Supplementary Information for

Effect of felzartamab anti-CD38 treatment on the molecular phenotype of antibody-mediated rejection in kidney transplant biopsies.

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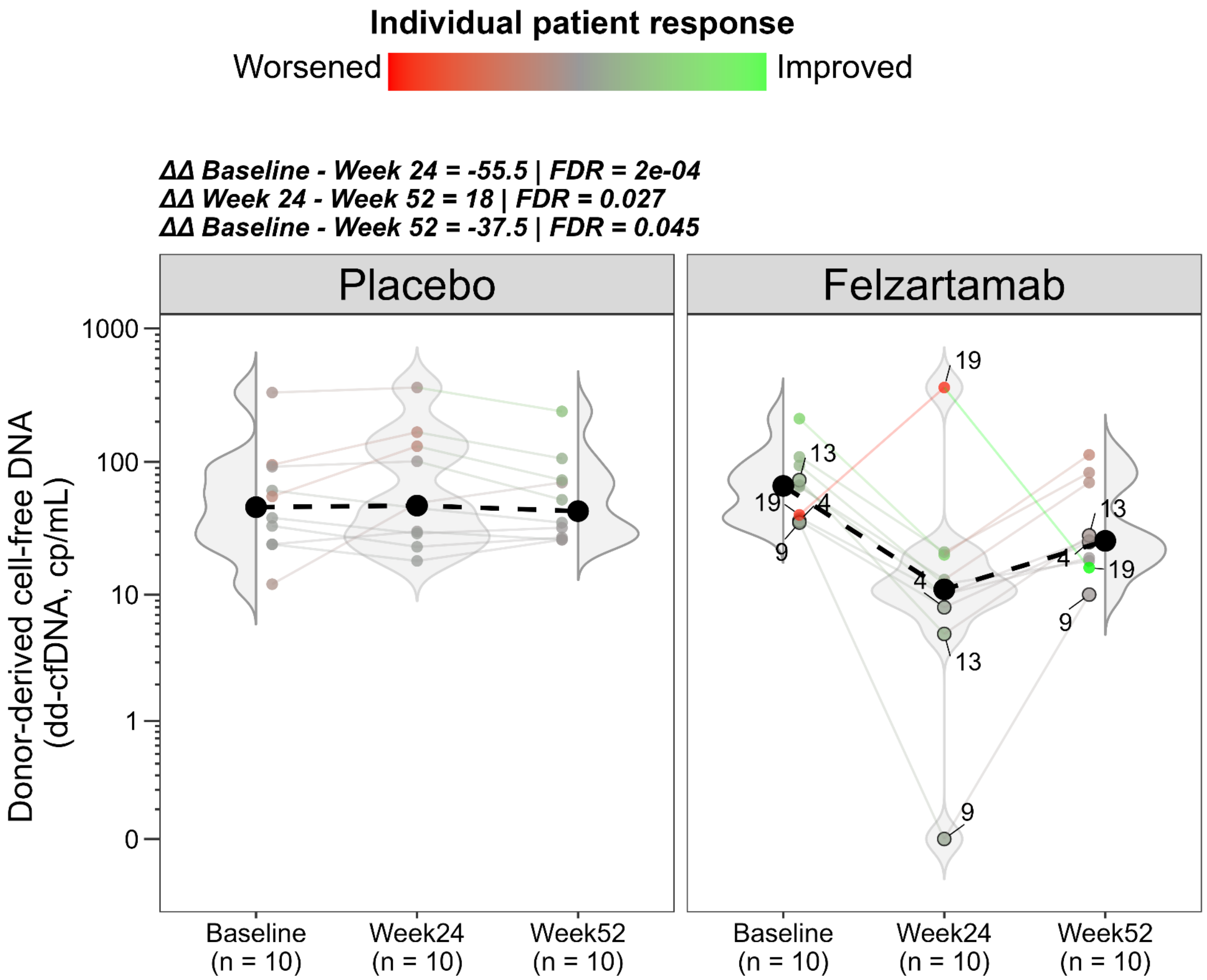

Figure S1. Effect of felzartamab treatment on donor-derived cell-free DNA (A) Shaded regions represent density estimates by group. Solid black circles represent the median scores within group. Dashed lines illustrate the changes in median scores (Δ) from baseline to week 24 to week 52 within treatment groups. Solid colored circles represent individual patient scores. Numbers identify patients of interest. Solid colored lines illustrate the change in individual patient scores from baseline to week 24 to week 52.

Supplementary Table 1. Demographic and characteristics of the participants at baseline

Variables	Placebo (n=10)	Felzartamab (n=10)	All patients (N=20)
Recorded at transplantation			
Female sex – no. (%)	7 (70.0)	3 (30.0)	10 (50.0)
Median recipient age (IQR) – yr	50 (17-59)	34 (5-58)	41 (5-59)
Mean recipient age (SD) - yr	45 (13)	35 (15)	40 (14)
Living donor – no. (%)	2 (20.0)	3 (30.0)	5 (25.0)
Median donor age (range) – yr	36 (3-63)	48 (18-55)	43 (3-63)
Mean donor age (SD) – yr	37 (18)	42 (14)	39 (16)
Median HLA (A, B, DR) mismatch (IQR)	3 (2 to 3)	2 (2 to 4)	3 (2 to 3)
Recorded at trial inclusion			
Median age of study patients (range) – yr	58 (36-74)	44 (31-65)	53 (31-74)
Mean age of study patients (SD) – yr	57 (11)	45 (11)	51 (12)
Median time to inclusion in the trial (IQR) – yr	11 (6 to 19)	8 (5 to 11)	9 (5 to 19)
Median eGFR (IQR) – mL/min/1.73 m2	36 (33 to 46)	63 (34 to 70)	37 (33 to 66)
Mean eGFR (SD) – mL/min/1.73 m2	42 (19)	54 (20)	48 (20)
Median protein/creatinine ratio (IQR) – mg/g	1227 (178 to 1475)	830 (421 to 1364)	993 (196 to 1489)
Mean protein/creatinine ratio (SD) – mg/g	1101 (1081)	1414 (1686)	1257 (1387)
Banff 2019 ABMR phenotypes (baseline biopsies) – no. (%)			
Active ABMR	3 (30.0)	4 (40.0)	7 (35.0)
Chronic active ABMR	7 (70.0)	6 (60.0)	13 (65.0)
Additional borderline lesion	2 (20.0)	0 (0.0)	2 (10.0)
MMDx signouts – no. (%)			
Moderate to severe early-stage ABMR	1 (10.0)	1 (10.0)	2 (10.0)
Severe early-stage ABMR	1 (10.0)	1 (10.0)	2 (10.0)
Moderate fully-developed ABMR	2 (20.0)	2 (20.0)	4 (20.0)
Severe fully-developed ABMR	4 (40.0)	4 (40.0)	8 (40.0)
Late-stage ABMR	1 (10.0)	2 (20.0)	3 (15.0)
Mixed rejection	1 (10.0)	0 (0.0)	1 (5.0)
DSA characteristics (screening visit)			
HLA class I DSA only – no. (%)	3 (30.0)	4 (40.0)	7 (35.0)
HLA class II DSA only – no. (%)	6 (60.0)	5 (50.0)	11 (55.0)
HLA class I and II DSA – no. (%)	1 (10.0)	1 (10.0)	2 (10.0)
Anti-DQ DSA – no. (%)	5 (50.0)	5 (50.0)	10 (50.0)
Peak MFI of DSA >10,000 – no. (%)	3 (30.0)	4 (40.0)	7 (35.0)
Median DSA (IQR) – n	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)

Abbreviations: ABMR, antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; IQR, interquartile range; MFI, mean fluorescence intensity; SD, standard deviation

Supplementary Table 2. Comparing MMDx diagnosis with histology diagnosis and lesions in patients who received felzartamab

Patient	Baseline biopsy						Week 24 biopsy (end of felzartamab treatment)						Week 52 biopsy (28 weeks after felzartamab treatment)						comments
	MMDx 1208	**ptc>0/g>0**	**ABMR$_{Prob}$**	**NKB**	**ABMR Phenotype Banff19**	**Lesions ptc/g/MVI/cg**	**MMDx 1208**	**ptc>0/g>0**	**ABMR$_{Prob}$**	**NKB**	**ABMR phenotype Banff19**	**Lesions ptc/g/MVI/cg**	**MMDx 1208**	**ptc>0/g>0**	**ABMR$_{Prob}$**	**NKB**	**ABMR phenotype Banff19**	**Lesions ptc/g/MVI/cg**	
2	Severe FABMR	0.89/0.89	0.86	1.9	C4d-neg caABMR	2/3/5/3	Moderate FABMR (Rej score is normal)	0.36/0.59	0.66	1.0	C4d-neg cABMR (inactive)	0/0/0/1	Severe FABMR	0.85/0.92	0.83	1.46	C4d-neg caABMR	2/1/3/1	
4	FABMR **(99% medulla)**	0.57/0.53	0.58	0.91	C4d-pos caABMR	1/1/2/?	Late ABMR (mild) **(90% medulla)**	0.31/0.44	0.17	0.71	C4d-neg cABMR (inactive)	0/1/1/3	Late ABMR (minimal)	0.37/0.39	0.17	0.57	C4d-neg cABMR (inactive)	0/1/1/1	No recurrence and no recovery of blood NK cells
5	Severe FABMR	0.79/0.82	0.84	1.34	C4d-neg aABMR	2/1/3/0	Moderate EABMR	0.65/0.62	0.50	0.95	No ABMR	0/0/0/0	Moderate EABMR	0.59/0.73	0.64	1.0	C4d-neg aABMR	1/1/2/0	
7	FABMR **(92% medulla)**	0.72/0.60	0.80	1.44	C4d-neg caABMR	0/3/3/2	NR	0.16/0.21	0.11	0.50	C4d-pos caABMR	0/1/1/3	Moderate/ Severe FABMR	0.71/0.59	0.77	1.22	C4d-pos caABMR	0/2/2/2	
9	LABMR (minimal)	0.25/0.27	0.18	0.50	C4d-neg caABMR	0/2/2/1	NR (LABMR+cg score)	0.12/0.24	0.16	0.22	C4d-neg cABMR (inactive)	0/1/1/2	NR	0.20/0.27	0.14	0.28	C4d-neg cABMR (inactive)	0/0/0/0	Minimal activity or recurrence
12	FABMR **(99% medulla)**	0.53/0.59	0.68	0.94	C4d-pos caABMR	1/1/2/1	NR **(99% medulla)**	0.07/0.11	0.09	0.50	C4d-neg cABMR (inactive)	0/0/0/0	Possible ABMR (Rej score is normal)	0.20/0.36	0.23	0.66	C4d-neg cABMR (inactive)	0/0/0/1	
13	Severe EABMR	0.87/0.89	0.90	1.20	C4d-pos aABMR	2/2/4/0	Moderate EABMR	0.75/0.59	0.56	1.32	C4d-pos aABMR	2/0/2/0	Severe FABMR	0.85/0.86	0.91	1.47	C4d-pos caABMR	1/1/2/1	Minimal effect of FLZ
16	Severe FABMR	0.89/0.88	0.80	1.67	C4d-pos aABMR	2/2/4/0	Mild ABMR (Rej score is normal) **(99% medulla)**	0.23/0.44	0.32	0.46	No ABMR	0/0/0/0	Severe EABMR	0.81/0.86	0.83	1.73	C4d-neg aABMR	2/0/2/0	
19	LABMR (mild)	0.50/0.44	0.36	0.91	C4d-neg caABMR	2/1/3/3	NR **(50% medulla)**	0.16/0.12	0.02	0.28	C4d-pos cABMR (inactive)	0/0/0/1	Moderate/ Severe FABMR	0.40/0.71	0.80	2.44	C4d-neg cABMR (inactive)	0/0/0/2	
22	EABMR	0.76/0.71	0.50	1.44	C4d-pos aABMR	2/1/3/0	NR	0.09/0.15	0.08	0.42	No ABMR	0/0/0/0	Mild EABMR	0.53/0.41	0.43	1.12	No ABMR	0/0/0/0	

Abbreviations: aABMR, active ABMR; ABMR, antibody-mediated rejection; ABMRProb, probability of ABMR; C4d-neg, C4d-negative; C4d-pos, C4d-positive; caABMR, chronic active ABMR; cABMR, chronic ABMR: cg, glomerular double contours; EABMR, early-stage ABMR; FABMR, fully-developed ABMR; g, glomerulitis; LABMR, late-stage ABMR; MMDx, Molecular Microscope® Diagnostic System; MVI, microvascular inflammation; NKB, natural killer-like B cells; NR, no rejection; ptc, peritubular capillaritis; Rej, rejection;

Supplementary Table 3. Molecular scores (PBTs, classifiers)

Category	Abbreviation	Description
TCMR-related	TCMR-RAT	TCMR-associated [1]
	QCAT	Cytotoxic T cell associated [2]
	TCB	T-cell burden related [3]
	$i>1_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic kidney i-lesion score > 1 [4]
	$t>1_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic kidney t-lesion score > 1 [4]
	$\mathrm{TCMR}_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic kidney TCMR diagnosis [4]
ABMR-related	NKB	Natural killer (NK) cell burden [5] (only valid if there is no TCMR)
	DSAST	Kidney derived DSA selective transcripts [3]
	$\mathrm{ABMR}_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic kidney ABMR diagnosis [4]
	$g>0_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic g-lesion score > 0 [4]
	$ptc>0_{\mathrm{Prob}}$	Top 20 transcripts in classifier of probability of histologic ptc-lesion score > 0 [4]
New ABMR-related PBTs	AAG	ABMR-associated activity genes
	IIAAG	IFNG-inducible ABMR-associated activity genes
	NKAAG	NK cell expressed ABMR-associated activity genes
	AEG	ABMR-associated endothelial cell genes
Macrophage-related	AMAT1	Alternatively activated macrophage transcripts [6]
	QCMAT	Constitutive macrophage transcripts [7]
Recent injury-related	IRITD3	Injury-repair induced, day 3 (IRITD3) [8]
	IRITD5	Injury-repair induced, day 5 (IRITD3) [8]
	IRRAT30	Injury-repair associated (IRRAT30) [9]
Atrophy-fibrosis-related	$ci>1_{\mathrm{Prob}}$	Fibrosis classifier [10]
	$ct>1_{\mathrm{Prob}}$	Atrophy classifier [10]
Normal parenchyma	KT1	Normal kidney transcripts (except solute carriers) [11]
	KT2	Normal kidney solute carrier transcripts [11]

[A] https://www.ualberta.ca/medicine/institutes-centres-groups/atagc/research/gene-lists.

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Abbreviations: pathogenesis-based transcript set (PBT); donor-derived cell-free DNA (dd-cfDNA); antibody-mediated rejection (ABMR); T cell mediated rejection (TCMR)

Supplementary Table 4. Median (IQR) molecular scores in baseline biopsies from felzartamab-treated vs placebo-treated patients

Annotation	Score	Placebo (N=10)	Felzartamab (N=10)	p	FDR*
cfDNA	Donor-derived cell-free DNA (dd-cfDNA, cp/mL)	46.50 (58)	66.00 (50.25)	0.284	0.560
	Donor-derived cell-free DNA (dd-cfDNA, %)	0.83 (0.88)	1.01 (1.42)	0.560	0.560
ABMR-related	ABMR classifier ($\text{ABMR}_{\text{Prob}}$)	0.67 (0.36)	0.74 (0.31)	0.942	1.000
	Glomerulitis classifier ($g>0_{\text{Prob}}$)	0.76 (0.2)	0.65 (0.32)	0.511	1.000
	Peritubular capillaritis classifier ($\text{ptc}>0_{\text{Prob}}$)	0.81 (0.18)	0.74 (0.31)	0.744	1.000
	DSA-selective transcripts (DSAST)	0.65 (0.24)	0.64 (0.16)	0.689	1.000
	NK cell burden (NKB)	1.17 (0.29)	1.27 (0.53)	1.000	1.000
TCMR-related	TCMR classifier ($\text{TCMR}_{\text{Prob}}$)	0.02 (0.03)	0.01 (0.01)	0.251	0.581
	Tubulitis classifier ($t>1_{\text{Prob}}$)	0.06 (0.07)	0.05 (0.05)	0.302	0.581
	Interstitial infiltrate classifier ($i>1_{\text{Prob}}$)	0.06 (0.05)	0.05 (0.05)	0.585	0.585
	Cytotoxic T cell-associated (QCAT)	1.37 (0.54)	1.25 (0.31)	0.379	0.581
	T cell burden (TCB)	1.88 (1.02)	1.71 (0.39)	0.465	0.581
Macrophage-related	Alternatively activated macrophage (AMAT1)	0.57 (0.16)	0.71 (0.3)	0.320	0.641
	Constitutive macrophage (QCMAT)	0.51 (0.14)	0.52 (0.24)	0.828	0.828
Injury-related	Injury-repair associated (IRRAT30)	0.27 (0.46)	0.03 (0.17)	0.268	0.447
	Injury-repair induced, day 3 (IRITD3)	0.08 (0.19)	0.00 (0.08)	0.662	0.828
	Injury-repair induced, day 5 (IRITD5)	0.37 (0.14)	0.33 (0.11)	1.000	1.000
	Fibrosis classifier ($\text{ci}>1_{\text{Prob}}$)	0.67 (0.29)	0.36 (0.15)	0.019	0.093
	Atrophy classifier ($\text{ct}>1_{\text{Prob}}$)	0.53 (0.39)	0.24 (0.28)	0.056	0.140
Parenchyma-related	Kidney parenchymal (KT1)	-0.17 (0.37)	-0.10 (0.18)	0.511	0.689
	Kidney parenchymal - no solute carriers (KT2)	-0.21 (0.61)	-0.19 (0.3)	0.689	0.689

FDR correction was carried out within each annotation grouping
Abbreviations: donor-derived cell-free DNA (dd-cfDNA); antibody-mediated rejection (ABMR); T cell mediated rejection (TCMR)

Supplementary Table 5. Natural killer (NK) cell counts in whole blood from felzartamab patients at Baseline, Week 24 and Week 52 of study

Felzartamab patients	CD16high NK cells (cell/ml)		
	Baseline	Week 24	Week 52
Patient 2	156	24	64
Patient 4	**62**	**27**	**23**
Patient 5	59	3	18
Patient 7	141	49	78
Patient 9	140	16	96
Patient 12	126	8	15
Patient 13	31	8	26
Patient 16	560	63	154
Patient 19	32	8	21
Patient 22	135	41	No data

Supplementary Table 6. Top 20 differentially expressed genes between baseline and week24 in biopsies from placebo and felzartamab treated patients sorted by treatment effect (selected by ΔΔ p, sorted by ΔΔlogFC).

Gene symbol	Gene	Annotation[1]	Differential expression				Mean expression by group				Cell panel expression[2]			
							Placebo		Felzartamab					
			Δ placebo logFC	Δ felzartamab logFC	ΔΔ logFC	ΔΔ P*	Baseline (N=10)	Week 24 (N=10)	Baseline (N=10)	Week 24 (N=10)	HUVEC	HUVEC (+IFNg)	RPTEC	RPTEC (+IFNg)
FABP5	fatty acid binding protein 5 (psoriasis-associated)	Broad, reduced in HUVECs by IFNG	-0.33	0.33	0.66	0.0203	147	93	103	161	3,647	1,947	426	524
SCGB2A1	secretoglobin, family 2A, member 1	Low expression	-0.13	0.45	0.59	0.0223	37	31	25	48	10	10	8	9
RGCC	regulator of cell cycle	Broad; decreased in ABMR	-0.18	0.34	0.52	0.0139	411	319	381	610	577	758	8	7
KCNK13	potassium channel, two pore domain subfamily K, member 13	Broad	-0.13	0.30	0.43	0.0142	39	33	36	54	15	17	9	15
SYBU	syntabulin (syntaxin-interacting)	Broad, reduced in RPTECs by IFNG	-0.13	0.27	0.41	0.0194	150	125	104	152	9	10	82	66
CCDC92	coiled-coil domain containing 92	Broad, reduced in HUVEC by IFNG	-0.23	0.15	0.38	0.0183	51	37	38	47	299	264	736	903
RARB	retinoic acid receptor, beta	HUVEC, reduced by IFNG	-0.17	0.18	0.35	0.0086	217	171	189	242	419	368	9	19
RECQL5	RecQ helicase-like 5	Broad, reduced in HUVEC by IFNG	-0.14	0.19	0.33	0.0155	167	137	138	180	142	126	123	153
TMEM97	transmembrane protein 97	Broad, reduced in HUVECs by IFNG	-0.06	0.24	0.30	0.0092	190	175	153	213	217	150	328	609
AVPR2	arginine vasopressin receptor 2	Broad, weakly decreased in ABMR	-0.09	0.21	0.30	0.0159	72	64	64	85	39	38	23	22
TRAV12-2	T cell receptor alpha variable 12-2	T cells; weakly expressed in cultured NK cells	0.25	-0.10	-0.35	0.0173	39	55	49	43	21	21	8	9
APOL1	apolipoprotein L1	ABMR-RAT,IFNG-inducible	0.07	-0.32	-0.39	0.0205	626	687	754	483	80	1,011	61	784
LOC339059	uncharacterized LOC339059	Weakly increased in EABMR	0.26	-0.15	-0.41	0.0203	51	73	66	53				
SH2D1B	SH2 domain containing 1B	NKAAG	0.07	-0.44	-0.51	0.001	38	42	40	22	17	16	7	9
GBP1	guanylate binding protein 1, interferon-inducible	IIAAG	-0.03	-0.61	-0.59	0.0096	678	655	909	389	153	6,985	92	6,274
GZMB	granzyme B	NKAAG	-0.01	-0.62	-0.61	0.0019	149	147	143	61	15	19	12	13
FCGR3A	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)	NKAAG	0.06	-0.58	-0.64	0.0167	550	602	571	256	15	14	7	6
IDO1	indoleamine 2,3-dioxygenase 1	IIAAG	-0.09	-0.77	-0.68	0.0103	338	298	409	140	47	9,620	14	4,381
CXCL10	chemokine (C-X-C motif) ligand 10	IIAAG	-0.21	-0.98	-0.77	0.0228	844	632	1,063	274	32	9,860	15	5,049
CXCL11	chemokine (C-X-C motif) ligand 11	IIAAG	-0.16	-1.01	-0.85	0.0176	494	395	617	153	14	6,842	5	2,161

[1] Gene annotations included membership in published pathogenesis-based transcript sets (PBTs) or phenotype associations in published reference sets of kidney transplant biopsies[2]

[2]

* All FDR > 0.05

Supplementary Table 7. Functional enrichment analysis of genes affects by felzartamab treatment between baseline and week 24 (by FDR)

library	ID	pathway	interpretation	n genes	NES	FDR	core enrichment genes
GO	GO:0006952	defense response	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0009605	response to external stimulus	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0009607	response to biotic stimulus	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0043207	response to external biotic stimulus	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0044419	biological process involved in interspecies interaction between organisms	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0051707	response to other organism	ABMR activity	20	-3.07	3e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO	GO:0006955	immune response	ABMR activity	23	-2.93	5e-05	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, TRAV12-2, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
GO8	GO:0002376	immune system process	ABMR activity	24	-2.75	0.0002	PTPRC, TRIM4, LYZ, PRF1, FCGR1A, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, APOL1, CXCL11, TRAV12-2, FCGR3A, IDO1, GBP1, GZMB, SH2D1B
Reactome	R-HSA-168256	Immune System	ABMR activity	14	-2.45	0.0002	PIK3AP1, PTPRC, TRIM4, KLRF1, LYZ, FCGR1A, KLRD1, GNLY, IL18RAP, CXCL10, FCGR3A, GBP1, SH2D1B
DOSE	DOID:2914	immune system disease	ABMR activity	10	-2.56	0.0007	PRF1, FCGR1A, CXCL9, IL18RAP, CXCL10, CXCL11, FCGR3A, IDO1, GZMB
DOSE	DOID:77	gastrointestinal system disease	ABMR activity	15	-2.59	0.0007	PTPRC, EPB41L3, LYZ, PRF1, KLRD1, CXCL9, GNLY, IL18RAP, CXCL10, CXCL11, FCGR3A, IDO1, GZMB
DOSE	DOID:1579	respiratory system disease	immune response	10	-2.56	0.0007	PRF1, FCGR1A, CXCL9, IL18RAP, CXCL10, CXCL11, FCGR3A, IDO1, GZMB

Abbreviations: normalized enrichment score (NES); false discovery rate (FDR)

Supplementary Table 8. Effect of treatment on interferon gamma-inducible antibody-mediated rejection activity genes (IIAAG)

Gene symbol	Gene	Baseline – Week 24				Week 24 – Week 52				Baseline – Week 52			
		Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p	Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p	Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p
GBP1	guanylate binding protein 1, interferon-inducible	-0.03	-0.61	-0.59	0.0094	-0.01	0.42	0.42	0.1074	-0.04	-0.36	-0.32	0.1533
IDO1	indoleamine 2,3-dioxygenase 1	-0.09	-0.77	-0.68	0.0106	-0.04	0.53	0.57	0.1124	-0.07	-0.26	-0.19	0.2765
CXCL11	chemokine (C-X-C motif) ligand 11	-0.16	-1.01	-0.85	0.0190	-0.07	0.21	0.28	0.1141	0.02	-0.35	-0.37	0.3080
CXCL10	chemokine (C-X-C motif) ligand 10	-0.21	-0.98	-0.77	0.0243	0.09	0.58	0.49	0.1502	-0.10	-0.35	-0.25	0.3281
CXCL9	chemokine (C-X-C motif) ligand 9	-0.14	-0.94	-0.79	0.0311	0.00	0.16	0.16	0.1966	-0.11	-0.39	-0.28	0.4057
GBP4	guanylate binding protein 4	-0.04	-0.38	-0.34	0.0737	-0.03	0.21	0.24	0.2103	-0.20	-0.48	-0.28	0.4366
CX3CL1	chemokine (C-X3-C motif) ligand 1	-0.01	-0.17	-0.16	0.0981	-0.01	0.26	0.27	0.2265	-0.15	-0.06	0.10	0.4435
PLA1A	phospholipase A1 member A	-0.09	-0.34	-0.25	0.1549	0.16	0.59	0.42	0.2485	-0.04	-0.10	-0.06	0.5587
WARS	tryptophanyl-tRNA synthetase	-0.08	-0.30	-0.22	0.1977	-0.03	0.08	0.11	0.2843	-0.07	-0.17	-0.10	0.5908
IL18BP	interleukin 18 binding protein	-0.15	-0.22	-0.07	0.5891	0.01	0.05	0.03	0.8439	-0.16	-0.13	0.03	0.8604
column means		-0.10	-0.57	-0.47		0.01	0.31	0.30		-0.09	-0.26	-0.17	

Supplementary Table 9. Effect of treatment on natural killer (NK) cell-expressed antibody-mediated rejection activity genes (NKAAG)

Gene symbol	Gene	Baseline – Week 24				Week 24 – Week 52				Baseline – Week 52			
		Δ logFC Placebo (N=10)	**Δ logFC Felzartamab (N=10)**	**ΔΔ logFC (N=20)**	**ΔΔ p**	**Δ logFC Placebo (N=10)**	**Δ logFC Felzartamab (N=10)**	**ΔΔ logFC (N=20)**	**ΔΔ p**	**Δ logFC Placebo (N=10)**	**Δ logFC Felzartamab (N=10)**	**ΔΔ logFC (N=20)**	**ΔΔ p**
SH2D1B	SH2 domain containing 1B	0.07	-0.44	-0.51	0.0007	-0.15	0.30	0.45	0.0029	-0.05	-0.19	-0.14	0.1652
GZMB	granzyme B	-0.01	-0.62	-0.61	0.0017	-0.09	0.45	0.54	0.0050	-0.11	0.12	0.22	0.1897
KIR2DL2	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 2	0.08	-0.21	-0.29	0.0051	-0.08	0.37	0.45	0.0225	-0.08	0.04	0.12	0.3093
KLRD1	killer cell lectin-like receptor subfamily D, member 1	-0.06	-0.49	-0.43	0.0280	-0.04	0.34	0.38	0.0522	-0.13	-0.42	-0.30	0.3353
GNLY	granulysin	-0.18	-0.75	-0.57	0.0291	-0.12	0.10	0.21	0.0644	-0.15	-0.04	0.11	0.5800
PRF1	perforin 1 (pore forming protein)	-0.02	-0.35	-0.33	0.0333	-0.06	0.23	0.29	0.0664	-0.26	-0.13	0.12	0.6094
KLRF1	killer cell lectin-like receptor subfamily F, member 1	0.00	-0.41	-0.41	0.0376	-0.08	0.39	0.46	0.0757	-0.08	-0.14	-0.06	0.6612
CCL4	chemokine (C-C motif) ligand 4	-0.23	-0.82	-0.59	0.0564	0.03	0.33	0.30	0.0787	-0.26	-0.36	-0.10	0.6824
TBX21	T-box 21	-0.10	-0.28	-0.18	0.1707	0.00	0.35	0.35	0.0799	-0.14	-0.07	0.08	0.7149
FGR	FGR proto-oncogene, Src family tyrosine kinase	-0.02	-0.16	-0.15	0.2127	-0.04	0.18	0.22	0.1010	-0.10	-0.17	-0.06	0.7316
TRDC	T cell receptor delta constant	-0.15	-0.39	-0.24	0.2199	-0.13	0.02	0.15	0.1419	-0.21	-0.17	0.05	0.7702
XCL1	chemokine (C motif) ligand 1	-0.20	-0.40	-0.20	0.2459	-0.04	0.31	0.35	0.1516	-0.14	-0.11	0.04	0.7704
FGFBP2	fibroblast growth factor binding protein 2	-0.22	-0.44	-0.23	0.3459	-0.01	0.27	0.27	0.1995	-0.08	-0.12	-0.04	0.7721
CD160	CD160 molecule	-0.14	-0.33	-0.20	0.3506	0.03	0.23	0.20	0.2497	-0.10	-0.15	-0.05	0.8013
S1PR5	sphingosine-1-phosphate receptor 5	0.04	-0.06	-0.10	0.3865	-0.08	0.04	0.12	0.3128	-0.09	-0.04	0.05	0.8135
NKG7	natural killer cell granule protein 7	-0.18	-0.28	-0.10	0.5045	0.10	0.40	0.29	0.3400	-0.10	-0.12	-0.03	0.8178
CST7	cystatin F (leukocystatin)	-0.24	-0.35	-0.11	0.5395	-0.03	0.12	0.15	0.3422	-0.20	-0.16	0.04	0.8409
GZMH	granzyme H	-0.09	-0.21	-0.12	0.5666	0.04	0.18	0.14	0.4199	0.00	0.00	0.00	0.9599
KIR2DL3	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 3	0.03	-0.03	-0.05	0.5852	-0.03	0.03	0.06	0.5547	-0.14	-0.15	0.00	0.9951
KLRC3	killer cell lectin-like receptor subfamily C, member 3	-0.14	-0.22	-0.08	0.6379	-0.06	0.06	0.11	0.5742	-0.17	-0.17	0.00	0.9990
	column means	-0.09	-0.36	-0.28		-0.04	0.24	0.27		-0.13	-0.13	0.00	

Supplementary Table 10. Effect of treatment on antibody-mediated rejection-associated endothelial genes (AEG)

Gene symbol	Gene	Baseline - Week24				Week24 - Week52				Baseline - Week52			
		Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p	Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p	Δ logFC Placebo (N=10)	Δ logFC Felzartamab (N=10)	ΔΔ logFC (N=20)	ΔΔ p
MALL	mal, T-cell differentiation protein-like	-0.01	-0.23	-0.22	0.0702	-0.07	0.15	0.21	0.0803	-0.21	-0.05	0.17	0.2882
NOS3	nitric oxide synthase 3 (endothelial cell)	0.02	0.11	0.08	0.3812	-0.10	0.01	0.11	0.3617	-0.12	0.02	0.14	0.3269
TM4SF18	transmembrane 4 L six family member 18	0.04	-0.05	-0.09	0.4501	-0.03	0.09	0.12	0.4457	-0.14	-0.05	0.08	0.4478
RASIP1	Ras interacting protein 1	-0.08	-0.01	0.07	0.5040	-0.13	-0.02	0.12	0.4607	-0.09	0.03	0.11	0.4601
CDH5	cadherin 5, type 2 (vascular endothelium)	-0.02	-0.09	-0.07	0.5497	-0.06	0.03	0.09	0.4849	-0.07	0.02	0.09	0.4957
PECAM1	platelet/endothelial cell adhesion molecule 1	-0.12	-0.05	0.07	0.6339	0.00	0.07	0.07	0.6120	0.09	0.14	0.06	0.5492
CDH13	cadherin 13	-0.04	-0.14	-0.10	0.6651	-0.05	0.00	0.06	0.6773	-0.13	-0.04	0.09	0.5853
TEK	TEK tyrosine kinase, endothelial	-0.08	-0.03	0.05	0.7444	0.03	0.09	0.06	0.7157	-0.12	-0.06	0.06	0.6446
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog	-0.02	0.02	0.04	0.7906	0.04	0.08	0.04	0.7264	-0.07	-0.12	-0.05	0.6886
MMRN2	multimerin 2	-0.06	-0.03	0.03	0.7933	0.06	0.04	-0.03	0.7845	-0.03	0.01	0.04	0.7442
ROBO4	roundabout guidance receptor 4	-0.07	-0.10	-0.03	0.8085	-0.05	-0.03	0.02	0.8458	0.03	-0.03	-0.06	0.7940
IFI27	interferon, alpha-inducible protein 27	-0.20	-0.24	-0.04	0.8454	-0.05	-0.03	0.02	0.8458	0.03	-0.03	-0.06	0.7940
ECSCR	endothelial cell surface expressed chemotaxis and apoptosis regulator	-0.16	-0.13	0.03	0.8563	0.07	0.11	0.04	0.8656	-0.06	-0.04	0.02	0.8682
ADGRL4	adhesion G protein-coupled receptor L4	-0.02	-0.04	-0.02	0.8964	0.04	0.06	0.02	0.8668	-0.09	-0.08	0.01	0.9103
RAPGEF5	Rap guanine nucleotide exchange factor 5	-0.06	-0.06	0.00	0.9779	-0.03	-0.05	-0.02	0.8827	-0.09	-0.08	0.01	0.9103
GNG11	guanine nucleotide binding protein (G protein), gamma 11	-0.07	-0.07	0.00	0.9798	-0.06	-0.05	0.01	0.9250	-0.08	-0.08	-0.01	0.9617
	column means	-0.06	-0.07	-0.01		-0.02	0.04	0.05		-0.07	-0.03	0.04	

Supplementary Table 11. Top 20 genes increased by felzartamab between baseline and week 24 (by P-value)

Gene symbol	Gene	Differential expression				Mean expression by group						Cell panel expression				Correlation with ABMR activity genesets in all K5086[1]							
						Placebo			Felzartamab							AAG		IIAAG		NKAAG		AEG	
		Δ placebo logFC	Δ felzartamab logFC	ΔΔ logFC	ΔΔ P	Baseline (N=10)	Week24 (N=10)	Week52 (N=10)	Baseline (N=10)	Week24 (N=10)	Week52 (N=10)	HUVEC	HUVEC (+IFNg)	RPTEC	RPTEC (+IFNg)	SCC	p	SCC	p	SCC	p	SCC	p
RARB	retinoic acid receptor, beta	-0.17	0.18	0.35	0.0086	217	171	193	189	242	207	419	368	9	19	0.03	8e-02	0.04	1e-02	0.04	3e-03	0.40	2e-195
TMEM97	transmembrane protein 97	-0.06	0.24	0.30	0.0092	190	175	152	153	213	180	217	150	328	609	-0.21	1e-50	-0.19	4e-44	-0.22	6e-57	0.03	2e-02
RGCC	regulator of cell cycle	-0.18	0.34	0.52	0.0139	411	319	349	381	610	401	577	758	8	7	-0.13	9e-20	-0.14	7e-23	-0.09	7e-11	0.14	2e-25
KCNK13	potassium channel, two pore domain subfamily K, member 13	-0.13	0.30	0.43	0.0142	39	33	30	36	54	38	15	17	9	15	-0.03	3e-02	-0.01	6e-01	-0.04	2e-03	0.17	2e-33
RECQL5	RecQ helicase-like 5	-0.14	0.19	0.33	0.0155	167	137	148	138	180	145	142	126	123	153	-0.08	1e-08	-0.10	1e-12	-0.06	6e-05	0.16	4e-31
AVPR2	arginine vasopressin receptor 2	-0.09	0.21	0.30	0.0159	72	64	60	64	85	71	39	38	23	22	-0.22	7e-57	-0.23	1e-61	-0.18	4e-38	0.09	6e-11
CCDC92	coiled-coil domain containing 92	-0.23	0.15	0.38	0.0183	51	37	43	38	47	38	299	264	736	903	-0.08	1e-08	-0.12	3e-18	-0.05	9e-04	0.07	2e-06
SYBU	syntabulin (syntaxin-interacting)	-0.13	0.27	0.41	0.0194	150	125	127	104	152	150	9	10	82	66	-0.07	3e-07	-0.10	4e-13	-0.03	3e-02	0.42	1e-211
FABP5	fatty acid binding protein 5 (psoriasis-associated)	-0.33	0.33	0.66	0.0203	147	93	125	103	161	91	3,647	1,947	426	524	0.33	4e-130	0.30	9e-107	0.33	3e-132	0.44	5e-240
SCGB2A1	secretoglobin, family 2A, member 1	-0.13	0.45	0.59	0.0223	37	31	40	25	48	35	10	10	8	9	-0.08	2e-08	-0.09	1e-09	-0.09	7e-10	0.17	6e-34
TRAV12-3	T cell receptor alpha variable 12-3	-0.22	0.17	0.39	0.0240	16	12	18	12	15	13	8	8	6	6	0.45	4e-250	0.40	2e-190	0.49	0e+00	0.09	2e-10
RASL11A	RAS-like, family 11, member A	-0.33	0.08	0.41	0.0242	100	63	67	85	95	95	30	33	10	16	-0.17	1e-33	-0.18	4e-39	-0.15	4e-27	0.04	3e-03
OLFM1	olfactomedin 1	-0.14	0.35	0.49	0.0260	157	129	158	107	173	134	64	64	36	48	0.13	1e-19	0.09	3e-11	0.19	5e-41	0.56	0e+00
CEMIP	cell migration inducing protein, hyaluronan binding	-0.15	0.23	0.38	0.0272	29	23	25	21	29	30	50	51	30	28	0.16	1e-29	0.10	7e-14	0.23	9e-63	0.20	2e-48
KAZN	kazrin, periplakin interacting protein	-0.15	0.14	0.29	0.0285	446	361	362	415	501	405	106	85	603	1,004	-0.22	1e-58	-0.22	8e-55	-0.26	1e-78	-0.06	4e-05
AMPH	amphiphysin	-0.06	0.32	0.38	0.0289	37	34	32	30	47	35	227	57	7	13	-0.22	3e-58	-0.22	4e-56	-0.19	9e-43	0.27	5e-85
RAB11FIP4	RAB11 family interacting protein 4 (class II)	-0.16	0.11	0.28	0.0323	113	90	83	91	106	87	31	36	19	23	-0.12	3e-19	-0.12	1e-17	-0.12	4e-17	-0.01	6e-01
MYZAP	myocardial zonula adherens protein	-0.21	0.24	0.44	0.0323	61	46	48	47	66	57	127	128	13	14	-0.10	1e-13	-0.10	3e-13	-0.06	4e-06	0.42	8e-221
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	-0.16	0.26	0.42	0.0367	403	324	276	293	422	397	10	10	8	12	-0.24	2e-69	-0.22	6e-57	-0.20	4e-48	0.16	2e-30
RPL35A	ribosomal protein L35a	-0.19	0.14	0.34	0.0370	159	122	153	128	155	109	6,482	5,672	2,696	3,454	0.16	3e-31	0.12	7e-19	0.14	4e-25	0.20	2e-49

[1] Cohort of 5086 kidney allograft biopsies

Abbreviations: pathogenesis-based transcript set (PBT); antibody-mediated rejection (ABMR); ABMR activity genes (AAG); interferon gamma ABMR activity genes (IIAAG); natural killer (NK) cell-expressed antibody mediated rejection genes (NKAAG); antibody-mediated rejection-associated endothelial genes (AEG); spearman correlation coefficient (SCC).

Supplementary Table 12A. Top 20 differentially expressed genes between baseline and week 52 in biopsies from placebo and felzartamab treated patients (selected by P-value, sorted by ΔΔlogFC)

Gene symbol	Gene	Annotation[1]	Differential expression				Mean expression by group					
							Placebo			Felzartamab		
			Δ placebo logFC	Δ felzartamab logFC	ΔΔ logFC	ΔΔ P*	Baseline (N=10)	Week24 (N=10)	Week52 (N=10)	Baseline (N=10)	Week24 (N=10)	Week52 (N=10)
HNRNPK	heterogeneous nuclear ribonucleoprotein K	injury-induced CKDAKI, AKI2	0.28	-0.38	-0.66	0.0055	818	1,044	1,203	1,096	1,059	649
COL1A1	collagen, type I, alpha 1	COLA1356,FICOL,IRITD5	0.38	-0.26	-0.64	0.0075	310	333	526	329	320	230
NFIX	nuclear factor I/X (CCAAT-binding transcription factor)	Injury induced in AKI	0.42	-0.15	-0.57	0.0012	162	179	289	221	167	180
RHOA	ras homolog family member A	IRRAT950	0.28	-0.29	-0.57	0.0049	691	803	1,017	923	809	620
COL1A2	collagen, type I, alpha 2	FICOL,IRITD5,LivGST_UP	0.26	-0.31	-0.57	0.0118	1,238	1,152	1,769	1,534	1,194	997
ITGB3	integrin beta 3	IRRAT30,IRRAT950	0.34	-0.21	-0.55	0.0100	105	137	169	110	103	82
LOC100129518	uncharacterized LOC100129518	GRIT3,IRRAT950	0.25	-0.22	-0.47	0.0050	429	546	605	527	461	390
ACTB	actin, beta	IRRAT950	0.15	-0.31	-0.47	0.0077	6,451	7,352	7,993	7,274	5,662	4,720
SPARC	secreted protein, acidic, cysteine-rich (osteonectin)	IRITD3	0.16	-0.30	-0.46	0.0100	2,411	2,532	3,011	2,343	2,094	1,550
DNAJA4	DnaJ (Hsp40) homolog, subfamily A, member 4	IRRAT950	0.27	-0.14	-0.42	0.0095	49	68	72	68	61	56
SLFN5	schlafen family member 5	injury-induced CKDAKI, AKI2	0.19	-0.20	-0.40	0.0050	39	44	51	49	38	37
CYR61	cysteine-rich, angiogenic inducer, 61	IRITD3,IRRAT950	0.14	-0.26	-0.40	0.0074	271	268	330	338	234	236
SDCBP	syndecan binding protein	Injury induced CKDAKI, AKI2	0.24	-0.14	-0.38	0.0120	1,135	1,404	1,582	1,478	1,358	1,224
SBSPON	somatomedin B and thrombospondin type 1 domain containing	Injury induced up in CKDAKI	0.31	-0.08	-0.38	0.0123	217	250	332	188	249	169
PAFAH1B2	platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 (30kDa)	injury-induced AKI2	0.23	-0.13	-0.36	0.0099	309	372	423	386	396	323
TMEM2	transmembrane protein 2	Injury induced CKDAKI, AKI2	0.10	-0.26	-0.36	0.0118	270	307	311	318	259	222
WNK1	WNK lysine deficient protein kinase 1	Injury induced up AKI2 down AKI1	0.26	-0.08	-0.34	0.0104	703	884	1,012	894	996	799
DACH2	dachshund family transcription factor 2	Suppressed in AKI2	-0.06	0.26	0.32	0.0106	32	32	29	29	33	42
AADACL4	arylacetamide deacetylase-like 4	Suppressed in AKI	-0.20	0.28	0.49	0.0040	19	13	14	14	15	21
RERGL	RERG/RAS-like	Suppressed in AKI	-0.35	0.30	0.65	0.0048	215	166	133	145	158	221

* All FDR > 0.05

[1] Gene annotations included membership in published pathogenesis-based transcript sets (PBTs) or phenotype associations in published reference sets of kidney transplant biopsies[2,3]

[2].Halloran, P.F., *et al.* Discovering novel injury features in kidney transplant biopsies associated with TCMR and donor aging. *Am J Transplant* **21**, 1725-1739 (2021).

[3].Halloran, P.F., *et al.* Archetypal Analysis of Injury in Kidney Transplant Biopsies Identifies Two Classes of Early AKI. *Front Med (Lausanne)* **9**, 817324 (2022).

Supplementary Table 12B. Top Hinze-defined injury genes differentially-expressed between baseline and week 52 biopsies from placebo and felzartamab treated patients (by P-value)

Gene symbol	**Gene**	**PBT annotation**	**Cellular expression in AKI**[1]	**ΔΔ logFC**	**ΔΔ FC**	**ΔΔ P**	**ΔΔ FDR**	**Mean expression by group**			
								Placebo		**Felzartamab**	
								Baseline (N=10)	**Week52 (N=10)**	**Baseline (N=10)**	**Week52 (N=10)**
SLFN5	schlafen family member 5		CNT-New2,CD-IC-New2	-0.40	0.76	**0.0050**	0.9625	39	51	49	37
CYR61	cysteine-rich, angiogenic inducer, 61	IRITD3,IRRAT950	CNT-New3	-0.40	0.76	**0.0074**	0.9625	271	330	338	236
SPARC	secreted protein, acidic, cysteine-rich (osteonectin)	IRITD3	**PT-New4**	-0.46	0.73	**0.0100**	0.9625	2,411	3,011	2,343	1,550
CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	IRITD3	CNT-New2,CD-IC-New1	-0.33	0.80	**0.0123**	0.9625	419	488	417	307
ADAM10	ADAM metallopeptidase domain 10	IRRAT950	CNT-New3	-0.41	0.75	**0.0148**	0.9625	157	235	210	177
VIM	vimentin	IRITD3,IRRAT950	**PT-New4**,CNT-New3	-0.34	0.79	**0.0244**	0.9625	7,744	9,738	7,479	5,842
LRRFIP1	leucine rich repeat (in FLII) interacting protein 1		CNT-New3,CD-PC-New2	-0.33	0.80	**0.0332**	0.9625	981	1,368	1,092	964
TPM4	tropomyosin 4	IRITD3	CNT-New1	-0.29	0.82	**0.0400**	0.9625	748	1,073	739	709
USP1	dual specificity phosphatase 1	IRRAT950	CNT-New1	-0.34	0.79	**0.0438**	0.9625	317	332	376	247
DOCK11	dedicator of cytokinesis 11		**PT-New4**	-0.34	0.79	**0.0445**	0.9625	301	430	311	277
HLA-DRB1	major histocompatibility complex, class II, DR beta 1	ABMR-RAT,GRIT3	PT-New1,CNT-New2,CD-IC-New2	-0.50	0.71	**0.0447**	0.9625	5,280	5,409	5,462	2,784
KLF6	Kruppel-like factor 6	IRITD3,IRRAT950	PT-New2,**TAL-New4**,DCT-New2,CNT-New3,others	-0.31	0.80	**0.0462**	0.9625	707	794	746	542
NRP1	neuropilin 1	IRRAT950	**DCT-New4**	-0.34	0.79	**0.0489**	0.9625	706	1,000	851	755
RARRES3	retinoic acid receptor responder (tazarotene induced) 3	GRIT3,TCMR-RAT	**PT-New4**,CNT-New2,CD-IC-New2	-0.40	0.76	**0.0493**	0.9625	1,421	1,375	1,664	922
ARL6IP5	ADP-ribosylation factor like GTPase 6 interacting protein 5	IRRAT950	CD-IC-New2	-0.25	0.84	0.0546	0.9625	1,182	1,410	1,454	1,221
FGFR1	fibroblast growth factor receptor 1		DCT-New2,CD-PC-New2,CD-IC-New1	-0.28	0.83	0.0569	0.9625	520	561	466	342
MMP7	matrix metallopeptidase 7	IRITD5	**PT-New4,TAL-New4**,CNT-New1,CD-IC-New2	-0.73	0.60	0.0574	0.9625	4,171	7,983	3,487	2,414
TSC22D1	TSC22 domain family, member 1	IRITD3	TAL-New3,CD-IC-New2	-0.25	0.84	0.0650	0.9625	2,422	2,979	2,793	2,437
WWC1	WW and C2 domain containing 1		**DCT-New4**,CNT-New3	-0.23	0.85	0.0668	0.9625	666	794	823	718
HLA-E	major histocompatibility complex, class I, E	ABMR-RAT, GRIT3	**PT-New4**,TAL-New3,DCT-New3,CNT-New2,others	-0.49	0.71	0.0692	0.9625	4,646	4,731	4,896	2,517

[1] In the genes differentially expressed at week 52 vs. baseline (figure 4), we identified as injury-related genes annotated by Hinze et al, and looked at the single cell expression of the top 20 by p value (Table S12A). All showed decreased expression vs. baseline (ΔΔ FC), 14 significant (ΔΔ P), i.e. blue symbols in figure 4. Seven had been designated in the new injury "new4" pathways that are associated with fibrosis and EMT.

Supplementary Table 13. Functional enrichment analysis of genes affected by felzartamab treatment between baseline and week 52 (by FDR)

library	ID	pathway	interpretation	n genes	NES	FDR	core enrichment genes
Reactome	R-HSA-168249	Innate Immune System	immune-related response to injury	20	-3.18	2e-06	LRRFIP1, C1QB, JUN, ATP6V1A, NCF2, CFI, EP300, FCGR1A, CAPZA1, CAPZA2, ADAM10, HSPA1A, STAT6, CALM2, SDCBP, PAFAH1B2, ACTB, RHOA
Reactome	R-HSA-168256	Immune System	immune-related response to injury	35	-3.08	2e-05	LRRFIP1, C1QB, CANX, JUN, ATP6V1A, RNF213, NCF2, PIK3AP1, VIM, CFI, EP300, FCGR1A, CAPZA1, CAPZA2, ADAM10, HSPA1A, IFNGR1, STAT6, CALM2, SDCBP, COL1A2, PAFAH1B2, ACTB, COL1A1, RHOA
Hinze[1]	AKI	Cellular response to acute kidney injury	response to injury	39	-2.75	4e-05	SPTBN1, NRP1, KLF6, HLA-DRB1, DOCK11, DUSP1, CHSY1, LDHA, CDC42SE2, TPM4, PTBP3, ARHGAP29, SYNE2, SERP1, CORO1C, LRRFIP1, PPFIBP1, CANX, JUN, SCOC, RNF213, SPP1, PIK3AP1, VIM, SVIL, TPM3, RAN, ANXA5, ADAM10, HSPA1A, CEBPB, SPARC, ACTB, HNRNPK, SLFN5, RHOA
Reactome	R-HSA-9006934	Signaling by Receptor Tyrosine Kinases	response to injury	19	-2.59	0.0002	ATP6V1A, SPP1, NCF2, SIN3A, EP300, ADAM10, STAT6, CALM2, COL1A2, SPARC, ITGB3, ACTB, COL1A1, RHOA
Reactome	R-HSA-1643685	Disease	immune-related response to injury	30	-2.68	0.0002	LRRFIP1, PPFIBP1, CANX, JUN, RNF213, CD163, PIK3AP1, TPM3, SIN3A, EP300, FCGR1A, RAN, ADAM10, HSPA1A, IFNGR1, CALM2, CEBPB, SBSPON, ITGB3, ACTB, HNRNPK
Reactome	R-HSA-597592	Post-translational protein modification	response to injury	17	-2.68	0.0002	CANX, SPP1, PRMT3, PPP6R3, SIN3A, EP300, CAPZA1, CAPZA2, ADAM10, CALM2, SBSPON, ACTB, HNRNPK, RHOA
Reactome	R-HSA-109582	Hemostasis	response to injury	17	-2.54	0.0005	SIN3A, CAPZA1, CAPZA2, ANXA5, CALM2, COL1A2, SPARC, ITGB3, ACTB, COL1A1, RHOA
Reactome	R-HSA-5653656	Vesicle-mediated transport	response to injury	15	-2.47	0.0005	SCOC, AP4B1, CD163, PPP6R3, CAPZA1, CAPZA2, CALM2, COL1A2, SPARC, PAFAH1B2, ACTB, COL1A1
Reactome	R-HSA-392499	Metabolism of proteins	response to injury	19	-2.42	0.0005	PRMT3, PPP6R3, SIN3A, EP300, CAPZA1, CAPZA2, ADAM10, CALM2, SBSPON, ACTB, HNRNPK, RHOA
Reactome	R-HSA-5663205	Infectious disease	immune-related response to injury	15	-2.45	0.0005	CANX, JUN, RNF213, CD163, EP300, FCGR1A, RAN, HSPA1A, IFNGR1, CALM2, ACTB, HNRNPK
Reactome	R-HSA-2262752	Cellular responses to stress	response to injury	14	-2.35	0.0008	DNAJB6, EIF2S3, SERP1, JUN, ATP6V1A, NCF2, SIN3A, EP300, CAPZA1, CAPZA2, HSPA1A, CEBPB, DNAJA4
Reactome	R-HSA-8953897	Cellular responses to stimuli	response to injury	14	-2.35	0.0008	DNAJB6, EIF2S3, SERP1, JUN, ATP6V1A, NCF2, SIN3A, EP300, CAPZA1, CAPZA2, HSPA1A, CEBPB, DNAJA4

[1] Hinze, C., et al. Single-cell transcriptomics reveals common epithelial response patterns in human acute kidney injury. Genome Med **14**(1), 103 (2022).

Abbreviations: normalized enrichment score (NES); false discovery rate (FDR)

Supplementary Table 14. Definition of ABMR activity genes

Gene symbol	Gene	PBT annotation	Cell panel expression					Correlation with ABMR in K5086[1]				Correlation with dd-cfDNA in N604[2]	
			NK	CD4	CD8	HUVEC (unstimulated)	HUVEC (IFNg stimulated)	SCC EABMR K5086	p EABMR K5086	SCC FABMR K5086	p FABMR K5086	SCC dd-cfDNA (cp/mL) N604	p dd-cfDNA (cp/mL) N604
FGFBP2	fibroblast growth factor binding protein 2	ABMR-RAT,DSAST	7,651	102	913	11	12	0.46	1e-259	0.48	2e-298	0.47	2e-21
GNLY	granulysin	ABMR-RAT,DSAST,QCAT	11,561	5,121	8,299	35	34	0.38	7e-175	0.46	5e-268	0.52	2e-26
CXCL11	chemokine (C-X-C motif) ligand 11	ABMR-RAT,GRIT3	9	7	7	14	6,842	0.31	4e-112	0.48	9e-290	0.58	5e-35
S1PR5	sphingosine-1-phosphate receptor 5	ABMR-RAT	347	19	18	31	32	0.31	4e-112	0.48	4e-299	0.50	1e-24
PLA1A	phospholipase A1 member A	ABMR-RAT,DSAST,GRIT3	18	13	15	17	545	0.29	1e-100	0.63	0e+00	0.58	2e-34
CXCL10	chemokine (C-X-C motif) ligand 10	ABMR-RAT,GRIT1	20	21	18	32	9,860	0.29	4e-98	0.45	3e-251	0.58	2e-34
CXCL9	chemokine (C-X-C motif) ligand 9	ABMR-RAT,GRIT1	27	18	23	41	11,888	0.29	5e-97	0.47	3e-275	0.58	8e-34
CCL4L1	chemokine (C-C motif) ligand 4-like 1	ABMR-RAT						0.28	6e-90	0.44	2e-239	0.54	4e-29
KLRD1	killer cell lectin-like receptor subfamily D, member 1	ABMR-RAT	1,465	22	119	26	22	0.28	2e-89	0.47	1e-283	0.55	5e-30
CCL4	chemokine (C-C motif) ligand 4	ABMR-RAT	3,200	266	1,977	35	30	0.27	2e-85	0.49	3e-308	0.60	5e-37
CCL3	chemokine (C-C motif) ligand 3	ABMR-RAT	622	243	2,098	18	15	0.26	2e-80	0.41	3e-210	0.55	7e-31
WARS	tryptophanyl-tRNA synthetase	ABMR-RAT,GRIT3	344	337	302	910	10,642	0.26	2e-78	0.49	0e+00	0.62	4e-41
NKG7	natural killer cell granule protein 7	ABMR-RAT,QCAT	8,535	369	3,138	21	25	0.26	1e-76	0.42	2e-222	0.50	5e-24
PRF1	perforin 1 (pore forming protein)	ABMR-RAT,QCAT	6,787	598	1,344	50	60	0.26	2e-76	0.49	7e-300	0.55	1e-30
GZMB	granzyme B	ABMR-RAT,QCAT	10,203	1,634	4,546	15	19	0.25	4e-74	0.45	2e-247	0.57	2e-32
GBP1	guanylate binding protein 1, interferon-inducible	ABMR-RAT,GRIT3	742	617	529	153	6,985	0.24	7e-68	0.44	1e-241	0.58	2e-34
IDO1	indoleamine 2,3-dioxygenase 1	ABMR-RAT,GRIT3	38	35	31	47	9,620	0.24	3e-66	0.48	4e-299	0.58	4e-35
GBP4	guanylate binding protein 4	ABMR-RAT,GRIT1,GRIT3	270	130	101	31	1,721	0.23	2e-63	0.49	7e-301	0.54	8e-29
RARRES3	retinoic acid receptor responder (tazarotene induced) 3	GRIT3,TCMR-RAT	3,162	1,403	1,427	44	3,157	0.23	3e-63	0.34	4e-136	0.50	2e-24
GZMH	granzyme H	RAT	7,166	90	1,351	27	24	0.23	2e-62	0.34	5e-135	0.39	2e-14
							average	0.28		0.46		0.54	

[1] Cohort of 5086 kidney allograft biopsies. Halloran, P.F., *et al.* Subthreshold rejection activity in many kidney transplants currently classified as having no rejection. *Am J Transplant* **in press**, (2024).

[2] Cohort of 604 kidney allograft biopsies and paired blood samples for donor-derived cell-free DNA (dd-cfDNA) testing. Gauthier et al. Distinct Molecular Processes Mediate Donor-derived Cell-free DNA Release From Kidney Transplants in Different Disease States. Transplantation **108**, 898-910 (2023).

Abbreviations: pathogenesis-based transcript set (PBT); natural killer (NK); antibody-mediated rejection (ABMR); early ABMR (EABMR); human umbilical vein endothelial cell (HUVEC); interferon gamma (IFNg); spearman correlation coefficient (SCC).

Supplementary Table 15. IFNG-inducible ABMR activity genes

Gene symbol	Gene	PBT annotation	Cell panel expression					Correlation with ABMR in K5086[1]				Correlation with dd-cfDNA in N604[2]	
			NK	CD4	CD8	HUVEC (unstimulated)	HUVEC (IFNg stimulated)	SCC EABMR K5086	p EABMR K5086	SCC FABMR K5086	p FABMR K5086	SCC dd-cfDNA (cp/mL) N604	p dd-cfDNA (cp/mL) N604
CXCL9	chemokine (C-X-C motif) ligand 9	ABMR-RAT,GRIT1	27	18	23	41	11,888	0.29	5e-97	0.47	3e-275	0.58	8e-34
WARS	tryptophanyl-tRNA synthetase	ABMR-RAT,GRIT3,	344	337	302	910	10,642	0.26	2e-78	0.49	0e+00	0.62	4e-41
CXCL10	chemokine (C-X-C motif) ligand 10	ABMR-RAT,GRIT1	20	21	18	32	9,860	0.29	4e-98	0.45	3e-251	0.58	2e-34
IDO1	indoleamine 2,3-dioxygenase 1	ABMR-RAT,GRIT3,	38	35	31	47	9,620	0.24	3e-66	0.48	4e-299	0.58	4e-35
GBP1	guanylate binding protein 1, interferon-inducible	ABMR-RAT,GRIT3,	667	752	598	127	8,616	0.24	7e-68	0.44	1e-241	0.58	2e-34
CXCL11	chemokine (C-X-C motif) ligand 11	ABMR-RAT,GRIT3,	9	6	6	12	7,317	0.31	4e-112	0.48	9e-290	0.58	5e-35
IL18BP	interleukin 18 binding protein	GRIT1,TCMR-RAT	168	70	67	70	3,270	0.22	1e-55	0.41	6e-200	0.50	8e-25
GBP4	guanylate binding protein 4	ABMR-RAT,GRIT3,	270	130	101	31	1,721	0.23	2e-63	0.49	7e-301	0.54	8e-29
PLA1A	phospholipase A1 member A	ABMR-RAT, DSAST,GRIT3,	18	13	15	17	545	0.29	1e-100	0.63	0e+00	0.58	2e-34
CX3CL1	chemokine (C-X3-C motif) ligand 1	ABMR-RAT,IRITD3	24	27	22	22	183	0.23	9e-61	0.49	0e+00	0.44	2e-18
							average	0.26		0.48		0.56	

[1] Cohort of 5086 kidney allograft biopsies. Halloran, P.F., *et al.* Subthreshold rejection activity in many kidney transplants currently classified as having no rejection. *Am J Transplant* **in press**, (2024).

[2] Cohort of 604 kidney allograft biopsies and paired blood samples for donor-derived cell-free DNA (dd-cfDNA) testing. Gauthier et al. Distinct Molecular Processes Mediate Donor-derived Cell-free DNA Release From Kidney Transplants in Different Disease States. Transplantation **108**, 898-910 (2023).

Abbreviations: pathogenesis-based transcript set (PBT); natural killer (NK); antibody-mediated rejection (ABMR); early ABMR (EABMR); human umbilical vein endothelial cell (HUVEC); interferon gamma (IFNg); spearman correlation coefficient (SCC).

Supplementary Table 16. Definition of NK cell-expressed ABMR activity genes

Gene symbol	Gene	PBT annotation	Cell panel expression					Correlation with ABMR in K5086[1]				Correlation with dd-cfDNA in N604[2]	
			NK	CD4	CD8	HUVEC (unstimulated)	HUVEC (IFNg stimulated)	SCC EABMR K5086	p EABMR K5086	SCC FABMR K5086	p FABMR K5086	SCC dd-cfDNA (cp/mL) N604	p dd-cfDNA (cp/mL) N604
PRF1	perforin 1 (pore forming protein)	ABMR-RAT,QCAT	16,872	2,596	4,955	50	56	0.26	2e-76	0.49	7e-300	0.55	1e-30
GNLY	granulysin	ABMR-RAT,DSAST,QCAT	11,561	5,121	8,299	35	34	0.38	7e-175	0.46	5e-268	0.52	2e-26
GZMB	granzyme B	ABMR-RAT,QCAT	10,203	1,634	4,546	15	19	0.25	4e-74	0.45	2e-247	0.57	2e-32
TRDC	T cell receptor delta constant	ABMR-RAT	9,333	214	372	19	20	0.21	3e-52	0.47	2e-280	0.48	2e-22
NKG7	natural killer cell granule protein 7	ABMR-RAT,QCAT	8,535	369	3,138	21	25	0.26	1e-76	0.42	2e-222	0.50	5e-24
FGFBP2	fibroblast growth factor binding protein 2	ABMR-RAT,DSAST	7,651	102	913	11	12	0.46	1e-259	0.48	2e-298	0.47	2e-21
CST7	cystatin F (leukocystatin)	ABMR-RAT,QCAT	7,421	2,469	2,904	22	28	0.18	8e-38	0.41	1e-203	0.49	3e-23
KLRF1	killer cell lectin-like receptor subfamily F, member 1	ABMR-RAT,DSAST,NKB	7,393	21	16	8	11	0.22	2e-54	0.49	0e+00	0.44	1e-18
GZMH	granzyme H	RAT	7,166	90	1,351	27	24	0.23	2e-62	0.34	5e-135	0.39	2e-14
KLRD1	killer cell lectin-like receptor subfamily D, member 1	ABMR-RAT	6,493	49	754	22	36	0.28	2e-89	0.47	1e-283	0.55	5e-30
SH2D1B	SH2 domain containing 1B	ABMR-RAT,DSAST,NKB	5,392	10	13	17	16	0.20	5e-45	0.50	0e+00	0.38	4e-14
S1PR5	sphingosine-1-phosphate receptor 5	ABMR-RAT	3,808	22	32	29	27	0.31	4e-112	0.48	4e-299	0.50	1e-24
XCL1	chemokine (C motif) ligand 1	ABMR-RAT	3,683	242	1,491	23	32	0.22	1e-54	0.45	3e-249	0.49	2e-23
CCL4	chemokine (C-C motif) ligand 4	ABMR-RAT	3,200	266	1,977	35	30	0.27	2e-85	0.49	3e-308	0.60	5e-37
FGR	FGR proto-oncogene, Src family tyrosine kinase	cIRIT	3,104	33	48	57	46	0.16	7e-32	0.43	8e-228	0.49	1e-23
CD160	CD160 molecule	ABMR-RAT	1,833	14	23	18	21	0.20	3e-45	0.42	1e-213	0.37	1e-13
TBX21	T-box 21	ABMR-RAT	1,803	165	408	35	41	0.22	9e-58	0.47	1e-280	0.47	2e-21
KIR2DL2	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 2		1,563	26	38	40	37	0.19	1e-43	0.32	5e-121	0.26	3e-07
KLRC3	killer cell lectin-like receptor subfamily C, member 3	ABMR-RAT	1,317	11	273	11	11	0.18	3e-40	0.42	8e-213	0.40	3e-15
KIR2DL3	killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 3		1,293	29	33	48	41	0.19	4e-41	0.25	3e-72	0.23	6e-06
							mean	0.24		0.44		0.46	

[1] Cohort of 5086 kidney allograft biopsies. Halloran, P.F., *et al.* Subthreshold rejection activity in many kidney transplants currently classified as having no rejection. *Am J Transplant* **in press**, (2024).

[2] Cohort of 604 kidney allograft biopsies and paired blood samples for donor-derived cell-free DNA (dd-cfDNA) testing. Gauthier et al. Distinct Molecular Processes Mediate Donor-derived Cell-free DNA Release From Kidney Transplants in Different Disease States. Transplantation **108**, 898-910 (2023).

Abbreviations: pathogenesis-based transcript set (PBT); natural killer (NK); antibody-mediated rejection (ABMR); early ABMR (EABMR); human umbilical vein endothelial cell (HUVEC); interferon gamma (IFNg); spearman correlation coefficient (SCC).

Supplementary Table 17. ABMR-associated endothelial genes

Gene symbol	Gene	PBT annotation	Cell panel expression					Correlation with ABMR in K5086[1]				Correlation with dd-cfDNA in N604[2]	
			NK	CD4	CD8	HUVEC (unstimulated)	HUVEC (IFNg stimulated)	SCC EABMR K5086	p EABMR K5086	SCC FABMR K5086	p FABMR K5086	SCC dd-cfDNA (cp/mL) N604	p dd-cfDNA (cp/mL) N604
GNG11	guanine nucleotide binding protein (G protein), gamma 11	ABMR-RAT,DSAST	66	23	25	5,182	4,144	-0.01	4e-01	0.45	6e-256	0.23	5e-06
PECAM1	platelet/endothelial cell adhesion molecule 1	ABMR-RAT,ENDAT,IRRAT950	344	105	350	3,178	3,034	-0.01	6e-01	0.41	2e-202	0.41	7e-16
CDH5	cadherin 5, type 2 (vascular endothelium)	ABMR-RAT,DSAST, ENDAT	19	17	17	2,845	2,224	0.14	2e-24	0.46	3e-260	0.37	3e-13
ECSCR	endothelial cell surface expressed chemotaxis and apoptosis regulator	ABMR-RAT,cIRIT	17	40	38	2,710	2,493	0.03	2e-02	0.47	2e-272	0.37	2e-13
ROBO4	roundabout guidance receptor 4	ABMR-RAT,DSAST	27	43	41	1,694	1,486	0.20	2e-47	0.55	0e+00	0.38	7e-14
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog		19	10	11	1,038	995	-0.02	2e-01	0.42	7e-217	0.22	2e-05
MALL	mal, T-cell differentiation protein-like	ABMR-RAT,DSAST	29	23	27	802	360	0.11	5e-15	0.46	2e-269	0.36	2e-12
RASIP1	Ras interacting protein 1	ABMR-RAT,ENDAT	43	26	38	635	446	0.06	3e-06	0.50	0e+00	0.16	3e-03
TEK	TEK tyrosine kinase, endothelial	ABMR-RAT,DSAST, ENDAT	12	10	11	567	367	0.07	1e-07	0.40	7e-197	0.09	7e-02
MMRN2	multimerin 2	ABMR-RAT	10	8	10	539	453	0.04	1e-02	0.43	7e-223	0.18	6e-04
TM4SF18	transmembrane 4 L six family member 18	ABMR-RAT,DSAST	15	14	16	415	389	-0.01	3e-01	0.40	5e-198	0.28	5e-08
RAPGEF5	Rap guanine nucleotide exchange factor 5	ABMR-RAT	13	17	29	301	151	0.09	1e-10	0.43	1e-229	0.30	8e-09
NOS3	nitric oxide synthase 3 (endothelial cell)	ENDAT	42	27	24	209	181	0.08	8e-09	0.42	8e-212	0.25	1e-06
CDH13	cadherin 13	ABMR-RAT,DSAST	11	9	10	127	125	-0.05	4e-04	0.41	7e-206	0.30	5e-09
							average	0.05		0.44		0.28	

[1] Cohort of 5086 kidney allograft biopsies. Halloran, P.F., *et al.* Subthreshold rejection activity in many kidney transplants currently classified as having no rejection. *Am J Transplant* **in press**, (2024).

[2] Cohort of 604 kidney allograft biopsies and paired blood samples for donor-derived cell-free DNA (dd-cfDNA) testing. Gauthier et al. Distinct Molecular Processes Mediate Donor-derived Cell-free DNA Release From Kidney Transplants in Different Disease States. Transplantation **108**, 898-910 (2023).

Abbreviations: pathogenesis-based transcript set (PBT); natural killer (NK); antibody-mediated rejection (ABMR); early ABMR (EABMR); human umbilical vein endothelial cell (HUVEC); interferon gamma (IFNg); spearman correlation coefficient (SCC).