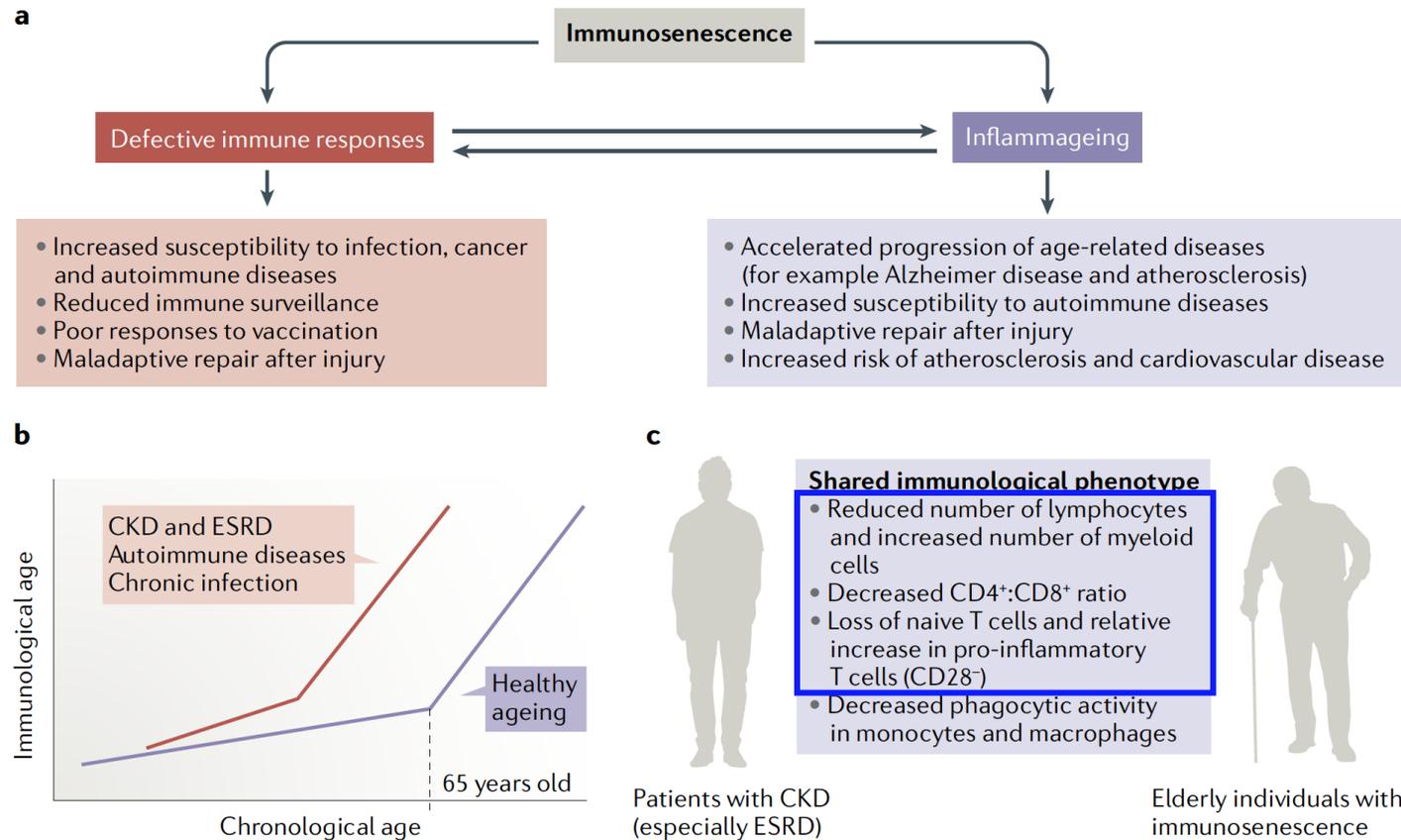


23 intraepithelial squamous cell carcinomas
3 infiltrative squamous cell carcinomas

Chronic and refractory PVB19 infection



Accelerated immune senescence in patients with CKD



Immunological age of T cells from ESRD patients is increased by 20 years compared with that of cells from age-matched healthy individuals

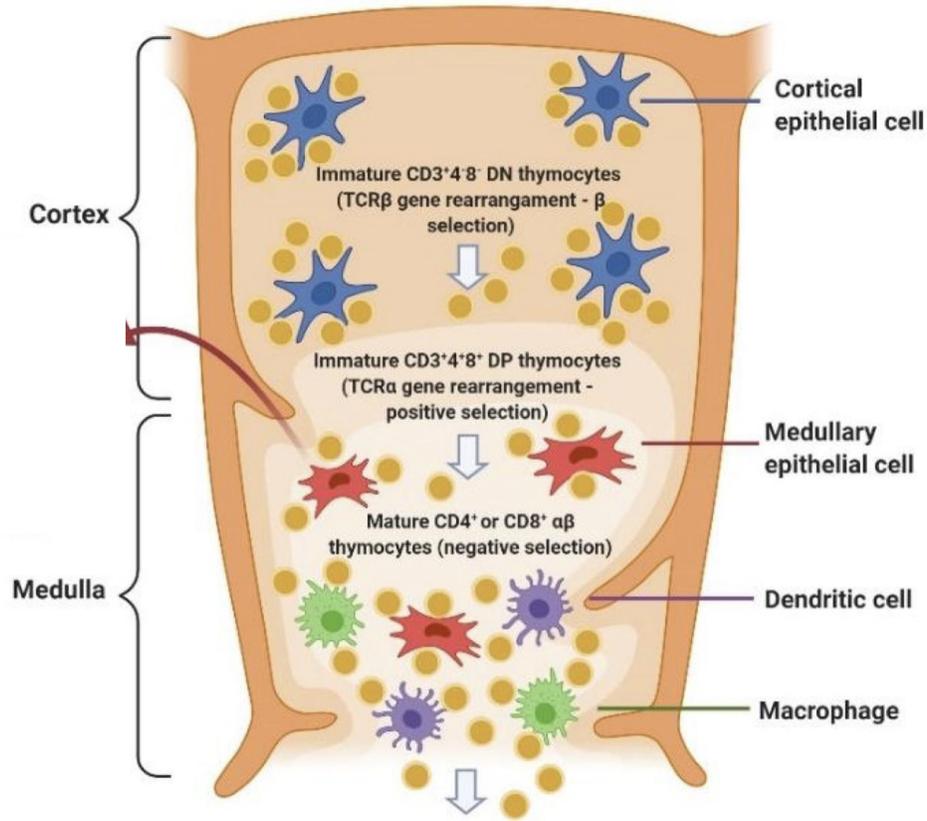
Uremia-induced immune senescence



D. Ducloux



Thymopoiesis



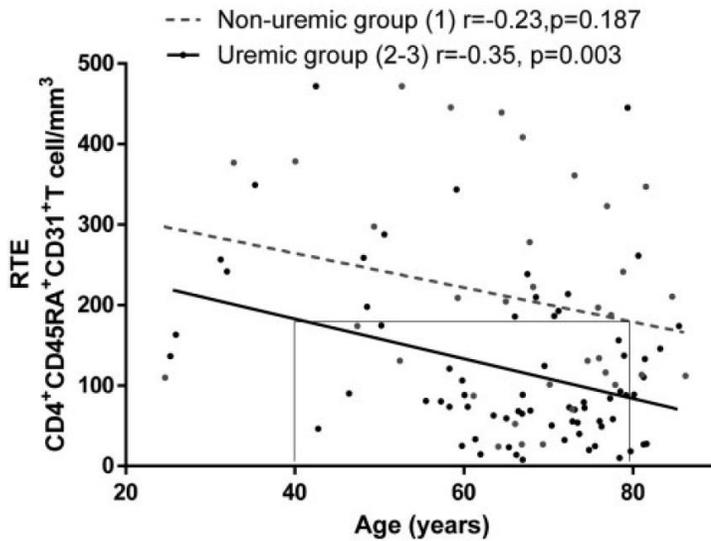
Positive selection

Rescues thymocytes able to interact with self-MHC-peptide complex from programmed cell death

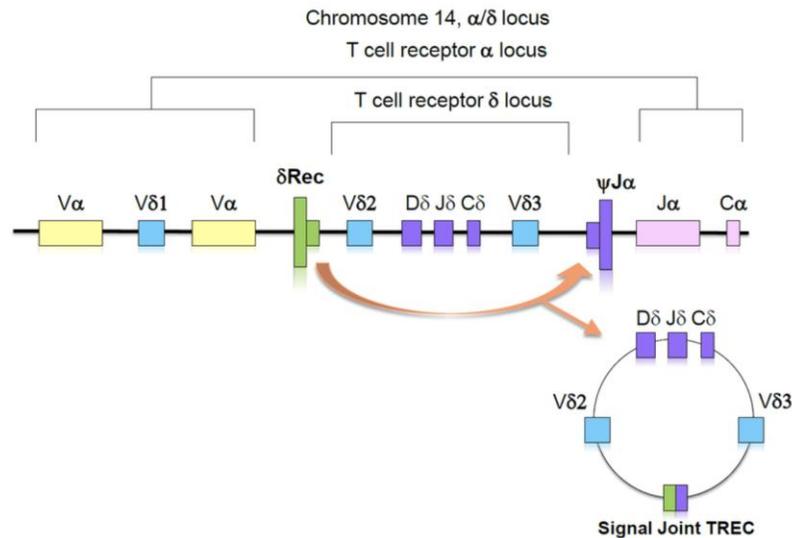
Negative selection

Active induction of apoptosis in thymocytes with a high affinity for self-MHC-peptide complex

Reduced thymic output



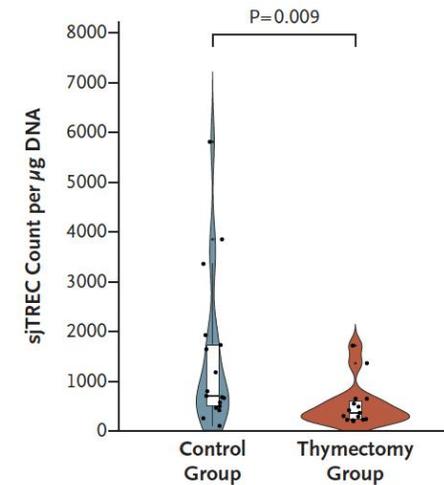
How to assess thymic function?



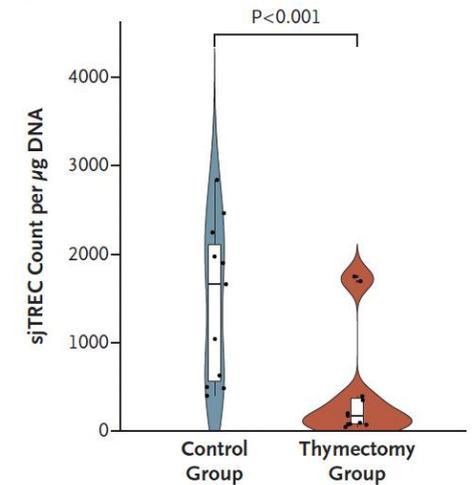
sjTREC (T cell receptor excision circles) are **small circles of DNA** generated by the rearrangement of the **alpha chain of the TCR** during thymic ontogeny

The detection of **sjTRECs** in peripheral blood is the most accurate surrogate marker of **thymic output**

A CD4+ Lymphocytes



B CD8+ Lymphocytes



Mean **sjTREC** count in CD4+ and CD8+ lymphocytes were much **lower among patients who had undergone thymectomy** than among controls

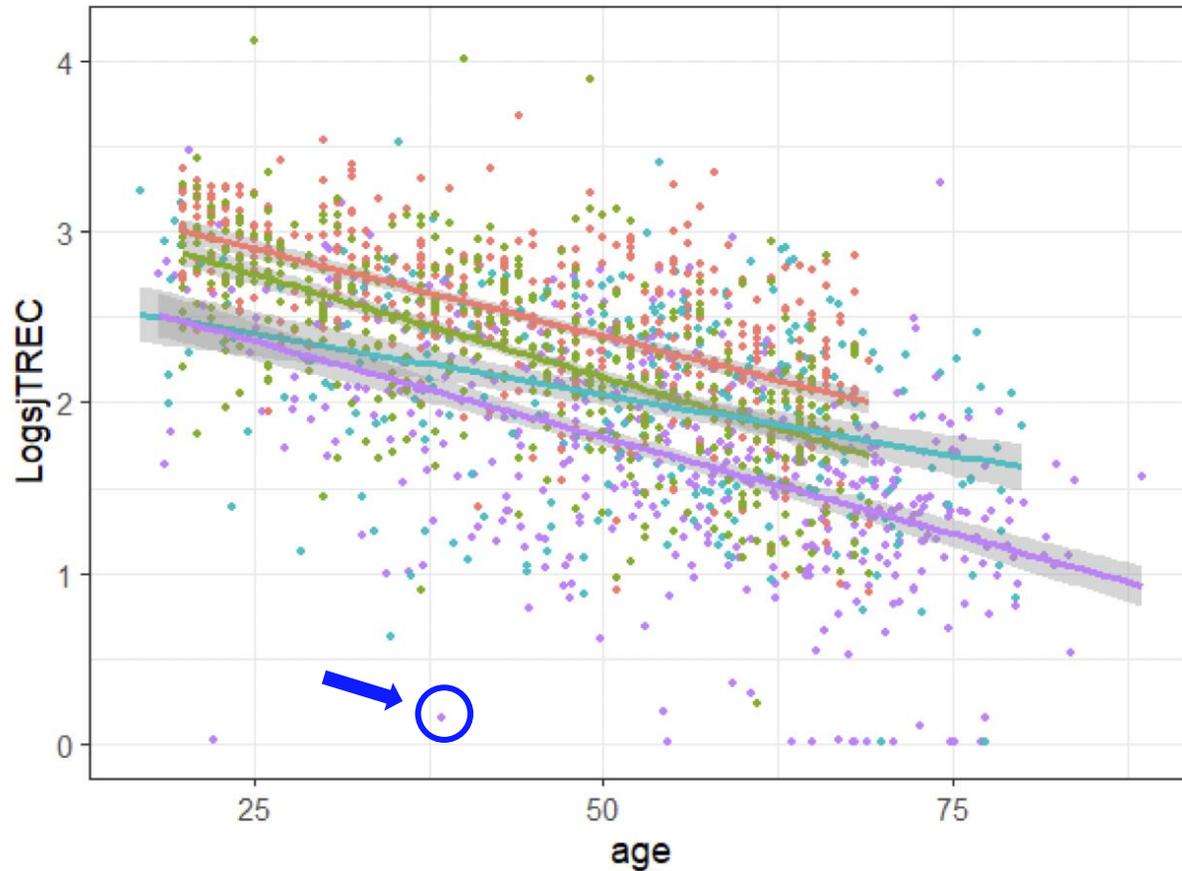
Uremia-induced thymic atrophy

Healthy controls (n=938)

- Women █
- Men █

CKD 5 (n=733)

- Women █
- Men █

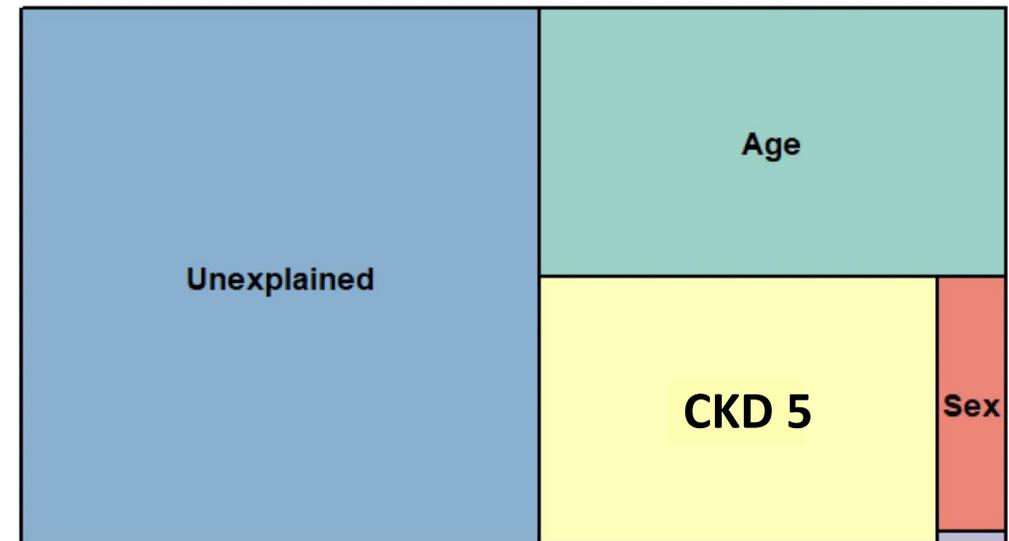


E. Clave



A. Toubert

Variables affecting the variance



unpublished



Thymic function provides lifelong protection, including after KTx



O. Aubert

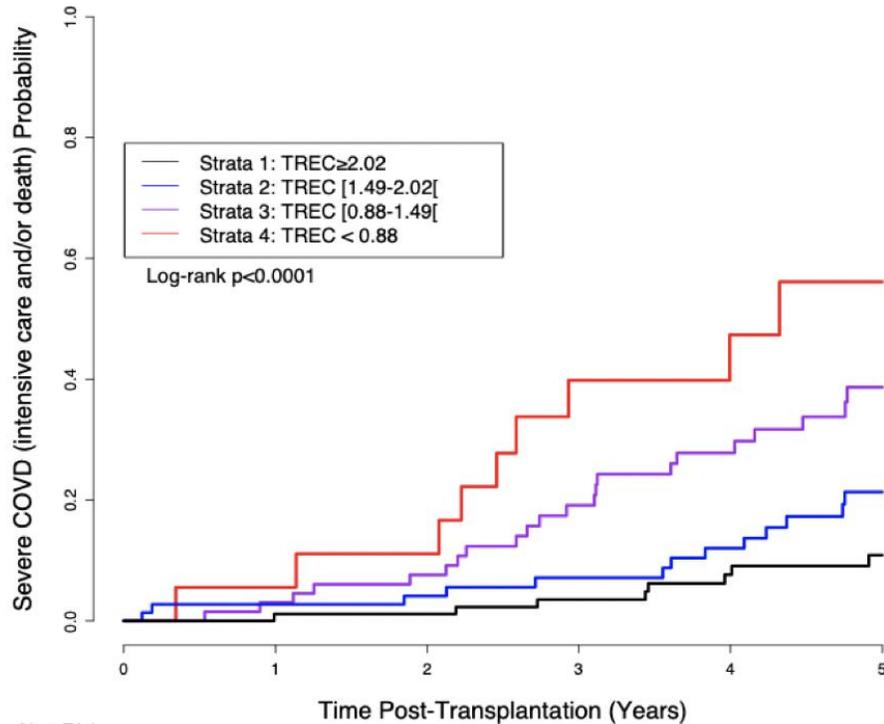


C. Kergaravat

Altered thymic function is associated with increased risk of severe COVID-19 in kidney transplant patients



A. Toubert



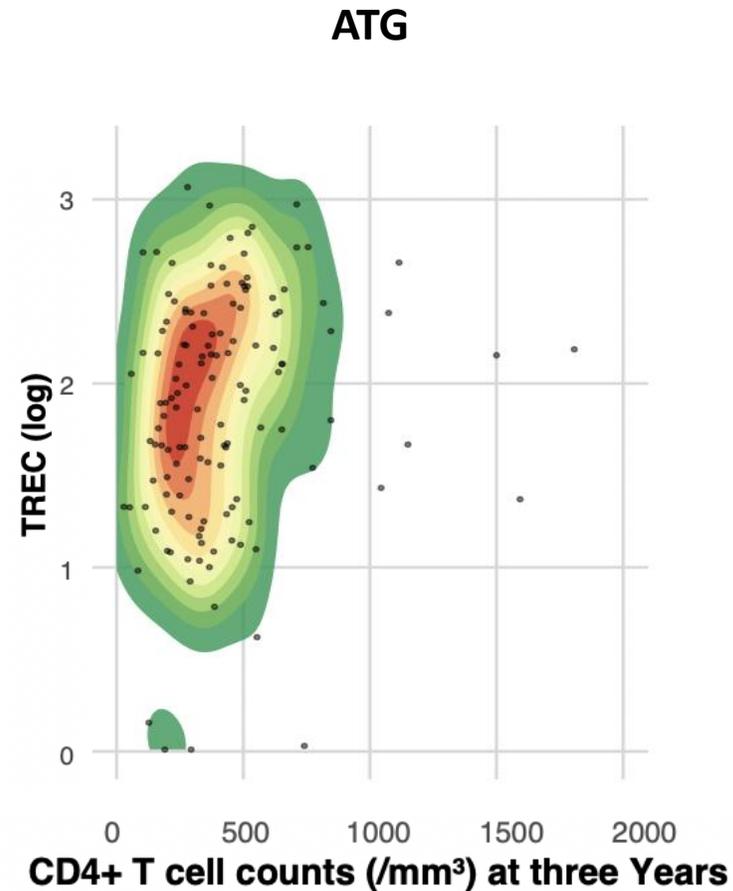
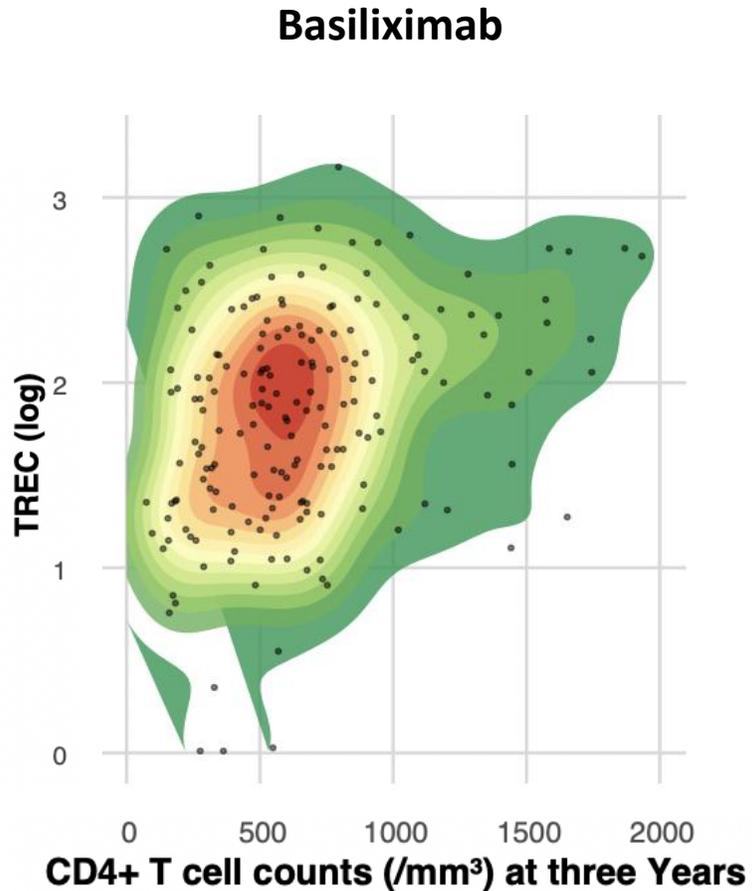
| | | Number of Patients | Number of events | HR | 95% CI | p* | HR 95% CI bootstrap BCA |
|----------------------------|-----|--------------------|------------------|------|-------------|------------------|-------------------------|
| Age (per 1-year increment) | | 731 | 62 | 1.03 | (1.01-1.06) | 0.004 | (1.01-1.06) |
| Body Mass Index | | 731 | 62 | 1.09 | (1.03-1.16) | 0.004 | (1.03-1.15) |
| Recipient Diabetes | No | 581 | 39 | 1 | - | - | - |
| | Yes | 150 | 23 | 1.76 | (1.04-3.00) | 0.034 | (1.02-3.03) |
| Prior kidney transplant | No | 623 | 46 | 1 | - | - | - |
| | Yes | 108 | 16 | 2.61 | (1.42-4.81) | 0.002 | (1.37-5.01) |
| TRECs (log transformation) | | 731 | 62 | 0.39 | (0.26-0.60) | <0.001 | (0.25-0.63) |



Pretransplant thymic function and immune reconstitution



O. Aubert



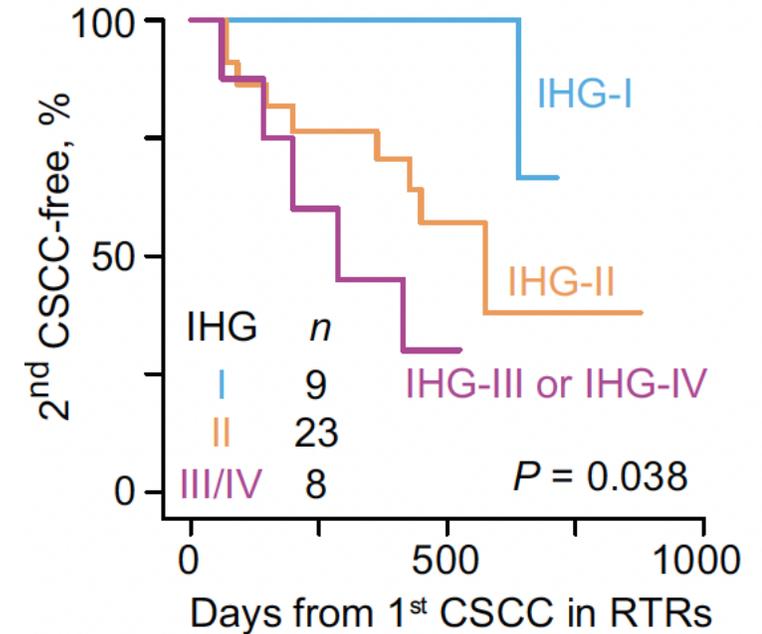
Both **low pre-transplant sjTRECs levels** and **ATG** were independently associated with **reduced CD4+ T cell counts at 3 year**



Low CD4+ T cell count is linked to increased rates of cutaneous SCC in KT recipients

CD4 T cell absolute count and CD4/CD8 ratio determine the **Immune Health Grades (IHGs)**

| IHG | Ratio ≥ 1.0 | CD4+ ≥ 800 | CD8+ level | CD4+ level | CD8-CD4 |
|-----|------------------|-----------------|------------------------|------------------------|----------------|
| I | + | + | CD8 ^{lower} | CD4 ^{highest} | equilibrium |
| II | + | - | CD8 ^{lowest} | CD4 ^{lower} | |
| III | - | + | CD8 ^{highest} | CD4 ^{higher} | disequilibrium |
| IV | - | - | CD8 ^{higher} | CD4 ^{lowest} | |

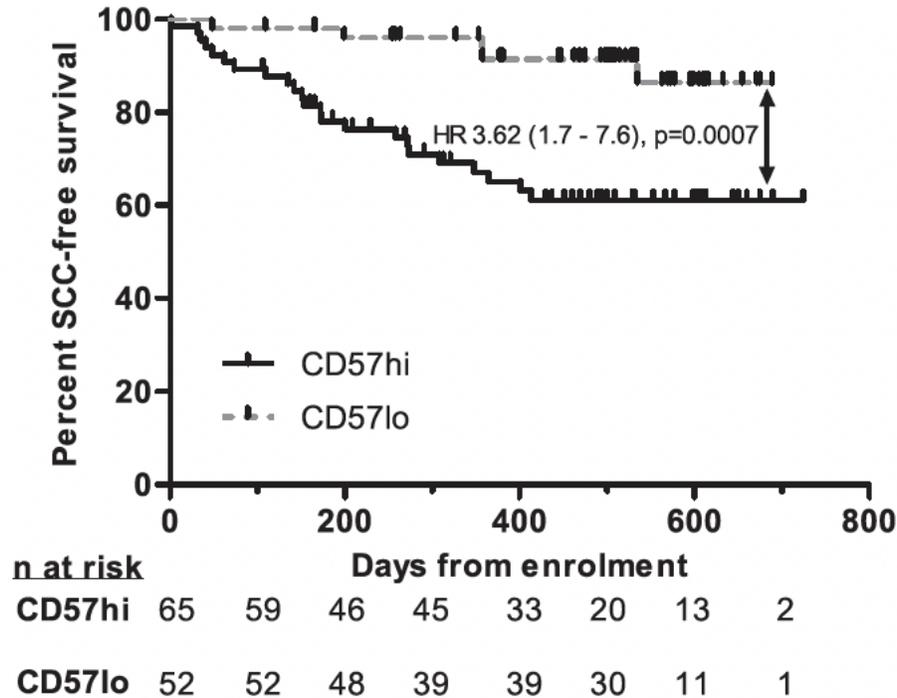


CD8+ Immunosenesence predicts post-transplant cutaneous SCC

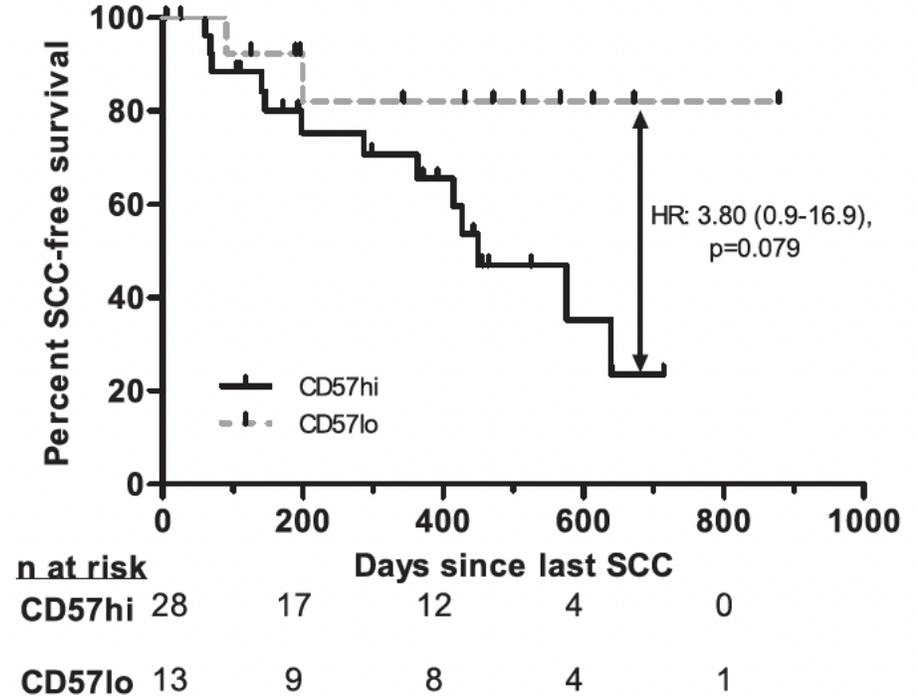


K. Wood

SCC occurrence in all KT recipients

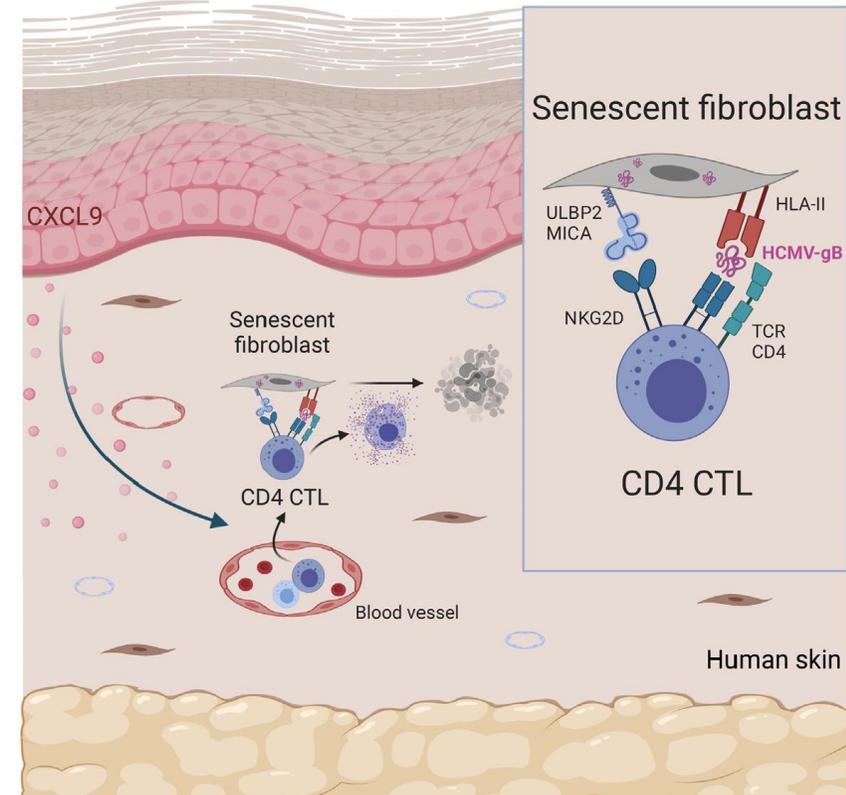
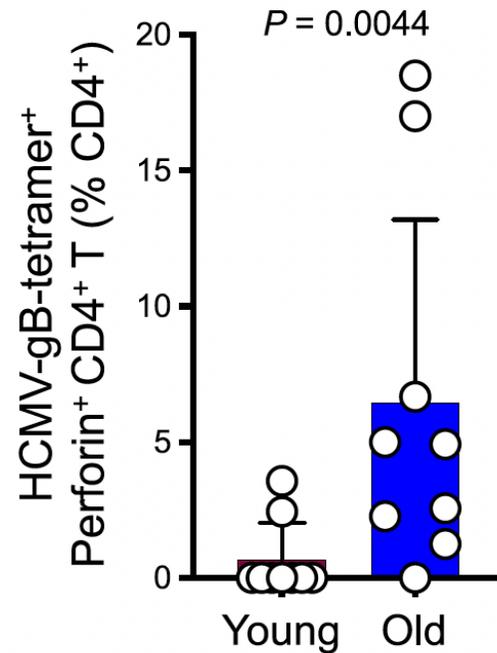
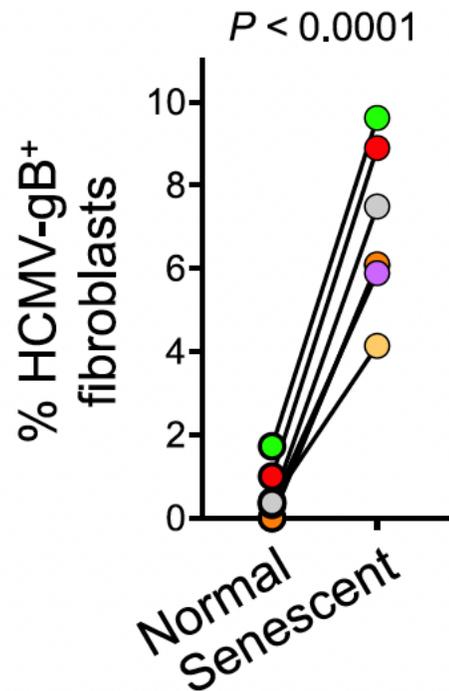


SCC recurrence in all KT recipients by time since previous SCC



CD57^{Hi} phenotype (>50% of CD8+ T cells) is stable with time and associated with **increasing age and CMV seropositivity**
CD57^{Hi} phenotype is a strong and independent predictor of SCC development and recurrence

CMV-specific CD4+ T cells eliminate senescent cells



- Senescent fibroblasts highly express HLA-II, NKG2D ligands, and HCMV-glycoprotein B
- CD4 CTLs eliminate HCMV-gB⁺ senescent fibroblasts in an HLA-II-dependent manner

Increased risk of cSCCs recurrence in KTx converted to belatacept



N. Chavarot

| Variables | Risk of developing at least one NMSC | | | Risk of NMSC recurrences | |
|--|--------------------------------------|------------------------------|------------------|-------------------------------|------------------|
| | Univariable p-value | Multivariable HR [95% CI] | p-value | Multivariable IRR [95% CI] | p-value |
| Age at KT | 0.015 | 1.03 [1.01-1.06] | 0.001 | 1.05 [1.0-1.1] | <0.001 |
| Belatacept conversion | 0.602 | | | 1.49 [1.1-1.9] | 0.004 |
| Follow-up post KT* | 0.003 | 1.14 [1.06-1.23] | <0.001 | * | * |
| Male gender | 0.392 | | | | |
| History of previous KT | 0.766 | | | | |
| Type I or II skin Fitzpatrick type (vs others) | <0.001 | 2.07 [1.1-3.69] | 0.012 | 2.01 [1.5-2.8] | <0.001 |
| Induction therapy (ATG versus others) | 0.475 | | | | |
| History of NMSC** | <0.001 | 15.0 [4.86 – 57.3] | <0.001 | 6.32 [4.6-8.6] | <0.001 |
| CNI use before NMSC | 0.618 | | | | |
| mTOR inhibitor use before NMSC | 0.261 | | | | |
| Steroids use before NMSC | 1.000 | | | | |
| AZA use before NMSC | 0.601 | | | | |



Conclusion-2

Advocacy for tailored immunosuppression based on **individual assessment of immune fitness**

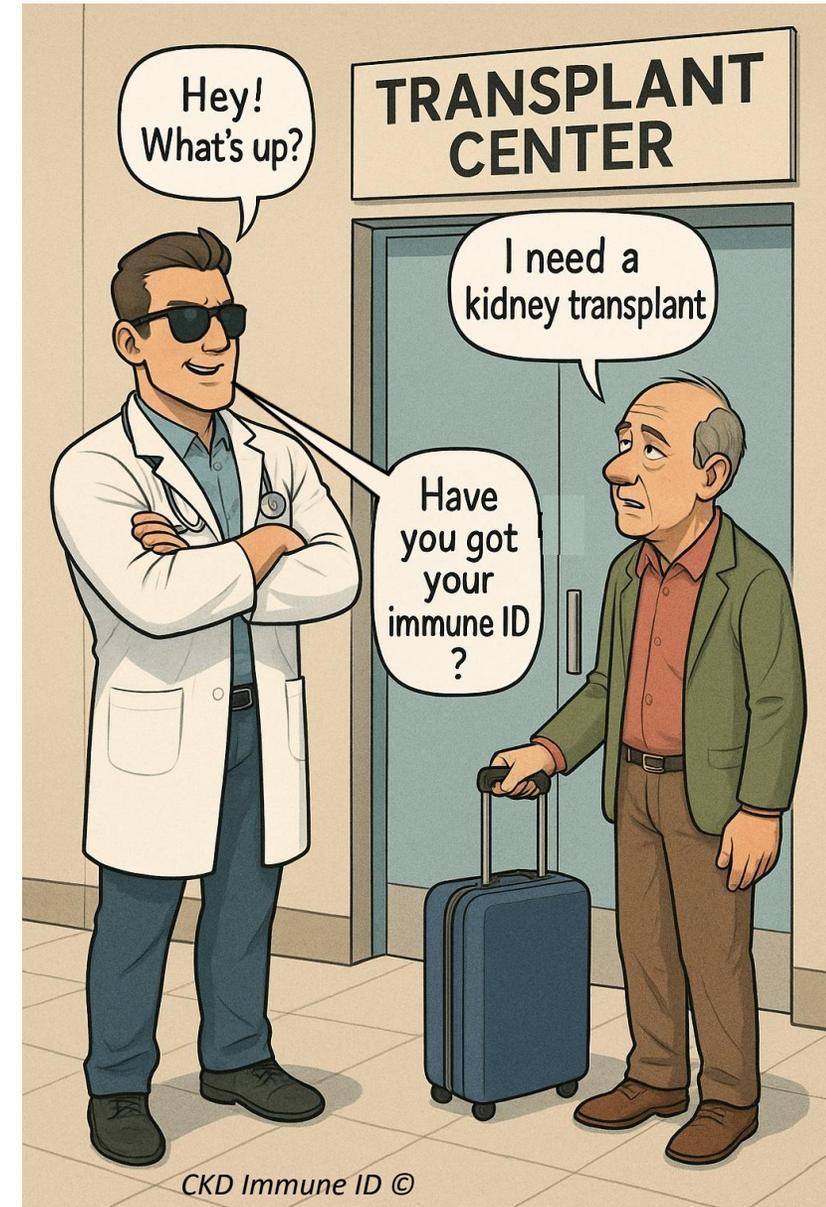
Need for **validated tools** to capture individual **immune profiles** before transplantation

Combination of **belatacept with mTOR inhibitors** in patients with preexisting T cell dysfunction / ageing

The Immune ID.



Your personal resistance passport



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