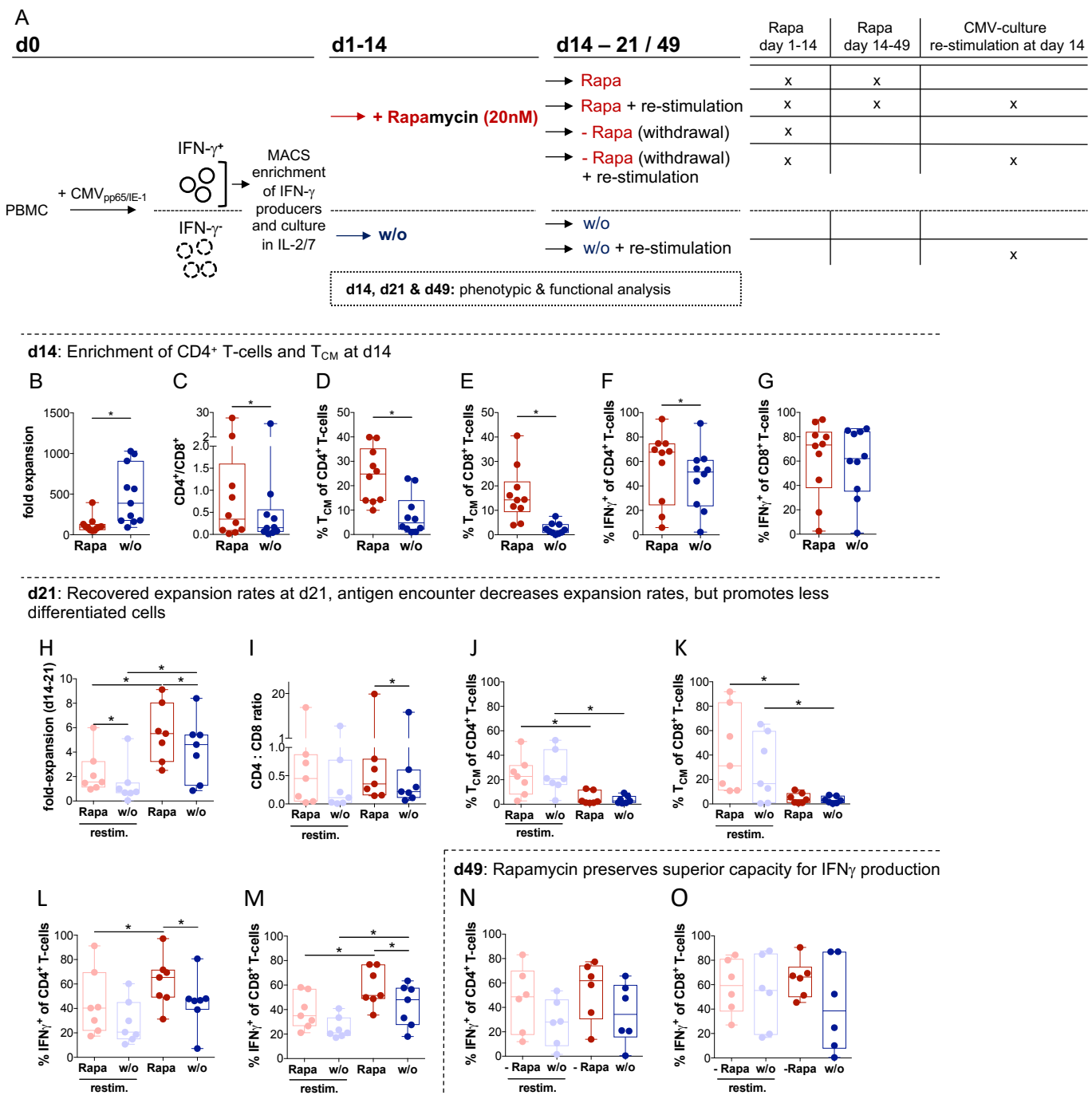

Figure S1: Effects of Rapamycin on IL-2/IL-7-expanded T-cell products: Expansion, phenotype and function

A: Schematic overview of experiments: T-cell products (TCPs) were generated from PBMCs isolated from venous blood of of healthy donors (HDs) by magnetically activated cell isolation sorting (MACS) of T-cells producing IFNγ in response to stimulation with $CMV_{IE-1/pp65}$ peptide pools and expanded in the presence of IL-2/IL-7 without (w/o; blue) or with addition of 20 nM of Rapamycin (Rapa; red). **B:** Expansion rates of IL-2/7-expanded Rapa-treated (Rapa-)TCPs (red) and untreated TCPs (blue) of n=10 healthy donors (HDs) calculated from yield at d14 divided by the number of seeded cells at d0. We gated flow cytometric data on lymphocytes → singlets → living $CD3^+$ T-cells. **C**: CD4/CD8 ratios in Rapa- (red) and untreated TCPs (blue) of n=10 HDs calculated from flow cytometry data as presented in Fig. 1C. **D-E**: Proportions of $CD4^+$ (**D**) and $CD8^+$ T_{CM} (**E**) among Rapa- (red) and untreated TCPs (blue) of n=10 HDs determined from flow cytometric data as shown in Fig. 1E at d14. **F-G:** To detect CMV-specific cytokine producers, TCPs were stimulated with $CMV_{IE-1/pp65}$ peptide-loaded autologous LCLs at a ratio of 1:10 for 6 h and BFA was added after 1 h. Proportions of CMV-specific IFNγ-producers among $CD4^+$ (**F**) and $CD8^+$ T-cells (**G**) in Rapa- (red) and untreated TCPs (blue) of n=10 HDs determined from flow cytometric data as shown in Fig. 1G at d14. **H-O**: For restimulation on d14 of culture, thawed $CD3^-$ autologous PBMCs were loaded with $CMV_{IE-1/pp65}$ peptide pools and added at 1:5 ratio to T-cells. **H:** Expansion rates of IL-2/7-expanded restimulated (pastel colors) or non-restimulated (dark colors) Rapa- (red) and untreated TCPs (blue) of n=7 HDs calculated from yield at d21 divided by the number of cells at d14. **I**: CD4/CD8 ratios in Rapa- (red) and untreated TCPs (blue) of n=7 HDs calculated from flow cytometric data as presented in Fig. 1C at d21. **J-K**: Proportions of $CD4^+$ (**J**) and $CD8^+$ T_{CM} (**K**) among Rapa- (red) and untreated TCPs (blue) of n = 7 HDs determined from flow cytometric data as shown in Fig. 1E at d21. **L-M**: To detect CMV-specific cytokine producers, TCPs were stimulated with $CMV_{IE-1/pp65}$ peptide-loaded autologous LCLs for 6 h and BFA was added after 1 h. Proportions of CMV-specific IFNγ-producers among $CD4^+$ (**L**) and $CD8^+$ T-cells (**M**) in Rapa- (red) and untreated TCPs (blue) of n=7 HDs determined from flow cytometric data as shown in Fig. 1G at d21. **N-O**: To mimic the situation after infusion, Rapa was withdrawn and TCPs were cultivated long-term until d49. Proportions of CMV-specific IFNγ-producers among $CD4^+$ (**N**) and $CD8^+$ T-cells (**O**) in TCPs withdrawn from Rapa (red) and untreated TCPs (blue) of n=6 HDs determined from flow cytometric data as shown in Fig. 1G at d49. For all graphs normal distribution of data points was tested with Kolmogorov-Smirnov test and paired t test was used to determine significance in normally distributed samples or Wilcoxon's matched-pairs signed rank test in not normally distributed samples, respectively. P-values below 0.05 are indicated by * and defined to be significant.

Table S1: Differentially expressed genes.
Log2-fold describes log2-fold expression of the respective gene in untreated *vs*. Rapa-TCPs.

	Ensemble ID	Gene	Function in T-cells	baseMean	log2Fold
LONG-LIVED MEMORY					
promoting					
	ENSG00000164530	PI16	unique subset of memory T helper $_{PC}$ cells with hyperproliferative and proinflammatory properties (1)	138.857891	-4.52567
	ENSG00000183813	CCR4	immature CD8 T-cell memory subset (2)	3238.81399	-3.97324
	ENSG00000126353	CCR7	T_{CM} marker (3)	2184.22723	-3.76273
	ENSG00000056736	IL17RB	highest expression in CD4$^+$ T_{CM} expressing prostaglandin receptor D2 (T_{H2}) (4)	3717.7612	-3.196748
	ENSG00000204252	HLA-DOA	non-classical MHC class II (peptide loading), higher expression in CD8 CD28$^+$ T-cells from young than from old subjects (5)	1385.33723	-2.298921
	ENSG00000073331	ALPK1	target of Tcf-1 (6) downstream of wnt (arresting memory CD8$^+$ T-cell differentiation [7])	404.02766	-1.892146
	ENSG00000135318	NT5E	CD73 catalyzes the conversion of extracellular nucleotides to membrane-permeable nucleosides, CD73$^+$ mouse memory CD4$^+$ T-cells make IL-2, but less IFNg than CD73$^-$ (8)	279.662059	-2.320378
	ENSG00000164362	TERT	Telomerase reverse transcriptase, overexpression extends proliferative potential of human T-cells (9)	27.7024907	-3.430006
	ENSG00000102096	PIM2	allows T_{mg} expansion in Rapamycin (10), antiapoptotic/upregulated in T_{CM} *vs.* T_{EM} (11)	7944.0909	-1.735721
	ENSG00000116016	EPAS1	accumulates upon early TCR signaling and hypoxia, accumulation increases glycolysis/GZB, expression diminished upon administration of IL-2, increased upon administration of IL-4, sustained effector function of CD8 CTLs (12)	3957.09145	-1.554453
	ENSG00000168685	IL7R	identifies the effector CD8 memory T-cell precursors that can persist and confer protective immunity (13)	11182.7835	-2.010491
	ENSG00000132170	PPARG	required for long-term persistence of CD8$^+$ T-cells in the skin, upregulated on T_{EM} (14)	391.15806	-2.143364
	ENSG00000072110	ACTN1	downregulated in effector/exhausted murine T-cells compared to memory T-cells (15)	1155.07765	-1.455754
	ENSG00000143674	MAP3K21	bivalent methylation in CD8$^+$ T_{CM} and T_{EM} allows rapid switch from a resting to activated state, transcription increased upon activation (16)	193.136063	-1.700155
	ENSG00000140443	IGF1R	increased in autoimmunity, increased upon TCR stimulation, ligand binding enhances proliferation and survival of CD45RO$^+$ T-cells (17)	797.424827	-1.791784
	ENSG00000115896	PLCL1	CpG methylation decreased in memory *vs.* naive CD4$^+$/upregulated upon activation with CD3/CD28 for 48 h (18), downregulated in SLE CD4$^+$ T-cells compared to controls (19)	2484.05367	-2.706713
antagonizing					
	ENSG00000162490	DRAXIN	antagonist of Wnt signaling (20)	221.619933	1.841851
	ENSG00000148053	NTRK2	downregulated on CD4$^+$ CD62L$^+$ T-cells compared to CD62L$^-$ (21)	608.962631	-2.751809
	ENSG00000149295	DRD2	dopamin receptor, drives T_{H1} differentiation *via* T-bet and IFNg production, decreases CD25 and CD69, advances T-cell differentiation, helps NFkB activation (22)	30.4424689	-3.125411
EFFECTOR FUNCTION					
	ENSG00000173334	TRIB1	in transplant patients marker of ongoing immune activation and an antibody response (23), d0 higher expression in T_{mg} than T_{GEM}, but d7 of culture higher expression in T_{GEM} than T_{mg} (24)	550.825277	-2.851495
	ENSG00000137265	IRF4	induced by TCR signaling → upregulation of inhibitory receptor/impairs metabolism → T-cell exhaustion (25); induction dependent on the signal strength of TCR signaling → glycolysis/clonal expansion/maintenance of effector function (26)	7024.41145	-1.335874
	ENSG00000189013	KIR2DL4	receptor for HLA-G, activation prevents cytolysis, HLA-G increases expression on CD4$^+$ T-cells (27), increased demethylation of promotor and expression in effector *vs.* memory T-cells (28)	19.9418867	3.054789
	ENSG00000124772	CPNE5	expression higher in effector than memory CD4$^+$ T-cells (29)	60.6283057	1.900004
	ENSG00000168229	PTGDR	higher expression in T_{SAMSA} than other T-cells (30)	371.569601	2.575663
	ENSG00000165025	SYK	switches TCR signaling from naive/memory to effector CD4$^+$ T-cells (31)	131.519078	2.816866
	ENSG00000170854	RIOX2	represses expression of IL-4 (32)	1604.81806	-1.44225
	ENSG00000099985	OSM	pro-inflammatory cytokine, attracts macrophages, induces antiviral response in epithelial cells (33; 34)	1983.6564	-1.986649
	ENSG00000182568	SATB1	required for suppressive function of T_{reg} and suppression of effector differentiation (35)	11007.1072	-1.273391
cytotoxicity					
	ENSG00000108176	DNAJC12	chaperone, co-factor of Hsp70 (36), which induces cytotoxic CD4$^+$ T-cells (37)	113.63151	-3.063666
	ENSG00000116016	EPAS1	accumulates upon early TCR signaling and hypoxia, accumulation increases glycolysis/GZB, expression diminished upon administration of IL-2, increased upon administration of IL-4, sustained effector function of CD8 CTLs (12)	3957.09145	-1.554453
IFNg					
	ENSG00000169194	IL13	synergizes with IL-2 in regulating interferon-gamma synthesis (38)	481.746448	-2.918254
	ENSG00000149295	DRD2	dopamin receptor, drives T_{H1} differentiation *via* T-bet and IFNg production, decreases CD25 and CD69, advances T-cell differentiation, helps NFkB activation (22)	30.4424689	-3.125411
	ENSG00000141655	TNFRSF11A	RANK, induces T-cell survival upon binding of RANKL (39); RANKL increases IFNg secretion in T-cells (40)	1997.55921	-2.813665
APOPTOSIS					
anti-apoptotic					
	ENSG00000118513	MYB	promotes memory T-cell development, antiapoptotic via Bcl-2 (41)	1103.23321	-3.78842
	ENSG00000141655	TNFRSF11A	RANK, induces T-cell survival upon binding of RANKL (39); RANKL increases IFNg secretion in effector and memory T-cells (40)	1997.55921	-2.813665
	ENSG00000134278	SPIRE1	involved in DNA repair (42)	295.111297	-2.942319
	ENSG00000134853	PDGFRA	anti-apoptotic signaling via PI3K/migration (43)	124.06083	-4.193055
	ENSG00000205755	CRLF2	thymic stromal lymphopoietin receptor, closely related to gamma chain, expression increased after TCR activation, signaling increases survival of T-cells and proliferation of activated CD4$^+$ T-cells (44)	130.168039	-1.904047
	ENSG00000126778	SIX1	anti-apoptotic (45)	95.8255104	-3.407385
	ENSG00000102096	PIM2	allows T_{mg} expansion in Rapamycin (10), antiapoptotic/upregulated in T_{CM} *vs.* T_{EM} (11)	7944.0909	-1.735721
	ENSG00000136026	CKAP4	p63, can suspress p73-dependent apoptosis (46)	825.271346	-2.023946
	ENSG00000140443	IGF1R	increased in autoimmunity, increased upon TCR stimulation, ligand binding enhances proliferation and survival of CD45RO$^+$ T-cells (17)	797.424827	-1.791784
	ENSG00000180543	TSPYL5	decreases p53 levels (47)	98.8277414	-1.991591
	ENSG00000133134	BEX2	protects against mitochondrial apoptosis, positively regulates Bcl-2/NFkB pathway and negatively regulates BAD, BAK1 and PUMA (48)	199.28867	-2.151393
	ENSG00000011028	MRC2	Mannose receptor, extends survival of mouse thymocytes/maintains cell growth (49)	268.370067	-3.100144
	ENSG00000171860	C3AR1	activation by C3a enhances naive CD4$^+$ T-cell activation, survival and proliferation *via* PI3K/Akt (50)	200.019164	2.171075
pro-apoptotic					
	ENSG00000101752	MIB1	E3 ubiquitin ligase, antagonizing anti-apoptotic effects of DAPK1 to promote TNF-induced apoptosis (51)	7311.96339	-1.07792
	ENSG00000163568	AIM2	sensor of cytoplasmic DNA activating inflammasome and cells death (52)	539.862663	-1.605941
T-CELL ACTIVATION					
	ENSG00000128322	IGLL1	downregulated within 48 - 96 h after T-cell activation (53)	28.8060963	-3.188403
	ENSG00000114739	ACVR2B	downregulated upon activation in naive T-cells (54)	800.556947	-1.03528
	ENSG00000183395	PMCH	expressed activation dependently in T_{H2}, but not T_{H1} cells (55), upregulated in induced Treg (56)	523.594842	-1.970519
enhancement					
	ENSG00000139946	PELI2	cooperates with Bcl-10 to activate NFkB in mice; can activate MAPK and AP-1/Elk-1 in humans (57)	2995.12322	-3.12598
	ENSG00000134460	IL2RA	CD25, sign for terminal differentiation in chronic viral response (58)	6206.12175	-2.47528
	ENSG00000105246	EBI3	part of IL-27 and IL-35, expressed in CD4/CD8 T-cells upon activation with phytohemagglutinin and IL-27 (59)	-4.276035	7.89E-09
	ENSG00000118263	KLF7	upregulated in activated CD8+ T-cells (60)	-2.276037	1.10E-08
	ENSG00000147408	CSGALNACT1	associated with EAE (61)	-2.046745	8.22E-07
	ENSG00000104427	ZC2HC1A	variant increases susceptibility to MS (62)	-2.444141	9.39E-07
	ENSG00000171860	C3AR1	activation by C3a enhances naive CD4$^+$ T-cell activation, survival and proliferation *via* PI3K/Akt (50)	2.171075	5.64E-06
	ENSG00000168811	IL12A	required for development of EAE (63), upregulates IL12R → signaling induces T-bet (64)	-2.749976	1.79E-05
	ENSG00000151748	SAV1	part of hippo signaling (induces a rather inflammatory T-cell phenotype (65))	-1.437997	2.07E-05
	ENSG00000214711	CAPN14	calpain, can generate constitutively active calcineurin (66)	-2.500567	3.49E-05
	ENSG00000174136	RGMB	ligand for PD-L2, not increased upon T-cell activation and absent in naive mice, sets down the threshold for activation and supports T-cell expansion (67)	-2.892547	0.000115
	ENSG00000127863	TNFRSF19	increases proliferation and NFkB signaling (68)	-2.607645	0.000155
	ENSG00000111252	SH2B3	LNK, involved in TCR signaling via PI3K/PLCg1/Ras (69)	1.245567	0.000290
negative regulation					
	ENSG00000188822	CNR2	cannabinoid receptor 2, inhibits inflammatory cytokines/proliferation of T-cells (70)	264.665093	2.458243
	ENSG00000133069	TMCC2	upregulated in the absence of Itk which is downstream of TCR signalling (71)	139.965562	-1.640783
	ENSG00000154127	UBASH3B	negatively regulates TCR signaling (72)	880.828175	1.94863
	ENSG00000107679	PLEKHA1	reduces activation of PI3K/Akt and STATs via PTPL1 (73)	1089.23164	1.942193
	ENSG00000071575	TRIB2	negative regulator of mitogen-activated protein kinases, differential expression in peripheral CD4$^+$ (higher) and CD8$^+$ T-cells (74)	2082.21767	1.612003
TRANSPORTERS / ION CHANNELS / GAP JUNCTIONS					
	ENSG00000092096	SLC22A17	iron transport, down-regulated in T_{SCM} compared to T_{N}(75)	52.2669151	-4.621821
	ENSG00000073150	PANX2	Structural component of the gap junctions and the hemichannels	38.9963951	-4.153572
	ENSG00000136052	SLC41A2	Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds, induced by TNF (76)	459.562097	-2.864748
	ENSG00000065923	SLC9A7	sodium and potassium/ proton antiporter, lower expression in non-human primate Ebola survivors than in non-survivors (77)	1991.43475	-1.612669
	ENSG00000144935	TRPC1	needed for intracellular calcium increase by THC in T-cells via DAG (78)	328.047316	-2.158811
	ENSG00000165474	GJB2	connexin 26, part of gap junctions	36.2806533	-3.677582
	ENSG00000121742	GJB6	connexin, part of gap junction	44.9584735	-3.42367
	ENSG00000075673	ATP12A	H$^+$/K$^+$-ATPase	231.196155	-3.834959
	ENSG00000185052	SLC24A3	Potassium-dependent sodium/calcium exchanger	49.8386818	3.227841
	ENSG00000122986	HVCN1	voltage-gated proton channel activity, downregulated in CD56$^+$ T-cells (able to kill CMV-infected cells), associated with metabolism (79)	469.805016	0.929571
	ENSG00000135750	KCNK1	contributes to passive transmembrane potassium transport	36.3729301	-2.730424
	ENSG00000160190	SLC37A1	Pi-linked G6P antiporter (80)	808.320349	1.500943
	ENSG00000182747	SLC35D3	Solute Carrier	12.9025324	-2.956685
	ENSG00000091137	SLC26A4	transmembrane transporter	125.843343	-2.113035
	ENSG00000186187	ZNRF1	regulates the sodium/potassium pump (Na+/K+ATPase) with ZNRF2 (81), high expression in conventional T-cells in the lymph node, but not skin or fat (82)	734.851294	-1.470285
	ENSG00000165449	SLC16A9	Proton-linked monocarboxylate transmembrane transporter	14.7881211	-2.481201

	Ensemble ID	Gene	Function in T-cells	baseMean	log2Fold
PROLIFERATION					
	ENSG00000196507	TCEAL3	transcription elongation factor	89.9871397	-2.190882
	ENSG00000175155	YPEL2	part of the mitotic apparatus required for cell division (83)	1404.32806	-1.179115
	ENSG00000064886	CHI3L2	activation of ERK1/2 phosphorylation by CHI3L2 inhibits cell mitogenesis and proliferation (84)	183.237313	1.318076
	ENSG00000103202	NME4	involved in Pyrimidine metabolism and Metabolism	325.668464	-1.872898
	ENSG00000174136	RGMB	ligand for PD-L2, not increased upon T-cell activation and absent in naive mice, sets down the threshold for activation and supports T-cell expansion (67)	181.825798	-2.892547
	ENSG00000127863	TNFRSF19	increases proliferation and NFkB signaling (68)	52.2866821	-2.607645
	ENSG00000100867	DHRS2	cell cycle regulated NADPH-dependent dicarbonyl reductase enzyme (85)	26.4152921	-2.540096
	ENSG00000174944	P2RY14	receptor for UDP-glucose, activation inhibits murine T-cell proliferation (86)	83.7383867	-2.181412
	ENSG00000164362	TERT	Telomerase Reverse Transcriptase, overexpression extends proliferative potential of human T-cells (9)	27.7024907	-3.430006
	ENSG00000171860	C3AR1	activation by C3a enhances naive CD4$^+$ T-cell activation, survival and proliferation *via* PI3K/Akt (50)	200.019164	2.171075
(CO-) STIMULATION					
	ENSG00000101017	CD40	required for CD8 T-cells to receive help from CD4 T-cells and activation enhances CTL response (87)	40.4430634	-2.698722
	ENSG00000114013	CD86	co-stimulation, upregulated on T-cells in Wegener's granulomatosis (generalized vasculitis) (88)	1042.09351	-2.500507
	ENSG00000120949	TNFRSF8	CD30, upregulated in 15% of stimulated T-cells, enhanced by IL-2 (needs TCR stimulus + IL-2), CD45RO positive T-cells, cross-linking induces Ca2+ release (89)	1077.91194	-3.220663
	ENSG00000197646	PDCD1LG2	PD1-L2, can confer co-stimulation (90)	202.44762	-1.595328
	ENSG00000196372	ASB13	Class I MHC mediated antigen processing and presentation	118.353047	-2.247595
	ENSG00000114455	HHLA2	undetectable on T-cells, binds to CD28H on T-cells (constitutively expressed on naive T-cells, lost in more differentiated memory T-cells) stimulates CD4 T-cell proliferation/increases cytokine production (91), inhibiting proliferation of TCR-stimulated T-cells/reduces cytokine production in T-cells (92)	290.1457	-2.415677
	ENSG00000179583	CIITA	induces expression of MHCII (93)	1949.31925	-0.996969
MIGRATION					
	ENSG00000065534	MYLK	myosin light chain kinase, role in ICAM-mediated cell migration (94)	158.762531	-2.480384
	ENSG00000154928	EPHB1	recruits c-Src and p52Shc to activate MAPK/ERK and promote chemotaxis (95), ephrins stimulate T-cell chemotaxis (96)	315.364149	-2.743718
	ENSG00000075391	RASAL2	activators of Ras superfamily of small GTPases, RET signaling and Cytoskeletal Signaling	792.724493	-2.702632
	ENSG00000196526	AFAP1	modulator of actin filament integrity in response to cellular signals, upregulated in the absence of Itk which is downstream of TCR signalling (71)	900.665659	-1.728868
	ENSG00000107719	PALD1	associated to actin,phosphorylation by Erk inhibits cell migration (97)	43.9082093	2.758423
	ENSG00000157827	FMNL2	involved in actin-dependenT-cell migration (98)	143.44854	-1.615625
	ENSG00000079112	CDH17	calcium-dependenT-cell adhesion protein	26.5219245	2.501369
	ENSG00000172164	SNTB1	actin binding	3080.4073	1.225121
ANERGY / EXHAUSTION					
	ENSG00000111796	KLRB1	CD161, high expression marks anergy on CD8 T-cells failing to secrete cytokines, proliferate, kill (99)	3183.52289	2.029115
	ENSG00000137265	IRF4	induced by TCR signaling → upregulation of inhibitory receptor/impairs metabolism → T-cell exhaustion (25); induction dependent on the signal strength of TCR signaling → glycolysis/clonal expansion/maintenance of effector function (26)	7024.41145	-1.335874
	ENSG00000204381	LAYN	exhaustion marker (downregulates IFNg), reduced cancer-free survival, upregulated in CD8$^+$ T-cells and T_{reg} upon CD3/28 stimulation (100); high expression in tumour infiltrating T_{reg} correlates with poor prognosis; upregulated in T_{RM} (101)	87.4738512	-2.672086
	ENSG00000120708	TGFBI	overexpressed in *post*-infusion *vs.* infusion of TCR engineered T-cells for melanoma (102)	111.986209	2.881898
	ENSG00000145246	ATP10D	metabolism, upregulated in exhausted CAR T-cells (103)	819.42255	1.292246
METABOLISM					
	ENSG00000107518	ATRNL1	role in melanocortin signaling pathways that regulate energy homeostasis	121.589335	-3.432412
	ENSG00000121039	RDH10	required for retinoic acid synthesis	1368.99121	-1.946465
	ENSG00000143845	ETNK2	Metabolism and Glycerophospholipid biosynthesis	115.851273	-2.544206
	ENSG00000164398	ACSL6	Fatty Acyl-CoA Biosynthesis	628.820036	1.453343
	ENSG00000016391	CHDH	part of oxidative phosphorylation (104)	946.804835	-2.952135
	ENSG00000103202	NME4	involved in Pyrimidine metabolism and Metabolism	325.668464	-1.872898
	ENSG00000122986	HVCN1	voltage-gated proton channel activity, downregulated in CD56$^+$ T-cells (able to kill CMV-infected cells), associated with metabolism (79)	469.805016	0.929571
	ENSG00000116016	EPAS1	accumulates upon early TCR signaling and hypoxia, accumulation increases glycolysis/GZB, expression diminished upon administration of IL-2, increased upon administration of IL-4, sustained effector function of CD8 CTLs (12)	3957.09145	-1.554453
CELLULAR ORGANIZATION					
	ENSG00000111052	LIN7A	generating and maintaining the asymmetric distribution of channels and receptors at the cell membrane	30.668353	-3.962803
	ENSG00000198932	GPRASP1	modulates lysosomal sorting and functional down-regulation of a variety of G-protein coupled receptors; variant linked to IPEX (105)	311.376694	-2.357607
	ENSG00000168502	MTCL1	microtubule binding	53.4993724	2.589775
	ENSG00000161835	GRASP	role in intracellular trafficking	1140.15859	-2.417493
	ENSG00000128578	STRIP2	cell morphology and cytoskeletal organization	778.705892	-1.75502
	ENSG00000080200	CRYBG3	mediates the subcellular compartmentation of protein kinase A	1797.12246	-1.542907
	ENSG00000114745	GORASP1	establishes the stacked structure of the Golgi apparatus, upregulated in biopsies of acute cellular rejection with acute hepatitis (106)	464.348531	-1.190619
	ENSG00000118200	CAMSAP2	microtubule binding	77.1979364	-2.558792
OTHERS					
	ENSG00000104921	FCER2	B-cell specific antigen, and a low-affinity receptor for IgE	70.5805133	-5.282302
	ENSG00000135919	SERPINE2	Thrombin, urokinase, plasmin and trypsin inhibitor	304.039786	3.215362
	ENSG00000123685	BATF3	on DCs needed for CD8 T-cell activation	629.085812	-3.290487
	ENSG00000177383	MAGEF1	Enhances ubiquitin ligase activity of RING-type zinc finger-containing E3 ubiquitin ligases	205.655947	-1.802055
	ENSG00000164742	ADCY1	regulated by calcium/calmodulin concentration, nucleotide binding and phosphorus-oxygen lyase activity	154.296726	-2.646613
	ENSG00000205002	AARD	Alanine And Arginine Rich Domain Containing Protein	87.2130341	-2.540349
	ENSG00000281938	CTB-127M13.1	???	599.808293	1.452842
	ENSG00000166432	ZMAT1	target gene of p53 (107)	171.866799	-1.551626
	ENSG00000220577	SAMD4A	Acts as a translational repressor of SRE-containing messengers	669.062337	-1.860179
	ENSG00000180044	C3orf80	???	7.29341353	-2.967343
	ENSG00000183570	PCBP3	binds to RNA with a specificity for C-rich pyrimidine regions, post-transcriptional regulation (108), transcriptional repressor (109)	206.493301	-2.534946
	ENSG00000043355	ZIC2	zinc-finger protein, regulates neurodevelopment	56.9453982	-3.618661
	ENSG00000060566	CREB3L3	transcriptional regulator downstream of cAMP, acute phase response	44.3122445	-3.955702
	ENSG00000169957	ZNF768	Zinc Finger	187.373087	-1.677774
	ENSG00000102870	ZNF629	DNA binding transcription factor activity	88.2902254	-2.112764
	ENSG00000173068	BNC2	transcription factor in Th22 cells (110)	36.5735491	3.196431
	ENSG00000186398	KIAA0355	???	1864.69372	-0.842476
	ENSG00000115271	GCA	calcium-binding on membrane and granules (111)	189.326058	-1.396011
	ENSG00000087258	GNAO1	alpha subunit of the Go heterotrimeric G-protein signal-transducing complex	180.918351	2.130565
	ENSG00000147180	ZNF711	zinc finger protein	74.2344179	-2.445459
	ENSG00000146416	AIG1	Androgen Induced 1	323.307154	-1.18446
	ENSG00000275342	PRAG1	tyrosine protein kinase	192.233186	1.636761
	ENSG00000111249	CUX2	RNA polymerase II regulatory region sequence-specific DNA binding	28.5203944	-2.487567
	ENSG00000108239	TBC1D12	acts as a GTPase-activating protein for Rab family protein(s)	83.3507848	-2.131095
	ENSG00000165138	ANKS6	ciliar protein	336.962981	-1.354375
	ENSG00000111962	UST	Uronyl 2-sulfotransferase	847.243661	-1.594802
	ENSG00000112246	SIM1	DNA binding transcription factor activity and obsolete signal transducer activity	219.600604	-5.050657
	ENSG00000145103	ILDR1	Ig-like receptor	171.851598	-4.569781

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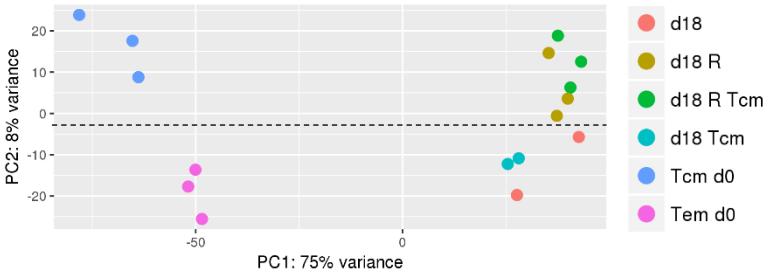

Figure S2: Rapamycin-treated cells are closer to *ex vivo* sorted T_{CM} and non-treated cultures resemble T_{EM} in dimension PC2.

Principle component (PC) analysis of RNA sequencing data of T_{CM} and T_{EM} sorted on d0 out of PBMCs derived from buffy coats of n = 3 HDs and untreated as well as Rapa-TCPs (R) and T_{CM}-like cells sorted on d18 of culture from the indicated TCP derived from the same n = 3 buffy coat donors. Lacking data points of d18 and d18 T_{CM} occurred due to failure at the quality control level.

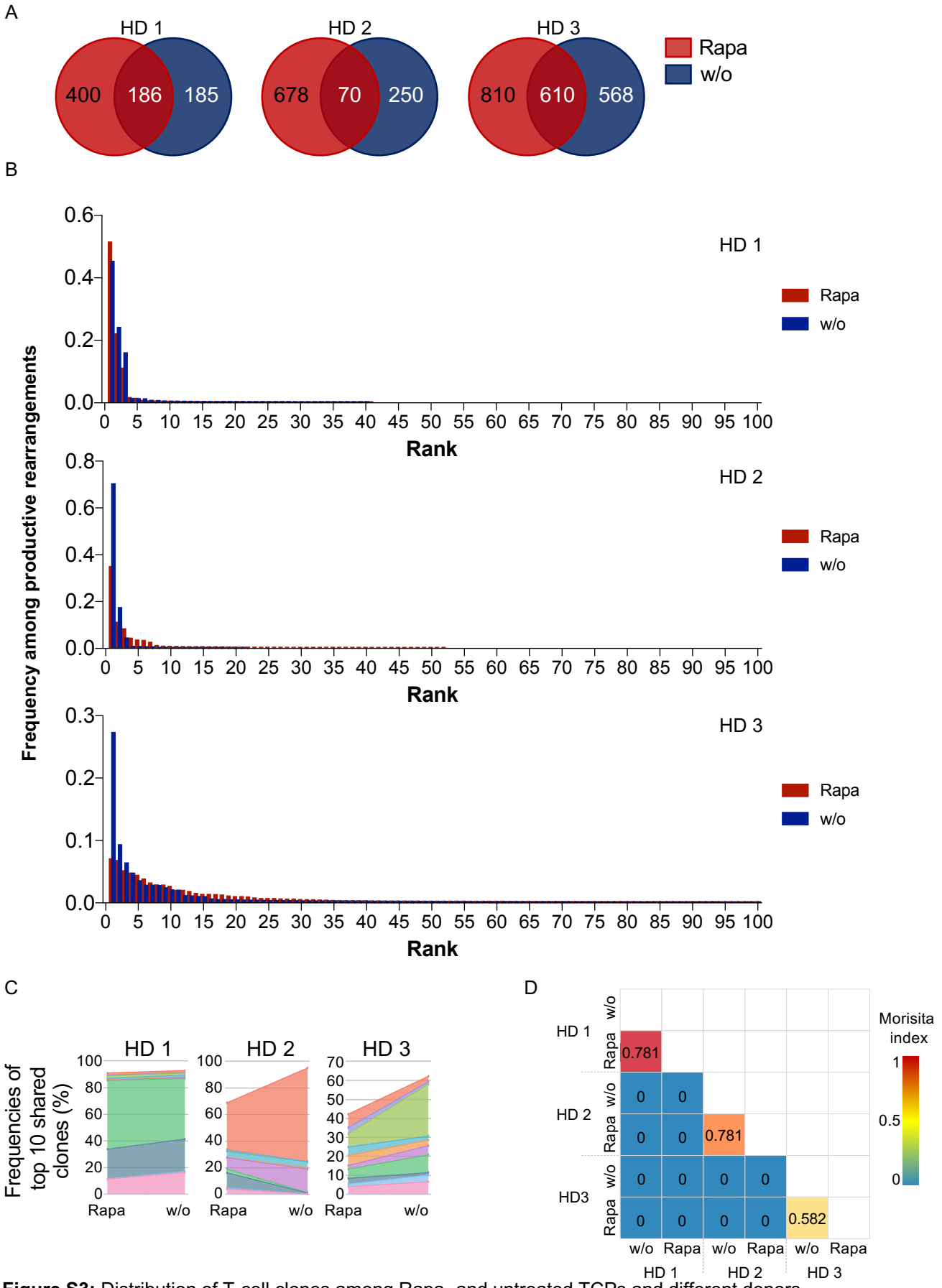

Figure S3: Distribution of T-cell clones among Rapa- and untreated TCPs and different donors.

A: Venn diagrams of all clones of Rapa- (red) and untreated TCPs (blue) of 3 HDs demonstrating individual and shared clones of each sample. **B**: Frequencies among productive rearrangements of the top100 clones of Rapa- (red) and untreated TCPs (blue) of 3 HDs. **C**: Stacked view of individual frequencies of the top 10 most represented shared clones in Rapa- and untreated TCPs (w/o) of 3 HDs. Shared clones were ranked based upon the maximum frequency achieved in either Rapa- or untreated TCPs." **D**: Morisita index matrix showing sample overlap between all samples, which is based on the presence of unique clones, individual frequencies of clones and the probability of a common origin of two samples. All data were calculated in ImmunoSEQ-Analyzer 3.0 based on TCRβ sequencing data.

Table S2: Patient details.

Pred. = Prednisolone; M-pred. = Methyl-prednisolone; Tac. = Tacrolimus; MMF = Mycophenolate mofetil; MPS = Mycophenolate sodium; CsA = Cyclosporine A; VGCV = Valganciclovir; ACV = Acyclovir; conc. = concentration; imcomp. = incompatible

No.		1	2	3	4	5	6	7	8	9		10	11	12	13		14	15	16	17	18	19
Age		58	45	42	53	29	45	51	44	46		78	56	52	46		63	70	66	67	34	60
Gender		M	F	F	F	M	M	F	M	M		M	M	M	M		M	M	F	F	F	F
time from KTx [d]		264	294	161	19	21	21	13	21	34		694	27	2499	28		1809	296	380	563	665	7418
Time from last CMV viremia [d]		-	-	-	-	-	-	-	-	-		0	0	13	9		1728	119	140	112	645	40
Tac. blood conc. [ng/ml]		8.5	6.4	7.2	11.3	10	8.35	5.2	9.7	9.8		6.5	11.5				5.9	5.5	8.5	11.3	4.1	4
Immuno-suppression at d0		Tac. (1 mg) MMF (1,5 g)	M-pred. (4 mg) Tac. (10,5 mg) MMF (2 g)	Tac. (3 mg) MMF (1,5 g)	Pred. (20 mg) Tac. (15 mg) MMF (2 g)	M-pred. (16 mg) Tac. (18 mg) MMF (2 g)	M-pred. (4 mg) Tac. (6 mg) MMF (2 g)	M-pred. (24 mg) Tac. (8 mg) MMF (2 g)	M-pred.(4 mg) Tac. (16 mg) MMF (2 g)	M-pred. (4 mg) Tac. (6,5 mg) MPS (2 g)		M-pred. (4 mg) Tac. (3 mg) MMF (1,5 g)	M-pred. (4 mg) Tac. (10 mg) MMFl (1,5 g)	M-pred. (4 mg) CsA (130 mg) MMF (2 g)	M-pred. (4 mg) CsA (250 mg) MPS (2 g)		M-pred. (4 mg) Tac. (4,5 mg)	M-pred. (4 mg) Tac. (7 mg) MMF (500 ng)	M-pred. (4 mg) Tac. (3,5 mg) MMF (1,5 g)	M-pred. (4 mg) Tac. (2,5 mg) MMF (2 g)	M-pred. (4 mg) Tac. (7 mg)	Pred. (5 mg) Tac. (4,5 mg) MPS (1,08 g)
Rejection [from d0]		acute cellular rejection (-245)	no	no	no	no	suspected acute (ATG-17 to -19)	no	no	no												
Antiviral therapy [from d0]		none	none	none	none	none	none	none	none	none		VGCV 900 mg (-468 to -420); 450 mg (+263 to +336); 225 mg (-668 to -599; +336 to +374)	VGCV 450 mg (19.01.2017 - 14.02.2017); 900 mg (23.11.2016 - 19.01.2017)	VGCV 450 mg (-2451 to -2423)	VGCV 900 mg (-7 to +5)		none	VGCV 450 mg (-1267 to -1218; -1372 to -1311)	VGCV 225 mg (-355 to -327)	none	none	ACV 200 mg (since -753)
Other detected CMV viremia [from d0]		none	none	none	none	none	+54	none	+112; +7	none		+400; +263; +261; +168; +119; +78; +49; +35; +16; -125; -292; -312; -348; -391; -412; -420; -475; -491; -496	+266; -7; -11; -14; -21	+468; +272; +97; -13; -22; -78; -267; -637; -813; -978; -1182; -1569; -2470; -2489	-18; -25		none	+325; +252; -524; -708; -888; -1255; -1269	+328; -253	-487; -526; -536	none	+297; +129; -207; -613; -641; -972; -2324
Lymphocyte count [/nl]		1.04	1.49	1.48	2.34	1.23	0.09	2.34	2.32	1.2		0.28	0.47	0.71	1.21		1.6	0.98	0.88	1.22	1.26	-
Donor		CMV-; living	CMV+; living	CMV-; living	CMV+; living	CMV+; living	CMV-; living	CMV+; living	CMV+; living	CMV-; living		CMV+; deceased	CMV+; living	CMV+; living	CMV+; living		CMV+; deceased	CMV+; deceased	CMV+; deceased	CMV-; deceased	CMV+; living	CMV+; deceased
CMV before KTx		+	+	+	+	+	+	+	+	+		-	+	+	+		+	-	+	+	+	+
Other							AB0 incomp. donation, delayed graft function					CMV colitis (-486 to -496-, +239 to + 275); VGCV resistance excluded		chronic hepatitis B			B cell lymphoma				missed abortion (-1)	anal carcinoma (diagnosed +289)
Underlying disease		IgA nephritis	hypertensive nephropathy	polycystic kidney disease	IgA nephritis	IgA nephritis	seronegative Lupus erythematosus	polycystic kidney disease	left nephrectomy after relapsed pyelonephritis, obstructive nephropathy	IgA nephritis		hypertensive nephropathy	IgA nephritis	unilateral renal agenesis and possibly obstructive nephropathy	Renal hypertensive angiopathy		Pauci immun-glumerulo-nephritis	unclear	Diabetic nephropathy	hypertensive nephropathy	IgA nephropathy	Diabetic nephropathy

Patients with so far no recorded CMV viremia

Patients with recent CMV viremia

Patients with history of CMV viremia

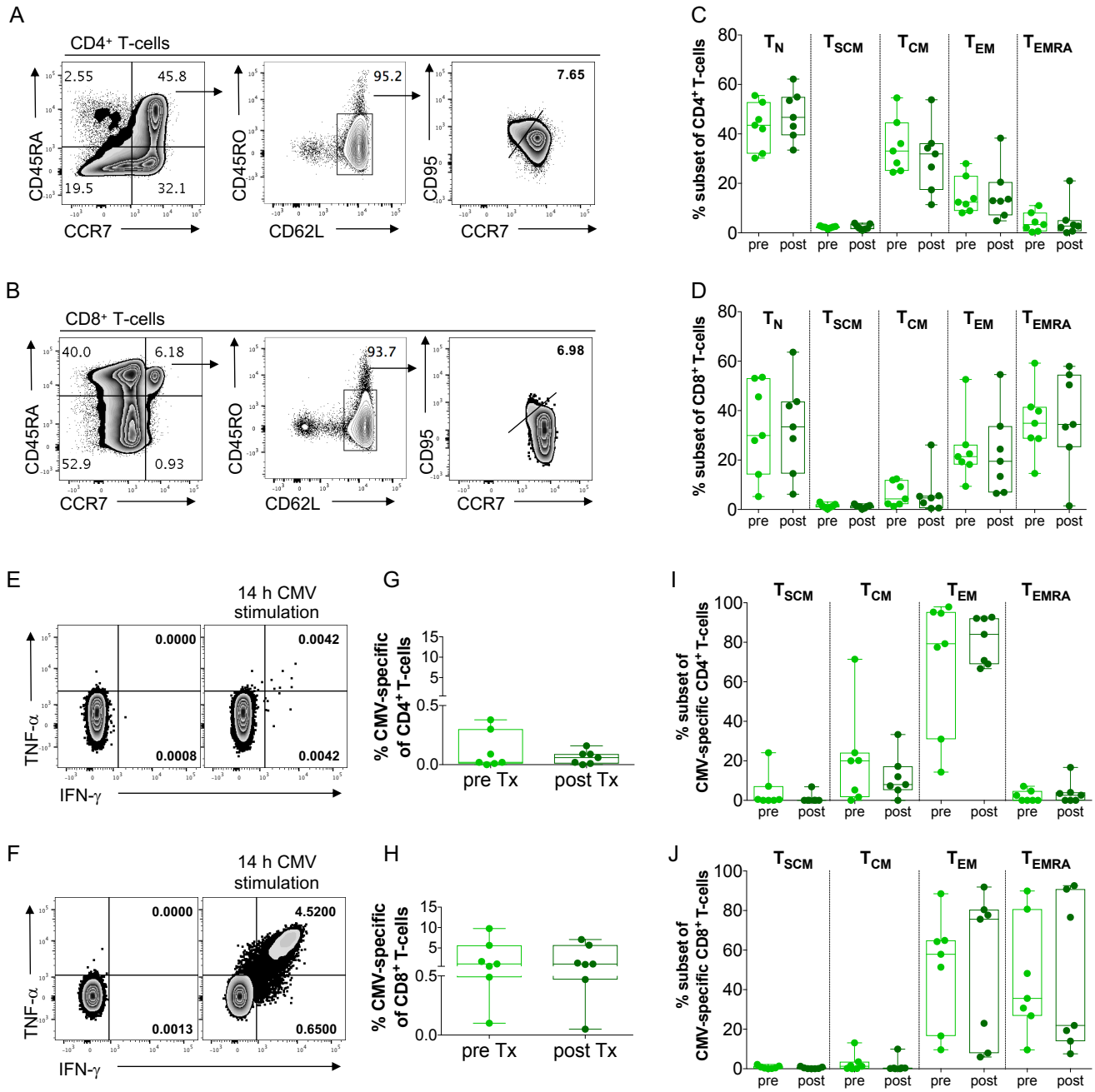

Figure S4: CMV-specific *ex vivo* response shifts to T_{EM} on the expense of T_{CM} within a few weeks after transplantation while the global subset composition remains stable.

N = 7 paired samples from the same patients before (pre; pastel green) and a few weeks after KTx (post; dark green). Gated on lymphocytes (FSC-A vs. SSC-A), single cells (FSC-H vs. FSC-A), living T-cells (CD3 vs. life/dead-discriminating dye) and as indicated on CD4⁺ or CD8⁺ T-cells, respectively. Gating strategy for discrimination of T-cell memory subsets for CD4⁺ (**A**) and CD8⁺ (**B**) subsets: T_N: CD45RA⁺ CCR7⁺ CD95⁻; T_{SCM}: CD45RA⁺ CCR7⁺ CD45RO⁻ CD62L⁺ CD95⁺; T_{CM}: CD45RA⁻ CCR7 ⁺; T_{EM}: CD45RA⁻ CCR7 ⁻; T_{EMRA}: CD45RA⁺ CCR7 ⁻. Global T-cell memory subset distribution of CD4⁺ (**C**) and CD8⁺ (**D**) T-cells from peripheral blood collected *pre*- and *post*-Tx. Subsets gated as shown in **A**/**B**. IFNγ and TNFα were stained intracellularly after 14 h stimulation of fresh PBMCs with $CMV_{IE\text{-}1/pp65}$ peptide pools and addition of BFA after 1 h. Exemplary dot plots and gating strategy for CD4⁺ (**E**) and CD8⁺ (**F**) T-cells. Summary of CMV-specific CD4⁺ (**G**) and CD8⁺ (**H**) T-cells identified as IFNγ⁺TNFα⁺ detected *ex vivo* in PBMCs of KTx patients based on the gating strategy shown in **E**/**F**. Proportions of subsets among CMV-responsive CD4⁺ (**I**) and CD8⁺ T-cells (**J**) determined by characteristic expression of CCR7, CD45RA and CD95. Gates were applied from gates set for global T-cell subset distribution (**A**/**B**).

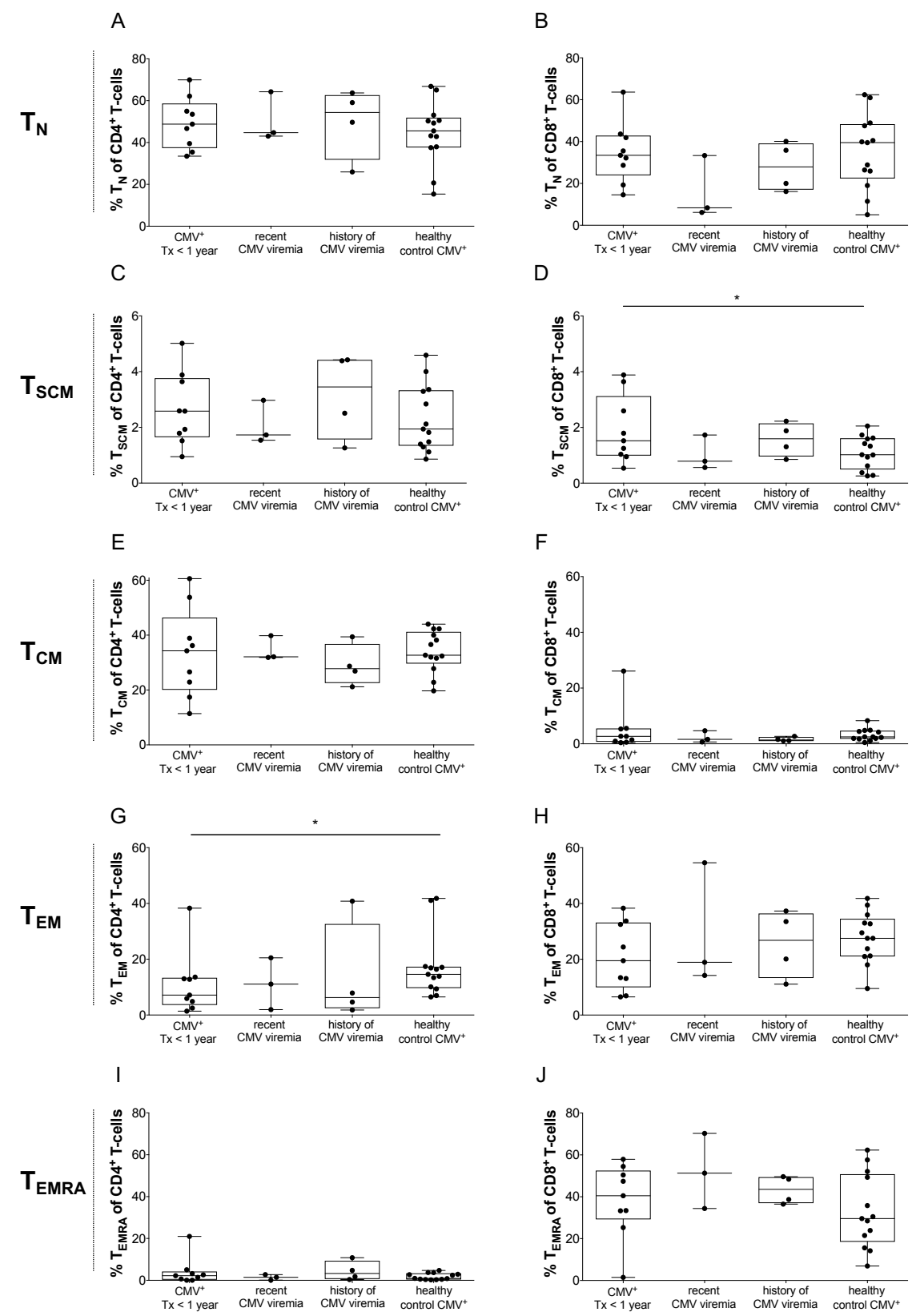

Figure S5: $CD8^+$ T_{SCM} are globally increased and $CD4^+$ T_{EM} globally decreased in the blood of patients without record of CMV viremia compared to the blood of healthy donors.

T-cell subset distribution of n = 19 patients (9 with so far no recorded CMV viremia; 4 with recent CMV viremia and 6 with a history of CMV viremia)/13 HDs. Global proportions of different $CD4^+$ (left panel) and $CD8^+$ T-cell (right panel) subsets determined by characteristic expression of CCR7, CD45RA, CD62L, CD45RO and CD95. N=19 patients (9 with so far no recorded CMV viremia; 4 with recent CMV viremia and 6 with a history of CMV viremia)/13 HDs. Gating strategy is shown in Fig. S4A/B. $CD4^+$ (**A**) and $CD8^+$ (**B**) $CD45RA^+$ $CCR7^+$ $CD95^-$ T_N. $CD4^+$ (**C**) and $CD8^+$ (**D**) $CD45RA^+$ $CCR7^+$ $CD62L^+$ $CD45RO^-$ $CD95^+$ T_{SCM}. $CD4^+$ (**E**) and $CD8^+$ (**F**) $CD45RA^-$ $CCR7^+$ T_{CM}. $CD4^+$ (**G**) and $CD8^+$ (**H**) $CD45RA^-$ $CCR7^-$ T_{EM}. $CD4^+$ (**I**) and $CD8^+$ (**J**) $CD45RA^+$ $CCR7^-$ T_{EMRA}. All data tested for normal distribution of data points with Kolmogorov-Smirnov test; significance determined with paired t test if normally distributed or Wilcoxon's matched-pairs signed rank test for not normally distributed samples. P-values below 0.05 are indicated by * and defined to be significant.

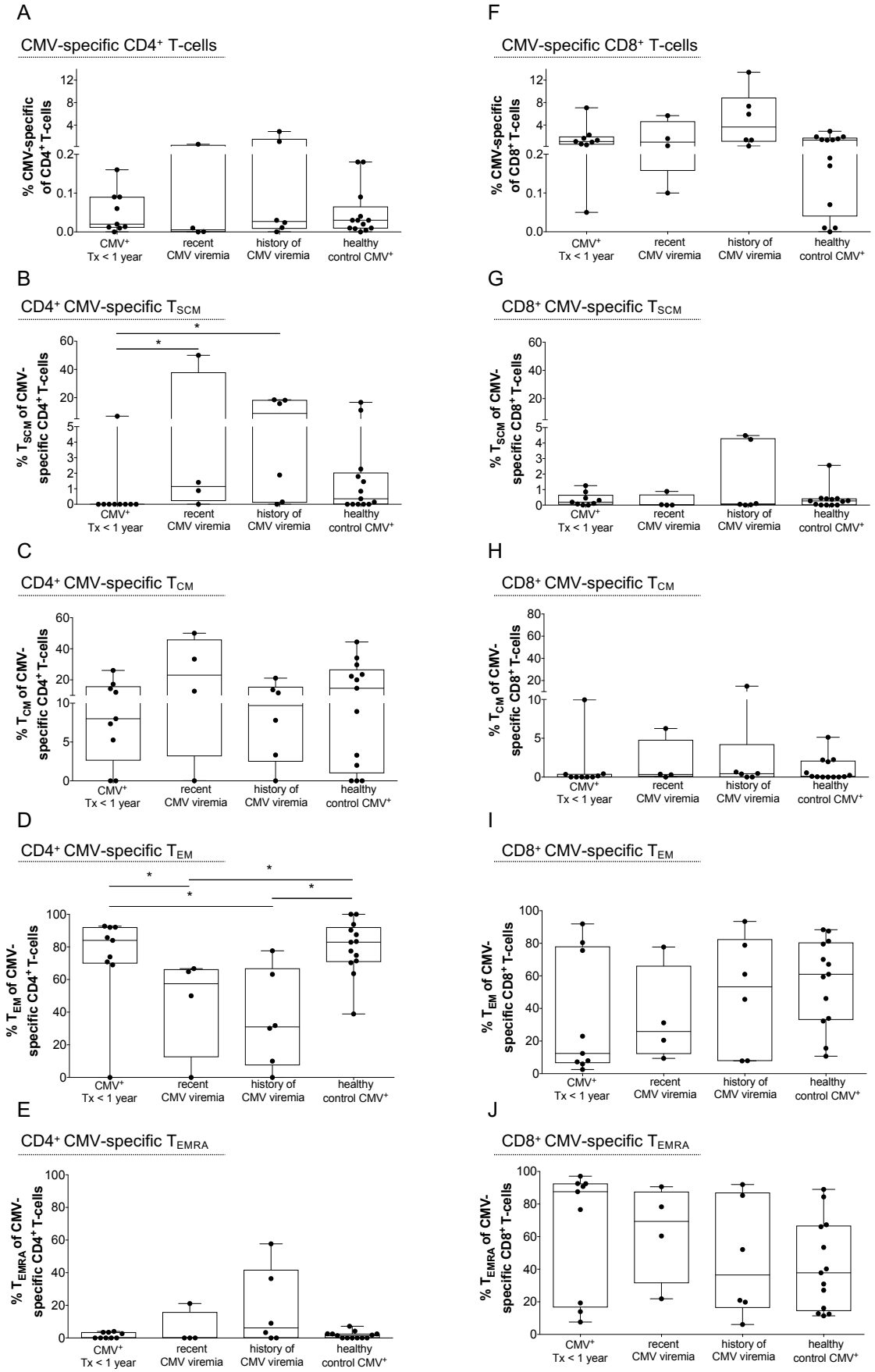

Figure S6: CD4+ CMV-specific T_{SCM} accumulate upon CMV reactivation and T_{EM} diminish after a history of CMV viremia in renal transplant recipients.

N=19 patients (9 with so far no recorded CMV viremia; 4 with recent CMV viremia and 6 with a history of CMV viremia)/13 healthy controls. Proportions of CMV-responsive among CD4+ (**A**) and CD8+ (**F**) T-cells detected by double positive intracellular staining for IFNγ and TNFα after 14 h stimulation of fresh PBMCs with $CMV_{IE\text{-}1/pp65}$ peptide pools and addition of BFA after 1 h (see dot plots Fig. 4E-F). T-cell memory subset distribution of CMV-reactive CD4+ (**B**-**E**) and CD8+ (**G**-**J**) T-cells following the gating strategy and subset definitions presented in Fig. S4A/B, applying gates for global subset distribution from Fig.S4. CMV-reactive CD4+ (**B**) and CD8+ (**G**) CD45RA+ CCR7+ CD62L+ CD45RO- CD95+ T_{SCM}. CMV-reactive CD4+ (**C**) and CD8+ (**H**) CD45RA- CCR7+ T_{CM}. CMV-reactive CD4+ (**D**) and CD8+ (**I**)) CD45RA- CCR7- T_{EM}. CMV-reactive CD4+ (**E**) and CD8+ (**J**) CD45RA+ CCR7- T_{EMRA}. All data tested for normal distribution of data points with Kolmogorov-Smirnov test; significance determined with paired t test if normally distributed or Wilcoxon's matched-pairs signed rank test for not normally distributed samples. P-values below 0.05 are indicated by * and defined to be significant.

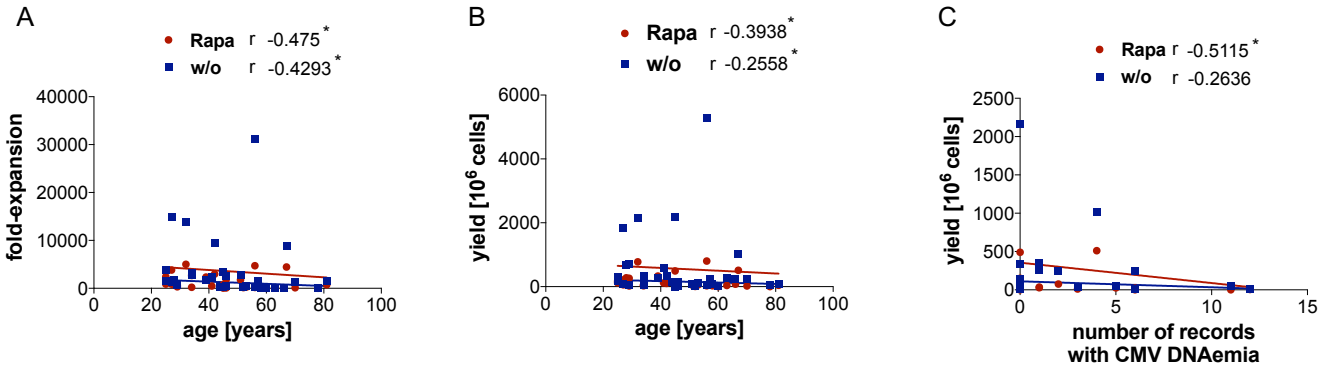

Figure S7: Decreased fold-expansion and yield correlate with increasing age and numbers of recorded reactivations.

Correlations of age and fold-expansion (**A**)/yield (**B**) as well as records of reactivations determined by viremia and yield (**C**) in untreated (blue) and Rapa (treated with 20 nM Rapamycin; red)-TCPs of 19 patients and 13 HDs; distributions tested for normality with Kolmogorov-Smirnov test, correlations of normally distributed data calculated with Pearson's correlation coefficient and of not normally distributed data with Spearman's rank correlation.

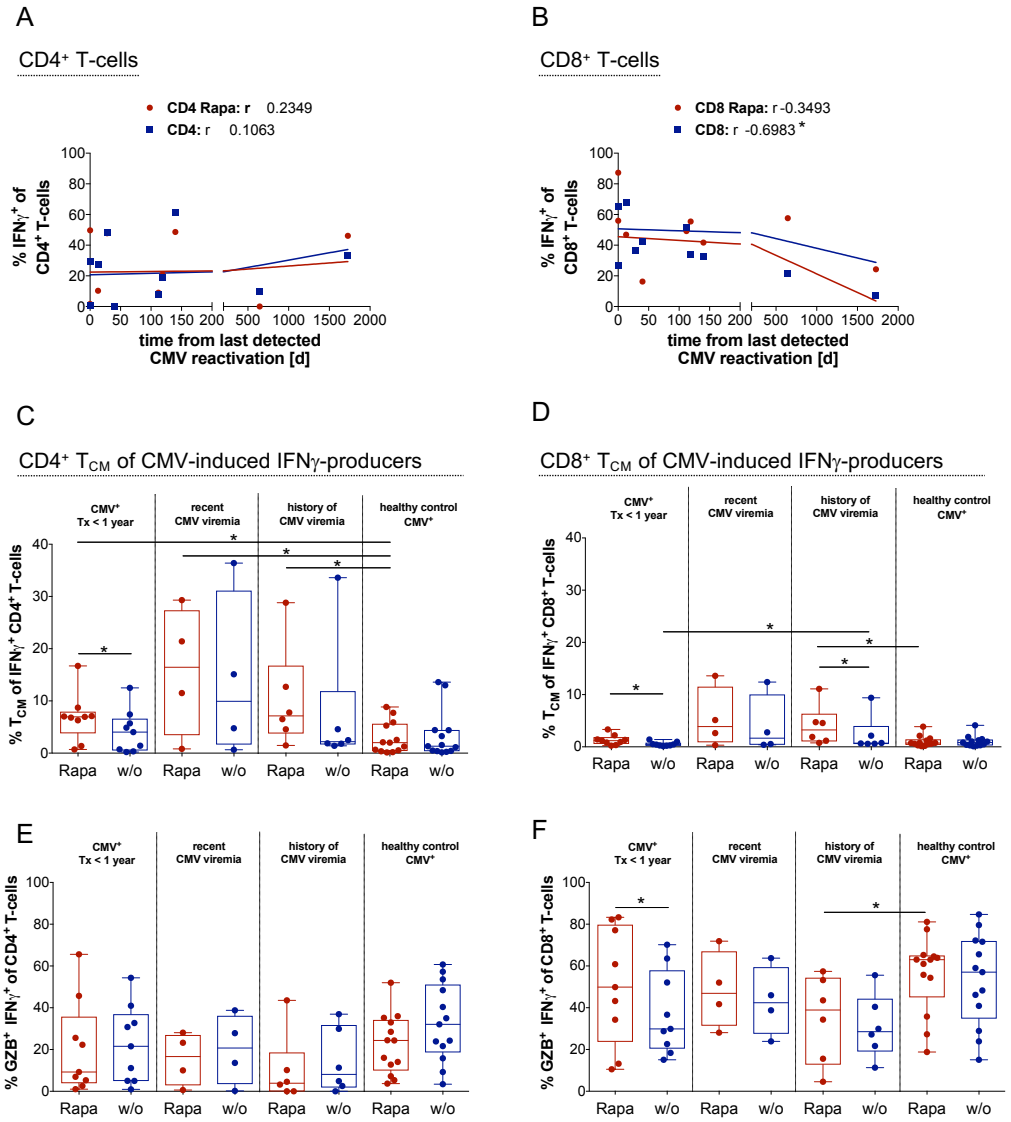

Figure S8: The proportion of IFNγ-producing CD8⁺ T-cells negatively correlates with the time from reactivation in *Rapa-TCP*s, among CMV-stimulated IFNγ responders the frequency of T_{CM} is increased in TCPs from patients with recorded CMV viremia and a substantial amount of cytotoxic CD4⁺ T-cells is abundant in TCPs.

Correlations of proportions of IFNγ-producing CD4⁺ (**A**) and CD8⁺ (**B**) T-cells from untreated (w/o, blue) and Rapa (red)-TCPs to time from last recorded CMV DNAemia from n = 10 patients (for whom a record of CMV DNAemia was available; Table S2); distributions tested for normality with Kolmogorov-Smirnov test, correlations of normally distributed data calculated with Pearson's correlation coefficient and of not normally distributed data with Spearman's rank correlation. Proportions of CD45RA⁻ CCR7⁺ T_{CM} among IFNγ producing CD4⁺ (**C**) and CD8⁺ (**D**) T-cells. Gates were applied from gates set for global T cell subset distribution (Fig.S4A-B). Proportions of CD4⁺ (**E**) and CD8⁺ (**F**) GZB-IFNγ-double-producers detected by intracellular staining after 6 h stimulation with autologous LCLs loaded $CMV_{IE\text{-}1/pp65}$ peptide pools and addition of BFA after 1 h on d21.

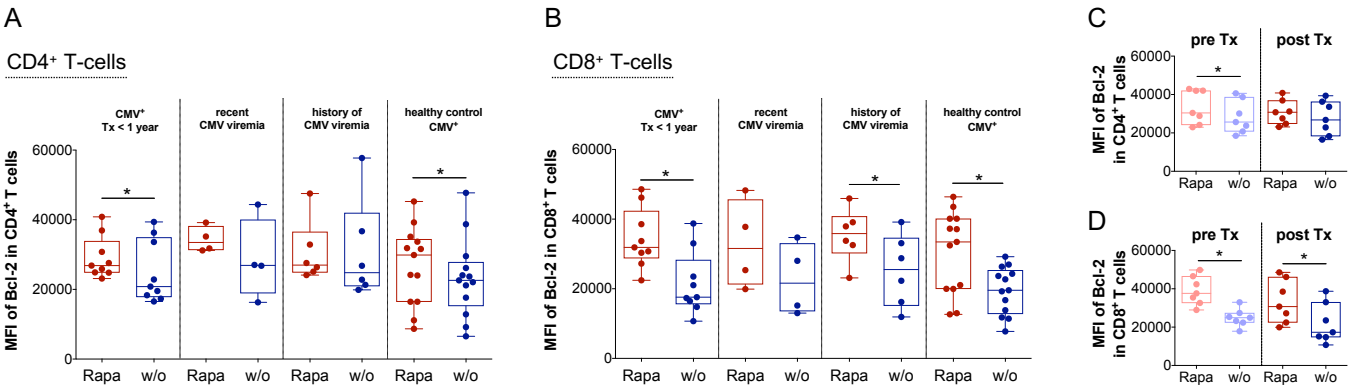

Figure S9: Bcl-2 is increased also in patient TCPs, especially in CD8$^+$ T-cells.

MFI of Bcl-2 in CD4$^+$ (**A**) and CD8$^+$ (**B**) T-cells of untreated (w/o, blue) and Rapa (red)-TCPs of n = 19 patients (9 with so far no recorded CMV viremia; 4 with recent CMV viremia and 6 with a history of CMV viremia)/13 healthy controls. MFI of Bcl-2 in CD4$^+$ (**C**) and CD8$^+$ (**D**) T-cells of untreated (w/o, blue) and Rapa (red)-TCPs of n = 7 patients for which TCPs were generated before and a few weeks after KTx.