Table S1: Data processing statistics

Data Processing	
Resolutions(Å)(Outer shell)	25–1.8 (2.00-1.80)
Cell constant(Å)(a, b, c)	43.86, 51.46, 102.85
Space group	$P2_12_12_1$
No. of measured reflections	211,670
No. of unique reflections	22,222 (5,907)
Completeness (%)	99.7 (99.4)
R_{merge} (%)	11.1 (33.8)
I/s(I)	10.33 (3.19)
Refinement	
Resolutions (Å) (Outer)	25.0–1.8(1.88-1.8)
No. of reflections used	22,219 (2,550)
R factor	0.1994 (0.2753)
R_{free}	0.2752 (0.3453)
Completeness (Outer)	1.0 (0.99)
No. of atoms	
Protein	1,835
Suger	28
Glycerol	12
Water	228
R. m. s. deviations	
Bond lengths(Å)	0.010
Bond angles(°)	1.2
Average B factors($Å^2$)	
Main chain	32.237
Side chain	36.497
Suger	59.504
Glycerol	48.485
Water	34.095

R_{merge} = S | I - <I> | / S<I>
R_{cryst} = S| | F_{obs} | - | F_{calc} | | / S| F_{obs} |
R_{free} = as for R_{cryst} but calculated for test set comprising reflections not used in refinement.

Root mean squared deviations (Rmsd) in bond length and angles are given from ideal values.

Table S2: Comparison of chains A and B of apo CTLA-4 and the CTLA-4 monomers in the CD80, CD86 and lipocalin complexes.

Structure comparisons			r.m.s.d. Å^2*	No. of residues
apo CTLA-4 mol A	-	apo CTLA-4 Mol B	1.13	117
		CTLA-4 mol C complexed with CD80	0.91	117
		CTLA-4 mol B complexed with CD80	0.91	116
		CTLA-4 mol C complexed with CD86	0.95	116
		CTLA-4 mol C complexed with CD86	1.02	108
		CTLA-4 complexed with lipocalin	1.26	116
		murine CTLA-4	1.46	116
		CD28	1.62	107
		PD-1	1.82	105
apo CTLA-4 Mol B	-	CTLA-4 mol C complexed with CD80	0.85	116
		CTLA-4 mol B complexed with CD80	0.93	116
		CTLA-4 mol C complexed with CD86	1.08	114
		CTLA-4 mol C complexed with CD86	0.85	107
		CTLA-4 complexed with lipocalin	1.03	113
		murine CTLA-4	1.23	112
		CD28	1.41	105
		PD-1	1.71	103

* R.m.s. differences were calculated using Coot (39).

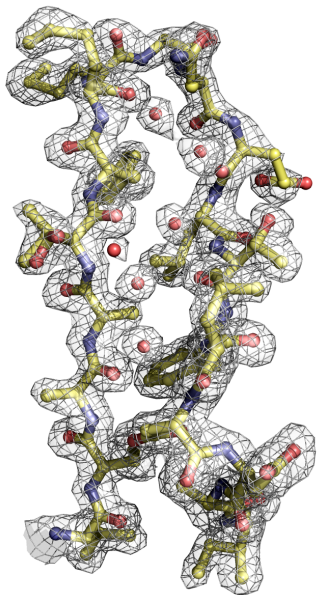

Figure S1. Electron density from the final model, showing the networked water spanning the C' and C" strands of CTLA-4 chain A. The view of the 2Fo-Fc map, contoured at σ1.0, is identical to that in Fig. 1d, main text.

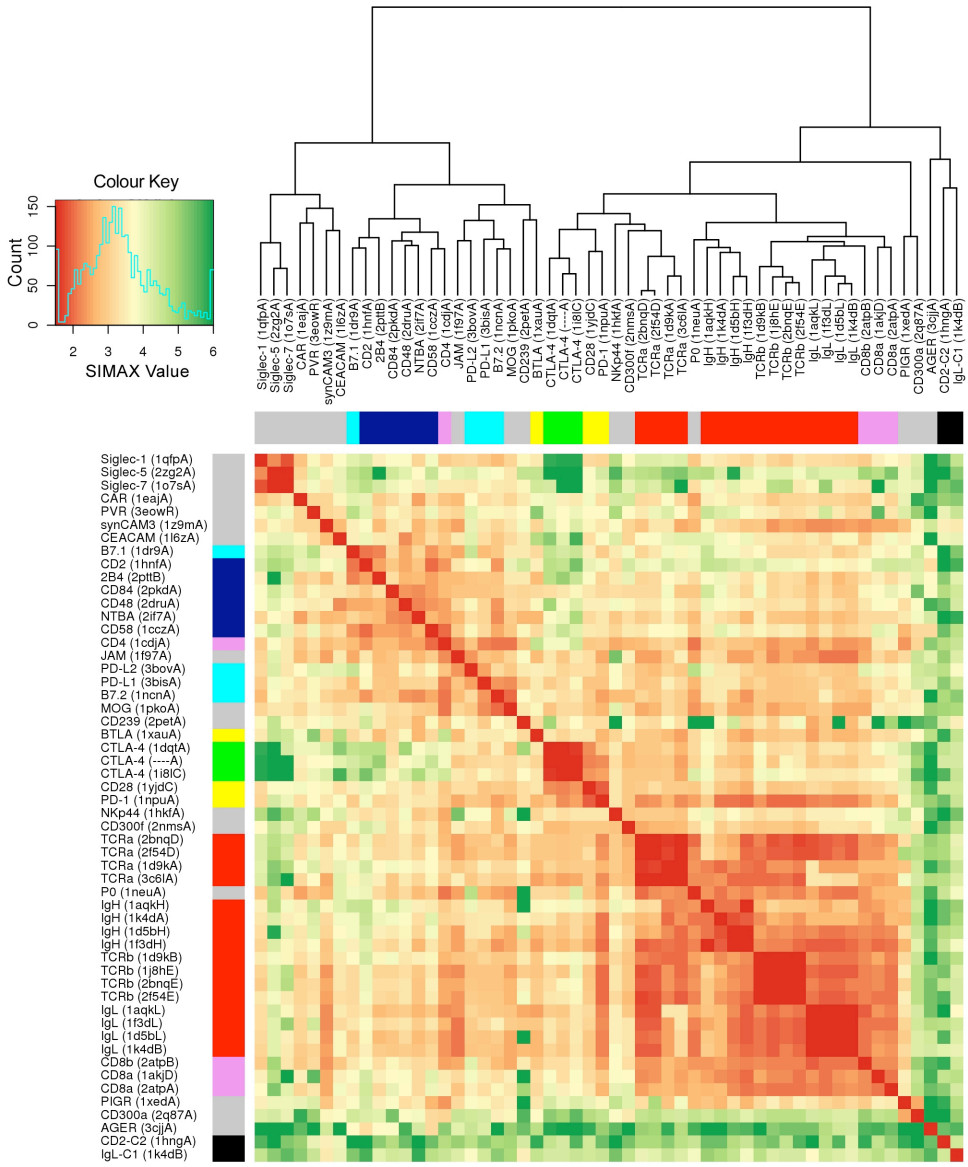

Fig. S2. Structural similarity dendrogram and heatmap among a selection of V-set IgSF domains, based on SIMAX scores. Domains are identified by the common short names of the proteins in which they occur, with the identifier and chain letter for the PDB structure used for comparison in brackets. Domains were order according to a dendrogram constructed using complete hierarchical clustering based on scores obtained from pairwise structural comparisons using SIMAX scoring (Dessailly et al., 2009). Colours in the heatmap range from red to dark green for high and low structural similarity, respectively (see colour key). A histogram in the colour key panel shows the frequency distribution of SIMAX scores in the set. Colour bars on the left and upper sides of the heatmap indicate known functional or family groupings: Green – CTLA-4, yellow – other members of the costimulatory/inhibitory family, red – antigen receptors, pink – coreceptors, dark blue – CD2 family, light blue – B7 family, black – outgroup (C1 and C2 set IgSF domains), grey – other V-set proteins.