Supplemental Data

# Mechanisms of recognition of Aβ monomer, oligomer, and fibril by homologous antibodies

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*Running title: *Amyloid Recognition by Homologous Antibodies*

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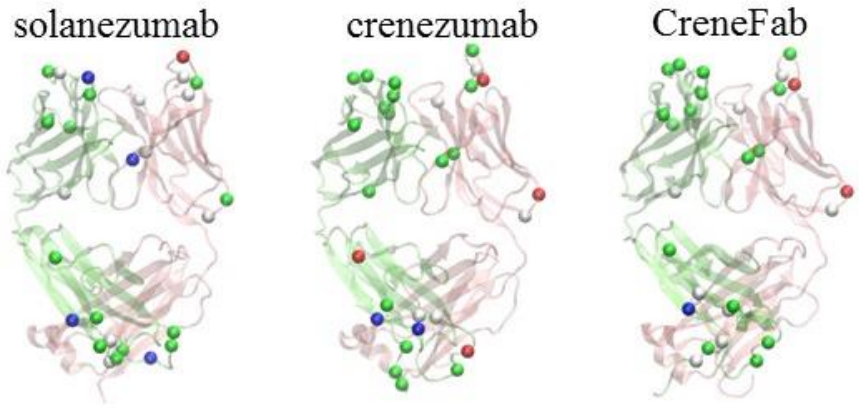


Fig. S1 Comparison of the corresponding mutational sites of the Fabs studied in this work. The light chain and heavy chain were colored in pink and lime respectively. Hydrophobic, hydrophilic, cationic, and anionic residues are colored in white, green, blue, and red respectively.

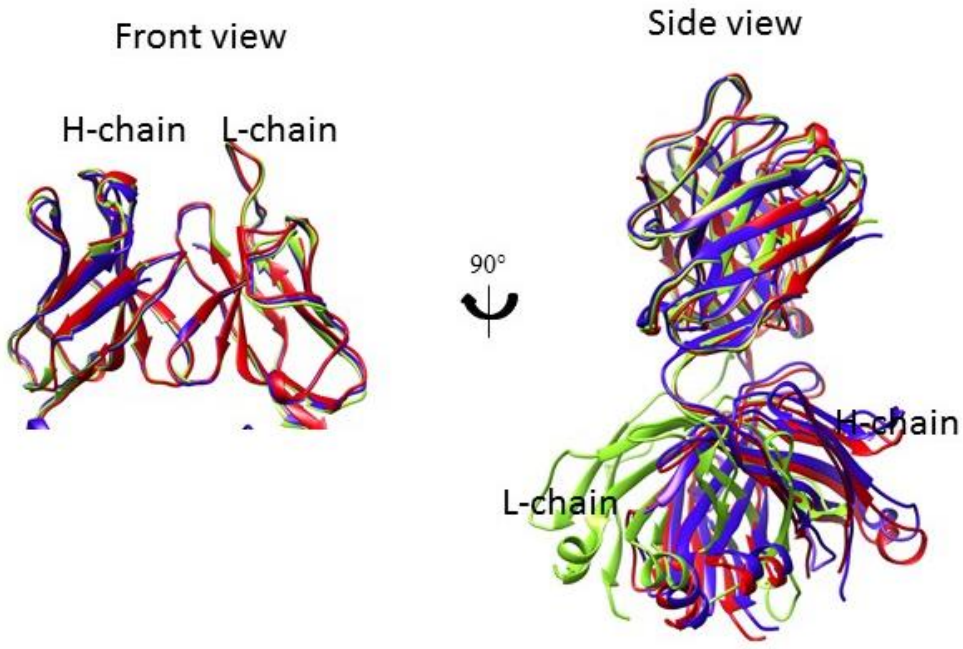


Fig. S2 Available crystal structures of solanezumab and CreneFab suggested similar V domain and different V-C domain orientation. The three crystal structures were superimposed on the V domain. The crystal structures of solanezumab-bind (4xxd), CreneFab-apo (4kmv), and CreneFab-bind (4kna) were colored by red, blue and green respectively.

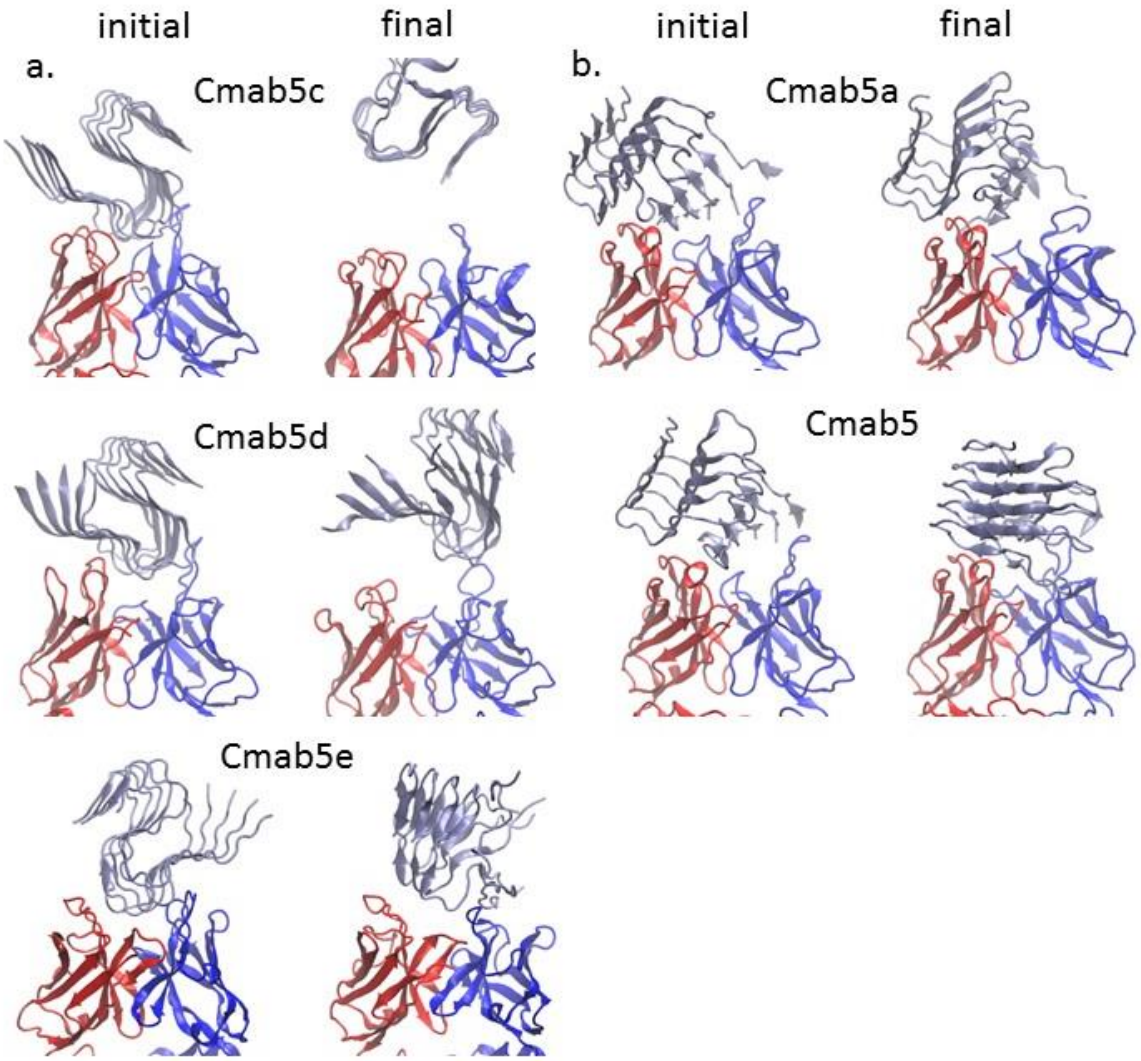


Fig. S3. Initial and final snapshots of the complexes between the Aβ-5mer and crenezumab with a.21-25 and b.13-15 as epitope. Light chain, heavy chain of Fab and Aβ 5mer are colored by blue, red, and grey respectively.

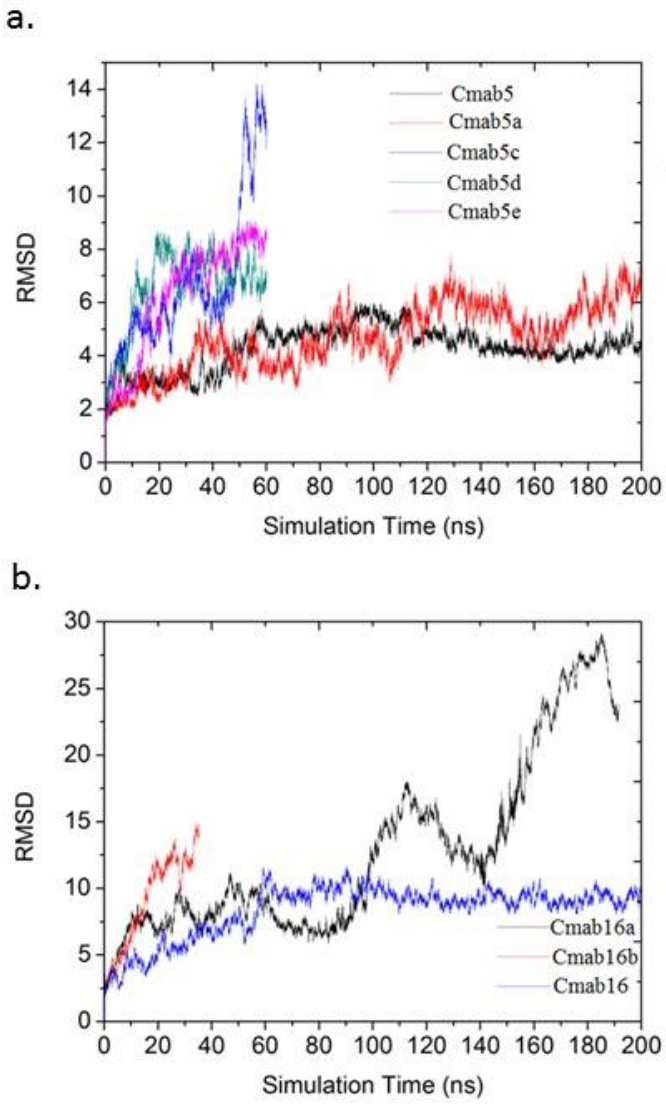


Fig. S4. RMSDs of the complexes between crenezumab and a. Aβ 5mer, b. Aβ 16mer during MD simulation.

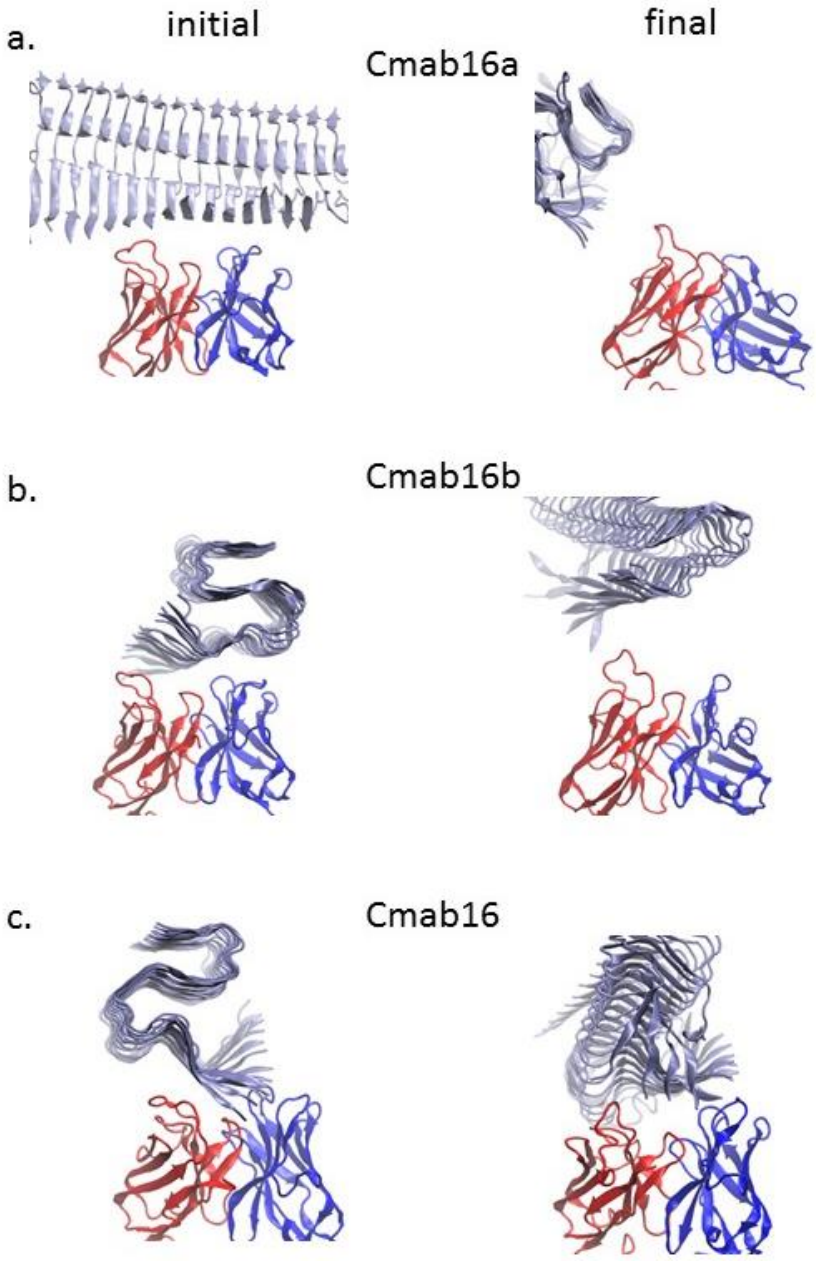


Fig. S5. Initial and final snapshots of three Aβ-16mer/crenezumab complexes. Light chain, heavy chain of Fab and Aβ 16mer are colored by blue, red, and grey respectively.

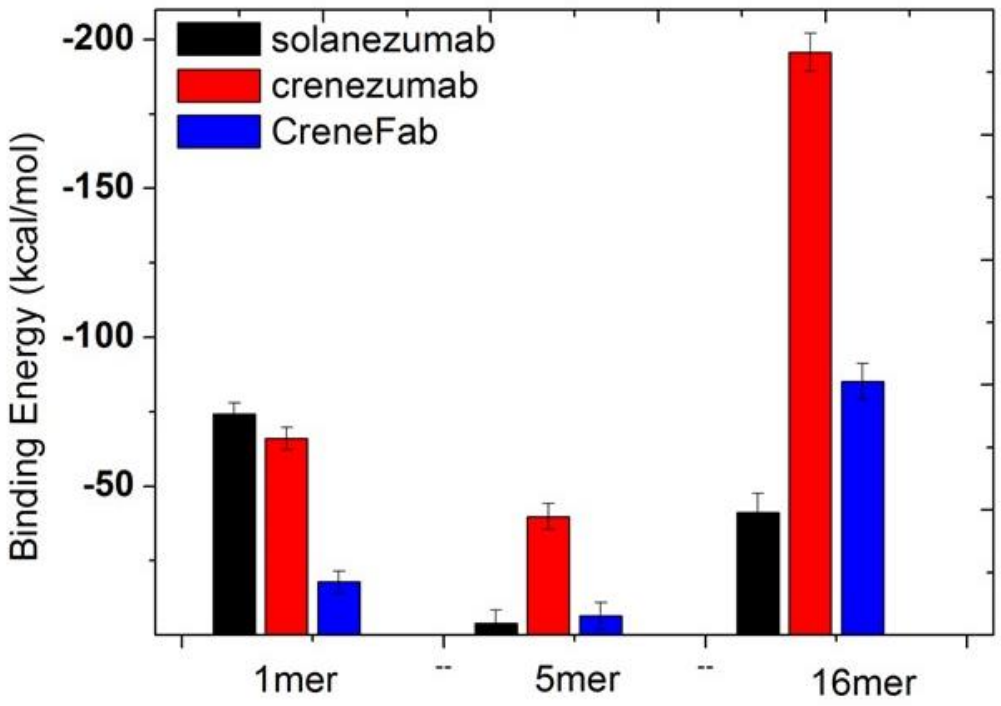


Fig. S6 Summary of the binding energies between Fabs and Aβ species. Binding energies of solanezumab, crenezumab, and CreneFab are colored by black, red and blue respectively.

Table S1. Sequence alignment of light chain and heavy chain (Fab region) of Solanezumab, Crenezumab, and chimera. Identical, similar and different residues are colored by black, grey, and white separately.

```
Solanezumab_LC    1  DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPR
Crenezumab_LC     1  DIVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGDTYLHWYLQKPGQSPQ
Chimera_LC        1  DIVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGDTYLHWYLQKPGQSPQ

Solanezumab_LC   51  LLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVP
Crenezumab_LC    51  LLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVP
Chimera_LC       51  LLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVP

Solanezumab_LC  101  WTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
Crenezumab_LC   101  WTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
Chimera_LC      101  WTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK

Solanezumab_LC  151  VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE
Crenezumab_LC   151  VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE
Chimera_LC      151  VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE

Solanezumab_LC  201  VTHQGLSSPVTKSFNRGEC
Crenezumab_LC   201  VTHQGLSSPVTKSFNRGEC
Chimera_LC      201  VTHQGLSSPVTKSFNRGEC

Solanezumab_HC  220  EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQ
Crenezumab_HC   220  EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLELVAS
Chimera_HC      220  EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLELVAS

Solanezumab_HC  270  INSVGNSTYYPDTVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGD
Crenezumab_HC   270  INSNGGSTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCASGD
Chimera_HC      270  INSNGGSTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCASGD

Solanezumab_HC  320  YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
Crenezumab_HC   320  YWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
Chimera_HC      320  YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT

Solanezumab_HC  370  VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
Crenezumab_HC   370  VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHK
Chimera_HC      370  VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK

Solanezumab_HC  420  PSNTKVDKKVEPKSC
Crenezumab_HC   420  PSNTKVDKRVESKYG
Chimera_HC      420  PSNTKVDKKVEPKSC
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Table S2. Sequence of solanezumab and crenezumab Fab region in the numbering system of Kabat and the simulation system.

| Light chain | | | | Heavy chain | | | |
|---|---|---|---|---|---|---|---|
| | Kabat | sola | cre | | Kabat | sola | cre |
| 1 | 1 | ASP | ASP | 220 | 1 | GLU | GLU |
| 2 | 2 | VAL | ILE | 221 | 2 | VAL | VAL |
| 3 | 3 | VAL | VAL | 222 | 3 | GLN | GLN |
| 4 | 4 | MET | MET | 223 | 4 | LEU | LEU |
| 5 | 5 | THR | THR | 224 | 5 | VAL | VAL |
| 6 | 6 | GLN | GLN | 225 | 6 | GLU | GLU |
| 7 | 7 | SER | SER | 226 | 7 | SER | SER |
| 8 | 8 | PRO | PRO | 227 | 8 | GLY | GLY |
| 9 | 9 | LEU | LEU | 228 | 9 | GLY | GLY |
| 10 | 10 | SER | SER | 229 | 10 | GLY | GLY |
| 11 | 11 | LEU | LEU | 230 | 11 | LEU | LEU |
| 12 | 12 | PRO | PRO | 231 | 12 | VAL | VAL |
| 13 | 13 | VAL | VAL | 232 | 13 | GLN | GLN |
| 14 | 14 | THR | THR | 233 | 14 | PRO | PRO |
| 15 | 15 | LEU | PRO | 234 | 15 | GLY | GLY |
| 16 | 16 | GLY | GLY | 235 | 16 | GLY | GLY |
| 17 | 17 | GLN | GLU | 236 | 17 | SER | SER |
| 18 | 18 | PRO | PRO | 237 | 18 | LEU | LEU |
| 19 | 19 | ALA | ALA | 238 | 19 | ARG | ARG |
| 20 | 20 | SER | SER | 239 | 20 | LEU | LEU |
| 21 | 21 | ILE | ILE | 240 | 21 | SER | SER |
| 22 | 22 | SER | SER | 241 | 22 | CYS | CYS |
| 23 | 23 | CYS | CYS | 242 | 23 | ALA | ALA |
| 24 | 24 | ARG | ARG | 243 | 24 | ALA | ALA |
| 25 | 25 | SER | SER | 244 | 25 | SER | SER |
| 26 | 26 | SER | SER | 245 | 26 | GLY | GLY |
| 27 | 27 | GLN | GLN | 246 | 27 | PHE | PHE |
| 28 | 27A | SER | SER | 247 | 28 | THR | THR |
| 29 | 27B | LEU | LEU | 248 | 29 | PHE | PHE |
| 30 | 27C | ILE | VAL | 249 | 30 | SER | SER |
| 31 | 27D | TYR | TYR | 250 | 31 | ARG | SER |
| 32 | 27E | SER | SER | 251 | 32 | TYR | TYR |
| 33 | 28 | ASP | ASN | 252 | 33 | SER | GLY |
| 34 | 29 | GLY | GLY | 253 | 34 | MET | MET |
| 35 | 30 | ASN | ASP | 254 | 35 | SER | SER |
| 36 | 31 | ALA | THR | 255 | 36 | TRP | TRP |
| 37 | 32 | TYR | TYR | 256 | 37 | VAL | VAL |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 38 | 33 | LEU | LEU | 257 | 38 | ARG | ARG |
| 39 | 34 | HSD | HSD | 258 | 39 | GLN | GLN |
| 40 | 35 | TRP | TRP | 259 | 40 | ALA | ALA |
| 41 | 36 | PHE | TYR | 260 | 41 | PRO | PRO |
| 42 | 37 | LEU | LEU | 261 | 42 | GLY | GLY |
| 43 | 38 | GLN | GLN | 262 | 43 | LYS | LYS |
| 44 | 39 | LYS | LYS | 263 | 44 | GLY | GLY |
| 45 | 40 | PRO | PRO | 264 | 45 | LEU | LEU |
| 46 | 41 | GLY | GLY | 265 | 46 | GLU | GLU |
| 47 | 42 | GLN | GLN | 266 | 47 | LEU | LEU |
| 48 | 43 | SER | SER | 267 | 48 | VAL | VAL |
| 49 | 44 | PRO | PRO | 268 | 49 | ALA | ALA |
| 50 | 45 | ARG | GLN | 269 | 50 | GLN | SER |
| 51 | 46 | LEU | LEU | 270 | 51 | ILE | ILE |
| 52 | 47 | LEU | LEU | 271 | 52 | ASN | ASN |
| 53 | 48 | ILE | ILE | 272 | 52A | SER | SER |
| 54 | 49 | TYR | TYR | 273 | 53 | VAL | ASN |
| 55 | 50 | LYS | LYS | 274 | 54 | GLY | GLY |
| 56 | 51 | VAL | VAL | 275 | 55 | ASN | GLY |
| 57 | 52 | SER | SER | 276 | 56 | SER | SER |
| 58 | 53 | ASN | ASN | 277 | 57 | THR | THR |
| 59 | 54 | ARG | ARG | 278 | 58 | TYR | TYR |
| 60 | 55 | PHE | PHE | 279 | 59 | TYR | TYR |
| 61 | 56 | SER | SER | 280 | 60 | PRO | PRO |
| 62 | 57 | GLY | GLY | 281 | 61 | ASP | ASP |
| 63 | 58 | VAL | VAL | 282 | 62 | THR | SER |
| 64 | 59 | PRO | PRO | 283 | 63 | VAL | VAL |
| 65 | 60 | ASP | ASP | 284 | 64 | LYS | LYS |
| 66 | 61 | ARG | ARG | 285 | 65 | GLY | GLY |
| 67 | 62 | PHE | PHE | 286 | 66 | ARG | ARG |
| 68 | 63 | SER | SER | 287 | 67 | PHE | PHE |
| 69 | 64 | GLY | GLY | 288 | 68 | THR | THR |
| 70 | 65 | SER | SER | 289 | 69 | ILE | ILE |
| 71 | 66 | GLY | GLY | 290 | 70 | SER | SER |
| 72 | 67 | SER | SER | 291 | 71 | ARG | ARG |
| 73 | 68 | GLY | GLY | 292 | 72 | ASP | ASP |
| 74 | 69 | THR | THR | 293 | 73 | ASN | ASN |
| 75 | 70 | ASP | ASP | 294 | 74 | ALA | ALA |
| 76 | 71 | PHE | PHE | 295 | 75 | LYS | LYS |
| 77 | 72 | THR | THR | 296 | 76 | ASN | ASN |
| 78 | 73 | LEU | LEU | 297 | 77 | THR | SER |
| 79 | 74 | LYS | LYS | 298 | 78 | LEU | LEU |
| 80 | 75 | ILE | ILE | 299 | 79 | TYR | TYR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 81 | 76 | SER | SER | 300 | 80 | LEU | LEU |
| 82 | 77 | ARG | ARG | 301 | 81 | GLN | GLN |
| 83 | 78 | VAL | VAL | 302 | 82 | MET | MET |
| 84 | 79 | GLU | GLU | 303 | 82A | ASN | ASN |
| 85 | 80 | ALA | ALA | 304 | 82B | SER | SER |
| 86 | 81 | GLU | GLU | 305 | 82C | LEU | LEU |
| 87 | 82 | ASP | ASP | 306 | 83 | ARG | ARG |
| 88 | 83 | VAL | VAL | 307 | 84 | ALA | ALA |
| 89 | 84 | GLY | GLY | 308 | 85 | GLU | GLU |
| 90 | 85 | VAL | VAL | 309 | 86 | ASP | ASP |
| 91 | 86 | TYR | TYR | 310 | 87 | THR | THR |
| 92 | 87 | TYR | TYR | 311 | 88 | ALA | ALA |
| 93 | 88 | CYS | CYS | 312 | 89 | VAL | VAL |
| 94 | 89 | SER | SER | 313 | 90 | TYR | TYR |
| 95 | 90 | GLN | GLN | 314 | 91 | TYR | TYR |
| 96 | 91 | SER | SER | 315 | 92 | CYS | CYS |
| 97 | 92 | THR | THR | 316 | 93 | ALA | ALA |
| 98 | 93 | HSD | HSD | 317 | 94 | SER | SER |
| 99 | 94 | VAL | VAL | 318 | 95 | GLY | GLY |
| 100 | 95 | PRO | PRO | 319 | 96 | ASP | ASP |
| 101 | 96 | TRP | TRP | 320 | 97 | TYR | TYR |
| 102 | 97 | THR | THR | 321 | 98 | TRP | TRP |
| 103 | 98 | PHE | PHE | 322 | 99 | GLY | GLY |
| 104 | 99 | GLY | GLY | 323 | 100 | GLN | GLN |
| 105 | 100 | GLN | GLN | 324 | 101 | GLY | GLY |
| 106 | 101 | GLY | GLY | 325 | 102 | THR | THR |
| 107 | 102 | THR | THR | 326 | 103 | LEU | THR |
| 108 | 103 | LYS | LYS | 327 | 104 | VAL | VAL |
| 109 | 104 | VAL | VAL | 328 | 105 | THR | THR |
| 110 | 105 | GLU | GLU | 329 | 106 | VAL | VAL |
| 111 | 106 | ILE | ILE | 330 | 107 | SER | SER |
| 112 | 107 | LYS | LYS | 331 | 108 | SER | SER |
| 113 | 108 | ARG | ARG | 332 | 109 | ALA | ALA |
| 114 | 109 | THR | THR | 333 | 110 | SER | SER |
| 115 | 110 | VAL | VAL | 334 | 111 | THR | THR |
| 116 | 111 | ALA | ALA | 335 | 112 | LYS | LYS |
| 117 | 112 | ALA | ALA | 336 | 113 | GLY | GLY |
| 118 | 113 | PRO | PRO | 337 | 114 | PRO | PRO |
| 119 | 114 | SER | SER | 338 | 115 | SER | SER |
| 120 | 115 | VAL | VAL | 339 | 116 | VAL | VAL |
| 121 | 116 | PHE | PHE | 340 | 117 | PHE | PHE |
| 122 | 117 | ILE | ILE | 341 | 118 | PRO | PRO |
| 123 | 118 | PHE | PHE | 342 | 119 | LEU | LEU |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 124 | 119 | PRO | PRO | 343 | 124 | ALA | ALA |
| 125 | 120 | PRO | PRO | 344 | 125 | PRO | PRO |
| 126 | 121 | SER | SER | 345 | 126 | SER | CYS |
| 127 | 122 | ASP | ASP | 346 | 127 | SER | SER |
| 128 | 123 | GLU | GLU | 347 | 128 | LYS | ARG |
| 129 | 124 | GLN | GLN | 348 | 129 | SER | SER |
| 130 | 125 | LEU | LEU | 349 | 130 | THR | THR |
| 131 | 126 | LYS | LYS | 350 | 131 | SER | SER |
| 132 | 127 | SER | SER | 351 | 132 | GLY | GLU |
| 133 | 128 | GLY | GLY | 352 | 133 | GLY | SER |
| 134 | 129 | THR | THR | 353 | 134 | THR | THR |
| 135 | 130 | ALA | ALA | 354 | 135 | ALA | ALA |
| 136 | 131 | SER | SER | 355 | 132 | ALA | ALA |
| 137 | 132 | VAL | VAL | 356 | 133 | LEU | LEU |
| 138 | 133 | VAL | VAL | 357 | 134 | GLY | GLY |
| 139 | 134 | CYS | CYS | 358 | 135 | CYS | CYS |
| 140 | 135 | LEU | LEU | 359 | 136 | LEU | LEU |
| 141 | 136 | LEU | LEU | 360 | 137 | VAL | VAL |
| 142 | 137 | ASN | ASN | 361 | 138 | LYS | LYS |
| 143 | 138 | ASN | ASN | 362 | 139 | ASP | ASP |
| 144 | 139 | PHE | PHE | 363 | 140 | TYR | TYR |
| 145 | 140 | TYR | TYR | 364 | 141 | PHE | PHE |
| 146 | 141 | PRO | PRO | 365 | 142 | PRO | PRO |
| 147 | 142 | ARG | ARG | 366 | 143 | GLU | GLU |
| 148 | 143 | GLU | GLU | 367 | 144 | PRO | PRO |
| 149 | 144 | ALA | ALA | 368 | 145 | VAL | VAL |
| 150 | 145 | LYS | LYS | 369 | 146 | THR | THR |
| 151 | 146 | VAL | VAL | 370 | 147 | VAL | VAL |
| 152 | 147 | GLN | GLN | 371 | 148 | SER | SER |
| 153 | 148 | TRP | TRP | 372 | 149 | TRP | TRP |
| 154 | 149 | LYS | LYS | 373 | 150 | ASN | ASN |
| 155 | 150 | VAL | VAL | 374 | 151 | SER | SER |
| 156 | 151 | ASP | ASP | 375 | 152 | GLY | GLY |
| 157 | 152 | ASN | ASN | 376 | 153 | ALA | ALA |
| 158 | 153 | ALA | ALA | 377 | 154 | LEU | LEU |
| 159 | 154 | LEU | LEU | 378 | 155 | THR | THR |
| 160 | 155 | GLN | GLN | 379 | 156 | SER | SER |
| 161 | 156 | SER | SER | 380 | 157 | GLY | GLY |
| 162 | 157 | GLY | GLY | 381 | 158 | VAL | VAL |
| 163 | 158 | ASN | ASN | 382 | 159 | HSD | HSD |
| 164 | 159 | SER | SER | 383 | 160 | THR | THR |
| 165 | 160 | GLN | GLN | 384 | 161 | PHE | PHE |
| 166 | 161 | GLU | GLU | 385 | 162 | PRO | PRO |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 167 | 162 | SER | SER | 386 | 163 | ALA | ALA |
| 168 | 163 | VAL | VAL | 387 | 164 | VAL | VAL |
| 169 | 164 | THR | THR | 388 | 165 | LEU | LEU |
| 170 | 165 | GLU | GLU | 389 | 166 | GLN | GLN |
| 171 | 166 | GLN | GLN | 390 | 167 | SER | SER |
| 172 | 167 | ASP | ASP | 391 | 168 | SER | SER |
| 173 | 168 | SER | SER | 392 | 169 | GLY | GLY |
| 174 | 169 | LYS | LYS | 393 | 170 | LEU | LEU |
| 175 | 170 | ASP | ASP | 394 | 171 | TYR | TYR |
| 176 | 171 | SER | SER | 395 | 172 | SER | SER |
| 177 | 172 | THR | THR | 396 | 173 | LEU | LEU |
| 178 | 173 | TYR | TYR | 397 | 174 | SER | SER |
| 179 | 174 | SER | SER | 398 | 175 | SER | SER |
| 180 | 175 | LEU | LEU | 399 | 176 | VAL | VAL |
| 181 | 176 | SER | SER | 400 | 177 | VAL | VAL |
| 182 | 177 | SER | SER | 401 | 178 | THR | THR |
| 183 | 178 | THR | THR | 402 | 179 | VAL | VAL |
| 184 | 179 | LEU | LEU | 403 | 180 | PRO | PRO |
| 185 | 180 | THR | THR | 404 | 181 | SER | SER |
| 186 | 181 | LEU | LEU | 405 | 182 | SER | SER |
| 187 | 182 | SER | SER | 406 | 183 | SER | SER |
| 188 | 183 | LYS | LYS | 407 | 184 | LEU | LEU |
| 189 | 184 | ALA | ALA | 408 | 185 | GLY | GLY |
| 190 | 185 | ASP | ASP | 409 | 186 | THR | THR |
| 191 | 186 | TYR | TYR | 410 | 187 | GLN | LYS |
| 192 | 187 | GLU | GLU | 411 | 188 | THR | THR |
| 193 | 188 | LYS | LYS | 412 | 189 | TYR | TYR |
| 194 | 189 | HSD | HSD | 413 | 190 | ILE | THR |
| 195 | 190 | LYS | LYS | 414 | 191 | CYS | CYS |
| 196 | 191 | VAL | VAL | 415 | 192 | ASN | ASN |
| 197 | 192 | TYR | TYR | 416 | 193 | VAL | VAL |
| 198 | 193 | ALA | ALA | 417 | 194 | ASN | ASP |
| 199 | 194 | CYS | CYS | 418 | 195 | HSD | HSD |
| 200 | 195 | GLU | GLU | 419 | 196 | LYS | LYS |
| 201 | 196 | VAL | VAL | 420 | 197 | PRO | PRO |
| 202 | 197 | THR | THR | 421 | 198 | SER | SER |
| 203 | 198 | HSD | HSD | 422 | 199 | ASN | ASN |
| 204 | 199 | GLN | GLN | 423 | 200 | THR | THR |
| 205 | 200 | GLY | GLY | 424 | 201 | LYS | LYS |
| 206 | 201 | LEU | LEU | 425 | 202 | VAL | VAL |
| 207 | 202 | SER | SER | 426 | 203 | ASP | ASP |
| 208 | 203 | SER | SER | 427 | 204 | LYS | LYS |
| 209 | 204 | PRO | PRO | 428 | 205 | LYS | ARG |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 210 | 205 | VAL | VAL | 429 | 206 | VAL | VAL |
| 211 | 206 | THR | THR | 430 | 211 | GLU | GLU |
| 212 | 207 | LYS | LYS | 431 | 212 | PRO | SER |
| 213 | 208 | SER | SER | 432 | 213 | LYS | LYS |
| 214 | 209 | PHE | PHE | 433 | 214 | SER | TYR |
| 215 | 210 | ASN | ASN | 434 | 215 | CYS | GLY |
| 216 | 211 | ARG | ARG | | | | |
| 217 | 212 | GLY | GLY | | | | |
| 218 | 213 | GLU | GLU | | | | |
| 219 | 214 | CYS | CYS | | | | |

Table S3 RMSD (Å) of the three crystal structures by comparing of full mab, V domain and C domain using Pymol align module.

| | 5kmv-5kna | 5kmv-4xxd | 5kna -4xxd |
|---|---|---|---|
| Full mab | 4.045 | 1.304 | 3.173 |
| V domain | 0.575 | 0.792 | 0.680 |
| C domain | 0.382 | 0.625 | 0.612 |

Table S4. Surface area of the antibody-antigen interface of selected complexes.

| Antibody | # of chains | [1]S_t | [2]S_LC | [2]S_HC | [3]H-bonds | | | [3]hydrophobic | | | [3]electrostatic | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| sola | 1mer | 1889.7 | 39.8% | 60.2% | 10.6 | 1.4 | 9.2 | 5.9 | 3.9 | 2 | 1.3 | 0 | 1.3 |
| | 5mer | 1456.8 | 38.6% | 61.4% | 9.2 | 5 | 4.2 | 8.2 | 0.1 | 8.2 | 2.1 | 1.2 | 0.8 |
| | 16mer | 1818.7 | 42.8% | 57.2% | 14.6 | 7.7 | 6.9 | 0 | 0 | 0 | 4.7 | 3.5 | 1.2 |
| Crenezumab | 1mer | 1785.2 | 51.7% | 48.3% | 7.0 | 1.4 | 5.6 | 7.2 | 4.1 | 3.1 | 1 | 0 | 1 |
| | 5mer | 1505.5 | 46.7% | 53.3% | 13.8 | 7.2 | 6.6 | 0.6 | 0.3 | 0.3 | 2.1 | 1.1 | 0.9 |
| | 16mer | 1667.3 | 34.1% | 65.9% | 9.2 | 2.1 | 7.1 | 0 | 0 | 0 | 1.6 | 1 | 0.6 |
| chimera | 1mer | 1989.2 | 55.4% | 44.6% | 9.9 | 2.0 | 8.0 | 8.4 | 5.0 | 3.4 | 1 | 0 | 1 |
| | 5mer | 1724.5 | 39.3% | 60.7% | 9.4 | 6.4 | 3 | 7.6 | 1 | 6.6 | 2.4 | 2.4 | 0 |
| | 16mer | 887.1 | 6% | 94% | 5.2 | 0.2 | 5 | 0 | 0 | 0 | 0 | 0 | 0 |

[1]. Total interface area.

[2]. Percentage of the surface area between light chain/heavy chain and Aβ.

[3]. H-bonds, hydrophobic and electrostatic interactions are listed in total, with light chain and heavy chain respectively.

Table S5. Contacts change between solanezumab and crenezumab in complex with Aβ12-28 Monomer.

| Res#[1] | Res#[2] | Resname[3] | Contact | Resname[4] | Contact | Δcontact[5] |
|---|---|---|---|---|---|---|
| 250[6] | 31[H] | ARG | 2.15 | SER | 0 | 2.15 |
| 54 | 49[L] | TYR | 2.4 | TYR | 0.86 | 1.54 |
| 220 | 1[H] | GLU | 0.98 | GLU | 0.05 | 0.93 |
| 252[6] | 33[H] | SER | 2.78 | GLY | 1.85 | 0.93 |
| 41[6] | 36[L] | PHE | 0.89 | TYR | 0 | 0.89 |
| 61 | 56[L] | SER | 1.07 | SER | 0.24 | 0.83 |
| 272 | 52A[H] | SER | 1.18 | SER | 0.37 | 0.81 |
| 39 | 34[L] | HIS | 0.79 | HIS | 0 | 0.79 |
| 317 | 94[H] | SER | 1.92 | SER | 1.13 | 0.79 |
| 251 | 32[H] | TYR | 3.9 | TYR | 3.12 | 0.78 |
| 221 | 2[H] | VAL | 1.05 | VAL | 0.4 | 0.65 |
| 320 | 97[H] | TYR | 2.14 | TYR | 1.53 | 0.61 |
| 318 | 95[H] | GLY | 1.39 | GLY | 0.88 | 0.51 |
| 96 | 91[L] | SER | 1.19 | SER | 1.69 | 0.5 |
| 254 | 35[H] | SER | 0.31 | SER | 0.77 | 0.46 |
| 31 | 27D[L] | TYR | 0.2 | TYR | 0.64 | 0.44 |
| 319 | 96[H] | ASP | 2.42 | ASP | 2 | 0.42 |
| 101 | 96[L] | TRP | 1.28 | TRP | 1.69 | 0.41 |
| 62 | 57[L] | GLY | 0.39 | GLY | 0 | 0.39 |
| 51 | 46[L] | LEU | 0.94 | LEU | 0.55 | 0.39 |
| 245 | 26[H] | GLY | 0.36 | GLY | 0 | 0.36 |
| 269[6] | 76[H] | GLN | 0.76 | SER | 0.45 | 0.31 |
| 271 | 52[H] | ASN | 0.93 | ASN | 0.67 | 0.26 |
| 99 | 94[L] | VAL | 0.27 | VAL | 0.52 | 0.25 |

1. Residue number in the MD simulation.

2. Residue number in the Kabat sequence numering.

3. The residue names in solanezumab

4. The residue names in crenezumab.

5. Contact difference between the specific residue in solanezumab and crenezumab. Only residues with Δcontact > 0.25 were listed

6. The residues at this site is different between solanezumab and crenezumab.

Table S6. Details about the simulation systems in the search of Aβ 5mer/16mer- Crenezumab complexes

| Model | Antibody | Antigen | epitope | Total atoms | Cations | Anion | water | Time (ns) | $E_{Binding}$ |
|---|---|---|---|---|---|---|---|---|---|
| Cmab5a | Crenezumab | Aβ11-42 pentamer | 13-15 | 227351 | 209 | 206 | 72695 | 100 | -37.2±4.5 |
| Cmab5 | Crenezumab | Aβ11-42 pentamer | 13-15 | 192947 | 176 | 173 | 61249 | 200 | -39.8±4.4 |
| Cmab5c | Crenezumab | Aβ11-42 pentamer | 21-25 | 206592 | 190 | 187 | 65788 | 100 | 2.4±4.5 |
| Cmab5d | Crenezumab | Aβ11-42 pentamer | 21-25 | 192978 | 176 | 174 | 61264 | 60 | 28.7±4.4 |
| Cmab5e | Crenezumab | Aβ11-42 pentamer | 21-25 | 196838 | 180 | 178 | 62548 | 60 | 78.2±4.3 |
| Cmab16a | Crenezumab | Aβ11-42 16mer | 13-15 | 286697 | 266 | 252 | 90690 | 100 | 54.3±6 |
| Cmab16b | Crenezumab | Aβ11-42 16mer | 13-15 | 222443 | 203 | 189 | 69314 | 80 | 139.2±6.2 |
| Cmab16 | Crenezumab | Aβ11-42 16mer | 13-15 | 286625 | 266 | 252 | 90666 | 100 | -195.8±6.3 |

Table S7. Contacts change between solanezumab and crenezumab in complex with Aβ5mer/16mer.

| | | | solanezumab | | crenezumab | | Δcontact[3] |
|---|---|---|---|---|---|---|---|
| | Res#[1] | Res#[2] | Resname | Contact | Resname | Contact | |
| 5mer | 32 | 27E$^{L}$ | SER | 0 | SER | 2.84 | 2.84 |
| | 247 | 28$^{H}$ | THR | 0 | THR | 2.33 | 2.33 |
| | 251 | 32$^{H}$ | TYR | 0 | TYR | 1.96 | 1.96 |
| | 31 | 27D$^{L}$ | TYR | 0 | TYR | 1.84 | 1.84 |
| | 250[4] | 31$^{H}$ | ARG | 2.2 | SER | 4.02 | 1.82 |
| | 33 | 28$^{L}$ | ASP | 0.09 | ASN | 1.84 | 1.75 |
| | 272 | 52A$^{H}$ | SER | 0 | SER | 0.99 | 0.99 |
| | 319 | 96$^{H}$ | ASP | 0 | ASP | 0.89 | 0.89 |
| | 61 | 56$^{L}$ | SER | 0 | SER | 0.88 | 0.88 |
| | 59 | 54$^{L}$ | ARG | 0 | ARG | 0.8 | 0.8 |
| | 34 | 29$^{L}$ | GLY | 0 | GLY | 0.58 | 0.58 |
| | 62 | 57$^{L}$ | GLY | 0 | GLY | 0.54 | 0.54 |
| | 37 | 32$^{L}$ | TYR | 0 | TYR | 0.43 | 0.43 |
| 16mer | 247 | 28$^{H}$ | THR | 0 | THR | 2.06 | 2.06 |
| | 35 | 30$^{L}$ | ASN | 0.04 | ASP | 1.8 | 1.76 |
| | 249 | 30$^{H}$ | SER | 0.11 | SER | 1.3 | 1.19 |
| | 220 | 1$^{H}$ | GLU | 0 | GLU | 1.01 | 1.01 |
| | 34 | 29$^{L}$ | GLY | 0.1 | GLY | 0.89 | 0.79 |
| | 276 | 56$^{H}$ | SER | 0.96 | SER | 1.6 | 0.64 |
| | 273 | 53$^{H}$ | VAL | 0.92 | ASN | 1.53 | 0.61 |
| | 33 | 28$^{L}$ | ASP | 0.75 | ASN | 1.34 | 0.59 |
| | 37 | 32$^{L}$ | TYR | 0.02 | TYR | 0.54 | 0.52 |
| | 98 | 93$^{L}$ | HIS | 0.01 | HIS | 0.31 | 0.3 |
| | 61 | 56$^{L}$ | SER | 0 | SER | 0.25 | 0.25 |
| | 319 | 96$^{H}$ | ASP | 0.95 | ASP | 0.4 | -0.55 |
| | 250 | 31$^{H}$ | ARG | 3.28 | SER | 2.88 | -0.4 |

1. Residue number in the MD simulation.

2. Residue number in the Kabat sequence numering.

3. Contact difference between the specific residue in solanezumab and crenezumab. Only residues with Δcontact > 0.25 were listed

4. The residues at this site is different between solanezumab and crenezumab.

Table S8. The shortest distance from distant sites to Phe20 of peptide in the Fab/Aβ monomer complex.

| [1]Res # | name | chain | Phe20 solan | cren | Lys16 chimera |
|---|---|---|---|---|---|
| 205 | [2]GLY/GLY | L | 485 | 432 | n/a |
| 347 | LYS/ARG | H | 525 | 388 | n/a |
| 410 | GLN/LYS | H | 333 | 275 | n/a |
| 351 | GLY/GLU | H | 449 | 330 | n/a |
| 352 | GLY/SER | H | 389 | 328 | n/a |
| 413 | ILE/THR | H | 305 | 262 | n/a |
| 417 | ASN/ASP | H | 280 | 239 | n/a |
| 428 | LYS/ARG | H | 313 | 269 | n/a |
| 431 | PRO/SER | H | 406 | 366 | n/a |
| 433 | SER/TYR | H | 472 | 442 | n/a |
| 434 | CYS/GLY | H | 461 | n/a | n/a |

1. Residue number in the MD simulation.

2. The two residues indicated that the there is mutation between sola and cre. The first residue is in solanezumab and the second one is in crenezumab.

Table S9. Details about the simulated antibody-antigen complexes.

| Model | Antibody | Antigen | Template pdb | Total atoms | Water/Cation/Anion | Time (ns) |
|---|---|---|---|---|---|---|
| Smab0 | Solanezumab | N/A | 4xxd | 99926 | 31084/85/91 | 200 |
| Smab1 | Solanezumab | Aβ12-28 monomer | 4xxd | 132308 | 41766/116/122 | 200 |
| Smab5 | Solanezumab | Aβ11-42 pentamer | 4xxd | 227351 | 72695/209/206 | 200 |
| Smab16 | Solanezumab | Aβ11-42 16mer | 4xxd | 286625 | 90666/266/252 | 200 |
| Cmab0a | Crenezumab | N/A | 5kmv | 97092 | 30153/85/87 | 100 |
| Cmab0b | Crenezumab | N/A | 5kna | 91058 | 28144/79/81 | 100 |
| Cmab1 | Crenezumab | Aβ12-28 monomer | 5kna | 112141 | 35067/99/101 | 100 |
| Cmab5 | Crenezumab | Aβ11-42 pentamer | 5kna | 201298 | 64025/185/182 | 200 |
| Cmab16 | Crenezumab | Aβ11-42 16mer | 5kna | 247395 | 77613/228/214 | 200 |
| CHmab0a | Crenezumab chimera | N/A | 5kmv | 143623 | 45609/129/132 | 100 |
| CHmab0b | Crenezumab chimera | N/A | 5kna | 102520 | 31934/90/93 | 100 |
| CHmab1 | Crenezumab chimera | Aβ12-28 monomer | 5kna | 124916 | 39294/111/114 | 100 |
| CHmab5 | Crenezumab chimera | Aβ11-42 pentamer | 5kna | 206839 | 65846/189/187 | 200 |
| CHmab16 | Crenezumab chimera | Aβ11-42 16mer | 5kna | 258732 | 81521/238/226 | 200 |