**Supporting Information**

Table S1. The calculated binding free energies of the five MD simulations both for the wild-type RBD and the E484K mutant, respectively, complexed with various neutralizing antibodies and nanobodiesa).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Neutralizing antibodies | RBD | $$∆E\_{vdw}$$ | $$∆E\_{ele}$$ | $$∆G\_{polar}$$ | $$∆G\_{nonpolar}$$ | $$∆E\_{vdw}+∆G\_{nonpolar}$$ | $$∆E\_{ele}+∆G\_{polar}$$ | $$∆G\_{bind}$$ |
| S2M11 | WTb)-1 | -72.29  | -71.41  | 98.34  | -9.50  | -81.79 | 26.93 | -54.86 |
| WT-2 | -71.07  | -72.95  | 94.55  | -9.54  | -80.61 | 21.60 | -59.01 |
| WT-3 | -71.07  | -85.19  | 104.31  | -9.23  | -80.30 | 19.12 | -61.18 |
| WT-4 | -71.69  | -66.35  | 91.62  | -9.15  | -80.84 | 25.27 | -55.57 |
| WT-5 | -71.84  | -74.90  | 96.47  | -9.23  | -81.07 | 21.57 | -59.50 |
| MTc)-1 | -68.94  | 39.78  | -4.97  | -8.01  | -76.95 | 34.81 | -42.14 |
| MT-2 | -76.81  | 18.20  | 21.16  | -8.84  | -85.65 | 39.36 | -46.29 |
| MT-3 | -76.59  | 29.57  | 13.49  | -9.20  | -85.79 | 43.06 | -42.73 |
| MT-4 | -76.24  | 31.80  | 11.58  | -8.79  | -85.03 | 43.38 | -41.65 |
| MT-5 | -65.36  | 36.52  | 1.70  | -7.68  | -73.04 | 38.22 | -34.82 |
| BD23 | WT-1 | -66.64  | -94.78  | 122.53  | -9.36  | -76.00 | 27.75 | -48.25 |
| WT-2 | -65.19  | -112.90  | 137.60  | -9.05  | -74.24 | 24.70 | -49.54 |
| WT-3 | -69.59  | -142.07  | 164.08  | -9.85  | -79.44 | 22.01 | -57.43 |
| WT-4 | -80.14  | -113.78  | 148.51  | -10.57  | -90.71 | 34.73 | -55.98 |
| WT-5 | -74.86  | -149.52  | 175.00  | -10.64  | -85.50 | 25.48 | -60.02 |
| MT-1 | -75.20  | 48.37  | 3.46  | -9.75  | -84.95 | 51.83 | -33.12 |
| MT-2 | -73.27  | 30.91  | 25.35  | -9.33  | -82.60 | 56.26 | -26.34 |
| MT-3 | -88.62  | 14.76  | 46.24  | -11.91  | -100.53 | 61.00 | -39.53 |
| MT-4 | -67.57  | 68.74  | -21.35  | -9.05  | -76.62 | 47.39 | -29.23 |
| MT-5 | -70.66  | 61.79  | -18.50  | -9.18  | -79.84 | 43.29 | -36.55 |
| [BD368-2](http://www1.rcsb.org/structure/7CHH) | WT-1 | -73.09  | -93.82  | 131.00  | -9.53  | -82.62 | 37.18 | -45.44 |
| WT-2 | -75.32  | -99.93  | 137.89  | -9.63  | -84.95 | 37.96 | -46.99 |
| WT-3 | -71.12  | -69.56  | 105.08  | -9.03  | -80.15 | 35.52 | -44.63 |
| WT-4 | -76.48  | -85.18  | 122.90  | -9.76  | -86.24 | 37.72 | -48.52 |
| WT-5 | -77.37  | -115.18  | 146.11  | -9.99  | -87.36 | 30.93 | -56.43 |
| MT-1 | -71.69  | -10.90  | 49.65  | -9.34  | -81.03 | 38.75 | -42.28 |
| MT-2 | -74.12  | 12.88  | 30.87  | -9.81  | -83.93 | 43.75 | -40.18 |
| MT-3 | -71.76  | -3.45  | 41.75  | -9.40  | -81.16 | 38.3 | -42.86 |
| MT-4 | -61.54  | 12.48  | 23.97  | -8.18  | -69.72 | 36.45 | -33.27 |
| MT-5 | -72.04  | 8.89  | 33.40  | -9.30  | -81.34 | 42.29 | -39.05 |
| nanobody Nb20 | WT-1 | -82.47  | -215.50  | 250.00  | -11.74  | -94.21 | 34.50 | -59.71 |
| WT-2 | -79.09  | -255.69  | 276.06  | -11.95  | -91.04 | 20.37 | -70.67 |
| WT-3 | -87.38  | -222.60  | 260.15  | -12.81  | -100.19 | 37.55 | -62.64 |
| WT-4 | -82.20  | -225.04  | 260.52  | -11.84  | -94.04 | 35.48 | -58.56 |
| WT-5 | -82.60  | -268.79  | 294.75  | -12.11  | -94.71 | 25.96 | -68.75 |
| MT-1 | -70.11  | -65.04  | 99.20  | -10.15  | -80.26 | 34.16 | -46.10 |
| MT-2 | -77.66  | 12.32  | 28.76  | -10.10  | -87.76 | 41.08 | -46.68 |
| MT-3 | -71.57  | -67.14  | 100.65  | -10.29  | -81.86 | 33.51 | -48.35 |
| MT-4 | -87.44  | -53.01  | 94.14  | -11.78  | -99.22 | 41.13 | -58.09 |
| MT-5 | -71.68  | -65.37  | 102.64  | -10.36  | -82.04 | 37.27 | -44.77 |
| Nanobody H11-D4 | WT-1 | -61.10  | -3.53  | 23.71  | -8.30  | -69.40 | 20.18 | -49.22 |
| WT-2 | -66.17  | -13.59  | 41.41  | -8.57  | -74.74 | 27.82 | -46.92 |
| WT-3 | -62.76  | -1.09  | 24.00  | -8.28  | -71.04 | 22.91 | -48.13 |
| WT-4 | -60.30  | 3.45  | 18.18  | -8.05  | -68.35 | 21.63 | -46.72 |
| WT-5 | -62.65  | 0.26  | 23.15  | -8.57  | -71.22 | 23.41 | -47.81 |
| MT-1 | -63.51  | 270.39  | -237.76  | -7.75  | -71.26 | 32.63 | -38.63 |
| MT-2 | -65.73  | 289.51  | -252.18  | -8.05  | -73.78 | 37.33 | -36.45 |
| MT-3 | -64.75  | 267.61  | -232.46  | -7.95  | -72.70 | 35.15 | -37.55 |
| MT-4 | -66.63  | 258.85  | -222.20  | -8.13  | -74.76 | 36.65 | -38.11 |
| MT-5 | -62.37  | 271.84  | -236.88  | -7.56  | -69.93 | 34.96 | -34.97 |
| Nanobody MR17-K99Y | WT-1 | -103.48  | -328.47  | 366.24  | -13.86  | -117.34 | 37.77 | -79.57 |
| WT-2 | -107.75  | -280.44  | 330.06  | -14.31  | -122.06 | 49.62 | -72.44 |
| WT-3 | -107.07  | -329.92  | 372.20  | -14.34  | -121.41 | 42.28 | -79.13 |
| WT-4 | -98.02  | -290.78  | 337.94  | -13.19  | -111.21 | 47.16 | -64.05 |
| WT-5 | -95.32  | -266.67  | 316.10  | -12.45  | -107.77 | 49.43 | -58.34 |
| MT-1 | -106.52  | -213.89  | 261.67  | -14.03  | -120.55 | 47.78 | -72.77 |
| MT-2 | -102.07  | -243.14  | 290.14  | -13.41  | -115.48 | 47.00 | -68.48 |
| MT-3 | -106.09  | -191.45  | 241.25  | -13.72  | -119.81 | 49.80 | -70.01 |
| MT-4 | -106.12  | -258.04  | 305.67  | -14.07  | -120.19 | 47.63 | -72.56 |
| MT-5 | -109.66  | -223.46  | 275.33  | -14.48  | -124.14 | 51.87 | -72.27 |

a)The unit of the values is kcal/mol; b)WT represents wild-type; c)MT represents mutant.