

Table S2. Interacting residue pair prediction performance for each protein-protein complex and characterization of each complex into enzyme, antibody, conformational change (RMSD) and interface size ( $\Delta$ ASA).

| Complex name | Difficulty level | Protein-1                  | Protein-2                     | RMSD ( $\text{\AA}$ ) | $\Delta$ ASA ( $\text{\AA}^2$ ) | AUC  | Category |
|--------------|------------------|----------------------------|-------------------------------|-----------------------|---------------------------------|------|----------|
| 1A2K_C_AB    | RB               | Ran GTPase                 | Nuclear transport factor 2    | 1.11                  | 1603                            | 0.63 | O        |
| 1ACB_E_I     | Medium           | Chymotrypsin               | Eglin C                       | 2.26                  | 1544                            | 0.78 | E        |
| 1AHW_AB_C    | RB               | Fab 5g9                    | Tissue factor                 | 0.69                  | 1899                            | 0.94 | A/B      |
| 1AK4_A_D     | RB               | Cyclophilin                | HIV capsid                    | 1.33                  | 1029                            | 0.74 | O        |
| 1AKJ_AB_DE   | RB               | MHC Class 1 HLA-A2         | T-cell CD8 coreceptor         | 1.14                  | 1995                            | 0.70 | O        |
| 1ATN_A_D     | Difficult        | Actin                      | Dnase I                       | 3.28                  | 1774                            | 0.55 | O        |
| 1AVX_A_B     | RB               | Porcine trypsin            | Soybean trypsin inhibitor     | 0.47                  | 1585                            | 0.82 | E        |
| 1AY7_A_B     | RB               | Barnase                    | Barstar                       | 0.54                  | 1237                            | 0.77 | E        |
| 1AZS_AB_C    | RB               | Adenylyl cyclase           | AC activator Gs alpha complex | 0.72                  | 1911                            | 0.69 | O        |
| 1B6C_A_B     | RB               | FKBP binding protein       | TGFbeta receptor              | 1.96                  | 1752                            | 0.61 | O        |
| 1BGX_HL_T    | Medium           | Fab                        | Taq polymerase                | 1.48                  | 5814                            | 0.73 | A/B      |
| 1BJ1_HL_VW   | RB               | Fab                        | vEGF                          | 0.5                   | 1731                            | 0.96 | A/B      |
| 1BKD_R_S     | Difficult        | Ras GTPase                 | Son of Sevenless              | 2.86                  | 3163                            | 0.65 | O        |
| 1BUH_A_B     | RB               | CDK2 kinase                | Ckshs1                        | 0.75                  | 1324                            | 0.70 | O        |
| 1BVK_DE_F    | RB               | Fv Hulys11                 | HEW lysozyme                  | 1.24                  | 1321                            | 0.86 | A/B      |
| 1BVN_P_T     | RB               | alpha-amylase              | Tendamistat                   | 0.87                  | 2222                            | 0.76 | E        |
| 1CGL_E_I     | RB               | Bovine chymotrypsinogen    | PSTI                          | 2.02                  | 2053                            | 0.78 | E        |
| 1D6R_A_I     | RB               | Bovine trypsin             | Bowman-Birk inhibitor         | 1.14                  | 1408                            | 0.79 | E        |
| 1DE4_AB_CF   | Difficult        | beta2-microglobulin        | Transferrin receptor ectodom. | 2.59                  | 2066                            | 0.59 | O        |
| 1DFJ_E_I     | RB               | Ribonuclease A             | Rnase inhibitor               | 1.02                  | 2582                            | 0.88 | E        |
| 1DQJ_AB_C    | RB               | Fab Hyhel63                | HEW lysozyme                  | 0.75                  | 1765                            | 0.93 | A/B      |
| 1E4K_AB_C    | Difficult        | FC fragment of human IgG 1 | Human FCGR III                | 2.59                  | 1634                            | 0.69 | A/B      |
| 1E6E_A_B     | RB               | Adrenoxin reductase        | Adrenoxin                     | 1.33                  | 2315                            | 0.56 | E        |
| 1E6J_HL_P    | RB               | Fab                        | HIV-1 capsid protein p24      | 1.05                  | 1245                            | 0.90 | A/B      |

|             |           |                               |                                 |      |      |      |     |
|-------------|-----------|-------------------------------|---------------------------------|------|------|------|-----|
| IE96_A_B    | RB        | Rac GTPase                    | p67 Phox                        | 0.71 | 1179 | 0.80 | O   |
| IEAW_A_B    | RB        | Matriptase                    | BPTI                            | 0.54 | 1866 | 0.79 | E   |
| IEER_A_BC   | Difficult | Erythropoietin                | EPO receptor                    | 2.44 | 3347 | 0.69 | O   |
| IEFN_B_A    | RB        | HIV-1-NEF protein             | SH3 domain                      | 0.77 | 1254 | 0.67 | O   |
| IEWY_A_C    | RB        | Ferredoxin reductase          | Ferredoxin                      | 0.8  | 1502 | 0.71 | E   |
| IEZU_C_AB   | RB        | D102N Trypsin                 | Ecotin                          | 1.21 | 2751 | 0.85 | E   |
| IF34_A_B    | RB        | Porcine pepsin                | Ascaris inhibitor 3             | 0.93 | 3038 | 0.75 | E   |
| IF51_AB_E   | RB        | Sporulation response factor B | Sporulation response factor F   | 0.74 | 2407 | 0.66 | O   |
| IFAK_HL_T   | Difficult | Coagulation factor VIIa       | Soluble tissue factor           | 6.18 | 3363 | 0.65 | O   |
| IFC2_C_D    | RB        | Staphylococcus Protein A      | Human Fc fragment               | 1.69 | 1307 | 0.69 | O   |
| IFQ1_A_B    | Difficult | CDK2 kinase                   | CDK inhibitor 3                 | 3.41 | 1832 | 0.59 | E   |
| IFQJ_A_B    | RB        | Gt-alpha                      | RGS9                            | 0.91 | 1806 | 0.65 | O   |
| IFSK_BC_A   | RB        | Fab                           | Birch pollen antigen Bet V1     | 0.45 | 1623 | 0.96 | A/B |
| IGCQ_B_C    | RB        | GRB2 C-ter SH3 domain         | GRB2 N-ter SH3 domain           | 0.92 | 1208 | 0.42 | O   |
| IGHQ_A_B    | RB        | Complement C3                 | Epstein-Barr virus receptor CR2 | 0.34 | 800  | 0.68 | O   |
| IGLA_G_F    | RB        | Glycerol Kinase               | Glucose specific phosphocARRIER | 0.98 | 1304 | 0.60 | O   |
| IGP2_A_BG   | Medium    | Gi-alpha                      | Gi-beta_gamma                   | 1.65 | 2287 | 0.72 | O   |
| IGPW_A_B    | RB        | HISF protein                  | Amidotransferase HISH           | 0.65 | 2097 | 0.65 | O   |
| IGRN_A_B    | Medium    | CDC42 GTPase                  | CDC42 GAP                       | 1.22 | 2332 | 0.71 | O   |
| IH1V_A_G    | Difficult | Actin                         | Gelsolin                        | 6.62 | 2071 | 0.48 | O   |
| IHE1_C_A    | RB        | Rac GTPase                    | Pseudomonas toxin GAP dom.      | 0.93 | 2113 | 0.70 | O   |
| IHE8_B_A    | Medium    | Ras GTPase                    | PIP3 kinase                     | 0.92 | 1305 | 0.61 | O   |
| IHIA_AB_I   | RB        | Kallikrein                    | Hirustatin                      | 1.4  | 1737 | 0.78 | E   |
| I12M_A_B    | Medium    | Ran GTPase                    | RCC1                            | 2.12 | 2779 | 0.87 | O   |
| I14D_D_AB   | RB        | Rac GTPase                    | Arfaptin                        | 1.41 | 1657 | 0.71 | O   |
| I19R_HL_ABC | RB        | Fab                           | Cd40 ligand                     | 1.3  | 1498 | 0.96 | A/B |
| I1B1_AB_E   | Medium    | 14-3-3 protein                | Serotonin N-acetylase           | 2.09 | 2808 | 0.62 | O   |
| I1BR_A_B    | Difficult | Ran GTPase                    | Importin beta                   | 2.54 | 2270 | 0.69 | O   |
| I1JK_A_BC   | Medium    | Von Willebrand Factor dom. A1 | Botrocetin                      | 0.68 | 1648 | 0.68 | E   |

|              |           |                               |   |      |      |      |     |
|--------------|-----------|-------------------------------|---|------|------|------|-----|
| 1IQD_AB_C    | RB        | Fab                           | Factor VIII domain C2                     | 0.48 | 1976 | 0.97 | A/B |
| 1IRA_Y_X     | Difficult | Interleukin-1 receptor        | Interleukin-1 receptor antagonist protein | 8.38 | 3367 | 0.53 | O   |
| 1J2J_A_B     | RB        | Arf1 GTPase                   | GAT domain of GGA1                        | 0.63 | 1209 | 0.68 | O   |
| 1JMO_A_HL    | Difficult | Heparin cofactor              | Thrombin                                  | 3.21 | 3461 | 0.75 | O   |
| 1JPS_HL_T    | RB        | Fab D3H44                     | Tissue factor                             | 0.51 | 1852 | 0.92 | A   |
| 1K4C_AB_C    | RB        | Fab                           | Potassium Channel Kcsa                    | 0.53 | 1601 | 0.92 | A/B |
| 1K5D_AB_C    | Medium    | Ran GTPase                    | Ran GAP                                   | 1.19 | 2527 | 0.80 | O   |
| 1K74_AB_DE   | RB        | RXR-alpha                     | PPAR-gamma                                | 0.8  | 2200 | 0.51 | O   |
| 1KAC_A_B     | RB        | Adenovirus fiber knob protein | Adenovirus receptor                       | 0.95 | 1456 | 0.75 | O   |
| 1KKL_ABC_H   | Medium    | HPr kinase C-ter domain       | HPr                                       | 2.2  | 1641 | 0.69 | E   |
| 1KLU_AB_D    | RB        | MHC class 2 HLA-DR1           | Staphylococcus enterotoxin C3             | 0.43 | 1254 | 0.52 | O   |
| 1KTZ_A_B     | RB        | TGF-beta                      | TGF-beta receptor                         | 0.39 | 989  | 0.66 | O   |
| 1KXP_A_D     | RB        | Actin                         | Vitamin D binding protein                 | 1.12 | 3341 | 0.66 | O   |
| 1KXQ_H_A     | RB        | camel VHH                     | Pancreatic alpha-amylase                  | 0.72 | 2172 | 0.85 | A/B |
| 1M10_A_B     | Medium    | Von Willebrand Factor dom. A1 | Glycoprotein IB-alpha                     | 2.1  | 2097 | 0.65 | E   |
| 1MAH_A_F     | RB        | Acetylcholinesterase          | Fasciculin                                | 0.61 | 2145 | 0.73 | E   |
| 1ML0_AA_D    | RB        | Viral chemokine binding p. M3 | Chemokine Mcp1                            | 1.02 | 2069 | 0.57 | O   |
| 1MLC_AB_E    | RB        | Fab44.1                       | HEW lysozyme                              | 0.6  | 1392 | 0.96 | A/B |
| 1N2C_ABCD_EF | Medium    | Nitrogenase Mo-Fe protein     | Nitrogenase Fe protein                    | 2.13 | 3635 | 0.59 | O   |
| 1N80_ABC_E   | RB        | Chymotrypsin                  | Ecotin                                    | 0.94 | 1851 | 0.88 | E   |
| 1NCA_HL_N    | RB        | Fab                           | Flu virus neuraminidase N9                | 0.24 | 1953 | 0.92 | A/B |
| 1NSN_HL_S    | RB        | Fab N10                       | Staphylococcal nuclease                   | 0.35 | 1776 | 0.86 | A/B |
| 1NW9_B_A     | Medium    | Capase-9                      | Ecotin                                    | 1.97 | 2112 | 0.75 | E   |
| 1OPH_A_B     | RB        | Alpha-1-antitrypsin           | Trypsinogen                               | 1.21 | 1360 | 0.91 | E   |
| 1PPE_E_I     | RB        | Bovine trypsin                | CMTI-1 squash inhibitor                   | 0.44 | 1688 | 0.77 | E   |
| 1PXV_A_C     | Difficult | Cystein protease              | Cystein protease                          | 2.63 | 2336 | 0.61 | E   |

|             |           |                            |  |      |      |      |     |
|-------------|-----------|----------------------------|--|------|------|------|-----|
|             |           |                            | inhibitor                                  |      |      |      |     |
| 1QA9_A_B    | RB        | CD2                        | CD58                                       | 0.73 | 1353 | 0.63 | O   |
| 1QFW_HL_AB  | RB        | Fv                         | Human chorionic gonadotropin               | 1.31 | 1580 | 0.91 | A/B |
| 1QFW_IM_AB  | RB        | Fv                         | Human chorionic gonadotropin               | 0.73 | 1637 | 0.77 | A/B |
| 1R0R_E_I    | RB        | Subtilisin Carlsberg       | OMTKY                                      | 0.45 | 1409 | 0.76 | E   |
| 1R8S_A_E    | Difficult | Arf1 GTPase                | Sec 7 domain                               | 3.73 | 2986 | 0.64 | O   |
| 1RLB_ABCD_E | RB        | Transthyretin              | Retinol binding protein                    | 0.66 | 1439 | 0.73 | O   |
| 1S1Q_A_B    | RB        | UEV domain                 | Ubiquitin                                  | 0.98 | 1288 | 0.61 | O   |
| 1SBB_A_B    | RB        | T-cell receptor beta       | Staphylococcus enterotoxin B               | 0.37 | 1064 | 0.71 | O   |
| 1T6B_X_Y    | RB        | Anthrax protective antigen | Anthrax toxin receptor                     | 0.62 | 1948 | 0.83 | O   |
| 1TMQ_A_B    | RB        | alpha-amylase              | RAG1 inhibitor                             | 0.86 | 2401 | 0.78 | E   |
| 1UDI_E_I    | RB        | Uracyl-DNA glycosylase     | Glycosylase inhibitor                      | 0.9  | 2022 | 0.59 | E   |
| 1VFB_AB_C   | RB        | Fv D1.3                    | HEW lysozyme                               | 1.02 | 1383 | 0.85 | A/B |
| 1WEJ_HL_F   | RB        | Fab E8                     | Cytochrome C                               | 0.31 | 1177 | 0.93 | A/B |
| 1WQ1_R_G    | Medium    | Ras GTPase                 | Ras GAP                                    | 1.16 | 2913 | 0.74 | O   |
| 1XD3_A_B    | RB        | UCH-L3                     | Ubiquitin                                  | 1.24 | 2281 | 0.63 | O   |
| 1XQS_A_C    | Medium    | HspBP1                     | Hsp70 ATPase domain                        | 1.77 | 2350 | 0.68 | O   |
| 1Y64_A_B    | Difficult | Actin                      | BNI1 protein                               | 4.69 | 2745 | 0.53 | O   |
| 1YVB_A_I    | RB        | Falcipain 2                | Cystatin                                   | 0.51 | 1743 | 0.75 | E   |
| 1Z0K_A_B    | RB        | Rab4A GTPase               | RAB4 binding domain of Rabenosyn           | 0.53 | 1787 | 0.62 | O   |
| 1Z5Y_D_E    | RB        | N-term of DsbD             | E.coli CCMG protein                        | 1.23 | 1346 | 0.77 | O   |
| 1ZHL_A_B    | RB        | BAH domain of Orc1         | Sir Orc-interaction domain                 | 0.68 | 1322 | 0.62 | O   |
| 2AJF_A_E    | RB        | ACE2                       | SARS spike protein receptor binding domain | 0.65 | 1704 | 0.70 | O   |
| 2B42_B_A    | RB        | Xylanase                   | Xylanase inhibitor                         | 0.72 | 2520 | 0.63 | E   |
| 2BTF_A_P    | RB        | Actin                      | Profilin                                   | 0.75 | 2063 | 0.58 | O   |

|            |           |                                      |                                   |      |      |      |     |
|------------|-----------|--------------------------------------|-----------------------------------|------|------|------|-----|
| 2COL_A_B   | Difficult | PTS1 and TRP region of PEX5          | SCP2                              | 2.62 | 2013 | 0.55 | O   |
| 2CFH_A_C   | Medium    | BET3                                 | TPC6                              | 1.55 | 2384 | 0.54 | O   |
| 2FD6_HL_U  | RB        | Plasminogen receptor antibody        | Plasminogen activator receptor    | 1.07 | 1139 | 0.94 | A/B |
| 2H7V_A_C   | Medium    | Rac GTPase                           | YpkA                              | 1.63 | 1574 | 0.73 | O   |
| 2HLE_A_B   | RB        | Ephrin B4 receptor                   | Ephrin B2 ectodomain              | 1.4  | 2116 | 0.54 | O   |
| 2HMI_CD_AB | Difficult | Fab 28                               | HIV1 reverse transcriptase        | 2.26 | 1234 | 0.96 | A/B |
| 2HQS_A_H   | RB        | ToIB                                 | Pal                               | 1.14 | 2333 | 0.80 | O   |
| 2HRK_A_B   | Medium    | Glutamyl-t-RNA synthetase            | GU-4 nucleic binding protein      | 2.03 | 1595 | 0.83 | O   |
| 2I25_N_L   | RB        | Shark single domain antigen receptor | Lysozyme                          | 1.21 | 1425 | 0.91 | A/B |
| 2JEL_HL_P  | RB        | Fab Jel42                            | HPr                               | 0.17 | 1501 | 0.89 | A/B |
| 2MTA_HL_A  | RB        | Methylamine dehydrogenase            | Amicyanin                         | 0.41 | 1461 | 0.77 | E   |
| 2NZ8_A_B   | Medium    | Rac GTPase                           | DH/PH domain of TRIO              | 2.13 | 2599 | 0.69 | O   |
| 2O8V_A_B   | RB        | PAPS reductase                       | Thioredoxin                       | 1.37 | 1619 | 0.68 | E   |
| 2OOB_A_B   | RB        | Ubiquitin ligase                     | Ubiquitin                         | 0.85 | 808  | 0.40 | O   |
| 2OT3_B_A   | Difficult | Rab21 GTPase                         | Rabex-5 VPS9 domain               | 2.79 | 2306 | 0.67 | O   |
| 2PCC_A_B   | RB        | Cyt C peroxidase                     | Cytochrome C                      | 0.39 | 1141 | 0.64 | E   |
| 2SIC_E_I   | RB        | Subtilisin                           | Streptomyces subtilisin inhibitor | 0.36 | 1617 | 0.85 | E   |
| 2SNI_E_I   | RB        | Subtilisin                           | Chymotrypsin inhibitor 2          | 0.35 | 1628 | 0.86 | E   |
| 2UUY_A_B   | RB        | Trypsin                              | Tryptase inhibitor from tick      | 0.43 | 1280 | 0.59 | E   |
| 2VIS_AB_C  | RB        | Fab                                  | Flu virus hemagglutinin           | 0.8  | 1296 | 0.96 | A/B |
| 7CEI_A_B   | RB        | Colicin E7 nuclease                  | Im7 immunity protein              | 0.7  | 1384 | 0.77 | E   |