Table S1. Summary of the preliminary evaluation of model performance for predicting ACE2 affinity and % human antibody escape using different types of models and featurization methods. Three types of featurization methods were used, namely one-hot encoding (OHE), biophysical descriptors, and amino acid indices. The details of the feature types and values are summarized in Table S2. Nine types of models were tested, namely ordinary least squares regression, Lasso, Bayesian Ridge, stochastic gradient descent (SGD), gaussian process classifier (GPC), kernel Ridge (radial basis function (RBF) and linear kernels), and elastic net. The average training and test Spearman's ρ values for each model trained with each type of feature set are reported based on 5-fold cross-validation. Based on this analysis, the Ridge Regression models trained with one-hot encoded features were further optimized and exclusively used in the remainder of this manuscript.

ACE2 affinity models		
One hot encoding	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.94	0.93
Ordinary least squares	0.93	0.81
Lasso	0.94	0.92
Bayesian Ridge	0.94	0.93
SGD	0.84	0.81
GPR	0.99	0.57
Kernel Ridge (RBF)	0.62	0.6
Kernel Ridge (Linear)	0.93	0.85
Elastic Net	0.93	0.89
Biophysical descriptors	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.85	0.84
Ordinary least squares	0.84	0.79
Lasso	0.94	0.93
Bayesian Ridge	0.84	0.79
SGD	0	0
GPR	0.99	0.34
Kernel Ridge (RBF)	0.77	0.74
Kernel Ridge (Linear)	0.77	0.74
Elastic Net	0.84	0.8
Amino acid indices	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.88	0.87
Ordinary least squares	0.87	0.81
Lasso	0.88	0.87
Bayesian Ridge	0.87	0.86
SGD	0.04	0.04
GPR	0.99	0.33
Kernel Ridge (RBF)	0.65	0.48
Kernel Ridge (Linear)	0.86	0.82
Elastic Net	0.87	0.82
Combined feature sets	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.94	0.92

Human serum antibody escape models		
One hot encoding	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.69	0.66
Ordinary least squares	0.67	0.45
Lasso	0.68	0.66
Bayesian Ridge	0.69	0.66
SGD	0.58	0.56
GPR	0.99	0.04
Kernel Ridge (RBF)	0.47	0.45
Kernel Ridge (Linear)	0.69	0.5
Elastic Net	0.64	0.57
Biophysical descriptors	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.64	0.62
Ordinary least squares	0.64	0.62
Lasso	0.63	0.62
Bayesian Ridge	0.63	0.62
SGD	0	0.1
GPR	0.99	-0.24
Kernel Ridge (RBF)	0.58	0.52
Kernel Ridge (Linear)	0.61	0.52
Elastic Net	0.61	0.53
Amino acid indices	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.65	0.63
Ordinary least squares	0.65	0.63
Lasso	0.64	0.63
Bayesian Ridge	0.65	0.63
SGD	-0.01	0
GPR	N/A	N/A
Kernel Ridge (RBF)	0.8	0.01
Kernel Ridge (Linear)	0.62	0.56
Elastic Net	0.65	0.63
Combined feature sets	Training data Spearman's ρ	Test data Spearman's ρ
Ridge Regression	0.69	0.64