SUPPLEMENTARY INFORMATION

Crystal structure of a heterodimer of editosome interaction proteins in complex with two copies of a cross-reacting nanobody

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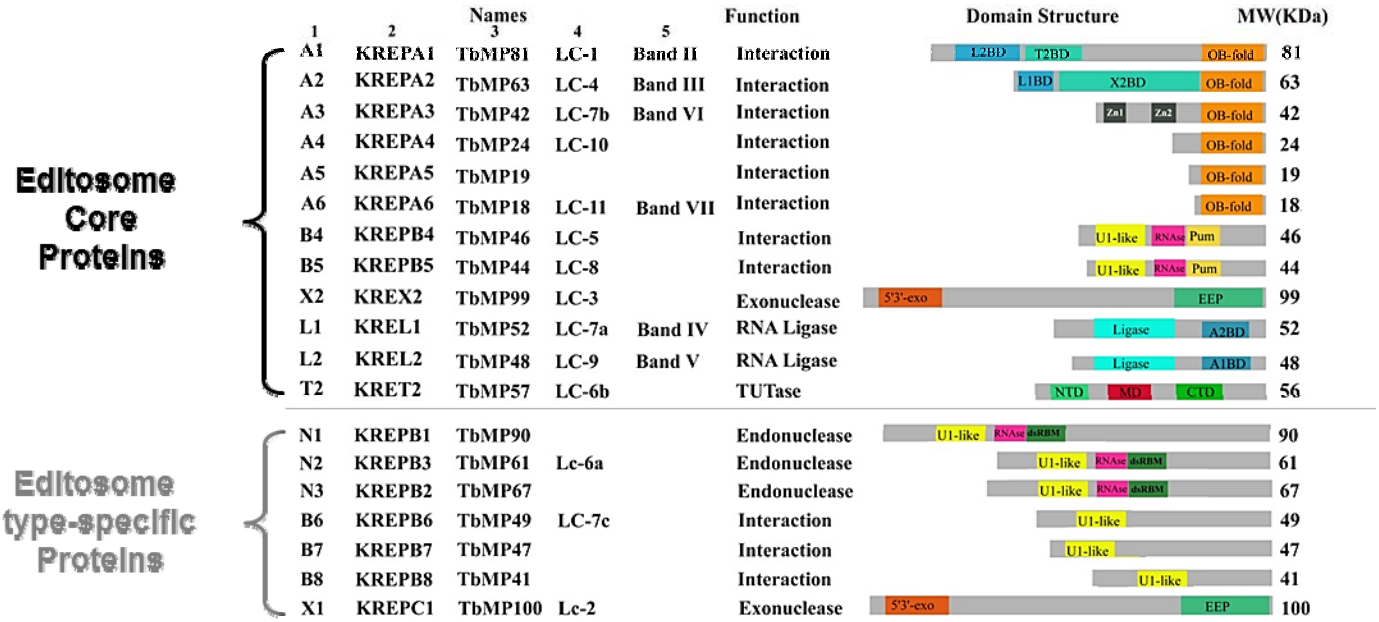
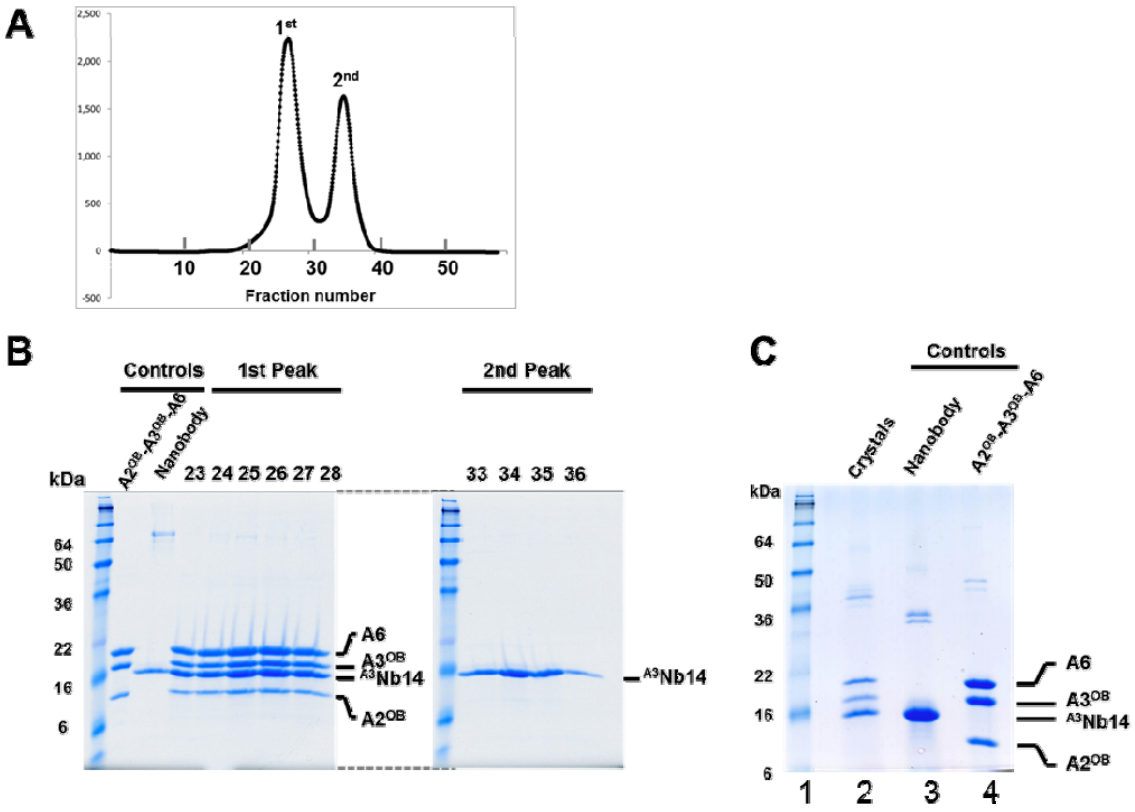
SUPPLEMENTARY FIGURES



Supplementary Figure S1. Editosome proteins in *T. brucei*. First column: the short protein names used in this application (1,2). **Second, third, fourth** and **fifth** columns: alternative nomenclatures from, respectively (3-7). **Last** column: molecular weights of full length proteins in *T. brucei.* The structurally identified (8-10) or putative (4) domains are: **L1BD** = L1-binding domain; **T2BD** = T2 binding domain; **OB-fold** in six OB-fold interaction proteins; **L2BD** = L2-binding domain; **X2BD** = X2-binding domain; **U1-like** = U1-like zinc-finger domains in the endonucleases **N1, N2, N3** and the interaction proteins **B4, B5, B6, B7 and B8**; **RNase III** = RNase-III-like motifs; **Pum** = Pumilio domain; **5′3′exo** = domain with structural homology to 5′→3′ exoribonuclease domain; **EEP** = endonuclease/exonuclease/phosphatase domain; **Ligase =** ligase domain; **A1BD** = A1-binding domain; **A2BD** = A2-binding domain; **NTD** = N-terminal, **MD** = middle and **CTD =** C-terminal domain of the 3'-terminal uridylyl transferase (TUTase) T2. **Zn1** in A3 is a Zn-finger motif which is also present in the L2BD of A1 and the L1BD of A2. **Zn2** in A3 is a Zn-finger motif which is also present in the T2BD of A1 and the X2BD of A2.

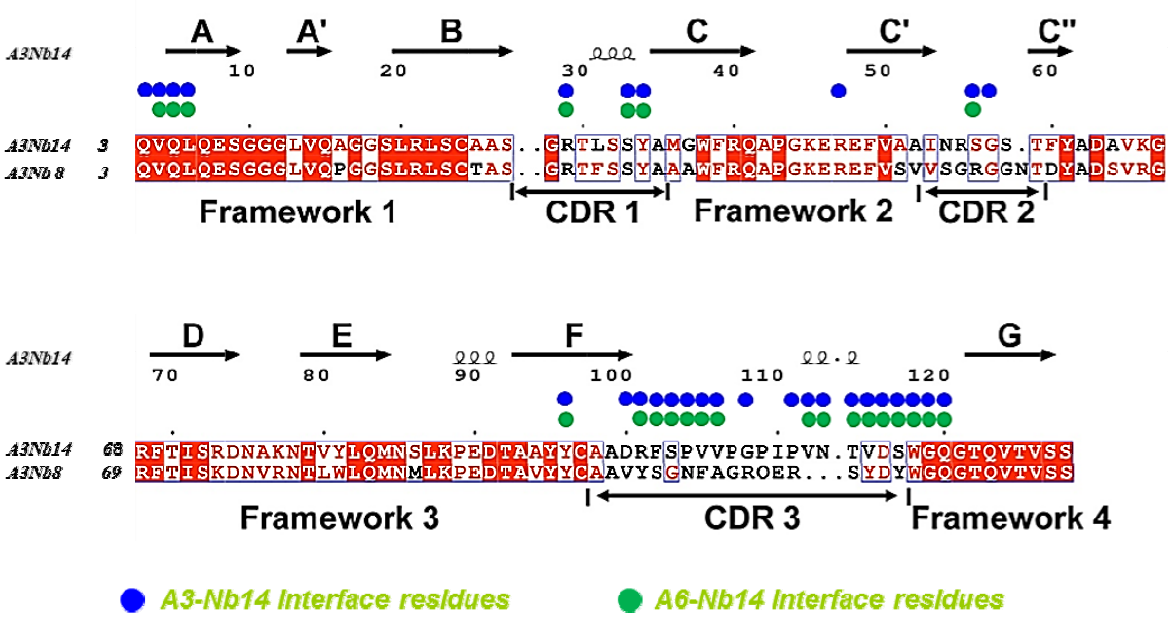


Supplementary Figure S2. Preparation of $A2^{OB}$-$A3^{OB}$-A6-^{A3}Nb14 complexes.

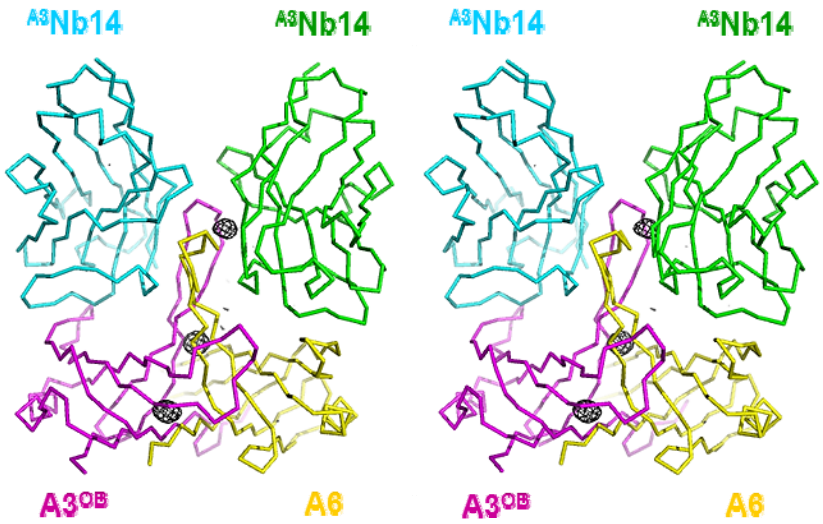
(A) SEC and SDS-PAGE of $A2^{OB}$-$A3^{OB}$-A6-^{A3}Nb14 complex. The $A2^{OB}$-$A3^{OB}$-A6-^{A3}Nb14 complex was purified by gel filtration over a Superdex 200 sizing column. Chromatographic absorbance traces at 280 nm are shown for the $A2^{OB}$-$A3^{OB}$-A6-^{A3}Nb14 complex (1st peak) and unbound ^{A3}Nb14 (2nd peak), as indicated.

(B) Proteins from the major peaks in (A) analyzed on an 8-16% SDS-PAGE gel. Lanes 1 and 10: Molecular weight markers; lanes 2 and 3:$A2^{OB}$-$A3^{OB}$-A6 and nanobody ^{A3}Nb14 as controls; lanes 4-9:1st gel filtration peak fractions 23 to 28; lanes 11-14: 2nd peak fractions 33 to 35. The lanes shown are all from the same gel – the gel has been split only to enable labeling in its center.

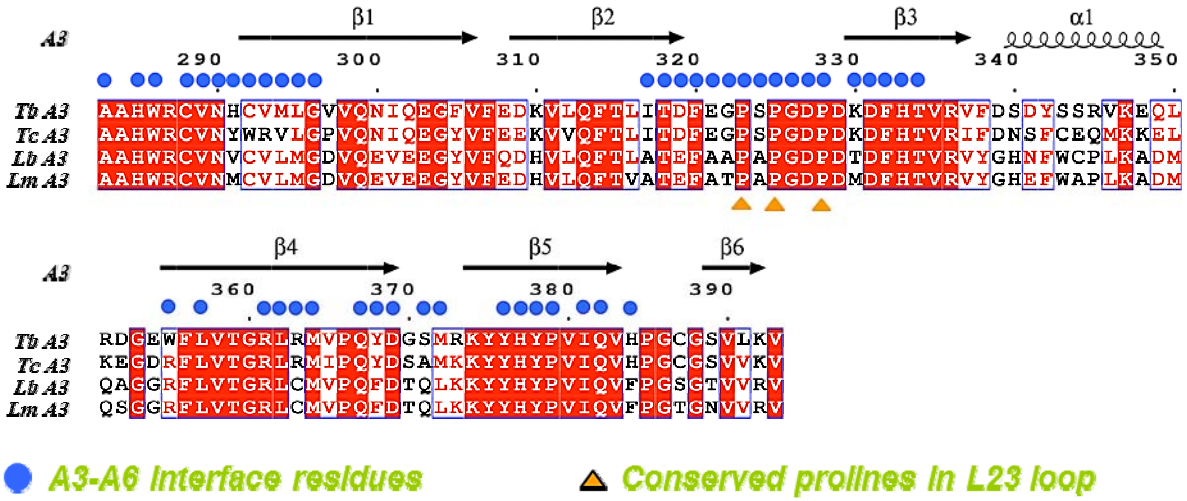
(C) SDS-PAGE of crystals containing $A3^{OB}$-A6-^{A3}Nb14. The crystals were carefully washed before electrophoresis. Dissolved crystals are shown in lane 2. Purified $A2^{OB}$-$A3^{OB}$-A6 and ^{A3}Nb14 are shown in lanes 3 and 4, as controls. Proteins were stained with Coomassie. The numbers to the left of lane 1 indicate the molecular weights of standard proteins.



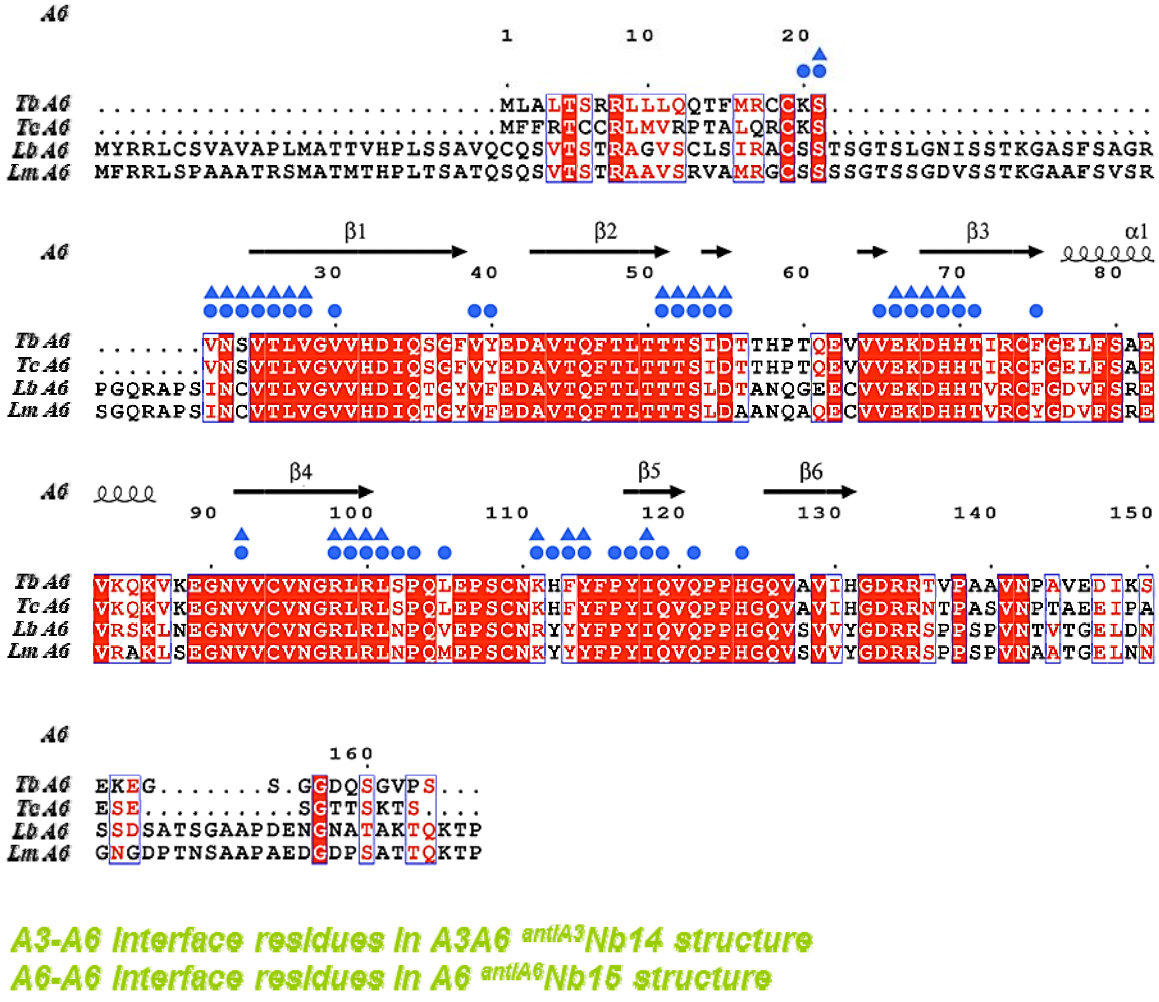
Supplementary Figure S3. Sequence alignment of anti-A3 nanobodies ^{A3}Nb8 and ^{A3}Nb14. The secondary structure elements correspond to the crystal structure of ^{A3}Nb14. Since each A3 and A6 monomer interacts with ^{A3}Nb14, the residues contacting A3^{OB} are labeled by blue circles, and residues contacting A6 by green circles. The three CDR's and framework regions of the nanobodies are indicated according to IMGT. (The double deletions after residue 113 derive from the fact that in the collection of 14 anti-A3 nanobodies obtained, several of these have a residue corresponding to this position).



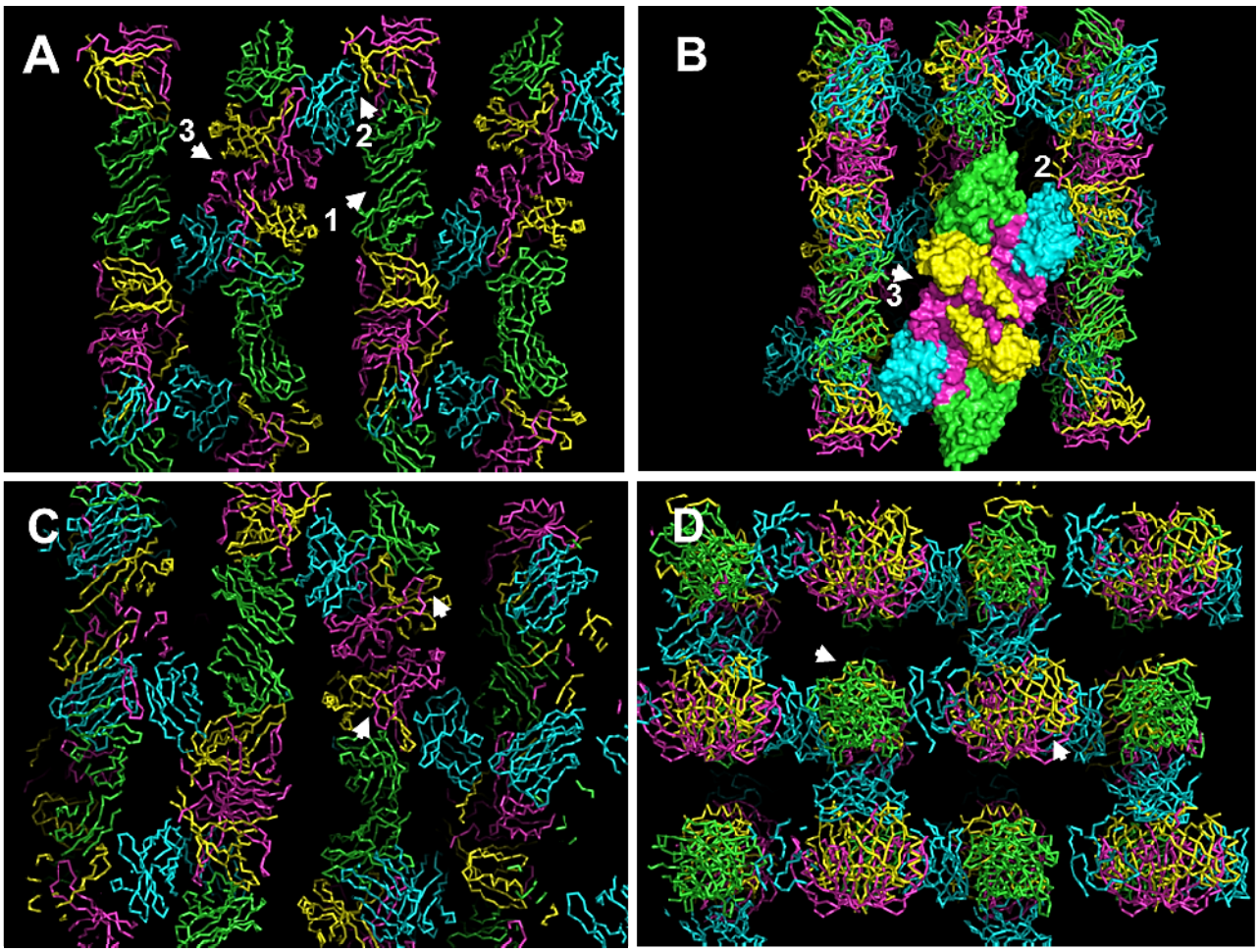
Supplementary Figure S4. Electron densities of Selenomethionines of A3. Stereo-view of the $A3^{OB}$-A6-^{A3}Nb14 complex and the anomalous difference map. The $A3^{OB}$-A6-^{A3}Nb14 heterotetrameric complex is shown as ribbons. The anomalous difference map calculated from the Se MAD data is shown in gray mesh as contoured at 4.0 σ. The three sites observed all occur in one chain thereby unambiguously identifying that the two OB folds are different. Colors: $A3^{OB}$ magenta with its ^{A3}Nb14 bound in blue, A6 yellow with its ^{A3}Nb14 bound in green.



Supplementary Figure S5. Family sequence alignments of A3. Multiple sequence alignment of C-terminal OB-domains from *T. brucei* A3 with orthologous proteins from other Kinetoplastida species. Lm, *Leishmania major*; Lb, *Leishmania brasiliensis*; Tc, *Trypanosoma cruzi*; Tb, *Trypanosoma brucei*. *T. brucei* A3 amino acids are numbered. The secondary structure elements correspond to the crystal structure of *T. brucei* A3. Strictly conserved residues are in the filled red boxes. A6-binding residues are depicted by blue circles above the sequences. Conserved prolines in the L23 loop are indicated by triangles below the sequences.



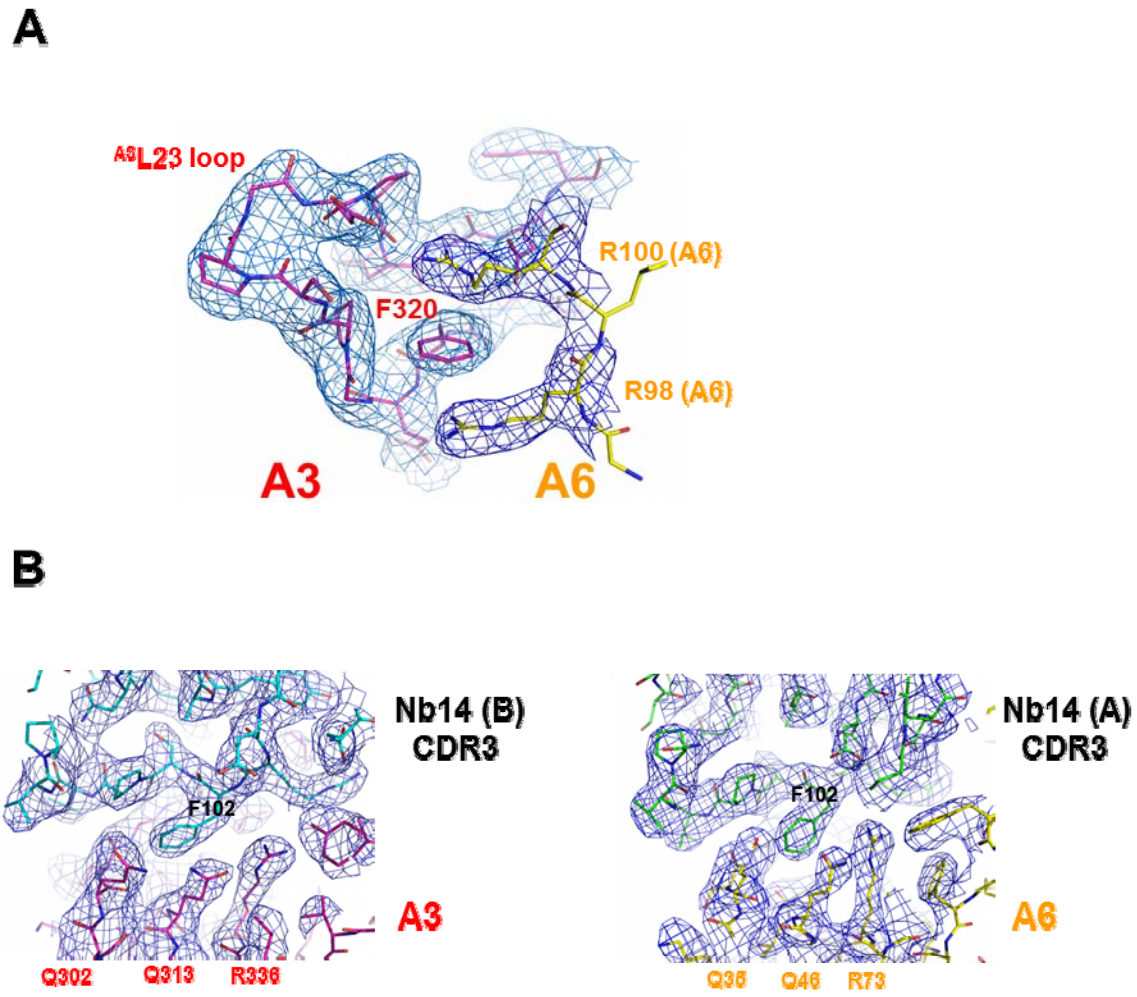
Supplementary Figure S6. Family sequence alignment of A6. Trypanosomatid species shown are: Lm, *Leishmania major*; Lb, *Leishmania brasiliensis*; Tc, *Trypanosoma cruzi*; Tb, *Trypanosoma brucei*. The *T. brucei* A6 amino acids are numbered. The secondary structure elements correspond to the crystal structure of *T. brucei* A6. Strictly conserved residues are in the filled red boxes. Contact residues involved in $A3^{OB}$-A6 heterodimer interface (current structure) and in the A6-A6 homodimer interface (PDB-ID: 3K7U)(10) are depicted by filled circles and triangles, respectively.



Supplementary Figure S7. Lattice contacts in the $A3^{OB}$-A6-^{A3}Nb14 crystals. Crystal lattice contacts are mediated by both nanobodies and the $A3^{OB}$-A6 dimer. Colors: $A3^{OB}$ magenta; A6 yellow; ^{A3}Nb14 bound to $A3^{OB}$ blue; ^{A3}Nb14 bound to A6 green.

(A and B). First arrow: the most extensive pairwise nanobody-nanobody interactions occur when two anti-parallel strands of one nanobody form a four-stranded antiparallel β-sheet with the two equivalent β-strands from a neighboring nanobody. Second arrow: in this crystal contact an ^{A3}Nb14 nanobody engages three nanobodies of neighboring heterotetramers. Third arrow: important crystal contacts are made between the β-surfaces of two adjacent $A3^{OB}$-A6 dimers, burying 2000 $Å^2$ surface area, leading to an $(A3^{OB}\text{-A6})_2$ heterotetramer of four OB folds of two different chain types.

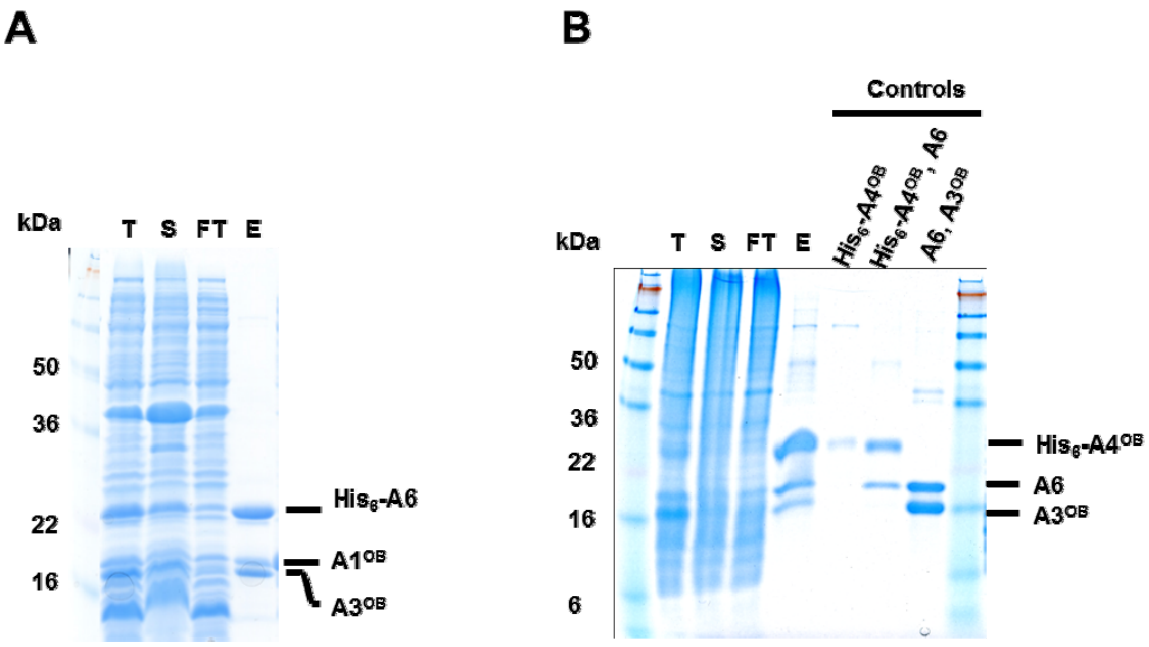
(C and D) The L23 loop positions of $A3^{OB}$ and A6 are indicated with arrows, showing that none of the L23 loops are engaged in crystal contacts.



Supplementary Figure S8. Electron density from the A3^{OB}-A6-^{A3}Nb14 complex.

(A) Electron density map of the A3^{OB}-A6-^{A3}Nb14 in a region at the dimer interface of A3 and A6.

(B) Electron density maps of the A3^{OB}-A6-^{A3}Nb14 in the vicinity of residue F102 at Interaction Region 1. $2mF_o - DF_c$ electron density maps are shown as a blue mesh, contoured at 1 σ. Selected residues from the A3, A6, and CDR3 are labeled.



Supplementary Figure S9. Formation of A1^{OB}-A3^{OB}-A6 and A4^{OB}-A3^{OB}-A6 ternary complexes.

(A) A1^{OB}-A3^{OB}-A6 ternary complex. The gene encoding residues 20-164 of *T. brucei* A6, preceded by an N-terminal 6xHistidine tag, was cloned into a pRSF vector (Novagen). The gene encoding residues 626-762 of *T. brucei* A1 (A1^{OB}) and the gene encoding residues 245-393 of *T. brucei* A3 (A3^{OB}) were cloned into the bi-cistronic expression vector pACYC (Novagen) without His-tag. His$_6$A6, A1^{OB} and A3^{OB} are co-expressed in *E. coli* and co-purified by Ni-NTA chromatography via an N-terminal His$_6$-tagged A6.

(B) A4^{OB}-A3^{OB}-A6 ternary complex. The gene encoding residues 34-218 of *T. brucei* A4 (A4^{OB}), preceded by an N-terminal 6xHistidine tag, was cloned into a pRSF vector. The gene encoding residues 20-164 of *T. brucei* A6 and the gene encoding residues 245-393 of *T. brucei* A3 (A3^{OB}) were cloned into the bi-cistronic expression vector pACYC without His-tag. His$_6$A4^{OB}, A3^{OB} and A6 are co-expressed in *E. coli* and co-purified by Ni-NTA chromatography via an N-terminal His$_6$-tagged A4^{OB}. The soluble lysates were applied to a Ni-NTA column, washed with 20 mM imidazole and subsequently eluted with 250 mM imidazole. Proteins were analyzed on 8-16% SDS-PAGE gel and stained with Coomassie. Molecular weight markers are indicated on the left. T: total lysate; S: soluble fraction; FT: flow-through Ni-NTA; E: Ni-NTA elution fraction.

SUPPLEMENTARY TABLES

Supplementary Table S1. A6 residues interacting with $A3^{OB}$ and A6

A6	A3 residue ($A3^{OB}$ -A6 dimer)[a]				
	BSA (Å²)	M-M	S-S	M-S	S-M
Lys20	30			Leu295 Trp355	
Ser21	88	Leu295	Thr318 Asp319 Trp355	Leu295 Trp355	Leu295 Gly296 Thr318 Asp319(H)
Val22	74	Val293 Met294 Leu295(H)	Val293 Leu295	Met294 Leu295 Thr318	Val293 Met294 Leu295
Asn23	57		Met294 Thr318 His333	Met294	
Ser24	48	Cys292 Val293(H)	Val293	Cys292 Val293 Met294	Val293
Val25	38	His291	Cys292 Met294 Leu362		His291
Thr26	45	Val289 Asn290 His291(H)	His291	His291	
Leu27	25	Val289	Asn290 Leu362		
Val28	55	Val289(H)	Val289	Val289	Cys288
Val30	15		Ala283		
Val39	4		Ser324		
Tyr40	66		Ser324 Pro325		
Thr51	20		Val289 Asn290		Val289
Thr52	21			Val289	
Ser53	32		Val289	Val289	
Asp55	15		Arg361		
Glu66	75		Arg361(H.SB) Arg363(H.SB)		
Lys67	2	Arg363			
Asp68	68		Arg363(H.SB) Met364		Leu362 Arg363 Met364
His69	31			Met364	
His70	43		Leu362 Met364		Leu362
Val92	10		Ala283		
Arg98	60		Phe320 Glu321		Glu321 Gly322
Leu99	61		His333 Leu362 Pro379	Asp331 His333	

A6	A6 residue (A6-A6 dimer)[b]				
	BSA (Å²)	M-M	S-S	M-S	S-M
Lys20					
Ser21					
Val22	112	Thr26 Leu27 Val28(H)	Ser53	Leu27 Thr51	Val28 Thr52
Asn23	43	Thr26	Leu27 Thr51 His70	Leu27	
Ser24	45	Val25 Thr26(H)	Thr26	Val25	Thr26
Val25	32	Ser24	Val25		Ser24
Thr26	39	Val22 Asn23 Ser24(H)	Ser24	Ser24	
Leu27	23	Val22	Asn23	Asn23	Val22
Val28		Val22(H)		Val22	
Val30					
Val39					
Tyr40					
Thr51	20		Asn23		Val22
Thr52	16			Val22	
Ser53	40		Val22 Arg98	Val22	
Asp55					
Glu66	70		Arg98(SB) Arg100(SB)		
Lys67	5			Arg100	
Asp68	62		Leu99 Arg100(H.SB) Leu101(H)		Leu99 Arg100(H) Leu101
His69	17			Leu101	
His70	46		Asn23 Leu99	Leu101	Leu99
Val92					
Arg98	39		Ser53 Glu66(SB)		
Leu99	79		His70	Asp68 His70	

A6	A3 residue (A3^{OB} -A6 dimer)[a]					A6	A6 residue (A6-A6 dimer)[b]				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**		**BSA (Å²)**	**M-M**	**S-S**	**M-S**	**S-M**
Arg100	132		Phe320 Pro323 Asp331(H.SB) Asp327	Asp331	Pro323 Pro328(H) Lys330	**Arg100**	56		Glu66(SB) Asp68(H.SB)	Asp68	Lys67
Leu101	74		Asp331 His333 Pro379	Asp331	Phe332	**Leu101**	84		Asp68(H) Pro116	Asp68	His69 His70
Pro103	14		Pro328			**Pro103**					
Leu105	58		Pro328		Gly326	**Leu105**					
Lys111	14		Tyr376			**Lys111**					
His112	24		Asp369(SB)			**His112**					
Phe113	116		Gln367 Asp369 Tyr376			**Phe113**					
Tyr114	58		Tyr378 Pro379		His377	**Tyr114**					
Phe115						**Phe115**	36		Phe115		
Pro116	54		Pro379 Met364	Pro379 Met364	His377 Pro379	**Pro116**	60		Pro116 Leu101	Pro116	
Tyr117	10		Asp327			**Tyr117**					
Gln119	22		Phe320			**Gln119**					
His124	18		Glu321			**His124**					

BSA: Buried surface area according to Pisa (11), **M-M**: Main chain - Main chain interactions; **S-S**: Side chain - Side chain interactions; **M-S**: Main chain - Side chain interactions; **S-M**: Side chain and Main chain interactions. **H**: Hydrogen bond; **SB**: Salt Bridge.

a: The interface residues in the A3^{OB}-A6 heterodimer structure (Current structure)

b: The interface residues in the A6 homodimer structure (PDB-ID: 3K7U)(10)

Supplementary Table S2. A3 residues interacting with A6 in the $A3^{OB}$-A6 heterodimer.

A3	A6 residue ($A3^{OB}$ -A6 dimer) [a]				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**
Ala283	27		Val30		
His285	33		Ile54		
Cys288	16		Val28	Thr26	
Val289	101	Thr26 Leu27 Val28(H)	Val28 Thr51 Ser53	Leu27 Val28 Thr51	Val28 Thr52
Asn290	43	Thr26 Leu27 Val28	Leu27 Thr51 Asp68 His70	Leu27	Thr26
His291	42	Ser24 Val25 Thr26(H) Leu27	Thr26	Thr26 Leu27	
Cys292	20	Ser24 Val25 Thr26	Val25	Ser24	Ser24 Val25 Thr26
Val293	42	Val22 Asn23 Ser24(H)	Val22 Ser24	Ser24	Ser24
Met294	46	Val22 Asn23 Ser24	Asn23 Val25	Val22	Val22 Asn23 Ser24 Val25
Leu295	48	Ser21 Val22(H) Asn23	Ser21 Val22	Ser21 Val22	Lys20 Ser21 Val22
Gly296	1	Ser21		Ser21	
Ile317	1			Ser21	
Thr318	21		Ser21 Asn23	Ser21	Val22
Asp319	25		Ser21	Ser21(H) Asn23	
Phe320	100		Arg98 Arg100 Gln119	Arg98	
Glu321	40		Arg98 His124	Arg98	
Gly322	18			Arg98 Gln119 Gln121	
Pro323	3		Arg100	Arg100	
Ser324	43		Val39 Tyr40 Phe75	Tyr40	
Pro325	27		Tyr40	Tyr40	
Gly326	34			Leu105	

A3	A6 residue ($A3^{OB}$ -A6 dimer) [a]				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**
Asp327	37		Tyr40 Arg100 Leu105 Tyr117	Leu105	
Pro328	45		Arg100 Leu105	Arg100(H) Leu105	
Lys330	4			Arg100(H)	
Asp331	52		Asn23 Arg100 Leu101	 Leu101	 Leu99 Arg100(H) Leu101 Ser102
Phe332	30	Tyr114		Leu101 Tyr114	
His333	46		Asn23 Leu99 Leu101	 Leu101	 Leu99
Trp355	31		Lys20 Ser21		Lys20 Ser21
Leu357	1		Val22		
Arg361	52		Ser53 Asp55 Glu66		
Leu362	75		Val25 Leu27 His70 Leu99 Ile118	 Asp68 His70	
Arg363	70		 Glu66 Asp68(H)	 Asp68	Val65 Glu66 Lys67 Asp68
Met364	79		Asp68 His69 His70 Pro116	Asp68	 His69
Gln367	28		Phe113		
Tyr368	4			Phe113	
Asp369	33		Phe113 His112	Phe113	
Tyr376	58		Lys111 Phe113	Lys111	Lys111 Tyr114
His377	28	Tyr114		Tyr114 Pro116	
Tyr378	21		Tyr114	Tyr114 Pro116	
Pro379	69		Leu99 Leu101 Tyr114 Pro116	Tyr114 Leu101 Pro116	Pro116
Gln382	4		Glu66		

BSA: Buried surface area according to Pisa (11), **M-M**: Main chain - Main chain interactions; **S-S**: Side chain - Side chain interactions; **M-S**: Main chain - Side chain interactions; **S-M**: Side chain and Main chain interactions. **H**: Hydrogen bond; **SB**: Salt Bridge.

a: The interface residues in the $A3^{OB}$-A6 heterodimer structure (Current structure)

Supplementary Table S3. A.^{A3}Nb14 residues interacting with A3 and A6 in the A3^{OB}- A6 - (^{A3}Nb14)$_2$ heterotetramer.

Nb14	A3 residue (A3^{OB} -A6 dimer)[a]				
	BSA (Å²)	M-M	S-S	M-S	S-M
Gln3	49		Pro366 Tyr368		Pro366 Gln367 Tyr368 Try375
Val4	3			Tyr368	
Gln5	49		Tyr368		Tyr368
Arg29	33		Phe307		
Ser33	20		Phe307	Phe307	Phe307
Tyr34	9		Phe307		
Arg55	64		Phe307 Glu308(SB)		Val306 Phe307(H) Glu308
Arg101	128	Phe307 Val365	Val306 Phe307 Arg336 Pro366 Val365 Tyr378	Phe305 Val306	Tyr378
Phe102	140	Phe305	Gln302 Gly304 Val306 Phe307 Val311 Gln313 Arg336	Val306	Gln302 Glu303 Gly304 Phe305 Gln313
Ser103	29	Gly304 Phe305(H)		Phe305	Phe305
Pro104	18	Glu303 Gly304	Gln302		Glu303
Val105	63	Glu303(H) Gly304	Glu303 Phe305		Gly304
Asn113	24			Gln367(H) Tyr378	
Thr114	68		Thr334 Tyr378	Gln367 Tyr378	
Val115	19			Gln367(H)	
Asp116	29	Pro366 Tyr368(H)	Val365 Try368	Gln367	Pro366 Tyr378
Ser117	16	Tyr368	Try368	Tyr368	Try368
Trp118	56	Tyr368(H) Gly370(H)	Asp369		Tyr368 Asp369 Gly370
Gly119	9	Gly370			
Gln120	48	Gly370 Ser371		Ser371	

Nb14	A6 residue (A3^{OB} -A6 dimer)[a]				
	BSA (Å²)	M-M	S-S	M-S	S-M
Gln3					
Val4	49	Ser108 Cys109		Glu106 Cys109	
Gln5	28	Ser108	Ser108	Ser108	Ser108
Arg29	46		Glu106(SB) Leu105 Tyr40		Tyr40
Ser33	25	Val39	Tyr40		
Tyr34	11		Tyr40		Tyr40
Arg55	60		Phe38 Glu41		Tyr40(H)
Arg101	124	Phe38 Val39(H)	Val39 Tyr40 Arg73 Tyr117	Val39	Tyr40
Phe102	125	Phe38	Gln35 Ser36 Val39 Val44 Gln46 Arg73	Val39	Ser36 Gly37 Val44 Gln46
Ser103	32	Gly37 Phe38(H)		Phe38	Phe38
Pro104	16	Ser36 Gly37	Gln35		Ser36
Val105	58	Ser36(H) Gly37	Ser36 Phe38		Ser36
Asn113	52			Lys111 Phe115	
Thr114	40		Arg73 Phe115		
Val115	19			Lys111	
Asp116	31	Cys109		Cys109 Lys111	
Ser117	14	Cys109	Cys109	Cys109	Cys109
Trp118	63	Cys109(H)	Cys109 Asn110 Lys111	Asn110	Asn110
Gly119	6			Ans110	
Gln120					

B. A3 and A6 residues interacting with ^{A3}Nb14 residues in the A3^{OB}- A6 - (^{A3}Nb14)$_2$ heterotetramer.

A3^{OB}	^{A3}Nb14				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**
Gln302	39		Phe102 Pro104 Val106	Phe102	Pro104 Val106
Glu303	41	Ser103 Pro104 Val105 Val106	Val105	Phe102 Pro104 Val105	
Gly304	26	Ser103 Pro104 Val105		Phe102 Val105	
Phe305	74	Arg101 Phe102 Ser103(H) Pro104	Arg55 Ser103 Val105	Arg55 Arg101 Phe102 Ser103	Ser103
Val306	29	Arg101 Phe102	Arg101 Phe102	Arg55 Arg101 Phe102	Arg101 Phe102
Phe307	157	Ser33 Arg55 Arg101	Arg29 Ser33 Tyr34 Arg101 Asp106	Ser33 Arg55(H)	Ser33 Tyr34 Arg101
Glu308	15		Ser33 Arg55	Arg55	
Val311	5		Phe102	Phe102	
Gln313	30		Phe102	Phe102	
Thr334	16		Thr114		
Arg336	31		Asp100 Arg101 Phe102		Phe102
Val365	36		Arg101 Asp116		
Pro366	40	Asp116	Arg101	Gln3 Arg101 Asp116	
Gln367	57	Val115 Asp116	Val115	Gln3	Asn113 Thr114 Val115(H) Asp116
Tyr368	103	Asp116 Ser117 Trp118(H)	Gln3 Gln5 Ser117	Gln3 Gln5 Ser117 Trp118	Val4 Gln5 Asp116 Ser117 Trp118
Asp369	23	Trp118	Trp118	Trp118	

A6	^{A3}Nb14				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**
Gln35	30		Phe102	Phe102	
Ser36	50	Ser103 Pro104 Val105 Val106	Phe102 Val105	Phe102 Val105	
Gly37	28	Ser103 Pro104 Val105		Phe102 Val105	
Phe38	70	Arg101 Phe102 Ser103(H) Pro104	Ser103 Val105	Phe102 Ser103	Ser103
Val39	49	Ser33 Arg101(H) Phe102	Phe102	Arg101	Arg101 Phe102
Tyr40	118	Ser33 Arg101	Ser33 Tyr34 Arg101	Arg29 Ser33 Tyr34 Arg101 Asp106	Ser33 Arg101
Val44	6		Phe102	Phe102	
Gln46	27		Phe102	Phe102	
Arg73	52		Asp100 Arg101 Phe102 Thr114		Phe102
Leu105	47		Val4 Arg29		
Glu106	23		Val4 Arg29		
Ser108	55	Val4 Gln5 Leu 6 Trp118	Gln5	Gln5 Ser117	Val4 Gln5
Cys109	59	Val4 Asp116 Ser117 Trp118(H)	Val4 Ser117	Val4 Ser117 Trp118	Val4 Asp116 Ser117
Asn110	69	Trp118	Trp118 Gln120	Trp118	Trp118 Gly119 Gln120
Lys111	78		Val115 Trp118	Trp118	Val112 Asn113 Val115 Asp116 Ser117
Tyr114	5	Asn113			

$A3^{OB}$	^{A3}Nb14					A6	^{A3}Nb14				
	BSA (Å²)	**M-M**	**S-S**	**M-S**	**S-M**		**BSA (Å²)**	**M-M**	**S-S**	**M-S**	**S-M**
Gly370	45	Trp118 Gly119 Gln120		Trp118 Gln120		**Phe115**	53	Asn113	Asn113 Thr114		Asn113 Thr114
Ser371	37	Trp118 Gly119 Gln120	Gln120	Gln120	Gly119 Gln120						
Arg373	21		Gln120								
Tyr375	15		Gln3	Gln5							
Tyr378	61	Thr114	Arg101 Thr114 Asp116	Asp100 Arg101 Thr114 Asp116	Asn113 Thr114 Val115 Asp116						

BSA: Buried surface area according to Pisa (11), **M-M**: Main chain - Main chain interactions; **S-S**: Side chain - Side chain interactions; **M-S**: Main chain - Side chain interactions; **S-M**: Side chain and Main chain interactions. **H**: Hydrogen bond; **SB**: Salt Bridge.

a: The interface residues in the $A3^{OB}$-A6 heterodimer structure (Current structure)

SUPPLEMENTARY REFERENCES

Note: Reference numbers 1-11 are those in the supplement. MT is the reference number of the same reference listed in the main text.

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