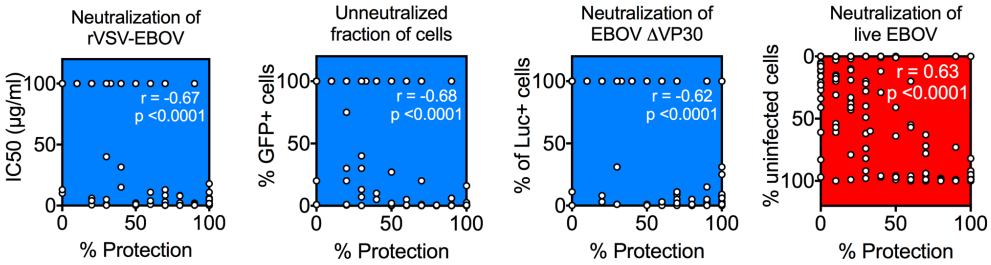
A.



B.

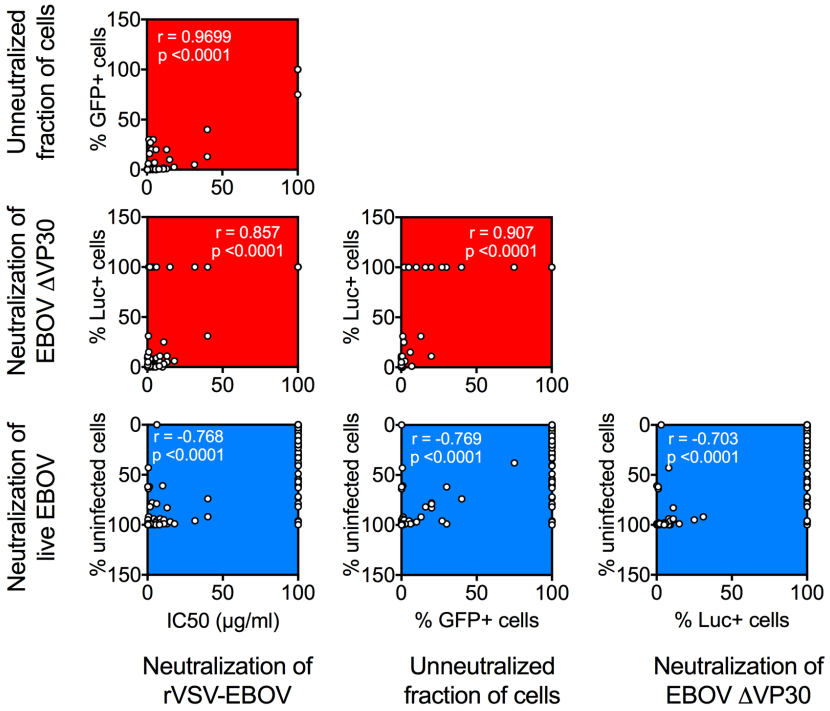


Figure S1. Neutralization activity is associated with mAb-mediated protection, related to Figure 3.

A. Spearman rho correlation analyses was used to determine significant associations between neutralizing activity in the four neutralization readouts and protection. Red background of graph indicates a significant positive association, a blue background indicates a significant negative association, and a white background indicates no significant association.

B. Spearman rho correlation analyses was used to determine if neutralization assays are correlated with each other. Red background of graph indicates a significant positive association, a blue background indicates a significant negative association, and a white background indicates no significant association.

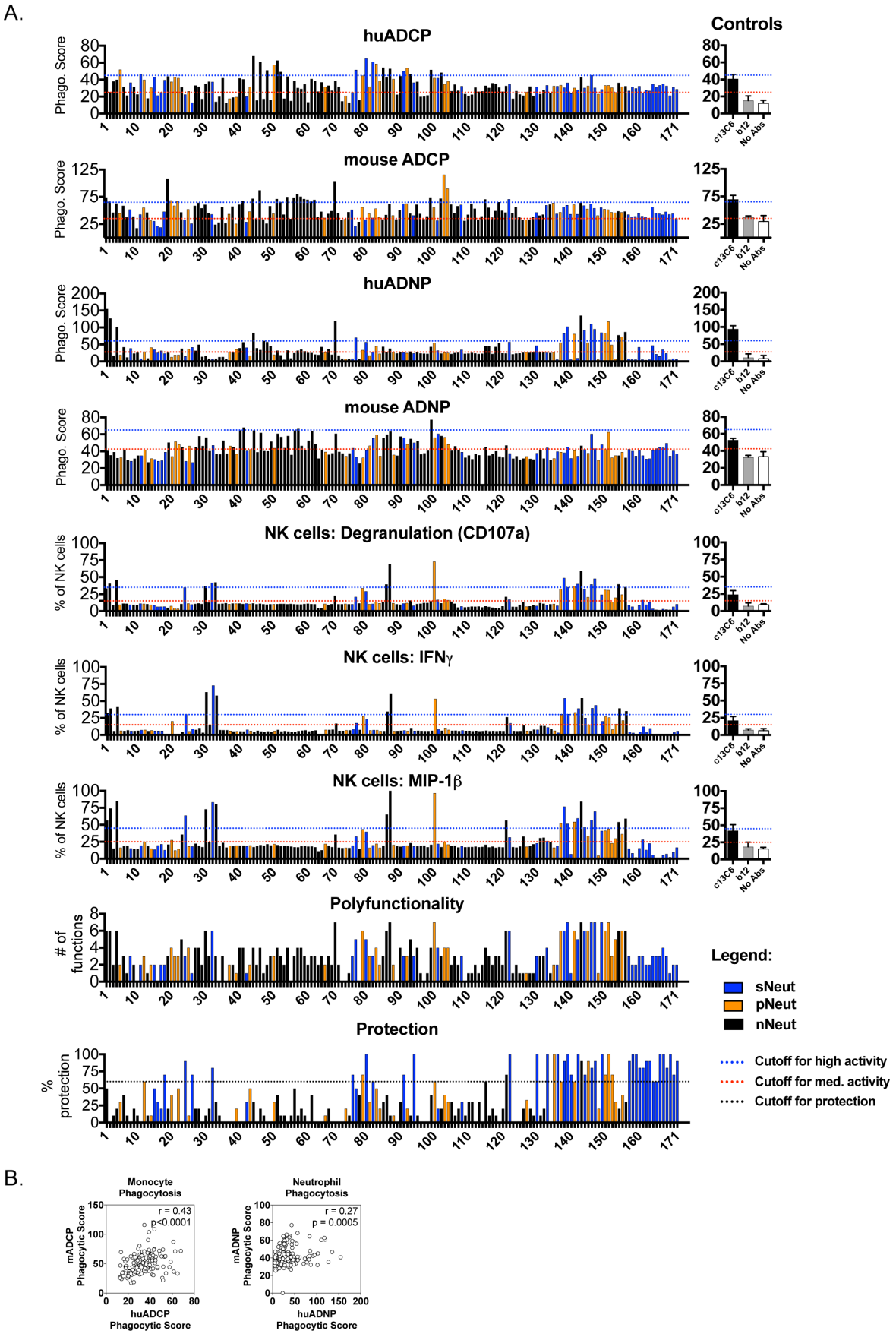
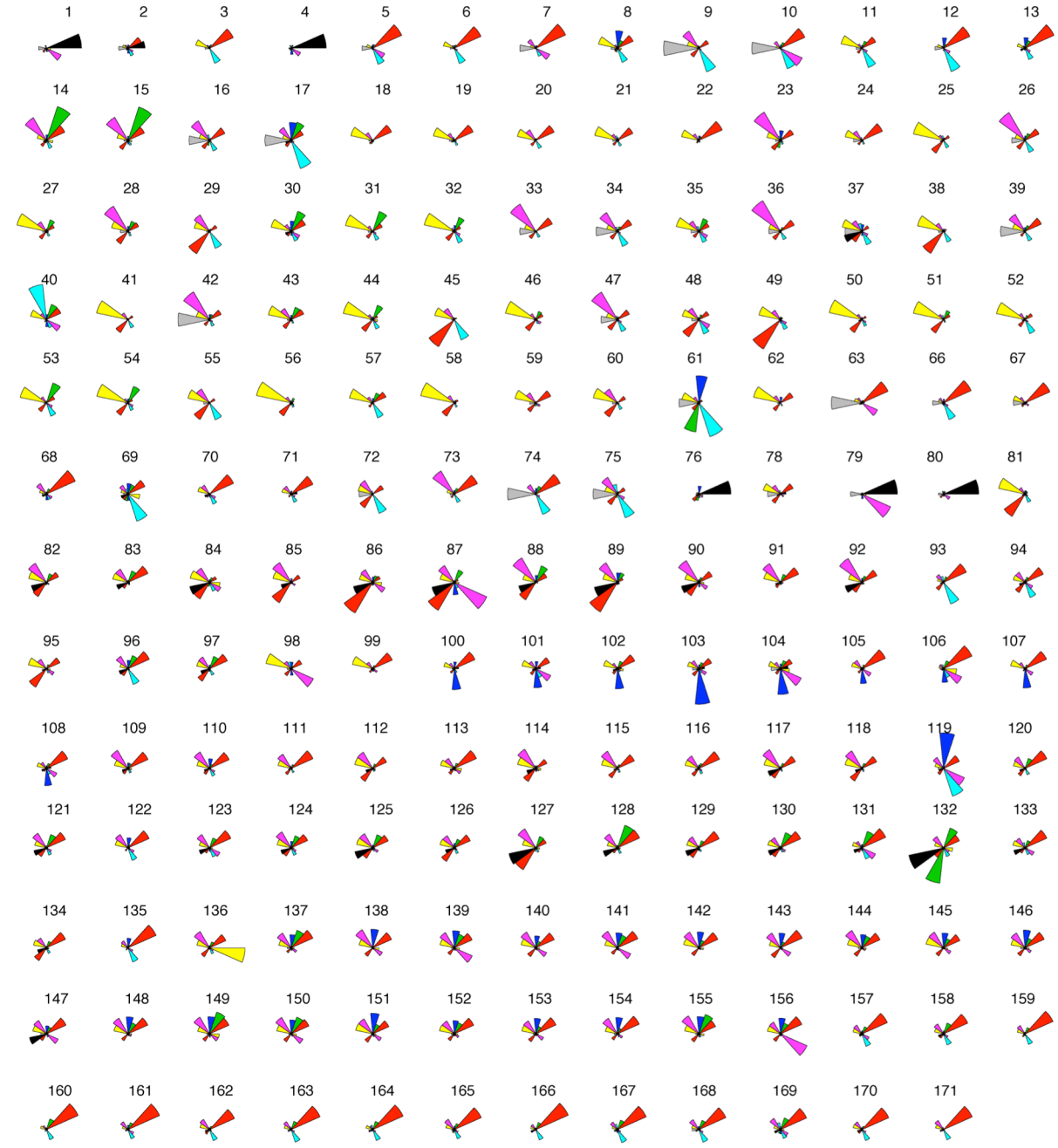


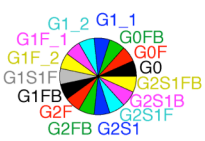
Figure S2. Raw data of VIC functional assays and protection, related to Figure 2.
Legend continued on next page.

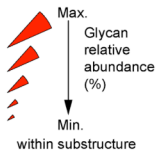
Figure S2. Raw data of VIC functional assays and protection, related to Figure 2 (con't).

A. The averaged raw values of technical duplicates for all VIC mAbs in each Fc-effector function assay, the number of functions (polyfunctionality), and protection are graphed. The color of each bar indicates the neutralization group (blue = sNeut; orange = pNeut; black = nNeut). The positive controls for each assay are graphed on the right (positive control = c13C6; negative control = b12 and no Abs). The cutoffs to define levels of functional activity are shown as dashed lines across the graphs (high activity = scores above blue dashed line; medium activity = scores between blue and red dashed lines; no activity = scores below dashed red line). The cutoff for protection is indicated with a black dashed line and is set at 60%.

B. Spearman rho correlation analyses was used to determine associations between the phagocytic scores of VIC mAbs in either mouse or human monocytes (left) or human and mouse neutrophils (right).







Glycan Structure

	G1_1	G0FB	G0F	G0	G2S1FB	G2S1B	G2S1F	G2S1
Minimum (%)	0.01	0.01	1.62	0	0	0.01	0	0.01
Maximum (%)	4.53	4.41	73.82	84.27	7.7	2.76	24.93	11.67

Glycan Structure

	G2FB	G2F	G1FB	G1S1F	G1F_2	G1F_1	G1_2
Minimum (%)	0.01	0.4	0	0.01	0.01	0.02	0.02
Maximum (%)	8.86	33.3	4.55	12.39	66.43	23.55	15.46

Figure S3. Fc glycan composition of each VIC mAb, related to Figure 3.

The relative abundance (%) of the indicated glycan structures on each VIC mAb was determined, and plotted by mAb in a star plot. Each wedge is color coded by the indicated glycan structure, and the size of the wedge corresponds to the abundance of that structure compared to the rest of the mAbs within the VIC. The table indicates the minimum and maximum relative abundance (%) of each glycan.

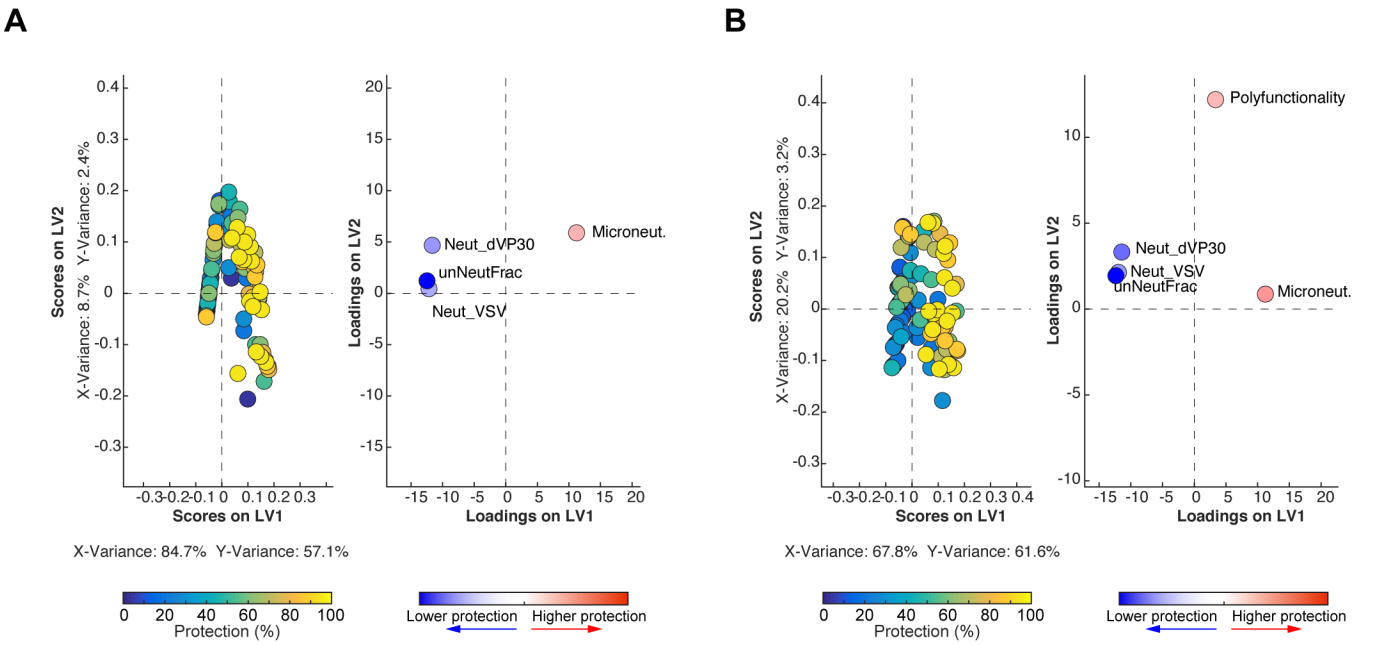


Figure S4. Neutralization and polyfunctionality can separate protective and non-protective mAbs, related to Figure 3.

Elastic Net/PLSR analysis of **(A)** neutralizing antibody features alone, or **(B)** neutralization and polyfunctionality features together. Each dot on the left graphs represents a different antibody, and are color coded to represent protective mAbs (green-yellow dots on left graph) from non-protective mAbs (light-dark blue dots). The mirror loadings plot (right graphs) show the features that drive the geographic location of the dots on the left graph. Features are color coded by importance to positively predicting protection (red) or negatively predicting protection (blue) as determined by variable influence on projection.

	PC1	PC2	PC3	PC4	PC5
NK cells: CD107a	0.981	-0.115	-0.153	0.033	-0.022
NK cells: IFNγ	0.966	-0.196	-0.130	0.102	0.015
NK cells: MIP-1β	0.960	-0.019	-0.246	-0.130	0.006
ADNP	0.762	-0.168	0.625	-0.024	0.000
ADCP	0.531	0.844	0.068	0.021	0.001

Table S1. Loading matrix for PCA of functionality of neutralizing and non-neutralizing Ebola-specific mAbs, related to Figure 1.

Loading matrix of functional features associated with principal components 1-5 (PC1-5) for Ebola-specific neutralizing and non-neutralizing mAbs.

Antibody features measured	
Epitope	Glycan: total G0
Binding affinity to GP (GP_EC50)	Glycan: total G1
Binding affinity to sGP (sGP_EC50)	Glycan: total G2
Cross reactivity	Glycan: total fucose
Subclass (huIgG1, huIgG3, mIgG1, mIgG2a, mIgG2b)	Glycan: total bisecting GlcNAc
Species (human, mouse)	Glycan: total sialic acid
Neutralization: rVSV-EBOV	Glycan: G0
Neutralization: Unneut. Fraction	Glycan: G0F
Neutralization: EBOVΔVP30	Glycan: G0FB
Neutralization: microneutralization (Microneut.)	Glycan: G1 (G1_1)
Effector function: human ADCP (huADCP)	Glycan: G1' (G1_2)
Effector function: mouse ADCP (mADCP)	Glycan: G1F (G1F_1)
Effector function: human ADNP (huADNP)	Glycan: G1F' (G1F_2)
Effector function: mouse ADNP (mADNP)	Glycan: G1FB
Effector function: NK cells CD107a	Glycan: G1S1F
Effector function: NK cells IFNγ (IFNγ)	Glycan: G1FB
Effector function: NK cells MIP-1β (MIP-1β)	Glycan: G2F
Effector function: polyfunctionality	Glycan: G2FB
	Glycan: G2S1
	Glycan: G2S1B
	Glycan: G2S1FB

Table S2. The antibody features measured through the VIC, related to Figure 3.
Abbreviations used in PLSR models are in parentheses.

		Activity in neutralization assay		
Neutralization assay	**Metric**	**High**	**Med/Low**	**None**
Neutralization of rVSV-EBOV GFP	IC50 µg/ml	≤5	>5-50	>50
Unneutralized fraction of rVSV-EBOV GFP	% GFP+ cells	<2%	≥2%-75%	>75%
Neutralization of EBOV ΔVP30-Luc	% Luc+ cells	≤5%	5%-50%	>50%
Microneutralization of EBOV	% uninfected cells	≥80%	35%-79%	<35%

Table S3. Neutralization parameters used to define neutralization categories, related to Figure 4.

The neutralizing activity of the VIC mAbs was evaluated in three neutralization assays, with four readouts of neutralization. Each mAbs was categorized into high, medium/low, and no activity according to assay standards.

sNeuts		pNeuts	nNeuts		
8	159	5	1	54	107
11	160	12	2	55	109
15	161	14	3	56	110
16	162	20	4	57	111
17	163	21	6	58	112
18	164	22	7	59	113
24	165	25	9	60	114
26	166	37	10	61	115
32	167	39	13	62	116
42	168	43	19	63	117
75	169	50	23	66	118
76	170	67	27	68	119
80	171	73	28	69	120
82		79	29	70	121
91		81	30	71	123
94		83	31	72	124
101		84	33	74	125
108		88	34	78	126
130		92	35	85	128
133		100	36	86	129
136		103	38	87	131
138		104	40	89	132
139		122	41	90	134
140		127	44	93	143
142		137	45	95	154
144		141	46	96	156
146		145	47	97	
147		148	48	98	
149		150	49	99	
157		151	51	102	
158		152	52	105	
		153	53	106	
		155			

Table S4. VIC mAbs in the sNeut, pNeut, or nNeut categories, related to Figure 4.

The VIC mAbs that were classified into the sNeut, pNeut, or nNeut categories according to the parameters defined by Table S3 and graphed in Figure 4A.

	All mAbs	Neut. only	Neut. and function	sNeut	pNeut	nNeut	IFNγ	mADCP
Figure	3	S4A	S4B	5A	5B	5C	6E	6F
# of features	10	4	5	5	3	6	8	7
Calibration RMSE	0.537	0.618	0.576	0.508	0.602	0.866	0.85	0.754
Calibration R^2	0.71	0.615	0.667	0.735	0.627	0.241	0.274	0.428
Leave-1-Out CV RMSE	0.565	0.642	0.604	0.617	0.648	0.925	0.881	0.788
Leave-1-Out CV R^2	0.679	0.585	0.633	0.618	0.567	0.143	0.221	0.377

Table S5. Cross-validation statistics for PLSR models related to Figures 3, 5, and 6, and Supplemental Figure S4.