

Additional file 4: Structure-based sequence alignment of all CSA-binding DBL domains from A4 and 3D7 *var2CSA*. The disulfide linkages are coloured in pairs. ‘S’ and ‘H’ denote sheet and helix region respectively in the A4 DBL 3X crystal structure (PDB code: 3BQK). The regions underlined in the N- and C-terminal regions could not be completely aligned. Residues underlined and in italics are disordered in A4 DBL 3X. Residues forming secondary structure in individual DBL domains are shown as bold.

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-----SSS-----
A4-DBL3X 1218 --SCDLNATNYIRGCQSKT-----YDGKIFPGKGGEKQWICCKD-TIIHG-D---- 1259
3D7-DBL3X 1209 --SCDCSEPIYIRGCQPKI-----YDGKIFPGKGGEKQWICCKD-TIIHG-D---- 1250
3D7-DBL2X 535 ASLTNCYKCDKCKSEQSKNNK-----NWIKKSSGKEGGLQ--KE----YA-N---- 576
A4-DBL2X 536 ASLTNGYKCDKCKSGTSRSKKN-----WIWKK--SSGNE--EGLQE 572
A4-DBL5ε 1989 DRCFDQDTKMKVCDLIADAIGCKDKTKLD---ELDEWNDMDLRGTYN-K---- 2033
3D7-DBL5ε 1983 DRCFPDDKSKMKVCDLIGDAIGCKHKTKLDEL---DEWNDVDMRDPYN-K---- 2027
A4-DBL6ε 2320 HHEYDKGNDYICNKYKNIHDRMK-----NNGNFVTDNFVKKSW-----E-I---- 2360
3D7-DBL6ε 2323 HHEYD-KGNDYI--C-NKY-----KNINVMKKNNDTWT--TD-LVKNSD---- 2361

-----SSS-----HHHHH---HHH---HHH-----HHHHHHHHHHHHHHHHHHHHHH
A4-DBL3X 1260 --TN-GACIPPRTQNLCVGELWDKSYGGRSNIKNDT---KELLKIKIKNAIHKETELLYEY 1314
3D7-DBL3X 1251 --TN-GACIPPRTQNLCVGELWDKRYGGRSNIKNDT---KESLKQKIKNAIQKETELLYEY 1305
3D7-DBL2X 577 --TI-G--LPPRTQSLCLVVCLDEKGGKQELKNIR-TNSELLKEWIIAFAFHGKLNKPS- 630
A4-DBL2X 573 EYAN-TIGLPPRTQSLYLGNLPLKLENCEDVKDINFDTKEKFLAGCLIVSFHEGKLNKKRY 632
A4-DBL5ε 2034 --HK-GVLIPPRRRLCFSRIVR---GPANLRN---LNEFKEEILKGAQSEGKFLGNY- 2082
3D7-DBL5ε 2028 --YK-GVLIPPRRRLCFSRIVR---GPANLRN---LKEFKEEILKGAQSEGKFLGNY- 2076
A4-DBL6ε 2361 --SN-GVLIPPRRKNLFLYIDPSK---ICEYKRD---PKLFDKFIYWSAFTEVERLKKK- 2410
3D7-DBL6ε 2362 --INKGVLLPPRRKNLFLKIDESD---ICKYKRD---PKLFDKFIYSSAI SEVERLKKV- 2412

-----HHHHHHHHHHHHHHHHHHHH---HH
A4-DBL3X 1315 HDTGTAIISKNDKKGQK---NDPNGLPKGFCHAVQRSFIDYKNMILGTSV---NIYEH 1368
3D7-DBL3X 1306 HDKGTAIISRNP MKGQKEEKNNSNGLPKGFCHAVQRSFIDYKNMILGTSV---NIYEH 1363
3D7-DBL2X 631 -----HEK-----K-----NDNG--KKLCKALEYSFADYGLIKGTSI---WDNEY 667
A4-DBL2X 633 PQKN-----SGNKENLCKALEYSFADYGLIKGTSI---WDNEY 669
A4-DBL5ε 2083 -----YKEHKDK-----EKALEAMKNSFYDYEDIIKGTDM---LTNIE 2117
3D7-DBL5ε 2077 Y-----NEDKDK-----EKALEAMKNSFYDYEYIIKGS DM---LTNIQ 2111
A4-DBL6ε 2411 Y-----GGARAKVVHAMKYSFTDIGSIIKGDMMEMKNSDK 2446
3D7-DBL6ε 2413 Y--GEA-----KTKVVHAMKYSFADIGSIIKGDMMEMNSDK 2443

HHHHHHHHHHHHHHHHHHHH-----HHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
A4-DBL3X 1369 IGKLOEDIKKIIIEKGTPOQKDK-----IGGVGSSSTENVNAWWKGIEREMWDAVRCAITKI 1422
3D7-DBL3X 1364 IGKLOEDIKKIIIEKGTTKQNGK-----T--VSGAENVNAWWKGI EGEMWDAVRCAITKI 1416
3D7-DBL2X 668 TKDLELNLQKIFGKLFKRYIKKNNTAEQDTSYSSLDELRESWNTNKKYIWLAMKHGAGMN 728
A4-DBL2X 670 TKDLELNLQNNFGKLFKGYIKKNNTAEQDTSYSSLDELRESWNTNKKYIWTAMKHGAEMN 730
A4-DBL5ε 2118 FKDIKIKLDRLLEKET--N-----NTKKAEDWWTNKKSIWNAMLCGYKKS 2161
3D7-DBL5ε 2112 FKDIKIKLDRLLEKET--N-----NTEKVDWWTNKKSIWNAMLCGYKKS 2154
A4-DBL6ε 2447 IGKILGD-----TDGQ-----N-EKRKKWDMNKYHIWESMLCGYRE- 2482
3D7-DBL6ε 2444 IGKILGDGVGQN-----EKRRKKWDMNKYHIWESMLCGYKHA 2485

HH-----HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
A4-DBL3X 1423 NK---KNNNSIFN-GDECGVSS--PPTGNDEDDQSVSWFKEWGEQFCIERLRYEQNI REACTI 1478
3D7-DBL3X 1417 NKK---QKNGTF-SIDECGIF--PPTGNDEDDQSVSWFKEWGEQFCIERLQYEQNI RACTN 1473
3D7-DBL2X 729 STTC-CGDGSVTGS SSSCDDI--PTI-DLIPQYLRFLQEWVEHFCKQROEKVKPV IENC-- 783
A4-DBL2X 731 ITTC-NADGSVTGS SSSCDDI--PTI-DLIPQYLRFLQEWVEHFCEQROAKVKDVITNC-- 785
A4-DBL5ε 2162 --GNKIID-PSWCTI-----PTT-ETPPQFLRWIKEWGTVNCIQKEEHKEYVVKSCSN 2210
3D7-DBL5ε 2155 -SGNKIID-PSWCTI-----PTT-ETPPQFLRWIKEWGTVNCIQKEEHKEYVVKSCSN 2204
A4-DBL6ε 2483 -AEGDTET-NENCRFPD-----IESV---PQFLRWFOEWSENFCDRRQKLYDKLNSECIS 2532
3D7-DBL6ε 2486 --YGNISE-NDRKMLD-----IPNNDDEHQFLRWFOEWTEHFCTKRNELYENMVTACNS 2536

-----HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
A4-DBL3X 1479 NGKNEKCKINSKSGQGDKI--QGACKRKCEKYKYYISEKKQEWKQKTKYENK-----Y 1530
3D7-DBL3X 1474 N-----GQ--GDKI---QGDCKRCEKYKYYISEKKQEWKQKTKYENK-----Y 1513
3D7-DBL2X 784 -----KSCKES-GGTNGECCKTECKNKCEVYKFFIEDCKGGDGTAGSSWVKRWDQIYKRS 838
A4-DBL2X 786 -----KSCKESGNKKTEC-KTKCKDECEKYKFFIEAGTAGGGIGTAGSPWVKRWDQIYK 840
A4-DBL5ε 2211 VTNLGA-----QASE-SNNCTSEIKKYQEWRSRKSIRWETISKRYKYYKRMDILKDV 2261
3D7-DBL5ε 2205 VTNLGA-----QESE-SKNCTSEIKKYQEWRSRKSIRWETISQYKYY-----KG 2248
A4-DBL6ε 2533 AECTN-----G--SVD-NSKCTHACVNYKNYILTKKTEYEIQTNKYDNE-----F 2574
3D7-DBL6ε 2537 ARCNT-----SNGSVDKKECTEACKNYSNFILIKKKEYQSLNSQYDMN---YKETKA 2585

-----HHHH
A4-DBL3X 1531 -----VGKS-----ASDLLKEN---YPECISAN-----PDFIFND-----NIEY 1561
3D7-DBL3X 1514 -----VGKS-----ASDLLKEN---YPECISAN-----PDFIFND-----NIEY 1543
3D7-DBL2X 839 KYIEDAKRNRKAGTKNCGPSSSTTNAENK-----VQSDIDSFFKH---LIDIGLTPS 889
A4-DBL2X 841 RYSKHIEDAKR-----NRKAGTKN-----GTSSTTNAASTDENKVQ--SDID 883
A4-DBL5ε 2262 KEPD-----ANTYLREH-----SK-----EPNANEYLKKHSK----- 2276
3D7-DBL5ε 2249 MDEF-----KNTFKNIK-----E-----DAN-----EPNANEYLKKHSK----- 2279
A4-DBL6ε 2575 KNKN SNDKD-----APDYLKEK-----NDNKCEC--LNKHIDDKNKTWKNPYETLED 2620
3D7-DBL6ε 2586 EKKE-----SPEYFKDKNGECSCLESEY-----PKDETRW-----KNEVKNN-- 2622

HHH---HHH-----
A4-DBL3X 1562 KTYYPYGDYSSICSCE----- 1577
3D7-DBL3X 1544 KTYYPYGDYSSICSCE----- 1559
3D7-DBL2X 890 -SYLSIVLDDNICGADK-APWTTYTYTTTEKN----- 921
A4-DBL2X 883 SFFKHLIDIGLTPSSYLSNVLDDNICGADKAPWTTYTYTTTEKCN 930
3D7-DBL5ε -----
A4-DBL5ε -----
A4-DBL6ε 2621 T--FKSKCDCPKP----- 2631
3D7-DBL6ε 2623 -----CMCKPP----- 2628

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